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The use of cannabinoids and alternative therapies in chronic pain management: a narrative review

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The use of cannabinoids and alternative therapies in chronic pain management: a narrative review

[Short title: The use of cannabinoids and alternative therapies in chronic pain management]

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Abstract

Palliative care patients experience pain daily which significantly lowers their quality of life. Chronic pain is one of the main reasons why people contact health professionals, and its prevalence is about 20% in Europe and the United States. Comprehensive and sufficient pain management is often limited to medical facilities whereas patients suffering from chronic pain staying in their households often receive incomplete analgesia. Pharmacological recommendations were described with specific indications and contraindications for therapeutic regimens in relation to cancer patients under palliative care. The addition of alternative pain management techniques to the pharmacological treatment can contribute to better pain control and even to lower doses of opioids administered. On the other hand, state-of-the-art studies evaluating their efficiency and mechanism of action are missing. This study summarizes a variety of alternative pain management methods and mechanisms behind their analgesic and co-analgesic effects that contribute to maximizing the pharmacological effect of analgesic drugs. The aim of this study was to gather alternative pain control options and assess their efficiency, status, and potential in palliative care settings. Moreover, this review tries to evaluate whether they are scientifically evidence-based or not.

Keywords: adjuvants, analgesics, pain, supportive care, palliative care, symptom management

Introduction

Pain is considered a major problem in the world affecting individual patients as well as the economy and medicine [1]. The chronic pain prevalence is estimated to be nearly 20% in the United States and Europe, while its management cost in 2010 was between 560 and 635 billion dollars solely in the US [2–5]. Chronic pain is one of the main reasons why people contact health professionals [2]. It indicates its high impact on both the physical and mental state and the patient's overall quality of life. On the other hand, both physical and mental state influence pain perception by mitigating or enhancing its sensation. It demonstrates how complex pain issue is [6]. Effective treatment of pain and concurret symptoms in patients receiving the end-of-life care and the palliative care is essential. It improves the patient's life quality significantly. The problem of pain in this group is very

prevalent, in advanced, metastatic, and terminal cancer 54.6% of patients experience pain in more than one location, exacerbating patients' distress and suffering [7, 8]. It often coexists with fatigue, insomnia, anxiety, anorexia, depression, nausea and vomiting [8, 9]. Inadequate treatment of the pain affects more than 30% of cancer patients and results from many reasons, related to both patients and providers [8]. The main problem seems to be the lack of knowledge of the available methods of pain treatment, analgesics, coping with side effects of the treatment [7, 8]. To improve the management of pain it is important to provide palliative care as soon as possible to those with life-limiting illnesses [10]. Older patients accept the pain as an integral part of their illness more often and cope better than younger patients, so they are at a higher risk of an inadequate pain management [11].

According to the reports made in Canada in 2017 and 2021 about 70% of seriously ill home care patients from Ontario suffer from severe pain [10]. The DEMETRA study including 865 patients with an advanced cancer has demonstrated how specialist palliative care helps reduce pain in patients treated at home, in hospital and in hospice [12]. The COVID-19 pandemic has also affected pain management. A study of 103 cancer patients determined that the patients with cancer had moderate to severe pain intensity with low levels of self-management and self-efficacy towards that pain during the pandemic. Thirty two percent (32.1%) of the patients needed additional help or support; 18.25% thought an epidemic affected pain management; 7.41% reported an increase in pain intensity [13]. The group was too small to make a general conclusion, but it shows that patients were concerned about pain managing during the pandemic. The pharmacological methods of pain management are crucial, however they should not be used alone, as simultaneous application of non-pharmacological techniques might improve the effect. Pharmacological treatment can be followed by supportive care such as rehabilitation, relaxation techniques and lifestyle modifications [9, 14]. Following review presents methods that are not commonly used and still are a matter of scientific discussion. The main aim of this review is, to sum up data about cannabinoids and alternative methods of pain management with a focus on the palliative care setting, indicate their efficiency, positives, and negatives, and draw conclusions about what should be done to make the patient's quality of life better.

Methods

This narrative review focuses on the problem of pain management in chronic

conditions, analyzing human clinical studies. The search was performed using MEDLINE and Google Scholar. Analyzing specific methods, the following search queries were used: “cannabinoids and pain”, “music therapy and pain”, “cognitive behavioral therapy and pain”, “physical exercise and pain”, “biofeedback and pain” and “acupuncture and pain”. All articles were assessed by title, and abstract and then qualified for full-text analysis. For every paragraph, full-text articles were reviewed at least by two co-authors. The studies focusing solely on acute pain, case reports, as well as studies published only as abstracts, posters or reports from conferences and studies written in a language other than English were excluded from the analysis. The studies published before the 2000 year were excluded from the analysis, except for one study (1999) we used to depict historical context.

