Integrative Therapies in Cancer Pain

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Anna Woodbury and Bati Myles

18.1 Introduction

Pain is inevitable; suffering is optional

–Haruki Murakami

The author of this quote, in 6 words, managed to encapsulate our current understanding of the complexity of pain. While pain is a universal experience, from stubbed toes to broken bones, the subjective experience and its meaning vary a great deal. Prior to advances in the field of neuroscience, pain was as mysterious and inevitable as most physical phenomena. With time, pain became less of an enigma as the structure and function of nerves, and their role in the perception of sensation became clear. Pain was one of many stories neurons shared with one another in the language of neurotransmitters and ions. Something so finite and understandable didn't have to be frightening anymore. However, we are coming to realize that even that isn't the entire story. The dance within the nervous system is not so predictable or choreographed. The brain does not passively receive information and faithfully respond in a standardized manner. Just as two individuals will respond to the same stimulus differently based on past experiences and personality, and the brain's response to pain reflects this variety. The brain is always changing, as prior experiences combine with new ones to shape and mold it into something slightly changed. The experience of pain itself changes how the brain responds to

A. Woodbury (✉)
Anesthesiology, Veterans Affairs Medical Center, Emory University School of Medicine, Atlanta Veterans Affairs Healthcare System, 1670 Clairmont Rd, Decatur, GA 30033, USA
e-mail: anna.woodbury@emory.edu

B. Myles
Emergency Medicine Physician, Palliative Care Fellow, Emory University School of Medicine, Atlanta, GA, USA

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that pain. So, not only will two different people respond to pain differently, the same person, with time, will as well.

The response to pain and its changes over time can be seen on a molecular level, as a sustained, intense, painful stimulus leads to upregulation of pain receptors and decreased firing thresholds in the peripheral nervous system [1, 2]. This central hypersensitization can lead to allodynia (innocuous stimulation causes pain) and hyperalgesia (stimulation causes pain out of proportion to the intensity of the stimulus). In the central nervous system, gene expression changes, establishing pathways that set up new, abnormal responses to pain [1, 2]. Further, it is not only the somatosensory areas of the brain that responds to pain; affective and cognitive regions respond as well, further described in neuroimaging studies of acute and chronic pain. Physical pain is not observed dispassionately from a distance; it has a significant emotional and cognitive impact that only grows with the intensity and duration of that pain. Because of this, for some people, physical pain breeds social, psychological and spiritual pain, which then breeds more physical pain and suffering. So we are beginning to understand that while pain is universal, suffering is not. Our individual histories and neural architecture determine what pain means to each of us.

The recognition of the individual experience of pain, and the impact that the mind has on that experience, has led to a growing acceptance of mind–body therapies. These modalities, which include meditation, art therapy, yoga and hypnotherapy, are designed to use the mind/body interface as a tool to facilitate healing. This has, in turn, fostered acceptance of a broader medical approach known as integrative medicine [3]. Integrative medicine embraces all effective treatments, including conventional western medicine and complementary treatments, which fall outside of that umbrella. Within the field of integrative medicine, there is also an emphasis on the patient as a whole person, with physical complaints considered equally as important as the impact of illness on a person's functioning in various aspects of life.

Patients are enthusiastically embracing integrative medicine in large numbers. According to a 2012 National Health Interview Survey (NHIS), 33.2% of Americans have used some form of complementary medicine in the past year [4]. The NHIS conducted in 2017 was not as broad, focusing on meditation, yoga and chiropractic, but showing increases in the percentage of the population using each of these therapies both in children and adults [5]. Among oncology patients, multiple studies show that more than 50% use complementary medicine after being diagnosed with cancer and up to 91% during chemotherapy [6, 7]. Complementary therapies available for integration into conventional medicine include 5 broad categories: Mind–Body Therapies, Energy Therapies, Alternative Medical Systems, Manipulative Therapies, and Biologicals/Nutraceuticals. Some of these therapies fall within more than one category, e.g., Tai Chi/QiGong which is considered both an Energy therapy as well as a Mind–Body therapy, and could also fall within Alternative Medical Systems as part of Traditional Chinese Medicine (TCM). Table 18.1 summarizes various complementary and alternative medicine therapies available to cancer patients. Though not entirely comprehensive given the wide

Table 18.1 Complementary and alternative medicine therapies for cancer patients

Mind–body	Energy	Alternative medical systems	Manipulative	Biologicals/Nutraceuticals	Other
Meditation	Acupuncture	Homeopathy	Chiropractic	Diet	Balneotherapy
Guided imagery	Acupressure	Traditional Chinese medicine	Massage	Herbal supplements	Hydrotherapy
Hypnotherapy	Magnet therapy	Ayurvedic medicine	Osteopathy	Vitamins	Hyperbaric therapy
Tai Chi/Qigong	Reiki				Cryotherapy
Yoga	Biofields				
Music therapy					
Art therapy					
Spirituality					

range of options available outside of conventional medical care, the table provides an idea of the broad range of therapies available. Not all of the therapies have sufficient evidence to justify their use, though most of the therapies carry a low risk of harm. It is important, however, to acknowledge that the potential for harm does indeed exist, and that "natural" does not necessarily mean "safe." Research regarding these therapies for cancer is ongoing and available trials can be found on the National Cancer Institute website [8].

