



European Monitoring Centre
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A summary of reviews of evidence on the efficacy and safety of medical use of cannabis and cannabinoids

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Medical use of cannabis and cannabinoids: questions and
answers for policymaking

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A summary of reviews of evidence on the efficacy and safety of medical use of cannabis and cannabinoids

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Introduction

This paper accompanies the report *Medical use of cannabis and cannabinoids — questions and answers for policymaking* and summarises the findings of major systematic reviews of the evidence on the effectiveness and safety of cannabis and cannabinoids when used to treat symptoms of various medical conditions. It provides more detail on topics summarised in the main report, in particular on the sections on the available evidence on the effectiveness of medical use of cannabis and cannabinoids and those on the health risks and potential unintended consequences associated with the medical use of cannabis and cannabinoids.

The first section of this paper summarises in detail the conclusions of three influential peer-reviewed publications (Koppel et al., 2014; NASEM, 2017; Whiting et al., 2015). These reviews evaluated all the published evidence on the efficacy and safety of cannabis for multiple medical uses. They used a clearly specified search strategy to identify studies, clear rules for deciding which studies to include and exclude, standardised criteria for evaluating the degree of bias in the studies and explicit criteria for synthesising the overall evidence.

The paper then summarises the findings of systematic reviews and meta-analyses of the evidence on the effectiveness of cannabinoids in treating chronic pain; chemotherapy induced nausea and vomiting in cancer patients; appetite stimulation in HIV/AIDS; intractable epilepsy; and palliative care for cancer. All these reviews used explicit search criteria, standardised tools for assessing study bias and explicit methods of synthesising the overall findings. Their degree of agreement is also summarised in a table.

A third section summarises reviews of the adverse effects of medical use of cannabis as indicated in randomised controlled clinical trials. The section includes the results of a meta-analysis of adverse effects reported in clinical trials conducted by Whiting et al. (2015). The section also considers long-term harms reported among recreational cannabis users that may be potential adverse effects of long-term medical use of cannabis and cannabinoids.

Finally, the paper includes an overview of studies, primarily conducted in the US, that explore the potential unintended consequences of the medical use of cannabis and cannabinoids.

Cannabis and cannabinoids have been made available in a wide range of forms, and the various products and preparations tended to be described in different ways in different publications. While the main report uses a new typology in describing the different forms in which cannabis and cannabinoids are made available, we have chosen in the background paper to use the original terminology from the studies under consideration.

1. Reviews of the evidence on the efficacy and safety of cannabis and cannabinoids for multiple disorders — three key evidence reviews

Koppel, B. S., et al. (2014)

Koppel, B. S., Brust, J. C., Fife, T., Bronstein, J., Youssof, S., Gronseth, G. and Gloss, D. (2014), 'Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology', *Neurology* 82, pp. 1556-1563.

These authors reviewed evidence on the safety and efficacy of cannabinoids in relieving or reducing spasticity in patients with multiple sclerosis (MS); central pain and painful spasms in MS; bladder dysfunction in MS; involuntary movements in MS; movement disorders in Huntington's disease and dyskinesia in Parkinson's disease; and seizure in epilepsy.

They conducted a systematic search up to November 2013 and included 33 clinical trials in their analysis. Clinical trials were classified into four categories defined by the American Academy of Neurology. Class I studies provided the strongest evidence, being double-blind randomised controlled trials (RCTs) in representative patients with similar symptom severity at baseline and the outcomes of which were assessed on objective measures. The remaining study classes provided weaker evidence because they lacked one or more of these desirable characteristics. For each symptom, the authors summarise the overall evidence in terms of the number of studies in classes I to IV, describe each study in detail and draw overall conclusions about the evidence. Only their conclusions are summarised below, along with any comments on the clinical context in which the cannabinoids might be used.

Spasticity in MS

This was the most extensively investigated symptom, with 4 class I, 4 class II and 9 class III studies. Koppel et al. summarised the results for each type of cannabinoid studied, that is, nabiximols; oral cannabis extract (OCE) and tetrahydrocannabinol (THC); oral cannabinoids; and 'smoked marijuana'. They concluded that OCE, THC and nabiximols are each 'probably effective' in reducing self-reported spasticity in the short term but 'probably ineffective' in reducing objective measures of spasticity. The effectiveness of smoked marijuana was 'uncertain'. They noted that the cannabinoids were used in addition to standard therapy, so no conclusion could be drawn on the comparative effectiveness of cannabinoids and standard treatments for spasticity. The outcomes were better when assessed by patient ratings of improvement. The authors suggested this might be because the cannabinoids improved mood or provided pain relief that allowed patients to move more freely.

Central pain in MS

This was the next most studied symptom, with 5 class I, 2 class II and 6 class III studies. The authors concluded that OCE was effective and that THC and nabiximols were 'probably effective' in reducing central pain. The efficacy of smoked marijuana was uncertain because there were too few studies.

Bladder dysfunction in MS

This symptom was assessed in a minority of the studies of cannabinoids in MS. The authors concluded that nabiximols was 'probably effective' in reducing the number of bladder voids per day at 10 weeks and that THC and OCE were 'probably ineffective'. Nabiximols was judged to be of uncertain effectiveness in reducing overall bladder symptoms because there were contradictory results from two class I trials that measured this outcome.

Tremor in MS

Tremor as a secondary symptom was assessed in six studies of cannabinoids in patients with MS. The authors concluded that THC and OCE were 'probably ineffective' and nabiximols was 'possibly ineffective' in reducing tremor in MS.

Involuntary movement disorders

There were very few studies of the effects of cannabinoids in Huntington's disease and the few that were available were underpowered to detect effects. Accordingly, no reliable conclusions could be drawn on the effectiveness of cannabinoids in this disease. The authors concluded that OCE was ineffective in reducing dyskinesia in Parkinson's disease. They found that there were insufficient data to assess the efficacy of cannabinoids in reducing symptoms of Tourette syndrome or cervical dystonia.

Epilepsy

There were no RCTs for review and only two low-quality studies that failed to detect any benefit of cannabinoids in reducing the frequency of seizures. The authors concluded that these studies provided insufficient evidence to assess the effectiveness of cannabinoids in epilepsy.

Adverse effects

The authors reviewed data on adverse events in studies of cannabinoid use for less than 6 months in 1 619 patients. They found that 6.9 % of patients in the cannabinoid groups withdrew from treatment because of adverse events compared with 2.2 % in the placebo groups. The adverse symptoms reported in at least two studies were nausea, weakness, behavioural or mood changes, suicidal ideation, hallucinations and dizziness.

Among these adverse events, the authors identified cognitive impairment as a concern with regard to the use of cannabinoids in patients with MS because many had cognitive impairment caused by their disease. They also expressed concern about the possibility that cannabinoids might increase suicidal ideation in MS patients who were at increased risk of suicide.

Recommendations for future research

The findings of the Koppel et al. review are summarised in Table 1. In discussing future research, Koppel et al. noted that a probable placebo effect from psychoactive cannabinoids complicated assessment of their therapeutic effects. They also acknowledged the major disincentives to doing clinical research on cannabinoids, namely regulatory requirements, a prohibition on patients driving and the need to rely on subjective assessment of patient outcomes. They nonetheless argued that we needed larger, better-designed RCTs to properly assess the efficacy of cannabinoids. They found the current literature hard to summarise because multiple cannabis products were used in varying doses, studies were often underpowered to detect effects and they often had high rates of patient dropout.

