This item is the archived peer-reviewed author-version of:

Treatment of pain following cancer : applying neuro-immunology in rehabilitation practice

Reference:

Nijs Jo, Leysen Laurence, Pas Roselien, Adriaenssens Nele, Meeus Mira, Hoelen Wouter, Ickmans Kelly, Moloney Niamh.- Treatment of pain following cancer : applying neuro-immunology in rehabilitation practice
Disability and rehabilitation - ISSN 0963-8288 - 40:6(2018), p. 714-721
Full text (Publisher's DOI): <https://doi.org/10.1080/09638288.2016.1261418>
To cite this reference: <http://hdl.handle.net/10067/1418210151162165141>

Treatment of Pain Following Cancer:

Applying Neuro-Immunology in Rehabilitation Practice

Jo Nijs^{1,2}, Laurence Leysen¹, Roselien Pas¹, Nele Adriaenssens^{1,3}, Mira Meeus^{4,5}, Wouter Hoelen^{6,7}, Kelly Ickmans^{1,2}, Niamh Moloney⁸

¹ Pain in Motion International Research Group, Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Belgium

² Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Belgium

³ Department of Oncology, University Hospital Brussels, Belgium

⁴ Rehabilitation Sciences and Physiotherapy, Faculty of Medicine, Antwerp University, Antwerp, Belgium

⁵ Department of Rehabilitation Sciences, Ghent University, Ghent, Belgium

⁶ De Berekuy, Private practice for physiotherapy in oncology & lymphology, the Netherlands

⁷ The Berekuy Academy, the Netherlands

⁸ Department of Health Professions, Faculty of Medicine and Health Sciences, Macquarie University, Australia

Address of correspondence and reprints requests to Jo Nijs, Vrije Universiteit Brussel, Building F-KIMA, Laarbeeklaan 103, BE-1090 Brussels, Belgium (phone +3224774489; fax +3226292876; e-mail: Jo.Nijs@vub.ac.be; website: www.paininmotion.be)

There are no conflict of interest disclosures from any authors.

Funding / Acknowledgements

Niamh Moloney was awarded by the International Association for the Study of Pain (IASP) with an Early Career Research Grant for the project entitled: 'Predicting the development of persistent pain after breast cancer treatment' (2015-2016). Jo Nijs is holder of a Chair funded by the Berekuy Academy / European College for Decongestive Lymphatic Therapy, the Netherlands.

Declaration of interest

The authors report no conflicts of interest.

Abstract

Purpose: Pain is the second most frequent persistent symptom following cancer treatment.

This paper aims at explaining how the implementation of contemporary pain neuroscience can benefit rehabilitation for adults following cancer treatment within an evidence-based perspective.

Materials and methods: Narrative review.

Results: First, pain education is an effective but underused strategy for treating cancer related pain. Second, our neuro-immunological understanding of how stress can influence pain, highlights the importance of integrating stress management into the rehabilitation approach for patients having cancer-related pain. The latter is supported by studies that have examined the effectiveness of various stress management programs in this population. Third, poor sleep is common and linked to pain in patients following cancer treatment. Sleep deprivation results in a low-grade inflammatory response and consequent increased sensitivity to pain. Cognitive behavioural therapy for sleep difficulties, stress management and exercise therapy improves sleep in patients following cancer treatment. Finally, exercise therapy is effective for decreasing pain in patients following cancer treatment, and may even decrease pain-related side effects of hormone treatments commonly used in cancer survivors.

Conclusions: Neuro-immunology has increased our understanding of pain and can benefit conservative pain treatment for adults following cancer treatment.

Key words: pain, neuropathic, sensitization, exercise, education, sleep

Abstract word count: 194

Introduction

Life expectancy for people following cancer treatment has increased due to the early detection and advances in cancer treatment[1, 2]. Unfortunately, cancer survivors often face long-term symptoms that arise or persist beyond the completion of treatment, making it an increasingly important population for the field of rehabilitation. In addition to fatigue, pain is the most frequent persistent symptom following cancer and cancer treatment[3]. The high prevalence of pain in the growing cancer survivor population is of considerable concern due to the fact that pain is associated with reduced quality of life and day-to-day functioning[4, 5, 6, 7, 8].

Modern pain neuroscience and neuro-immunology has advanced our understanding about pain. Early paradigms of pain being proportional to injury i.e. nociceptive input have evolved over the decades to include Wall and Melzack's gate control theory,[9] with more recent insights on the role of nervous system sensitization[10] (defined as "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity"[11]), and the complex interactions between nociceptive pathways and the immune system i.e. neuro-immunology [12, 13]. Pain neuroscience has evolved, and rehabilitation clinicians around the globe are at the front line for implementing contemporary pain neuroscience in clinical practice.

Implementation of pain neuroscience in clinical practice has gained wide attention in the area of musculoskeletal physiotherapy, but not so much in other areas like oncology.

Therefore, here we explain how implementation of contemporary pain neuroscience and neuro-immunology can benefit conservative treatment for people having pain following cancer (treatment). The first part of the paper provides an update of our current understanding of pain following cancer (treatment). The next part explores new pain treatment strategies within an evidence-based perspective.

Pain in patients following cancer (treatment)

Pain in patients following cancer (treatment) is often neuropathic in nature[14]; mainly peripheral neuropathic pain. Cancer-related neuropathic pain syndromes may be subdivided into (1) cancer-related neuropathic pain, (2) cancer-therapy-induced neuropathic pain, and (3) cancer-associated neuropathic pain. Examples of the first are paraneoplastic neurological syndromes and tumor/metastasis infiltration or compression of the central and/or peripheral nervous system[15], however further detail is beyond the scope of this article. Neuropathic pain is often a side effect or complication of various life-preserving treatments for cancer[16, 17, 18] like surgery[16, 17]. Post-mastectomy pain syndrome[19, 20, 21] is a common example of cancer-therapy-induced neuropathic pain which often relates to damage to the long thoracic or thoracodorsal nerve, intercostobrachial nerve[22] or due to a neuroma. In cancer survivors with a history of thoracotomy, intercostal nerve injury is a common type of cancer-therapy-induced neuropathic pain, possibly explaining chronic chest wall pain[21].

