INTRODUCTION

The medical applications of marijuana have long been a focus of public and scientific interest. The use of marijuana as a medicinal or therapeutic herb has been advocated in modern medicine for over a century (1,2). Remarkable advances have been made toward understanding the neu- rochemistry of cannabinoids, sparked by the discovery of endogenous cannabinoids and receptors (3–7). This has led to further hypotheses regarding potential therapeutic applications for cannabinoids (8,9).

Extensive evaluations of the pharmacology and biochemistry of cannabinoids have been published (8–11). The precise physiological role of the endogenous cannabinoid system in humans remains incompletely understood. Current opinion suggests it may represent a delicate tuning system of numerous finely regulated physiological processes, and has led to speculation that there may be a role for novel cannabinoid drugs in therapy for various pathological conditions (12).

There is, at present, evidence supporting modest clinical benefit for cannabinoids, particularly in an oral formulation, as an antiemetic for cancer therapy-related nausea and as an appetite stimulant for AIDS-associated anorexia/cachexia (13–17).

Further claims exist for the therapeutic benefit of marijuana to alleviate symptoms of spasticity associated with multiple sclerosis or spinal cord injury, glaucoma, epilepsy, hiccups, pain, and other conditions (18). Unfortunately, many of these claims are based on incomplete evidence and are, to date, of unproven efficacy in the clinical setting.

With the exception of cannabinoids as antiemetics, few randomized placebo-controlled clinical trials, considered necessary to demonstrate the clinical efficacy and safety of a symptom control drug in humans, have been conducted on the use of oral cannabinoids or smoked marijuana. This is, in part, attributable to the enormous time and expense of completing large human studies. Further, since marijuana is not an approved drug and is prohibited under the Controlled Drugs and Substances Act (CDSA) in Canada, acquiring it for clinical trials is a challenge (19). At present, in Canada, there are two drugs containing the active ingredients from marijuana approved for clinical use as antiemetics for chemotherapy-induced nausea: oral THC (Marinol®) and naboline (Cesamet®) (20).

Caution regarding the clinical use of marijuana is derived from strong but polarized public opinion, and the limited and sometimes conflicting scientific basis for its use. There is at least some evidence to support the hypothesis that smoked marijuana is unsafe, although complete characterization of its health effects remains to be determined (21–37).

Recent public interest in the medical use of marijuana has escalated (38), particularly in relation to reports in the popular media and to Health Canada initiatives for intensified research (39). Though acknowledging that scientific data establishing the safety and efficacy of smoked marijuana is inconclusive, Health Canada has made smoked marijuana accessible on a compassionate, case-by-case basis (40). Patients can apply, under section 56 of the CDSA, for an exemption permitting the cultivation and possession of crude marijuana for personal medical use. Patients with symptoms deemed refractory to all other medical therapies considered the standard of care, and with a statement of support by their treating physician are able to apply for the exemption (40). Recently, Health Canada announced amendments to the current exemption, effective as of July 15, 2001, that permit a broader availability for those applying.

However, policy towards the use of marijuana as medicine is, at present, clouded by conflicting information in several arenas, including an unclear definition of what constitutes a clinical indication for marijuana, incomplete epidemiological data on the prevalence of use, risk of personal harm and long-term effects, polarized interpreta-
tion of existing clinical evidence, and conflicting opinion in the public and scientific communities (41).

In order to address queries surrounding the medical use of marijuana—in particular, with respect to palliative care—we sought to provide a comprehensive review of human clinical trials using marijuana, or any of its active constituents, as an antiemetic, appetite stimulant, antispasmodic agent, anticonvulsant, or analgesic. Based on the best available evidence, we provide a summary of recommendations for the indications for medical therapeutic uses for marijuana in palliative care, in oral or smoked form.

METHODS

The authors obtained data on the medical applications of smoked marijuana, delta-9-tetrahydrocannabinol (THC) or other related cannabinoid compounds. Resources were identified from PREMEDLINE, MEDLINE 1966–December 2000, CANCERLIT 1975–November 2000, and AIDSLINE 1980–December 2000 using the following search terms: marijuana, cannabis, cannabinoid(s), and smoked marijuana. The search yielded 9,715, 461, and 385 citations from each database, respectively. These titles were meshed with the following subject headings: nausea, vomiting, or antiemetic; cachexia, anorexia, or appetite; pain, analgesic, or analgesia; palliative, terminal, or care; seizure(s), epilepsy or anticonvulsant(s); hiccups(s), spasticity, or multiple sclerosis. The results were subsequently limited to human and clinical trials.

