QUERI

Evidence Map of Acupuncture

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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EVIDENCE MAP OF ACUPUNCTURE

BACKGROUND

Many Veterans desire complementary and alternative medicine or integrative medicine modalities such as acupuncture, both for treatment and for the promotion of wellness. However, the effectiveness and adverse events associated with acupuncture are not firmly established. Given the VA's desire to promote evidence-based practice, this evidence mapping project will help provide guidance to VA leadership about the distribution of evidence to inform policy and clinical decision making.

In general, acupuncture is the stimulation of specific acupuncture points through penetration of the skin with needles, which aims to correct imbalances in the flow of *qi*, a concept of energy in traditional Chinese medicine (TCM), through meridians (ie, energy channels). The available published literature on acupuncture is extensive. PubMed searches in 2013 identified almost 20,000 citations with the term "acupuncture" and almost 1,500 randomized controlled trials (RCTs) with "acupuncture" in the title. Not surprisingly, a large number of systematic reviews and meta-analyses have been published to-date, and even a number of "reviews of reviews" are available in the published literature on acupuncture in general[1-6] or for a specific clinical condition.[4,7-20]

Results from existing reviews of reviews about the effectiveness of acupuncture are non-conclusive. A systematic review of systematic reviews of acupuncture published between 1996 and 2005 included 35 reviews.[1] The overview noted that 12 reviews reported support for acupuncture and 6 reported strong support; however, when applying strict inclusion criteria, such as randomized and double blind studies, good evidence of no benefit was shown. In 2007, Adams compiled a "Brief Overview – A summary of the evidence for use of acupuncture from systematic reviews and meta-analyses" for the Veterans Health Administration Office of Patient Care Services Technology Assessment Program.[21] The report included 42 systematic reviews published since 2002 and concluded that higher quality studies are only beginning to emerge, the evidence base is heterogeneous, and the review results highlight the overall poor quality of studies and reporting. Thus, it is timely to assess the current state of reviews of acupuncture.

KEY QUESTIONS/SCOPE OF PROJECT

The project deliverables are:

- An evidence map that provides a visual overview of the distribution of evidence (both what is known and where there is little or no evidence base) for acupuncture; and
- A set of executive summaries that would help stakeholders interpret the state of the evidence to inform policy and clinical decision making.

This project maps the literature for the indications Pain, Mental Health and Wellness; as well as any clinical area for which at least 3 reviews and/or recent large RCTs exist.

METHODS

This systematic review of systematic reviews provides an overview of the existing literature on acupuncture.

INCLUSION CRITERIA

To be included in the review of reviews, studies had to meet the following criteria:

- Participants: Reviews and new RCTs including human adult participants undergoing acupuncture for any health-related indication were eligible for inclusion in the evidence map. Reviews and new RCTs in adult participants or not further specified age groups were included; reviews and new RCTs exclusively focusing on animals and exclusively focusing on children were excluded.
- Intervention: Reviews and new RCTs of effects of acupuncture using needles, including traditional Chinese acupuncture and other related acupuncture concepts, with or without electro stimulation, with or without moxibustion, and whole body as well as microsystem acupuncture, were eligible. Reviews or RCTs exclusively targeting acupressure, laser acupuncture, transcutaneous electrical nerve simulation, or dry needling were excluded. Reviews on the effectiveness of acupuncture, alone or in combination with other traditional Chinese medicine approaches, were included. Reviews of clinical indications that included studies of acupuncture among many other interventions, and broad reviews on complementary and alternative medicine approaches without particular focus on acupuncture were not sought. Studies addressing the mechanism of action and correlates of acupuncture (eg, brain activity), or investigating the comparative effectiveness of different acupuncture regimes were excluded.
- Comparator (design): Systematic reviews focusing on acupuncture and summarizing primary research studies were eligible. Reviews either identified as "systematic review" in the title or abstract of the publication or reporting the search sources in the abstract were included. In addition, recent, large (N≥500 participants) RCTs focusing on acupuncture, reporting patient outcomes, and not yet included in existing reviews were included. RCTs had to report on the sample size or be described as a multicenter study in the title or abstract to be considered.
- Outcome: Patient outcomes addressed in reviews or trials were eligible. Reviews and RCTs of provider outcomes, acceptance, prevalence, use, costs, study design features, or intervention features not reporting patient health outcomes in the abstract were excluded.
- Timing: Reviews and new RCTs including any intervention duration and any follow-up point were eligible for inclusion. Reviews had to be published in or after 2005 to be included, regardless of the publication date of the included studies in the review. Of the recent RCTs, only those not yet included in existing systematic reviews were considered.
- Setting: Reviews and recent RCTs in healthcare-related settings were eligible.
- English-language reviews, regardless of the language of the included studies, and recent, large RCTs were eligible for inclusion in the review of reviews.

SEARCH

For this project, we searched the electronic databases PubMed using the systematic review clinical query; the Database of Abstracts of Reviews of Effects (DARE), a database dedicated

to catalogue systematic reviews in healthcare; the Cochrane Library of Systematic Reviews which keeps a record of all ongoing and completed Cochrane reviews; and AMED, the Allied and Complementary Medicine database, in March 2013 to identify English-language systematic reviews published since 2005 focusing on acupuncture. In addition, we identified relevant reviews through the review registry PROSPERO, published reviews of reviews, and topic experts.

Recently published, large acupuncture RCTs indexed in PubMed and not yet included in existing systematic review were identified in topic specific searches using the Randomized Controlled Trial filter in PubMed.

PROCEDURE

In the first step, we identified systematic reviews meeting the inclusion criteria and removed data duplicates from the database so that the data from each review entered the dataset only once. This entailed identifying and consolidating online-only and final publication of articles, Cochrane reviews published in the Cochrane database and in a journal article, multiple updates of Cochrane reviews, and references to systematic reviews differently indexed in general and specialist systematic review databases. Where originals and updates of systematic reviews by the same author group were available only the most recent version was considered. These systematic reviews were then coded by clinical topic.

Reviews and recent RCTs identified as potentially relevant and all unclear citations were ordered as full text to evaluate the publication against the specified inclusion criteria. The literature flow was documented in an electronic database. Reasons for exclusion of full text publications were recorded. Results of individual reviews and recent RCTs were extracted in an online database for systematic reviews.

DATA SYNTHESIS

We grouped the identified reviews and trials into the 3 VA priority areas: Pain, Wellness, and Mental Health. In addition, we added categories for Other Indications and for Adverse Events. General acupuncture reviews that could not be categorized as addressing pain, wellness, or mental health were included in the Other Indication domain. Topics of other indications were only eligible for synthesis if at least 3 systematic reviews or recent large RCTs were available for the specific topic.

Topic grouping into the priority domains was guided by a technical expert panel. All reviews focusing on pain regardless of the underlying condition were assigned to the Pain domain. The Wellness domain was used as a broad category covering a wide range of clinical indications and outcomes. This included reviews of indication-unspecific outcomes such as quality of life, reviews of treatments for chronic conditions that reported on symptoms that could be experienced by generally healthy people such as nausea, and reviews of very common conditions such as insomnia. The Mental Health domain covered core mental health conditions and chronic fatigue syndrome due to the use of mental health outcomes in the review. Topics were classified as Other Indication if they did not fit into the VA priority groups. Reviews on adverse

events were assigned to the Adverse Event category if they did not report on the therapeutic effectiveness of acupuncture as well. Where possible, reviews were assigned to one topic only based on the primary focus of the review rather than incorporated multiple times into the evidence synthesis.

BUBBLE PLOTS

The evidence base was distilled into a visual overview of each of the 3 VA priority areas using a bubble plot format. In order to be included in the bubble plots, reviews had to report effect sizes for patient health outcomes for each included study or a pooled result across included studies; present the citations for included studies so that the evidence was identifiable; report on RCT data; and report the effects of passive-controlled studies. We extracted the specific topic (eg, depression treatment), the number of included RCTs, and the size of the treatment effect for the main patient outcomes according to passive-controlled RCT data, from each included systematic review with bubble plot-relevant data. We also extracted additional review characteristics such as whether the review was a Cochrane review or an independent patient data (IPD) review, whether the review showed a positive treatment effect in assessor-blinded RCTs, and whether a majority of studies included in the review not indexed in PubMed.

The bubble plots displays information about the research area in 3 dimensions: the estimated literature size (y-axis), the estimated treatment effect (x-axis), and the confidence in the reported effect (bubble size). Given the format, the large number of existing reviews, and the scope of this project, the bubble plots can only represent limited information.

Literature size

First, the bubble plots provide an overview of the research volume or quantity for the included topics in each priority area. For this estimate, we used the number of included RCTs per review, selecting the systematic review with the most included acupuncture RCTs for the individual topic as the research volume estimate. Reviews vary in their inclusion criteria for study designs (for example whether or not they include observational studies) and providing the volume for a well-established research design such as RCT that is always likely to be included should provide a broad estimate. Furthermore, the number of RCTs should provide an indicator of the overall research volume sufficient for this map of the literature. A pilot test showed that an alternative method, cumulatively adding all studies included in reviews on a particular clinical indication to a database to determine the complete research pool, is immensely time consuming and not feasible for large-scale evidence maps. In the case of acupuncture research, hundreds of individual studies need to be cross-checked against dozens of reviews to prevent duplication, but the lack of unique study identifiers and differences in translation of study titles make such cross-checking impractical within the project timeframe and resources.

Clinical effectiveness

Secondly, the bubble plots provide a broad estimate of the clinical effectiveness of acupuncture for each differentiated clinical indication. This estimate of clinical effectiveness should ideally be a continuous measure representing the summary effect size for the clinical indication. However, in trying to apply this display method to reviews of acupuncture, we were unable to

use a continuous measure such as effect size. Because the studies included in individual reviews may overlap, results of reviews cannot be pooled across reviews and meta-analyses (included studies are not all independent units, and individual studies may be included in more than one review). In addition, different reviews use different summary measures, such as weighted mean differences, odds ratios, or relative risks to summarize treatment effects; individual reviews focused on a variety of different condition-specific continuous or categorical outcome measures (e.g., treatment response, Beck Depression Inventory, Hamilton Depression Rating Scale among hundreds of other measures); inclusion criteria for eligible RCTs differed across reviews; and the review authors' conclusions were often inconsistent across reviews. Therefore, for this application, the bubble plots simply differentiate the findings according to 4 categories: "evidence of no effect," "unclear evidence," "evidence of a potential positive effect," and "evidence of a positive effect."

