Context for Current Treatments of Pain (I): Evidence-based Pain Medicine and Pain Management

NASEM Topical Pain Cream Workshop

May 20, 2019

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Tufts University School of Medicine

Topics (15-20 min)

- Prevalence of pain in the US population
- Trends over past 5-10 years
  - Pain management in general
  - Topical pain products specifically
- Subpopulations that would especially benefit from topical pain cream products
- Perspective on any patient preferences, in regard to pain management
- Safety or effectiveness of topical pain cream medications
- Specific recommendations (if any) would you like to see in the committee's report

AARP Magazine Apr-May 2019

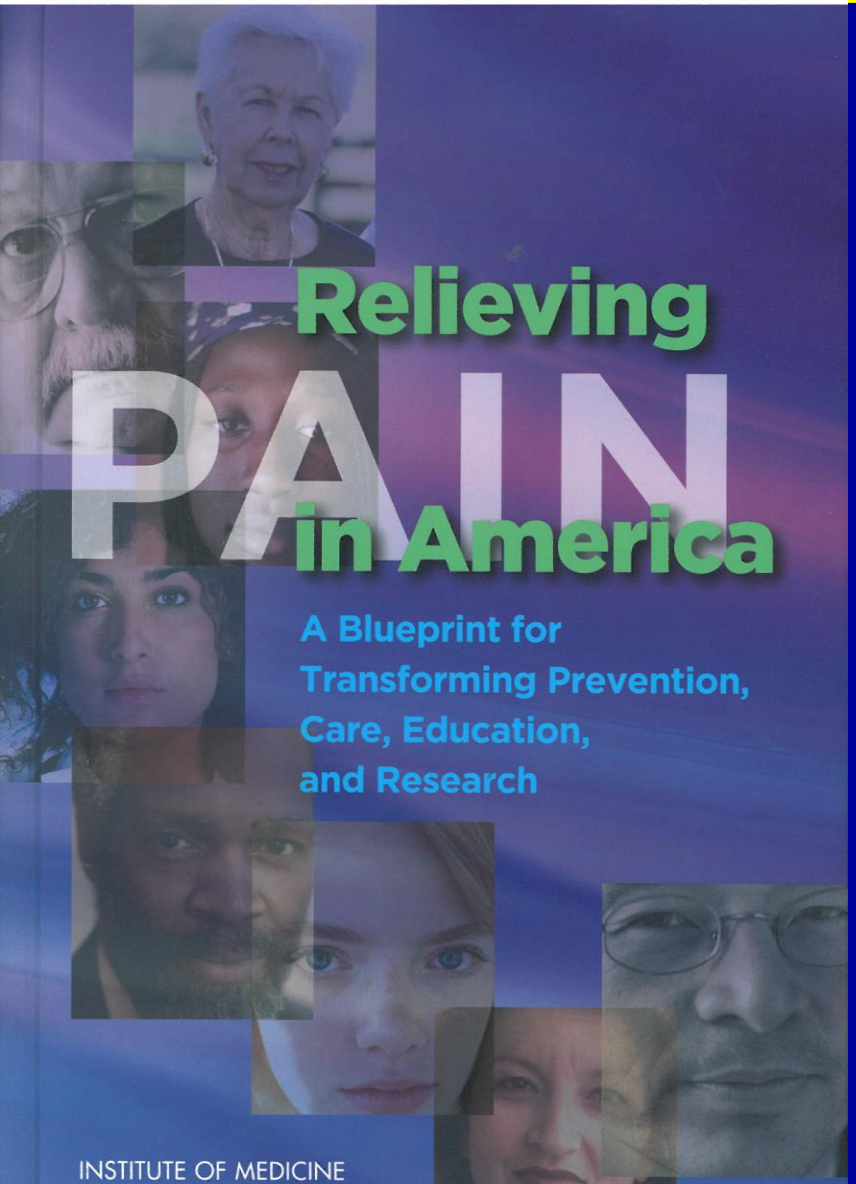
SCIATICA BACK OR LEG PAIN?

