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# Should more patients be offered treatment with cannabinoids?

KRONIKK

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Today, a small but growing number of patients in Norway are prescribed cannabinoids for medical use. Despite the large focus on their potential as medicines, there is limited scientific knowledge about the positive effects, adverse effects, long-term effects and interaction potential of cannabinoids.

Interest in the medical use of the cannabis plant and its active ingredients – the cannabinoids – has grown in recent years, both on the national and international stage. Since the Journal of the Norwegian Medical Association last mentioned the use of 'cannabis as a medicine' in 2015 (1), several clinical studies and systematic literature reviews on the efficacy of medical use of cannabinoids have been published. In addition, a cannabinoid-based medicine intended for use in children was recently launched in the USA (2).

The potential of cannabinoid use as an adjunctive therapy for some diseases seems to be an established fact in the current evidence base. This is particularly the case for seriously ill patients who do not respond to, or have an insufficient effect from, conventional therapy. However, the studies have weaknesses, such as a small effect size for most of the conditions studied, and reduced transferability due to the broad diversity of the product used and small study populations. For many of the diseases, only subjectively perceived

improvements have been measured, making the results less reliable. There is also a great need for interaction studies and longitudinal studies in order to better identify the safety aspect. It is important that prescribing doctors are aware of these limitations so that they can give relevant patients a realistic picture of expected treatment outcomes.

## Medical use of cannabis

The cannabis plant (Cannabis sativa, Cannabis indica) is described in texts dating back to 2700 BC, and has historically been used to treat pain, aid sleep and reduce anxiety and depression. Today, we know that the plant contains more than 80 different cannabinoids, of which the psychoactive delta-9-tetrahydrocannabinol (THC) and the non-psychoactive cannabidiol (CBD) are the best known (3). The discovery of endocannabinoids and the endocannabinoid system in the early 1990s led to a growing scientific interest in the potential use of cannabis as a medicine. Various compositions of cannabinoids have been studied as treatment alternatives for a wide range of diseases.

Medical use of the cannabis plant was first permitted in parts of the USA in the mid-1990s, and has since become legal in many countries in America and Europe, including Norway. However, the degree of regulation surrounding its use varies considerably (4).

Worldwide, there are several cannabinoid-containing medicines. At present, the only cannabis extract marketed in Norway is nabiximols, with spasticity in multiple sclerosis as the only indication. All doctors with prescription rights for prescription group A can prescribe nabiximols and apply for requisition rights and approval exemptions for other cannabinoid-based medicines. The use of cannabis products that are not approved as medicinal products, and consequently regarded as narcotic drugs, is permitted in special cases (5). Only specialists in hospitals can apply for approval exemptions for such products if they contain more than 1 % of delta-9-tetrahydrocannabinol. The authorities have not drawn up an exhaustive list of patients who may be eligible for such treatment. It is the prescribing doctor who has to justify why the treatment is necessary and why other treatment cannot be used. A selection of cannabinoid-containing medicines is presented in Table 1 (4).

**Table 1**

A selection of cannabinoid-containing medicines

| Active ingredient (product name) | Description |
|---|---|
| Dronabinol (Marinol, Syndros) | Synthetically produced delta-9-tetrahydrocannabinol. |
| Nabilone (Cesamet, Canemes) | Synthetic cannabinoid with a similar effect to delta-9-tetrahydrocannabinol. |
| Nabiximols (Sativex) | Plant-based. Contains roughly similar amounts of delta-9-tetrahydrocannabinol and cannabidiol. |
| Cannabidiol (Epodiolex) | Plant-based. Natural component of cannabis with no delta-9-tetrahydrocannabinol. |

Figures from the Norwegian Medicines Agency show that a small but increasing number of patients are granted approval exemptions for products with a high content of delta-9-tetrahydrocannabinol (adviser in the Norwegian Medicines Agency, personal communication, 16 January 2019). In the period 2016–18, a total of 35 patients received such an approval exemption. Most of these applied to use dried cannabis plants from the Dutch company Bedrocan. In our experience, it is also not uncommon for Norwegians to be prescribed cannabis products by doctors in the Netherlands. Anyone listed in the National Registry in Norway can bring up to a one-week supply (according to the specified dosage) of narcotic medicines acquired abroad back into Norway (6).

## Chronic pain conditions

Prolonged pain affects approximately 30 % of the adult population in Norway, and is a major cause of long-term sick leave and disability (7). Several studies have shown that cannabinoids are probably better than placebo for chronic, non-malignant pain conditions.