Given the widespread use of complementary therapies, it is important that medical providers be prepared to discuss the risks, benefits and evidence supporting these treatments. Moreover, it is important that clinicians initiate discussions about the use of complementary medicine with patients. In one study, more than two-thirds of physicians were unaware of their patients' use of complementary therapies, suggesting a significant disconnect between patients and their physicians [9]. Patients seem to be reluctant to share their use of integrative therapies, while physicians may not feel like they have adequate time or knowledge to broach this subject. By initiating discussions about all therapies being used, clinicians foster a supportive environment in which patients have permission to disclose their use of less traditional treatments. Resources from the National Institutes of Health include regularly updated summaries on complementary therapies from the National Cancer Institute (https://www.cancer.gov/about-cancer/treatment/cam/patient) as well as from the National Center for Complementary and Integrative Health (https://nccih.nih.gov/health/integrative-health).

Web References:

National Cancer Institute. *Complementary and Alternative Medicine for Patients.* 20 Sep. 2020: https://www.cancer.gov/about-cancer/treatment/cam/patient

National Center for Complementary and Integrative Health. *Complementary, Alternative, or Integrative Health: What's in a Name?* 20 Sep. 2020: https://nccih.nih.gov/health/integrative-health

In this chapter, we will discuss some of the most studied and commonly used complementary therapies available for the treatment of cancer-related pain and symptoms. Our goal is to provide a framework for discussions between medical providers and their patients to ensure safety, discussion of all available treatments, and open lines of communication. By improving our understanding of complementary and alternative treatments, we exponentially expand the arsenal of therapies that can be explored to improve a patient's ability to better manage pain and reduce suffering.

18.2 Nutritional Supplements

The term nutritional supplement, in the context of integrative medicine, is very broad. This can refer to herbs of various kinds, plant products such as aloe vera, vitamins, minerals and amino acids among others. Anything that is edible and used for medicinal purposes falls under this category. Because of the wide variety of products and traditions that inform their use, it is unsurprising that there is a great deal of anecdotal evidence supporting an array of supplements, but a relatively small amount of literature supporting their efficacy. As these are compounds being introduced into the body, they pose a particular threat, while being the complementary therapy most commonly used by patients. It is important to note both the potential side effects as well as benefits from these therapies, and evaluate the available evidence that would support or should prevent their use in specific patients.

18.2.1 Supplements for Neuroprotection

Vitamin E is a commonly used supplement that can increase the risk of bleeding, but has also been found to be neuroprotective and may have applications for the prevention of chemotherapy-induced neuropathy [9, 10]. Neuropathy is a common, dose-limiting complication of treatment with platinum-based chemotherapy (PBC). While the mechanism of action is unknown, there is evidence that mitochondrial dysfunction from oxidative stress damages peripheral nerves and causes neuropathic pain. Vitamin E is a naturally occurring antioxidant that has been shown to be significantly reduced in patients being treated with PBC [11]. Additionally, the peripheral neuropathy that develops in some patients receiving PBC is similar to symptoms experienced by people with vitamin E deficiency. These observations have led to a number of randomized trials examining the efficacy of vitamin E supplementation in the prevention of chemotherapy-induced neuropathy. One such study by Pace et al. involved 108 patients receiving at least 300 mg/m^2 cumulative dose of cisplatin. These patients had to be free of baseline neuropathy and naïve to chemotherapy. They also had to ultimately receive at least 300 mg/m^2 cumulative dose of cisplatin therapy. The subjects were randomized to receive 300 mg of vitamin E daily and for 3 months after completion of chemotherapy or placebo. Patients were then evaluated for the presence and severity of neurotoxicity using a validated neurotoxicity score (Total Neuropathy Score) as well as electrophysiologic nerve conduction and nerve potential amplitude studies. The study showed that patients who had received vitamin E had significantly lower mean neurotoxicity scores and a 0.14 relative risk of developing signs or symptoms of neurotoxicity. Additionally, the treatment group had no significant change from baseline on electrophysiological examination, while patients in the control group had significantly decreased mean sural and sensory median nerve amplitude values. This is supported by the findings of other similar studies [12–14].

Oral glutamine, both a potent antioxidant and the most abundant amino acid in the serum and skeletal muscle, has also been shown in multiple studies to prevent neurotoxicity. Glutamine is a precursor to two important neurotransmitters: glutamate and gamma-aminobutyric acid (GABA). A 2007 study by Wang et al. found that it prevented oxaliplatin-induced neuropathy in colorectal cancer patients [15]. In this study, 86 patients with metastatic colorectal cancer receiving oxaliplatin, 5-fluorouracil and folinic acid were randomized to receive glutamine or nothing as controls. The glutamine group received 15 g of glutamine twice daily for 7 consecutive days every 2 weeks starting the day of initiation of oxaliplatin infusions. Response to chemotherapy, neurologic toxicity and electrophysiological changes were all measured with the glutamine groups having significantly less neurotoxicity compared to controls without any differences in chemotherapy response and non-neurologic toxicity or survival. Since glutamine is a precursor to glutamate, a major excitatory neurotransmitter, glutamate has also been studied for neuroprotection. A 2009 study by Loven et al. showed no evidence of protection from 1.5 g daily dose of glutamate, but did provide evidence that in patients treated with glutamate who had neuropathy symptoms, and this population had significantly less painful neuropathy compared to placebo [16].