The category "evidence of no effect" was used for research areas that provided evidence for no positive effect, that is to say reviews which showed that results in the control groups are equivocal or better than in the acupuncture group. The "unclear evidence" category was used for conflicting results across reviews that could not be resolved or for conflicting results within reviews with authors summarizing the evidence as inconclusive. The "evidence of a potential positive effect" category was used for those areas where reviews showed that all individual RCTs or the pooled effect across RCTs were positive, but the best available secondary evidence or all systematic reviews concluded that the evidence base was insufficient to draw firm conclusions despite the statistically significant positive treatment effect. For example, several systematic reviews produced pooled estimates of effects that were statistically significantly positive, yet the review authors judged the evidence insufficient due to limitations of the included trials. The final category, "evidence of a positive effect," was used for clinical areas with evidence of a statistically significant positive effect of acupuncture and where authors of the best available secondary literature recommended the intervention without major concerns regarding the existing evidence.

For each clinical topic, all available systematic reviews and recently published trials were reviewed. Most emphasis was given to Cochrane reviews, individual patient data reviews, and the largest review or recent trial. For topics with narrative reviews without statistical meta-analysis, conflicting results across or within reviews that could be resolved by a synthesis including all relevant RCTs, and for areas where a recent large trial was identified that was not yet incorporated into existing reviews, a statistician checked whether studies could be pooled and performed a meta-analysis to determine the treatment effect. The reanalysis used the data documented in the systematic reviews; it was not feasible to obtain primary study data from several hundred RCTs included in existing reviews. In many cases, it was not possible to resolve the conflicting evidence. Furthermore, the bubble plots summarize dozens of clinical areas, of which each area is represented by up to 10 recent reviews, each review potentially summarizing a large number of individual research studies. Hence the clinical effectiveness category should not be construed as a definitive answer of the effectiveness but rather represents a broad overview, or trend, to broadly summarize the research field.

The effect determination focused on the effectiveness of acupuncture compared to that of "passive" control groups, such as a waiting list group, no treatment, placebo / sham acupuncture,

prescription-free or provider-independent interventions, usual care not further specified, and treatments given to both RCT arms. As we discuss in the future research section, what constitutes a valid control group for acupuncture intervention studies is an area of controversy. For this broad map of the literature we did not favor one control modality over another and had to rely on the published reviews to differentiate or pool across passive comparators. In order to provide a coherent and easy-to-interpret bubble plot across individual topics, we did not include the comparative effectiveness of acupuncture, that is to say acupuncture compared to active comparators such as medication interventions (e.g., equivalence or superiority assessments for acupuncture versus antidepressants). Instead, identified comparative effectiveness results were summarized in the narrative synthesis.

Confidence

Finally, our confidence in the effect for each clinical indicator is represented by the size of the corresponding bubble. By default, we categorized our level of confidence as "Medium". We changed the confidence to "High" only if an effect was shown in a Cochrane review adhering to strict methodological criteria or in an IPD systematic review not subject to typical meta-analytic limitations, based on the assumption that both of these kinds of reviews represent stronger evidence than an average systematic review. We changed the confidence to "Low" if the reported treatment effect was based primarily on studies not indexed in the largest medical database PubMed (defined as more than 50% of relevant RCTs not indexed) based on the assumption that studies in journals and other outlets not indexed in PubMed are more likely to be of low quality than studies published in PubMed-indexed journals. This issue has been shown to be of particular relevance to the research area acupuncture.[22,23]

Given the large number of clinical topics, the large number of reviews, and the fact that some clinical topics were associated with up to 10 current systematic reviews from independent author groups, this assessment could take only very limited information into account.

OTHER RESULTS

Results from comparative effectiveness reviews (ie, reviews comparing acupuncture to other active treatments) were summarized in a narrative synthesis for each of the domains.

Adverse events of acupuncture interventions were summarized in a narrative synthesis. For this broad overview we only included reviews addressing adverse events in the title or the abstract of the publication and thereby indicating that adverse events were one of the main research questions addressed by the review.

FUTURE RESEARCH

We identified evidence gaps by documenting clinical indications for which there is conflicting evidence across identified reviews or where reviews concluded that the existing evidence base is insufficient to come to firm conclusions. In addition, we documented those topic areas for which systematic reviews exist, but for which the reviews did not identify relevant RCTs. For the non-priority areas we highlighted where research on acupuncture was available but there were only

one or 2 systematic reviews published since 2005 to provide a current estimate of the evidence. Finally, we checked the literature for ongoing systematic reviews that may become available to summarize a topic area in the near future.

TECHNICAL EXPERT PANEL

The technical expert panel (TEP] for the project included Dr. Stephen Ezeji-Okoye, VHA CO Field Advisory Committee on Complementary and Alternative Medicine; Laura Krejci, Associate Director Office of Patient Centered Care and Cultural Transformation; Dr. Edward Seunghoon Lee; Dr. Marc Goldstein; Dr. An-Fu Hsiao; and Dr. Walter Fricke.

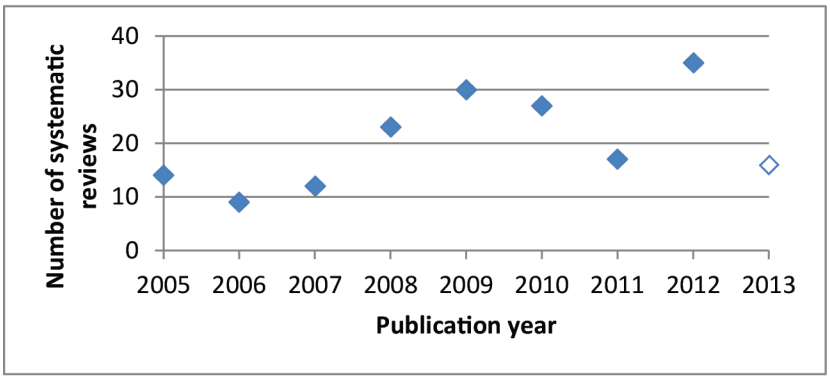
PEER REVIEW

A draft version of the deliverables was reviewed by technical experts, as well as clinical leadership. Reviewer comments were addressed in the final product and are documented in the appendix.

RESULTS

The electronic literature search identified 1,223 citations. Of these, 183 citations were classified as unique systematic review citations meeting the inclusion criteria.[24-205] The number of systematic review publications by year is shown in Figure 1 below.

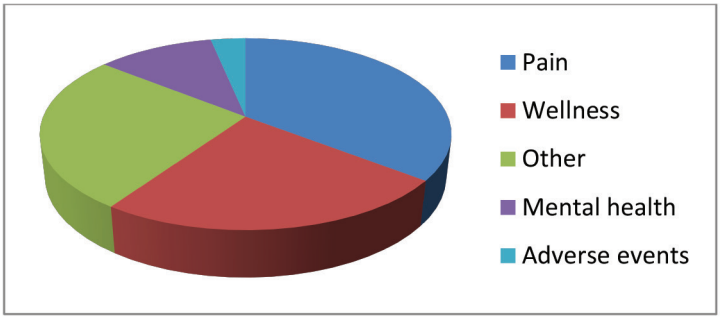
Figure 1: Systematic reviews on acupuncture published January 2005 to March 2013



The number of published reviews is increasing, between 9 and 35 reviews were published each year with a peak at 2012. The 2013 column only shows systematic reviews published between January and March 2013.

For the evidence map, the results of the existing systematic reviews are presented in the priority areas: Pain, Wellness, and Mental Health. The distribution of topics is shown in Figure 2 below.

Figure 2: Research volume by priority topic areas



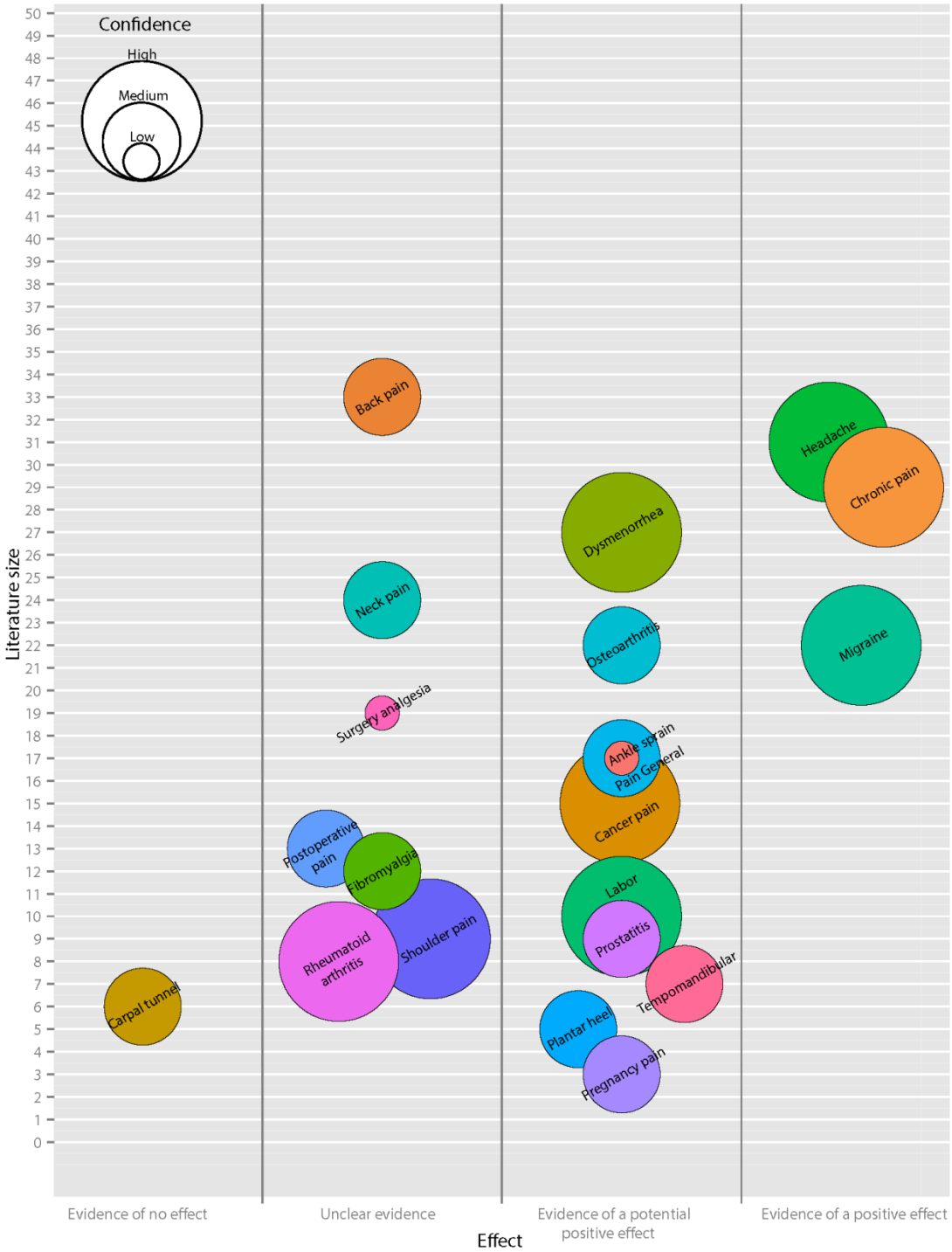
Of the identified priority areas, the most systematic reviews were published relevant to the indication Pain (N=65). In total, 44 reviews were classified as relevant to Wellness. For the indication Mental Health, the fewest systematic reviews were identified (N=20). A large number of systematic review did not appear to be relevant to any of the priority areas (Other Indication N=48). Six systematic reviews focused on Adverse Events, not the clinical effectiveness of acupuncture.

