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Chronic Persistent Pain and Health Related Quality of Life in Breast Cancer Survivors: Current Concepts and Future Directions

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Abstract

Breast cancer is a major cause of physical and mental disturbances in women. Cancer and its treatment, exert not only a serious physical as well as mental toll on the body but also may leave behind permanent painful reminders of their presence. With improved medical diagnostic, treatment methodology as well as broad cancer research, health practitioners provide better cancer management with enhanced lifestyle in breast cancer patients and breast cancer survivors. The prevalence rate of chronic neuropathic pain following breast cancer surgery may exceed 50% and with an increase in life expectancy of BCS, providing adequate pain relief is of paramount importance to improve their quality of life. A large number of risk factors associated to predispose to chronic postsurgical pain. The severity of post-surgical pain also varies on the type of surgery performed. All treatment methodology like radiotherapy, chemotherapy, and surgery etc. have their own associate complications and intensity of pain during treatment, even after treatment. The genetic makeup of patients also influences the pain occurrence and pain intensity, as well as the efficacy of treatment methodology. Intensive cancer research and pharmacokinetic studies open personalized treatment methodology based on their genetic constituents, as well as their interaction with the environment to the most effective treatment methodology and pain management during treatment or post-treatment till her life. A comprehensive association of drug, therapy, surgery, and their genetic polymorphism will guide the suitable treatment methodology for the better management of pain and life quality.

Keywords: Breast cancer, Breast cancer survivor, Chronic pain, Pain management, Life quality.

Introduction

Breast cancer is one of the frequently encountered cancer affecting women globally. Cancer itself and its treatment broadly speaking, exert not only a heavy physical as well as mental toll on the body, but also may leave behind permanent reminders of their presence, with "chronic pain" being the commonest and most dreadful sequelae. Women may encounter pain at any stage of cancer as well as during treatment. As a consequence of advancement in medical research, diagnostics and improved health care system, a 10-year survival rate of breast cancer survivors (BCS) in the most developed nations, has been reported to be as high as 83% [1,2]. It was also reported that these patients have a poor health related quality of life (HRQOL) for multiple reasons [3]. Saxena et al [4] , published a review way back in 2007, which reflected that the prevalence rate of chronic neuropathic pain following breast cancer surgery may exceed 50% and with an increase in life expectancy of BCS, providing adequate pain relief is of paramount importance to improve their quality of life. According to a recent meta-analysis concluded for questionnaire data, Emra Ilhan concluded that, the pooled prevalence of neuropathic pain among BCS was 32.6% - 58.2 % and for Neuropathic Pain Special Interest group criteria reported prevalence rates were 29.5% to 57.1%.

Our population is continuously expanding and this is coupled with an increase in the number of women surviving breast cancer because of advance in health sector. Pain during or after breast cancer treatment can be temporary, which fades away with time or for some people will develop into chronic persistent pain either during or immediately after cessation of treatment or even months or years after treatment. Chronic pain is due to a de-arrangement occurring within the nervous system, classically a stimulus instigating a process of emanating from a peripheral damage or nociceptive, mechanical or inflammatory, neural damage or neuropathy.

Breast cancer itself leads to serious sequelae on HRQOL. There are major psychological, psychosocial, emotional and physical effects among BCS since diagnosis, to throughout the treatment course and also immediately or years after cessation of treatment. This significantly impacts daily life adversely and is proven to be detrimental to the HRQOL of BCS. Recently, Enien et al [5] observed globally a lower quality of life among BCS .Also, Aguiar et al [6] demonstrated a significant poor HRQOL among the females surviving breast cancer while, Weaver et al [7] reported in another study the physical and mental HRQOL among BCS as poor as 24.5% and 10.1% respectively. In an interesting study, Foley et al [8] emphasize on increased attention that needs to be focused on augmentation of the quality of life of BCS and targeting towards improvement in physical function, mental health and social support.

In a very recent study, Cox-Martin et al [9] concluded with a sample size of 1702 cancer survivors, who had already completed therapy, that chronic pain among cancer survivors is inversely related to HRQOL. Another systemic literature search involving 52 females BCS by Armoogum et al, [10] observed that chronic persistent pain is intrinsically interlinked with the women's perception of cancer and also, added that these BCS did not get enough support. In a recent survey involving 1,488 young adult cancer survivors(YACSs), it was concluded that a large percentage of long term YACSs do not actually fulfill the criteria for life style modifications guidelines for physical

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activities [11].

Persistent pain after breast cancer treatment (PPBCT) is potentially a debilitating problem among BCS with prevalence as high as 50% as reported by Hofso et al [12] and Burton et al [13]. More recently, Wang et al [14] reported that 25% to 60% of patients surviving after breast cancer surgery continue to suffer from persistent post-surgical pain. Many other researchers also supported and published data stating that a large majority of breast cancer patients continue to experience post-surgical pain [15-20]. It was also reported by clinicians that these patients have reduced quality of life.[21-24]

Recently, Hamood et al [25] conducted a study, with the purpose to investigate the prevalence and risk factors associated with self-reported chronic pain and symptoms related to breast cancer or its treatment. In their cross-sectional study, among a total of 410 women who survived breast cancer, 305 women (i.e., 74%) with a median of 7.4 years after diagnosis complained of chronic pain. Other symptoms commonly reported among BCS, were namely paresthesia (63%), allodynia (48%) and phantom sensation (15%). Chronic pain alone or along with other symptoms was observed to be significantly associated with poorer quality of life. Jensen et al [26] concluded that improved pain management among BCS would result in a better quality of life. The findings of their study among the females with a history of breast cancer on the active patients list of Seatle Cancer Care Alliance Women's Wellness Follow Up Clinic reported that chronic pain is the most frequent problem encountered in BCS. They also found a positive association between intensity of pain and quality of life, patients with severe pain having poor HRQOL.

Van den Beuken et al [27] conducted a systematic review of past 40 years among cancer patients and reported in 2007 that the pooled prevalence of pain is more than 50%.However, in 2016 same group of authors, Van den Beuken et al [28] conducted a systematic review meta-analysis and updated the earlier study, with the comment that the prevalence rate of pain among cancer survivors were 39.3% after curative cancer treatment, while 55.0% during ongoing treatment and 66.4% in case of advanced or metastatic stage of cancer.

Thus, despite increased advancements in research and health care facilities on assessment and management of cancer, chronic pain still continues to be a major troublesome symptom among BCS. The main purpose of this review article is to examine and update on prevalence of chronic persistent pain in BCS and to delineate the risk factors involved in the underlying mechanism for development of chronic persistent pain. Moreover, this review article will cover up the management of Persistent Pain after Breast Cancer Treatment (PPBCT), Post Mastectomy Pain Syndrome (PMPS), Chemotherapy Induced Neuropathic Pain (CINeP) and Radiation Induced Neuropathic Pain (RINeP). (Table 1) shows the frequently encountered chronic persistent pain syndromes observed in Breast Cancer Survivors.

Characteristics of chronic persistent pain among breast cancersurvivors

BCS experience many symptoms and problems during their treatment course, which may even persist for months and years after the treatment, resulting in poorer HRQOL. In an interesting study by Smith et al [19] common cancer treatment related effects observed were upper extremity lymphedema, cognitive impairment, depression, fatigue, pain, sleep disturbance, nausea, vomiting, bone loss, fractures and also cardiotoxicity, responsible for compromising patient's daily routine, regular activities and quality of life in BCS. Among all the common symptoms in BCS, chronic PPBCT is a potentially the most debilitating problem among BCS.

Post-mastectomy pain syndrome (PMPS), by definition is the chronic pain experienced after breast surgery and is typically neuropathic in nature. It was first reported in 1970, characterized by a dull aching pain and burning sensation confined to anterior chest wall and radiating to arm and gets exacerbated on movement. [29] Recently, Belfer et al [30] conducted a cross-sectional cohort study and reported that out of 611 total patients who were included in the study, one third i.e. 32.5% complained of PMPS of severity of more than 3/10 on NRS-pain. [28] The exact cause of PMPS remain unknown, but various proposed etiological theories include surgical dissection of ipsilateral inter-costo-brachial nerve, damage to axillary nerve or possible formation of neuroma. [15] The typical character of pain in PMPS was assessed and reported as neuropathic in nature having numbness, burning, stabbing or pins and needle sensation. [31] Also, there are different type of sensory disturbances like allodynia, hyperalgesia, burning and sensory loss which may occur associated as a sequel to the surgical procedures.[32]

The IASP (International Association for Study of Pain) defines persistent post-surgical pain as the pain that develops after surgery and persists at least 2 months.[14] According to IASP Taxonomy, that when pain is associated with cancer, 3 months is too long to wait before considering pain as chronic.[33] However, recently IASP task force has drawn a consensus to define the period as 3 months for referring to it as chronic pain, which is consistent with the definition of chronicity in other types of chronic pain, that is the pain persistent beyond the normal healing time of 3 months.[34]

Macrae et al [35] proposed a better four-point definition for Chronic Post-Surgical Pain (CPSP) as: (1) the pain which has developed as a consequence of a surgery, (2) a duration of at least 2 months, (3) no other explanation exists for the pain and (4) the pain is not a continuation of a pre-existing chronic pain condition for which the surgery was performed.Furthermore, in 2012, Peuckmann et al [36] observed in a survey conducted in Denmark, that radiotherapy and younger age group are risk factors for developing PPBCT. Anderson et al [17] also published a critical review pointing out radiation therapy and nerve damage as significant risk factors for development of chronic pain among BCS.

Table 1: Frequently encountered chronic persistent pain syndromes observed in Breast Cancer Survivors.

a	Post-SurgicalPain Syndromes	Post- Surgical scar pain with primary and secondary hyperalgesia Chronic Post-Surgical Pain (CPSP) or Chronic Persistent Post Surgical Pain (CPPP). Post Mastectomy Pain Syndrome (CMPS)
b	Post Radiation related Chronic Pain Syndromes(PRCP)	Radiation- induced Neuropathic Pain Radiation-induced Brachial Pain OTHER PRCP: post radiation peripheral nerve entrapment, radiculopathy, myelopathy, nancardiac chest pain, pelvic pain, osteonecrosis and pain. Due to pelvic insufficiency fracture, enteritis orabdominal visceral pain.
c	Post Chemotherapy related Chronic Pain syndrome	Chemotherapy-induced peripheral neuropathy (CIPN)

There is absence of an exact global data of PPBCT because of lack of its recognition. The incidence of PPBCT is underestimated, as there are multiple barriers that interfere with patients reporting to their physicians with pain. Onset or occurrence of pain during treatment brings along high degree of anxiety among BCS of cancer recurrence. [37] One of the major barriers still lack of awareness and the belief that "pain is inevitable". Peretti-Watel et al [38] conducted an interesting interview based survey among breast cancer survivors in French women, and observed 50% of cancer survivors suffer from chronic pain. Chronic persistent pain among BCS lead to distress, fatigue, reduced appetite, insomnia, irritability, depression subsequently responsible for a poor quality of life. It was concluded in a questionnaire-based study, that pain is necessary on the "road to recovery" and one should learn to "live with it only", though we are aware that this s a myth. Women learn to deal with pain by taking precautions, avoiding certain activities and thus, limiting their routine daily chores. This eventually leads to other psychosocial problems namely depression. Depression is not just a symptom but can lead to life-threatening situation, as patients with severe depression also get suicidal tendencies.

The International classification of diseases defines persistent post-operative pain as the pain having greater intensity or different character than preoperative pain and is a continuation of post-operative pain. [39] Persistent pain among BCS (PPBCS) may also develop after or during chemotherapy because of chemotherapy-induced peripheral neuropathy (CIPN), after or during radiotherapy due to radiation induced peripheral neuropathy (RIPN), hormone therapy, or stem-cell transplantation, with an overall prevalence of approximately 30% [40].

Thus, in order to benefit the BCS and improve their quality of life, we need to address pain systematically from the preoperative to postoperative period for those undergoing surgery for breast cancer. Clinicians must also, provide pain relief throughout the ongoing treatment period and also, must follow up and must essentially provide pain alleviation remedies months to years after cessation of treatment.

