Palliative cancer patients pain reduction methods during opioid epidemic era

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Abstract

Introduction: Opioids are the most commonly used medication in palliative cancer pain treatment due to their proven effectiveness. However, modern anti-pain treatment concentrates not only on analgesics, but simultaneously on the detection of conditions affecting and intensifying pain sensation. Many studies have shown potential of other, non-opioidal palliative cancer pain treatment with additional positive effect on patient’s general quality of life.

Aim of the study: The purpose of our review is to introduce the issue of the use of opioids and draw attention to other non-opioidal pain reduction methods as well as to indicate directions for further potential researches.

Methods and materials: We have reviewed the literature available in the PubMed, Google Scholar, Science Direct database using the keywords: „cancer patients and opioids”; „pain and cancer”; „chronic pain”; „palliative cancer”. We excluded abstracts, comments, and non-English language articles.

Results:

The methods outlined in this review will not affect pain reduction to the same extent as opioids, but they offer a chance to reduce it to a level that allows patients to maintain a normal life. In the light of opioid epidemic era literature shows new approaches to treating pain such as analgesics, including antidepresants, anticonvulsants, Vitamins, cannabis and nonpharmacological methods and showing their potential for wider use in palliative cancer patients treatment.

Conclusion: Besides opioids, there are many factors that affect pain reduction, however, their analgesic potential require additional studies on larger groups of patients.

Key words: cancer patients and opioids; pain and cancer; chronic pain; palliative cancer
I. Introduction

International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in relation to such damage [1]. Uninterrupted pain negatively affects patients’ activities, motivation, interactions with family and friends, and overall quality of life [2]. Medical literature more and more often shows us that quality of life and survival are associated with early and effective palliative care, and therefore also with pain management [3]. Unfortunately, cancer patients still experience pain and in many cases it is not adequately relieved. According to available sources pain is prevalent in 59% of patients who receive cancer-directed therapies and in 64% of patients who have advanced stages of illness [4].

Opioids have remained the mainstay of treatment because of their rapid effectiveness in treating moderate to severe pain [5], lack of ceiling effect, and no direct detrimental effects on organ functions. Even though the opioid treatment has many advantages, in time it may become problematic: Firstly to reach the full potential of the opioids physician has to be able to titrate both immediate release and long-acting opioid, and foresee and manage the possible side effects. The most common mistakes are dosing immediate release opioids in too long intervals (and concentrating on increasing their doses instead of replacing them with long-acting opioids) and adjusting long-acting opioids faster than its required [6]. For safety reasons, a patient should always reach steady state on the current opioid dose before an additional titration is completed. It takes 4 to 5 half-lives for a medication to reach steady state [7], thus an immediate-release opioid reaches steady state in approximately 24 hours, whereas an extended-release opioid takes between 2 to 5 days to reach steady state. Long-acting opioids should never be added faster than the time to reach steady state [8]. Furthermore the drug tolerance may occur which leads to increase the dose of the drug and as a result to the higher risk of side effects or even addiction [9].

Many palliative cancer patients suffer chronic pain which is not easy to manage. However patients in general, do not expect their pain to be fully relieved [10]. The more important for them is full comprehension of the cancer pain cause, what to expect, methods of pain control, and how to handle cancer pain including talking with others and finding help. Patients expect their pain to be controlled enough to maintain their daily activities and relationships with family and friends [11].

Taking into account abovementioned consideration our review will focus on possible alternatives or adjuvant methods of palliative patients pain treatment such as antidepressants, anticonvulsants, cannabinoids as well as draw attention to comorbidity between conditions and pain: depression, VD deficiency.

II. Aim of the study: The purpose of our review is to introduce the issues of opioids and draw attention to other non-opioid pain reduction methods as well as to indicate directions for further potential researches.

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IV. State of knowledge

IVA. Comorbidity, depression and pain

Besides opioids, anti-pain treatment includes not only analgesics, but simultaneously the early detection of conditions affecting and intensifying pain sensation. Among cancer patients during or after treatment pooled mean prevalence of depression estimated to 8-24% (compared with the 4% found in the general population) and the prevalence was dependent on cancer type and treatment phase [12]. Managing depression in palliative cancer patients is challenging for various reasons. Firstly diagnosis is difficult due to many similar symptoms such as fatigue, sleep disturbance and loss of appetite [13]. Secondly, emotional disorders may negatively impact the severity and persistence of chronic pain [14]. Currently, it is unclear whether pain causes depression or whether depression amplifies pain. The researchers proposed many hypotheses to explain this phenomenon, however without unambiguous answer. Literature shows that chronic pain can trigger depressive symptoms and that depression can manifest as both physical and emotional pain [15].

