

Chapter 4

Acupuncture for the Treatment of Hot Flashes in Cancer Patients

Francesco C. Peluso, Paul R. Graves and Hani Ashamalla

Abstract Hot flashes, a phenomenon characterized by an intense feeling of heat and visible reddening in the upper body, have frequently been described in cancer patients undergoing hormonal deprivation or hormonal ablation therapy. The occurrence of hot flashes can substantially affect the quality of life in such patients. Though several treatments are available to reduce hot flashes, many have significant side effects of their own. Acupuncture has emerged as a promising treatment modality to alleviate hot flashes in cancer patients. In prostate cancer patients, six different studies concluded that acupuncture reduces the incidence and severity of hot flashes well beyond the estimated placebo effect and the effects of alternative treatments such as venlafaxine with minimal side effects. In breast cancer patients, acupuncture trials have yielded similar results. However, there are more conflicting results among randomized clinical trials which use sham acupuncture as a control; with one study concluding that actual acupuncture is no better than sham acupuncture in reducing hot flash incidence. In fact, two systematic reviews concluded that current evidence did not suggest that acupuncture was an effective treatment for hot flashes in breast cancer and prostate cancer patients due to the paucity and poor quality of the primary data (Lee et al., *Breast Cancer Research Treatments*, 115:497–503, 2009; *Supportive Care Cancer*, 17:763–770, 2009). These conclusions are at least partly due to the inherent difficulties involved in the proper blinding of acupuncture practitioners and the development of an adequate placebo to mimic the therapeutic experience of acupuncture. Because the overall evidence from well-controlled, randomized clinical trials is currently limited, it is not possible to unequivocally state that acupuncture is more effective than venlafaxine for hot flashes – the medication that has yielded the most impressive benefits in treating hot flashes. However, since the majority of acupuncture trials have provided very encouraging results with minimal side effects, future studies are warranted to further investigate and assess the potential role of acupuncture in the treatment of hot flashes in cancer patients.

H. Ashamalla (✉) · P. R. Graves
Radiation Oncology Department, New York Methodist Hospital and Weill Medical
College of Cornell University, Brooklyn, NY 11215, USA
e-mail: hashamalla@gmail.com

F. C. Peluso
State University of New York Downstate Medical Center, Brooklyn, NY, USA

4.1 Introduction

Prostate and breast cancer are two of the most common types of cancer. Treatment of these cancers frequently involves hormonal reduction and/or ablation. One consequence of the sudden deprivation of sex hormones is the ensuing predisposition for hot flashes or vasomotor instability.

A significant number of cancer patients undergoing hormonal deprivation therapy experience hot flashes. Androgen deprivation therapy (ADT) is now considered the gold standard treatment for metastatic cancer of the prostate (Spetz et al. 2003). Men with prostatic cancer can undergo either surgical or medical castration (treatment with GnRH analogues) castration coupled with anti-androgens for total androgen ablation. A systematic review (Spetz et al. 2003) of 143 randomized, prospective studies has shown that hot flash incidence is 45% in men receiving GnRH analogue coupled with anti-androgens; whereas individual studies report hot flash incidence ranging between 14–74.3%. One Scandinavian group (Spetz et al. 2001) reported a 74.3% incidence of hot flashes in 452 men undergoing complete androgen ablation.

Premenopausal women undergoing treatment for breast cancer can experience more frequent and severe hot flashes than women in the menopausal population (Carpenter et al. 1998). Overall, hot flashes occur in >65% of all breast cancer survivors and one study reported that 72% of women taking tamoxifen experienced hot flashes (Carpenter et al. 1998).

The occurrence of hot flashes is often associated with insomnia, fatigue, and irritability—with great detriment to the quality of life of the patients who incur them (Casper and Yen 1985). As a result, various pharmacologic interventions to reduce hot flash frequency and severity have been tested. However, many of these have the potential for significant adverse side effects (Sicat and Brokaw 2004). Consequently, a great deal of research has gone into evaluating the effectiveness of alternative treatment options, such as acupuncture.

Acupuncture, a 25-century-old treatment modality developed in China, has emerged as one strategy for the treatment of hot flashes in cancer patients. If practiced correctly, acupuncture is regarded as safe and has minimal side effects. This chapter will review the potential role of acupuncture as a method to reduce hot flashes in cancer patients.

4.2 Treatment Modalities of Acupuncture

Acupuncture is a technique in which very thin needles of varying lengths are inserted through the skin to treat a variety of conditions. This ancient form of traditional Chinese medicine has been used to treat myriad conditions. It has been used to reduce pain, combat addictive behaviors, and promote rehabilitation from strokes or other injuries (Lin and Chen 2008). With regard to cancer, acupuncture has been most widely applied to reduce the untoward effects of cancer treatments. Examples include the application of acupuncture to reduce nausea and vomiting from chemotherapy

(Collins and Thomas 2004) and to provide pain relief and improve movement (He et al. 1999; Deng et al. 2004; Capodice 2010; Morrow et al. 2011).

In traditional acupuncture, needles are inserted at specific locations termed acupoints, as defined by traditional Chinese medicine. Needles are inserted at acupoints just deep enough into the skin to keep them from falling out. They are usually left in place for less than half an hour. Skilled acupuncturists cause virtually no pain. The acupuncturist may twirl the needles, apply heat or a weak electrical current to enhance the effects of the therapy. Modern acupuncture needles are made of very thin stainless steel and are disposable. In 1996, the FDA approved the use of acupuncture by licensed practitioners (Lanfrey et al. 1996). By law, needles must be labeled for one-time use only.

