Back to the Future – Medical Reversals with 2020 Vision

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Faculty/Presenter Disclosure

- **Presenter:** Cody Magnusson

- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

Learning Objectives

- Briefly review the concept of Medical Reversals and how they can occur in modern practice
- Review and analyze recent medical trials that question the gold standard of care, and evaluate if a reversal either has already taken place or soon will
- For fun, we'll try to predict some future reversals at the end, as a treat

WARNING

- This talk will likely contain several very bad puns and terrible jokes
- Is this professional? Debatable.
- I’m just a dumb person who makes dumb jokes
- Could I simply not do this? No, unfortunately this is a deep seated character flaw.

What is a Medical Reversal?

- A medical reversal occurs when new evidence (most often from a high-quality RCT) reveals that an existing clinical practice is ineffective (or in some cases, harmful)
  - This evidence may offer a novel treatment, a reversion to an old treatment, or reveal that no treatment is preferred
- How can this happen? Consider that many interventions:
  - have been in use since before the dawning of the robust levels of evidence we now consider standard
  - are approved based on changes in surrogate markers
  - are based on single studies with varying levels of bias
  - are based on meta-analyses of small and poor RCTs (GIGO Principal)

Examples of Historic Medical Reversals

- Flecainide post-MI
  - Was used to prevent post-MI PVCs, which were associated with sudden cardiac death
  - Usage was based on theoretical physiology in the early 80s
  - In 1991, it was finally formally tested, and CAST was published showing that flecainide actually increased mortality
- Very-Early Cancer Screening
  - Both PSA in middle-aged men and early mammography (age 40) in women were instituted to try to catch prostate and breast cancer sooner
  - After decades of use, observational studies have shown that we are catching a lot of benign pre-cancerous cells and lab values, leading to a lot of unnecessary surgeries, and both tests have been largely changed and/or discouraged.

- In 2013 Vinay Prasad and colleagues published a paper entitled “A Decade of Reversal: An Analysis of 146 Contradicted Medical Practices”
  - They screened 2044 articles published between 2001-2010
  - Within them, 363 tested a standard of care
    - 146 of those (40.2%) reversed the practice, 79 (21.8%) were inconclusive, and only 138 (38%) reaffirmed the practice
    - Reversals included the cardiac risks of COX-2 inhibitors, routine hormonal therapy in postmenopausal women, stenting for stable CAD, arthroscopic surgery for knee OA, and insertion of tympanostomy tubes in children
- 2019 update paper: “Meta-Research: A Comprehensive review of randomized clinical trials in three medical journals reveals 396 reversals”

Abscond with Aspirin!

- In 2018, also known as the Year of the Trial Dumping on ASA, 3 landmark studies evaluated use of aspirin for primary prophylaxis of cardiovascular disease in specific populations
  - ARRIVE (Lancet, Sept 2018) found that in patients at moderate risk (10-19% Framingham) of an initial CV-event, use of ASA did not confer benefit, but did have a NNH=196 for bleeding events
    - They found one significant reduction in MI as a secondary outcome, but they also ran 18 secondary analyses without adjustment for multiple testing, so the likelihood of getting a false positive was 90%. This is an important concept to remember
  - ASPREE (NEJM, Oct 2018) also found no benefit in the healthy elderly (age>70), and had a NNH=100 for major hemorrhage
  - ASCEND (NEJM, Oct 2018) found that in diabetics age >40, there was a small benefit (NNT=91), but also a harm of major bleeding (NNH=111) with nearly identical absolute risks (ARR = 1.1%, ARI =0.9%), making the usage a wash

Modern Medical Reversals

1. Vitamin D supplementation to reduce mortality, cardiovascular disease, and cancer
2. Gabapentinoids for Sciatica
3. IV vs PO Antibiotics for Osteomyelitis and Endocarditis

Routine Vitamin D Supplementation for Mortality Reduction

BECAUSE THIS TURNED INTO A THING SOMEHOW? REMEMBER BIOLOGIC PLAUSIBILITY? I MISS THAT IN SCIENCE.

Vitamin D-elightful or D-etestable?

- Routine vitamin D supplementation has been used with increasing frequency over the past decade, without rigorous evidence
- Vitamin D supplementation was once thought to reduce the risk of falls in the community dwelling elderly, but this has since been refuted
- Vitamin D deficiency was once thought to be more rampant in Canadians due to our long, sunless winters, but this has never been shown to be clinically meaningful
- Even for osteoporotic fracture prevention, the USPSTF 2018 recommendation update found that they no longer supported the use of Calcium/Vitamin D

Vitamin D-efeating D-eath?

