National Academy of Science:

Summary of Report on Therapeutic Uses of Cannabis and Cannabinoids

Wayne Hall, Centre for Youth Substance Abuse Research, UQ

Megan Weier, National Drug and Alcohol Research Centre, UNSW

A Committee of the National Academy of Science of the USA was asked by US Federal and State government agencies and philanthropic bodies to undertake a comprehensive review of the evidence on the health effects of cannabis and its constituents. They were asked to review research that had been published since the Academy last reviewed the literature on medical uses of cannabis in 1999 and to consider the medical uses of cannabis and cannabinoids and the health risks of recreational cannabis use (National Academies of Science, 2017). Only the findings on the first are summarised here.

The committee's approach was to review high quality systematic reviews and meta-analyses of the research literature. They also examined high quality research studies that not been included in the systematic reviews or that had appeared after the most recent systematic review. In the absence of any systematic reviews, the Committee reviewed primary research published between January 1999 and August 2016. The Committee drew on the findings of 16 good- to fair-quality systematic reviews and 21 primary literature articles when formulating their conclusions.

The committee synthesised the evidence by defining the weight of evidence that would warrant varying levels of confidence in the conclusion that cannabis or cannabinoids were or were not effective in treating a medical condition, namely, conclusive, substantial, moderate, limited and insufficient. The type of evidence that was required to warrant each of these descriptors is shown in Box 1.

Box1:

Strength of conclusion	RCT evidence on efficacy from	Support from other studies	Role of chance, bias, and confounding
Conclusive	Strong study designs	Many studies; no opposing findings	Can be ruled out with reasonable confidence
Substantial	Strong study designs	Several studies; no opposing findings	Cannot be ruled out but minor
Moderate	Some good- to fair-quality studies	Several studies; very few or no opposing findings	Cannot be ruled out with confidence
Limited	Weak study designs	Mixed findings from other studies	Significantly uncertain
Insufficient	None or evidence from single poor study	Mixed findings or none	Substantial concerns

The committee examined twenty-four groups of medical conditions for which medical use of cannabis or cannabinoids have been advocated. These were: chronic pain; cancer; nausea and vomiting produced by cancer therapy; appetite stimulation in HIV/AIDS, Cancer and Anorexia Nervosa; Irritable Bowel Syndrome; Epilepsy; Spasticity in Multiple Sclerosis and Spinal Cord Injury; Tourette's Syndrome; Amyotropic Lateral Sclerosis; Huntington's Disease; Parkinson's Disease; Dystonia; Alzheimer's Disease; Glaucoma; Traumatic Brain Injury and Spinal Cord Injury; Addiction; Anxiety Disorders, Depressive disorders; sleep disorders; Post-Traumatic Stress Disorder; and Schizophrenia. These conditions were selected for review because they were among the indications for which medical cannabis users in the USA reported using cannabis.

The following cannabis products and cannabinoids were included in the review: cannabis smoked and inhaled; synthetic tetrahydrocannabinol (dronabinol); THC analogues (nabilone); cannabidiol (CBD); and medicinal cannabis plant extracts that included nabiximols (plant extracts with equal ratios of THC and CB) and epidiolex (a CBD-based plant extract).

Chronic pain

Rationale

The treatment of chronic pain is the most commonly reported reason for the medical use of cannabis in the USA. This use has biological plausibility in that the cannabinoids have been shown to reduce pain in animals, the endocannabinoid system appears to be implicated in pain, and cannabinoid receptors are found in brain regions involved in the expression of pain.

Evidence

The Committee found five systematic reviews of fair to good quality. It gave greatest weight to the findings of the most comprehensive high quality review, that of Whiting et al (2015). Whiting et al restricted their review to parallel group randomised controlled trials that had been conducted to a reasonable standard of rigor. Their findings were consistent with those of the other reviews (many of which included studies of weaker design, such as, cross over studies) in suggesting that cannabinoids have a modest effect in reducing various types of pain.

Whiting identified 28 RCTs that included a total of 2,454 patients with various types of chronic pain in which patients were randomly assigned to receive either cannabis or a cannabinoid and some control intervention. In all but one case, the comparison condition was a placebo. Whiting et al did not find any differences in efficacy between different cannabinoids in treating different pain conditions but the small sample sizes of the studies provided limited statistical power to detect any differences. There was only one trial of inhaled cannabis flowers which showed one of the largest effects of cannabis on pain.