Medical cannabis and cannabinoids

A constantly growing number of analgesics abuse, including the worldwide opioid crisis creates the need for new treatment modalities and active substances, incorporating medical cannabis and cannabinoids use for pain [15–17]. Two main active substances in cannabis are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), both causing analgesia, but, most importantly, CBD does not have psychoactive effect [18]. There are also endogenous cannabinoids, anandamide (arachidonoyl ethanolamide) and 2-Ara-Gl (2-arachidonoglycerol). They regulate signal transduction pathways by binding cannabinoid receptors CB_1 (expressed mainly in the central nervous system and sensory neurons of dorsal root ganglia) and CB_2 (mainly in the cells of immune system, microglia, astrocytes, and peripheral nerves), causing activation of G_i protein which inhibits adenyl cyclase. The precise localization and effects of receptor CB_3 are still the subject of intensive studies. Endogenous cannabinoids can be produced in several body tissues and affect synergistically via different mechanisms, preventing the degradation of the active form or initiate binding to a specific receptor. It’s called the “entourage effect” [19]. Chronic pain increases the amount of CB_2 receptors on peripheral cells, which changes the pain signals pathway and is one of the impacts of cannabinoids on pain processing [20]. Anandamide can reduce cisplatin-induced CIPN (chemotherapy–induced neuropathic pain) by affecting CB_1. Increasing the level of anandamide with using an inhibitor of specific hydrolysis prevent hyperalgesia [21, 22]. The neuropathic component can be up to 40% of pain in cancer patients, so cannabinoids can potentially be effective in therapy [21].

Using cannabinoids has yet to be standardized globally, primarily due to the contradicting findings of various studies. Legalization of medical cannabis and cannabinoids for treating chronic pain (mainly non-cancer related) in some countries (U.S., Australia) has resulted with many studies investigating its use. There is only moderate evidence on cannabinoids' effectiveness in chronic pain control and cannabinoids are not strongly recommended in therapy of cancer patients, due to potential reduction of quality of life and change of survival caused by ineffective therapy [23]. Moreover, it can be very difficult to obtain long-term conclusions.

A systemic review and meta-analysis of randomized clinical trials with moderate to high certainty evidence shows that using non-inhaled medical cannabis or cannabinoids by patients living with chronic pain, compared with placebo, may cause small and very small increase of pain relief, but in fact does not improve functioning [24]. Adding cannabinoids may be recommended by some experts to reduce opioid doses in patients with severe side-effects and ineffective pain control, but placebo-controlled, randomized clinical trials are needed [25]. The placebo-controlled randomized study of 25 patients receiving methadone therapy for opioid use disorder showed that adding delta-9-tetrahydrocannabinol (THC) (especially in a dose of 20 mg) modulated pain sensitivity in this cohort. However, it changed self-reported rather than experimental pain sensitivity measures [26, 27]. Medical cannabis legalization in some states in the U.S. has indeed reduced opioid use and mortality from opioid overdose [28]. However, there are also some negative reports about the synergistic effect of opioids with THC. Within-subject, double-blind, randomized, placebo-controlled study of 37 subjects with knee osteoarthritis-related pain revealed no significantly improved analgesic effect for clinical pain severity and physical functioning with the use of hydrmorphone-dronabinol combination [29]. Another meta-analysis of pre-clinical and clinical studies by Nielsen et al. [30] proved no effect of cannabinoids on opioid-sparing. Noori et al. [31] meta-analysis showed low certainty in this matter.

Recently, many systematic reviews and meta-analyses were published. McParland et al. [32] demonstrated that THC might reduce the peripheal or cental neuropathic pain wih moderate grade certainty of evidence based on the group of 1051 patients in comparison to placebo. Conversely, the newest studies have the opposite results. Oral capsules of THC alone and in combination with cannabidiol had no effect on peripheral neuropathic pain in the group of 145 patients with at least one prior line of evidence-based treatment [33]. Although

the systematic review with meta-analysis and trial sequential analysis conducted by Barakji based on 7017 participants confirmed the positive impact on chronic pain, both effect sizes were below predefined minimal important differences. These results are supported in Wang's et al. [22] meta-analysis. Moreover, the analysis indicated no influence on cancer and acute pain with an increased risk of non-serious adverse events [34]. Zeraatkar meta-analysis defined this risk as limited, but emphasisized the risk of rare serious adverse events [35]. Another meta-analysis by Bilbao et al. [36] proved that dronabinol and nabiximols reduced chronic pain with moderate evidence. This inconsistency raise the issue of risk related to generalized conlusions in this group of drugs. Every applied active substance should be investigated in a specific setting and clinical apllication.

