

# Mechanisms of Action for Acupuncture in the Oncology Setting

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## Opinion statement

A growing body of literature supports the use of acupuncture in the oncology clinic for the relief of symptoms caused by cancer treatments. Several clinical trials are currently supported by the National Institutes of Health to assess the efficacy of such treatments, as evidenced by the listings in the National Institutes of Health Computer Retrieval of Information on Scientific Projects (CRISP) database. However, little is known about the mechanisms of action behind the effects of acupuncture. A biomedical database search for articles in the English-language literature revealed studies examining the effect of acupuncture on fibroblast cells, a decrease of inflammatory cytokines, an increase of T-lymphocytes, and increasing adenosine, neuropeptides, opioid peptides, peptide hormones, and stem cells. This limited review attempts to reveal some possible mechanisms of action for the effects of acupuncture for symptom relief in the oncology setting.

## Introduction

Acupuncture is a procedure in which fine needles are inserted into chosen specific points on the body to relieve pain and promote homeostasis. Acupuncture practiced today originated in China and is the result of more than 4,000 years of empirical evidence. The World Health Organization reports 28 diseases, symptoms or conditions for which acupuncture has been shown to be an effective treatment through controlled trials [1]. In 1991, the Office of Alternative Medicine (OAM) was established at the National Institutes of Health (NIH) to investigate and evaluate promising unconventional medical practices. Acupuncture gained popularity in the United States in the late 1990s, when the NIH

issued a consensus statement: "...promising results have emerged, for example, showing efficacy of acupuncture in adult postoperative and chemotherapy nausea and vomiting and in postoperative dental pain. There were other situations such as addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain, osteoarthritis, low back pain, carpal tunnel syndrome, and asthma, in which acupuncture may be useful as an adjunct treatment or an acceptable alternative..." [2]. In 1998, The National Center for Complementary and Alternative Medicine (NCCAM) was established at the NIH elevating the status of the OAM to an NIH Center.

Although further information supporting the use of acupuncture in oncology is needed [3], evidence does support the use of acupuncture for symptoms associated with cancer and cancer treatments. Examples include chemotherapy-induced neuropathy [4], nausea and vomiting associated with chemotherapy [5], xerostomia [6], and chemother-

apy-induced fatigue [7], neutropenia, and leucopenia [8•].

Although acupuncture is applied and studied worldwide in human and animal models, little is known about its mechanisms of action. In the last 4–5 years, some interesting data have emerged, which begin to explain acupuncture's therapeutic effects.

### Sensory neuropathy

- Common chemotherapeutic agents such as thalidomide, bortezomib, and taxanes can cause sensory neuropathy, as well as surgical procedures, often produce neuropathy. Neuropathy is a distressing and painful problem, and one that may become sufficiently severe as to limit the course of therapy.
- Cancer patients also experience severe fatigue, mood disturbances, and insomnia. These problems tend to exacerbate pain and other symptoms [9]. The literature contains a wealth of information on the use of acupuncture for peripheral neuropathy [4, 10, 11], but studies investigating the effect of acupuncture on chemotherapy-induced neuropathy are limited [4, 11].

### Post-surgical pain and dysfunction

- A recent study conducted at Memorial-Sloan Kettering Cancer Center examined the effect of acupuncture on pain and dysfunction in 58 cancer patients with head and neck cancer treated surgically. The neck dissection procedure often involves removal of or damage to the spinal accessory nerve and the salivary glands. Damage to the nerve leads to shoulder problems, including limited neck and shoulder function, winged scapula, weak abduction, and pain in the neck and shoulder. Even dissection that preserves the nerve may lead to sequelae. Complaints of neck or shoulder pain and dysfunction are common in 30–70% of patients after classical radical neck dissection. In this study, subjects were also assessed for improvement in xerostomia, a common result of radiation to the head and neck area. Significant reductions in pain and dysfunction, as well as increased saliva, were observed in patients receiving acupuncture vs usual care [12•].

### Joint pain from aromatase inhibitors

- Aromatase inhibitors are a standard of care in breast cancer treatment, but because of the pain that results from this agent, many women stop their treatment prematurely. A recent clinical study showed acupuncture to be effective in relieving joint pain and inflammation associated with aromatase-inhibitor therapy [13•]. Although this study confirmed the usefulness of acupuncture, the mechanism of action remains unknown.

