An exploratory review of the electroacupuncture literature: clinical applications and endorphin mechanisms

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/acupmed-2013-010324).

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Received 1 February 2013
Accepted 1 July 2013
Published Online First 5 August 2013

ABSTRACT

Electroacupuncture (EA) is widely used in clinical practice and research, as well as in experimental investigations into the mechanisms of acupuncture. This study explores publication trends in clinical and experimental studies of EA (1975–2011) for pain and non-pain research; EA use for different clinical conditions (1974–2012); and the relation of EA research, including stimulation frequency, to opioid peptide mechanisms. Appropriate PubMed 'all fields' searches were conducted, identified studies were classified using PubMed filters and manually, and data extracted into tables. A total of 2916 clinical studies were located, of which 19% involved EA. Additionally, 3344 animal studies were located, of which 48% involved EA. The publication rate of EA studies per year has risen over time, but the percentage of studies of pain has fallen from 60% to 25%. The conditions most commonly treated with EA are musculoskeletal, neurological, obstetric and gastrointestinal, along with intraoperative and postoperative analgesia. EA studies, particularly with low frequency stimulation, are more likely to support the role of endogenous opioid mechanisms than manual acupuncture studies, and opioid release is more likely in the central nervous system than the circulation. EA is increasingly used in clinical and especially experimental research, particularly for non-pain conditions. Acupuncture does release endogenous opioids, but this probably depends on 'dosage', with the evidence more consistent and convincing for EA than for manual acupuncture. Different frequencies of EA appear to activate different endogenous opioid mechanisms.

INTRODUCTION

Acupuncture may involve manual or electrical stimulation. Electroacupuncture (EA) is widely used in clinical practice, although usage varies, depending on local convention. It is frequently used in experimental investigations into the mechanisms of acupuncture.

In preparation for new editions of two textbooks,[1 2] and in order to update an online EA resource,[3] the literature on EA was explored through PubMed searches. This paper reports three aspects of this literature: trends in the publication rates of studies on EA for the period 1975–2011, including in pain and non-pain research; the conditions treated with EA (1974–2012); and to what extent findings on the endogenous opioid mechanisms (EOM) of acupuncture are limited to EA. Each aspect is reported separately.

TRENDS IN PUBLICATION

Methods

Various PubMed searches (searches 1–6) were conducted between March and December 2012 for different aspects of the study, as described, together with results, in the web-only supplementary appendix. Resources were insufficient to include other electronic databases to maximise inclusion of non-English papers. In addition, information on clinical conditions treated, and on EA frequencies used, was gained from cumulative PubMed searches from 2003 onward by several researchers in compiling an EA database,[3] together with searches of personal files. Data were classified using search filters where possible (as described below); other data were extracted by hand from abstracts or the full paper when necessary. Studies in all languages were considered, and salient passages of non-English papers translated

To cite: Mayor D. *Acupunct Med* 2013;**31**:409–415.

where possible. Studies not available in UK libraries were excluded. Also excluded when assessing trends were studies published prior to 1975 (when annual EA publication rates were in single figures) or after 2011 (when not all published studies would be indexed by the search date).

Results

Just over 16 600 items on acupuncture published between 1975 and 2011 are included in PubMed (search 1), of which 2916 are classified as clinical trials using the appropriate filter. Of the clinical trials, 548, or 18.8%, include the term 'electroacupuncture' or 'electro-acupuncture' (search 2).

A total of 2962 items labelled as EA (search 3) and then hand counted for the same period included 836 (28.2%) clinical studies (in patients) and 1710 (57.7%) experimental studies in healthy volunteers or animals; the remainder were reviews, editorials, or unclassifiable. Of the 3344 animal acupuncture studies published during the period, the large majority of which were experimental, 1607 (48.1%) were identified as EA by PubMed searches (search 4). However, it seems likely that manual inspection paper by paper would have discovered that a higher proportion used EA.

These data are presented in figure 1 which shows that EA plays an important and increasing part in acupuncture publication, with experimental studies outnumbering clinical ones by approximately 2 : 1 overall, and by more in the 1990s (figure 1).

EA was initially introduced for its analgesic effects, and was the usual stimulation method in early experiments on the role of EOM. However, its effects are not limited to analgesia, and it has become widely used in a range of clinical conditions, as illustrated in figure 2. Whereas initially at least half the studies identified were concerned with pain (annually, 59.9 SD 13.7% for 1975–1984), this proportion has gradually reduced since about 1990, and is now 25.2, SD 4.2% over the past decade.