Epidemiology and risk factors of chronic pain among breast cancer survivors

Various studies have been conducted in the past as regard to prevalence of pain among BCS, and reported a prevalence of chronic pain in BCS from 25% to 60%. Moreover, a large number of risk factors have also been reported to predispose to chronic postsurgical pain [14-15]. Peuckmann and colleagues [36] in their comprehensive survey reported the prevalence rate of chronic pain as 42% among BCS. Also, Seigel et al[41]reported that out 226,870 women diagnosed with breast cancer almost all required surgery as a preliminary treatment, thus raising our concerns for PPBCS. In another study, conducted by Gartner et al [32] incidence of PPBCS after breast cancer treatment was also 25-60%.In a very recent observation study, published in 2020, of 261 female BCS, Divella et al [42] observed that, among the risk factors surgical complications and weight of the excised breast tissue were two of the important risk factors for development of chronic neuropathic pain among BCS.

It was concluded by Wang et al [14] that there exist a high quality evidence to support a strong association of younger age, radiotherapy, Axillary Lymph Node Dissection (ALND), presence of pre-operative pain and acute post-operative pain with persistent pain after breast surgery. However, ALND has the strongest association for development of persistent pain, with a risk of 21% of developing persistent post-surgical pain and the type of surgery namely, breast conserving surgery, simple mastectomy or modified radical mastectomy were not strong predictive factors. Also, according to this meta-analysis study Body Mass Index (BMI), Chemotherapy, Endocrine or hormonal therapy were found not to be strongly associated with development of chronic pain [14]. As mentioned in initial part of this review, Gartner et al [32] reported 74% as prevalence of chronic pain among BCS, they also observed a positive association of persistent pain with mastectomy, radiotherapy, stage of cancer at diagnosis and inverse correlation with age.

Fabro et al [43] recently conducted a prospective cohort study on women undergoing surgery for breast cancer treatment and reported that the incidence of pain syndrome was 52%. They also reported that younger age group women (<40 years) and those who underwent ALND (>15 lymph nodes excision) are at greater risk of developing chronic pain after surgery. Macdonald et al [31] reported after conducting a questionnaire-based cohort study among 175 women who complained of PMPS that the cumulative prevalence of PMPS at a mean of 9 years post operatively was 52%. Also, there was a statistically significant lower quality of life score (SF -36), reflecting a poorer quality of life among BCS.

The severity of post-surgical pain varies depending on the type of surgery performed [32]. A survey was conducted by Gartner and colleagues [32] enrolling 3,754 women, between 18-70 years. Among them, a total of 47% patients reported pain in one or more areas, 13% reported severe pain of score 8-10/10, 59% had moderate pain of score 4-7/10 and 48% had mild pain of 1-3/10. Among the women who complaint of severe pain, 77% of them experienced pain daily while 36% of women had mild pain daily. PPBCS is a different pain from other chronic post-surgical pain syndromes, because it is typically localised to a particular area. The frequently reported area is over the breast or anterior chest wall (86%) followed by ipsilateral axilla (63%), then arm (57%) and same side of body (56%) [32].

Jung et al [15] reported that one of the risk factors for persistent pain among breast cancer was adjuvant chemotherapy and radiotherapy. The estimated possible risk of painful neuroma formation after breast cancer surgery was 23-49%. The main risk factors for prevalence of pain in breast cancer survivors include age of less than 40 years, preoperative breast pain, psychological status, intensity of acute post-operative pain [44-45]. This is in contrast to a more recent study conducted by Juhl et al [46] who reported that younger age was not an associated risk factor for development of PPBCT. However, growing evidences support that, younger women have increasedlevel of anxiety, offered more aggressive adjuvant treatment and thus a lower tolerance of pain. According to a cohort study by Smith et al [47] radiation therapy was reported to be significantly associated with development of post mastectomy pain syndrome.

Juhl et al [46] enrolled 305 women who underwent a unilateral mastectomy between 2009-2013 and were evaluated for prevalence, location, intensity and frequency of pain at surgical site. They found that 38.3% presented with persistent pain at one area. More frequently complained area of pain being axilla followed by surgical site of excised breast, medial arm, thorax and scar area, supporting previously available data. Among the women who complained of pain, 26% reported pain over one area while 74% reported over more than one area. The average pain intensity 4.7+2-3/10 on NRS pain scoring scale 34% complained of mild pain (1-3/10 NRS), 50% complained of moderate pain then 16% complained of severe pain (8-10/10 NRS). Of all women, who complained of post-operative pain, 58% experienced pain every day [46]. In this particular study, an interesting finding noted was that out of 100 patients who reported pain, 13% had a high enough PDQ (Pain Detect Questionnaire) score, to indicate a likely

neuropathic pain, while 16% scored in an ambiguous range and 71% scored low on PDQ scale indicating nociceptive type of pain. These authors also reported the factors that seem to be associated with PPBCT significantly were BMI > 30 kg/m2, patients receiving radiation therapy and patients who underwent ALND. There was a significant association observed between dysesthesia and PPBCT. Moreover, 16% of women experienced phantom breast sensation, and out of which 5% reported phantom breast pain [46].

However, 9.3% patients had preoperative breast pain which was not found significantly associated with PPBCT. On the other hand, various researchers observed that, PPBCT was often reported by some patients as burning, shooting, stabbing in nature indicating neuropathic pain [15,31,46,48]. Hence, there observation was contradictory to less neuropathic component reported by Juhl et al. [46]. This was explained by Juhl et al, as there was a significant difference among the study populations. Julh et al, also observed pain among BCS patients, there is a highly significant positive correlation between higher pain intensity and the neuropathic pain score.

In an attempt to provide a data on prevalence rate of neuropathic pain in postoperative breast cancer survivors, Bokhari et al [49] conducted a prospective, quantitative and longitudinal pilot survey and reported that 23% of patients developed neuropathic pain following breast cancer surgery. Patients of age less than 50 years, undergoing extensive and invasive surgery, complaining of acute postoperative pain and inadequate use of analgesics during immediate acute postoperative period are the potential risk factors for development of chronic persistent post-surgical pain among BCS. These observations were further corroborated by the study of Gartner et al [32] who reported that, the major risk factors associated with chronic post-surgical pain after breast surgery includes–young age (18-39 years), adjuvant radiotherapy more than chemotherapy and axillary lymph node dissection (ALND) more than sentinel lymph node dissection (SLND).

In 1996, a study specifically demonstrated pain after breast reconstruction surgery was conducted, by Wallace et al. [50] Women who had breast implants had a higher prevalence of postoperative pain (53%) than those who didn't have implants for breast reconstruction or underwent mastectomy without reconstruction.

Vilholm et al [51] observed women who complained of PPBCT, and noted that they also had a higher thermal detection threshold, increased frequency of cold allodynia and an increase in temporal pain summation evoked by multiple pin pricks. Gutrup et al [52] demonstrated that patients with PPBCT had increased frequency of temporal pain summation at operated site. Thus, both indicating a role of "neuropathic pain" in the overall mechanism of PPBCT.

Hormonal disturbances also contribute to development of breast cancer and thus, hormonal replacements remain one of the treatment strategies for breast cancer. Hormonal therapy is also associated with chronic pain, namely involving the musculoskeletal system. Aromatase Inhibitor (AI) are commonly responsible for arthralgia, that can lead to painful mobility restrictions and limiting daily activities [53]. AI such as Anastrazole, Letrozole and Exemestane have shown promising results in limiting breast cancer, thus are part of standard adjuvant endocrine therapy [54].

Din et al [55]reviewed the incidence of any musculoskeletal symptoms in clinical trials of hormonal adjuvants and reported women on AIs have higher rates of incidence of arthralgia than with Tamoxifen. Crew et al [56]reported among patients on AIs experience stiffness, bodyaches or symmetric pain of hands, arms, knees, feet [56,57]. They may also develop tenosynovial changes like fluid in tendon sheet, increasing tendon thickness or even carpal tunnel syndrome [58-60]. Robidoux et al conducted a prospective pilot study among post-menopausal breast cancer patients on AI and observed 67% patient showed no symptoms of pain, 17% experienced low to moderate pain at base line which did not increase with AI treatment. Thus, assessment of muscular skeletal pain at baseline and prompt intervention may help optimize health related HRQOL. Also gene expression profile in peripheral blood need to be further explored on a larger scale study in order to stratify markers to identify patients at high risk of developing arthralgia [61].

These studies reflect high incidence and prevalence of postoperative pain among breast cancer survivors and those undergoing ongoing treatment. Pain varies from mild to severe and results in a poor health related quality of life. To sum up, significant predictors of chronic pain and poor HRQOL among BCS being younger age, BMI>30kg/m2, extensive surgery, radiotherapy, lack of awareness, time since operation, breast implants and ALND more than SLND. The common risk factor for development of chronic persistent pain among BCS is listed in (Table 2).

We need to draw a more scrupulous attention towards identification and treatment of pain among BCS in order to improve their quality and standard of life.

Mechanism of chronic post-surgical pain among breast cancer survivors

There are multiple factors responsible for PPBCT. Breast cancer treatment option includes various types of surgical intervention for example-mastectomy, lumpectomy, sentinel lymph node biopsy and axillary lymph node dissection and adjuvant therapies like chemotherapy, radiotherapy as well as hormonal or endocrine therapy. The exact mechanism of persistent pain remains unclear. Multiple surveys and genetic studies have been conducted to elucidate the mechanism of generation of persistent pain post-operatively.

Saxena et al [62] concluded in a follow up observational study among females undergoing staging laparotomy for ovarian carcinoma that 90.5%, 38.1% and 38.1% of patients had moderate pain at 30th, 60th and 90th day post operatively respectively. They concluded, 38.1% incidence of chronic persistent post-surgical pain (CPPP). The functional status and quality of life of these women was significantly reduced.

Kehlet et al [16] in 2006 asserted in a review that postsurgical pain is due to ongoing inflammation or surgical injury to major nerves resulting in neuropathic pain [13]. The pathophysiology of CPPP can be based on peripheral and central neuro-plastic changes that arises as a result of damage and injury to tissue or nerve. The surgical procedure like mastectomy itself or along with ALND/SLND may lead severe inter-costo-brachial nerve and thoracic intercostal nerve damage. This

Table 2: Frequently encountered chronic persistent pain syndromes observed in Breast Cancer Survivors

1. Young age (18-39 years),
2. BMI › 30Kg/m^2 ,
3. Heavy breast,
4. Extensive dissection/ invasive surgery,
5. Adjuvant chemotherapy (CIPN),
6. Axillary Lymph Node Dissection,
7. Breast implants.

Survivor

gives an impression that PPBCT is of neuropathic in origin [15]. In the neuropathic pain there is the plasticity of the nervous system which is responsible for pain without any painful stimuli, thus spontaneous pain or allodynia (i.e, pain caused by non-painful stimuli) or hyperalgesia (i.e, increased sensation of pain from a mild painful stimuli).

It is known that pain is a psychological experience and factors like nociceptive, inflammatory and neuropathic may be involved in its generation. It is well established fact that inflammation and nerve injury lead to long term synaptic plasticity which generally multiplies and maintains the pain signalling and the phenomenon is referred as pain sensitization. After surgery, pain sensitization occurs, which causes an increase in post-operative pain through expression of wound hyperalgesia and thus, considered as an important factor for development of CPPP [63]. Therefore, analgesic treatment must focus on drugs or procedures to produce pain desensitization.

The process of transition of acute post-operative pain is complex and involves multiple factors like biological, psychological and socioeconomic factors. In the primary efferent sensory neurons of dorsal root ganglion (DRG), there are nociceptive inputs because of surgery producing a local molecular change such as release of nerve growth factors (NGF) and cytokines. These influence tissue remodelling, wound healing and reinnervation [64]. NGF acts through its receptor tropomyosin kinase, an activating mitogen–activated protein kinase p38 in DRG, resulting in an increased expression of cation channels in the free nerve endings making it hyper sensitive.[65] Other factors like cytokines mostly interleukin–1ß and chemokines are responsible for the incision pain. There are changes observed in the ionotropic channel's expression in sensory neurons.

Cao and Wang et al [66] reported that peri-incisional stress appears to regulate the phosphorylation and trafficking of -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainite receptors. Thus, peri-operative stress may contribute to the molecular mechanism of persistent pain after surgery. Post-operative pain can also be linked to the activity of hypothalamic-pituitary-adrenal axis, by blocking the spinal glucocorticoids receptor complexes which prevents the effects of peri-incisional stress on incision induced pain hypersensitivity.

All these factors possibly are synergistically responsible for peripheral sensitization that produces primary hyperalgesia and leads to subsequent changes responsible for development of central sensitization. Central sensitization is a type of neuro plasticity that enhances pain signalling by effecting neurons in the spinal cord, resulting in a long-term adaptive form pain memory. This is mainly responsible for secondary hyperalgesia that is basically increased pain sensitivity outside the primary area of injury[67].