4.3 Clinical Trials

To date, the most significant studies done to assess the efficacy of acupuncture in cancer patients have been conducted in the form of clinical trials. Quality systematic reviews have been published evaluating trials in both prostate cancer patients and breast cancer patients, both concluding that the limited evidence does not suggest that acupuncture is an effective treatment for hot flashes in cancer patients (Lee et al. 2009a,b). We have focused our discussion on the published studies contained in these reviews. The observational studies by Ashamalla et al. and Beer et al. discussed below, are articles published after the 2009 systematic review of acupuncture for prostate cancer patients. These studies were only available in abstract form at the time of Lee's systematic review but are provided here for completeness. Here we provide a review of these clinical trials that have been published as journal articles separated according to the type of cancer being treated and discussed in chronological order.

4.3.1 *Acupuncture Trials in Prostate Cancer Patients*

At the time of this writing, a total of six clinical studies have addressed the efficacy of acupuncture for the treatment of hot flashes in prostate cancer patients (Lee et al. 2009b). These studies, including their study designs, results and conclusions are summarized in Table 4.1.

The first clinical trial to suggest that acupuncture may reduce the incidence of hot flashes in men undergoing prostate cancer therapy was conducted by Hammar and colleagues (1999). In this pilot study, a total of seven men with vasomotor symptoms due to castration therapy underwent acupuncture therapy and the frequency of hot flashes was recorded in personal logbooks. Of the seven men, six completed a 10-week course of acupuncture. The frequency of hot flashes was reduced by 50–70% at various points with no adverse effect reported. This study did not include a placebo control group.

Table 4.1 Acupuncture trials for hot flashes in prostate cancer

Author	Therapy	Duration	No. of patients	HF measurement used	Acupuncture points	Percent reduction from baseline (%)	Control	Side effects
Hammar et al. (1999)	TA + electro-acupuncture	Weeks 1–2: twice weekly Weeks 3–12: once weekly	6	HF Frequency	B/L: BL15, BL23 ^a , BL32 ^a U/L: GV20, HT7, PC6, LR3, SP6, SP9	70	None	NS
Hayes et al. (2005)	TA + electro-acupuncture	Weeks 1–2: twice weekly Weeks 3–12: once weekly	10	Mean HFS	B/L: GB34, BL15, BL23 ^a , BL32 ^a U/L: GV20, HT7, PC6, LR2, SP6	43	None	NS
Harding et al. (2009)	AA	AA once weekly for 10 weeks	60	Daily record (at 0, 4 and 10 weeks). Frequency of HF during night and day	B/L: Auricular: autonomic, kidney, Shenmen, lung and liver	58	None	None
Frisk et al. (2009)	Electro-acupuncture	Weeks 1–2: twice weekly Weeks 3–12: once weekly	14	Mean HFS	B/L: BL15, BL23 ^a , BL32 ^a U/L: GV20, HT7, PC6, LR3, SP6, SP9	78	None	b
TA	Same as electroacupuncture arm	Same as electroacupuncture arm	15	Mean HFS	Same as above but without electroacupuncture	73	None	Mild or grade 1 adverse events
Beer et al. (2010)	TA + electro-acupuncture	Weeks 1–4: twice weekly Weeks 5–10: once weekly	22	Mean HFS	B/L: GB34, BL15, BL23 ^a , BL32 ^a U/L: GV20, HT7, PC6, LR2, SP6	>50	None	Mild or grade 1 adverse events
Ashmalla et al. (2011)	TA + electro-acupuncture	Twice weekly for 4 weeks	14	Mean HFS	B/L: GB34, SP6 ^a , KI3, ST36 ^a , BL15 ^a BL23 ^a , Taiyang, HT7, PC6, LI11	89.2	None	None

All acupuncture studies used 30 min sessions (except for Harding et al.'s study which used 40 min sessions). AA auricular acupuncture, B/L bilateral, BL bladder, GB gall bladder, HFS hot flash score, HT heart, KI kidney, NS not stated, PC pericardium, SP spleen, ST stomach, TA traditional acupuncture, U/L unilateral^aAcupuncture point that received 2 Hz electrostimulation

^bOne patient felt that treatment caused distress, another reported fatigue on the day of treatment, and a third reported a centimeter sided hematoma at the insertion site of an acupuncture needles

In the clinical trial conducted by Hayes and colleagues that was published in abstract form only, ten patients were enrolled and treated with acupuncture twice weekly for 4 weeks. A 43% reduction in mean hot flash score—number of daily hot flashes multiplied by severity on a scale of 1 (mild) to 4 (very severe)—was reported with seven of the ten men experiencing at least a 50% reduction in hot flash score (HFS) at any time during a 16-week evaluation. No significant side effects were reported. This study did not include a placebo control group.

A study by Frisk and colleagues (2009) evaluated the ability of acupuncture to reduce hot flashes in prostate cancer patients. In this study, 31 men with hot flashes were recruited and randomized into two groups: one that received electroacupuncture (EA) and another that received traditional acupuncture (TA) weekly for 12 weeks. Of the 29 men that completed the treatment, the HFS decreased by 78% and 73% in the EA and TA groups respectively. Only a few minor side effects were reported including one local centimeter-sized hematoma, one episode of distress and one episode of fatigue among three separate patients. This study did not have a placebo control. Instead, a small group of patients were asked to record their HFS 6 weeks prior to treatment. The efficacies of EA and TA were evaluated by comparing the HFS before and after the respective treatments.

A larger study conducted by Harding and colleagues (2009) analyzed 60 patients for reduction of hot flashes after treatment with auriculo-acupuncture (AA). The study selected patients receiving luteinizing-hormone releasing hormone (LHRH) analogues for carcinoma of the prostate. Patients underwent weekly AA for a period of 10 weeks and consented to a questionnaire to assess their sense of well-being both before and after treatment. All men completed the treatment without any adverse effects and 95% of patients reported a significant decrease in the severity of symptoms. The mean reduction of hot flashes in this group was 58%. This study also did not have a placebo control.

