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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Pitfalls of disproportionality analysis

PROTECT Symposium tutorial

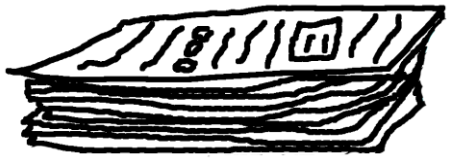
Niklas Norén, PhD

Uppsala Monitoring Centre

Feb 18, 2015

All models are wrong – but some are useful

- G. E. P. Box

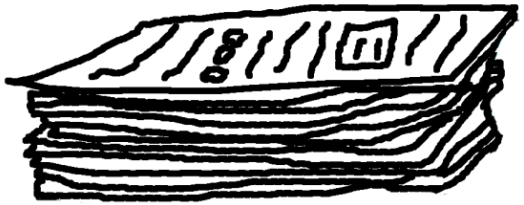


VS

How useful is this?

Growth retarded with poliovirus vaccine

17



VS

7

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Growth retarded with poliovirus vaccine

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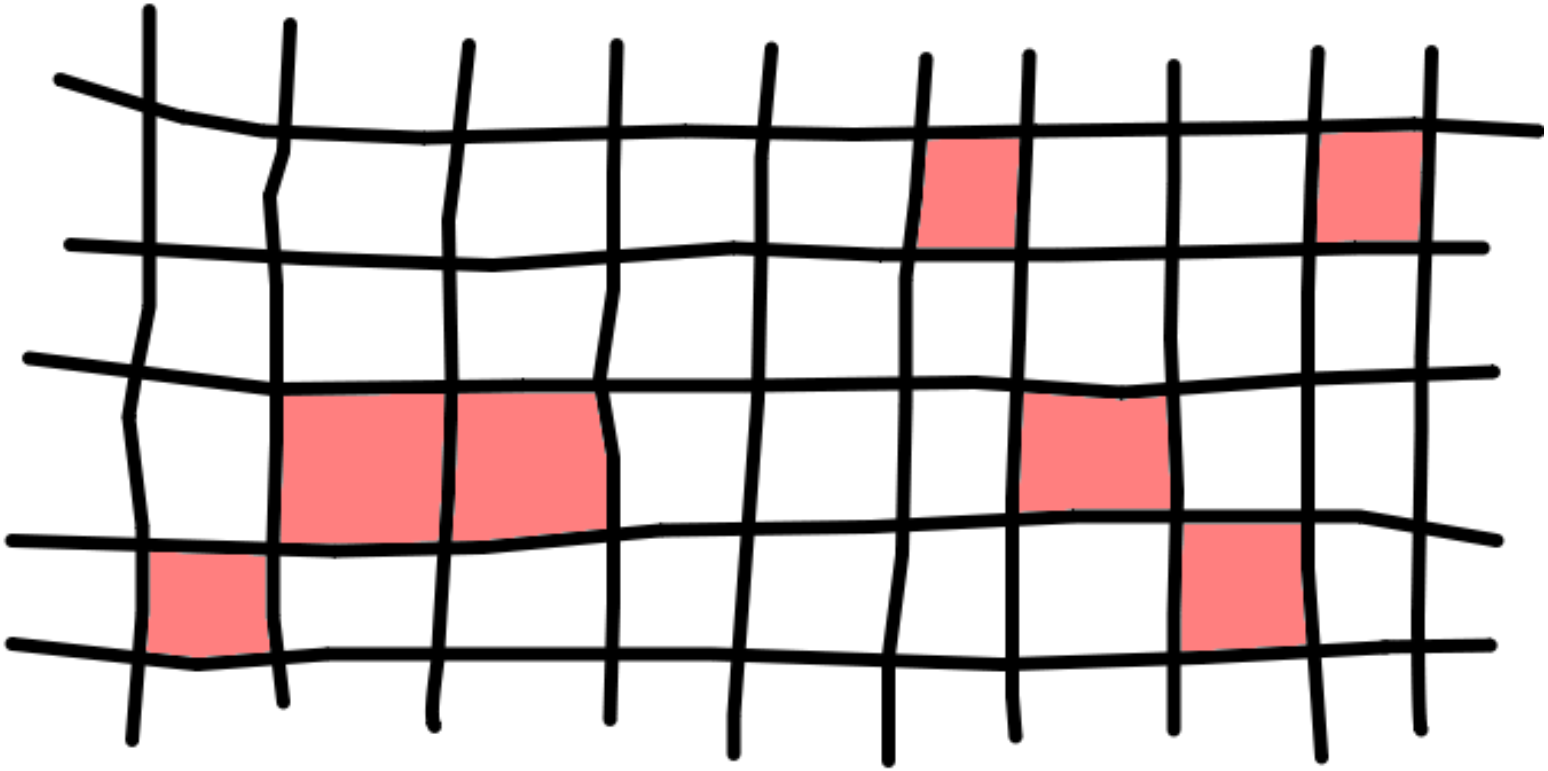
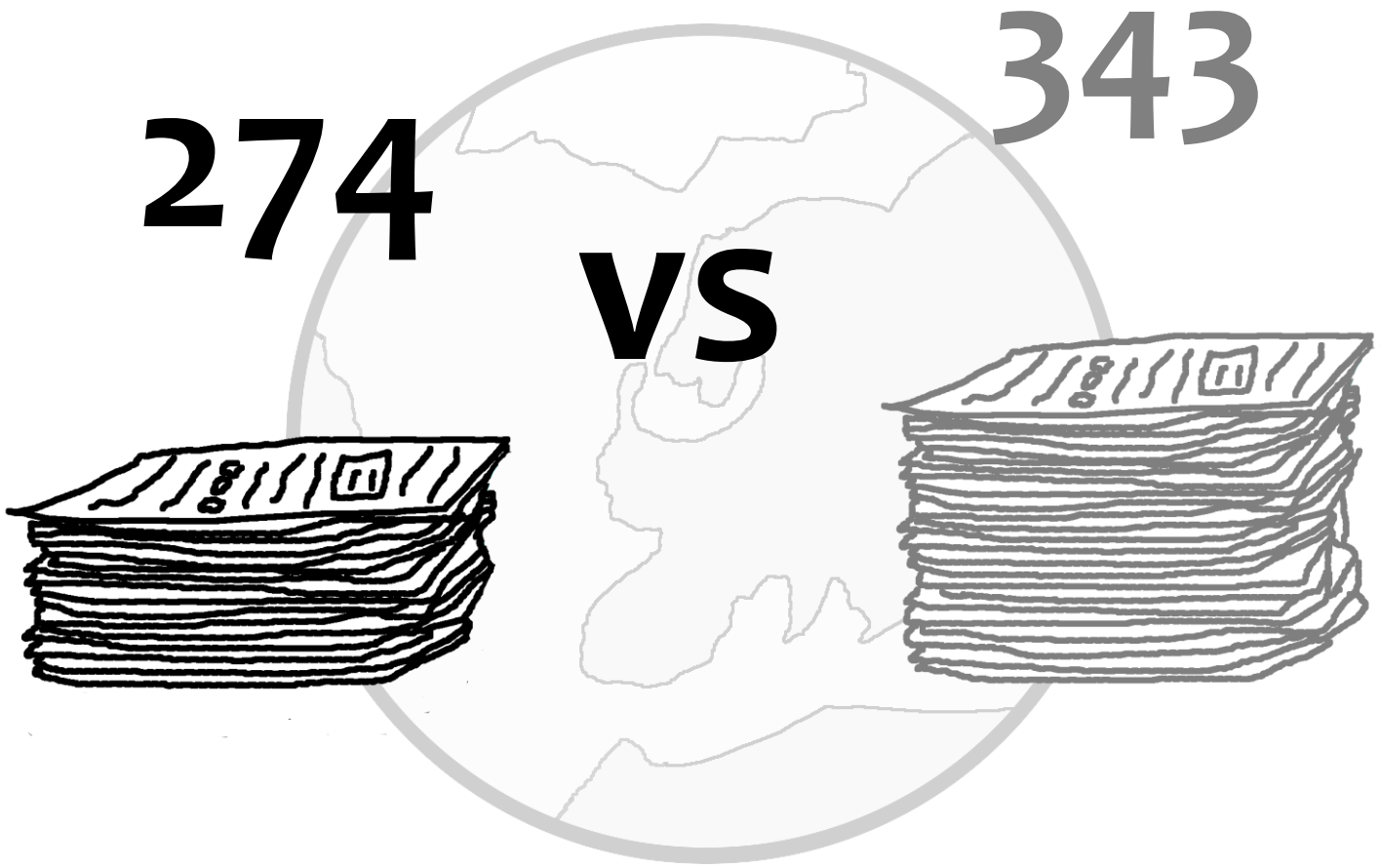
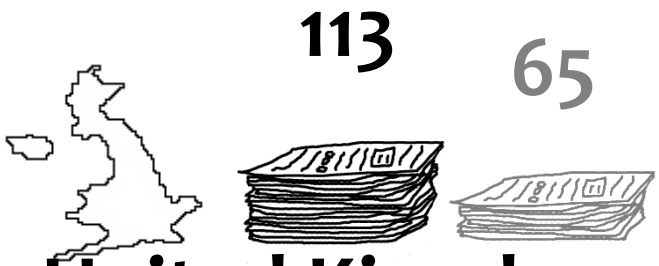
‘De-confounded’ pattern