The tinel's sign, is pain along the lateral chest wall and on local regional blocks this pain is significantly reduced, suggestive on painful neuroma formation as a potential cause of post-operative chronic pain. Neuroma pain may arise following surgery, greater risk in lumpectomy than mastectomy [68]. On resection of intercostal neuroma among BCS successfully reduces intensity of pain, indicating possible role of neuroma formation in development of chronic post-surgical pain among BCS [69].

Mechanism of chemotherapy induced peripheral neuropathy among breast cancer survivors

One of the frequently occurring side-effects among BCS on anti-neoplastic agents is chemotherapy induced peripheral neuropathy (CIPN), responsible for significant pain and reduced quality of life. Antineoplastic drugs are an effective tool to arrest the progression of multiplying cancer cells, by targeting various actions. These agents subsequently also damage the structure of nervous system namely the large and small neural fibres, sensory and motor fibres, cranial and autonomic system, demyelinating and axonal structures leading to neuropathies, commonest being CIPN [70,71].

These changes depend on the properties, dosage and duration of exposure of chemotherapeutic drugs [72]. Fallon et al [73] reported that CIPN is agent dependent, with a prevalence rate of 19-85%.It is almost 70-100% and is the highest in the case of chemotherapeutic drugs that are platinum- based, while 11-87% in case of taxanes, 20-60% in thalidomide and 60-65% in ixabepilone [72]. Although chemotherapeutic agents may lead to neurotoxicity in both central and peripheral nervous system, neuropathy is still more prevalent in peripheral nerves, affecting almost 10-100% patients and the degree of severity depends on factors mainly duration, dosage and co-existing comorbidities [74].

CIPN can result from a single high dose or multiple cumulative exposures of chemotherapeutic agents. It is predominantly sensory with or without motor or autonomic changes [75]. Recent researchers have highlighted that the prevalence of CIPN at approximately one month after treatment is 68.1%, at three months is 60.0% and after six months is 30.0% [75]. The chemotherapeutic drugs, are an effective tool against progression of cancer but unfortunately are responsible for number of side-effects like nausea, vomiting, diarrhoea, anaemia, immunosuppression, recurrent infections, hair loss, fatigue, infertility, peripheral neuropathy and most importantly chronic persistent pain [76]. Paclitaxel and Oxaliplatin, manifest acute pain immediately or even during treatment [77] but other anti-neoplastic drugs manifest CIPN symptoms late, i.e. weeks or months after cessations of treatment, with severity in proportion to the cumulative dose of the agent used [78]. Thus, women with breast cancer may get free from cancer but develop debilitating neuropathy during treatment, immediately or late after cessation of treatment.

The pathophysiology behind CIPN is complex and dependent on causative agent i.e. the chemotherapeutic drug. According to a critical analysis by Park et al [79] CIPN may be sensory, motor and or autonomic with varied severity. Typical signs and symptoms of CIPN includes characteristics glove and stocking neuropathy, involving feet and hands. Sensory symptoms develop first and effect the distal most parts of limbs. They would complain of numbness, tingling, altered touch, impaired vibration, burning, thermal allodynia, dysesthesia or paraesthesia, hyperalgesia or electric shock like pain [77]. There can be paradoxical worsening of symptoms after completion of treatment. This is referred to as "coasting", where mild neuropathy deteriorates or a fresh onset CIPN develops [80]. Pain and sensory deficits may persist for long after cessation of treatment, i.e., months to years, leaving these women cancer free but in pain [81]. Patients may experience painful sensations like spontaneous burning, shooting or even electric shock like pain, thermal allodynia or hyperalgesia. There can even be sensory loss of percaption [82]. Motor symptoms are rare and may be in the form of distal weakness, altered gate or disturbances in maintaining balance [83]. In worst cases, these patients may experience paresis or severe disability and immobilization [73].

The chemotherapeutic agents exert neurotoxic effects, mainly of peripheral nervous system and responsible for causing neuropathic changes. These can be grouped into-

1. Platinum based antineoplastic drugs namely Oxaliplatin and Cisplatin,

2. Vinca alkaloids particularly vincristine and vinblastine,

3. Taxens-Paclitexel, docetaxel,

4. Protease inhibitors like Bortizomib,

5. Epothilones namely Ixabepilone, and

6. Immunomodulatory drugs like thalidomide. The most neurotoxic drug is platinum-based agents, Taxens, Thalidomide and Ixabepilone. Bortezomib and Vinca alkaloids are known to be comparatively safer and hence frequently used [80].

The mechanism of CIPN is multifactorial involving disruptions of microtubules, oxidative stress and mitochondrial damage. There are also evidences suggestive of myelin sheath disruption, altered ion channels and its activities, DNA distortion, immunological changes and neuroinflammation [84]. There is a characteristic axonal sensory motor neuropathy. Genetic role in CIPN, have also been reported with advances in Genome-Wide Association studies (GWAs). They identified and reported few single nucleotide polymorphism (SNPs) which are associated with development of CIPN. EPHA5 and FZD3 have been implicated as genes responsible for paclitaxel-induced CIPN, VAC14 gene associated with docetaxel-induced peripheral neuropathy, FOXC1 and ITGA1 identified for oxaliplatin-induced neuropathy and CEP72 association with vincristine induced neurotoxicity[85].

The platinum-based drugs, bind with nuclear DNA to inhibit DNA replication and arrest multiplication of cancer cells. Also, there is disruption of respiratory cyclical chains, increase in reactive oxygen species and mitochondrial DNA damage. In addition, they have influence on calcium signalling pathways and protein kinase function. These agents also show changes in neuronal and glial cells by altering their functioning. In interesting study, Janes et al [86]suggested that inhibition of an astrocyte associated neuro-inflammatory response predisposes to the protective action of A3AR signalling and this supports the scientific basis for use of selective A3AR agonist as adjunct to Oxaliplatin therapy in reducing Oxaliplatin-induced peripheral neuropathy.[86] In another interesting study, Li C et al[87] studied in rat model and concluded that, there is a specific signalling pathway which leads to neuropathic pain produced by Bortezomib. They also suggest that blockage of TRPA1 and TNF is of neuropathic pain produced by Bortezomib [87]. These mediators can also disrupt blood brain barrier along with reactive oxygen species and involves in toxicity induced by chemotherapeutic agents [88]. Thus, there are several alterations occurring at the level of intracellular organelles, membrane receptors, ion channels, signalling and neurotransmission, all resulting in neuro-inflammation, DNA damage and axonal degeneration leading to development of CIPN.

Cisplatin-induced peripheral neuropathy usually after a cumulative dose of more than 350mg/m2 [89]. Oxaliplatin-induced peripheral neuropathy (OIPN) may be acute transient and may develop within hours of Oxaliplatin infusion at dose of 85-130 mg/m2 [90]. A cumulative dose, two hours of expansion, low body weight and duration of exposure are risk factors for developing OIPN[91].

Immunomodulatory drugs, namely Thalidomide, a glutamate acid derivative, acts as an anticancer drug by blocking the production of tumour necrosis factor alpha (TNF-□), blocking the activation of nuclear factor kappa B (NF-□B), or blocking angiogenesis through inhibition of fibroblast growth factor (FbGF) or vascular endothelial growth factor (VEGF). Thalidomide typically shows dose dependent Thalidomide-induced peripheral neuropathy (TIPN), almost in 25 to 75% patients [92]. The risk of developing TIPN increased in a dose dependent fashion and may develop at a cumulative dose of 20 grms, limiting maximum daily dose to 200mg [93]. The antiangiogenic effect of thalidomide is also proposed to be responsible for secondary ischemia and hypoxia of nerve fibres followed by irreversible neuronal damage [94,95]. There is additional downregulation of TNF-□ and inhibition of NF-□B, causing dysregulation of neuro-tropins and their receptors and which brings subsequently neuronal cell death [96].

Taxens class of antineoplastic drugs including Paclitaxel, Docetaxel and Carbazitaxel interfere with microtubules depolymerisation and re-polymerization impairing cancer cell growth, CIPN incidence with use of Taxens is 11-87%, highest with paclitaxel, [72] and predominantly sensory neuropathy. Mechanism behind CIPN with Taxens principally is microtubule disruption, mitochondrial damage both in neurons and non-neuronal cells, axon degeneration, altered calcium homeostasis and neuroinflammation [97-99].

Epothilones, mainly Ixabepilone shows similar mechanism in development of CIPN as taxens.There is mild to moderate sensory neuropathy and less frequent motor involvement and rarely autonomic symptoms [100]. Mitochondrial dysfunction because of oxidative stress is postulated mechanism for development of CIPN in women suffering from breast cancer on Epothilones.

Vinca alkaloids, namely Vincristine, Vinblastine, Vindesin and Vinorelbine, primarily inhibit the assembly of microtubules and disrupt axonal transport of neuronal signals. Vincristine induced axonal neuropathy is also dose dependent [101]. Its mechanism of action is simple, binding to intracellular tubulin and blocking its polymerization and further formation of microtubules, inhibiting both fast and slow transports in peripheral nervous system, inducing distal axonopathy [70]. The significant relation between Charcot-Marie-Tooth disease type 1A (CMT1A) and vincristine must be mentioned here, a single dose of vincristine can result in significant weakness due to transformation of an asymptomatic carrier. CMT patients cannot be treated with vincristine. Patients with CMT and ERG2 gene mutation or CEP72 gene polymorphism are highly sensitive to vincristine induced neuropathy [102-104]. Neuropathic doses of Vinca alkaloids are 1.4 mg/m2 per week that may lead to sensory symptoms of painful paresthesia and distal weakness may occur after dose above 6-8 mg/m2.

Bortezomib and Carfilzomib, reversible proteasome inhibitors can lead to very painful condition due to sensory neuropathy, with or without demyelinating neuropathic weakness [105]. Patients on Bortezomib may develop neuropathic pain syndrome characterized by chronic, distal and symmetrical neuropathy, that may last for weeks, months or even after years of cessation of treatment [106]. They may exhibit dose-dependent or dose adjusted neurotoxicity, length dependent, mixed small and large fibres sensory axonal neuropathies. Within the peripheral nervous system, Bortezomib increases the production of TNF-□ and interleukin-1□, which actwithin astrocytes to augment sphingolipid metabolism releasing sphingosine-1- phosphate (SIP), that binds to SIP receptors, ultimately leading to increase in presynaptic glutamate release at dorsal horn of spinal cord resulting in neuropathic pain [107]. SIP also has a nociceptive and inflammatory action contributing to development of neuro-inflammation and hence, neuropathies [108]. It is suggested to monitor Vitamin D levels in patients on Bortezomib, as those with low Vitamin D levels are associated with greater intensity of Bortezomib- induces neuropathy [109].

Thus, patients undergoing chemotherapy need to be monitored carefully not only throughout the treatment duration, also after cessation of treatment. They must be followed up weeks, months and

year after treatment even though they might be rendered cancer free. They must be aware and counselled about different signs and treatment of CIPN, and neuropathic pain should be treated vigorously as it may further deteriorate their quality of life if not paid adequate attention.

Mechanism of radiation induced neuropathic pain among breast cancer survivors

Breast cancer survivors may experience a rare but frightening, progressive and usually irreversible neuropathic pain that may appear even after several years of radiation therapy. There is compression of nerves due to radiation induced fibrosis along with direct injury to nerves caused by axonal damage or demyelination or ischemic changes [110]. A well-known and more frequently encountered radiation induced neuropathy (RIPN) is radiation induced brachial plexopathy (RIBP) following radiation therapy for breast cancer. The patients of breast cancer treated with radiation therapy typically complaint of numbness, paraesthesia, dysesthesia, lymphedema or even motor weakness over shoulder to proximal arm. This is a typical complaint of radiation induced brachial plexopathy. It is a form of neurogenic pain that may vary from mild to severe intensity of pain. The onset of neuropathic pain may vary from as early as six months to twenty years after radiation therapy [111]. Stoll and Andrew et al reported back in 1966 the first case of radiation induced brachial plexus neuropathy (RIBPN), following radiotherapy in women who underwent surgery for breast cancer [112]. With advancement in medical sciences and invention of various adjuvant techniques and surgeries for treating carcinomas longevity of patients with primary as well as secondary cancer have improved to a much larger extent. There are higher rates of patient compliance for conservative surgery among breast cancer patients for obvious cosmetic and psychological reasons, increasing the demand of opting for radiotherapy at an early stage of breast cancer. Thus, the incidence of RIBPN has also unfortunately increased drastically with a reported index of 1.2% among BCS who received radiation therapy [113-115]. RIBPN is a neurological impairment which may be transient or permanent.