Considering the above clinicians should not overlook depression hiding under the mask of fatigue, lost of appetite, sleep disturbances commonly found in palliative cancer patients what cause not sufficient pain control.

The main common characteristic of pain and depression is their influence on serotonergic and norepinephrine system. Brain structures that transfer information about pain through nervous system are also involved in mood. As a result serotonergic and norepinephrine antidepressants are strategies commonly employed to mitigate pain both as adjuvants and single treatment. Tricyclic antidepressants (TCAs) are more effective in reducing pain than Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs).

IVB. Adjuvants and antidepressants

Adjuvants can be used as a single medication treatment to treat neuropathic pain and can have additive effects when used in combination with opioids Neurupathic Cancer Pain NCP is pain arising from direct damage to the nervous system by cancer per se or cancer treatment, which includes chemotherapy (Cancer Induced Neuropathy - CIPN), radiation therapy and surgery [16]. Neuropathic pain affects between 20% and 40% of cancer patients [17] and is more often caused by sensory than motor damage [18]. Even though the incidence of CIPN varies by medication, a systematic review noted that approximately 68% of patients developed CIPN within 30 days of any chemotherapy, and up to 6 months, 30% of patients continued to have CIPN [19].

The presence of pain arises from many receptors activity such as norepinephrine, serotonin, opioids, and N-methyl-D-aspartic acid. In consequence, treating neuropathic pain may be effective using antidepressants with impact at these receptors [20]. It has been noticed that amitriptyline, imipramine, nortriptyline, and maprotiline, considering their ability to inhibit norepinephrine reuptake, are more suitable in pain reduction than antidepressants without this action [21].

Tricyclic antidepressants

Amitriptyline is the most knows substance among tricyclic antidepressant (TCA) and the most researched as well. It was estimated in a Cochrane review study that amitriptyline may have more effectiveness on neuropathic pain treatment than placebo. Unfortunately, the study also showed slightly lower capability to reduce pain caused by antineoplastic treatments [22]. However, the American Society of Clinical Oncology (ASCO) guidelines note that, in light of limited treatment options, TCAs may be prescribed to some patients after considering the risks and benefits [23]. In addition, TCAs may have positive effect on patients who have multiple causes of neuropathy (for example, a patient with neuropathy from diabetes, multiple myeloma).

Selective Serotonin Reuptake Inhibitors SSRI

Contrary to TCAs, SSRI action involves a wide variety od mechanisms that contribute to their analgesic effect but also increase their tendency to cause side effects. Fluoxetine, citalopram, and paroxetine are medications belong to SSRI, although they are used in headaches,
migraines, and other non-neuropathic forms of chronic pain treatment, the studies showed their less effectiveness in palliative care but they may act like an adjuvants. SSRIs can act through the serotonergic system as well as through its interaction with the opioid system but Naloxone - an opioid antagonist did not block the antinociceptive effects of fluoxetine, fluoxetine, and citalopram [24] unlike paroxetine. Another study showed that fluvoxamine, paroxetine, fluoxetine and citalopram caused an antinociceptive effect, in contrast to escitalopram, which had no effect. Additionally, the results of the the trials also revealed that fluvoxamine exerted a dose-dependent effect, contrary to citalopram and fluoxetine which both had a very insignificant effect. [25]

Although SSRIs are the most prescribed medications in depression disorder, they are not suggested as the main method of chronic pain treatment when it comes to palliative cancer patients because of their increased risk of serious side effects such as hemorrhages.

Serotonin Norepinephrine Reuptake Inhibitors SNRI

Duloxetine and Venlafaxine are the most recognized SNRI medicines. Recent studies showed promising anagelics effect. Duloxetine has been shown to be superior to placebo in treating CIPN. One study demonstrated that 59% of patients who received duloxetine reported “any decrease” in pain compared with 38% of patients who received placebo; the relative risk of a 30% reduction in pain was 1.96 with duloxetine versus placebo. Beside the above researchers noted decrease in pain interfering with daily function, decrease in numbness/tingling, and improvement in pain-related quality of life [26]. Venlafaxine has shown to be superior to placebo in treating CIPN secondary to taxane agent and adjuvant analgesics. The study demonstrated greater efficacy in minimizing neuropathic cancer pain. In a randomized, double-blind, placebo-controlled study, patients who received Naloxone had less pain, needed less PRN morphine, and had improved functional status compared with those who received gabapentin or amitriptyline [29].

