Sobańska, Natalia, Bednarz, Katarzyna, Banaś, Patryk, Banasiak, Aleksandra Paulina, Teichman, Rafał, Kasprowicz, Jakub, Pierzchała, Jakub Rafał, Abram, Kamila, Adamus, Justyna & Hyjek, Michał. Palliative cancer patients pain reduction methods during opioid epidemic era. Journal of Education, Health and Sport. 2022;12(12):193-198. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2022.12.12.030
https://apcz.umk.pl/JEHS/article/view/40803
https://zenodo.org/record/7334034

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 07.11.2022. Revised: 10.11.2022. Accepted: 18.11.2022.

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 antidepressants, 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 menage 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, Vit D deficiency.

II. 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.

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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 Neuropathic 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 can 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 Cohrane 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. SSRI 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 fluvoxamine, 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 tests 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 analgesic 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 been shown to be superior to placebo in treating CIPN secondary to taxane agents and oxaliplatin. The study demonstrated greater than 75% relief of symptoms; the most striking responses were for patients who had received a taxane and reported “burning-tingling-stabbing” and patients who received oxaliplatin and reported “pain triggered by cold’’ [27]. Although it can be difficult to decrease the numerical pain score when treating neuropathy, the improvement in secondary outcomes may be clinically significant in improving quality of life for patients.

IVC. Anticonvulsants

Gabapentin and pregabalin are the most commonly used anticonvulsant medications for the treatment of cancer pain. Neuronal hyperexcitability plays a relevant role in the pathophysiology of neuropathic pain. Gabapentinoids reduce pain transmission in the spinal pathways and also modulate the central nervous system to inhibit pain pathways resulting in wide use for the treatment of neuropathic pain.

The efficacy of the anticonvulsants have been studied primarily in noncancer neuropathy syndromes, although data exist supporting their use for treatment of cancer pain in conjunction with opioids or even instead of opioids. When compared in a prospective, randomized, open-label trial, pregabalin relieved neuropathic cancer-related pain more effectively than transdermal fentanyl [28]. Pregabalin has been shown to be superior to gabapentin and amitriptyline in managing neuropathic cancer pain. In a randomized, double-blind, placebo-controlled study, patients who received pregabalin 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 anticonvulsants 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 studies 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 µg less fentanyl/h per week with vitamin D treatment [33]. Vitamin D reduced 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.

IVE. 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 mechanism 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 crossectional 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.

One 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 intently 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 with functioning, and that quality-controlled psychosocial interventions should be considered in multimodal approaches to 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 showed 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 antidepressants, 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.

References

1. Merskey H, Bugduk N. Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms, 2nd Ed. IASP Press, Seattle, WA. 1994.

2.Te Boveldt N, Vernooij-Dassen M, Burger N, et al.. Pain and its interference with daily activities in medical oncology outpatients. Pain Physician 2013;16:379–389. PMID: 23877454.

3.Grudzen CR, Richardson LD, Johnson PN, et al. Emergency Department-Initiated Palliative Care in Advanced Cancer: A Randomized Clinical Trial. JAMA Oncol. 2016 May 1;2(5):591-598. doi: 10.1001/jamaoncol.2015.5252. PMID: 26768772; PMCID: PMC9252442.

4. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007 Sep;18(9):1437-49. doi: 10.1093/annonc/mdm056. Epub 2007 Mar 12. PMID: 17355955.

5. Bennett M, Paice JA, Wallace M. Pain and Opioids in Cancer Care: Benefits, Risks, and Alternatives. Am Soc Clin Oncol Educ Book. 2017;37:705-713. doi: 10.1200/EDBK_180469. PMID: 28561731.

6. Hjermstad MJ, Kaasa S, Caraceni A, et al; European Palliative Care Research Collaborative (EPCRC). Characteristics of breakthrough cancer pain and its influence on quality of life in an international cohort of patients with cancer. BMJ Support Palliat Care. 2016 Sep;6(3):344-52. doi: 10.1136/bmjspcare-2015-000887. Epub 2016 Jun 24. PMID: 27342412.

