Evidence-Based Medicine Brain Teasers: How Conundrums drive us to better medical decision making

Caring for the Ages
2014 Geriatric & Long-Term Care Conference

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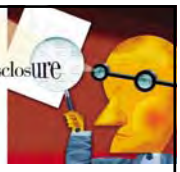
Disclaimer



- I have no conflict of interest relating in the material covered today.
- I do not serve on any speaker bureau.
- I do not have any personal grants concerning the area of discussion today.

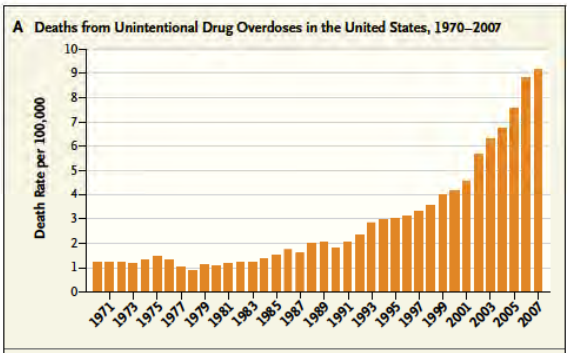
Conundrum

- What is a conundrum?
- a confusing or difficult problem
- a riddle, especially one whose answer makes a play on words
- Synonym = brain-teaser

- I like to think of it as a TENSION!
- They often have an ethical bent!

Medicine is full of conundrums

- The patient does not have a pulse
- "Hiccups, a medical conundrum"
- Treating RA and Crohn's disease with a TNF-blocker, increases the risk of psoriasis
- The mobile/medical conundrum
  - Having information at your fingertips vs security issues
  - Patient privacy issues
- Using placebo in medical practice
- Overdiagnosis
- Going to the doctor when you feel well
- Preventative medicine
  - Risk issues



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NEJM 2010;363(21):1981-3

Prescription Drug Abuse

- FDA and FDA advisory boards urge that training in appropriate use of opioids be mandatory for all physicians who prescribe them.
- REMS: Risk Evaluation and Mitigation Strategy
  - REMS example - www.nucyntaerrems.com
- Tension
  - undertreatment vs harmful access
  - Our rate of narcotic use is 45,000 daily doses/million/day (2007-2009). It is the highest in the world (Canada 25,000; Germany 22,000)

6

Using evidence to lift the haze!

- We can get a better handle on the conundrums of medicine when we use the principles of evidence-based medicine (EBM).
- We make better medical decisions, often bringing the patient in on the decision-making.
- It helps us deal with the hard decisions

Conundrum #1

- How do you know what you know?
- Oh no, beliefs enter in. Can you check them out by the door before patient care?
- The area of study of this question is known as:

Epistemology

Epistemology

- Should physician-assisted suicide be allowed in some situations?
- Should it be legal for people to buy organs for transplant, if they would not be able to receive an organ by waiting their turn through a national database?
- A woman has the right to choose an abortion.
- A woman does not have the right to choose an abortion.
- A woman has the right to choose an abortion in certain situations.

Knowing what we know!

- In medicine, we utilize several things:
- Experience
- Opinion (although watch out for GOBSAT)
- Empirical evidence
  - we should utilize evidence when we have it

You are responsible!

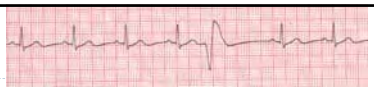
- Be like "Yoda"
- Your Own Data Analyzer

Conundrum #2

- Not all research changes my practice!
- Just because you change a lab value does not mean the patient is helped!
- DOEs:
  - Disease-oriented evidence
    - Pharmacology, pathophysiology, etiology
    - Surrogate markers for disease
      - Lowering cholesterol, lowering BP or blood glucose, increasing BMD, improved drug bioavailability, etc.

JFP. 38(5):505-13, 1994

CAST Trial



- CAST evaluated the effect of antiarrhythmic therapy (encainide, flecainide, or moricizine) in patients with asymptomatic or mildly symptomatic ventricular arrhythmia (six or more PVC's per hour) after myocardial infarction.
- Results
  - 75% reduction in PVC's
  - Increase total mortality with encainide, flecainide
  - RRI = 60%
  - ARI = 4.7%

NEJM 1989;321:406-12

DOEs and POEMs

- POEMs:
  - Patient-oriented evidence that MATTERS
    - Morbidity, mortality and quality of life
    - Final outcomes of disease
      - Stroke, heart attack, hip fracture, admission to the hospital or SNF, performance of ADLs
  - POEMs should result in a change in your practice

JFP. 38(5):505-13, 1994

Conundrum #3

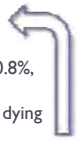
- Lowering outcomes does not mean the patient lives longer.
- All-cause mortality is a difficult reduction to make.
- So, are we just switching what people die of?