In addition to surgery, other cancer-therapy-induced neuropathic pain syndromes like radiation therapy may also affect surrounding structures including nerves and neural plexi

(e.g. the lumbosacral plexus during irradiation of pelvic organs[17]). The prevalence of radiation-induced neuropathy has decreased substantially over the past 70 years[23]. However, radiation-induced peripheral neuropathy usually appears several years after radiotherapy[23], which makes it still prevalent these days. Finally, due to chemo-toxicity, chemotherapy is a third common cause of neuropathy in patients following cancer treatment[21, 23]. Clinical signs include sensory signs (numbness and burning feeling) rather than pain per se; pain can be present but is reported less commonly[21]. Neuropathies related to treatment are most common and are thus mainly due to damage at the peripheral nerve system, resulting in complaints localized in the respective regions.

Post-herpetic neuralgia is the most common example of cancer-associated neuropathic pain, and is developed by approximately 25% to 50% of cancer patients following an acute herpes zoster infection. Indeed, because of the higher incidence of immunosuppression in cancer patients, acute herpes zoster is more likely to occur in cancer patients than in the general population[24].

In addition to neuropathic pain, nociceptive pain is also possible in patients following cancer treatment. Common sources of nociception in these patients include connective tissue fibrosis[25, 26, 27], skeletal-related events[28], oedema[29], rashes, ulcers, myofascial pain and movement dysfunctions e.g. scapular dyskinesis[30]. Finally, emerging evidence suggests a role for central sensitization in explaining pain in a subgroup of cancer survivors[31, 32, 33]. These studies revealed widespread pressure pain hypersensitivity in people treated for breast or colon cancer[31, 32, 33]. However, some studies found only local hypersensitivity[33, 34] and studies investigating other features of central sensitization

pain (peripherally-driven central excitability and dysfunctional endogenous analgesia) are inconclusive[35, 36, 37]. Together these findings suggest that pain following cancer treatment is not always dominated by central sensitization, but instead may be present in a subgroup. Moreover, pain following cancer (treatment) is likely a mixed pain condition. Guidelines for identifying the relevant or even dominant type of pain in patients following cancer treatment have been proposed[38].

Traditionally, rehabilitation clinicians have been involved in optimizing muscle & joint function in patients following cancer treatment. This includes restoring upper limb function in patients following breast cancer surgery[39]. However, rehabilitation clinicians can do much more than providing hands-on treatment for improving joint function in adults following cancer treatment. The next sections explore the treatment options for implementing contemporary pain neuroscience and neuro-immunology within evidence-based treatment for adults suffering from pain following cancer treatment.

Educating patients following cancer treatment about their pain

A meta-analysis of 21 trials concluded that patient-based educational interventions are effective but underused for treating cancer related pain[40]. Equivocal evidence was found for a positive effect on pain severity, knowledge and self-efficacy[40], each of which are crucial for preparing patients for subsequent phases of the rehabilitation program. It is notable that the positive effects noted in this review were modest, thus integration with other aspects of pain management appears appropriate. Moreover the content of the included education is variable and poorly established, as highlighted in the meta-analysis of

Bennett et al.[40]. Up to now, most of the educational interventions for cancer patients have been restricted to more biomedical pain management instructions (e.g. use of analgesics) [40].

When providing education to patients following cancer treatment, implementation of contemporary pain neuroscience into the educational program seems warranted (Table 1 provides key messages). Pain neuroscience education includes explaining to patients that pain is an output product of the brain resulting from input from multiple central and peripheral nervous system processes and leading to the perception of threat rather than pain being a reflection of current tissue damage[41]. Pain *neuroscience* education intends to transfer that knowledge to patients, allowing them to understand their pain and hence to effectively cope with their pain[41]. This includes explaining to patients that the pain is the sum of many processes within the nervous system and brain, which may or may not include nociception, and thus frequently poorly reflects current tissue damage. In non-cancer population with pain, pain neuroscience education is welcomed very positively by patients,[42, 43] and is effective in changing pain beliefs and improving health status as well as pain coping strategies[42, 43, 44, 45, 46, 47, 48, 49, 50]. However, studies examining the effectiveness of pain neuroscience education in patients following cancer treatment are lacking and are therefore an important research priority (Table 2 provides a research agenda).

According to the meta-analysis mentioned previously, education for cancer related pain did not result in positive effects on interference with daily activities[40], indicating that

education can be a first and important step but requires follow-up with more active interventions including stress management as well as exercise and functional activity interventions.

Stress management

Some people will show blunted cortisol responses to psychological stress[51, 52], flatter diurnal cortisol rhythms[53] and lower heart rate variability[54, 55] following cancer treatment. These findings are suggestive of a subtle hypothalamus-pituitary adrenal axis dysfunction and decreased vagal activity in these patients. How does this relate to pain?

Several potential mechanisms included in our current understanding of cancer pathophysiology[56, 57] (e.g. oxidative stress and the role of inflammation), explain why decreased vagal activity may contribute to pain[58]. Low vagal nerve activity implies less inhibition of inflammation (including oxidative stress), higher sympathetic activity and low activity in brain regions capable of modulating nociceptive input[58], thereby explaining in part how the pain experience may be magnified in the presence of stress.

In addition, the stress response system is capable of influencing nociceptive processing through various pathways[59, 60, 61, 62, 63, 64, 65]. In addition to its anti-inflammatory effects, cortisol (“the” stress hormone) holds analgesic effects as well: e.g. the dorsal horn glucocorticoid receptors have analgesic capacities[65]. Second, in primary afferent nociceptors, stress triggers a switch in second messenger signaling for pro-nociceptive immune mediators, possibly explaining stress-induced symptom flares[59]. Stress activates the dorsomedial nucleus of the hypothalamus and subsequent activation of ON-cells (neurons increasing pain) plus suppression of OFF-cells (neurons decreasing pain)[64]. Finally, chronic stress has detrimental effects on gamma-amino-butyric acid (GABA)-

neurotransmission both at the spinal and supraspinal level, resulting in generalized hyperalgesia and disinhibition of the hypothalamic-pituitary-adrenal axis[63]. Together these neuro-immune reactions can result in stress-induced hyperalgesia (augmented nociceptive facilitation and suppressed nociceptive inhibition) rather than stress-induced hypoalgesia[64].

Our neuro-immunological understanding of how stress can influence pain highlights the importance of examining whether dysfunctional stress mechanisms demonstrated by patients following cancer treatment [51, 52, 53, 54, 55] account for (in part) or contribute to the individual's pain. Therefore, it seems warranted to integrate stress management into the management of pain following cancer treatment. Stress management is an evidence-based intervention for patients following cancer treatment. In breast cancer populations, there is some evidence to support the use of cognitive behavioural stress management[66]. Also, a stress management intervention comprising relaxation, cognitive restructuring and coping skills training was found to be effective in patients following surgical breast cancer treatment[67], while mindfulness-based stress reduction has been shown to be effective in general cancer populations[68, 69].

