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# Systematic Review of Acupuncture in Cancer Care: A Synthesis of the Evidence

M. Kay Garcia, Jennifer McQuade, Robin Haddad, Sonya Patel, Richard Lee, Peiying Yang, J. Lynn Palmer, and Lorenzo Cohen

A B S T R A C T

#### Purpose

Many cancer centers offer acupuncture services. To date, a comprehensive systematic review of acupuncture in cancer care has not been conducted. The purpose of this review was to evaluate the efficacy of acupuncture for symptom management in patients with cancer.

#### Methods

Medline, Embase, CINAHL, Cochrane (all databases), Scopus, and PubMed were searched from inception through December 2011 for prospective randomized clinical trials (RCT) evaluating acupuncture for symptom management in cancer care. Only studies involving needle insertion into acupuncture points were included. No language limitations were applied. Studies were assessed for risk of bias (ROB) according to Cochrane criteria. Outcomes by symptom were designated as positive, negative, or unclear.

#### Results

A total of 2,151 publications were screened. Of those, 41 RCTs involving eight symptoms (pain, nausea, hot flashes, fatigue, radiation-induced xerostomia, prolonged postoperative ileus, anxiety/ mood disorders, and sleep disturbance) met all inclusion criteria. One positive trial of acupuncture for chemotherapy-induced nausea and vomiting had low ROB. Of the remaining studies, eight had unclear ROB (four positive, three negative, and one with unclear outcomes). Thirty-three studies had high ROB (19 positive, 11 negative, and three with both positive and negative outcomes depending on the symptom).

#### Conclusion

Acupuncture is an appropriate adjunctive treatment for chemotherapy-induced nausea/vomiting, but additional studies are needed. For other symptoms, efficacy remains undetermined owing to high ROB among studies. Future research should focus on standardizing comparison groups and treatment methods, be at least single-blinded, assess biologic mechanisms, have adequate statistical power, and involve multiple acupuncturists.

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## INTRODUCTION

The use of complementary therapies is common among patients with cancer.<sup>1</sup> Although some approaches may be helpful, making informed decisions about their use can be difficult, particularly when mechanisms of approaches such as acupuncture remain elusive.

According to the World Health Organization, acupuncture is used in at least 78 countries.<sup>2</sup> It involves the placement of solid, sterile, stainless steel needles into specific points on the body that are believed to have reduced bioelectrical resistance and increased conductance.<sup>3,4</sup> Various techniques are used to stimulate the needles such as manual manipulation or adding a mild electrical current.<sup>3-5</sup> Stainless steel or gold (semi-permanent) needles, or

"studs," are also sometimes placed at points on the ears and left in place for several days. When performed correctly, acupuncture has been shown to be safe, minimally invasive, and have few adverse effects.<sup>6-13</sup> Most serious adverse events are as a result of a lack of education or negligence on the part of the practitioner rather than the treatment itself.

The mechanisms of acupuncture are not well understood and may be dependent on the specific symptom being treated, point selection, and type of needle stimulation. In pain control, for example, activation of opioid systems and autonomic and CNS has been shown to cause the release of various neurotransmitters and neurohormones.<sup>3,14</sup> For nausea, fatigue, hot flashes, xerostomia, or other symptoms, the mechanisms may be quite different than for pain. Although studies are under way to

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parse-out the specific effects of acupuncture, until strong correlations can be made between objective physiologic outcomes and subjective, patient-reported measures, optimizing treatment approaches is challenging.

In 1998, a National Institutes of Health consensus panel reported acupuncture was effective in controlling postoperative pain and chemotherapy-related nausea and vomiting.<sup>15</sup> Since then, both the National Cancer Institute and the National Center for Complementary and Alternative Medicine have sponsored several clinical trials evaluating the use of acupuncture for symptom management. More recent reviews have focused on one or two specific symptoms and have included multiple acupuncture techniques, such as acupuncture point stimulation with acupressure, electrical stimulation with/without needles, or the use of magnets.<sup>16</sup> Therefore, discerning the specific benefits of acupuncture point needling per se is difficult.

Many major cancer centers in the United States now offer acupuncture services. Yet, it can be difficult for physicians to make informed decisions about whether or not to add it to a patient's treatment plan. The purpose of this systematic review was to: identify prospective randomized clinical trials (RCTs) investigating the use of acupuncture for symptom management among patients with cancer; evaluate risk of bias (ROB) for the included studies; provide a synthesis of conclusions for included studies by symptom; and provide recommendations for physicians, researchers, and acupuncturists regarding the study and use of acupuncture for symptom management in patients with cancer. The heterogeneity of study designs and treatment methods does not allow for meta-analysis. The intent, therefore, is to provide synthesis to the broad area of acupuncture for symptom management in patients with cancer and to evaluate the overall level of evidence.