We also conducted informal searches for studies that were known to us or to our colleagues, scanned reference lists of published articles and reviews, and inquired with experts in the field as a source of potential unpublished trial results to further minimize any publication bias.

To be included in this review, studies had to be human clinical trials and include patients treated with smoked marijuana, delta-9-tetrahydrocannabinol (THC), or related cannabinoid compounds. If the search detected very few citations, subject headings were re-expanded to include all citations, in order to detect possible case series or reports (e.g., MEDLINE: cannabinoid + hiccup(s) limited to human and clinical trial).

The primary outcome was the efficacy of oral THC or related compounds, or of smoked marijuana in attenuating or relieving symptoms. Secondary outcomes of interest were the incidence of adverse effects and risks associated with short and prolonged exposure (Table 1).

The potential therapeutic roles of medical marijuana in palliative care to manage nausea, pain, migraine, anorexia-cachexia, spasticity, seizures, and hiccups are summarized below.

RESULTS

The total number of studies of medical marijuana evaluated in this comprehensive review is 80, including 10 case reports.

Nausea and Vomiting

The majority of clinical trials on cannabinoids have examined their efficacy as antiemetics for cancer-related nausea and vomiting (42–90). Our search yielded 42 clinical trials and three case reports of smoked marijuana, THC, or other cannabinoids for use in cancer or AIDS-related nausea.

Despite many clinical trials with cannabinoids, none have compared their antiemetic efficacy against newer generation antiemetics such as the serotonin (5HT,) antagonists, ondansetron, granisetron, and dolasetron.

THC versus placebo. Four clinical trials have compared the antiemetic efficacy of oral THC to placebo (44–47). One randomized cross-over trial of 22 patients observed antiemetic effects in 70% versus 0% of cancer patients when compared with placebo. However, adverse effects were reportedly higher in those receiving THC, with euphoria in 81%, sedation in 67%, and dysphoria in 9% (44). A non-randomized pilot study of 54 patients with various malignancies and chemotherapy-induced nausea refractory to standard antiemetic regimens, who were given oral THC 5 mg/m² every four hours initiated prior to chemotherapy, showed partial or complete responses and improvement in nausea (72% vs. 28%) (46). Xerostomia and sedation were common (53% and 26%), while 16% had severe toxicity including bedridden somnolence, postural hypotension, and dysphoria. A small trial compared oral and smoked THC to placebo for chemotherapy-related nausea and did not find benefit (48). In general, these studies concluded that oral THC was an effective antiemetic superior to placebo, however, dose-related adverse sedating and psychotropic effects frequently limited its use.

| Table 1 / DOSE-LIMITING ADVERSE EFFECTS OF ORAL DELTA-9-TETRAHYDROCANNABINOL OR RELATED CANNABINOIDS AND SMOKED MARIJUANA REPORTED IN CLINICAL TRIALS REVIEWED |
|-------------------------------------------------|-----------------------------------------------|
| Physiologic Adverse Effects                     | Psychotropic Adverse Effects                  |
| Dizziness                                       | Somnolence                                    |
| Hypotension                                     | Dysphoria                                     |
| Dry mouth                                       | Abnormal thinking                             |
| Blurred vision                                  | Hallucinations/psychosis                       |
| Ataxia                                          | Depersonalization                             |

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Prochlorperazine. Ten clinical trials have compared the antiemetic efficacy of cannabinoids to prochlorperazine. Two randomized double-blind trials found oral THC produced equivocal results relative to prochlorperazine (49,50), and four suggested that oral THC was superior to prochlorperazine (51–54).

One randomized crossover trial of 24 patients receiving cisplatin-based chemotherapy for lung cancer compared nabilone 2 mg to prochlorperazine 15 mg, started 12 hours prior to initiation of chemotherapy (55). Nabilone was superior to prochlorperazine for reduction in vomiting episodes and preferred by two-thirds of patients. However, dose-limiting effects were evident in nearly 50%, causing three patients to withdraw due to ataxia and hallucinations. Herman et al. compared oral nabilone (4 mg every 8 hours) to prochlorperazine in a randomized double-blind crossover study of 113 cancer patients (56). Nabilone proved more effective for relief of nausea and vomiting (80% vs. 32%), with 8% achieving complete relief versus none with prochlorperazine. Adverse effects reported included somnolence (85%), xerostomia (84%), dizziness (69%), ataxia (68%), and 4.5% discontinued nabilone due to severe toxicity requiring medical attention.

