Review Article

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Breast cancer pain management - A review of current & novel therapies

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Breast cancer is one of the most prevalent cancers amongst women in the world. Unfortunately, even after adequate treatment, some patients experience severe pain either due to disease progression or due to treatment related side effects. The persistent pain causes a negative physical and psychosocial impact on patients' lives. Current rational pain management is patient-centred and requires a thorough psychological assessment. Usually adequate analgesia is achieved by adopting the WHO's three step analgesic ladder. As the disease progresses, the pain experienced by the patient also increases. This necessitates the administration of opioids and adjuvant analgesics to the breast cancer patients experiencing severe pain. However, opioid use is associated with intolerable side effects like constipation, nausea, vomiting, fear of dependence, and tolerance. Concomitant medications are required to combat these unacceptable side effects. Adjuvant analgesics need to be added to provide adequate and satisfactory analgesia. These factors worsen the psychological state of patients and deteriorate their quality of life. Hence, there is a need to develop therapeutic modalities to provide adequate analgesia with minimum side effects. This review article focuses on the current treatments available for cancer pain management, their limitations, and novel targets and non-pharmacological measures under investigation which have the potential to produce a radical change in pain management measures for the breast cancer patients.

Key words Breast cancer - cancer pain - pain management

Introduction

The variation observed in rates of incidence as well as mortality due to breast cancer, is due to a number of contributing factors like age, race, socio-economic status, life style, reproductive history, family history, *etc*[1]. According to GLOBOCAN 2008 cancer fact sheet[2], incidence of breast cancer was approximately 1.38 million (23% of all neoplasms). Developed countries (except Japan) have a higher incidence (more than 80 for every 100,000 persons) as compared to developing nations (less than 40 for every 100,000 persons)[2].

As a consequence of advancements in diagnostic procedures and treatments available, the rate of survival of patients has increased. Hence, it is expected that the population susceptible to develop pain as a complication would increase[3]. It has been estimated that in developing nations 70 per cent of new breast cancer cases would be seen by 2020[4]. Pain arising in advanced stage of

breast cancer can cause emotional suffering and affects quality of life of patients[5]. As per the estimates of the International Association for the Study of Pain (IASP) the prevalence of pain in breast cancer ranges from 40-89 per cent[6]. It has been found that persistent pain after surgical treatment is quite common and is higher among young patients, those undergoing radiotherapy and axillary lymph node dissection[3,7], and about 20-50 per cent women are affected by persistent neuropathic pain after their surgical treatment[8].

Symptoms

Pain usually does not occur in early breast cancer. A painless lump may be the first symptom. In later stages, pain may occur due to involvement of deeper structures like muscles, ribs, *etc.,* resulting in severe excruciating pain which increases with chest movements. Patients undergoing mastectomy may develop chronic neuropathic pain which may be either phantom breast pain, or intercostobrachial neuralgia (including post-mastectomy pain syndrome), or neuroma pain (including scar pain) or pain due to other nerve injury[3]. During radiotherapy, there may be active painful skin lesions at the radiation site and later cervical or brachial plexopathy may develop. Involvement of brachial plexus by tumour results in pain and Horner's syndrome, whereas sensory symptoms like paresthesia, numbness, dysesthesia and swelling and weakness of arm occur in radiation induced injury to brachial plexus[9]. Depending upon the measurement tool used, 2-83 per cent of breast cancer survivors suffer from lymphoedema over the chest or arm[10]. Breast cancer metastasis commonly involves bones, lungs, brain and liver[11], which respectively results in bony pain, pain in hypochondrium, headache and other symptoms in areas of cancer invasion.

There may be sudden exacerbations of pain, termed as breakthrough cancer pain (BTcP). A patient is supposed to have BTcP only when he/she has adequately controlled background cancer pain and is still experiencing transient exacerbations of pain. It can either occur unexpectedly (idiopathic pain) with involuntary acts like coughing, or expectedly (volitional pain) with voluntary acts like walking[12]. The site and pathophysiology of BTcP is usually the same site as that of background pain[13]. It is relatively common in advanced disease, painful vertebral metastasis and pain originating from nerve plexuses[14].