Glutathione is a molecule made in the body from cysteine, glutamate and glycine that works as an antioxidant, neutralizing free radicals. It has been shown to decrease the incidence and severity of platinum chemotherapy-induced peripheral neuropathy in multiple oncologic cancers. The 2002 paper published by Cascinu et al. demonstrated that glutathione reduced the incidence of neurotoxicity in patients with colorectal cancer being treated with oxaliplatin [17]. 52 patients receiving oxaliplatin chemotherapy for their colorectal cancer were randomized to receive 1500 mg/m^2 glutathione in a 15-min infusion prior to chemotherapy or normal saline. Electrophysiological investigations were performed at baseline and after four, eight and 12 cycles of treatment. After 8 and 12 cycles, the glutathione-treated group had statistically significant lower rates of grade 2 and higher neuropathy as graded by the National Cancer Institute's common toxicity criteria [18]. Moreover, sural nerve conduction studies showed a significant increase in latency (ms) and decrease in sensory amplitude potential (μV) and conduction velocity (m/sec) after 8 cycles of chemotherapy in the placebo group but not the treated group. In the placebo group, latency increased from 3.07 ± 0.33 to 3.19 ± 1.70 ($P = 0.03$), sensory amplitude potential decreased from 10.98 ± 6.92 to 7.20 ± 5.05 ($P = 0.05$) and conduction velocity decreased from 45.91 ± 4.59 to 39.33 ± 11.66 ($P = 0.01$) after 8 cycles. There was no significant decrease after only 4 cycles. In the treatment group latency increased from 2.98 ± 0.97 to 3.08 ± 0.99 (P = NS), sensory amplitude potential decreased from 9.09 ± 6.34 to 8.71 ± 5.50 (P = NS) and conduction velocity decreased from 39.87 ± 13.0 to 39.13 ± 11.63 (NS).

Melatonin, a neurohormone secreted by the pineal gland, plays an important role in physiologic and neuroendocrine functions such as regulating the circadian rhythm. It has also been recognized as possessing antioxidant properties, with recent animal studies supporting a role for melatonin in the prevention and

treatment of chemotherapy-induced neuropathy [19–21]. Unfortunately, there have been fewer human studies confirming these findings, particularly in patients with cancer. However, there was one large 1999 study of 250 cancer patients receiving chemotherapy that demonstrated a significant decrease in the incidence of neuropathy in patients treated with melatonin [22]. Patients with non-small cell lung cancer, breast cancer, gastrointestinal (GI) tumors and head and neck cancers receiving a standardized chemotherapy directed at their type of tumor were then randomized to either receive chemotherapy alone or with melatonin given orally at a dose of 20 mg/day every evening starting 7 days prior to chemotherapy and then continued until disease progression occurred. Along with developing significantly less neurotoxicity, patients treated with melatonin also developed significantly less thrombocytopenia, cardiotoxicity and stomatitis compared to controls.

In a systematic review of herbs used for chemotherapy induced peripheral neuropathy (CIPN), 17 trials involving 2174 patients were assessed, and it was found that herbal medicines could potentially prevent or treat CIPN with only two cases of adverse events [23]. The herbal medicines tested in these trials were primarily East Asian formulations stemming from traditional Chinese medicine (TCM), rather than the nutraceuticals and supplements described above. As such, these therapies should probably be used only under the supervision of a practitioner of TCM as an alternative medical system. A 2015 review, on the other hand, summarized research on individual herbs such as Gingko biloba 50–150 mg/kg, green tea 300 mg/kg, *Ocimum sanctum* 100–200 mg/kg, *Matricaria chamomilla* 25 mg/kg, *Butea monosperma* 400 mg/kg, Walnut 6%, *Xylopia aethiopica* 30–300 mg/kg and Curcumin 10 mg/kg, showing evidence of a positive effect in animal models of CIPN [24].

18.2.2 Supplements for Mucositis

Glutamine is an amino acid that may have beneficial effects for mucositis. Mucositis is a painful complication related to both cytotoxic chemotherapy and radiation therapy. This occurs due to damage to rapidly proliferating cells such as those in the mouth and GI system with these treatments. Multiple studies have shown that glutamine, when given in a "swish and swallow" formulation shows a consistent reduction in the frequency and severity of mucositis caused by chemotherapy and radiation therapy. One 2005 study by Aquino et al. was performed in 120 children undergoing hematopoietic stem cell transplant [25]. These children underwent a variety of treatments including whole body radiation and high-dose cytotoxic therapy. Prior to treatment, they were randomized to receive either glutamine 2 g/m^2/dose twice daily until 28 days post-transplant or a glycine placebo taken in a "swish and swallow" method started at admission for transplantation. The glutamine treatment group had a trend toward less severe mucositis, fewer days of total parenteral nutrition (TPN), and a reduction in the mean number of days of intravenous opiate use. Another 1998 study by Anderson et al. [26] studied 24 patients undergoing bone marrow transplant. In this study, patients were