Another randomized trial of 37 cancer patients showed smaller doses of nabilone (2 mg every 12 hours) were superior to slow-release prochlorperazine for patients not receiving cisplatin. For those receiving cisplatin, the drugs were equivalent (57). Dose-limiting adverse effects occurred in 25% of the nabilone patients. Two additional randomized clinical trials demonstrated nabilone was superior to prochlorperazine for both cisplatin chemotherapy and in controlling nausea, retching, and episodes of vomiting (58,59). The most common adverse effects reported were somnolence (57%) and dizziness (38%) (59).

Four clinical trials have examined the antiemetic efficacy of combination oral cannabinoids and prochlorperazine for various malignancies and chemotherapy regimens (60–63). Overall, these trials suggest that combination therapy of cannabinoids with prochlorperazine has superiority over either administered alone and contributed to reducing the incidence of dose-limiting adverse effects common to oral cannabinoids. One open crossover trial of 80 patients receiving cisplatin-based chemotherapy found greater control of nausea and vomiting with metoclopramide and dexamethasone compared to nabilone and prochlorperazine (32% vs. 19%, respectively) (63). These trials support a recent case report of the benefit of THC in a 50-year-old palliative patient with widespread metastatic malignant melanoma and otherwise refractory nausea and vomiting (64).

Pediatrics. Four clinical trials have examined the efficacy of cannabinoids in pediatric populations (65–67). Ekert et al., in two double-blind trials, found oral THC superior to metoclopramide (83% vs. 16%) and prochlorperazine (33% vs. 0%) for reducing chemotherapy-induced nausea in 19 pediatric cancer patients. Somnolence was, however, more common with oral THC (30% vs. 0%) (65). Nabilone was shown to be preferred and superior to domperidone in a randomized crossover trial of 18 pediatric patients (66). Chan et al. determined that nabilone was more efficacious than prochlorperazine in a randomized crossover trial of 30 children (improvement 70% vs. 30%, respectively) (67). Somnolence (67% vs. 17%) and dizziness (50% vs. 3%) were more common with nabilone.

Metoclopramide. Metoclopramide has been compared to oral cannabinoids in four clinical trials, one being in children discussed previously (65). A randomized study of 35 cancer patients compared the antiemetic efficacy of oral THC, oral thiemethylperazine, and intravenous metoclopramide (68). Results showed no difference in antiemetic efficacy. Further, adverse effects were greater for those receiving THC, including, most commonly, drowsiness, ataxia, and feelings of dysphoria. High-dose intravenous metoclopramide alone and with dexamethasone was shown to be an effective antiemetic for potent emetogenic chemotherapy regimens, in particular those containing cisplatin (69–71). In one randomized double-blind study of 27 cancer patients, Gralla et al. showed intravenous metoclopramide to be superior to oral THC (72). In another randomized crossover trial of 80 cancer patients receiving their first course of cisplatin chemotherapy, oral nabilone plus prochlorperazine was inferior antiemetic therapy to intravenous metoclopramide and dexamethasone (73).

Smoked marijuana. Four clinical trials have examined the efficacy of smoked marijuana, as an antiemetic. A prospective pilot study of 56 patients with various malignancies, where smoked marijuana (estimated dosage THC 5 mg/m²) was provided prior to and during chemotherapy for a total of four doses, suggested moderate effectiveness in 78% of patients. These results should, however, be viewed with caution. This trial was not randomized, symptoms were self-rated by a non-validated estimation, and those rated as responders were more likely to be smok-
ers (53% vs. 38%) and had prior marijuana exposure (52% vs. 17%) (74). Adverse effects were common, including sedation (88%), dizziness (39%), and dizziness (39%). In another trial, 15 patients receiving methotrexate were randomized to smoked marijuana (THC 1.93% or 17.4 mg) if vomiting occurred with oral THC, and were compared with patients receiving placebo (75). Higher plasma levels of THC were associated with lower subjective sensations of nausea, but an increased incidence of adverse effects overall, including sedation in 80%. In contrast, two small trials have found that smoked marijuana did not effectively reduce nausea and vomiting when compared to oral cannabinoids or placebo (48,76).

**Other.** Oral THC demonstrated no differences in efficacy when compared to halol (77) or domperidone (78). Neither levonantral nor chlorpromazine was effective for preventing nausea and vomiting following upper abdominal palliative radiotherapy (79). The THC analogue (BRI-4664), a synthetic cannabinoid, was shown to have weak antiemetic properties in a small non-randomized, non-placebo-controlled trial (80). Nine clinical trials examined the efficacy of parenteral levonantral, a synthetic cannabinoid. Though levonantral demonstrates antiemetic properties, it is associated with a high incidence of adverse effects and is not available for clinical use (81-88).