In clinical practice, engaging patients in such stress management programs is often a challenge – use of stress management skills sometimes contradicts patients' illness beliefs. Explaining to patients that stress is closely related to their (exacerbation of) symptoms is often misinterpreted as 'it's all in my mind'. One way to overcome this is by integrating the above outlined neuro-immunology behind stress and pain to show that the stress response

system is 'real' (i.e. holds a biological nature) and that it involves part of the central nervous system (e.g. the autonomic branch of the central nervous system) and complex endocrine axes (including the hypothalamic-pituitary-adrenal axis). Stress management should incorporate acknowledgement that inherent stress response systems may not be functioning properly, and that external assistance is required in order to cope better with everyday stressors. If the illness perception regarding the role of stress is adopted properly, and if the patient can see how the approaches outlined can assist or strengthen the stress response system, then improved adherence with stress self-management interventions might be achievable.

The inability to cope with everyday stressors is a frequent cause of sleeping difficulties [70, 71]. Conversely, effective stress management improves sleep [72, 73]. How this applies to (pain in) the cancer survivor population will be addressed in the next section.

Sleep self-management

Poor sleep is common in patients following cancer treatment[74, 75] even in adult survivors of childhood cancer[76, 77]. This illustrates that sleep difficulties, when left untreated, do not always naturally resolve in this population. Poor sleep in patients following cancer treatment is accompanied with poor physical health and anxiety[76, 77].

Poor sleep has been linked to pain in the cancer[74] (survivor[78]) population and is associated with headache in cancer survivors[76]. Our current understanding of sleep neuro-immunology provides potential links between sleep difficulties and (the onset of) pain. While proper sleep facilitates immune health, sleep deprivation results in low-grade inflammatory responses[79, 80, 81]. This low-grade inflammatory response as a consequence of sleep deprivation includes increased levels of interleukin 6, prostaglandin E2[80, 81] and nitric oxide[82] possibly mediated by cerebral microglia[82]. Even low levels of inflammatory cytokines are known to affect brain function[83] which correlates with observations of increased sensitivity to painful stimuli following sleep restriction[80, 84, 85]. Taken together, sleep deprivation imparts a low-grade inflammatory response leading towards increased sensitivity to pain as typically seen in chronic pain sufferers. Our neuro-immunologic understanding of the link between sleep and pain may be important for inclusion in pain education for patients with pain following cancer treatment (i.e. to empower patients to invest time in specific sleep interventions known to benefit sleep problems in this population).

Cognitive behavioural therapy is effective, with large effect sizes, for improving sleep in patients following cancer treatment[86]. Such cognitive behavioural therapy for sleep typically includes sleep hygiene and can be provided in face-to-face sessions or using online programs[87]. Such interventions are not limited to a specific discipline but available for any therapist willing to learn more about the role of sleep and how to improve it. In addition to cognitive behavioural therapy for sleep difficulties, stress management[74] and exercise therapy[74, 88] can also improve sleep in patients following cancer treatment.

Exercise therapy

Exercise therapy has been shown to be effective for improving quality of life in cancer survivors[88, 89, 90, 91]. Systematic evaluation of the effects of exercise on a multitude of cancer-related concerns e.g., fatigue, sleep and mood reveals it is effective for these impairments, but also shows some efficacy for decreasing pain in this population[88]. Exercise therapy may be beneficial to cancer survivors due to its positive effects on the cardiovascular system, immune functioning and musculoskeletal system, but may also target central pain (inhibitory) mechanisms[92]. Given these benefits, exercise may hold value for treatment of pain related side effects of hormone treatments commonly used in cancer survivors[93].

Postmenopausal women with hormone receptor-positive breast cancer receive hormone therapy as part of their (post-)cancer treatment. One of the most frequently used and evidence-based[94, 95, 96] hormone treatments are aromatase inhibitors (inhibitors of the enzyme aromatase) that inhibit the conversion of androgens to estrogens. This results in decreased availability of estrogens and slowed progression of breast cancer. Exercise / physical activity also decreases the availability of estrogens in healthy women[97]. Unfortunately, aromatase inhibitors often result in debilitating side effects like pain: approximately 50% of breast cancer survivors on aromatase inhibitor therapy report musculoskeletal pain[98]. Such musculoskeletal pain remains even after stopping the hormone therapy.

The reason for this common side effect of aromatase inhibitors is still an active area of research, and advances have been made. Recent animal work suggests that aromatase inhibitors selectively target the transient receptor potential ankyrin 1 (TRPA1) channel, a major pathway in pain transmission and neurogenic inflammation[99]. Aromatase inhibitors activate TRPA1 channels in nociceptors, resulting in the release of sensory neuropeptides (i.e. neuro-inflammation) and mechanical hypersensitivity, together corresponding to a picture of generalized peripheral sensitization. Indeed, TRPA1 is not only expressed on the distal, but also on the central endings of the primary afferent nociceptive fibers, located within the spinal dorsal horn[100].

As pain is one of the main reasons for low treatment adherence and high aromatase inhibitor discontinuation, combining drug treatment with exercise therapy might overcome this problem. A high-quality randomized controlled trial showed that exercise therapy (comprising a combination of aerobic and strengthening exercise) is effective in decreasing aromatase inhibitors-induced arthralgia in breast cancer survivors[93]. More specifically, breast cancer survivors performed a home-based aerobic exercise program of 150 minutes per week (walking or cycling) at 50 to 80% of maximal heart rate. The strength training included supervised resistance training of lower and upper limb muscles and was performed twice per week. The control group received usual care and showed little pain severity changes throughout the study period. The treatment group improved markedly in pain severity and disability scores, with a mean improvement of 29% in pain severity[93]. This number is most likely to reflect a clinically important improvement, but given the capacity of

the placebo effect to generate large improvements in pain severity, a placebo-controlled trial with similar treatment time for both arms is required to confirm these findings.