Beer and colleagues' study (2010) analyzed the effect of acupuncture on HFS, quality of life, and sleep quality in patients undergoing hormonal therapy for prostate cancer. Patients were treated with TA and EA biweekly for 4 weeks then weekly for 6 weeks. Patients recorded their response during the course of treatment and hot flash scores were calculated from the patient's daily diaries. Of the patients in the study, 44% reported a 50% reduction in HFS by week 4 and 55% reported a 50% reduction in HFS upon completing 10 weeks of therapy.

Ashamalla and colleagues' study (2011) included 14 men treated with TA plus electrostimulation of select acupoints twice weekly for 4 weeks. The study recorded the mean HFS at 2 weeks, 6 weeks, and 8 months from the initiation of treatment. The mean percent HFS reduction at weeks 2 and 6 were 68.4% and 89.2%, respectively. In patients with adequate follow-up at 8-months, significant improvement of the HFS was still evident as there was a continued 80.3% reduction from mean baseline HFS. This study, like all those listed above, did not employ placebo control.

4.3.2 *Acupuncture Trials in Breast Cancer Patients*

A significant number of studies have been conducted addressing the efficacy of acupuncture in the treatment of hot flashes in breast cancer patients. Among these, there are a relatively small number of randomized, placebo-controlled, clinical trials (Lee et al. 2009a) using sham acupuncture. These studies, including their study designs, results and conclusions are summarized in Table 4.2.

In the study by Nedstrand and colleagues (2005), a total of 38 post-menopausal women with breast cancer were randomized into two groups. One received EA and the other received applied relaxation therapy for 12 weeks. The number of hot flashes was recorded daily in personal logbooks before and during treatment and at 3 and 6 months post-treatment. Of the 19 women in the acupuncture group, it was reported that hot flashes were reduced by 52% after 12 weeks of acupuncture, and by 58% after 6 months of follow up. Applied relaxation techniques also reduced hot flashes by 51% after 12 weeks and by 58% at 6-months follow-up.

In the prospective, randomized, controlled trial conducted by Deng and colleagues (2007), a total of 72 women with breast cancer were randomly assigned to obtain either sham acupuncture with retractable needles or true acupuncture. Treatment was given twice weekly for a period of 4 consecutive weeks. The frequency of hot flashes was evaluated at baseline, at 6 weeks and at 6 months after initiation of treatment. The mean number of hot flashes was reported to decrease from 8.7 to 6.2 (29%) in the true acupuncture group and from 10 to 7.6 in the sham group (24%). Although there were fewer hot flashes in the true acupuncture group (0.8 per day), it did not reach statistical significance. In this study the effectiveness of acupuncture was not significantly better than sham treatment but the authors suggested that longer and more intense acupuncture might produce a larger reduction of hot flashes.

Frisk and colleagues (2008) conducted a randomized, controlled study to compare acupuncture to hormonal therapy in reducing hot flashes in patients with a history of breast cancer. This study was part of an international multicenter study from three centers in Sweden. Forty-five women were randomized to receive either EA for 12 weeks or hormone therapy (HT) for 24 months. The number and severity of hot flash episodes were registered daily before, during, and up to 24 months after the initiation of treatment. For the 19 women that completed the EA treatment for 12 weeks, the median number of daily hot flashes decreased from 9.6 (baseline) to 4.3 at 12 weeks. Long-term follow-up also demonstrated a continued benefit for patients after EA therapy. Twelve months after the start of treatment, 14 women had a median of 4.9 daily hot flashes. At 24 months follow-up, seven women had a median of 2.1 daily hot flashes. The 18 women who received HT had the number of daily hot flashes reduced from a baseline of 6.6 to 0 at 12 weeks after initiation of HT. Therefore, acupuncture was shown to have a beneficial long-term effect in reducing hot flashes but was not as effective as hormone therapy. Nevertheless, hormone therapy is contraindicated in women with hormone receptor-positive breast cancer and has well-documented adverse cardiovascular effects in post-menopausal women.

In the prospective, randomized, controlled trial conducted by Hervik and Mjaland (2009), acupuncture was shown to provide effective relief from hot flashes in women

Table 4.2 Acupuncture trials for hot flashes in breast cancer

Author	Therapy	Treatment and Duration	No. of patients	HF measurement used in study	Acupoints	Percent reduction from baseline	Control	Side effects
Nedstrand et al. (2005)	electro-acupuncture	Weeks 1–2: twice weekly Weeks 3–12: once weekly	38	Mean HF frequency	B/L: BL15, BL23 ^a , BL32 ^a U/L: GV20, HT7, PC6, LR3, SP6, SP9	50%	Applied relaxation (60 min, once weekly for 12 weeks)	NS
Deng et al. (2007)	TA	Twice weekly for 4 weeks	72	Mean HF frequency	B/L: GB20, BL13, PC7, HT6, KI7, ST36, SP6, ear Shenmen, ear sympathetic point U/L: GV14	29%	Sham TA (non-penetrating, non-acupoint)	Minor adverse effects. Slight bleeding at needle site
Frisk et al. (2008)	TA + electro-acupuncture	Weeks 1–2: twice weekly Weeks 3–10: once weekly	45	Median HF frequency	B/L: BL15, BL23 ^a , BL32 ^a U/L: GV20, HT7, PC6, LR3, SP6, SP9	55%	Hormone therapy	NS
Hervik and Mjaland et al. (2009)	TA	Weeks 1–5: twice weekly Weeks 6–10: once weekly	59	Mean HF frequency	U/L: GB20, LU7, KI3, SP6, CV4, PC7, LR4, LR8	50% day, 60% night	Sham TA (2–3 mm penetration at non-acu points)	NS
Walker et al. (2010)	TA	12 weeks	47	Mean HFS	NS	50%	Venlafaxine (12 weeks course)	None

All acupuncture studies used 30 min sessions (except for Deng et al.'s study which used 20 min sessions) *BL* bilateral, *BL* bladder, *GB* gall bladder, *GV* governor vessel, *HFS* hot flash score, *HT* heart, *KI* kidney, *LI* large Intestine, *LR* liver, *LU* lung, *NS* not stated, *PC* pericardium, *SP* spleen, *ST* stomach, *TA* traditional acupuncture, *U/L* unilateral