Table 1: Summary table, Koppel et al., 2014

Symptoms studied	Conclusions reached
Symptoms of MS	
Muscle spasticity	Nabiximols probably effective in reducing subjective symptoms
Central pain	Nabiximols probably effective in reducing central pain
Bladder dysfunction	Nabiximols probably effective in reducing frequency of voiding; their effects on other bladder symptoms were uncertain
Tremor	Nabiximols probably ineffective in reducing tremor
Movement disorders	
Huntington's disease	Insufficient evidence to draw reliable conclusions
Parkinson's disease	Cannabinoids probably ineffective in treating dyskinesia
Tourette syndrome	Insufficient evidence to draw reliable conclusions
Cervical dystonia	Insufficient evidence to draw reliable conclusions
Epilepsy	Insufficient evidence to assess the effectiveness of cannabidiol

Whiting, P. F., et al. (2015)

Whiting, P. F. Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., et al. (2015), 'Cannabinoids for medical use: a systematic review and meta-analysis', *JAMA* 313, pp. 2456-2473.

Whiting et al. (2015) conducted a systematic review of randomised controlled clinical trials of cannabinoids for various medical uses. They conducted meta-analyses when there were two or more RCTs that compared cannabis or a cannabinoid with another treatment such as usual care, placebo or no treatment. The review was commissioned by the Swiss Federal Office of Public Health and published in *JAMA*.

The authors evaluated evidence on the safety and efficacy of cannabinoids in treating the following disorders:

- nausea and vomiting in patients undergoing chemotherapy for cancer
- appetite stimulation in HIV/AIDS patients
- chronic pain
- spasticity due to MS or paraplegia
- depression

- anxiety disorder
- sleep disorder
- psychosis
- intraocular pressure in glaucoma
- Tourette syndrome

The authors searched electronic databases of scientific studies in all languages and identified RCTs. They used the Cochrane Collaboration tool to assess the risk of bias in each of the studies. They classified studies as having a high risk of bias if there was a high risk of bias in at least one domain (e.g. sampling, design, missing data, patients' awareness of treatment) and as having a low risk of bias if there was no risk of bias in any of these domains. They conducted meta-analyses if there were two or more RCTs for a specific health outcome with one or more cannabinoids. They also conducted a meta-analysis of adverse events reported for all cannabinoids in clinical trials for all conditions reviewed.

In Whiting et al.'s review, 79 studies met the criteria for inclusion. They screened 505 studies that were potentially relevant from 23 754 papers identified in their initial searches. These studies included 34 parallel group studies (with 4 436 patients) and 45 crossover trials (with 2 026 patients).

Only 5 of the trials were rated as having a low risk of bias; 55 were rated as having a high risk of bias. In the remainder, the degree of bias was unclear because of poor reporting of trial methods. The major sources of bias were incomplete outcome data (in more than half of the studies), uncertainty about whether patients were blind as to the treatment they received (57 %) and selective reporting of study outcomes (16 %).

Nausea and vomiting

Whiting et al. analysed data from 28 studies involving 1 772 patients that assessed the effectiveness of cannabinoids in treating nausea and vomiting related to chemotherapy for cancer. These included 14 trials of nabilone, 3 of dronabinol, 1 of nabiximols, 4 of levonantradol and 6 of THC. All trials included a placebo. Some trials also included an active treatment comparison, most often the anti-emetic drug prochlorperazine (15 studies).

The risk of bias was rated as high in 23 out of 28 studies and unclear in the remainder. A meta-analysis of all these studies showed that cannabinoids achieved more complete control of nausea than placebo (odds ratio (OR) = 3.82 (95 % confidence interval (CI) 1.65 to 9.42)).

Appetite stimulation

This outcome was assessed in only four studies that included 255 patients, primarily with AIDS-related wasting. All the studies compared dronabinol with placebo in stimulating appetite. All were judged to have a high risk of bias and hence considered to provide weak evidence of efficacy.

Chronic pain

Whiting et al. reviewed 28 studies involving 2 454 patients of cannabinoids used to treat chronic pain. Seventeen trials were judged to have a high risk of bias. The trials evaluated nabiximols (13), THC (4), dronabinol (2), vaporised cannabis (1), ajulemic acid (1), oral THC (1) and nabilone (1). Only one study used an active treatment comparison (amitriptyline); the remainder looked at efficacy in comparison with a placebo.

The studies involved the following chronic pain conditions: neuropathic pain (12); cancer pain (3); diabetic neuropathy (3); fibromyalgia (2) HIV neuropathy (2), refractory pain in MS (1), rheumatoid arthritis (1), non-cancer pain (1), central pain (1) and musculoskeletal pain (1).

A meta-analysis indicated that the cannabinoids were superior to placebo in reducing pain and that there were no differences in responses for different types of pain or different cannabinoids.

Spasticity due to MS or paraplegia

A total of 14 studies evaluated the effects of cannabinoids on muscle spasticity: 11 studies in patients with MS and 3 in patients with paraplegia. They included 2 280 patients. All were placebo-controlled studies. Seven were judged to have a high risk of bias, two were considered to have a low risk of bias and the degree of bias was unclear in five studies.

The cannabinoids evaluated included nabiximols (6 studies), dronabinol (3 studies), nabilone (1 study); THC/CBD combinations (4 studies) and smoked THC (1 study).

A meta-analysis found greater improvements in self-reported spasticity in those treated with cannabinoids than in those given a placebo, but there was weak evidence of improved clinician ratings of muscle spasticity.

Depression

The review did not include any RCTs that evaluated the effects of cannabinoids on depression as a primary disorder, but five RCTs of patients treated with cannabinoids for other medical conditions assessed depression as a secondary endpoint. This included four trials in patients with chronic pain and one trial looking at muscle spasticity in MS. Three of the trials were judged to have a high risk of bias. The cannabinoids evaluated were dronabinol (1 study), nabiximols (3 studies) and nabilone (1 study). No trial found a significantly greater reduction in depression in the patients treated with a cannabinoid than in those given a placebo.

Anxiety

There was only one small RCT that evaluated the effects of a cannabinoid in treating anxiety in general anxiety disorder. It was judged to have a high risk of bias and found only a small difference compared with placebo.

Sleep disorder

There were two studies of cannabinoids used to treat sleep disorders. They included one parallel group RCT and one crossover study, both of which were judged to have a high risk of bias. These studies provided some evidence that cannabinoids improved sleep.

Psychosis

Two studies were included on the effects of cannabidiol (CBD) on psychotic symptoms. These included 71 patients and were judged to have a high risk of bias. There were no differences in outcomes between patients given the cannabinoid and those given a placebo.

Intra-ocular pressure in glaucoma

Only one small crossover study involving six patients was included. It was judged to have a high risk of bias and it did not find any difference between the cannabinoid and placebo.

Tourette syndrome

Two small placebo-controlled studies involving 36 patients reported suggestive evidence that there were fewer tics reported by patients receiving the cannabinoid than by those receiving the placebo.

Summary

Whiting et al. concluded that there was:

- moderate-quality evidence that cannabinoids were effective in treating chronic neuropathic and cancer pain and muscle spasticity in patients with MS;
- low-quality evidence that cannabinoids improved nausea and vomiting in cancer patients, increased appetite and weight gain in AIDS patients, improved symptoms of sleep disorders and improved symptoms of Tourette syndrome;
- low-quality evidence for the efficacy of cannabinoids in treating anxiety, psychosis and depression;
- an increased risk of adverse events for all cannabinoids;
- a need for large, robust well-controlled RCTs to confirm that cannabinoids were effective in treating most of these clinical outcomes.

NASEM (2017)

US National Academies of Sciences, Engineering, and Medicine (NASEM) (2017), *The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research*, National Academies Press, Washington, DC.

A committee of the US National Academy of Sciences (NASEM, 2017) reviewed research that had been published since the Academy had last reviewed the medical use of cannabis, in 1999. The committee conducted a review of reviews, that is, they summarised findings of high-quality systematic reviews and meta-analyses of the research literature. They also assessed high-quality research studies not included in the systematic reviews or published after the most recent systematic review. If there were no systematic reviews, the committee reviewed primary research published between January 1999 and August 2016. The committee synthesised the evidence using the following levels of confidence in conclusions that cannabis or cannabinoids were or were not effective in treating a medical condition (Table 2).

