

Medicine: Where science ends and art begins

*An Academy of Life Long Learning presentation
January 11, 2018, Corvallis, OR*

Objectives of the presentation

To review :

1. How medical studies are conducted, interpreted, and how “evidence-based” recommendations are made;
2. the merits and limitations of **scientific studies**;
- and
3. to discuss what is meant by the **art of medicine**

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It is **NOT** the purpose
of this presentation to:



- 1. Offer a fix for our dysfunctional healthcare system.*
- 2. Expose the business or profit motives of the “medical industrial complex”*
- 3. Question the integrity and value of our medical institutions, their scientists and clinical experts*



Neither is this presentation is about:

- *Minimizing the recent progress and future benefits of modern medicine, or turning you into a diagnostic or therapeutic nihilist.*
- *Questioning the trust you should have in your healthcare providers.*
- *Giving medical advice on your personal healthcare and specific medical decisions*

This presentation is only a cautionary tale on how to understand medical recommendations

“To believe in medicine would be the height of folly, if not to believe in it were not a greater folly still.”

Marcel Proust (1871-1922)



Medicine: Where science ends and art begins

Take home messages:

- 1. There is a great deal of **good science** in medicine, but let's be careful how we draw conclusions.*
- 2. The **art** of medicine is no different than that of other art forms: to make sense of our complex human nature, to connect with others, and learn to accept our human condition*

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What motivates me to make this presentation:

- There is a confidence crisis in the medical establishment – not just with our healthcare insurance system
- At the national level: *The issue of “over-use” and cost control of healthcare is highly complex and ripe of vigorous debate*
- At our individual level: *Understanding how medical recommendations are made might allow us to make better healthcare choices.*

Erosion of public trust in the medical profession

| Survey question | 1966 | 2012 | 2014 |
|---|------|------|------|
| “Great confidence in leaders of the medical profession” | 73% | 34% | |
| “High trust in physician integrity” | | | 58% |
| “Very satisfied with last doctor visit” | | 56% | |
| Public confidence in US healthcare system | | | 23% |

Note: **Overall, the US ranks 24/29 of industrialized countries surveyed**, even when US patient satisfaction with their doctors is high

Source: Blendon RJ et al: NEJM, Oct 23, 2014

Why are we seeing a confidence crisis in the medical profession?

- **Media exposure of scandalous and unethical behavior of a few – *lack of accountability***
- **Critical peer analysis: *Only 50% of patients receive “standards of care”; patient frustration with the “system”- fragmented care, too much for some, too little for others***
- **“Hidden epidemic” in the “Gray Zone” of medicine: *Conflicting health recommendations that raise issues of incompetence, lack of transparency, and conflict of interest***

Unintended consequences of pain management practices and the misguided “the “war on drugs”: *The opioid epidemic in the USA*

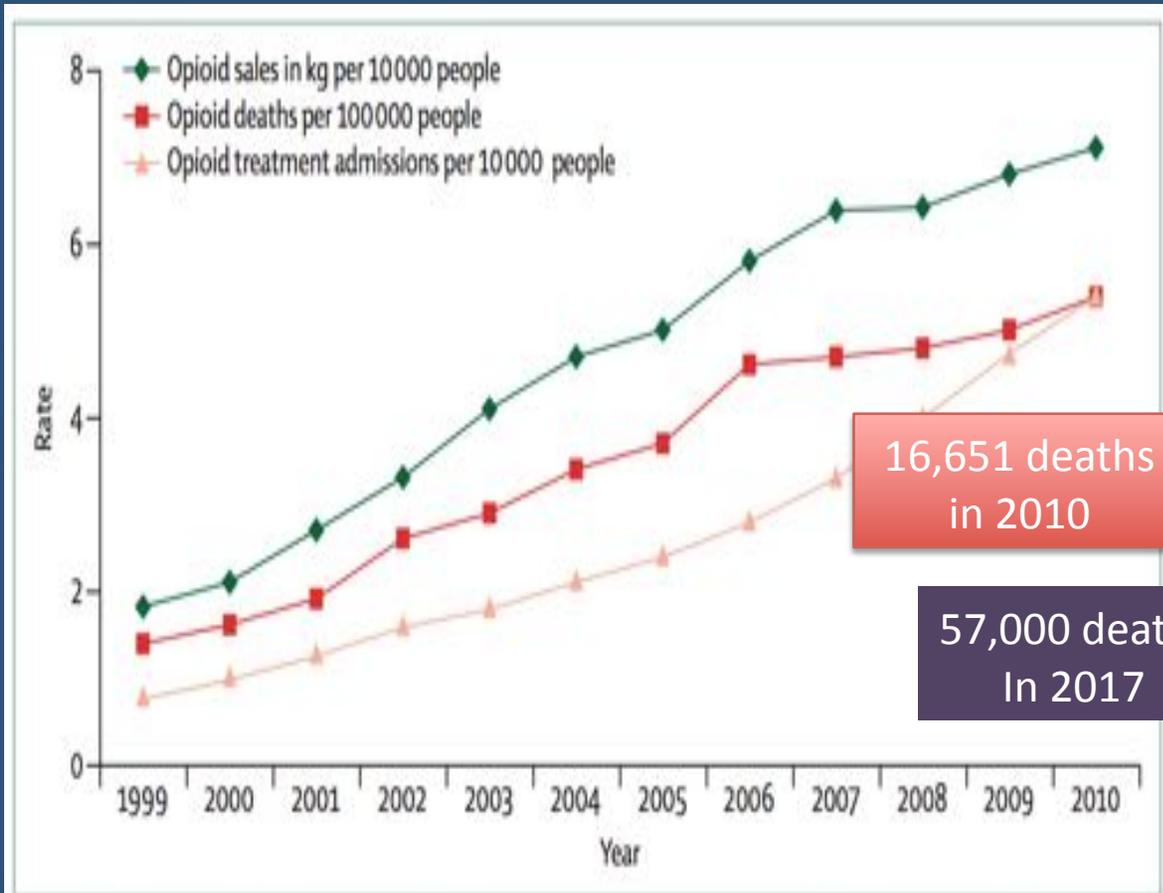
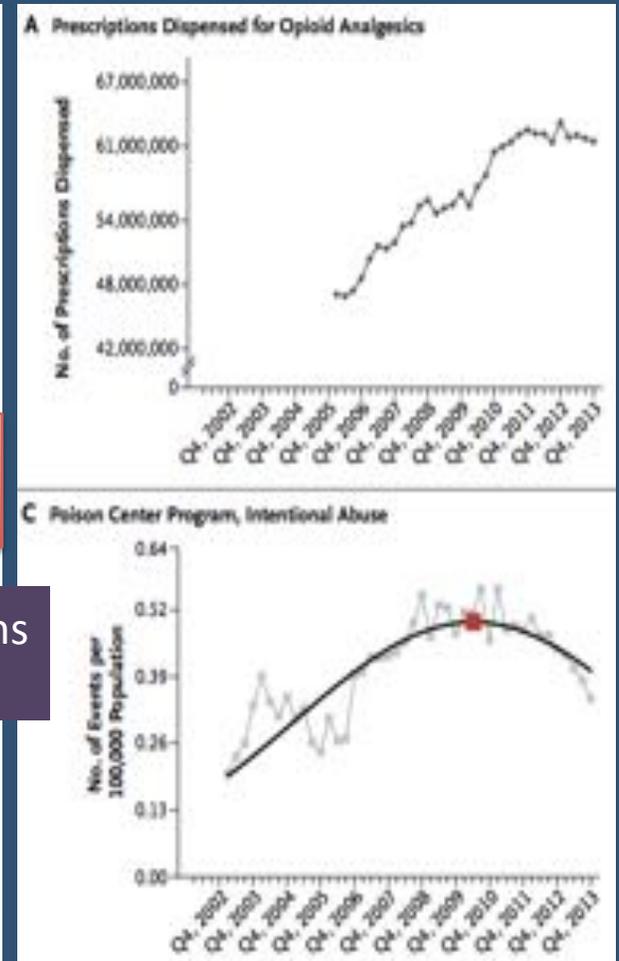
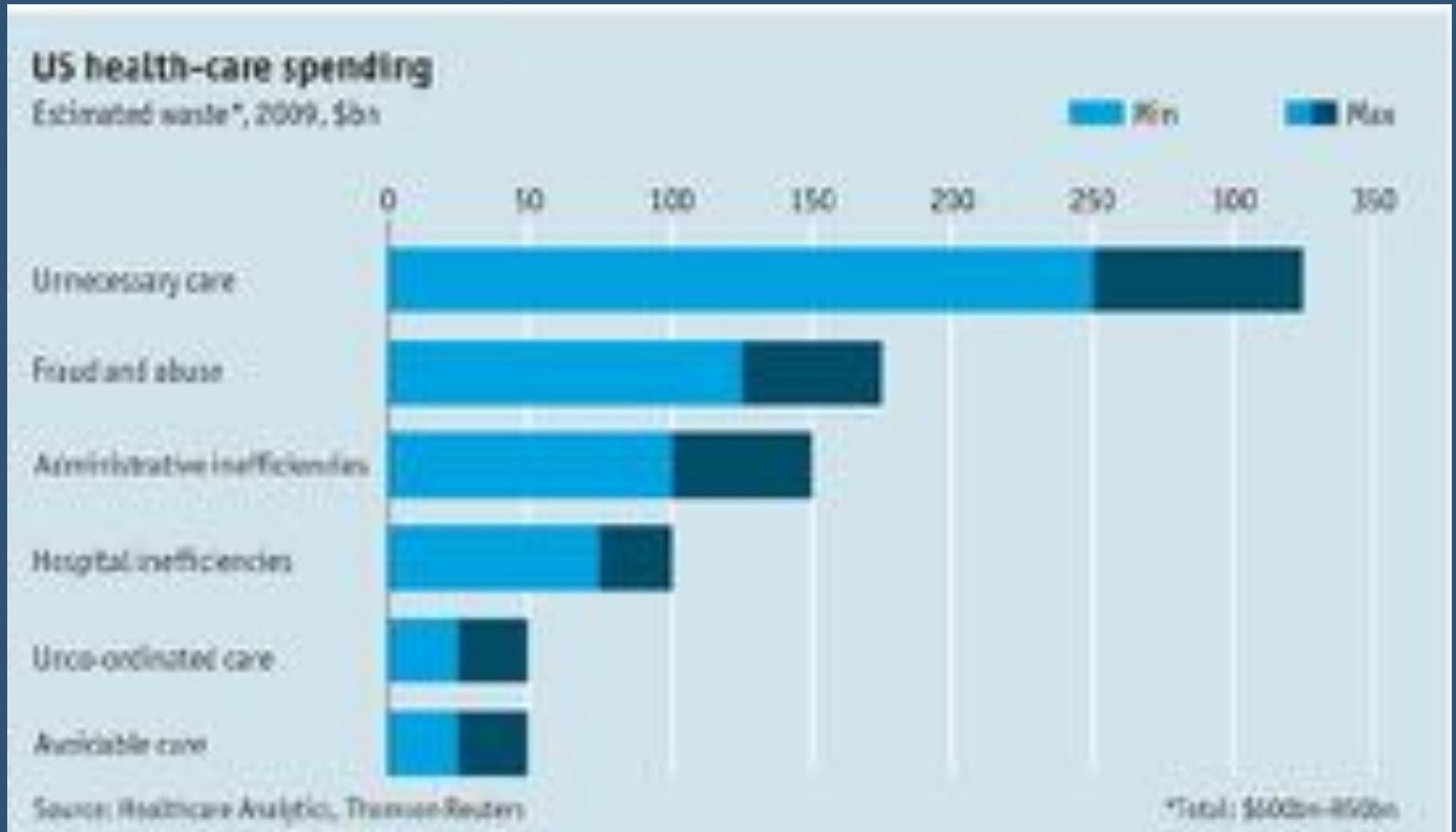


Figure 3: Rates of opioid overdose deaths, sales, and treatment admissions in the USA, 1999-2010



Sources: Jones CM, JAMA 2013 Vol 309:657-59; Dart RC: NEJM:372, Jan 15, 2015

Estimate waste in US healthcare: 30% of total health expenditures



Source: The Dartmouth Atlas of Health Care (<http://www.dartmouthatlas.org/keyissues/issue.aspx?con=1338>)

“Low-value health care” ...

The triple sins of the US medical profession (*)

- Over-testing
 - Over-diagnosing
 - Over-treating
- Potentially can create risks > benefits for patients
 - Increase healthcare costs to society
 - Increase health inequities

PS: “a little bit like pornography: while easy to define in concept, it can be hard to know when you see it...”

(Former Supreme Court Justice Potter Stewart)

() Welch: JAMA July 2017; for a counter-argument, read Rosenbaum; NEJM, Dec 14, 2017*

| Age groups | % of individuals taking 5 or more prescription drugs |
|------------|--|
| All ages | Year 2000 = 8% Year 2012 = 15% |
| 65-69 | 25% |
| 70-79 | 49% |

(Source: Kaiser Health News, Dec 12, 2017)

Are we over-prescribing medications?

“To write a prescription is easy, but to come to an understanding with people is hard”



Franz Kafka
 (“The Country Doctor”)



One of the first duties
of the physician
is to educate the masses
not to take medicine



- William Osler -
(1849 - 1919)

DRUG-FREE AMERICA



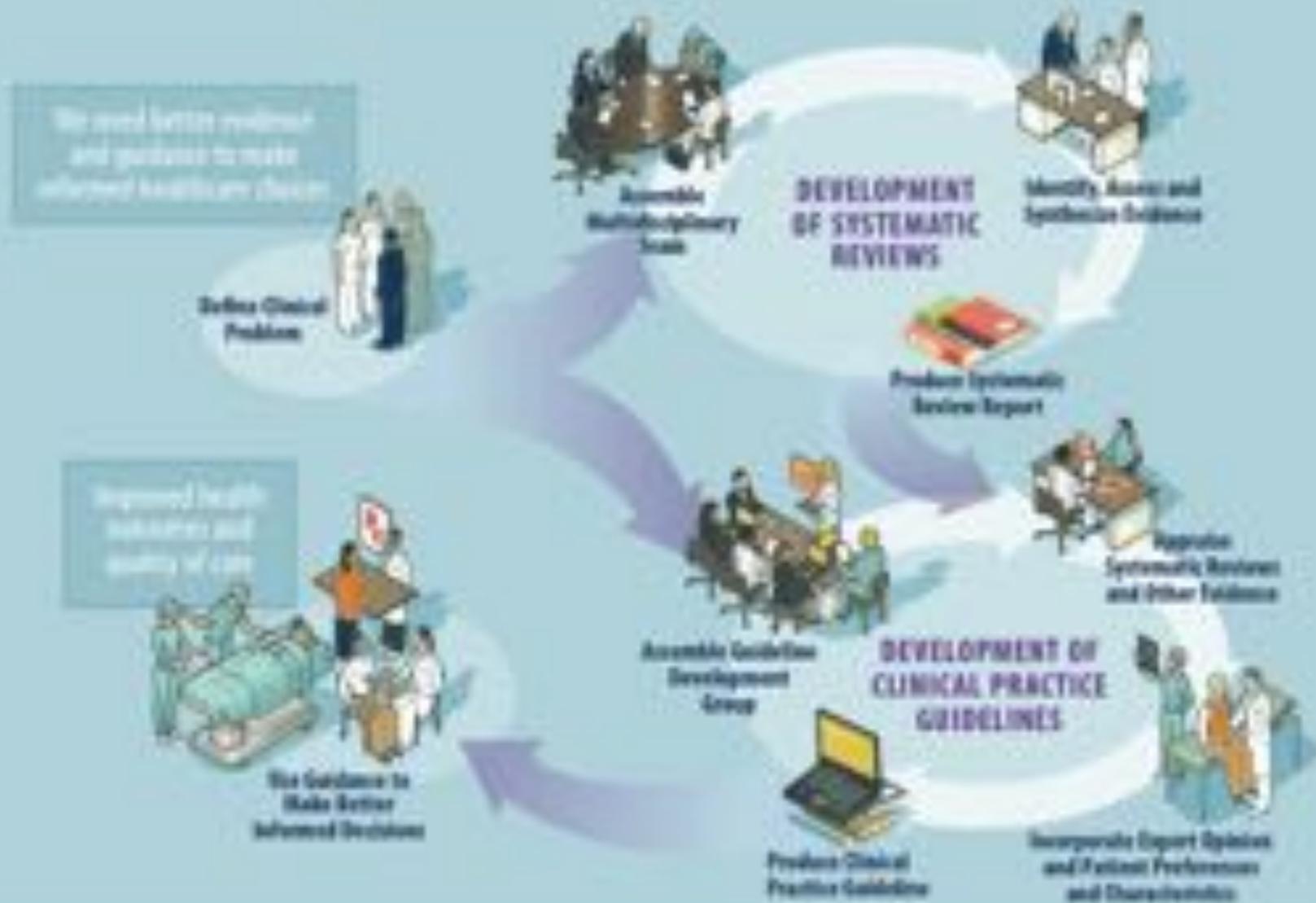
| | | | | | | |
|----------------|-------------|--------------------------|--------------|--------------|------------------|--------------------|
| <u>AGE 0-4</u> | <u>4-12</u> | <u>12-18</u> | <u>18-24</u> | <u>24-38</u> | <u>38-65</u> | <u>65 —</u> |
| AMOXICILIN | RITALIN | APPETITE SUPPRESSANTS | NO-DOZ | PROZAC | ZANIAC VIAGRA | EVERYTHING ELSE |