**AIDS.** One case report describes a terminal AIDS patient with nausea refractory to conventional management strategies who rapidly responded to daily oral nabilone (2 mg twice daily) without significant adverse effects (89). This observation supported previous anecdotal reports of the potential effectiveness of oral cannabinoids in refractory AIDS-related nausea and vomiting (90).

**Analgesia.**

Cannabinoids have proven analgesic properties in animal models (91,92). Cannabinoid-induced antinociception is principally mediated through CB1 receptors (93) in the brain, spinal cord, and peripheral nerves (94-98). Brain regions suggested to modulate antinociception include the thalamus, amygdala, rostral ventromedial medulla, and periaqueductal gray area—an important structure in both descending and ascending pain transmission (94,99).

Animal studies further suggest that endogenous cannabinoid systems may modulate antinociceptive processes in isolation, or via simultaneous activation or potentiation of specific opioid receptors (100-105; reviews: 9,10,106,107).
Cannabinoid systems represent potentially novel targets for analgesic development. Cannabinoids have reportedly been used as therapies for various chronic pain syndromes including pain associated with diabetic neuropathy, multiple sclerosis, phantom limb, spinal injury, and cancer. Our search yielded eight clinical trials and two case reports (Table 2).

In a pilot study of 10 advanced cancer patients with moderate pain, Noyes et al. administered single oral doses of THC at 5 mg, 10 mg, 15 mg, and 20 mg. Results suggested superior pain relief with oral THC over placebo. Higher dosages were, however, complicated by substantial somnolence and mental clouding (108).

In a follow-up study, Noyes et al. compared the analgesic effect of single doses of oral THC to oral codeine in 34 advanced cancer patients with moderate to severe pain syndromes (109). Analgesic superiority over placebo was shown with THC 20 mg and codeine 120 mg. However, patients receiving THC reported dose-limiting effects compared with placebo, including somnolence (94% vs. 29%), dizziness (97% vs. 26%), blurred vision (64% vs. 9%), and feelings of dysphoria (66% vs. 18%). Though small, this trial does suggest an analgesic effect of THC greater than placebo, although use was limited by an unacceptable rate of adverse effects.

Jochimsen et al. studied benzopyranoperdine (BPP), a THC cogener, and codeine compared with placebo in a double-blind crossover trial of 35 patients with cancer-related pain syndromes (110). Only patients receiving 120 mg of codeine had significant pain relief and reductions in pain intensity compared to placebo (54% vs. 26% for BPP and 34% placebo). BPP was no better than placebo for analgesia, but psychotropic adverse effects were more common.

Staquet et al., in two double-blinded crossover trials, compared the analgesic efficacy of a nitrogen analogue of THC (NIB) with 50 mg of codeine, 50 mg of secobarbital, and placebo in patients with advanced cancer and moderate to severe pain syndromes (111). NIB was superior to placebo in both trials, equivalent to codeine, and superior to secobarbital for pain relief in single doses. Adverse effects, including somnolence, were equivalent between groups (40% for NIB, 44% for codeine, 33% for secobarbital, and 21% for placebo, respectively).

Several studies have assessed the analgesic potential of opioids for non-malignant pain. Raft et al. studied pain threshold during dental extraction in 10 volunteers, and found intravenous THC (0.022 mg/kg or 0.044 mg/kg) was an inferior analgesic to intravenous diazepam (0.157 mg/kg), and equivalent to placebo (112). Hill et al. applied cutaneous electrical stimulation to assess pain and sensation thresholds in 24 experienced marijuana users following administration of smoked marijuana (THC 1.4% or approximately 12 mg) (113). Results suggested that smoked marijuana increased sensitivity to such painful stimuli when compared with placebo. In a similar series of studies, Milstein et al. assessed the effect of smoked marijuana (THC 1.3%) on absolute pressure and pain sensitivity in 16 marijuana users and non-users, demonstrating trends towards increased pain tolerance for experienced marijuana users (16% vs. 8% for non-users, respectively) (114).

A patient with chronic neuropathic pain relieved by nabilone failed to have reversal of analgesia by intravenous naloxone, suggesting that the analgesic properties of cannabinoids are not completely mediated through opioid receptor systems (115). Finally, a 29-year-old male with familial Mediterranean fever with chronic relapsing abdominal pain refractory to several standard therapies had significant analgesic benefit following an n-of-1 double-blinded randomized trial of oral THC (mean daily dose 23 mg) (116).