Aetiology

The aetiology of cancer pain is multi-factorial. It may arise due to *(i)* cancer itself due to release of inflammatory mediators or due to metastases to distant tissues including bones and neuronal tissue[15], and *(ii)* cancer treatment. Sensory neurons are degenerated after chemotherapy and lead to neuropathic pain. Radiotherapy induced pain arises as a result of microvascular changes and nerve compression[15]. The main causes for surgery induced pain are damage to the intercostobrachial nerves and neuroma formation[3]. Estrogen deficiency caused by aromatase inhibitors leads to arthralgias[16].

Pain management

Pain management for cancer patients requires critical pain assessment and thorough patient evaluation including psychological assessment. Depending upon the aetiology of pain, the approach to pain management can be customised for the patient. Various approaches for pain management and treatment are given in Table I[17]. In about 85-90 per cent of the patients, the pain can be controlled by oral analgesics given according to the World Health Organization (WHO) analgesic ladder, while in others interventions may be required[18].

Currently available treatments

According to WHO[17], pharmacotherapy constitutes the main treatment for cancer pain (Table II). The analgesics are used as per five principles: 'by mouth', 'by the clock', 'by the ladder', 'for the individual' and 'attention to detail'. According to the WHO analgesic ladder, the treatment for cancer pain should follow a sequential order (Figure)[17]. It is initiated by non-opioid drugs, *e.g.* paracetamol, ibuprofen, which constitute Step I. If adequate analgesia is not achieved, weak opioids like codeine, tramadol should be added. If the pain is still not properly controlled, strong opioids such as morphine, oxycodone can be given (Table II), which constitute Step III of WHO analgesic ladder.

Table I. Various approaches for cancer pain management

Approach	Treatment given
Modification of underlying pathology	Surgery, chemotherapy, radiotherapy, hormone therapy
Pharmacotherapy	NSAIDS (Non-steroidal anti-inflammatory drugs), anticonvulsants, opioids, anti-depressants, corticosteroids
Interventional techniques	Local anaesthetics, neurolytic agents

Source: Adapted from Ref. 17

Table II. List of basic drugs prescribed for cancer pain

Drug category	Examples
Non-opioids	Paracetamol, Acetyl salicylic acid, Indomethacin, Ibuprofen, Diclofenac, Naproxen
Weak opioids for mild to moderate pain	Codeine, Tramadol, Dihydrocodeine
Strong opioids for moderate to severe pain	Morphine, Methadone, Oxycodone

Source: Adapted from Ref. 17

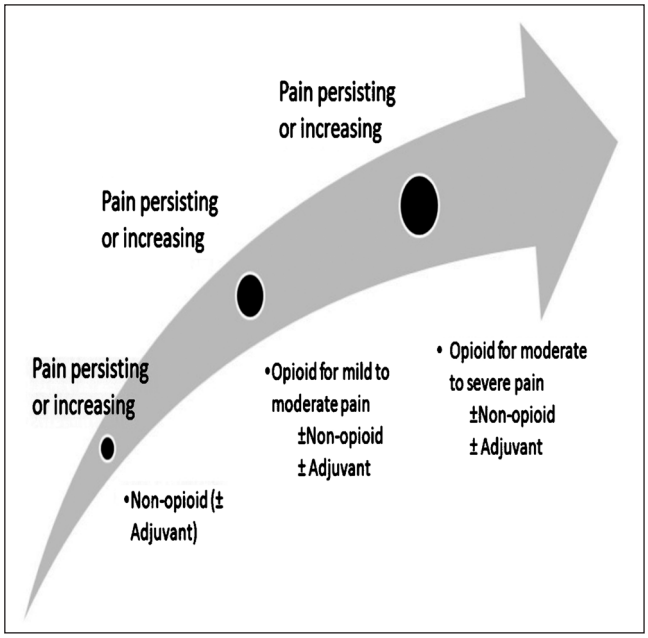

Fig. WHO's ladder for relief of cancer pain.
Source: Adapted from Ref.17.

Adjuvant medications for pain relief are also provided for different types of pain (Table III)[19].

Amongst strong opioids, morphine is the most commonly used. Oral formulations are available as immediate release (IR) morphine and sustained release (SR) morphine sulphate or hydrochloride. Maximum analgesic effect is obtained in 1.5 to 2 h for IR preparations and 3 to 4 h for SR preparations. Usually, opioid therapy is started with IR formulations, though some physicians prefer to start with controlled release formulation, and reserve IR formulations for BTcP[20]. Steady state of the drug is reached only after five half lives, so dose changes are advised only after 24 h for IR and in 2-3 days for SR formulations[20]. There is no maximum safe dose for morphine due to absence of ceiling effect to analgesia. Wide individual variations exist to provide same endpoint of pain relief[21]. The recommended correct dose is the dose which relieves pain adequately without intolerable side effects[22].