Still, the positive effects of exercise therapy in patients following cancer treatment[88, 89, 90, 91] are not just limited to breast cancer but also apply to head and neck cancer, brain and spinal cord cancer, Myeloma, osteogenic cancers and blood cancer, among others. Another important consideration when prescribing exercise is the presence of signs of central sensitization. The presence of central sensitization may reduce the effectiveness of exercise interventions. Although emerging evidence suggests a role for central sensitization in explaining pain in a subgroup of patients following cancer treatment[31, 32, 33], evidence concerning the effects of exercise therapy on pain processing in cancer survivors is limited. To our knowledge, only two studies evaluated the effect of exercise therapy on signs of central sensitization in cancer patients. The first one found that widespread hypersensitivity in patients following breast cancer treatment did not improve in response to an 8-week water therapy exercise program, even though the number of myofascial trigger points decreased and the neck/shoulder/axillary pain improved[101]. The second study demonstrated that hydrotherapy resulted in a significant increase in pressure pain threshold levels of the affected and non-affected side in breast cancer survivors with hormone therapy-associated arthralgia[102]. More studies examining whether exercise therapy is capable of decreasing hypersensitivity of the nervous system in patients following cancer treatment are needed, including studies using exercise therapy adopted to our current understanding of pain neuroscience[103, 104]. Further research is warranted to investigate

both the presence of central sensitization in this group, and whether exercise can help to improve pain in this scenario.

Conclusions

Pain neuroscience and neuro-immunology has increased our understanding of pain following cancer treatment, but the latter stays an underestimated clinical problem in a fast growing population. It is time to implement contemporary pain neuroscience to care for patients with pain following cancer and cancer treatment. Rehabilitation clinicians are perfectly situated within the health care system to implement contemporary pain neuroscience and neuro-immunology in this population.

First, pain education is a potentially effective but underused strategy for treating cancer related pain[40]. When providing pain education to patients following cancer treatment, implementation of contemporary pain neuroscience into the educational program seems warranted for yielding positive effects on interference with daily activities. When doing so, rehabilitation clinicians are advised to take into account that pain in cancer survivors is contextualised by the serious condition that has been a precursor for pain. In many cases, the pain experienced by these patients has often, at least initially, been associated with real damage and danger and therefore, has potentially a higher threat value compared to other (chronic) pain populations. Secondly, in this population, there is often a constant fear for recurrence, so it might be harder to reconceptualise the pain as an unreliable and harmless signal. Therefore, it is very important for both patient and therapist to be confident/reassured about that issue. Finally, it is possible that cancer survivors are less

admissive about their pain, due to the enormous psychological burden caused by the disease.

Second, some patients following cancer treatment show a subtle hypothalamus-pituitary adrenal axis dysfunction and decreased vagal activity[51, 52, 53, 54, 55]. Our neuro-immunological understanding of how stress can influence pain highlights the importance of integrating stress management into the treatment approach for patients having pain following cancer, a notion underscored by the available evidence supporting the use of various stress management programs for this population of survivors[66, 67, 68, 69].

Third, poor sleep is common[74, 75, 76, 77] and linked to pain[74, 76, 78] in patients following cancer treatment. Sleep deprivation imparts a low-grade inflammatory response possibly leading towards increased sensitivity to pain as typically seen in chronic pain sufferers. Cognitive behavioural therapy for sleep difficulties[86, 87], stress management[74] and exercise therapy[74, 88] improves sleep in patients following cancer treatment. Finally, exercise therapy is effective for decreasing pain in patients following cancer treatment[88], and may even decrease pain-related side effects of hormone treatments commonly used in cancer survivors[93]. More studies examining whether exercise therapy is capable of decreasing the hypersensitivity of the nervous system in a subgroup of patients with predominant central sensitization pain in patients following cancer treatment[32, 33] are emerging. Likewise, there is a need for studies examining the role of pain in explaining quality of life after stopping all cancer treatment, especially given the increasing survivorship time. Will rehabilitation clinicians take the lead in implementing and researching pain

neuroscience in people following cancer treatment like they did in the area of musculoskeletal pain, taking into account the specific profile of these people?

References

1. Ghoncheh M, Mirzaei M, Salehiniya H. Incidence and Mortality of Breast Cancer and their Relationship with the Human Development Index (HDI) in the World in 2012. *Asian Pacific journal of cancer prevention : APJCP*. 2015;16:8439-43. Epub 2016/01/09.
2. Krok-Schoen JL, Fisher JL, Baltic RD, Paskett ED. White-Black Differences in Cancer Incidence, Stage at Diagnosis, and Survival among Adults Aged 85 Years and Older in the United States. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2016;25:1517-23. Epub 2016/11/03.
3. Harrington S, Gilchrist L, Sander A. Breast Cancer EDGE Task Force Outcomes: Clinical Measures of Pain. *Rehabilitation oncology*. 2014;32:13-21. Epub 2014/10/28.
4. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. Pain and its treatment in outpatients with metastatic cancer. *The New England journal of medicine*. 1994;330:592-6. Epub 1994/03/03.
5. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. *Jama*. 1998;280:147-51.
6. Avis NE, Crawford S, Manuel J. Quality of life among younger women with breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005;23:3322-30. Epub 2005/05/24.
7. Arnow BA, Hunkeler EM, Blasey CM, Lee J, Constantino MJ, Fireman B, Kraemer HC, Dea R, Robinson R, Hayward C. Comorbid depression, chronic pain, and disability in primary care. *Psychosomatic medicine*. 2006;68:262-8. Epub 2006/03/24.
8. Rudy TE, Kerns RD, Turk DC. Chronic pain and depression: toward a cognitive-behavioral mediation model. *Pain*. 1988;35:129-40. Epub 1988/11/01.
9. Wall B, Melzack R. *Textbook of Pain*. 3rd ed ed. London 1994.
10. Woolf CJ. Central sensitization: uncovering the relation between pain and plasticity. *Anesthesiology*. 2007;106:864-7. Epub 2007/04/07.
11. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152:S2-15. Epub 2010/10/22.
12. Verma V, Sheikh Z, Ahmed AS. Nociception and role of immune system in pain. *Acta neurologica Belgica*. 2015;115:213-20. Epub 2014/12/31.
13. Austin PJ, Moalem-Taylor G. The neuro-immune balance in neuropathic pain: involvement of inflammatory immune cells, immune-like glial cells and cytokines. *Journal of neuroimmunology*. 2010;229:26-50. Epub 2010/09/28.
14. Bennett MI, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. *Pain*. 2012;153:359-65. Epub 2011/11/26.
15. Naleschinski DB, R.; Miaskowski, C. Identification and treatment of neuropathic pain in patients with cancer. . *Pain Clin Updates*. 2012;20:1-5.
16. Peuckmann V, Ekholm O, Rasmussen NK, Groenvold M, Christiansen P, Moller S, Eriksen J, Sjogren P. Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. *European journal of pain (London, England)*. 2009;13:478-85. Epub 2008/07/19.
17. Kim JH, Dougherty PM, Abdi S. Basic science and clinical management of painful and non-painful chemotherapy-related neuropathy. *Gynecologic oncology*. 2015;136:453-9. Epub 2015/01/15.
18. Chen AM, Wang PC, Daly ME, Cui J, Hall WH, Vijayakumar S, Phillips TL, Farwell DG, Purdy JA. Dose--volume modeling of brachial plexus-associated neuropathy after radiation therapy for head-and-neck cancer: findings from a prospective screening protocol.

