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Use of Medical Cannabis in Palliative & Supportive Care

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ABSTRACT

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Introduction

The need for palliative care is increasing rapidly in the context of an aging population and where 75% of deaths are caused by chronic and progressive diseases (McNamara B, 2006). In general, people with terminal illnesses experience a significant burden of symptoms that often increases in severity over time. In contemporary studies, patients report 8-12 symptoms, with fatigue, pain, anorexia, cachexia, shortness of breath, anxiety and depression being particularly common (Portenoy RK, 1994; Van Lancker A, 2014). There are many opportunities to improve palliative and palliative care using both pharmacological and non-pharmacological means. Inadequate symptom control and / or intolerable side effects attributed to opioids and other drugs encourage the search for other treatment strategies, such as cannabinoid-based drugs (CBMs). These include approved cannabinoids such as Nabilone (Cesamet®), Nabiximols (Sativex®), Dronabinol (Marinol® - no longer available in Canada) and medical cannabis products, such as dried flowers or edible oils. The integration of medical cannabis into palliative care has been delayed by many obstacles, including a lack of clinical research data, poor clinical knowledge on how to initiate and monitor cannabinoid therapies, and conflicting or confusing regulatory frameworks.

This situation is further complicated by political and public views that either stigmatize cannabis use or claim that cannabinoids of various formulations are extremely effective in palliative care for a number of other conditions. In addition, a study published in 2017 on adult cancer patients at a major cancer center in Seattle, WA found high rates of active cannabis use (24% in the last year) and also showed that cancer patients want but do not receive cannabis information from providers. oncology of healthcare (Pergam SA, [1]). Interestingly, a more recent survey of 237 U.S. oncologists published in May 2018 showed that while only 30% felt sufficiently informed to make recommendations about CBM, 80% of oncologists discussed CBM with patients and 46% recommended CBM clinically. In addition, 67% considered it a useful adjunct to standard pain management strategies and 65% considered CBM to be equally or more effective than standard treatments for anorexia and cachexia (Braun IM, 2018). Meanwhile, the Dutch government recently agreed to fully reimburse medical cannabis for terminally ill patients starting in January 2019 (Government agrees to free medical cannabis for terminally-ill patients 2018). In this context, we addressed these challenges through expert consensus and systematic review of the literature and organized them to reflect the patient counseling process.Thus, in this work we will: Consider current challenges when considering CBD in palliative care. Provide a systematic review of current general knowledge about cannabis and cannabinoids in relation to these specific challenges, and provide practical recommendations and clinical data on the appropriate and supportive use of CBD in palliative care.

Systematic Review

Methodology

Strategies have been devised to include all potentially relevant studies using both Medical Subject Terms (MeSH) terms and text word searches to increase search sensitivity. The terms "cannabis / cannabinoids", "cancer / neoplasms" and "pain" were combined to identify related studies. Search terms for cannabinoids included individual drug names and the general terms "cannabinoids" and "cannabis". Cancer search included the term MeSH "exp neoplasms /" and text search for synonyms for cancer. The search for "pain" included terms and synonyms for pain. Studies included RCTs evaluating the effect of cannabinoids (THC: CBD, THC extract, nabiximols, Sativex, medical cannabis) compared with placebo or other active agents for the treatment of cancer-related pain in adults with as a primary result (Flow Chart 1). Before considering the use of medical cannabis in palliative care, a good clinical judgment should always determine whether the timing and indications for the introduction of this treatment are appropriate. For example, it is important to determine if there will be sufficient time to evaluate the potential therapeutic benefits of cannabinoid therapy. In addition, in the late stages of cancer, delirium is a common finding, and this could be exacerbated by the use of CBD.

Flow Chart 1: Current Challenges During the Cannabis Examination in A.F.