There were also some clinical trials in specific diseases. Cannabidiol chewing gum was ineffective in the treatment of perceived pain in irritable bowel syndrome [37]. However, meta-analysis by Doeve et al. [39] revealed allieviating effect on patient-reported symptoms and increased quality of life scores after cannabinoids and phase 2b randomized placebo-controlled trial (CAPTIVATE) showed the significant impact of olorinab (agonist of cannabinoid receptor 2) on abdominal pain (moderate to severe) reduction [38, 39]. Similarly, the inhaled cannabis had no effect on pain in the randomized clinical trial of patients with sickle cell disease [40]. The THC-CBD spray improved pain and spasticity in secondary progressive multiple sclerosis patients, but the conclusions of this study are limited by low (n = 15) number of subjects [41]. However, another study (n = 20) confirmed it [42]. The effect on pain in fibromyalgia was also limited [43] and the lack of impact on abdominal pain was observed in a phase 2 study [44]. On the other hand, multicentre, open-label, follow-on study (n = 380) proved therapeutic effect of THC/CBD oromucosal spray in the management of neuropathic pain related to diabetes or allodynia [45] and this observation was further confirmed by double-blind, randomized, placebo-controlled parallel grorup study (n = 303) [46]. Study by Wallace [47] indicated that patients with low and high THC levels in blood did not experience decrease in pain intensity in diabetic neuropathy, whereas those whose THC levels were in the therapeutic range, experienced positive effect, indicating the importance of appropriate dose. Study by Almog [48] also confirmed the determining effect of dose on the efficiency in chronic pain management.

Medical cannabis and cannabinoids may be considered as a part of pain management, especially in cases where neuropathic component of ailments is highly probable. Adding

cannabinoids can also potentially reduce doses of opioids. Combination of THC/CBD seems to be more effective than THC extract, possibly because of the “entourage effect”. However, there are some negative meta-analyses that limits its applicability and shows the lack of efficiency of this group, suggesting the use cannabinoids only in some cases of non-cancer chronic pain [49]. Interestingly, Gedin et al. [50] indicated that a placebo might affect the outcome of many cannabinoid clinical trials, contributing significantly to pain reduction. Another problem might be the appropriate dose [51]. Therefore, there is a need for careful design of future studies, taking this effects into consideration.

Non-pharmacological methods of alternative pain management

There are numerous methods of pain management that are non-pharmacological. Some of them were tested in clinical trials and they are summarized below.

Music therapy

One of the potential methods of alleviating pain and supporting basic therapy is music therapy. The mechanism behind music therapy effectiveness may be explained by the descending pain modulatory system (DPMS) [52, 53], which has the ability to alter pain perception. By evoking an emotional response, music stimulates the central nervous system to down-regulate stress, anxiety and pain via endocrine, autonomous and immune system [54, 55]. Rhythm creates brain waves modulating the autonomous nervous system to lower heart rate, respiratory rate and both, systolic and diastolic pressure [54], to relax muscles [56], which the patient interpret as anxiety relief and fatigue reduction [57]. By shifting the balance from sympathetic to parasympathetic nervous system music therapy succeed in increasing high-frequency variation in heart rate and improving peripheral circulation [57].

There are two methods to introduce music into treatment process — music medicine and music therapy [58]. Music medicine involves passive listening to pre-recorded music. Music therapy requires more active participation — while listening to live music, the patient works with a trained music therapist, such as performs breathing exercises, visualization or plays an instrument themselves. A meta-analysis summarized the outcomes of different studies comparing both methods and concluded that music therapy tends to be more engaging and better in changing patient’s pain perception, and music medicine allowed to administer lower dosages of analgesics and normalized vital parameters such as heart rate, respiration

rate and blood pressure [58]. Despite varying strengths of each method, there was no statistically significant difference in effectiveness between music medicine and music therapy in pain reduction [55, 58].

A randomized controlled trial conducted by Gutgsell et al. [59] investigated the efficiency of music therapy plus standard therapy vs standard therapy alone in the reduction of pain in a group of 200 palliative care patients. Interestingly, a significant decrease in numeric rating scale pain was observed in the patients who underwent a single music therapy intervention based on therapist-guided autogenic relaxation and live music [59]. In a meta-analysis Li et al. [60] tried to establish the exact duration of music therapy for it to be the most effective in managing pain — it should last from 1 to 2 months.

