Personalised medicine? Don’t hold your breath

Stephen Senn

LUXEMBOURG INSTITUTE OF HEALTH
RESEARCH DEDICATED TO LIFE

Acknowledgements

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A previous Prime Minister of the UK speaks

This agreement will see the UK lead the world in genetic research within years. I am determined to do all I can to support the health and scientific sector to unlock the power of DNA, turning an important scientific breakthrough into something that will help deliver better tests, better drugs and above all better care for patients....

David Cameron, August 2014 (my emphasis)

Genes, Means and Screens

It will soon be possible for patients in clinical trials to undergo *genetic tests* to identify those *individuals who will respond favourably to the drug* candidate, *based on their genotype*…. This will translate into *smaller, more effective clinical trials* with corresponding *cost savings* and ultimately better treatment in general practice. … *individual patients will be targeted* with specific treatment and personalised dosing regimens to maximise efficacy and minimise pharmacokinetic problems and other side-effects.

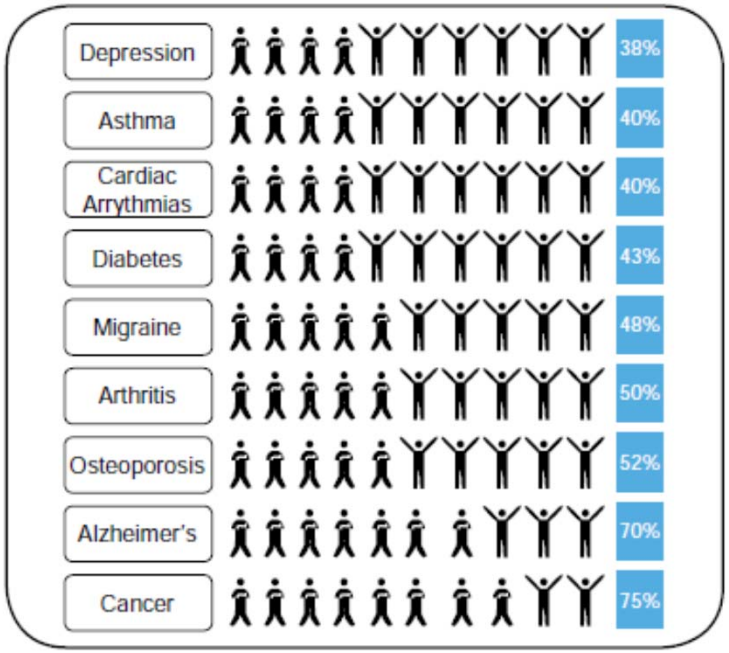
Sir Richard Sykes, FRS, 1997

My emphasis

Zombie statistics 1

Percentage of non-responders

What the FDA says



Paving the way for personalized medicine, FDA Oct 2013

Where they got it

Table 1. Response rates of patients to a major drug for a selected group of therapeutic areas[1]

Therapeutic area	Efficacy rate (%)
Alzheimer's	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrythmias	60
Depression (SSRI)	62
Diabetes	57
HCV	47
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Spear, Heath-Chiozzi & Huff, *Trends in Molecular Medicine*, May 2001

Zombie statistics 2

Where they got it

Where those who got it got it

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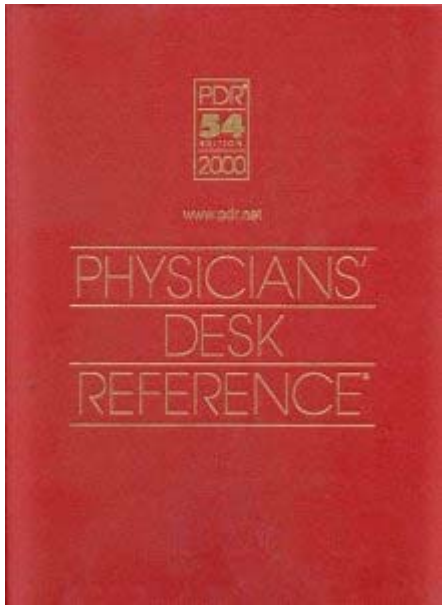