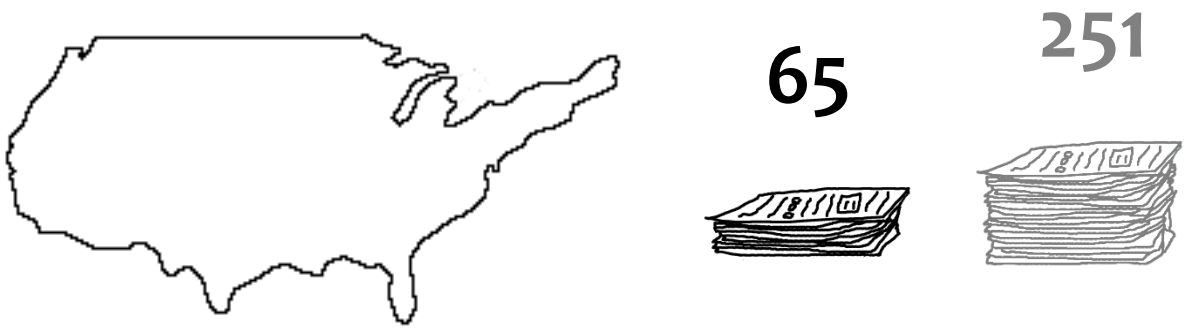
Alopecia with fluoxetine



Alopecia with fluoxetine



Alopecia with fluoxetine



United States

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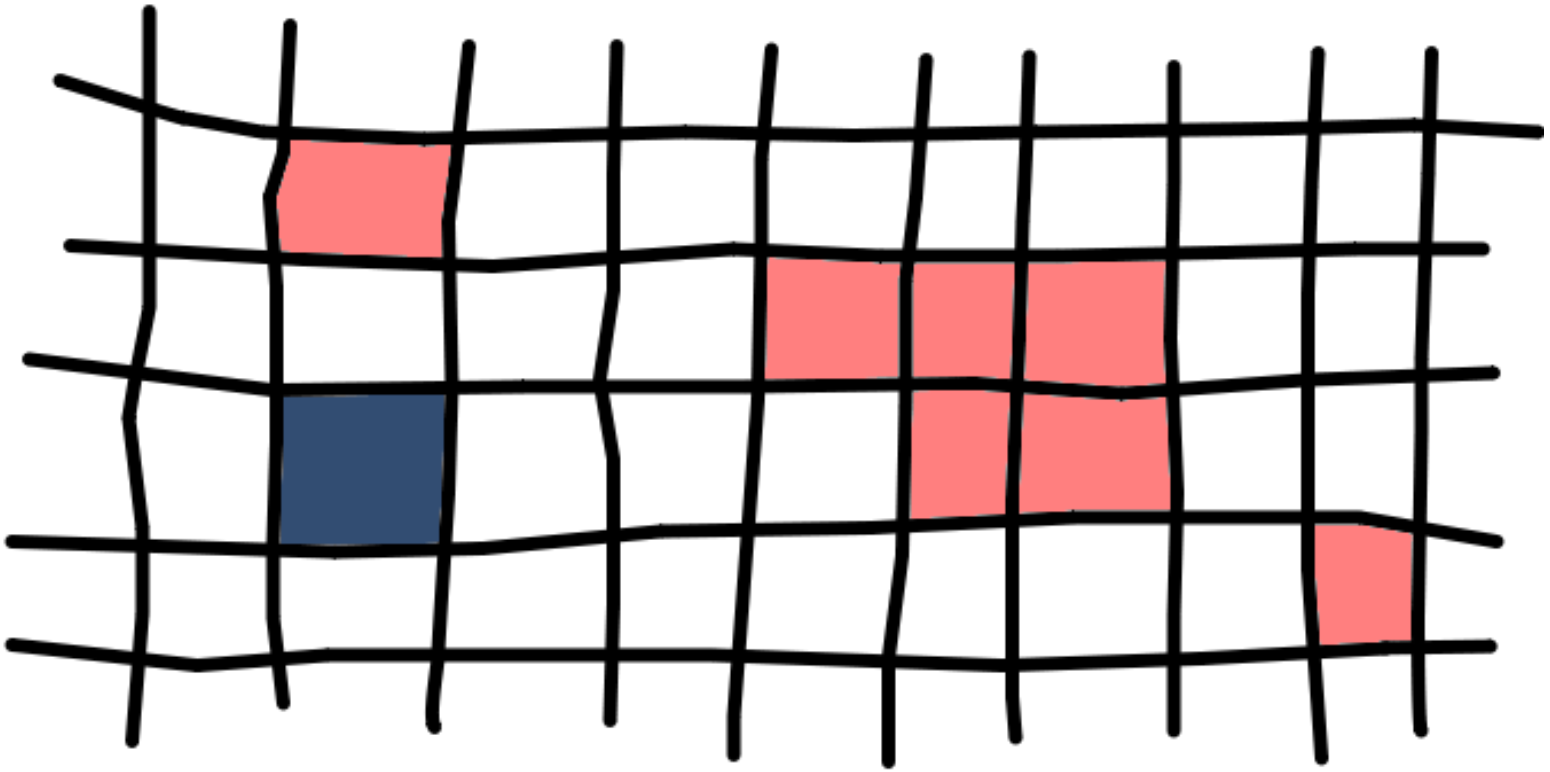
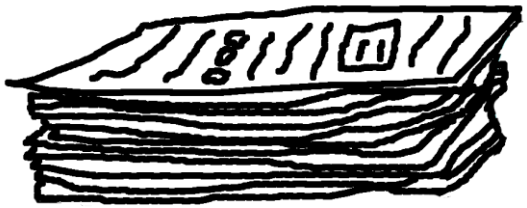
Hopstadius & Norén, 2012.