What is “Standard of care” today often discarded tomorrow

Past Examples:

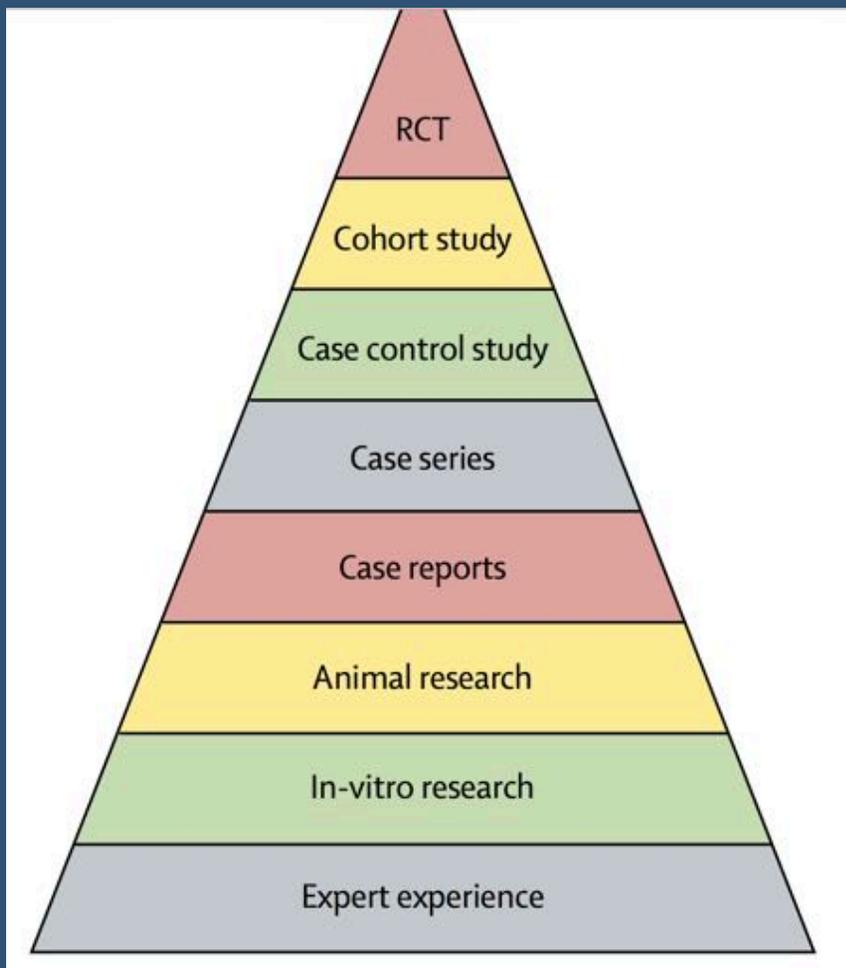
- Routine hormone replacement therapy for women after menopause.
- “ABC” of CPR techniques
- Use of anti-arrhythmic drugs after a heart attack
- Home use of syrup of ipecac in pediatric poisoning
- Various infant feeding advices
- Nutritional recommendations (“Food Pyramid”)

Systematic Reviews and Clinical Practice Guidelines Improve Healthcare Decision Making



How are recommendations made?

1. Review the quality of evidence from scientific studies



(Djubelevic B, Guyatt. The Lancet July 22, 2017)

2. Develop practice guidelines from:

- Summary of the systemic review of all the evidence
- Assessment of benefits and harms
- Determination of the certainty and magnitude of the net benefit/risk ratio

3. Assign a letter GRADE Recommendation

Clinical studies are key tools in medical sciences, *but have their challenges and limitations*

Factors that effect study results:

- Methodology:
 - *Variations in demographics; study design; timing of intervention; outcome measurements; sample size and bias; length of follow-up, and data collection.*
- Statistical analysis:
 - *Methodology*
- Result interpretations: “Quality of the evidence”
 - *Correlation vs. causality; Opinions and biases*
- Applications in the “real world”:
 - *Extrapolating results from a population-study to personalized medicine*

Evidence-based medicine

- *First goal was to educate providers in the use of published medical literature to optimize clinical care*
- *Has evolved into **developing systematic reviews and clinical guidelines***
- *Helps providers with **information to patients***
- *In some cases, being used as **bench marks for quality of care and re-imbursement incentives to providers.***

(Adapted from B Djulbegovic, The Lancet, July 22, 2017)

Gray-zone medicine

“Evidence-based medicine”: *whose evidence?*

- Sciences quoted for public consumption:
 - *“latest research shows...”*
- Practice recommendations and guidelines:
 - *Who make them?*
 - *How are they made?*
 - *Are they followed?*
- Dilemmas in medicine: Whose “VALUE” ?
 - Individual considerations: *Ratio of Benefits / Risks + Costs*
 - Population-wide benefits: *Cost-effectiveness to society*

Quality of the evidence *should matter*:

Yet, a review of 190 treatment recommendations made by the American Academy of Pediatrics revealed that

- Only 43 % were based on solid experimental studies
- 30% were based on observational, “weaker” studies
- And 27% were expert opinions, or had no reference

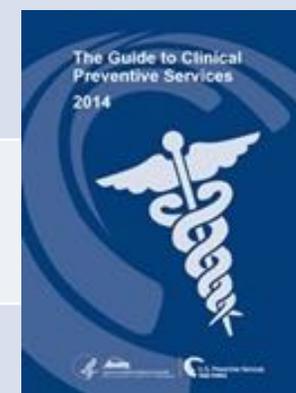
(Source: Isaac A, et al. Pediatrics, March 25, 2013)

The majority of medical professional societies use the following processes in developing evidence-based guidelines:

- Establish transparency
- Publish guideline group composition
- Manage conflicts of interest
- Review-analyst and clinical-practice intersection
- Establish foundation and rating strength of evidence used
- External review
- Articulation of recommendations; practical tools to improve decision making
- Implementation issues, respect for patients' values
- Updating

US Preventive Services Task Force : Recommendation criteria and guidelines, 2014 edition

| Grade and recommendations | Benefit of service | Level of Certainty |
|---|---|---|
| A = Recommend | substantial | High |
| B = Recommend <i>(Note: The ACA requires private health insurers to cover A and B at no costs to their beneficiaries)</i> | High certainty that benefit is moderate; or moderate certainty that benefit is high | Moderate: <ul style="list-style-type: none"> •Quality of studies not optimal •Inconsistency , incoherence, or limited generalizability of findings between studies |
| C = Optional, based on professional judgment and patient preference | Small benefit for most persons | Moderate |
| D = Recommend against | No net benefit, or harms outweigh benefit | High or moderate |
| I No recommendation | Insufficient or conflicting evidence | Low |



Types of medical studies

- **Observational studies**
 - *Longitudinal, epidemiologic population studies*
 - *Short-termed, narrowly focused, case-controlled studies*
- **Randomized controlled trials (RCT): the Gold Standard**
 - *with or without placebo; cross-over trials*
 - *Single or multiple interventions and/or dosing variations*
 - *single-blinded or double-blinded*
 - *Most difficult and most expensive to do*
- **Meta-analysis studies / systematic reviews**

Examples of observational longitudinal studies

| | Year started | Study populations | Correlation of some of the health outcomes and risk factors examined |
|-------------------------------------|-----------------------------|---|--|
| Framingham Heart Study | 1948 | Starting with 5,209 adults in MA, now into its 3 rd generation | Cardiovascular, smoking, cholesterol, obesity, life styles... |
| Seven-Countries Study | 1958 | 12,763 male adults US, Europe, Japan | Cardiovascular, cancer, diet, life styles |
| Nurses' Health Study | 1976;1989; 2010 | > 160,000, US | Cardiovascular, bone health, cancer, hormone use, diet, environment... |
| British Birth Cohort Studies | 1946; 1958;1970; 2000 | > 70,000 British children | Effects of family poverty and parenting |

Randomized clinical trials

- Most stringent “gold standard” to test the effectiveness of a medical intervention: Compare effect of Rx one group, vs placebo or a different intervention in another group

But:

- Very expensive to conduct
- Participants selected according to very restrictive criteria
- Results not always clear when situations involve multiple interventions, or multiple outcome evaluations
- Use of placebo not always feasible for ethical reasons
- Results may not reflect “real life” situations

Meta-analysis studies/ systematic reviews

- Benefits: *Combine findings of multiple studies to increase statistical power behind the results of an observation or an intervention*
- Pitfalls and dangers:
 - *Studies vary greatly in demographics and designs*
 - *Mixing apples and oranges*

Conclusions may stand on shaky grounds. Most difficult to interpret are studies for dietary recommendations and behavioral sciences

Examples of evidence-based medicine that have changed patient care

- Stop the use of lidocaine and other anti-arrhythmic drugs to prevent ventricular fibrillation in patients with myocardial infarction
- Change the “ABC” of CPR practice
- Stop the routine recommendation of hormone replacement therapy for post-menopausal women
- Infant sleep positioning
- Timing of introduction of peanut feeding to children
- Home use of ipecac for accidental poisonous ingestion in children

The story of hormonal prophylaxis for post-menopausal women

- **1963:** “Beneficial estrogen level should be continued throughout life” – estrogen Rx sales increased by x4 folds
- **Mid 1970s:** associated with increased risk of endometrial cancer
- **1989:** recommended for women at risk for osteoporosis
- **1992:** recommended for women who had undergone hysterectomy or who are at increased risk for coronary heart disease
- **1996:** “B” recommendation: counseling for benefits/risks
- **1998, 2002, 2004, 2006:** RCTs showed no benefits for CVD; increased risk of venous thrombosis, gall bladder disease and dementia; slight decreased risk in colon cancer and hip fractures
- **2005; 2012; and 2017:** USPSTF “D” recommendation (ineffective, risks > benefits)

(Adapted from Lewis CE Wellons MF: JAMA Dec 12, 2017)

The problem with science...

“Science is not about certainty. Science is about finding the most reliable way of thinking, at the present level of knowledge.”

Carlo Rovelli

Theoretical physicist,

University of the Mediterranean,

Marseille, France

“I know that half of what I teach today will prove false in the next 10 years.

The hard part is I don't know which half”.

Confession of

a medical hubris

Examples of USPSTF recommendations for primary care, 2014

- Aspirin for prevention of CVD, for men age 45-79, with risks stratified by age group (>4% to >12%) (A)
- Screen for breast cancer BRCA mutations: women with family history for increased risk (B)
- Primary care interventions to promote breast feeding (B)
- Screening for depression in children, adolescents and adults: (B)
- Behavioral counseling to promote a healthful diet and physical activity for CVD prevention in adults (C)
- Screening for lung cancer in smoking history with low-dose CT scan (B)
- Use of statins for primary CVD prevention according to risk calculations (B and C)

(Note: The ACA requires private health insurers to cover A and B at no costs to their beneficiaries)

Statistics vilified?

“A statistician is a fellow who says that if you ate a chicken and I ate none, we each ate, on average, half a chicken”

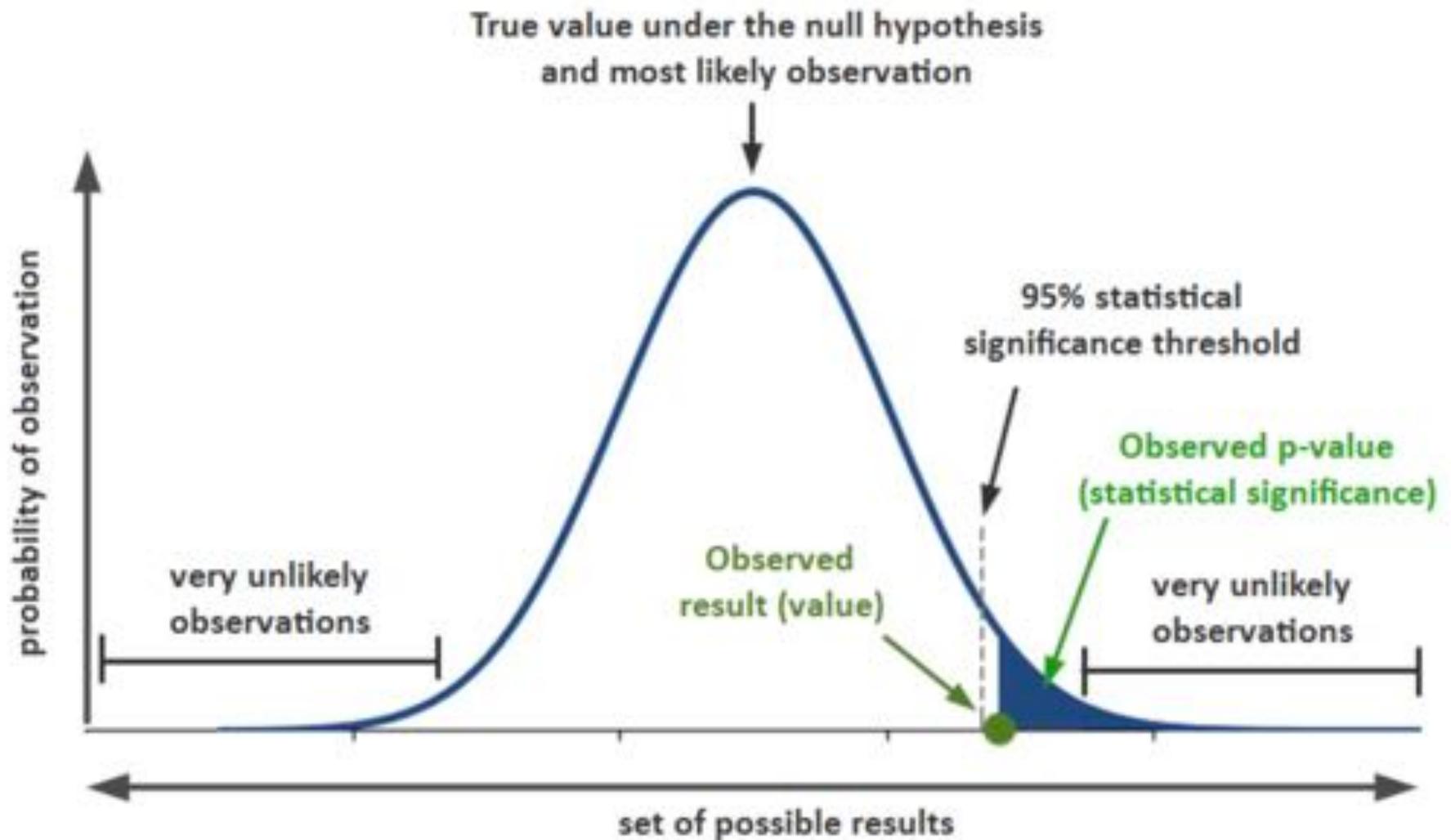
*(Author unknown,
quoted by Lawrence Mohr, Prof
of Political Science,
U Michigan)*

“There are more quacks practicing medical statistics than there are quacks practicing medicine, and they do their damage wholesale rather than retail.”

