How to Identify Low Value and Ineffective Medical Care

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Disclosure

Funding:

@vpplenarysesh
Disclosure

• Some of this talk is controversial.
• It is not my purpose to disparage any particular practice
• Broad patterns of medical progress/innovation/evidence (& hijacked) and missteps in medicine
What is Medical Reversal?

Often in medicine new practices replace older ones.

H2 -> PPI
MOMP -> MOPP -> ABVD
Streptokinase -> TPA -> PCA BM stent/-> drug eluting
What is Medical Reversal?

Many other times, something we had been doing is found to be no better or worse than a prior or lesser standard of care (incd. doing nothing)

Routine use of Swan Ganz for monitoring ICU patients
Routine HT for post-menopausal women
Routine PCA for stable angina
What is Medical Reversal?

Is much more like this....
Definition of Medical Reversal

A large, well done study; typically RCT (with better blinding/controls/ power/ endpoints aka less bias) contradicts current medical practice.
Talk outline

- Select examples of reversal
- Frequency estimates
- Harms
- Origins
- Solutions
- Objections
- What will EBM look like in the age of recognition of Medical Reversal
Talk outline

• Select examples of reversal
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Atherosclerotic plaque buildup:

- Fat, calcium, and immune cells
Renal artery narrowed by plaque deposits

Stent placed to restore blood flow
Revascularization versus Medical Therapy for Renal-Artery Stenosis

The ASTRAL Investigators

A First Renal Event

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Patients with Renal Event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical therapy</td>
</tr>
<tr>
<td>0</td>
<td>10</td>
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<tr>
<td>1</td>
<td>20</td>
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<td>50</td>
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<td>5</td>
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No. at Risk

<table>
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<tr>
<th></th>
<th>Revascularization</th>
<th>Medical therapy</th>
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<tbody>
<tr>
<td>Years since Randomization</td>
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<td>99</td>
<td>84</td>
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<td>39</td>
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B First Cardiovascular Event

<table>
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<tr>
<th>Years since Randomization</th>
<th>Patients with Cardiovascular Event (%)</th>
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<tbody>
<tr>
<td></td>
<td>Medical therapy</td>
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<th>Medical therapy</th>
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<tbody>
<tr>
<td>Years since Randomization</td>
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<td>133</td>
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<td>3</td>
<td>77</td>
<td>61</td>
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<tr>
<td>4</td>
<td>33</td>
<td>27</td>
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</tbody>
</table>

Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cullip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators

Stent plus medical therapy | Medical therapy alone

Event-free Survival (%)

Hazard ratio with stenting, 0.94 (95% CI, 0.76–1.17) P=0.58 by log-rank test

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Stent plus medical therapy</th>
<th>Medical therapy alone</th>
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</thead>
<tbody>
<tr>
<td>Years from Enrollment</td>
<td>459</td>
<td>472</td>
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<tr>
<td>0</td>
<td>362</td>
<td>371</td>
</tr>
<tr>
<td>1</td>
<td>318</td>
<td>314</td>
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<td>224</td>
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<td>3</td>
<td>131</td>
<td>115</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>40</td>
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</table>

Medical therapy alone

Stent plus medical therapy

Medical therapy
Steroid injection for spinal stenosis
Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial.


<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise time (s)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients assessed</td>
<td>104</td>
<td>90</td>
</tr>
<tr>
<td>Pre-randomisation</td>
<td>528.0 (178.7)</td>
<td>490.0 (195.0)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>556.3 (178.7)</td>
<td>501.8 (190.9)</td>
</tr>
<tr>
<td>Increment (pre-randomisation to follow-up)</td>
<td>28.4 (95% CI 11.6 to 45.1)</td>
<td>11.8 (95% CI -7.8 to 31.3)</td>
</tr>
<tr>
<td>Difference in increment between groups</td>
<td>16.6 (95% CI -8.9 to 42.0)</td>
<td>..</td>
</tr>
<tr>
<td>p value</td>
<td>0.200</td>
<td>..</td>
</tr>
</tbody>
</table>
Talk outline