Embase	1201
Ovid medline	646
PSYCINFO	147
Web of science	382
Clinical trials gov	124
ISTCTN registry	7
Cochrane database of systematic reviews protocols	4
Cochrane database of systematic reviews	37
Cochrane central register of controlled trials	119
Database of abstracts of reviews of effect	10
Bielefeld academic search engine base	294
Open grey	19
Mednar	533

Systematic reviews of the benefits of CBD for pain management reveal mixed recommendations [1-4]. A recent review aimed at evaluating the effectiveness of CBD in relieving pain in patients with malignant disease showed significant analgesic effect in 15 of the 18 trials compared with placebo [5]. However, a recent review by the Canadian College of Family Physicians (CFPC) recommended that CBD not be used as a first- or second-line treatment for cancer pain relief (a strong recommendation) [6]. According to the CFPC, clinicians could only consider CBM for refractory cancer if the following considerations are met: Discuss the risks and benefits of CBM with patients. Patients had a reasonable therapeutic trial with more than two prescription analgesics and had persistent problem pain despite optimized analgesic therapy. CBD is additive to other prescription analgesics. The CFPC also recommends approved CBD Nabilone or Nabiximols as initial agents (strong recommendation), although only the latter is indicated for cancer pain by Health Canada. Although it is fair to argue that the effectiveness of CBD in treating pain in palliative care settings is not yet well established compared to other therapies, the position of CFPC is debatable for a number of reasons. Although most patients taking cannabis medication do so to reduce pain, a recent Israeli study of cannabis use in more than 3,000 cancer patients showed a significant improvement in controlling other common symptoms, including sleep problems (70.8%), fatigue (55.9%), anxiety and depression (74.1%) and nausea and vomiting (54.7%). Only 18.7% of patients reported a good quality of life before starting treatment, while 69.5% reported a good quality of life at 6 months. In addition, 36% of patients discontinued opioid use and less than 20% discontinued cannabis treatment. Of these, only 19.3% stopped due to side effects [7]. Thus, the clinical utility of CBM, which is still considered by many to be limited to pain control, appears to include a much wider range of symptoms found in palliative care settings. In light of these recent findings, it may now be time to reconsider not only the role of CBM in controlling symptoms, but also whether these compounds should be offered earlier during an integrated palliative care strategy, especially for patients who have previously had positive experience of relieving symptoms other than pain.

In addition, if CBM were to be considered, we question whether the recommended CBM Nabilone and Nabiximols should be used as first-line agents. Nabilone is a synthetic tetrahydrocannabinol (THC) analogue in oral form that is 10 times more potent than natural THC. It is approved for nausea and vomiting caused by chemotherapy and has been used off-label for pain [8-10]. Since it is often reimbursed by public and private insurance schemes (at least in Canada), an initial trial with this product could reasonably be considered. However, this is not necessarily the case with Nabiximols, a whole plant extract of Cannabis sativa in the form of 1: 1 THC and cannabidiol (CBD) oral mucosal spray. In Canada, it is reported for the management of cancer pain, neuropathic pain and spasticity in multiple sclerosis [11,12]. Although the purity and potency of uncontrolled cannabis products can often be unreliable or inaccurate compared to Nabiximols, Canadian law requires that medical cannabis supplied by licensed manufacturers comply with many of the same standards. expected from the pharmaceutical industry. As a result, many available products from licensed manufacturers exhibit potency of the active cannabinoids THC and CBD that are similar to Nabiximols. Since these are the two most abundant cannabinoids found