Spear, Heath-Chiozzi & Huff, *Trends in Molecular Medicine*, May 2001

1 Physicians' Desk Reference, 54th Edn., 2000

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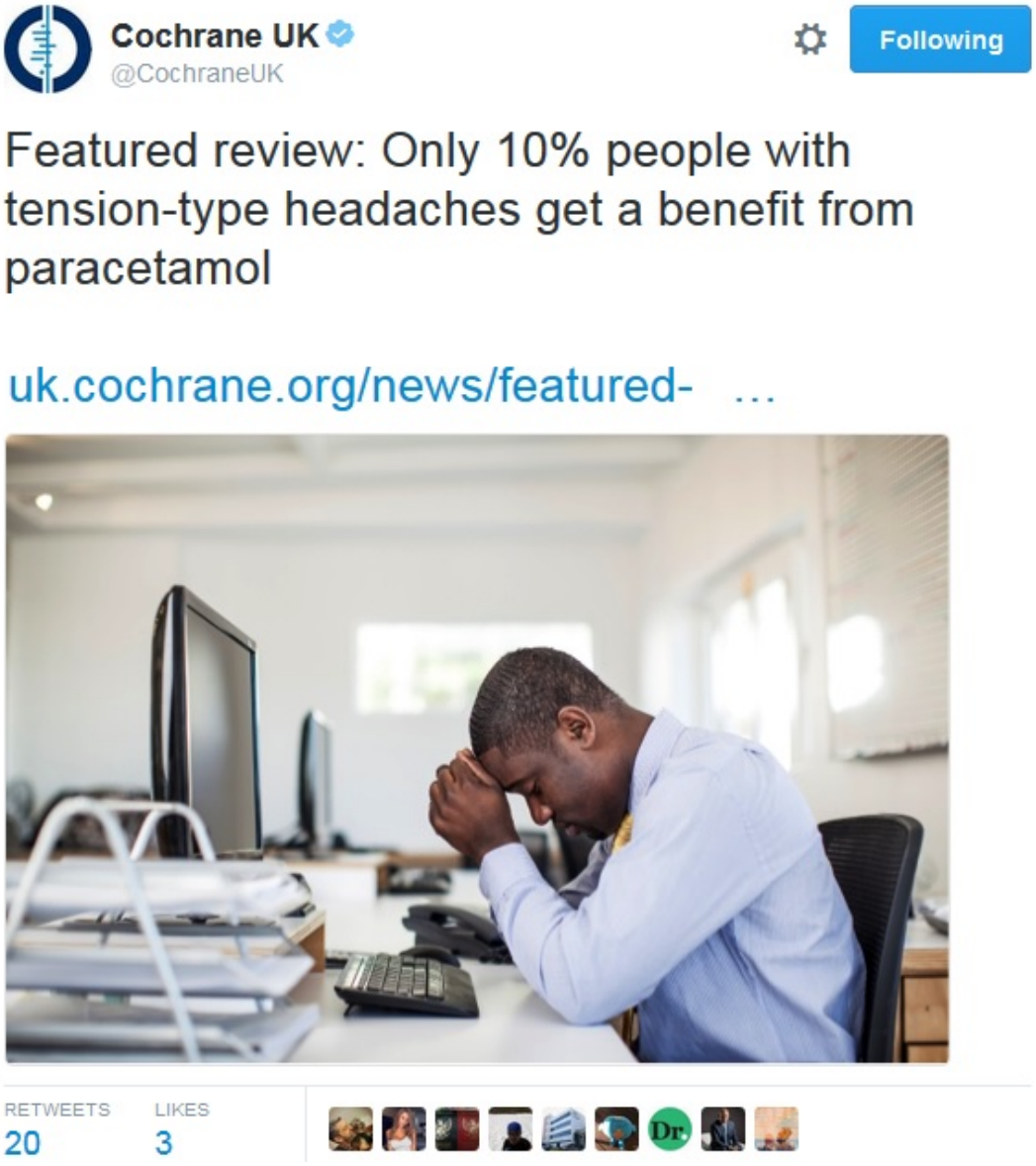
The Real Truth