The pathophysiology behind RIPN can be attributed to local damage of nervous tissue due to initial microvascular injury followed by fibrosis, also known as radiation induced fibrosis (RIF) [116]. RIPN involves gradual changes leading to worsening of neural tissues over a period of several years. Firstly, there is an asymptomatic early phase or the pre-fibrotic phase of chronic inflammation followed by organised fibrotic phase, characterized by deposits of extensive extracellular matrix around the involved nerve tissue. Then there is a late fibro-atrophic phase of poorly vascularized and refractile fibrosis, [117] which involves cellular proliferation, deposition of extracellular matrix, production of cytokines like TGF and CTGF. Further reactive oxygen species play additive role in neural tissue damage. Heightened free radical generation results into oxidative stress, which accelerates fibrogenesis. On subsequent repetitive oxidative stress, intensified fibrogenesis is induced which is responsible for RIPN.

The pathophysiological stages of RIPN basically involves an initial step of electrophysiological and histochemical changes, which is later followed by the second step of fibrosis around the nerve along with injury to vessels supplying these nerves. The endoneurium is also often thickened with extensive loss of myelin and hyalinization [118]. Following radiation therapy there is failure of cellular proliferation along with local ischemia, resulting in fibrosis of neural and perineural tissues with microvascular insufficiency, that progressing towards nerve entrapment and responsible for conduction blockade.

RIBPN/RIPN is dose dependent phenomenon, i.e. development of fibrosis is under the control of radiation dosage, specifically of more than 50Gy or radiation fraction of more than 2Gy per fraction, and use of concomitant chemotherapy or associated with any vascular diseases like diabetes and hypertension [118-122].

Role of genetic factors predisposing to post surgical pain among breast cancer survivors

A recent study evaluating the association between persistent postoperative pain and 90 genetic markers after varied type of surgeries, no difference was observed between patients with CPPP and controls [123-124]. The presence of carriers of minor allele of single nucleotide polymorphism (SNP) in interleukin 1 receptor (IL-1) were less prone to pain after breast surgery. While presence of carriers of minor allele for SNP in IL3 were more prone to develop pain after breast surgery [125].

In an interesting study conducted by Saxena et al [62] on patients undergoing staging laparotomy for carcinoma ovary, it was concluded that genetic predisposition is an important predictive risk factor for the CPPP development. A total of 21 patients of ASA grade 1-3, between age 20-70, undergoing staging laparotomy (hysterectomy, bilateral salpingo-oophorectomy, omentectomy and lymphadenectomy) for carcinoma ovary with a midline incision were included for the study. The recruited patients were followed up for 4 months for a detailed evaluation and assessment of pain. The intensity and quality of pain was assessed at post-operative day 1,3,14,30,60 and 120, using Visual Analog Scale (VAS), Numerical Rating Scale- sleep (NRS-sleep) and Global Perceived Scale (GPE). To assess the neuropathic component Neuropathic Pain Symptoms Inventory (NPSI) and pain DETECT questionnaire (PDQ) were used. Also, using Short Form-12 questionnaires (SF-12) and Activity Assessment Scale (AAS), the functional status and quality of life were assessed. Estimation of PKA, PKC and ERK mRNA expression study were done to find out the role of genetic expression in development of chronic post-surgical pain. It was observed in their study that 38.1% surgical patients had incidence of development of chronic post-surgical pain and reflected an up-regulation in mRNA expression of signal transduction gene (PKA, PKC and PRK) which was responsible for the development of CPPP [62]. This demonstrated a positive correlation in mRNA expression of these three signal transduction gene and CPPP.

Hinriches–Rocker et al focussed on psychological factors, which involved in development of CPPP, like anxiety, depression, fear for surgery and pain, lack of awareness, lack of support in patient's environment, peri-operative stress are the general psychological factors responsible for stress induced pain sensitization contributing to development of CPPP [126].

The generation of chronic post-surgical pain is complex and multifactorial, involving molecular and genetic interplay with other physiological factors. There are complex underlying changes triggered by surgical insults, which predispose to development of post-operative pain. The transcriptional and post translational changes that occur in DRG resulting in release of glutamate leading to long term activity of spinal afferent neurons responsible for central sensitization. These changes not only are influenced by stress, but also modulated by use of drugs like opioids and pre-emptive analgesia, regulating the development of CPPP [63]. NMDA receptors play a crucial role in establishment of long-term pain, and blockade of NMDA receptors completely neutralises stress induced hyperalgesia[67].

A large number of studies have proven a strong association of chronic post-surgical persistent pain among BCS with ALND,

LRRT (loco-regional chemotherapy) and chemotherapy. It is to be emphasized that certain co-morbidities in breast cancer survivors, such as myalgia, chronic low back pain, migraine, osteoarthritis and rheumatoid arthritis are important risk factors for the development of chronic pain following breast cancer treatment. In the opinion of Bredal et al it is yet not established that, in any case the anxiety or depression are important risk factors for development of chronic pain among BCS [127]. The women who received ALND, chemotherapy and LRRT to the axilla had a much higher risk of developing chronic pain, than who received one or two of these therapeutic options. However, endocrine therapy has less or no such risk for development of chronic pain. It is yet to be explored further, whether anxiety or depression or both are risk factors of chronic pain post operatively in BCS.

Management of chronic persistent pain among breast cancer survivors

In-spite of major advancement in understanding and treatment of chronic pain, it still remains an unsolved and also a common persistent problem which is potentially debilitating among BCS. Chronic persistent pain is still an ongoing challenge. The major obstacle in successful pain management among BCS is variable reporting of patients to their clinician, variable response to treatment or fear susceptibility to adverse effects and seek consultation for chronic pain. Therefore, a rational personalized pain management is necessary, which consider not only the physical and mental status of patients but also, the pharmacogenetics and pharmacokinetics of patient and analgesics.

Pre-operative identification and targeted intervention of women with high risk factors for developing chronic pain following post breast cancer surgery, must be done to enhance the post-operative quality of life of BCS. Strategies aiming at alleviating chronic pain, post breast cancer surgery among BCS includes, minimal invasive therapies, such as breast conserving techniques of mastectomy, breast reconstruction, sentinel lymph nodes dissection over axillary lymph dissection, early treatment with radiation and chemotherapy, adequate and prompt use of analgesics peri-operatively and post-operatively.

Saxena and Kumar et al [4] highlighted on the need for proper assessment of pain in identification of pain syndromes among BCS. Pain being the most distressing symptoms among BCS, its identification would guide in formulating adequate treatment strategies. They stress on the benefits of multimodal analgesia in cooperating pharmacological, intervention as well as non-conventional techniques that may be employed prior to or along with and after primary treatment of breast cancer.

(a) Potential for Prevention of Chronic Persistent Pain Among Breast Cancer Survivors

Neuropathic pain is a neurodegenerative disease majorly of iatrogenic origin, and thus, a neuroprotective treatment would help to reduce post-operative pain. A combination of therapies targeting the injured nerve to control or reduce the neuropathic changes subsequently arising in central nervous system (CNS). With aggressive pain management at the time of surgery and throughout the perioperative and postoperative period, targeting not just the disturbances in sensations produced but also at the progression mechanism of pain. The sensory inflow from the site of nerve injury may be interrupted with local or regional anaesthetic blocks. This would probably help to prevent the activity dependent neuroplastic changes of CNS. Other treatment modalities available are administration of growth factors, glial cell line–derived neurotropic factor (GDNF), prevention of microglial activation with drugs like minocycline and preventing apoptosis in dorsal root ganglion. However, these neuroprotective strategies still need further evaluation and research.

The pharmacological therapies to prevent CPPP should include blockade of sodium channels (Na 1.3, Na 1.7, Na 1.8), potassium channels openers in sensory neurons, N- type calcium channel (Ca 2.2) blockers, 2 binding drugs, P2X4 and P2X7 purinergic receptor antagonist receptor present in microglial cells, caspase inhibitor and drugs binding to activate glutamate transporters. It has been well established that damage to major nerve during surgery is associated with high risk of developing persistent pain post-operatively. Thus, more precise dissection avoiding nerve damage would drastically reduce post-operative pain among BCS. In patients undergoing mastectomy, there has been significant observation made that preservation of inter-costal brachial nerve might to a large extent help in alleviating post-operative pain [128-129]. On similar ground, sentinel lymph node biopsy (SLNB) thereby should be done prior to ANLD in order to prevent inter-costal nervedamage.

There occurs acute neuroplastic responses and central sensitization following any injury to tissue is another major proven mechanism responsible for development of CPPP after breast cancer surgery. Pre-emptive and aggressive multimodal analgesia play a role in preventing these changes, thus is favourable for patients to prevent post-operative pain [130]. COX inhibitors and opioids are suitable therapeutic agents available at present for pre-emptive multimodal analgesia. In addition, peri-operative use of intra vascular NMDA antagonist-ketamine, GABA analogue pregabalin and gabapentin, COX inhibitors–NSAIDS, acetaminophen, alpha 2 agonist dexmedetomidine and clonidine, afferent neural blockade with epidural block and analgesia or regional blocks, all have the potential to prevent central neuroplasticity, contributing in lower post-operative pain [131-133].

Reuben et al [134] obtained a promising result that peri-operative administration of Venlafexine is effective in reduction of chronic pain after breast surgery. Similar results were observed by Fassaulaki et al in three different studies using peri-operative–mexilitine with gabapentin and in other EMLA only and in third one EMLA with gabapentin [135-137].

Thus, primary focus to prevent CPPP and of pivotal role is avoiding nerve injury, reducing inflammatory responses and use of minimally invasive surgical techniques. The surgeons should be made aware of the same and encouraged to adopt techniques minimizing nerve damage. The secondary focus should be at strategic peri-operative pre-emptive and multimodal analgesia techniques.

(b) Pharmacological Therapies For Chronic Persistent Pain in Breast Cancer Survivors

Use of topical capsaicin for CPPP in BCS has been observed to be associated with significant pain relife. [138]. Anti-epileptic drugs, gabapentin and serotonin non epinephrine reuptake inhibitors, venlafaxine had appeared to be effective for CPPP [139-140]. Gabapentin administration prior to surgery shows a lower pain score in post-operative period and also reduces the use of adjuvant analgesics. However, its efficacy in long term chronic pain management remains unclear [141]. Amitryptiline is another good choice of drug for neuropathic pain, following breast cancer treatment. Pain relief was greater among BCS on Amitryptiline among BCS on placebo, in a randomised, double blind, placebo controlled trial by Kalso et al [142]. On the other hand, in another double-blind placebo controlled trial by Tasmuth et al [140] Venlafexine did not have a significant on the

daily pain diary ratings, but did have a greater relief and maximum pain incidence.

Use of Eutectic Mixture of Local Anaesthetics (EMLA), Mexiletine or Gabapentin peri-operatively appeared to reduce acute post-operative pain, movement associated pain and also reduces post-operative analgesic consumptions or intensity of persistent pain among BCS. According to Fassoulaki et al [136]EMLA alone proved to be effective in preventing CPPP among BCS. On topical application to breast and arm areas of the site to be operated one day prior to the surgery reduced analgesic consumption between two to six days post-operatively. It was also found to decrease the incidence as well as intensity of pain up-to three months post-surgery [136]. These findings were supported by another trial in 2005 on multimodal analgesia using combination of Gabapentin and local anaesthetics [137].

Intravascular peri-operative lidocaine, was found to reduce the incidence and severity of persistent pain among BCS. According to a prospective randomised, double blind, placebo controlled trial by Grigoras et al[143] it was reported that 11.8% patients in lidocaine group and 47.4% patients in controlled group reported persistent pain following BCS at three months followup.

Park et al [144] observed, Dexmedetomidine has a dose dependent anti-allodynic effect on cold as well as mechanical stimuli in Vincristine evoked neuropathic model of rats. To study the role of peri-operative dexmedetomidine on CPPP among BCS, Jain et al [144] conducted a prospective double-blind trial among women who underwent breast cancer surgery. The consumption of analgesics and inhalational agents intra-operatively and post-operatively was significantly lower among Dexmedetomidine group. Also, the numerical pain score, brief pain inventory (BPI) score and the short-form of revised McGill Pain Questionnaire (SF-MPQ2) scores at rest and with movement was lower in dexmedetomidine group, with a better quality of life [135]. Thus, Jain et al concluded that peri-operatively Dexmedetomidine infusion have a very important role in prevention of chronic pain among BCS and improving the quality oflife.

