Medical Acupuncture In Pain Medicine

OBJECTIVES

1 What Critical Population Health Challenges do we face in pain medicine today?
2 How can Medical Acupuncture help to solve those challenges?

FINANCIAL DISCLOSURES

• Boston Scientific: PI - Research Support
• Mainstay Medical: PI - Research Support

OFF-LABEL / INVESTIGATIONAL USE

• NONE
1997 NIH CONSENSUS STATEMENT

| Strong Evidence | 1 Headache | 8 Dental Pain |
| Strong Evidence | 2 Fibromyalgia | 9 Menstrual Cramps |
| Strong Evidence | 3 Myofascial Pain | 10 Addiction |
| Strong Evidence | 4 Tennis Elbow | 11 Nausea/Vomiting |
| Strong Evidence | 5 Osteoarthritis | 12 Stroke Rehab |
| Strong Evidence | 6 Low Back Pain | 13 Asthma |
| Strong Evidence | 7 Carpal Tunnel Sx | |


600+ Published Clinical Trials

| Human Research | 1997 | 2010 |
| Animal Research | Large Scale RCT |
| Anti-nociceptive networks | Limbic system |
| Anti-nociceptive networks | Hypothalamus |
| Anti-nociceptive networks | Brainstem |

Fig. 1. Number of SCI-Expanded journals' papers referring to "electroacupuncture", "electroacupuncture", "acupoint", "acupunctur", and "percutaneous electrical nerve stimulation" since 1900.

Critical Challenges

- Opioid Epidemic
- Aging Population
**Fig 1. Drug Poisoning Mortality Rates by manner of death - US 1979–2002**


**Fig 2. Drug Overdose Deaths Involving Opioids by type of opioid - US 2000–2014**

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm (Accessed 8/20/2017)

2015 OPIOID RELATED DEATHS: 33,091

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C.O.T. = DIFFICULT PATIENT?

1. Behavioral
2. Social
3. Pain Mechanism
4. Physiologic
5. Genetic

The epidemiology of pain in elderly people

**ACUTE PAIN** Incidence:
- Same across age groups

**CHRONIC PAIN** Incidence:
- Increases with age
- Up to the 7th decade

Table 1: Prevalence of pain according to demographic and health characteristics in adults 65 years and older

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. in the United States with pain</th>
<th>% Prevalence of pain (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total in the older adult population</td>
<td>59,660,000</td>
<td>52.5 (51.5–54.3)</td>
</tr>
</tbody>
</table>

Bothersome pain afflicts half of the community-dwelling US older adult population and is associated with significant reduction in physical function, particularly in those with multisite pain.


Fig 5a: Most Commonly Reported Body Locations And Causes Of Pain

Case 1

- 55 yo M
- Top-Gun Instructor
- Commercial Pilot
- Cockpit Ejection
- Neck Trauma
- s/p 8 Neck Surgeries
- s/p Lumbar Discectomy

PRESENTATION:
- Rt Neck Pain ➔ Scapula
- Rt Headache ➔ Eye
- LBP ➔ Right Great Toe
- Fatigue
- Insomnia
- Agitation
- Depression

Electroacupuncture suppresses a nociceptive reflex: naltrexone prevents but does not reverse this effect.

Suppression of noxious responses in single neurons of cat spinal cord by electroacupuncture and its reversal by the opiate antagonist naloxone.

Electroacupuncture treatment of morphine-dependent mice reduces signs of withdrawal, without showing cross-tolerance.

Increased cerebrospinal fluid levels of endorphins after electro-acupuncture.

Low CSF met-enkephalin levels in cluster headache are elevated by acupuncture.

C-fos expression in the hypothalamo-pituitary system induced by electroacupuncture or noxious stimulation.

Increased beta-endorphin but not met-enkephalin levels in human cerebrospinal fluid after acupuncture for recurrent pain.

Acupuncture in heroin addicts; changes in Met-enkephalin and beta-endorphin in blood and cerebrospinal fluid.

Neurochemical basis of acupuncture analgesia.

Electroacupuncture markedly increases proenkephalin mRNA in rat striatum and pituitary.

Increased release of immunoreactive CCK-8 by electroacupuncture and enhancement of electroacupuncture analgesia by CCK-B antagonist in rat spinal cord.

Interacting brain stem components of opiate-activated, descending, pain-inhibitory systems.