## METHODS

Medline, Embase, CINAHL, Cochrane (all databases), Scopus, and PubMed were searched from inception through December 2011 by a professional medical research librarian for prospective RCTs related to acupuncture in cancer care. No language limitations were applied. Key search terms were acupuncture, electroacupuncture, moxibustion, Chinese medicine, Asian medicine, cancer, neoplasms, randomized controlled trial, controlled clinical trial, and symptom management. Additional terms were used to target specific symptoms (ie, pain, nausea, hot flashes, hot flushes, fatigue, xerostomia, ileus, anxiety, depression, mood disorder, sleep disturbance, insomnia, dyspnea, shortness of breath, peripheral neuropathy, hiccups, and hiccoughs).

#### Study Selection

Two authors (K.G. and S.P.) independently screened articles for inclusion. Studies were included if they were prospective RCTs, evaluated the use of acupuncture for symptom management in patients with cancer, and involved needle insertion into acupuncture points. Unpublished reports, letters to the editor, retrospective chart reviews, studies for which only interim data analyses were available, and studies that did not evaluate acupuncture for cancerrelated symptom management were excluded. If contact information was available for abstracts with interim analyses only, the first author was contacted via e-mail and was asked if final results were published elsewhere. Studies using therapies similar to acupuncture but that did not involve needle insertion (ie, acupressure, laser acupuncture, and electrostimulation without needles) or studies that only compared two types of active acupuncture were excluded. Likewise, studies evaluating acupuncture for the treatment of disease or effects on immunity rather than cancer-related symptom management were excluded.

## Data Abstraction and Rating of Articles for ROB

Studies were placed into predefined subgroups according to symptom. To best inform clinical decision making, studies with more than one RCT within the symptom category are emphasized. For articles published in English, two authors (K.G. and R.H.) abstracted data and rated articles for sequence generation/randomization, allocation concealment, blinding, missing data, selective outcome reporting, and other sources of bias. Articles written in Chinese were evaluated by two reviewers fluent in the language (J.M. and P.Y.). Each article was independently rated using the Cochrane ROB criteria<sup>17</sup> (Table 1). To be rated as low ROB, a study had to meet all criteria in all domains. Studies were rated as unclear ROB if there was unclear risk in one or more domains with no high risk. High risk in one or more domains was rated as high ROB.

After determining ROB, two reviewers (K.G. and R.H.) also independently evaluated each study according to whether findings for primary outcomes were positive, negative, or unclear. Although some studies reported statistical analyses for within group changes from baseline, between-group

Domain	Criteria	Examples			
Sequence generation	Allocation sequence was adequately generated	<ul> <li>Random number table used</li> <li>Computer random number generator used</li> <li>Used coin tossing</li> <li>Shuffled cards or envelopes</li> <li>Drew lots</li> </ul>			
Allocation concealment	Allocation of group assignment could not be foreseen prior to randomization	<ul> <li>Used central allocation such as telephone or Web-based randomization</li> <li>Used sequentially numbered opaque, sealed envelopes</li> </ul>			
Blinding of participants, personnel, and outcome assessors	Knowledge of the allocated intervention was adequately prevented during the study	<ul> <li>Blinding was ensured for participants and key study personnel and unlikely to have been broken</li> <li>No blinding, but the outcom was unlikely to have been influenced</li> </ul>			
Incomplete outcome data	Incomplete outcome data were adequately addressed	<ul> <li>No missing outcome data</li> <li>Missing outcome data unlikely to be related to true outcome</li> <li>Missing outcome data balanced across groups with similar reasons for missing data across groups</li> </ul>			
Selective outcome reporting	The study was free of apparent selective outcome reporting	<ul> <li>Study protocol available and all prespecified outcomes of interest reported</li> <li>Study protocol not available but reported all expected prespecified outcomes</li> </ul>			
Other sources of bias	The study was free of other problems that could introduce bias	<ul> <li>Small sample size (&lt; 30/group randomly assigned One acupuncturist provided all treatments to active and sham groups</li> <li>Baseline group differences</li> <li>Inconsistent or unclear recruitment strategies or treatment methods</li> <li>Study stopped early</li> <li>Vague/unclear outcome measures</li> <li>Short washout period in a crossover design</li> </ul>			

