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Evidence Based Science
(Excerpts)

Prescription Only Medicines

WORLD HEALTH ORGANISATION AND CANNABIS

Cannabis

Terminology

Cannabis is a generic term used to denote the several psychoactive preparations of the plant Cannabis sativa. The major psychoactive constituent in cannabis is Δ-9 tetrahydrocannabinol (THC). Compounds which are structurally similar to THC are referred to as cannabinoids. In addition, a number of recently identified compounds that differ structurally from cannabinoids nevertheless share many of their pharmacological properties. The Mexican term 'marijuana' is frequently used in referring to cannabis leaves or other crude plant material in many countries. The unpollinated female plants are called hashish. Cannabis oil (hashish oil) is a concentrate of cannabinoids obtained by solvent extraction of the crude plant material or of the resin.

Epidemiology

Cannabis is by far the most widely cultivated, trafficked and abused illicit drug. Half of all drug seizures worldwide are cannabis seizures. The geographical spread of those seizures is also global, covering practically every country of the world. About 147 million people, 2.5% of the world population, consume cannabis (annual prevalence) compared with 0.2% consuming cocaine and 0.2% consuming opiates. In the present decade, cannabis abuse has grown more rapidly than cocaine and opiate abuse. The most rapid growth in cannabis abuse since the 1960s has been in developed countries in North America, Western Europe and Australia. Cannabis has become more closely linked to youth culture and the age of initiation is usually lower than for other drugs. An analysis of cannabis markets shows that low prices coincide with high levels of abuse, and vice versa. Cannabis appears to be price-inelastic in the short term, but fairly elastic over the longer term. Though the number of cannabis consumers is greater than opiate and cocaine consumers, the lower prices of cannabis mean that, in economic terms, the cannabis market is much smaller than the opiate or cocaine market.

Acute health effects of cannabis use

The acute effects of cannabis use has been recognized for many years, and recent studies have confirmed and extended earlier findings. These may be summarized as follows:

- Cannabis impairs cognitive development (capabilities of learning), including associative processes; free recall of previously learned items is often impaired when cannabis is used both during learning and recall periods;
- Cannabis impairs psychomotor performance in a wide variety of tasks, such as motor coordination, divided attention, and operative tasks of many types; human performance on complex machinery can be impaired for as long as 24 hours after smoking as little as 20 mg of THC in cannabis; there is an increased risk of motor vehicle accidents among persons who drive when intoxicated by cannabis.

Chronic health effects of cannabis use

- Selective impairment of cognitive functioning which include the organization and integration of complex information involving various mechanisms of attention and memory processes;
- Prolonged use may lead to greater impairment, which may not recover with cessation of use, and which could affect daily life functions;
- Development of a cannabis dependence syndrome characterized by a loss of control over cannabis use is likely in chronic users;
- Cannabis use can exacerbate schizophrenia in affected individuals;
- Epithelial injury of the trachea and major bronchi is caused by long-term cannabis smoking;
- airway injury, lung inflammation, and impaired pulmonary defence against infection from persistent cannabis consumption over prolonged periods;
- Heavy cannabis consumption is associated with a higher prevalence of symptoms of chronic bronchitis and a higher incidence of acute bronchitis than in the non-smoking cohort;

- Cannabis used during pregnancy is associated with impairment in fetal development leading to a reduction in birth weight;
- Cannabis use during pregnancy may lead to postnatal risk of rare forms of cancer although more research is needed in this area.

The health consequences of cannabis use in developing countries are largely unknown because of limited and non-systematic research, but there is no reason a priori to expect that biological effects on individuals in these populations would be substantially different to what has been observed in developed countries. However, other consequences might be different given the cultural and social differences between countries.

Therapeutic uses of cannabinoids

Several studies have demonstrated the therapeutic effects of cannabinoids for nausea and vomiting in the advanced stages of illnesses such as cancer and AIDS. Dronabinol (tetrahydrocannabinol) has been available by prescription for more than a decade in the USA. Other therapeutic uses of cannabinoids are being demonstrated by controlled studies, including treatment of asthma and glaucoma, as an antidepressant, appetite stimulant, anticonvulsant and anti-spasmodic, research in this area should continue. For example, more basic research on the central and peripheral mechanisms of the effects of cannabinoids on gastrointestinal function may improve the ability to alleviate nausea and emesis. More research is needed on the basic neuropharmacology of THC and other cannabinoids so that better therapeutic agents can be found.

