General

Acupuncture as Part of Multimodal Analgesia for Chronic Pain

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Background

Chronic pain is a multifactorial condition that is afflicting populations worldwide causing an increasing economic, physical, mental, and emotional burden. Treatments range from medications to interventional procedures to complementary and alternative medicine (CAM), such as acupuncture. This review aims to discuss the use of acupuncture in the treatment of chronic pain, proposed mechanisms, indications, and efficacy for various chronic pain conditions.

Results

Evidence is varied on the efficacy and quality of data on the use of acupuncture in the treatment of chronic pain. Recent studies have demonstrated promising results in the support of acupuncture for the use in the treatment of cancer, neck, and back pain, functional dyspepsia, and various chronic abdominal pain syndromes.

Conclusion

Acupuncture, deemed well-tolerated and safe to use, has been increasingly studied and is regarded as effective in clinical practice, but its efficacy is limited by the lack of well-conducted, high-quality clinical trials, lower quality evidence, and conflicting study results. Additionally, the exact analgesic mechanism of acupuncture remains to be fully elucidated. Increasing evidence supports the role of acupuncture as therapy in the treatment of cancer, neck, and back pain and functional dyspepsia. Further rigorous studies are needed to fully assess the use of acupuncture in various chronic pain conditions, determine its indications, and optimal treatment schedule. Overall, future studies could benefit from better designed experimental studies, larger groups, and more objectives ways to measure pain reduction and symptom improvement.

INTRODUCTION

Chronic pain is generally defined as pain that lasts for more than 3 months, or pain that lasts beyond the time that is expected for the pain to resolve.[1,2] The prevalence of chronic pain is approximately 35-50% worldwide and 11-40% in the United States.[2,3] The annual cost of chronic pain including medical care, lost productivity, and family burden is estimated to be $560-635 billion in the US.[3] Patients suffering from chronic pain typically experience psychiatric symptoms such as anxiety and depression, constitutional symptoms such as fatigue and sleep disturbance, as well as other limitations in life, such as self-care, social interactions, and overall lower quality of life.[3,4]

The etiology of chronic pain is multifactorial and incompletely understood. Chronic pain may develop from an acute pain that does not resolve, even after a successful treatment of its underlying condition.[3] The development of chronic pain may, for example, in chronic abdominal pain, result from the development of sensitization of pain or dys-

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regulation of endogenous pain modulation.[5,6] Treatment options include both single and multimodal approaches, encompassing pharmacological, surgical, psychological, behavioral, and complementary and alternative facets of management.[3] Pharmacologic treatments of chronic pain include psychoactive agents, antiepileptics, anti-inflammatories, opioids, neuropathic agents, and muscle relaxants.[7,8] Interventional strategies for pain management include surgery, nerve blocks, and denervation techniques.[3,9,10] Psychological and behavioral approaches include, but are not limited to, psychotherapy, cognitive-behavioral therapy, exercise, physical therapy, and biofeedback.[5,8,11,12]

Complementary and alternative medicine (CAM) is defined as a treatment framework that is not recognized as a conventional treatment for a condition.[13] CAM includes, but is not limited to, acupuncture, botanical products, "energy medicine", and chiropractic manipulation.[13] Acupuncture is a CAM modality that originated as a traditional Chinese medicine technique.[14] It involves needle insertion into the body at specific body points defined as acupoints.[2] The efficacy of acupuncture on pain management has been extensively studied, and in clinical practice, acupuncture is generally regarded as effective.[14] However, the degree of acupuncture efficacy is varied at best due to a lack of well-conducted, high-quality trials.[14,15] The mechanism of analgesia provided by acupuncture has yet to be elucidated, although there are many credible theories, including hormonal changes, immunomodulation, and release of endogenous opioids.[15] Acupuncture research is limited due to difficulty designing high-quality randomized controlled trials (RCT).[15] This review describes an overview of chronic pain and the role of acupuncture in its management, including proposed mechanisms, indications, and efficacy for different chronic pain conditions.

CHRONIC PAIN

In contrast to acute pain, which is precipitated by distinct injury, chronic pain has in many ways come to be regarded to be a syndrome of its own.[16] The International Classification of Diseases recognizes both chronic pain as a symptom due to another disease as well as chronic pain as a syndrome.[4] Three International Classification of Diseases (ICD) codes were recently added to denote chronic pain, which is defined as pain that persists or returns for greater than three months.[4] Chronic pain persists after healing and resolution of the inciting affliction, or pain that exists beyond the extent of inflicted damage.[17] It may include unremitting physical pain as well as associations such as disability and emotional distress, all of which may impact an individual's social functioning.[18]

Cancer pain is a broad term that can encompass a variety of definitions depending on setting.[4] The term includes pain that is due to tumor burden as well as pain that results from treatment and therapeutic interventions or their adverse events – for example, chemotherapy treatments that come with side effects such as painful mucositis, or wounds from surgical tumor resection.[19] Statistics show that 40-70% of cancer survivors will suffer from chronic pain, which may often be inadequately controlled.[4,19] Furthermore, cancer pain, like other forms of chronic pain, can interfere with quality of sleep, lifestyle, and activities of daily living, and increases the likelihood of depression and anxiety.[19]

PATHOPHYSIOLOGY OF CHRONIC PAIN

While acute pain can typically be attributed to direct tissue injury, chronic pain is a persistent pain perception that results from nervous system remodeling.[16] With continued stimulation from a painful stimulus, the central nervous system can demonstrate plasticity, causing alterations in sensitization and excitability.[20] Increased excitability and heightened sensitization can lead to hyperalgesia and allodynia, which are increased pain responses and aberrant pain responses, respectively.[20] Long-term potentiation mechanisms may also play a role in maintaining increased sensitivity to pain; some theories postulate that more NMDA receptors may be in their activated state.[20]

SYNDROMES OF CHRONIC PAIN

Persistent tension-type headaches were found to be the most common chronic pain condition according to a global study in 2016 afflicting nearly 2 billion people.[21] However, musculoskeletal complaints are also frequent manifestations of chronic pain. Neck pain is a common presenting form of chronic pain that has been reported to affect up to 50% of the population with 37% of those who suffer from it identifying it as a persistent condition.[22] Though neck pain is a frequent ailment, lower back pain is the largest contributor to disability across the globe.[23] While the majority of individuals will recover with few to no sequelae, up to 20% of patients with acute lower back pain will eventually develop chronic lower back pain.[23]

The prevalence of fibromyalgia increases with age and is more common in women .[24] The condition is a chronic widespread musculoskeletal pain that cannot be attributed to a different etiology.[25] Patients who suffer from fibromyalgia, as well as their family members, are more likely to be affected by other chronic conditions, such as chronic fatigue syndrome, irritable bowel syndrome, irritable bladder syndrome, and temporomandibular disorder.[25] Patients with fibromyalgia have evidence of hyperalgesia, or increased responsiveness to painful stimuli, as well as allodynia (painful response to nonpainful stimulus).[25] Chronic widespread pain is a phenomenon affecting multiple areas of the body; it may also be an independent condition or associated with fibromyalgia.[1] Chronic abdominal pain can arise as a result of pathologies such irritable bowel syndrome (IBS), or as part of abdominal cutaneous nerve syndrome.[26] Though not exhaustive, these are examples of chronic pain syndromes.