^a Acupuncture point that received 2 Hz electrostimulation

following surgical intervention and treated with tamoxifen. In this study, 59 women were randomized into two groups: those receiving traditional acupuncture or those receiving sham acupuncture. Sham acupuncture for this study was defined as the insertion of needles superficially (2–3 mm deep) at non-acupoints: 5, 10 and 15 cm proximal to the upper border of the patella and over the highest point of the trapezius muscle. Women were treated for a period of 10 weeks. The mean number of hot flashes was recorded both before the treatment, during treatment, and 12 weeks post-treatment. The mean number of daytime and nighttime hot flashes was reported to decrease by 50% and 60% respectively, in the acupuncture group. The women in the sham acupuncture group experienced a 25% decrease in daily hot flashes during treatment, which reversed during the following 12 weeks. The Kupperman index, a validated health score, was reduced by 44% in the acupuncture group at the end of treatment while no changes were observed in the sham acupuncture group.

In the study conducted by Walker and colleagues (2010), 50 hormone receptor-positive breast cancer patients were randomly assigned to two groups, one that received 12 weeks of acupuncture ($n = 25$) and one that received venlafaxine (Effexor), ($n = 25$) treatment. Outcomes, including hot flash score, depression and other quality of life symptoms were measured for up to 1 year post treatment. It was reported that both treatment groups experienced significant decreases in hot flashes, depression, and had improvement in quality of life symptoms including mental health. Although acupuncture was found to be equally effective as venlafaxine in reducing hot flashes, the acupuncture group experienced significantly fewer side effects than the venlafaxine group. Whereas 18 of the 25 patients in the venlafaxine group experienced nausea, dry mouth, dizziness and anxiety, the acupuncture group experienced no significant adverse effects.

4.4 Review and Evaluation of Results

4.4.1 *Review of Acupuncture Trials in Prostate Cancer Patients*

All of the six clinical trials mentioned above demonstrated a significant reduction in hot flashes among prostate cancer patients compared to their occurrence prior to treatment. Most of these studies used the HFS as a tool to measure the efficacy of acupuncture treatment. The HFS is a nationally accredited system that has been used in numerous studies and has been proven to be reliable in estimating the quality and quantity of hot flashes experienced by cancer patients (Sloan et al. 2001).

The reported reduction in hot flashes from baseline in all of these studies approach or exceed the efficacy of SNRIs (namely venlafaxine) which have proven to be very effective in the alleviation of hot flashes in both men and women undergoing hormonal deprivation therapy for cancer. Studies of the efficacy of venlafaxine for alleviation of hot flashes have demonstrated decreases in median HFS of 54% and 45.5% among men and women respectively (Quella et al. 1999; Loprinzi et al.

2009a,b). In addition, acupuncture treatment was reported to be very well tolerated in the prostate cancer studies in Table 4.1, whereas venlafaxine treatment has been associated with a number of undesirable side effects including nausea, altered sexual drive, and sleeplessness (Quella et al. 1999; Nelson et al. 2006).

Acupuncture may have long-lasting effects on hot flashes in ADT patients which last well beyond treatment duration. This has been evidenced by follow-up studies conducted by Hammar et al. (1999), Frisk et al. (2009) and Ashamalla et al. (2011), Hammar et al. (1999) reported that at 6-month follow-up, the mean number of hot flashes per day was 50% lower than before therapy while 33% of patients still experienced greater than a 50% reduction. Frisk et al. (2009) reported that at 6-month follow-up, 33% of EA patients and 43% of TA patients experienced > 50% reduction in the mean number of hot flashes per day. At 12-month follow-up, 18% of the available EA patients and 46% of the available TA patients still experienced a 50% decrease from their baseline. Ashamalla et al. (2011) reported that at 8-month follow-up, there was still an 80.3% decrease in HFS among patients and 91% of the men continued to experience a greater than 50% improvement.

4.4.2 Review of Acupuncture Trials in Breast Cancer Patients

The results of the acupuncture trials listed above for the treatment of hot flashes in breast cancer patients generally show significant reductions in hot flashes approaching that of venlafaxine treatment (50–60%). These acupuncture trials report minimal adverse side effects compared with both venlafaxine and hormonal therapies (Table 4.2).

The randomized, controlled study by Deng et al. (2007) stands out in concluding that there is no statistically significant difference between the effects of actual acupuncture and sham acupuncture. Deng's trial employed the use of retractable needles, which never pierce the skin while the device itself is kept upright by a tiny adhesive ring at its base. These sham devices were placed several centimeters away from the proper acupoints. Patients in the true acupuncture group had a mean daily hot flash decrease of 33% while those in the sham group experienced a decrease of 24%. When those who initially received the sham treatment were crossed over to true acupuncture at 7 weeks, they experienced another 9% decrease resulting in a 33% decrease overall. These results were not deemed statistically significant because they are within the range of placebo effect observed for hot flash treatment that ranges from 20–35% with 4 weeks of placebo treatment.

Another approach to conducting sham acupuncture has been to needle the skin at non-acupoints, such as the trial conducted by Vincent et al. (2007). This trial studied the efficacy of acupuncture on hot flashes in postmenopausal women. This randomized, sham-controlled clinical study also concluded that there is no difference between acupuncture and sham acupuncture for hot flashes. Of note, the study of Vincent et al. (2007) used different definitions for sham acupuncture. Their trial defined sham acupuncture as needling administered in non-acupuncture, non-meridian areas, whenever possible 5 cm or more away from the actual acupuncture point. 103

participants were randomized to either true or sham acupuncture for biweekly treatments for 5 weeks with another 7 weeks of follow-up for each arm of the study. At week 6, patients receiving true acupuncture experienced a 40% decrease in hot flashes while those receiving sham acupuncture experienced a 38% decrease in hot flashes. At week 12, the true acupuncture group had 13% more hot flashes than they did at week 6; those in the sham group continued to experience a decrease of another 5%. Therefore, at the end of 12 weeks, those who received true acupuncture only experienced a net decrease in hot flashes of 27% from baseline, while those who received sham had 45% decrease from baseline. The authors concluded that the results of the study suggest medical acupuncture was not any more effective for reducing hot flashes than was the chosen sham acupuncture.

