Auriculotherapy for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Gary N. Asher, MD, MPH,^{1,2} Daniel E. Jonas, MD, MPH,³ Remy R. Coeytaux, MD, PhD,⁴
Aimee C. Reilly, LAc,¹ Yen L. Loh, MD,¹ Alison A. Motsinger-Reif, PhD,⁵ and Stacey J. Winham, MS⁵

Abstract

Objectives: Side-effects of standard pain medications can limit their use. Therefore, nonpharmacologic pain relief techniques such as auriculotherapy may play an important role in pain management. Our aim was to conduct a systematic review and meta-analysis of studies evaluating auriculotherapy for pain management.

Design: MEDLINE,[®] ISI Web of Science, CINAHL, AMED, and Cochrane Library were searched through December 2008. Randomized trials comparing auriculotherapy to sham, placebo, or standard-of-care control were included that measured outcomes of pain or medication use and were published in English. Two (2) reviewers independently assessed trial eligibility, quality, and abstracted data to a standardized form. Standardized mean differences (SMD) were calculated for studies using a pain score or analgesic requirement as a primary outcome.

Results: Seventeen (17) studies met inclusion criteria (8 perioperative, 4 acute, and 5 chronic pain). Auriculotherapy was superior to controls for studies evaluating pain intensity (SMD, 1.56 [95% confidence interval (CI): 0.85, 2.26]; 8 studies). For perioperative pain, auriculotherapy reduced analgesic use (SMD, 0.54 [95% CI: 0.30, 0.77]; 5 studies). For acute pain and chronic pain, auriculotherapy reduced pain intensity (SMD for acute pain, 1.35 [95% CI: 0.08, 2.64], 2 studies; SMD for chronic pain, 1.84 [95% CI: 0.60, 3.07], 5 studies). Removal of poor quality studies did not alter the conclusions. Significant heterogeneity existed among studies of acute and chronic pain, but not perioperative pain.

Conclusions: Auriculotherapy may be effective for the treatment of a variety of types of pain, especially postoperative pain. However, a more accurate estimate of the effect will require further large, well-designed trials.

Introduction

PAIN AFFECTS MORE AMERICANS than diabetes, heart disease, and cancer combined,¹ and accounts for more than 20% of medical visits and 10% of prescription drug sales.² One of the most common approaches to managing pain relief, the World Health Organization analgesic ladder,³ details the use of both opioid and nonopioid medications in a stepwise fashion. However, up to 80% of patients receiving opioid medications experience at least one adverse event, most commonly constipation (41%), nausea (32%), or somnolence (29%); the number needed to harm for these common events is

between three and five.⁴ Additionally, gastrointestinal toxicity related to the use of nonsteroidal anti-inflammatory drugs (NSAID) is estimated to cause more than 100,000 hospitalizations and over 16,000 deaths annually in the United States.⁵ Cardiovascular risk is also elevated with use of most NSAIDs.⁶ For these reasons, methods of nonpharmacologic pain relief, such as acupuncture, mind-body interventions, and manipulative therapies, have been advocated as adjuncts to pharmacologic therapy.^{7–9}

Acupuncture has been shown to be effective for pain relief due to a variety of causes including low back pain,^{10,11} osteoarthritis,¹² and headache.¹³ Auriculotherapy is an adjunct to

¹Department of Family Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC.

²Program on Integrative Medicine, Department of Physical Medicine and Rehabilitation, University of North Carolina at Chapel Hill, Chapel Hill, NC.

³Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC.

⁴Department of Community and Family Medicine, Duke University, Durham, NC.

⁵Department of Statistics, North Carolina State University, Raleigh, NC.

traditional acupuncture and over the last 60 years has developed into a distinct treatment system of its own. It is based on a set of anatomical maps superimposed onto the ear. Stimulating a point on the map is proposed to affect the gross anatomical organ associated with that point. For the ear, auricular points may be stimulated with needles (auricular acupuncture); *Vaccaria* seeds, probes, or fingers (acupressure); electrical units attached to auricular needles (percutaneous electrical nerve stimulation) or directly to the skin (TENS—transdermal electrical nerve stimulation or auricular electroacupuncture); or laser; all of which may be considered forms of auriculotherapy.

Early studies of auriculotherapy have demonstrated beneficial effects on both pain and anxiety including pain associated with cancer,¹⁴ knee arthroscopy,¹⁵ and hip fracture and hip arthroplasty.¹⁶ Several recent small studies have suggested that auricular acupuncture alone can relieve pain and anxiety in the prehospital transport phase of hip fracture^{16,17} and reduce acute pain due to a variety of causes in the emergency department setting.¹⁸ Recently, a systematic review of auriculotherapy for perioperative pain concluded that the evidence for efficacy was “promising but not compelling.”¹⁹ However, because auriculotherapy is currently used in a wide range of acute and chronic pain conditions beyond the perioperative period, it is important to assess its clinical utility in general. Therefore, in this review our primary objective was to conduct a systematic review and meta-analysis of the efficacy of auriculotherapy for all types of pain. We present these data as a whole and also by category of pain (perioperative, acute, and chronic).

Materials and Methods

Data sources and searches

We searched MEDLINE,[®] Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, AMED, ISI Web of Science, and CINAHL from inception through December 2008, using the following terms: “auricular acupuncture,” “ear acupuncture,” and “auriculotherapy.” We limited the electronic searches to human subjects and, due to resource constraints, English language. We attempted to identify additional studies through hand searches of reference lists, as well as our own files. All citations were imported into an electronic database (Endnote v. X1).

Study selection

Trials were included if they (1) were randomized; (2) compared auriculotherapy to sham auriculotherapy control, standard medical care, or waiting-list control; (3) measured the effect on pain or medication use; (4) and were published in English in a peer-reviewed journal. We chose to exclude studies that compared auriculotherapy to a nonauriculotherapy active control treatment that did not have clear evidence of efficacy. Two (2) reviewers independently assessed titles and abstracts, which were excluded only if both reviewers agreed that the trial did not meet eligibility criteria. Full-text articles of remaining citations were retrieved and assessed for inclusion by 2 reviewers. Disagreements were resolved by consensus. Results published only in abstract form were not included unless adequate details were available for quality assessment.