EPIDEMIOLOGY

Chronic pain disorders are most common among women.[25] Moreover, women report higher rates of neck pain.[23] Older

age, higher level of baseline pain, and depression are all associated with increased likelihood of persistent pain.[23] Age can also play a role, as a longer life increases the odds of exposure to an inciting event.[21] A study of patients recovering from shingles found that individuals > 80 years of age had more than twice the chance of developing post-herpetic neuralgia than those aged 50-54.[21]

COMMON PAIN TREATMENTS

In general, oral analgesic medications are typically the first-line pharmacologic approach to treatment of chronic pain.[18] Typical oral pharmacologic options for back and neck pain include non-steroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants such as cyclobenzaprine.[27] Topical analgesics, such as fentanyl, buprenorphine, and lidocaine, may also be prescribed.[18] The World Health Organization has published a stepwise ladder approach to analgesic therapy that begins with NSAIDs, followed by weak opioids, and for persistent or increasing pain, progression to stronger opioids.[18] Despite limited evidence for its efficacy and devastating potential for abuse and misuse, short and long-acting opioid therapy continues to be prescribed for chronic pain, despite.[16] Adjuvant analgesics include medications such as antidepressants, particularly the tricyclics (TCA) and serotonin/noradrenaline reuptake inhibitors (SNRI).[18]

Other approaches that have demonstrated evidence of benefit in treatment of chronic neck pain include proprioceptive and strengthening exercises.[27] Physical therapy and cognitive behavioral therapy are also employed.[18] Recently, cannabinoids and CBD have also become attractive treatment options in both cancer and non-cancer chronic pain, though they still carry a substantial set of limitations.[28] Additionally, application of heat or cold, capsaicin cream, and electrical nerve stimulation (both trans- and percutaneous) have all been used for treatment of pain which is believed to function by a mechanism known as "counter-irritation" which has been practiced in traditional medicine.[18]

INTERVENTIONAL APPROACHES

There are multiple interventional approaches for the treatment of chronic pain, most of which are generally reserved for patients whose pain has failed to respond to conservative medical management.[18] Common options include but are not limited to nerve block and steroid injections, surgically implanted medication delivery devices, denervation surgeries, and implantable nerve stimulators.[18] Denervation surgery at facet joints may also be used to relieve neck and/or back pain in some cases.[18] Implantable nerve stimulators have been recommended in the United Kingdom for treatment of neuropathic pain that does not respond to first-line treatments.[18] These stimulators work by inhibiting spinothalamic tract neurons responsible for pain signaling.[18] Finally, deep brain stimulation involves insertion of electrodes into brain structures that are thought to contribute to pain transmission. This therapy is currently not approved in the US but has shown efficacy in the UK and Europe for treatment of chronic and neuropathic pain.[18]

ACUPUNCTURE

Acupuncture takes its roots in Chinese rituals, where it was developed as a healing technique drawing from philosophic principles, such as those of Confucianism and Taoism.[29] It was first adopted by Korean and Japanese culture and eventually made its way into Western society by the 1500s.[30] In 2008, an estimated 4% of the US population had used acupuncture at some point in their lifetime.[31] Acupuncture embraces the idea of different channels, known as meridians and collaterals, in the human body that connect to organs and extremities.[32] Through these conduits, the balance of yin and yang is maintained by the flow of one's "vital energy," known as "qi," which helps maintain homeostatic function.[32] Acupoints located along these meridians are selected for targeting a particular area of ailment.[32] Needle insertion is therefore meant to identify certain points that will remedy any disturbance to balance.[29]

Acupuncture involves insertion of fine needles into designated anatomical locations, known as acupoints.[33] Chinese meridian teachings identify 361 acupoints on the human body.[34] Certain techniques may combine it with heat application, known as moxibustion, or the use of pressure. Sites of insertion are targeted for specific therapeutic purposes. During a typical session, between 5 and 15 needles may be inserted, but most acupuncturists are trained in up to 150 sites of insertion on the human body.[29] A variety of techniques and approaches exist in acupuncture – variations include pulsation, herbal therapies, electrical stimulation, and "microsystem" approaches, which identify a more focused target.[35] Dry needling has been considered a variant of acupuncture that uses solid needles, is less invasive, and for some providers, easier to learn.[36] Needles have ranged in various metal composition with the most widely used being stainless steel.[32]

In the 1990s, an NIH counsel deemed that acupuncture was effective in treating dental pain.[36] In 1996, the United States Food and Drug Administration (FDA)-approved the use of acupuncture by trained professionals. Currently, there are several society groups and councils that have positions on the use of acupuncture. The American College of Physicians recommends acupuncture as an option for treatment of low back pain, supported albeit by low quality evidence.[36] The American Academy of Family Physicians rated the evidence for clinical recommendation of acupuncture in treatment of chronic low back pain and chronic headache as grade A, citing "consistent, good-quality, patient-oriented" findings.[36] The National Comprehensive Cancer Network supports the use of acupuncture therapy in combination with pharmacologic treatment for alleviation of cancer pain.[33]

The mechanism of action of acupuncture's possible therapeutic benefit is not entirely known.[36] Proposed mechanisms suggest that acupuncture may lead to the release of endogenous opioids as well as neurotransmitters serotonin and norepinephrine, all of which may help tamper inflammatory responses and alter nociceptive processes in the body, perhaps leading to pain suppression.[36] Other studies have demonstrated that the release of adenosine is pro-

voked by electrical and mechanical acupuncture technique, which then inhibit nociceptive fibers.[34]

Clinical trials have illustrated repeatedly the presence of a placebo response (Table 1).[36] Sham procedures have posed a perennial challenge to RCTs, as needle insertion often produce similar responses to acupuncture procedures.[36] For example, in a study of acupuncture for treatment of knee osteoarthritis, acupuncture was superior to lack of treatment, but when compared with sham needle insertion, the clinical significance disappeared.[36] Increased number of treatments led to greater improvements in pain scores.[36] Thus, it is possible that sham needle insertion may actually improve pain, similarly to acupuncture. However, a systematic review of acupuncture for the treatment of low back pain found a statistically significant improvement in pain in those treated with acupuncture versus placebo/sham as well as against anti-inflammatory medications, though the differences were small.[36] The study concluded that the differences to be "borderline" in clinical significance.[36] A 2017 systematic review and meta-analysis of 29 RCTs found that acupuncture was an effective treatment option for cancer pain and resulted in statistically significant reduction in cancer pain due to both surgery and malignancy.[33] One posed theory for this was the neuropathic nature of chemotherapy and radiation therapy-induced pain, both of which can be harder to treat or adequately control.[33]

Acupuncture is deemed to be well-tolerated and safe with minimal serious adverse events based on 17 systematic reviews compiled by the American Academy of Family Physicians.[36] A consensus statement published by the National Institutes of Health deemed that acupuncture offered fewer side effects than many pharmacologic options for pain management; this sentiment was echoed by a separate study that also concluded acupuncture had fewer adverse events than medication in treatment of migraines.[31,57] In a study of acupuncture for use in treatment of depression, adverse events were limited to headache, syncope, and some bleeding, bruising, and/or irritation at needle sites.[58] Patients with clotting disorders, bleeding disorders, warfarin use, skin trauma, or local skin infections should not receive acupuncture due to the invasive nature of acupuncture.[59]

ACUPUNCTURE FOR CHRONIC MUSCULOSKELETAL PAIN

The evidence for the clinical efficacy of acupuncture in the treatment of musculoskeletal (MSK) pain comes from the results of phase II and III clinical trials as well as smaller crossover and comparative studies[12,39,41,42,44,45,50,53,55] which are summarized in Table 1; it includes strong evidence to support acupuncture for use in both back[60] and neck pain.[61] Other clinical trials have been proposed or are currently being pursued for acupuncture and its efficacy in narrower clinical contexts such as cervical spondylosis, osteoporosis, spinal cord injury, or more specific control parameters.[47–49,51,56]

A 2018 trial using electromyography and subjective pain outcomes found no significant difference between traditional and sham acupuncture.[37] Similar results were found in a 2020 trial using video-guided acupuncture, which were compared with results from a previous study on sham acupuncture, finding no difference in outcomes between modalities.[38] A 2013 multi-center study (n = 130) found that traditional acupuncture resulted in a greater reduction in the visual analogue score (3.36) than sham acupuncture (2.27), indicating efficacy of traditional acupuncture in reducing pain in patients with chronic lower back pain.[41] A 2017 single-center trial (n = 154) found a greater reduction in neck pain from traditional acupuncture at both 2 and 6 week marks (intergroup mean differences: -5.75; 95% confidence interval [CI], -9.48 to -2.03; p = 0.008 than sham acupuncture -8.65; 95% CI, -12.13 to -5.16; P < 0.001, respectively).[44] A 2016 sham-controlled trial examining acupuncture in the treatment of osteoporosis (n = 53; 87% female) found that pain was reduced by 61% according to the visual analogue scale in the true acupuncture group while pain was reduced by 49% in the sham control group.[49]