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Cochrane Database of Systematic Reviews

Cannabis-based medicines and medical cannabis for adults with cancer pain (Review)

Häuser W, Welsch P, Radbruch L, Fisher E, Bell RF, Moore RA

Häuser W, Welsch P, Radbruch L, Fisher E, Bell RF, Moore RA.
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[Intervention Review]

Cannabis-based medicines and medical cannabis for adults with cancer pain

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ABSTRACT

Background

Pain is a common symptom in people with cancer; 30% to 50% of people with cancer will experience moderate-to-severe pain. This can have a major negative impact on their quality of life. Opioid (morphine-like) medications are commonly used to treat moderate or severe cancer pain, and are recommended for this purpose in the World Health Organization (WHO) pain treatment ladder. Pain is not sufficiently relieved by opioid medications in 10% to 15% of people with cancer. In people with insufficient relief of cancer pain, new analgesics are needed to effectively and safely supplement or replace opioids.

Objectives

To evaluate the benefits and harms of cannabis-based medicines, including medical cannabis, for treating pain and other symptoms in adults with cancer compared to placebo or any other established analgesic for cancer pain.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 26 January 2023.

Selection criteria

We selected double-blind randomised, controlled trials (RCT) of medical cannabis, plant-derived and synthetic cannabis-based medicines against placebo or any other active treatment for cancer pain in adults, with any treatment duration and at least 10 participants per treatment arm.

Data collection and analysis

We used standard Cochrane methods. The primary outcomes were 1. proportions of participants reporting no worse than mild pain; 2. Patient Global Impression of Change (PGIC) of much improved or very much improved and 3. withdrawals due to adverse events. Secondary outcomes were 4. number of participants who reported pain relief of 30% or greater and overall opioid use reduced or stable; 5. number of participants who reported pain relief of 30% or greater, or 50% or greater; 6. pain intensity; 7. sleep problems; 8. depression and anxiety; 9. daily maintenance and breakthrough opioid dosage; 10. dropouts due to lack of efficacy; 11. all central nervous system adverse events. We used GRADE to assess certainty of evidence for each outcome.

Main results

We identified 14 studies involving 1823 participants. No study assessed the proportions of participants reporting no worse than mild pain on treatment by 14 days after start of treatment.

We found five RCTs assessing oromucosal nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) or THC alone involving 1539 participants with moderate or severe pain despite opioid therapy. The double-blind periods of the RCTs ranged between two and five weeks. Four studies with a parallel design and 1333 participants were available for meta-analysis.

There was moderate-certainty evidence that there was no clinically relevant benefit for proportions of PGIC much or very much improved (risk difference (RD) 0.06, 95% confidence interval (CI) 0.01 to 0.12; number needed to treat for an additional beneficial outcome (NNTB) 16, 95% CI 8 to 100). There was moderate-certainty evidence for no clinically relevant difference in the proportion of withdrawals due to adverse events (RD 0.04, 95% CI 0 to 0.08; number needed to treat for an additional harmful outcome (NNTH) 25, 95% CI 16 to endless). There was moderate-certainty evidence for no difference between nabiximols or THC and placebo in the frequency of serious adverse events (RD 0.02, 95% CI −0.03 to 0.07). There was moderate-certainty evidence that nabiximols and THC used as add-on treatment for opioid-refractory cancer pain did not differ from placebo in reducing mean pain intensity (standardised mean difference (SMD) −0.19, 95% CI −0.40 to 0.02).

There was low-certainty evidence that a synthetic THC analogue (nabilone) delivered over eight weeks was not superior to placebo in reducing pain associated with chemotherapy or radiochemotherapy in people with head and neck cancer and non-small cell lung cancer (2 studies, 89 participants, qualitative analysis). Analyses of tolerability and safety were not possible for these studies.

There was low-certainty evidence that synthetic THC analogues were superior to placebo (SMD −0.98, 95% CI −1.36 to −0.60), but not superior to low-dose codeine (SMD 0.03, 95% CI −0.25 to 0.32; 5 single-dose trials; 126 participants) in reducing moderate-to-severe cancer pain after cessation of previous analgesic treatment for three to four and a half hours (2 single-dose trials; 66 participants). Analyses of tolerability and safety were not possible for these studies.