It should be noted that the above results are limited by restriction of the search to PubMed. The changes over time are likely to be reasonably valid, though new journals were included in PubMed over these years; the changes reflect only part of the global literature on acupuncture.

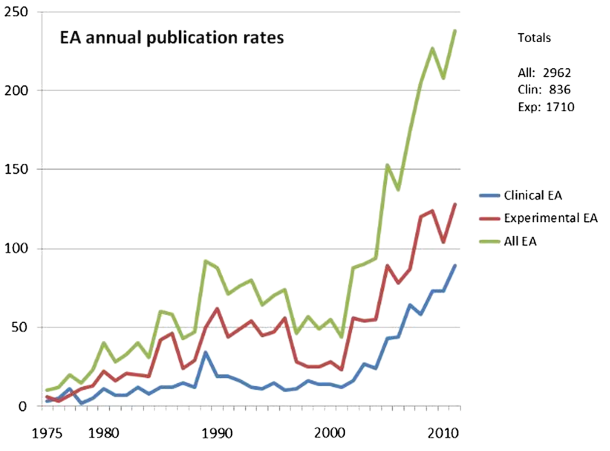

Figure 1 Annual publication rates for electroacupuncture (EA) papers, 1975–2011: clinical and experimental studies.

CONDITIONS TREATED WITH EA

Methods

The results of the updated cumulative review of EA randomised controlled trials (RCTs) (Filshie and White[2], White[4] and PubMed search 2) were combined with searches of studies included in the open-access 'electroacupunctureknowledge' (EAK) database (1959–2001).[3] It should be noted that use of the term 'randomisation' is not always identical in Western and Chinese contexts,[5] although since 2010 there appears to be greater awareness of this issue in at least some Chinese journals.

Results

Table 1 shows numbers of RCTs in PubMed for different categories of condition, and the numbers of studies in EAK. These numbers, together with the proportion (%) of RCTs to all EAK studies, give some indication of where further rigorous research is needed. The median publication date suggests, for example, that addiction has not received much research attention recently, while low numbers of RCTs indicate a need for further research into the use of EA in the treatment of neuropathic pain and chronic fatigue. Further details on the conditions for which EA has been used may be found in the web-only supplementary appendix to this paper.

ACUPUNCTURE AND THE ENDORPHIN HYPOTHESIS REVISITED

Background

Acupuncture and the endorphins simultaneously became hot topics of research in the mid-1970s, and it is often stated that acupuncture 'releases

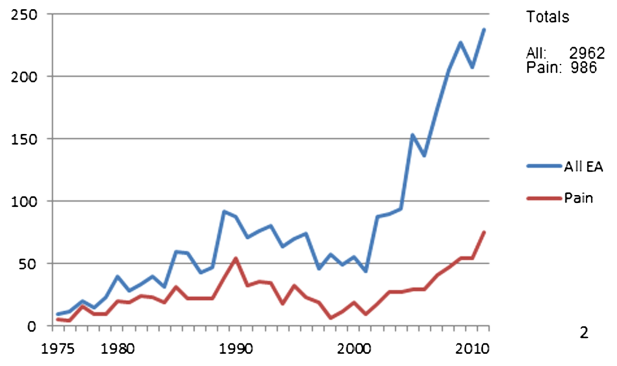

Figure 2 Annual publication rates for electroacupuncture (EA) papers, 1975–2011: studies on pain.

Table 1 Summary data on RCTs of EA for different conditions, 1974 to early 2012, including types of points and electrical parameters used