Are radiating pains down the back of your leg, or pain in your lower back or buttocks making it uncomfortable to sit, walk or sleep? Many are suffering unnecessarily because they are not aware of this effective, topical treatment.

MagniLife® Leg & Back Pain Relief Cream combines seven active ingredients, such as Colocynthis to relieve burning pains and tingling sensations. Although this product is not intended to treat or cure sciatica, it can help with the painful symptoms. *"I am no longer the 'Screaming Lady'! My legs are not in pain. I would not know what to do without the Leg & Back Pain Relief Cream."* - Dolores, AZ.

MagniLife® Leg & Back Pain Relief Cream is **sold at CVS, Rite Aid and Amazon,** or check your local retailer. Order risk free for $19.99 +$5.95 S&H for a 4 oz jar. Get a **FREE** jar when you order two for $39.98 +$5.95 S&H. Send payment to: MagniLife SC-AG3, PO Box 6789, McKinney, TX 75071 or call **1-800-679-3481**. Satisfaction guaranteed. **Order now at www.LegBackCream.com**

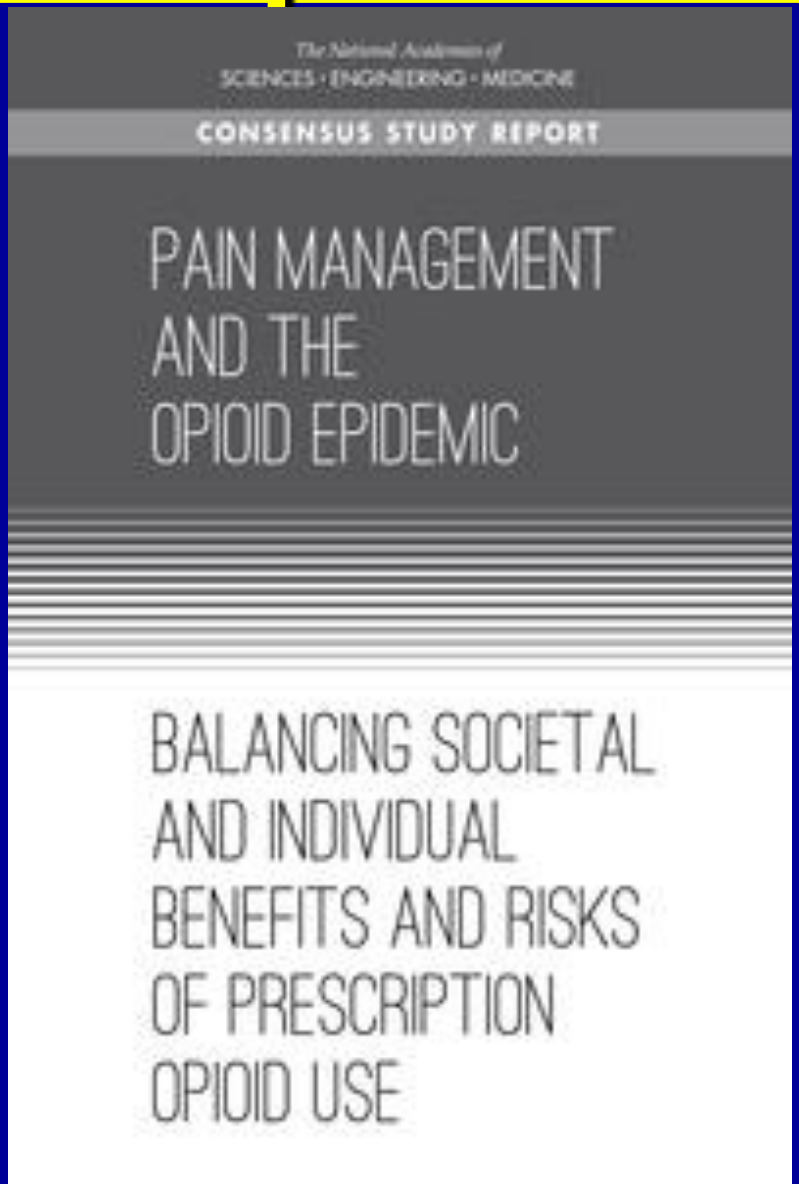
Pain: a Public Health Issue

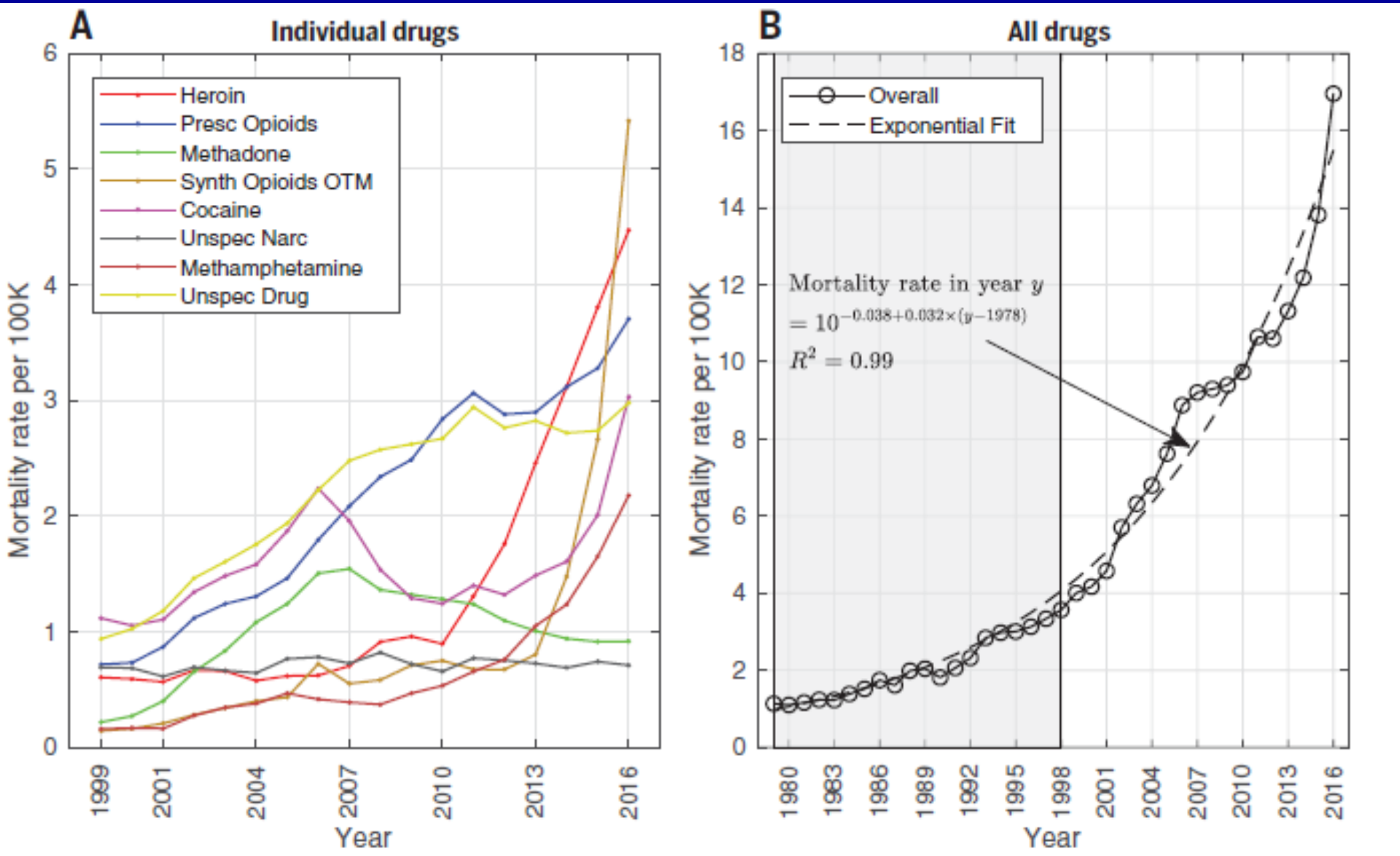


IOM, WHO have declared pain a public health issue:

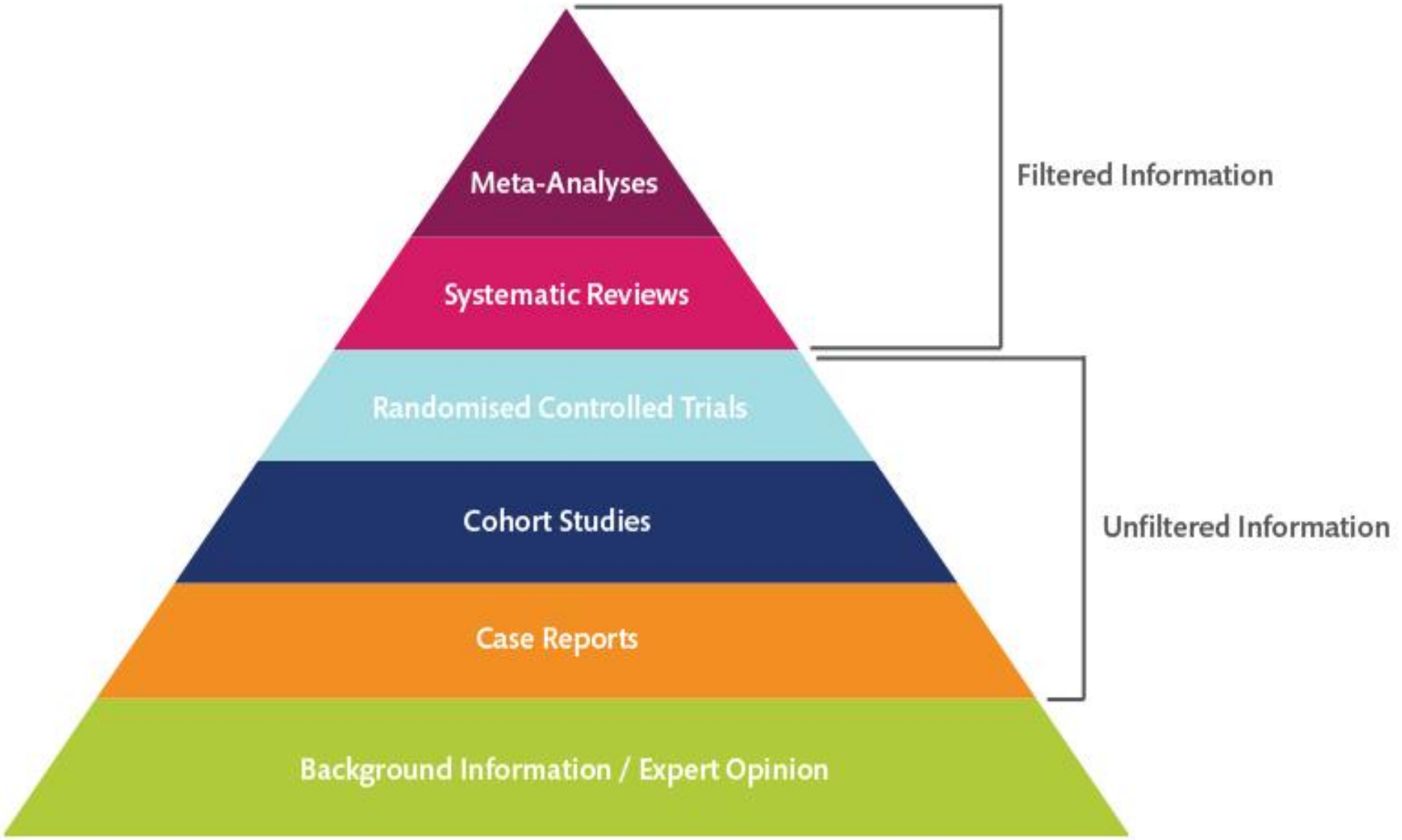
- High prevalence, burden
- Amenable to prevention (e.g., acute-to-chronic)
- Population-based, clear relation to SES
- Human rights dimension including inequities
- Moral imperative to transform our thinking

Pain Management and the Opioid Epidemic (2017)




