“It’s only a case report” and related nonsense

David Juurlink
University of Toronto
CSIM 2018
Obligatory Disclosure Slide

Personal income
  Clinical billings
  Salary support
    UofT, Sunnybrook DOM, ICES, Ontario Poison Centre
  The Medical Letter
  Medicolegal
Obligatory Disclosure Slide

Personal income
  Clinical billings
  Salary support
    UofT, Sunnybrook DOM, ICES, Ontario Poison Centre
  The Medical Letter
  Medicolegal

No dealings with industry
Hemodialysis in lithium poisoning: there is no evidence. Full stop.

September 29, 2015, 2:44 pm
Stronger evidence
More believable
“Only way to show cause-effect”
Weaker evidence
Bias / confounding
“Can’t prove cause-effect”
“That’s nice.”
We’re trying to answer questions

Effects of interventions

Prognosis

Role of agents (or characteristics) in health and disease
“Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”
RCTs

Intervention

No intervention
RCTs

Randomized (!)
Conceptually simple
Tailored
Measures of effect
  Relative
  Absolute

Cost / duration
May be impossible
May be unethical
Selected patients
Quasi-ideal setting
“Drugs are tested by the people who manufacture them... on hopelessly small numbers of weird, unrepresentative patients... in such a way that they exaggerate the benefits of treatments. Unsurprisingly, these trials tend to produce results that favour the manufacturer. When trials yield results that companies don’t like, they are perfectly entitled to hide them... so we only ever see a distorted picture of any drug’s true effects.”

- Ben Goldacre, Bad Pharma
Case series, Case reports

Cross-sectional studies
Case-Control
Cohort studies
RCT’s
Systematic Reviews-Metaanalysis
Ideas, opinions, editorials, anecdotal
“Always note and record the unusual. Publish it. Place it on permanent record as a short, concise note. Such communications are always of value.”
“But remember: It’s only a case report so it probably won’t get published anywhere good.”
The headache of teenage acne

The Case: A 15-year-old woman presented to hospital with a 1-month history of worsening bilateral headache and a perception of intracranial noise. The headaches were nonpulsatile, more severe in the morning and in the supine position and were associated with double vision on lateral gaze. On examination, she was alert, oriented and looked well. She was mildly overweight. There were no meningeal signs, and her vital signs were normal. There was an absence of papilledema (Fig. 1), with loss of physiologic cupping, indistinct disc margins and small retinal hemorrhages bilaterally. Visual acuity was reduced in the right eye (20/60), but her visual fields were full. She also had bilateral abducens palsy upon extreme lateral gaze. Her physical examination was otherwise normal.

A rare presentation of an ancient disease: scurvy presenting as orthostatic hypotension

Jonathan Samuel Zipursky,1 Ahmad Alhashemi,1 David Juurlink2

SUMMARY

A 49-year-old man presented to hospital with severe orthostatic hypotension, gingival dysplasia and a purpuric rash involving his extremities. The orthostatic hypotension failed to respond to fluids and, on the basis of physical examination and dietary history, the patient was given a preliminary diagnosis of scurvy (ascorbic acid deficiency). Serum ascorbic acid levels were undetectable and the orthostasis was resolved within 24 h of ascorbic acid replacement. The pathogenesis of orthostatic hypotension in the setting of scurvy appears to involve impaired catecholamine synthesis and attenuated vasomotor response to α-adrenergic stimulation. We believe that this case describes a rare presentation of scurvy and highlights a previously under- reported connection between scurvy and vasomotor instability.

TREATMENT

The patient received 2 L of intravenous crystalloid in the emergency room (ER) with no improvement.

A case of recurrent meningitis

A 20-year-old man presented to the emergency department with a 4-hour history of severe bifrontal headache, neck pain and vomiting associated with fever and a 1-week history of productive cough. About 5 months earlier he had been admitted to another hospital with Streptococcus pneumoniae meningitis.

Pseudoephedrine-induced Toxic Epidermal Necrolysis

Pseudoephedrine is a sympathomimetic agent that is commonly found in over-the-counter cough and cold preparations. We describe the first reported case of toxic epidermal necrolysis (TEN) associated with the use of pseudoephedrine, confirmed by inadvertent rechallenge and supported by patch testing.