NOTE. Complete criteria for judgment of high, low, or unclear risk of bias may be accessed at Part 2, Chapter 8, Section 8.5, Table 8.5.d, "Criteria for judging risk of bias in the 'risk of bias' assessment tool" at www.cochrane-handbook.org/.<sup>17</sup>

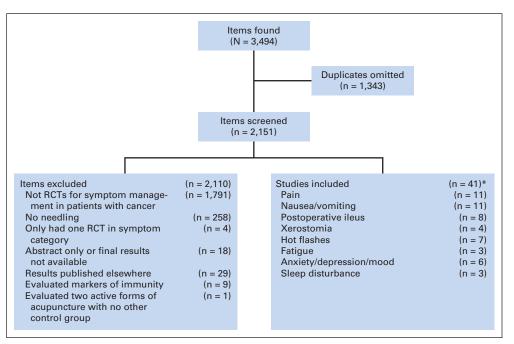


Fig 1. Flow chart for selection of studies. RCT, randomized clinical trial. (\*) Some studies included more than one symptom.

differences were emphasized in determining study outcomes. In some situations, such as when acupuncture was compared with hormone-replacement therapy for the treatment of hot flashes, a lack of between-group differences indicates a positive trial. Differences in rating were settled by discussion or by a third person (English, L.C.; Chinese, J.M.) if consensus was not achieved by the two primary reviewers.

To determine the magnitude of the effect of acupuncture in any of the positive trials, we identified a subset of studies for which effect sizes could be estimated. Studies that had at least 20 patients per group, compared acupuncture to usual care and/or active acupuncture to sham/placebo, did not involve a cross-over design, and presented adequate data for calculating effect size (Cohen's *d* within or between groups) were evaluated.

## RESULTS

A total of 3,494 articles were identified; 1,343 duplicates were omitted, leaving 2,151 articles that were screened. Of those, 41 RCTs involving eight symptoms (pain, nausea, hot flashes, fatigue, radiation-induced xerostomia, prolonged postoperative ileus, anxiety/mood disorders, and sleep disturbance) met all inclusion criteria and were evaluated for ROB (see Fig 1). Four of the included studies were written in Chinese and 37 in English. Some studies investigated the use of acupuncture for multiple symptoms.

For four symptoms (dyspnea, chemotherapy-induced peripheral neuropathy, unremitting hiccups, and lower urinary-tract symptoms), only one RCT was identified. Two of these (chemotherapy-induced peripheral neuropathy and hiccups) were unblinded trials with high ROB. The studies evaluating acupuncture for dyspnea and lower urinary-tract symptoms were methodologically sound but had high ROB because of small sample sizes (N = 47 and N = 30, respectively).

Of the 41 studies that met all inclusion criteria, one positive trial evaluating the use of acupuncture for chemotherapy-induced emesis was identified as having low ROB (Table 2). Of those remaining, eight had unclear ROB (four positive, three negative, and one with unclear conclusions). Thirty-three studies had high ROB (19 positive, 11 negative, and three with both positive and negative outcomes, depending on the symptom). Of the 41 studies, 16 studies (39%) had small sample sizes with fewer than 60 participants. A total of nine studies (five symptoms)<sup>18-26</sup> met criteria for effect size calculation and are discussed in the relevant sections of this article.

Tables 3 and 4 present ROB ratings for included trials by symptom and indicates whether conclusions for major outcomes were positive, negative, or unclear. Of 17 studies with at least one negative or unclear outcome, nine reported negative between- and within-group findings and eight reported clinically significant positive within-group findings. There was also considerable heterogeneity in study design among studies: acupuncture versus control (16 studies, one crossover), true acupuncture versus sham (12 studies), acupuncture versus other types of treatment (two studies), acupuncture versus other treatment versus control (three studies), acupuncture versus sham versus control (two studies), true acupuncture versus sham versus other treatment (three studies), acupuncture versus sham versus other

	Risk of Bias (No. of studies)						
Symptom	High	Unclear	Low	Total			
Pain	10	1	0	11			
Nausea	8	2	1	11			
Postoperative ileus	6	2	0	8			
Xerostomia	4	0	0	4			
Hot flashes	5	2	0	7			
Fatigue	3	0	0	3			
Anxiety/depression/mood	6	0	0	6			
Sleep disturbance	3	0	0	3			