The study by Vincent's group is intriguing because the placebo still involves piercing of the skin and although the areas were deemed non-acupuncture and non-meridian according to traditional Chinese medicine, they could still affect afferent nerve fibers in the skin. By stimulating afferent nerve fibers, there is potential release of β -endorphins which may contribute to the alleviation of hot flashes according to the current pathophysiologic model of hot flashes discussed later in this chapter (Zhao 2008). Furthermore, although this method of placebo was defined as a needling in non-meridian points, there was no mention of whether manual stimulation was used to achieve the Deqi sensation—the characteristic numbness or soreness experienced by the patient during true acupuncture (Vincent et al. 2007). If Deqi was induced, then the same physiological mechanism which is produced by manual acupuncture at normal acupoints may have been activated, and could explain why placebo patients in this trial still experienced a 45% reduction in hot flashes. If this was the case, the statistical differences observed in the reduction of hot flashes between the true acupuncture group and the sham acupuncture group may simply reflect different efficacy in placement of acupuncture needles rather than a difference between a true acupuncture treatment and a feigned one. Lastly, the 45% reduction experienced by the sham group is quite comparable to the effects of venlafaxine and suggests that acupuncture, regardless of acupoint placement, may still be clinically useful.

The sham retractable needle acupuncture device used in Deng's trial (2007) is a good placebo in the sense that it does not pierce the skin and thus there is no potential for inadvertent afferent nerve stimulation. However, it does not allow for adequate blinding. While neither the patient nor the doctor may know if the patient actually received true acupuncture or placebo, the acupuncturist cannot be effectively blinded as he/she will obviously be aware of the fact that the needles are authentic or sham devices. Although a single acupuncturist coached all acupuncturists conducting the sham acupuncture and also observed treatments periodically for integrity, this obviously leaves the study results vulnerable to bias (Ernst 2006). This problem is simply inherent in acupuncture research and there may be no way to provide a better placebo than the device used by Deng's group. However, the fact that Deng's trial is deemed placebo-controlled should not lend it any more authority than other non-controlled trials in light of this essential flaw in methodology.

4.5 Safety and Adverse Effects

As of 1996, acupuncture needles are deemed Class II medical devices by the FDA—permitting their use by licensed, registered, or certified practitioners. Needles are required by the FDA to have proper labeling and manufacturers must follow strict practices in their production. About 7–11% of patients may experience needling pain or bleeding at the site of needling. Major complications such as pneumothorax, cardiac tamponade, human immunodeficiency virus and hepatitis C infection are exceedingly rare especially if the procedure is performed by a well-trained acupuncturist with sterile, one-time use needles (Ernst 2006). Most of the serious side effects documented are the result of poor training and the large number of paramedics practicing non-sterile techniques. When considering acupuncture therapy for their patients, it is essential that physicians confirm that the licensed acupuncturist has adequate accreditation in accordance with the appropriate state legislature.

4.6 The Theoretical Pathophysiologic Model of Hot Flashes and the Biochemical Action of Acupuncture

Studies of the hot flash mechanism have been limited to postmenopausal women but it has been suggested that an analogous mechanism applies for the triggering of hot flashes in men and women receiving hormonal deprivation therapy. This is because hot flashes in both menopausal women and cancer patients are subjectively and objectively similar and are associated with the sudden withdrawal of sex hormones (Spetz et al. 2001). Estrogen and testosterone stimulate the production of endorphins, which modulate norepinephrine—a neurotransmitter thought to play a key role in the hot flash mechanism of Shanafelt and colleagues (Shanafelt et al. 2002).

Shanafelt et al. (2002) have presented a theoretical model for the hot flash mechanism that incorporates the findings and theories published by experts on the subject through 2002. Hot flashes are the result of dysfunction of the thermoregulatory nucleus located in the medial preoptic area of the hypothalamus. This nucleus is responsible for maintaining body temperature within a normal range termed the thermoregulatory zone. If body temperature increases, the nucleus initiates heat loss mechanisms such as peripheral vasodilation—occasionally resulting in a hot flash.

Shanafelt et al. (2002) proposes that norepinephrine is the primary neurotransmitter for lowering the thermoregulatory set point, citing that plasma levels of norepinephrine metabolites are increased before and during hot flashes, and intrahypothalamic injection of norepinephrine can induce a heat loss response. Following sex hormone withdrawal, the level of endorphins will decrease and may no longer be sufficient to effectively modulate hypothalamic norepinephrine. This relative excess of norepinephrine in the thermoregulatory nucleus triggers hot flashes when minor stimuli (emotional stress, caffeine, alcohol, etc.) are present.

Serotonin (5-HT) also plays a significant role in Shanafelt's model—explained in more detail in a work by Berendsen (2000). Both Shanafelt and Berendsen cite a number of studies demonstrating that blood serotonin levels are drastically lowered in women who experience menopause and return to normal with the injection of an estrogen (Berendsen 2000). This low blood serotonin level leads to the increase of 5-HT_{2A} receptors on blood platelets—possibly reflecting an increase of hypothalamic 5-HT_{2A} receptors. This is significant because 5-HT_{2A} receptors have been shown to mediate heat loss and an increased number of these receptors in the hypothalamus render it hypersensitive to serotonin (Berendsen 2000). This predisposes the hypothalamus to trigger autonomic heat loss mechanisms in response to relatively small increases of serotonin. In addition, mild stressors such as emotional stress, alcohol, and caffeine release 5-HT modulin, which by blocking 5-HT_{1B} auto-receptors, perpetuate a further release of serotonin (Shanafelt et al. 2002).