A
Individual drugs
Heroin
Presc Opioids
Methadone
Synth Opioids OTM
Cocaine
Unspec Narc
Methamphetamine
Unspec Drug
Mortality rate per 100K
Year
B
All drugs
Overall
Exponential Fit
Mortality rate in year y
$= 10^{-0.038+0.032\times(y-1978)}$
$R^2 = 0.99$
Mortality rate per 100K
Year

Evidence Pyramid (simple)



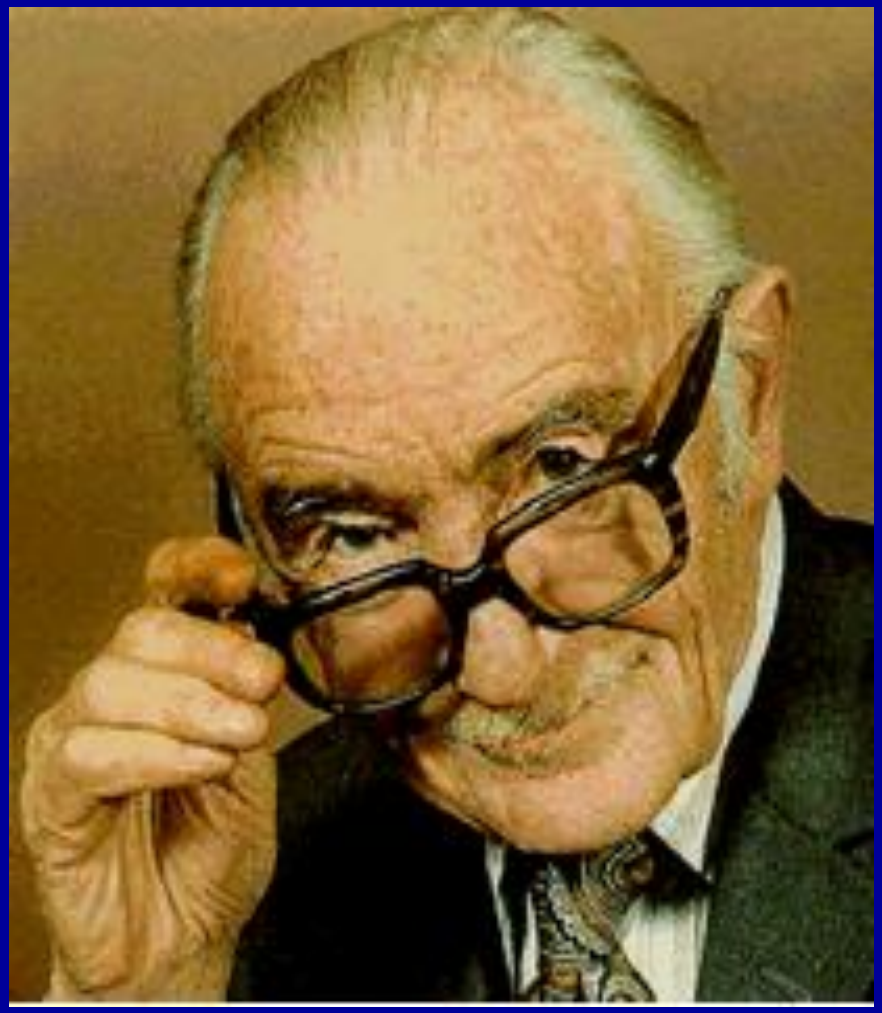
Efficacious Topical Analgesics

- TRPV-1 agonist: capsaicin
- Alpha-2 agonist: clonidine
- NSAIDs: aspirin and diclofenac
- Local anesthetics (including abrasion, suturing)
- Single drug or combinations: TCAs (amitriptyline, doxepin), ketamine, baclofen, gabapentin
- Botulinum toxin type A
- Topical opioids: morphine, loperamide
- Antioxidants: dimethyl sulfoxide
- Palmitoylethanolamide
- Sources: Cochrane Library, Argoff et al, Peppin et al

INDIVIDUAL RESPONSES VARY

- Case reports/ series/ clinical trials indicate wide interindividual variability according to etiology and within etiologies
- Settings in which topical analgesics are used often have large effect sizes for placebo including counterstimulation while applied
- Consider relaxing prevailing P-value approach for efficacy indication and emphasizing safety more
- Benefit from crises re: P-values, causality