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Outcome		Level of Risk/ Conclusions
Pain							
Li 1994 (see ileus) <sup>27</sup>	0	-	0	0	+	-	H/N
Poulain 1997 (see ileus) <sup>28</sup> *	+	+	-	+	+	0	H/P
Dang 1998 <sup>29</sup>	0	0	_	-	0	_	H/P
Alimi 2003 <sup>18</sup>	+	+	0	+	+	0	U/P
Wong 2006 <sup>30</sup>	+	+	+	+	+	-	H/P
Crew 2007 <sup>31</sup>	0	0	_	+	_	_	H/P
He 2007 (see ileus) <sup>32*</sup>	0	0	0	0	+	_	H/P
Mehling 2007 (see nausea, anxiety/depression/mood disorder in Table 4) <sup>33*</sup>	+	+	-	0	0	-	H/P
Deng 2008 <sup>34</sup>	+	+	+	+	+	0	U/N
Crew 2010 <sup>19</sup>	+	+	+	+	+	_	H/P
Pfister 2010 (see xerostomia) <sup>20</sup> *	+	+	_	+	+	+	H/P
Nausea							
Xia 1986 <sup>35</sup>	0	0	-	-	_	_	H/N
Dundee 1987 <sup>36</sup>	+	0	_	0	_	_	H/P
Dundee 1988 <sup>37</sup>	+	0	_	0	_	_	H/N
Shen 2000 <sup>21</sup>	+	+	+	+	+	+	L/P
Streitberger 2003 <sup>38</sup>	+	+	+	+	+	_	H/N
Melchart 2006 <sup>39</sup>	+	+	+	+	+	_	H/N
Mehling 2007 (see pain, anxiety/depression/mood disorder in Table 4) <sup>33</sup>	+	+	_	0	0	_	H/N
Gottschling 2008 <sup>40</sup>	+	+	0	+	+	_	H/P
Yang 2009 <sup>22</sup>	+	+	+	+	+	0	U/P
Enblom 2011 <sup>41</sup>	+	0	+	+	+	_	H/P
Enblom 2011 <sup>42</sup>	+	0	+	+	+	+	U/N
lleus							
Li 1994 (see pain) <sup>27</sup>	0	_	0	0	+	_	H/P
Poulain 1997 (see pain) <sup>28</sup>	+	0	_	+	+	0	H/N
He 2007 (see pain) <sup>32</sup>	0	0	0	0	+	_	H/P
Garcia 2008 <sup>43</sup>	0	0	0	+	+	_	H/N
Yin 2009 <sup>44</sup>	0	0	_	+	+	0	H/P
Meng 2010 <sup>45</sup>	+	+	0	+	+	0	U/N
Sun 2010 <sup>46</sup>	0	0	0	+	+	0	U/P
Du 2011 <sup>23</sup>	0	0	_	0	0	_	H/P
Xerostomia	Ŭ			Ŭ	Ŭ		, .
Blom 1996 <sup>47</sup>	+	0	+	+	+	_	H/N
Cho 2008 <sup>48</sup>	0	0	_	0	+	_	H/N
Pfister 2010 (see pain) <sup>20</sup>	+	+	_	+	+	+	H/P
Meng 2011 <sup>24</sup>	+	+	_	+	+		H/P

NOTE. 0 represents unclear ROB, - represents high ROB, and + represents low ROB.

Abbreviations: H, high ROB for one or more domains; L, low ROB for all domains; N, conclusions negative for symptoms; P, conclusions positive for symptoms; ROB, risk of bias; U, unclear ROB for one or more domains.

\*Indicates primary outcome if multiple symptoms were evaluated.

groups (one study), acupuncture plus acupressure versus sham plus acupressure (one study), and acupuncture versus other treatment versus acupuncture plus other treatment (one study).

## **Results by Symptom**

*Pain.* Pain is the most common symptom treated by acupuncture. This review included 11 RCTs<sup>18-20,27-34</sup> on pain (Table 3). No large trials were identified that had low ROB and positive results. The most common reasons reviewers assigned high ROB were problems with blinding patients and small sample size. Within-group effect size estimates for significant pain studies ranged from 1.11 to 2.10 for true acupuncture and from -0.45 to 0.45 for sham acupuncture.<sup>18-20</sup>