Table 2: Criteria that NASEM used for summarising strength of evidence

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	Opposing findings from other studies	Significantly uncertain
Insufficient	No studies or a single poor study	Mixed or no findings	Substantial concerns

The committee examined evidence on conditions for which medical use of cannabis or cannabinoids has been advocated in the US. These included the following groups of medical conditions: 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 MS and spinal cord injury; Tourette syndrome; amyotrophic 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.

The committee reviewed evidence on cannabis that was smoked and inhaled, synthetic THC (dronabinol), THC analogues (nabilone), CBD, and medicinal cannabis plant extracts that included nabiximols (plant extract with equal ratios of THC and CBD) and Epidiolex (a CBD-based plant extract).

Chronic pain

The committee found five systematic reviews of fair to good quality. They gave the greatest weight to the most comprehensive high-quality review (Whiting et al., 2015). Its findings were consistent with those of other reviews (many of which included studies with weaker designs, such as crossover studies) in suggesting that cannabinoids have a modest effect in reducing some types of pain.

Whiting et al. identified 28 RCTs that included 2 454 patients with various types of chronic pain, who were randomly assigned to receive either cannabis (or a cannabinoid) or a comparison treatment. The comparison was placebo in all but one trial. Whiting et al. did not find any differences in efficacy between different cannabinoids, but the small sample sizes of the studies limited the statistical power to detect differences.

Two RCTs had been published since the Whiting et al. review. These compared the effects of varying doses of inhaled cannabis flower and placebo 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).

The committee concluded that there was 'substantial evidence that cannabis is an effective treatment for chronic pain in adults'. It noted that most trials evaluated nabiximols in treating neuropathic pain in MS. Less was known about the effectiveness and side effects of cannabis products sold in US medical cannabis dispensaries, such as vaporised cannabis flower, concentrates and edible forms of cannabis.

Nausea and vomiting in patients undergoing chemotherapy for cancer

The committee relied on the review of Whiting et al. (2015) and a Cochrane Collaboration review by Smith et al. (2015). Whiting et al. (2015) summarised 28 RCTs comparing various cannabinoids with placebo or an anti-emetic drug (most often prochlorperazine). In most of these trials, cannabinoids produced greater reductions in nausea than a placebo and they provided control as good as and

sometimes better than that provided by the anti-emetic drug with which they were compared.

The Cochrane review included 23 clinical trials, 19 of which were crossover studies. Smith et al. (2015) concluded that cannabinoids were more effective than placebo and similar in effectiveness to conventional anti-emetics. They also found that cannabinoids caused more adverse events, such as dizziness, dysphoria, euphoria, 'feeling high' and sedation. They found a weak patient preference for cannabinoids over placebo and a stronger preference for cannabinoids over other anti-emetics. They concluded that cannabinoids should be used only when other anti-emetics had failed.

The committee identified one additional study, conducted in 2007, that had not been included in either of these reviews. It compared the anti-emetic effects of dronabinol with those of ondansetron and found the two drugs to be equally effective (Meiri et al., 2007). The committee concluded that there was 'conclusive evidence that oral cannabinoids are effective anti-emetics in the treatment of chemotherapy-induced nausea and vomiting' (pp. 4-7).

[Anorexia and weight loss in HIV/AIDS, cancer and anorexia nervosa](#)

The committee relied on two systematic reviews. Whiting et al. (2015) reviewed four RCTs of cannabinoids as appetite stimulants in 255 patients with HIV/AIDS. All were judged to have a high risk of bias. Lutge 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 AIDS-related anorexia. No additional studies were identified because the syndrome had disappeared 'since effective antiretroviral therapies became available in the mid-1990s' (NASEM, 2017, pp. 4-8).

There were no systematic reviews of controlled trials of cannabis or cannabinoids in cancer-related anorexia. Two controlled studies were reviewed. The first was discontinued because of high patient attrition due to side effects and a lack of efficacy (Strasser et al., 2006). Another larger trial found that megestrol acetate was better than dronabinol in stimulating appetite in cancer patients (Jatoi et al., 2002). There were no systematic reviews and only a small number of small-sample trials of cannabinoids in anorexia nervosa (Andries, 2014).

The committee concluded that there was (1) 'limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS' and (2) 'insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa' (pp. 4-10).

[Epilepsy](#)

The committee found two fair-quality reviews of cannabis and cannabinoids as single or added treatments for epilepsy (Gloss and Vickrey, 2014; Koppel et al., 2014). These summarised a small number of poor-quality studies in 48 patients. No

additional RCTs or other studies had been published, but several clinical trials had been completed without reporting their results at the time of the review.

One open-label study of oral CBD had been published since the Whiting et al. and NASEM reviews (Devinsky et al., 2016; Rosenberg, 2015). It examined the efficacy of oral CBD in reducing seizures in 162 children with intractable epilepsy and found a 37 % reduction in the frequency of seizures. A case series was reported from Israel (Tzadok et al., 2016). Neither of these was a double-blind study and there were no comparison groups.

The committee assessed the evidence on epilepsy as highly subject to bias because neither doctors nor patients were blind to treatment and in the absence of a comparison group it was difficult to be sure that the apparent benefits of CBD 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' (pp. 4-13).

Spasticity

The committee relied on Whiting et al.'s 2015 review of 11 parallel group studies of nabilone and nabiximols in patients with MS and three studies of cannabinoids in patients with paraplegia. A meta-analysis of three studies of nabiximols in MS found reasonably consistent evidence of clinical improvement in patient-rated symptoms of spasticity. There was no difference between cannabinoids and placebo when spasticity was rated by physicians. Koppel et al. (2014) concluded after reviewing 14 studies in MS that oral cannabinoids and nabiximols was 'probably effective in reducing severity of patient-rated spasticity but not physician-rated symptoms'.

The committee concluded that nabiximols and cannabinoids were 'probably effective' in reducing the patient-rated severity of spasticity in MS but found that there was insufficient evidence to judge their efficacy in treating spasticity in people with spinal cord injuries (pp. 4-15).

Sleep disorders

Whiting et al. (2015) reviewed evidence from two RCTs with 54 participants who received nabilone and dronabinol for sleep problems. A trial with a high risk of bias in 22 patients with obstructive sleep apnoea showed greater benefits from dronabinol than placebo. A crossover trial with a low risk of bias in 32 patients with fibromyalgia found that nabilone resulted in greater reductions in insomnia than amitriptyline.

Nineteen trials of 3 231 participants with chronic pain or MS reported sleep outcomes. In these trials, nabiximols (13 studies), THC/CBD capsules (2 studies), smoked THC (2 studies), and dronabinol or nabilone were compared with placebo. Eleven of nineteen trials had a high risk of bias, six had an uncertain risk of bias and two had a low risk of bias. A meta-analysis found that cannabinoids produced greater improvements than placebo in sleep quality in eight trials and less sleep disturbance in three trials. There were small improvements on a 10-point scale.

The committee concluded that there was moderate evidence that cannabinoids, primarily nabiximols, are effective in improving short-term sleep outcomes in individuals with obstructive sleep apnoea syndrome.

Conditions for which there was insufficient or limited evidence

The committee concluded that there was limited evidence of effectiveness for the following:

- behavioural disturbance in dementia
- glaucoma
- cannabis use disorders
- spinal cord injury and intracranial haemorrhage
- anxiety symptoms
- depression
- post-traumatic stress disorder
- schizophrenia and other psychoses.

The committee concluded that there was insufficient evidence to evaluate the effectiveness of cannabinoids in treating the following conditions:

- brain cancer, glioma
- irritable bowel syndrome
- Tourette syndrome
- amyotrophic lateral sclerosis
- Huntington's disease
- Parkinson's disease
- dystonia.