There were an additional two RCTs published since the Whiting et al review. These compared the effects of varying doses of inhaled cannabis flower and placebo in the effects on acute pain. One found that inhaled cannabis produced a dose-related reduction in pain (Wallace et al., 2015); the other did not (Wilsey et al., 2016). These findings were consistent with those from the Whiting et al review.

Conclusions

The committee concluded that there was "substantial evidence that cannabis is an effective treatment of chronic pain in adults". It noted that this much of this evidence came from trials of nabiximols in patients with multiple sclerosis. Much less was known about the effectiveness and side effects of the forms of cannabis that were most often sold in US medical cannabis dispensaries to treat a wide variety of different types of pain, viz vaporised cannabis flower, cannabis concentrates and edibles forms of cannabis.

Cancer

Cannabinoids as curative anti-cancer agents

Rationale

Cancers include a wide range of disorders of abnormal, unregulated cell division that often result in tumour growth. Preclinical studies of the effects of cannabinoids on cancer cell preparations suggest that the endocannabinoid system may play a role in regulating cell growth. This has encouraged research into the possibility that cannabinoids may be used to treat some cancers.

Evidence

The committee only identified one systematic review of primarily preclinical animal research on the use of cannabinoids to treat one type of brain cancer, glioma (Rocha et al., 2014) . This review summarised suggestive pre-clinical evidence that cannabinoids had anti-tumour effects in animal models of glioma. One small human trial of cannabinoids in patients with this cancer was inconclusive. No further primary research studies were identified.

Conclusions

The Committee concluded that there was too little research to make a judgment about the efficacy of cannabinoids in treating gliomas. There was a signal from preclinical research that cannabinoids may have a therapeutic effects in glioma but more clinical research was required to evaluate it.

Nausea and vomiting in cancer chemotherapy

Rationale

The motivation for this medical use came from patient reports in the 1970s that smoking cannabis relieved the nausea produced by cancer chemotherapy. These reports prompted researchers to conduct randomised controlled trials of the efficacy of oral cannabinoids (principally dronabinol) in controlling chemotherapy-induced nausea and vomiting (CINV).

Evidence

The Committee relied on the reviews of Whiting et al (2015) and a systematic review of studies cannabinoids undertaken as part of the Cochrane Collaboration by Smith et al (2015). The Whiting et al (2015) review summarised the findings of 28 randomised controlled trials that compared various cannabinoids (nabilone (14), tetrahydrocannabinol (6),

levonantradol (4), dronabinol (3) and nabiximols (1) with placebo and another anti-emetic drug (most often prochlorperazine) Most of these studies found that cannabinoids produced greater reductions in nausea than placebo. They also produce at least as good if not better control over CINV than the anti-emetic drugs with which they were compared. Whiting et al did not make any specific recommendations on the clinical use of cannabinoids to treat CINV.

The Cochrane reviewed included 23 clinical trials, 19 of which were cross-over studies. Smith et al (2015) concluded that cannabinoids were more effective than placebo and similar to conventional anti-emetics in treating CINV but they also caused more adverse events such as dizziness, dysphoria, euphoria, "feeling high," and sedation. They found a weak patient preference for cannabinoids over placebo and stronger preference for cannabinoids over other anti-emetics. They nonetheless concluded that cannabinoids should not be used as a first line treatment for CINV, suggesting that they only be used when other anti-emetics had failed. There have only been three clinical trials of the use of cannabinoids in children experiencing CINV and their results have been equivocal.

The Committee identified one additional study that was conducted in 2007 and not included in either of these reviews. It compared the anti-emetic effects of dronabinol with those of ondansetron and found that the two drugs equally effective in reducing CINV (Meiri et al., 2007).

Conclusions

The Committee noted that nabilone and dronabinol have been found to be superior in efficacy to placebo and equivalent in efficacy to the anti-emetic drugs used when the trials were conducted (prochlorperazine in most cases). The 2007 study found that cannabinoids were equivalent in efficacy to ondansetron but no studies had compared the efficacy of cannabinoids with the newer widely used anti-emetics, the neurokinin-1-inhibitors. It noted the dearth of trials of inhaled cannabis and concluded that there is "conclusive evidence that oral cannabinoids are effective anti-emetics in the treatment of chemotherapy-induced nausea and vomiting" (p4-7).