- More recently, observational data and smaller systematic reviews have suggested mortality benefits of routine Vitamin D supplementation, only adding to how widespread its use is
  - Benefits in reducing the incidence and mortality of cancer have also been suggested
- Worst of all, Vitamin D is dirt cheap and essentially side-effect free, making it very easy to give out even with a paucity of evidence

Association between vitamin D supplementation and mortality: systematic review and meta-analysis

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2019;366:l4673
http://dx.doi.org/10.1136/bmj.l4673

Accepted: 5 July 2019

ABSTRACT

OBJECTIVE

To investigate whether vitamin D supplementation is associated with lower mortality in adults.

DESIGN

Systematic review and meta-analysis of randomised controlled trials.

DATA SOURCES

Medline, Embase, and the Cochrane Central Register from their inception to 26 December 2018.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Randomised controlled trials comparing vitamin D supplementation with a placebo or no treatment for mortality were included. Independent data extraction was conducted and study quality assessed. A meta-analysis was carried out by using fixed effects and random effects models to calculate risk ratio of death in the group receiving vitamin D supplementation and the control group.

MAIN OUTCOME MEASURES

All cause mortality.

RESULTS

reduced the risk of cancer death by 16%. Additional large clinical studies are needed to determine whether vitamin D_3 supplementation is associated with lower all cause mortality.

STUDY REGISTRATION

PROSPERO registration number CRD42018117823.

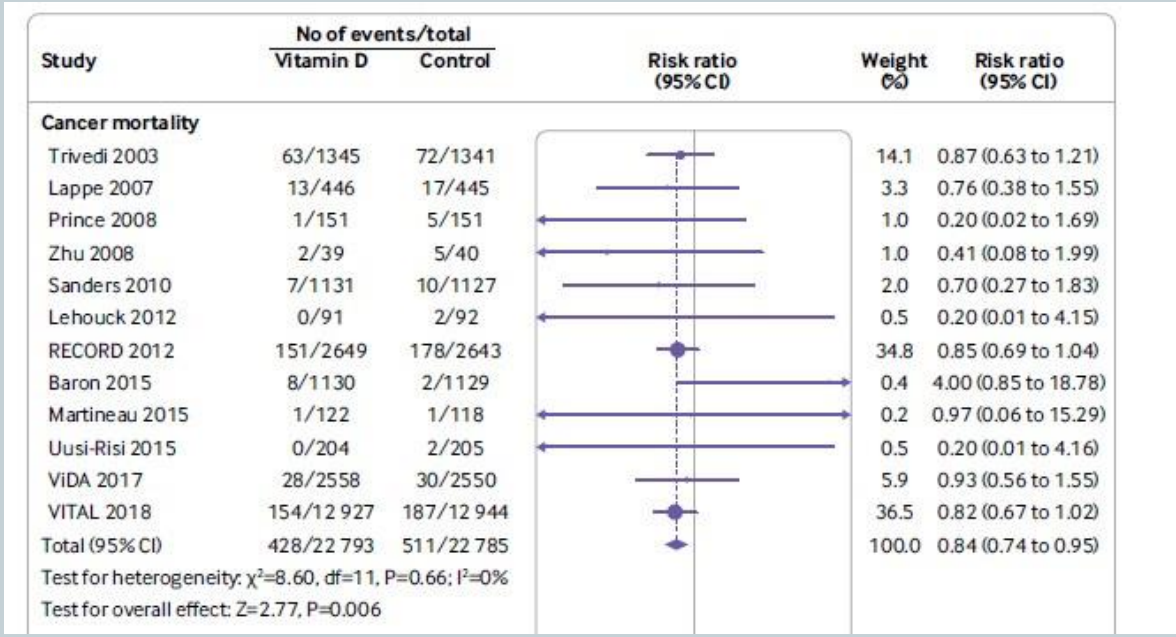
Introduction

Vitamin D supplementation has been advocated for maintaining or even improving musculoskeletal health. Evidence from observational studies indicates that low vitamin D status is associated with higher mortality from life threatening conditions such as cancer and cardiovascular disease.[1 2] Therefore, supplemental vitamin D has been viewed as a potential strategy for preventing non-skeletal chronic diseases.[3-5] If adequate vitamin D concentrations were to reduce risk of death from a wide variety of medical conditions, vitamin D supplementation would be a safe, economical, and widely available method to reduce mortality.