'But one' pattern



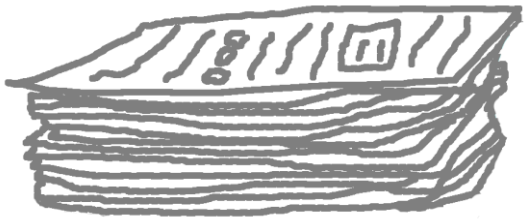
Rhabdomyolysis with venlafaxine

48



vs

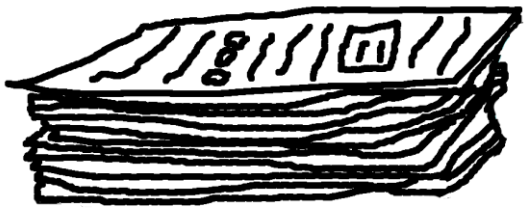
58



Rhabdomyolysis with venlafaxine

~~statins~~

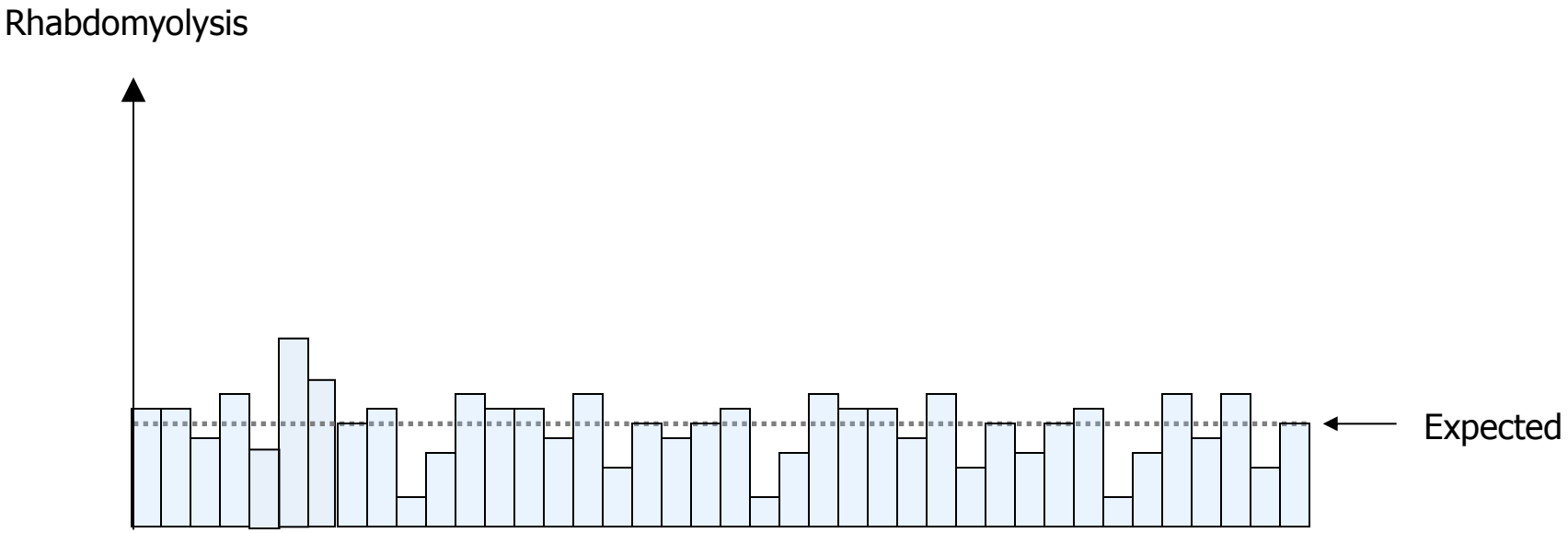
45



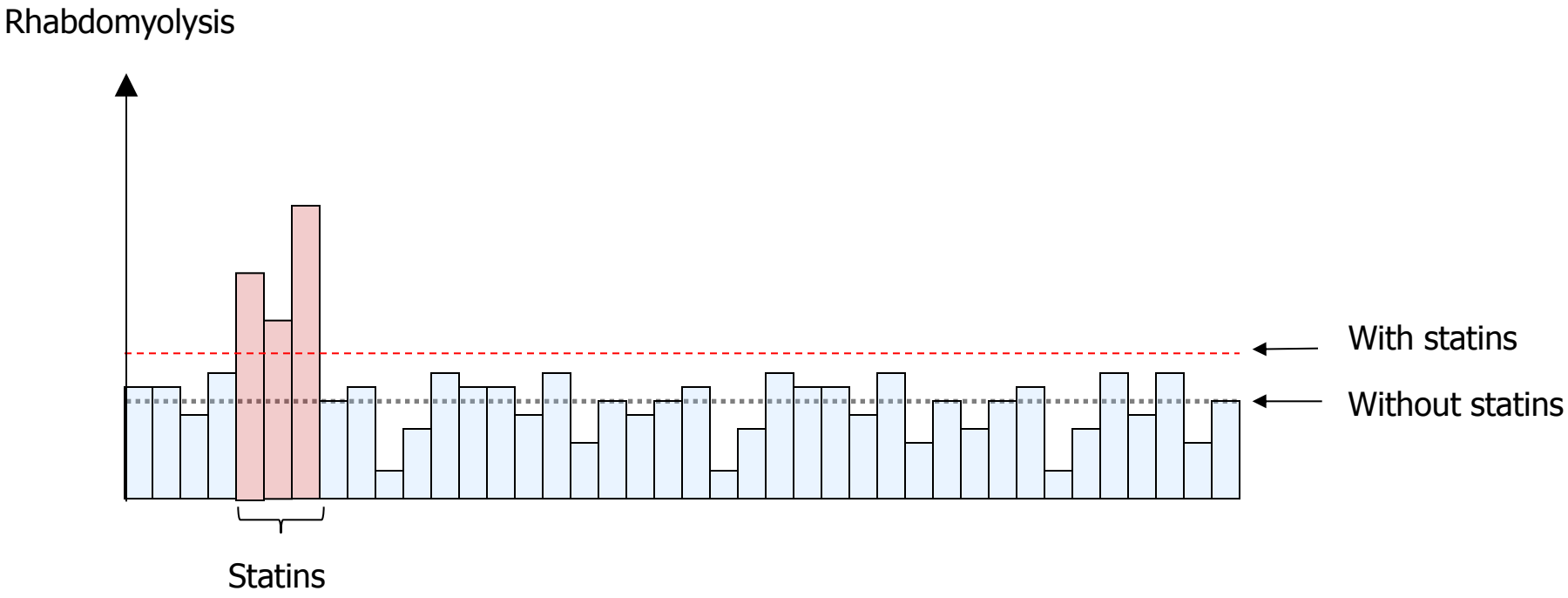
vs

15

Masking



Masking



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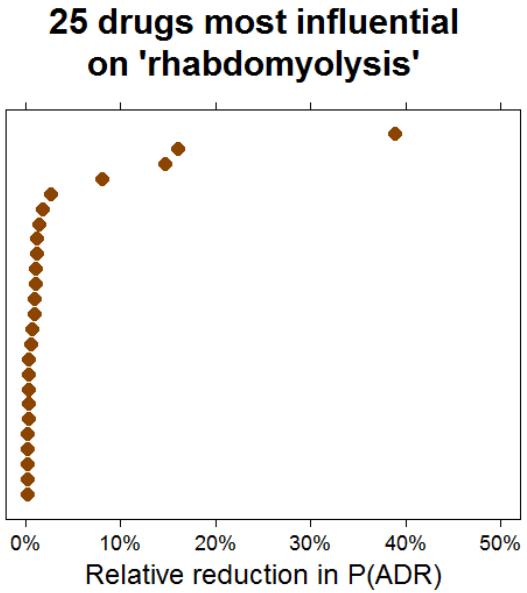
Caster et al. 2009.