Migraine

Marijuana has historically been endorsed as symptomatic and prophylactic therapy for migraine headaches (2). More recently, claims for marijuana's efficacy, based largely on anecdotal data, have been renewed (117). Our search yielded one clinical trial, one case report, and one survey (118–120). To date, no randomized clinical trials in humans have established a role for either smoked or oral formulations of cannabinoids for use as acute or prophylactic therapy in patients suffering from migraine.

The mechanisms by which cannabinoids could potentially interfere with effects of migraines are not known. Studies have suggested that specific cannabinoid compounds may have a role in inhibition of serotonin release and platelet stabilization during migraine attacks (118).

In one case report of three young patients, abrupt discontinuation of chronic daily smoked marijuana use was linked with precipitation of migraine headaches (119). Though a prophylactic role of smoked marijuana for prevention is theorized, no comment is made concerning the possible role of marijuana withdrawal in precipitating subsequent migraines. One small survey of 54 patients at a drug treatment centre suggested marijuana use is commonly employed as a method of self-medication for migraine sufferers (120).
Anorexia-cachexia Syndrome

Cannabinoids may possess stimulating effects on appetite for patients with anorexia/cachexia syndrome associated with advanced cancer or AIDS (121–123).

Anorexia-cachexia syndrome is a complex and incompletely understood phenomenon, likely involving aberrant metabolic, immune, and cytokine function, and is common in both cancer and AIDS patients (123). Early small clinical trials in young healthy adults described an association with marijuana and increased appetite (124–127). Our search yielded 13 mostly small and open-label clinical trials, including those aforementioned (Table 3).

Cancer. In a double-blind placebo-controlled crossover study of 54 advanced cancer patients, THC 0.1 mg/kg three times daily one hour before meals was reported to be effective for both weight gain and improvement of depression. There were, however, problems with the study design (128). Only 34 patients finished the two-week trial, and only 16 could be evaluated for changes in weight.

An open-label non-randomized pilot study of 19 patients with various malignancies started on oral THC 2.5 mg given three times daily after meals suggested subjective improved in appetite, however clinical anorexia was not defined on inclusion, most patients had a ECOG performance status of two or better, and only 10 patients completed the study (122).

Plasse et al., in two open-label cross-over studies of 42 mostly THC-naive cancer patients with overall good performance status (median Karnofsky scores 70–90), reported no weight gains and only trends toward subjective appetite improvement after three weeks of oral THC. Adverse effects were reported in 65% receiving low dose (>7 mg/m²) and in 58% receiving high-dose (>7 mg/m²) THC, with dysphoric effects in 12% and 28%, respectively (129).

AIDS. Abrams et al. reported clinically significant increases in caloric intake and weight gain in 62 HIV-positive patients randomized to smoked marijuana or oral THC versus placebo over a 21-day period. These patients did not have clinical defined wasting (i.e., >10% weight loss in six months prior to entry) (17).

One non-randomized pilot study of 10 HIV-positive patients with AIDS-defining illnesses, all of whom received oral THC 2.5 mg three times daily, titrated to minimize adverse effects, for a median duration of 12 weeks, suggested a stabilization or modest increase in weight (+0.54