### Fatigue

- Fatigue is a common complaint of patients receiving chemotherapy and radiation. The exact cause of cancer-related fatigue is unknown and is likely the consequence of many variables. Acupuncture for cancer-related fatigue was studied in a randomized controlled trial. Patients with fatigue were randomized to an acupuncture group, an

acupressure group, and a sham acupressure group. Acupuncture was shown to be more effective than acupressure or sham acupressure [7]. These data are promising, but additional research is needed to assess the potential benefits of acupuncture for cancer-related fatigue.

## Hyperemesis

- High-dose chemotherapy poses challenges to emesis management. In a study published in the *Journal of American Medical Association*, 104 women with high-risk breast cancer were randomized into three groups: electro-acupuncture at antiemetic points, minimal stimulation acupuncture with mock-electricity, and no needling. All the patients received concurrent triple antiemetic pharmacotherapy and high-dose chemotherapy (cyclophosphamide, cisplatin, and carmustine). The number of emesis episodes occurring during the 5-day study period was significantly lower for patients receiving electro-acupuncture vs those who received minimal needling or pharmacotherapy alone (median number of episodes, 5, 10, and 15, respectively;  $P < .001$ ) [5]. New advances in pharmacotherapy for emesis are encouraging, although in some patients, emesis remains resistant to pharmacologic management. These data support the use of acupuncture as an adjunct to pharmacotherapy for emesis.

## Possible mechanisms

### The local inflammatory and immune response

- Little is known about the numerous biochemical and neurochemical changes that occur during acupuncture. However, it appears that the cascade of events originates as a result of the needle pricking the skin. The body responds to the needle invasion with the release of numerous chemical signals. Mast cells release histamine, which triggers dilation and increased permeability of the capillaries. Macrophages discharge prostaglandins, which promote blood flow to the site. The vascular changes allow larger antimicrobial proteins to the site. Blood vessel endothelial cells secrete chemokines which direct the migration of phagocytes and signal them to increase production [14]. Considering that each needle stick stimulates local inflammatory and immune responses, it becomes clear why both true and sham acupuncture produced significant positive effects.

### Explaining meridians acupuncture points and Qi

- Western scientists theorize that Qi, characterized in Traditional Chinese Medicine as “vital energy,” can be explained in western terms as the sum of all body energetic phenomena, such as metabolism, movement, signaling, and information exchange. Meridian Qi, energy that flows in pathways that correspond to organs and systems, is described by scientists as connective tissue biochemical/bioelectrical signaling, and blockage or “stagnation” of Qi has been described as altered connective tissue matrix composition leading to altered signal transduction [15].
- Extensive data have been collected at the University of Vermont College of Medicine since 2001 on the local effect of acupuncture stimulation on connective tissue [15, 16]. Through the use of ultrasound, acupuncture points were located on a convergence of

connective tissue planes. Interstitial “loose” connective tissue (including subcutaneous tissue) constitute a continuous network enveloping all limb muscles, bones, and tendons, extending into connective tissue planes of pelvic and shoulder girdles, abdominal and chest walls, neck, and head. This tissue network is also continuous with more specialized connective tissues such as periosteum, perimysium, perineurium, pleura, peritoneum, and meninges. A form of signaling (mechanical, bioelectrical, and/or biochemical) transmitted through interstitial connective tissue, therefore, may have potentially powerful integrative functions [15]. Such data help explain why acupuncture points located on the peripheral or the internal meridian system affect areas, organs, and systems distant from the original point. Additional research is needed to explore this hypothesis.

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### **Fibroblasts and cytoskeletal remodeling**

- An investigation of acupuncture’s effect on connective tissue revealed that acupuncture with needle rotation induces extensive fibroblast spreading and lamellipodia formation. Fibroblasts, the most common of connective tissue cells, secrete an extracellular matrix, a web rich in collagen and other macromolecules. Fibroblasts also play an important role in wound healing [17]. The effect of acupuncture was quantified by morphometric analysis of mouse tissue explants imaged with confocal microscopy. The response expanded several centimeters laterally. The active cytoskeletal response of fibroblasts uncovered supports a model for the mechanism of acupuncture involving connective tissue mechanotransduction [16].