- Examples:
- TNT trial tells us that 80 mg atorvastatin is better than 10 mg atorvastatin
  - Major coronary events composite of death from CHD + nonfatal non-procedure-related MI + resuscitation after cardiac arrest + fatal/nonfatal stroke, NNT 45
  - All-cause mortality, p = NS

JFP. 38(5):505-13, 1994

Medicine is a gray science

- PROSPER Trial
  - Statin therapy in elderly
  - NNT = 48 for CV event reduction
  - NNH = 58 for cancer diagnosis
- HYVETT Trial
  - Treatment of hypertension in the elderly
  - Goal is <150/90 with drug or placebo
  - Primary outcome – any stroke, p = NS
  - All-cause mortality, ARR 2.2%, NNT 45
  - Death from stroke was reduced with treatment, ARR 0.8%, NNT 125
  - Conundrum! Do I really want to reduce patients from dying from a stroke? I really want to reduce all strokes.



Conundrum #4 – The RRR!

RRR vs ARR

- RRR vs ARR
- Most benefit reductions are reported as relative risk reduction (RRR)
- This number is often misleading. Overestimates the benefit as it does with shopping. As you need to know the price of a product, you need to know the prevalence of the disease being treated.

Analyze the Research

We need perspective

RRR vs ARR

Risk vs Benefit

Do you understand risk?

- What is the risk of an elderly female breaking a hip between the ages of 70 to 79?
  - Fosamax® reduces hip fracture 50%
- What's her risk of stroke?
- A female age 70 yrs, BP ~174/86
- 44% reduction of stroke when treated
- In the Syst-Eur trial, the risk of having a stroke in this type patient over 4 years was 2.5%
- A 44% reduction is 1.4%

Ms. FIT Trial Lancet 1996;348:1535
Syst-Eur Study Group. Lancet 1997;350:757-64 (Sept 13)

What's the risk of a nonfatal MI in this patient?

- male, 60 years of age, white, nonsmoker, BP = 165/95, BMI = 29, glucose = 112, SCr = 1.3, baseline TC = 212, baseline LDL = 130, HDL = 50, diabetes in family
- Lipitor® 10 mg reduces nonfatal MI by 37%
- Risk is ~ 3% over 5 years
- 37% reduction = 3% to 1.9%

The Numbers of EBM

- Incidence of hip fracture (Lancet 1996;348:1535)
- Placebo 2.2%
  - Must always use event rate which is the number of events divided by the total in group ("n")
- Alendronate 1.1%
- RRR 50%
  - RRR = control - treatment / control (2.2%-1.1%/2.2% = 50%)
- ARR 1.1%
  - ARR = control - treatment (2.2% - 1.1% = 1.1%)
- NNT 91
  - NNT = 1/ARR (100/1.1% = 91)

The advantage of the absolute risk reduction

- takes into account the internal incidence of the condition being treated or prevented
  - Often not reported in research trials
  - Need to learn how to calculate this!!!

Conundrum #5

- Weigh the risk/benefit of a treatment.
- We must look at medications based on harm and not just efficacy.
- We weigh risk/benefit every day.

Our values will dictate our presupposition!

- If we like the medication, we stand on efficacy.
- If we don't like the medication, we stand on side effects.
- We need balance!
- We need to understand our values.
  - Also our patient values.
- Are you an optimist?
- Are you a pessimist?

Do you prescribe hormones??

- The Women's Health Initiative
  - Stopped early because of a 26% increase in risk of breast cancer in women using HT
  - What you saw on the "Today Show"… 26%!!!
- Incidence of the Outcome
  - Placebo Group 0.30%
  - Hormone Therapy Group 0.38%
- RRI = 0.38% - 0.30% / 0.30% = 26%
- ARI - 0.38% - 0.30% = 0.08%
- NNH = 100 / 0.08% = 1250
  - Assume 10,000 women - 10,000 / 1250 = 8

JAMA 2002;288(3):321-33 (July 17)

Conundrum #6

Medication risk must be balanced with benefit not FEAR!