• Select examples of reversal
• **Frequency estimates**
• Harms
• Origins
• Solutions
• Objections
• What will EBM look like in the age of recognition of Medical Reversal
A Decade of Reversal: An Analysis of 146 Contradicted Medical Practices

Vinay Prasad, MD; Andrae Vandross, MD; Caitlin Toomey, MD; Michael Cheung, MD; Jason Rho, MD; Steven Quinn, MD; Satish Jacob Chacko, MD; Durga Borkar, MD; Victor Gall, MD; Senthil Selvaraj, MD; Nancy Ho, MD; and Adam Cifu, MD

Abstract

Objective: To identify medical practices that offer no net benefits.

Methods: We reviewed all original articles published in 10 years (2001-2010) in one high-impact journal. Articles were classified on the basis of whether they addressed a medical practice, whether they tested a new or existing therapy, and whether results were positive or negative. Articles were then classified as 1 of 4 types: replacement, when a new practice surpasses standard of care; back to the drawing board, when a new practice is no better than current practice; reaffirmation, when an existing practice is found to be better than a lesser standard; and reversal, when an existing practice is found to be no better than a lesser therapy. This study was conducted from August 1, 2011, through October 31, 2012.

Results: We reviewed 2044 original articles, 1344 of which concerned a medical practice. Of these, 981 articles (73.0%) examined a new medical practice, whereas 363 (27.0%) tested an established practice. A total of 947 studies (70.5%) had positive findings, whereas 397 (29.5%) reached a negative conclusion. A total of 756 articles addressing a medical practice constituted replacement, 165 were back to the drawing board, 146 were medical reversals, 138 were reaffirmations, and 139 were inconclusive. Of the 363 articles testing standard of care, 146 (40.2%) reversed that practice, whereas 138 (38.0%) reaffirmed it.

Conclusion: The reversal of established medical practice is common and occurs across all classes of medical practice. This investigation sheds light on low-value practices and patterns of medical research.
How often does it happen?

- 2044 Articles
- 1344 (65.8%) Concern a medical practice
How often does it happen?

2044 Articles

1344 (65.8%) Concern a medical practice

981 (73.0%) Test a new practice
How often does it happen?

**FIGURE 1.** A breakdown of articles concerning a medical practice.
How often does it happen?

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FIGURE 1. A breakdown of articles concerning a medical practice.
How often does it happen?
We detail all 146 Reversals in the Supplementary Appendix.