A 57-year-old woman was admitted to the hospital with a pruritic, generalized maculopapular eruption. Her medi-
THALIDOMIDE AND CONGENITAL ABNORMALITIES

Sir,—Congenital abnormalities are present in approximately 1.5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (‘Distaval’) during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales.

W. G. McBride.
Epi 6 mg
\[\text{11X}\]
Amio 300 mg
Mg 1g

Systolic Blood Pressure, mmHg

NaHCO₃ 50mEq

Time, minutes
Figure.
Correlation of octreotide therapy with resolution of recurent hypoglycemia.
The diagram illustrates a hierarchy of evidence levels in research. At the top, labeled "Sys Reviews - Metaanalysis," comes at the peak, followed by "RCT’s," "Cohort studies," "Case-Control," "Cross-sectional studies," "Case series, Case reports," and finally, at the base, "Ideas, opinions, editorials, anecdotal."
Cross sectional studies

POPULATION

With attribute

Without attribute
THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIZ ZAINAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAGNE, M.D., ALFONSO PEPEZ, M.D., JULE PALENSKEY, M.S., AND JANET WITTE, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*

ABSTRACT

Background and Methods. Aldosterone is important in the pathophysiology of heart failure. In a double-blind study, we enrolled 1863 patients who had severe heart failure and a left ventricular ejection fraction of no more than 35 percent and who were being treated with an angiotensin-converting-enzyme inhibitor, a loop diuretic, and in most cases digoxin. A total of 822 patients were randomly assigned to receive 25 mg of spironolactone daily, and 841 to receive placebo. The primary end point was death from all causes.

Results. The trial was discontinued early, after a

Aldosterone has an important role in the pathophysiology of heart failure. Aldosterone promotes the retention of sodium, the loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, and vascular damage and impairs arterial compliance. Many physicians have assumed that inhibition of the renin–angiotensin–aldosterone system by an angiotensin-converting-enzyme (ACE) inhibitor will suppress the formation of aldosterone.

No. at Risk
Placebo 841 775 723 678 628 592 565 538 483 379 280 179 92 36
Spironolactone 822 766 739 698 669 630 608 526 419 316 193 122 43

Probability of Survival

Months
Online release of RALES
Online release of RALES
What RALES said

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SLOW HEART FAILURE

Bertam Pitt, M.D., Faiez Zannah, M.D., Willem J. Remine, M.D., Robert Cody, M.D., Alain Castaigne, M.D., Alfonso Perez, M.D., Jolie Palensky, M.S., and Janet Wittes, Ph.D., ALDOSTERONE EVALUATION STUDY INSTITUTE

ABSTRACT

Background and Methods: Aldosterone is important in the pathophysiology of heart failure. In a double-blind study, we enrolled 1663 patients who had severe heart failure and a left ventricular ejection fraction of no more than 35 percent and who were being treated with an angiotensin-converting–enzyme inhibitor, a loop diuretic, and in most cases digoxin. A total of 822 patients were randomly assigned to receive 25 mg of spironolactone daily, and 841 to receive placebo.

What we heard

ALDOSTERONE has an important role in the pathophysiology of heart failure. Aldosterone promotes the retention of sodium, the loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, and vascular damage and impairs arterial compliance. Many physicians have assumed that inhibition of the renin–angiotensin–aldosterone system...
Epilogue

Spironolactone + ACEI (> 66 y with CHF)

RALES 1999

NEJM 2004
Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone

Irfan A. Dhalla MD MSc, Muhammad M. Mamdani PharmD MPH, Marco L.A. Sivilotti MD MSc, Alex Kopp BA, Omar Qureshi MD, David N. Juurlink MD PhD

Figure 1: Annual number of opioid analgesics prescribed on an outpatient basis in Ontario from 1991 to 2007.
Opioid deaths, Ontario
1991 - 2015
% of all deaths involving an opioid

2000

0-14 15-24 25-34 35-44 45-54 55-64 65+
% of all deaths involving an opioid
% of all deaths involving an opioid
Case-control studies
Case-control studies
Case-control studies