Condition	*N* RCTs (N in EAK database) percentage	Median publication date	Points used	Parameters used	DD type
Addiction	13 (266) 4.9%	1997	9a 6m 5s (3 sa) 1t	4LF 5HF 4DD	1×HF-LF 3×10-HF
Weight loss	14 (49) 28.6%	2007	5a 7m 9s 11t	7LF 2HF 4DD 1×20Hz	1×15-HF 2×50-HF
Cardiovascular	8 (459) 1.7%	2009	1a 4m 1s 6t	2LF 2HF 2DD 1×20Hz	2×HF-LF
ENT	10 (224) 4.5%	2008	3a 6m 8s (3 sa) 4t	4LF 1HF 3DD 2×10Hz	3×HF-LF
Peripheral motor disorders	15 (266) 5.6%	2009	7m 15s (1 sa) 8t	8LF 1HF 4DD 1i	2×HF-LF
Gastrointestinal	32 (440) 7.3%	2007	2a 21m 20s 25t	9LF 5HF 10DD 4×10 Hz 1r	7×HF-LF 1×LF-20 2×LF-15
Musculoskeletal	90 (1413) 6.4%	2007	3a 20m 79s (3 sa) 21t	37LF 5HF 16DD 5×10 Hz 4×15 Hz 1×20 Hz 3×(30–50 Hz) 3r	7×HF-LF 3×LF-15 1×LF-10 2×LF-20 1×15–50 2×15-HF
Neurology	47 (658) 7.1%	2008	1a 24m 42s (23 sa) 11t	16LF 13HF 6DD 1×10 Hz 3×15 Hz 1×20 Hz 1r 2i	1×LF-15 1×LF-45
Peripheral neuropathic pain	3 (141) 2.1%	2010	2m 3s	2LF 1HF 1DD	1×15–30
Chronic/neuropathic pain (other)	2 (171) 1.2%	2007	1m 1s	2DD	2 HF-LF
Mixed pain	1 (93) 1.1%	1999	1m 1s	1LF 1HF	
Head/facial pain	6 (466) 1.3%	2008	1a 1m 2s 3t	1LF 1HF 3DD	3 HF-LF
Obstetrics and Gynaecology	32 (349) 9.2%	2008	1a 24m 25s 20t	10LF 3HF 14DD 1×10 Hz 1×15 Hz 1×20 Hz 1×50 Hz 1i	10 HF-LF 1×LF-20 1×LF-50
Genitourinary	16 (261) 6.1%	2009	8m 16s (3sa) 9t	9LF 1HF 3DD 2×10 Hz 1×20 Hz 1i	1×HF-LF 1×LF-15 1×LF-20
Psychiatry	26 (272) 9.6%	2009	2a 4m 24s (25sa) 7t	15LF 4HF 4DD 1r	1×HF-LF 1×LF-10 1×LF-15 1×LF-20
Respiratory	3 (237) 1.3%	2007	1m 2s 2t	1HF 2DD	2×HF-LF
Intraoperative analgesia &c	32 (1730) 1.8%	2008	3a 27m 22s (1sa) 9t	12LF 9HF 14DD 1×10 Hz 1r	10×HF-LF 4×LF-15 1×LF-20
Postoperative analgesia &c	32 (285) 11.2%	2009	5a 22m 19s (1sa) 12t	11LF 7HF 5DD 1×10 Hz 1×20 Hz 4r	6×HF-LF 1×LF-15 3×LF-20 1×LF-30 3×10-HF
Cancer care	1 (145) 0.7%	2011	1a 1m 1s 1t	1LF	
Endocrinology and chronic fatigue	3 (40) 7.5%	2011	3m 2s (1sa) 3t	1LF 1HF 1×20 Hz 1×50 Hz	
Dermatology	3 (158) 1.9%	2009	1a 2s 2t	2DD 1r	2×HF-LF
Animal studies	2 (-)	2010	1m 2s 1t	2DD	2×LF-15
Totals	391 (8123) 4.8%	-	38a 191m 301s (63sa) 156t	150LF 63HF 101DD 17×10 Hz etc.	60×HF-LF 11×LF-15 9×LF-20 etc.

'Peripheral motor disorders' includes conditions such as facial paralysis, hiccup, muscle spasm and contracture, myasthenia gravis, muscular dystrophy and some peripheral nerve injury. 'Neurology' includes disorders of the central nervous system (excluding headache). Numbers of studies for each category in the EAK database are approximate, in that some studies covered several conditions and others were reported more than once; such duplicates were not removed. Point abbreviations are as follows: 'a' (auricular), 'm' ('major', an informal term for the common points PC6, TE5, LR3, LI4, ST36 and SP6), 's' (segmental), 'sa' (scalp acupuncture, including traditional head points) and 't' traditional/channel (mostly non-segmental). Some of these categories overlap, but virtually no points are excluded using these groupings.
'10-LF'=alternating 10 Hz and low frequency, etc.; DD, dense-disperse (alternating frequencies); EA, electroacupuncture; EAK, 'electroacupunctureknowledge' database; ENT, ear, nose and throat; HF, high frequency; HF-LF, alternating high and low frequency; il, intermittent; LF, low frequency; r, range; RCT, randomised controlled trial.