However, the effect size is small. A Cochrane summary of studies on cannabinoids (all containing delta-9-tetrahydrocannabinol) as pain relief for chronic neuropathic pain suggests that the number of patients that need to be treated (Number Needed to Treat - NNT) for one patient to achieve 50 % pain reduction is about 20 (8). In another literature review from 2018, with a large sample of chronic pain conditions, it was found that 24 patients had to be treated to achieve 30 % pain reduction in one patient, which is significantly higher than for conventional analgesics (9). Both summaries conclude that the evidence of positive effects from cannabinoids in the treatment of chronic pain conditions is modest and that they are likely to be overshadowed by the risk of adverse effects.

## Oncology problems

Cancer treatment often involves intense and aggressive chemotherapy, which can cause severe nausea and vomiting. In a Cochrane summary of 23 randomised controlled trials from the period 1975–91, cannabinoids, mainly dronabinol and nabilone, were found to be more effective than placebo, and probably just as effective for treating chemotherapy-induced nausea as the antiemetic prochlorperazine (10). We are not aware of any large-scale studies comparing cannabinoids with novel antiemetics. Their potential role in modern chemotherapy regimens therefore remains uncertain.

There is also a great need for interaction studies and longitudinal studies in order to better identify the safety aspect.

In a 2018 literature review analysing nine studies involving a total of 1561 participants, no significant difference was found between cannabinoids (all containing delta-9-tetrahydrocannabinol) and placebo in terms of calorie intake, appetite, nausea, dizziness, sleep quality, mental health or pain in palliative cancer patients (11). Furthermore, cannabinoids did not appear to improve participants' quality of life any more than placebo.

## Sleep disorders

Few studies have directly investigated the efficacy of cannabinoids for sleep disorders. Studies examining sleep as part of a wider investigation indicate that the use of cannabinoids with delta-9- tetrahydrocannabinol may be associated with improved sleep quality (12). However, one concern is that prolonged use may lead users to develop a tolerance for its sleep-inducing properties (13).

## Epilepsy in children

The psychoactive properties of delta-9-tetrahydrocannabinol limit its use to a certain extent, especially in children. However, cannabidiol has shown promising results in the treatment of drug-resistant epilepsy in children (14). In the USA, four randomised controlled trials showed reduced seizure frequency. As a result, cannabidiol was recently approved as an adjunctive therapy for Lennox-Gastaut syndrome and Dravet syndrome (2). A recent literature review found cannabidiol to be more effective than placebo in reducing the frequency of seizures and improving quality of life in intractable epilepsy. The NNT for a 50 % seizure reduction in one patient in this study was estimated at eight (15).

## Adverse effects

The authors of a literature review of 79 studies involving a total of 6462 participants concluded that adverse effects occurred more frequently in the treatment groups than the

placebo groups, and that patients receiving cannabinoids (all containing delta-9-tetrahydrocannabinol) were at higher risk of withdrawal from the treatment (12). However, the cannabinoids appeared to be relatively well tolerated since the majority of adverse reactions reported could be classified as mild. The most common were dizziness, dry mouth, nausea, fatigue, drowsiness, euphoria and depression.

At present, there is little to suggest that we should be aiming for the broad use of cannabinoids in medicine

In most studies of adverse effects, the follow-up time has been short. The evidence of the potential harm during long-term use is therefore limited. A follow-up study of 146 users of nabiximols, which followed patients for up to three years after the original six-week study, found that 94.5 % of users experienced adverse effects (16). Most of these were mild to moderate, but 18.5 % also reported serious events, including one case of delusional and paranoid behaviour. A total of 16 % of patients withdrew from the study due to adverse events, and only four of the original 146 patients continued to use the medicine for three years. There was no evidence to suggest tolerance development or withdrawal symptoms at the end of the course of treatment. It is worth noting that patients with a previous psychiatric or substance abuse disorder were excluded from the study.

Relatively few drug interaction studies have been conducted on cannabinoids. In vitro studies have shown that both delta-9-tetrahydrocannabinol and cannabidiol can affect important CYP enzymes involved in drug metabolism (17). Since cannabinoids are generally used as an adjunct to conventional therapy, more in vivo studies on the interaction potential are needed. This is particularly the case for cancer drugs and antiepileptic drugs, where changes in serum concentration can have serious consequences.

## Limited evidence base

At present, there is little evidence implying that we should be aiming for the broad use of cannabinoids in medicine. Doctors who prescribe cannabinoids outside approved indications assume a special medical and legal responsibility for the treatment. It is therefore important to be aware of the limitations of the current evidence base, particularly in relation to adverse effects and drug interactions.

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