Data abstraction and quality (internal validity) assessment

We designed and used a structured data abstraction form. Trained reviewers abstracted data from each study and assigned an initial quality rating. A second reviewer read each abstracted article, evaluated the completeness of the data abstraction, and confirmed the quality rating. Differences in quality ratings were resolved by discussion or by involving a third senior reviewer. The following data were extracted: study design, setting, population characteristics (including age, sex, and race), inclusion and exclusion criteria, interventions, comparisons, additional medications or interventions allowed, outcome assessments, attrition, withdrawals attributed to adverse events, results, and adverse events reported. We recorded intention-to-treat results if available.

For the auriculotherapy interventions, we abstracted details based on the STRICTA (Standards for Reporting Interventions in Controlled Trials of Acupuncture) criteria for the reporting of acupuncture trials,²⁰ including point selection method, point locations, number of points per ear, needle type, use of electrical or laser stimulation, number of treatments, treatment frequency, and duration of each treatment. We also abstracted data on the practitioner type, years of experience, and acupuncture style. For the control intervention, we abstracted similar details. The country of the study was also recorded.

We assessed the quality of trials based on the criteria of the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.).^{21,22} Quality assessment elements included randomization method, allocation concealment, and blinding; similarity of compared groups at baseline; maintenance of comparable groups; reporting of dropouts, crossover, adherence, and contamination; overall and differential loss to follow-up; and intention-to-treat analysis. Attrition was defined as the number of randomized subjects who did not reach the study endpoint.²³

Trials that met all criteria were rated “good quality,” while those that failed to meet combinations of items were rated “poor quality.” The remainder received a quality rating of “fair.” This includes studies that presumably fulfilled all quality criteria but did not report their methodologies to an extent that answered all of our questions. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. A poor-quality trial is not likely to be valid—the results are at least as likely to reflect flaws in the study design as the true difference between the intervention and control.

Data synthesis and analysis

We summarized the overall strength of evidence for the efficacy of auriculotherapy for each set of pain indications into evidence profiles. The overall strength of evidence for a particular key question reflects the design, quality, consistency, and magnitude of effect of the set of studies relevant to the question. We rated the overall strength of evidence as low, moderate, high, or insufficient using an approach established by the Agency for Healthcare Research and Quality Evidence-Based Practice Centers.²⁴ High strength of evidence indicates high confidence in the estimate of effect and that the evidence reflects the true effect; further research is unlikely to change

our confidence. Moderate strength of evidence indicates moderate confidence, and further research may change our confidence in the estimate as well as the estimate itself. Low strength of evidence indicates low confidence in the estimate and further research is likely to change our confidence in the estimate and is likely to change the estimate. Insufficient indicates that evidence is unavailable or does not permit estimation of an effect.

Standardized mean differences (SMD) and 95% confidence intervals (CI) were calculated for all comparisons. A standardized mean difference refers to the raw difference in the sample treatment mean and the sample control mean divided by the pooled standard deviation of both the treatment and control groups. Because the times to study endpoints greatly varied among the studies, weighted mean differences were not calculated. The use of the pooled standard deviation in the SMD accounts for the inconsistent study endpoints by placing the treatment differences on the same comparable scale. SMDs therefore are not interpreted on the original scale, but are interpreted in terms of number of standard deviations. For example, an SMD of 3.0 would mean that the treatment mean is approximately 3.0 standard deviations higher than the control mean. Mean differences around 0.2 are often considered small while those ≥ 0.8 are considered large.²⁵ For example, a mean difference of 0.5 indicates that the mean of the treated group is at the 69th percentile of the comparison group—a moderate effect—while a difference of 1.5 indicates that the mean of the treated group is at the 93% of the comparison group—a large effect.

Study comparisons based on pain scales compared the standardized difference in mean decrease in pain from baseline (to end of study) between the treatment and control group. The numerical rating scale (NRS) was converted to a 100-point scale for comparisons with the 100-point visual analogue scale (VAS). Study comparisons based on pain medication use compared the percentage decrease in pain medication use between treatment and control groups. We tested whether these decreases, in either pain scale or pain medication use, were significantly different from zero across studies. For the overall meta-analysis comparing acupuncture to a control, only the studies that utilized a pain scale measure were included because of concerns of comparability between the pain scale and analgesic use outcomes. For all comparisons, an SMD of zero indicates no difference between groups.

Study results were combined using the two-tailed *p*-values reported from each individual study. If a *p*-value was not reported, it was calculated from the reported standard error. Because study sample sizes and variances were not constant, reported differences were converted to standardized mean differences; studies were weighted by the inverse of the study variance so that studies with lower variance received more weight. A formal hypothesis test for heterogeneity was performed using Cochran's *Q* statistic.²⁶ As an alternative to *Q*, the inconsistency index I^2 is reported,²⁷ as well as τ^2 ,²⁸ the between-study variance. Results for both random and fixed-effects models were calculated, but because significant heterogeneity among studies was often found, we report the results from random effects models only.²⁹ To further investigate heterogeneity, studies that employed multiple control groups^{14,30,31} were compared using the control group with the least active intervention, and studies that used an active control known to be efficacious for pain were excluded.^{32,33}

Analysis was performed using the software package Comprehensive Meta Analysis (www.meta-analysis.com).

Subgroup analyses were performed for perioperative studies reporting pain medication use, studies of acute pain, and studies of chronic pain. Although other subgroups may be important to consider, too few studies were available for such analyses.

Forest plots and funnel plots were created for the overall results and for each subgroup analysis. Sensitivity analysis was performed by removing each study and recalculating the overall results of the analysis. Cumulative analysis was performed to assess the possible treatment effect over time. Comparisons were performed with and without poor quality studies to assess the effect of study quality. This study was approved by the University of North Carolina institutional review board.