Statins and rhabdomyolysis



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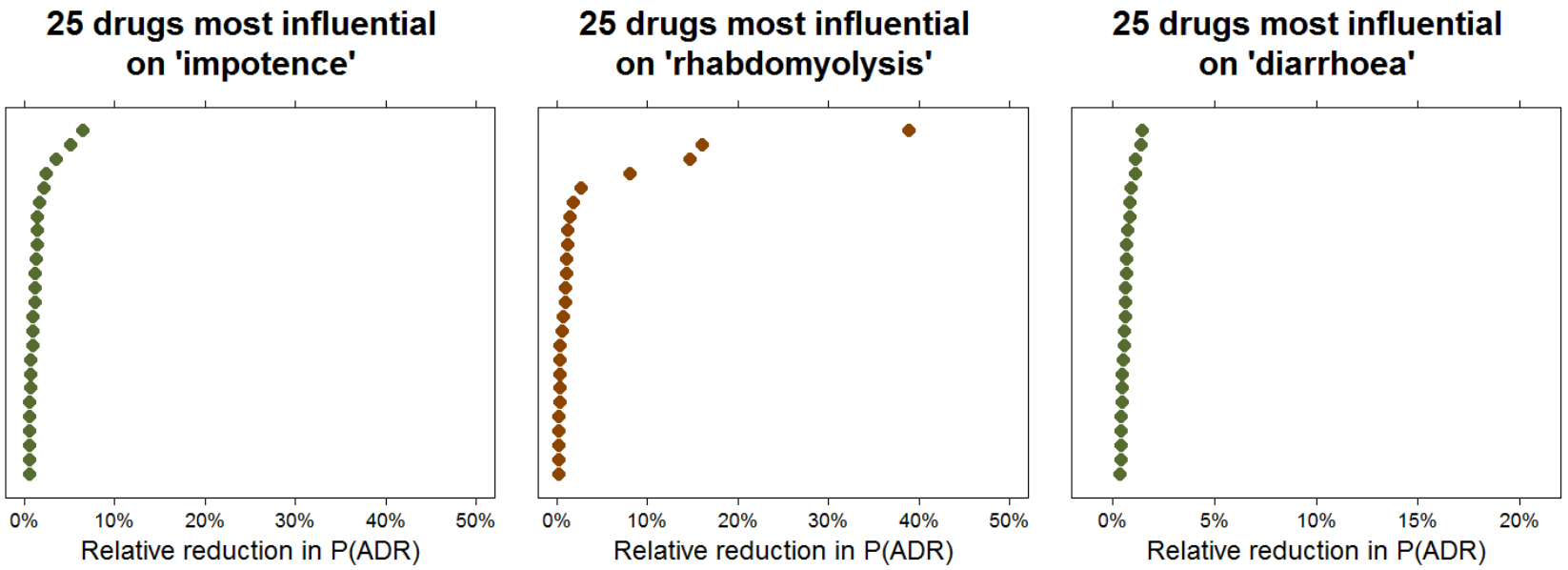
Caster et al. 2009.

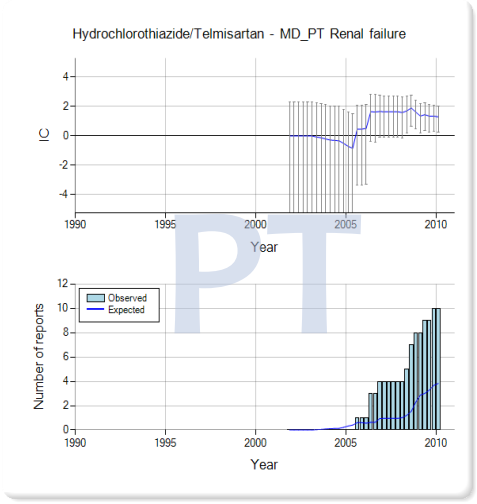
Statins and rhabdomyolysis

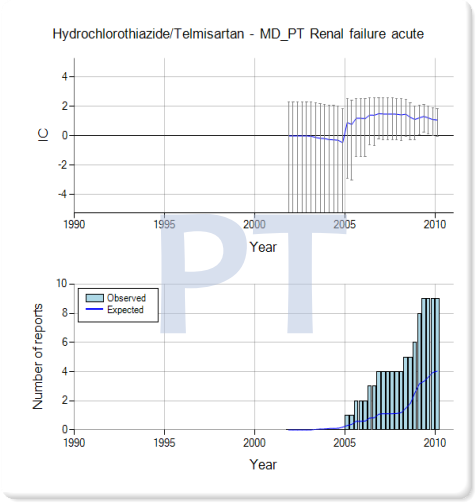


Hill et al. 2009.

Acute renal failure with Hydrochlorothiazide/Telmisartan

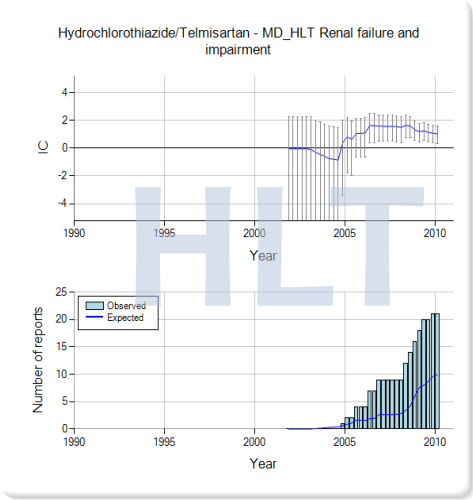
- Highlighted by the first PT in 2nd quarter 2008





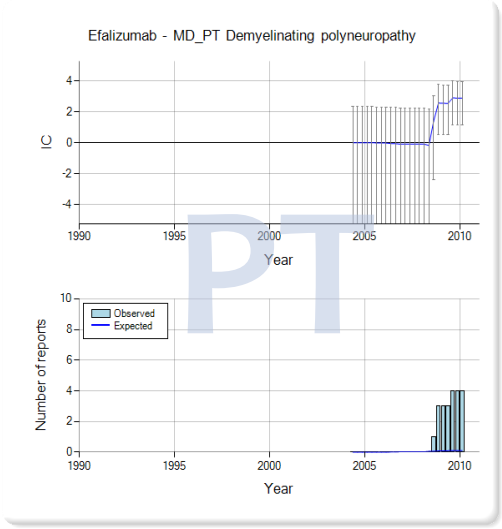
Acute renal failure with Hydrochlorothiazide/Telmisartan