Study Features

Of the six RCTs included (two reported in a single publication), one was a small cross-sectional pilot randomized study, two were phase II studies, and three were phase III studies (Table 1). Of the two early randomized double-blind phase II studies in patients with advanced cancer and pain not relieved by opioids (Johnson JR, et al. [11-13]), one reported that cannabinoids had analgesic effects (Johnson JR [13]). and the main outcome of the other was negative (Portenoy RK [11]). Following these studies, three Phase III placebo RCTs with similar methodology have been reported. Data from two RCTs were reported in a single publication, with primary efficacy endpoints (improvement rate (study 1) and mean change (study 2) in mean daily NRS pain scores) .18 Neither these nor the third RCT (primary endpoint) point: per cent change in mean pain score (NRS) (Lichtman AH [14]) reported a positive effect of nabiximols compared to placebo at their main endpoints. These studies had a low risk of bias. The small cross-sectional pilot study (n = 18) evaluated nabiximoles versus placebo for use in the treatment of neuropathic pain caused by chemotherapy and did not report a statistically significant difference between nabiximoles and placebo in NRS. : mean score before treatment = 6.75. and at the end of 4 weeks, the score of the nabiximols group = 6.00 while the score of the placebo group = 6,380, (Lynch ME [15]). However, further analysis in five patients who responded to treatment showed an average reduction of 2.6 in an NRS of 11 degrees for pain intensity (Lynch ME, [15]). The studies used a pump-acting oral mucosa spray that used a THC: CBD 1: 1 extract versus placebo. Some studies have had extra strands, for example, THC extract (Johnson JR, [13]). Dose titration differed between studies. Patients self-titrated to the optimal dose (Johnson JR, et al. [13-15]) or randomly divided into different doses (Portenoy RK [11]). In Phase III studies, patients titrated medication according to a predetermined dose escalation protocol until they achieved pain relief, developed side effects, or reached a maximum dose of 10 sprays / day (Fallon MT, et al. [12-14]).

Quality of study

The quality evaluation of the included studies was performed using the Cochrane Risk of Bias Tool (online supplementary table 1). The studies included had a low risk of bias. Although studies have been funded (or have been medicated) by industry, and publication bias is more common when most of the published studies are industry-funded, based on the results, these are generally negative studies that make it less likely that post bias. The pipeline diagram (online supplement chart 1) showed that the distribution was approximately symmetric, indicating that there was no possibility of publication bias.

Pain

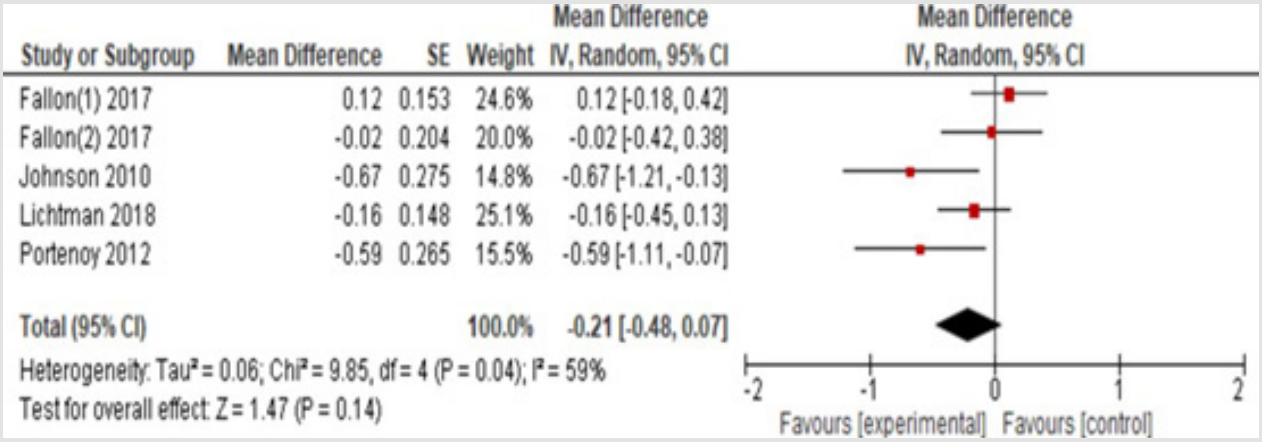

Figure 1: Change in pain intensity for the Phase II and III studies.