Opioids are good choice of drug for moderate to severe pain. While choosing the opioid, we need to take into consideration its mechanism of action of along with intensity of pain, patients age, co-morbidities, as well as other medication and psychological status. Opioids can be classified based on its affinity for opioid receptor, into complete agonist or agonist – antagonist. Buprenorphine, partial agonist of μ & receptor and antagonist at receptor, is a commonly used opioid for pain among cancer survivors. Pure agonists, with a strong affinity for μ receptor, namely morphine and fentanyl, are preferred for management of chronic pain among cancer survivors. Opioids are administered orally via plain or sustained release formulations, through transdermal patches, epidural route or even intravenously in acute or palliative care among cancer survivors. Tapentadol, is the latest and centrally acting opioid preparation with a strong analgesic available for management of pain among cancer survivors [145].

CIPN is one of the major dose-limiting adverse reaction of chemotherapeutic agents, which are the first line of treatment for breast carcinoma. The key area of concern with CIPN is its management, whether it is possible to even prevent it or at-least alleviate the chemotherapy induced symptoms. Zajączkowska et al [146] reported that, patients on life saving chemotherapeutic agents are on potential risk of developing CIPN. They should have the knowledge about signs and symptoms of neuropathic pain and instructed to report immediately on onset of any symptom. These patients should be counselled before commencement of treatment and advised to report, to their clinician in case they experience any sign suggestive of neuropathic changes like altered perception to sensory stimuli.

Patients having high risk of developing CIPN that are: older age group, co-existing other neuropathies like diabetic neuropath, history of chronic smoking, impaired creatinine clearance reflecting deranged renal functions and/or history of cancer related neuropathies must be identified. These patients should be given additional care and neurological or electrophysiological examination must be carried out at each visit to oncologist. The key idea is to prevent the onset of CIPN and identify it at an early stage. The American Society of Clinical Oncology (ASCO) does not recommend any particular agent for CIPN management, however, “duloxetine” has proved to be effective. There are studies suggestive of use of topical gel containing baclofen, amitriptyline and ketamine [147-148]. There are limited options available for treatment of CIPN, hence a better understanding of its mechanism including the genetic role need to be explored and strategies for its prevention as well as treatment must be formulated [146].

Despite limited availability of evidence for use of other anti-neuropathic drugs, published guidelines are available for use of both amitriptyline and gabapentin with proven efficacy for treating CIPN after trial for neuropathy by Hershman [139]. Topical preparation available for CIPN are capsaicin 0.025% cream, 5% lidocaine patches. The use of cannabinoid receptor agonist is still under trail and evaluation. The other potential treatments under evaluation includes topical menthol, an in-activator of voltage gated sodium channel of nociception and tetrodotoxin [149]. Also, Vitamin B1 to B6, B12 and physical therapy are often routinely advised and have proved to be helpful [110-150].

Psychological support and counselling first and foremost important part of management for RIPN and RBPN chronic pain. Non-opioid analgesics available are benzodiazepines, tricyclic antidepressants, anti-epileptics and membrane stabilizing drugs, like carbamazepine. Avoiding aggravating factors like lifting heavy weight, controlling co-morbid conditions namely high blood pressure, diabetes, stopping alcohol consumption, smoking or fibrogenic drugs may be useful in preventing and delaying RIPN and RIBPN. Acute inflammation may be prevented with corticosteroids [151-152]. Patients should be counselled on strictly avoiding local trauma to the radiated area as far as possible. Hyperbaric oxygen therapy reduces tissue oedema and promotes angiogenesis, fibroblast growth and extra-cellular tissue matrix, and so may be considered for persistent symptoms of pain, oedema or erythema. Carl et al [153] conducted a study of 32 women who underwent breast conserving radiation therapy after 25 hyperbaric oxygen therapy sessions and 9 months follow up, has significantly reduced pain as compared to 12 controls, however fibrosis and telangiectasia were not affected.Glantz et al [154] demonstrated, successful use of heparin and warfarin as an attempt to halt progression and necrosis due to ischemic changes around involved nerve. Recently,the combined use of pentoxifyllin-tocopherol to significantly reduce RIPN has been proven by Delanian et al [155] and Hamama et al [156].

Non-pharmacological and non-invasive techniques are also available for pain management of RIPN origin pain, namely transcutaneous electric nerve stimulation (TENS), physiotherapy and muscle strengthening exercises, which are very useful in alleviating symptoms of neuropathic pain among BCS presenting with RIPN [115]. It should be noted that neuropathic pain arising as a consequence of radiation is relatively insensitive to conventional analgesics, like non-steroidal anti-inflammatory drugs or Acetoaminophen. Pregabalin

i.e., -isobutyl–G–aminobutyric acid is the drug of choice for RIPN. Also, tricyclic anti-depressants, amitriptyline and anticonvulsant like carbamazepine and sodium valproate have shown promising results in alleviation of paraesthesia and neuropathic pain in RIPN [111]. They may reduce hyper-excitability of membrane like myokymia, thus acting as membrane stabilizing drug especially carbamazepine.Myokymia is a spontaneous, involuntary and localized quivering of muscles, but insufficient for any movement. Invasive procedures available for treatment of chronic pain of neurogenic nature, which includes epidural blocks and injection of steroids as well as local anaesthetic agents, brachial plexus block and even spinal cordstimulation.

In cases where BCSs fail to respond to non-pharmacological or pharmacological modalities of treatment of chronic pain. Surgical treatment is also available for such severe refractory neuropathic pain, which unresponsive to conventional therapies and/or associated with neurological motor deficits are external neurolysis. It is a surgical technique of excising a peri-neural fibrosis and scar tissues from around the entrapped nerve [157-161].

Another minimally invasive intervention that is paravertebral nerve blocks during breast cancer surgery have been reported by Kairaluoma et al, [162] Moller et al, [163] and Coveney et al [164] to reduce acute post-operative pain and opioid consumption. In a Cochrane review, Andreae et al [165] compared use of local or regional anaesthetics to conventional analgesia interventions, and pain was assessed at 6 and 12 months after surgery. They concluded; paravertebral regional nerve block may have pivotal role in attenuating risk of developing CPPP after breast surgery in breast cancer. (Table 3) summarizes the available treatment options.

Future directions-pharmacogenetics and personalized pain management

World-wide leading cause of mortality at present is cancer, according to a report by ASCO, the State of Cancer Care in America, 2014 [166]. Although, with advancements in medical sciences, the number of cancer survivors also have increased tremendously, and is expected to rise by 35%, from 13.7 million in 2012 to 18 million in 2022 [147]. In the upcoming years, we need to focus our attention to overcome the barriers in health care for an effective pain treatment and strategically implement interventions to optimize pain among BCS. There is need of awareness programme among women (breast cancer patient) about risk factors of developing chronic pain, and pharmacological as well as non-pharmacological therapies to attenuate pain.

The therapeutic efficacy varies among BCS to different treatments, which may be modulated and determined by pharmacogenetics, as specific genetic traits affect the metabolism of a drug, by different pharmacokinetic and pharmacodynamics i.e., the mechanism through which drug affects the human physiology [167]. Different allelic variations (SNPs) have been identified in a major enzyme cytochrome p4502D6, which, involved in opioid metabolism [168]. Genetic polymorphism in opioid receptor gene is linked with clinical variation in response to opioid analgesics. Similarly, for NSAIDS metabolism, CYP2CP and CYP2CA enzymes are responsible and they also have shown differential effects of genetic polymorphism [169-170]. Genetic variations in case of Selective Serotonin Reuptake Inhibitor (SSRI) also play an important role in its bioavailability. Polymorphism of gene coding for Catechol-O-methyltransferase (COMT) enzyme is effectively linked to variation in pain perception among individuals. Thus, genetic polymorphism affects pain experience as well as therapeutic response of patients to differentanalgesics.

Bach-Rojecky et al [171] reported that, there is a e influence of epigenetic modulations, in chronic persistent pain and its treatment efficacy. There is a strong influence of dietary habits, exercise, yoga, toxins, stress, medication and other similar factors which modulates the genes involved with pain perception, and predisposing to painful stimulus. Further, epigenetic modulations may contribute to the onset of opioid analgesic adverse effects such as addiction or hyperalgesia. Thus, a universal approach to pain management will not be a successful story, as all patients have different response to medication due to varied pharmacogenomics based on genetic polymorphism and epigenetic modulations. An individualised patient care, monitoring patients for any side effects and possible review of patient's single nucleotide polymorphism of genes related to pain management can be an ideal approach [172].

Webster et al [173] concluded that each individual carries his/her own genetic imprint, that determines possibility of developing

Table 3: The holistic approach to treat chronic pain among BCS.

(I) Pharmacological
• Non-opioids: e.g., Acetaminophen, Non-steroidal anti-inflammatorydrugs, Naproxen sodium. • Opioids: e.g., Oxymorphone, Morphine, Hydromorphone, Fentanyl • Co-analgesics includes: o Anti-depressants (Amitriptyline) o Anti-convulsants (Carbamazipine) o Corticosteroids (Dexamethasone) o Amphetamine (Caffeine, Modafinil) o Anti-anxiety (Diazepam, Lorazepam) oBisphosphonates (Zoledronic acid, Risedronate) Tropical analgesics eg., EMLA, Lidocaine patch, Cream
(II) Invasive techniques
• Regional Nerve blocks • Epidural blocks / Epidural analgesics • Nerve stimulation with cold or heat, vibration, menthol, Capsaicin. • TENS (Trans Cutaneous Electrical Nerve Stimulation)
(III) Surgical
• Excising peri-neural fibrosis • Radiation, ablation
(IV) Physical therapy
• Cognitive Behavioral Therapy (CBT), Massage, Stretching, Strength training exercise and Yoga.

chronic pain, its intensity, pain perception and response to prescribed analgesic. The expression of an individual genetic profile is further influenced by various environmental factor. The gene-gene and gene-environment interaction also able to influence pain perception as well as response to analgesics [173]. Banerjee et al in their studies of gene environment interaction reported that genetic polymorphism play crucial role in the development of different cancer as well as cancer progression [174]. In a recent study, Smith et al [175] concluded that pharmacogenetics guided therapy for management of chronic pain has been adopted in few institutions for selective medications that are metabolised by enzyme CYP2D6. With this personalised approach of patient care, clinician can use individual's genotype and phenotype of specific drug metabolism enzymes to identify predisposing risk factors to chronic pain and design a possible therapeutic strategy. Hence in future, medical research in this area would be highly beneficial for the holistic management of chronic pain among BCS.

The differences in response to various analgesics among BCS at the molecular level can be explained by genetic influence on drug response, that is through drug metabolising enzyme drug transporters, structural alteration in opioid receptors and other analgesic receptor and/or variability in processing and modulation of perception of pain. Also, the most important aspect of personalized pain medicine is a holistic multidisciplinary team approach and evaluation of patients presenting with chronic persistent pain.

Conclusion

The agony of chronic pain persistent among BCS is undisputedly and certainly a major issue of concern. It interferes with routine day to day activities, hampering their physical, mental and social health, eventually resulting in a poor quality of life. The clinician must draw an equal attention towards pain management among the survivors and not just entirely focussed on treating just the cancer. The belief that pain during or after cancer treatment is inevitable and the fear of women to come to their clinician for complain of pain must be addressed. Even mild pain can interfere with daily routine and gradually progress to other effects like fatigue, anxiety, depression, etc. Pain control is thus, an important part of health care and women should not hesitate to let their health care provider know about any discomfort their experience during or after breast cancer treatment. There has to be an early implementation of appropriate analgesics and adjuvant drugs. We should counsel the BCS, that pain is easier to treat when it is mild and addressed at an early stage and thus, one should not wait for the mild pain to get severe before seekingrelief.

Pain after surgeries is like lumpectomy, mastectomy or breast reconstructionistemporaryandduetoacuteinjurytoskin, subcutaneous tissue or muscles. Mild analgesics such as NSAIDS, acetaminophen may show good pain relief. For severe pain a multimodal analgesic approach, combining opioids (tramadol, fentanyl, morphine, etc.) and non-opioids (NSAIDS, pregabalin, gabapentin, etc.) might show positive results in reducing pain. In addition, non-pharmacological methods that includes yoga, acupuncture, meditation, relaxation and physical therapy, all are extremely beneficial and must be incorporated in the regimen of treating persistent pain after breast cancer treatment, which not only helps the women surviving breast cancer to get psychological strength but also improves their physical well-being.