The specific clinical topics targeted in the existing systematic reviews included pain, headache, migraine, fibromyalgia, myofascial trigger point pain, burning mouth syndrome, ankle sprain, neck disorder, dysmenorrhea, trigeminal neuralgia, analgesia during surgery, anxiety, schizophrenia, depression, posttraumatic stress disorder, dementia, Alzheimer's Disease, chronic

fatigue syndrome, addiction in general, cocaine addiction, alcohol addiction, opiate addiction, smoking, opioid withdrawal symptoms, quality of life, exercise performance, hiccups, hot flushes, cancer, menopause-related effects, insomnia, cancer-related fatigue, nausea, cancer treatment-related adverse events, uremic pruritus, vasomotor menopausal symptoms, dry eye, dry mouth, premenstrual syndrome, erectile dysfunction, obesity, irritable bowel syndrome, constipation, Ménière's disease, allergic rhinitis, tinnitus, restless legs, temporomandibular disorders, stroke, Bell's palsy, fertility treatment, arthritis, Parkinson, uterine fibroids, pressure ulcer, traumatic brain injury, spinal cord injury, fetal breech presentation, labor induction, aphasia, blood pressure, glaucoma, epilepsy, respiratory disease, asthma, facial spasm, cervical spondylotic radiculopathy, polycystic ovarian syndrome, and angina pectoris symptoms.

EVIDENCE MAP OF ACUPUNCTURE FOR PAIN

The results for the clinical indication Pain are presented in the bubble plot and a text summary below. The bubble plot summarizes the results of 59 systematic reviews for 21 distinct indications relevant to the outcome pain [search date: March 2013].



Legend: The bubble plot shows an estimate of the evidence base for pain-related indications judging from systematic reviews and recent large RCTs. The plot depicts the estimated size of the literature (y-axis, number of RCTs included in largest review), the estimated effect (x-axis), and the confidence in the estimate (bubble size).

The figure provides a broad visual overview over the evidence base. The bubble plot depicts the estimated research volume based on the number of acupuncture RCTs included in the largest review summarizing the clinical indication, the estimated treatment effect of acupuncture compared to passive control, and the confidence in the effect, judging from published systematic reviews. Estimates of the size of the treatment effect based on specific individual reviews as well as reason for classifying the evidence base as inconclusive are reported in the narrative synthesis. The evidence map used the clinical topics as addressed in existing reviews, and individual research studies may have contributed to a number of included reviews and clinical indications. All 3 depicted dimensions (literature size, effect, and confidence) are estimates and can only provide a broad overview of the evidence base.

EXECUTIVE SUMMARY: PAIN

As shown in the bubble plot, a large number of studies have addressed the treatment of **headaches** with acupuncture; a 2008 review included 31 RCTs[124] and 5 independent systematic reviews have been published since 2005. A Cochrane review on tension-type headache by Linde et al., last updated in 2009, reported that 3 to 4 months after randomization, the pooled responder rate ratio was 1.24 (95% confidence interval [CI]: 1.05, 1.46) with 50% responders in the acupuncture groups compared to 41% in sham groups across 4 RCTs.[120] The review concluded that acupuncture could be a valuable non-pharmacological tool in patients with frequent episodic or chronic tension-type headaches. A 2012 individual patient data meta-analysis published by Vickers et al for the Acupuncture Trialists' Collaboration included data from 29 RCTs evaluating acupuncture for **chronic pain**.[47] The review reported that patients receiving acupuncture had less pain, with scores that were 0.23 (95% CI: 0.13, 0.33), 0.16 (95% CI: 0.07, 0.25) and 0.15 (95% CI: 0.07, 0.24) standard deviations lower than sham controls for back and neck pain, osteoarthritis, and chronic headache. The review concluded that acupuncture is effective for the treatment of chronic pain and is a reasonable referral option. However, the most recent available best evidence syntheses concentrating on back pain, neck pain, or osteoarthritis individually do not summarize the evidence as equally unrestrictedly positive, as outlined further below. Thus, the conclusion that acupuncture had evidence of effectiveness with high confidence for chronic pain patients is currently still limited by the lack of conclusive evidence syntheses for the individual conditions that make up 50-65% of chronic pain, namely back pain and neck pain. There is considerable research available for **migraine** prophylaxis; a 2009 Cochrane review by the same author group working on headaches included 22 acupuncture RCTs.[121] The review reported sufficient detail for a reanalysis and a positive effect across all passive controlled RCTs as defined in this review of reviews was identified. However, it should be noted that effects were driven by RCTs comparing acupuncture to no acupuncture (relative risk [RR] 2.33; 95% CI: 2.02, 2.69), not RCTs comparing acupuncture and sham (RR 1.13; 95% CI: 0.95, 1.35). The review concluded that acupuncture should be considered a treatment option for patients willing to undergo this treatment. More than half of the 7 included RCTs on chronic headaches included in the chronic pain IPD meta-analysis[47] are also included in the Cochrane reviews on headaches and migraine.

Dysmenorrhea has also been addressed in a large number of primary studies; a 2010 systematic review on primary dysmenorrhea included 27 RCTs.[92] A Cochrane review on dysmenorrhea last

updated in 2012 reported an improvement in pain relief from acupuncture compared with placebo control (odds ratio [OR] 9.5, 95% CI: 21.17, 51.8) and concluded that acupuncture may reduce period pain but further well-designed RCTs are needed.[72] **Osteoarthritis** has also been targeted in a large number of systematic reviews (we identified 6 recent reviews from independent author groups) and individual research studies; a 2012 Centre for Reviews and Dissemination (CRD) network meta-analysis on the relief of chronic pain due to osteoarthritis of the knee included 22 acupuncture RCTs.[174] The report, comparing different physical treatments, concluded that acupuncture is one of a number of physical treatments that produces a clinically-relevant effect in alleviating pain in the short-term, and although further research is needed to substantiate these conclusions, acupuncture should be considered as an evidence-based treatment option for relieving pain due to osteoarthritis of the knee. A 2010 Cochrane review on acupuncture for peripheral joint osteoarthritis reported positive results for acupuncture in comparison to sham and waiting list control but not as add-on treatment compared to exercise-based physiotherapy alone. The review concluded that benefits compared to shame were small, did not meet pre-defined thresholds for clinical relevance, and were probably due at least partially to placebo effects from incomplete blinding, while effects compared to waiting list were clinically relevant but could be associated with expectation or placebo effects.[97] A recent RCT[206] not yet included in the existing systematic reviews and one of the largest available studies on acupuncture and osteoarthritis (N=527) reported no statistically significant differences between acupuncture and sham, but a reanalysis combining the largest review and this trial showed that the pooled treatment effect would remain positive if included in an updated meta-analysis. The IPD meta-analysis on chronic pain[47] included 9 osteoarthritis RCTs. Acupuncture for **pain management** regardless of the underlying conditions has been addressed in some of the identified reviews; the largest review on auriculotherapy for pain management included 17 RCTs.[78] The review reported auriculotherapy was superior to controls for studies evaluating pain intensity (standardized mean difference [SMD] 1.56, 95% CI: 0.85, 2.26) but concluded that a more accurate estimate of the effect requires further large, well-designed trials. A 2009 systematic review on acupuncture for pain treatment published in the *BMJ* concluded that a small analgesic effect of acupuncture was found, which seems to lack clinical relevance and cannot be clearly distinguished from bias.[119] A 2013 review on acupuncture for **ankle sprain** included 17 RCTs.[30] The review found that significantly more participants in acupuncture groups reported global symptom improvement compared with no acupuncture (RR 0.56, 95% CI: 0.42, 0.77), but the review was primarily based on non-indexed publications, trial quality was poor, no sham controlled RCT was identified, and the review concluded that given methodological shortcomings and the small number of high-quality primary studies, the available evidence is insufficient to recommend acupuncture as an evidence-based treatment option. **Cancer-associated pain** has been addressed in 15 RCTs according to the largest recent review.[59] A 2012 Cochrane review identified one relevant RCT that showed statistically significant differences between the acupuncture and placebo groups but the review concluded there is insufficient evidence to judge whether acupuncture is effective in treating cancer pain in adults.[73] **Labor pain** has also been addressed in a number of primary studies; a 2010 review included 10 RCTs.[85] A 2011 Cochrane review reported less intense pain from acupuncture compared with no intervention (SMD -1.00, 95% CI: -1.33, -.067) and positive effects for other outcomes and comparators; however, all comparisons were based on one RCT each and the review concluded acupuncture may have a role in relieving pain during labor but more research is needed.[67]