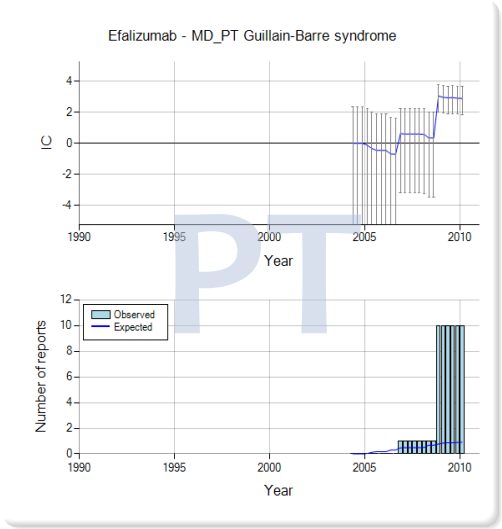
- Highlighted by the HLT in 2nd quarter 2006



Peripheral neuropathy with efalizumab

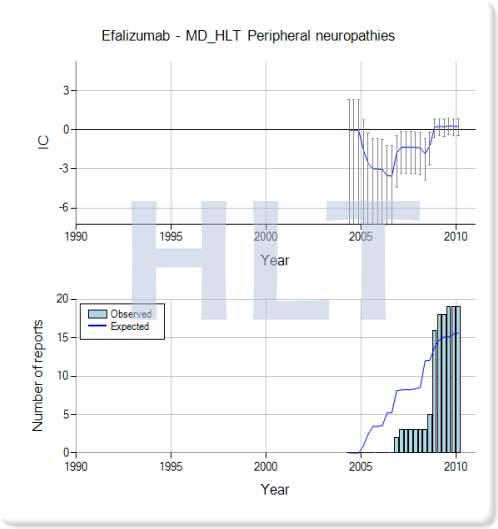
- Highlighted by two PTs in 4th quarter 2008