Besides many promising studies in this matter, literature statements can be found that contradicts their positive effect in managing pain. In double-blind randomized, placebo-controlled trial gabapentin was found to be barely effective in treating CIPN [30]. Despite this, ASCO recommend using anatcovulsants in cancer patients in light of lack of alternative, effective treatment options and contraindications on opioid use [31].

IVD. Vit D deficiency

Vitamin D plays a role in a wide range of processes in the body. Here we review the possible role of vitamin D in CIPN and inflammatory pain. In observational studies, low vitamin D levels have been associated with increased pain and higher opioid doses [32]. Recent interventional trials have shown promising effects of vitamin D supplementation on cancer pain and muscular pain but only in patients with insufficient levels of vitamin D when starting intervention. Vitamin D-supplemented patients increased their opioid doses at a significantly slower rate than patients receiving placebo, patients needed 0.56 mg less fentanyl/h per week with vitamin D treatment [33]. Vitamin D reduces self-assessed fatigue but did not affect antibiotic use or self-assessed Quality of life. The treatment was safe and well-tolerated. Possible mechanisms for vitamin D in pain management are the anti-inflammatory effects mediated by reduced cytokine and prostaglandin release and effects on T-cell responses.

The major limitation of this analysis is that the original study was not designed for subgroup analysis in women and men, constituting a risk of both type I and type II statistical errors. Thus, the results must be interpreted with caution and are only hypothesis-generating. In addition, the small numbers of patients who completed the study highlights the difficulties in performing trials in a palliative cohort with a high attrition rate due to death. However, several observational studies show that cancer patients generally have lower vitamin D levels than healthy controls [34] [35], thus Vit D insufficiency examination should be introduced as a standard procedure for palliative cancer patients.

IVF. Cannabinoids

In Poland, cannabinoids are registered for the treatment of spasticity associated with multiple sclerosis. In recent years, the CBD oils massive popularity and the need to find safer, nonopioid pain reduction method prompted researchers to look for other uses for cannabinoids. Several preclinical studies have been conducted in animal models, investigating the mechanism of cannabinoid modulation of pain pathways. The interaction mechanisms of these compounds with one of the body’s endogenous signaling systems, known as the “endocannabinoid” system was identified [36], [37]. Said system acts separately from the opioid pathway to control pain signaling, immune activation, and inflammation [38]. A recent retrospective cross-sectional survey of patients with chronic pain using medicinal cannabis showed a 64% decreased opioid use and an improved quality of life [39]. Other studies of cannabinoid-opioid interaction were conducted when 21 subjects with chronic pain taking twice-daily sustained-release morphine or oxycodone inhaled vaporized cannabis three times daily for 5 days which as a consequence resulted in a 27% reduction in pain with no altered plasma opioid levels [40]. In addition states with medicinal cannabis legalization have actually seen a reduction in opioid analgesic overdose.

Consistency across studies is that there is often some form of methodological flaw, including preparation quality and/or risk of bias. There is lack of sufficient high-quality evidence showing effectiveness of cannabinoids in cancer-related pain treatment, clinicians should always consider side effects such us sedation, dizziness, dry mouth, dysphoria, cognitive impairment, anxiety, and psychosis when suggesting marijuana for the management of cancer-related pain.

IVF. Nonpharmacological

The management of pain in cancer patients should include pharmacological and non-pharmacological interventions. The therapies of integrative medicine, such as mind-body practice, acupuncture, massage therapy and music therapy, have been studied for their role in pain management. Randomized controlled trial data support the effect of hypnosis, acupuncture and music therapy in reducing pain. Mindfulness meditation, yoga, qigong, and massage therapy, although may not reduce pain per se but can relieve anxiety and mood changes which are commonly associated with pain. When deciding whether integrative medicine therapy has clinical value in clinical practice, it is also important to consider patient burden and risk, patient preference and the presence or absence of better alternatives. For patients who have strong spiritual needs, who desire a more naturalistic approach to health, and patients who have experienced the benefits of these therapies before, they are more open to integrative therapies and appreciate their availability. If the clinician cooperates with the patient and appreciates his or her point of view on how to deal with pain, he or she will find that the therapeutic relationship between them is better. Only by taking into account what is truly
important to the patient as an individual physicians can provide optimal patient-centered care, improve the quality of pain management, and make the patient as comfortable as it is possible.