Archie Cochrane (1909-1988)



All effective treatment must be free…The main job of the [NHS] is to choose between alternatives. The RCT is a very beautiful technique… but as with everything else there are snags:

- Bias
- Statistics (P-values vs N)
- Inapplicable (e.g., ethics)
- When outcomes subjective
- Rare conditions
- Culture, geography

Lou Lasagna's Plea (1974)

[RCTs], while of clear utility in establishing efficacy, are nevertheless remarkably artificial in the sense of not resembling the real-life application of medicaments to treatment of the ill. Once marketed, a drug will be used by doctors of all levels of expertise and wisdom, on heterogeneous populations, usually in conjunction with other drugs, without informed consent, protocol forms, or specified lab tests as criteria for success or failure.

Lou Lasagna's Plea (contd)

Given these differences, it seems inevitable that the prediction of "naturalistic" performance from controlled clinical trials will be faulty, the only point at issue is how flawed will be the prognostications.

What, then, is needed? Certainly not *more* clinical trials. Rather, we must study the medicine in its natural habitat, i.e. the doctor's office, the patient's home, and the hospital.


Causation in Population Health Informatics and Data Science
Olaf Dammann
Benjamin Smart
Springer

"Methodological Pluralism"

- "Precision medicine (PM) = prevention, diagnosis and treatment strategies that take individual variability into account …PM takes into account genes, environment and lifestyle" [Collins & Varmus, *NEJM* 2015]
- "PM differs greatly from EBM, which seeks the best course of action based on population-based studies." [Tonelli & Shirts, Knowledge for PM, *JAMA* 2017]
- [In PM] "case-based reasoning and understanding of mechanisms will figure more prominently." [Tonelli & Shirts]

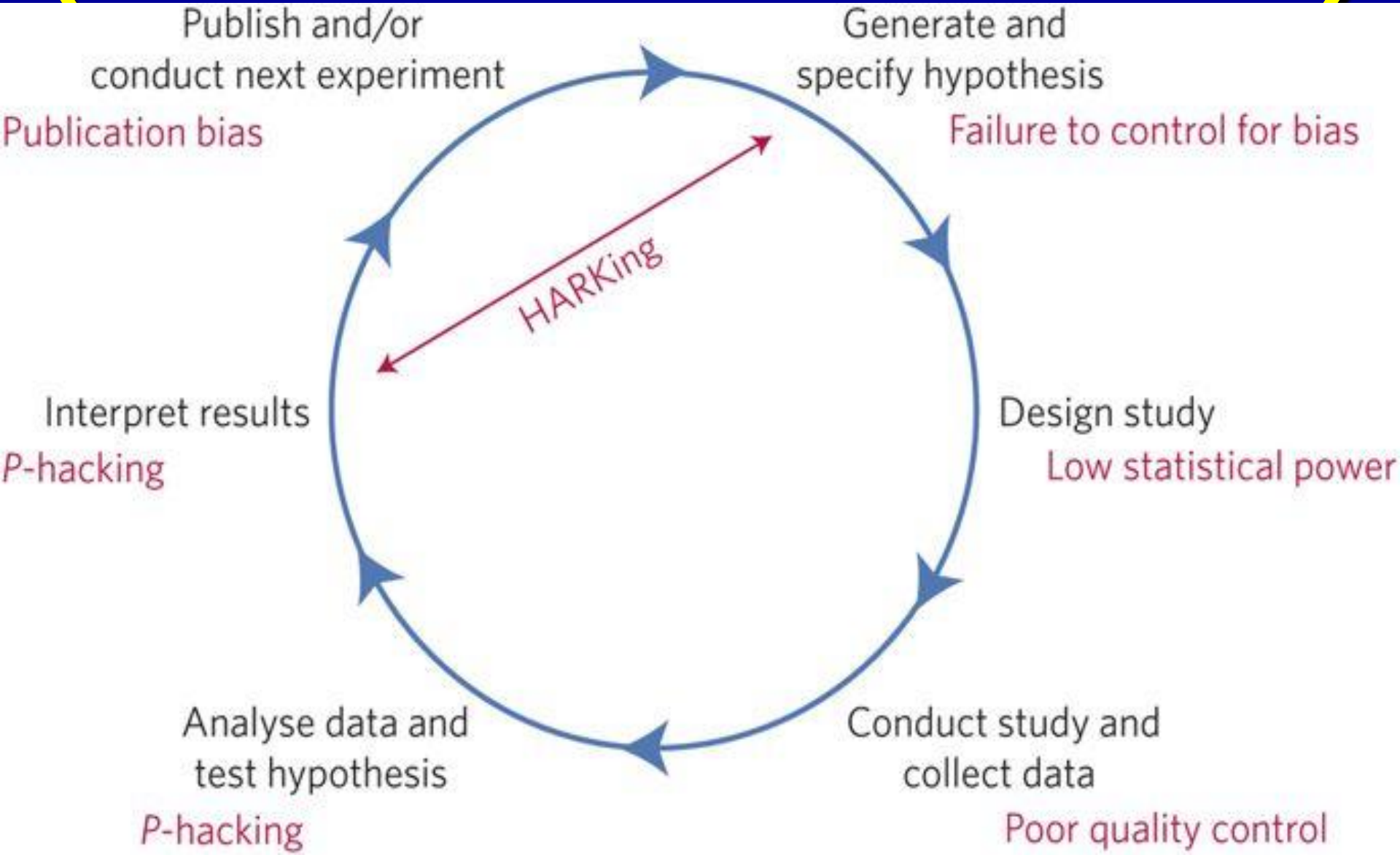
"Faces or the Crowd?" (IASP AP SIG 2014 Satellite)