There was low-certainty evidence that CBD oil did not add value to specialist palliative care alone in the reduction of pain intensity in people with advanced cancer. There was no difference in the number of dropouts due to adverse events and serious adverse events (1 study, 144 participants, qualitative analysis).

We found no studies using herbal cannabis.

Authors' conclusions

There is moderate-certainty evidence that oromucosal nabiximols and THC are ineffective in relieving moderate-to-severe opioid-refractory cancer pain. There is low-certainty evidence that nabilone is ineffective in reducing pain associated with (radio-) chemotherapy in people with head and neck cancer and non-small cell lung cancer. There is low-certainty evidence that a single dose of synthetic THC analogues is not superior to a single low-dose morphine equivalent in reducing moderate-to-severe cancer pain. There is low-certainty evidence that CBD does not add value to specialist palliative care alone in the reduction of pain in people with advanced cancer.

PLAIN LANGUAGE SUMMARY

Cannabis-based medicines for cancer pain

Do medicines based on cannabis help adults with cancer pain?

Key messages

Cannabis-based medicines (CbMs) did not relieve cancer pain that did not respond to morphine-like medicines.

The studies analysed did not allow any statement to be made on the place of these medications in the World Health Organization (WHO) analgesic ladder for cancer pain.

Trials with CbMs in cancer need to be very much better designed than those conducted so far.

Pain in cancer and its treatment

One person in two or three who gets cancer will have pain that becomes moderate or severe in intensity. The pain tends to get worse as the cancer progresses.

The WHO recommends taking morphine-like medicines for moderate-to-severe pain from cancer, but 1 in 6 to 10 people with cancer pain do not experience sufficient pain relief from morphine-like medicines. Several products based on the cannabis plant have been suggested as treatment for cancer pain. These products include inhaled or orally ingested herbal cannabis, and various oils, sprays or tablets containing active cannabis ingredients obtained from the plant, or made synthetically. Some people with cancer pain have reported that CbMs are effective for them, and that is often highlighted in the media.

What did we want to find out?

If CbMs relieved cancer pain in people living with cancer.

If CbMs were associated with any unwanted or harmful effects.

What did we do?

We searched for clinical trials that examined CbMs compared to other medications to treat cancer pain in adults.

We summarised the results of the studies and rated our confidence in the evidence, based on factors such as the methods and size of studies.

What did we find?

We found 14 studies involving 1823 people. The biggest study included 399 people and the smallest study included 10 people.

Studies were conducted in countries around the world; most (six) were based in North America.

Five studies used one dose of CbM and lasted less than one day. Other studies lasted between two and eight weeks.

Pharmaceutical companies funded seven studies.

Six studies compared a mouth spray with a plant-derived combination of tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis, and cannabidiol (CBD), an anti-inflammatory ingredient of cannabis, against a fake medication (placebo). Seven studies compared an artificial cannabinoid mimicking the effects of THC against placebo. Of these seven studies, two studies compared against a morphine-like medication (codeine), too. One study compared CBD against placebo.

We did not find studies with herbal cannabis.

Main results

Mouth spray with a plant-derived combination of THC and CBD was probably not better than placebo in reducing pain in people with moderate-to-severe cancer pain despite opioid treatment. Thirty-two out of 100 people reported to be much or very much improved by cannabis-based mouth spray and 23 out of 100 people with mouth spray with placebo. A total of 19 out of 100 people withdrew early because of side effects by cannabis-based mouth spray and 16 out of 100 people by mouth spray with placebo. There was no difference in serious side effects between the cannabis-based mouth spray and a placebo mouth spray.

Artificial cannabinoid mimicking the effects of THC may not be better than a fake medication in reducing pain associated with chemotherapy or radiochemotherapy in people with head and neck cancer and a certain type of lung cancer.

A single dose of an artificial cannabinoid mimicking the effects of THC may be better than a single dose of placebo, but may not differ from a single small dose of a morphine-like medication in reducing moderate-to-severe cancer pain after cessation of previous analgesic treatment for three to four and a half hours.

CBD may not add value to specialist palliative care alone in the reduction of pain in people with advanced cancer.