The change in pain intensity was the primary result of interest in this systematic review. The change in pain intensity was the primary result in the studies of Johnson et al, [13] Fallon et al [12] and Lichtman et al, [14] and a secondary effect in Portenoy et al. [11]. Lynch et al measured the change in NRS for pain intensity and reported that there was no statistically significant difference between treatment and placebo groups, but as this study included only people with chronic neuropathic pain and was a small exploratory study, was not included in the meta-analysis (Lynch ME [15]). The meta-analysis is shown in Figure 1. There was no difference between cannabinoids and placebo for the difference in the mean NRS pain scores: mean difference −0.21 (−0.48 to 0.07, p = 0.14) . Including only phase III studies in the meta-analysis, there was no benefit from cannabinoid use: mean difference −0.02 (−0.21 to 0.16, p = 0.80) (Figure 2) (Fallon MT, [12]- Lichtman, [14]). Was the change in pain intensity a secondary outcome in Portenoy et

al? their main outcome (30% reduction in initial pain) was not statistically different between cannabinoids and placebo (p = 0.59) (Portenoy RK [11]). In Portenoy et al, data were not available on the mean pain difference of all three doses combined (Portenoy RK [11]) so only low dose (1–4 sprays) was used in the meta-analysis as this was the most effective dose (Figure 3).

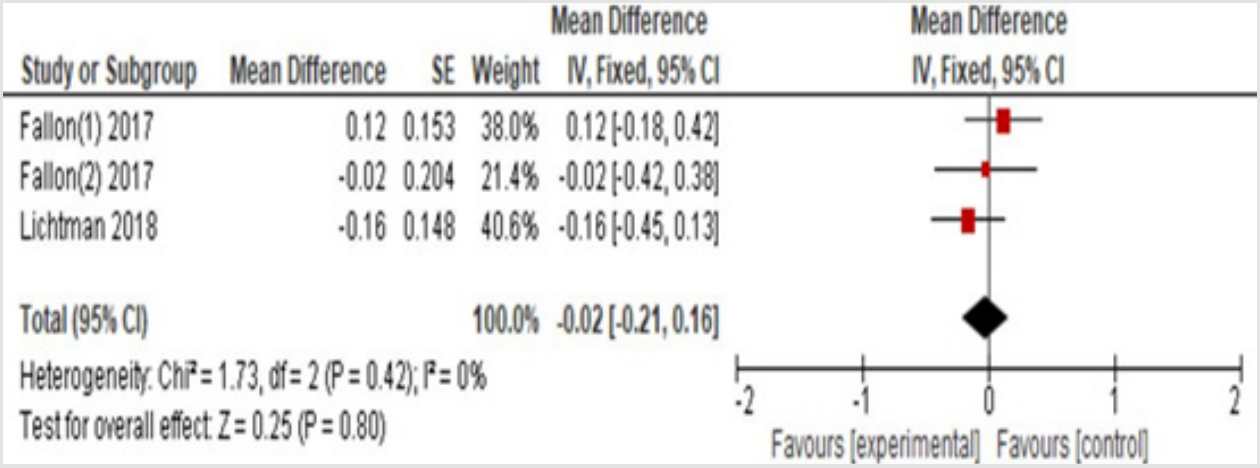

Figure 2: Change in pain intensity for phase III studies.