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### **Cytokines**

- Cytokines, released by cells during phagocytosis, are signaling proteins that help activate lymphocytes and other immune cells. The presence of cytokines indicates an inflammatory and immune response, and could help explain acupuncture’s analgesic and anti-inflammatory effect.
- A study designed to test the anti-inflammatory effects of acupuncture on acute inflammation induced by injection of carrageenan to the paw of a rat found that acupuncture decreased the expression of three cytokines: interleukin-6, beta-nerve growth factor, and tissue inhibitors of metalloproteinase-1 [18]. The acupuncture point studied in this experiment, Zusanli (ST36), was several centimeters away from the inflamed paw, thereby, eliminating the likelihood of a local response. Such data begin to shed light on acupuncture’s systemic anti-inflammatory effects.

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### **Adenosine**

- New data help us explain why acupuncture is useful in the treatment of chemotherapy-induced neuropathy. Scientists at the University of Rochester Medical Center found that the purine adenosine, a neuro-modulator with anti-nociceptive properties, is released during acupuncture [19•]. Samples of interstitial fluid were collected from the tibialis anterior muscle/subcutis of adult mice 0.5 mm from the

Zusanli (ST36) point before, during, and after acupuncture. Adenine nucleotides and adenosine were quantified using high-performance liquid chromatography with ultraviolet absorbance. During acupuncture, ATP, ADP, AMP, and adenosine sharply increased to approximately 24-fold.

- When it was established that adenosine is released during acupuncture, investigations focused on whether this reflected acupuncture's anti-nociceptive effects. After injecting an inflammatory agent (CFA) into the right paw, symptoms of mechanical allodynia to innocuous stimulation and thermal allodynia were produced. Administration of an adenosine A1 receptor agonist, 2-chloro-*N*(6)-cyclopentyladenosine (CCPA) evoked a sharp increase in the threshold to touch and thermal pain. CFA and CCPA also were tested on mice lacking adenosine A1 receptors; for these mice, CCPA failed to produce any clinical benefit [19]. The above studies support the use of acupuncture for mechanical and thermal allodynia which is often experienced by cancer patients as a result of chemotherapy-induced neuropathy.

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### Neuromodulation and the brain

- Both subjective reports and objective measures, such as nerve conduction studies, indicate that acupuncture has a positive effect on peripheral neuropathy [10]. Some study results might be explained by modulation through local neurochemical reactions to the acupuncture needle, such as release of adenosine and cytokines, although new evidence suggests that deeper, more systemic changes occur.
- Historically, it was theorized that acupuncture's neuromodulatory effects may be explained by the Melzack-Wall gate theory of pain [20]. Both thin "sharp pain" nerve fibers and larger diameter "touch, pressure, vibration" nerve fibers transport information to the two types of cells in the dorsal horn of the spinal cord: transmission cells that transmit pain; and inhibitory cells that repress pain transmission. The gate theory proposes that stimulation of the larger innocuous fibers stimulates inhibitory cells, "closing the gate" on the transmission of the thin nerve fibers that are perceived as sharp pain [20]. It is thought that the light pressure sensation produced by the acupuncture needle utilizes the larger diameter nerve fibers, exciting inhibitory cells in the dorsal horn and thus "closing the gate" on sharp pain sensation.
- Sequentially applied acupuncture and sham acupuncture at bilateral Zusanli (ST36) and Chize (LU5) points during PET scanning revealed that acupuncture, but not sham treatment, activated the left anterior cingulum, superior frontal gyrus, bilateral cerebellum, and insula, as well as the right medial and inferior frontal gyri [21]. These are the areas activated by acute and chronic pain [22]. This observation suggests a possible systemic neuromodulatory mechanism for acupuncture analgesia.
- Extensive research has explored the impact of acupuncture on dopamine [23, 24]. Investigations of the neuroprotective role of acupuncture found that electro-acupuncture stimulation protects dopaminergic neurons from inflammation-mediated damage in the medial forebrain of bundle-transected rats [23]. Another study examined the effect of six different acupoints on dopamine in the brains of rats. One of the points, P7, stimulated dopamine in the brain. Further studies revealed that various frequencies of P7 electrostimulation released varying levels of dopamine [24].