Results

Our search revealed 554 citations, of which 133 full-text articles were reviewed. A total of 17 studies (1009 subjects) met our inclusion criteria (Fig. 1) and were included in the review. Attempts were made to contact the authors of an additional three publications that may have been eligible for inclusion but were not because no replies were elicited.^{34–36} For 5 of the 17 included studies, additional data were obtained from the authors to enable inclusion in the meta-analysis.^{30–33,37} Four (4) studies included in the review were excluded from the meta-analysis due to incomplete data.^{17,38–40}

The 17 included studies encompassed a wide variety of auriculotherapy interventions (Table 1) including auricular needles that were placed and removed after a single session (two studies); indwelling auricular needles that could remain in place for up to 30 days (six studies); electrical stimulation of either indwelling auricular needles (five studies) or transcutaneously without needles (two studies); laser stimulation (one study); and acupressure (one study). Most studies used either a VAS (10/17) or measures of the amount of pain medication use (5/17) as a primary outcome measure. The remaining studies used other measures, including a NRS and reports of "pain relief" or "pain decrease."

Thirty-five percent (6/17) of trials were rated as good quality, 24% (4/17) were fair quality, and 41% (7/17) were poor quality (see Appendix). Selection of auricular acupoints were varied among the studies based on the type and location of pain being treated; however, *shenmen* was the most commonly included point (10 studies) followed by *thalamus* (4). Visual inspection of the funnel plots for each comparison did not indicate substantial publication bias. Table 1 lists type of intervention and control treatments, primary outcome measures, and acupoints for each study.

All pain types

Overall, 12 studies reported primary outcome effects in favor of auriculotherapy, 3 studies found mixed results (different direction of outcomes for multiple outcome scales or multiple times of outcome measurement), and 2 studies reported no difference between auriculotherapy and control interventions (Table 1). Of the 17 studies included in our review, 8 reported sufficient data for change in pain intensity to be included in an overall meta-analysis; 3 studies that did report on pain intensity did not provide enough data to be

FIG. 1. Flow chart of screened, excluded, and analyzed studies. RCT, randomized controlled trial; AT, auriculotherapy.

included in the meta-analysis.^{17,39,40} Auriculotherapy interventions for studies incorporated into the meta-analysis included auricular acupuncture with and without electrical stimulation, TENS, and laser auriculotherapy; control group treatments included sham auriculotherapy, placebo pill, and standard medical care. Auriculotherapy was significantly more effective than control procedures at decreasing pain intensity as measured by VAS or NRS (SMD 1.56; 95% CI: 0.85, 2.26; eight studies) (Fig. 2A). Though significant heterogeneity existed among the studies (Q-value = 58.6, $p < 0.001$, $I^2 = 88$), sensitivity analyses indicated no difference in conclusions with any single study removed, and cumulative analysis showed that results become more positive over time. When poor quality studies were removed, results remained statistically significant (SMD 2.17; 95% CI: 1.20, 3.13; five studies) and heterogeneity remained (Q-value = 43.4, $p < 0.001$, $I^2 = 91$). Two (2) studies were clear outliers.^{32,33} These studies included 21 and 61 participants, respectively (10% of our sample) and utilized a summed weekly pain score in addition to including only subjects with high baseline pain scores. When removed from the analysis, heterogeneity was reduced nominally (Q-value = 19.18, $p < 0.002$, $I^2 = 74$) and

the SMD dropped to 1.01 (95% CI: 0.51, 1.51). The overall strength of evidence for efficacy of auriculotherapy for pain was rated as moderate (Table 2).

Perioperative pain

Eight (8) studies assessed perioperative auriculotherapy. Two (2) studies assessed intraoperative use for anesthetic requirement,^{31,41} and six studies reported on the effects of postoperative auriculotherapy on pain relief or pain medication use.^{15,16,30,37,39,40} Three (3) of these studies were rated as high quality, three were rated fair, and two were rated poor (Table 1).

Three (3) studies in this subgroup were excluded from the meta-analysis due to missing data or an outcome measure other than analgesic use.^{31,39,40} Analgesic consumption was significantly lower in the auriculotherapy group compared to controls (SMD 0.54; 95% CI: 0.30, 0.77; five studies) (Fig. 2B). Statistical heterogeneity did not exist for this subgroup of studies (Q-value = 4.48, $p = 0.35$, $I^2 = 10.62$, $\tau^2 = 0.007$). Sensitivity analyses indicated no differences in the conclusions with any single study removed. All studies included

TABLE 1. STUDIES OF AURICULOTHERAPY FOR PAIN MANAGEMENT

<i>Author,^a year country</i>	<i>Indication, sample size</i>	<i>Quality rating^b</i>	<i>Result</i>	<i>Intervention treatment</i>	<i>Control treatment^c</i>	<i>Primary outcome measure</i>	<i>Acupoints</i>
Perioperative pain							
Li ³⁹ 1994 China	Postoperative pain (liver resection) 16 ^d	Poor	Mixed	AA, herbs, epidural morphine	Placebo pill	VAS, pethidine use	Heart, lung, and <i>shenmen</i>
Michalek-Sauberer ³⁰ 2007 ^e Austria	Tooth extraction 149	Fair	–	Indwelling EA	Indwelling AA + mock EA and no-needle mock EA	Tylenol [®] use	Tooth, mouth, <i>shenmen</i>
Sator-Katzenshlager ³¹ 2006 ^f Austria	Intraoperative pain (oocyte aspiration) 94	Good	+	Indwelling EA	Indwelling AA + mock EA & no-needle mock EA	VAS	Uterus, <i>shenmen</i> , cushion
Usichenko ¹⁶ 2005 ^e Germany	Postoperative pain (THA) 61	Fair	+	Indwelling AA	Indwelling AA at nonacupuncture points	Piritramide use	<i>Shenmen</i> , thalamus, lung, hip
Usichenko ³⁷ 2005 ^e Germany	Postoperative pain (knee arthroscopy) 18	Fair	+	Indwelling AA	Indwelling AA at nonacupuncture points	Ibuprofen use	<i>Shenmen</i> , lung, knee
Usichenko ⁴¹ 2006 ^e Germany	Intraoperative pain (THA) 64	Good	+	Indwelling AA	Indwelling AA at nonacupuncture points	Fentanyl requirement	<i>Shenmen</i> , lung, hip, forehead
Usichenko ¹⁵ 2007 ^e Germany	Postoperative pain (knee arthroscopy) 120	Good	+	Indwelling AA	Indwelling AA at nonacupuncture points	Ibuprofen use	<i>Shenmen</i> , lung, knee
Wigram ⁴⁰ 1986 U.K.	Postoperative pain (abd. surgery) 34	Poor	–	Indwelling EA	Standard medical care	VAS	NR
Acute pain							
Barker ¹⁷ 2006 Austria	Hip fracture (prehospital transport) 38	Good	+	AP	Sham AP (nonindicated points)	VAS	<i>Shenmen</i> , hip, valium
Goertz ¹⁸ 2006 ^{e,f} USA	Acute pain syndromes 100	Fair	Mixed	Indwelling AA	Standard medical care	NRS	Cingulate gyrus, thalamus
Gu ³⁸ 1993 China	Acute biliary colic 48	Poor	+	AA	IM atropine and phenergan	Pain relief or decrease	Point zero