- These are zombie statistics
- They refuse to die
- Not only is the FDA's claim not right, it's not even wrong
- It's impossible to establish what it might mean even if it were true

88.2% of all statistics are made up on the spot

Vic Reeves



59% had no headache after 2 hours when treated with paracetamol

49% had no headache after 2 hours when treated with placebo

59%-49% = 10%

Therefore 10% benefitted

The number needed to treat for one extra patient to have a benefit is 10

SIGNIFICANCE

In Practice

Jump to...

The drugs don't work ... or do they? (pages 38–41)

Corine Baayen

Version of Record online: 1 AUG 2016 | DOI: 10.1111/j.1740-9713.2016.00940.x

When testing new drugs, researchers are asked to specify their statistical analysis plan before seeing their results. This can be a gamble if little is known about how a drug might work. But there is a way for researchers to keep their analysis options open, says Corine Baayen

Abstract | Article | PDF(331K) | References | Request Permissions

'It tells us we can help about 35% of migraine patients'

Painful comparison

Cochrane Collaboration meta-analysis

- Meta-analysis of placebo-controlled trials of paracetamol in tension headache
- 23 studies
- 6000 patients in total
- Outcome measure:
  - Pain free by 2 hours

Baayen *Significance* article

- Explanation of Novartis's MCP-Mod dose-finding approach using a trial run by Merck
- 7 doses + placebo
- 517 patients in total
- Outcome measure
  - Pain free by 2 hours

In both cases

- The patients were only studied once
- A dichotomy of a continuous measure was made
- Patients were labelled as responders and non-responders
- A causal conclusion was drawn that went beyond simply comparing proportions
  - Baayen talked about the proportion of patients who would respond
  - Cochrane talked about the proportion of patients to whom it would make a difference in terms of response

What I propose to do

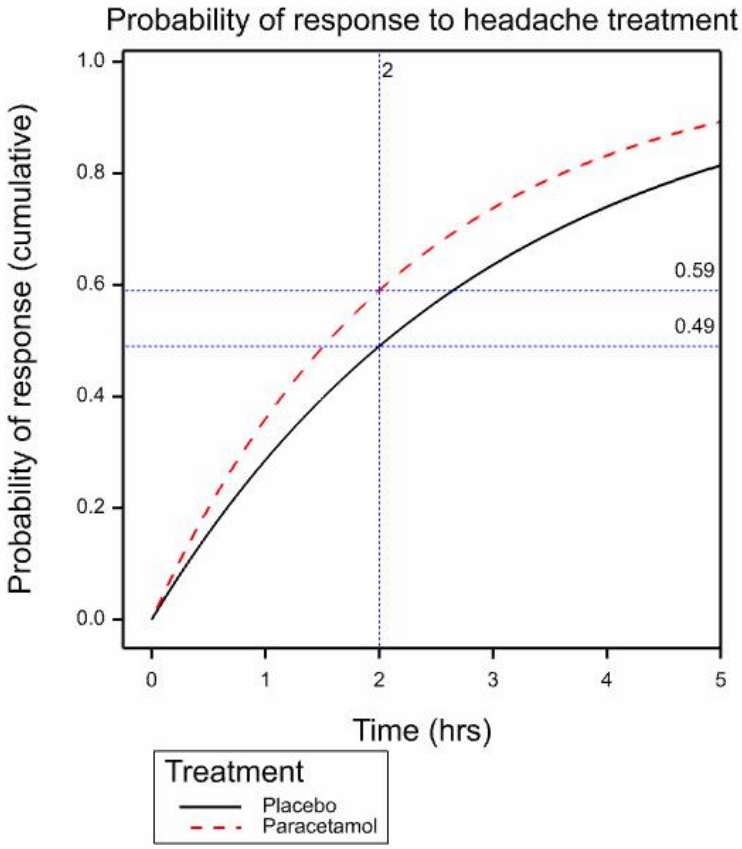
- Create a simple statistical model to mimic the Cochrane result
  - In terms of time to pain resolution *every* patient will have the same proportional benefit
    - In fact I shall be using a form of *proportional hazards model*
  - The dichotomy will classify patients as responders or non-responders
  - We will be tempted to conclude that some don't benefit and some do and that this is a permanent feature of each patient