Summary of the committee's conclusions

The committee summarised its conclusions on medical use of cannabinoids as follows:

- *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.*

The findings of the Whiting et al. and NASEM reviews are shown for comparison in Table 3.

Table 3: Comparison of conclusions in the Whiting et al. and NASEM reviews

Symptom or disorder	Whiting et al., 2015	NASEM, 2017
Nausea and vomiting	Low-quality evidence that THC is superior to placebo in reducing symptoms	Conclusive evidence that oral cannabinoids are effective in the treatment of chemotherapy-induced nausea and vomiting
Appetite stimulation	Low-quality evidence that THC increases appetite in AIDS	Limited evidence that cannabinoids are effective in increasing appetite and decreasing weight loss in HIV/AIDS
Chronic pain	Moderate-quality evidence that cannabinoids are superior to placebo in reducing chronic pain and cancer pain	Substantial evidence that cannabis is effective for chronic pain, especially neuropathic pain in MS
Muscle spasticity	Moderate-quality evidence that nabiximols is superior to placebo in reducing subjective symptoms in MS; weak evidence for clinician-rated symptoms	Cannabinoids are probably effective in reducing patient-rated spasticity in MS; insufficient evidence to assess efficacy in spinal cord injuries
Epilepsy	Not assessed because no RCTs	Insufficient evidence to assess effectiveness
Sleep	Low-quality evidence that cannabinoids improve sleep	Nabiximols is effective in improving short-term sleep outcomes in obstructive sleep apnoea
Depression	No evidence that cannabinoids are superior to placebo	Limited evidence of effectiveness
Anxiety	Insufficient evidence to assess effectiveness	Limited evidence of effectiveness
Psychosis	Insufficient evidence to assess effectiveness	Limited evidence of effectiveness
Glaucoma	Insufficient evidence to assess effectiveness	Limited evidence of effectiveness
Tourette syndrome	Low-quality evidence that cannabinoids improved symptoms	Insufficient evidence to assess effectiveness

2. Reviews of the evidence on the efficacy and safety of cannabis and cannabinoids for specific disorders

Chronic pain

Andrae, M., Carter, G. M., Shaparin, N., Suslov, K., Ellis, R. J., Ware, M. A. et al., (2015), 'Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data', *Journal of Pain* 16, pp. 1221-1232.

Andrae et al. (2015) reported a Bayesian meta-analysis using data from 178 patients who participated in five RCTs of inhaled vaporised herbal cannabis and were assessed for up to 2 weeks. This included two studies of patients with AIDS-related neuropathy and three studies of patients with various types of neuropathic pain caused by, for example, spinal cord injury, diabetes and trauma. All the trials used inhaled herbal cannabis that was supplied by the US National Institute on Drug Abuse. Participants were generally not blind to the treatment that they received.

The conclusion of this review was more positive than those of the systematic reviews of larger numbers of studies of cannabinoids reviewed below. The odds ratio for a 30 % reduction in pain was 3.2 and it was estimated that 1 in every 5 or 6 patients benefited from the treatment, an effect that the authors argued was comparable to that of gabapentin. They acknowledged that the sample sizes in these trials were small and recommended larger, pragmatic and longer term clinical studies to see whether these good short-term effects were sustained for longer than the 2 weeks observed in these studies.

Nugent, S. M., Morasco, B. J., O'Neil, M. E., Freeman, M., Low, A., Kondo, K. et al. (2017), 'The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review', *Annals of Internal Medicine* 167, pp. 319-331.

Nugent et al. (2017) reviewed only controlled clinical trials of the effectiveness of plant-based cannabis medicines. These included nabiximols, herbal cannabis and cannabis-based oils. They argued that controlled trials of synthetic cannabinoids had been reviewed by other groups. Their review included the findings of 13 systematic reviews of the evidence from 62 primary studies and their review of evidence from 22 RCTs included in recent reviews and 8 studies published since these reviews, as well as 3 cohort studies of patients with chronic pain.

Thirteen of the trials examined cannabinoids in chronic neuropathic pain. Eleven trials were described as having a low risk of bias, in one trial the risk of bias was unclear and there was a high risk of bias in the other. The authors found a very small difference in the mean change on a visual analogue scale for pain (VAS) between cannabinoids and placebo; the difference was judged to be of limited clinical significance. Only a small proportion of patients achieved a 30 % or greater

reduction in pain. A 1-year prospective study of patients treated with nabiximols found a very small reduction in VAS rating that was not clinically significant.

Nugent et al. also analysed nine trials of neuropathic pain in MS. Three were rated as having a low risk of bias, five were rated as having an unclear risk of bias and one was rated as having a high risk of bias. They concluded that there was 'insufficient evidence to characterise the effects of cannabis on pain in patients with MS' (p. 321), largely because of the small number of rigorous studies, the lack of evidence on long-term patient outcomes and the small numbers of patients included in the trials. They also considered three trials of cannabinoids for treating cancer pain that involved 547 patients. Two of these studies had an unclear risk of bias and one had a high risk of bias. They concluded that these studies provided 'insufficient evidence' because of the small number of studies and high patient attrition rate.

They also reviewed adverse events reported in these trials. They described most of the effects as minor and did not find the rate of adverse events significantly different between cannabinoids and placebo used to treat chronic pain. Their overall conclusion was that there was 'limited evidence on the potential benefits and harms of cannabis use in chronic pain populations' (p. 325) and only low-quality evidence that nabiximols reduced neuropathic pain.

Meng, H., Johnston, B., Englesakis, M., Moulin, D. E. and Bhatia, A. (2017), 'Selective cannabinoids for chronic neuropathic pain: a systematic review and meta-analysis', *Anesthesia and Analgesia* 125, pp. 1638-1652.

Meng et al. (2017) conducted a systematic review and meta-analysis of 11 RCTs that evaluated cannabinoids as treatments for chronic neuropathic pain (NP). These included studies of dronabinol (1 trial), nabilone (3 trials) and nabiximols (7 trials). In all trials, the cannabinoids were adjunctive treatments, that is, they were added to other analgesics. The trials include 1 219 patients (614 receiving a cannabinoid and 605 receiving a comparison treatment (placebo in 10 out of 11 trials). The authors used Cochrane Collaboration criteria to rate the degree of study bias and the GRADE (Grading of Recommendation Assessment, Development and Evaluation) system to synthesise the evidence. The primary outcome was a change in a numerical rating scale of pain that was used in all but one of the trials. Secondary outcomes included quality of life, sleep and physical activity. Patients in the trials suffered from either central neuropathic pain, for example as a consequence of MS or brachial plexus avulsion, or peripheral neuropathic pain due to diabetes or other causes.

Meng et al. assessed the overall risk of bias as low in 10 out of 11 trials. One trial had a high risk because it was unclear how patients had been randomised or if patients and assessors had been blind as to treatment. Six of the eleven trials found that the cannabinoid was superior to placebo, but the mean difference in pain ratings between the two was only 0.65 on an 11-point scale. The authors examined

differences in efficacy between different cannabinoids and different types of neuropathic pain, but these comparisons were limited by the small number of trials and the small sample sizes in the trials. There was suggestive evidence that nabiximols was superior to nabilone. In five of the eight studies that assessed quality of life and sleep, the cannabinoids were superior to placebo.

Adverse events were more commonly reported in the cannabinoid group, but these were mostly mild to moderate, and the most common involved dizziness, somnolence and dry mouth. The severity of adverse events decreased with use, suggesting that tolerance developed. There were two severe events reported: agitation and paranoid ideation.

The reviewers' recommendation was that 'cannabinoids can be recommended in patients with NP syndromes (GRADE: weak recommendation; moderate-quality evidence)' (p. 1648). They described the mean difference in numerical rating scale pain scores (on a 10-point scale) between patients receiving cannabinoids and those receiving a placebo as 'significant but clinically small' (p. 1648). They recommended larger RCTs comparing different cannabinoids (THC, varying combinations of THC and CBD) in their effects on chronic neuropathic pain.