Another multicenter randomized controlled trial of 104 palliative care patients called “Song of Life” was based on a three-session music therapy intervention working with a biographically meaningful song [61]. Although psychological quality of life was not improved, participants reported higher spiritual well-being and lower distress than in the control group [61]. Moreover, the reduction of cortisol and lower mean heart rate were confirmed [61]. Future studies should further evaluate the efficiency and cost-effectiveness of music therapy to assess the potential of the introduction of this treatment into clinical practice. Especially, when music therapy complementary to pharmacological treatment, has been described to enable opioid and non-opioid analgesic dosage reduction [52]. The possibility of minimizing requirement of analgesics should be treated with reserve as not every study found this statistically significant [52]. Familiarity of the music is also a valid aspect of music therapy — as it gives the patient comfort and feeling of “control” over their treatment, further amplifying the analgesic effect [52, 59]. However, not every study which observed and admitted its relevance, found it statistically significant [52].

Addition of music therapy to pharmacological methods of pain management is promising, enabling to reduce pain, alleviate anxiety, improve sleep quality, and overall quality of life [55, 60]. The main issue is heterogeneity between studies reporting on its use — each study has its own music therapy regimen. They differ in almost every aspect of therapy, e.g.: type of music, frequency and duration of each intervention, time of the follow-up, scales used to assess the pain intensity, chosen control group. It is also prone to bias as most of the patients are already on analgesics when starting music therapy, making it almost impossible to distinguish the role of each treatment in pain management. The research on

music therapy needs standardization in order to objectively state the extent of its use.

Cognitive behavioral therapy

Another interesting psychological method of pain management is cognitive behavioral therapy (CBT) [61]. The mechanism behind CBT is explained by several theories one of them being Gate Control Theory of Pain [62]. Aforementioned theory states that by stimulating various areas of the brain responsible for cognition, emotion and endocrine regulation, it is possible to down-regulate pain gating in dorsal horns of the spinal cord [62]. Neuromatrix Theory developed from Gate Control Theory of Pain, and went further and stated that stressful external stimuli can distort the structure of tissues, including neural circuits [63]. Seminowicz et al. tested whether CBT can alter the structure of the brain using MRI-imaging which revealed changes in the prefrontal cortex, potentially leading to different pain perception [62, 64].

Saxena et al. [65] in a pilot study compared the efficiency of CBT in combination with pregabalin vs pregabalin alone in the management of neuropathic pain in post-therapeutic neuralgia. In equally divided group of 40 patients, a significant decrease in pain intensity, depressive symptoms, and pain-related catastrophizing and the improvement in the quality of life were noted in the group receiving both, pharmacological and psychological treatment. NRS pain score was not significantly different in the two groups. However, significant downregulation of IL-6 was observed [66], which is one of the factors considered to be correlated with the prognosis and occurrence of pain [67, 68].

Another study by Rodin et al. [68] tested a modification of CBT called Emotion and symptom-focus management (EASA) intervention based on 8 weeks of psychotherapy in a group of palliative care patients with acute leukemia. The investigators compared EASE in combination with standard care *vs.* standard care alone. The study showed a reduction of pain intensity and interference at 12 weeks as well as an alleviation of traumatic stress symptoms [68]. The pain improvement after CBT treatment was also confirmed in studies regarding chronic low back pain and haemophilia [69, 70]. Although better management of pain after CBT was confirmed in fibromyalgia by Serrat et al. [71], a study by McCrae et al. [72] showed the opposite results with no improvement in pain management. The CBT use seems to be reasonable in terms of palliative care pain treatment and other symptom management in most patients. However, the level of evidence regarding efficiency varies. Comparison of studies on CBT and chronic pain is impeded by use of different pain scales, etiology of the

pain, methods used in therapy, frequency and duration of the therapy, and time of the follow-up's. Therefore, the utility of this method should be carefully considered in every case due to the limited availability of qualified personnel.

Physical exercise

The commonly advised method in any disease prevention is physical exercise. Borisovskaya et al. described many probable mechanisms behind physical exercise's analgesic effect [73]. According to the Neuromatrix Theory, chronic pain is a result of central nervous system's structural maladaptation to constant stressful stimuli, including pain [63]. The plasticity of nervous system allows for those changes to be reversed, by providing frequent positive stimuli, like physical exercise, over-riding negative input. Studies have shown that consistency is much more important than intensity or duration of a physical training in achieving better pain management [73, 74]. It has been suggested by Geneen et al. that long — term application of physical exercise regimen may be more effective [75].