Clinical data examining the effect of vitamin

- Meta-analysis of 52 trials containing 75,454 patients with a median follow-up of 1.2 years
  - 14/52 trials containing 56429 patients had at least 3 years of follow-up on average
- Primary outcome was all-cause mortality
  - Secondary outcomes included cancer mortality, CV-mortality, non-cancer or non-CV mortality, cerebrovascular disease mortality, and ischemic heart disease mortality
- No difference was found for all-cause mortality
  - A small benefit (RRR=16%) in cancer mortality in a subgroup of patients taking D3 (but not D2) supplements was found
  - All other secondary outcomes were also negative

- 2 major trials show no difference, but a mess of small trials with absurd CI's somehow gain significance?
  - GIGO
- RRR=16%, but the ARR is 0.36%, giving an unimpressive NNT=278
- The authors spin this as a positive analysis
  - A mortality-benefit in a subgroup of a secondary outcome in a meta-analysis? Call me skeptical



Study	No of events/total: Vitamin D	No of events/total: Control	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
Cancer mortality					
Trivedi 2003	63/1345	72/1341		14.1	0.87 (0.63 to 1.21)
Lappe 2007	13/446	17/445		3.3	0.76 (0.38 to 1.55)
Prince 2008	1/151	5/151		1.0	0.20 (0.02 to 1.69)
Zhu 2008	2/39	5/40		1.0	0.41 (0.08 to 1.99)
Sanders 2010	7/1131	10/1127		2.0	0.70 (0.27 to 1.83)
Lehouck 2012	0/91	2/92		0.5	0.20 (0.01 to 4.15)
RECORD 2012	151/2649	178/2643		34.8	0.85 (0.69 to 1.04)
Baron 2015	8/1130	2/1129		0.4	4.00 (0.85 to 18.78)
Martineau 2015	1/122	1/118		0.2	0.97 (0.06 to 15.29)
Uusi-Risi 2015	0/204	2/205		0.5	0.20 (0.01 to 4.16)
ViDA 2017	28/2558	30/2550		5.9	0.93 (0.56 to 1.55)
VITAL 2018	154/12 927	187/12 944		36.5	0.82 (0.67 to 1.02)
Total (95% CI)	428/22 793	511/22 785		100.0	0.84 (0.74 to 0.95)
Test for heterogeneity: χ^2=8.60, df=11, P=0.66; I^2=0%					
Test for overall effect: Z=2.77, P=0.006					

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ORIGINAL ARTICLE

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

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ABSTRACT

BACKGROUND

It is unclear whether supplementation with vitamin D reduces the risk of cancer or cardiovascular disease, and data from randomized trials are limited.

METHODS

We conducted a nationwide, randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D_3 (cholecalciferol) at a dose of 2000 IU per day and marine n–3 (also called omega-3) fatty acids at a dose of 1 g per day for the prevention of cancer and cardiovascular disease among men 50 years of age or older and women 55 years of age or older in the United States. Primary end points were invasive cancer of any type and major cardiovascular events (a composite of myo-

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- P – 25,871 patients, males aged >50 and females aged >55, goal to include at least 5000 black patients, with no cancer or CVD at trial entry
- I – 2x2 factorial design of 2000 units VitD and 1 g daily of marine omega-3 fatty acids as the two interventions
- C – Placebo controlled (4 groups: D+O, D+Op, Dp+O, Dp+Op)
- O – 2 Primary endpoints were incidence of invasive cancer and MACE
  - Secondary outcomes included components of the primary (ex/ breast cancer incidence, rate of non-fatal MI, etc), cancer mortality, and an expanded-MACE
- Median follow-up was 5.3 years
  - ~137K years worth of patient data

- In the Vitamin D focussed paper, neither primary outcome was found to be significant
  - The only significant secondary outcome was death from cancer, but only once the first 2 years of follow-up was excluded in an investigation for a delayed effect
    - RRR = 25%, but ARR = 0.29% and NNT = 345
    - Once again, a subgroup of a secondary outcome (at least in a well done RCT this time?)
- However, they report that they did <u>not</u> control for multiple tests
  - So for the primary/secondary outcomes, running 19 tests at $p<0.05$ without proper adjustment has an ~95% chance of finding a false positive by statistical chance
  - By the same notion, they ran 40 patient subgroup analyses and found significant results for Cancer incidence in those with a BMI<25 and <27.1, but should have found 2 results by chance anyway