endorphins'. However, most of the evidence for the acupuncture–endorphin connection has been derived from studies on EA, not manual acupuncture (MA).[6] More specifically, initial research indicated that low frequency (LF) EA leads to supraspinal release of the μ opioid receptor (OR) ligand β-endorphin (from the medial arcuate nucleus of the hypothalamus (NArc)), whereas high frequency (HF) EA is associated with release of the κ receptor ligand dynorphin (in the dorsal horn of the spinal cord). Low doses of the opioid antagonist naloxone may inhibit release of β-endorphin, higher doses that of dynorphin.[1] Even this is rather an oversimplification, however, and in order to evaluate whether acupuncture does release endorphins and to what extent this is limited to EA, the literature was assessed in more detail.

Methods

As a first step, PubMed searches were conducted to locate studies on the EOM of MA (searches 5a, 5b), followed by searches for EA and 'transcutaneous electrical acupoint stimulation' (TEAS) (searches 6a, 6b), to include studies involving the NArc or pituitary (these being the principal sources of β-endorphin in the brain and peripheral circulation, respectively) (search 6c).

Studies were categorised as MA or EA by hand. 'All fields' searches for MA EOM studies (595 hits), even when designed to exclude 'EA', included many which, on perusal of the actual papers, turned out to be on EA, not MA (always a problem with searches that are not 'full text'). Others were reviews, or mentioned EOM only in passing, and a number were not retrievable to determine whether they were on MA or other forms of acupuncture.

The studies were then categorised according to whether the results confirmed the involvement of EOM in some way (positive) or not (negative), and if positive, at what level: peripheral (blood, tissue), spinal cord or brain. Finally, studies were categorised according to stimulation frequency (table 2).

Results

Those studies exclusively or primarily on the involvement of EOM in MA are shown in the upper part of table 3, which also shows the rather larger number of studies of EA and transcutaneous electrical nerve stimulation (TENS) at acupuncture points ('TEAS' or 'Acu-TENS') inadvertently identified by searching for MA alone. One study included MA and EA arms. Similar PubMed searches for EA EOM studies (searches 6a, 6b) located 476 papers, of which only 292 were confirmed to be studies on EA (9 also with MA arms, 3 with TEAS arms), 1 on MA only and 2 on TEAS only. These are summarised in the lower part of table 3. The remainder were either reviews, editorials, or unclassifiable, or studies on other topics which only mentioned EA. Most of the 'pituitary' studies found (search 6c) concerned the hypothalamo–pituitary–adrenal axis and so adrenergic and endocrine rather than opioid mechanisms, and none were definite MA EOM studies, although 11 were positive (on or confirming the EOM of EA within the brain). Numbers in parentheses are negative studies in tables 2 and 3. The final two columns show the proportion (%) of negative studies and approximate total number of EOM studies for each treatment modality (row).

Taking the figures in both parts of table 3 (all five searches) together, the percentage of studies that are negative—that is, do not confirm the involvement of EOM—is 34% for MA, but only 17% for EA/TEAS.

Discussion

The tables presenting evidence on EOM in EA are complex, and at first sight may not appear to give a consistent picture that EOM is involved in acupuncture mechanisms. However, a number of potential confounding factors need to be taken into account, such as gender differences,[9] pre-existing individual endorphinergic state,[10] and individual variations in responsiveness,[11 12] including the presence of pathology and its type.[13 14] In addition (table 2), results may be affected by situational context, such as stress-induced analgesia (footnote ‡)[15] or cumulative effects (footnote §§),[16–19] order[20] and antagonist dosage (footnotes ¶, ††, †††, ‡‡‡, ††††), or the use of non-standard stimulation parameters (footnotes §, ‡‡, §§§). Even so, and bearing in mind the evident preponderance of EA studies in EOM research, likely publication bias (eg, non-publication of negative outcomes or 'political correctness'[21 22]) and errors or misinterpretations when dealing with the multiple neural circuits involved,[9] certain trends are apparent: (1) EA studies are more likely to be positive for EOM than MA studies; (2) increased levels of endorphins in the central nervous system in response to EA—whether HF or LF—are more likely than increased levels in the blood, although this may not be the case for MA; and (3) LF, or acupuncture-like stimulation (ALS), involves EOM relatively consistently, whereas HF, or TENS-like stimulation (TLS), even at around 45–50 Hz, is less likely to do so.