The therapies of integrative medicine involve little physical risk. In general, they are safe if provided by properly trained practitioners. However, they can place a financial burden on patients.

Hypnosis

Hypnosis is a practice by which a therapist induces, or instructs the patient on how to self-induce, a mental state of focused attention or altered consciousness between wakefulness and sleep. In this state, distractions are blocked, allowing the patient to concentrate intensely on a particular subject, memory, sensation, or problem. Patients may receive suggestions, or self-suggest, changes in perceptions toward sensations, thoughts, and behaviors.

In a systematic review of 31 studies (21 RCTs- Randomized Controlled Trials, 2 non-RCTs, and 8 case series), self-hypnosis provided pain relief in cancer patients and dying patients among metastatic breast cancer and after breast cancer surgery[41], [42]. Besides the above promising conclusions there are studies that not share such enthusiasm at this topic and thus draw attention to the poor quality of studies evaluated, and the heterogeneity of study populations which limited further evaluation [43]. A meta-analysis of 37 studies (N=4199) on psychosocial interventions, including hypnosis, concluded that these modalities have a significant medium-size effect on both pain severity and pain interference. In both face normal and face quality-control, interventions should be considered in multidisciplinary pain management for cancer patients [44]. Interestingly, patients who are highly hypnotizable reported greater benefits from hypnosis, used self-hypnosis more often outside of group therapy, and applied it to manage other symptoms in addition to pain, indicating selection of likely responders may be important in clinical practice [45].

Acupuncture

Acupuncture is an old method derived from Traditional Chinese Medicine. When receiving acupuncture treatment, filigree needles are inserted into specific points on the body and stimulated using manual manipulation (twisting, pulling and pressing), heat or electrical impulses. Strong evidence exists to support its analgesic effect on musculoskeletal pain and CIPN. The studies have shown that acupuncture reduced the severity of acute and chronic low back pain to a greater extent than sham acupuncture (form of placebo acupuncture). According to a meta-analysis including 20,827 patients from 39 RCTs, the analgesic effect size of acupuncture was 0.5 SDs compared to non-acupuncture controls and close to 0.2 SDs compared to sham [46], [47]. In accordance with neurobiological studies, mechanisms of action of acupuncture appear to be increased production of endogenous analgesic neurotransmitters, such as endorphins and adenosine, and modulation of the neuronal matrix involved in pain perception [48].

When opioid therapy produces adverse effects such as sedation, constipation, fatigue, nausea and vomiting, the addition of acupuncture has the potential to reduce the required dose of painkillers and thus their side effects.

Music therapy

Music therapy can be receptive – patients listening to recorded or live music selected by a music therapist, or active – patients participate in making music guided by a music therapist, either by singing or playing instruments. The therapist assesses the patient's needs and conditions before designing and providing a tailored intervention regimen. Through music, patients can express and communicate in ways that words cannot. Many randomized, controlled trials of music therapy have been conducted to evaluate its effects on pain. From a meta-analysis of 97 studies, it was shown that music therapy significantly reduces pain, pain-related emotional distress, anesthesia use and opioid use in the general population [49]. With regard to cancer patients, a Cochrane review of 52 music therapy studies involving 3731 patients showed that the average pain score was 0.91 SMD lower (95% CI -1.46 to -0.36) in the music therapy group than in the usual care control group [50]. An SMD of 0.91 is regarded as an effect size greater than moderate. Music therapy proved to be an inexpensive, safe method to help manage pain.

Summary

Cancer pain remains prevalent, yet undertreatment continues, in part due to concerns regarding the use of opioids. The efficacy of opioids in advanced disease has been clearly established, however, questions remain about the safety and effectiveness of opioids in palliative care. As a result of challenges surrounding opioids, alternative analgesics, including antidepressans, anticonvulsants, Vitamins, cannabis and nonpharmacological methods are being studied. Risks and benefits, as well as regulatory and legal issues, must be carefully considered when recommending these treatment options.

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