Studies comparing the efficacy of traditional (true) acupuncture or sham acupuncture versus placebo have found that both traditional acupuncture and sham acupuncture resulted in greater gains of patient outcomes than conventional care alone, defined as education and physical therapy.[39,43,45,53] A 2019 trial compared conventional care (spinal manipulations, analgesics, physical therapy, and massage) with thread-embedding acupuncture with polydioxanone and demonstrated a 17.46 [11.15–23.76] (p < 0.0001) reduction in the neck pain and disability scale after 9 weeks.[45] A 2012 trial compared 3 acupuncture modalities with conventional treatment (analgesics, nonsteroidal anti-inflammatory drugs, myorelaxant drugs, and posture recommendations) and found no significant difference between the acupuncture modalities, but a more significant reduction in pain and disability in the true acupuncture group (RR = 5.04) versus conventional care (RR = 2.57).[53] However, a 2017 trial comparing dry needling to manual pressure found no significant difference in pain outcomes between the two techniques; however, both techniques did result in improved pain pressure threshold, muscle elasticity, and stiffness (p < 0.001).[42] A 2011 study with patients with neuropathic pain following a spinal cord injury found that pain ratings improved significantly after acupuncture treatment compared with massage alone (19 scale units for acupuncture; 8 scale units for massage).[47] A 2020 trial comparing acupuncture with biofeedback therapy integrated with conventional therapy in the treatment of neck and upper back myofascial pain found clinical benefit for both acupuncture and biofeedback treatments but better gains in pain scale and range of motion in the lower trapezius muscle were found in the acupuncture group (p < 0.05).[12]

Serious adverse effects due to acupuncture are rare.[59] In several multicenter RCT, patients with chronic low back pain, who received acupuncture, reported no major or systemic adverse effects.[53,62,63] Likewise, patients with chronic neck pain, who received acupuncture, have not re-

Table 1. Acupuncture in Musculoskeletal Pain

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Calamita et al. 2018[37]	15 healthy patients and 15 patients with nonspecific neck pain, 1 session of acupuncture and 1 session of sham acupuncture. EMG signal of the upper trapezius was measured before and after acupuncture sessions.	Decreased EMG amplitude in both healthy and nonspecific neck pain patient groups. Numerical pain score improved among patients with nonspecific neck pain after acupuncture and sham acupuncture sessions. No difference was found between acupuncture and sham acupuncture treatments in regards to the numerical pain score. No systemic adverse effects were observed.	Acupuncture resulted in resistance to muscle fatigue and decrease of muscle activity as measured by EMG and was well tolerated. Pain improved with both acupuncture and sham acupuncture. Further investigation is warranted.
Cao et al. 2020[38]	18 patients, including 12 females, with chronic low back pain. Subjects received 6 treatments of video-guided acupuncture imagery treatment (VGAIT) over 4 weeks. Results were compared with a previous trial involving real acupuncture and sham acupuncture in chronic low back pain patients (n = 50, 31 females).	The three treatments studied (VGAIT, real, and sham acupuncture) resulted in decreased pain severity as measured by chronic low back pain severity score. No statistical difference in pain relief was found between VGAIT, real acupuncture, or sham acupuncture. No systemic adverse effects were noted.	VGAIT provided pain relief and shows promise. No control was used, the results should be viewed as preliminary.
Cerezo-Tellaz et al. 2016[39]	130 adult patients with nonspecific neck pain, with active myofascial trigger points in their cervical muscles. One group (n = 65) received deep dry needling (DDN) plus stretching while the second group (n = 65) received stretching only.	Subjective pain intensity significantly decreased in both trial groups after treatment. At a 6-month follow-up, the DDN trial group had neck disability index score reported (2.48 vs. 1.60). No adverse effects were observed.	Dry deep needling and muscle stretching alone relieved subjective pain in chronic neck pain patients. More studies are warranted.
Chi et al. 2016[40]	Single center study. 60 adults, including 55 females, with diagnosed and self-perceived chronic neck pain were followed for 5 months. 30 patients received dry cupping therapy while 30 control patients received rest only. Cupping therapy was administered at 3 acupuncture points (SI 15, GB 21, and LI 15) over 20 minutes.	Skin surface temperature (SST), blood pressure, and pain intensity was measured and compared to baseline. SST was elevated at each site in the cupping group. Neck pain intensity decreased more in the cupping group (baseline of 9.7 decreased by 6.1). Blood pressure differences were not significant, however systolic blood pressure was reduced in the cupping group (117.7 mmHg to 111.8 mmHg). No study participant reported adverse effects in the treatment regions.	Subjective neck pain relief was observed after treatment with cupping performed at traditional acupuncture sites. An analgesic effect is possible with no known adverse effects. Further studies on long-term effects of cupping are recommended.
Cho et al. 2013[41]	Multicenter study with 130 adults suffering from nonspecific chronic low back pain. Participants received either real acupuncture or sham acupuncture for 6 weeks with 2 treatments performed each week. The primary outcome was visual analogue score (VAS) for bothersomeness for chronic low back pain.	116 patients maintained follow-up over a 6-month period. Mean VAS decreased by 3.36 points in the real acupuncture group, compared with 2.27 in the sham control group. Adverse effects were monitored, and 16 participants reported minor to moderate events related to treatment. No systemic or serious adverse effects were reported.	Real acupuncture reduced chronic low back pain bothersomeness and pain intensity better than sham acupuncture. Adverse effects were minor, such as worsened low back pain, pain, or bruising, and

			did not last greater than 1 week. The physicians who administered the acupuncture were not blinded.
De Meulemeester et al. 2017[42]	42 female office-worker participants with existing myofascial neck/shoulder pain. Randomly assigned to dry needling (DN) group or the manual pressure (MP) control group. Evaluated with Neck Disability Index (NDS), a numeric rating scale, pressure pain threshold, and muscle characteristics before and after treatment.	No significant differences were found between DN and MP. Symptoms and rating scales improved in both groups after 4 treatments performed over 3 months. No adverse effects were reported.	DN was found to be no more effective than manual pressure. Reduced long term and short-term disability was found in both groups.
Eslamian et al. 2020[12]	Patients between 25-55 of both sexes (n = 50, 39 women and 11 men); diagnosed with myofascial pain syndrome (MPS). Treatment group (n = 25) exposed to electroacupuncture. Control group (n = 25) exposed to visual electromyography and biofeedback. Pain severity based on VAS and functional status assessed with the NDI. Inclinometer and algometer used to measure range of motion and pressure pain threshold.	All parameters improved significantly in both groups, except for pressure pain threshold of lower trapezius and paravertebral muscles. Outcomes improved significantly in acupuncture (20 subjects) versus biofeedback (10 subjects) (rate ratio=2, CI of 1.19-3.36). Intervention lasted 3 months.	Both electroacupuncture and biofeedback were effective in reducing pain severity and neck disability. Electroacupuncture performed better in some parameters and shows promise in the treatment of myofascial pain syndromes of the neck and upper back.
Foster et al. 2016[43]	Two phase study assessing acupuncture in the treatment of chronic low back pain in pregnant women in the UK. Phase I consisted of a questionnaire survey, interview of patients and providers, to assess feasibility of study. Phase II consisted of a single-center randomized controlled trial (n = 125) comparing real acupuncture (n = 42) versus sham acupuncture (n = 42) versus standard care alone (n = 41). Both acupuncture groups received standard care for chronic low back pain (education and physical therapy). Acupuncture (real and sham) regimen consisted of 6 to 8 treatments.	Phase I results showed that 24% of physical therapists administered acupuncture. Women reported no concerns with exploring acupuncture as a treatment of chronic low back pain. Phase II patient reported that outcomes (pain, function, and quality of life) improved with acupuncture overall at the 8-week follow-up. Mean score differences were adjusted for baseline scores and baseline covariates obtained through regression. No severe adverse events were reported. All participants resumed treatment after any hospitalization or medical intervention not related to the study. No neonatal adverse effects were reported. Minor side effects reported include bleeding at the site of acupuncture (21% of true acupuncture, 0.5% in non-penetrating acupuncture arm). 86% of the women were still pregnant at the end of the 8-week follow-up.	Pain reduction and functionality improvement were achieved with true acupuncture and non-penetrative acupuncture.
Ho et al. 2017[44]	Patient and assessor-blind, sham-controlled single center trial. Patients ages 18-65 (n = 154) were assigned to receive abdominal (n = 77) or non-penetrating sham (n = 77) acupuncture. Each group received treatments in six sessions by Registered Chinese Medicine Practitioners. Mean improvement in neck pain disability scores (Northwick Park Neck Pain Questionnaire) and quality of life were obtained. The abdominal acupuncture group had additional follow-up at 14 weeks.	True abdominal acupuncture group exhibited greater improvement in neck pain and disability scores at both 2- and 6-week periods (mean difference -5.75 at 2 weeks; -8.65 at 6 weeks). Patients in the true abdominal acupuncture group also reported greater improvement in pain intensity and quality-of-life measures than those in the sham control group. There were no severe adverse effects. 11 participants in the true abdominal acupuncture group reported transient bruises that did not persist or require treatment.	Abdominal acupuncture resulted in greater decrease in neck pain and disability as compared with sham non-penetrative acupuncture. Further multicenter studies on abdominal acupuncture are needed, however abdominal