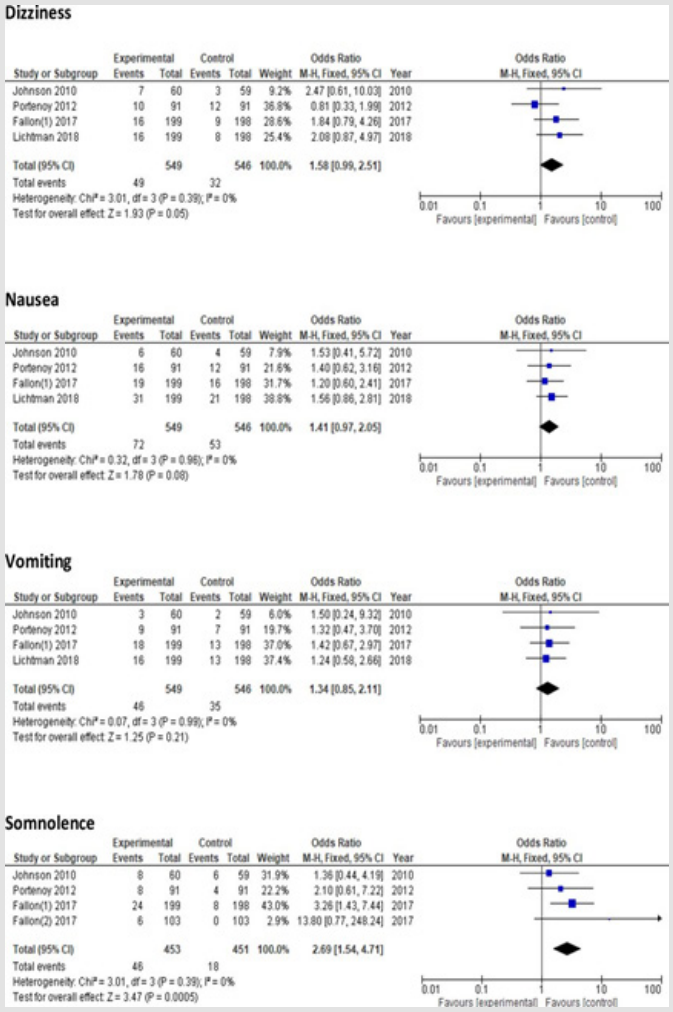

Figure 3: Adverse effects for phase II and III studies (Fallon 2 study not included for adverse reactions where <5% had adverse effects).

Adverse Effects

All studies reported adverse reactions (Table 3). Dizziness, nausea, vomiting, drowsiness and fatigue were the main side effects reported. In general, cannabinoids have been reported to have a higher risk of side effects compared to placebo. Fallon et al, Lichtman et al and Portenoy et al reported only adverse reactions in ≥5% of patients (Portenoy RK, et al. [11-15]). In Johnson et al, they are the only ones reported in three or more patients (Johnson JR, [13]). Lynch et al reported more adverse reactions than placebo, but as this study included only people with chronic neuropathic pain and was a small pilot study, it was not included in the meta-analysis (Lynch ME [15]). In the meta-analysis, only the low dose (1–4 sprays) was used by Portenoy et al for consistency with the pain score meta-analysis (Figure 4).

