# Conflicts of interest

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I have no conflicts of interest

# Our drug epidemic

8 mio daily doses in Denmark; 5.5 mio inhabitants

One of eight get at least 5 drugs every day

NSAIDs: one of eight get one every year

SSRIs: 450.000 people per year or 6 years of our lives

SSRIs: sales 1992-2007 reflected number of drugs (r = 0.97)

Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing, 2013.

# Polypharmacy


"Is there a pill I can take to feel better about all the pills I take?"

# Our drugs kill us

## In the United States and Europe

Prescription drugs are the third leading cause of death after heart disease and cancer

200,000 die in the United States each year

What if the drug epidemic had been a microbial epidemic?

Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing, 2013.

# Industry behaviour

Organised crime

Racketeering is the act of engaging in a certain type of offence more than once, e.g. extortion, fraud, federal drug offences, bribery, embezzlement, obstruction of justice, obstruction of law enforcement, tampering with witnesses, and political corruption.

Pfizer convicted of organised crime and a conspiracy in 2010 for Neurontin (gabapentin) fraud.

# Industry crimes

Compared to other industries, the pharmaceutical industry is the biggest defrauder of the US federal government under the False Claims Act.

In the United States, drug companies have more than three times as many serious or moderately serious law violations as other companies, and this record holds after adjustment for company size. Big pharma has a worse record than other companies for international bribery and corruption.

The crimes are increasing.

# Pfizer fraud

In 2009, Pfizer entered a Corporate Integrity Agreement with the US Department of Health and Human Services, which means that good behaviour is required for the next 5 years.

Pfizer had previously entered into three such agreements, and when Pfizer promised the federal prosecutors not to market drugs illegally again in 2004, Pfizer was busily doing exactly this while they signed the agreement.

# FDA's approach to safety

The way FDA approaches safety is to virtually disregard it. FDA believes there is no risk that cannot be managed in the post-marketing setting.

What FDA says is: We can't be 95 percent certain this drug will kill you, therefore we will assume it doesn't – and they let it on the market.

*David Graham, Associate Director, FDA's Office of Drug Safety*

FDA approved Vioxx because it lacked 'complete certainty' that the drug increased cardiovascular risk, although this was expected based on the drug's mode of action.

# FDA's fake fixes

Warnings, precautions, contraindications, etc.

Warfarin is used when contraindicated.

Cisapride (Propulsid), black box warning in 1998 about contraindications. Contraindicated for users:

Before warning: 26%, 30% and 60% (at three sites)
One year after warning: 24%, 28% and 58%.

# What about?

Selective reporting and analysis
Are RCTs science?
Marketing-based medicine

Statistical alchemy cannot make gold of garbage

# Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

## Comparison of Protocols to Published Articles

An-Wen Chan, MD, DPhil
Asbjørn Hrobjartsson, MD, PhD
Mette T. Haahr, BSc
Peter C. Gøtzsche, MD, DrMedSci
Douglas G. Altman, DSc

(JAMA 2004;291:2457-65)

# Outcome reporting bias

Full outcome reporting is associated with $p<0.05$

Odds ratio 2.4 (1.4 - 4.0) for efficacy
Odds ratio 4.7 (1.8 - 12) for harms

# Are primary outcomes consistent between protocols and publications?

| Discrepancy in primary outcomes | Proportion (%) of trials with inconsistencies |
|---|---|
| Changes to protocol-defined outcome | 53% (40/76) |
| New publication-defined outcome | 33% (21/63) |
| Change in power calculation outcome | 29% (10/38) |
| ANY INCONSISTENCY | 63% (52/82) |

None of the reports acknowledged modifications

# Antidepressants, any benefits?

2006 FDA analysis of 100,000 patients in placebo controlled trials:

- only 4% on active drug got tricyclics
- half of the patients had depression
- 50% responded on drug, 40% on placebo
- the 40% is NOT a placebo effect!

www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf

# Antidepressants, any benefits?

The effect is measured on highly subjective scales, e.g. Hamilton.

Systematic review of 21 trials in a variety of disease areas that had both blinded and nonblinded outcome assessors.

Most trials had used subjective outcomes.

The effect was exaggerated by 36% on average (measured as odds ratio) by the nonblinded observers.

What if the blinding has been broken for all patients?

The 10% difference in effect becomes zero (odds ratio 1.02)

Hróbjartsson et al, BMJ 2012;344:e1119.

# Antidepressants, any benefits?

Cochrane review with an active placebo (atropine)

- 9 trials, 751 patients
- tricyclic antidepressants
- one trial had an implausibly large effect
- omitting this trial, the SMD was 0.17
- this corresponds to 1.3 on the Hamilton 17 scale, i.e. no effect (as 5-6 is the minimum that can be perceived)
- included studies: 7 from 1961-66, 2 from 1970s, 1 from 1984

Moncrieff et al, Cochrane review,CD003012 and Leucht et al., J Affect Disord 2013;148:243-8.