Anorexia and Weight Loss in HIV/AIDS, Cancer and Anorexia Nervosa

Rationale

Recreational cannabis users often report that cannabis use stimulates their appetite, a phenomenon colloquially knows as "the munchies". There were also reports from patients with the AIDS syndrome that smoking cannabis stimulated their appetite. These reports prompted a number of controlled clinical trials in the 1980s that led to dronabinol being approved for this indication in the USA in the mid-1980s.

Evidence

The Committee identified two systematic reviews of the small research literature on this health outcome. Whiting et al (2015) reviewed the outcomes of four RCTs of cannabinoids as appetite stimulants that involved 255 patients with HIV/AIDS. All of these studies were judged to be at high risk of bias. Lutje et al (2013) reviewed seven clinical trials and concluded that there was a lack of evidence for the efficacy and safety of cannabis and cannabinoids in treating AIDS-related anorexia. No additional primary studies were

identified because of "the virtual disappearance of the syndrome since effective antiretroviral therapies became available in the mid-1990s" (NAS, p 4-8).

There were no systematic reviews of controlled trials of the effectiveness of cannabis or cannabinoids in treating cancer-related anorexia. Two controlled studies were reviewed by the Committee. The first was discontinued before completion because of patient attrition due to side effects and a lack of evidence of efficacy (Strasser et al., 2006). Another larger trial found megestrol acetate superior to dronabinol in stimulating appetite and weight gain in cancer patients (Jatoi et al., 2002). There were no systematic reviews and only a small number of small sample studies of the use of cannabinoids as appetite stimulants in anorexia nervosa (Andries et al., 2014). Their results were equivocal, namely, small weight gain but no improvement in the clinical condition or in the patients' quality of life.

Conclusions

The Committee concluded that there was: "limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS". It also concluded that there was "insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancer associate cachexia or anorexia nervosa" (p 4-10).

Irritable Bowel Syndrome

Rationale

There is some biological plausibility for a clinical role of cannabinoids in the treatment of inflammatory bowel disease (IBS). CB1 receptors are found in the mucosa of the colon and endocannabinoids inhibit the activity of these CB1 receptors.

Evidence

No systematic reviews have been published because there has only been one small trial of dronabinol in 36 patients with IBS (Wong et al., 2012). This study failed to find any evidence that dronabinol improved bowel function or reduced the symptoms of IBS.

Conclusions

The committee concluded that there was "insufficient evidence to support of refute effectiveness of dronabinol in treating symptoms of IBS." (p4-11).

Epilepsy

Rationale:

Epilepsy is a common neurological disorder the symptoms of which are not well controlled in around one third of cases by current anti-convulsant drugs. There is a reasonable rationale for using cannabinoids to treat epilepsy, namely, animal studies suggest that THC and CBD have anti-convulsant effects, and there are patient reports that the use of cannabis and cannabis preparations reduce the frequency of seizures.

Evidence

The committee found two fair quality reviews of evidence assessing the efficacy of cannabis and cannabinoids as monotherapies or adjunctive treatments for epilepsy (Gloss and Vickrey, 2014, Koppel et al., 2014). These reviews summarised a small number of reports of poor quality studies that included a total of 48 patients. No RCTs had been published at the time of these reviews (or the Committee's consideration of the reviews). Several clinical trials have reportedly been completed but their results have yet to be published.

One open label study of oral cannabidiol has been published since the two reviews were completed. Results have been reported on different numbers of participants in two papers (Devinsky et al., 2016, Rosenberg et al., 2015). These authors examined the efficacy of oral cannabidiol in reducing seizures in 162 children with intractable epilepsy treated in US epilepsy treatment centres and found a 37% reduction in the frequency of seizures.

A case series was also reported from Israel (Tzadok et al., 2016). In this report patients with epilepsy were observed after being treated for six months with an oral preparation of cannabidiol and tetrahydrocannabinol (at a 20:1 ratio). Patients were clinically classified into groups on the basis of clinical judgment about the degree of control achieved over seizures. Neither study was double blind. Because they were case series there were no comparison groups with which to compare the effects of cannabinoids on seizure frequency or severity.

Conclusions

The committee assessed the available evidence on the efficacy of cannabinoids in epilepsy as highly subject to bias. This was because in the available studies neither the doctors nor patients were blind to the treatment received and, in the absence of a placebo or another treatment, it was difficult to be ensure that the apparent benefits of cannabidiol were not due to placebo effects or regression to the mean. The committee concluded that there was "insufficient evidence to support or refute the conclusion that cannabinoids are effective in the treatment of epilepsy" (p4-13).