Positive effects were also reported for other clinical indications; however the evidence base was considerably smaller. A review on **prostatitis** / chronic pelvic pain syndrome included 9 acupuncture RCTs in total and reported a positive effect of acupuncture compared to sham (RR 1.56, 95% CI: 1.09, 2.24); however this result was based on one RCT only.[71] The largest of 4 recent reviews on **temporomandibular** joint disorders included 7 RCTs in total.[195] The review reported significant improvements in pain intensity for a visual analogue scale (weighted mean difference [WMD] -12.6, 95% CI: -21.2, -6.1) but concluded that further rigorous studies are required to establish beyond doubt whether acupuncture has therapeutic value for this indication. A review on acupuncture for **plantar heel pain** included 5 RCTs and the passive controlled RCTs reported statistically significant positive results for pain outcomes, but only 2 RCTs were classified as high quality and no pooled result was presented to determine the size of the treatment effect.[44] A review specific to p**regnancy**-associated pelvic and back pain included 3 RCTs in total and both acupuncture as add-on treatment RCTs reported statistically significant results. However, no pooled effect was presented to estimate the size of the treatment effect.[143]

Acupuncture for the treatment of **back pain** has received a great deal of research attention but the evidence base regarding the effectiveness of acupuncture remains unclear judging from the available systematic reviews. We identified 10 recent systematic reviews on acupuncture for back pain and the largest review, a review on the efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine published by Furlan et al in 2012, included 33 acupuncture RCTs.[62] The review showed a positive effect of acupuncture compared to no treatment but noted that sham-acupuncture controlled trials tended towards statistically nonsignificant results. A 2005 evidence synthesis on low back pain within the framework of the Cochrane Collaboration concluded that the data do not allow firm conclusions regarding the effectiveness of acupuncture for acute low back pain.[170] It is noteworthy that the IPD meta-analysis (see above) on chronic pain which concluded that acupuncture is effective for treating chronic pain also included 10 back pain studies. The largest review on **neck pain** is the review by Furlan et al. [62] published in 2012; it includes 24 acupuncture RCTs. The review came to the same conclusion as for back pain while 2 smaller reviews reported favorable results for acupuncture. The IPD meta-analysis by Vickers at al included some back pain and neck pain studies but was limited to chronic pain (defined as the current episode of pain being of at least 4 weeks' duration), a pooled result was only given for a combined back and neck pain analysis, and indication-specific effects or the individual size of the treatment effect are not known. Acupuncture effects on **analgesia during surgery** were reviewed by Lee and Ernst in 2005; the review included 19 RCTs and the evidence was judged to be inconclusive. Two systematic reviews on **postoperative pain** were published in 2008. The study selection was not identical across reviews and there were inconsistent results across included studies; one of the review concluded the evidence that auricular acupuncture reduces postoperative pain is promising but not compelling.[123] **Fibromyalgia** has been addressed in 12 RCTs according to one of 3 recent systematic reviews; effectiveness results are inconsistent within and across reviews. Results regarding **shoulder pain** are also inconclusive. A 2012 review on shoulder pain after stroke included 3 relevant acupuncture RCTs but did not report a pooled treatment effect estimate; a Cochrane review on shoulder pain, last updated in 2005, identified 9 RCTs with varying results and concluded that due to a small number of clinical and methodological diverse trials, little can be concluded from the review.[167,207] The evidence base for **rheumatoid arthritis** is also unclear

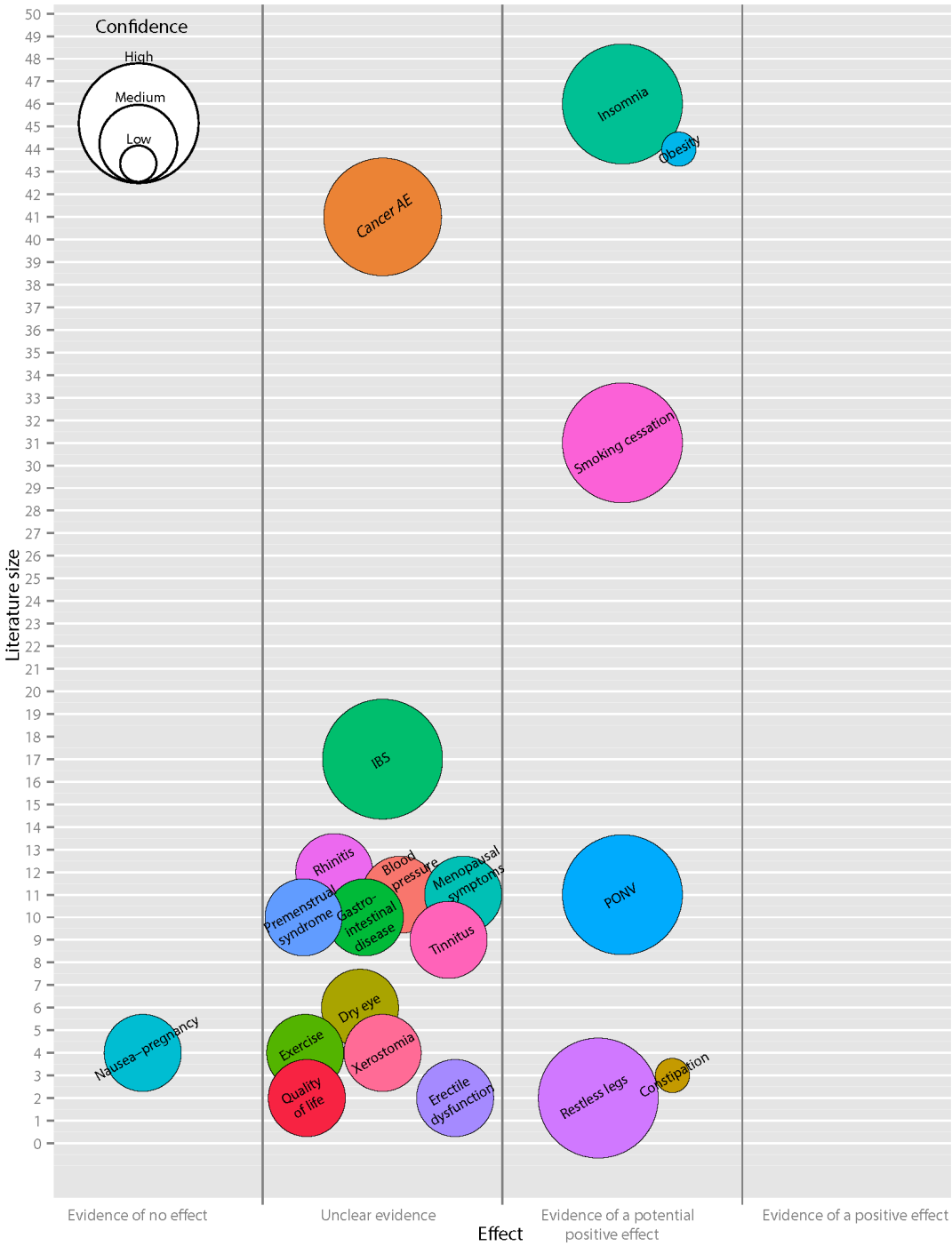
and insufficient data were reported to determine the effectiveness across reviews and included trials. A Cochrane review last updated in 2005 highlighted that conclusions are limited by methodological considerations such as the type of acupuncture, the site of intervention, the small number of clinical trials, and the small sample size of the included studies.[165]

A single review on **carpal tunnel syndrome** was identified that included 6 RCTs. The review did not find statistically significant differences in 2 sham controlled RCTs and conflicting results across outcomes for acupuncture as an add-on treatment in a further RCT.

In addition, a small number of reviews were identified that could not be incorporated in the bubble plot. They addressed primarily the comparative effectiveness of acupuncture in relation to other treatments. The reviews reported that acupuncture was more effective than conventional pharmacological therapies in the treatment of gouty arthritis[35] and neurovascular headache (although this is based on a very limited number of studies),[69] more effective than Chinese herbal medicine for endometriosis,[65] but no more effective than pharmacological sedation for egg retrieval during assisted reproductive therapy[173] and of similar efficacy as carbamazepine for trigeminal neuralgia in the existing low-quality studies.[181] One systematic review on myofascial trigger point pain reported positive results. However, the number of traditional acupuncture trials, rather than trials on dry needling inserted directly into the trigger points, supporting the result was not reported. A systematic review on acupuncture or acupoint injection for management of burning mouth syndrome[180] found injections to be superior to laser acupuncture; no passive controlled acupuncture RCTs were identified.

EVIDENCE MAP OF ACUPUNCTURE FOR WELLNESS

The results for Wellness-relevant indications and outcomes are presented in the bubble plot and text summary below. The bubble plot represents 43 systematic reviews and 3 recent large RCTs not yet incorporated in existing reviews summarizing effects for 20 distinct clinical indications relevant to Wellness [search date: March 2013].



Legend: The bubble plot shows an estimate of the evidence base for wellness-related indications judging from systematic reviews and recent large trials. The plot shows the estimated size of the literature (y-axis, number of RCTs included in largest review), the estimated effect (x-axis), and the confidence in the estimate (bubble size).

The figure provides a visual overview of the evidence base of acupuncture for wellness indications. The bubble plot depicts the estimated research volume based on the number of acupuncture RCTs included in the largest review for each of the differentiated clinical areas, the estimated treatment effect compared to passive control, and the confidence in the effect estimate, judging from published systematic reviews. Effect size estimates of the treatment effect based on specific individual reviews, as well as reason for classifying the evidence base as inconclusive, are reported in the narrative synthesis. The evidence map used the clinical topics as addressed in existing reviews and individual research studies may have contributed to a number of included reviews and clinical indications. All 3 depicted dimensions (literature size, effect, and confidence) are estimates and can only provide a broad overview of the evidence base.