We found no studies with medical cannabis.

What are the limitations of the evidence?

We are moderately confident in the evidence that a mouth spray with a plant-derived combination of THC and CBD does not reduce severe cancer pain despite opioid treatment because studies did not provide information about everything that we could have used.

We have little confidence in the evidence that an artificial cannabinoid mimicking the effects of THC (nabilone) does not reduce pain associated with chemotherapy or radiochemotherapy because the studies did not provide data about everything that we could have used, and because the studies were small.

We have little confidence in the evidence that artificial cannabinoids mimicking the effects of THC reduce cancer pain after the previous pain-relieving medication was stopped some hours before because the studies did not provide data about everything that we could have used, and because the studies were small.

We have little confidence in the evidence that CBD added to standard palliative care does not reduce cancer pain because there was only one study available.

How up to date is the evidence?

The evidence is up to date to January 2023.

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Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy (Review)

Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S

Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S.
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[Intervention Review]

Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

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ABSTRACT

Background

Cannabis has a long history of medicinal use. Cannabis-based medications (cannabinoids) are based on its active element, delta-9-tetrahydrocannabinol (THC), and have been approved for medical purposes. Cannabinoids may be a useful therapeutic option for people with chemotherapy-induced nausea and vomiting that respond poorly to commonly used anti-emetic agents (anti-sickness drugs). However, unpleasant adverse effects may limit their widespread use.

Objectives

To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer.

Search methods

We identified studies by searching the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO and LILACS from inception to January 2015. We also searched reference lists of reviews and included studies. We did not restrict the search by language of publication.

Selection criteria

We included randomised controlled trials (RCTs) that compared a cannabis-based medication with either placebo or with a conventional anti-emetic in adults receiving chemotherapy.

Data collection and analysis

At least two review authors independently conducted eligibility and risk of bias assessment, and extracted data. We grouped studies based on control groups for meta-analyses conducted using random effects. We expressed efficacy and tolerability outcomes as risk ratio (RR) with 95% confidence intervals (CI).

Main results

We included 23 RCTs. Most were of cross-over design, on adults undergoing a variety of chemotherapeutic regimens ranging from moderate to high emetic potential for a variety of cancers. The majority of the studies were at risk of bias due to either lack of allocation concealment or attrition. Trials were conducted between 1975 and 1991. No trials involved comparison with newer anti-emetic drugs such as ondansetron.

Comparison with placebo
People had more chance of reporting complete absence of vomiting (3 trials; 168 participants; RR 5.7; 95% CI 2.6 to 12.6; low quality evidence) and complete absence of nausea and vomiting (3 trials; 288 participants; RR 2.9; 95% CI 1.8 to 4.7; moderate quality evidence) when they received cannabinoids compared with placebo. The percentage of variability in effect estimates that was due to heterogeneity rather than chance was not important (I^2 = 0% in both analyses).

People had more chance of withdrawing due to an adverse event (2 trials; 276 participants; RR 6.9; 95% CI 1.96 to 24; I^2 = 0%; very low quality evidence) and less chance of withdrawing due to lack of efficacy when they received cannabinoids, compared with placebo (1 trial; 228 participants; RR 0.05; 95% CI 0.0 to 0.89; low quality evidence). In addition, people had more chance of 'feeling high' when they received cannabinoids compared with placebo (3 trials; 137 participants; RR 31; 95% CI 6.4 to 152; I^2 = 0%).

People reported a preference for cannabinoids rather than placebo (2 trials; 256 participants; RR 4.8; 95% CI 1.7 to 13; low quality evidence).

Comparison with other anti-emetics
There was no evidence of a difference between cannabinoids and prochlorperazine in the proportion of participants reporting no nausea (5 trials; 258 participants; RR 1.5; 95% CI 0.67 to 3.2; I^2 = 63%; low quality evidence), no vomiting (4 trials; 209 participants; RR 1.11; 95% CI 0.86 to 1.44; I^2 = 0%; moderate quality evidence), or complete absence of nausea and vomiting (4 trials; 414 participants; RR 2.0; 95% CI 0.74 to 5.4; I^2 = 60%; low quality evidence). Sensitivity analysis where the two parallel group trials were pooled after removal of the five cross-over trials showed no difference (RR 1.1; 95% CI 0.70 to 1.7) with no heterogeneity (I^2 = 0%).