TABLE 2. Key Reversals, 2001-2010

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial treatment in diabetic women with asymptomatic bacteriuria (Harding et al. 48, 2002)</td>
<td>In contrast to European societies, several groups 49, 50 in the United States recommended screening and treating for asymptomatic bacteriuria in women with diabetes. This randomized trial found that although this practice leads to more antibiotic use, it did not reduce complications or improve the time to symptomatic infection.</td>
</tr>
<tr>
<td>Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer (Van Herpen et al. 51, 2003)</td>
<td>Multiple studies have claimed that high-dose chemotherapy with stem cell transplantation improves disease-free survival at 3 years to 65%-70%, an improvement of 20%-30% beyond standard adjuvant chemotherapy. 52, 53 High-dose chemotherapy and autologous stem cell transplantation became a common, costly, and controversial practice for more than a decade. This trial randomized patients with primary breast cancer with involvement of at least 10 ipsilateral axillary lymph nodes to standard adjuvant chemotherapy vs adjuvant chemotherapy followed by high-dose chemotherapy and stem cell transplant. The study arm was found to breast cancer (Van Herpen et al. 51, 2003)</td>
</tr>
<tr>
<td>Control of exposure to allergen and allergic rhinitis in adults with asthma (Woodcock et al. 54, 2003)</td>
<td>The cause of vestibular neuritis is presumed to be a viral infection, 59 and yet it is unknown whether corticosteroids, an antiviral medication, or a combination of both have any benefit in treating this disease. At the time of this publication, physicians prescribed either or both. A prospective, randomized, double-blind, 2-by-2 factorial trial was performed assessing whether placebo, methylprednisolone, valacyclovir, or a combination of the 2 would improve symptoms. Only the corticosteroids, and not the antiviral, improved the recovery of patients with vestibular neuritis.</td>
</tr>
<tr>
<td>Methylprednisolone, valacyclovir, or the combination for vestibular neuritis (Strupp et al. 58, 2004)</td>
<td>Hypothermia was found to be helpful as a neurosurgical adjunct in 1955, especially for ischemic and traumatic insults. At the time of this publication, the practice was used in nearly 50% of aneurysm surgeries. 61 This large randomized study, the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST), found no improvement in neurologic outcomes with hypothermia, while noting an increase in bacterial infections with the intervention.</td>
</tr>
<tr>
<td>Mild intraoperative hypothermia during surgery for intracranial aneurysm (Todd et al. 60, 2005)</td>
<td>Although treatment guidelines recommended an initial approach of intensive medical therapy, reduction of risk factors, and lifestyle modification (optimal medical therapy) for patients with stable coronary artery disease, percutaneous coronary intervention (PCI) was still a common initial treatment strategy for patients with stable coronary artery disease at the time this study was performed. 62, 63 The authors found that PCI added to optimal medical therapy did not reduce the risk of death, myocardial infarction, or other major cardiovascular events.</td>
</tr>
<tr>
<td>Optimal medical therapy with or without PCI for stable coronary disease (Boden et al. 35, 2007)</td>
<td></td>
</tr>
</tbody>
</table>
Reversals include

• Medications/ Procedures/ Devices/ Surgeries/ Screening tests/ OTC medications/ Vitamins/ Supplements/ Treatment algorithms (P2y12 testing)/ Diagnostic instruments (Swan Ganz)/ Systems interventions/ Quality and performance measures

• In short, every corner of health care
Talk outline

- Select examples of reversal
- Frequency estimates
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- What will EBM look like in the age of recognition of Medical Reversal
What are the harms of reversal

- Harms are threefold:
- People who undergo the practice during the years it fell in favor
- People who undergo the practice during the lag time before it falls out of favor
  Ten years of inertia
- Loss of trust in medical system
What are the harms of reversal

- Harms are threefold:
  
- People who undergo the practice during the years it fell in favor
  
- People who undergo the practice during the lag time before it falls out of favor
  
  Ten years of inertia

- Loss of trust in medical system
Why is reversal problematic?

- No benefit to patients in years it was in favor
- Lag time to reversal
- Loss of trust in medical system
Why is reversal problematic?

- No benefit to patients in years it was in favor
- Lag time to reversal
- Loss of trust in medical system (mammography)
Talk outline

• Select examples of reversal
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Why does Reversal happen?

- We adopted something based on inadequate & biased studies (w/o definitive trials ongoing or forthcoming)
  - Pathophysiology alone
  - Pathophysiology plus anecdotal evidence
  - Epidemiological evidence (with residual confounding)
  - Historical controlled evidence
  - Randomized trials
    - Inappropriate controls (too young/ non representative)
    - Inappropriate dosing/ comparators/ concom. medications
    - Single center
    - Drug run periods
    - Inappropriate endpoints (surrogates)
    - Early termination
    - Selective reporting/ publication bias
  - Meta-analysis – based on caliber of included studies & completeness
Sham controls needed for subjective endpoints

- Meniscectomy for knee OA
- Debridement for knee OA
- RV pacing for HOCM
- Vertebroplasty
- Lumbar steroid injections
- PCA for stable angina (IMA ligation, Cobb)
Drug run in periods

- Test a different question: whether it is better to stay on Entresto or switch to enalapril after exposure to both agents for unequal time
Vitamin E increases all-cause mortality