EXECUTIVE SUMMARY: WELLNESS

As shown in the bubble plot, the largest research area was the indication **insomnia**. We identified 7 recent systematic reviews by independent author groups; the largest review, published in 2009, included 46 acupuncture RCTs.[24] A 2012 Cochrane review reported that compared with other treatment alone, acupuncture as an adjunct might marginally increase the proportion of people with improved sleep quality (OR 3.1, 95% CI: 1.9, 4.9) but concluded that the current evidence is not sufficiently rigorous to support or refute acupuncture for treating insomnia. The role of acupuncture in **obesity** has also been evaluated in a large number of studies; a 2012 review included 44 primarily non-PubMed indexed acupuncture RCTs.[60] The review reported a risk ratio of 2.14 (95% CI: 1.58, 2.90) in favor of body weight reduction with a mean difference in body weight reduction of 2.76kg (95% CI: 1.61, 3.83) but noted that the majority of included studies was of low quality. A competing review including 31 acupuncture RCTs concluded that results suggested that acupuncture is an effective treatment for obesity; however, the amount of evidence is not fully convincing because of the poor methodological quality of trials reviewed.[122] **Smoking cessation** has also been addressed in a large number of studies; a 2011 Cochrane review included 31 acupuncture RCTs. The review reported that compared with sham acupuncture the risk ratio for short-term effects was 1.18 (95% CI: 1.03, 1.34) and 1.05 (CI: 0.82, 1.35) for long-term effects[74] but concluded there is no consistent, bias-free evidence that acupuncture, acupressure, laser therapy, or electro-stimulation are effective for smoking cessation and no firm conclusions can be drawn. A 2012 review reported positive effects of acupoint stimulation at immediate, 3- and 6-month follow-up but did not differentiate effects of acupuncture, acupressure, electro-acupuncture, or percutaneous electrical nerve stimulation.[53] Nausea and vomiting was addressed in a number of publications for a variety of indications and results appear to depend on the underlying condition causing the symptom. A 2009 Cochrane review included 11 acupuncture RCTs evaluating the effect of wrist acupuncture point P6 stimulation (acupressure, acupuncture, electro-acupuncture, transcutaneous nerve stimulation, laser stimulation, capsicum plaster, acustimulation device) for preventing postoperative nausea and vomiting (**PONV**).[111] The review reported a pooled effect size of 0.65 (95% CI: 0.48, 0.89) for acupuncture trials compared to sham for nausea and 0.60 (95% CI: 0.43, 0.84) for vomiting. The review concluded that P6 acupoint stimulation prevents post-operative nausea and vomiting; however the majority of included studies evaluated acupressure or other treatments and no conclusions specific to acupuncture were presented.

Positive effects were also reported for other clinical indications; however, the effects are based on only a small number of primary research studies. A Cochrane review on acupuncture for **restless legs syndrome** reported dermal needle therapy in combination with medications and massage was more effective than medications and massage alone in terms of remission of unpleasant sensation in the legs (RR 1.36, 95% CI: 1.06 to 1.75). However, the result was based on a single RCT and the review concluded that the evidence is insufficient.[130] A systematic review on the efficacy of TCM for the management of **constipation** included 3 acupuncture RCTs.[99] The RCTs comparing acupuncture treatment with patients taking lactulose or Folium Sennae reported statistically significant benefits in favor of acupuncture but no pooled effect was reported to estimate the size of the acupuncture treatment effect.

The clinical effectiveness is unclear for a number of wellness-relevant indications. Several primary studies and systematic reviews have been published on **cancer treatment-associated physical adverse events**; a 2013 review included 41 RCTs addressing a variety of adverse events such as pain, nausea, hot flashes, fatigue, xerostomia, prolonged postoperative ileus, anxiety / mood disorders, and sleep disturbance.[38] The review concluded that acupuncture is an appropriate adjunctive treatment for chemotherapy-induced nausea / vomiting but additional studies are needed, and for other symptoms efficacy remains undetermined due to the high risk of bias of existing studies. A Cochrane review specific to chemotherapy-induced nausea or vomiting reported that stimulation with needles reduced the proportion of acute vomiting (RR 0.74, 95% CI: 0.58, 0.94) but not acute nausea severity. Results were inconsistent for elector-acupuncture and manual acupuncture, and studies combining electro-acupuncture with state-of-the-art antiemetics and in patients with refractory symptoms are needed to determine clinical relevance.[161] The evidence base across and within 5 additional reviews on cancer and cancer-treatment related adverse events or specific conditions such as cancer-related fatigue, hot flashes in breast cancer survivors, and hiccups in cancer patients was judged to be insufficient to draw firm conclusions by the review authors. A Cochrane review on **irritable bowel syndrome (IBS)** included 17 RCTs[57]. The review indicated that acupuncture was more effective than no specific therapy (RR 2.11, 95% CI: 1.18, 3.79) and Chinese medicine treatment alone (RR 1.17, 95% CI: 1.02, 1.33), but not sham acupuncture for symptom severity (SMD -0.11, 95% CI: -0.35, 0.013) or quality of life (SMD -0.03, 95% CI: -0.27, 0.22). Results of effects of acupuncture on **rhinitis** were judged to be inconsistent in 3 systematic reviews; the largest review included 12 acupuncture RCTs. A recent, large RCT, commissioned by German health insurance companies as part of the "Acupuncture in Routine Care" study and not yet included in existing reviews, included 981 randomized participants with allergic rhinitis. The study reported a mean improvement of 1.48 (SE 0.06) on a rhinitis quality of life questionnaire in the acupuncture group and 0.50 (SE 0.06) in the control group ($p<0.001$).[208] The existing reviews did not report sufficient data to allow a reanalysis of all available RCTs. A 2006 systematic review on acupuncture treatment in g**astrointestinal diseases** included 10 RCTs covering a wide range of indications and reported that quality of life improved independently from the treatment, real or sham acupuncture, while a recent large RCT on functional dyspepsia and a trial on gastroesophageal reflux disease reported superior effects of true acupuncture, and a meta-analytic reanalysis for the purpose of this review of reviews was not possible.[209,210] Two reviews on acupuncture effects on **blood pressure** and one review on **tinnitus** concluded that the evidence is inconclusive. Reviews on **menopausal symptoms**, **premenstrual syndrome**,

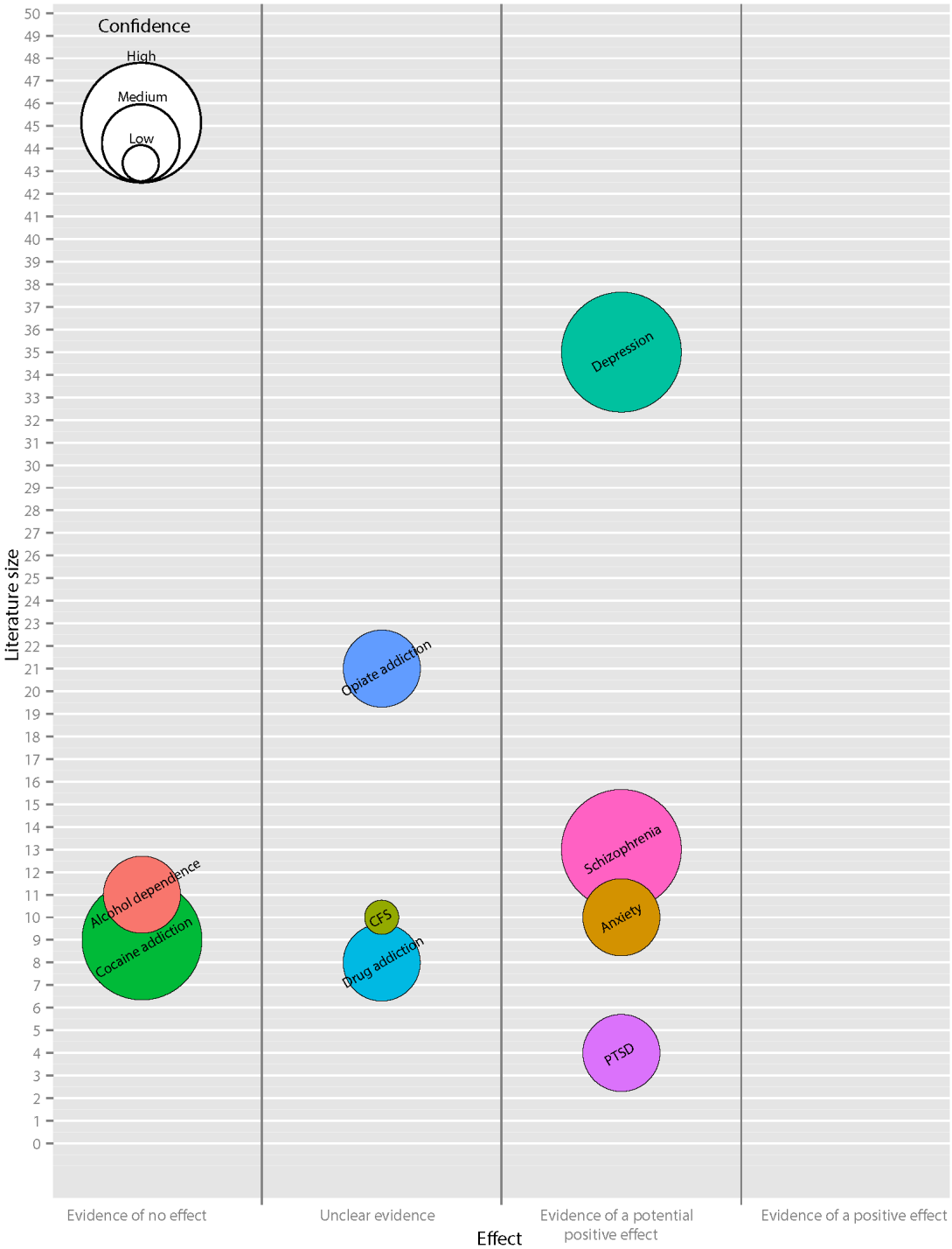
and **xerostomia** showed conflicting results across reviews; each topic was targeted in 2 to 3 reviews by independent researcher groups. Reviews on **dry eye**, **exercise performance**, **rrectile dysfunction** and **quality of life** found conflicting results across included studies, did not pool results, and provided insufficient details for a reanalysis without obtaining original trials data. The reviews indicate that only a limited number of individual studies are available, ranging from 2 to 6 included acupuncture RCTs.

A review on acustimulation effects on nausea and vomiting in pregnant women (**nausea-pregnancy**) included 4 acupuncture RCTs and reported no effect in reducing nausea and vomiting.[154]

In addition, a small number of reviews were identified that could not be incorporated in the bubble plots. They primarily addressed the comparative effectiveness of acupuncture in comparison to other active treatments. One review concluded, based on individual RCTs and existing meta-analyses, that acupuncture was as effective as pharmacological therapies or acupressure in addressing postoperative nausea but not vomiting.[54] A review of the effects of acupuncture on hot flushes in men with prostate cancer[117] and reviews of auriculotherapy (either acupuncture or auricular taping) for managing constipation[87, 211] concluded most studies were too methodologically flawed to reach a conclusion. A recent Chinese-language RCT (N=577 participants) not yet included in existing reviews on acupuncture for pulmonary function concluded that the effect of acupuncture is equal to salbutamol aerosol inhalation.[211] A systematic review on acupuncture for respiratory disease in Japan [197] included 2 relevant RCTs, and the evidence tables indicated that acupuncture was superior to waiting list controls for cold prevention. However, no numerical values were reported and the statistical significance is not known.