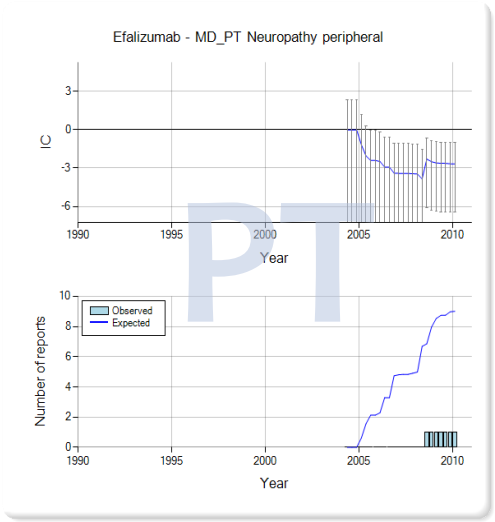
Peripheral neuropathy with efalizumab

- Not highlighted by the HLT at all



Peripheral neuropathy with efalizumab

- High expected count for HLT due to another PT



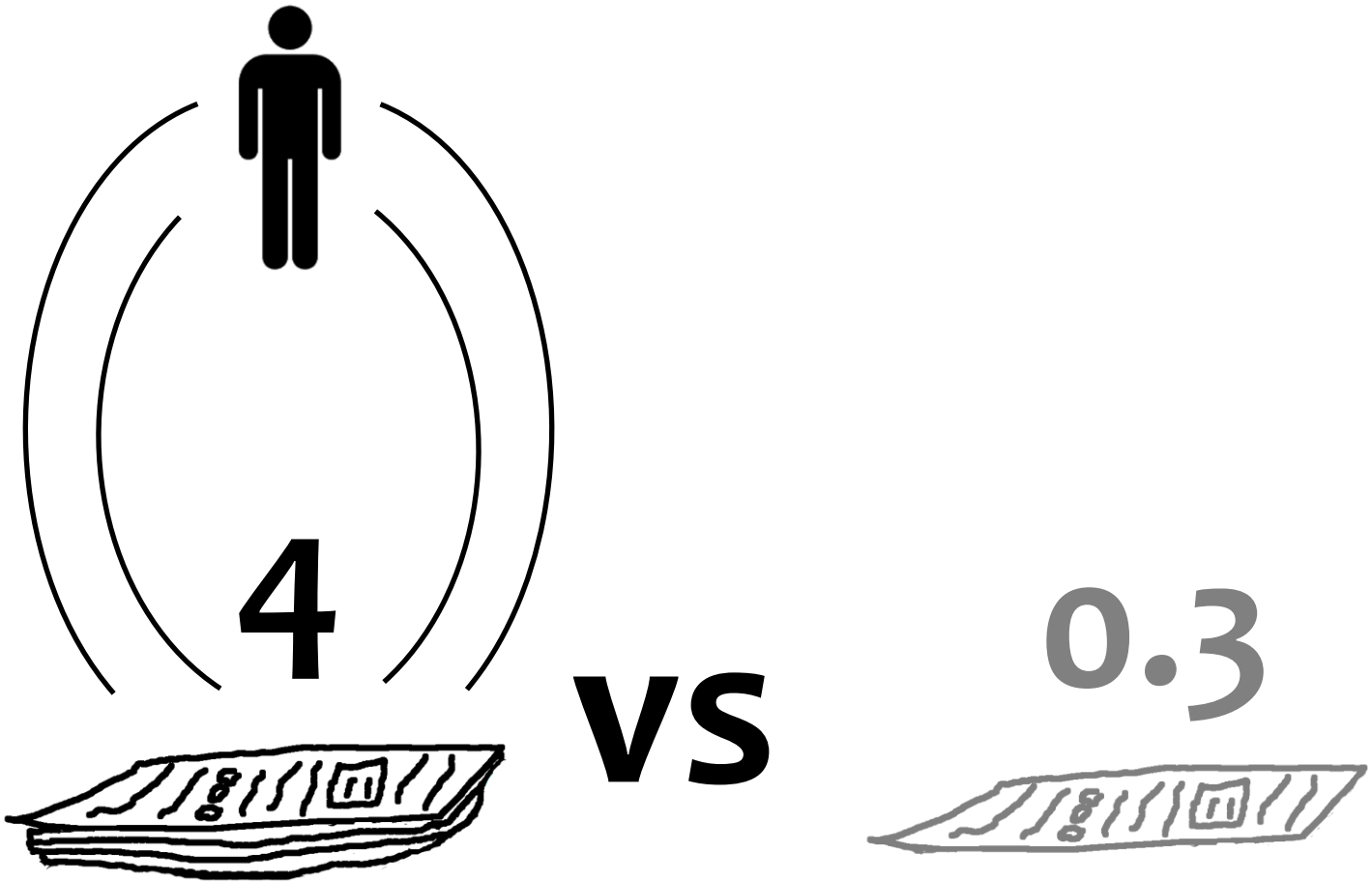
Face pain with epinephrine

4

vs

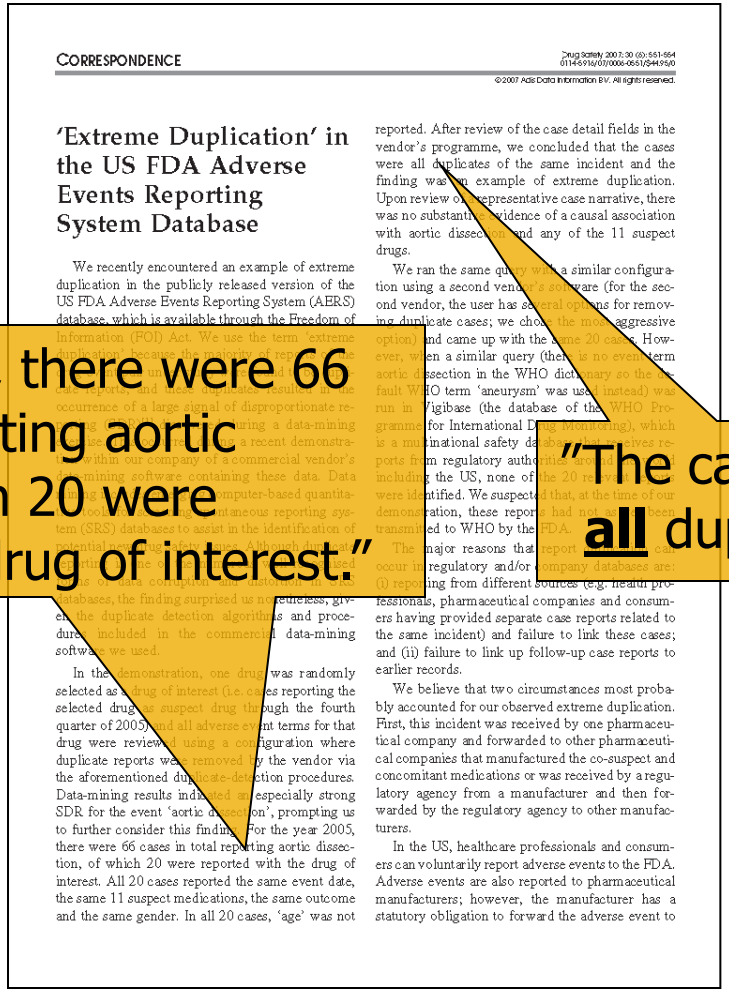
0.3

Face pain with epinephrine



Extreme duplication

Hauben et al.
Drug Safety, 2007.



CORRESPONDENCE

Drug Safety 2007; 30 (6): 551-554
0114-5916/07/0006-0551/$44.95/0

'Extreme Duplication' in the US FDA Adverse Events Reporting System Database

We recently encountered an example of extreme duplication in the publicly released version of the US FDA Adverse Events Reporting System (AERS) database, which is available through the Freedom of Information (FOI) Act. We use the term 'extreme duplication' because the majority of reports [illegible] occurrence of a large signal of disproportionate reporting (SDR) during a data-mining [illegible] within our company of a commercial vendor's data-mining software containing these data. Data mining is a computer-based quantitative procedure that scans [illegible] spontaneous reporting system (SRS) databases to assist in the identification of potential new drug safety issues. Although duplicate reports are [illegible] databases, the finding surprised us nonetheless, given the duplicate detection algorithms and procedures included in the commercial data-mining software we used.

In the demonstration, one drug was randomly selected as a drug of interest (i.e. cases reporting the selected drug as suspect drug through the fourth quarter of 2005) and all adverse event terms for that drug were reviewed using a configuration where duplicate reports were removed by the vendor via the aforementioned duplicate-detection procedures. Data-mining results indicated an especially