



Treatment options for persistent pain and numbness in cancer survivors

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Comment on: Abe H, Inoue R, Tsuchida R, *et al.* Efficacy of treatments for pain and numbness in cancer survivors: a systematic review and meta-analysis. *Ann Palliat Med* 2022. [Epub ahead of print]. doi: 10.21037/apm-22-420.

Keywords: Pain; numbness; cancer survivors; exercise; alternative medicine

Submitted Dec 06, 2022. Accepted for publication Dec 19, 2022. Published online Jan 16, 2023.

doi: 10.21037/apm-22-1392

View this article at: <https://dx.doi.org/10.21037/apm-22-1392>

With improvements in cancer screening and treatment, the number of cancer survivors is increasing (1). Cancer treatments, such as radiation, hormonal treatment, and chemotherapy, can result in roughly 40% of cancer survivors experiencing chronic pain and numbness persistent after treatment (2). Other common causes of persistent pain in cancer survivors included aromatase inhibitor (AI) associated arthralgia, chemotherapy-induced peripheral neuropathy (CIPN), post-surgical pain, postmastectomy pain syndrome (PMPS), and other non-specific pain complications, which have an impact on psychological well-being, functional status, and overall quality of life (3).

The management of chronic pain and numbness in cancer survivors can pose challenges for healthcare providers. The detailed, systematic review and meta-analysis conducted by Abe and colleagues, “Efficacy of treatments for pain and numbness in cancer survivors: a systematic review and meta-analysis”, provides a much-needed critical assessment of treatment modalities including—opioid therapy, non-opioid pharmacotherapy, interventional treatments, acupuncture, education and cognitive behavioral therapy, physical exercise, and alternative medicine—for pain and numbness in cancer survivors (4). In their systematic review, cancer survivors were characterized as being aged 18 years or older, completed active cancer treatment, and were noted to have stable disease with no evidence of recurrence or progression and excluded studies with participants who had greater than 50% advanced cancer, stage III-IV or terminal

disease and ongoing active cancer treatment. The meta-analysis included 36 randomized controlled trials (RCTs) (2,870 cancer survivors) with a predominance of studies, 24 RCTs, involving breast cancer survivors indicating the need for more research in patients other than breast malignancies in order to improve generalizability.

Abe and colleagues’ review highlight a remarkable lack of studies evaluating the benefits of opioids for the management of persistent pain in cancer survivors. In the current setting of an ongoing opioid epidemic in the United States, the use of opioid therapy for chronic pain in cancer survivors is controversial. ASCO guidelines for the management of chronic pain in adult cancer survivors do advocate for cautious use of opioids for patients who fail conservative management (5). Of note, among cancer survivors, in a cross-sectional, retrospective, population-based study, the rates of non-medical opioid use (NMOU) were reported to be low and similar to non-cancer patient population; however, NMOU was associated with younger age (18–34 years), prior history of alcohol and substance use disorders (6). In addition, cancer survivors with mental health disorders and complications of pain or numbness present a challenge to healthcare providers due to lack of adherence to treatment plans and increased risk of chemical coping, the use of opioids for emotional pain and psychological distress, and researchers advocate for an individualized approach, informed consent, and a shared decision-making model to manage these difficult

scenarios (7). In addition, a recent study of patients with non-cancer pain on chronic opioid therapy reported opioid tapering, defined as 15% or more relative reduction in mean daily opioid dose, was associated with increased risk for substance use disorders and a mental health crisis (8) suggesting that if an alternative, healthy, coping mechanism is not supplemented for opioid use, the risk of substance use disorders or emotional and psychological distress may increase.

Chronic post-surgical pain, including post-thoracotomy pain syndrome, chronic pain after neck dissection or colorectal surgery, and post-nephrectomy syndrome, in cancer survivors is a clinical challenge for healthcare providers to treat and often needs a different approach than the management of cancer pain in patients with active or advanced disease. The use of long-term opioids in cancer survivors experiencing pain has raised concerns for issues of NMOU and chemical coping, like the non-cancer pain population where long-term opioids are no longer recommended (9). Also, long-term opioid use exposes cancer survivors to risks of constipation, hypogonadism and loss of sexual desire, delirium, hyperalgesia, and can also potentially interfere with employment. The use of analgesics other than opioids and non-pharmacological interventions is advised as first line therapy for chronic pain in cancer survivors and when opioids are prescribed, using the lowest effective dose with close monitoring is recommended (10).

Breast cancer affects over 250,000 patients per year with advances in treatment leading to increased survival and a subset of patients with complications of post-mastectomy pain syndrome, affecting 20–50% of patients (11). For pain and neuropathy due to PMPS, non-pharmacological therapy including physical activity, massage therapy, and acupuncture have been endorsed, and pharmacological interventions include acetaminophen or non-steroidal inflammatory drugs, and duloxetine for neuropathy and underlying depression and anxiety, while opioids have been suggested to avoid (11). Others have recommended gabapentinoids for PMPS as a component of multi-modality therapy (12); however, gabapentin, which has recently been increasingly prescribed for off-label treatment of nerve pain and other conditions resulting in the doubling of prescriptions from 13 to 37 per 1,000 insurance beneficiaries between 2009 and 2106, has been increasingly detected, along with opioids, in 1 in 10 overdose deaths between 2019 and 2020 (13) and may best be used cautiously at low doses or avoided altogether in favor of antidepressants such as

duloxetine or non-pharmacological interventions.