Mucke, M., Phillips, T., Radbruch, L., Petzke, F. and Hauser, W. (2018a), 'Cannabis-based medicines for chronic neuropathic pain in adults', *Cochrane Database of Systematic Reviews* 3, CD012182.

Mucke et al. (2018a) assessed studies that compared the efficacy of cannabis-based medicines (herbal, plant-based and synthetic) with placebo in chronic neuropathic pain in adults. They restricted their search to randomised double-blind controlled trials with minimum treatment duration of at least 2 weeks and a minimum of 10 participants per treatment arm.

The outcomes that they assessed were the proportion of patients who achieved 50 % and 30 % reductions in pain and the number who needed to be treated to benefit. They included 16 studies with 1 750 participants who received a cannabis-based medicine or placebo for 2 to 26 weeks. The cannabinoids studied included nabiximols (10 studies), nabilone (2 studies), herbal cannabis (2 studies) and dronabinol (2 studies). The comparison treatment was placebo in 15 studies and dihydrocodeine in 1 study. The authors rated the study quality as low in 2 studies, moderate in 12 studies and high in 2 studies. Nine studies were assessed as having a high risk of bias because of small sample sizes.

Mucke et al. found that the percentage of patients who achieved a 50 % reduction in pain when treated with cannabinoids was 21 %, compared with 17 % for placebo. The number who needed to be treated to benefit was 20. There was weaker evidence of benefit on secondary outcomes that included the Patient Global Impression of Change scale (26 % vs. 21 %) and the percentage who achieved a

30 % reduction in pain (39 % vs. 33 %), for which the number who needed to be treated to benefit was 11. They found more withdrawals from treatment because of adverse events in the cannabinoid condition than in the placebo condition (10 % vs. 5 %).

The authors concluded that the potential benefits of cannabinoids in treating chronic neuropathic pain might be outweighed by the harms. They found the quality of evidence poor because most studies excluded patients with a history of substance abuse and used small samples. Their 'bottom line' was that 'there is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain'.

Stockings, E., Campbell, G., Hall, W. D., Nielsen, S., Zagic, D., Rahman, R. et al. (2018a), 'Cannabis and cannabinoids for the treatment of people with chronic non-cancer pain conditions: a systematic review and meta-analysis of controlled and observational studies', *Pain* 159, pp. 1932-1954.

Stockings et al. (2018a) examined evidence from controlled clinical trials and observational studies on the efficacy of cannabinoids in treating chronic non-cancer pain (CNCP). They also considered differences in outcomes between different types of cannabinoid in treating specific CNCP conditions. They included RCTs and non-RCTs and used the IMMPACT guidelines to assess the clinical significance of CNCP outcomes (IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials).

Their review included 91 publications that reported 104 studies. These included 9 958 participants in 47 RCTs (24 parallel group studies and 23 crossover trials) and 57 observational studies that did not involve random assignment to treatment.

Of the studies, 48 were of patients with neuropathic pain (16 in patients with MS and 32 in patients with neuropathic pain other than MS-related). They also included 7 studies of patients with fibromyalgia, 1 study of patients with rheumatoid arthritis and 48 studies of other types of CNCP (13 of MS-related pain, 6 of visceral pain and 29 of mixed or undefined CNCP).

The percentage of CNCP patients who achieved a 30 % reduction in pain intensity when averaged across RCTs was 29 % for patients treated with cannabinoids versus 26 % in those who received a placebo. This difference was statistically significant. The number of patients who needed to be treated to benefit was 24 when a 50 % reduction in pain was used as the outcome. The proportion achieving this level of pain reduction was 18 % in those who received a cannabinoid and 14 % in those who received a placebo. This difference was not statistically significant. The overall change in pain intensity was equivalent to a 3 mm greater reduction on a 100 mm visual analogue scale in those treated with a cannabinoid than in those given a placebo.

In the RCTs, the proportion of patients reporting any adverse event was 81 % in those who received a cannabinoid compared with 66 % in those who received a placebo. The number of patients who needed to be treated to harm was six. There were no significant effects of cannabinoids on physical or emotional functioning, and there was only low-quality evidence that cannabinoids improved sleep or patients' global impression of change.

Stockings et al. concluded that the evidence for the effectiveness of cannabinoids in treating CNCP was limited. The number of patients who needed to be treated to benefit was high, while the number who needed to be treated to harm was low. There was limited evidence of benefit in other pain-related domains. The authors' summary was that it was 'unlikely that cannabinoids are highly effective medicines for CNCP'.

Chemotherapy-induced nausea and vomiting in cancer patients

Smith, L., Azariah, F., Lavender, V. T., Stoner, N. S. and Bettioli, S. (2015), 'Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy', *Cochrane Database of Systematic Reviews* 11, CD009464.

Smith et al. (2015) reviewed 23 RCTs that compared the effectiveness of a cannabinoid (most often dronabinol) with either placebo or an active treatment for nausea and vomiting in cancer patients who were undergoing chemotherapy. Most of the studies were crossover trials and the majority were assessed as having a high risk of bias because of a lack of clarity about how patients were allocated to treatment, a lack of participant blindness to treatment or high rates of subject attrition. The trials were conducted between 1975 and 1991, so none could compare cannabinoids with the more effective anti-emetic drugs developed since that time.

Complete control of vomiting was assessed in three trials with 168 participants. The cannabinoid was found to completely control vomiting in a larger proportion of patients than placebo, but these studies were described as of low quality. The outcome of complete control of nausea and vomiting was assessed in two trials with 288 participants and cannabinoids were found to be superior to placebo. Patients who received the cannabinoid were more likely to withdraw from treatment because of adverse events than those who received the placebo, but this effect was not statistically significant.

An analysis of trials that compared cannabinoids with other anti-emetics did not find any difference between the cannabinoid and prochlorperazine on any measure of control of nausea and vomiting. The sample sizes in these studies were small, however, so the statistical power of these comparisons was low. Patients who received a cannabinoid were more likely to withdraw because of adverse events than those taking prochlorperazine.

The overall quality of the evidence was low because most studies had a moderate risk of bias and they did not reflect current chemotherapy and anti-emetic regimens. The evidence was graded as low for the majority of outcomes, indicating that the reviewers were not very confident of the results. They also believed that research on cannabinoids in newer chemotherapy regimens and in comparison with newer anti-emetic drugs could modify the conclusions.

Studies of appetite stimulation in HIV/AIDS

Lutge, E., Gray, A. and Siegfried, N. (2013), 'The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS', *Cochrane Database of Systematic Reviews* 4, CD005175.

Lutge et al. (2013) reviewed seven RCTs that compared cannabinoids (dronabinol and nabilone) with a placebo. These included four parallel group and three crossover trials, all with small sample sizes and short durations of treatment (21 to 84 days). Only three clearly randomised patients to treatment. Outcomes that were assessed included weight gain and self-reported appetite. The authors assessed the evidence as very weak and noted that all the studies had been done before effective antiretroviral treatment was introduced for AIDS.

Intractable epilepsy

Gloss, D. and Vickrey, B. (2014), 'Cannabinoids for epilepsy', *Cochrane Database of Systematic Reviews* 3, CD009270.

Gloss and Vickrey (2014) reviewed four RCTs that compared the effects of adding a cannabinoid or placebo to conventional anti-epileptic drugs in treatment-resistant epilepsy. These trials included 48 patients and all evaluated the effects of adding CBD to an anti-convulsant, which was continued in all the studies. The primary outcome measured was freedom from seizures. All the studies were judged to be of low quality. The authors concluded that no reliable conclusions could be drawn about the efficacy and safety of CBD in intractable epilepsy.

Stockings, E., Zagic, D., Campbell, G., Weier, M., Hall, W. D., Nielsen, S. et al. (2018b), 'Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence', *Journal of Neurology, Neurosurgery, and Psychiatry* 89, pp. 741-753.