# Antidepressants, any benefits?

It seems likely to me that antidepressants don't work.

Many patients and doctors think they work but they forget about the natural cause of the depression.

Do they have any meaningful effect on outcomes that matter,

e.g. saving relationships and getting people back to work?

They cause sexual problems in half of those treated and who did not have problems before they were treated.

Is it likely that they help saving intimate relationships?

Montejo, J Clin Psychiatry 2001;62(Suppl. 3):10–21.

# One week later, placebo equals active drug

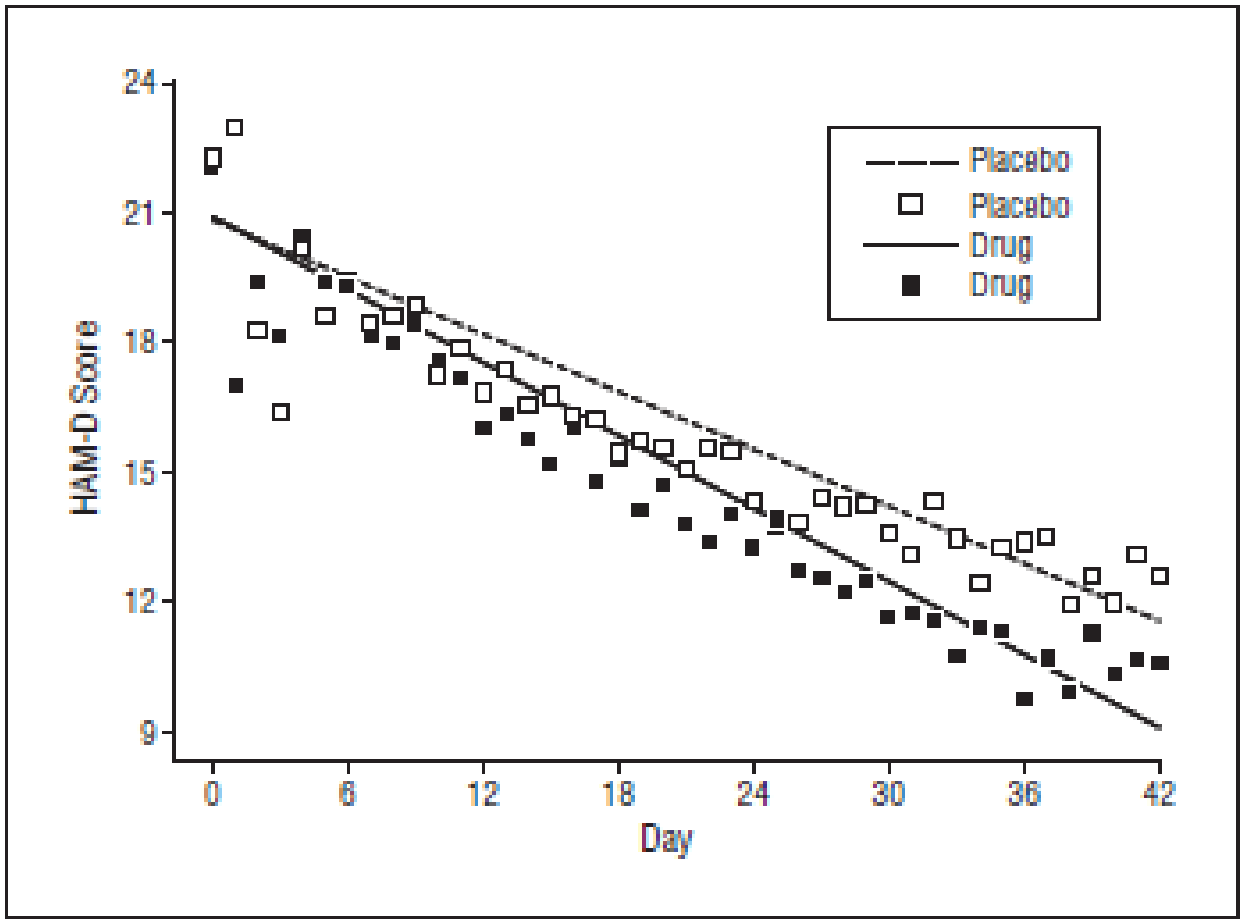



**Figure.** Observed vs estimated depression severity time trends for drug vs placebo in 37 adult and geriatric studies. HAM-D indicates Hamilton Depression Scale.