Jones KW. Medication Risk Must be Balanced with Benefit Not Fear Annals of Pharmacotherapy. 2010;44(4):737-9.

Medications are NOT perfect!

- Why does FEAR creep in to motivate people for change instead of good thinking and analysis?
- Just check your email! Check out the daily FDA alerts.
- The latest is that ceftaroline (Teflaro®) increases the risk of death.
- Tylenol® kills livers!
- Testosterone causes heart attacks!
- Caffeine is bad one day, good one day.
- Salt is good one day, bad one day!
- Fear definitely motivates people to get the flu shot.

H1N1 fear has reached the church!

Albuquerque, New Mexico

Fear is striking hard on the prescription pads of America!

- Phenylpropanolamine
- OTC Cough and Cold medications in children
- Acetaminophen
- Intranasal Zinc - Zicam®
- Tegasterod (Zelnorm®)
- Quinine
- Propoxyphene (Darvocet®)

Killed by the FDA!

- Murder weapon: QT elongation
- Death reports from propoxyphene are primarily due to overdose and suicides, NOT SUDDEN DEATH from Torsades de pointes
  - Been on the market since 1957
    - 91 deaths, 74 linked to multi-drug overdoses (The MJ-PK Effect)

Bad decision?

My Opinion

- The issue for me is that FDA alerts cross our desk daily but there is never a fair analysis of the benefit of the medication.

FDA Cough and Cold Advisory

- Released 1/17/08
- "FDA recommends that OTC cough and cold products not be used for infants and children under 2 years of age."
  - FDA vote was 13 to 9 in favor of above
- This statement is based on public advisory meeting in October of 2007

Good decision?

FDA Cough and Cold Advisory

- Consumer Healthcare Products Association (CHPA) has issued a statement to the FDA
  - Represents OTC cough and cold medicines
  - They have voluntarily modified the product labels for consumers of cough and cold medicines to state:
  - "do not use in children under 4 years of age"
- Manufacturers are introducing new child-resistant packaging and measuring devices.

Issues

- Multiple products given to the child
  - Ingredient duplication
- Multiple doses of long-acting preps
- Poor dose measurement
- Failure of child-proof containers
- Parent attitudes
  - Preps will cure child
  - Intentional sedation
  - Parent literacy

FDA records

- 1969 to 2006
  - 54 deaths in children associated with cold medicines made with decongestants.
  - 69 deaths associated with antihistamines
  - Total = 123 cases in 37 years
  - Most < 2 years of age
- Denominator?
  - 95 million packages of cold medicines are purchased each year for children.
  - 3.5 billion in 37 years

FDA.gov website

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...but not **causal**

FDA.gov website

Arizona Program

- Arizona Child Fatality Review Program
- 2006
  - Reviewed all records of infant deaths
  - 10 unexpected infant deaths associated with cold-medication
    - 17 days old to 10 months
  - Only 4 had prior medical care
  - 1 patient was prescribed an OTC cold med
  - No denominator

Pediatrics 2008;122(2):318-22

MMWR Data

- 2004-2005
  - 1,519 (estimate) children < 2 were treated in US emergency departments for adverse events and overdoses associated with cold medications.
  - 3 infant (<6 mths) deaths from cold medications reported in 2005 by medical examiners in US.
  - No denominator

MMWR 2007;56:1:1-4

CDC: Division of Healthcare Quality

- ED visits for adverse events from cough and cold medications in children < 12 years old.
- N = 63 emergency departments, 2004-2005
- 7091 patient visits, annual estimate
  - 6% of all ED visits related to cold medications for children < 12
  - 64% were 2 to 5 years old
  - 66% unsupervised ingestions
  - No required admission

Pediatrics 2008;121(4):783-7

FDA Hearing Part 15

- Testimony
- Efficacy
  - Product's don't work
  - No data to supporting efficacy in young children
- Adverse events
  - Data underreported

Now we are talking!!!!
You just had to dig it out of FDA testimony!!!

Quotes from Testimony

- "Although many medical experts may agree that the risks from pediatric cough and cold medications may be low, some experts still feel the recommendations are need."
- "Obviously the events are rare, It's true the denominator is huge, but these products do not save lives."
- "When a treatment is ineffective, its risks - if not zero - will always exceed its benefit."

We need perspective!