Stockings et al. (2018b) reviewed 6 clinical trials (involving 555 patients) and 30 observational studies (involving 2 865 patients) that evaluated CBD in intractable epilepsy (primarily in children). All participants, whose average age was 13 years, had a rare form of epilepsy that had not responded to treatment with other anti-epileptic drugs. A pooled analysis showed that CBD was more effective than placebo in reducing seizure frequency by 50 % or more and in improving quality of life. Eight patients needed to receive CBD for one to reduce their seizure frequency by 50 % or

more. CBD was also more effective than placebo at completely controlling seizures, but this was a very rare outcome.

The risk of side effects (dizziness and drowsiness), was 24 % higher for CBD than placebo. Serious side effects occurred at twice the rate in those taking CBD compared with those given a placebo. Pooled data from the 17 observational studies indicated that seizure frequency decreased by 50 % or more in just under half of the patients and disappeared in 8.5 %. Quality of life improved for half of the patients in 12 of the observational studies.

Palliative care for cancer

Mucke, M., Weier, M., Carter, C., Copeland, J., Degenhardt, L., Cuhls, H. et al. (2018b), 'Systematic review and meta-analysis of cannabinoids in palliative medicine', *Journal of Cachexia, Sarcopenia, and Muscle* 9, pp. 220-234.

Mucke et al. (2018b) reported a systematic review and meta-analysis of studies of the efficacy, tolerability and safety of cannabinoids in palliative medicine for cancer and AIDS. They found nine studies with 1 561 participants, all of which were judged to have a moderate risk of bias. The quality of evidence comparing cannabinoids with placebo was rated as low or very low because of imprecision and potential reporting bias. In cancer patients, there were no significant differences between cannabinoids and placebo in improving caloric intake (standardised mean difference (SMD): 0.2 (95 % CI -0.66 to 1.06)), appetite (SMD: 0.81 (95 % CI -1.14 to 2.75)) or nausea/vomiting (SMD: 0.21 (95 % CI -0.10 to 0.52)), or in achieving a greater than 30 % decrease in pain severity (risk difference (RD): 0.07 (95 % CI -0.01 to 0.16)) or improving sleep problems (SMD: -0.09 (95 % CI -0.62 to 0.43)). In the case of HIV patients, the authors found that cannabinoids were superior to placebo for weight gain (SMD: 0.57 (95 % CI 0.22 to 0.92) and improving appetite (SMD: 0.57 (95 % CI 0.11 to 1.03)) but not for reducing nausea/vomiting (SMD: 0.20 (95 % CI -0.15 to 0.54); $p = 0.26$). In cancer patients, they found no differences between cannabinoids and placebo in relation to dizziness (RD: 0.03 (95 % CI -0.02 to 0.08)) or poor mental health (RD: -0.01 (95 % CI -0.04 to 0.03)). In HIV patients, there was an increase in mental health symptoms in those given cannabinoids (RD: 0.05 (95 % CI 0.00 to 0.11)). The number of patients who withdrew from treatment because of adverse events did not differ significantly between cannabinoid and placebo in cancer patients (RD: 1.15 (95 % CI 0.80 to 1.66)) or HIV patients (RD: 1.87 (95 % CI 0.60 to 5.84)).

There was a high degree of uncertainty about patient safety because of the small sample sizes in many of the studies. The authors 'found no convincing, unbiased, high quality evidence suggesting that cannabinoids are of value for anorexia or cachexia in cancer or HIV patients'. They also 'did not find any significant differences

between cannabinoids and placebo in improving caloric intake, appetite, nausea or vomiting, pain, or sleep in terminally ill cancer patients'. Their confidence in their conclusions was limited by the small number of high-quality studies in the review and the small sample sizes of the studies, both of which reduced the chances of finding any differences between cannabinoids and placebo. Larger, better-designed trials are needed to assess the value of cannabis and cannabinoids in palliative cancer care.

3. Adverse effects of the medical use of cannabis and cannabinoids

Short-term risks

The short-term effects of medical use of cannabinoids and cannabis have been studied in a substantial number of randomised controlled clinical trials in a diverse range of medical conditions, typically for periods of 8 to 12 weeks. The trial length has varied with condition: trials looking at nausea and vomiting due to chemotherapy lasted from 1 to 6 days, while trials looking at conditions such as appetite, pain or spasticity associated with MS lasted from 8 to 15 weeks (Whiting et al., 2015).

Wang et al. (2008) conducted a meta-analytic review of adverse effects reported in RCTs of cannabinoids and cannabis extracts for various medical uses. They also considered case reports of adverse events among cannabis users and observational studies of adverse events among recreational cannabis users. Most adverse events (97 %) reported in the clinical trials were very minor, with dizziness (20 %) being the most common. The authors did not find any elevated risk of serious adverse events in patients using cannabinoid drugs (either plant extracts or THC preparations) compared with placebo (Wang et al., 2008).

These findings supported the conclusion reached in a 1999 report (Institute of Medicine, 1999) that the short-term use of cannabinoids for medical purposes had an acceptable profile of adverse effects. The review was unable to provide information on the longer term use of cannabinoids for chronic disorders, such as MS, because the available trials had been relatively short term (8 hours to 12 months) (Wang et al., 2008).

Whiting et al. (2015) reported a meta-analysis on the adverse events reported in 79 trials that evaluated the medical use of cannabinoids for nausea and vomiting, appetite stimulation, chronic pain, spasticity due to MS, depression, anxiety, sleep disorder, psychosis, glaucoma or movement disorder due to Tourette syndrome. Table 4 summarises the prevalence of any adverse effects, serious adverse effects and withdrawal from studies. It also indicates the number of studies and the number of patients on which the estimates are based and uses the odds ratio to express the difference in the likelihood of these events between patients receiving a cannabinoid and those receiving a placebo.

Table 4: Prevalence of any adverse effects, serious adverse effects and withdrawal (based on Whiting et al., 2015)

	Studies (n)	Patients (n)	OR
Any adverse effects	29	3 714	3.03
Serious adverse effects	34	3 248	1.41
Withdrawal	23	2 755	2.94

Adverse events were more common among patients who received a cannabinoid than among those who received a placebo. So were serious adverse events, although the difference in odds was smaller. Patients who received a cannabinoid were also more likely to withdraw from the study.

Table 5 shows the most commonly reported adverse effects and the number of studies and patients in whom they were reported. The adverse effects reported most often by patients who received cannabinoids were dizziness, dry mouth, nausea, fatigue, somnolence and euphoria.

Table 5: Most commonly reported adverse effects (based on Whiting et al., 2015)

	Studies (n)	Patients (n)	OR
Dizziness	41	4 243	5.09
Dry mouth	36	4 181	3.50
Nausea	30	3 579	2.08
Fatigue	20	2 717	2.00
Somnolence	26	3 168	2.83
Euphoria	27	2 420	4.08
Depression	15	2 353	1.32
Vomiting	17	2 191	1.67
Diarrhoea	17	2 077	1.65
Disorientation	12	1 736	5.41
Asthenia	15	1 717	2.03

Information is lacking in many reviews on possible interactions between cannabinoids and other drugs (Martin and Bonomo, 2016). This is an important evidence gap because cannabinoids are most often used as adjunctive treatments in combination with other drugs, such as opioids and other analgesics in the case of chronic pain, immunosuppressant drugs in the case of MS and anti-epileptic drugs in the case of intractable epilepsy.

Long-term risks

There is very little evidence on the longer term adverse effects reported by patients who use cannabis-based medicines regularly over months or years. One study by Serpell et al. (2013) reported the adverse events experienced by patients taking part in an open-label trial of Sativex for spasticity due to MS. Patients who had previously taken part in a 6-week RCT of Sativex were invited to continue to receive the drug in an open-label extension trial for up to 3 years. Eighty-four per cent ($n = 145$) of the patients who finished the RCT continued in the open-label trial; 35 patients used Sativex for up to 1 year, 43 patients used it for up to 2 years, and 4 patients used it for up to 3 years. Ninety-five per cent of patients experienced an adverse event, but the majority of these were mild to moderate in severity. The most common involved dizziness, fatigue or headache. A total of 23 patients (16 %) withdrew from the study due to adverse events.