EVIDENCE MAP OF ACUPUNCTURE FOR MENTAL HEALTH

The results for mental health indications are presented in the bubble plot and text summary below. The bubble plot represents 17 systematic reviews summarizing evidence for 9 clinical indications relevant to mental health [search date: March 2013].



Legend: The bubble plot shows an estimate of the evidence base for mental health-related indications judging from systematic reviews and recent large trials. The plot depicts the estimated size of the literature (y-axis, number of RCTs included in largest review), the estimated effect (x-axis), and the confidence in the estimate (bubble size).

The figure provides a broad visual overview of the evidence base of acupuncture for mental health. The bubble plot depicts the estimated research volume based on the number of acupuncture RCTs included in the largest review for each of the 10 depicted clinical indications, the estimated treatment effect of acupuncture compared to passive control, and the confidence in the effect estimate, judging from published systematic reviews. Effect sizes based on specific individual reviews, as well as reason for classifying the evidence bases as inconclusive, are reported in the narrative synthesis. The evidence map used the clinical topics as addressed in existing reviews and individual research studies may have contributed to a number of included reviews and clinical indications. All 3 depicted dimensions (literature size, effect, and confidence) are estimates and can only provide a broad overview of the evidence base.

EXECUTIVE SUMMARY: MENTAL HEALTH

As shown in the bubble plot, acupuncture for the treatment of **depression** has been evaluated in a large number of studies; a 2010 systematic review on acupuncture therapy in depressive disorders included 35 RCTs meeting an initial quality threshold.[103] Across studies and across the most recent of the 5 identified systematic reviews positive effects were shown. However, effects depend on the comparator – a 2010 Cochrane review reported that acupuncture may have an additive benefit when combined with medication compared with medication alone but noted inconsistent effects from acupuncture compared with a waitlist control or sham acupuncture control. The review also noted a high risk of bias in the majority of included trials and concluded that evidence to recommend the use of acupuncture for people with depression is insufficient.[96] **Schizophrenia** has also been addressed in a number of studies; a 2009 systematic review included 13 RCTs.[101] A Cochrane review with literature searches up to April 2005 reported that Brief Psychiatric Rating Scale (BPRS) data favored a combined acupuncture and antipsychotic group (WMD -4.3, 95% CI: -7.0, -1.6). However data for global state outcomes, leaving the study early, and dichotomized BPRS data (improved versus not improved) were equivocal and the review concluded that there is insufficient evidence to recommend the use of acupuncture for people with schizophrenia.[164] A review on acupuncture for **anxiety** and anxiety disorders included 10 RCTs.[147] The review reported that all studies indicated positive findings; however, the review also pointed out that studies lacked many basic methodological details and concluded that there is insufficient research evidence for firm conclusions.

Regarding topics with fewer primary research studies and positive results, a review on **posttraumatic stress disorder (PTSD)** was identified that included 4 RCTs. The review found that acupuncture was superior to waitlist control (posttraumatic symptom scale-self report effect size [ES] -0.98, $p=0.001$) and cognitive behavioral therapy alone (Revised Impact on Event Scale ES -1.56, $p<0.001$) based on one RCT each.[31]

The role of acupuncture for **opiate addiction** has been addressed in a substantial number of studies; a 2009 systematic review included 21 RCTs of acupuncture therapy combined with opioid receptor agonists for heroin detoxification,[188] but the evidence base regarding the effectiveness of acupuncture is unclear. The largest review reported no effects on relapse rate after 6 months and the methodology of some included trials was poor; however, positive effects for withdrawal symptoms, side effects, and medication dosage were shown. A competing review concluded that the review results cannot be used to establish the efficacy of acupuncture in the

treatment of opiate addiction because the majority of included studies were classified as having low quality.[58] A review on auricular acupuncture for not further specified **drug addiction** and a review on acupuncture for **chronic fatigue syndrome (CFS)** showed conflicting results across included studies and did neither pool the data nor report sufficient detail for a reanalysis. The reviews included 10 or fewer studies.

Three recent reviews on **cocaine addiction**, including a Cochrane review last updated in 2006,[162] did not support the use of acupuncture for the treatment of cocaine dependence; the largest review included 9 RCTs. A single review on **alcohol dependence** was identified reviewing 11 RCTs; it did not report favorable results and concluded that the existing studies do not allow any conclusion about acupuncture treatment efficacy.

In addition, 2 reviews were identified that could not be incorporated into the bubble plot. One review concluded that acupuncture was no more effective than other treatments in treating opiate addiction.[159] A review comparing acupuncture and Western medicine for post-stroke depression[190] found mixed results depending on the selected patient outcome.

OTHER INDICATIONS

Only 2 indications that were not already included in the priority areas Pain, Wellness, or Mental Health were identified that were addressed in 3 or more systematic reviews. The unique topics are presented in the Future Research section.

A large number of individual studies and 9 recent systematic reviews have been published relating to **stroke** rehabilitation; a 2012 meta-analysis on the efficacy of acupuncture in treating dysphagia in patients with a stroke included 72 RCTs. The review reported that the effectiveness of treatment was higher in the acupuncture group compared to control (OR 5.17, CI: 4.18, 6.38).[45] However, the review was primarily based on non-PubMed indexed studies; a 2008 Cochrane review on the same topic included only one RCT and concluded that there is not enough evidence to make any conclusion about the therapeutic effect of acupuncture. A review published in 2012 which aimed to update the Cochrane review included 9 RCTs; it reported that acupuncture combined with conventional rehabilitation has positive effects on dysphagia but given the methodology of the studies more research is needed before recommending acupuncture as a standard treatment to patients.[199] A further Cochrane review, last updated in 2009, on stroke rehabilitation concluded there is no clear evidence on the effects of acupuncture on subacute or chronic stroke.[157] A third, independent Cochrane review on acupuncture for acute stroke concluded that there is no clear evidence of benefit.[168]

In addition, one systematic review on apoplectic aphasia rehabilitation was identified that did not provide sufficient data to be combined with the other stroke reviews; the review concluded that controlled clinical studies and a systematic review demonstrate that acupuncture has therapeutic effects on aphasia after stroke.[40]

A second topic, acupuncture to support **fertility** treatment, has also received substantial research attention; a systematic review on effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization included 24 RCTs.[61] There were conflicting results across the 6 recent systematic reviews on the topic performed by independent researcher groups. While the largest review concluded that acupuncture improves clinical pregnancy rate and live birth rate, a 2010 publication based on a Cochrane review concluded that there is no evidence of benefit in the use of acupuncture during assisted conception.[98]

In addition, one relevant systematic review was identified that did not report on a passive control group; the review concluded that although acupuncture has gained increasing popularity in the management of subfertility, its effectiveness has remained controversial.[141]

ADVERSE EVENTS OF ACUPUNCTURE

We identified 6 systematic reviews summarizing adverse events of acupuncture. In addition, a number of effectiveness systematic reviews addressed adverse events in the title or the abstract of the publication, indicating that adverse events was one of the main research questions addressed by the review.

REVIEWS OF ADVERSE EVENTS OF ACUPUNCTURE

All 6 independent systematic reviews on adverse events of acupuncture focused on case studies. Because no denominator was reported (number of patients exposed), it is not possible to determine rates of adverse events from these data. In addition, no control group data were available; hence the results are difficult to interpret. The first adverse event review searched Medline through 2011 for literature on vascular injuries caused by acupuncture and found 31 cases, 3 of which resulted in death.[201] This was an update of a prior review, and included all the cases found in the prior review.[212] A second review focused on cardiac tamponade caused by acupuncture, and searched Embase, Medline, AMED, CENTRAL and the Chinese Journal Full-Text Database through January 2010.[204] Of the 26 cases of cardiac tamponade found in 17 articles, 14 deaths were reported. All fatal instances were deemed to have certain causality linking the deaths to acupuncture treatment. A further review searched 4 major Chinese databases through 2010 for literature on adverse events more generally and found 1,038 cases in 167 papers.[202] An acupuncture-related adverse event was defined as any unfavorable and unintended sign, symptom, or disease that presents during or after treatment with acupuncture regardless of causal relationship, and adverse events were classified in one of 4 categories: syncope (N=468), organ or tissue injury (N=451), infection (N=38), and others (N=81). Deaths were reported for 35 cases: 21 of 26 organ or tissue injury-related deaths were judged as having a "certain" likelihood of causality by 2 reviewers, and 3 of the 9 infection-related deaths were judged as certain. One review on acupuncture, moxibustion, and cupping searched 6 databases for English language case reports to 2011.[200] Of the 117 reports published since 2000, 103 reports including 294 cases were related to acupuncture. Adverse events were categorized as either complications, including infections or organ or tissue injury, or adverse reactions. Three deaths were reported with case analysis supporting the causal link between the acupuncture treatment and the fatal outcome. A review that focused on the safety of acupuncture for osteoarthritis of the knee searched PubMed and a Japanese literature database through 2006 and found 12 relevant RCTs, of which 7 included adverse event information.[205] This review found no serious adverse events. A final review of Chinese language literature on acupuncture-related adverse events searched 3 Chinese databases through 2009 and included 115 articles that identified a total of 479 cases.[203] Adverse events were categorized as traumatic, infectious and other, and although 14 deaths were reported, the category and causality were not specified for all these fatal cases. Reviews called for more standardized procedures, including adverse event reporting mechanisms, safe practice procedures, and acupuncturist's qualifications and training, and warned that although adverse events are rare occurrences, a lack of regular reporting makes establishing a frequency difficult.