7. Hernandez MA, Rathinavelu A. Basic Pharmacology: Understanding Drug Actions and Reactions: Boca Raton, FL: CRC Press; 2017.

8. Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. CA Cancer J Clin. 2018 May;68(3):182-196. doi: 10.3322/caac.21453. Epub 2018 Mar 30. PMID: 29603142; PMCID: PMC5980731.

9. Ganguly A, Michael M, Goschin S, et al. Cancer Pain and Opioid Use Disorder. Oncology (Williston Park). 2022 Sep 7;36(9):535-541. doi: 10.46883/2022.25920973. PMID: 36107782.

10. Gibbins J, Bhatia R, Forbes K, et al. What do patients with advanced incurable cancer want from the management of their pain? A qualitative study. Palliat Med. 2014 Jan;28(1):71-8. doi: 10.1177/0269216313486310. Epub 2013 May 13. PMID: 23670721.

11. Jacqueline L. Bender, Joanne Hohenadel, Jennifer Wong, et al. What Patients with Cancer Want to Know About Pain: A Qualitative Study, Journal of Pain and Symptom Management, Volume 35, Issue 2, 2008, Pages 177-187, ISSN 0885-3924, https://doi.org/10.1016/j.jpainsymman.2007.03.011.

12. Krebber AM, Buffart LM, Kleijn G, et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology. 2014 Feb;23(2):121-30. doi: 10.1002/pon.3409. Epub 2013 Sep 16. PMID: 24105788; PMCID: PMC4282549.

13. Newport DJ, Nemeroff CB. Assessment and treatment of depression in the cancer patient. J Psychosom Res. 1998 Sep;45(3):215-37. doi: 10.1016/s0022-3999(98)00011-7. PMID: 9776368

14. Bair MJ, Robinson RL, Katon W, et al. Depression and Pain Comorbidity: A Literature Review. Arch Intern Med. 2003;163(20):2433–2445. doi:10.1001/archinte.163.20.2433
Lachlan A. McWilliams, Renee D. Goodwin, Brian J. Cox,

15. Fasick V, Spengler RN, Samankan S, Nader ND, Ignatowski TA. The hippocampus and TNF: Common links between chronic pain and depression. Neurosci Biobehav Rev. 2015 Jun;53:139-59. doi: 10.1016/j.neubiorev.2015.03.014. Epub 2015 Apr 7. PMID: 25857253.

16. Yoon SY, Oh J. Neuropathic cancer pain: prevalence, pathophysiology, and management. Korean J Intern Med. 2018 Nov;33(6):1058-1069. doi: 10.3904/kjim.2018.162. Epub 2018 Jun 25. PMID: 29929349; PMCID: PMC6234399.

17. Bennett MI, Rayment C, Hjermstad M, et al. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain. 2012 Feb;153(2):359-365. doi: 10.1016/j.pain.2011.10.028. Epub 2011 Nov 23. PMID: 22115921.

18. Hershman DL, Lacchetti C, Dworkin RH, et al. American Society of Clinical Oncology. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jun 20;32(18):1941-67. doi: 10.1200/JCO.2013.54.0914. Epub 2014 Apr 14. PMID: 24733808.

19. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain. 2014 Dec;155(12):2461-2470. doi: 10.1016/j.pain.2014.09.020. Epub 2014 Sep 23. PMID: 25261162.

20. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010 Aug;9(8):807-19. doi: 10.1016/S1474-4422(10)70143-5. PMID: 20650402.

21. McCleane G. Antidepressants as analgesics. CNS Drugs. 2008;22(2):139-56. doi: 10.2165/00023210-200822020-00005. PMID: 18193925.

22. Moore RA, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015 Jul 6;2015(7):CD008242. doi: 10.1002/14651858.CD008242.pub3. PMID: 26146793; PMCID: PMC6447238.