Opioid rotation is done when inadequate analgesia or intolerable side effects are experienced. The new opioid dose is usually reduced to 66 per cent of the calculated equivalent dose due to incomplete cross-tolerance between the two. Moreover, opioids can be discontinued if appropriate pain relief is achieved by other alternatives like radiation therapy or neurolytic blocks[20]. Opioids can be discontinued slowly either by decreasing the daily dose by up to 10 to 20 per cent per day or over several weeks to minimize withdrawal symptoms[23].

Transdermal fentanyl (TDF) is used for managing patients with stable cancer pain who cannot take oral medications[24]. Patches are available with a delivery rate of 25, 50, 75 and 100 µg/h, and need to be changed after every 72 h. The dose increase is usually 30-50 per cent, but sometimes 100 per cent (from 25 to 50 µg patch) [20].

Table III. Adjuvant medications and their side effects

Drug category	Examples	Side effects
Tricyclic antidepressants	Amitriptyline, Desipramine	Constipation, blurred vision, dry mouth, urinary retention, tachycardia, cognitive impairment
Anti-convulsants	Gabapentin	Weight gain, ataxia, dizziness, somnolence, fatigue
Local anaesthetics	Mexilitine	Nausea, dizziness
Corticosteroids*	Prednisolone, Dexamethasone	Gastrointestinal discomfort, immunosuppression, hyperglycaemia
Bisphosphonates	Clodronate, Pamidronate, Zoledronic acid, Ibandronate	Bone/joint/ muscle pain, bisphosphonate-associated osteonecrosis

*The possibility of side effects is dependent on the duration of therapy
Source: Ref. 19

Adjuvant medications

Adjuvant medications can be added at any stage of the WHO ladder. For management of cancer induced neuropathic pain antidepressants, gabapentinoids (gabapentin, pregabalin), or other anti-epileptic drugs can be used. Primary tricyclic antidepressants (TCA) like amitriptyline are more effective in neuropathic cancer pain, whereas secondary amines like nortriptyline and desipramine which produce lesser analgesia have fewer side effects. Neuroleptics like haloperidol, chlorpromazine, selective serotonin reuptake inhibitor-fluoxetine, and antiepileptic-carbamazepine are also recommended for treating neuropathic cancer pain[25].

N-methyl-D-aspartate (NMDA) receptor antagonists like ketamine and amantadine provide an alternative for management of opioid resistant cancer pain[25]. When pain is not responding to opioids, oral ketamine can be used; only after improvement with a trial of low-dose intra venous ketamine[26]. However, a systematic review revealed that evidence is insufficient to determine the role of ketamine as an adjuvant to opioids for cancer pain relief[27].

The 5 per cent lidocaine patch and 8 per cent capsaicin patch have been found beneficial in treating neuropathic pain. These are safe and well tolerated, and adverse events are attributed to local application of the patch[25].

Corticosteroids are also used for managing neuropathic cancer pain. Longer duration of action and least mineralocorticoid effect favour dexamethasone to be frequently used. However, long term use is inhibited by adverse effects like immunosuppression, proximal muscle wasting and endocrine effects[25].

Management of breakthrough cancer pain (BTcP)

BTcP can be controlled by treating the underlying aetiology, optimising around the clock medications and using specific medications. In patients with well controlled baseline pain having BTcP episodes, increase in baseline opioid dose results in better pain relief[28]. For BTcP episodes, about one-sixth (17%) of the daily dose of morphine can be used[21].

Faster onset of action is desirable to control BTcP episodes. Effervescent morphine tablets provide faster analgesia as compared to IR oral morphine, hence, can be alternatively used[29]. Nasal morphine-chitosan spray is rapidly absorbed through nasal mucosa and has plasma profile similar to slow iv administration of morphine[30]. It provides a faster and convenient alternative than oral morphine for managing episodic pain[31].