People had more chance of withdrawing due to an adverse event (5 trials; 664 participants; RR 3.9; 95% CI 1.3 to 12; I^2 = 17%; low quality evidence), due to lack of efficacy (1 trial; 42 participants; RR 3.5; 95% CI 1.4 to 8.9; very low quality evidence) and for any reason (1 trial; 42 participants; RR 3.5; 95% CI 1.4 to 8.9; low quality evidence) when they received cannabinoids compared with prochlorperazine.

People had more chance of reporting dizziness (7 trials; 675 participants; RR 2.4; 95% CI 1.8 to 3.1; I^2 = 12%), dysphoria (3 trials; 192 participants; RR 7.2; 95% CI 1.3 to 39; I^2 = 0%), euphoria (2 trials; 280 participants; RR 18; 95% CI 2.4 to 133; I^2 = 0%), 'feeling high' (4 trials; 389 participants; RR 6.2; 95% CI 3.5 to 11; I^2 = 0%) and sedation (8 trials; 947 participants; RR 1.4; 95% CI 1.2 to 1.8; I^2 = 31%), with significantly more participants reporting the incidence of these adverse events with cannabinoids compared with prochlorperazine.

People reported a preference for cannabinoids rather than prochlorperazine (7 trials; 695 participants; RR 3.3; 95% CI 2.2 to 4.8; I^2 = 51%; low quality evidence).

In comparisons with metoclopramide, domperidone and chlorpromazine, there was weaker evidence, based on fewer trials and participants, for higher incidence of dizziness with cannabinoids.

Two trials with 141 participants compared an anti-emetic drug alone with a cannabinoid added to the anti-emetic drug. There was no evidence of differences between groups; however, the majority of the analyses were based on one small trial with few events.

Quality of the evidence
The trials were generally at low to moderate risk of bias in terms of how they were designed and do not reflect current chemotherapy and anti-emetic treatment regimens. Furthermore, the quality of evidence arising from meta-analyses was graded as low for the majority of the outcomes analysed, indicating that we are not very confident in our ability to say how well the medications worked. Further research is likely to have an important impact on the results.

Authors' conclusions

Cannabis-based medications may be useful for treating refractory chemotherapy-induced nausea and vomiting. However, methodological limitations of the trials limit our conclusions and further research reflecting current chemotherapy regimens and newer anti-emetic drugs is likely to modify these conclusions.

PLAIN LANGUAGE SUMMARY

Cannabis-based medicine for nausea and vomiting in people treated with chemotherapy for cancer

Background
As many as three-quarters of people who receive chemotherapy experience nausea (feeling sick) and vomiting (being sick), which many find distressing. While conventional anti-sickness medicines are effective, they do not work for everyone, all of the time. Therapeutic drugs based on the active ingredient of cannabis, known as THC (delta-9-tetrahydrocannabinol), have been approved for use as anti-sickness medicines in some countries.

Review question
This review evaluated how well cannabis-based medicines work for treating nausea and vomiting due to chemotherapy treatment in people with cancer, and what the side effects were.

Main findings

This review of 23 randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) found that fewer people who received cannabis-based medicines experienced nausea and vomiting than people who received placebo (a pretend medicine). The proportion of people who experienced nausea and vomiting who received cannabis-based medicines was similar to conventional anti-nausea medicines. However, more people experienced side effects such as 'feeling high', dizziness, sedation (feeling relaxed or sleepy) and dysphoria (feeling uneasy or dissatisfied) and left the study due to the side effects with cannabis-based medicines, compared with either placebo or other anti-nausea medicines. In trials where people received cannabis-based medicines and conventional medicines in turn, overall people preferred the cannabis-based medicines.

Quality of the evidence

The trials were of generally of low to moderate quality and reflected chemotherapy treatments and anti-sickness medicines that were around in the 1980s and 1990s. Also, the results from combining studies on the whole were of low quality. This means that we are not very confident in our ability to say how well the anti-sickness medicines worked, and further research reflecting modern treatment approaches is likely to have an important impact on the results.

Cannabis-based medicines may be useful for treating chemotherapy-induced nausea and vomiting that responds poorly to commonly used anti-sickness medicines.


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