Shelley Wood
November 10, 2004

**New Orleans, LA** - Driving a final nail in the coffin for vitamin E, a meta-analysis of the popular supplement indicates that doses >400 IU/day can increase the risk of death from any cause. Vitamin-E capsules typically contain 400 to 800 IU.
A new study questions whether Vitamin E supplements are really correlated with an increased mortality risk
Y = Mortality

X1 = Vitamin E exposure
X2 = Age
X3 = Sex
X4 = Race
• Y = Mortality
• X1 = Vitamin E exposure
• X2 = Age
• X3 = Sex
• X4 = Race
• X5 = Income
• Y = Mortality
• X1 = Vitamin E exposure
• X2 = Age
• X3 = Sex
• X4 = Race
• X5 = Income
• X6 = Smoking
• Y = Mortality

• X1 = Vitamin E exposure
• X2 = Age
• X3 = Sex
• X4 = Income
• X5 = Smoking
• X6 = body mass index (BMI), hypertension, diabetes, cholesterol, alcohol consumption, education, family history of heart disease, heart disease, any cancer, physical activity) and race/ethnicity
Data Source
NHANES 1999-2004
417 variables of interest
time to death
N=1000 (≥100 deaths)

Variable of Interest
1 SD of log(serum Vitamin D)

Adjusting Variable Set
n=13
SES (3rd tertile)
education (>HS)
race (white)
BMI (normal)
total cholesterol
any heart disease
family heart disease
any hypertension
any diabetes
any cancer
current/past smoker
[no smoking]
drink 5/day
physical activity

All-subsets Cox regression
$2^{13} = 8,192$ models

Vibration of Effects
Relative Hazard Ratio (RHR)=$HR_{gg}/HR_1$
Range of P-value (RP)= $-\log_{10}(p-value_1) + \log_{10}(pvalue_{gg})$
Observational/ Epidemiology studies can say anything
Media Coverage of Medical Journals: Do the Best Articles Make the News?

Senthil Selvaraj¹, Durga S. Borkar², Vinay Prasad³ *

¹ Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, United States of America, ² Department of Medicine, Beth Israel Deaconess - Brockton, Brockton, Massachusetts, United States of America, ³ Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, United States of America

Table 1. Characteristics of Clinical Investigations Covered by High Circulation Newspapers and High Impact Medical Journals.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Investigations from High Circulation Newspapers (N=75)</th>
<th>Investigations from High Impact Medical Journals (N=75)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal impact factor*</td>
<td>5.4 (4.1–30.0)</td>
<td>30.0 (16.7–33.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Participants, n*</td>
<td>1034 (112–17408)</td>
<td>1901 (412–32608)</td>
<td>0.14</td>
</tr>
<tr>
<td>Pharmaceutical funding, n (%)</td>
<td>5 (7)</td>
<td>12 (16)</td>
<td>0.12</td>
</tr>
<tr>
<td>Randomized controlled trials, n (%)</td>
<td>13 (17)</td>
<td>26 (35)</td>
<td>0.016</td>
</tr>
<tr>
<td>Observational studies, n (%)</td>
<td>56 (75)</td>
<td>35 (47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Studies assessing mortality, n (%)</td>
<td>17 (23)</td>
<td>19 (25)</td>
<td>0.70</td>
</tr>
<tr>
<td>Cross-sectional studies, n (%)</td>
<td>45 (60)</td>
<td>22 (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of follow-up in longitudinal studies, y*</td>
<td>1.80 (0.42–6.00)</td>
<td>1.00 (0.21–4.00)</td>
<td>0.22</td>
</tr>
<tr>
<td>Study design rating, n (%)</td>
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</tr>
<tr>
<td>1</td>
<td>13 (17)</td>
<td>30 (40)</td>
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<td>3</td>
<td>51 (68)</td>
<td>38 (51)</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>4 (5)</td>
<td>6 (8)</td>
<td></td>
</tr>
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</table>

* Randomized trials
Observational trials
Talk outline

• Select examples of reversal
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Solutions*

• New costly technologies that are being introduced to health systems are ideal for testing in RCTs
Solutions*

• New costly technologies that are being introduced to health systems are ideal for testing in RCTs