- International journal of radiation oncology, biology, physics. 2014;88:771-7. Epub 2014/03/13.
19. Couceiro TC, Valenca MM, Raposo MC, Orange FA, Amorim MM. Prevalence of post-mastectomy pain syndrome and associated risk factors: a cross-sectional cohort study. *Pain management nursing : official journal of the American Society of Pain Management Nurses*. 2014;15:731-7. Epub 2013/10/23.
 20. Alves Nogueira Fabro E, Bergmann A, do Amaral ESB, Padula Ribeiro AC, de Souza Abrahao K, da Costa Leite Ferreira MG, de Almeida Dias R, Santos Thuler LC. Post-mastectomy pain syndrome: incidence and risks. *Breast (Edinburgh, Scotland)*. 2012;21:321-5. Epub 2012/03/02.
 21. Burton AW, Fanciullo GJ, Beasley RD, Fisch MJ. Chronic pain in the cancer survivor: a new frontier. *Pain medicine (Malden, Mass)*. 2007;8:189-98. Epub 2007/02/20.
 22. Loukas M, Louis RG, Jr., Wartmann CT. T2 contributions to the brachial plexus. *Neurosurgery*. 2007;60:ONS13-8; discussion ONS8. Epub 2007/02/14.
 23. Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2012;105:273-82. Epub 2012/12/19.
 24. Miaskowski CC, J.; Burney, R.; Coyne, P.; Finley, R.; Foster, R.; Grossman, S.; Janjan, N.; Ray, J.; Syrjala, K.; Weisman, S.; Zahrbock, C. . Guideline for the management of cancer pain in adults and children. Glenview, IL, U.S.A.: American Pain Society; 2005.
 25. Orlik JR, Horwich P, Bartlett C, Trites J, Hart R, Taylor SM. Long-term functional donor site morbidity of the free radial forearm flap in head and neck cancer survivors. *Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale*. 2014;43:1. Epub 2014/01/15.
 26. Kinahan KE, Sharp LK, Seidel K, Leisenring W, Didwania A, Lacouture ME, Stovall M, Haryani A, Robison LL, Krull KR. Scarring, disfigurement, and quality of life in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30:2466-74. Epub 2012/05/23.
 27. Westbury CB, Yarnold JR. Radiation fibrosis--current clinical and therapeutic perspectives. *Clinical oncology (Royal College of Radiologists (Great Britain))*. 2012;24:657-72. Epub 2012/05/23.
 28. Jensen AO, Jacobsen JB, Norgaard M, Yong M, Fryzek JP, Sorensen HT. Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark. *BMC cancer*. 2011;11:29. Epub 2011/01/26.
 29. Kim SJ, Park YD. Effects of complex decongestive physiotherapy on the oedema and the quality of life of lower unilateral lymphoedema following treatment for gynecological cancer. *European journal of cancer care*. 2008;17:463-8. Epub 2008/07/19.
 30. Crosbie J, Kilbreath SL, Dylke E, Refshauge KM, Nicholson LL, Beith JM, Spillane AJ, White K. Effects of mastectomy on shoulder and spinal kinematics during bilateral upper-limb movement. *Physical therapy*. 2010;90:679-92. Epub 2010/03/13.
 31. Caro-Moran E, Diaz-Rodriguez L, Cantarero-Villanueva I, Galiano-Castillo N, Arroyo-Morales M, Fernandez-Lao C. Nerve pressure pain hypersensitivity and upper limb mechanosensitivity in breast cancer survivors: a case-control study. *Pain medicine (Malden, Mass)*. 2014;15:1715-23. Epub 2014/09/23.
 32. Fernandez-Lao C, Cantarero-Villanueva I, Fernandez-de-las-Penas C, Del-Moral-Avila R, Menjon-Beltran S, Arroyo-Morales M. Widespread mechanical pain hypersensitivity as a sign of central sensitization after breast cancer surgery: comparison between mastectomy and lumpectomy. *Pain medicine (Malden, Mass)*. 2011;12:72-8. Epub 2010/12/15.