Adverse Events in Reviews on Acupuncture for Pain

In the domain relating to Pain, 12 reviews addressed adverse events. One review of 10 RCTs of acupuncture for pain relief in labor found no events in the 6 trials that reported on adverse

events.[85] The other 11 reviews all found low rates of adverse event reporting, and of those reported, all events were minor symptoms such as bruising, nausea, temporary pain, dizziness or faintness, or discomfort.[30,50,62,88,94,97,121,140,143,167,182] Three reviews noted that these symptoms were comparable to control groups,[94,97,167] and one review of acupuncture for migraine prophylaxis found that acupuncture resulted in fewer adverse events than prophylactic drug treatment.[121]

Adverse Events in Reviews on Acupuncture for Wellness

Thirteen reviews in the Wellness-relevant domain focused on adverse events as well as the clinical effectiveness. Three reviews on acupuncture treatment for insomnia found low rates of reporting of adverse events, and of the few reports, all but one event were minor events such as bruising.[24,46,112] One instance of a patient dropping out of a study due to pain associated with acupuncture was reported by 2 of the reviews.[46,112] The rest of the reviews in the wellness-relevant category also found low rates of adverse event reporting, and of those events that were reported, the events were minor such as temporary pain, nausea, dizziness, discomfort, or bruising.[52,60,68,86,102,109,111,122,130,142]

Adverse Events in Reviews on Acupuncture for Mental Health

Of the Mental Health reviews, 6 focused on adverse events.[96,103,110,162,164,179] Three reviews of alcohol dependence[110], cocaine dependence[162], and drug addiction[179] found low levels of adverse event reporting (3 of 11 studies, 0 of 7 studies, and 5 of 8 RCTs, respectively), and those studies that did report adverse events mentioned mild levels of symptoms such as pain, bleeding, nausea and dizziness. Two reviews of depression mentioned adverse events. The first included 30 studies, of which one reported on adverse events, and found no statistical difference between acupuncture and the control group.[96] The second review found 21 of the 35 included studies reported on adverse events, and in a pooled analysis acupuncture (including both active and sham) had a statistically significantly lower incidence of adverse events when compared to anti-depressants (10.2% vs 40.4%; $P<0.001$).[103] The final review was of acupuncture for schizophrenia, and of the 5 trials included, 2 small trials reported on adverse events and found favorable results for acupuncture, both when used alone in comparison to antipsychotics and when used in combination with antipsychotics compared to antipsychotics alone.[164]

Adverse Events in Reviews on Acupuncture for Other Indications

Four reviews in the Other Indication category were identified. Two small reviews including 5 and 8 studies of acupuncture for stroke found no included studies reported adverse events.[41,157] A third review including 14 studies on acupuncture for acute stroke found 9 studies reported adverse events, the majority of which were minor.[168] Of 386 cases, 6 were moderate to severe, with no mentions of fatal adverse events. Finally, a review of emergency department acupuncture adverse events found that 2 of the 4 included studies reported adverse events, but that all reports were minor (eg, bruising, dizziness).[36]

FUTURE RESEARCH

We identified evidence gaps by highlighting inconclusive evidence across or within reviews or a lack of primary research according to identified reviews.

However, an overarching theme and source of heterogeneity in results appeared to be the selection of the comparator against which the treatment effects of acupuncture was compared. The bubble plots summarize data from all passive controlled RCTs to determine the effectiveness of acupuncture. Passive controls included no treatment, waiting list assignment, acupuncture as add-on treatment to a treatment plan received by both treatment groups, and placebo control such as sham acupuncture. Clinical effectiveness estimates may depend on the chosen comparator. In research studies, placebo controls are used to blind participants ensuring that treatment effect estimates are not biased. However, in acupuncture trials there are additional considerations.

Sham acupuncture may include needles inserted superficially rather than deep at non-acupoints nearby; true needling at points not thought to influence the desired outcome; acupuncture devices with needles that retract into the handle rather than penetrate the skin; the use of blunt devices to apply pressure without penetration (Streitberger placebo acupuncture); or non-needle approaches, such as deactivated electrical stimulation or detuned laser.[17,213] The type of sham acupuncture may already be a source of heterogeneity among studies assessing the effectiveness of acupuncture. Several authors have suggested that a noninvasive placebo needle at acupoints, such as that used in the Streitberger method, and sham involving needle penetration at non-acupoints may both elicit physiological effects similar to those of acupressure; thus the "sham" acupuncture would be more similar to acupressure than a true control for acupuncture.[47,214,215] Zheng et al (2012)[213] argues that surface stimulation at acupoints, such as acupressure or transcutaneous electrostimulation, should be considered as the adjunctive treatment rather than as a control. Other authors have suggested that the specific acupoints are not as relevant as traditionally assumed[216] and the recent IPD meta-analysis on chronic pain concluded that differences between true and sham acupuncture are relatively modest suggesting that factors in addition to the specific effects of needling are important contributors to the therapeutic effects of acupuncture.[47]

Future research is needed to help distinguish between the effectiveness and cost-effectiveness of acupuncture and sham acupuncture. If the explanation for the observation of little difference in effectiveness between true and sham acupuncture is that both true and sham acupuncture have positive effects, then the specific implication for the VA could be that there is no need for training in acupuncture and for VA to hire licensed acupuncturists, since the sham acupuncture could be performed by a technician with minimal training. The scientific debate is ongoing; a number of reviews highlight clear differences between sham and true acupuncture and counter arguments that sham interventions involving needle penetration result in large nonspecific effects.[119,217,218] Nonetheless, there is currently no universal standard for what constitutes an appropriate method or procedure for a sham acupuncture control, and that this may contribute to the discrepancy between observed clinical effectiveness of acupuncture and the lack of rigorous research supporting these observations.[217]

Further sources of heterogeneity appeared to be the inclusion criteria across reviews and the electronic databases searched. Reviews published in the same year did not use the same study pool and newer reviews rarely included all studies included in previous reviews, therefore simply

accumulating additional evidence. A number of authors have pointed to publication bias ("do certain countries produce only positive results?")[23] For this broad overview we could only flag the concern and highlight inconsistencies across reviews. A number of authors have summarized challenges in acupuncture research that may contribute to the apparent complexity of the research area.[219-221]

FUTURE RESEARCH: PAIN DOMAIN

In the Pain domain, we had to conclude for a number of specific clinical indications that the evidence base is currently unclear and a systematic review stratifying by comparator and outcome is needed to determine the effectiveness and size of the treatment effect. Clinical indications included acupuncture for back pain, neck pain, surgery analgesia, postoperative pain, fibromyalgia, shoulder pain, and rheumatoid arthritis.

Although we classified chronic pain as one of the conditions for which acupuncture has evidence of a positive effect and high confidence, this conclusion is limited by the lack of a consistent signal of positive effect in the individual pain categories that must make up any "chronic pain" population. Back pain alone usually accounts for 50% or more of chronic pain patients, and therefore if acupuncture has a positive effect in chronic pain patients then one would expect acupuncture to have a positive effect in chronic low back pain patients. Yet, we did not identify a definitive evidence synthesis for acupuncture and back pain. Similarly, one of the next most common conditions within a population of chronic pain patients is neck pain, and yet again the best available evidence synthesis of the effectiveness of acupuncture for neck pain is not equally positive as it is for the area chronic pain. This review of reviews suggests the need for an additional systematic review to resolve the discrepancy.

Furthermore, a Cochrane review for endometriosis did not identify any placebo or sham controlled RCTs.[65] One comparative effectiveness review noted that although exercise, spinal manipulation therapy, and acupuncture are widely used interventions in the treatment of chronic low back pain, no study comparing acupuncture head-to-head with the alternative treatments was identified.[63] A large 2013 RCT including 501 participants diagnosed with primary dysmenorrhea concluded that traditional Chinese medicine pattern might affect acupoint-specific effects on pain, however, the main results of the trial are not published yet.[222]

FUTURE RESEARCH: WELLNESS DOMAIN

In the Wellness-relevant domain, we concluded for a substantial number of specific clinical indications that the therapeutic effectiveness of acupuncture is unclear and further research is needed. Topics included acupuncture for cancer treatment adverse events, IBS, rhinitis, blood pressure, menopausal symptoms, premenstrual symptoms, gastrointestinal diseases, tinnitus, dry eye, xerostomia, exercise, quality of life, and erectile dysfunction. For some of the clinical indications the evidence base appeared to be unclear due to the lack of research studies. However, the evidence base for physical symptoms of cancer treatment associated adverse events was unclear despite a large number of research studies. Inconclusive results were potentially due to the diversity of reviewed outcomes. Future systematic reviews and/or future individual studies may determine whether acupuncture has a role in these clinical indications and for which clinical outcome.

FUTURE RESEARCH: MENTAL HEALTH DOMAIN

In the smallest research domain, Mental Health, the effect of acupuncture on CFS and its role in the treatment of addiction, in particularly opiate addiction, remained unclear. Systematic reviews should to differentiate effects on relapse rates and effects on drug withdrawal symptoms.

FUTURE RESEARCH: OTHER INDICATIONS

In the Other Indication domain there were a number of clinical indications with only one or 2 reviews published in recent years. Topics included acupuncture for chemotherapy-induced leukopenia,[196] Bell's Palsy,[64,223] brain injury,[28,70] asthma,[79,160] epilepsy,[131] breech presentation,[115,139] facial spasm,[198] angina pectoris therapy,[34] spinal cord injury,[32] Parkinson's disease,[135] induction of labor,[100] Alzheimer's disease,[107] uremic pruritus,[66] Meniere's syndrome,[106] and the use of acupuncture in emergency departments.[36]

A Cochrane review on acupuncture for vascular dementia,[150] assessed as up to date in April 2011, identified no randomized placebo-controlled trial that could inform the review question. Acupuncture for glaucoma was targeted in a 2009 Cochrane review[145] but the review did not identify any RCT meeting inclusion criteria. A Cochrane review last updated in 2010 did not identify any RCTs on acupuncture for uterine fibroids.[95] Pressure ulcers were addressed in a 2012 publication but no acupuncture study meeting inclusion criteria was identified.[56] A 2010 review on polycystic ovarian syndrome did not identify any relevant RCTs.[91]

A couple of systematic reviews on broad topics such as sham acupuncture compared to true acupuncture exist but could not be considered in this review of reviews due to insufficient reporting and the lack of a sufficient number of relevant systematic reviews.[114,128,137]

Finally, the reviewed topics acupuncture for stroke rehabilitation and the role of acupuncture in supporting fertility treatment both had to be classified as unclear despite the large number of existing primary studies and systematic reviews.