Another mechanism of action involves restoring the balance between inflammatory and anti–inflammatory factors. Physical exercise reduces inflammation, which has been proven to ease the chronic pain [73, 76]. A study on a group of 126 women suffering from breast cancer who underwent mastectomy, showed that adequate physical activity reduced the pain experienced in the post-mastectomy pain syndrome and also correlated with reduction of inflammation markers such as IL-6, IL-8, tumor necrosis factor and CRP [77].

Commonly known phenomenon of exercise–induced endogenous opioids secretion, could also contribute to physical exercise's analgesic effect [75, 76, 78]. However, the process may be disrupted in patients suffering from chronic diseases such as fibromyalgia [73, 76, 79, 80], deeming the treatment ineffective. Therefore, it is worth remembering that not every patient may benefit from adding exercise to pain management regimen. Apart from endogenous opioids, physical activity promotes secretion of other neurotransmitters with analgesic effect such as serotonin [73, 76], dopamine and norepinephrine [73, 81].

Some patients may experience kinesiophobia due to fear of pain exacerbation during exercise. It is important to give the patient time to learn their safe, pain-free range of motion and to adjust the training's intensity gradually, under medical supervision [73, 82] and with patient's consent [73, 74, 83]. A randomized controlled trial comparing manual therapy and therapeutic exercise in treatment of non-specific chronic neck pain showed that patients with

certain disorders may need many different types of exercise included in the training plan to achieve the best analgesic effect possible. Both methods were proven to be statistically significant in reducing pain. However, the therapeutic exercise group regained cervical mobility faster and the manual therapy group achieved pain relief first, suggesting that both methods combined should bring the best clinical results [84].

Despite many limitations of analyzed studies, including lack of blinding of the intervention/therapist, different time of follow-up, not including all coexisting factors potentially altering the pain intensity (such as diet, analgesic or anti-inflammatory drugs, other chronic diseases), the clinical application of physical exercises in pain management and reducing disability was statistically significant comparing to no intervention at all, education or pharmacological treatment only [85]. The great benefits from regular exercise (irrespective of its intensity or duration) to patient's overall health, physical fitness and pain control support the recommendation of adopting physical activity as a part of chronic pain treatment [74, 86, 87].

It may improve sleep quality and subsequently lower pain sensitivity (poor sleep enhances the risk of higher pain sensitivity) [88, 89]. This method seems to be more effective in the reduction of musculoskeletal or diffuse rather than neuropathic pain phenotype. In addition, the exercise treatment should be adjusted to specific diseases [2]. For example, the pain improvement with the use of exercises was confirmed in fibromyalgia and cancer patients [90, 91]. However, there is still a need of further research on effectiveness of physical therapy in reducing chronic pain present in specific types of cancer and detailed guidelines for prescribing physical exercises in chronic pain control is emphasized in many studies [74, 92].

Biofeedback

Another tested pain treatment modality is a method named biofeedback. It is an instrument-based learning process, where an autonomic and neuromuscular activity is measured and visual, acoustic, or verbal feedback is provided, to promote self-control over physiological processes, which are otherwise outside awareness or under less voluntary control [93]. The method is based on the training of psychological responding and may be divided depending on the type of signal on different variants such as electromyography electrodermal activity, skin temperature, heart rate variability (HRV), respiratory of end–tidal CO_2, and electroencephalography (EEG) biofeedback. There is also a modality with the use

of functional magnetic resonance imaging and blood-oxygen-level dependent method [94].

The randomized controlled trial of neurofeedback (EEG) by Prinsloo et al. [95] in a group of 71 cancer survivors suffering from chemotherapy-induced peripheral neuropathy compared patients who underwent 20 sessions of EEG-biofeedback as a control group. Interestingly, a significant decrease in the worst pain, average pain and pain interference were confirmed in the EEG biofeedback group. In addition, neurological changes in the cortical location and in the bandwidth targeted by intervention and differences in EEG activity were observed and considered as predictive of symptom reduction [95]. The impact of HRV biofeedback was investigated in irritable bowel syndrome (IBS) and functional abdominal pain (FAP) in the pediatric setting [96]. The 69.2% of patients with IBS declared full remission and 30.8% partial remission of the disease, whereas patients with FAP reported full remission in 63.6% of cases and partial remission in 36.4% of cases [96]. A pilot study of HRV biofeedback therapy for children and adolescents with chronic pain also showed promising results [97]. In the group of 21 patients' significant reduction of self-reported pain intensity and higher levels of self-reported school functioning were confirmed. In addition, the control patients in the waitlist group noted enhanced pain intensity during the waiting period [97]. Taking into consideration these promising results in adult and pediatric populations, different modalities of biofeedback ought to be tested in the palliative care setting. Further clinical trials with a higher number of enrolled participants should determine the future of this relatively simple and cost-effective method.