administered 2 g glutamine/m^2/dose swish and swallow four times a day with glycine serving as a control. This was taken on days of chemotherapy and for 14 days following completion of treatment. Glutamine treatment was associated with a significant 4.5 day reduction in duration of mouth pain and reduction in pain severity. Similar results were seen in a 2000 study by Huang et al. in patients receiving radiation therapy for head and neck cancer [27]. A 2009 review by Noe et al. reported the reduction in the incidence and severity of mucositis using a regimen of 20–30 g of glutamine, divided BID, taken daily at the start of radiation or chemotherapy through 2 weeks after completion of chemotherapy [28]. The review also noted a lack of toxicity when glutamine was given at even higher levels.

Honey has also been found to be an effective preventative treatment for mucositis. A recent systematic review and meta-analysis revealed an 80% relative risk reduction in radiation induced oral mucositis in patients treated with honey versus controls [29]. One of the most recent studies cited involved 40 patients with oral cancer [30]. These patients were randomized to receive honey or lignocaine gel 15 min before and after radiation therapy and once before bed. A visual assessment of the oral cavity using the Radiation Therapy Oncology Group (RTOG) rating scale from 0 to 4, with 0 being normal and 4 being most severe, to rate mucositis. Strikingly, only 1/20 patients treated with honey developed grade 3 or 4 mucositis compared to 15/20 patients in the control group. This was a significant difference with a relative risk of severe mucositis in patients treated with honey of 0.067. Similar findings were seen in 2 other studies with similar treatment regimens and mucositis rating scales [21]. In all studies, patients applied honey to the inside of their mouths before, directly after, and several hours after radiation therapy. A Cochrane review draws similar conclusions [31], though clinicians are advised to be cautious when using this therapy given small study sizes and the risk of bias in all supporting studies. Because honey has such a distinct flavor and texture, recipients could not be blinded to the treatment they received.

Calendula, a type of marigold with antioxidant properties, has demonstrated utility in the prevention of dermatologic and mucosal side effects of radiation therapy [32]. In a 2013 study by Babaee et al., 40 patients were randomized to receive 2% calendula extract mouthwash or placebo given twice daily starting at the beginning of radiotherapy and continuing until its completion [33]. Oropharyngeal mucositis, as graded by the oral mucositis assessment scale, was significantly less severe in the treatment group compared to the placebo group at weeks 2, 3 and 6. It was also found to be effective in another randomized controlled trial of 254 patients scheduled to receive postoperative radiation for breast cancer [34]. The patients were randomized to have calendula or trolamine ointment applied to irradiated fields after each session, at least twice a day (more if needed), until completion of radiation therapy. The occurrence of acute dermatitis of grade 2 (moderate) or higher was significantly lower (41 vs 63%) in the patients treated with calendula.

18.2.3 Caution with Supplements

As many of these supplements are ingested, particular attention must be paid to toxicity and drug interactions. Most of the aforementioned supplements are known to be safe, with benign side effect profiles. There are known risks associated with the ingestion of glutamine and Vitamin E. Glutamine has been shown to reduce clearance and increase tissue concentrations of methotrexate in in vivo rat cancer models [35, 36]. In humans, vitamin E has been shown to reduce through levels of cyclosporine and the bioavailability of tamoxifen [37–39]. Therefore, dietary supplements should be treated similarly to prescribed medications with safety, necessity and possible drug-drug interactions being considered.

While larger controlled trials are necessary to further explore the utility of these and other supplements, the evidence supporting the use of therapies such as glutamine and vitamin E are strong. The added benefit of these products being safe and inexpensive should encourage both further investigation and use in appropriate patient populations.

18.3 Cryotherapy

Oral cryotherapy is a simple, yet effective method for preventing the painful complication of mucositis in cancer patients receiving certain types of chemotherapy. A 2015 Cochrane meta-analysis concluded confidently that cryotherapy reduces the incidence of mucositis of all severities in patients receiving 5 fluorouracil based chemotherapy for solid tumors [40]. The review included 14 RCTs involving 1280 patients, most of whom were receiving cytotoxic chemotherapy, though one study included people receiving radiation therapy to the head and neck. The overall effect was a RR of 0.61 for all severities of mucositis in the treatment group with the relative risk for moderate to severe and severe mucositis in the treatment group being 0.52 and 0.40, respectively. Generally, the cryotherapy intervention in these studies involved placing ice chips, ice cubes or ice water in the mouth 5 min prior to chemotherapy and continuing for 30 min.

The mechanism of action is unclear, but one hypothesis is that the cold decreases blood flow to the mouth and prevents exposure of the tissue to the cytotoxic effects of both radiation and chemotherapy.