*(Bailar JC III.
Clin Pharmacol Ther
1990;20:113-9)*

*Statistical tools are essential to understand data, but not humans.
Like any tool we use, they can help, or hurt.*

Probability & Statistical Significance Explained



Common statistical tools

(Stats 101 much simplified)

| Calculations | What they indicate |
|--|---|
| Multivariable regression analyses: Logistic regression odd risk ratio (OD) Cox regression hazard rate ratio (HR) | Models to establish correlation between a variable (<i>blood glucose</i>) and an outcome (<i>diabetes</i>); and to estimate the probability or relative risk of an event (Odd Ratio) or of a relative incidence rate (HR) |
| P value (<0.05) | Probability of an observed result arising by chance |
| Confidence interval (95% CI) | Range of values that gives a 95% certainty that the mean value is within that range |

***When to be cautious about medical recommendations:
over-reaching conclusions, or under-stating knowledge gaps***

| Situations | |
|--|--|
| Expert opinions and empirical experience as dogmas | |
| Over-estimating product effectiveness | |
| Dealing with conflicting observations and data | |
| Same data, conflicting recommendations | |
| Cherry-picking what study findings to emphasize | |

When to be cautious about medical recommendations:

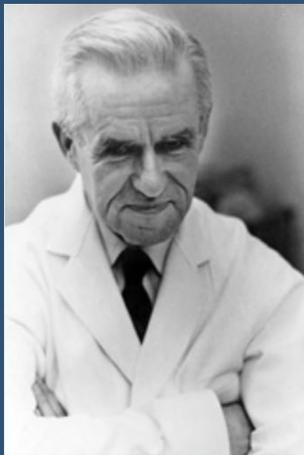
| Situations | Examples |
|--|---|
| Expert opinions used as dogmas to fill in knowledge gaps | <i>Empirical use of anti-microbial agents</i> |
| Over-estimating product effectiveness | <i>Influenza vaccine and medications</i> |
| Dealing with conflicting observations and data | <i>Prevention of dementia Rx of hypertension</i> |
| Same data, conflicting recommendations | <i>Cancer screening</i> |
| Cherry-picking what study results to emphasize | <i>Use of statins and Rx of hypertension to prevent cardiovascular diseases</i> |

Antimicrobial use and the development of resistant organisms



- “...the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with penicillin-resistant organism. I hope this evil can be averted”.

(Alexander Fleming, 1945)



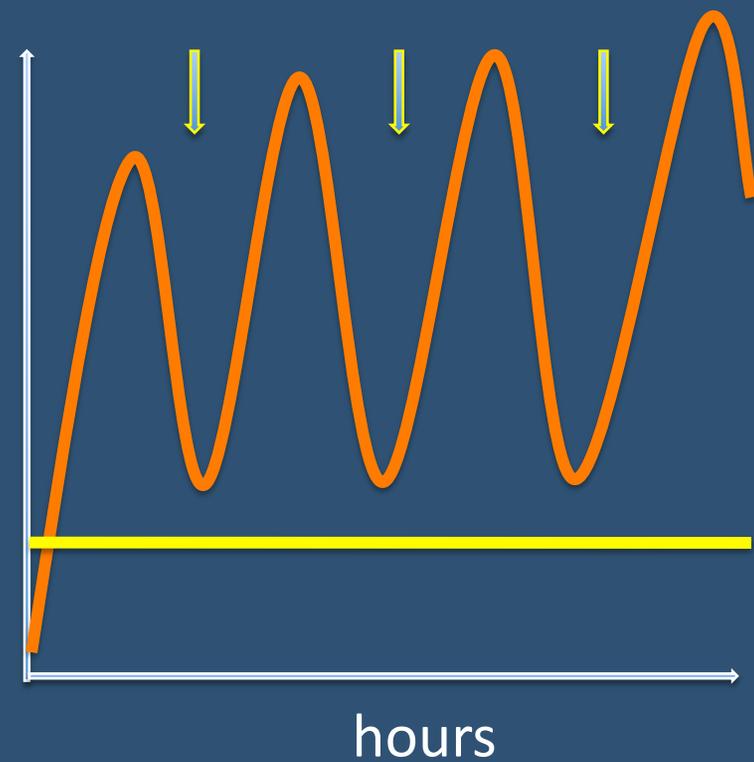
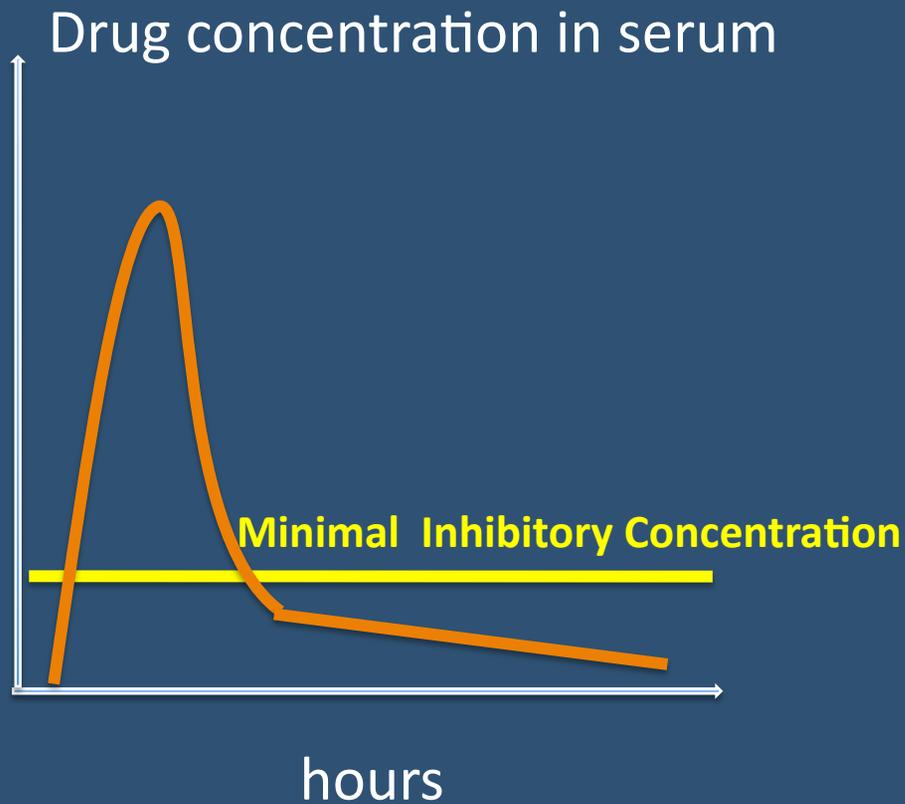
- “We know all about antibiotics, except when and how much to use them”
(Maxwell Finland, First President of the Inf Dis Soc of Amer 1965)
- 30-50% of antibiotics prescribed today to people in the US are either not needed or inappropriately “

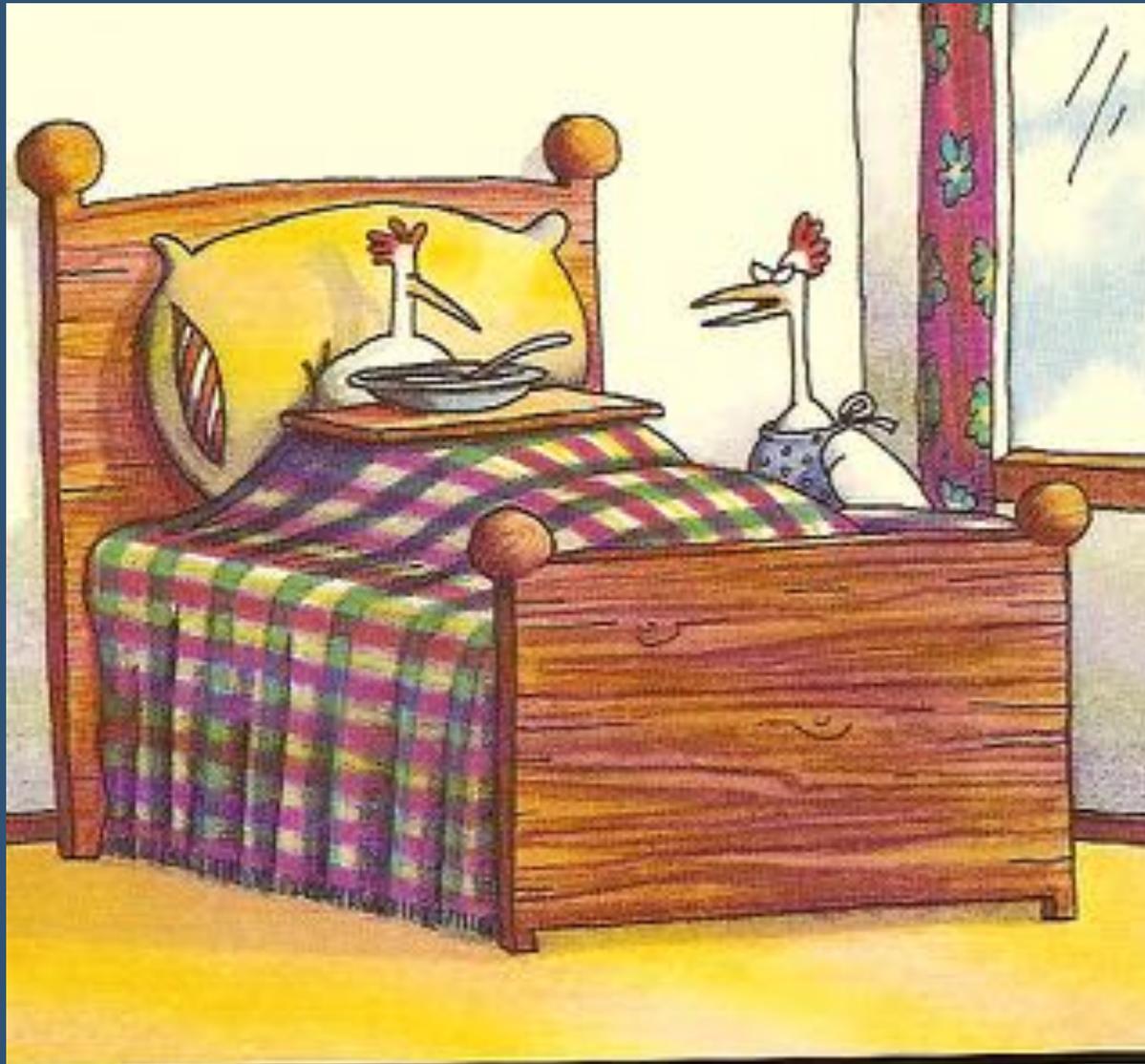
(R Khabbakz, CDC, in IOM report, Oct 2014)

Dogmas in antibiotic use

- **Dosing** (how much, how often to give) usually based on pharmacokinetic studies.
- For many decades, **duration** of treatment is “empirical”, i.e. based on extrapolation of experience gained from other situations, or from “expert opinion” (*...it all started with the Rx of strept throat...*)
- Only in the past 2 decades there has been (small) RCTs to fine-tune the Rx of common infections like ear, respiratory and urinary tract infections.

Antibiotic pharmacokinetics and dosing





"Quit complaining and eat it! . . . Number one, chicken soup is good for the flu — and number two, it's nobody we know."

Vaccine Efficacy (VE) calculation

$$VE = (1 - \text{Odds Ratio}_{\text{Exposure}}) \times 100\%$$

Example: Efficacy of varicella (chickenpox) vaccine:

Observation: For children who had previously received the vaccine, the rate of getting chicken pox after exposure is 1/10 that of unvaccinated children.

Odds Ratio = .10

$VE = [1 - (.1)] \times 100\% = 90\%$

Special challenges in evaluating vaccine efficacy/ Vaccine efficacy is often inflated

- Variations in disease epidemiology
 - *Disease incidence may vary year by year*
 - *Population characteristics may not be the same as in studies*
- Measuring study endpoints
 - *Which clinical outcomes are most relevant?*
 - *Biological markers (antibodies...) may not correlate with level of protection*
 - *Statistical methodology can bias results*
- Duration of protection
- Vaccine uptake once licensed
- Indirect impact : *Effect on herd immunity*

Influenza vaccine effectiveness in the elderly

| Author (publication) | Setting | Decrease in risk of hospitalization for pneumonia - influenza | Decrease in risk in all causes of death |
|---|--|---|---|
| Nichol (NEJM, 2007) | HMOs in WI, MN, Pacific NW , and NYC (1990-2000) (Uncontrolled for confounding factors) | 27 % | 48 % |
| Jefferson Lancet, 2005)- <i>well matched vaccines</i> | Nursing home | 46% | 60% |
| | Community living | 22-27% | 47% |
| Baxter (Vaccine , 2010) | KP No. CA (1997-2008, (population of 10 million member-years) | age 50-64 = 12.4 % age 65 or > = 8.5 % | 4.6 % |

Vaccine efficacy results may be strongly influenced by study methodology

| Methodology | Characteristics | Effect on results |
|--|---|---|
| Observational studies using logistic regression modeling | Case controls often contains epidemiologic bias (<i>“unmeasured confounding factors”</i>) even after controlling for demographic variables and other medical conditions | Over-estimate the vaccine protective effect |
| Instrumental variable analysis method – using large population cohorts | Randomized study that neutralizes the effect of patient selection, prognostic variables and outcome | Recently found to be more accurate |

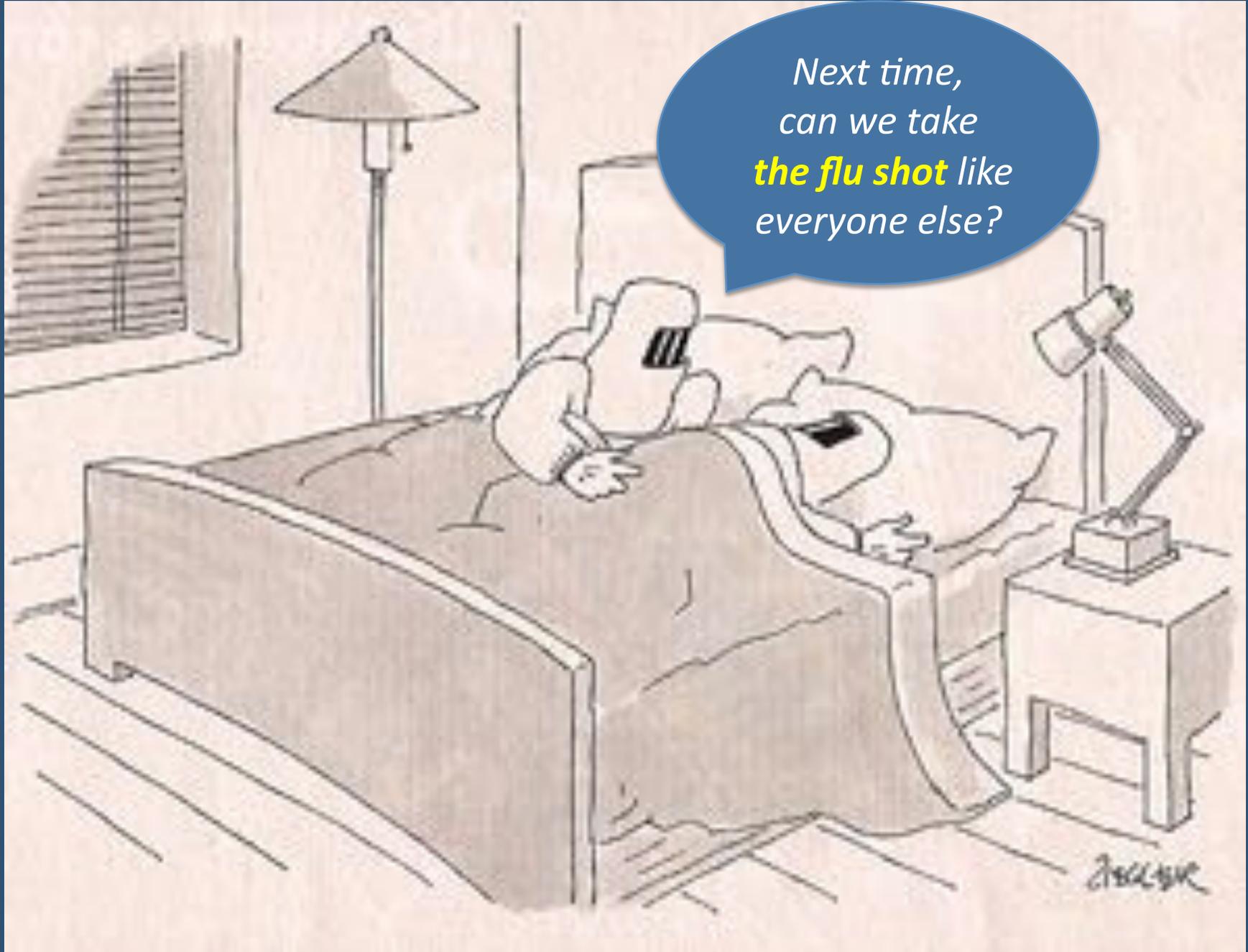
Sources: Wong K, and Brookhart et al: Arch Int Med, March 26, 2012)

Influenza vaccine effectiveness in community-dwelling elderly patients , Ontario, Canada 2000-2009

| Same data, Different, analysis methodology | Adjusted Odd Ratio (95% CI) for all causes of mortality | Adjusted Odd Ratio (95% CI) for pneumonia + influenza + death |
|---|---|--|
| Case control, Logistic regression | 0.67 (0.62 – 0.72) or a 33% reduction | 0.74 (0.70 – 0.78) or a 26% reduction |
| Randomized population, Instrumental variable | 0.94 (0.84 – 1.03) or a 6% reduction | 0.86 (0.79- 0.92) or a 14% reduction |

Source: Wong K, et al: Arch Int Med, March 26, 2012 – studying nine influenza seasons , 1.4 million individuals per season)

Next time,
can we take
the flu shot like
everyone else?