23. Accordino MK, Neugut AI, Hershman DL. Cardiac effects of anticancer therapy in the elderly. J Clin Oncol. 2014 Aug 20;32(24):2654-61. doi: 10.1200/JCO.2013.55.0459. Epub 2014 Jul 28. PMID: 25071122; PMCID: PMC4876340.

24. Duman EN, Kesim M, Kadioglu M, Yaris E, Et al. Possible involvement of opioidergic and serotonergic mechanisms in antinociceptive effect of paroxetine in acute pain. J Pharmacol Sci. 2004 Feb;94(2):161-5. doi: 10.1254/jphs.94.161. PMID: 14978354.

25. Schreiber S, Pick CG. From selective to highly selective SSRIs: a comparison of the antinociceptive properties of fluoxetine, fluvoxamine, citalopram and escitalopram. Eur Neuropsychopharmacol. 2006 Aug;16(6):464-8. doi: 10.1016/j.euroneuro.2005.11.013. Epub 2006 Jan 18. PMID: 16413173.

26. Smith EM, Pang H, Cirrincione C, et al. Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013 Apr 3;309(13):1359-67. doi: 10.1001/jama.2013.2813. PMID: 23549581; PMCID: PMC3912515.

27. Kus T, Aktas G, Alpak G, et al. Efficacy of venlafaxine for the relief of taxane and oxaliplatin-induced acute neurotoxicity: a single-center retrospective case-control study. Support Care Cancer. 2016 May;24(5):2085-2091. doi: 10.1007/s00520-015-3009-x. Epub 2015 Nov 7. PMID: 26546457.

28. Raptis E, Vadalouca A, Stavropoulou E, et al. Pregabalin vs. opioids for the treatment of neuropathic cancer pain: a prospective, head-to-head, randomized, open-label study. Pain Pract. 2014 Jan;14(1):32-42. doi: 10.1111/papr.12045. Epub 2013 Mar 6. PMID: 23464813.

29. Mishra, Seema, et al. "A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study." American Journal of Hospice and Palliative Medicine® 29.3 (2012): 177-182.

30. Rao RD, Michalak JC, Sloan JA, et al; North Central Cancer Treatment Group. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer. 2007 Nov 1;110(9):2110-8. doi: 10.1002/cncr.23008. PMID: 17853395.

31. Hershman DL, Lacchetti C, Dworkin RH, et al; American Society of Clinical Oncology. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jun 20;32(18):1941-67. doi: 10.1200/JCO.2013.54.0914. Epub 2014 Apr 14. PMID: 24733808.

32. Bergman P, Sperneder S, Höijer J, Bergqvist J, et al. Low vitamin D levels are associated with higher opioid dose in palliative cancer patients--results from an observational study in Sweden. PLoS One. 2015 May 27;10(5):e0128223. doi: 10.1371/journal.pone.0128223. PMID: 26018761; PMCID: PMC4446094.

33. Helde Frankling M, Klasson C, Sandberg C, et al. 'Palliative-D'-Vitamin D Supplementation to Palliative Cancer Patients: A Double Blind, Randomized Placebo-Controlled Multicenter Trial. Cancers (Basel). 2021 Jul 23;13(15):3707. doi: 10.3390/cancers13153707. PMID: 34359609; PMCID: PMC8345220.

34.Dev R, Del Fabbro E, Schwartz GG, et al. Preliminary report: vitamin D deficiency in advanced cancer patients with symptoms of fatigue or anorexia. Oncologist. 2011;16(11):1637-41. doi: 10.1634/theoncologist.2011-0151. Epub 2011 Sep 30. PMID: 21964001; PMCID: PMC3233299.

35. Shi L, Nechuta S, Gao YT,et al. Correlates of 25-hydroxyvitamin D among Chinese breast cancer patients. PLoS One. 2014 Jan 21;9(1):e86467. doi: 10.1371/journal.pone.0086467. PMID: 24466109; PMCID: PMC3897707.

36.Ward SJ, McAllister SD, Kawamura R, et al. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy. Br J Pharmacol. 2014 Feb;171(3):636-45. doi: 10.1111/bph.12439. PMID: 24117398; PMCID: PMC3969077.