18.4 Acupuncture

Acupuncture is a technique rooted in traditional Chinese medicine. The first recorded description of acupuncture comes from the *Huang Di Nei Jing*, an ancient Chinese medical text, written in 200 BC. The practice of acupuncture is based on a view of the body that differs from conventional allopathic medical understanding.

Acupuncture functions by altering the flow of qi (chee). Qi is conceptualized as an energy force present in the body that flows through channels known as meridians and regulates the body's functions. Illness is thought to occur when there is an imbalance in the flow of qi, either an excess or a blockage. Acupuncture, by acting upon particular points within meridians that lie on the surface of the body, is intended to return balance to the flow of qi. Acupuncture specifically involves the insertion of sterile needles at meridian points to influence qi, but a variety of other techniques exist to manipulate the flow of qi including laser acupuncture, cupping, tui na massage, Gua Sha, Tai Chi and acupressure [41].

In 1998, the National Institutes of Health released a consensus statement concluding that acupuncture is effective for postoperative and chemotherapy-induced nausea and vomiting as well as for postoperative dental pain [32]. This statement reflects recognition of the role that acupuncture can play in disease and symptom management, despite its philosophical differences from those of mainstream allopathic medicine. It also reflects the extensive amount of work that has been done in this field. Along with evidence for the use of acupuncture in the management of nausea, vomiting, and postoperative dental pain, there is also literature supporting the use of acupuncture in a variety of other pain complaints including: migraines, TMJ, fibromyalgia, osteoarthritis, low back pain and myofascial pain [42].

Both molecular and fMRI studies have shed light on the potential mechanism of action of acupuncture in relieving pain. In a study by Sjolund [43], the cerebrospinal fluid of humans was analyzed following electroacupuncture, revealing increased levels of endorphins. Multiple animal studies have demonstrated the release of the endogenous opiates, enkephalin, beta-endorphin, endomorphin and dynorphin during acupuncture. This suggests that the analgesic effects of acupuncture are mediated by the release of these endogenous opiates. This hypothesis is further supported by a human study demonstrating that the analgesic effects of acupuncture are reversed by the administration of naloxone [44].

Functional MRI studies have further demonstrated distinct effects of acupuncture on the brain. In a 1999 study by Wu et al. [45], acupuncture was performed on patients using both true acupuncture sites (LI.4 and ST.36, analgesic acupuncture points) and a non-acupuncture site. They found that when patients were subjected to true acupuncture, areas of the descending antinociceptive pathways in the hypothalamus and nucleus accumbens were activated, while areas important for pain association (the limbic system) were deactivated. This suggests that the mechanism of action of acupuncture, in the case of analgesia, may be a combination of the release of endogenous pain modulators and the activation of inhibitory impulses that disassociate the emotional and cognitive pain response.

When it comes specifically to treatment of cancer-related pain, there is an extensive collection of studies focusing on the use of acupuncture for this purpose. There is evidence of its effectiveness in the treatment of bone, visceral and neuropathic pain associated with a variety of cancers and their treatments.

In a 2013 RCT by Chen et al., [46] 60 patients with pancreatic cancer were randomized to acupuncture treatment or control. The acupuncture group was treated with insertion of sterile acupuncture needles on Jiaji points T8–T12 bilaterally,

which were attached to an acupoint nerve stimulator for 30 min once a day for 3 days. The control group had sham needles pushed onto the same acupuncture points without puncturing the skin. Patient pain was measured using numerical rates scales before treatment, after 3 treatments, and 2 days after treatment was completed. Patients who had undergone acupuncture treatment had significantly improved pain scores after 3 days of treatment with a 1.67 point difference from baseline in the acupuncture group, and no change in the control group; this was consistent when patients were followed 2 days later.

A 1995 case series by Guo et al. [47] found that 74.2% of 286 patients with cancer pain due to bony metastasis experienced decreased pain levels and analgesic medication use after electroacupuncture, with the analgesic effect lasting an average of 3.6 h.

A 2008 RCT of 70 patients by Pfister et al. [48] involved 58 patients with chronic pain or dysfunction related to neck dissection for head and neck cancer. These patients were randomly assigned to weekly acupuncture versus usual care including physical therapy, analgesia and/or anti-inflammatory drugs. The patients receiving acupuncture received treatment once a week for 4 weeks. During treatment, sterile acupuncture needles were inserted at points L1-4, SP-6, GV-20, luzhen and auricular shenman and allowed to remain for 30 min The Constat-Murley score, a composite of pain, function and activities of daily living was measured. This composite score decreased significantly in the group treated with acupuncture, providing evidence that acupuncture resulted in a significant reduction in pain in head and neck cancer patients after neck dissection compared with non-acupuncture controls.

A 2003 RCT by Alimi et al. [49] studied the effectiveness of auricular acupuncture in decreasing pain in 90 patients with chronic neuropathic pain occurring after treatment for cancer. A baseline visual analog score of 30 mm and on stable analgesic therapy for at least a month was required for patients to be included in the study. Most patients had neuropathic pain, though a minority were also experiencing nociceptive pain. The treatment arm received two courses of acupuncture using steel spear-headed implants (semi-permanent needles applied to the ear). There were two control arms: one group receiving acupuncture at placebo points and another with auricular seeds attached to placebo points. It was found that neuropathic pain intensity decreased significantly by 36% at 2 months compared to baseline in the auricular acupuncture group, with no decrease occurring in the placebo arms.