Lesson from the *Tamiflu (osteltamivir) story*

- Drug approved in 1999 for treatment of uncomplicated influenza within 48 hours of symptom onset, based on 2 randomized studies (849 patients) reporting the drug shortened illness by 1.3 day.
- Drug also decreases viral shedding, and observational studies reported decrease in mortality of influenza-hospitalized patients
- In 2010, WHO added *osteltamivir* to its list of “essential drugs”. In the fear of worldwide influenza pandemics, many governments stock-piled the drug (1/2 of the drug total \$18bn global sales)
- In 2013, a meta-analysis study and a Cochrane review - including many studies whose publications were suppressed by Roche pharmaceutical - found the drug relieved symptoms by only 20 hours, and did not prevent influenza complications.
- In 2017, WHO dropped *osteltamivir* from its essential drug list.

(Sources: Hurt AC, Kelly H: *Emerg Inf Dis* June 2016; Ebell MH: *Brit Med Journal*, July 13, 2017)

Reasons cited for screening mammography for breast cancer

- The most common form of cancer , and the second cause of cancer deaths in women
- 75% of newly diagnosed breast cancer have no known risk factors ; 50% of all breast cancers are found via screening mammography
- Annual screening of women (age 40-84) is associated with up to 40% mortality reduction; biennial screening of women aged 50-74 is associated with a 23% mortality reduction
- Early detection = less advanced stage of cancer = less “aggressive” treatment needed

(Adapted from Leslie Arpin, MD- Good Sam Reg Med Center, Corvallis, OR - Oct 10, 2014)

**Quantifying the benefits and potential harms
of yearly screening mammography,
for 1000 women, over a 10-year period**

| Age starting screen | # of avoided deaths from breast cancer (lower estimate, 5% reduction; upper estimate, 36% reduction) | # of women given at least one “false alarm” | # of women who would receive unnecessary treatment |
|----------------------------|---|--|---|
| 40 years | 0.1-1.6 | 510-690 | ? - 11 |
| 50 years | 0.3-3.2 | 490-670 | 3 - 14 |
| 60 years | 0.5 – 4.9 | 390-540 | 6 - 20 |

*Gilbert HG. Passow HJ (Dartmouth Inst of Health Policy and Clinical Practice):
JAMA Int Med. April 2014;174:448-453*

Comparison of guidelines on breast cancer screening: “Mammography Wars”

| Country | Starting age | Frequency of mammograms (total #) | Stopping age |
|--|---|-----------------------------------|--------------|
| UK (2012) | 50 | Every 3 yrs (7) | 70 |
| Canada (2011) | 50 | Every 2-3 yrs (10-12) | 75 |
| US Preventive Services Task Force (2009, 2016) (B) | 50 (C for 40) | Every 2 yrs (13) | 75 |
| Switzerland (2014) | No routine screening | | |
| American Cancer Society (re-affirmed in 2014) | “Women age 40 and older should have a mammogram every year and should continue to do so for as long as they are in good health” | | |

Sources: A Bleyer, MD –OHSU, September 12, 2014; Siu AL et al, Ann Int Med Jan 2016

Benefit/risk data for screening colonoscopy for colorectal cancer

| | Colonoscopy group | No-screening control |
|---|--|-------------------------------|
| Colorectal cancer incidence | Reduced by 20% in screened individuals | |
| Cancer-specific mortality rate | Reduced by 27% in screened individuals | |
| Mortality from colorectal cancer | 3/per 1000 individuals | 4/per 1000 individuals |
| Risks associated with screening colonoscopy | Discomfort; cost Removal of low-grade adenomas that do not influence mortality Rarely, bowel perforation (but reported as high as 1/450 procedures ?) | |

Source: JAMA, Aug 13, 2014 –(patients followed for over an average of 11 years)

Value-based health care: *Patient-focused, socially responsible*

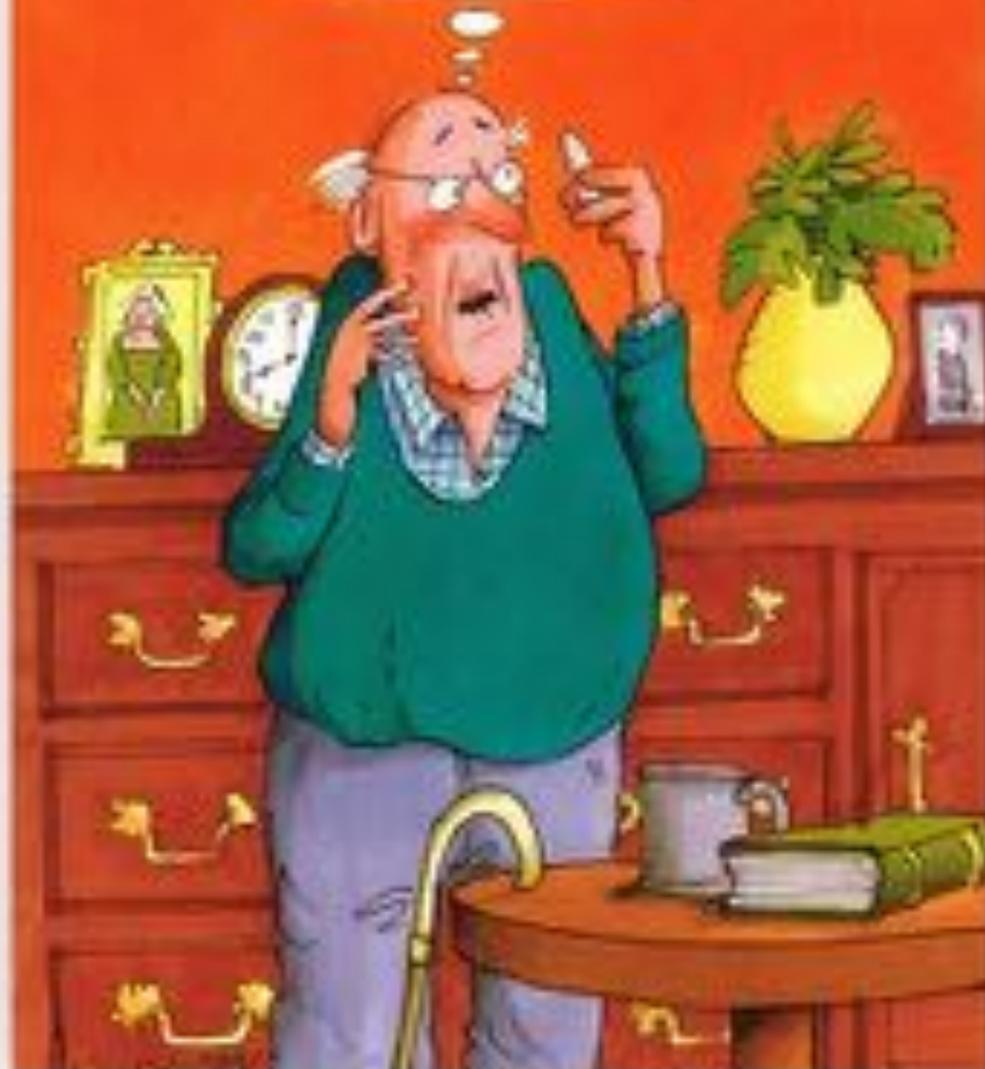
$$\frac{\text{Outcomes that matter to patients}}{\text{Cost per patient}} = \text{Value}$$

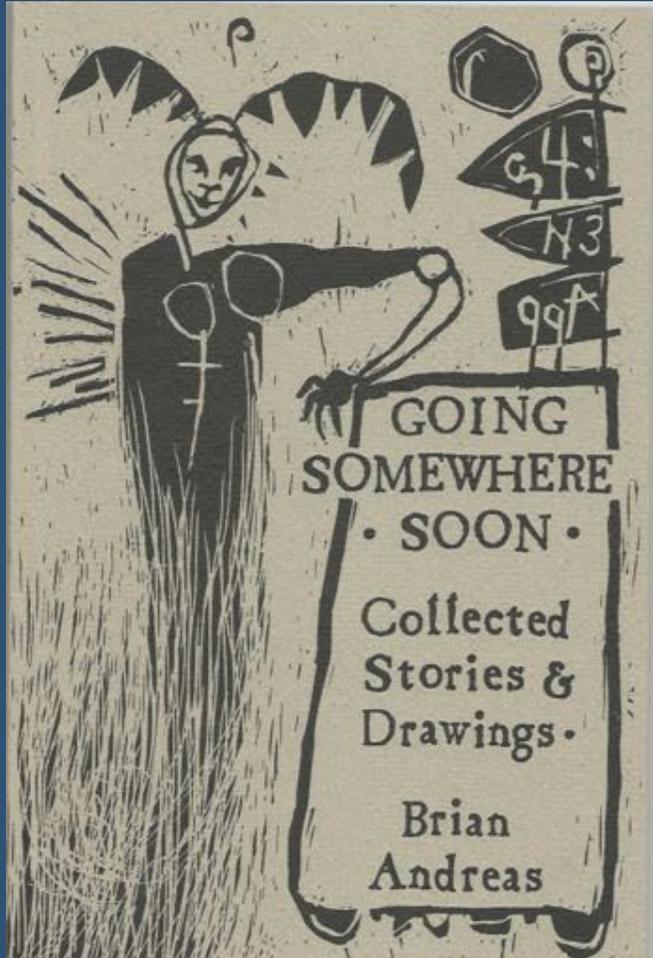
Benefits to patient
and to society

= -----

- **Risks** associated with medical intervention
- **Costs** to patient and to society:
 - Number needed-to-treat
 - Competing priorities
 - Costs for not acting

HOLD ON...IF I'VE
GOT A SUPPOSITORY IN MY
EAR - WHERE THE HELL IS
MY HEARING-AID?





Make sure you got
clean underwear, she
always said, in case
you get in an accident
& I always figured
that'd be the least
of my worries, but
now I'm older & I
see there's a lot you
can't control & some
you can control &
clean underwear is
one of those you can.

Cognitive decline and dementia(*)

- A decline in one or more cognitive areas (learning and memory, language, executive function, complex attention, perceptual-motor, social cognition).
 - Dementia: severe enough to interfere with daily activities, social functioning, and independence
 - In AD, preclinical stage may begin years before symptoms
- 60-80% caused by Alzheimer's disease (AD)
 - Other causes:
 - Vascular dementia
 - Dementia with Lewy bodies
 - Parkinson's disease
 - Fronto-temporal (Pick's) dementia
 - Heavy metal poisoning, some chronic infections, vitamin or hormone deficiencies, medications etc...

* from Latin word “*de*” (out of); and “*mens*” (mind)

Increased risks of dementia

- Modifiable risk factors (35%)
 - *Life style*
 - *Environmental*
 - *Co-morbid medical conditions*
- Non-modifiable risk factors (65%)
 - *apolipoprotein E (ApoE) e-4 allele increases by 3x (in heterozygotes) to 15x (in homozygotes) the risk for late-onset Alzheimer's disease , but its presence alone does not cause AD*
 - *other unknowns*

(Source: The Lancet Commission on Dementia Prevention, Intervention and Care, July 20, 2017)

Modifiable factors that correlate with dementia

| | <u>RR</u> (95% CI) |
|------------------------------|--------------------|
| • In early life (age <18) | |
| education <secondary school | 1.6 (1.26-2.01) |
| • In middle (age 45-65 yrs) | |
| hypertension | 1.6 (1.16-2.24) |
| obesity | 1.6 (1.34-1.92) |
| Hearing loss | 1.9 (1.38-2.73) |
| • In later life (age>65 yrs) | |
| smoking | 1.6 (1.15-2.20) |
| depression | 1.9 (1.55-2.33) |
| physical inactivity | 1.4 (1.16-1.67) |
| social isolation | 1.6 (1.32-1.85) |
| diabetes | 1.5 (1.33-1.79) |

(Source: The Lancet Commission, July 20, 2017)

Neuro-protective effect of physical activity is still unproven

- Prospective cohort study involving 10,308 participants enrolled at the age of 35-55 years, assessed 7 times over 27 years (1985-88)
- Findings: No association between physical activity (up to 2.5 hours/week of vigorous exercise) and subsequent cognitive decline or development of dementia

(Source BMJ: Sabia S: BMJ, June 2017- Whitehall Cohort Study, England)

Benefits of interventions to prevent cognitive decline and dementia: *“encouraging, but inconclusive”*

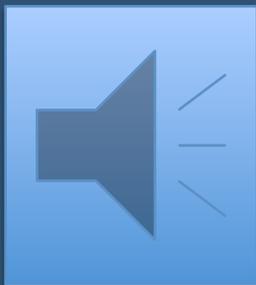
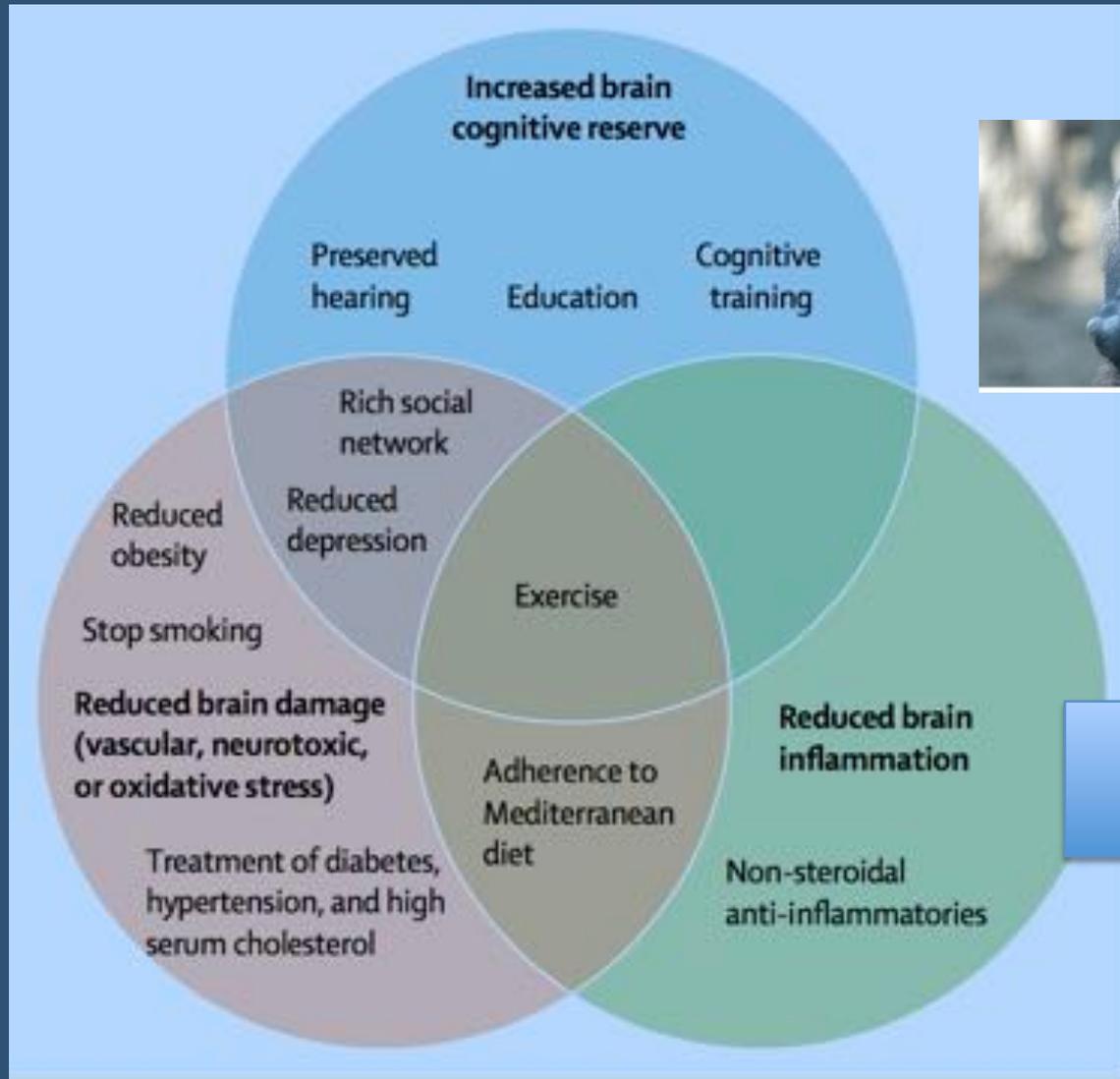
| | Strength of evidence from RCTs | Strength from observational studies | National Academy of Sciences recommendations |
|--|--------------------------------|-------------------------------------|--|
| Cognitive training (“brain games”) | Low-moderate | | No endorsement |
| BP management in people with hypertension | weak | moderate | Promote, but not enough evidence to mount an assertive public health campaign |
| Increased physical activities | weak | moderate | |

(RCTs= randomized Controlled Trials)

Source: National Academic Press 2017

Potential strategies to prevent dementia

In the absence of vigorous science : use common sense and intuition ?