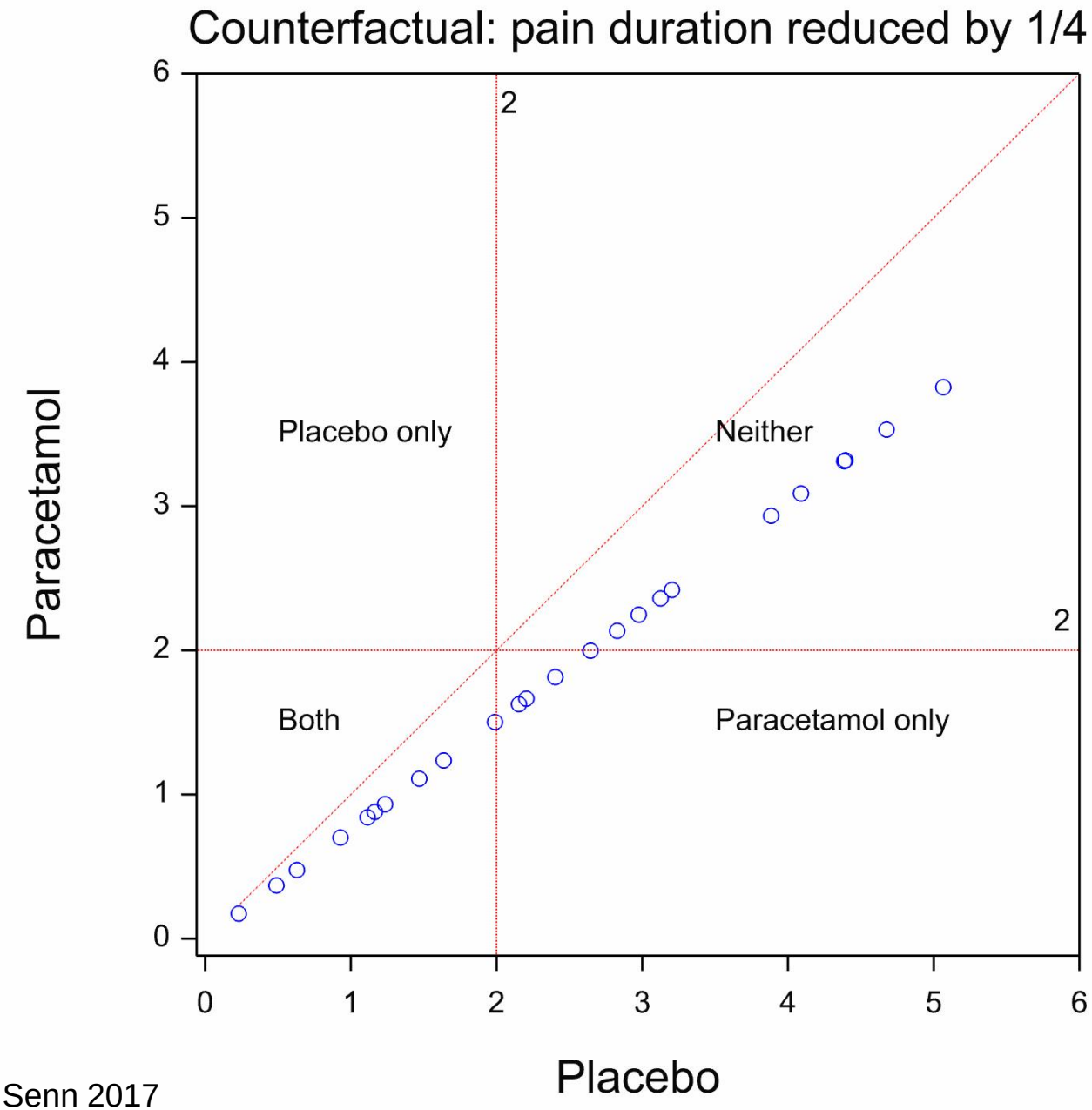
The Numerical Recipe

- I shall generate pain duration times for 6000 headaches treated with placebo
  - This will be done using an exponential distribution with a mean of just under 3 hours (2.97 hrs to be exact)
  - Each such duration will then be multiplied by just over ¾ (0.755 to be exact) to create 6000 durations under paracetamol
- I shall then take the 6000 pairs and randomly erase one member of the pair to leave 3000 unpaired placebo values and 3000 unpaired paracetamol values
- I shall then analyse the data

Why this recipe?

- The exponential distribution with mean 2.970 is chosen so that the probability of response in less than two hours is 0.49
  - This is the placebo distribution