There have also been multiple case series (Wong 2006, Bao 2011 and Donald 2011) of patients with chemotherapy-induced peripheral neuropathy having significantly decreased or resolved pain after acupuncture therapy, though this is subject to reporting and publication bias [50–52].

An intriguing 2012 pilot study by Schroeder et al. [53] involved 11 patients with CIPN; 6 patients chose acupuncture therapy and 5 opted out. The treatment arm received acupuncture for 10 weeks at ST34, EX-LE12 and EX-LE8 points. Five of the 6 treated patients had significantly improved nerve conduction velocity and mean amplitude compared to the control group. A more recent 2019 pilot study

regarding CIPN specifically in breast cancer survivors who had been treated with taxane-containing adjuvant chemotherapy found significantly improved subjective sensory symptoms with reduced neuropathic pain and paresthesia in women randomized to immediate acupuncture (18 treatments over 8 weeks) as opposed to the waiting-list group [54].

In a 2017 meta-analysis, 5 studies involving 181 patients showed significant pain reduction after 6–8 weeks of acupuncture treatment with significant decreases in BPI (Brief pain index) score and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score [55]. One of the studies was a 2010 randomized, controlled, blinded study by Crew et al. [56] comparing sham acupuncture twice weekly for 6 weeks in postmenopausal women with breast cancer who had self-reported musculoskeletal pain related to aromatase inhibitors. Aromatase inhibitors have been shown to be more effective than tamoxifen in preventing breast cancer recurrence. As such, they are routine adjuvant therapy used in postmenopausal women with estrogen receptor positive breast cancer. Unfortunately, 50% of patients report musculoskeletal discomfort, leading to discontinuation rates as high as 13%. In the 2010 study by Crew et al. the treatment arm (TA) received full body/auricular acupuncture and joint specific point treatment. Sham acupuncture (SA) involved superficial needle insertion at non-acupoint locations. Pain was measured using the brief pain inventory short form (BPI-SF), WOMAC. The TA experienced significantly larger reductions in pain severity and pain-related interference at 6 weeks compared to the SA using BPI-SF and WOMAC at 3 and 6 weeks.

Most recently, a systematic review and meta-analysis evaluating 386 cancer patients gathered from 6 randomized control trials (high quality, by a modified Jadad scale) showed that acupuncture led to statistically significant improvements in pain scores (-1.21, $P < 0.00001$) and nervous system symptoms from "Functional Assessment of Cancer Therapy/Neurotoxicity" questionnaire scores (-2.02, $P < 0.00001$). Though the decrease in pain score may not meet criteria for a minimally clinically important difference, this review does suggest that acupuncture may be a reasonable, evidence-based treatment in cancer patients suffering from chemotherapy-induced peripheral neuropathy [57].

There are some risks associated with acupuncture. One 2010 study revealed that 6.8% of patients receiving acupuncture experienced negative short-term reactions such as pain, tiredness and dizziness [58]. In another study, in which 8.6% of patients reported an adverse effect, bleeding or hematoma were the most common [59]. In 2015, a large scale review of case reports of acupuncture related adverse events and complications in China between 1980 and 2013 was published [60]. This review identified 182 patients over 33 years who experienced adverse events with spinal cord injury being the most commonly reported complication. There were also instances of infection and hemorrhage reported. Though this doesn't capture all instances of complications experienced due to acupuncture, the fact that only 182 serious complications were reported in the literature after millions of people had been treated with acupuncture over that time frame suggests that these complications are rare.

18.5 Hypnosis

Hypnosis is the practice whereby a hypnotist moves a person to a trance-like state in which the patient is more aware, focused and open to suggestion. Multiple studies have examined the effectiveness of hypnosis on postoperative pain, mucositis, chronic pain and metastatic cancer pain.

Functional MRI studies have suggested that two structures in the brain appear to play a particularly important role in the analgesic effects of hypnosis: the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) [61]. The prefrontal cortex plays an important role in decision making and has been found to exhibit hyperactivation in patients receiving pain-directed hypnosis. Changes in the PFC were particularly noticeable when the hypnotic suggestion involved the patient remembering a pleasant autobiographical memory or invoking some other pleasant imagery. The ACC is most involved in attention and motivation, and plays an important role as it integrates sensory experience with cognitive, emotional and behavioral regions of the brain such as the PFC.

These studies focusing specifically on a population with cancer, hypnosis has been shown to be associated with a significant decrease in pain scores among patients with post-surgical, bone, and mucositis pain among others.

In a recent study in 2009 by Butler et al. [62] of 124 women with metastatic breast cancer who were followed for 12 months, patients who received hypnosis in a supportive group therapy environment were found to have significantly less increase in the intensity of pain compared to controls. Both groups had similar pain scores at the beginning of the intervention, and while the average pain scores in the control group increased over the year, those of the patient's receiving hypnosis did not significantly change.