(continued)

TABLE 1. (CONTINUED)

Author, ^a year country	Indication, sample size	Quality rating ^b	Result	Intervention treatment	Control treatment ^c	Primary outcome measure	Acupoints
Lewis ⁴² 1990 ^{e,f} USA	Acute burn 11 ^g	Poor	+	TENS	Placebo pill	VAS	Shenmen, lung, and thalamus
Chronic pain Alimi ¹⁴ 2003 ^{c,f} France	Neuropathic pain 90	Good	+	Indwelling AA	Indwelling AA & AP at nonconductance pts	VAS	Individualized based on dermal conductance
Longobardi ⁴⁴ 1989 ^{e,f} USA	Distal extremity pain 15	Poor	Mixed	TENS	Placebo pill	VAS, PRI	Shenmen, lung, thalamus, + 2: toe, ankle, knee; or finger, wrist, elbow
Mazzetto ⁴³ 2007 ^{e,f} Brazil	TMJ pain 48	Poor	+	LAT	Mock LAT	VAS	External auditory canal just poste- rior to the tragus
Sator-Katzenshlager ³³ 2003 ^{e,f} Austria	Chronic neck pain 21	Good	+	Indwelling EA	Indwelling AA + mock EA	VAS	Cervical spine, shenmen, cushion
Sator-Katzenshlager ³² 2004 ^{e,f} Austria	Chronic low-back pain 87	Fair	+	Indwelling EA	Indwelling AA	VAS	Cushion, shenmen, lumbar spine

AA, auricular acupuncture; VAS, visual analog scale; Indwelling, AA using ASP needles, press tacks, or typical needles; EA, electroacupuncture; THA, total hip arthroplasty; NR, not reported; NRS, numerical rating scale; IM, intramuscular; TENS, transdermal electrical nerve stimulation; AP, acupuncture; PRI, pain rating index; TMJ, temporomandibular joint; LAT, laser auriculotherapy; +, benefit from auriculotherapy; -, no benefit from auriculotherapy.

^aAll studies were randomized controlled trials.

^bQuality ratings were based on Agency for Healthcare Research and Quality (AHRQ) guidelines.

^cAcupoints for control and treatment groups were the same unless otherwise indicated.

^d3×2 factorial design.

^eStudies used for subgroup analyses.

^fStudies used in overall meta-analysis.

^gCrossover design.

A Comparison: Auriculotherapy for all types of pain versus control Outcome: Pain score

Study name	Statistics for each study							Sample size	
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Treatment	Control
Alimi 2003	0.752	0.272	0.074	0.220	1.285	2.768	0.008	29	29
Goertz 2006	1.959	0.243	0.059	1.482	2.436	8.052	0.000	50	50
Lewis 1990	0.641	0.437	0.191	-0.216	1.498	1.465	0.143	11	11
Longobardi 1989	0.083	0.518	0.268	-0.932	1.097	0.160	0.873	8	7
Mazzetto 2007	0.970	0.305	0.093	0.372	1.569	3.180	0.001	24	24
Sator-Katzenschlager 2003	5.361	0.936	0.875	3.528	7.195	5.731	0.000	10	11
Sator-Katzenschlager 2004	2.955	0.370	0.137	2.229	3.681	7.979	0.000	31	30
Sator-Katzenschlager 2006	1.192	0.276	0.076	0.652	1.733	4.323	0.000	32	30
	1.555	0.361	0.130	0.848	2.263	4.310	0.000		

Test for heterogeneity:

Q-value	df (Q)	p-value	F	τ^2
58.57	7	<0.001	88.05	0.86

B Comparison: Auriculotherapy for perioperative pain versus control Outcome: Pain medication use

Study name	Statistics for each study							Sample size	
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Treatment	Control
Michalek-Sauberer 2007	0.200	0.229	0.053	-0.249	0.650	0.873	0.383		
Usichenko 2005a	0.747	0.265	0.070	0.228	1.266	2.820	0.005		
Usichenko 2005b	1.043	0.505	0.255	0.053	2.033	2.064	0.039		
Usichenko 2006	0.728	0.258	0.067	0.222	1.234	2.819	0.005		
Usichenko 2007	0.466	0.185	0.034	0.103	0.829	2.518	0.012		
	0.536	0.119	0.014	0.302	0.769	4.495	0.000		

Test for heterogeneity:

Q-value	df (Q)	p-value	F	τ^2
4.48	4	0.35	10.62	0.007

C Comparison: Auriculotherapy for acute pain versus control Outcome: Pain score

Study name	Statistics for each study							Sample size	
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Treatment	Control
Goertz 2006	1.959	0.243	0.059	1.482	2.436	8.052	0.000		
Lewis 1990	0.641	0.437	0.191	-0.216	1.498	1.465	0.143		
	1.350	0.657	0.432	0.062	2.638	2.054	0.040		

Test for heterogeneity:

Q-value	df (Q)	p-value	F	τ^2
6.94	1	<0.001	85.60	0.74

D Comparison: Auriculotherapy for chronic pain versus control Outcome: Pain score

Study name	Statistics for each study							Sample size	
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Treatment	Control
Alimi 2003	0.752	0.272	0.074	0.220	1.285	2.768	0.006		
Longobardi 1989	0.083	0.518	0.268	-0.932	1.097	0.160	0.873		
Mazzetto 2007	0.970	0.305	0.093	0.372	1.569	3.180	0.001		
Sator-Katzenschlager 2003	5.361	0.936	0.875	3.528	7.195	5.731	0.000		
Sator-Katzenschlager 2004	2.955	0.370	0.137	2.229	3.681	7.979	0.000		
	1.836	0.629	0.396	0.603	3.069	2.918	0.004		

Test for heterogeneity:

Q-value	df (Q)	p-value	F	τ^2
49.54	4	<0.001	91.93	1.73

FIG. 2. Standardized mean differences (SMD) and 95% confidence interval (CI) (lower limit, upper limit). A SMD >0 indicates less pain (pain score) or less analgesic use (pain medication use) with auriculotherapy compared to control. A larger forest plot point reflects a study with heavier relative weight. The final row in each table represents the test for overall effect.