strong SDR for the event 'aortic dissection', prompting us to further consider this finding. For the year 2005, there were 66 cases in total reporting aortic dissection, of which 20 were reported with the drug of interest. All 20 cases reported the same event date, the same 11 suspect medications, the same outcome and the same gender. In all 20 cases, 'age' was not reported. After review of the case detail fields in the vendor's programme, we concluded that the cases were all duplicates of the same incident and the finding was an example of extreme duplication. Upon review of the representative case narrative, there was no substantial evidence of a causal association with aortic dissection and any of the 11 suspect drugs.

We ran the same query with a similar configuration using a second vendor's software (for the second vendor, the user has several options for removing duplicate cases; we chose the most aggressive option) and came up with the same 20 cases. However, when a similar query (there is no event term aortic dissection in the WHO dictionary so the default WHO term 'aneurysm' was used instead) was run in Vigibase (the database of the WHO Programme for International Drug Monitoring), which is a multinational safety database that receives reports from regulatory authorities around the world including the US, none of the 20 reports were identified. We suspected that, at the time of our demonstration, these reports had not yet been transmitted to WHO by the FDA.

The major reasons that report duplication can occur in regulatory and/or company databases are: (i) reporting from different sources (e.g. health professionals, pharmaceutical companies and consumers having provided separate case reports related to the same incident) and failure to link these cases; and (ii) failure to link up follow-up case reports to earlier records.