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Population</th>
<th>Patients (n)</th>
<th>Design</th>
<th>Dose/From THC</th>
<th>Results</th>
<th>Adverse Effects</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Timpon et al. (131)</td>
<td>AIDS</td>
<td>52</td>
<td>R, non-DB with Megace, four arms</td>
<td>THC 2.5 mg PO bid +/- Megace</td>
<td>THC less effective than Megace</td>
<td>confusion, anxiety, euphoria, psychosis</td>
<td>39/52 completed</td>
</tr>
<tr>
<td>Beal et al. (132)</td>
<td>AIDS</td>
<td>139</td>
<td>R, PL</td>
<td>THC 2.5 mg PO bid</td>
<td>THC improved VASH; not weight</td>
<td>reported as mild</td>
<td>88/139 completed</td>
</tr>
<tr>
<td>Beal et al. (121)</td>
<td>AIDS</td>
<td>94</td>
<td>non-R open-label</td>
<td>THC 2.5 mg PO bid</td>
<td>THC improved VASH and weight (only 1 month)</td>
<td>psychosis, sedation, dysphoria (44%)</td>
<td>22/94 completed, results NS, only trends on weight stabilizing</td>
</tr>
<tr>
<td>Abrams et al. (17)</td>
<td>HIV</td>
<td>62</td>
<td>R, DB, PL</td>
<td>THC 2.5 mg PO bid or smoked marijuana</td>
<td>increased caloric intake and weight gain</td>
<td>mild</td>
<td>not clinically cachexic</td>
</tr>
<tr>
<td>Gorter et al. (130)</td>
<td>HIV/ AIDS</td>
<td>10</td>
<td>non-R</td>
<td>THC 2.5 mg PO tid</td>
<td>increased/stabilized weight</td>
<td>mild</td>
<td>NR</td>
</tr>
<tr>
<td>Nelson et al. (122)</td>
<td>Cancer</td>
<td>19</td>
<td>non-R open-label</td>
<td>THC 2.5 mg PO tid after meals</td>
<td>THC improved appetite, trends for weight/caloric intake</td>
<td>common</td>
<td></td>
</tr>
<tr>
<td>Regelson et al. (128)</td>
<td>Cancer</td>
<td>54</td>
<td>R, DB</td>
<td>THC 0.1 mg/kg PO tid before meals</td>
<td>THC improved appetite and weight</td>
<td>sedation, confusion, dizziness</td>
<td>34/54 completed, both in and out patients</td>
</tr>
<tr>
<td>Plasse et al. (129)</td>
<td>Cancer</td>
<td>42</td>
<td>non-R open-label</td>
<td>THC 2.5–5.0 mg PO bid</td>
<td>THC improved appetite and weight</td>
<td>10 patients withdrew</td>
<td>design NR, results NS</td>
</tr>
</tbody>
</table>

THC=delta-9-tetrahydrocannabinol; VASH=visual analogue scale for hunger; HIV=human immunodeficiency virus; AIDS=acquired immune deficiency syndrome; PO=orally administered; bid=twice daily; tid=three times daily; PL=placebo; NS=nsignificant; R=randomized.
kg/month). Limitations of this study include no clear definition for clinical anorexia-cachexia, three patients taking or having previously taken megestrol acetate, and exclusion of data on adverse effects (130).

An open-label trial of 52 patients with AIDS compared oral THC and megestrol acetate, as single agents and in combination, on quality of life and weight gain (131). Of 39 patients evaluable, only patients receiving megestrol acetate had improved gains in weight and quality of life scores. Adverse effects of those receiving oral THC were common, including hallucinations, confusion, and euphoria.

Beal et al. randomized 139 patients with AIDS to oral THC 2.5 mg or placebo, twice daily over a six-week period (132). Primary outcomes were changes in appetite based on visual analogue scale (VAS) and weight. Only 88 patients were evaluable. Improvements in appetite were reported at four weeks, with no changes in weight for those receiving oral THC. Adverse effects with oral THC were common, with 17 patients requiring dose reductions.

As follow up, an open-label non-randomized study of 94 patients evaluated the long-term efficacy and safety of oral THC on appetite and weight in patients with AIDS (121). All patients were started on oral THC, however, only 22 patients completed the 12-month course. Oral THC was associated with improved appetite, but conclusive data on stabilization or gains in weight cannot be inferred due to loss of follow up. Further, 44% of patients experienced adverse effects including depersonalization, confusion, and euphoria.

Central Nervous System Disease and Spasticity

Endogenous cannabinoid systems have been proposed as potential targets for therapy of spasticity and other neurologic disorders (10,133). Animal studies and anecdotal reports suggest evidence exists for a role for cannabinoids in attenuating symptoms of central nervous system disease (134). To date, few clinical trials have examined its safety and efficacy in humans. Our search yielded four clinical trials, one n-of-1 trial, and one case report (Table 4).

A small study of nine marijuana-naïve patients with spasticity from multiple sclerosis (MS) examined the effect of either 5 mg or 10 mg oral THC or placebo on muscle tone, strength, reflexes, and EMG studies (135). Patients who received 10 mg THC showed some improvement in spasticity by clinical measurement, however, overall EMG studies of most patients were not performed. Adverse effects at higher doses of THC (10 mg doses) were reported.

In a randomized trial of 13 patients with spasticity from MS, patients received 2.5 mg–15 mg oral THC or placebo for five consecutive days, followed by crossover with a two-day washout (136). Subjective improvements were reported at doses greater than 7.5 mg THC, but these doses were also correlated with a greater incidence of adverse effects.