Cholecalciferol? More like dontgiveoutthisatall

- Right now, there is no good evidence for routine Vitamin D supplementation in the average patient
  - This includes the community dwelling elderly at risk of falls or osteoporotic fracture
- Vitamin D deficiency is rare, and routine testing for such is not recommended, even in Canada
- There is a small but real risk of kidney stones from excess vitamin D supplementation
  - Especially in those taking commonly used mega-doses like 100,000 units weekly/monthly
  - Risk of both this and hypercalcemia are possible in those with renal disease

Conclusion?

- Vitamin D-on't do it!
- The only signal of benefit is an incredibly small and delayed benefit to cancer mortality, but those signals should generate hypotheses for further study and not be a clinical indication
- In addition to a complete lack of benefit and the previously discussed harms, there are also the tangible harms of being on a thing rather than not
  - Cost, in acquisition dollars, health system dollars, patient/caregiver time
  - Pill burden and the mortality/morbidity risks of polypharmacy
  - Clout/Capital as a provider
    - How many of you have heard "I'm not taking anything else, if you want to add something you need to get rid of something else!!"

Gabapentinoids for the Treatment of Sciatica

IN WHICH I COULDN'T THINK OF ANY GOOD PUNS BEYOND "GABA SOUNDS LIKE ABBA" SO I JUST STARTED WEDGING SONG LYRICS IN BECAUSE I HAVE SHTICK TO ABIDE BY

Mamma Mia! Here we Gabago again…

- Gabapentin and other gabapentinoid drugs (pregabalin, mirogabalin) are widely used for varying types of neuropathic pain with mixed levels of evidence
- Sciatica lifetime incidence is as high as 40%, and is likely the most common form of neuropathic pain
- Because of this, gabapentinoids are widely used for sciatic nerve pain disorders, but have not been widely studied
  - Across the board, epidemiologic evidence has shown use of pregabalin/gabapentin increasing without much evidence
  - Further, gabapentinoids are become more common as drugs of abuse/misuse as well
- Several treatment guidelines, including the most recent 2017 NICE LBP/Sciatica guideline, recommend considering neuropathic pain agents after NSAIDs/weak opioids

Take a Chance on Me?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 23, 2017 VOL. 376 NO. 12

Trial of Pregabalin for Acute and Chronic Sciatica

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ABSTRACT

BACKGROUND

Sciatica can be disabling, and evidence regarding medical treatments is limited. Pregabalin is effective in the treatment of some types of neuropathic pain. This study examined whether pregabalin may reduce the intensity of sciatica.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial of pregabalin in patients with sciatica. Patients were randomly assigned to receive either pregabalin at a dose of 150 mg per day that was adjusted to a maximum dose of 600 mg per day or matching placebo for up to 8 weeks. The primary outcome was the leg-pain intensity

From the George Institute for Global Health and Sydney Medical School (S.M., C.G.M., J.L., L.B., S.J., C.-W.C.L.) and Faculty of Pharmacy and Centre for Education and Research on Ageing (A.J.M.), University of Sydney, Faculty of Medicine and Health Science, Macquarie University (M.J.H.), the Ingham Institute for Applied Medical Research, South Western Sydney Clinical School (I.H.), and St. Vincent's Clinical School (R.O.D.), Faculty of Medi-

Gimme! Gimme! Gimme! A well designed RCT.

- Also known as the PRECISE (Pregabalin in Addition to Usual Care for Sciatica) trial
  - $20 to anyone that can figure out how they spelled PRECISE from those letters in that order
- P – 204 Patients age >18 with mod/severe sciatica lasting >1 wk but <1 yr
- I – Pregabalin 75 mg BID (titrated weekly by 150 mg/day to a max of 600 mg/day)
- C – Placebo
- O – Average leg-pain over the last 24 hours by a 0-10 NPRS at 8 weeks
  - Secondary outcomes include a week 52 pain score, disability score (RDQS), back pain intensity, global perceived effect, quality of life score (SFHS), workplace absenteeism, and health care utilization

Thank You for the Evidence

- At both 8 and 52 weeks, there were no significant differences in any of the primary or secondary outcomes
  - Post-hoc analysis of use of additional pain medications was also no different
- 80% of patients were in the acute group of leg pain lasting <3 months
  - Previous trials in chronic patients have also shown no effect
- There were significantly more adverse events in the pregabalin group (227 in 68 patients) vs the placebo group (124 in 43 patients)
  - Almost entirely driven by dizziness
  - No difference in serious adverse events

What about for all the non-Dancing Queens?