			acupuncture appears to be an effective treatment of neck pain.
Kim et al. 2019[45]	Single-center, assessor blinded, two-armed trial with 106 adults suffering from chronic neck pain. Trial patients (n = 51) received thread-embedding acupuncture (TEA) with polydioxanone in conjunction with usual care (UC). Control group received usual care only. TEA treatments were given once a week for a 4-week period with usual care as needed. The primary outcome measured was neck pain and disability scale (NPDS) score. Patients were assessed at 0,3,5, and 9 weeks.	The TEA treatment group showed significant improvement in NPDS at week 5 (13.74) and at week 9 (17.46) than the UC control group. 12 patients reported adverse effects that occurred during the 191 TEA treatment sessions. These included stiffness (22.6%), bruising (8%), irritation (8%), skin flare (4%), pruritus (1%). No severe adverse events were reported.	TEA therapy resulted in significant improvements in NPDS scores. Psychological distress and quality of life improvements were also observed. Although some patients reported mild adverse effects related to treatments, TEA is a promising therapy for chronic nonspecific neck pain.
Nasb et al. 2020[46]	Pilot trial with 24 adult patients possessing trigger points and nonspecific neck pain. Randomly assigned to a cupping therapy group, ischemic compression therapy group, and a combination therapy group. Pressure pain threshold, neck range of motion, and neck disability index were assessed.	All treatment groups experienced improvement in neck disability index, pressure pain threshold, and neck range of motion. No significant difference was observed between dry cupping and ischemic compression, although the combination therapy achieved the most improvement.	A larger RCT on the efficacy of dry cupping and ischemic compression is indicated. No adverse effects were observed.
Norrbrink et al. 2011[47]	Pilot trial with 30 adult patients, with neuropathic pain following a spinal cord injury, assigned to acupuncture group (n = 15) or massage group (n = 15). Both groups received treatments twice weekly for 6 weeks. Patients received follow-up at end of treatments and 2 months later. Ratings of present pain, general pain, pain unpleasantness, and coping were monitored. Ratings were obtained using the multidimensional pain inventory and the patient global impression of change scale.	Pain ratings improved significantly at the end of treatment after acupuncture as compared with baseline. Ratings of pain interference on the multidimensional pain inventory improved after massage. No significant improvements were found after the 2-month follow-up, however 6 acupuncture patients reported subjective improvement. Few side effects were reported, and no subjects dropped out due to adverse effects.	It is possible that acupuncture may improve neck pain after spinal cord injuries. Larger trials are warranted to examine this issue.
Que et al. 2013[48] Protocol	Protocol for a double blinded, parallel group, placebo-controlled trial comparing active acupuncture with sham acupuncture. 456 adult patients diagnosed with cervical spondylosis and suffering from neck pain. Patients will be treated 5 times a week for 2 weeks. Northwick Pain Neck Pain Questionaire (NPQ), Short-Form 36 (SF-36), and McGill pain scale will be used. Patients will be followed up at 4,8, and 12 weeks after intervention.	-	-
Schiller et al. 2016[49]	Sham controlled trial. 53 adult patients (87% female) with osteoporosis, received 10 sessions of acupuncture over a period of 5 weeks. Pain score (VAS) and quality of life score (QUALEFFO-41) were recorded.	Pain reduced by 61%, by the end of the study, in the true acupuncture group. Pain reduced by 49% in the control sham group. Serious side effects did not occur during the study.	Both true and sham acupuncture were effective in producing pain relief in osteoporosis

			patients. True acupuncture had longer lasting effects. No adverse effects were reported. Larger sample sizes are warranted.
Shin et al. 2013[50]	Multicenter study with 58 adult patients with acute low back pain, with severe functional disability, assigned to motion style acupuncture treatment or conventional diclofenac injection. Improvement in lower back pain was assessed using 10-point numerical score. Patients were assessed at 2,4, and 24 weeks after treatment.	Numerical rating scale decreased by 3.12 in the acupuncture group while the disability score decreased by 32.95%. The differences with the diclofenac group were statistically different at the 2 and 4 week assessments. No adverse effects were reported.	Motion style acupuncture is an effective method for initial pain relief in acute lower back pain. Adverse effects were not reported.
Sun et al. 2019[51] Planned	Protocol for a multicenter trial that will feature 716 adult patients with chronic neck pain. Acupuncture will be applied to sensitive acupoints. Participants assigned to one of 4 groups (highly sensitive acupoints group, low/non-sensitive acupoints group, sham acupuncture group, and waiting list-control group). Patients evaluated before treatment, after treatment, and at 4, 8, 12, 16, 20 weeks.	Primary outcome is the VAS while the secondary outcome is the NPQ and McGill pain questionnaire. Adverse effects will be recorded.	-
Sun et al. 2019[52] Planned	Protocol for a multicenter observational study that will feature 224 adult patients with chronic neck pain. Study will attempt types of sensitization and the distribution of sensitized points. Body surface temperature, mechanical pain threshold, pressure pain threshold, and skin resistance will be assessed at 15 acupoints.	Acupoint sensitization will be determined using odds ratio between neck pain patients and healthy controls and acupoint sensitization rate of all patients.	-
Vas et al. 2012[53]	Multicenter trial that evaluated the efficacy of acupuncture in 275 patients with acute low back pain. Patients assigned to either conventional treatment alone or conventional treatment plus true acupuncture, sham acupuncture, or placebo acupuncture. Roland Morris Disability Questionnaire (RMDQ) score was scored, and patients were followed up at 3, 12, and 48 weeks.	RMDQ score reduced by 35% or more after 2 weeks of treatment. All modalities of acupuncture treatment resulted in greater pain reduction than conventional treatment alone. There was no significant difference between sham acupuncture and true acupuncture. No serious adverse effects reported. 12 patients (4.4%) had possible adverse effects including epigastralgias and nausea. 8 patients (3.9%) reported pain after the treatment session.	True acupuncture and sham acupuncture were effective in reducing pain and disability in patients with acute low back pain. No serious adverse effects were reported however minor discomfort was observed in a small number of patients (3.9%).
Wand et al. 2013[54]	Cross-over experiment in 25 adult patients with chronic low back pain. Compared effects of acupuncture with sensory discrimination training component against acupuncture without. Patients rated pain intensity using a numerical rating scale. Treatments were given during two phases.	The average reported pain intensity was less in the sensory discrimination group (2.8) than the acupuncture alone group (3.6). Adverse effects were not considered.	Patients subjectively reported less pain when given acupuncture with sensory discrimination training than with acupuncture alone. Acupuncture may favorably influence pain

			through improvement of self-perception.
Weiß et al. 2013[55]	143 adult patients with chronic low back pain (67% men). Assigned to 2 groups: acupuncture plus standard rehabilitation and standard rehabilitation only. Short-Form Health Survey-36 (SF-36) used to measure outcomes (physical functioning, general health, vitality, quality of life, and pain).	Acupuncture treatment group reported better quality of life outcomes than control group. Pain outcomes improved compared with control group.	Acupuncture was accepted by study participants as a viable treatment option and showed better improvement in subjective pain symptoms and quality of life outcomes than standard rehabilitation alone. There were no major adverse effects reported.
Yang et al. 2017[56] Protocol	Protocol for five-arm, parallel, single-blinded, sham-controlled trial. 175 adult patients with chronic neck pain. Groups will include traditional acupuncture, shallow-puncture, non-acupoint acupuncture, non-acupoint shallow-puncture, and sham acupuncture. Sessions will last 20 minutes and will be carried out twice a week for 5 weeks.	NPQ and Short Form McGill Pain Questionnaire (SF-MPQ-2) will be used to measure outcomes. Safety will be evaluated at each treatment period.	Intent is to measure efficacy of traditional acupuncture vs placebo.