The limitations noted earlier also apply here: only studies located by searches of PubMed were included, so many non-English studies are likely to be excluded. The first trend is probably explained by the fact that EA delivers a higher dose (more prolonged and intense) of stimulation than MA, and neither low-intensity stimulation,[20] nor a brief, single treatment[23] may activate EOM. ALS is indeed considered to involve central opioid mechanisms, including upregulation of β-endorphin within the hypothalamic arcuate nucleus and enhanced enkephalin synthesis in other hypothalamic nuclei and elsewhere in the brain. At the spinal level, the δ OR agonist met-enkephalin and the μ

Table 2 Effect of stimulation frequency on endogenous opioid mechanisms

Studies	Brain	Spinal cord	Blood	Tissue	Non-specific	Percentage negative	Total EOM studies for modality
LF (1–7 Hz)	81 (2)	27 (3*)	20† (8‡,§)	6 (0)	56 (13¶,**)	14%	190
8–10 Hz	12 (0)	6 (0)	2 (2)	1 (1)	5 (3††)	23%	26
14–17 Hz	6 (1)	2 (0)	5 (0)	0 (0)	6 (0)	5%	19
20–30 Hz	5 (0)	1 (0)	1 (0)	3 (0)	7‡‡ (0)	0%	17
43–50 Hz	2 (1)	0 (0)	2 (1‡)	0 (0)	5 (1)	33%	9
HF (≥80 Hz)	22§§,¶¶ (3)	11*** (3†††)	2 (1)	1 (0)	16‡‡‡ (11†††)	35%	52
DD (2/15 Hz§§§)	15 (0)	8 (0)	2X (1)	1¶¶¶ (0)	5 (0)	3%	31
DD (10/ 20 Hz****)	6 (0)	0 (0)	2 (2)	1 (0)	0 (0)	22%	9
DD (LF/HF)	6 (0)	3 (0)	3 (2X) (2)	2 (0)	4 (1††††)	17%	18
DD (undefined)	6 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0%	8
Other	3 (0)	1 (0)	3 (1)	0 (0)	2 (0)	11%	9
Parameters unknown	8 (2)	2 (1)	2X‡‡‡‡ (0)	0 (0)	10 (0)	14%	22

Numbers of electroacupuncture/transcutaneous electrical acupoint stimulation (EA/TEAS) studies located when searching PubMed for endogenous opioid mechanisms (EOM), categorised by stimulation frequency (negative studies in parentheses). X indicates a decrease in blood β-endorphin in response to stimulation.
*One low frequency (LF) study showed no involvement of κ opioid receptors.
†Four studies demonstrated decreased blood or plasma β-endorphin, one unchanged blood β-endorphin in patients with positive outcome (EA-induced ovulation) but increased β-endorphin in those who did not ovulate[8]; three other studies demonstrated altered β-endorphin activity in circulating lymphocytes.
‡In one study, GV26 was strongly stimulated.
§In one study, only weak stimulation was used.
¶In four of these studies, naloxone/naltrexone was applied during or after stimulation, in one only a low dose was used.
**Two studies involved inflammatory pain.
††In one study, prior naloxone/naltrexone potentiated EA, but applied afterwards reduced its effect; another involved inflammatory pain.
‡‡In five of these studies, stimulation was with 20 Hz trains.
§§Only positive with repeated stimulation in one study.
¶¶In three studies, effects with high frequency (HF) stimulation were less than with LF stimulation.
***In two studies, effects with HF were less than with LF stimulation.
†††In one study, naloxone was applied during stimulation.
‡‡‡In five of these studies, high-dose naloxone was used.
§§§Including 2/12 and 6/18 Hz.
¶¶¶Increase in heart muscle.
****Including 6/25, 5/30 and 10/30 Hz.
††††Naloxone/naltrexone applied after stimulation.
‡‡‡‡In one study, an initial decrease was followed (after 1 h) by an increase.
DD, dense-disperse (alternating frequencies).