Experimental basis of acupuncture analgesia.

C-fos expression in spinal cord and brainstem following noxious stimulation and electroacupuncture plus noxious stimulation.

Electroacupuncture elevates blood cortisol levels in naive horses; sham treatment has no effect.

A mesolimbic loop of analgesia. A neuronal pathway from nucleus accumbens to periaqueductal gray.

Increased release of serotonin during electroacupuncture of spinal cord nerve roots in rats; effects blocked by L-glutamate injections into forebrain structures.


ACUPUNCTURE PHYSIOLOGY

- Naloxone Reversal of Acup. Analgesia
- CSF & Serum Endorphin Levels
- Reversal of Opioid Withdrawal

Early Acupuncture Research

A Meta-Analysis of Acupuncture Combined with Opioid Receptor Agonists for Treatment of Opiate-Withdrawal Symptoms

Yingfeng Liu - Ju Shi - Daxiao H. Liu

- Meta Analysis: 11 RCT
- N= 1105
- Heroin Addiction / Detox
- POM: WITHDRAWAL SYMPTOM SCORE

WITHDRAWAL SYMPTOMS

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>WMD</th>
<th>95% CI</th>
<th>NR(p=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.21</td>
<td>-0.58, 0.90</td>
<td>12.09</td>
</tr>
<tr>
<td>1</td>
<td>-0.32</td>
<td>-0.65, 0.00</td>
<td>16.42</td>
</tr>
<tr>
<td>2</td>
<td>-0.30</td>
<td>-0.63, 0.03</td>
<td>1.76</td>
</tr>
<tr>
<td>3</td>
<td>-0.44</td>
<td>-0.78, 0.00</td>
<td>2.37</td>
</tr>
<tr>
<td>4</td>
<td>-0.50</td>
<td>-0.83, 0.00</td>
<td>3.09</td>
</tr>
<tr>
<td>5</td>
<td>-0.50</td>
<td>-0.83, 0.00</td>
<td>3.61</td>
</tr>
<tr>
<td>6</td>
<td>-0.50</td>
<td>-0.83, 0.00</td>
<td>4.12</td>
</tr>
<tr>
<td>7</td>
<td>-0.50</td>
<td>-0.83, 0.00</td>
<td>4.63</td>
</tr>
<tr>
<td>8</td>
<td>-0.50</td>
<td>-0.83, 0.00</td>
<td>5.14</td>
</tr>
</tbody>
</table>

Fig. 1. Efficacy of acupuncture therapy plus opioid receptor agonists (A+ORA) versus ORA in alleviating opioid withdrawal symptoms. The success rate of the weighted mean differences (WMDs) and their 95% CIs are given by day. D0 indicates the baseline, and D1 was analyzed with fixed-effect models. The other time points were analyzed with random-effect models. NR indicates the failsafe number, i.e., the number of unpublished negative studies that would be required to negate each significant finding at an alpha level of 0.05.

AT + ORA > ORA

P = 0.05

WITHDRAWAL SYMPTOMS

Efficacy of AT plus ORA compared with ORA in alleviating opioid withdrawal symptoms.
Fig. 2 Efficacy of acupuncture therapy plus opioid receptor agonists (AT ± ORA) versus ORA in reducing rate of relapse at 6 months. Summary estimates of the relative risk (RR) and its 95% CI were analyzed with random-effect Models.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>AT+ORA</th>
<th>ORA</th>
<th>RR (random)</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang 2016 B</td>
<td>16/60</td>
<td>20/44</td>
<td>1</td>
<td>25.07 (9.29, 67.77)</td>
<td>39.67</td>
</tr>
<tr>
<td>McEvedy et al. 2017</td>
<td>47/76</td>
<td>46/75</td>
<td>1</td>
<td>25.07 (9.29, 67.77)</td>
<td>39.67</td>
</tr>
<tr>
<td>Total (66%)</td>
<td>112/240</td>
<td>166/229</td>
<td>1</td>
<td>25.07 (9.29, 67.77)</td>
<td>39.67</td>
</tr>
</tbody>
</table>

Test for heterogeneity: X^2 = 4.15 (df = 1) (P = 0.041), I^2 = 10.2%

Test for overall effect: Z = 1.00 (P = 0.15)