Spasticity

Rationale

The main reason for exploring the clinical use of cannabinoids to treat spasticity were reports by patients with multiple sclerosis that the severity of their spasticity symptoms was reduced when they smoked cannabis. These reports led to clinical trials of nabiximols in the United Kingdom.

Evidence

The major systematic review of these studies is Whiting et al (2015). They reviewed 11 parallel group studies of cannabinoids (nabilone and nabiximols) in patients with MS and 3 studies in patients with paraplegia. They were able to perform a meta-analysis of 3 studies of nabiximols in patients with MS. They found reasonably consistent evidence of clinical improvement on patient rated symptoms of spasticity but did not find a difference between cannabinoids and placebo when spasticity was rated by physicians and they did not find any difference in efficacy between nabilone and nabiximols.

A review by Koppel et al (2014) of studies in MS came to the same conclusion as Whiting et al (2015), namely, that orally administered cannabinoids and nabiximols were "probably effective in reducing severity of patient rated spasticity but not physician rated symptoms". The Committee noted doubts in the literature about the sensitivity of the Ashworth scale for physician ratings and a lack of agreement on how large a change on this scale represented a clinically significant improvement.

One further cross over RCT has been reported since these reviews but it had a high rate of loss to follow up so it was judged to be at high risk of bias (Leocani et al., 2015). Its findings were not given much weight by the Committee.

Conclusions

The Committee concluded that nabiximols and cannabinoids were "probably effective" in reducing patient rated severity of spasticity in MS but there was insufficient evidence to judge their efficacy in treating spasticity in persons with spinal cord injuries (p4-15).

Tourette's Syndrome

Rationale

The rationale for this clinical use of cannabinoids in treating Tourette's syndrome is weak. Its use seems to depend upon the possibility that the anti-convulsant properties of cannabinoids may reduce the frequencies of tics.

Evidence

The Committee identified two good-quality systematic reviews (Koppel et al., 2014, Whiting et al., 2015) that evaluated medical cannabis for Tourette syndrome. Both reviewed the same trials and the committee focused on the more recent Whiting et al (2015) review which considered two RCTs (4 reports) that were conducted by the same research group (Müller-Vahl et al., 2001, Müller-Vahl et al., 2003a, Müller-Vahl et al., 2002, Müller-Vahl et al., 2003b). They compared THC capsules (maximum dose 10 mg daily) to placebo in 36 patients with Tourette syndrome. Tic severity was improved with THC capsules but the benefit was modest, less than 1 point on a 0–6 severity scale. The committee expressed concerns about bias in the assessment of outcome at 6 weeks because the data were incomplete and there was no clear description of the randomisation process or how the nature of treatment received was concealed form patients. No further primary research studies were identified.

Conclusions

The committee concluded that were was "limited evidence" that oral cannabinoids were an effective treatment for Tourette's syndrome (p4-16).

Amyotropic Lateral Sclerosis

Rationale

The rationale for using cannabinoids to treat symptoms of ALS depends on the possibility that some cannabinoids have neuroprotective effects they could be useful in treating this inflammatory degenerative neurological disease that affects motor neurons in the spinal cord, brain stem and motor cortex.

Evidence

No systematic reviews had been done because there were insufficient studies to justify a review. The primary literature consisted of two small studies of dronabinol with a weak study design. One was a randomized, double-blind crossover study of 19 patients with ALS (Gelinas et al., 2002). Participants noted improvement in appetite and sleep but not in cramps or fasiculations (involuntary muscle twitches). The second study enrolled 27 patients with ALS who had moderate to severe cramps in a randomized, double-blind trial of dronabinol 5 mg twice daily or placebo, each given for 2 weeks with an intervening 2-week washout period (Weber et al., 2010). There was no difference between dronabinol and placebo in the primary endpoint, cramp intensity, or in any secondary endpoints such as cramp number, intensity of fasciculations, quality of life, sleep, appetite, and depression. The committee noted that there were too few participants to detect anything other than a large effect.

Conclusions

The committee concluded that was "insufficient evidence" to decide whether cannabinoids were an effective treatment for ALS (p4-17).