33. Sanchez-Jimenez A, Cantarero-Villanueva I, Molina-Barea R, Fernandez-Lao C, Galiano-Castillo N, Arroyo-Morales M. Widespread pressure pain hypersensitivity and ultrasound imaging evaluation of abdominal area after colon cancer treatment. *Pain medicine* (Malden, Mass). 2014;15:233-40. Epub 2014/02/15.
34. Fernandez-Lao C, Cantarero-Villanueva I, Fernandez-de-Las-Penas C, Del-Moral-Avila R, Arendt-Nielsen L, Arroyo-Morales M. Myofascial trigger points in neck and shoulder muscles and widespread pressure pain hypersensitivity in patients with postmastectomy pain: evidence of peripheral and central sensitization. *The Clinical journal of pain*. 2010;26:798-806. Epub 2010/09/16.
35. Edwards RR, Mensing G, Cahalan C, Greenbaum S, Narang S, Belfer I, Schreiber KL, Campbell C, Wasan AD, Jamison RN. Alteration in pain modulation in women with persistent pain after lumpectomy: influence of catastrophizing. *Journal of pain and symptom management*. 2013;46:30-42. Epub 2012/10/30.
36. Schreiber KL, Martel MO, Shnol H, Shaffer JR, Greco C, Viray N, Taylor LN, McLaughlin M, Brufsky A, Ahrendt G, Bovbjerg D, Edwards RR, Belfer I. Persistent pain in postmastectomy patients: comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. *Pain*. 2013;154:660-8. Epub 2013/01/08.
37. Vilholm OJ, Cold S, Rasmussen L, Sindrup SH. Sensory function and pain in a population of patients treated for breast cancer. *Acta anaesthesiologica Scandinavica*. 2009;53:800-6. Epub 2009/04/29.
38. Nijs J, Leysen L, Adriaenssens N, Aguilar Ferrandiz ME, Devoogdt N, Tassenoy A, Ickmans K, Goubert D, van Wilgen CP, Wijma AJ, Kuppens K, Hoelen W, Hoelen A, Moloney N, Meeus M. Pain following cancer treatment: Guidelines for the clinical classification of predominant neuropathic, nociceptive and central sensitization pain. *Acta oncologica* (Stockholm, Sweden). 2016:1-5. Epub 2016/05/05.
39. De Groef A, Van Kampen M, Dieltjens E, Christiaens MR, Neven P, Geraerts I, Devoogdt N. Effectiveness of postoperative physical therapy for upper-limb impairments after breast cancer treatment: a systematic review. *Archives of physical medicine and rehabilitation*. 2015;96:1140-53. Epub 2015/01/18.
40. Bennett MI, Bagnall AM, Jose Closs S. How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. *Pain*. 2009;143:192-9. Epub 2009/03/17.
41. Moseley GL, Butler DS. Fifteen Years of Explaining Pain: The Past, Present, and Future. *The journal of pain : official journal of the American Pain Society*. 2015;16:807-13. Epub 2015/06/09.
42. Louw A, Diener I, Butler DS, Puentedura EJ. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Archives of physical medicine and rehabilitation*. 2011;92:2041-56. Epub 2011/12/03.
43. Nijs J, Paul van Wilgen C, Van Oosterwijck J, van Ittersum M, Meeus M. How to explain central sensitization to patients with 'unexplained' chronic musculoskeletal pain: practice guidelines. *Manual therapy*. 2011;16:413-8. Epub 2011/06/03.
44. Van Oosterwijck J, Meeus M, Paul L, De Schryver M, Pascal A, Lambrecht L, Nijs J. Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: a double-blind randomized controlled trial. *The Clinical journal of pain*. 2013;29:873-82. Epub 2013/02/02.
45. Van Oosterwijck J, Nijs J, Meeus M, Truijen S, Craps J, Van den Keybus N, Paul L. Pain neurophysiology education improves cognitions, pain thresholds, and movement performance in people with chronic whiplash: a pilot study. *J Rehabil Res Dev*. 2011;48:43-58. Epub 2011/02/18.

46. Moseley GL. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. *European journal of pain* (London, England). 2004;8:39-45.
47. Moseley GL. Widespread brain activity during an abdominal task markedly reduced after pain physiology education: fMRI evaluation of a single patient with chronic low back pain. *The Australian journal of physiotherapy*. 2005;51:49-52.
48. Moseley GL. Joining forces – combining cognition-targeted motor control training with group or individual pain physiology education: a successful treatment for chronic low back pain. *J Manual Manipulative Ther*. 2003;11:88-94.
49. Moseley GL, Nicholas MK, Hodges PW. A randomized controlled trial of intensive neurophysiology education in chronic low back pain. *The Clinical journal of pain*. 2004;20:324-30.
50. Moseley GL. Combined physiotherapy and education is efficacious for chronic low back pain. *The Australian journal of physiotherapy*. 2002;48:297-302.
51. Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosomatic medicine*. 2005;67:277-80. Epub 2005/03/24.
52. Porter LS, Mishel M, Neelon V, Belyea M, Pisano E, Soo MS. Cortisol levels and responses to mammography screening in breast cancer survivors: a pilot study. *Psychosomatic medicine*. 2003;65:842-8. Epub 2003/09/26.
53. Bower JE, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL. Diurnal cortisol rhythm and fatigue in breast cancer survivors. *Psychoneuroendocrinology*. 2005;30:92-100. Epub 2004/09/11.
54. Caro-Moran E, Fernandez-Lao C, Galiano-Castillo N, Cantarero-Villanueva I, Arroyo-Morales M, Diaz-Rodriguez L. Heart Rate Variability in Breast Cancer Survivors After the First Year of Treatments: A Case-Controlled Study. *Biological research for nursing*. 2015. Epub 2015/01/27.
55. Crosswell AD, Lockwood KG, Ganz PA, Bower JE. Low heart rate variability and cancer-related fatigue in breast cancer survivors. *Psychoneuroendocrinology*. 2014;45:58-66. Epub 2014/05/23.
56. Gidron Y, De Couck M, De Greve J. If you have an active vagus nerve, cancer stage may no longer be important. *Journal of biological regulators and homeostatic agents*. 2014;28:195-201. Epub 2014/07/09.
57. Gidron Y, Perry H, Glennie M. Does the vagus nerve inform the brain about preclinical tumours and modulate them? *The Lancet Oncology*. 2005;6:245-8. Epub 2005/04/07.
58. De Couck M, Nijs J, Gidron Y. You may need a nerve to treat pain: the neurobiological rationale for vagal nerve activation in pain management. *The Clinical journal of pain*. 2014;30:1099-105. Epub 2014/01/24.
59. Khasar SG, Burkham J, Dina OA, Brown AS, Bogen O, Alessandri-Haber N, Green PG, Reichling DB, Levine JD. Stress induces a switch of intracellular signaling in sensory neurons in a model of generalized pain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2008;28:5721-30. Epub 2008/05/30.
60. Quintero L, Moreno M, Avila C, Arcaya J, Maixner W, Suarez-Roca H. Long-lasting delayed hyperalgesia after subchronic swim stress. *Pharmacol Biochem Behav*. 2000;67:449-58. Epub 2001/02/13.
61. Quintero L, Cardenas R, Suarez-Roca H. Stress-induced hyperalgesia is associated with a reduced and delayed GABA inhibitory control that enhances post-synaptic NMDA receptor activation in the spinal cord. *Pain*. 2011;152:1909-22. Epub 2011/06/04.