ONGOING RESEARCH

This broad overview over the evidence on acupuncture concentrated on the clinical effectiveness of acupuncture. This did not consider systematic reviews on the more refined existing open questions such as the optimal acupuncture pattern and pressure points,[224] the comparative effectiveness of existing acupuncture protocols,[225] effects of the practitioner,[226] cost-effectiveness considerations,[227] or the optimal intervention time for acupuncture.[228] Furthermore, the use of standardized treatments may not be the optimal treatment for individual patients. Traditional acupuncture involves tailoring treatments to the individual person and innovative methods may be necessary to evaluate acupuncture within the framework of evidence-based medicine.[229]

Individual future research studies on the clinical effectiveness of acupuncture should comply with the revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).[230]

We identified Cochrane review protocols for acupuncture published in the last 3 years for treating plantar heel pain,[231] renal colic,[232] primary hypercholesterolaemia,[233] hearing loss,[234] breech baby in pregnancy,[235] gastroparesis,[236] chronic constipation,[237] urinary incontinence,[238] neuropathic pain,[239] post-stroke upper limb pain,[240] allergic rhinitis,[241] ankle sprains,[242] angina pectoris,[243] chronic kidney disease,[244] back pain,[245] hypertension,[246] obesity,[247] dyspepsia,[248] and multiple sclerosis[249] indicating ongoing reviews. A search of the international registry of systematic reviews PROSPERO in September 2013 identified 9 ongoing systematic reviews on acupuncture and postoperative gastroparesis syndrome, osteoarthritis, chronic pulmonary obstruction disease, headache, neck pain, phantom limb pain, heel pain, cortisol levels, and pregnancy rates; 2 ongoing reviews of reviews on stroke rehabilitation and surgical conditions; and 2 reviews on semen quality and on diabetic peripheral neuropathy were listed as completed but not published in time for this evidence map [web access 9/23/2013].

SUMMARY AND LIMITATIONS

This broad overview of the evidence base on acupuncture included 183 systematic reviews published since 2005. The most secondary literature and primary research is available for the clinical indication Pain. The most promising evidence for the effectiveness of acupuncture was also identified for this outcome. However, it should be noted that we did not review the evidence base with standard evidence synthesis methods (ie, a systematic review). This broad evidence map only estimated the research volume and effectiveness of acupuncture judging from published reviews. We had no control over the scope, inclusion criteria, or methodological rigor of the reviews. Across reviews there is overlap as individual primary studies have contributed to multiple reviews (most prominently in the systematic reviews on pain) and reviews differed widely (in selected areas reviews on the same topic included between one versus 72 studies). Furthermore, the choice of comparator is the subject of an ongoing scientific debate and adds to the complexity of the evidence base on acupuncture.

Evidence maps are only meant as a broad overview over the evidence base indicating in which areas research has been conducted. This report was not designed to inform policies regarding the use of acupuncture or precluding acupuncture for specific conditions within the VA. More detailed and definitive answers, as well as information on differences in effects based on the type of acupuncture intervention, the type of comparator, competing outcomes, or the study design, can only be obtained by carrying out individual systematic reviews for each of the numerous clinical indications. Full systematic reviews would involve targeted electronic searches, inclusion screening titles and abstracts and full text publications to identify primary research studies, numerous steps to minimize reviewer errors and bias such as screening in duplicate, extracting the outcomes of interest from each available primary study for an independent meta-analysis, differentiating comparators and intervention modalities and other potential moderators in subgroup and meta-regressions, quality assessing the included studies, synthesizing the available studies, and evaluating the overall body of evidence in detail. Finally, assessments to evaluate the value of acupuncture need to take into account multiple factors such as the clinical efficacy, risks and benefits compared to standard treatment, costs and cost-effectiveness, as well as patient satisfaction and patient preferences for a particular clinical diagnosis.

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APPENDIX. PEER REVIEW COMMENTS/AUTHOR RESPONSES

Comment	Response
The scope here states that acupuncture is "one type of Traditional Chinese Medicine" (TCM). In fact, acupuncture is one aspect of Chinese or Oriental Medicine, (which includes multiple modalities including herbal medicine, manual therapies, and movement therapies) and TCM is school of thought in Chinese Medicine. There are other schools of thought as well. Acupuncture is practiced by practitioners of traditional Japanese Medicine as well as practitioners of Medical Acupuncture.	We have revised the sentence accordingly.
paragraph 1 The reviewers use the terms "effectiveness and harms" in …. this biases the reader toward negative bias. The usual terms are risk and benefit.	We have replaced the term "harms" with the broader, more accurate, and more common term "adverse events" to avoid any notion of bias.
page 4: Bubble Plots Review methods described on page 4 are somewhat difficult to follow. I would suggest editing for clarification.	The section has been edited for clarity and revised accordingly.
Reasoning for confidence of effect seems somewhat arbitrary. I am not sure that rating a systematic review low based only on the included studies not being indexed in PubMed is the best indicator available for assessing quality of evidence, although I do understand the reasoning.	With hundreds of reviews and RCTs we needed a simple system and used an issue that was both widely discussed as well as easy to follow up. We have added more references addressing the use of publically available studies in acupuncture research to provide more information on the rationale.
Also, it is unclear how the investigators controlled for the same RCTs being included in multiple SRs, as this could potentially alter the strength of the effect size.	For evidence maps we rely on the systematic reviews as published and have no control over the inclusion criteria of the review. To address this point, we have added a note following each of the three evidence maps and the limitation section alerting the reader to this issue.
Pg 6 ln 32 title should be VHA CO Field Advisory Committee.	changed
Pg12 ln 35 back pain is listed as unclear, yet included in part of positive effect seen in chronic pain. Is there a distinction between acute back pain and chronic back pain which would account for this? Given that back pain is the leading cause of chronic pain it seems surprising the evidence would be so different for back pain and chronic pain.	We have added a comparison of the studies included in the IPD review on chronic pain and the back pain, neck pain, headache, and osteoarthritis reviews. We have also highlighted issues surrounding the unique scope of reviews and the overlap of reviewed studies across reviews in each of the evidence maps and in the limitation section of the report.
In one of the reviews on the use of acupuncture for opioid addiction (page 22), which was not incorporated in the bubble plot, the issue of comparative effectiveness studies is raised – the conclusion was that acupuncture was no better than other treatment, but non-inferiority could be considered a positive finding.	To address this point, we have added a sentence to the limitation section of the report clarifying that an assessment of acupuncture need to take the clinical efficacy but also risks and benefits compared to standard treatment into account.
Pg 28 ln 2-3 and 20-21 in discussion on further research the evidence base is listed as unclear. With trend to positive in pain and wellness as well as some findings of positive evidence in pain it would have seemed that at least for the indications where the evidence is positive a more definitive statement than the evidence is unclear could have been made.	To address the point, we have specified in the future research section that the unclear evidence refers to specific clinical indications within the domains, not the domains itself.

When this report is made public services and facilities will be trying to determine what conditions have sufficient research to support their use. Those conditions with positive findings would appear to be conditions where use would be justified while those trending towards positive it could be considered. However, by reporting that the evidence base is unclear it would make all use seem questionable. It may be that policy will need to be written on how to use these findings and it may be that such guidance would be better than having each facility interpret the data individually. If there were any trends on patterns of usage both in frequency and duration of treatment that were seen that would be useful information for the field	We have moved the limitation section to the end of the report and stated more clearly that the evidence maps are not designed to give definitive answers regarding the effectiveness of acupuncture. We have made more explicit that we did not review the evidence base ourselves with standard methods, i.e. a systematic review; we only estimated the effectiveness of acupuncture judging from published reviews and recent trials. Consequently the evidence map is only meant as a broad overview over the evidence base indicating in which areas research has been conducted and we broadly summarized the results of the 184 included reviews.
Ernst E, White AR: A review of problems in clinical acupuncture research. Am J Chin Med 1997; 25(1):3-11	We have cited the paper illustrating the complexity of the research area in the Future Research study.
Acupuncture trials are frequently inconclusive. Although the gold standard in clinical research is the double- blinded, placebo- controlled trial, yet this was designed to evaluate pharmaceuticals and not acupuncture, which includes and operator and individualization of treatment. One article concludes that "Problems in clinical acupuncture research include the diversity of forms of therapy, need for individualization, blinding and control procedures. " (see above- Ernst E, White : Am J Chin Med 1997; 25(1):3-11) . Because our research methods are not yet adequate, it is important to consider supporting veteran demand at the same time sponsoring research activity in order to clarify the issues.	We agree, however the issue about supporting veteran demands while at the same time sponsoring research is a decision for VA policy makers.
I would suggest writing a set of "take home points" for each of the medical indications for which acupuncture was assessed. That is, using plain language, briefly describe the indications for which the VA should offer acupuncture to patients and which indications need further study.	We have added a summary to the report and clarified that guidance on how acupuncture should be offered within the VA is outside the scope of the evidence map.
Assessment needs to be done that can assess overall value of acupuncture taking into account multiple factors: clinical efficacy, cost savings, patient satisfaction, risk vs benefit compared to standard treatment for a particular clinical diagnosis. Most acupuncture studies look at clinical efficacy only.	We have added this point to the limitation section.
The bias is simply that the review sets randomized, placebo-control trials as the gold standard, when there are multiple issues with using placebo for acupuncture studies. Simply stating that there is no significant difference between sham and true acupuncture obscures the possibility that both sham and true acupuncture actually had positive effects. The effects of both should be reported.	For this reason we have not limited the evidence map to reviews of placebo-controlled trials and instead have focused on reviews on all passive-controlled comparators, including no control treatment, waiting lists, and add-on trials where acupuncture was added to a common treatment in one group only while the control group received no additional treatment. We have added the choice of comparator issue to the limitation section to highlight that it adds to the complexity of the research area. Future research is needed to help distinguish between the effectiveness and cost-effectiveness of acupuncture and sham acupuncture. If the explanation for the observation of little difference in effectiveness between true and sham acupuncture is that both have positive effects, then it may be that there is no need for training in acupuncture and for VA to hire licensed acupuncturists, since the sham acupuncture could be performed by a technician with minimal training.

Furthermore, the use of standardized treatments for the treatment arm may not be the optimal treatment for any given patient. Traditional acupuncture involves tailoring treatments to a person based on several factors, apart from the conventional medical diagnosis. Not all patients with the same symptom are given the same Chinese medical diagnosis. Because of this, each patient may be treated with different points.	We have added this point to the Future Research section (see Ongoing Research).
I am concerned that the supposed lack of evidence for some indications would be used to set policy precluding using acupuncture for specific conditions. For instance, in my experience, carpal tunnel syndrome responds very well to acupuncture. I am curious about the data that they examined. I believe that a trial of treatment is always warranted, as the risks and benefits to the patient are much more favorable than more invasive interventions.	To address this point, we have added that this report was not designed to inform policies regarding the use of acupuncture or precluding acupuncture for specific conditions within the VA to the limitation section. We have added more information regarding the carpal tunnel review.