Two observational studies have reported on adverse effects in cancer patients (Bar-Lev Schleider et al., 2018) and elderly patients (Abuhasira et al., 2018) treated in a leading Israeli cancer hospital between January 2015 and October 2017. Adverse events were assessed in a telephone interview conducted 6 months after treatment started. Among cancer patients, 31 % reported an adverse event; these most commonly related to dizziness (8.0 %), dry mouth (7.3 %), increased appetite (3.6%), sleepiness (3.3 %) and psychoactive effects (2.8 %) (Bar-Lev Schleider et al., 2018). The prevalence and type of adverse events were very similar in older patients treated with cannabis for more varied medical conditions (Abuhasira et al., 2018).

There have not yet been any studies of adverse events associated with the regular use of CBD in children treated for intractable epilepsy. This should be a research priority given concerns about the possible effects of long-term medication use on brain development in children and adolescents.

Risks associated with long-term recreational cannabis use

In the light of the sparse evidence on the long-term harms that may be associated with medical use, a number of reviews have reviewed evidence of harms from long-term recreational use to identify possible harms that should be monitored in medical treatment using cannabinoids (see, for example, Wang et al., 2008). Observational population-based cohort studies of recreational cannabis users may provide an indication of possible adverse effects of long-term cannabis use. There are major

uncertainties, however, about the extent to which these risks apply to the use of cannabinoid medicines. Cannabis preparations for medical purposes are typically used in lower doses by older adults using an oral route, whereas recreational users are generally younger adults who smoke potent cannabis products, often daily.

Respiratory diseases

Long-term cannabis smoking is associated with the development of chronic bronchitis (Hall et al., 2016; NASEM, 2017). There have been more mixed reports on the risk of chronic obstructive pulmonary disease (Hall et al., 2016; NASEM, 2017). The potential respiratory risks primarily arise because cannabis is smoked in a combustible cigarette and, in many instances, combined with tobacco (Tan et al., 2009). If the patient consumes the cannabinoid orally in the form of a capsule or in an oil, then respiratory risks will not arise. The use of vaporisers would probably also reduce this risk, but it is unclear by how much.

Cognitive impairment

Long-term heavy use of cannabis for recreational purposes has also been associated with poorer cognitive function — specifically memory, attention, decision-making and planning (Crean et al., 2011; Solowij et al., 2002). This risk may be a concern for patients who are using cannabinoids over the long term and wish to continue activities in which reduced cognitive performance may be an issue.

Psychiatric disorders

Longitudinal and cohort studies have indicated that long-term or heavy cannabis use is associated with a greater prevalence of symptoms of depression (Degenhardt et al., 2003), mania (Henquet et al., 2006) and psychosis (van Os et al., 2002). Long-term regular cannabis use is associated with the development of depression, anxiety, mania and hypomania in individuals with bipolar disorder, suicidal thoughts and suicide completion, social anxiety, and PTSD symptoms (NASEM, 2017) (see Table 5). Debate continues about which of these associations are causal. There is limited evidence from prospective cohort studies for most of these disorders, so it is difficult to exclude the possibility that cannabis is used to self-medicate symptoms of the disorders.

There is support for a causal relationship in the case of psychosis (Hall et al., 2016; NASEM, 2017). Prospective studies suggest that long term daily cannabis use may precipitate psychotic symptoms or disorders in young people who are vulnerable because of personal or family history (Degenhardt and Hall, 2006; NASEM, 2017). Again, this evidence is derived from people who have used cannabis for recreational purposes, typically daily from their mid-teens and into young adulthood. It remains uncertain whether the same risks would arise from daily use of a synthetic cannabinoid or cannabis preparation that was consumed in controlled doses by an older patient. Nevertheless, people who have a personal or family history of psychosis might be wise to avoid using cannabis for any reason (Degenhardt and Hall, 2006; Hall et al., 2016).

Cannabis dependence

One possible consequence of long-term medical use of cannabis is the risk of developing cannabis dependence. The risk is highest (Hall, 2015; Hall et al., 2001) among recreational cannabis users who began using in adolescence and early adulthood, and who used the most potent cannabis products. These users have probably smoked cannabis with a greater frequency and intensity than would older adults using smaller doses for symptom relief (Hall et al., 2016). We know nothing of the incidence of cannabis dependence in long-term, medically supervised medical use, such as that which might occur if cannabis were used to treat chronic pain. Here, the risk of dependence could plausibly be considered higher than in more episodic medical use, such as for chemotherapy-induced nausea, although it is unclear by how much.

Cardiovascular risk

The cardiovascular disease risk posed by cannabis and cannabinoids is a concern in relation to medical use of cannabis because the risk of these diseases is higher in the older populations that are likely to use cannabis for medical reasons (Hall and Degenhardt, 2003). One epidemiological study found that heavy cannabis users (who were also heavy tobacco and alcohol users and had other elevated risk factors for adverse outcomes) were at slightly elevated risk of mortality at later follow-up, but their deaths were not related to cardiovascular causes (Mukamal et al., 2008). More recent reviews have suggested that cannabis use, both short term and long term, increases the risk of triggering a myocardial infarction (Franz and Frishman, 2016; Hall et al., 2016; NASEM, 2017) and may also do so for stroke (Hall et al., 2016).

Cancers

The cancer risks posed by cannabis smoking remain uncertain. There have been inconsistent findings in epidemiological studies: some have suggested no increased cancer risk, and some case-control studies have suggested some elevation of risk in very heavy long-term smokers (Aldington et al., 2008; Hashibe et al., 2006). Some evidence suggests that long-term recreational use may be associated with an increased risk of developing testicular, prostate or ovarian cancer (Hall et al., 2016). However, these associations are most pertinent to cannabis smoking and probably less of an issue for oral use of cannabis oils or cannabinoids.

Summary

Based on the current data, the risk of adverse effects from the short-term use of medical cannabinoids and cannabis extracts is greater than that from placebo, but the most common adverse events are minor, for example involving dizziness or somnolence, and serious adverse events are rare. The risk may be marginally greater for oral THC than for combinations of CBD and THC or for cannabis extract preparations (Wang et al., 2008). CBD may counteract some of the adverse effects of THC (Zuardi et al., 2006). We need better information on the adverse effects of more sustained use of cannabinoids and cannabis preparations from follow-up studies of patients using these preparations for chronic pain and epilepsy, so that we

can assess the risks of cannabis dependence and cardiovascular disease in medical cannabis users.

4. Focus on the US — potential unintended consequences of the medical use of cannabis and cannabinoids

When considering the outcomes of regulatory changes to allow access to cannabis and cannabinoids for medical use, in addition to considering health risks and benefits for patients it is important to consider potential broader social and public health impacts. There are now a growing number of studies, primarily from the US, investigating these wider impacts. However, as with the evidence concerning the clinical effectiveness of different cannabis products and preparations, variations in approaches, definitions and data sources makes drawing firm conclusions difficult, with studies often having contradictory outcomes or inconclusive results.

In this section, a few issues considered in medical cannabis studies to date are discussed to illustrate the types of potential unintended consequences, both positive and negative, that may need to be considered when making cannabis or cannabinoids available for medical use.