- Depends on where you are sitting!
- Office desk
  - Population driven
  - We think in populations, but treat individuals!
- Couch
  - Individual driven
  - N = 1
- To gain perspective we turn to Nicholas Sparks!
- Nights in Rodanthe
  - Movie Clip at min 46 and min 59

Do we live in a no risk world?

- 2005 data
  - Odds of dying from any injury - 1 in 2,517
  - Odds of dying from a fall - 1 in 15,085
  - Odds of dying from an auto injury - 1 in 20,331
  - Odds of dying from complications from medical and surgical care - 1 in 111,763
  - Odds of dying from a firearm - 1 in 375,801
  - Odds of having unintentional liver injury from acetaminophen - 1 in 850,000 (NOT "odds of dying")
  - Odds of dying from fireworks - 1 in 57,588,244

National Safety Council. The odds of dying in 2005 http://www.nsc.org/research/odds.aspx

The Big Picture

- Has safety become intrusive in the care of patients?
- When safety is the presupposition in medical decision-making, then there is risk of sensationalism.
- We want safe outcomes, but risks are unavoidable in any area of life.
- We need good evidence to help give us perspective of the benefit to risk ratio. One way to use the calculated NNT and NNH.

The meaning of risk medicine

- "Risk is basic to medical progress."
- "Where risk medicine is abolished, medical advance is also abolished."
- "A society which wants good innovations and *no* risks is asking for the impossible. It is denying the freedom to progress."
- "To deny the possibility of failure is to deny the reality of success."

RJ Rushdoony,
Roots of Reconstruction

Becoming a *Jedi*

- Putting it all together
- Evidence-based medicine thinking allows the practitioner to begin making better "medical decision making"
  - NOT disease-state management
- Secrets of the Jedi
  1. Patient-focused
  2. Efficacy-Safety-Cost
  3. NNT-NNH-Cost

Conundrum #7
Data does not rule!




NNT RRI CI ARI

They are just NUMBERS

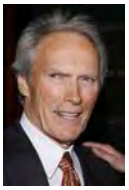
OR HR NNH RRR ARR P-value

Conundrum #8

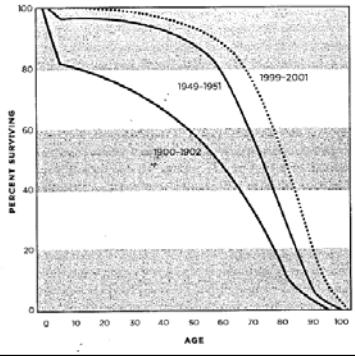
- We can use evidence to help us make good medical decisions in the elderly.
- Why?
- The quality of their dying becomes as important as their living!

Living to a ripe old age!

- "One is old when one is ripe"
  - Ripe = Octogenarian
- Ours is not our grandparents longevity.

Another Presupposition
Changes in US Longevity Rates



20th Century Survival Curves

US Public Health Service National Vital Statistic Reports 2008;57(1) August 5, 2008

From 1902 to 1949 mean age went from 47 to 68

Is it longevity that matters?

- The issue is no longer longevity but quality of life of the aged.
  - **"In your ninth decade of life, both the quality of living and the quality of dying are primary health concerns."
- Who cares how many diseases you can list when you are an octogenarian.
  - Disease transforms to dis-ease
- Let's rejoice when we arrive at the "ripe old age".
- The question really is not how we can be assured we will live to be 85, but how can we aspire to be purposeful and self-assured for those 85 years?
  - Does preventative medicine have a role in the aged?

**Hadler NM Rethinking Aging, 2011 ISBN 978-0-8078-3506-7

Mortal Hazards

- Obesity, smoking, high cholesterol, health-adverse diet, inactivity are adverse heath behaviors.
- These account for 20-25% of one's mortal hazard = the years one falls short of a ripe old age.
- The other 75% relates to the circumstance of community and these big time chip away at longevity.
  - Socio-economic status
  - You hate your job
  - Poor
  - Ostracized
  - Faced with uncertainty
  - Lonely or alone
    - Lack of interpersonal networks
    - Not being married
  - Lack of faith

"The secret to longevity are in the fine structures of human ecology"
Hadler, 2011

Hadler NM Rethinking Aging, 2011 ISBN 978-0-8078-3506-7

Making Great Medical Decisions

- Can we use evidence to help us make these decisions?
- Statin use after age 80?
- ASA use over age 80?
- "She been on the bisphosphonate how long?"
- "She is demented and very poorly functional and still on donepezil and memantine?"
- Hyperpharmacotherapy?