In summary, sex hormone withdrawal causes dysfunction in the thermoregulatory nucleus by two proposed mechanisms. Firstly, through decreased production of endorphins, increasing norepinephrine and decreasing the hypothalamic thermoregulatory set point. Secondly, through upregulation of 5HT_{2A} receptors that leads to the hypersensitivity of the thermoregulatory nucleus towards serotonin (Berendsen 2000; Shanafelt et al. 2002).

A review by Lin and Chen (2008) of mechanisms of acupuncture analgesia provides a thorough overview of the evidence supporting the theory that the release of endorphins and serotonin are induced by acupuncture. Lin and Chen cite studies in the mid to late 1970s conducted by Pomeranz (Pomeranz and Cheng 1979; Pomeranz and Paley 1979) which suggest that EA causes the pituitary to release endogenous opioids into the plasma and exerts an analgesic effect on the central nervous system. Following Pomeranz's suggestion that different frequencies applied to acupuncture needles may release different endogenous opioids such as β -endorphin, enkephalin, endomorphin and dynorphin, research began to focus on establishing the relationship between specific endogenous opioids with specific EA frequencies.

Han's review (2004) of the results of studies attempting to link the release of opioid peptides to specific electrical frequencies concludes that EA at 2 Hz stimulates a strong release of enkephalin, beta-endorphin, and endomorphin but no release of dynorphin while EA at 100 Hz stimulates a strong release of dynorphin but not the release of any of the other three substances. It was also discovered that alternating between frequencies of 2 Hz and 100 Hz using a pulse generator significantly increases acupuncture's analgesic effect compared to the use of 2 Hz or 100 Hz exclusively. The relationship between different frequencies of EA and endogenous opiates produced suggests that different frequencies of electroacupuncture used for hot flash treatment may have varying efficacy depending on which opioid is most effective in suppressing norepinephrine.

Two hertz EA is the modality most utilized in hot flash acupuncture trials and may be preferable for its ability to stimulate the release a variety of endogenous opioids. Furthermore, studies by Tsai et al. have suggested that the analgesic effect of EA at 2 Hz is also mediated by serotonin, since the effect diminished after a serotonin synthesis inhibitor injection—suggesting that serotonin may also be released as a result of EA at 2 Hz (Lin and Chen 2008). This conclusion is further evidenced by

the increase of serotonin in the spinal cord following 2 Hz EA and that serotonin's precursor responds to enhanced analgesia at 2 Hz EA (Lin and Chen 2008).

Among the trials listed in Tables 4.1 and 4.2, those that implemented 2 Hz EA tended to report greater reductions in hot flashes than those using manual stimulation exclusively—with the exception of Frisk's prostate cancer study (2009) which showed a slightly higher decrease in mean hot flash score among men receiving TA than EA. If these mechanisms for acupuncture analgesia are accurate, acupuncture may have the potential to alleviate hot flashes by two possible mechanisms: by increasing centrally acting endorphins which modulate norepinephrine and by increasing circulating 5-HT which decreases central 5-HT_{2A} receptor hypersensitivity and hyperdensity (Fig. 4.1).

4.7 Conclusion and Future Prospectives

In conclusion, to design a randomized, well-controlled study of acupuncture for the alleviation of hot flashes in cancer patients is a particularly challenging enterprise. The mechanisms for both hot flashes and the physiologic effects of acupuncture are not entirely known. There are inherent problems in developing an ideal placebo device for acupuncture—one that effectively blinds the acupuncturist as well as the patient and prescribing physician. This prevents effective double-blind studies in clinical trials for hot flash treatment. Loose definitions given to acupuncture and sham acupuncture may cause confusion when comparing various studies because different acupuncture techniques may have varying physiological effects on the body. In addition, chosen sham placebos which needle the skin may still stimulate affect afferent nerves—making it difficult to determine whether hot flash improvement is due to placebo effect or something more. Methods for blinding and controlling acupuncture studies must be further improved in the future to allow for more objective meta-analysis of acupuncture trials.

The measured outcomes of hot flashes should be standardized as well in order to more objectively compare the efficacy of different treatment modalities. Several studies found in both Tables 4.1 and 4.2 measure reduction in hot flash frequency, which does not take into account the severity of each hot flash. HFS is preferable as it gives a more comprehensive picture of the morbidity of hot flashes in cancer patients. It also provides more insight into the utility of a given treatment modality—as the ability to reduce the severity of a patient's hot flashes can be just as clinically meaningful as decreasing the frequency of his/her hot flashes alone.

The many variables in acupuncture studies including differing acupuncture protocols and measured study outcomes may undermine the credibility of study results and prevent researchers from coming to a consensus on the value of acupuncture in treating hot flashes. Future studies must seek to standardize the acupuncture protocol to the finest detail in order to allow their results to be interpreted more objectively and compared to those of other studies. The studies in Tables 4.1 and 4.2 suggest that the most promising protocol for hot flash acupuncture treatment should employ

Proposed Pathophysiologic Mechanism of Hot Flashes and Possible Sites of Action for Acupuncture Therapy*