(Source: The Lancet Commission on Dementia Prevention, Intervention and Care, July 20, 2017)



“Poor fool with all the sweated lore,
I stand no wiser than I was before”

JW von Goethe -Faust – Part One, 1806

There are times
I think I'm doing
things on principle,
but mostly I just
do what feels
good.

But that's a
principle, too.

Brian Andreas

*“Going Somewhere Soon”
Collected Stories and Drawings*

2017 definition of normal Blood Pressure and Hypertension (regardless of age or co-morbid health conditions)

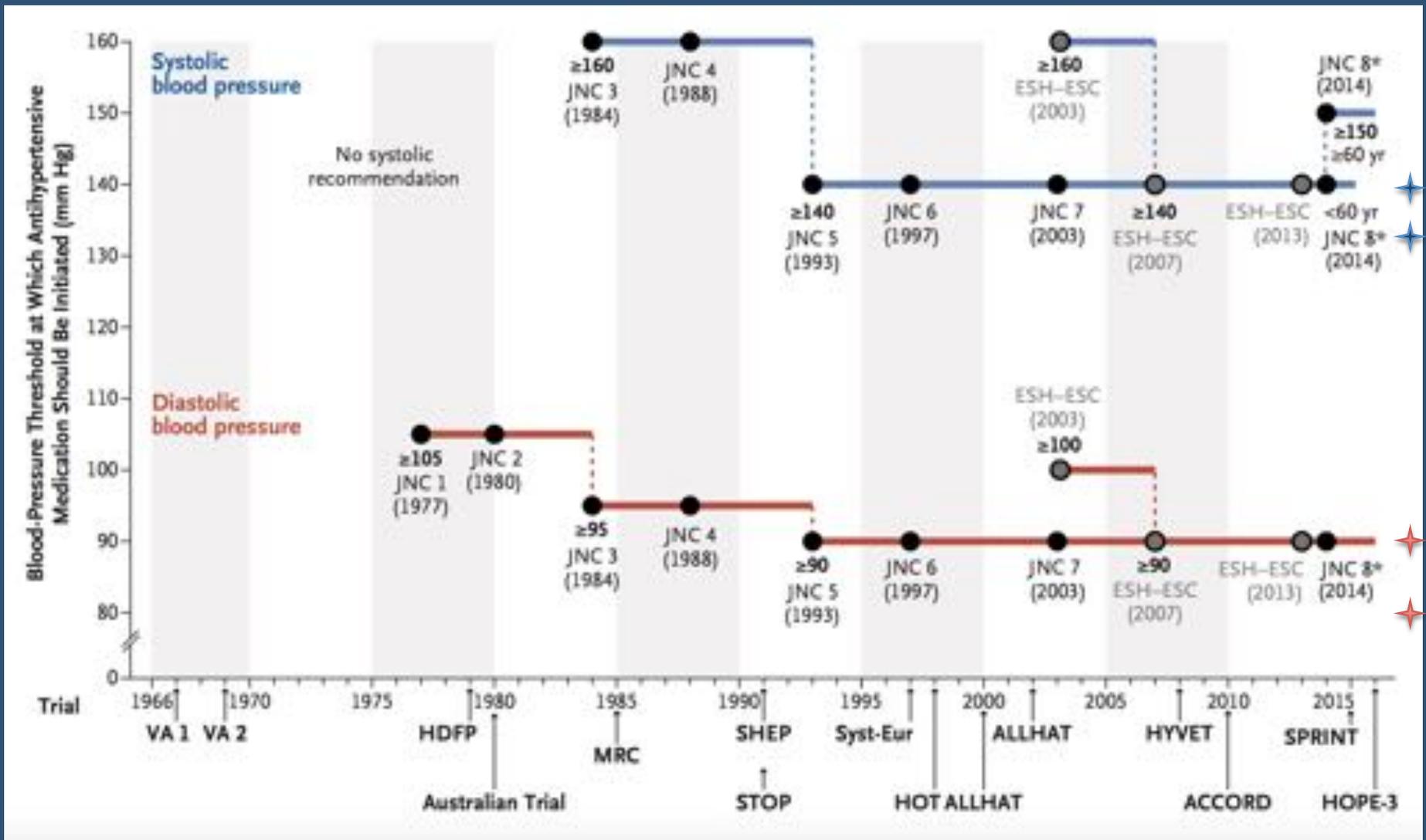
| BLOOD PRESSURE CATEGORY | SYSTOLIC mm Hg (upper number) | | DIASTOLIC mm Hg (lower number) |
|--|----------------------------------|---------------|-----------------------------------|
| NORMAL | LESS THAN 120 | and | LESS THAN 80 |
| ELEVATED | 120 - 129 | and | LESS THAN 80 |
| HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1 | 130 - 139 | or | 80 - 89 |
| HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2 | 140 OR HIGHER | or | 90 OR HIGHER |
| HYPERTENSIVE CRISIS (consult your doctor immediately) | HIGHER THAN 180 | and/or | HIGHER THAN 120 |

Source: American Heart Association and American College of Cardiology, JAMA Nov 20, 2017

Recommendations for control of high blood pressure, 2017

- First and foremost, life-style changes
- If low CVD risk (<10% in next 10 years), aim at BP <140/90
- If BP >140/90, **drug Rx** regardless of risk factors
- **Drug Rx** recommended – aiming at BP <130/80, if:
 - If CVD risk is >10% in next 10 years, or
 - aged >65, or
 - patients with diabetes or chronic kidney disease

Trials influencing guidelines for Rx for hypertension



(Pfeffer, McMurray: NEJM, Nov 3, 2016)

A Randomized Trial of Intensive vs Standard Blood-Pressure Control (SPRINT study) (slide 1)

- 9361 individuals, aged >50
- Systolic BP =130-180 mg Hg, and
- With one or more increased Cardio-Vascular (CV) risks:
 - *Clinical or subclinical CV disease*
 - *Chronic kidney disease*
 - *A 10 year-risk of CV disease = or > 15%, or*
 - *Age >75*
- Patients with diabetes or prior stroke excluded

- Goals:
 - Intensive: BP <120
 - Standard: BP <140
- Outcomes measured:
Primary composite of events:
Myocardial infarction, stroke, heart failure, or death from CV disease

(Source :NEJM Nov 9, 2015; updated Sept 2017)

Blood pressure control *Sprint* study (slide #2)

| | Intensive Rx (mean 2.8) | Standard Rx (mean 1.8) | Hazard ratio (95% CI) | Relative reduction |
|-------------------------------|-------------------------------------|--------------------------------------|-----------------------------|-----------------------|
| CVD event | 243/4678 1.6% per year | 319/4633 2.19% per year | 0.75 (0.64-0.89) | 25% |
| Death All causes | 155 | 210 | 0.73 (0.6-0.9) | 27% |
| Renal damage | 1.21% per year | 0.35% per year | 3.49 (2.4-5.1) | |
| Serious adverse effects | 4.7% per year | 2.5% per year | 1.88 P <0.001 | |

Association of BP lowering and CVD outcomes: *strongest for baseline systolic BP = or > 140*

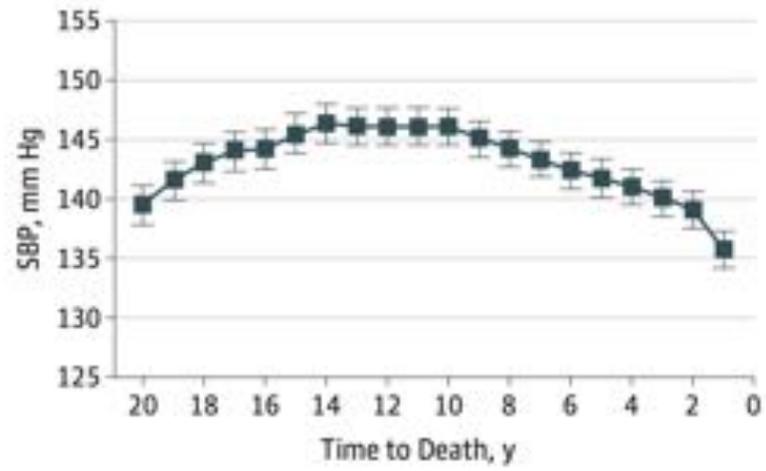
| Baseline systolic BP | Reduction in mortality RR (95% CI) | Reduction in CVD events RR (95%) | Relative risk reduction in CVD events |
|----------------------|---------------------------------------|-------------------------------------|---------------------------------------|
| > 160 | 0.93 (0.87-1.00) | 0.78 (0.7-0.87) | 22% |
| 140-159 | 0.87 (0.75-1.00) | 0.88 (0.8-0.96) | 12% |
| <140 | 0.98 (0.9-1.06) | 0.97 (0.9-1.04) | 3% |

(Meta-analysis of 74 trials involving >306,000 participants, primary intervention, 60% men, mean age 63.6 yrs)

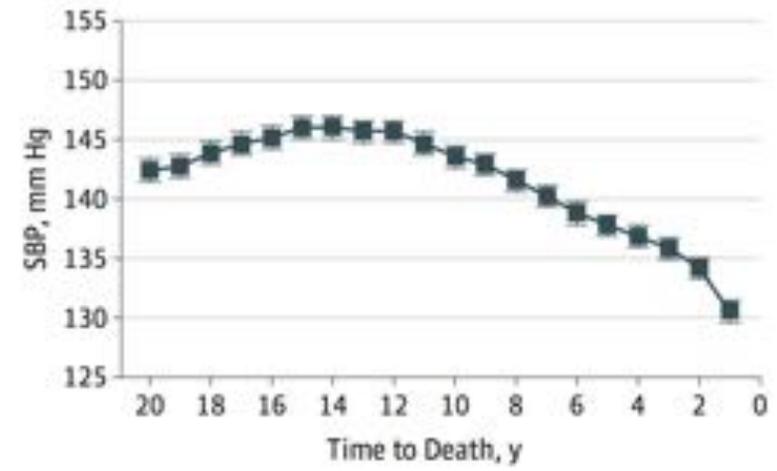
(Brunstrom: JAMA Int Med. Jan 2, 2018 - and commentary by Moran)

Blood Pressure trajectory 20 years before death

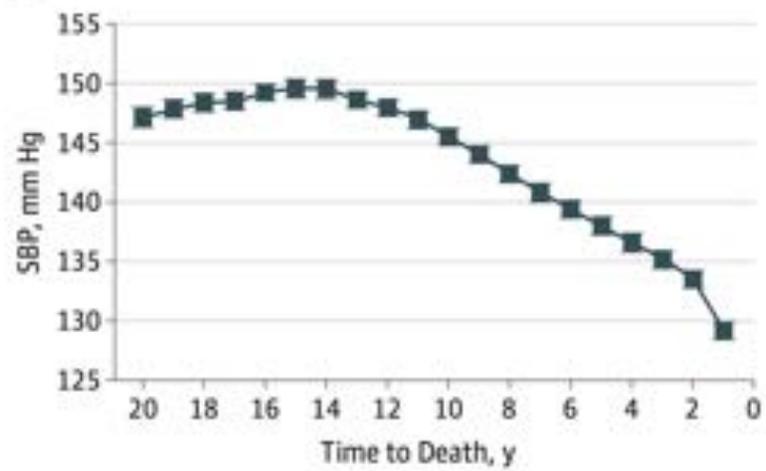
A 60 to 69 years



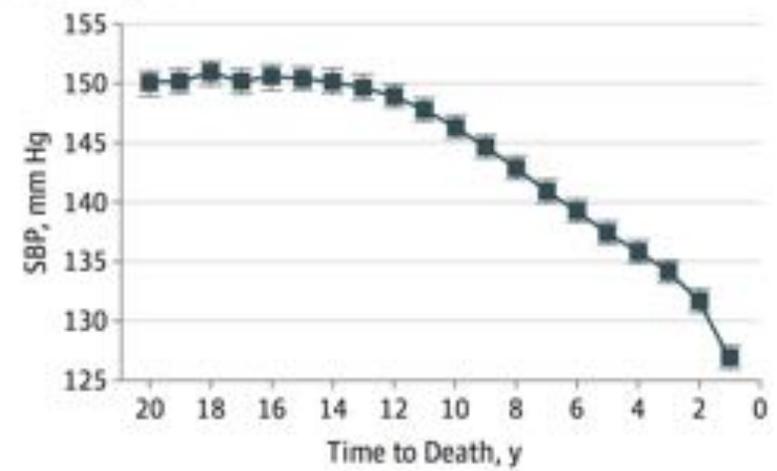
B 70 to 79 years



C 80 to 89 years



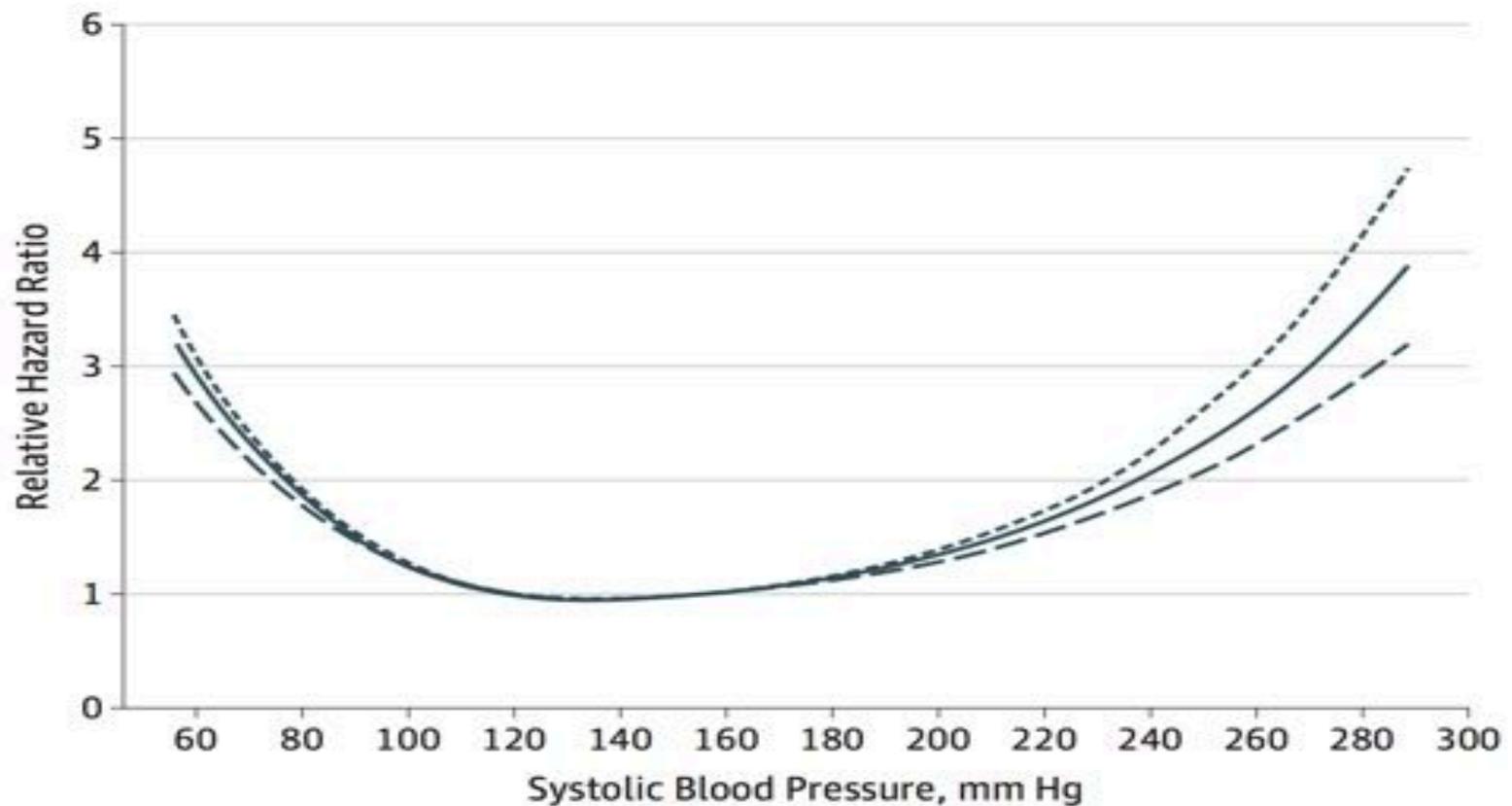
D ≥90 years



>46,000 participants in UK; results not attributable to antihypertensive Rx
(Delgado: JAMA Int Med Dec 4, 2017)

Ideal BP target for patients with chronic kidney diseases

Figure. Mortality Hazard Ratios Associated With Various Baseline Systolic Blood Pressures



The illustrated cohort consisted of 651 749 US veterans, each with an estimated glomerular filtration rate lower than mL/min/1.73 m². This graph was adapted from Kovesdy et al.²

Source: C Kovesky. JAMA Oct 2017, vol 177(10)

A low sodium intake and a diet rich in fruits, veggies, low fat (DASH diet) might work better than meds (?)