Transmucosal administration of fentanyl provides rapid onset of action via non-invasive route. Oral transmucosal fentanyl citrate (OTFC) is a fentanyl-impregnated lozenge, available in six dosage strengths (200, 400, 600, 800, 1200 and 1600 µg)[29]. Absorption rate and bioavailability of OTFC is greater than oral absorption and serum fentanyl levels increase linearly with dose. Intranasal fentanyl spray (INFS) has faster onset of action (at 10 min), attaining peak effect at 12-15 min. It can be self administered, is acceptable to patients with reduced salivary flow and has greater preference than OTFC[29]. Fentanyl buccal tablet (FBT) is an effervescent drug delivery system employed to augment the rate and extent of fentanyl absorption across the buccal mucosa. Its absolute bioavailability is greater than OTFC. Sublingual fentanyl (SLF) is rapidly absorbed due to high vascularity and permeability of sublingual mucosa. It directly reaches systemic circulation and plasma concentration increases linearly with increase in dose. Ease of administration makes it popular amongst patients[29]. Fentanyl buccal soluble film (FBSF) is available in strengths of 200-1200 µg. It delivers fentanyl via buccal mucosa, thereby providing fast onset of pain relief, and decrease in pain intensity persists for about 60 min[32]. All these formulations are more effective in reducing episodic pain. These provide faster analgesia, relieve more episodes of BTcP, are easier to use and are usually well tolerated[29].

Management of disorders commonly seen with breast cancer

Brachial plexopathy: Radiotherapy is useful in relieving pain from metastatic plexopathy, whereas surgery provides pain relief in radiation plexopathy, but without any improvement in neurological deficit[9,33]. In addition, dorsal column stimulators, transdermal electrical nerve stimulation, neurolysis with omentoplasty are helpful in managing radiation plexopathy. Contrarily, metastatic plexopathy can be managed by dorsal root entry zone procedure, paravertebral nerve blocks, dorsal rhizotomy and contralateral cordotomy[34].

Painful bony metastasis: Palliative radiotherapy, namely external beam radiotherapy is useful in patients with painful bony metastasis. Both single (8-10 Gy) and fractionated (20-30 Gy in 5-10 fractions) radiotherapy provide good analgesia[35]. Bisphosphonates like zoledronic acid, pamidronate, ibandronate, or denosumab (human monoclonal antibody) not only

provide relief from bony pain but reduce the risk of skeletal complications and the need of radiotherapy. Rarely, gastrointestinal toxicity, renal toxicity, and osteonecrosis of the jaw may be seen[36]. Radioisotopes such as samarium[153], strontium[89] and rhenium[186] are also used in patients with painful bony metastases[37]. These reduce the bony pain over one to six months, but bone marrow suppression is frequent. Therefore, these should be reserved for patients with painful bone metastases not responding to established treatments like radiotherapy, hormone therapy or bisphosphonates[38].

Post-mastectomy pain syndrome (PMPS): PMPS can be prevented by multimodal approaches using local anaesthetics with gabapentin and pregabalin[39] and with antidepressants like amitriptyline, venlafaxine[25]. Stellate ganglion block has been found to be useful in some patients to treat PMPS[40,41].

Lymphoedema: Complex decongestive therapy and exercises like range of motion, resistance and strengthening, compression garments and weight reduction are helpful in decreasing lymphoedema. Therapies like endermologie, flexitouch, deep oscillation, acupuncture, liposuction and autologous stem cell transplant are recent treatment options[10].

Brain metastasis: Single metastasis is usually treated by surgery followed by whole brain radiotherapy (WBRT), whereas multiple (2-4) metastases are treated by stereotactic surgery, with or without WBRT[42].

Liver metastasis: Liver metastasis is usually treated by chemotherapeutic agents or TACE (Transarterial Chemoembolization) [43].

Limitations of pharmacotherapy

Non-steroidal anti-inflammatory drugs (NSAIDS) usually are tolerable and have a few side effects like nausea, vomiting, gastric disturbances, hepatic or renal dysfunction[17]. These exhibit ceiling effect and should be used with caution in high risk patients including elderly; patients with gastrointestinal disorders, renal and hepatic impairment and/or those receiving other medications[44].

Opioid use is associated with many side effects. The most common ones are nausea/vomiting and constipation. Tolerance does not develop to constipation. It necessitates life-long treatment with bulk laxatives, stool softeners, osmotic laxatives and stimulant laxatives. Sedation may occur at the initiation and rapid dose escalation. It can be decreased by reducing the opioid dose, opioid rotation, or using psychosomatic stimulants. Psychomotor performance is normally impaired at the start of opioid therapy, but once a stable dose is reached, it does not result in any impairment even immediately after taking the opioid dose[45]. Respiratory depression occurs rarely in chronic cancer pain patients receiving opioids regularly. It may occur when pain is relieved suddenly, *e.g.* non-titration of opioid dose after successful nerve block[46]. Tolerance develops to analgesic action of opioids when administered for a long time. In order to relieve the pain, the dose has to be increased[45,46]. As a result of these side effects, there may be either under-dosing or early discontinuation of opioids leading to inadequate pain relief[45].