Exposure

Cases

Controls
Case-control studies

Rare diseases
Long latency
Fast, inexpensive
Multiple exposures
Few ethical issues

Can’t estimate incidence
Biases
- Subject identification
- Exposure assessment
Confounding
- “Association ≠ causation”
Association of Tequin (gatifloxacin) with serious hypoglycemia and hyperglycemia - For Health Professionals - Bristol-Myers Squibb Canada
<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Patients</th>
<th>Controls</th>
<th>Univariate Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>788 (100)</td>
<td>3791</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>61 (7.7)</td>
<td>77 (2.0)</td>
<td>4.4 (3.0–6.3)</td>
<td>4.3 (2.9–6.3)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>114 (14.5)</td>
<td>341 (9.0)</td>
<td>1.7 (1.4–2.2)</td>
<td>1.5 (1.2–2.0)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>24 (3.0)</td>
<td>162 (4.3)</td>
<td>0.8 (0.5–1.3)</td>
<td>0.8 (0.5–1.3)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>209 (26.5)</td>
<td>1075 (28.4)</td>
<td>1.1 (0.9–1.3)</td>
<td>0.9 (0.8–1.1)</td>
</tr>
<tr>
<td>Cephalosporins†</td>
<td>62 (7.9)</td>
<td>397 (10.5)</td>
<td>0.9 (0.6–1.2)</td>
<td>0.9 (0.6–1.2)</td>
</tr>
<tr>
<td>Macrolides‡</td>
<td>318 (40.4)</td>
<td>1739 (45.9)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Variable</td>
<td>Case Patients</td>
<td>Controls</td>
<td>Univariate Odds Ratio (95% CI)</td>
<td>Adjusted Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------</td>
<td>----------</td>
<td>-------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>470 (16.7%)</td>
<td>2280</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>86 (18.3)</td>
<td>42 (1.8)</td>
<td>16.3 (10.4–25.4)</td>
<td>16.7 (10.4–26.8)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>52 (11.1)</td>
<td>233 (10.2)</td>
<td>1.6 (1.1–2.3)</td>
<td>1.3 (0.9–1.9)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>20 (4.3)</td>
<td>70 (3.1)</td>
<td>2.0 (1.2–3.5)</td>
<td>1.7 (1.0–3.0)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>113 (24.0)</td>
<td>576 (25.3)</td>
<td>1.4 (1.0–1.8)</td>
<td>1.1 (0.9–1.5)</td>
</tr>
<tr>
<td>Cephalosporins†</td>
<td>38 (8.1)</td>
<td>235 (10.3)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.2 (0.8–1.7)</td>
</tr>
<tr>
<td>Macrolides‡</td>
<td>161 (34.3)</td>
<td>1124 (49.3)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women

Laura Y. Park-Wyllie, PharmD, MSc

Context: Osteoporosis is associated with significant morbidity and mortality. Oral bis-

~200,000 women ≥66 years initiating a bisphosphonate
716 ‘atypical’ fracture; 3580 controls

Table 2. Risk of Subtrochanteric or Femoral Shaft Fractures Among Women Taking Bisphosphonate Therapy

<table>
<thead>
<tr>
<th>Duration of Bisphosphonate Therapy</th>
<th>Transient, &lt;100 days</th>
<th>Short-term Use, 100 days to 3 years</th>
<th>Intermediate Use, 3 to 5 Years</th>
<th>Long-Term Use, ≥5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (% of patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n = 716)</td>
<td>42 (5.9)</td>
<td>349 (48.7)</td>
<td>204 (28.5)</td>
<td>121 (16.9)</td>
</tr>
<tr>
<td>Control (n = 3580)</td>
<td>218 (6.1)</td>
<td>1832 (51.2)</td>
<td>1070 (29.9)</td>
<td>460 (12.9)</td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.0 [Reference]</td>
<td>1.00 (0.70-1.43)</td>
<td>1.08 (0.73-1.59)</td>
<td>1.74 (1.11-2.73)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.0 [Reference]</td>
<td>0.90 (0.48-1.68)</td>
<td>1.59 (0.80-3.15)</td>
<td>2.74 (1.25-6.02)</td>
</tr>
</tbody>
</table>