ported major adverse effects.[44,64] Minor adverse effects, occurring in less than 0.1% of cases, include needle-site pain, nausea, vomiting, dizziness, and fainting.[59] In a study examining the safety of polydioxanone thread-embedding acupuncture in chronic neck pain, 22.6% of patients (n = 51) reported an adverse effect with neck stiffness being the most common (8.2%). Other symptoms included bruise, irritation, skin flare, and pruritus.[45] A 2017 systemic review and metanalysis found no major adverse effects in studies with acupuncture in chronic neck pain.[65] The overall safety profile of acupuncture and trigger point needling appears to be safe.[66] Evidence for cost-effectiveness and impact on mental health outcomes is limited.[67] In patients suffering from osteoporosis, no studies have reported any adverse effects due to acupuncture therapy.[68] As of 2017, pneumothorax and 5 cases of acupuncture related deaths have been reported.[14]

ACUPUNCTURE FOR CHRONIC ABDOMINAL PAIN

There are a variety of conditions that can underlie chronic abdominal pain, such as gastroparesis, inflammatory conditions such as Crohn disease and ulcerative colitis, and gynecologic pathologies. The role of acupuncture and its efficacy in treatment of pain is variable (Table 2). Although there are many RCTs evaluating the efficacy and safety of acupuncture on chronic pain, a majority of the trials either have low-quality evidence or are flawed methodologically.[69]

There have been individual RCTs that attempt to quantify the efficacy of acupuncture on chronic abdominal pain. Biochemical markers of inflammation, including α_1-acid glycoprotein and C-reactive protein, were measured in an attempt to quantify the effectiveness of acupuncture on pain secondary to Crohn disease and ulcerative colitis.[72,75] The Crohn disease activity index (CDAI) and the colitis activity index (CAI) were used to quantify symptoms associated with the respective conditions.[73,74] The acupuncture treatment group and the control sham acupuncture group (using anatomical sites not considered to be acupuncture sites on the body) both showed an improvement in CDAI and CAI scores post-treatment in comparison to pre-treatment.[72–74] This result is most likely explained by a placebo effect, with the act of needling, a component of both acupuncture and sham acupuncture, contributing to an improvement in the well-being and quality of life reported by study participants.[72] Inflammatory biomarkers were found to have significantly decreased after the completion of acupuncture in comparison to sham treatment, signifying overall effectiveness of acupuncture in treating disease activity, rather than subjective reports from study participants[72,74] Furthermore, another study utilized functional magnetic resonance imaging (fMRI) data to assess changes in neurophysiology following treatment.[71] Study participants were randomized into an acupuncture group or a moxibustion group, and participants were further randomized to receive resting-state fMRI pre- and post-treatment to evaluate neurological mechanisms of symptom modulation.[71] The CDAI and an inflammatory bowel disease questionnaire were used to determine participant's disease severity and quality of life.[71] Acupuncture was found to be effective in treating the symptoms associated with Crohn disease via possible modulation of the homeostatic afferent processing network.[71] Participants with irritable bowel syndrome (IBS) with diarrhea were randomized to treatment with acupuncture or treatment with moxibustion; patients that underwent acupuncture reported a significant improvement in abdominal pain following 1 month after treatment and 3 months after treatment.[70] In addition, fMRI was also used to evaluate neurophysiological changes during treatment, and acupuncture was found to be associated with prefrontal cortex changes, demonstrating possible effective therapy of acupuncture.[70] Overall, acupuncture demonstrated good therapeutic effect for the treatment of abdominal pain secondary to IBS.[70] No serious adverse events associated with acupuncture in the previous studies.[72–74] One patient did the formation of a hematoma during acupuncture.[74]

There have been many systematic reviews and meta-analyses assessing the efficacy and safety of acupuncture on various conditions contributing to chronic abdominal pain. In a meta-analysis of 32 RCTs, the effect of acupuncture in patients with abdominal pain secondary to gastroparesis of any etiology was evaluated.[76] This study demonstrated that symptoms associated with gastroparesis were improved, although this improvement was poorly defined and categorized among the studies.[76] It was found that acupuncture, either alone or combined with gastrokinetic agents, resulted in short-term improvement, which was defined as less than 4 to 5 weeks of symptom improvement.[76] There was a lack of safety reporting in the majority of the included RCTs, with only 7 RCTs reporting minor adverse events; there were no other major adverse events reported.[76] Overall, the safety of acupuncture could not be evaluated due to incomplete data and the lack of inclusion in the majority of RCTs.[76] The role of acupuncture is uncertain in improving symptoms of gastroparesis due to very low-certainty evidence.[76] Meta-analyses evaluating the effectiveness of acupuncture on IBS revealed acupuncture to be an effective and safe treatment for symptoms associated with IBS in comparison conventional Western medicine treatment.[77–79]

No significant differences were found between acupuncture and sham treatment in the improvement of IBS symptoms and quality of life, demonstrating possible placebo effect.[77] However, after pooling results, acupuncture appeared to show a better improvement in treating IBS symptoms over sham treatment.[77] Acupuncture resulted in a significant improvement of IBS symptoms in comparison to treatment with Western medicine with symptom alleviation estimated to last for 3 months.[77] Another meta-analysis concluded that acupuncture seemed to result in a more favorable improvement and showed promising long-term efficacy in comparison to treatment with Western medicine.[78] Unfortunately, many of the included RCTs were of questionable quality and design, which limited the strength of the evidence.[78]

Table 2. Acupuncture for Chronic Abdominal Pain

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Zhao et al., 2015[70]	60 patients with irritable bowel syndrome (IBS) with diarrhea. 30 patients were treated with electroacupuncture and 30 patients were treated with moxibustion.	Patients that underwent electroacupuncture reported a significant improvement in abdominal pain at 1 month and 3 months after treatment. There were no reported adverse events during this trial.	In patients with abdominal pain secondary to IBS, electroacupuncture demonstrated good therapeutic effect.
Bao et al., 2017[71]	65 patients with Crohn disease were randomly divided into acupuncture and moxibustion treatment groups. Patients in each group were randomly selected to undergo functional magnetic resonance imaging at baseline and after treatment.	Acupuncture was effective in treating the symptoms associated with Crohn disease by possibly modulating the homeostatic afferent processing network.	Patients with Crohn disease can be treated effectively with acupuncture. The safety of acupuncture in this condition was not evaluated.
Joos et al., 2004[72]	51 patients with active mild to moderate Crohn disease were randomized to acupuncture or sham treatment groups. Serum markers of inflammation were collected as a measurement of a secondary outcome.	Both acupuncture and sham treatment groups reported an improvement in well-being and quality of life. α_1-acid glycoprotein concentration decreased significantly in the acupuncture group.	The act of needling is associated with an improvement in well-being and quality of life in patients with active mild to moderate Crohn disease, demonstrating a placebo effect. However, biochemical markers of inflammation showed a statistically and clinically significant improvement in disease activity. There were no serious adverse events reported.
Joos et al., 2006[73]	29 patients with active mild to moderate ulcerative colitis were randomly assigned to acupuncture and moxibustion or sham treatment groups. The colitis activity index (CAI) was used to assess clinical activity of ulcerative colitis as a primary outcome measure. Serum markers of inflammation were collected to assess secondary outcome measures.	Patients who received acupuncture were found to have a statistically significant decrease in CAI and statistically significant superiority in treatment of disease activity. There was no significant difference regarding inflammatory markers found between the two groups.	Acupuncture, including sham acupuncture, improved the symptoms associated with ulcerative colitis. There were no reports of adverse events.
Bao et al., 2014[74]	92 patients with active Crohn disease were randomly assigned to acupuncture and moxibustion or sham acupuncture and moxibustion treatment groups. The Crohn disease activity index (CDAI) was used as a primary outcome measure, and biomarkers of inflammation were used as a secondary outcome measure.	Both the treatment and control groups had a statistically significant reduction of CDAI scores post-treatment. Treatment with acupuncture and moxibustion had a significantly larger degree of improvement in comparison to the sham treatment group. In addition, the treatment group demonstrated significantly improvements in levels of inflammatory biomarkers in comparison to the control group.	Acupuncture is an effective and safe treatment for patients with active Crohn disease. There were no serious adverse events, although one patient encountered the formation of a hematoma during acupuncture.