### Acupuncture for chronic pain and depression in primary care: a programme of research

Hugh MacPherson,^1,4 Andrew Vickers,^2 Martin Bland,^1 David Torgerson,^1 Mark Corbett,^7 Eldon Spackman,^4 Pedro Saramago,^8 Beth Woods,^9 Helen Weatherley,^4 Mark Sculpher,^4 Andrea Mance,^4 Stewart Richmond,^1 Ann Hopkin,^1 Janet Eldred^1 and Ian Watt^1

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^3Centre for Reviews and Dissemination, University of York, York, UK
^4Centre for Health Economics, University of York, York, UK
^5Department of Health Sciences, York Medical School, University of York, York, UK

### Effect size of acupuncture for chronic pain

IS ACUPUNCTURE PLACEBO?

- 29 High-Quality RCT / 955 Screened
- 17,922 Patients
- IPD – Individual Patient Data Meta Analysis
Our principal finding is that there are statistically significant differences between acupuncture and sham acupuncture, and between acupuncture and non-acupuncture controls for all of the pain types studied.

**TABLE 2 Primary analyses of effect sizes**

<table>
<thead>
<tr>
<th>Indication</th>
<th>n</th>
<th>Fixed effects (95% CI)</th>
<th>Non-significant</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture vs. sham acupuncture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back and neck</td>
<td>8</td>
<td>0.81 (0.67 to 0.95)</td>
<td>0.67 (0.52 to 0.86)</td>
<td>0.80 (0.57 to 0.93)</td>
</tr>
<tr>
<td>Chronic headache</td>
<td>5</td>
<td>0.62 (0.51 to 0.73)</td>
<td>0.62 (0.50 to 0.75)</td>
<td>0.81 (0.57 to 0.93)</td>
</tr>
<tr>
<td>Shoulder pain**</td>
<td>3</td>
<td>0.62 (0.49 to 0.77)</td>
<td>0.62 (0.49 to 0.77)</td>
<td>0.81 (0.57 to 0.93)</td>
</tr>
</tbody>
</table>

*Sham acupuncture vs. no acupuncture control

<table>
<thead>
<tr>
<th>Indication</th>
<th>n</th>
<th>Fixed effects (95% CI)</th>
<th>Non-significant</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back and neck</td>
<td>7</td>
<td>0.33 (0.25 to 0.41)</td>
<td>0.33 (0.25 to 0.41)</td>
<td>0.81 (0.57 to 0.93)</td>
</tr>
<tr>
<td>Chronic headache</td>
<td>6</td>
<td>0.62 (0.51 to 0.73)</td>
<td>0.62 (0.50 to 0.75)</td>
<td>0.81 (0.57 to 0.93)</td>
</tr>
<tr>
<td>Shoulder pain**</td>
<td>5</td>
<td>0.62 (0.49 to 0.77)</td>
<td>0.62 (0.49 to 0.77)</td>
<td>0.81 (0.57 to 0.93)</td>
</tr>
<tr>
<td>MUSCULOSKELETAL PAIN</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Figure 2** Forest plots comparing acupuncture with no acupuncture controls (see Table 2 for references): (a) osteoarthritis; (b) chronic headache; and (c) musculoskeletal pain. No forest plot is available for shoulder pain as there were fewer than three trials and therefore no meta-analysis was performed. TTH, tension-type headache.

**Figure 3** Forest plots comparing acupuncture with sham acupuncture (see Table 2 for references): (a) osteoarthritis; (b) chronic headache; (c) musculoskeletal pain; and (d) shoulder pain. TTH, tension-type headache.
**EFFECT SIZE OF ACUPUNCTURE FOR CHRONIC PAIN**

**IS ACUPUNCTURE PLACEBO?**

- ACU statistically superior to Sham-ACU Control
- ACU statistically superior to Non-ACU Controls
- Differences were clinically meaningful
  - Standardized Differences
  - Pain Scale

**KNEE OA: Physical Interventions**

- Among most common pain syndromes
- Among the best indications for ACU

- Network Meta-Analysis
- Standardized Mean Differences in Effect
- Variety of Treatments for Knee Pain

**KNEE OA: Physical Interventions**

- **Studies of Any Quality**
- **TX vs Standard Care**
- **Standardized Mean Differences**
  - 8/22 statistically superior to SOC
  - **ACU- superior to all**
  - Except Interferential Tx- (1 Study)
FIGURE 7: Standardised mean differences of each treatment compared with acupuncture for the analysis including studies of any quality. Numbers in parentheses indicate the numbers of studies. AE EX, aerobic exercise; BAL, balneotherapy; BRA, braces; HEA, heat treatment; ICE, ice/cooling treatment; INS, insoles; INT, inferential therapy; LAS, laser therapy; MAG, static magnets; MAN, manual therapy; MU EX, muscle-strengthening exercise; NO MED, no intervention; PLA, placebo; SH ACU, sham acupuncture; STC, standard care; TAI, t’ai chi; WEI, weight loss.