Table 3 Numbers of acupuncture studies located (numbers with negative results in parentheses) from searching PubMed for endogenous opioid mechanisms (EOM)

Studies	Brain	Spinal cord	Blood	Tissue	Non-specific	Percentage negative	Total EOM studies for modality
Search for MA studies (attempted exclusion of EA)							
MA	8 (1)	2 (0)	14 (2)	1 (0)	27 (14)	33%	52
EA/TEAS:	28 (0)	4 (0)	6 (6*)	0 (0)	26 (10*)	25%	64
Search for EA studies (attempted exclusion of MA)							
MA	1 (1)	2† (0)	5‡ (4)	1 (0)	4§ (0)	38%	13
EA/TEAS All	119 (5)	52 (5)	24¶ (14)	13 (2)	59 (15**)	15%	267††

*A total of 13 of these 16 negative studies used HF (6) or low amplitude (2) EA, or TEAS (2), low dose naloxone (2), or naloxone application during rather than prior to EA (1).
†Effect less than that of EA in one study.
‡Transient effect only in one study (in contrast to EA).
§In one study,[7] only one of three (mechanised) needle techniques tested involved EOM.
¶Included nine studies showing decreased blood opioid levels following stimulation.
**A total of 11 of these 15 negative results involved 10 Hz (2) or HF(4) stimulation, low dose naloxone (1) and application of naloxone after rather than before stimulation (4).
††Several EA studies investigated more than one modality of stimulation (eg, MA and EA, or EA and TEAS).
EA, electroacupuncture; HF, high frequency; TEAS, transcutaneous electrical acupoint stimulation.

OR agonist endomorphin-1 are involved (see the extra materials in Mayor[1] for a review).

The second trend is more difficult to disentangle. Although the blood/brain barrier is relatively impermeable to endorphins,[24] they are released into the peripheral circulation from the anterior pituitary and adrenal glands in response to stress (and may also be present in circulating lymphocytes). Thus, non-stressful EA may actually reduce plasma β-endorphin when it is already raised (for instance, during surgery[25]), whereas strong EA may increase circulating β-endorphin (and result in so-called stress-induced analgesia). 'No change' might then result from the counterbalancing of the stress response by EA.

As for the third trend, HF provides 'more' stimulation (charge per second) than LF EA of the same amplitude and pulse duration,[26] so that as frequency is increased stimulation may be experienced as stronger, possibly even with greater analgesic effect.[27 28] However, most patients will not tolerate HF, high amplitude EA for any length of time, so that the total dosage delivered will in general be less than that of ALS. The apparent lack of involvement of EOM in HF stimulation can also be explained in many cases by the use of low doses of the opioid antagonists naloxone and naltrexone. As Han's group has repeatedly demonstrated, much higher levels are required to inactivate κ ORs within the spinal cord than the μ or δ ORs, and here it is the κ OR agonist dynorphin rather than the μ or δ OR agonists that is selectively released by 100 Hz EA or TEAS.[29] Thus ALS is usually explained—mostly, but not exclusively, on the basis of animal studies—as activating various endorphinergic 'long-loop' supraspinal pathways (some of which may also be involved in the EOM of MA), with μ or δ ORs involved in the spinal cord,[30] and HF or TLS as promoting dynorphin release at the spinal level (dense-disperse (DD) at 2/15 Hz may involve both mechanisms[31]).

CONCLUSIONS

EA is frequently reported in the literature, the term being used in around 18% of all published acupuncture papers located in this study. It is used increasingly frequently in clinical studies, although usage is still about twice as high in experimental as in clinical studies. In clinical RCTs, EA is most commonly reported—in ranked order (number of publications)—for musculoskeletal conditions (90), intraoperative and postoperative analgesia (64), in neurology (47), obstetrics and gynaecology (32), gastroenterology (32), psychiatry (26), genitourinary disorders (16) and peripheral motor disorders (15). It has also been used for weight loss (14) and addiction (13). Acupuncture does release endogenous opioids, but this probably depends on acupuncture 'dosage', with nearly half of MA studies being negative for EOM. In contrast, evidence on EA involvement of EOM is more consistent and convincing. In particular, different frequencies of EA appear to activate different EOM.

Acknowledgements I would like to thank Nicolas Chadwick and Gerald Dennett for help with translating technical details from studies published in Russian, Hu Xiaoyang for similar assistance with Chinese studies, various authors for responding to queries about their published work, and librarians John Moffett (Needham Research Institute, Cambridge) and Lynn Saliba (British Library, London) for their help in locating even the most obscure of references. I would also like to thank Adrian White and Mike Cummings for early PubMed searches and for their editorial suggestions, and Karen Pilkington for critical comments on earlier versions of this paper.

Competing interests This paper is a revised version of part of a commissioned chapter on EA written for a textbook on Medical Acupuncture coedited by Adrian White, Mike Cummings and Jackie Filshie, to be published by Churchill Livingstone (Elsevier).

Provenance and peer review Not commissioned; internally peer reviewed.

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