Research

JAMA Neurology | Original Investigation

Effect of Gabapentin vs Pregabalin on Pain Intensity in Adults With Chronic Sciatica

A Randomized Clinical Trial

Kelvin Robertson, BPharm, MClinTRes; Laurence A. G. Marshman, MBBS, MD; David Plummer, MBBS, PhD; Elena Downs, MBBS

Supplemental content

IMPORTANCE Optimal pharmacologic treatment for chronic sciatica (CS) is currently unclear. While gabapentin (GBP) and pregabalin (PGB) are both used to treat CS, equipoise exists. Nevertheless, pharmaceutical regulation authorities typically subsidize one drug over the other. This hinders interchange wherever the favored drug is either ineffective or ill-tolerated.

OBJECTIVE To assess GBP vs PGB head to head for the treatment of CS.

DESIGN, SETTING, AND PARTICIPANTS A preplanned interim analysis of a randomized, double-blind, double-dummy crossover trial of PGB vs GBP for management of CS at half the estimated final sample size was performed in a single-center, tertiary referral public hospital. A total of 20 patients underwent randomization from March 2016 to March 2018, and 2 were excluded with 1 lost to follow-up and the other requiring urgent surgery unrelated to the study. Patients attending a specialist neurosurgery clinic with unilateral CS were considered for trial recruitment. Chronic sciatica was defined as pain lasting for at least 3 months

Fernando! (I don't have a joke that's just a good song)

- P – 18 patients >age 18with chronic (>3 months) sciatica
- I/C – Crossover design with 1 week washout, groups were:
  - Gabapentin 400-800 mg TID
  - Pregabalin 150-300 mg BID
- O – Primary outcome was leg pain from 0-10 by VAS
  - Key secondary outcome was the Oswestry Disability Index questionnaire

- This trial cites the last trial in it's introduction claiming it had too many acute patients
  - Note that 20% of the last trial population is ~41 patients, which is still over double the size of this trial

Does Your Mother Know?

- That at 8 weeks, gabapentin reduced pain significantly better than pregabalin but was not superior for disability scores
- Gabapentin reduced pain by 1.72cm (SD=1.17 cm) and pregabalin by 0.94 (1.09)
  - This trial chose a 1.5 cm change on the VAS as a MCID based on a single emergency medicine trial, but referencing a variety of literature reveals values from 1-3cm, or more commonly a 30% change, so the whether either is clinically important is questionable
    - Remember that a 95%CI comprises 1.96SD in either direction, so both scores would cross 0
- Disability scores were also not significantly clinically important changes

- Fun Fact: This trial was stopped early for significant signs of superiority on the first interim analysis. Woof.

When All is Said and Done…

- Sciatica is not treatable with gabapentinoid drugs
- There is a very small chance that gabapentin may have a very small effect in chronic sciatica, but the rate of adverse reactions likely mean the risk-benefit ratio is not favourable
- In the first trial, the authors actually posit that sciatica may not truly be "neuropathic pain" despite the nerve involvement, due to it's difference in causal physiology and lack of response to agents that are otherwise effective for neuropathic pain

Oral vs Intravenous Antibiotics for Osteomyelitis and Endocarditis

I'VE GOT A 'BONE' TO PICK WITH PEOPLE THAT PRESCRIBE WITH THEIR 'HEART' INSTEAD OF WITH THE EVIDENCE

What you don't know can heart you

- Both osteomyelitis and endocarditis have long been treated predominantly with IV antibiotics of at least 4-6 weeks, based on a belief that the IV route is inherently superior
  - This started in the 60s and 70s when having evidence of your claims before stating a standard of care was largely optional
- IV therapy is associated with prolonged hospital stays, increased risk of complications including secondary bacteremia, and greatly increased costs
  - Outpatient IV clinics avoid institutionalization, but still carry all the other risks

A Joint Evaluation

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

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ABSTRACT

BACKGROUND

The management of complex orthopedic infections usually includes a prolonged course of intravenous antibiotic agents. We investigated whether oral antibiotic therapy is noninferior to intravenous antibiotic therapy for this indication.