Concerns about opioid availability and accessibility have been raised. Various regulations have been imposed for prescribing opioids. Only licensed practitioners have the authority to prescribe opioids. License is required by the pharmacies also to dispense opioids. Extensive regulatory requirements lead to reluctance on the part of pharmacists to dispense opioids[47]. With the collaborative efforts of the WHO Collaborating Centre at the Pain and Policy Studies Group (PPSG), and the Indian Association of Palliative Care narcotic regulations were eased in India in 1998.

The usefulness of WHO ladder has been questioned by many studies. The addition of weak opioids to NSAIDs is questionable. In one meta-analysis, the addition of weak opioids to NSAIDs resulted in no improvement of analgesia, while another review demonstrated that NSAIDs and weak opioids produce similar analgesia, when given alone or in combination[48,49]. The role of strong opioids as step I analgesic in advanced cancer has also been put forward. A randomized trial compared pain relief in advanced cancer cases when treated either according to the WHO ladder or with strong opioids as a first line treatment[50]. Patients treated with strong opioids as first line treatment had considerably more relief in pain intensity, greater satisfaction and improvement in general condition as compared to the patients treated as per WHO analgesic ladder.

Non-pharmacological therapies

Apart from the conventional pharmacotherapy, many non-pharmacological measures are available to manage breast cancer pain. The prevalence of complementary or alternative therapies to improve health is increasing. Their usage amongst breast cancer survivors has been found high as compared to

the general population and those suffering from other types of cancer[51].

With the recognition of objective and subjective component of cancer pain, cognitive behavioural therapy is being adopted by many breast cancer patients for pain relief. It includes various techniques like relaxation training, progressive muscle relaxation, hypnosis, distraction, guided imagery, problem solving, *etc*[52]. Pre-surgery hypnotic intervention is supposed to reduce post-surgery pain in patients[53]. Guided imagery modulates pain and alters transmission and perception of pain stimulus by distracting attention from it[54]. Moore and Spiegel[55] demonstrated in African-American and White women with metastatic breast cancer, that they used this technique to re-connect to the self, manage cancer pain and develop a sense of control over their lives. Individual variations in improvement in pain score by using imagery necessitate the need to customise the intervention given to the patient[54]. A meta-analysis conducted by Tatrow and Montgomery[56] revealed that breast cancer patients receiving various cognitive behavioural therapies experienced lesser pain as compared to control groups.

Thoracic paravertebral nerve block technique reduces post-operative pain and lessens the chances of developing chronic mastectomy pain syndrome[57]. It helps in pain relief and improves the quality of life of breast cancer patients after surgery when combined with glucocorticoids[58].

Novel therapies

Various forms of pharmacological and non-pharmacological treatments are being developed to aid in cancer pain relief. Some of these are described below:

Pharmacological therapies

CB2 agonist: Cannabinoid receptor 2 (CB2) agonist is a novel therapeutic target, which has proved efficacious against neuropathic pain. Low dose of delta-9-tetrahydrocannabinol (THC) produces mild analgesic effects on cancer patients, but higher dose results in side effects in the form of somnolence, dizziness, ataxia, and blurred vision[59]. Johnson *et al*[60] found in a multicentric trial that tetrahydrocannabinol: cannabidiol (THC:CBD) extract is efficacious for pain relief in patients with advanced cancer pain refractory to opioids. A phase III clinical trial to determine effect of cannabinoid extract (Sativex) in reducing chemotherapy induced neuropathic pain is being conducted (*ClinicalTrials.gov #NCT00872144*)[61].

(ii) Tetrodotoxin: Upregulation of voltage gated sodium (Na^+) channels has been seen in metastatic cancers including breast cancer[62]. Their expression is inhibited by selective Na^+ channel blocker - tetrodotoxin, which produces the analgesic effect by blocking action potential propagation or ectopic discharges. A recent trial suggests that tetrodotoxin may alleviate moderate to severe, treatment-resistant cancer pain even for prolonged periods following treatment, with acceptable toxicity[63].