FDA requirement for new antihypertensive drugs (13)

Angiotensin-converting enzyme inhibitors (12)

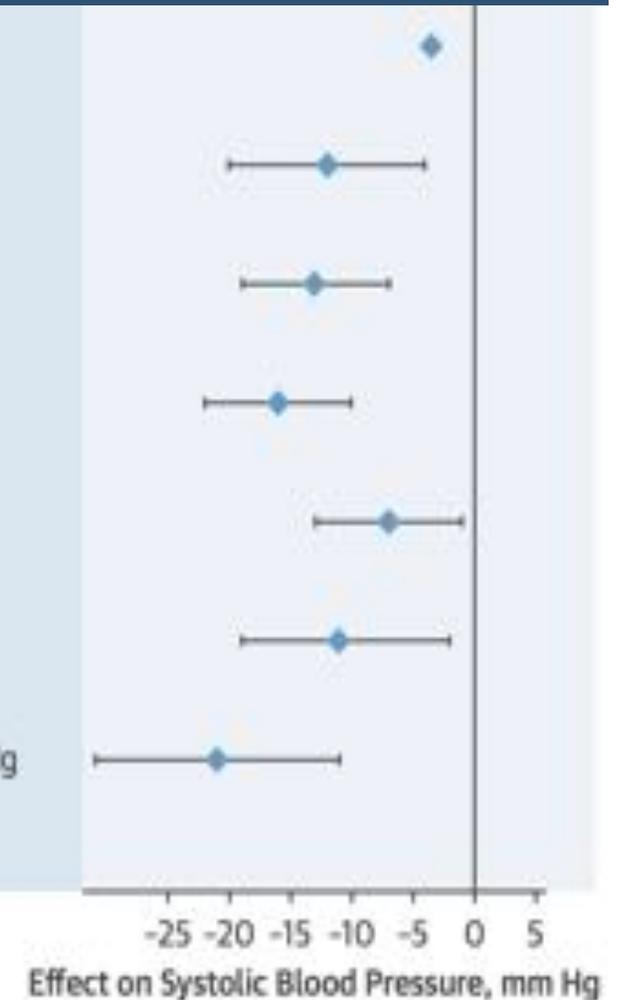
Beta blockers (12)

Calcium-channel blockers (12)

Sodium reduction (on a control diet) in participants with a baseline SBP ≥ 150 mm Hg

DASH versus control (at high sodium) in participants with a baseline SBP ≥ 150 mm Hg

DASH-low sodium (vs control-high sodium) in participants with a baseline SBP ≥ 150 mm Hg



412 participants with Stage 1 or pre-hypertension, mean age 48 yrs; studied for 4 weeks
(Source: *J Amer Coll Cardiology*, Vol 70 (23): 2017)

Benefits of statin Rx for primary prevention of cardio-vascular diseases (CVD)

Results from 19 RCTs (71,344 participants, aged 40-75)
without known CVD, mean duration of follow-up = 3 years

| Outcome | Pooled Risk Ratio (95%CI) | Relative reduction |
|---------------------------|------------------------------|-----------------------|
| Cardio-vascular mortality | 0.69 (0.54-0.88) | 31% |
| Stroke | 0.71 (0.62—0.82) | 29% |
| Non-fatal heart attack | 0.64 (0.57-0.71) | 36% |
| Mortality, all causes | 0.86 (0.80-.0.93) | 14% |
| Composite CV outcome | 0.70 (0.63-0.78) | 30% |

(Source: JAMA Nov 15, 2016)

Guidelines for use of statin Rx for primary prevention of CVD

| | Target population | With following conditions |
|---|--------------------------|--|
| Amer Coll Cardiology/ Am Heart Assoc (2013) | Age 40-75 | LDC-C 70-189 mg/l and diabetes, or a 10-yr CVD risk >7.5% |
| USPSTF (JAMA Nov 2016) | Age 40-75 Age >76 | 1 or more CVD risk factor, and 10-yr CVD risk = or >10% (B recommendation); 10-yr CVD risk of 7.5% – 10% (C recommendation) |
| Canada (2013) | Men >40, women >50 | 10-yr CVD risk >20%; or LDL-C >135-190mg/l and risk 10-20% |
| United Kingdom (2016) | >40 | 10-yr CVD risk = or > 10% |

(risk for CVD = dyslipidemia (LDC-C >130 mg/l or HDL-C<40mg/l; diabetes; hypertension; smoking); Use ACA-AHA “risk calculator”

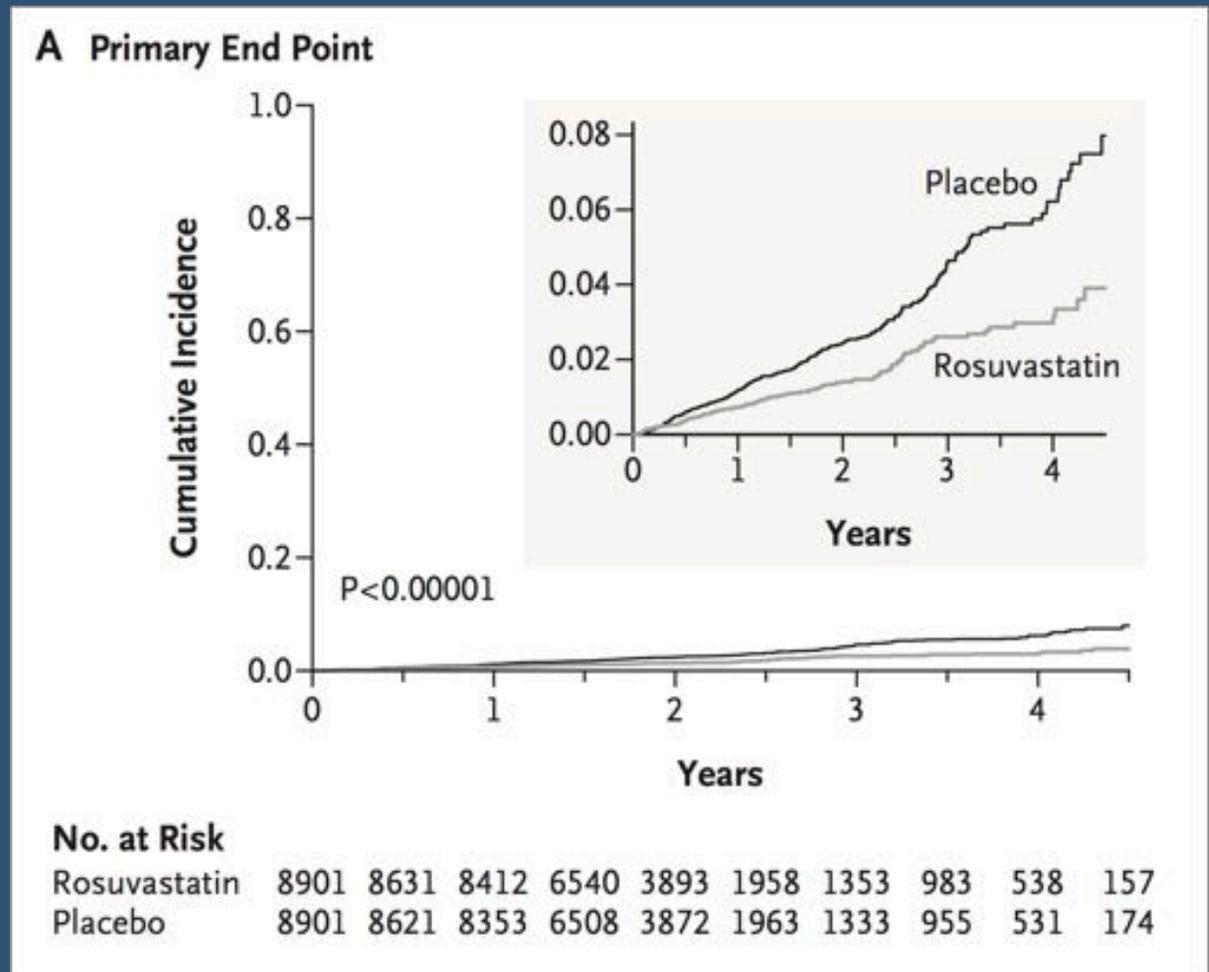
Statin Rx for the primary prevention of vascular events (JUPITER trial, *NEJM* Nov 20, 2008)

- 17,802 participants from 26 countries, highly selected by strict exclusion criteria

Inclusion criteria:

- Healthy men >60, women >50
- hs C-Reactive Protein >2mg/l)
- LDL-C <130 mg/dl

Median follow-up=1.9 years



CVD events per 100 person-year

Statin

placebo

HR (95% CI)

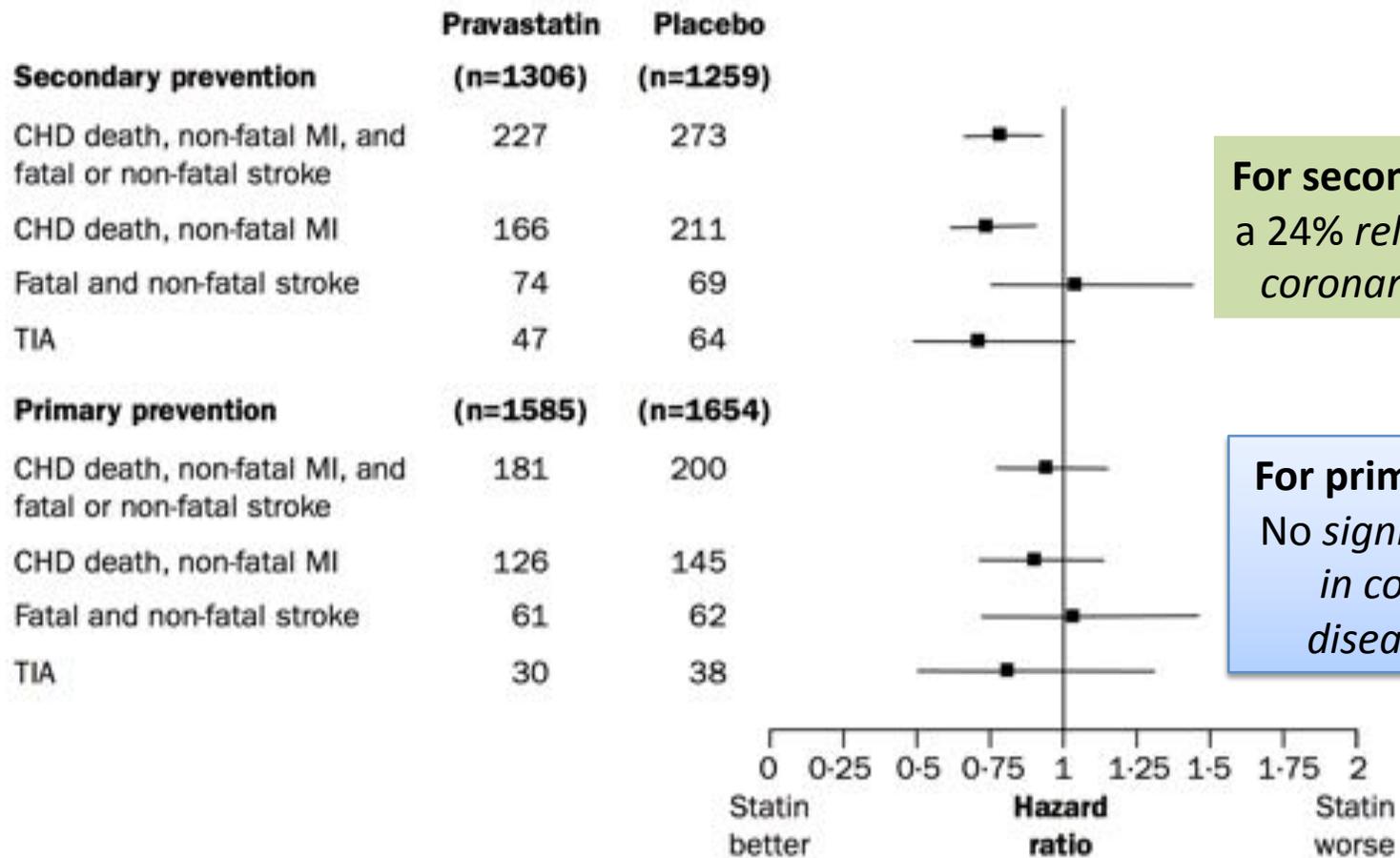
0.77

1.36

0.56 (0.46-0.69) or a **34% risk reduction**

Use of statin Rx for prevention of cardiovascular diseases:

The PROSPER randomized controlled trial (2002)



For secondary prevention:
a 24% relative reduction in coronary heart diseases

For primary prevention:
No significant reduction in coronary heart diseases or strokes

Figure 4: Major cardiovascular outcomes, according to primary or secondary prevention status of participants

CHD=coronary heart disease. MI=myocardial infarction. TIA=transient ischaemic attack. The primary endpoint of the study is reproduced for comparative purposes.

(Source: *The Lancet*: Nov 23, 2002)- participants aged 70-82

RCTs of use of statins in primary prevention of CVD (slide #2)

| Study | Population | Mortality rate / 5-year follow-up | | |
|---|--------------------------------------|-----------------------------------|-----------------------|---------------------|
| | | Statin Rx (#1467) | Usual care (#1400) | HR (95% CI) |
| ALLHAT-LLT US (JAMA May 22, 2017) | With hypertension and hyperlipidemia | | | |
| | Aged 65-74 | 15.5% | 14.2% | 1.08 (0.85-1.37) |
| | Aged >75 | 24.5% | 18.5% | 1.34 (0.98-1.84) |

| Study | Population | Heart attack or stroke/ 5.6 years | | HR (95% CI) |
|---|---|--------------------------------------|-------------------|--|
| | | Statin Rx # 6361 | Placebo # 6344 | |
| HOPE-3 21 countries (NEJM May 26, 2016) | Males >55 Females > 60 With 1 or > CV risk factors | # 235 | # 304 | 0.76 (0.64-0.91) |
| | | (3.7%) | (4.8%) | Relative risk reduction = 24% |

“Number to treat”:

“For each patient we may help, how many might we potentially harm without clear benefits?”

| | Relative reduction | # to treat to prevent |
|--|--------------------|---|
| Use of statin drug for primary prevention of CVD <i>(systematic review from 19 RCTs)</i> | 30% | 1 CVD event = 72 1 death = 244 individuals, for 5 years |

(Source: USPSTF guideline evidence / JAMA 2016;316(19):2008-24)

| | Risk reduction | Absolute reduction |
|---|--|--|
| More intense drug Rx for hypertension <i>(SPRINT study)</i> | Decrease incidence of CVD from 8% to 6% over 4 years, or 25% relative reduction | 2 CVD events prevented for every 100 treated individuals |

(Source: Welch HG, Dartmouth Inst Health Policy and Clinical Practice, NYT Nov 15, 2017)

RISK CALCULATOR
for cardio-vascular
events (heart attack,
stroke, death...) in
the next 10 years

**American College of
Cardiology/
American Heart
Association**

Input:

- Age
- Gender
- Race (African American?)
- Total Cholesterol
- HDL
- Systolic BP
- Diastolic BP
- Treated for high BP ?
- Diabetes?
- Smoker?