62. Quintero L, Cuesta MC, Silva JA, Arcaya JL, Pinerua-Suhaibar L, Maixner W, Suarez-Roca H. Repeated swim stress increases pain-induced expression of c-Fos in the rat lumbar cord. *Brain Res.* 2003;965:259-68. Epub 2003/02/20.
63. Suarez-Roca H, Leal L, Silva JA, Pinerua-Shuhaibar L, Quintero L. Reduced GABA neurotransmission underlies hyperalgesia induced by repeated forced swimming stress. *Behav Brain Res.* 2008;189:159-69. Epub 2008/02/08.
64. Martenson ME, Cetas JS, Heinricher MM. A possible neural basis for stress-induced hyperalgesia. *Pain.* 2009;142:236-44. Epub 2009/02/24.
65. McLean SA, Clauw DJ, Abelson JL, Liberzon I. The development of persistent pain and psychological morbidity after motor vehicle collision: Integrating the potential role of stress response systems into a biopsychosocial model. *Psychosomatic medicine.* 2005;67:783-90.
66. Stagl JM, Bouchard LC, Lechner SC, Blomberg BB, Gudenkauf LM, Jutagir DR, Gluck S, Derhagopian RP, Carver CS, Antoni MH. Long-term psychological benefits of cognitive-behavioral stress management for women with breast cancer: 11-year follow-up of a randomized controlled trial. *Cancer.* 2015;121:1873-81. Epub 2015/03/27.
67. Phillips KM, Antoni MH, Lechner SC, Blomberg BB, Llabre MM, Avisar E, Gluck S, DerHagopian R, Carver CS. Stress management intervention reduces serum cortisol and increases relaxation during treatment for nonmetastatic breast cancer. *Psychosomatic medicine.* 2008;70:1044-9. Epub 2008/10/10.
68. Carlson LE, Tamagawa R, Stephen J, Doll R, Faris P, Dirkse D, Specia M. Tailoring mind-body therapies to individual needs: patients' program preference and psychological traits as moderators of the effects of mindfulness-based cancer recovery and supportive-expressive therapy in distressed breast cancer survivors. *Journal of the National Cancer Institute Monographs.* 2014;2014:308-14. Epub 2015/03/10.
69. Zernicke KA, Campbell TS, Specia M, McCabe-Ruff K, Flowers S, Carlson LE. A randomized wait-list controlled trial of feasibility and efficacy of an online mindfulness-based cancer recovery program: the eTherapy for cancer applying mindfulness trial. *Psychosomatic medicine.* 2014;76:257-67. Epub 2014/05/09.
70. Gelaye B, Kajeepeta S, Zhong QY, Borba CP, Rondon MB, Sanchez SE, Henderson DC, Williams MA. Childhood abuse is associated with stress-related sleep disturbance and poor sleep quality in pregnancy. *Sleep medicine.* 2015;16:1274-80. Epub 2015/10/03.
71. Sawah MA, Ruffin N, Rimawi M, Concerto C, Aguglia E, Chusid E, Infortuna C, Battaglia F. Perceived Stress and Coffee and Energy Drink Consumption Predict Poor Sleep Quality in Podiatric Medical Students A Cross-sectional Study. *Journal of the American Podiatric Medical Association.* 2015;105:429-34. Epub 2015/10/03.
72. Fang R, Li X. A regular yoga intervention for staff nurse sleep quality and work stress: a randomised controlled trial. *Journal of clinical nursing.* 2015. Epub 2015/10/20.
73. Halpern J, Cohen M, Kennedy G, Reece J, Cahan C, Baharav A. Yoga for improving sleep quality and quality of life for older adults. *Alternative therapies in health and medicine.* 2014;20:37-46. Epub 2014/04/24.
74. Davis MP, Goforth HW. Long-term and short-term effects of insomnia in cancer and effective interventions. *Cancer journal (Sudbury, Mass).* 2014;20:330-44. Epub 2014/10/10.
75. Taylor TR, Huntley ED, Makambi K, Sween J, Adams-Campbell LL, Frederick W, Mellman TA. Understanding sleep disturbances in African-American breast cancer survivors: a pilot study. *Psycho-oncology.* 2012;21:896-902. Epub 2011/06/08.
76. Zhou ES, Manley PE, Marcus KJ, Recklitis CJ. Medical and Psychosocial Correlates of Insomnia Symptoms in Adult Survivors of Pediatric Brain Tumors. *Journal of pediatric psychology.* 2015. Epub 2015/08/16.

77. Zhou ES, Recklitis CJ. Insomnia in adult survivors of childhood cancer: a report from project REACH. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2014;22:3061-9. Epub 2014/06/18.
78. Ferreira VT, Dibai-Filho AV, Kelly de Oliveira A, Gomes CA, Melo ES, Maria de Almeida A. Assessing the impact of pain on the life of breast cancer survivors using the Brief Pain Inventory. Journal of physical therapy science. 2015;27:1361-3. Epub 2015/07/15.
79. Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. Best practice & research Clinical endocrinology & metabolism. 2010;24:775-84. Epub 2010/11/30.
80. Haack M, Lee E, Cohen DA, Mullington JM. Activation of the prostaglandin system in response to sleep loss in healthy humans: potential mediator of increased spontaneous pain. Pain. 2009;145:136-41. Epub 2009/06/30.
81. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. Sleep. 2007;30:1145-52. Epub 2007/10/04.
82. Wisor JP, Schmidt MA, Clegern WC. Cerebral microglia mediate sleep/wake and neuroinflammatory effects of methamphetamine. Brain, behavior, and immunity. 2011;25:767-76. Epub 2011/02/22.
83. Pollmacher T, Haack M, Schuld A, Reichenberg A, Yirmiya R. Low levels of circulating inflammatory cytokines--do they affect human brain functions? Brain, behavior, and immunity. 2002;16:525-32. Epub 2002/10/29.
84. Wodarski R, Schuh-Hofer S, Yurek DA, Wafford KA, Gilmour G, Treede RD, Kennedy JD. Development and pharmacological characterization of a model of sleep disruption-induced hypersensitivity in the rat. European journal of pain (London, England). 2015;19:554-66. Epub 2014/09/10.
85. Schuh-Hofer S, Wodarski R, Pfau DB, Caspani O, Magerl W, Kennedy JD, Treede RD. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. Pain. 2013;154:1613-21. Epub 2013/05/28.
86. Johnson JA, Rash JA, Campbell TS, Savard J, Gehrman PR, Perlis M, Carlson LE, Garland SN. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors. Sleep medicine reviews. 2015;27:20-8. Epub 2015/10/06.
87. Ritterband LM, Bailey ET, Thorndike FP, Lord HR, Farrell-Carnahan L, Baum LD. Initial evaluation of an Internet intervention to improve the sleep of cancer survivors with insomnia. Psycho-oncology. 2012;21:695-705. Epub 2011/05/04.
88. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC, Snyder C. Exercise interventions on health-related quality of life for cancer survivors. The Cochrane database of systematic reviews. 2012;8:CD007566. Epub 2012/08/17.
89. Zeng Y, Huang M, Cheng AS, Zhou Y, So WK. Meta-analysis of the effects of exercise intervention on quality of life in breast cancer survivors. Breast cancer (Tokyo, Japan). 2014;21:262-74. Epub 2014/02/27.
90. Bourke L, Boorjian SA, Briganti A, Klotz L, Mucci L, Resnick MJ, Rosario DJ, Skolarus TA, Penson DF. Survivorship and Improving Quality of Life in Men with Prostate Cancer. European urology. 2015;68:374-83. Epub 2015/05/06.
91. Mishra SI, Scherer RW, Snyder C, Geigle P, Gotay C. Are exercise programs effective for improving health-related quality of life among cancer survivors? A systematic review and meta-analysis. Oncology nursing forum. 2014;41:E326-42. Epub 2014/10/31.