METHODS

We enrolled adults who were being treated for bone or joint infection at 26 U.K. centers. Within 7 days after surgery (or, if the infection was being managed without surgery,

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. M. Scarborough at Microbiology Level 6, John Radcliffe Hospital, Oxford OX3 9DL, United Kingdom.

*A complete list of the OVIVA trial collaborators is provided in the Supplementary

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2019 VOL. 380 NO. 5

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

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ABSTRACT

BACKGROUND

Patients with infective endocarditis on the left side of the heart are typically treated with intravenous antibiotic agents for up to 6 weeks. Whether a shift from intravenous to oral antibiotics once the patient is in stable condition would result in efficacy and safety similar to those with continued intravenous treatment is unknown.

METHODS

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Bundgaard at the Department of Cardiology B 2141, the Heart Center, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark, or at henning.bundgaard@

There's nothing humerus about antibiotic stewardship

- P – 1054 patients age >18 with a bone or joint infection normally needed 6 weeks of IV Abx
  - NB: prosthetic joints were included
- I – Oral antibiotics x 6 weeks
- C – IV antibiotics x 6 weeks
- O – Primary: definitive treatment failure within 1 year
  - Key Secondary: probable/possible failure, early discontinuation of Tx, IV-line complications, C diff, adherence

- P – 400 patients age >18 getting IV antibiotics for non-surgical left-sided endocarditis (native or prosthetic valve) from streptococcus, E faecalis, Staph aureus, or coag-neg Staph in stable condition
- I – Change to PO antibiotics ASAP after 10 days
- C – IV antibiotics for duration of Tx
- O – All-cause mortality, unplanned cardiac surgery, embolic events, or bacteremia relapse within 6 months

Harry Potter and the Heart Chamber of Results

- There was no difference in the primary endpoint of definitive failure, showing non-inferiority of oral antibiotics
- The only significant secondary outcomes were all in favour of oral treatment
  - IV was associated with prolonged hospital stay, more IV-line complications, and higher rate of early discontinuation
- Duration of treatment did not significantly differ

- There was no difference in the primary endpoint of mortality, surgery, embolism, or relapse, showing non-inferiority of oral antibiotics
- There were no differences in safety outcomes or adverse effects
- Randomization occurred, on average, on day 17 of treatment
  - Treatment duration was for an average of 34 totally days in the IV group, and 36 in the partial oral group

A bone-afide alternative to long IV courses

- For BJI, there is no good reason to subject stable patients, who are able to take antibiotics as dictated by cultures, to prolonged courses of IV antibiotics
  - We have a wealth of information on bone-penetration of various oral antibiotics and any pharmacist worth their stuff can appropriately dose them
- For left-sided Endocarditis cause by non-HACEK organisms, after an initial 10-17 day period of IV treatment, switching to oral is justified, safe, and effective
  - Normal pharmacokinetic/dynamic calculations can be used as blood levels will correlate directly with valve-tissue exposure

Conclusion?

- Switch to oral ASAP and send people home!!
  - Can start on the day you get the final C&S for BJI, and as early as day 10 of treatment (but probably do 2 weeks to be safe) for endocarditis
  - Prosthetic vs Native joints/valves makes no difference, no matter what the surgeon thinks
- Utilize your local ID pharmacist to pick agents that have the highest bioavailability and tissue penetration

Looking to the future?

- Focus on treatments that have been used for a long time as first to third line therapy
- Focus on disease states that have had big therapeutic improvements in the last 10-15 years
- Focus on treatments where we have known harms, however small, that we have still used because of the benefits, be they perceived or real
- Focus on routine/preventative medicine that does not have a rigorous evidence base

My Predictions

1. The routine physical exam will be a relic, as will the ordering of non-targeted lab work (ex CBC, Chem-7, LFTs)
2. Opioids for the vast majority of non-acute pain conditions will be tossed aside
3. Anticholinergics for OAB will become last line therapy
4. Once SGLT-2's and GLP-1's are affordable/covered, sulfonylureas will be cast aside and considered one of the most harmful interventions of the last 30 years

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Questions?

THANK YOU