Primary dysmenorrhea is a common etiology of chronic abdominal pain, and many systematic reviews and meta-analyses have evaluated the effect of acupuncture on treatment of symptoms. Unfortunately, while many of these reviews and meta-analyses reported favorable and effective outcomes with acupuncture in the treatment of the symptoms associated with primary dysmenorrhea, all included studies were deemed to have inconclusive evidence due to a high-risk of bias.[80] The included studies reported that acupuncture, either in comparison to sham treatment, conventional pharmacologic treatment, or other non-acupuncture treatment was effective in treating pain from primary dysmenorrhea.[81–84] All studies reported that overall results were limited by low-quality designs of included RCTs.[81–84]

Acupuncture may be effective in treating symptoms of chronic prostatitis.[85] A systematic review assessed studies comparing standard medical therapy, sham procedure, and acupuncture and found that acupuncture alleviated symptoms in a clinically meaningful manner.[85] In addition, acupuncture had little to no difference in adverse safety events when compared to sham treatment or treatment with standard medical therapy.[85] Unfortunately, the included studies were of low quality, limiting overall conclusions.[85]

Abdominal pain secondary to functional dyspepsia may also be effectively treated by acupuncture.[86] A systematic review of 35 RCTs revealed that acupuncture was found to be more effective in treating functional dyspepsia symptoms in comparison to sham procedure, as well as treatment by standard medical therapy. The acupuncture treatment group was found to have an improvement of questionnaire and survey scores pre- and post-treatment in comparison to sham and conventional treatment groups.[86] Adverse events reported in the included RCTs included hematoma formation with the overall risk of serious adverse events deemed to be minimal and self-resolving.[86] Acupuncture was found to be effective in the treatment of functional dyspepsia, including a positive long-term effect, as evidenced by scoring from various questionnaires and surveys.[86] Additionally, it can be considered as an alternative therapy for functional dyspepsia for patients who cannot tolerate conventional prokinetic agents.[86]

A single meta-analysis assessing functional constipation and acupuncture concluded that acupuncture was an effective and safe treatment.[87] Acupuncture was compared with sham treatment in reducing symptoms associated with functional constipation.[88] The studies included in this meta-analysis were limited by low quality of evidence, and thus the overall conclusion was limited.[88] A systematic review evaluating the effectiveness of acupuncture for the treatment of post-cholecystectomy syndrome found that in combination with conventional treatment, acupuncture did not show a statistically significant reduction in pain associated with post-cholecystectomy syndrome.[89] Based on the limited data describing the efficacy of acupuncture in treating post-cholecystectomy syndrome, no conclusion could be drawn.[89]

There are no specific guidelines for acupuncture therapy for the treatment of chronic abdominal pain, and the decision to perform acupuncture is entirely subjective to the clinical practioner.[86] Moreover, effects seen with acupuncture are reliant on the skill and experience of the acupuncture practioner.[86] It is generally agreed that acupuncture intervention should be performed under sterile procedure.[70] Even then, complications can occur with any surgical procedure, as evidenced by the aforementioned minor adverse events during acupuncture.

ACUPUNCTURE FOR CANCER PAIN

Improving cure rates, survival rates and quality of life are the main therapeutic goals when treating patients with cancer. Quality of life is critical as it has been shown to improve the prognosis in patients with cancer.[90] Unfortunately, 50% of the pain in cancer patients is inadequately controlled.[19] The failure to control pain pharmacologically has led to the use of alternative non-drug treatments including acupuncture.

Acupuncture has now filled a significant role in this respect as a means to relieve symptoms associated with cancer including post-operative nausea and vomiting, chemotherapy-induced emesis, opioid-induced constipation and pruritus, hot flushes, shortness of breath, fatigue, and pain.[91,92] Clinically, acupuncture analgesia has been used to alleviate cancer pain as well as decrease the dose and side effects of pharmacologic analgesics.[93] These conditions include but is not limited to post-operative pain, chemotherapy-induced neuropathy, aromatase inhibitor-associated joint pain, and neck dissection-related pain and dysfunction.[94]

Research into acupuncture and their application specifically for cancer pain has been growing but the findings thus far have been limited and inconsistent (Table 3). A recent systematic review and meta-analysis found that acupuncture was significantly associated with reduced cancer pain and decreased used of pharmacologic analgesics.[91,95] However, this conclusion is supported with suboptimal quality of evidence which can be attributed to the substantial heterogeneity in study methodologies, cancer populations, and acupuncture techniques across the available studies.[96] Small sample sizes, introduction of biases due to lack of or different implementation of controls, and different preferred acupuncture acupoints are among some of the examples that suggest more rigorous trials are needed to better characterize the association between acupuncture and reducing cancer pain.[97,98]

Acupuncture for cancer pain has a very low incidence of adverse effects.[99] Mild adverse effects that have been reported include nausea, fainting, dizziness, sweating, vomiting, pain and bruising.[111] Severe adverse event rates are estimated to be less than 1.1 per 10,000 treatments.[111] The risk developing complications with acupuncture is likely increased in patients undergoing cancer treatment.[112] A cancer patient receiving treatment with chemotherapy can become severely immunosuppressed and vulnerable to infection and bleeding[113-].[114] While this represents a known risk, the risk is still low when appropriate guidelines and recommendations are followed.

Safety issues concerning acupuncture in oncology patients due to their more complicated medical status and higher risk of adverse reactions highlight the importance of identifying indications against treatment. Patients with lymphoedema, neutropenia, thrombocytopenia, spinal instability, spinal cord injuries, bleeding tendencies, history of cerebrovascular accidents, and valvular heart disease should avoid acupuncture treatment[99,111,112] Needling into areas of ulceration, scarring, and prosthesis should be avoided as well as electroacupuncture in patients with intracardiac defibrillators.[115,116]

Though acupuncture in conjunction with pharmacologic interventions is commonly used to treat cancer-related pain, how best to integrate it into pain and symptom management plans remains a challenge. The National Comprehensive Cancer Network (NCCN) only provides recommendations that acupuncture be used as part of an integrative intervention approach for adult cancer pain.[117] Specific guidelines on optimal dosage, point selection and treatment frequency and length are not provided. The previously mentioned heterogeneity in studies likely contributes to the difficulty in reaching a consensus on a standardized plan.

Table 3. Acupuncture in Cancer Pain

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Chen et al. 2013[99]	Single-center RCT N = 60 stage III-IV pancreatic cancer 2 groups: 30 electroacupuncture; 30 non-penetrative needle Treatment: once daily for 30 minutes for 3 days Outcome measure: Pain intensity measured by a numeric rated scale (NRS) from 0-10 at baseline, after each treatment and 2 days after the last treatment Miscellaneous: * Patient required to have NRS from 3-6, be on stable dose of analgesics at least 72 hrs prior randomization with estimated survival time more than 1 mo and never treated by acupuncture * Blinding was not reported	Pain intensity in the electroacupuncture group decreased compared to baseline after the third day of treatment (-1.67, 95% CI -1.46 to-1.87) with little change in the control group (-0.13, 95% CI 0.08 to -0.35). There was a statistically significant difference between the two groups after the third treatment and the two-day post-treatment follow-up (P-value < 0.001). No adverse effects were observed.	Electroacupuncture can relieve mild to moderate forms of pain in patients with pancreatic cancer but cannot provide evidence of sustained benefit.
Greenlee et al. 2016[100]	Single-center RCT n = 63 women stage I-III breast cancer receiving adjuvant or new-adjuvant paclitaxel weekly for 12 cycles enrolled, 48 completed week 16 assessment 2 groups: 31 electroacupuncture (EA); 32 sham non-penetrative electroacupuncture (SEA) Treatment: once weekly for 30 minutes for 12 weeks Outcome measure: Neuropathic pain measured by Brief Pain Inventory-Short Form (BPI-SF) and quality of life domains by Functional Assessment of Cancer Therapy-Taxane neurotoxicity sub scale (FACT-NTX) at baseline, 6, 12 and 16 weeks; clinically meaningful change Miscellaneous: * Patient excluded if prior treatment of acupuncture within 12 mo * An change of ≥ 2 points in BPI-SF and ≥ 5 points in FACT-NTX score was considered clinically meaningful	At week 12, both groups reported increase in mean BPI-SF worst pain score but no statistical difference between groups (EA 2.6 vs SEA 2.8, p = 0.86) At week 16, BPI-SF worse pain score of SEA returned to baseline while EA continued to worsen (EA 3.4 vs SEA 1.7, p = 0.03) No difference between groups with respect to the FACT-NTX sub scale score at weeks 6, 12, and 16 weeks. No difference in taxane adherence reported One grade 1 adverse event reported; needle site exhibited minor swelling and bruising after needle removal	Unable to identify a protective effect or an improvement in pain with electroacupuncture on chemotherapy-induced peripheral neuropathy symptoms in women with breast cancer over the course of chemotherapy
Mao et al. 2013[101]	Single-center Phase II RCT n=67 women stage I-III breast cancer with self-reported arthralgia attributed to aromatase inhibitors 3 groups: 22 electroacupuncture; 22 sham non-penetrative electroacupuncture; 23 waitlist control (WLC) Treatment: 30 minute sessions twice a week for 2 weeks then once a week for 6 weeks for a total of 10 treatments over 8 weeks Outcome measure: Pain measured by BPI at baseline, week 8 and 12	Mean reduction in pain severity was greater in the EA group than in the WLC group at week 8 (2.2 vs 0.2, p = 0.0004) and at week 12 (2.4 vs 0.2, p< 0.0001). The SEA group also showed a statistically significant greater decrease in the BPI severity score compared to the WLC group at both Week 8 (p < 0.001) and Week 12 (p = 0.0036). EA and SEA showed no statistical difference in all study outcomes at Week 8. 18 adverse events reported by 8 subjects which were mild in severity and spontaneously resolved.	Electroacupuncture produces a clinically significant reduction in arthralgias related to aromatase inhibitors in patients with breast cancer, however, sham electroacupuncture elicits a similar effect.