Acupuncture

Acupuncture is an old Chinese technique that nowadays is one of alternative pain management options available to patients. In ancient China it was believed that every illness was caused by imbalance in the Qi energy circulating in human body and that by inserting needles into specific points on the body (acupoints) the energy flow in meridian to which the targeted point belongs would be restored [98].

Studies show that it can have analgesic effect and lower the dosage of analgesics needed to alleviate pain [99, 100]. There are several theories of mechanism behind acupuncture. The first one argues that acupuncture stimulates the central nervous system and causes endorphins release [101, 102]. Acupuncture was reported to elevate levels of β-endorphin, metenkephalin and dynorphins in cerebrospinal fluid [98, 102]. The analgesic effect can be maximized if D-phenylalanine (inhibitor of enkaphalinazes) is administered

before acupuncture [102]. The analgesic effect is achieved after a while, lasts a period and reaches areas different than the acupuncture was performed on, supporting the neuromodulation theory [98, 102]. It was observed that naloxone reverses the effect of acupuncture [98, 101], giving the grounds for theory about acupuncture regulating expression of opioid production [102]. Study of acupuncture on rats showed an increased dopamine release in striatum, supporting a theory that acupuncture modulates pain *via* monoamine release [101]. The involvement of noradrenergic and serotonergic pathways is another area of studies [102] due to serotonin, oxytocin secretion following acupuncture [102–104]. Anti-inflammatory effect of ST36 point electroacupuncture has been researched on model of breast tumor in mice [103]. The ST36 point is located on the anterior surface of the lower limb, its electrostimulation caused a reduction of IL-1beta, TNF-alpha (inflammatory agents) and an increase of IL-10 (anti-inflammatory agent) in the serum and in the tumor tissue, lowered the expression of Arg-1 and COX-2 protein that take part in suppression of T cells and NK cells function [103].

There are different types of acupuncture used. The first one is traditional acupuncture performed by insertion of the needle. In electroacupuncture after insertion of the needle, electric current is delivered through it. In other types of different stimuli are used on the acupoint instead of a needle — pressure in acupressure, electric stimulation in TEAS, heat in moxibustion or laser energy. Electroacupuncture is the most effective among them [99, 104]. Studies on acupuncture focus on finding areas for its clinical application. There are clinical trials researching usage of acupuncture in perioperative and postoperative treatment [99, 105, 106], chronic pain management [107], depression [108], irritable bowel syndrome [109], fibromyalgia [110], rheumatoid arthritis [99], neuropathy [111, 112]. A study on 107 patients showed that the group of patients who received epidural analgesia and acupuncture reported significantly better pain management scoring low on pain scales (postoperatively on the day of operation and two days after) that the control group who received epidural analgesia only [99, 105]. Acupuncture also lowered the dosage of opioids needed to uphold analgesic effect [99, 105]. In another trial, focused on recovery of 81 gastric cancer patients after surgery, the test group, which received transcutaneous electrical acupoint stimulation (TEAS), reported lower pain, regained gastrointestinal peristalsis faster [106]. The application of acupuncture is also researched in pain relief for cancer patients [113].

In the USA National Comprehensive Cancer Network (NCCN) guidelines listed

acupuncture as one of alternative methods that can be used as a supplementation treatment when patient experiences neuropathic pain, arthralgia or myalgia [100, 114–116]. The Society for Integrative Oncology in ASCO Guidelines recommends (moderate strength of the recommendation) acupuncture to patients suffering from joint-pain after aromatase-inhibitor therapy in breast cancer survivors; general pain or musculoskeletal pain caused by cancer; pain during systemic cancer therapy. The strength of recommendation for acupuncture for patients with chemotherapy-induced peripheral neuropathy and patients undergoing cancer surgery or other invasive procedures is weak [117]. Nevertheless, there are studies that reported on acupuncture reducing taxane-induced peripheral neuropathy (tingling, numbness, pain in distal extremities) and overall well-being [111, 112].