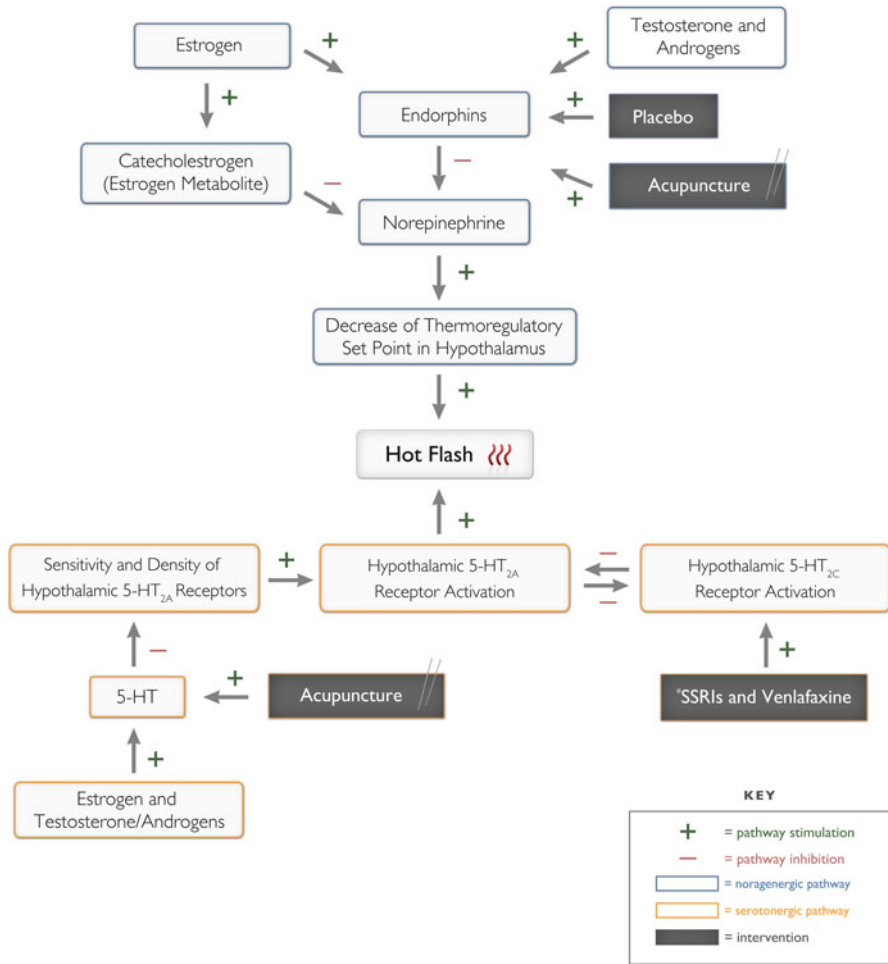


Fig. 4.1 Sex hormone withdrawal causes dysfunction in the thermoregulatory nucleus by two proposed mechanisms. Firstly, through decreased production of endorphins, increasing norepinephrine and decreasing the hypothalamic thermoregulatory set point. Secondly, through upregulation of 5-HT_{2A} receptors that leads to the hypersensitivity of the thermoregulatory nucleus towards serotonin. Acupuncture may have the potential to alleviate hot flashes by two possible mechanisms: by increasing centrally acting endorphins which modulate norepinephrine and by increasing circulating 5-HT which decreases central 5-HT_{2A} receptor hypersensitivity and hyperdensity

2 Hz electrostimulation at multiple acupoints during biweekly sessions for at least 4 weeks to achieve the maximum anticipated effect that acupuncture therapy may provide. Attempts at standardizing acupuncture research methodology and developing improved placebo devices will help to advance our knowledge of the potential that

acupuncture may have in improving the quality of life for cancer patients suffering from hot flashes.

References

- Ashamalla, H., Jiang, M. L., Guirguis, A., Peluso, F., Ashamalla, M. (2011). Acupuncture for the alleviation of hot flashes in men treated with androgen ablation therapy. *International Journal of Radiation Oncology, Biology, Physics*, 79, 1358–1363.
- Beer, T. M., Benavides, M., Emmons, S. L., Hayes, M., Liu, G., Garzotto, M., et al. (2010). Acupuncture for hot flashes in patients with prostate cancer. *Urology*, 76, 1182–1188.
- Berendsen, H. H. (2000). The role of serotonin in hot flashes. *Maturitas*, 36, 155–164.
- Capodice, J. L. (2010). Acupuncture in the oncology setting: clinical trial update. *Current Treatment Options of Oncology*, 11, 87–94.
- Carpenter, J. S., Andrykowski, M. A., Cordova, M., Cunningham, L., Studts, J., McGrath, P., et al. (1998). Hot flashes in postmenopausal women treated for breast carcinoma: prevalence, severity, correlates, management, and relation to quality of life. *Cancer*, 82, 1682–1691.
- Casper, R. F., & Yen, S. S. (1985). Neuroendocrinology of menopausal flushes: an hypothesis of flush mechanism. *Clinical Endocrinology (Oxf)*, 22, 293–312.
- Collins, K. B., & Thomas, D. J. (2004). Acupuncture and acupressure for the management of chemotherapy-induced nausea and vomiting. *Journal of American Academic Nurse Practise*, 16, 76–80.
- Deng, G., Cassileth, B. R., & Yeung, K. S. (2004). Complementary therapies for cancer-related symptoms. *Journal of Supportive Oncology*, 2, 419–426; discussion 427–429.
- Deng, G., Vickers, A., Yeung, S., D’Andrea, G. M., Xiao, H., Heerd, A. S., et al. (2007). Randomized, controlled trial of acupuncture for the treatment of hot flashes in breast cancer patients. *Journal of Clinical Oncology*, 25, 5584–5590.
- Ernst, E. (2006). Acupuncture—a critical analysis. *Journal of International Medicine*, 259, 125–137.
- Frisk, J., Carlhall, S., Kallstrom, A. C., Lindh-Astrand, L., Malmstrom, A., & Hammar, M. (2008). Long-term follow-up of acupuncture and hormone therapy on hot flashes in women with breast cancer: a prospective, randomized, controlled multicenter trial. *Climacteric*, 11, 166–174.
- Frisk, J., Spetz, A. C., Hjertberg, H., Petersson, B., & Hammar, M. (2009). Two modes of acupuncture as a treatment for hot flashes in men with prostate cancer—a prospective multicenter study with long-term follow-up. *European Journal of Urology*, 55, 156–163.
- Hammar, M., Frisk, J., Grimmas, O., Hook, M., Spetz, A. C., & Wyon, Y. (1999). Acupuncture treatment of vasomotor symptoms in men with prostatic carcinoma: a pilot study. *Journal of Urology*, 161, 853–856.
- Han, S. J. (2004). Acupuncture and endorphins. *Neuroscience Letters*, 361, 258–261.
- Harding, C., Harris, A., & Chadwick, D. (2009). Auricular acupuncture: a novel treatment for vasomotor symptoms associated with luteinizing-hormone releasing hormone agonist treatment for prostate cancer. *BJU International*, 103, 186–190.
- Hayes, M., Katovic, N. M., Donovan D., Emmons S., Benavides M., Montalto M., et al. (2005). Acupuncture for hot flashes in prostate cancer patients. *Journal of Clinical Oncology*, 23, 8160.
- He, J. P., Friedrich, M., Ertan, A. K., Muller, K., & Schmidt, W. (1999). Pain-relief and movement improvement by acupuncture after ablation and axillary lymphadenectomy in patients with mammary cancer. *Clinical and Experimental Obstetrics Gynecology*, 26, 81–84
- Hervik, J., & Mjaland, O. (2009). Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial. *Breast Cancer Research Treatments*, 116, 311–316.
- Lanfrey, P., Mottet, N., Dagues, F., Bennaoum, K., Costa, P., Louis, J. F., et al. (1996). Hot flashes and hormonal treatment of prostate cancer. *Progrès en Urologie*, 6, 17–22.