- Age= 69 years
- Gender: Male
- Race: not Afr Amer
- Total Cholesterol= 220
- HDL= 49
- Systolic BP =122
- Diastolic BP= 78
- Treated for high BP: No
- Diabetes: No
- Smoker: No

My ACC/AHA Risk Calculator

- My risk is **16.6%** for having heart disease or a stroke in the next 10 years
- The USPSTF recommends low dose-aspirin
- AHA/ACC recommend: start Rx with a moderate-high intensity statin



Impacts of new guidelines

85% of US adults have at least one of the risks associated with adverse cardio-vascular events: *high cholesterol; diabetes; smoking; or high BP*

- New definition means that ½ of all American adults, and 80% of aged >65 have hypertension
- Simply being aged >65 brings a 10% risk of CVD in the next 10 years

Under current guidelines:

- 103 million Americans (from 72M before definition change) now carry the diagnosis of hypertension, and 4.2M more will need drug Rx
- Statin Rx would be recommended for 96.4% of men; and 65.8% of women by 65 ½ years of age

After intermission

- The new frontiers of medical sciences
 - Will they improve health outcomes?
- Medical care as the art of medicine
 - Drawing the contrast between science and art
 - Where the practice of medicine joins other art forms
- Open forum

What you can do
during this break

#1



*Ask your doctor if **Preparation H** is right for you*

What you can do during this break
#2

Take a walk

Walking can add minutes to your life every year. This enables you at 85 years of age to spend an additional 5 months in a nursing home at \$5,000 per month.

(Anonymous Internet author)

What you can do
during this break:
#3

Re-connect



Monica Pizzarelli



**What you can do
during this break:
#4**

Redefine yourself

When radiologists take a selfie

memee.com



New technologies in medicine

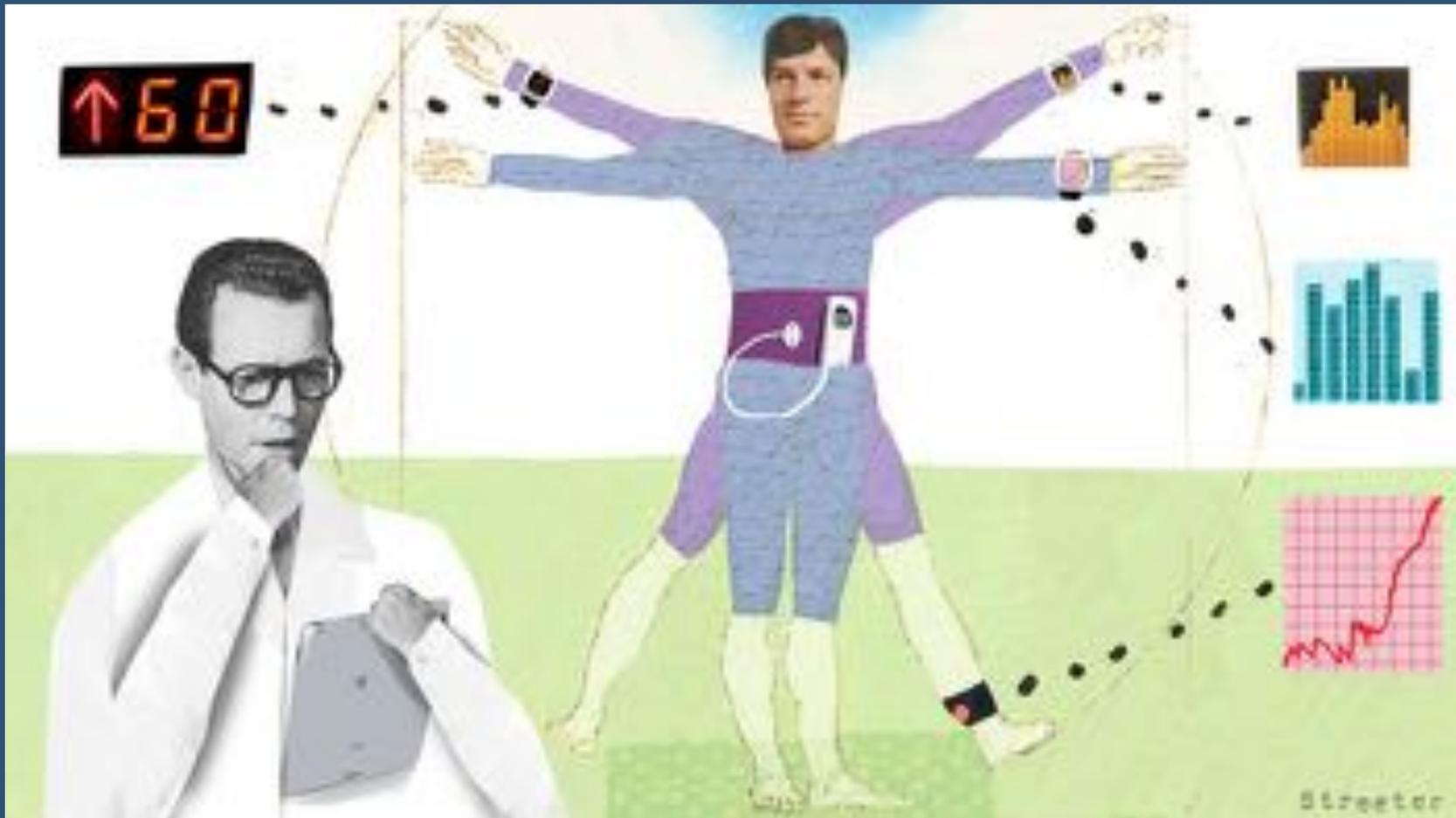
- Information Technology (IT) innovations in patient digital monitoring and communications
- Tele-medicine consultations
- Web-based repository of medical information
- Robotic surgeries
- Artificial Intelligence



... Like any tool, they can help ...or hurt

Medicine in the twenty first century...

Would e-gadgets know and connect with patients better ?



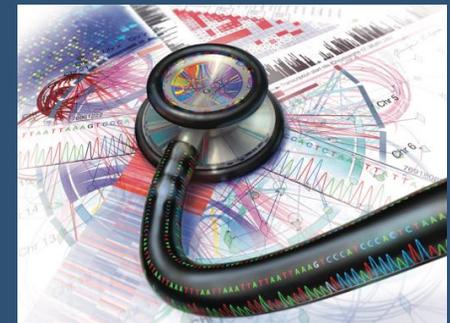
Expanding the frontiers of medical sciences

- New foci in basic research and therapeutics:
 - Genetics and immunology
 - Human microbiomes



- Beyond the limitations of current evidence-based medicine:

- Making use of “Big Data”
- “Precision medicine”



Examples of new technologies expanding the frontiers of medical sciences

1. Digital monitoring, big-data, artificial intelligence:

- Apps for “digital monitoring” patient’s pattern of Rx use
- “Data mining” : Pool huge amount of data from large number of individuals, allowing stronger bases for statistical analysis
- “Machine-learning”: Build clinical algorithms with better predictive value and accuracy than current guidelines
- Clinical trial stimulators : Use of mathematical models of disease progression to explore potential outcomes

Examples of new technologies expanding the frontiers of medical sciences

- 2. “Precision medicine”
 - Identify mechanisms of health and diseases (“biomarkers”) and aim at specific “targets” for drug or vaccine development
 - Examples: monoclonal antibodies; genomics and gene therapy; viral bacteriophage cocktails for antibiotic-resistant bacteria

Would new informative technologies improve health outcomes?

Probably not with the current level of functional literacy !



| Functional literacy level | Sample tasks |
|---------------------------|---|
| Basic quantitative | Use TV guide to find out what programs are on at a specific time; compare ticket prices for 2 events ; add cost of salad + sandwich from a menu |
| Intermediate | Consult reference materials to determine vitamin content of foods; calculate total cost of ordering office supplies from a catalog |
| Proficient | Compare viewpoints in 2 newspaper editorials; interpret a table about BP, age, and physical activity; compute and compare the cost per ounce of food items, or credit card offers at different interest rates |



Source: Am Inst Res and Pew Charitable Foundation: Functional literacy of US college graduates – a 2006 report

Physician-patient communication – *Then*

Trust me,
I am a
doctor

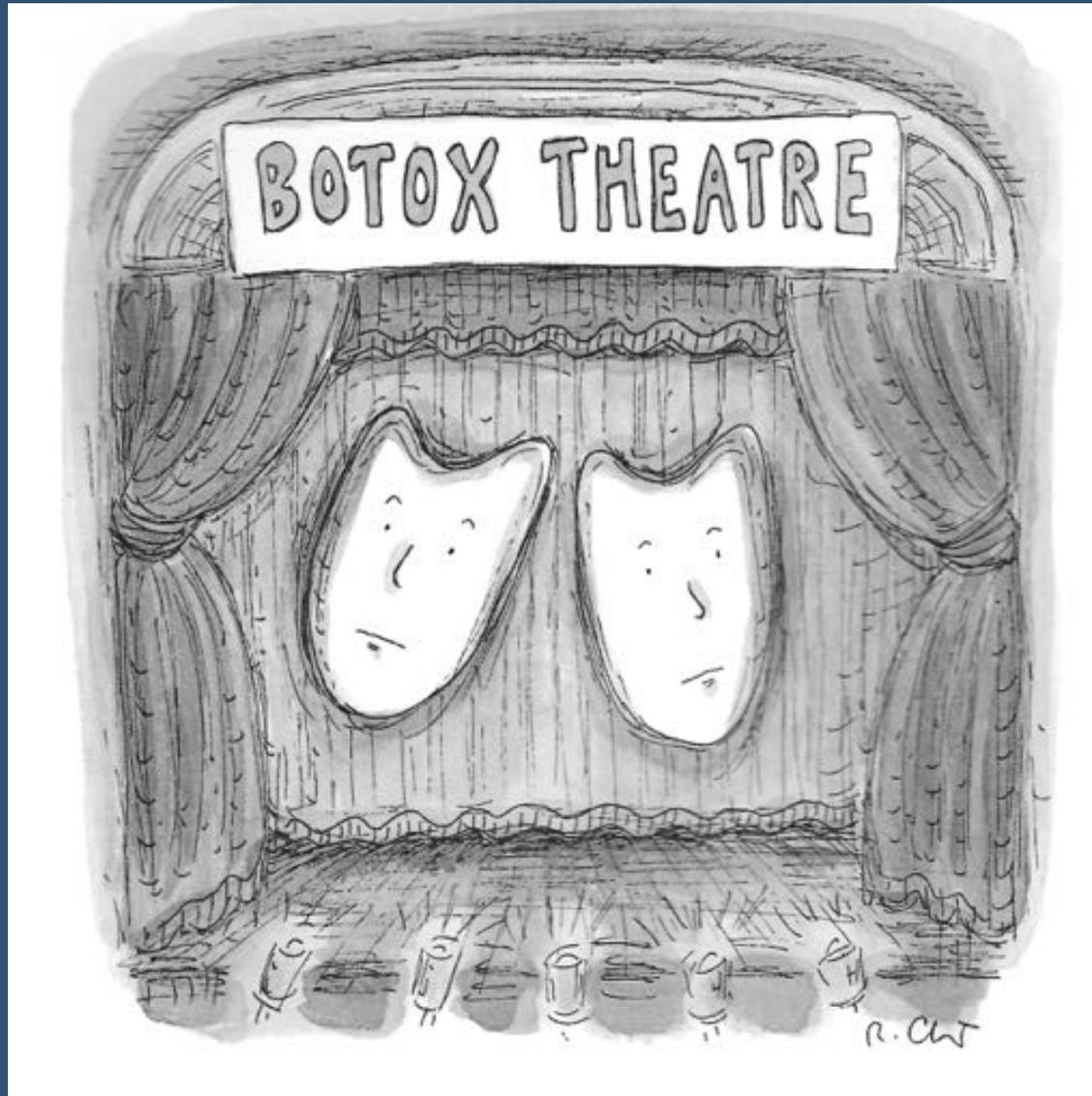
! # ?

\$\$

*!??



*Making patients aware of potential side effects
of medical interventions*



Another joy of medical practice:
helping patients see life realities

Lesson from the Ebola:



“Failure to communicate”

- 2/3 patients are discharged from the hospital without even knowing their diagnosis
- > 60% of patients misunderstood directions after a visit to their doctor’s office
- On average, physicians wait just 18 seconds before interrupting patient’s narratives of their symptoms

(Source: Nirmal Joshi, MD – NY Times, Jan 4, 2015)