It is uncertain how much placebo effect contributes to acupuncture effectiveness. There was a study that compared position emission tomography [with (11)C–carfentanil] images of patients who received acupuncture and patients who received sham acupuncture, before and after 4 weeks of acupuncture treatment [118]. Short and long-term effect of increased mu-opioid receptors binding potential was only observed after real acupuncture [118]. An interesting point was made in a cross-cultural study which measured brain activity in patients in USA and patients in China who received acupuncture or sham acupuncture [119]. Strong placebo effect was noticed in patients from USA as the difference between real and sham acupuncture in brain activity was small [119]. In Chinese patients the difference was more significant [119]. Even though the study was carried out on small group of patients it brought to attention the impact of patients' cultural background. Placebo effect gives pain relief instantly, contrary to maximal analgesic effect of acupuncture which is reached up to 24h [98].

To sum up, the research on acupuncture effectiveness is still controversial as it lacks standardization, leading to various, often contradicting results [120]. There are also discrepancies in establishing a credible control group. In sham acupuncture the skin is not penetrated, but the point where the pressure is applied can be an actual acupoint or sham point. The need of further research concerning the effectiveness and long-term application of acupuncture is mentioned in many articles [117, 118, 120–122]. A summary the main conclusions is demonstrated in Table 1. Additionally, information about ongoing and completed clinical trials is available as the supplementary material (Supplementary Table 1).

Table 1. Key aspects of new directions in pain management in palliative care patients

Method	Possible mechanism	Conclusions
Medical cannabis and cannabinoids	Increasing the amount of CB2 receptors on peripheral cells "Entourage effect"	May be considered as a part of pain management, especially in cases with neuropathic component
Music therapy	Reduction of cortisol Lower mean heart rate	May provide to higher spiritual well-being and lower distress
Cognitive behavioral therapy	Down regulation of IL-6	The utility of this method should be carefully considered in every case due to the limited availability of qualified personnel
Physical exercise	Improve sleep quality and subsequently lower pain sensitivity	This method seems to be more effective in the reduction of musculoskeletal or diffuse rather than neuropathic pain phenotype
Biofeedback	Promote self-control over physiological processes, which are otherwise outside awareness orunder less voluntary control	Promising results in adult and pediatric populations, differed modalities of biofeedback ought to be tested. Further clinical trials with higher number of enrolled participants should determine the future of this relatively simple and cost-effective method
Acupuncture	Stimulation of the central nervous system Endorphin release Regulating expression of opioid production	The research on acupuncture effectiveness isstill controversial as it lacks standardization, leading to contradicting results. The need offurther research concerning the effectivenessand long-term application of acupuncture isneeded. Overall, acupuncture is perceived asa complementary method of pharmacologicalpain management beneficial to patients' quality of life and well-being

Conclusions

The complexity of pain necessitates a multifaceted approach for its effective management, which should not be limited to pharmacology and the use of analgesics. There is a need to explore diverse strategies and incorporate new and innovative methods. In this review cannabinoids and non-pharmacological methods of pain management, were discussed.

We observe plenty of alternative methods and mechanisms behind their analgesic and co-analgesic effects that might contribute to maximizing the effect of pain management strategies. However, the existing research studies does not provide conclusive evidence regarding their effectiveness. Therefore, these methods may be considered with caution, in combination with evidence-based, standard methods to finally determine their efficiency in clinical practice.

Article information and declarations

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Author contributions

GŁ, MG, and BKS designed the work. GŁ, MG, ZB, OS, and BKS analyzed and interpreted data, drafted the work, and wrote the manuscript. BKS supervised the manuscript. All authors approved the final version for publication and have agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Table 1. The studies registered in the ClinicalTrials.gov system and regard pain management in palliative care, including new and alternative methods