- Rescaling these figures by 0.755 produces another exponential distribution with a probability of response in under two hours of 0.59
  - This is the paracetamol distribution




Counterfactual: pain duration reduced by 1/4
Paracetamol
Placebo
Placebo only
Neither
Both
Paracetamol only
2
2
0
1
2
3
4
5
6

Dichotomania

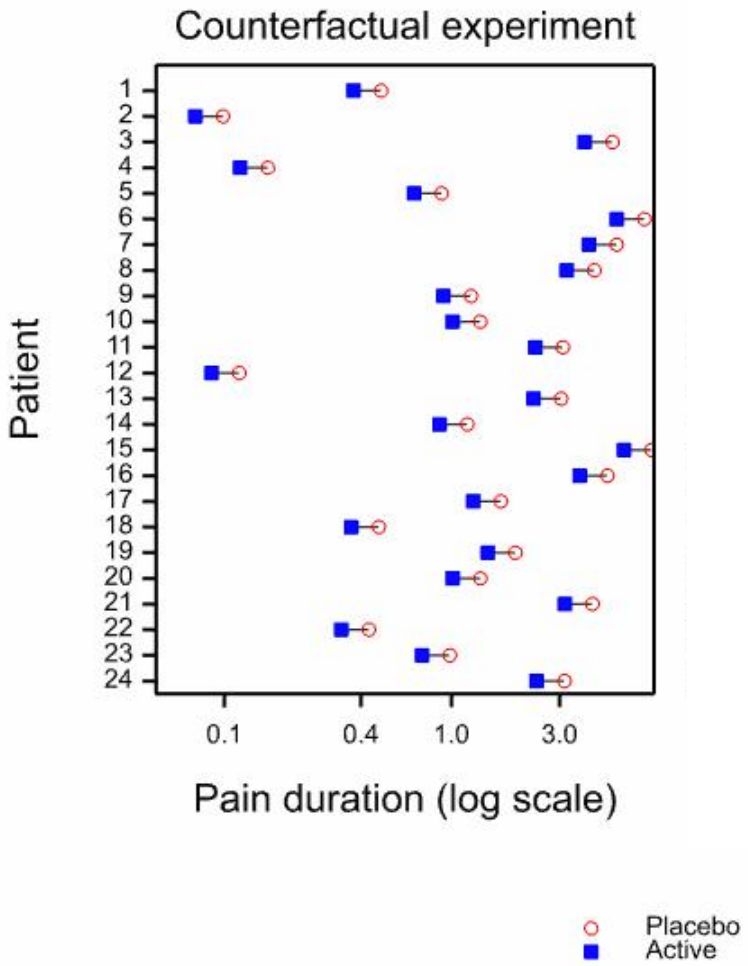
Some simulated pain headache durations

Placebo duration	Paracetamol duration	Benefit
0.230	0.174	
0.489	0.369	
0.630	0.476	
0.929	0.701	
1.115	0.842	
1.165	0.880	
1.235	0.933	
1.470	1.110	
1.637	1.236	
1.989	1.502	
2.154	1.627	Yes
2.205	1.665	Yes
2.403	1.815	Yes
2.645	1.998	Yes
2.828	2.136	
2.976	2.247	
3.125	2.360	
3.204	2.420	
3.884	2.933	
4.089	3.088	
4.386	3.312	
4.394	3.318	
4.676	3.532	
5.066	3.826	
6.085	4.595	
7.024	5.305	
8.017	6.055	
9.999	7.551	
10.122	7.644	
10.989	8.299	