Physician-patient communication –

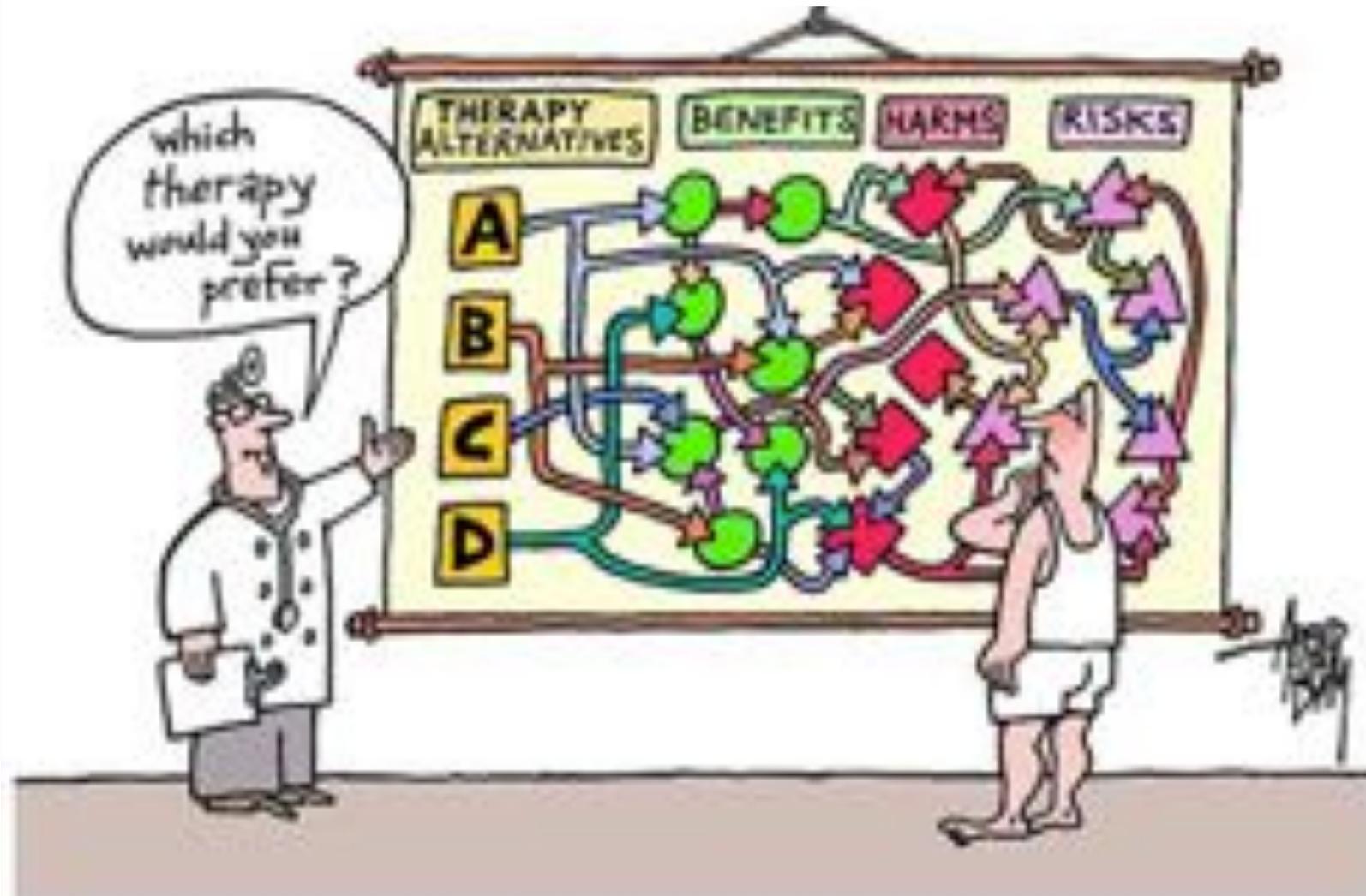
Now

LESS IS MORE

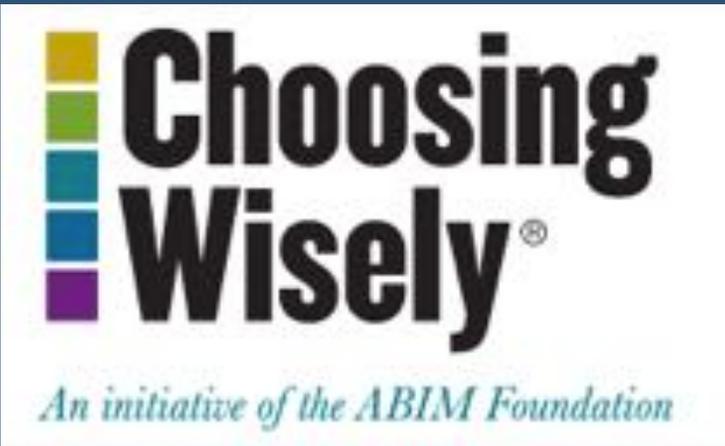
Shared Decision-Making

Easy to Evoke, Challenging to Implement

Miriam Kuppermann, PhD, MPH¹; George F. Sawaya, MD¹

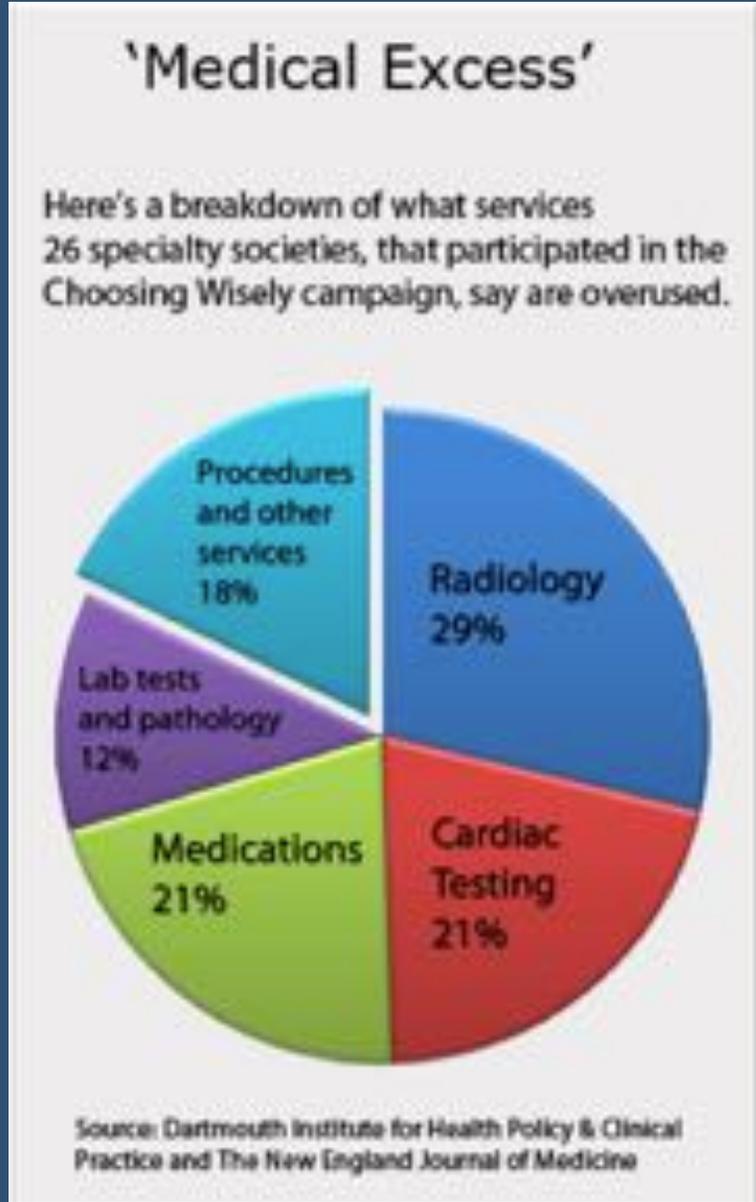


informed consent



Aims to promote conversation between providers and patients to choose care that is:

1. supported by evidence
2. not duplicated services
3. free from harm
4. truly necessary
(...still, be aware...!!!)



Risk of breast cancer in women currently using hormonal contraception (HC)(*)

Absolute risk:

68 (HC users) vs 55 (non-users) breast cancer cases –
or 13 more cases per
100,000 person-year

Relative Risk: 1.20

(95% CI, 1.14-1.26) or a 20% ↑

***Or 1 extra breast cancer case
for every 7690 women
using HC per year***

How do we rationally
make choices?

Benefits >> risks + costs

(*) A study of 1.8 million Danish women followed for >10 years – NEJM Dec 7, 2017

What is meant - the “art of medicine”?

- The myth: Medicine is a “healing art”
- A better answer might be: Being able to connect well with patients is at the heart of clinical care.
- **To connect** means:
 - Listening
 - Understanding each other’s mindset
 - Having empathy (*): helping patients overcome difficulties, while nursing their pains and wounds
 - Engaging in a fair process in “shared-decision” making

(*)empathy – from the German word *Einführung*, meaning “feeling into”



"If it's all the same to you, I'd rather eat this not knowing what the latest science suggests."

Mindsets

- Mindsets are lenses or frames of mind that orient an individual to a particular set of beliefs, association, expectations and behavior
- Mindsets are more visceral than we care to admit, as they are created and influenced by
 - Culture: family, religion, educational background and mentors
 - Past experiences
 - Social media and support groups

How others can take advantage of your mindset

“My leverage came from confirming an impression they were already predisposed to believe”

(Donald Trump, in “the Art of the Deal” 1987)

“Perception is more important than reality. If someone perceives something to be true, it is more important than if it is in fact true. This doesn't mean you should be duplicitous or deceitful, but don't go out of your way to correct a false assumption if it plays to your advantage.”

Ivanka Trump,

(in “The Trump Card: Playing to Win in Work and Life”, 2009)

Dangers of mindsets

- Accepting simplified versions of what's right or possible, to make sense of the incredible complex world.
- Assumes that wisdom resides with us (righteousness)
- Heuristics (mental short cuts to arrive quickly at an answer)
- Limit one's ability to analyze or accept rational information that conflicts with one's entrenched biases
- Creates anxiety when faced with needed changes

Reading mindset?



“Why We Lie”: The Science Behind Our Deceptive Ways”
(National Geographic, June 2017 - photo by Dan Winters)

Medical implications of mindsets

Providers

- Are quick at adopting new technology, and slow at shedding outdated practices
- Give patients the “benefit of the doubt” if risk of adverse effects may be less than potential benefits
- “Defensive medicine” - Giving in patients’ demands and expectations
- Therapeutic illusions: over-estimating the effects of one’s actions
- Tend to overestimate benefits and underestimate harms of medical intervention (*JAMA Int Med Jan 9, 2017*)

Patients

- **Confirmation biases:**
Reinforce expectations about diagnostic and treatment outcomes (accuracy, efficacy, side effects)
- **Therapeutic illusions:**
Placebo effect
Nocebo effect

Patients' expectations of benefits and harms of medical interventions: *the Polly Anna effect*

A systematic review of 36 studies:

- 14 studies on cancer screening
- 15 studies on treatment (surgical, cardiovascular, medications...)
- 3 studies on testing (diagnostic imaging)
- 3 studies on screening and treatment

Overall observations:

- Patients over-estimated the outcome benefits 65% of the time, and
- Under-estimated potential harm 67% of the time

(Source: Hoffman TC, and Korenstein D : JAMA Int Med, Dec 22, 2014)

Provider and patient communications: “Shared Decisions” have their own illusions

- Outcome of virtually all medical decisions is at least partly outside of physician control
- Providers usually don't change patients' mindsets that are deeply embedded, but may be able to minimize them.
- Providers' words can also inadvertently amplify patient's symptoms and distress

“The cure... May it be not as bad as the disease”

Miguel de Cervantes (1547-1616)



How:

Reframe mindsets:

“More is not better.”

Balance Benefits/costs+risks : *“Less is more”*

Examples:

Avoid over-testing

Allow “Mother Nature” to do some healing

Shorter course of therapy

Avoid sledgehammer approach

Consider active surveillance for low-grade cancers

“I long for a day, when instead of our complex guidelines, doctors are simply given summaries of evidence, with clear indications of the limitations and extent of uncertainty, and always acknowledging possible harm”

- *(Iona Heath, MD, Brit Med J, Nov 01, 2016)*

“I still find the best way to understand a patient is not by staring at a computer screen, but going to see that patient. For it is at the bedside that I can figure out what is important to the patient and how the data you have accumulated makes sense.”

Abraham Verghese, MD

*Professor of the Theory and Practice
of Medicine , Stanford University*

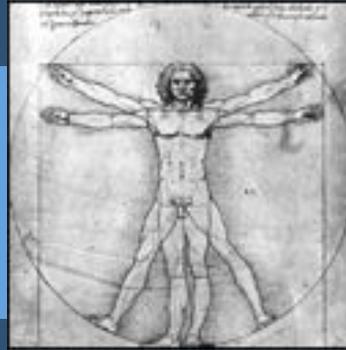


**“Medicine is
a science of uncertainty and
an art of probability”**

*Sir William Osler
(1849-1919)*



**Sciences:
to explain, using**



**Arts:
to connect, using**

- ***Objective*** analyses
- Quantifiable variables
- Precise measurements
- Logical calculations
- Rationality
- Reproducible results
- Seek consensus

- ***Subjective*** impressions
- Personal interpretations
- Fluid dimensions
- Spontaneous imagination
- Emotions
- Best when “one of a kind”
- Unique appeal to individuals

Science is about fighting uncertainty.

Art helps us accept uncertainties in our lives.

Point and counter-point:

**“It doesn’t count
unless you can
count it”**

*Leonard Abramson,
former chairman of
US Healthcare.*

*(In 1996, he made \$1 billion
on a \$ 8.3 billion sale of his
company to Aetna Life)*

**“Not everything
that can be
counted counts,
and not
everything that
counts can be
counted”**

Albert Einstein

**“It doesn’t count
unless you can
count it” ...**

*So, how do you count
or measure:*

despair

suffering

Hope

empathy

“feeling
vulnerable”

grief

“feeling
lost”

Unbearable pain

*“Not everything that can be counted counts,
and not everything that counts can be counted”*

What does the typical study of risk factors for cardiovascular events often fail to consider?

Typical medical studies try to correlate health outcomes with measurable data:

- Metabolic numbers:
 - Glucose, BP, cholesterol, Body Mass Index (BMI)...
- Life style:
 - Diet, smoking, exercise...
- Physical environment:
 - Air pollution
- Medications prescribed

But Intangible co-variants that might be just as important:

- Social determinants of health
 - Education
 - Early childhood experience
 - Inter-personal relationships:
 - Social isolation / support
- Mental health
 - Personality type
 - Stressful life events and coping behavior

Point and counter-point:
the art of healing

**“Words of comfort,
skillfully administered,
are the oldest therapy
known to men”**

Louis Nizer
(1902-1994)

*In “Perspective in Biology
and Medicine”, 1985*

“Caring without
science is well-
intentioned
kindness, but not
medicine”

B. Lown

*in “The lost art of healing:
practicing compassion in
medicine”, 1996)*

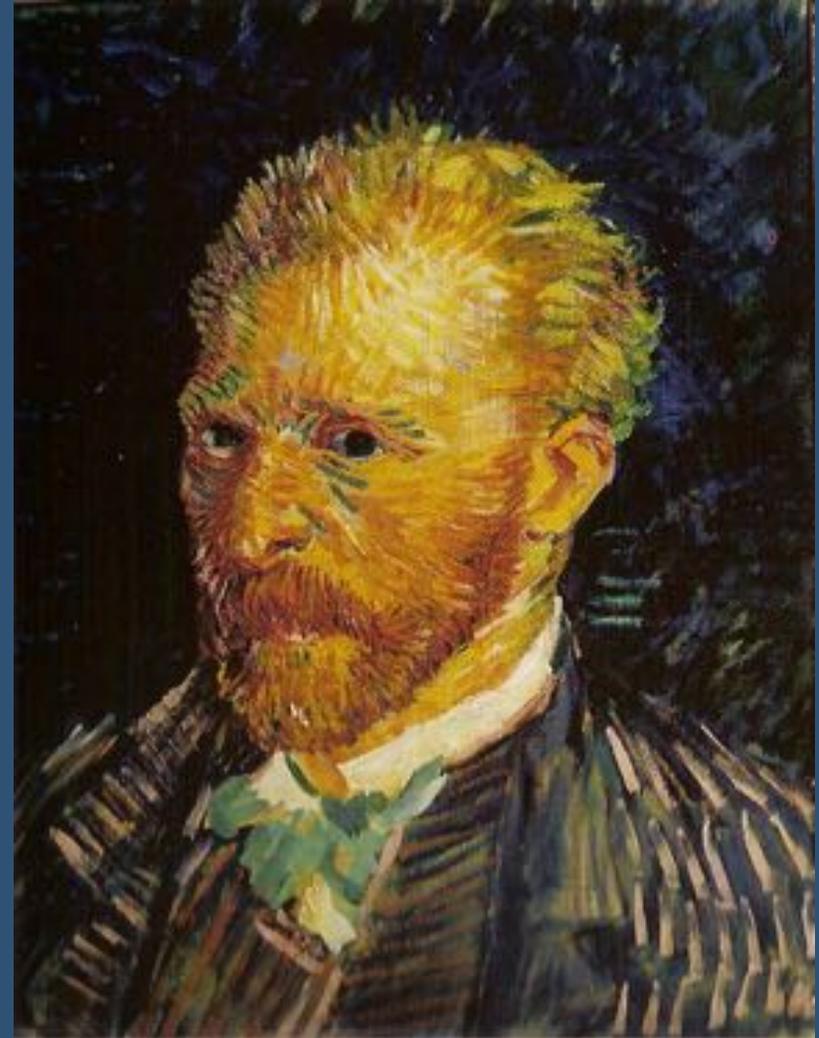
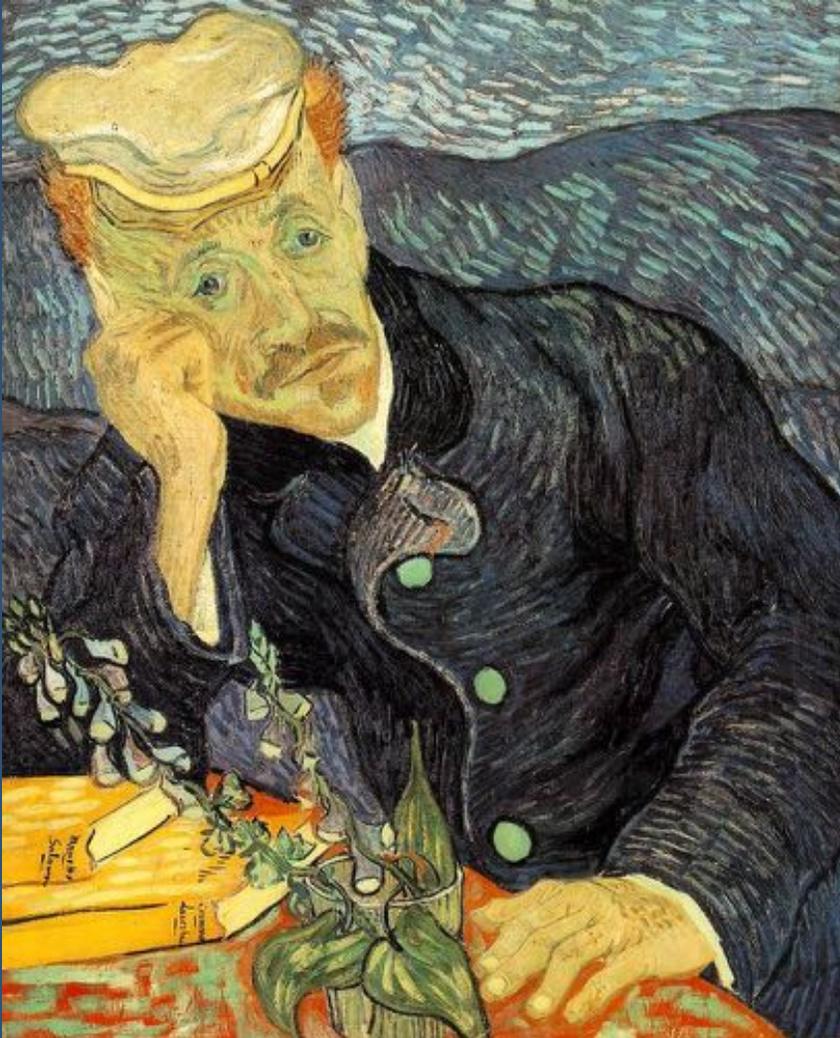
Medicine is a social contract built on science and artfully delivered

Medical sciences
help us understand
how we intersect
with the world,
and try to solve
problems of life with
information and
technology



The art of medicine
is to help us make better
choices in life, and
accept what we cannot
understand
nor change, such as the
existential challenges
of loss and our own
mortality

*Under a starry, starry night,
a common path: empathy*





“People don’t remember what you do, or what you say, but they will always remember how you make them feel”.



Freddie Wiggins
St Thomas Hospital, Nashville, TN
*(as reported on NBC Nightly News, June 21,
2017)*