KNEE OA: Physical Interventions

- Studies of Any Quality
- TX vs ACU
- Standardized Mean Differences

- ACU- superior to all
- Except Interferential Tx- (1 Study)

FIGURE 8: Standardised mean differences of each treatment compared with standard care for the analysis including studies of better quality. Numbers in parentheses indicate the numbers of studies. ACU, acupuncture; AE EX, aerobic exercise; BAL, balneotherapy; MU EX, muscle-strengthening exercise; NO TREAT, no intervention; SH ACU, sham acupuncture; STC, standard care; TAI, t’ai chi; WEI, weight loss.

KNEE OA: Physical Interventions

- Better-Quality Studies
- TX vs Standard Care
- Standardized Mean Differences

- ACU- superior to all

FIGURE 9: Standardised mean differences of each treatment compared with acupuncture for the analysis including better-quality studies. Numbers in parentheses indicate the numbers of studies. ACU, acupuncture; AE EX, aerobic exercise; BAL, balneotherapy; MU EX, muscle-strengthening exercise; NO TREAT, no intervention; SH ACU, sham acupuncture; STC, standard care; TAI, t’ai chi; WEI, weight loss.

KNEE OA: Physical Interventions

- Better-Quality Studies
- TX vs ACU
- Standardized Mean Differences

- ACU- superior to all
KNEE OA: Physical Interventions

Based on current evidence:

- ACU is one of the more effective physical modalities for pain due to knee OA
- Data is for short-term relief
- Overall strength of data for most interventions was weak

Chapter 6: Acupuncture, Counselling or Usual Care for Depression (ACUDep): a randomised controlled trial

- 3-Arm RCT
  - 2 (266) ACU+ Usual Care
  - 2 (231) Counselling+ Usual Care
  - 1 (151) Usual Care Alone

- Mod – Sev Depression w/in 5 years (BDI-II > 20)
- Concealed Allocation (Blinded Investigators)
- Up to 12 sessions Tx offered (Acu or Counselling)
- POM: PHQ-9 @ 3 mo (PH Health Questionnaire-9 items)
- F/U: 3, 6, 9, 12 mo

Programme Grant A5 3 2017 (53)

<table>
<thead>
<tr>
<th>TABLE 36</th>
<th>Effect of trial arm on PHQ-9 depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acu &gt; UC P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Counsel &gt; UC P = 0.008</td>
</tr>
<tr>
<td></td>
<td>ACU – Counsel P = 0.140</td>
</tr>
</tbody>
</table>
**FIGURE 28** Mean PHQ-9 scores by treatment, comparing the pain and no-pain groups

(a) patients with moderate to extreme pain at baseline (n = 384)

(b) patients pain free at baseline (n = 371)

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Why Functional Connectivity (FC)?

1. Chronic pain - disrupt FC [1-4]
2. ACU - modulate FC [7-16]
3. Analgesics - modulate FC [17,18]
4. FC - useful tool in acupuncture & chronic pain research

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SUBJECTS
1. Mod-Sev Knee OA Grade 2 or 3 Kellgren-Lawrence Scale
2. Acupuncture Naïve
3. No Interventions x6 MO

RANDOMIZATION
1. ACU
   • High Dose - 6 points
   • Low Dose - 2 points
2. Sham ACU
   • No Interventions x6 MO
   • Placebo Needles

METHODS
1. 6 ACU TX in 1 MO
2. Tx 1, 3, 6 in fMRI (3T)
3. POM: KOOS- Pain, Fxn (Knee injury and Osteoarthritis Outcome Score)
4. Blinded Subjects
5. Blinded Investigators

BLINDING MAINTAINED?
90% Believed needle inserted all sessions
10% Believed needle not inserted
• Real ACU- Low Dose