Neuropathic pain mainly because of extensive dissection or neural damage can betreated with a combination of analgesics, antidepressants, membrane stabilizing agents and gaba-amino-butyric acid. For severe neuropathic pain lignocaine patch, nerve blocks, epidural blocks and steroids may be beneficial. CIPN is a significant limiting side-effect of commonly used chemotherapeutic agents. Patients should be counselled to report at the earliest for any symptoms of neuropathic pain like numbness or altered sensory perception. If any signs are detected detailed neuropathic examination needed to be conducted. The specific doses of chemotherapeutic agents should then be revised. Pain as consequence to chemotherapy is characteristically burning, shooting pain, numbness may respond to duloxetine, as per moderate recommendation by ASCO and topical gel containing Amitryptiline, baclofen and ketamine, weak recommendation of ASCO. A3AR agonist may be useful for OIPN. But because of their limited role, we need to develop an alternative effective therapeutic approach. It is equally important that "translation" of various gene identified by GWAs will show us pattern for prediction of CIPN occurrence after chemotherapeutic agents.

The process of finding an optimum treatment strategy for each patient among BCS has been traditionally a hit and trial method. With advancement and progress in medical sciences a more rational; approach to pain can be adapted. A physician attending women presenting with persistent pain after breast cancer treatment, should obtain a detailed data regarding duration of pain, time since cessation of treatment, presence of co-morbidities, additional medicines and/or any predisposing factors. A tailor-made strategy to combat pain should then be planned. Further research has to be done on epigenetic mechanism involved in pain perception and analgesic drug action. Although enormous effort has been put towards pain management but still chronic pain persists to be an immense challenge for both clinician and researchers. A new and less explored area is the epigenetic mechanisms related to pain.

There has been a tremendous progress in the gene targeted therapy for therapeutic management of malignancy of carcinoma breast. Gene targeted therapy of pain management is very much in infancy and yet to see the light of the day. Thus, genome wide association studies need to be conducted to identify full genetic mapping for pain and analgesia before making it a widespread part of clinical practice towards pain management. However, psychological as well as emotional support is key and most important step towards treatment of chronic pain among BCS. Patients must be counselled and encouraged to adopt various non pharmacological techniques for improving the quality of life post cancer treatment.

In conclusion, the actual recognition of females who are highly prone to the development of chronic pain following various types of treatment for breast cancer is essential for chronic persistent pain by arranging various specific interventions, for reducing the sequelae of the various types of cancer treatment. In future, this shall also include the identification of pain genes involved in the pathogenesis of chronic pain in BCS and subsequently one can plan for gene target therapy. No doubt more prospective multi-centric scientifically designed clinical trials and research studies involving larger number of patients, are required to explore the efficacy of multimodal approach in further minimizing the development of chronic pain among BCS. In next 5-10 years genes identified by GWAs for CIPN shall determine the role of gene target therapy.

Hence, this will go a long way in providing a prolonged support system to expedite the recovery in BCS. In intractable cases of chronic pain in BCS one should always integrate strategies of cognitive behavioural therapy, meditation, deep breathing exercises, and yogic exercises. There is no doubt we should continue our attention for more advanced research to be able to determine whether improvement in pain management strategies would also result in enhanced quality of

life in BCS. Last but not the least all breast cancer survivors should be counselled and oriented about the possibility of development of chronic pain and various strategies to alleviateit.

Reference

1. Canadian Cancer Society (2014). Canadian cancer statistics. Toronto, ON.
2. American Cancer Society AC. Breast cancer facts and figures (2019–2020):1-44
3. Naughton M. and Shumaker S. A. (2003). The case for domains of function in quality of life assessment. Quality of life research. 12: 73-80.
4. Saxena A. K and Kumar S. (2007). Management strategies for pain in breast carcinoma patients: current opinions and future perspectives. Pain practice. 7: 163-177.
5. Enien M. A, Ibrahim N, Makar W, Darwish D, Gaber M. (2018). Health-related quality of life: Impact of surgery and treatment modality in breast cancer. Journal of cancer research and therapeutics. 14: 957.
6. De Aguiar S. S, Bergmann A and Mattos I. E. (2014). Quality of life as a predictor of overall survival after breast cancer treatment. Quality of Life Research. 23: 627-637.
7. 7. Weaver K. E, Forsythe L. P, Reeve B. B, Alfano C. M, Rodriguez J. L. et al. (2012). Mental and physical health–related quality of life among US cancer survivors: population estimates from the 2010 National Health Interview Survey. Cancer Epidemiology and Prevention Biomarkers. 21:2108-2117.
8. Montazeri A. (2008). Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. Journal of experimental & clinical cancer research. 27: 32.
9. Cox-Martin E, Anderson-Mellies A, Borges V, Bradley C. (2019). Chronic pain, health-related quality of life, and employment in working-age cancer survivors. Journal of Cancer Survivorship.1-9.
10. Armoogum J, Harcourt D, Foster C, Llewellyn A, McCabe CS. (2020). The experience of persistent pain in adult cancer survivors: A qualitative evidence synthesis. European Journal of Cancer Care. 29:13192.
11. Bøhn S-KH, Lie HC, Reinertsen KV, Fosså SD, Haugnes HS. et al. (2020). Lifestyle among long-term survivors of cancers in young adulthood. cancer. 3:5.
12. Hofsø K, Rustøen T, Cooper BA, Bjordal K, Miaskowski C. (2013). Changes over time in occurrence, severity, and distress of common symptoms during and after radiation therapy for breast cancer. Journal of pain and symptom management. 45:980-1006.
13. Burton AW, Fanciullo GJ, Beasley RD, Fisch MJ. (2007). Chronic pain in the cancer survivor: a new frontier. Pain Medicine. 8:189-98.
14. Wang L, Guyatt GH, Kennedy SA, Romerosa B, Kwon HY. et al. (2016). Predictors of persistent pain after breast cancer surgery: a systematic review and meta-analysis of observational studies. Cmaj. 188:E352-E61.
15. Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. (2003). Neuropathic pain following breast cancer surgery: proposed classification and research update. Pain. 104:1-13.
16. 16. Kehlet H, Jensen TS, Woolf CJ. (2006). Persistent postsurgical pain: risk factors and prevention. The lancet. 367:1618-25.
17. Andersen KG, Kehlet H. (2011). Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. The Journal of Pain. 12:725-46.
18. 18. Brummett CM. (2011). Chronic pain following breast surgery. Techniques in Regional Anesthesia and Pain Management.15:124-32.
19. Smith HS, Wu S-X. (2012). Persistent pain after breast cancer treatment. Ann Palliat Med. 1:182-94.
20. Cregg R, Anwar S, Farquhar-Smith P. Persistent postsurgical pain. Current opinion in supportive and palliative care 2013;7:144-52.
21. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. (2013). The neuropathic component in persistent postsurgical pain: a systematic literature review. PAIN. 154:95-102.
22. Hidding JT, Beurskens CH, van der Wees PJ, van Laarhoven HW, Nijhuis-van der et al. (2014). Treatment related impairments in arm and shoulder in patients with breast cancer: a systematic review. PloS one. 9.
23. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GK. et al. (2009). The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. Annals of surgical oncology.16:1959-72.
24. Liu C-q, Guo Y, Shi J-y, Sheng Y. (2009). Late morbidity associated with a tumour-negative sentinel lymph node biopsy in primary breast cancer patients: a systematic review. European journal of cancer. 45:1560-8.
25. Hamood R, Hamood H, Merhasin I, Keinan-Boker L. (2018). Chronic pain and other symptoms among breast cancer survivors: prevalence, predictors, and effects on quality of life. Breast cancer research and treatment. 167:157-69.
26. Jensen MP, Chang H-Y, Lai Y-H, Syrjala KL, Fann JR. et al. (2010). Pain in long-term breast cancer survivors: frequency, severity, and impact. Pain medicine.11:1099-106.
27. Van den Beuken-van, Everdingen M, De Rijke J, Kessels A, Schouten H. et al. (2007). J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Annals of oncology.18:1437-49.
28. Van Den Beuken-Van MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. (2016). Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. Journal of pain and symptom management. 51:1070-90.
29. 29. Wood K. (1978). Intercostobrachial nerve entrapment syndrome. Southern medical journal. 71:662-3.
30. Belfer I, Schreiber KL, Shaffer JR, Shnol H, Blaney K, Morando A, et al. (2013). Persistent postmastectomy pain in breast cancer survivors: analysis of clinical, demographic, and psychosocial factors. The journal ofpain.14:1185-95.
31. Macdonald L, Bruce J, Scott NW , Smith WCS, Chambers W. (2005). Long-term follow-up of breast cancer survivors with post-mastectomy pain syndrome. British journal of cancer. 92:225-30.
32. Gärtner R, Jensen M-B, Nielsen J, Ewertz M, Kroman N. et al. (2009). Prevalence of and factors associated with persistent pain following breast cancer surgery. Jama. 302:1985-92.
33. Pain CoC. (1986). Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. Pain Suppl. 3.
34. TREEDE R-d. (2015). A classification of chronic pain for ICD-11. Pain,[sl]. mar.
35. Macrae W. (2008). Chronic post-surgical pain: 10 years on. British journal of anaesthesia. 101:77-86.
36. Peuckmann V, Ekholm O, Rasmussen NK, Groenvold M, Christiansen P, Møller S, et al. (2009). Chronic pain and other sequelae in long- term breast cancer survivors: nationwide survey in Denmark. European journal of pain. 13:478-85.
37. Rosedale M, Fu MR. (2010). Confronting the unexpected: temporal, situational, and attributive dimensions of distressing symptom experience for breast cancer survivors. Oncology nursing forum.
38. Peretti-Watel P, Bendiane M-K, Spica L, Rey D. (2012). Pain narratives in breast cancer survivors. Pain research and treatment.
39. Katz J, Seltzer Ze. (2009). Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert review of neurotherapeutics. 9:723-44.
40. Glare PA, Davies PS, Finlay E, Gulati A, Lemanne D, Moryl N, et al. (2014). Pain in cancer survivors. Journal of clinical oncology. 32:1739.
41. Siegel R, Naishadham D, Jemal A. (2012). Cancer statistics for hispanics/ latinos, CA: a cancer journal for clinicians. 62:283-98.
42. Divella M, Vetrugno L, Bertozzi S, Seriau L, Carla C, Bove T. (2020). Patient-reported pain and other symptoms among breast cancer survivors: prevalence and risk factors. Tumori Journal. 0300891620908930.
43. Fabro EAN, Bergmann A, e Silva BdA, Ribeiro ACP, de Souza Abrahão K, et al. (2012). Post-mastectomy pain syndrome: incidence and risks. The Breast. 21:321-5.
44. Kudel I, Edwards RR, Kozachik S, Block BM, Agarwal S, Heinberg LJ, et al. (2007). Predictors and consequences of multiple persistent postmastectomy pains. Journal of pain and symptom management. 34:619-27.
45. Poleshuck EL, Katz J, Andrus CH, Hogan LA, Jung BF, et al. (2006). Risk factors for chronic pain following breast cancer surgery: a prospective study. The Journal of Pain.7:626-34.
46. Juhl AA, Christiansen P, Damsgaard TE. (2016). Persistent pain after breast

cancer treatment: a questionnaire-based study on the prevalence, associated treatment variables, and pain type. Journal of breast cancer.19:447-54.

47. Smith WCS, Bourne D, Squair J, Phillips DO, Chambers WA. (1999). A retrospective cohort study of post mastectomy pain syndrome. Pain. 83:91-5.

48. Carpenter JS, Andrykowski MA, Sloan P, Cunningham L, Cordova MJ, Studts JL, et al. (1998). Postmastectomy/postlumpectomy pain in breast cancer survivors. Journal of clinical epidemiology. 51:1285-92.

49. Bokhari FN, McMillan DE, Daeninck PJ. (2012). Pilot study of a survey to identify the prevalence of and risk factors for chronic neuropathic pain following breast cancer surgery. Oncology nursing forum: Oncology Nursing Society. 141.