Case – 69 year old female
HTN, Bipolar, Arthritis

- Meds as on MAR – in assisted living situation
  - Amitriptyline 25 mg bid
  - Baclofen 5 mg tid
  - Caltrate bid
  - Cetirizine 10 mg daily
  - Cyclobenzaprine 5 mg tid
  - Detrol LA 4 mg daily
  - Fluticasone 50 mcg nasal spray daily
  - Lidoderm 5% patch daily for 12 hours
  - Lipitor 20 mg daily
  - Lyrica 50 mg tid
  - Metoprolol 50 mg bid
  - Morphine ER 30 mg bid
  - Metanx 2 tabs daily
  - Nexium 40 mg daily
  - Oxybutynin 5 mg tid
  - Senna plus 2 tabs daily
  - Therems-M daily
  - Toviaz ER 8 mg daily
  - Vitamin B-12 125 mcg daily
  - Voltaren gel to knee QID
  - Lamotrigine 200 mg qhs
  - Mirtazapine 15 mg qhs
  - Ropinirole 2 mg qhs
  - Sertraline 250 mg daily
  - **PRN Meds**
  - Albuterol inhaler
  - Promethazine syrup 6.25 mg
  - Hydrocodone APAP
  - Tramadol 50 mg tid prn
  - Zolpidem 5 mg qhs prn
  - New – Ciprofloxacin 250 mg

Our Last Conundrum #9

- Do we use the guideline?
- Many prescribers are being "paid for performance"
- The payors have latched on to guidelines as a standard of care.
- The term "guideline" was borrowed from a mountain-climbing technique in which experienced guides mark the best and safest paths for hikers to take by placing ropes along the way.
- In medicine, guidelines were formed to suggest safe direction when managing difficult clinical situations.
- So… should these type guidelines be distilled into performance measures?
  - "…deviations from guidelines have become less tolerated"
  - They need to be cognizant of unintended consequences

Peterson Editorial, JAMA, Published online, December 18, 2013

JNC-8 Guidelines

- The new JNC-8 and Cholesterol guidelines are for the first time truly evidenced-based!
- They tells us more about what we need to research than actually how to treat…….conundrum

Kelso's Wow Factor on the JNC-8!

- 140/90 is a reasonable goal
- 150/90 in those > 60 years
- The benefit of treating to lower BP levels with pharmacotherapy is NOT established!
- *"…these recommendations are not a substitute for clinical judgment, and decisions about care must be considered and incorporate the clinical characteristics and circumstances of <u>each individual patient</u>."*
  - *Page E13, last paragraph*

Guidelines are just that – guides!

- We need to harmonize these guidelines with other cardiovascular risk guidelines and recommendations to assess a more comprehensive CV risk profile.
  - JNC 8 recommendation is based on a single risk factor - BP
- Guidelines never integrate care for many of the actual patients we see.

Some guidelines have been called to question!

- June 2013 – NHLBI announced its decision to discontinue development of clinical guidelines, but to partner with organizations to develop guidelines.
  - Why? IDSA complicated legal proceedings concerning a Lyme Disease guideline – concerns disclosure issues.
  - IDSA physicians testifying against physicians who are not complying with these guidelines.
  - Recent mammography screening issue from USPSTF
- Dronedarone in atrial fibrillation

The End

E-mail questions:
kjones@mcleodhealth.org
Or
PharmReach.org

Master Yoda

Self-Assessment Questions

- 1. The ACCOMPLISH Trial showed that benazepril-amlodipine combination was superior than benazepril-HCTZ combination in reducing cardiovascular events in patients with hypertension. This is an example of which kind of trial?
  - a. POEM
  - b. DOE
  - c. Retrospective trial
  - d. Case-control trial

Self-Assessment Questions

- 2. For every 40 people treated with Pravachol, one patient would not have a myocardial infarction over a 5-year period. This is an explanation of?
  - a. NNH
  - b. RRR
  - c. ARR
  - d. NNT

Self-Assessment Questions

- 3. You have a down moment during lunch one day and you open up one of your journals and come across an article titled – "**Aspirin for preventing recurrence of venous thromboembolism". Would you read this article?**
  - a. Yes because it is a POEM
  - b. No because it is a DOE
  - c. Yes because it is a DOE
  - d. No because it is a POEM