TABLE 2. COMPARATIVE EFFICACY OF AURICULOTHERAPY FOR TREATMENT OF PAIN

Number of studies (no. of subjects)	Design	Quality	Consistency	Magnitude of effect (95% CI; no. of studies in meta-analysis)	Other modifying factors ^a	Overall strength of evidence
All pain types combined						
Outcomes: analgesic use or change in pain score						
17 (1009)	RCT	Good (6); Fair (5); Poor (6)	High	For change in pain score: SMD 1.56 (0.85, 2.26; eight)	None	Moderate
Perioperative pain						
Outcomes: analgesic use or change in pain score						
8 (551)	RCT	Good (3); Fair (3); Poor (2)	High	For analgesic use: SMD 0.54 (0.30, 0.77; five)	Most studies were done by same research team. Analgesic use is a proxy for pain intensity.	Moderate
Acute pain						
Outcome: change in pain score						
4 (197)	RCT	Good (1); Fair (1); Poor (2)	High	SMD 1.35 (0.08, 2.64; two)	none	Low
Chronic pain						
Outcome: change in pain score						
5 (261)	RCT	Good (2); Fair (1); Poor (2)	High	SMD 1.84 (0.60, 3.07; five)	none	Low

^aImprecise or sparse data, a strong or very strong association, high risk of reporting bias, evidence of a dose response gradient, effect of plausible residual confounding.

CI, confidence interval; RCT, randomized controlled trial; SMD, standardized mean differences.

for this analysis were rated either good or fair quality. Of the three studies not included, two were rated poor and reported either mixed or negative results, and one study was rated good that reported favorable results. The strength of evidence for efficacy for this subgroup was rated as moderate (Table 2).

Four of the five studies included in the perioperative subgroup^{15,16,37,41} examined the effect of auricular acupuncture at true acupoints compared to sham points, allowing for a comparison of the effect of point specificity. Meta-analysis for these studies show a significant reduction in analgesic use for the true acupuncture group (SMD 0.63; 95% CI: 0.88, 4.97; four studies). Significant heterogeneity was not detected among this subgroup of studies (Q -value = 1.79, $p = 0.62$, $I^2 < 0.001$, $\tau^2 < 0.001$), and sensitivity analysis indicated no differences in conclusions with any single study removed. This was the only group of studies that compared the effects of penetrating true and sham acupuncture.

Acute pain

We identified four eligible studies of auriculotherapy for acute pain. One (1) study, however, did not provide enough data to be included in the meta-analysis.¹⁷ The pain etiologies studied were the following: hip fracture¹⁷; biliary colic³⁸; wound debridement in burn patients⁴²; and acute pain from a variety of different pain etiologies among patients in an emergency care center.¹⁸ We rated only one study as good quality. Of the remaining three studies, one was rated fair, and two were rated poor (Table 1).

Because of the different scales used for primary outcome measures within this group, only two studies reported sufficient data for meta-analysis (Fig. 2C).^{18,42} The results com-

paring SMD for decrease in pain from baseline to end of study between treatment and control group favor auriculotherapy (SMD 1.35; 95% CI: 0.08, 2.64; two studies). There was significant heterogeneity between these two studies (Q -value = 6.94, $p < 0.001$). The two studies not included in this subgroup analysis both reported positive effects for auriculotherapy. The strength of evidence for efficacy of this subgroup was rated as low (Table 2).

Chronic pain

Five (5) studies using auriculotherapy to treat chronic musculoskeletal pain met our inclusion criteria. The range of conditions studied included chronic neck,³³ low back,³² cancer,¹⁴ temporomandibular joint,⁴³ and distal extremity pain.⁴⁴ Of the five studies, two were rated good, one was rated fair, and two were rated poor (Table 1).

The overall change in pain score shows significant improvement for acupuncture treatment versus control (SMD 1.84; 95% CI: 0.60, 3.07; five studies). Significant heterogeneity was detected among the studies (Q -value = 49.54, $p < 0.001$) (Fig. 2D). However, sensitivity analysis indicated no differences in the conclusions with any single study removed, and cumulative analysis showed that effect estimates became larger with later publication dates. When poor quality studies were removed, results still favored auriculotherapy (SMD 2.86; 95% CI 0.70, 5.02; three studies). The strength of evidence for efficacy of this subgroup was rated as low (Table 2).

Adverse events

Of the 17 studies included in this review, 7 (41%) did not report on adverse events, 5 (29%) reported no adverse events,

and 5 (29%) reported some acupuncture-related adverse event. All 10 studies that reported on adverse events (4445 needle punctures) used indwelling auricular needles for both the intervention and control procedures, except for one study³⁹ that used auricular needles for the intervention procedure and placebo pill for the control. The most commonly reported events were ear pain ($n = 16$) and tiredness ($n = 16$). Other events reported include local minor bleeding ($n = 2$), dizziness and nausea ($n = 1$), and headache ($n = 1$). No infections or other serious adverse events associated with auriculotherapy were reported.