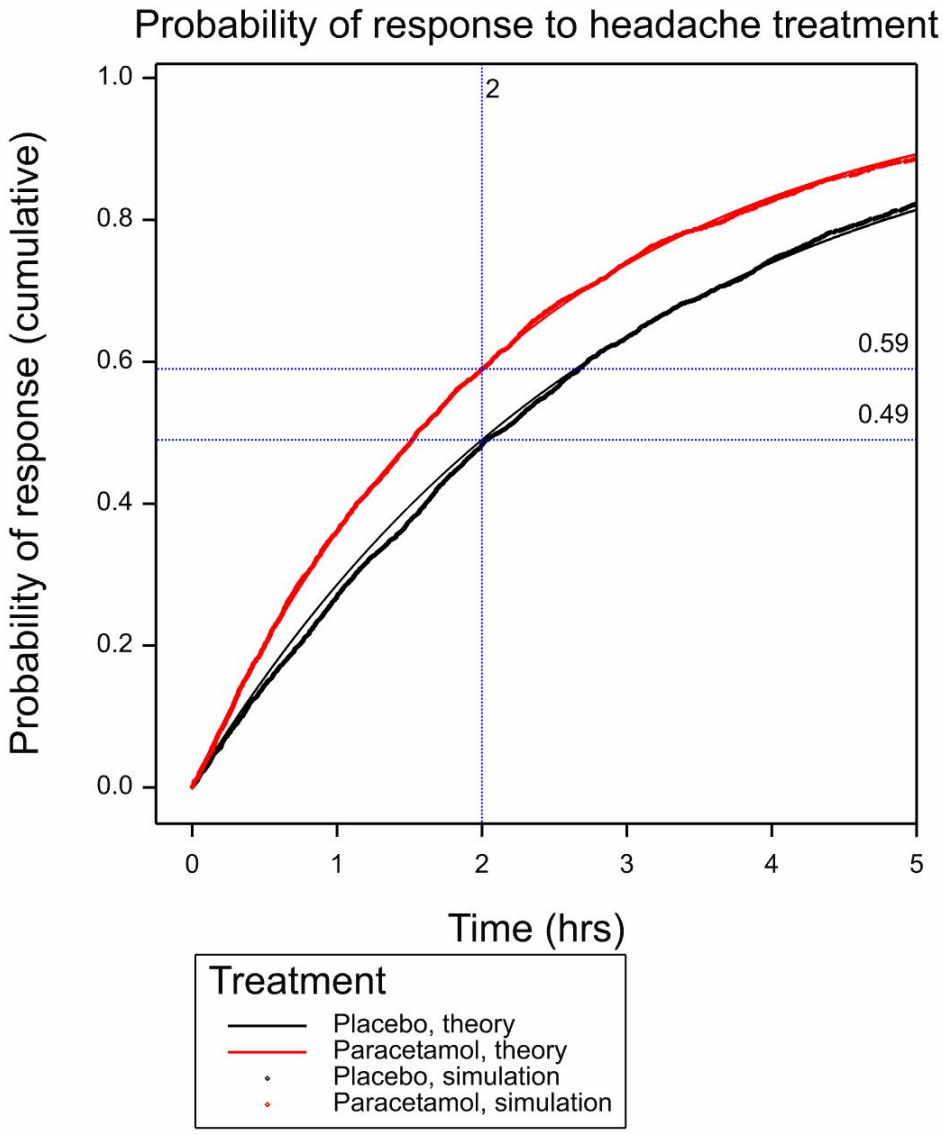
- We lose information through such dichotomies
- We tend to believe our own nonsense labels
  - Response
  - Non-response
- We then delude ourselves that Nature also believes our nonsense
- Next stop: *personalised medicine*