- Lee, M. S., Kim, K. H., Choi, S. M., & Ernst, E. (2009a). Acupuncture for treating hot flashes in breast cancer patients: a systematic review. *Breast Cancer Research Treatments*, *115*, 497–503.
- Lee, M. S., Kim, K. H., Shin, B. C., Choi, S. M., & Ernst, E. (2009b). Acupuncture for treating hot flashes in men with prostate cancer: a systematic review. *Supportive Care Cancer*, *17*, 763–770.
- Lin, J. G., & Chen, W. L. (2008). Acupuncture analgesia: a review of its mechanisms of actions. *American Journal of Chinese Medicine*, *36*, 635–645.
- Loprinzi, C. L., Dueck, A. C., Khoyratty, B. S., Barton, D. L., Jafar, S., Rowland, K. M. Jr., et al. (2009a). A Phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB). *Annals of Oncology*, *20*, 542–559.
- Loprinzi, C. L., Sloan, J., Stearns, V., Slack, R., Iyengar, M., Diekmann, B., et al. (2009b). Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. *Journal of Clinical Oncology*, *27*, 2831–2837.
- Morrow, P. K., Mattair, D. N., & Hortobagyi, G. N. (2011). Hot flashes: a review of pathophysiology and treatment modalities. *Oncologist*, *16*, 1658–1664.
- Nedstrand, E., Wijma, K., Wyon, Y., & Hammar, M. (2005). Vasomotor symptoms decrease in women with breast cancer randomized to treatment with applied relaxation or electro-acupuncture: a preliminary study. *Climacteric*, *8*, 243–250.
- Nelson, H. D., Vesco, K. K., Haney, E., Fu, R., Nedrow, A., Miller, J., et al. (2006). Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA*, *295*, 2057–2071.
- Pomeranz, B., & Cheng, R. (1979). Suppression of noxious responses in single neurons of cat spinal cord by electroacupuncture and its reversal by the opiate antagonist naloxone. *Experimental Neurology*, *64*, 327–341.
- Pomeranz, B., & Paley, D. (1979). Electroacupuncture hypalgesia is mediated by afferent nerve impulses: an electrophysiological study in mice. *Experimental Neurology*, *66*, 398–402.
- Quella, S. K., Loprinzi, C. L., Sloan, J., Novotny, P., Perez, E. A., Burch, P. A., et al. (1999). Pilot evaluation of venlafaxine for the treatment of hot flashes in men undergoing androgen ablation therapy for prostate cancer. *Journal of Urology*, *162*, 98–102.
- Shanafelt, T. D., Barton, D. L., Adjei, A. A., & Loprinzi, C. L. (2002). Pathophysiology and treatment of hot flashes. *Mayo Clinic Proceedings*, *77*, 1207–1218.
- Sicat, B. L., & Brokaw, D. K. (2004). Nonhormonal alternatives for the treatment of hot flashes. *Pharmacotherapy*, *24*, 79–93.
- Sloan, J. A., Loprinzi, C. L., Novotny, P. J., Barton, D. L., Lavoisier, B. I., & Windschitl, H. (2001). Methodologic lessons learned from hot flash studies. *Journal of Clinical Oncology*, *19*, 4280–4290.
- Spetz, A. C., Hammar, M., Lindberg, B., Spangberg, A., & Varenhorst, E. (2001). Prospective evaluation of hot flashes during treatment with parenteral estrogen or complete androgen ablation for metastatic carcinoma of the prostate. *Journal of Urology*, *166*, 517–520.
- Spetz, A. C., Zetterlund, E. L., Varenhorst, E., & Hammar, M. (2003). Incidence and management of hot flashes in prostate cancer. *Journal of Supportive Oncology*, *1*, 263–6, 269–70, 272–3; discussion 267–8, 271–2.
- Vincent, A., Barton, D. L., Mandrekar, J. N., Cha, S. S., Zais, T., Wahner-Roedler, D. L., et al. (2007). Acupuncture for hot flashes: a randomized, sham-controlled clinical study. *Menopause*, *14*, 45–52.
- Walker, E. M., Rodriguez, A. I., Kohn, B., Ball, R. M., Pegg, J., Pocock, J. R., et al. (2010). Acupuncture versus venlafaxine for the management of vasomotor symptoms in patients with hormone receptor-positive breast cancer: a randomized controlled trial. *Journal of Clinical Oncology*, *28*, 634–640.
- Zhao, Z. Q. (2008). Neural mechanism underlying acupuncture analgesia. *Progress in Neurobiology*, *85*, 355–375.