Another randomized trial of smoked marijuana (1.54% delta-9-THC) in 20 healthy and MS patients with spasticity compared postural responsiveness and response speed (137). Objective postural tracking error increased after smoked marijuana in both groups, and worsened for patients with pre-existing spasticity. Increased tracking error was associated with decreased response speed. These findings are consistent with previously reported declines in mental, motor, and postural stance in normal volunteers, suggesting that marijuana can further impair posture and balance in normal sub-

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**Table 4 / STUDIES THAT USED ORAL DELTA-9-TETRAHYDROCANNABINOL OR SMOKED MARIJUANA FOR SPASTICITY**

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Population</th>
<th>Patients (n)</th>
<th>Design</th>
<th>Dose/Form THC</th>
<th>Results</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petro et al. (135)</td>
<td>Spasticity due to MS</td>
<td>9</td>
<td>DB</td>
<td>THC 5, 10 mg vs. PL</td>
<td>improved clinically but not by EMG</td>
<td>common at higher doses</td>
</tr>
<tr>
<td>Ungerfeider et al. (136)</td>
<td>Spasticity due to MS</td>
<td>13</td>
<td>R, DB, crossover</td>
<td>THC 2.5–15 mg vs. PL</td>
<td>subjective improvement at THC &gt;7.5 mg</td>
<td></td>
</tr>
<tr>
<td>Greenberg et al. (137)</td>
<td>Spasticity due to MS</td>
<td>20</td>
<td>R, DB</td>
<td>smoked marijuana (1.54% THC)</td>
<td>increased postural tracking error, decreased response speed</td>
<td></td>
</tr>
<tr>
<td>Martyn et al. (139)</td>
<td>Spasticity due to MS</td>
<td>1</td>
<td>n-of-1, R</td>
<td>nabilone 1 mg vs. PL</td>
<td>improvement in pain from spasticity by VAS</td>
<td>mild sedation</td>
</tr>
<tr>
<td>Clifford et al. (141)</td>
<td>Tremor and ataxia due to MS</td>
<td>8</td>
<td>non-R, non-DB</td>
<td>THC 5 mg, titrated by 5 mg increments</td>
<td>subjective improvement</td>
<td>50% prior users</td>
</tr>
</tbody>
</table>

MS=multiple sclerosis; THC=delta-9-tetrahydrocannabinol; PL=placebo; VAS=visual analogue score; R=randomized; DB=double blind.
jects and worsen nervous system performance in patients with multiple sclerosis (138).

In an n-of-1 trial of a patient with MS-related spasticity, nocturia, and malaise, administration of oral nabilone provided subjective improvements in all symptoms, in particular, pain from spasticity (139). One case reported improvements in both subjective and objective measures (EMG studies) in a 30-year-old MS patient following administration of a single smoked marijuana cigarette (140).

Although not a trial assessing spasticity, one small study of eight MS patients examined the efficacy of oral THC on ataxia and tremors (141). Results suggested five patients experienced mild subjective improvement in tremor. Overall, none reported objective improvement in symptoms.

Seizures and Epilepsy

Various cannabinoids may possess anticonvulsive activity, and the endogenous cannabinoid system may represent a potential avenue for new drug development (142,143). There is, however, a general paucity of available literature in this area and what there is contains contradictory findings (144,145).

Studies in animal models (146–148) have suggested potential role of certain cannabinoids in controlling anticonvulsant activity. Differing data suggest cannabinoids may theoretically contribute to lowering of seizure thresholds (146,147,149–152). Our search yielded one clinical trial and two case reports.

Cunha et al. randomized 15 patients with generalized epilepsy with a temporal focus refractory to standard therapy to either cannabidiol (200 mg–300 mg daily) or placebo, in addition to their routine anticonvulsants, for up to 4.5 months (143). Seven of the eight patients in the cannabidiol group improved, four improved considerably in terms of seizure activity. Four patients reported difficulty with somnolence associated with cannabidiol.

A case report of a 24-year-old patient with difficult-to-control epilepsy, despite phenytoin and phenobarbital, reported complete control of seizures when smoked marijuana (two to five marijuana cigarettes per night) was added to the therapy. Further, the patient experienced breakthrough seizures when his prescribed medication was discontinued, suggesting synergy of the phenytoin, phenobarbital, and smoked marijuana (153). Another case report of a 29-year-old male with known bipolar disorder, alcoholism, and chronic daily marijuana use reported new-onset complex partial seizures and EEG abnormalities following abrupt discontinuation of marijuana use (154).