- EBM, Precision Medicine at odds.
- Policymakers now look "beyond RCTs" to cohort studies, case-control studies, case series, registries, pragmatic trials etc (Frieden *NEJM* 2017; Tonelli & Shirts *JAMA* 2017).
- ***Inversion of "evidence pyramid"?***

"Beyond RCTs" – Alternative Designs (Frieden NEJM 2017)

- Sysrevs, M-As
- Prospective cohort studies
- Retrospective cohort studies
- Case-control studies
- Cross-sectional studies
- Ecologic studies
- Pragmatic trials
- Large observational studies
- Program-based evidence
- Case reports, series
- Registries

Nonreproducibility Crisis (Ioannidis 2017: P<0.005?)



Improving Pain Evidence (NPS, NIH, IPRCC, FPRS, HEAL)

- Study quality (numbers accrued, design heterogeneity, duration) not on par with primary therapy trials
- More “PICOTS” studies in sub-populations, settings: genetics, gender, age, race, ethnicity, culture, integrative
  - Pain etiologies
  - Drug combinations/ interactions
  - Self-care versus passive
  - Naturalistic data (outcomes, N-of-1, registries)
- Derive NNT, NNH, intrinsic analgesic potencies while allowing for “methodological pluralism”
- Integration into practice guidelines, decision support
- Don’t throw out baby (case-level benefit) with bathwater (reliance upon population-based statistics)

Topical Analgesia in Hospice (c/o Dr. J. Winegarden)

- 98 yo female with vulvar cancer recurrence, metastases externally to rectum and internally to bowel
  - Prior treatment with neurolytic ganglion impar nerve block, pudendal nerve block, tramadol, hydrocodone-acetaminophen and benzocaine gel
  - Attempted suicide with tramadol
  - Pain 9/10 with lidocaine 5% gel q 1-3 hours

- Treatment with ketamine 10%/ clonidine 0.2 mg/ gabapentin 6 mg (all /ml) cream applied topically q 4-8 hours
  - Vulvar pain reduction to 2/10 pain but experienced breakthrough pain at 2-3 hours

- Treatment with ketamine 10%/ clonidine 0.2 mg/ gabapentin 6 mg/ bupivacaine 2 mg/ methadone 0.2 mg (all /ml) applied topically q 4 hours
  - Vulvar pain remained < 3/10 through remainder of life; patient able to lie down, sit up, have perineal care without pain

THANK YOU