(iii) Botulinum toxin: Botulinum toxin has ability to suppress the release of neurotransmitters involved in transmission of pain impulses/nociception *i.e.* endothelin-1, substance P, and calcitonin gene related peptide (CGRP) and neuropeptide Y[64]. It has been used to control post-mastectomy pain[65] and has potential to reduce cancer induced bone pain[64].

(iv) Caffeine: Caffeine is an antagonist of adenosine receptors-A[1], A[2A], A[2B]. It has shown beneficial effects when given as an adjuvant with NSAIDs and opioids[66]. Clinical trials to establish the efficacy of caffeine as an adjuvant to opioids in reducing pain (*ClinicalTrials.gov #NCT00879775*)[67] and in alleviating post-operative pain after breast surgery are being carried out (*ClinicalTrials.gov #NCT00299039*)[68].

(v) Soy isoflavones: Some studies have shown analgesic effect of soy isoflavones in animal models[69,70]. A clinical trial was being conducted to determine the outcome of soy isoflavones consumption as analgesic after surgery for breast carcinoma (*ClinicalTrials.gov #NCT01047774*)[71].

Non-pharmacological therapies

(i) Gene therapy: Improved understanding of signalling pathways underlying pain generation and transmission, and significant advances in the viral vector designs have led to the development of gene-based approach to modulate nociception[72]. Fink *et al*[73] conducted a phase I clinical trial of NP2, a replication-defective herpes simplex virus (HSV) based vector expressing human preproenkephalin (PENK) in cancer pain subjects. The intervention was well tolerated by the subjects. Phase II of this clinical trial for treating intractable pain due to malignancy is currently being carried out (*ClinicalTrials.gov #NCT01291901*)[74].

(ii) Yoga: Yoga has shown positive results on behavioural outcomes like pain, fatigue, depression, mood and quality of life[75]. Galantino *et al*[76] demonstrated that yoga could reduce joint pain due to aromatase inhibitors in breast cancer survivors. Carson

et al[75] demonstrated that women with metastatic breast cancer reported improvement in pain when given yoga as intervention. However, the sustainability of pain relief after yoga based intervention needs more investigation.

(iii) Music therapy: Music therapy reduces pain through physiological, psychological and socio-emotional mechanisms. Li *et al*[77] reported that music therapy significantly reduced pain scores in breast cancer patients following mastectomy. Due to the advantage of absence of any adverse effects from music therapy, it can be combined with other interventions for pain relief to obtain maximum benefit. This non-invasive non-pharmacological intervention can be customised according to the patient's cultural background and familiarity; and can prove beneficial in not just reducing cancer induced pain but also to reduce anxiety and depression[78].

(iv) Acupuncture: Analgesic activity of acupuncture is attributed to various mechanisms like discharges of polymodal receptors, increase in circulatory levels of opioid peptides, blood flow improvement and mechano-transduction-based responses[79]. Auricular acupuncture has been found to reduce pain intensity in subjects with neuropathic cancer pain[80]. Studies have demonstrated analgesic activity of acupuncture and electro-acupuncture in breast cancer survivors experiencing arthralgia due to aromatase inhibitors[81,82]. Clinical trials investigating the role of acupuncture/ electro-acupuncture in reducing taxane induced neuropathic pain in breast cancer patients are being carried out (*ClinicalTrials.gov # NCT01163682, NCT01050075*)[83,84].

(v) Scrambler therapy: Scrambler therapy is an electro-analgesic technique to regulate pain. Ricci *et al*[85] demonstrated its safety and efficacy in controlling cancer pain in advanced cases. Chronic neuropathic pain was shown to be better relieved by scrambler therapy than standard pharmacotherapy in a pilot study conducted by Marineo *et al*[86]. The results of these preliminary studies need to be confirmed via clinical trials to be used in cancer subjects including breast cancer survivors. A phase II study to determine its effect in managing chronic chemotherapy-induced peripheral neuropathy has been conducted[87].

Conclusion

The life expectancy of breast cancer patients is increased due to effective treatment options available today. Nonetheless, persistent chronic pain of oncologic origin has depreciated the quality of life in advanced stage breast cancer survivors after treatment. A range of analgesics and adjuvant medications are accessible to the patients. These medicines provide satisfactory analgesia but are allied to a number of side effects. Hence, more effective ways for managing breast cancer pain are needed. However, further studies are needed for the novel therapies and agents to assure fast and adequate pain relief with minimum side effects.

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