92. Nijs J, Kosek E, Van Oosterwijck J, Meeus M. Dysfunctional endogenous analgesia during exercise in patients with chronic pain: to exercise or not to exercise? *Pain physician*. 2012;15:ES205-13. Epub 2012/07/20.
93. Irwin ML, Cartmel B, Gross CP, Ercolano E, Li F, Yao X, Fiellin M, Capozza S, Rothbard M, Zhou Y, Harrigan M, Sanft T, Schmitz K, Neogi T, Hershman D, Ligibel J. Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33:1104-11. Epub 2014/12/03.
94. Franik S, Kremer JA, Nelen WL, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. *The Cochrane database of systematic reviews*. 2014;2:CD010287. Epub 2014/02/25.
95. John-Baptiste AA, Wu W, Rochon P, Anderson GM, Bell CM. A systematic review and methodological evaluation of published cost-effectiveness analyses of aromatase inhibitors versus tamoxifen in early stage breast cancer. *PloS one*. 2013;8:e62614. Epub 2013/05/15.
96. Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L. Hormonal therapies for early breast cancer: systematic review and economic evaluation. *Health technology assessment (Winchester, England)*. 2007;11:iii-iv, ix-xi, 1-134. Epub 2007/07/06.
97. Ennour-Idrissi K, Maunsell E, Diorio C. Effect of physical activity on sex hormones in women: a systematic review and meta-analysis of randomized controlled trials. *Breast cancer research : BCR*. 2015;17:139. Epub 2015/11/07.
98. Peppone LJ, Janelins MC, Kamen C, Mohile SG, Sprod LK, Gewandter JS, Kirshner JJ, Gaur R, Ruzich J, Esparaz BT, Mustian KM. The effect of YOCAS(c)((R)) yoga for musculoskeletal symptoms among breast cancer survivors on hormonal therapy. *Breast cancer research and treatment*. 2015;150:597-604. Epub 2015/03/31.
99. Fusi C, Materazzi S, Benemei S, Coppi E, Trevisan G, Marone IM, Minocci D, De Logu F, Tuccinardi T, Di Tommaso MR, Susini T, Moneti G, Pieraccini G, Geppetti P, Nassini R. Steroidal and non-steroidal third-generation aromatase inhibitors induce pain-like symptoms via TRPA1. *Nature communications*. 2014;5:5736. Epub 2014/12/09.
100. Pertovaara A, Koivisto A. TRPA1 ion channel in the spinal dorsal horn as a therapeutic target in central pain hypersensitivity and cutaneous neurogenic inflammation. *Eur J Pharmacol*. 2011;666:1-4. Epub 2011/06/07.
101. Cantarero-Villanueva I, Fernandez-Lao C, Fernandez-de-Las-Penas C, Lopez-Barajas IB, Del-Moral-Avila R, de la-Llave-Rincon AI, Arroyo-Morales M. Effectiveness of water physical therapy on pain, pressure pain sensitivity, and myofascial trigger points in breast cancer survivors: a randomized, controlled clinical trial. *Pain medicine (Malden, Mass)*. 2012;13:1509-19. Epub 2012/09/11.
102. Cantarero-Villanueva I, Fernandez-Lao C, Caro-Moran E, Morillas-Ruiz J, Galiano-Castillo N, Diaz-Rodriguez L, Arroyo-Morales M. Aquatic exercise in a chest-high pool for hormone therapy-induced arthralgia in breast cancer survivors: a pragmatic controlled trial. *Clinical Rehabilitation*. 2013;27:123-32.
103. Nijs J, Meeus M, Cagnie B, Roussel NA, Dolphens M, Van Oosterwijck J, Danneels L. A modern neuroscience approach to chronic spinal pain: combining pain neuroscience education with cognition-targeted motor control training. *Physical therapy*. 2014;94:730-8. Epub 2014/02/01.
104. Nijs J, Lluch Girbes E, Lundberg M, Malfliet A, Sterling M. Exercise therapy for chronic musculoskeletal pain: Innovation by altering pain memories. *Manual therapy*. 2015;20:216-20. Epub 2014/08/06.

Table 1: Key messages

1. Pain is often ignored in the field of oncology, but pain is very common and debilitating in cancer survivors.
2. Implementation of pain neuroscience in rehabilitation practice has gained little attention in the field of oncology.
3. Pain education is effective for improving cancer pain; implementation of contemporary pain neuroscience into the educational program seems warranted.
4. The dysfunctional stress response as seen in some patients following cancer treatment may relate to pain (increases), provides a theoretical basis for implementing stress management into the treatment of pain in this population.
5. Various types of stress management are effective for treating patients following cancer treatment.
6. Poor sleep is common in patients following cancer treatment, and rehabilitation specialists can address this by providing exercise therapy, sleep hygiene and/or cognitive behavioural therapy.
7. Exercise therapy is effective for decreasing pain in patients following cancer treatment, including the treatment of pain as a common side effect of hormone treatments for breast cancer survivors.

Table 2: Research agenda

Hypotheses

- 1.** Pain neuroscience education is more effective than standard pain education for decreasing pain and improving pain cognitions/beliefs in patients following cancer treatment.
- 2.** The dysfunctional stress response as seen in some patients following cancer treatment relates to pain (increases) and the hyperexcitability of the central nervous system.
- 3.** Stress management is effective for decreasing pain and the hyperexcitability of the central nervous system in patients following cancer treatment.
- 4.** Specific conservative treatment for improving sleep in cancer survivors will not only result in sleep improvements, but also in decreased hyperexcitability of the central nervous system and decreased pain severity.
- 5.** Exercise therapy is effective in improving endogenous analgesia and the physiological stress response systems in patients following cancer treatment.