Hiccups

Our search yielded one case report of a patient with AIDS and esophageal candidiasis, who developed refractory hiccups following minor surgery (155). Following courses of several standard anti-singultus therapies, the patient, who had previously used marijuana, smoked marijuana with subsequent complete relief of hiccups. Persistent hiccups has been reported as a rare complication of AIDS, most frequently as a symptom of an underlying opportunistic infection, particularly of the esophagus or central nervous system (156).

CONCLUSIONS

Palliation of symptoms is an ethical imperative for physicians and other providers caring for patients with advanced illness. Comprehensive patient assessment, identification, and treatment of the underlying cause of symptoms, and a multidisciplinary and pathophysiologically based approach to symptom management are foundations of palliative care delivery. No single drug will be a panacea for palliative patients. Further, currently available information on medical marijuana is incomplete for the palliative care setting. Many palliative patients in need of symptom control may not tolerate the serious toxicity of cannabinoids, particularly marijuana-naïve patients with multisystem disease who are receiving other medications with a potential for side effects.

Based on a comprehensive review of published literature, there is evidence to support the following recommendations for medical use of cannabinoids in the palliative setting:

1. Nausea and Vomiting: Cannabinoids have antiemetic properties. There is evidence that oral formulations are superior to placebo and equivalent to some antiemetics such as prochlorperazine. However, dose-related adverse effects frequently limit their use. Further, certain patient populations have proven more susceptible to psychotropic adverse effects, in particular in medication-naïve and elderly patients. Their use in these patients, therefore, warrants caution. There is evidence to suggest that oral formulations in combination with other antiemetic agents are effective and may contribute to lowering the incidence of adverse effects. Based on the available evidence, we would not recommend that oral cannabinoids be used as first-line antiemetics. They may, however, prove effective for refractory nausea or as an adjuvant to other antiemetics. To date, there is no evidence for
superiority of smoked marijuana over oral cannabinoids or other antiemetics for cancer or AIDS-associated nausea and vomiting.

2. Analgesia: Cannabinoids have analgesic activity, however, the magnitude of effect appears modest at best, with no evidence of superiority over weak opioids such as codeine. Further, significant adverse effects that limit their use commonly complicate their administration at dosages sufficient for analgesic benefit. It is unclear whether the analgesic effect is clinically evident in the absence of the neuropsychiatric effects of cannabinoids. There appears to be little or no justification to use cannabinoids for pain in palliative patients outside of the clinical scenario of medically refractory pain (157). It is hoped that further understanding of the intrinsic neurochemistry of cannabinoid systems will provide avenues for development of novel analgesic therapies with lower adverse effect profiles.

3. Migraine: To date, there exists only scant anecdotal evidence and no randomized clinical trials in humans that have established a role for either oral or smoked cannabinoids for use as acute or prophylactic therapy in patients suffering from migraine.

4. Anorexia-cachexia Syndrome: There is some evidence of improvement in appetite reported with cannabinoids, however, the evidence is not conclusive for stabilization or gain in weight, or nutritional improvement in the setting of clinically significant anorexia-cachexia. Further clinical trials are essential to clearly define the role for cannabinoids in the treatment of cancer- or AIDS-associated anorexia-cachexia syndrome.

5. Spasticity: There is low level and conflicting evidence for the use of cannabinoids for relief of spasticity, and there is little compelling evidence to support their use for relief of pain in spasticity in palliative care patients. Except in extraordinary circumstances, we do not recommend the use of cannabinoids for spasticity. However, relief of spasticity-related pain is an area of intense research interest, and further information in this area is expected.

6. Seizures and Epilepsy: Some evidence suggests that specific cannabinoid compounds may, in the future, yield potential targets for drug development. Based on current published evidence, there is insufficient evidence on the use of oral THC or related cannabinoids, or smoked marijuana for chronic seizure control, either alone or in combination with conventional anticonvulsants. Therefore, its use cannot be recommended. Further, animal studies and anecdotal data suggest that THC, and therefore smoked marijuana, may decrease seizure threshold, in particular during periods of withdrawal. We recommend that patients with severe forms of epilepsy should be counselled about the possible proconvulsant effects of THC and smoked marijuana.

7. Hiccups: There is no evidence, at present, to suggest that either oral or smoked marijuana is equivalent to or better than standard interventions for hiccups in the palliative care setting. Therefore, there is no justification for their recommendation.

Although currently published information does not support the use of cannabinoids in palliative care in most clinical settings, there is reason to hope that further basic and clinical research will demonstrate opportunity for the use of currently available or novel cannabinoids for improved symptom control in palliative care.

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