Title of Project	ClinicalTrials.gov	Participants (n)	Conditions	Treatment	Study type	Locations	Current status
Paracetamol Route in Palliative Care Patients	NCT03944044	20	Patients in a palliative care situation	Possibility to not take paracetamol in the previous 24 hours before inclusion	Interventional	University Hospital, Caen, France	Recruiting
Remote Self-Reporting of Symptoms by Patients With Palliative Care Needs (RELIEF): A Mixed-Methods Implementation Study	NCT05806255	600	Patient has palliative care needs	nd	Interventional	nd	Not yet recruiting
Resiniferatoxi to Treat Severe Pain Associated With Advanced Cancer	NCT00804154	45	People at least 18 years of age with severe pain from advanced cancer at or below the level of the chest that cannot be controlled with standard treatments	nd	Interventional	National Institutes of Health Clinical Cente, Bethesda, Maryland, United States	Recruiting
Effects of Nurse-led Telephone Based Service For Early Palliative Care Patients With Advanced Cancer: The Paltel Randomized Controlled Trial	NCT05434208	140	Early Palliative Care cancer patients	nd	Interventional	Istituto Scientifico Romagnolo per lo Studio e la cura dei Tumori, Meldola, Forlì-Cesena, Italy	Not yet recruiting
Medical Hypnosis and Music for Palliative Care	NCT05951257	40	Adults in Palliative home care	nd	Interventional	Laval University, Montréal, Quebec, Canada	Recruiting
Assessment of the Interest of ANI in the Non-communicating Patient in Palliative Care (ANI-CARE)	NCT05454202	20	Non-communicating end-of-life patient hospitalized in palliative care	nd	Observational	University Hospital, Lille, France	Recruiting
MR Guided Focused Ultrasound vs Radiotherapy for Palliative Pain Tx in Bone Metastases	NCT05250687	50	Solitary painful metastatic bone lesion or multiple metastatic lesions with one predominantly painful target lesion	nd	Interventional	Stanford University, Palo Alto, California, United States	Not yet recruiting
Percutaneous Cordotomy for Pain Palliation in Advanced Cancer	NCT04119037	42	Has undergone 3 palliative care evaluations.Pain intensity ≥ 4 on a 0–10 numerical scale.Unilateral pain due to cancer below the shoulder level	Drug: Morphine	Interventional	M.D. Anderson Cancer Center, Houston, Texas, United States	Recruiting

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Technology-Enhanced Palliative Care for Advanced Cancer Patients	NCT04989556	150	Diagnosis of advanced solid tumor	nd	Interventional	M.D. Anderson Cancer Center, Houston, Texas, United States	Recruiting
Psilocybin Combined With Multidisciplinary Palliative Care in Demoralized Cancer Survivors With Chronic Pain	NCT05506982	10	Diagnosis of solid or liquid cancer made ≥ 1 year at any stage in cancer survivorship	nd	Interventional	Emory University, Atlanta, Georgia, United States	Recruiting
Patients Referred to the Chronic Pain Unit for Palliative Treatment With Ozone Therapy Between 2022 and 2025 (EPOOzo)	NCT05417737	105	Patients submitted to the Chronic Pain Unit of the Hospital Universitario de Gran Canaria Dr. Negrín for symptomatic/palliative treatment with ozone therapy because conventional treatment does not exist, it has been unsuccessful, or it is associated with high risk or high morbidity	nd	Observational	Dr. Negrin University Hospital, Las Palmas, Spain	Recruiting
Cannabinoids in Pediatric Oncology (CAN-PONC)	NCT05754840	60	Diagnosed with relapsed or refractory solid or hematologic malignancy. Currently Receiving active cancer treatment or palliative care	nd	Interventional	University of Manitoba, Canada	Not yet recruiting
Subcutaneous Versus Intravenous Morphine When Switching From Or to Parenteral Route in Palliative Cancer Patients (SIM)	NCT05236647	60	Patients admitted to a Hospital palliative medicine unit with an indication for parenteraladministration of morphine	Unsatisfactory pain control despite titration of oral or transdermal opioids	Interventional	University Hospital, Akershus, Lørenskog, Norway	Recruiting
Cannabis For Cancer-Related Symptoms (CAFCARS)	NCT03948074	150	Must have at least one of the following cancer-relatedsymptoms or a cancer treatment-related symptoms: Nausea; Pain; Anxiety; Sleep Disturbance	nd	Interventional	British Columbia Cancer Agency, Canada	Recruiting
Transcranial Direct-current Stimulation (tDCS) Efficacy in Refractory Cancer Pain.(STIMPAL)	NCT04683172	70	Patient with a confirmed cancer at a palliativestage	nd	Interventional	Elsan, Nantes, France	Recruiting
Pain Assessment	NCT04726228	40	Home care	Patients	Observational	National Cancer	Recruiting

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in Cancer Patients by Machine Learning (PASCALE)			patients diagnosed with advanced cancer disease and life expectancy ≤ 1 year	Receiving treatment for cancer pain		Institute, Naples, Italy	
Benefits of Morphine Gel for Pain Reduction in Patients With Cancer Wounds (MorphineGEL)	NCT05800834	106	Malignant neoplastic wound in breast or head and neck	Make use of systemic morphine	Interventional	Instituto Nacional de Cancer, Brazil	Recruiting