Huntington's Disease

Rationale

The rationale for the clinical use of cannabis and cannabinoids in HD also depends upon the possible neuroprotective effects of some cannabinoids in treating a progressive neurological disorder and preclinical evidence than cannabinoids may be involved in the pathophysiology of the disorder.

Evidence

One systematic review was considered (Koppel et al., 2014) that reviewed two small sample clinical trials of nabilone and cannabidiol compared to placebo. The first assigned 22 patients to receive nabilone for 5 weeks followed by 5 weeks of placebo and another 22 patients receive placebo followed by nabilone for 5 weeks in each case. The primary endpoint was the total motor score of the (UHDRS). There was no significant difference in the primary endpoint, a total motor score on Unified Huntington's Disease Rating Scale, in the 37 patients who could be evaluated. There was some improvements on some secondary endpoints but the Committee argued that the wide confidence intervals around these differences reduced their confidence in nabilone's effectiveness.

The second study included in the systematic review was a lower-quality, 15-patient randomized, double-blind, placebo-controlled trial investigating the effect of cannabidiol capsules at a dose of 10 mg/kg/day in two divided doses (Consroe et al., 1991). There were no statistically significant differences between cannabidiol and placebo in any outcomes.

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the declines in motor function and cognitive performance associated with Huntington's disease.

Conclusions

The committee regarded these studies as underpowered and their duration was too short to assess any effects of cannabinoids on HD. It accordingly concluded that were was "insufficient evidence" that cannabinoids were an effective treatment for HD (p4-18).

Parkinson's Disease

Rationale

The rationale for the clinical use of cannabis and cannabinoids in PD relied upon the possible neuroprotective and anti-inflammatory properties of cannabinoids that may make them useful in treating a progressive neurological disorder.

Evidence

The systematic review of Koppel et al., (2014) identified two trials of cannabinoid therapies in patients with levodopa-induced dyskinesias. Nineteen patients were randomized in a double-blind, placebo-controlled crossover trial to receive Cannador capsules (containing THC) or placebo (Carroll et al., 2004). The primary endpoint was the dyskinesia score of the UPDRS. The overall treatment effect suggested a worsening with Cannador but this was not statistically significant. No effects were seen on the secondary outcomes and there were more adverse events on the drug than placebo. The study had limited statistical power to detect anything but a large treatment effect because of its small sample size.

The second study was a smaller, low-quality randomized, double-blind, placebo-controlled crossover trial with seven patients with Parkinson's disease who had levodopa-induced dyskinesia (Sieradzan et al., 2001). Nabilone or a placebo was administered 12 hours and 1 hour before levodopa at a dose of 200 mg. The primary endpoint was total dyskinesia disability as measured using the Rush Dyskinesia Disability Scale. The anti-Parkinsonian actions of levodopa were not affected by nabilone pretreatment but nabilone significantly reduced total levodopa-induced dyskinesia compared with placebo (Sieradzan et al., 2001). The committee cautioned that because these results came from only seven patients who received only two doses of nabilone one could not draw any conclusions about efficacy.

Conclusions

The committee concluded that there was “insufficient evidence” that cannabinoids are an effective treatment for the motor system symptoms associated with Parkinson’s disease or the levodopa-induced dyskinesia. (p4-20).

Dystonia

Rationale

Dystonia is a disorder characterized by sustained or repetitive muscle contractions which result in abnormal fixed postures or twisting, repetitive movements. Idiopathic cervical dystonia is the most common cause of focal dystonia. Stimulation of the cannabinoid receptors has been postulated as a way to reduce dystonia. Clinical reports suggested that cannabis may alleviate symptoms associated with dystonia. A small open pilot study in five patients who received cannabidiol reported dose-related improvements in patients.

Evidence

Koppel et al., (2014) identified one study of the effect of dronabinol on cervical dystonia in 9 patients who participated in an 8 week cross over study. The review described the study as underpowered to detect any differences between dronabinol and the placebo. There was no statistically significant effect of dronabinol on the dystonia compared with placebo. The primary literature consisted of very small studies of very weak design

The Committee identified another study in 15 patients with a clinical diagnosis of primary dystonia who received a single dose of nabilone or placebo on the study day (Fox et al., 2002, Carroll et al., 2004). Treatment with nabilone did not produce a significantly greater reduction in the total dystonia movement scale score than placebo

Conclusions

The committee concluded that was “insufficient evidence” to support or refute the conclusion that nabilone or dronabinol were effective treatments for dystonia (p4-21).