Aromatase inhibitor (AI) associated musculoskeletal joint pain can be a challenge to treat in cancer survivors. Musculoskeletal pain due to AI is often treated with non-steroidal anti-inflammatory medications or acetaminophen, antidepressants, anticonvulsants, and other non-pharmacological approaches. Non-pharmacological interventions for joint pain due to AI with evidence of benefit include physical exercise consisting of aerobic or endurance exercises and resistance training (14), less support of stretching exercises such as yoga (15), mixed results to treatment with acupuncture (16,17) and omega-3 fatty acid supplementation was not superior to placebo control in one study (18). One strategy to manage musculoskeletal pain due to AI involves switching treatments (19); however, it is not uncommon for patients to discontinue AIs due to arthralgia (20). The systematic review by Abe's group also reports alternative treatment such as myofascial therapy and neuromuscular taping resulted in significant improvement of joint pain due to AI, but the number and quality of trials were low. Finding effective and safe strategies for AI associated joint pain may allow for greater compliance with treatment.

CIPN is the most common neurological complication of cancer treatment and associated with decrease functional impairment and quality of life (21). Cancer survivors who had complications of oxaliplatin or paclitaxel-induced peripheral neuropathy may show no resolution of pain or numbness even after completing therapy with a subset of patients, up to 30–40%, experience persistence symptoms (21,22). ASCO guidelines for the management of CIPN in adult cancer survivors confirmed no pharmacological agents beneficial for prevention of CIPN and only some, limited evidence to support duloxetine to control pain due to CIPN (23). In cancer survivors, the systematic review reports moderate support for physical exercise for pain control, including the management of CIPN. Both aerobic and resistance exercises showed significant benefits with less support for stretching exercise, but the studies reviewed had notable variations in frequency and duration of exercise (1) and more research is needed to determine frequency and intensity of specific exercise modalities. Of note, in a recent survey of cancer survivors, the majority with advanced disease and on active treatment, lack of motivation or interest and limited self-discipline were noted barriers to engaging in the American College of Sports Medicine recommendations which encourages 150 minutes of moderate-intensity aerobic activity and 2–3 weekly sessions

of resistance training (24).

Abe and colleagues' review highlights preliminary studies, although limited in number, with potential benefits of various non-pharmacological interventions for pain in cancer survivors including acupuncture, yoga, neurofeedback, compression and cryotherapy and transcutaneous electrical nerve stimulation devices, but lack of evidence to support mindfulness or coping skills training. In addition, the review highlights the lack of evidence to support non-opioid pharmacotherapy including capsaicin or ketamine plus amitriptyline cream for neuropathic pain, vitamin D3 supplementation or Yi Shen Jian Gu, a Chinese medicine, for AI associated musculoskeletal joint pain, botulinum toxin A for upper extremity pain, and pH-balanced vaginal gel for dyspareunia for pain in cancer survivors (1). For numbness due to CIPN in cancer survivors, acupuncture and yoga did not show benefits compared to placebo with only 1 potentially beneficial pilot study reporting biofeedback superior to usual care (25).

Since non-pharmacological interventions may have a potentially better safety profiles compared with opioids, more studies are needed in cancer survivors examining their benefits. Effective non-pharmacological treatments may potentially prevent cancer survivors from being exposed to long-term opioid or pharmacological therapy or pursue risky interventional procedures, which were also were noted to have no clinical trials to support their use for pain control (1).

In conclusion, pain and persistent numbness has significant impact on physical function and quality of life in cancer survivors. Unfortunately, breast cancer patients are predominant patient population in these studies of cancer survivors making it difficult to generalize findings to other types of malignancies and many studies are small and of low quality. Currently, a shift away from opioid therapy due to the opioid epidemic makes analgesics other than opioids and non-pharmacological interventions the focus of future research in the treatment of pain in cancer survivors; however, the uncertainty of the durability of response in certain cancers would suggest that healthcare providers need to be vigilant and conduct a thorough clinical and physical examination to formulate a treatment plan when pain persists or increases. Despite the lack of evidence, opioid therapy may be needed and prescribed cautiously in some cancer survivors with complications of pain who don't respond to other analgesics or non-pharmacological interventions such as exercise, but more research is needed to guide treatment.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Palliative Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-1392/coif>). Both authors report that in the past 36 months, they have received royalties or licenses from UpToDate. Both authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Dev R, Bruera E. Treatment options for persistent pain and numbness in cancer survivors. *Ann Palliat Med* 2023;12(1):32-35. doi: 10.21037/apm-22-1392