50. Wallace MS, Wallace AM, Lee J, Dobke MK. (1996). Pain after breast surgery: a survey of 282 women. PAIN. 66:195-205.

51. Vilholm O, Cold S, Rasmussen L, Sindrup S. (2009). Sensory function and pain in a population of patients treated for breast cancer. Acta anaesthesiologica scandinavica. 53:800-6.

52. Gottrup H, Andersen J, Arendt-Nielsen L, Jensen TS. (2000). Psychophysical examination in patients with post-mastectomy pain. Pain. 87:275-84.

53. Winters- Stone KM, Schwartz AL, Hayes SC, Fabian CJ, Campbell KL. (2012). A prospective model of care for breast cancer rehabilitation: bone health and arthralgias. Cancer. 118:2288-99.

54. Burstein HJ, Griggs JJ, Prestrud AA, Temin S. (2010). American society of clinical oncology clinical practice guideline update on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer. Journal of oncology practice. 6:243-6.

55. Din OS, Dodwell D, Wakefield RJ, Coleman RE. (2010). Aromatase inhibitor-induced arthralgia in early breast cancer: what do we know and how can we find out more? Breast cancer research and treatment. 120:525-38.

56. Crew KD, Greenlee H, Capodice J, Raptis G, Brafman L, Fuentes D, et al. (2007). Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. Journal of Clinical Oncology. 25:3877-83.

57. Burstein HJ, Winer EP. (2007). Aromatase inhibitors and arthralgias: a new frontier in symptom management for breast cancer survivors. American Society of Clinical Oncology.

58. Henry NL, Giles JT, Ang D, Mohan M, Dadabhoy D, Robarge J, et al. (2008). Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. Breast cancer research and treatment. 111:365-72.

59. Morales L, Pans S, Paridaens R, Westhovens R, Timmerman D, Verhaeghe J, et al. (2007). Debilitating musculoskeletal pain and stiffness with letrozole and exemestane: associated tenosynovial changes on magnetic resonance imaging. Breast cancer research and treatment. 104:87-91.

60. Sestak I, Sapunar F, Cuzick J. (2009). Aromatase Inhibitor–Induced Carpal Tunnel Syndrome: Results From the ATAC Trial. Journal of clinical oncology. 27:4961-5.

61. Robidoux A, Rich E, Bureau N, Mader S, Laperriere D, Bail M, et al. (2011). A prospective pilot study investigating the musculoskeletal pain in postmenopausal breast cancer patients receiving aromatase inhibitor therapy. Current Oncology. 18:285.

62. Saxena AK, Chilkoti GT, Chopra AK, Banerjee BD, Sharma T. (2016). Chronic persistent post-surgical pain following staging laparotomy for carcinoma of ovary and its relationship to signal transduction genes. The Korean journal of pain. 29:239.

63. Richebé P, Capdevila X, Rivat C. (2018). Persistent Postsurgical Pain Pathophysiology and Preventative Pharmacologic. Anesthesiology. 129:590.

64. Spofford CM, Brennan TJ. (2012). Gene expression in skin, muscle, and dorsal root ganglion after plantar incision in the rat. Anesthesiology: The Journal of the American Society of Anesthesiologists. 117:161-72.

65. Ji R-R, Samad TA, Jin S-X, Schmoll R, Woolf CJ. (2002). MAPK activation by NGF in primary sensory neurons after inflammation increases TRPV1 levels and maintains heat hyperalgesia. Neuron. 36:57-68.

66. Cao J, Wang P-K, Tiwari V, Liang L, Lutz BM, Shieh K-R, et al. (2015). Short-term pre-and post-operative stress prolongs incision-induced pain hypersensitivity without changing basal pain perception. Molecular pain. 11:s12990-015-0077-3.

67. Rivat C, Laboureyras E, Laulin J-P, Le Roy C, Richebé P, Simonnet G. (2007). Non-nociceptive environmental stress induces hyperalgesia, not analgesia, in pain and opioid-experienced rats. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 32:2217-28.

68. Tasmuth T, Von Smitten K, Hietanen P, Kataja M, Kalso E. (1995). Pain and other symptoms after different treatment modalities of breast cancer. Annals of Oncology. 6:453-9.

69. Wong L. (2001). Intercostal neuromas: a treatable cause of postoperative breast surgery pain. Annals of plastic surgery. 46:481-4.

70. Cioroiu C, Weimer LH. (2017). Update on chemotherapy-induced peripheral neuropathy. Current neurology and neuroscience reports. 17:47.

71. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J. et al. (2014). Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. Journal of Clinical Oncology. 32:1941-67.

72. Banach M, Juranek JK, Zygulska AL. (2017). Chemotherapy- induced neuropathies—a growing problem for patients and health care providers. Brain and behavior. 7:00558.

73. Fallon M. (2013). Neuropathic pain in cancer. British journal of anaesthesia. 111:105-11.

74. Van Wilgen CP, Dijkstra PU, van der Laan BF, Plukker JT, Roodenburg JL. (2004). Morbidity of the neck after head and neck cancer therapy. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck. 26:785-91.

75. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, et al. (2014). Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. PAIN. 155:2461-70.

76. Health UNIo. (2010). National Cancer Institute. Chemotherapy Side Effects Fact Sheets.

77. Argyriou AA, Cavaletti G, Briani C, Velasco R, Bruna J, Campagnolo M, et al. (2013). Clinical pattern and associations of oxaliplatin acute neurotoxicity: a prospective study in 170 patients with colorectal cancer. Cancer. 119:438-44.

78. Maestri A, De Pasquale Ceratti A, Cundari S, Zanna C, Cortesi E. et al. (2005). A pilot study on the effect of acetyl-L-carnitine in paclitaxel-and cisplatin-induced peripheral neuropathy. Tumori Journal. 91:135-8.

79. Park SB, Goldstein D, Krishnan AV, Lin CSY, Friedlander ML. et al. (2013). Chemotherapy- induced peripheral neurotoxicity: a critical analysis. CA: a cancer journal for clinicians. 63:419-37.

80. Starobova H, Vetter I. (2017). Pathophysiology of chemotherapy-induced peripheral neuropathy. Frontiers in molecular neuroscience. 10:174.

81. Flatters S, Dougherty PM, Colvin L. (2017). Clinical and preclinical perspectives on chemotherapy-induced peripheral neuropathy (CIPN): a narrative review. BJA: British Journal of Anaesthesia. 119:737-49.

82. Bernhardson B-M, Tishelman C, Rutqvist LE. (2007). Chemosensory changes experienced by patients undergoing cancer chemotherapy: a qualitative interview study. Journal of pain and symptom management. 34:403-12.

83. Kolb NA, Smith AG, Singleton JR, Beck SL, Stoddard GJ. et al. (2016). The association of chemotherapy-induced peripheral neuropathy symptoms and the risk of falling. JAMA neurology. 73:860-6.

84. Areti A, Yerra VG, Naidu V, Kumar A. (2014). Oxidative stress and nerve damage: role in chemotherapy induced peripheral neuropathy. Redox biology. 2:289-95.

85. Chua KC, Kroetz DL. (2017). Genetic advances uncover mechanisms of chemotherapy- induced peripheral neuropathy. Clinical Pharmacology & Therapeutics. 101:450-2.

86. Janes K, Wahlman C, Little JW, Doyle T, Tosh DK. et al. (2015). Spinal neuroimmune activation is independent of T-cell infiltration and attenuated by A3 adenosine receptor agonists in a model of oxaliplatin-induced peripheral neuropathy. Brain, behavior, and immunity. 44:91-9.

87. Li C, Deng T, Shang Z, Wang D, Xiao Y. (2018). Blocking TRPA1 and TNF-α Signal Improves Bortezomib-Induced Neuropathic Pain. Cellular Physiology and Biochemistry. 51:2098-110.

88. Rochfort KD, Collins LE, Murphy RP, Cummins PM. (20140. Downregulation of blood-brain barrier phenotype by proinflammatory cytokines involves NADPH

oxidase-dependent ROS generation: consequences for interendothelial adherens and tight junctions. PloS one. 9.

89. Krarup-Hansen A, Helweg-Larsen S, Schmalbruch H, Rørth M, Krarup C. (2007). Neuronal involvement in cisplatin neuropathy: prospective clinical and neurophysiological studies. Brain : a journal of neurology. 130:1076-88.

90. Leonard GD, Wright MA, Quinn MG, Fioravanti S, Harold N, Schuler B, et al. (2005). Survey of oxaliplatin-associated neurotoxicity using an interview-based questionnaire in patients with metastatic colorectal cancer. BMC cancer. 5:116.

91. Gebremedhn EG, Shortland PJ, Mahns DA. (2018). The incidence of acute oxaliplatin-induced neuropathy and its impact on treatment in the first cycle: a systematic review. BMC cancer. 18:410.

92. 92. Morawska M, Grzasko N, Kostyra M, Wojciechowicz J, Hus M. (2015). Therapy- related peripheral neuropathy in multiple myeloma patients. Hematological oncology. 33:113-9.

93. Wechalekar AD, Chen C, Sutton D, Reece D, Voralia M. et al. (2003). Intermediate dose thalidomide (200 mg daily) has comparable efficacy and less toxicity than higher doses in relapsed multiple myeloma. Leukemia & lymphoma. 44:1147-9.

94. Tamilarasan K, Kolluru GK, Rajaram M, Indhumathy M, Saranya R. et al. (2006). Thalidomide attenuates nitric oxide mediated angiogenesis by blocking migration of endothelial cells. BMC cell biology. 7:17.

95. Jongen JLM, Broijl A, Sonneveld P. (2015). Chemotherapy-induced peripheral neuropathies in hematological malignancies. Journal of neuro-oncology. 121:229-37.

96. Keifer JA, Guttridge DC, Ashburner BP, Baldwin AS. (2001). Inhibition of NF-κB activity by thalidomide through suppression of IκB kinase activity. Journal of Biological Chemistry. 276:22382-7.

97. Gornstein EL, Schwarz TL. (2017). Neurotoxic mechanisms of paclitaxel are local to the distal axon and independent of transport defects. Experimental neurology. 288:153-66.

98. Yilmaz E, Watkins SC, Gold MS. (2017). Paclitaxel-induced increase in mitochondrial volume mediates dysregulation of intracellular Ca2+ in putative nociceptive glabrous skin neurons from the rat. Cell calcium. 62:16-28.

99. Okubo K, Takahashi T, Sekiguchi F, Kanaoka D, Matsunami M. et al. (2011). Inhibition of T-type calcium channels and hydrogen sulfide-forming enzyme reverses paclitaxel-evoked neuropathic hyperalgesia in rats. Neuroscience. 188:148-56.

100. Vahdat LT, Thomas ES, Roché HH, Hortobagyi GN, Sparano JA. et al. (2012). Ixabepilone-associated peripheral neuropathy: data from across the phase II and III clinical trials. Supportive Care in Cancer. 20:2661-8.

101. Boyette-Davis JA, Hou S, Abdi S, Dougherty PM. (2018). An updated understanding of the mechanisms involved in chemotherapy-induced neuropathy. Pain management. 8:363-75.

102. Graf WD, Chance PF, Lensch MW, Eng LJ, Lipe HP. et al. (1996). Severe vincristine neuropathy in charcot- marie- tooth disease type 1A. Cancer: Interdisciplinary International Journal of the American Cancer Society. 77:1356-62.

103. Nakamura T, Hashiguchi A, Suzuki S, Uozumi K, Tokunaga S. et al. (2012). Vincristine exacerbates asymptomatic Charcot–Marie–Tooth disease with a novel EGR2 mutation. Neurogenetics. 13:77-82.

104. Diouf B, Crews KR, Lew G, Pei D, Cheng C. et al. (2015). Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. Jama. 313:815-23.

105. Saifee TA, Elliott KJ, Lunn MP, Blake J, Reilly MM. et al. (2010). Bortezomib-induced inflammatory neuropathy. Journal of the Peripheral Nervous System. 15:366-8.

106. Thawani SP, Tanji K, De Sousa EA, Weimer LH, Brannagan III TH. (2015). Bortezomib-associated demyelinating neuropathy—clinical and pathologic features. Journal of clinical neuromuscular disease. 16:202-9.

107. Stockstill K, Doyle TM, Yan X, Chen Z, Janes K. et al. (2018). Dysregulation of sphingolipid metabolism contributes to bortezomib-induced neuropathic pain. Journal of Experimental Medicine. 215:1301-13.

108. Dawkins JL, Hulme DJ, Brahmbhatt SB, Auer-Grumbach M, Nicholson GA. (2001). Mutations in SPTLC1, encoding serine palmitoyltransferase, long chain base subunit-1, cause hereditary sensory neuropathy type I. Nature genetics. 27:309-12.