Hershman et al. 2018[102]	Multi-center RCT; 11 sites n = 226 women stage I-III breast cancer on aromatase inhibitors; 206 completed trial 3 groups: 110 true acupuncture; 59 sham acupuncture; 57 waitlist control (WLC) Treatment: 30-45 minute sessions twice per week for 6 weeks followed by 1 session per week for 6 weeks; total of 18 sessions Outcome measure: Pain measured by BPI-WP at baseline, 6, 12, 16, 20, 24 and 52 weeks Miscellaneous: * Patient excluded if scored under 3 on the Brief Pain Inventory Worst Pain (BPI-WP) * A change of ≥2 points in BPI-SF was considered clinically meaningful	Combined mean baseline BPI-WP score = 6.6 After 6 weeks, the mean BPI-WP score in the true acupuncture group decreased by 2.05 points, in the sham acupuncture group by 1.07 points, and in the waitlist control group by 0.99 points. The adjusted difference for true acupuncture vs sham acupuncture was 0.92 points (95% CI, 0.20-1.65; P = .01) and for true acupuncture vs waitlist control was 0.96 points (95% CI, 0.24-1.67; P = .01). 2 episodes of grade 2 presyncope reported. Bruising at acupuncture sties was the most common adverse effect.	Acupuncture in women with breast cancer and aromatase inhibitor-related arthralgias, true acupuncture compared with sham acupuncture or with waitlist control resulted in a statistically significant reduction in joint pain, however, the change was of uncertain clinical importance.
Crew et al. 2010[103]	Single-center RCT n = 38 women with history of stage I-III breast cancer on aromatase inhibitors 2 groups: 20 true acupuncture; 18 sham acupuncture Treatment: 30 minute sessions twice a week for 6 weeks Outcome measure: Pain measured by BPI-SF. Joint pain, stiffness and function of the knees and hands measured by Western-Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands (M-SACRAH) respectively. Patient's surveyed at baseline, 3 and 6 weeks Miscellaneous: * Patient excluded if scored under 3 on the Brief Pain Inventory Worst Pain (BPI-WP)	Mean BPI-SF worse pain score at 6 weeks was lower in the true acupuncture group than in the sham acupuncture group (3.0 vs 5.5; P=0.001) The true acupuncture group had up to a 70% decrease in the WOMAC and M-SACRAH scores compared with baseline. No adverse effects were observed.	Women with aromatase inhibitor induced arthralgias who were treated with true acupuncture exhibited significant improvement with the pain. Objective functional assessments should in incorporated into the study in addition to the current patient reported outcomes.
Lam et al. 2017[98]	Dual-center RCT n = 42 patients with moderate to severe cancer pain 3 groups: 14 *si guan xue* acupoint; 12 *si guan zue* acupoint; 14 common acupoints Treatment: 7 30 minute sessions Outcome measure: Pain measured by NRS from 0-10 measured daily and patient subjective improvement measured by the Patient Global Impression of Change (PGIC) scale measured at baseline and day 7	With a repeated measures design approach, there was no difference in pain score among the three treatment groups. Differences in PGIC scores across the three treatment arms indicate no statistically significant difference. There was a statistically significant improvement in the pain score in treatment using the *si guan xue* acupoints after the fifth day of treatment ($p < 0.05$). No adverse effects were observed.	The trial had a limited sample size did not blind or use a non-treatment control. Thus, the results should be considered preliminary.
Lu et al. 2012[97]	Dual-center parallel pilot RCT n=21 women with ovarian cancer receiving chemotherapy 2 groups: 11 electroacupuncture; 10 sham acupuncture Treatment: 10 30 minute sessions 2-3 times per week beginning 1 week prior 2nd cycle of chemotherapy and ending prior patient's 3rd	Original recruitment target was not achieved. No statistically significance between the two treatment groups was found in any subscore. After adjusting for baseline EORTC-QLQ-C30 score differences, only the social function	Electroacupuncture may hav a role in improving quality of life during chemotherapy but no firm conclusions can be drawn due to the limited sample size and high drop out rates.

	cycle of chemotherapy Outcome measure: Quality of life measured by the European Organization for Research and Treatment of Cancer-Quality-of-Life Questionnaire-Core 30 Item (EORTC-QLQ-C30) and the Quality of Life Questionnaire–Ovarian Cancer Module-28 Item (QLQ-OV28) was measured at baseline and after the last acupuncture session. Miscellaneous: * A change of ≥10 points was considered clinically meaningful	subscore was significantly higher in the electroacupuncture arm, compared with the sham acupuncture arm. And after adjusting for baseline QLQ-OV28 differences, only the score of peripheral neuropathy was still significantly higher in the electroacupuncture group, compared with the sham acupuncture group. No adverse effects were observed.	
Alimi et al. 2003[104]	Single-centered RCT n = 90 patients with chronic central or peripheral neuropathic pain after treatment of cancer 3 groups: 29 auricular acupuncture;30 sham auricular acupuncture; 31 sham non-penetrative auricular acupuncture Treatment: 2 sessions a month apart averaging of 44 minute each session. Acupuncture points were selected individually for each patient based on electrodermal response; same sites were used for the second treatment Outcome measure: Pain intensity by a VAS scaled from 0 to 100 mm measured at baseline and month 1 and 2. Miscellaneous: * Patients excluded if pain intensity <30 mm on VAS * The sham non-penetrative control group were visually identifiable from the two other groups	More than 2/3 of patients were women treated for breast cancer. A 36% statistically significant decrease (58 mm to 37 mm on VAS) was observed after two months in the acupuncture group compared to the limited change observed in the sham non-penetrative acupuncture group (58 mm to 55 mm on VAS) ($p < 0.0001$). The decrease in pain intensity correlated with the decrease in the average electrical potential difference at the auricular points in the acupuncture group ($R^2 > 0.76$). No adverse effects were observed.	Auricular acupuncture in adult patients with neuropathic pain after treatment of cancer provides statistically significant pain relief when compared to placebo acupuncture. The study suggests that the reduction in pain may be associated with a decrease in average electrodermal signal on the ear.
Bao et al. 2013[105]	Dual-center RCT n = 47 women with stage 0-III breast cancer on aromatase inhibitor therapy with associated musculoskeletal symptoms 2 groups: 23 true acupuncture; 24 sham non-penetrating acupuncture Treatment: 8 20 minute weekly sessions Health outcome: Health Assessment Questionnaire Disability Index (HAQ-DI) and VAS measured at baseline and at 8 weeks. Miscellaneous: * Patients were required to have a baseline Health Assessment Questionnaire Disability Index (HAQ-DI) score ≥0.3 and/or pain using a 100 point VAS ≥20 * A change of ≥0.22 points in HAQ-DI was considered clinically meaningful	No statistically significant difference in HAQ-DI ($p = 0.30$) and VAS ($p = 0.31$) at week 8 was observed between true acupuncture and sham acupuncture with respect to aromatase inhibitor associated musculoskeletal symptoms (AIMSS). A statistically significant reduction of IL-17 ($p = 0.009$) was observed in both groups. No adverse effects were observed.	Statistically significant reduction of IL-17 offers preliminary evidence that both real and sham acupuncture may reduce the severity of AIMSS through modulation of IL-17.
Han et al. 2017[106]	Single-center RCT n = 104 patients with multiple myeloma who developed new onset peripheral neuropathy grade II-IV (as defined by NCI CTCAE neuropathy severity assessment) during chemotherapy 2 groups: 52 acupuncture + methylcobalamin; 52 methylcobalamin only Treatment: 3 cycles of 30 minute sessions daily for 3 days then every	The VAS pain score decreased more significantly in the treatment group than compared to the control group ($p < 0.01$) The patients' daily activity measured by the Fact/GOG-Ntx questionnaire indicated significant improvement in the treatment ($p < 0.001$).	Significant decrease in pain and improvement in patient daily activity when acupuncture is combined with methylcobalamin to address chemotherapy induced peripheral neuropathy during treatment of multiple myeloma.