Among pain studies, two blinded, sham-controlled trials (N = 25: 13 electroacupuncture and 12 sham; N = 38: 20 acupuncture

and 18 sham)<sup>19,30</sup> with positive findings were methodologically sound but had small sample sizes. In the earlier trial, Wong et al<sup>30</sup> found patients who received electroacupuncture after thoracotomy used significantly less pain medication than patients who received sham treatment (P < .05). A later cross-over trial (N = 106 at 30-day follow-up; 52 acupuncture and 54 sham)<sup>34</sup> did not find perioperative stimulation with intradermal acupuncture needles was more effective than sham for post-thoracotomy pain, but authors concluded the specific technique used may have provided less intense stimulation than the electroacupuncture used in the previous trial.<sup>30</sup> In later studies, Crew et al evaluated the use of acupuncture for management of aromatase inhibitor–associated joint pain in women with breast cancer.<sup>19,31</sup> In an initial pilot cross-over study (N = 19),<sup>31</sup> the authors

### Garcia et al

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Level of Risk/ Conclusions
Hot flashes							
Nedstrand 2006 (see anxiety/depression/mood disorder)49*	+	+	-	+	+	-	H/P
Deng 2007 <sup>50</sup>	+	+	+	+	+	0	U/?
Frisk 2008 <sup>51</sup>	+	+	-	+	+	-	H/N
Hervik 2009 <sup>25</sup>	+	+	+	+	+	0	U/P
Liljegren 2010 <sup>26</sup>	+	+	-	+	+	0	H/P
Walker 2010 (see anxiety/depression/mood disorder) <sup>52*</sup>	+	0	-	+	-	-	H/P
Frisk 2011 (see sleep, anxiety/depression/mood disorder)53*	+	+	-	+	+	-	H/P
Fatigue							
Molassiotis 2007 <sup>54</sup>	+	+	+	+	+	_	H/P
Balk 2009 (see anxiety/depression/mood disorder)55*	+	+	+	0	+	_	H/N
Johnston 2011 <sup>56</sup>	+	+	-	+	+	-	H/N
Anxiety/depression/mood disorder							
Nedstrand 2006 (see hot flashes) <sup>49</sup>	+	+	-	+	+	-	H/P
Mehling 2007 (see pain, nausea in Table 3) <sup>33</sup>	+	+	-	0	0	-	H/P
Balk 2009 (see fatigue) <sup>55</sup>	+	+	+	0	+	-	H/N
Walker 2010 (see hot flashes) <sup>52</sup>	0	0	-	+	_	-	H/P
Feng 2011 (see sleep disturbance) <sup>57*</sup>	+	0	-	_	+	0	H/P
Sleep disturbance							
Cui 2003 <sup>58</sup>	0	0	-	0	0	-	H/P
Frisk 2011 (see hot flashes, anxiety/depression/mood disorder) <sup>53</sup>	+	+	_	+	+	_	H/P
Feng 2011 (see anxiety/depression/mood disorder) <sup>57</sup>	+	0	_	_	+	0	H/P

NOTE. 0 represents unclear ROB, - represents high ROB, and + represents low ROB.

Abbreviations: H, high ROB for one or more domains; N, conclusions negative for symptoms; P, conclusions positive for symptoms; ROB, risk of bias; U, unclear ROB for one or more domains; ?, conclusions unclear for symptoms.

\*Indicates primary outcome if multiple symptoms were evaluated.

concluded acupuncture reduced joint symptoms and improved functional ability. A subsequent blinded, sham-controlled trial  $(N = 38)^{19}$ showed worst pain scores were significantly lower in the true acupuncture versus sham group (P < .003).

One trial (N = 87; 29 acupuncture, 28 sham needles, and 30 sham ear seeds)<sup>18</sup> with positive results compared auricular acupuncture with two placebo groups (ear studs at sham points and ear seeds at sham points). ROB was unclear because issues of blinding were not discussed, and after the study began, the recruitment strategy was changed.

*Nausea and vomiting.* Nausea and vomiting are among the top three most commonly reported adverse effects of cancer treatment. In our search, 11 RCTs<sup>21,22,33,35-42</sup> on nausea and vomiting met the inclusion criteria (Table 3). One three-arm, parallel group RCT (N = 104; 37 electroacupuncture, 33 sham, and 34 antiemetic medications) with positive findings for the use of electroacupuncture to control myeloablative chemotherapy-induced emesis among women with breast cancer was considered to have low ROB.<sup>21</sup> At 5 days, the electroacupuncture group had significantly fewer episodes of emesis versus minimal needling (P < .001). Furthermore, the minimalneedling group had significantly fewer episodes of emesis than the medication group (P = .01). The between-group effect size estimate for acupuncture versus sham was 0.80 and for acupuncture versus usual care was 1.10.