Note: Crude: Crude odds ratio.
“Typical” fractures
N=9723

Table 3. Risk of Femoral Neck or Intertrochanteric Hip Fractures Among Women Taking Bisphosphonate Therapy

<table>
<thead>
<tr>
<th>Duration of Bisphosphonate Therapy</th>
<th>Transient, &lt;100 days</th>
<th>Short-term Use, 100 days to 3 years</th>
<th>Intermediate Use, 3 to 5 Years</th>
<th>Long-Term Use, ≥5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case (n = 9723)</td>
<td>817 (8.4)</td>
<td>5587 (57.5)</td>
<td>2438 (25.1)</td>
<td>881 (9.1)</td>
</tr>
<tr>
<td>Control (n = 48564)</td>
<td>3434 (7.1)</td>
<td>27086 (55.8)</td>
<td>13148 (27.1)</td>
<td>4896 (10.1)</td>
</tr>
</tbody>
</table>

Odds Ratio (95% CI)

- Crude: 1.0 [Reference] 0.87 (0.80-0.94) 0.72 (0.65-0.79) 0.65 (0.58-0.74)
- Adjusted* 1.0 [Reference] 0.93 (0.81-1.07) 0.86 (0.73-1.00) 0.76 (0.63-0.93)

Abbreviation: CI, confidence interval.

*The full list of covariates for the adjusted model are given in eAppendix 2 (available at http://www.jama.com).
Cohort studies

OUTCOME

+++
Cohort studies

Can establish incidence
Clinically logical
Exposure not biased by outcome
Can study multiple outcomes

Inefficient
Expensive
Delayed findings
Biases
Estimating incidence

Incidence (IR) = \( \frac{3}{107.7} = 0.028 \) person-yr
\[ = \frac{28}{1000} \text{ p-yrs} \]

Total time at risk = 107.7 person-yrs
Risk of Suicide Following Deliberate Self-poisoning

7 per 100,000 p-y

278 per 100,000 p-y

adjusted HR ~42

N=65,784

JAMA Psych 2015
Predictors of suicide

Recurrent poisoning aHR 2.85
Male aHR 1.87
Saw a psychiatrist aHR 1.65
Advancing age

<table>
<thead>
<tr>
<th>Age group, y</th>
<th>aHR</th>
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<tr>
<td>≤20</td>
<td>1</td>
</tr>
<tr>
<td>21-30</td>
<td>1.71</td>
</tr>
<tr>
<td></td>
<td>(1.32-2.20)</td>
</tr>
<tr>
<td>31-40</td>
<td>2.57</td>
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<tr>
<td></td>
<td>(2.02-3.25)</td>
</tr>
<tr>
<td>41-50</td>
<td>3.09</td>
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<td></td>
<td>(2.45-3.89)</td>
</tr>
<tr>
<td>51-60</td>
<td>4.60</td>
</tr>
<tr>
<td></td>
<td>(3.60-5.88)</td>
</tr>
<tr>
<td>61-70</td>
<td>4.85</td>
</tr>
<tr>
<td></td>
<td>(3.52-6.68)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>5.10</td>
</tr>
<tr>
<td></td>
<td>(3.56-7.31)</td>
</tr>
</tbody>
</table>

Finkelstein JAMA Psych 2015
Best way to evaluate causality / determine if an intervention can work
Best way to evaluate causality / determine if an intervention can work

Real-world insights not obtainable any other way
Best way to evaluate causality / determine if an intervention can work

Real-world insights not obtainable any other way

Sometimes awesome
“That thing I said about case reports? Still solid 120 years later.”
Self-matched designs

Subject is his or her own control

**Example**: The case-crossover design

- Identify event (case)
- Look back for exposure at different intervals
Macrolide-CCB interaction

- **7-day risk interval**
- **7-day control interval**
- **21-day “washout” interval**

Hospitalized with hypotension

- CCB therapy

Erythromycin OR 5.8 (2.3 to 15.0)
Clarithromycin OR 3.7 (2.3 to 6.1)
Azithromycin OR 1.5 (0.8 to 2.8)
High-dose insulin in verapamil poisoning

LV Efficiency

LD$_{100}$