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### Arginine vasopressin

- Since the early 1990s, extensive research has addressed the effect acupuncture on arginine vasopressin in the rat hypothalamic paraventricular nucleus (PVH), and the role of vasopressin in acupuncture analgesia [25]. Vasopressin, an anti-diuretic peptide hormone, controls the reabsorption of molecules in kidney tubules by affecting tissue permeability. It also increases peripheral vascular resistance, which in turn increases arterial blood pressure. Recent studies suggest that microinjection of L-glutamate sodium into the PVH, which excites the PVH neurons, could dose-dependently enhance the analgesic effects of acupuncture [26]. The question of whether vasopressin acts through anti-diuretic or anti-nociceptive actions to effect acupuncture analgesia requires additional research.

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### Opioid peptides

- Previous attempts to explain the mechanism of acupuncture's analgesic effects indicate that acupuncture increases endomorphin-1, beta endorphin, enkephalin, and serotonin levels in plasma and brain tissue [11, 27]. The impact of acupuncture on opioid peptides was an early discovery. In 1995, it was reported that the pain threshold and the level of Leu5 enkephalin or beta-endorphin released in the perfusate were increased during electro-acupuncture, but that noradrenaline release from the preoptic area was decreased. Naloxone (15  $\mu$ M) perfusion significantly reversed the increased pain threshold and the decreased noradrenaline release induced by acupuncture. The inhibition of nociceptive neuronal discharges produced by electro-acupuncture was closely related to the endorphine-sensitive neurons, and reversed by naloxone. These important results suggest that the inhibitory effects of electro-acupuncture may be mediated by opioid peptides in the preoptic area [27].

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### Immunomodulation

- Many studies have investigated the impact of acupuncture on immune response. In both human and animal models, flow cytometry reveals that acupuncture reduces levels of CD4+ and CD8+ cells, which are known to suppress overactive immune response and to increase cytotoxic NK cell activity [28, 29]. One study of reaction to immune- and non-immune-related acupuncture points revealed not only T-cell modulation, but also an increase of soluble interleukin-2 receptor, and a decrease of cytokines interleukin-4 and interleukin-6. This indicates that acupuncture may modulate both peripheral blood lymphocyte populations and serum cytokine levels of the immune system [30]. In another study, electro-acupuncture normalized two opposing leukocyte/granulocyte patterns, suggesting that acupuncture may modulate abnormal leukocyte and granulocyte patterns [31].
- Because it is understood that emotional disturbances impact immune function, scientists in Brazil investigated the impact of acupuncture on the impaired immune functions in anxious women. Acupuncture significantly improved chemotaxis, phagocytosis, lymphoproliferation, and NK activity, and normalized immune parameters, such as superoxide anion levels and lymphoproliferation, in patients with elevated

baseline values. Optimal immune function effects appeared 72-h post treatment and persisted for 1 month post treatment [31]. Another study investigated acupuncture's effect on white blood cells and absolute neutrophil count during myelosuppressive chemotherapy. The incidence of grade 2–4 leukopenia was less in the acupuncture arm than the sham arm (30% vs 90%;  $P = 0.02$ ), although no statistical differences were detected in absolute neutrophil count or plasma granulocyte colony-stimulating factor [8•]. These studies support the use of acupuncture for chemotherapy-induced leukopenia.

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### Autonomic nervous system