Discussion

We found a large difference between auriculotherapy and control for reduction in pain scores for a wide variety of types of pain. The overall SMD was 1.56 (95% CI: 0.85, 2.26), indicating that on average, the mean decrease in pain score for the auriculotherapy group was 1.56 standard deviations greater than the mean decrease for the control group (i.e., the mean of the auriculotherapy group was at the 94th percentile of the control group). Removing two outliers reduced the effect size somewhat (SMD 1.01), but for either estimate, the effect size is considerably large. For comparison, a recent meta-analysis of traditional acupuncture for all types of pain found effect sizes (SMD) of 0.17 for body acupuncture versus placebo acupuncture, and 0.42 for placebo acupuncture versus no acupuncture.⁴⁵ It is unclear what accounts for the large effect sizes found for these studies. Adequate blinding procedures are often challenging for studies of acupuncture, with acupuncturists often unblinded and questionable blinding of participants. However, the studies with the best blinding procedures tended to have the highest effect estimates.^{16,31–33,37,43} Additionally, when poor quality studies were removed, which are more likely to contain unmeasured bias, the effect estimates remained relatively unchanged.

Subgroup analyses for postoperative, acute, and chronic pain also revealed significant reductions in either pain scores or analgesic consumption. In addition, the estimates did not change significantly when poor quality studies were removed. These results are further supported by the results of the random effects overall test for effect, sensitivity analyses, and cumulative analyses (Fig. 2).

Postoperative pain was the largest subgroup we analyzed and contained the only results that were not statistically heterogeneous. We conducted two analyses of this group: studies measuring analgesic use, and studies comparing penetrating auricular acupuncture at true acupoints versus nonacupuncture points. Similar to a recent review of auriculotherapy for postoperative pain,¹⁹ results for analgesic use suggest that auriculotherapy, specifically indwelling auricular acupuncture, is effective at reducing postoperative pain.

Perhaps more interesting are the comparisons for penetrating auricular acupuncture at true acupoints versus nonacupuncture points, since this comparison controls for the effects of needle puncture, demonstrating the effect of true acupuncture points. Our results suggest that for auricular acupuncture, pain relief may be dependent on the use of true acupuncture points. In contrast, the results of several recent studies of full body acupuncture suggest that the effects of acupuncture may be related simply to skin penetration and not to the use of true acupuncture points.^{13,46–48} Two (2)

considerations may help explain these discordant findings: (1) the effects of auriculotherapy may indeed be point specific and work through different mechanisms than full body acupuncture, or (2) auriculotherapy is not point specific but may have regional specificity.

The regional innervations of the ear remain an unexplored area of investigation for auriculotherapy. The auricle receives nerve fibers from three distinct but overlapping groups: fibers from the superior cervical plexus largely innervate the helix and lobe; the pinna is innervated by the trigeminal nerve; and the conchae are predominantly innervated by the vagus nerve with some facial and glossopharyngeal nerve innervations.⁴⁹ It is possible that the effects noted in the subgroup analysis comparing auricular acupuncture at true acupoints versus nonacupuncture points are due to the regional grouping of the needles. In all four of these studies, the intervention treatment points were located in the conchae, while the control points were located along the helix. It has been demonstrated that needle stimulation of the conchae can induce significant parasympathetic stimulation.⁵⁰ It is possible that regional specificity, and not point specificity, is responsible for the results of these studies.

The results from studies of acute pain, though in favor of auriculotherapy, are difficult to generalize because only two studies were included in that meta-analysis. Likewise, because of the clinical heterogeneity among the studies of chronic pain, interpretation and generalizability of these results are limited. While it is possible that auriculotherapy analgesia works via central mechanisms that are independent of the type of pain experienced, there are a paucity of data on the mechanisms that might be responsible for auriculotherapy analgesia and there are not yet enough high quality studies across the wide spectrum of chronic pain syndromes to be confident that our results are generalizable to all chronic pain conditions. However, the positive results from analyses of these two subgroups do add a little information, in favor of auriculotherapy, to our overall conclusion that auriculotherapy appears to be beneficial for pain reduction across a wide spectrum of pain conditions. Further studies to elucidate the mechanisms responsible for acupuncture analgesia, and high quality studies of clinical pain syndromes will help to further clarify the benefits of auriculotherapy.

Overall, we rated the strength of evidence for efficacy of auriculotherapy compared to control for the treatment of pain as moderate (Table 2). This was based on the magnitude of the mean differences we found overall and for each subgroup, the high consistency in direction and magnitude of effects noted throughout the studies, the lack of evidence of publication bias, the preponderance of good and fair quality studies, and the stability of our estimates with poor quality studies removed. Although we acknowledge the generally low strength of evidence of efficacy for acute and chronic pain subcategories, overall we note that the direction of effect appears to favor efficacy of auriculotherapy.

Limitations

Our search identified two studies that may have been appropriate to include in our review but were unavailable in English.^{51,52} Additionally, since our search strategy included only U.S. and European databases, we may have overlooked studies contained in the Asian literature.⁵³ However, it has

been noted that studies of acupuncture that are indexed in MEDLINE and published in English score significantly higher on standardized quality scales than those that do not meet these criteria,⁵⁴ and some countries have been shown to publish exclusively positive results for studies of acupuncture.⁵⁵ For these reasons, we believe our results likely reflect the results of higher quality studies and reduced publication bias. For the meta-analyses, significant heterogeneity existed for all groups analyzed except for the perioperative subgroup. Though heterogeneity among pooled results may limit the strength of our findings, we note that most trials showed positive effects for auriculotherapy, sensitivity analyses revealed that results were not influenced by any single study, and cumulative analyses most often showed that studies became more significant over time. Additionally, because random-effects models were used for the conclusions of the current study, homogeneity was not assumed for these analyses.²⁹ However, we recognize that the magnitude of the effect estimates found may reflect biases that are difficult to overcome in studies of acupuncture.

Conclusions

The evidence from this review suggests that auriculotherapy may be effective for the treatment of a variety of types of pain, especially postoperative pain, and may be a reasonable adjunct for patients having difficulties with pharmacologic pain therapies.

Acknowledgments

We would like to thank Denise Esserman, PhD for her help in reviewing some of the trials, and participants of the University of North Carolina NRSA Primary Care Research fellowship for reviews of the manuscript. Financial support was provided by National Institutes of Health/National Center for Complementary and Alternative Medicine grant T32AT003378 (GNA), and NIH/NIGMS grant T32GM081057 (SJW).

Disclosure Statement

No competing financial interests exist.