109. Wang J, Udd KA, Vidisheva A, Swift RA, Spektor TM. et al. (2016). Low serum vitamin D occurs commonly among multiple myeloma patients treated with bortezomib and/or thalidomide and is associated with severe neuropathy. Supportive Care in Cancer. 24:3105-10.

110. Delanian S, Lefaix J-L, Pradat P-F. (2012). Radiation-induced neuropathy in cancer survivors. Radiotherapy and Oncology. 105:273-82.

111. Warade AC, Jha AK, Pattankar S, Desai K. (20190. Radiation-induced brachial plexus neuropathy: A review. Neurology India. 67:47.

112. Stoll BA, Andrews JT. (1966). Radiation-induced peripheral neuropathy. British Medical Journal. 1:834.

113. Schierle C, Winograd JM. (2004). Radiation-induced brachial plexopathy: review. Complication without a cure. Journal of reconstructive microsurgery. 20:149-52.

114. Fathers E, Thrush D, Huson SM, Norman A. (2002). Radiation-induced brachial plexopathy in women treated for carcinoma of the breast. Clinical rehabilitation. 16:160-5.

115. Gosk J, Rutowski R, Reichert P, Rabczynski J. (2007). Radiation-induced brachial plexus neuropathy-aetiopathogenesis, risk factors, differential diagnostics, symptoms and treatment. Folia neuropathologica. 45:26.

116. Cavanagh J. (1968). Effects of X-irradiation on the proliferation of cells in peripheral nerve during allerian degeneration in the rat. The British journal of radiology. 41:275-81.

117. Delanian S, Lefaix J-L. (2004). The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. Radiotherapy and oncology. 73:119-31.

118. Bowen BC, Verma A, Brandon AH, Fiedler JA. (1996). Radiation-induced brachial plexopathy: MR and clinical findings. American journal of neuroradiology. 17:1932-6.

119. Thomas JE, Colby MY. (1972). Radiation-induced or metastatic brachial plexopathy?: a diagnostic dilemma. Jama. 222:1392-5.

120. Salner A, Botnick L, Herzog A, Goldstein M, Harris J. et al. (1981). Reversible brachial plexopathy following primary radiation therapy for breast cancer. Cancer treatment reports. 65:797-802.

121. Gerard J-M, Franck N, Moussa Z, Hildebrand J. (1989). Acute ischemic brachial plexus neuropathy following radiation therapy. Neurology. 39:450-.

122. Lu L, Gong X, Liu Z, Wang D, Zhang Z. (2002). Diagnosis and operative treatment of radiation-induced brachial plexopathy. Chinese journal of traumatology= Zhonghua chuang shang za zhi. 5:329-32.

123. Mogil JS, Wilson SG, Chesler EJ, Rankin AL, Nemmani KV. et al. (2003). The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. Proceedings of the National Academy of Sciences. 100:4867-72.

124. 124. Montes A, Roca G, Sabate S, Lao JI, Navarro A. et al. (2015). Genetic and Clinical Factors Associated with Chronic Postsurgical Pain after Hernia Repair, Hysterectomy, and ThoracotomyA Two-year Multicenter Cohort Study. Anesthesiology: The Journal of the American Society of Anesthesiologists. 122:1123-41.

125. McCann B, Miaskowski C, Koetters T, Baggott C, West C. et al. (2012). Associations between pro-and anti-inflammatory cytokine genes and breast pain in women prior to breast cancer surgery. The Journal of Pain. 13:425-37.

126. Hinrichs- Rocker A, Schulz K, Järvinen I, Lefering R, Simanski C. et al. (2009). Psychosocial predictors and correlates for chronic post- surgical pain (CPSP)–a systematic review. European journal of pain. 13:719-30.

127. Bredal IS, Smeby NA, Ottesen S, Warncke T, Schlichting E. (2014). Chronic pain in breast cancer survivors: comparison of psychosocial, surgical, and medical characteristics between survivors with and without pain. Journal of pain and symptom management. 48:852-62.

128. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN. et al. (2004). Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. Journal of neuroscience. 24:10410-5.

129. Jung BF, Johnson RW, Griffin DR, Dworkin RH. (2004). Risk factors for postherpetic neuralgia in patients with herpes zoster. Neurology. 62:1545-51.

130. Coderre TJ, Katz J. (1997). Peripheral and central hyperexcitability: differential signs and symptoms in persistent pain. Behavioral and Brain Sciences. 20:404-19.

131. Subramaniam K, Subramaniam B, Steinbrook RA. (2004). Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesthesia & Analgesia. 99:482-95.

132. McCartney CJ, Sinha A, Katz J. (2004). A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesthesia & Analgesia. 98:1385-400.

133. Dahl JB, Mathiesen O, Møiniche S. (2004). 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post- operative pain. Acta Anaesthesiologica Scandinavica. 48:1130-6.

134. Reuben SS, Makari-Judson G, Lurie SD. (2004). Evaluation of efficacy of the perioperative administration of venlafaxine XR in the prevention of postmastectomy pain syndrome. Journal of pain and symptom management. 27:133-9.

135. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. (2002). The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesthesia & Analgesia. 95:985-91.

136. Fassoulaki A, Sarantopoulos C, Melemeni A, Hogan Q. (2000). EMLA reduces acute and chronic pain after breast surgery for cancer. Regional anesthesia and pain medicine. 25:350-5.

137. Fassoulaki A, Triga A, Melemeni A, Sarantopoulos C. (2005). Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. Anesthesia & Analgesia. 101:1427-32.

138. Watson CPN, Evans RJ. (1992). The postmastectomy pain syndrome and topical capsaicin: a randomized trial. Pain. 51:375-9.

139. Patarica-Huber E, Boskov N, Pjevic M. (2011). Multimodal approach to therapy-related neuropathic pain in breast cancer. Journal of BU ON: official journal of the Balkan Union of Oncology. 16:40-5.

140. Tasmuth T, Härtel B, Kalso E. (2002). Venlafaxine in neuropathic pain following treatment of breast cancer. European Journal of Pain. 6:17-24.

141. Amr YM, Yousef AAA-M. (2010). Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain. The Clinical journal of pain. 26:381-5.

142. Tiina T. (1996). Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain. 64:293-302.

143. Grigoras A, Lee P, Sattar F, Shorten G. (2012). Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. The Clinical journal of pain. 28:567-72.

144. Park HJ, Kim YH, Koh HJ, Park C-S, Kang S-h. et al. (2012). Analgesic effects of dexmedetomidine in vincristine-evoked painful neuropathic rats. Journal of Korean medical science. 27:1411-7.

145. Góraj E. (2018). The efficacy of tapentadol prolonged release in the treatment of mixed cancer pain. Nowotwory Journal of Oncology. 68:146-51.

146. Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J. et al. (2019). Mechanisms of chemotherapy-induced peripheral neuropathy. International Journal of Molecular Sciences. 20:1451.

147. De Moor JS, Mariotto AB, Parry C, Alfano CM, Padgett L. et al. (2013). Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. Cancer Epidemiology and Prevention Biomarkers. 22:561-70.

148. Azhary H, Farooq MU, Bhanushali M, Majid A, Kassab MY. (2010). Peripheral neuropathy: differential diagnosis and management. American family physician. 81:887-92.

149. Boland EG, Ahmedzai SH. (2017). Persistent pain in cancer survivors. Current opinion in supportive and palliative care. 11:181-90.

150. Schloss J, Colosimo M. (2017). B vitamin complex and chemotherapy-induced peripheral neuropathy. Current oncology reports. 19:76.

151. Evans ML, Graham MM, Mahler PA, Rasey JS. (1987). Use of steroids to suppress vascular response to radiation. International Journal of Radiation Oncology Biology Physics. 13:563-7.

152. DELATTRE JY, ROSENBLUM MK, THALER HT, MANDELL L, SHAPIRO WR. et al. (1988). A model of radiation myelopathy in the rat: pathology, regional capillary permeability changes and treatment with dexamethasone. Brain : a journal of neurology. 111:1319-36.

153. Carl UM, Feldmeier JJ, Schmitt G, Hartmann KA. (2001). Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery. International Journal of Radiation Oncology* Biology* Physics. 49:1029-31.

154. Glantz MJ, Burger P, Friedman A, Radtke R, Massey E. et al. (1994). Treatment of radiation- induced nervous system injury with heparin and warfarin. Neurology. 44

155. Delanian S, Porcher R, Balla-Mekias S, Lefaix J-L. (2003). Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. Journal of Clinical Oncology. 21:2545-50.

156. Hamama S, Gilbert-Sirieix M, Vozenin M-C, Delanian S. (2012). Radiation-induced enteropathy: Molecular basis of pentoxifylline–vitamin E anti-fibrotic effect involved TGF-β1 cascade inhibition. Radiotherapy and Oncology. 105:305-12.

157. Tung TH, Liu DZ, Mackinnon SE. (2009). Nerve transfer for elbow flexion in radiation-induced brachial plexopathy: a case report. Hand. 4:123-8.

158. Tung TH, Novak CB, Mackinnon SE. (2003). Nerve transfers to the biceps and brachialis branches to improve elbow flexion strength after brachial plexus injuries. Journal of neurosurgery. 98:313-8.

159. LeQuang C. (1989). Postirradiation lesions of the brachial plexus. Results of surgical treatment. Hand clinics. 5:23-32.

160. Brunelli G, Brunelli F. (1985). Surgical treatment of actinic brachial plexus lesions: free microvascular transfer of the greater omentum. Journal of reconstructive microsurgery. 1:197-200.

161. Gillette E, Mahler P, Powers B, Gillette S, Vujaskovic Z. (1995). Late radiation injury to muscle and peripheral nerves. International Journal of Radiation Oncology• Biology• Physics. 31:1309-18.

162. Kairaluoma PM, Bachmann MS, Rosenberg PH, Pere PJ. (2006). Preincisional paravertebral block reduces the prevalence of chronic pain after breast surgery. Anesthesia & Analgesia. 103:703-8.

163. Moller JF, Nikolajsen L, Rodt SA, Ronning H, Carlsson PS. (2007). Thoracic paravertebral block for breast cancer surgery: a randomized double-blind study. Anesthesia & Analgesia. 105:1848-51.

164. Coveney E, Weltz CR, Greengrass R, Iglehart JD, Leight GS, Steele SM, et al. (1998). Use of paravertebral block anesthesia in the surgical management of breast cancer: experience in 156 cases. Annals of surgery. 227:496.

165. Andreae MH, Andreae DA. (2012). Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery. Cochrane Database of Systematic Reviews.

166. Oncology ASoC. (2014). The state of cancer care in Americ: a report by the American Society of Clinical Oncology. Journal of Oncology Practice. 10:119-42.

167. Ablin JN, Buskila D. (2013). Personalized treatment of pain. Current rheumatology reports. 15:298.

168. Klepstad P, Rakvåg T, Kaasa S, Holthe M, Dale O. et al. (2004). The 118 A> G polymorphism in the human μ- opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiologica Scandinavica. 48:1232-9.

169. Stamer UM, Zhang L, Stüber F. (2010). Personalized therapy in pain management: where do we stand? Pharmacogenomics. 11:843-64.

170. Ali ZK, Kim RJ, Ysla FM. (2009). CYP2C9 polymorphisms: considerations in NSAID therapy. Current opinion in drug discovery & development. 12:108-14.

171. Bach-Rojecky L, Vađunec D, Žunić K, Kurija J, Šipicki S. et al. (2019). Continuing war on pain: a personalized approach to the therapy with nonsteroidal anti-inflammatory drugs and opioids. Personalized medicine. 16:171-84.

172. Kaye AD, Garcia AJ, Hall OM, Jeha GM, Cramer KD, Granier AL, et al. (2019). Update on the pharmacogenomics of pain management. Pharmacogenomics and personalized medicine. 12:125.

173. Webster LR, Belfer I. (2016). Pharmacogenetics and personalized medicine in pain management. Clinics in laboratory medicine. 36:493-506.

174. Banerjee B, Kumar R, Thamineni K, Shah H, Thakur G. et al. (2020). Effect of Environmental Exposure and Pharmacogenomics on Drug Metabolism. Current drug metabolism.

175. Smith DM, Weitzel KW, Cavallari LH, Elsey AR, Schmidt SO. (2018). Clinical application of pharmacogenetics in pain management. Personalized medicine. 15:117-26.