We believe that two circumstances most probably accounted for our observed extreme duplication. First, this incident was received by one pharmaceutical company and forwarded to other pharmaceutical companies that manufactured the co-suspect and concomitant medications or was received by a regulatory agency from a manufacturer and then forwarded by the regulatory agency to other manufacturers.

In the US, healthcare professionals and consumers can voluntarily report adverse events to the FDA. Adverse events are also reported to pharmaceutical manufacturers; however, the manufacturer has a statutory obligation to forward the adverse event to

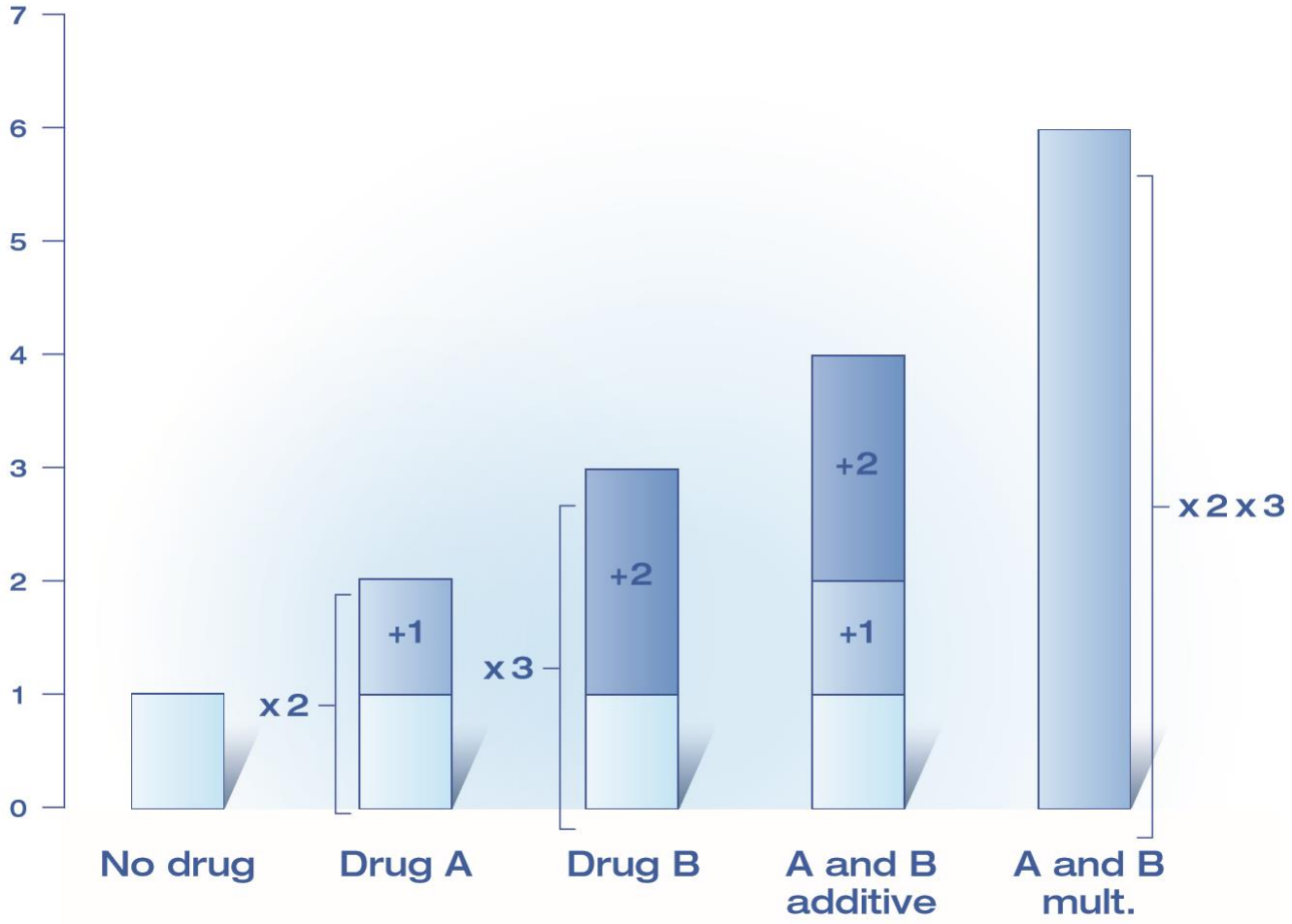
"For the year 2005, there were 66 cases in total reporting aortic dissection, of which 20 were reported with the drug of interest."

"The cases were **all** duplicates"

Drug interactions

1+1=3 ?

Interaction compared to what?



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Disproportionality analysis is

a good servant

but a terrible master!

Watch your step!

References

1. Hopstadius J, Norén GN. **Robust discovery of local patterns: subsets and stratification in adverse drug reaction surveillance**. Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium, 2012.
2. Caster O, Star K, Hill R, Norén GN. **Using Regression To Find Otherwise Undetected Drug Safety Issues** [abstract]. *Pharmacoepidemiology and drug safety*, 2008. **18(**S1).
3. Hauben M, Reich L, DeMicco J, Kim K. **Extreme duplication in the US FDA Adverse Events Reporting System database**. *Drug Safety*. 2007; **30**(6):551-554.
4. Norén GN, Orre R, Bate A, Edwards IR. **Duplicate detection in adverse drug reaction surveillance**. *Data Mining and Knowledge Discovery*, 2007. **14**(3):305-328.

References

5. Caster O, Norén GN, Madigan D, Bate A. **Large-Scale Regression-Based Pattern Discovery: The Example of Screening the WHO Global Drug Safety Database**. *Statistical Analysis and Data Mining* 2010; **3**(4):197-208.
6. Norén GN, Sundberg R, Bate A, Edwards IR. **A statistical methodology for drug-drug interaction surveillance**. *Statistics in Medicine*, 2008. **27**(16):3057-3070.