Dementia

Rationale

The main intended clinical use for cannabinoids in dementia is to treat the common behavioural problems of agitation, aggression and food refusal that can prove distressing to patients and their families and can be a common reason for patients receiving institutional care. The available drug treatment for these symptoms involve using anxiolytic and anti-psychotic (typical and atypical) medications. The latter are only modestly effective and can have potentially serious adverse side effects, including falls and cardiovascular death.

Evidence

The Committee identified two systematic reviews that assessed two small trials of cannabinoids in 15 and 6 dementia patients respectively (Krishnan et al., 2009, van den Elsen et al., 2014). The first was a small randomized crossover trial (Volicer et al., 1997) that assessed the effects of dronabinol on behavioural disturbance and food refusal in 15 hospitalized patients with probable Alzheimer's disease. Patients were randomized to dronabinol for 6 weeks or placebo. The patients gained some weight but there were no differences between dronabinol and placebo in the frequency of behavioural disturbances. The other study was an open-label pilot study (Walther et al., 2006), which evaluated six patients with severe dementia for the effects of dronabinol on nighttime agitation. It did not meet eligibility criteria for the review by Krishnan et al (2009). The methods of both trials were poorly reported so they were judged to be a high risk of bias.

Since these reviews a RCT which assessed the effects of THC three times daily on behavioural symptoms in 50 dementia patient (van den Elsen et al., 2015). It failed to find any improvement in the behavioural or any other symptoms in these patients and no improvement in their quality of life.

Conclusions

The committee concluded that there was "limited evidence" that cannabinoids were effective treatments of behavioural disturbance in dementia (p4-23).

Glaucoma

Rationale

Glaucoma is a common eye disorder in which increase intra-ocular pressure gradually damages vision. There is preclinical evidence that cannabinoids and THC in particular acutely reduce intra-ocular pressure. This raises the possibility that the regular use of THC and other cannabinoids could have therapeutic effects in glaucoma.

Evidence

The committee identified one systematic review (Whiting et al., 2015). It evaluated a single randomized crossover trial in six patients with glaucoma that compared the effects on intra-ocular pressure of: THC (5 mg oromucosal spray), cannabidiol (20 mg oromucosal spray), cannabidiol spray (40 mg oromucosal spray) and a placebo. It assessed intraocular pressure intermittently until12 hours after treatment. No differences in intraocular pressure were found between the effects of placebo and any of these cannabinoids. There were no additional studies identified by a literature search.

Conclusions

The committee concluded that there was "limited evidence" that cannabinoids were an ineffective treatment for glaucoma.

Spinal Cord Injury and Intracranial Haemorrhage

Rationale

The main reason for exploring the clinical use of cannabinoids in these conditions is animal evidence that some cannabinoids have neuroprotective effects in brain injury.

Evidence

There were no systematic reviews and no randomised controlled clinical trials on the effectiveness of cannabinoids in these conditions. The only available evidence consisted of two observational studies. One assessed rates of survival and recovery in 446 patients who had suffered brain and spinal cord injuries (Nguyen et al., 2014) and compared patients who did and did not have cannabinoids detected in their blood. The other study involved a similar comparison among 725 patients who had suffered an intra-cranial haemorrhage (Di Napoli et al., 2016). Both studies found a higher survival rate in patients with cannabinoids present in their blood. Both were observational studies, however, so it is difficult to be sure that all confounding variables that may have influenced patient survival or recovery were adequately controlled for in these comparisons.

Conclusions

The committee concluded that there was "limited evidence" of a statistical association between cannabinoids and better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial haemorrhage" (p4-25).

Addiction

Rationale

Cannabinoids may be potentially useful in treating cannabis disorders by assisting patients to withdraw from cannabis while experiencing minimal withdrawal symptoms. They could also potentially be used to treat other forms of addiction because the endocannabinoid system appears to be implicated in the drug reward system believed to be involved in all addiction.

Evidence

Two systematic reviews have been published that have reviewed two RCTs of the efficacy of cannabinoids (nabiximols and dronabinol) in treating cannabis dependence (Marshall et al., 2014, Prud'homme et al., 2014). One small trial has also been reported in cigarette smokers (Morgan et al., 2013).