A randomized clinical trial by Montgomery et al. in 2007 [63] examined the effectiveness of a brief, 15-min presurgery hypnosis session conducted by a psychologist compared to empathetic listening (control) in women undergoing breast cancer surgery. Patients in the hypnosis group required less intraoperative propofol and lidocaine than the control group. They also reported less pain intensity, pain unpleasantness, nausea and fatigue.

In a 2004 a prospective, randomized study by Elkins et al. [64] of 39 patients with advanced cancer (stage III or IV) and malignant bone disease were studied. These patients were randomized to receive weekly sessions of supportive attention or a hypnosis intervention. Those in the hypnotic group received at least 4 weekly sessions and demonstrated a significant decrease in pain compared to the control group.

A 1992 study of 67 patients who underwent bone marrow transplantation were randomized to hypnosis training, cognitive behavioral coping skills training, therapist contact control or usual care. The hypnosis group had significantly reduced pain from oral mucositis [65].

18.6 Guided Imagery

Guided imagery is the use of mental visualization to improve mood and physical wellbeing. During a guided imagery session, the patient is guided through an imagery technique or script designed to invoke one or more senses. This can be done one on one, in a group setting or by tape. By invoking these senses, patients can alter their perception of ongoing experiences. It is often used in conjunction with progressive muscle relaxation, a nursing intervention facilitating the tensing and releasing of successive muscle groups, while attending to the resulting difference in sensation.

There have been multiple studies detailing the effectiveness of guided imagery in improving pain in both chronic pain conditions like migraines and osteoarthritis as well as in patients with cancer pain.

A 2016 study by Charalambous et.al [66] was a randomized controlled trial of 208 cancer patients undergoing chemotherapy. Patients were randomized to an intervention group trained in guided imagery and progressive muscle relaxation and a control group that received standard care. Inclusion criteria were patients with breast or prostate cancer experiencing symptoms like pain, fatigue, depression, nausea, vomiting and anxiety. Measurements for control and intervention groups were collected at baseline and after completion of the intervention. The intervention group had significantly less pain and fatigue compared to the control group, with pain scores at the end of the intervention being an average of 2.5 and 4.8, respectively.

A 2015 study by Chen et al. [67] examined the utility of guided imagery in the management of a variety of symptoms in women with breast cancer undergoing chemotherapy. 65 women were randomly assigned to experimental or usual therapy groups. The experimental group received 1 h of relaxation with guided imagery training before chemotherapy and a CD to practice the guided imagery 20 min daily for 7 days after chemotherapy. These patients exhibited a significant decrease in insomnia, pain, restlessness, difficulty concentrating, numbness, anxiety and depression compared to usual therapy.

18.7 Music Therapy

Music therapy is the use of music to tackle various aspects of a patient's pain, including the physical, emotional, cognitive and social needs associated with serious illness. It must be administered by a qualified music therapist who assesses patients' strengths and needs and provides indicated treatment. It can be passive, such as listening, or active, e.g., playing music or composing original work.

A 2016 Cochrane meta-analysis of randomized controlled trials examined the impact of music interventions on physical and psychological outcomes in people with cancer [68]. The analysis revealed that along with significant improvements in both anxiety and depression in patients exposed to music therapy, and there was an

overall large and statistically significant pain-reducing effect among 7 studies including 528 participants.

One example of the supporting studies was one 2010 study by Huang et al. [69]. In this study, 126 patients with cancer pain were randomized to either an experimental group receiving music therapy or a control group. Music choices included folk songs, Buddhist hymns, harp and piano. The experimental group listened to music for 30 min, while the control group rested in bed. Sensation and distress of pain were rated on a 100 mm VAS before and after music. The intervention group had significantly less post-test pain compared to controls. Also, 30 min of music provided 50% relief in 42% of the music group compared to 8% of controls.

Another 2013 study by Gutsell et al. [70] was performed in 200 palliative care patients. Participants were treated with standard care or standard care with music therapy. The music therapy intervention involved music therapist guided relaxation and live music. The intervention group had significantly greater decreases in pain scores and mean changes on the functional pain scale.

18.8 Massage

Massage involves a therapist stroking, kneading, applying friction and stretching specific muscles and connective tissues with varying levels of pressure. The purpose of this can be relaxation or treatment of musculoskeletal complaints. There are many forms of massage including: Swedish, deep tissue and Shiatsu. Many studies have explored the ability of massage to promote relaxation and mental well-being, while the number of studies exploring its ability to mitigate physical pain has been smaller. There are, however, multiple studies showing massage to be effective in the treatment of lower back pain during pregnancy to labor pain, migraine headaches, premenstrual syndrome, chronic fatigue, fibromyalgia, carpal tunnel syndrome and rheumatoid arthritis [71].