37. Deng L, Guindon J, Cornett BL, et al. Chronic cannabinoid receptor 2 activation reverses paclitaxel neuropathy without tolerance or cannabinoid receptor 1-dependent withdrawal. Biol Psychiatry. 2015 Mar 1;77(5):475-87. doi: 10.1016/j.biopsych.2014.04.009. Epub 2014 Apr 25. PMID: 24853387; PMCID: PMC4209205.

38. Huang WJ, Chen WW, Zhang X. Endocannabinoid system: Role in depression, reward and pain control (Review). Mol Med Rep. 2016 Oct;14(4):2899-903. doi: 10.3892/mmr.2016.5585. Epub 2016 Aug 1. PMID: 27484193; PMCID: PMC5042796.

39. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain. 2016 Jun;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002. Epub 2016 Mar 19. PMID: 27001005.

40. Abrams DI, Jay CA, Shade SB, Et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007 Feb 13;68(7):515-21. doi: 10.1212/01.wnl.0000253187.66183.9c. PMID: 17296917.

41. 41. Pan CX, Morrison RS, Ness J, Et al. Complementary and alternative medicine in the management of pain, dyspnea, and nausea and vomiting near the end of life. A systematic review. J Pain Symptom Manage. 2000 Nov;20(5):374-87. doi: 10.1016/s0885-3924(00)00190-1. PMID: 11068159.

42. Cramer H, Lauche R, Paul A, et al. Hypnosis in breast cancer care: a systematic review of randomized controlled trials. Integr Cancer Ther. 2015 Jan;14(1):5-15. doi: 10.1177/1534735414550035. Epub 2014 Sep 18. PMID: 25233905.

43. Rajasekaran M, Edmonds PM, Higginson IL. Systematic review of hypnotherapy for treating symptoms in terminally ill adult cancer patients. Palliat Med. 2005 Jul;19(5):418-26. doi: 10.1191/0269216305pm1030oa. PMID: 16111066.

44. Sheinfeld Gorin S, Krebs P, Badr H, Et al. Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. J Clin Oncol. 2012 Feb 10;30(5):539-47. doi: 10.1200/JCO.2011.37.0437. Epub 2012 Jan 17. PMID: 22253460; PMCID: PMC6815997.

45. Butler LD, Koopman C, Neri E, Et al. Effects of supportive-expressive group therapy on pain in women with metastatic breast cancer. Health Psychol. 2009 Sep;28(5):579-87. doi: 10.1037/a0016124. PMID: 19751084.

46. Vickers AJ, Linde K. Acupuncture for chronic pain. JAMA. 2014 Mar 5;311(9):955-6. doi: 10.1001/jama.2013.285478. PMID: 24595780; PMCID: PMC4036643.

47. Vickers AJ, Vertosick EA, Lewith G, et al. Acupuncture Trialists' Collaboration. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. J Pain. 2018 May;19(5):455-474. doi: 10.1016/j.jpain.2017.11.005. Epub 2017 Dec 2. PMID: 29198932; PMCID: PMC5927830.

48. Sawynok J. Adenosine receptor targets for pain. Neuroscience. 2016 Dec 3;338:1-18. doi: 10.1016/j.neuroscience.2015.10.031. Epub 2015 Oct 21. PMID: 26500181.

49. Lee JH. The Effects of Music on Pain: A Meta-Analysis. J Music Ther. 2016 Winter;53(4):430-477. doi: 10.1093/jmt/thw012. Epub 2016 Oct 19. Erratum in: J Music Ther. 2021 Aug 24;58(3):372. PMID: 27760797.

50. Bradt J, Dileo C, Magill L, Teague A. Music interventions for improving psychological and physical outcomes in cancer patients. Cochrane Database Syst Rev. 2016 Aug 15;(8):CD006911. doi: 10.1002/14651858.CD006911.pub3. Update in: Cochrane Database Syst Rev. 2021 Oct 12;10:CD006911. PMID: 27524661.