These reviews concluded that the two RCTs (Levin et al. (2011) examining dronabinol and Allsop et al. (2014) examining nabiximols) have shown that dronabinol and nabiximols reduced the severity of withdrawal symptoms experienced by cannabis dependent persons, increased retention in treatment and increased the chances of completing withdrawal. There were no differences, however, in the proportion of patients who were abstinent in the longer term (six months). The small study of cigarette smoking by Morgan et al. (2013) reportedly

found that inhaled cannabidiol reduced craving but it did not assess its effects on smoking cessation. No additional primary research studies has been published since these reviews.

Conclusions

The committee concluded that there was "no evidence to support or refute the conclusion that cannabinoids are effective in achieving abstinence in substance use disorders" (p4-27).

Anxiety Symptoms

Rationale

Anxiety disorders are very common disorders of mood in which excessive fear and anxiety and physical symptoms can cause significant distress or interfere with social, occupational, and other areas of functioning. Given the role of the endocannabinoid system in mood regulation, the committee explored the relationship between anxiety and cannabis.

Evidence

Whiting et al. (2015) identified one randomized trial with a high risk of bias that compared a single 600 mg dose of cannabidiol to placebo in 24 participants with generalized social anxiety disorder. Cannabidiol was associated with a greater improvement on the anxiety factor of a 100-point visual analogue mood scale compared with a placebo during a simulated public speaking test.

Four other randomized controlled trials (232 participants) enrolled patients with chronic pain also reported on the effects of different cannaboinoids on anxiety symptoms. The cannabinoids studied included dronabinol, nabilone, and nabiximols. Outcomes were assessed from 8 hours to 6 weeks after randomization. Three of the four trials were judged to have a high risk of bias. All trials found greater short-term reductions in anxiety with cannabinoids than placebo. The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the improvement of anxiety symptoms.

Conclusions

The committee concluded that there is "limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders." (p4-28).

Depression

Depression is one of the most common mental disorders in which feelings of sadness, emptiness, or irritable mood, and somatic and cognitive changes may affect the individual's capacity to function. The endocannabinoid system is known to play a role in mood regulation so the committee explored the association between cannabis use and depressive disorders or symptoms.

Evidence Reviews

The review by Whiting et al. (2015) was the most recent good-quality review. No RCTs were identified that specifically evaluated cannabis in patients with a depressive disorder but there were five RCTs involving 634 participants with other conditions (chronic pain or multiple sclerosis with spasticity) that assessed the effects of cannabinoids on depressive symptoms. Only one study reported depressive symptoms at baseline and these symptoms were mild.

Nabiximols (n = 3), dronabinol and nabilone capsules were compared to placebo; and nabilone was compared to dihydrocodeine. Outcomes were assessed from 8 hours to 9 weeks after randomization. Three of the five trials were judged to have a high risk of bias and the other two as unclear risk. Three studies (nabiximols, dronabinol) showed no effect on validated symptom scales. One study of three doses of nabiximols found that the highest dose increased depressive symptoms but there was no difference between nabiximols and placebo at lower doses. The comparison of nabilone to dihydrocodone did not find any difference in depressive symptoms.

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment to reduce depressive symptoms.

Conclusions

The committee concluded that there is "limited evidence" that nabiximols, dronabinol, and nabilone are *ineffective* treatments for depressive symptoms in individuals with chronic pain or multiple sclerosis (p4-29).

Sleep disorders

Rationale

Sleep disorders are very common and there is some evidence that the endocannabinoid system may play a role in sleep. THC is associated in a dose-dependent manner with changes in slow-wave sleep and cannabis may decrease time to sleep onset at low doses. For these reasons the committee decided that it was worth assessing if cannabinoids have a role in treating sleep disorders.

Evidence

The review by Whiting et al. (2015) was the most recent good-quality review. Two RCTs involving 54 participants evaluated nabilone and dronabinol for the treatment of sleep problems. A trial deemed to have a high risk of bias was conducted in 22 patients with obstructive sleep apnoea showed a greater benefit of dronabinol than with a placebo on sleep apnoea/hypopnea index.

A crossover trial deemed to have a low risk of bias was conducted in 32 patients with fibromyalgia. It found greater reductions in insomnia for nabilone daily compared with amitriptyline. Nineteen trials of 3,231 participants with other conditions (chronic pain or multiple sclerosis) also reported on sleep outcomes. In these nabiximols (13 studies), THC/CBD capsules (2 studies), smoked THC (2 studies), and dronabinol or nabilone were compared to placebo. Sleep outcomes were assessed at 2–15 weeks after randomization. Eleven of the 19 trials were judged to have a high risk of bias, 6 had an uncertain risk of bias and 2 had a low risk of bias. The meta-analysis found that cannabinoids produced greater improvements than placebo in sleep quality in 8 trials and greater reductions in sleep disturbance in 3 trials. These represented small improvements on a 10-point scale.