However

- So far I have only gone half way in my simulation recipe
- I have simulated a placebo headache and a corresponding paracetamol headache
- However I can’t treat the same headache twice
- One of the two is *counterfactual*
- I now need to get rid of one member of each factual/counterfactual pair



Note log scale


Probability of response to headache treatment
Probability of response (cumulative)
1.0
0.8
0.6
0.4
0.2
0.0
2
0.59
0.49
0
1
2
3
4
5
Time (hrs)
Treatment
Placebo, theory
Paracetamol, theory
Placebo, simulation
Paracetamol, simulation

To sum up

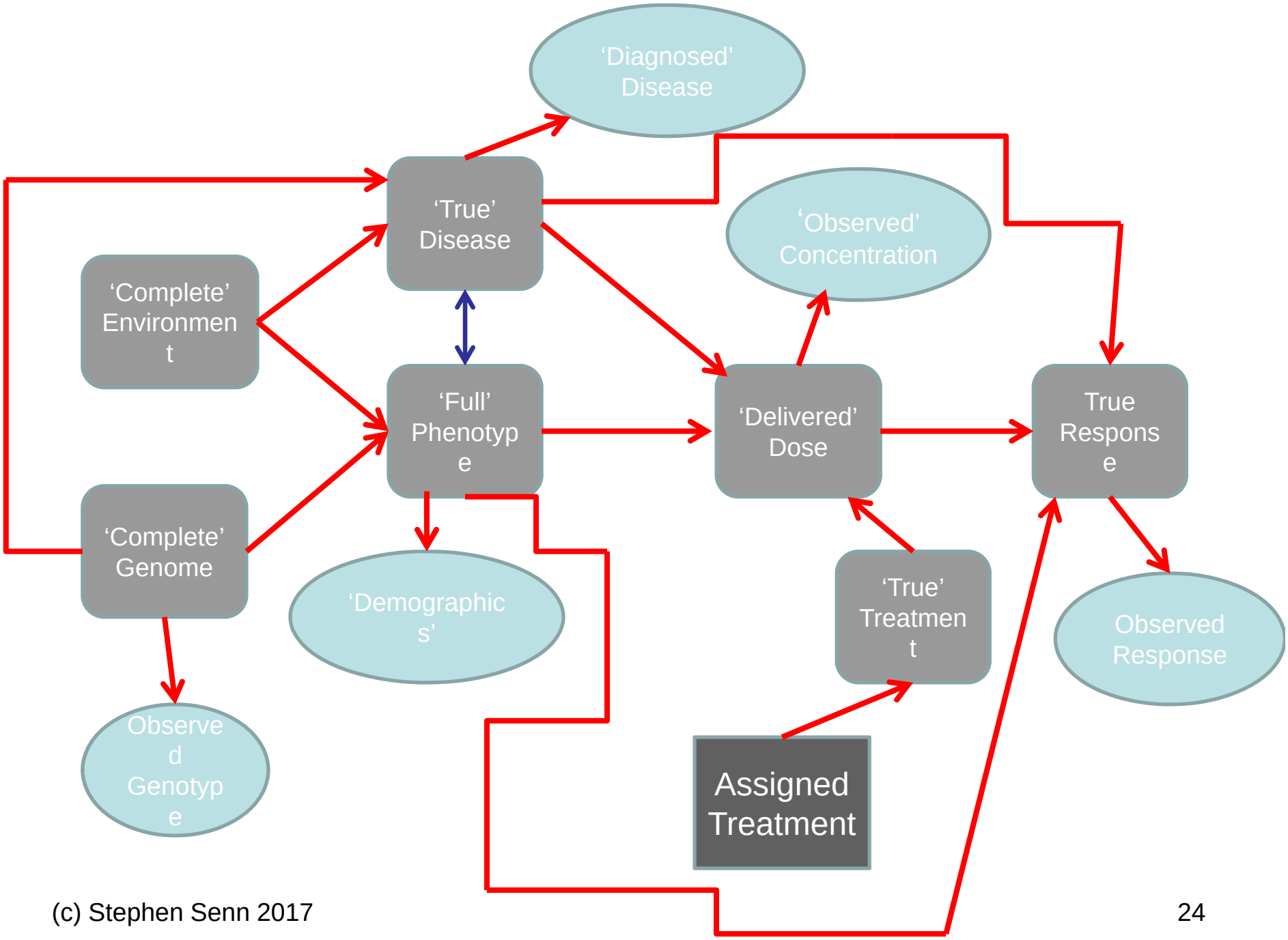
- The results reported are perfectly consistent with paracetamol having the same effect on *every* single headache
- This does not have to be the case but we don't know that it isn't
- The combination of dichotomies and responder analysis has great potential to mislead
- Researchers are assuming that because some patients 'responded' in terms of an arbitrary dichotomy there is scope for personalised medicine