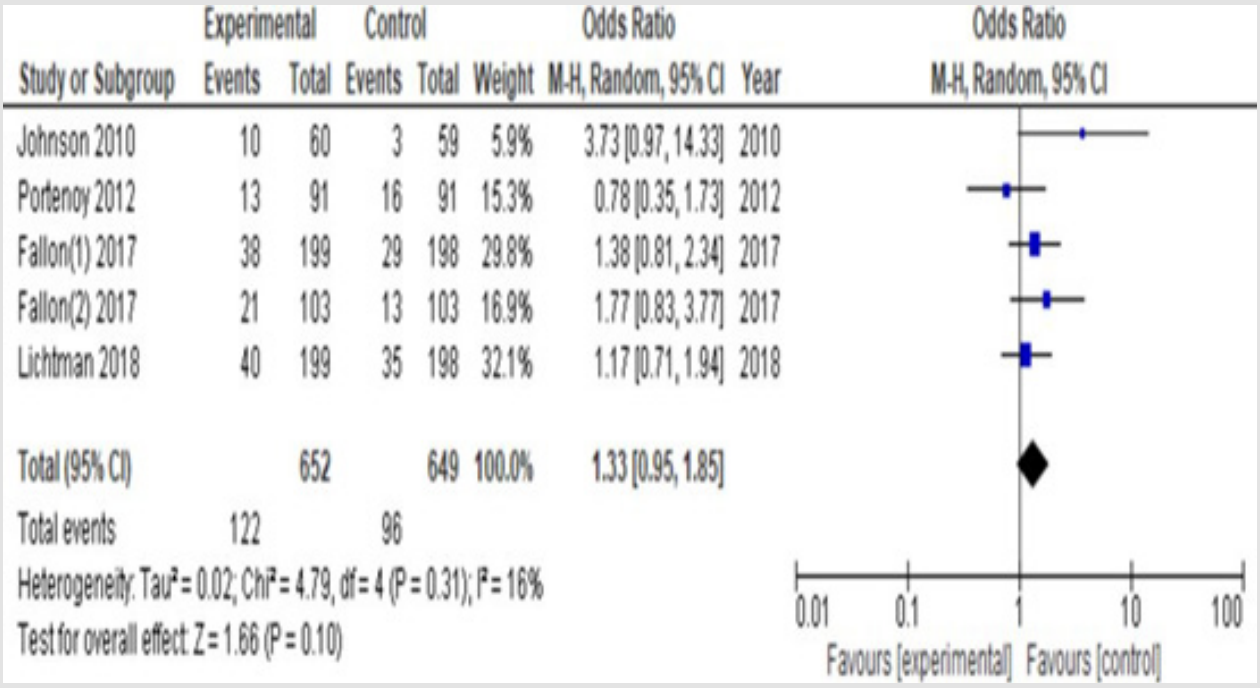

Figure 4: Departures due to adverse events.

Departures Due to Adverse Events

In Johnson et al, [13] discontinuation due to adverse reactions was 16.7% in the THC: CBD group and 5% in the placebo group (Johnson JR, [13]). In Portenoy et al, discontinuation of adverse reactions was dose-dependent: 19.8% in all patients receiving nabiximols and 17.6% in the placebo group (Portenoy RK [11]). In Study 1 by Fallon et al, 19% of patients with Sativex and 14.6% of placebo patients discontinued treatment due to adverse reactions. 17.5% of patients discontinued Sativex due to adverse reactions (Fallon MT, [12]). During the treatment period, 20.4% withdrew from the Sativex group and 12.6% from the placebo group (Fallon MT, [12]). In Lichtman et al, discontinuation due to adverse reactions was 20.1% in the Sativex group and 17.7% in the placebo group (Lichtman AH, [15]). No treatment-related deaths were reported in any study. The following Figure shows the side effects due to side effects, which shows a higher probability of side effects due to side effects in the cannabinoid group (OR 1.33 (0.95 to 1.85, p = 0.10)), but not statistically significant. In the meta-analysis, only the low dose (1–4 sprays) was used by Portenoy et al for consistency with the pain score meta-analysis.

Discussion

Studies with a low risk of bias have shown that for adults with advanced cancer, the addition of cannabinoids to opioids did not reduce cancer pain compared with placebo. This work complements and is based on the systematic review of Häuser et al. [2]. Although the same overall conclusions were drawn, this systematic review and meta-analysis is based on additional methodological information and is therefore supported by higher quality data (as the included studies were considered to have a lower risk of bias). In addition, the primary outcome in this systematic review is a more sensitive outcome for detecting minimal changes in pain (Moore RA [16]). This systematic review provides good evidence that cannabinoids have no role in cancer-related pain. In all RCTs included, pain was the main reason for cannabinoid administration and the change in pain score or pain intensity was the main outcome. Five RCTs were included in the meta-analysis (n = 1442) where cannabinoids were administered as adjunctive therapy in addition to their existing fixed dose of opioids. In the meta-analysis, the two phase II studies and the three phase III studies included patients with chronic cancer pain (mean pain duration of all studies