Among studies that were blinded, two trials (N = 246: 127 electroacupuncture plus medications and 119 medications alone; N = 205: 103 acupuncture and 102 sham)<sup>22,42</sup> were rated as having unclear ROB. In one study<sup>22</sup> published in Chinese, patients who

received electroacupuncture plus antiemetics experienced significantly less nausea than patients who received antiemetics alone (P < .001). Reviewers rated this study as unclear ROB because there was no mention of who conducted the acupuncture treatments, and detail was lacking in the descriptions of some study procedures. Within-group effect size estimate was 2.35 for true acupuncture and 1.26 for medications alone. In the second trial,<sup>42</sup> penetrating acupuncture to elicit "de qi" sensation was compared with a nonpenetrating sham procedure. Although findings were negative for between-group differences, there was no usual care control group, and the authors stated more than 95% of patients reported the treatments helped relieve nausea. ROB in this study was unclear because there was not sufficient detail to determine how investigators were prevented from foreseeing group allocations before randomization.

All other studies evaluating acupuncture for nausea/vomiting had high ROB (three positive and five negative outcomes). One trial was a randomized, multicenter, cross-over pilot study evaluating the use of acupuncture for chemotherapy-induced nausea and vomiting in a pediatric oncology population.<sup>40</sup> Although this was a positive trial, lack of patient blinding was cause for concern when interpreting results. Of the five trials with high ROB and negative findings, two were underpowered,<sup>37,39</sup> one was stopped early,<sup>38</sup> one had positive outcomes for pain and anxiety,<sup>33</sup> and one,<sup>35</sup> published in 1986, had numerous reporting insufficiencies.

*Postoperative ileus.* Eight RCTs<sup>23,27,28,32,43-46</sup> evaluated the use of acupuncture to treat or prevent prolonged postoperative ileus (Table 3). Six<sup>23,27,28,32,43,44</sup> were assessed as having high ROB (four with positive and two with negative outcomes) and two<sup>45,46</sup> (one positive

and one negative) had unclear ROB because of a lack of information about blinding or who performed the acupuncture treatments. For one study with high ROB<sup>23</sup> (35 acupuncture and 35 usual care; P < .05), the between-group effect size estimate was 1.05. No RCTs meeting our inclusion criteria evaluated the use of acupuncture to treat diarrhea, constipation, or loss of appetite among patients with cancer.

*Xerostomia.* Four studies<sup>20,24,47,48</sup> evaluating xerostomia (dry mouth) were included (Table 3). Three evaluated the use of acupuncture to treat radiation-induced xerostomia and one evaluated whether or not acupuncture administered during a course of radiation could reduce the incidence and severity of symptoms. All had high ROB (two positive and two with negative outcomes) owing to low statistical power or problems with patient blinding. For two of the studies, an effect size could be estimated. The between-group (acupuncture, N = 39; usual care, N = 45; *P* = .003) effect size estimate for one study<sup>24</sup> was 0.94, and the within-group effect size estimate for the other was 0.35 for true acupuncture and 0.08 for usual care (*P* < .02).<sup>20</sup>

Although not included in this review because the population consisted of healthy volunteers, an interesting study conducted by Deng et al<sup>59</sup> used functional magnetic resonance imaging to evaluate changes in saliva production associated with acupuncture at point LI-2. Manual stimulation of LI-2 was associated with neuronal activations that were absent during sham acupuncture. Furthermore, neuroimaging signal changes appeared to correlate with saliva production. Mean saliva production in grams during the true versus sham acupuncture was 2.72 (standard deviation, 1.42) and 2.38 (standard deviation, 1.43), respectively.

*Vasomotor symptoms (hot flashes).* Hot flashes experienced by patients receiving treatment for cancer may significantly interfere with quality of life. For this review, seven RCTs<sup>25,26,49-53</sup> studying vasomotor symptoms were included (Table 4). No studies had low ROB.