The Pharmacogenomic Revolution?

- Clinical trials
  - Cleaner signal
  - Non-responders eliminated
- Treatment strategies
  - “Theranostics”
- Markets
  - Lower volume
  - Higher price per patient day

Implicit Assumptions

- Most variability seen in clinical trials is genetic
  - Furthermore it is not revealed in obvious phenotypes
    - Example: height and forced expiratory volume (FEV_1) in one second
    - Height predicts FEV_1 and height is partly genetically determined but you don't need pharmacogenetics to measure height
- We are going to be able to find it
  - Small number of genes responsible
  - Low (or no) interactive effects (genes act singly)
  - We will know where to look
- We are going to be able to do something about it
  - May require high degree of dose flexibility
- In fact we simply don't know if most variation in clinical trials is due to individual response let alone genetic variability


‘Diagnosed’ Disease
‘True’ Disease
‘Observed’ Concentration
‘Complete’ Environment
‘Full’ Phenotype
‘Delivered’ Dose
True Response
‘Complete’ Genome
‘Demographics’
‘True’ Treatment
Observed Response
Observed Genotype
Assigned Treatment

Sources of Variation in Clinical Trials

Label	Source	Description
A	Between treatments	The difference between treatments averaged over all patients
B	Between patients	The difference between patients given the same treatment
C	Patient-by-Treatment Interaction	The extent to which the effect of treatment varies from patient to patient
D	Within patients	The extent to which the results vary from occasion to occasion for patients given the same treatment

Senn SJ. Individual Therapy: New Dawn or False Dawn. *Drug Information Journal* 2001;35(4):1479-1494.

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Identifiability and Clinical Trials

Type of Trial	Description	Identifiable Effects	Error Term
Parallel	Each patient is randomised to receive one treatment	A	B+C+D
Cross-over	Each patient receives each treatment in one period only	A and B	C+D
Repeated cross-overs	Each patient receives each treatment in at least two periods	A and B and C	D

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Giving this medicine to children:

It is important to know how much your child weighs to make sure you give them the correct amount of medicine. As a guide a child of 9 years of age will weigh about 30 kg (four and a half stone). If in doubt weigh your child, then follow the instructions in the table.

Do not give to children who weigh less than 30 kg.

Do not give to children under 2 years.

Age	How many to take	How often to take
Adults and children of 12 years and over	One tablet	Once a day
Children of 2 to 11 years who weigh **more than** 30 kg	One tablet	Once a day
Children of 2 to 11 years who weigh **less than** 30 kg	**Do not give** this medicine. For children over 2 years of age and who weigh less than 30 kg a syrup form of this medicine may be more suitable.	

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The supply of truth always greatly exceeds its demand

John F Moffitt

Advice

- Don’t let the label ‘responder’ infect your brain
- A ‘responder’ is a patient who was *observed* to get better by some arbitrary standard
- A ‘responder’ is not a patient who was *caused* to get better by the drug
- Subsequence is *not* consequence
- To establish who really responds and who does not you need to work very hard
- You need smart design and smart statistics