There are different theories regarding the mechanism by which massage exerts its analgesic properties. One is called the Gate Control Theory (also applicable to acupuncture). This theory holds that because pressure is carried to the brain by quick firing, longer, myelinated nerves versus the shorter, less myelinated fibers used for pain sensation transmittal, the pressure sensation (in the case of massage) "closes the gate" to the pain by reaching the brain first. Another theory relates to sleep deprivation. Substance *P*, a common mediator of pain, is released at reduced levels during deeper sleep states. Massage therapy leads to lower substance *P* levels in the saliva of patients receiving massages as well as more time in deep sleep. Finally, there is a hypothesis that by increasing serotonin levels, massage therapy exerts its analgesic effect by decreasing substance *P*, cortisol or depression. Further studies need to be done to further clarify the veracity of these theories.

In regards to the effectiveness of massage in improving cancer-related pain, a 2015 meta-analysis including 12 studies and 559 participants concluded that there was strong evidence showing that massage is effective for the relief of cancer pain [72].

One 2011 study by Jane et al. [73] was a randomized controlled trial in 72 Taiwanese cancer patients with metastatic bone pain of at least an intensity of 4 on a 0–10 scale. These patients were randomized to massage therapy or social attention (a caring professional there to allow the patient to discuss their feelings and thoughts) which served as the control group. Patients in the intervention group received 3 consecutive days of a 45 min massage session with the same therapist on all 3 days. Improvement of pain over time compared to baseline was significantly improved in patients receiving massage therapy. The control group did not show a similar improvement.

A 2008 study by Currin and Meister [74] examined the impact of Swedish massage on patient reported levels of distress in four areas (pain, physical discomfort, emotional discomfort and fatigue) among 251 patients. This study was a non-randomized single group pre and post-test design with 251 participants. The study showed statistically significant reductions in distress in all areas.

A large 2004 outcome study by Cassileth an Vickers of 1290 patients over 3 years showed that massage therapy decreased symptom scores, including pain, by half [75].

18.9 Exercise

Exercise covers a wide range of activities including walking, strength training, tai chi and yoga. Multiple studies support the role of exercise, regardless of type, in the elevation of mood, reduction in stress and improved sleep. In concert with theories regarding the connection between mind and body, there have been studies further exploring if activities known to calm the mind have a demonstrable effect on the body apart from the expected improvements in strength and cardiovascular capacity. There also exists a collection of studies exploring the role of exercise in pain management and more specifically in cancer patients. A recent meta-analysis specifically analyzed the data supporting the use of tai chi in symptom management in cancer patients, and showed a trend toward decreased pain in these patients.

Two 2012 Cochrane reviews explored this question more broadly in reviews about the effectiveness of exercise of all types in the management of symptoms in both cancer survivors and patients undergoing active treatment [76, 77]. The meta-analysis involving patients undergoing active treatment included 56 trials and 4826 participants. Cancer diagnoses included breast, prostate, gynecologic, hematologic and others. The types of exercise interventions varied including cycling, yoga, Qigong, resistance training or some combination thereof. Significant improvements in fatigue, physical functioning, anxiety, depression, emotional wellbeing and physical functioning were found. Regarding pain, there was only one

RCT identified demonstrating a significant improvement in pain with exercise. The review of exercise intervention in cancer survivors included 40 trials with 3694 participants with history of breast, colorectal, head and neck, lymphoma and other cancers. They found that exercise interventions improved body image/self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, fatigue, and pain at varying follow-up periods. The effect on pain was small and only significant at 12 weeks follow-up, but still a promising result.

One of the included papers, a 2009 study by Griffith et al. [78] studied 126 patients mostly with stage I-III prostate or breast cancer undergoing treatment including radiation and chemotherapy. These patients were divided into either a control group or a group performing a customized walking program based on baseline function and fitness. The exercise intervention was a moderate intensity walking program. This showed that along with significant improvements in cardiovascular fitness and physical function, and there was significantly less pain.

A recent meta-analysis was published detailing the effectiveness of Tai Chi and Qigong for cancer-related symptoms and quality of life [79]. This included 22 studies including 15 RCTs evaluating 1283 participants with breast, prostate, lymphoma, lung or combined cancers. Time of intervention ranged from 3–12 weeks. This intervention was associated with significantly improved decreases in sleep difficulty, depression and improved overall quality of life. There was also a statistically non-significant trend of improvement in pain with this exercise intervention. Another included study was a non-randomized trial of 67 patients with breast cancer receiving chemotherapy. The experimental group practiced a qigong regimen and had symptoms and psychological distress recorded on days 8, 15 and 22 of chemotherapy. The intervention group had significant improvements in pain, numbness, heartburn, and dizziness, compared with the control group. The authors of the meta-analysis conclude that larger, better designed studies need to occur to further solidify the role of these exercises in symptom relief for cancer patients.

18.10 Conclusion

Complementary medicine challenges us as scientists and providers to embrace the knowledge of our limitations. Acupuncture and guided imagery may not fit well in the conventional medicine paradigm, and their mechanisms of action aren't well understood, but there is a plethora of evidence to support their benefits. As clinicians, we have little choice but to inform ourselves of these therapeutic modalities, given the number of cancer patients who pursue complementary treatments. While more research is necessary to fully elucidate optimal treatment regimens, and larger, more powerful studies are needed to support preliminary results, we believe this chapter provided information regarding many safe and efficacious complementary treatments available to ease or even prevent symptom burden.

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