	other day for 10 days Health outcome: Patient daily activity and degree of neuropathy evaluated by VAS pain score, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire and electromyographic (EMG) nerve conduction velocity (NCV) determinations measured at baseline and after completion of final treatment	NCV measured by EMG in the treatment group improved significantly. No adverse effects were observed.	
Rostock et al. 2013[107]	Single-center RCT n = 60 patients after treatment of chemotherapy exhibiting symptoms of chemotherapy-induced peripheral neuropathy (CIPN) 4 groups: 14 electroacupuncture; 14 hydroelectric baths; 15 vitamin B1/B6; 17 placebo capsule Treatment: 8 ± 1 - 15 minute sessions over 3 weeks for electroacupuncture and hydroelectric baths; 3 capsules per day for 3 weeks for vitamin B1/B6 and placebo Health outcome: Neuropathic pain intensity measured by NRS from 0-10 and quality of life measured by EORTC QLQ-C30 at baseline, day 21 and 84.	CIPN related NRS score improved in electroacupuncture by 0.8 ± 1.2, in hydroelectric baths by 1.7 ± 1.7, in vitamin B1/B6 by 1.6 ± 2.0, and in placebo by 1.3 ± 1.3 points without significant difference between the groups or placebo. By day 21, health-related quality of life metrics improved moderately in all groups but no significant differences were identified by EORTC QLQ-C30 scores between groups.	Electroacupuncture, hydroelectric baths or vitamins B1/B6 was not shown to be superior to placebo in treatment of CIPN in cancer patients
Pfister et al. 2010[108]	Single-center RCT n = 58 patients with cancer with history of neck dissection associated moderate to severe pain and dysfunction for at least 3 months (Constant-Murley score ≤ 70) 2 groups: 28 acupuncture; 30 usual care Treatment: 4 30 minute acupuncture sessions weekly; usual care includes physical therapy, analgesia and/or anti-inflammatory drugs Health outcome: Pain and function measured by the Constant-Murley score from 0-100 and pain measured by NRS from 0-10 at baseline and after completion of last treatment Miscellaneous: * Randomization stratified by neck procedure type * Baseline NRS score was an average of two surveys 7 days apart within 1 week of starting treatment	Post hoc analysis adjusted for large baseline differences between groups with respect to medication use. Medication use defined by the medication quantification scale decreased in both groups. The differences between the groups were not statistically significant (P=0.4) Acupuncture was significantly superior compared to control for nearly all outcome measures. Patients receiving acupuncture had Constant-Murley scores 11.2 higher than the usual care group (95% CI, 3.0-19.3; p = 0.008) No adverse effects attributed to acupuncture were observed.	Findings suggest significant reductions in pain and dysfunction was observed in patients receiving acupuncture compared to usual care in patients with history of cancer and moderate to severe pain after neck dissection, however, further studies with larger sample size required.
Meng and Feng. 2018[109]	Single-center retrospective chart review n = 64 patients with stage II-IV cervical cancer 2 groups: 32 pain-specific acupoints; 32 regular acupoints Treatment: 30 minute sessions daily for 14 days Health outcome: Pain measured by NRS from 0-10, quality of life measured by EORTC QLQ-C30, and efficacy by Karnofsky Performance Status (KPS) from 0-100 measured at baseline and day 14	Patients in the pain-specific acupoint group exhibited a -4.2 point decrease in pain after day 14 compared to the -2.2 point decrease in the regular acupoint group and observed to be a statistically significant difference (p = 0.01). No significant difference observed between groups with respect to EORTC QLQ-C30 and KPS scores No adverse effects were observed.	The study suggests that patients with cervical cancer who receive acupuncture at pain specific acupoints exhibited a greater decrease in pain compared to those receiving acupuncture at regular acupoints. However, the findings may be limited by lack of randomization and selection bias.
Miller et al. 2019[110]	Single-center retrospective chart review n=68 adult patients with cancer or history of cancer referred to palliative care and received acupuncture	Range of 1-13 acupuncture treatments; median = 2; 81% of patients had between 1 - 3 treatments	Patients with advanced cancer and higher baseline pain scores receiving acupuncture are more likely to achieve clinically meaningful pain reduction. However, these

	1 group: paired t-test Treatment: Acupuncture for median of 28 minute sessions (15 - 40 minute range) Outcome measure: Edmonton Symptom Assessment Scale (ESAS) measured at baseline and after last treatment Miscellaneous: * A change of ≥2 points in ESAS was considered clinically meaningful	Significant reductions in mean pain scores determined by ESAS were observed after the first treatment (1.9+1.8; $p < 0.001$) and across all treatments (1.7+1.9; $p < 0.001$). Multivariable analysis demonstrated clinically meaningful pain improvement in patient with stage III/IV cancer (OR: 3.23, 95% CI 1.11-9.40; $p < .001$) The percent pain reduction between those with no disease and active cancer showed no significant difference ($p = 0.54$) No adverse effects were observed.	findings may be limited by concomitant pain medications confounding the pain scores.

CONCLUSION

Chronic pain is an increasingly prevalent syndrome that takes a toll on the lives of patients not only affecting the physical but having devastating effects on the psychiatric, emotional, and economic aspects of the patient. The economic burden in the USA alone amounts to over half a trillion dollars a year. Treatment aimed at chronic pain is varied due to it being multifactorial and not well understood. Therapeutic approaches utilize non-opioid and opioid medications, interventional, psychological, and behavioral techniques and CAM. Acupuncture, a CAM modality, is a technique utilizing needle insertions at various acupoints in the body to achieve pain reduction.

Numerous studies have been undertaken to assess the statistical and clinical significance in pain reduction with the use of acupuncture in various chronic pain syndromes but have been limited by the lack of well-conducted, high-quality clinical trials. The level of evidence ranges from low quality evidence to high quality depending on the organization supporting the use of acupuncture. The use of sham procedures as a control have continued to produce conflicting results as trials have demonstrated placebo responses or significance is removed once the sham procedure is introduced.

When applied to lower back pain, the sham procedure did not affect significance though the differences were small and borderline in clinical significance. Phase II and III clinical trials further support the use of acupuncture with strong evidence for back and neck pain with studies for narrower indications in progress. Despite this, there exists other clinical trials demonstrating no significance differences, but the overwhelming numbers support acupuncture in neck and back pain. The sides effects are minimal, and the procedure is well tolerated with support from the National Institutes of Health deeming that it had lower side effects than pharmacologic options, though there still remains a subset of patients in which acupuncture remains a risky procedure.

With respect to abdominal pain, there lies numerous different conditions in which acupuncture was applied with its efficacy being variable and the RCTs being low quality or flawed. In Crohn disease, there was an improvement in CADI and CAI scores but it was attributed to possible placebo effect. In a subsequent study, objective measures of disease activity showed a response to treatment. In IBS, both pain and neurophysiological changes as seen on fMRI were observed indicating objectives measures of change. Finally, in functional dyspepsia, acupuncture was shown to be more effective than sham or even standard medical therapy.

In addition, acupuncture demonstrated a statistically significant difference when used as a treatment option for cancer pain. Of all the indications, acupuncture appears to hold the greatest promise in cancer pain and symptom management as doses of pain medications were decreased. Despite the strong support for acupuncture in cancer, there still remains the issue of low quality evidence, heterogeneity of study methodologies, and small sample sizes. Extensive research is underway to better elucidate the association between acupuncture and cancer pain reduction.

Though extensive studies have been performed, there still remains much to be learned from acupuncture including the mechanisms of action, and if these mechanisms change based on the location of the body it is performed and how much the skills of the acupuncturist influence the results. More robust studies are needed to demonstrate statistical and clinical significance with objective outcomes though this may be difficult as pain is highly subjective. Therein lies the question whether acupuncture is only effective for some ailments while ineffective for others.

AUTHOR CONTRIBUTIONS

All authors were involved in the writing and editing of the manuscript.

DISCLOSURES

There are no conflict of interests with the authors.

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