Figure 3: Changes in KOOS subscale scores from baseline to endpoint. Improvement in each of the 5 domains is indicated by a positive value. (a) The interaction between group (high versus low versus sham) and time (baseline versus endpoint) showed a trend for the KOOS pain subscale (F(2, 27) = 2.709, P = .085) but not for either function in daily living (F(2, 27) = 1.778, P = .193) or function in sport (F(2, 26) = 2.441, P = .149). (b) The interaction between group (real versus sham) and time (baseline versus endpoint) was significant for the KOOS subscale scores for pain (F(1, 28) = 5.936, P = .025), function in sport (F(1, 27) = 4.232, P = .049), and quality of life (QOL) (F(1, 28) = 4.852, P = .039).

Fig. 1. Comparison of the pre-acupuncture scans in treatments 6 and 1. (a) Connectivity between the right frontoparietal network and the rACC increases more in the verum group than in the sham group. (X = 12) (b) Executive control network showed stronger connectivity with rACC after treatment in the verum group than in the sham group. (X = 4) (c) Sensory-motor network showed reduced connectivity with dACC after real acupuncture treatment compared with sham group. (X = −8) (d) Results in a, b, c controlled for age and duration of pain.

rFPN = Right Frontal Parietal Network
ECN = Executive Control Network
SMN = Sensori Motor Network
rACC = Rostral Anterior Cingulate Cortex
MPFC = Medial Prefrontal Cortex
dACC = dorsal Anterior Cingulate Cortex

Verum ACU > Sham ACU (Tx + Time)

<table>
<thead>
<tr>
<th></th>
<th>rFPN</th>
<th>ECN</th>
<th>SMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++ FC</td>
<td>+++ FC</td>
<td>- - - FC</td>
<td></td>
</tr>
<tr>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Shown in green: after treatment, the increase in functional connectivity between the rFPN and left insula/putamen positively correlated with the change in KOOS pain scores. Shown in red: the verum group showed significant increase in connectivity between the rFPN and left insula/putamen compared to sham group. (X = −30) (d) Results in a after adjusting for age and duration of pain. The comparison between verum and sham shown in red were at a less conservative threshold of voxel-wise Z > 1.96 and a corrected cluster significance threshold of P < 0.05.

FC $\propto$ Clinical Outcome
- Regression Analysis
  - r = 0.61
  - P < 0.001

Qi $\propto$ FC?
Case 1

DIAGNOSIS:
- Cervical Dystonia
- Myofascial Pain
- Cervical Spondylosis
- Opioid Induced Hyperalgesia
- Opioid Induced Hypogonadism
- Depression / Anxiety
- Lumbar Radiculopathy
- Lumbar Spondylosis

TIME | ACU Tx | DOSE | OUTCOME
---|---|---|---
0-3 MO | Q 3 D X 1 MO, Q 1 Wk X 1 MO, Q 2 Wk X 1 MO | MSO4 600 mg/Day, ↓ MSO4 360 mg/Day | ↓ Pain 30%-40%, ↑ Sleep, ↑ Mood, ↑ Cognition/ Memory
3-12 MO | Q 4 Wk, Drug Holiday | MSO4 ↓ 300 mg/Day | ↓ Pain 40%-50%, Mood Normalized, ↑ Energy (Hormone Repl), ↑ Exercise
1-8 YR | Q 4 Wk | MSO4 300 mg/Day | Pain Stable/ Tolerable, Mood Stable, Stopped Interventions

TIME | ACU Tx | DOSE | OUTCOME
---|---|---|---
Age 65 | Medicare Beneficiary, Lost Acupuncture Coverage, Chose to Pay Out of Pocket, But reduce # Treatments | | |
9-14 YR | Quarterly Sch: 1st MO - ACU, 2nd MO - TPI | MSO4 300 mg/Day, ↓ MSO4 120-180 mg/Day | ↓ Pain Euthymic, ↑ Energy
Two Decades of Transformation

CRITICAL CHALLENGES
- Opioid Epidemic
- Aging Population
- Chronic Pain
- Disability
- Health Economics

UNPRECEDEMT ADVANCES
- Rapid
- Rigorous
- Quality
- Intrinsic Opioids
- Musculoskeletal

Time for Integrative Solutions

ACUPUNCTURE
- Permanent Addition to Tool Box
- Full Potential :: Fully Integrated