1.2–2.0 years), with mean pain ≥4 and ≤8 at 0– 10 NRS pain scores, regularly taking opioids, were randomized to the same THC: CBD medication and had comparative placebo. Five trials from four publications in the 1970s (including a total of 128 participants) were ruled out as single-dose studies evaluating the short-term effects of cannabinoids in 6-7 hours (Noyes R, et al. [17,18]). Four of these studies evaluated delta-9-tetrahydrocannabinol (THC) or nitrogen-containing benzopyran derivative, a modification of delta-1-trans-tetrahydrocannabinol (NIB) (Noyes R, et al. [17,19]). The fifth study used the cannabinoid benzopyranoperidine (Jochimsen PR [20]). Of these five single-dose studies evaluating efficacy for hours, three used THC or NIB and reported no difference in efficacy compared to codeine (Noyes R, et al. [18,19]). The fifth study used the cannabinoid benzopyranoperidine and reported that approximately 30% of patients had increased pain intensity with this drug (Jochimsen PR [20]). Side effects Cannabinoids are associated with short-term side effects such as drowsiness, dizziness, confusion, hallucinations, euphoria, nausea and vomiting and diarrhea (Whiting PF [21]). A systematic review evaluating the side effects of medical cannabinoids found that patients taking medical cannabinoids had a 1.86-fold higher risk of developing serious side effects compared with controls and there was no significant difference between serious active side effects. . Our analysis reflected this, showing that cannabinoids were generally reported to have a higher risk of side effects than placebo, with drowsiness and dizziness being statistically significant.

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Possibilities and Limitations

This are a rigorous systematic review that included "gray" literature and contacted authors when data and methodological information were not included in the publication. This allowed the included studies to be considered with a low risk of bias. The studies included were RCTs that evaluated clinically relevant cannabinoids as adjunctive drugs for opioids in advanced cancer patients who had mixed causes of pain due to their cancer. The change in pain score was used as the main result to assess whether cannabinoids had an effect on pain, as this is more sensitive to changes compared to a 30% or 50% reduction in pain. Despite the detailed search strategy, not all relevant studies may be included. There were inconsistencies between the studies in the patients included, the interventions, the comparators and the results. In the meta-analysis, a side effect was used for Portenoy et al (as this was the primary result for this systematic review) (Johnson JR, et al [10,11]). The studies included had several possible limitations. The self-reported NRS pain index may not be the best measure for such tests, as this simple instrument does not record the complexity of the pain, especially when it comes to a long-term problem.

The fidelity of the use of the oral mucosa spray, which affects the absorption and pharmacokinetics, was not evaluated and this may also affect the effectiveness of the drug used and the result measured. Some of the included studies had maintained maintenance doses of opioids and other drugs throughout the trial. Dosage reduction options should be considered when needed, as this may also have an impact on side effects. Negative results from some of the RCTs could be due to the relatively high number of patient withdrawals and high mortality rate (Johnson

JR, et al. [10-14]). Publication bias is most common when most of the published studies are industry-funded. However, the primary outcome for most of these studies was negative, making publication bias for these studies less likely [22-28]. In addition to the lack of therapeutic efficacy, adverse outcomes from some of the RCTs could also be due to the relatively high number of patients leaving the studies, as well as the high mortality rate and increased number of lost patients (Johnson JR, et al. [10-14]).

Conclusion

For a drug to be useful, there must be a clear overall benefit, with the positive effects (analgesia) outweighing the negative effects. None of the included phase III studies show any benefit from cannabinoids. One of the phase II studies showed benefit in its primary outcome (Johnson JR, [10]). The other was negative in its main outcome, although a side effect was positive (Portenoy RK [11]). When statistics were collected, there was no reduction in cannabinoid pain scores. There are, however, significant side effects and leaks reported by cannabinoids. Based on data with a low risk of bias, cannabinoids may not be recommended for the treatment of cancer-related pain.

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