References

- Health, United States, National Center for Health Statistics Report. National Center for Health Statistics Report. Online document at: www.cdc.gov/nchs/data/abus/abus07.pdf Accessed July 17, 2008.
- Max MB. How to move pain and symptom research from the margin to the mainstream. *J Pain* 2003;4:355–360.
- National Cancer Control Programmes: Policies and Managerial Guidelines. Geneva, Switzerland: World Health Organization, 2002.
- Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain* 2004;112:372–380.
- Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *NEJM* 1999; 340:1888–1899.
- Schlansky B, Hwang JH. Prevention of nonsteroidal anti-inflammatory drug-induced gastropathy. *J Gastroenterol* 2009;44(suppl 19):44–52.
- Li JM. Pain management in the hospitalized patient. *Med Clin North Am* 2008;92:371–385, ix.
- McCarberg BH. Rheumatic diseases in the elderly: Dealing with rheumatic pain in extended care facilities. *Rheum Dis Clin North Am* 2007;33:87–108.
- Tyring SK. Management of herpes zoster and postherpetic neuralgia. *J Am Acad Dermatol* 2007;57(6 suppl):S136–S142.
- Brinkhaus B, Witt CM, Jena S, et al. Acupuncture in patients with chronic low back pain: A randomized controlled trial. *Arch Intern Med* 2006;166:450–457.
- Haake M, Muller HH, Schade-Brittinger C, et al. German Acupuncture Trials (GERAC) for chronic low back pain: Randomized, multicenter, blinded, parallel-group trial with 3 groups. *Arch Intern Med* 2007;167:1892–1898.
- Manheimer E, Linde K, Lao L, et al. Meta-analysis: Acupuncture for osteoarthritis of the knee. *Ann Intern Med* 2007;146:868–877.
- Linde K, Streng A, Jurgens S, et al. Acupuncture for patients with migraine: A randomized controlled trial. *JAMA* 2005; 293:2118–2125.
- Alimi D, Rubino C, Pichard-Leandri E, et al. Analgesic effect of auricular acupuncture for cancer pain: A randomized, blinded, controlled trial. *J Clin Oncol* 2003;21:4120–4126.
- Usichenko TI, Kuchling S, Witstruck T, et al. Auricular acupuncture for pain relief after ambulatory knee surgery: A randomized trial. *CMAJ* 2007;176:179–183.
- Usichenko TI, Dinse M, Hermesen M, et al. Auricular acupuncture for pain relief after total hip arthroplasty: A randomized controlled study. *Pain* 2005;114:320–327.
- Barker R, Kober A, Hoerauf K, et al. Out-of-hospital auricular acupressure in elder patients with hip fracture: A randomized double-blinded trial. *Acad Emerg Med* 2006;13:19–23.
- Goertz CM, Niemtzow R, Burns SM, et al. Auricular acupuncture in the treatment of acute pain syndromes: A pilot study. *Mil Med* 2006;171:1010–1014.
- Usichenko TI, Lehmann C, Ernst E. Auricular acupuncture for postoperative pain control: A systematic review of randomised clinical trials. *Anaesthesia* 2008;63:1343–1348.
- MacPherson H, White A, Cummings M, et al. Standards for Reporting Interventions in Controlled Trials of Acupuncture: The STRICTA recommendations. *J Altern Complement Med* 2002;8:85–89.
- Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: A review of the process. *Am J Prev Med* 2001;20(3 suppl):21–35.
- Khan KS, ter Riet G, Glanville J, et al., eds. Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Those Carrying Out or Commissioning Reviews. York, UK: Centre for Reviews and Dissemination, University of York, 2001.
- Egger M, Smith G, Altman D. Systematic Reviews in Health Care, 2nd ed. London: BMJ Books, 2001.
- U.S. Preventive Services Task Force Grade Definitions, Agency for Healthcare Research and Quality, Rockville, MD. May 2008. Online document at: www.ahrq.gov/clinic/uspstf/grades.htm Accessed December 17, 2008.
- Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Mahwah, NJ: Lawrence Erlbaum, 1988.
- Glasziou P, Irwig L, Bain C, Colditz. Systemic Reviews in Health Care: A Practical Guide. Cambridge: Cambridge University Press, 2001.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–1558.

28. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-188.
29. Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res* 1993;2:121-145.
30. Michalek-Sauberer A, Heinzl H, Sator-Katzenschlager SM, et al. Perioperative auricular electroacupuncture has no effect on pain and analgesic consumption after third molar tooth extraction. *Anesth Analg* 2007;104:542-547.
31. Sator-Katzenschlager SM, Wolfner MM, Kozek-Langenecker SA, et al. Auricular electro-acupuncture as an additional perioperative analgesic method during oocyte aspiration in IVF treatment. *Hum Reprod* 2006;21:2114-2120.
32. Sator-Katzenschlager SM, Scharbert G, Kozek-Langenecker SA, et al. The short- and long-term benefit in chronic low back pain through adjuvant electrical versus manual auricular acupuncture. *Anesth Analg* 2004;98:1359-1364.
33. Sator-Katzenschlager SM, Szeles JC, Scharbert G, et al. Electrical stimulation of auricular acupuncture points is more effective than conventional manual auricular acupuncture in chronic cervical pain: A pilot study. *Anesth Analg* 2003;97:1469-1473.
34. Alimi D, Rubino C, Leandri EP, Brule SF. Analgesic effects of auricular acupuncture for cancer pain. *J Pain Symptom Manage* 2000;19:81-82.
35. Kou WT. The effects of low-energy laser in the auriculotherapy in individuals with chronic low back pain. *Dissertation Abstracts Int* 1991;4:1946.
36. Gori L, Firenzuoli F. Ear acupuncture in the treatment of low back pain in cancer patients. *J Soc Integr Oncol* 2005;3:130.
37. Usichenko TI, Hermesen M, Witstruck T, et al. Auricular acupuncture for pain relief after ambulatory knee arthroscopy: A pilot study. *Evid Based Complement Alternat Med* 2005;2:185-189.
38. Gu XD. Clinical-study on analgesia for biliary colic with ear acupuncture at point erzong. *Am J Acupuncture* 1993;21:237-239.
39. Li QS, Cao SH, Xie GM, et al. Combined traditional Chinese medicine and Western medicine: Relieving effects of Chinese herbs, ear-acupuncture and epidural morphine on postoperative pain in liver cancer. *Chin Med J (Engl)* 1994;107:289-294.
40. Wigram JR, Lewith GT, Machin D, Church JJ. Electroacupuncture for postoperative pain. *Physiother-Pract* 1986;2:83-88.
41. Usichenko TI, Dinse M, Lysenyuk VP, et al. Auricular acupuncture reduces intraoperative fentanyl requirement during hip arthroplasty: A randomized double-blinded study. *Acupunct Electrother Res* 2006;31:213-221.
42. Lewis SM, Clelland JA, Knowles CJ, et al. Effects of auricular acupuncture-like transcutaneous electric nerve stimulation on pain levels following wound care in patients with burns: A pilot study. *J Burn Care Rehabil* 1990;11:322-329.
43. Mazzetto MO, Carrasco TG, Bidinelo EF, et al. Low intensity laser application in temporomandibular disorders: A phase I double-blind study. *Cranio J Craniomandib Pract* 2007;25:186-192.
44. Longobardi AG, Clelland JA, Knowles CJ, Jackson JR. Effects of auricular transcutaneous electrical nerve stimulation on distal extremity pain: A pilot study. *Phys Ther* 1989;69:10-17.
45. Madsen MV, Gotzsche PC, Hrobjartsson A. Acupuncture treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. *BMJ* 2009;338:a3115.
46. Witt C, Brinkhaus B, Jena S, et al. Acupuncture in patients with osteoarthritis of the knee: A randomised trial. *Lancet* 2005;366:136-143.
47. Melchart D, Streng A, Hoppe A, et al. Acupuncture in patients with tension-type headache: Randomised controlled trial. *BMJ* 2005;331:376-382.
48. Scharf HP, Mansmann U, Streitberger K, et al. Acupuncture and knee osteoarthritis: A three-armed randomized trial. *Ann Intern Med* 2006;145:12-20.
49. Peuker ET, Filler TJ. The nerve supply of the human auricle. *Clin Anat* 2002;15:35-37.
50. Haker E, Egekvist H, Bjerring P. Effect of sensory stimulation (acupuncture) on sympathetic and parasympathetic activities in healthy subjects. *J Auton Nerv Syst* 2000;79:52-59.
51. Ceccherelli F, Ambrosio F, Adami MG, et al. Failure of high frequency auricular electrical stimulation to relieve postoperative pain after cholecystectomy: Results not improved by administration of aprotinin (double blind trial). *Dtsch Z Akupunktur* 1985;4:87-92.
52. Strom H. Controlled triple-blind investigation of the effect of electro-ear-acupuncture on movement and pain in the knee after meniscectomy. *Ugeskr-Laeg* 1977;39:2326-2329.
53. Kim YS, Jun H, Chae Y, et al. The practice of Korean medicine: An overview of clinical trials in acupuncture. *Evid Based Complement Alternat Med* 2005;2:325-352.
54. Linde K, Jonas WB, Melchart D, Willich S. The methodological quality of randomized controlled trials of homeopathy, herbal medicines and acupuncture. *Int J Epidemiol* 2001;30:526-531.
55. Vickers A, Goyal N, Harland R, Rees R. Do certain countries produce only positive results? A systematic review of controlled trials. *Control Clin Trials* 1998;19:159-166.

Address correspondence to:

Gary N. Asher, MD, MPH

Department of Family Medicine

University of North Carolina at Chapel Hill

590 Manning Drive, CB#7595

Chapel Hill, NC 27599

E-mail: gasher@med.unc.edu

APPENDIX. QUALITY RATINGS AND ASSESSMENT ITEMS

<i>Author</i>	<i>Quality rating</i>	<i>A</i>	<i>B</i>	<i>C</i>	<i>D</i>	<i>E</i>	<i>F</i>	<i>G</i>	<i>H</i>	<i>I</i>	<i>J</i>	<i>K</i>	<i>L</i>
Alimi ¹⁴	Good	+	+	Yes	+	+/-	NR	+	+	Mod	Yes	+	+
Barker ¹⁷	Good	+	+	Yes	+	NR	+	+	+	None	No	-	+
Sator-Katzenshlager ³³	Good	+	+	No	+	+	+	+	+	Low	No	+	+
Sator-Katzenshlager ³¹	Good	+	+	Yes	+	+	+	+	+	Low	No	+	+
Usichenko ⁴¹	Good	+	+	Yes	+	+	-	+	+	Low	No	+	NR
Usichenko ¹⁵	Good	+	+	Yes	+	+	-	+	NR	Low	No	+	+
Goertz ¹⁸	Fair	+	+	No	+	+	-	-	+	Mod	NR	+	NR
Michalek-Sauberer ³⁰	Fair	+	NR	No	+	NR	+	+	+	Mod	No	+	NR
Sator-Katzenshlager ³²	Fair	+	+/-	No	+	NR	-	-	+	Low	No	+	+
Usichenko ¹⁶	Fair	+	+	Yes	+	+	+	+	NR	Mod	No	-	+
Usichenko ³⁷	Fair	+	+	No	+	+	+	+	NR	Low	No	-	+
Gu ³⁸	Poor	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lewis ⁴²	Poor	+/-	+	NR	+	NR	NR	+	NR	High	No	NR	NR
Li ³⁹	Poor	+	NR	Yes	+/-	NR	+/-	+/-	NR	None	NR	NR	NR
Longobardi ⁴⁴	Poor	+/-	+	No	+	NR	NR	+	NR	None	No	+	NR
Mazzetto ⁴³	Poor	+/-	+/-	NR	+	+	+	+	NR	None	No	+	+
Wigram ⁴⁰	Poor	+/-	NR	No	-	NR	NR	NR	+	None	No	-	NR

A, randomization; B, allocation concealment; C, groups similar at baseline; D, eligibility criteria; E, outcome assessors blinded; F, care providers blinded; G, participants blinded; H, reporting of adherence; I, attrition; J, high differential attrition (>15%); K, intention-to-treat analysis; L, postrandomization exclusions.

+, item adequately reported; -, item reported but not performed; +/-, item performed but method not fully described; NR, not reported.