The committee did not identify any good-quality primary literature on medical cannabis as an effective treatment for sleep outcomes. It concluded that there is moderate evidence that cannabinoids, primarily nabiximols, are an effective treatment to improve short-term sleep outcomes in individuals with obstructive sleep apnoea syndrome.

Post-Traumatic Stress Disorder

PTSD is a disorder that can occur among persons exposed to a traumatic event (e.g., the threat of death, serious injury, or sexual violence) who experience psychological distress as a result of that exposure (e.g., intrusion symptoms, such as distressing memories; avoidance of stimuli that are associated with the traumatic event; negative alterations in mood and cognition; alterations in arousal and reactivity associated with the traumatic event; functional impairment). The committee decided to explore the association between PTSD and cannabis use because of cannabis has psychoactive effects and patients with PTSD reportedly use cannabis to treat their symptoms.

Evidence

The committee did not identify any good- or fair-quality systematic reviews on cannabis in the treatment of PTSD symptoms. They found a fair-quality double-blind randomized crossover trial (Jetly et al., 2015) in Canadian male military personnel with trauma-related nightmares who had not responded to standard PTSD treatments. Ten participants were randomized to nabilone or placebo for 7 weeks. Following a 2-week washout period, subjects were then treated with the other treatment and followed for an additional 7 weeks. Nightmares, global clinical state, and general well-being were improved more with nabilone treatment than placebo treatment. There was no effect on sleep quality and quantity. Global clinical state was rated as very much improved or much improved for 7 of 10 subjects during nabilone treatment and for 2 of 10 subjects in the placebo period.

Conclusion

The committee concluded that there is "limited evidence" that nabilone is effective for improving symptoms of posttraumatic stress disorder.

Schizophrenia and Other Psychoses

Rationale

There is suggestive evidence that the cannabinoid system is disturbed in persons with schizophrenia and some evidence that CBD is protective against the psychotogenic effects of THC. Most research interest has been in the possible anti-psychotic effects of CBD.

Evidence

The Committee identified two fair to good quality systematic reviews but focused on that of Whiting et al., (2015) because they judged it to be the stronger and more current. The review only included two randomised controlled trials. These involved a total of 71 patients with schizophrenia or schizophreniform psychosis who were treated with CBD or an atypical antipsychotic drug (amisulpride). These studies were judged to be at high risk of bias. One found that CBD was superior to placebo in reducing psychotic symptoms on the Brief Psychiatric Rating Scale. The other study which used a cross over design failed to find a difference between CBD and placebo in their impact of psychotic symptoms. No further primary studies were found.

Conclusion

The committee concluded that there was "insufficient evidence to support or refute the conclusion that cannabidiol is an effective treatment for the mental health outcomes in individuals with schizophrenia or schizophreniform psychoses. "

Summary of Committee's Conclusions

The Committee provided the following summary in the highlights of its chapter on medical uses of cannabinoids:

- "In adults with chemotherapy induced nausea and vomiting, oral cannabinoids are effective antiemetics.
- In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms
- In adults with multiple sclerosis (MS) related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.
- For these conditions the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess their effects." (p4-1)

A more detailed list of the Committee's detailed findings on each medical endpoint classified is shown in a series of boxes in Appendix B classified by the degree of confidence that the Committee had in each conclusion.

Appendix A: **Abbreviated Weight-of-Evidence Categories for therapeutic effects used by the National Academy of Science**

"CONCLUSIVE EVIDENCE
There is strong evidence from randomized controlled trials … that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

… there are many supportive findings from good-quality studies with no credible opposing findings.

A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE
There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

… there are several supportive findings from good-quality studies with very few or no credible opposing findings.

A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE
There is some evidence … that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

… there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings.

A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE
There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

… there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion.

A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

… there are mixed findings, a single poor study, or health endpoint has not been studied at all.

No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors."

Appendix B:

Box 1:

"There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As anti-emetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

Box 2:

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

Box 3:

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids)(4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; one single, small fair quality trial) (4-20)

Box 4:

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids
- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

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