• We need to prioritize unproven medical practice (Value of information) and run a large, non-conflicted trials agenda
Solutions*

• New costly technologies that are being introduced to health systems are ideal for testing in RCTs
• We need to prioritize unproven medical practice (Value of information) and run a large, non-conflicted trials agenda
• Design and conduct of clinical trials should move to third party agency
Rapid Randomization in the TASTE Trial, with Enrollment of Most Patients Receiving Primary Percutaneous Coronary Intervention (PCI).
Adapted from the Institute of Medicine (www.iom.edu/~media/Files/ActivityFiles/Quality/Vsrt/Lst20Workshop/Presentations/Granger.pdf). The incremental cost of the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial was $300,000, or $50 for each participant who underwent randomization.
Talk outline

• Select examples of reversal
• Frequency estimates
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• Solutions

• Objections

• What will EBM look like in the age of recognition of Medical Reversal
What about RCTs of parachutes

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Main outcome measure Death or major trauma, defined as an injury severity score > 15.

Results We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.
What about RCTs of parachutes

• Two limits of the analogy
• 1. A single clear etiology (BCR-ABL)
  – Trauma –
• 2. A huge effect size
Prior “parachutes” were no such thing

Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials

Results Four randomised controlled trials with a total of 900 patients (470 antibiotic treatment, 430 appendicectomy) met the inclusion criteria. Antibiotic treatment was associated with a 63% (277/438) success rate at one year. Meta-analysis of complications showed a relative risk reduction of 31% for antibiotic treatment compared with appendicectomy (risk ratio (Mantel-Haenszel, fixed) 0.69 (95% confidence interval 0.54 to 0.89); I²=0%; P=0.004). A secondary analysis, excluding the study with crossover of patients between the two interventions after randomisation, showed a significant relative risk reduction of 39% for antibiotic therapy (risk ratio 0.61 (0.40 to 0.92); I²=0%; P=0.02). Of the 65 (20%) patients who had appendicectomy after readmission, nine had perforated appendicitis and four had gangrenous appendicitis. No significant differences were seen for treatment efficacy, length of stay, or risk of developing complicated appendicitis.

Conclusion Antibiotics are both effective and safe as primary treatment for patients with uncomplicated acute appendicitis. Initial antibiotic treatment merits consideration as a primary treatment option for early uncomplicated appendicitis.
Most medical practices don’t have large treatment effects
Some advances have been tested without RCT

When are randomised trials unnecessary? Picking signal from noise

The relation between a treatment and its effect is sometimes so dramatic that bias can be ruled out as an explanation. Paul Glasziou and colleagues suggest how to determine when observations speak for themselves

Some historical examples of treatments with dramatic effects

- Insulin for diabetes\textsuperscript{w1}
- Blood transfusion for severe haemorrhagic shock\textsuperscript{w2}
- Sulphanilamide for puerperal sepsis\textsuperscript{w3}
- Streptomycin for tuberculous meningitis\textsuperscript{w4}
- Defibrillation for ventricular fibrillation\textsuperscript{w5}
- Closed reduction and splinting for fracture of long bones with displacement
- Salicin for acute rheumatism\textsuperscript{w6}
- Neostigmine for myasthenia gravis\textsuperscript{w7}
- Tracheostomy for tracheal obstruction\textsuperscript{w8}
- Suturing for repairing large wounds
- Drainage for pain associated with abscesses
- Pressure or suturing for arresting haemorrhage
- Ether for anaesthesia
- One way valve or underwater seal drainage for pneumothorax and haemothorax\textsuperscript{w9}
- Phototherapy for skin tuberculosis\textsuperscript{w10}
- Combination chemotherapy with cisplatin, vinblastine, and bleomycin for disseminated testicular cancer
Final thought

• History has taught us that the arc of medicine bends towards higher standards of evidence
Purpose of this talk is not to litigate any *particular* practice

But to speak broadly about patterns of medical progress and missteps.

If you liked the talk, check out the book

Questions