Two sham-controlled trials<sup>25,50</sup> had unclear ROB (one with positive and one with unclear outcomes). The positive trial (N = 59; 30 acupuncture, 29 sham)<sup>25</sup> was rated as having unclear ROB because of the small sample size, and only one acupuncturist gave all treatments to both true and sham groups. The within-group effect size estimate for true acupuncture was 1.29 and 0.03 for sham (P < .001). In the other study,<sup>50</sup> ROB was unclear because it was a cross-over design, with short treatment and wash-out periods. Outcomes were unclear because even though between-group differences were not significant, when participants in the sham group were crossed-over to true acupuncture, a further reduction in the frequency of hot flashes was seen which persisted for up to 6 months after completion of treatment. Finally, one blinded study for hot flashes with positive outcomes was rated as having high ROB<sup>26</sup> because 64.9% of patients in the control group correctly guessed they were getting the inactive treatment. For nighttime hot flash severity in this trial, the within-group effect size estimate for true acupuncture was 0.56 and 0.36 for sham (P = .03).

*Fatigue.* Fatigue in patients with cancer is difficult to manage and can have a major impact on quality of life. For this review, three studies<sup>54-56</sup> of fatigue were included (Table 4). All were assessed as having high ROB. Two studies with negative outcomes<sup>55,56</sup> were underpowered (N = 26: 15 acupuncture and 11 sham; N = 12: five acupuncture plus lifestyle education and seven usual care). The latter study also had problems with recruitment. In a third study with positive outcomes (N = 38; 13 acupuncture, 12 acupressure, and 13

sham acupressure),<sup>54</sup> there were questions about possible group differences at baseline. In addition, a single acupuncturist acquired the consent of and treated all participants.

Anxiety/depression. Although acupuncture is frequently used in the community for anxiety and stress management, relatively few studies have evaluated its use for these symptoms in patients with cancer. Six trials<sup>33,49,52,53,55,57</sup> met the inclusion criteria (Table 4). All evaluated additional symptoms such as pain, hot flashes, nausea, fatigue, or sleep; therefore, treatment specificity for anxiety, depression, or other mood disturbances was questionable. Five<sup>33,49,52,53,57</sup> of the trials with positive outcomes were unblinded and, thus, assessed as having high ROB. One<sup>55</sup> negative trial with high ROB was blinded but underpowered (N = 26; 15 acupuncture and 11 sham).

*Sleep quality.* Poor sleep quality is common among patients undergoing cancer treatment. Few studies have evaluated the use of acupuncture to improve sleep, and only three studies<sup>53,57,58</sup> met our inclusion criteria. All three reported positive outcomes, but they were unblinded studies with high ROB (Table 4).

## DISCUSSION

According to this review, the strongest evidence for the use of acupuncture in patients with cancer was for control of nausea/vomiting. One positive trial with a large between-group effect size (0.80) in patients with breast cancer on high-dose chemotherapy was rated as having low ROB.<sup>21</sup> A second multicenter blinded trial published in Chinese (N = 246),<sup>22</sup> reported positive outcomes but was rated as unclear ROB because there was no mention of who provided the acupuncture treatments and a lack of detail in reporting. Overall, among studies for which we could estimate an effect size, the betweengroup effect size for significant studies for acupuncture versus usual care ranged from 0.94 to  $1.10.^{21,23,24}$  The within-group effect size estimates ranged from 0.35 to 2.35 for active acupuncture and from -0.45 to 1.26 for sham acupuncture. This suggests there are nonspecific aspects contributing to acupuncture, yet the specific effects are larger.

Lack of reporting on who conducted the acupuncture treatments was a common problem across studies. The specific effects of acupuncture needling are not well understood, and there is clearly a strong placebo component, especially in symptom management among patients with cancer. Kaptchuk et al<sup>60</sup> evaluated the multiple elements of placebo (ie, assessment and observation, therapeutic ritual, and supportive patient-practitioner relationship) and found the patient-practitioner relationship is the most robust of these components. Therefore, it is imperative that studies report information about who provided treatments. Studies in which a single unblinded acupuncturist provides all treatments may be at risk of introducing bias, especially if one individual provides treatment to both active and inactive groups in a sham-controlled trial. While utilization of multiple acupuncturists introduces some degree of variability in treatment methods, findings will have greater generalizability. The ethics of providing a sham treatment are of concern to some acupuncturists whose professional standard of care may be different from allopathic medicine; thus, acupuncturists may need reassurance that care has been taken to avoid deception when patients are recruited to clinical trials.