The impact of medical use of cannabis on recreational cannabis use and cannabis disorders

One of the possible issues is the impact of medical use of cannabis on recreational cannabis use. Data from US household surveys suggest that cannabis use may have increased among adults over the age of 21 years between 2004 and 2012 after laws on the medical use of cannabis were passed (Wen et al., 2015). There were no differences in rates of new adult cannabis users between states with laws on the medical use of cannabis and states without such laws, but adults in states with laws on the medical use of cannabis were more likely to report higher rates of cannabis use in the past 30 days (an increase of 1.3 %), higher rates of daily cannabis use (an increase of 0.6 %) and higher rates of cannabis abuse/dependence (an increase of 10 %) than adults who lived in states that had not passed laws on the medical use of cannabis.

There are conflicting findings on whether cannabis dependence has increased overall in the US adult population over the two decades in which laws on the medical use of cannabis have been enacted. The National Epidemiologic Survey of Alcohol and Related Conditions concluded that the prevalence of cannabis use disorders increased between 1991-1992 and 2001-2002 (Compton et al., 2004) but that rates of cannabis use remained stable. The prevalence of cannabis use disorders increased again between 2001-2002 and 2012-2013, and so did the prevalence of cannabis use (Hasin et al., 2015).

These studies were not supported by Compton et al.'s 2016 analysis of trends in cannabis use in US adults aged 18 years and older in annual surveys between 2002 and 2014 (Compton et al., 2016). The prevalence of past year cannabis use increased from 10 % in 2002 to 13 % in 2014, with rates increasing most steeply

after 2007. Rates of initiation of cannabis use in the past 12 months increased from 0.7 % to 1.1 % and the prevalence of daily or near daily cannabis use increased from 1.9 % to 3.5 %, again beginning in 2007.

Surprisingly, despite the increased prevalence of adult cannabis use, the prevalence of cannabis use disorders in the past year remained at 1.5 % in adults across this period. More surprisingly, the risk of disorders *declined* among adults who had used cannabis in the past year from 15 % in 2002 to 11.0 % in 2014. This finding is surprising because one might expect an increase in these disorders among users when the prevalence and frequency of cannabis use and the use of more potent cannabis products increase (Freeman and Winstock, 2015; Mehmedic et al., 2010).

There are a number of possible explanations for the decreased prevalence of cannabis use disorders found in Compton et al.'s 2016 study despite the increase in the prevalence of near daily cannabis use. First, there could be an age cohort effect. Grucza et al. (2016) found a decline in use among 12- to 17-year-olds, who are at a higher risk of developing cannabis use disorder. Compton et al. (2016) found increased use in those over the age of 18 years. Younger users are more likely to develop dependence, whereas older users may be more likely to use cannabis without developing dependence. A second possibility is that liberalisation of cannabis policy has increased the number of cannabis users among older adults, possibly by increasing the number of former users who resume cannabis use. Older adults generally use less often, and so the proportion of current users who meet criteria for cannabis use disorders could have been reduced.

One study has examined the effects of laws on the medical use of cannabis on treatment seeking for cannabis use disorders. Choo et al. (2014) compared the number of people seeking first-time treatment for cannabis problems between 1992 and 2011 in states that did and did not have these laws. They found a 15-21 % increase in new treatment episodes for primary cannabis use problems in people who had *not* been referred by the criminal justice system after laws on the medical use of cannabis were passed.

The impact of medical use of cannabis on use among young people

An additional concern has been that these laws will increase adolescent cannabis use by making cannabis more available to young people and sending the unintended message that cannabis use is not risky. Researchers have evaluated these concerns using survey data to compare trends in cannabis use in adolescents in states that have and have not legalised medical cannabis use. These surveys were not primarily designed for this task. They were designed to provide representative samples of the US high school population nationally, as opposed to profiling the high school populations of individual states. In order to compare populations in states that have legalised and not legalised medical marijuana, data often have to be averaged over two survey years to produce stable estimates.

Comparisons of adolescent cannabis use in household and school-based surveys have generally not found differences in use between states with and without medical marijuana laws (MMLs) (see, for example, Ammerman et al., 2015; Cerda et al., 2012; Choo et al., 2014; Harper et al., 2012; Lynne-Landsman et al., 2013; Schuermeyer et al., 2014; Wall et al., 2011; Wall et al., 2012).

The largest study of adolescent cannabis use in the US to date was based on national surveys of secondary school students funded by the National Institute on Drug Abuse. Using data from Monitoring the Future Surveys run between 1991 and 2014, Hasin et al. (2015) compared trends in past 30 day cannabis use in the 21 states that had legalised medical marijuana use with those in the 27 mainland US states that had not, while controlling for social, economic and demographic differences between states and schools. Hasin et al. found that states that had passed MMLs had higher rates of past 30 day cannabis use *before* the laws were passed (16 % vs. 13 %) than states that had not. There was no change in adolescent cannabis use before and after the passage of MMLs (16.3 % pre to 15.5 % post). Indeed, there was a *reduction* in rates of cannabis use in eighth grade students in states with MMLs.

Comparisons of trends in cannabis use among young people aged 12 to 20 years in the US National Survey on Drug Use and Health show similar results (Wen et al., 2015). The proportion of young people in MML states who reported using cannabis in the year after the MMLs were passed marginally increased between 2004 and 2012, but there was no increase in cannabis use in the past 30 days and no increase in daily use.

The medical use of cannabis and cannabis-related motor vehicle fatalities

Studies evaluating the effects of MMLs on cannabis-related motor vehicle fatalities have produced mixed results. Some (Masten and Guenzburger, 2014) have found an increase in the percentage of cannabis-impaired drivers detected in fatal crashes in states that have passed MMLs. The complication is that testing drivers for cannabis use became more common after MMLs were enacted.

Anderson et al. (2013) examined the role of alcohol in car crashes between 1990 and 2010 in US states that did and did not have MMLs. They found an 8-11 % greater *decrease* in total traffic fatalities and in fatalities with a blood alcohol concentration greater than 0.08 % in states with MMLs. They argued that this effect was the result of young males substituting cannabis for alcohol because cannabis was cheaper in MML states. They cited as supporting evidence that there were larger reductions in alcohol consumption and beer sales in states that had passed MMLs.

A comparison of trends in fatal motor vehicle crashes in Colorado and 34 states without MMLs between 1994 and 2011 produced inconsistent results (Salomonsen-Sautel et al., 2014). The authors found a larger increase in cannabis-positive fatalities in Colorado after 2009 than in the 34 states without MMLs. They also found no change in alcohol-related motor vehicle fatalities in Colorado or the 34 states without MMLs.

Medical use of cannabis and suicides

Anderson et al. (2014) reported steeper declines in suicides among males aged 20 to 30 years in US states that had legalised medical marijuana than in those that had not. An analysis that controlled for differences between states did not support their finding (Grucza et al., 2015). Rylander et al. (2014) did not find any association between suicide rates and the number of medical marijuana patients in US states between 2004 and 2010.

Medical use of cannabis and other substances

A number of studies of MMLs have examined trends in alcohol-related harm to see if young men may be using cannabis as a substitute for alcohol in states with MMLs (Anderson et al., 2014). Wen et al.'s 2015 analysis of National Survey on Drug Use and Health data did not find a greater reduction in alcohol use among people under the age of 21 years in states with MMLs. Indeed, they found more binge drinking, and more concurrent use of alcohol and cannabis, among adults aged over 21 years in states with MMLs.

An analysis of opioid overdose deaths in the US found lower rates of these deaths in states with MMLs than in those without such laws, and the difference in overdose death rates increased over time (Bachhuber et al., 2014). This finding has been interpreted as evidence that the substitution of cannabis for opioids in pain relief has reduced the number of fatal opioid overdoses. However, a correlation between time series data on opioid overdose deaths and state MMLs is weak evidence for a causal relationship (Finney et al., 2015). Better evidence is needed, namely that cannabis and opioid use have changed in the ways required for a causal relationship, and that the association is not explained by other policy differences (e.g. rates of imprisonment of opioid users and provision of methadone-assisted treatment) between states that have and have not passed MMLs (Hall et al., 2018; Hayes and Brown, 2014).

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