- Research supports the theory that acupuncture affects the sympathetic nervous system. Autonomic nervous system modulation may explain some of acupuncture's effects on the gastrointestinal system. Neuroimaging PET-CT studies of patients with functional dyspepsia (FD) found that the anterior cingulate cortex, the prefrontal cortices, and the caudate tail (somatosensory areas) are involved in processing noxious gastric perceptions in the FD patients. Manual acupuncture at points Liangqui (ST34), Zusanli (ST36), Fenglong (ST40), and Chongyang (ST42) showed a decrease in activity in the postcentral gyrus, and the cerebellum. These results suggest that acupuncture contributes to the deactivation of the primary somatosensory area [32•].
- In a study examining the mechanisms by which acupuncture decreases heart rate, the decrease was found to result from reciprocal coordination of increased cardiac vagal activity and decreased cardiac sympathetic activity [33]. This phenomenon may be associated with the stimulation of parasympathetic nerves by acupuncture and the subsequent normalization of blood circulation [29], which may help explain the effect of acupuncture on heart rate, blood pressure and hyperemesis [32•–34].
- A study of the neural mechanisms of acupuncture-induced gastric relaxation addressed the effects of acupuncture on muscle contractions in the stomach. Strain gauge transducers were implanted on the serosal surface of the stomach to record circular muscle contractions during acupuncture in thiobarbital-anesthetized rats. It was discovered that acupuncture caused transient relaxation of the stomach and increased the number of c-Fos immunopositive cells at the ventrolateral medulla (VLM). These researchers concluded that acupuncture-induced gastric relaxations are mediated via the somatosympathetic reflex [34].

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### Neuropeptide Y and corticotrophin-releasing factor

- Neuropeptide Y (NPY) and Corticotrophin-releasing factor (CRF) are the two key neuropeptides involved in the stress response. These two peptides act in opposing directions in the biological cascade of stress. Upon activation of the flight-or-fight response, CRF is increased to initiate the full biologic and behavioral response, then NPY is activated to counterbalance the effects of CRF. Both CRF and NPY receptors as well as the respective mRNAs have been found within nuclei implicated in the mediation of fear/anxiety behaviors such as the amygdala. NPY and CRF interact to create a steady state of emotionality [35].

- The effect of acupuncture on anxiety and CRF and NPY mRNA expression in the amygdala of the rat has been studied extensively [36, 37]. For example, changes in NPY levels were investigated following stimulation of acupuncture points, Shenmen (H7) and Zusanli (ST36), in rats undergoing maternal deprivation stress. The investigators assessed the anxiety-like behavior using the elevated plus-maze, a standardized test for anxiety, as well as changes in NPY in the basolateral amygdala (BLA). Stimulation of H7 was found to significantly increase NPY levels in the amygdala, while the control site ST36 did not affect NPY. These findings suggest that acupuncture treatment may reduce anxiety-like behavior in adult rats following maternal separation by modulating the NPY system in the amygdala [36]. In another study examining the effect of acupuncture on anxiety-like behavior during nicotine withdrawal in rats, researchers found that acupuncture at H7 reduced the levels of CRF mRNA compared with the control group [37]. These findings support the use of acupuncture as a complementary therapy for the treatment of anxiety.

### Stem cells

- The first study of acupuncture-related stem cell mobilization recently was reported. In an investigation of acupuncture for the treatment of spinal cord injury, 14 healthy subjects were given one whole body acupuncture treatment tailored to treat spinal cord injury. Subjects returned at a later date to undergo a counterpoint control acupuncture treatment. Serial levels of CD133 and CD34 cells, matrix metalloproteinase (MMP-9), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and IL-6 were obtained immediately before and after 24 and 48 h of acupuncture at both sessions. The results showed an increase in stem cells which were CD133+ and CD34- and a decrease in BDNF and MMP-9 levels [38•]. CD133 and CD34 cells are young, non-differentiated progenitor or stem cells, which have the ability to proliferate and differentiate into several cell types, depending on the growth factors present in an environment. The concentration of these cells in peripheral blood normally is very low. The results of this study indicate that acupuncture mobilized CD133+ and CD34- cells, which paralleled a decrease in serum BDNF and MMP-9 levels. No CD133+ and CD34- mobilization or decreases in BDNF and MMP-9 occurred when the same individuals were acupunctured on control counterpoints [38•]. It is unknown as regards where the cells originated, how they will mature, or whether they have neurogenic potential. Further study is needed in this exciting new area.

### Conclusion

- Many acupuncture trials lack western methodologic vigor. What is known from methodologically sound research, however, suggests that acupuncture is effective due to various simultaneous local and systemic biochemical reactions and bioelectric changes. The evidence supports the use of acupuncture for the treatment of symptoms associated with cancer treatment, including pain, neuropathy, anxiety, leucopenia, gastrointestinal complaints, hyperemesis, and fatigue. Research is beginning to emerge on the mechanisms of action behind these effects.



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Papers of particular interest, published recently, have been highlighted as:

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