In 1998, a National Institutes of Health consensus statement on acupuncture stated, "There is clear evidence that needle acupuncture is efficacious for adult postoperative and chemotherapy nausea and vomiting and probably for the nausea of pregnancy,"<sup>15</sup> but acupuncture is still not accepted as a standard treatment. This is in part because putative mechanisms are not well understood, and the placebo response is a contributing mechanism. Regardless of the specific molecular basis of the effects, acupuncture for nausea/vomiting is a safe and inexpensive treatment that can relieve considerable suffering and may be an especially important option for patients who do not get good symptom control with pharmaceuticals. Although more research is needed, findings from this review are supportive for the use of acupuncture as an adjunctive treatment to manage nausea in patients with cancer. For other symptoms, positive trials with low ROB were not found.

Of the 11 trials examining acupuncture for pain, nine were positive, but eight had high ROB. Two blinded, sham-controlled trials<sup>19,30</sup> had positive findings and were methodologically sound but underpowered. Other reviews and meta-analyses have been published suggesting the utility of acupuncture for pain control in noncancer populations,<sup>61</sup> but studies with low ROB are needed to definitively assess its efficacy for pain management in patients with cancer.

Conclusions for studies with high ROB should be viewed with caution, but it should be noted the most common reasons for high ROB were lack of statistical power and inadequate blinding. Although acupuncturists cannot be blinded, patients and assessors can be through the use of placebo needle devices.<sup>62,63</sup> Other problems identified among studies were lack of a usual care comparison group and lack of detail in reporting. Although more recent publications were better at following recommended guidelines,<sup>64</sup> descriptions of randomization procedures and allocation concealment, missing data, and drop outs are still problematic. While it is reasonable to assume rigorous procedures were unlikely to have been performed if not mentioned, it is possible that limits on journal space precluded detailed descriptions. To accurately assess bias in future trials, diligent reporting is necessary.

Two important questions for physicians are: when should I refer patients for acupuncture, and what specific guidelines are available to help make informed decisions? Based on this review, physicians should refer patients for acupuncture if they are experiencing uncontrolled nausea/vomiting, and there are no contraindications. For other symptoms such as pain, hot flashes, xerostomia, anxiety, or fatigue, efficacy is undetermined largely owing to high ROB among studies. As Ernst<sup>65</sup> aptly reminds us, a lack of evidence does not necessarily mean lack of effect.

Specific guidelines for providing acupuncture treatment to patients with cancer have been published by Filshie and Hester.<sup>66</sup> Treatment should always be provided by a credentialed practitioner, and needles should never be placed directly into a tumor or ulcerated area. In general, needles should not be placed in limbs prone to lymphedema, but studies are underway to assess the potential safety and efficacy of using acupuncture to treat this problem. Care should be taken when needling over the chest wall in cachetic patients and when treating neutropenic patients or patients with bleeding disorders. Electroacupuncture should not be used in patients with an intracardiac defibrillator or pacemaker, and finally, special care and attention should be provided when treating pregnant patients, patients with seizure disorders, and confused patients.<sup>66,67</sup>

Evidence-based practice helps improve patient outcomes, and acupuncturists should increase their awareness of research findings. For acupuncturists who participate in clinical trials, it is important to be knowledgeable about human subject considerations and potential sources of bias that can be introduced during a treatment session.

Overall, the quality of acupuncture trials is improving. The guiding research agenda of the future should focus on standardizing comparison groups and treatment methods, ensuring that at least single blinding is used, using multiple acupuncturists, identifying biologic mechanisms, and conducting trials with adequate statistical power.

It is as important for authors of systematic reviews to assess their own ROB as it is to assess the ROB of the RCTs they evaluate. Although reviewers were not blinded as to the authorship of articles that were rated, we attempted to limit that risk by involving multiple reviewers throughout the process. With a project of this magnitude, however, relevant information may be overlooked, and unintended errors may occur. Publication bias is also of concern. Finally, although we attempted to include databases that the study team thought would be most inclusive of related literature, other databases may have produced a different listing of RCTs.

The use of acupuncture as an adjunct for symptom control in oncology is important to consider. Studies with adequate power, duration, and controls are necessary to evaluate its applications for general symptom management. According to this review, acupuncture is an appropriate adjunctive treatment for chemotherapy-induced nausea/vomiting, but additional research is needed to increase the reliability of these findings. For other symptom management, efficacy remains undetermined because of unclear or high ROB among studies.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

Conception and design: M. Kay Garcia, Jennifer McQuade, Richard Lee, J. Lynn Palmer, Lorenzo Cohen Collection and assembly of data: M. Kay Garcia, Jennifer McQuade, Robin Haddad, Sonya Patel, Peiying Yang, J. Lynn Palmer Data analysis and interpretation: All authors Manuscript writing: All authors Final approval of manuscript: All authors

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