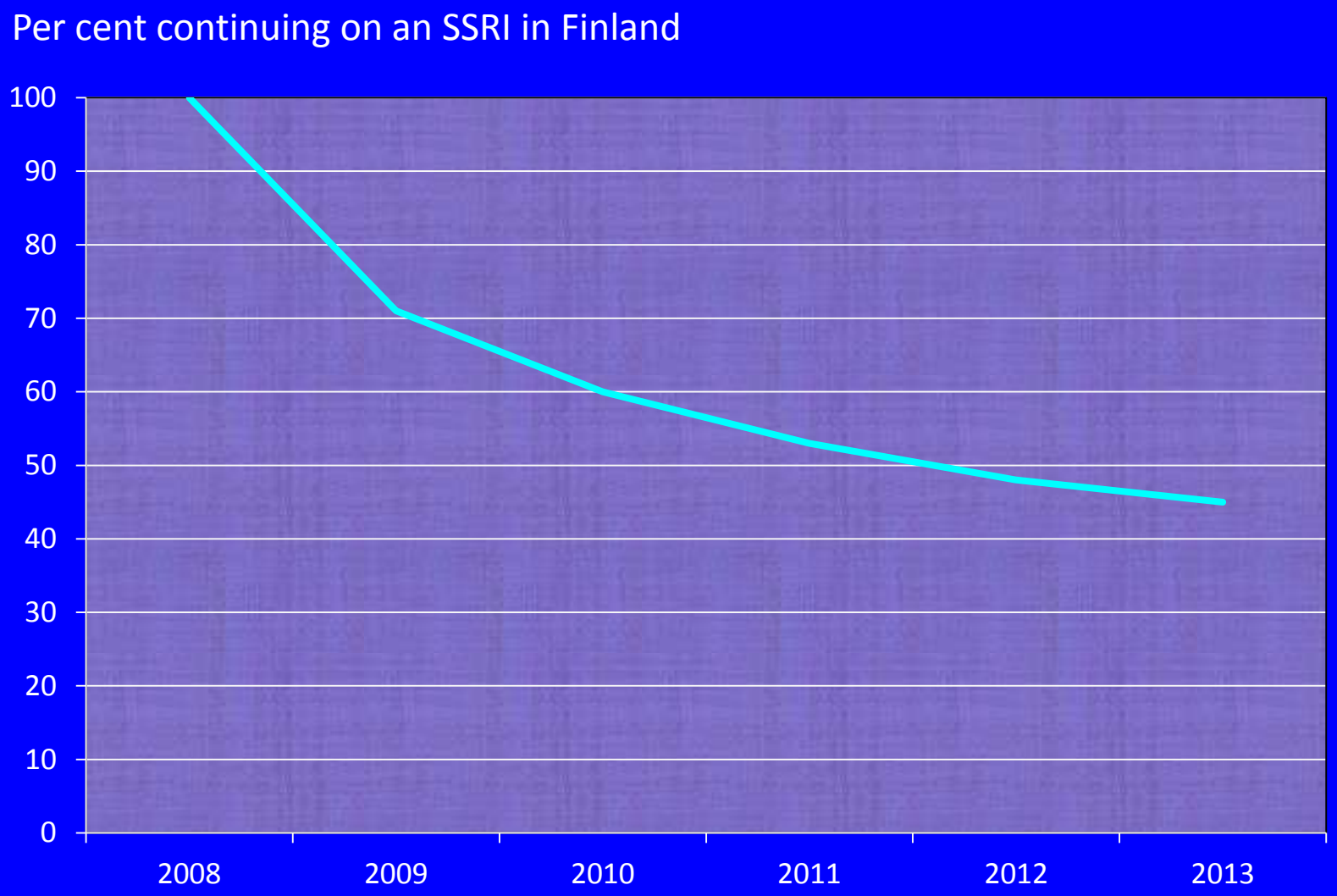
Sponsor-conducted RCTs of fluoxetine and venlafaxine.

OBS: Linear regression is wrong on these data

Gibbons et al,
Arch Gen Psychiatry.
Online March 5, 2012.

doi:10.1001/archgenpsychiatry.2011.2044

# People go on and on and on…



# Suicide risk is far worse than what the FDA found

Suicides in the trials:

5 suicides in 52,960 patients on antidepressants in 2004 FDA analysis, 1 per 10,000

5 suicides in 2,963 patients on paroxetine in 1993 meta-analysis, 17 per 10,000

2 suicides in 1,427 patients on fluoxetine in 1984 , 14 per 10,000

9 suicides in 6,993 patients on fluoxetine in 1990, 13 per 10,000

Laughren 2006 FDA analysis: 1 per 10,000

Laughren 2001 FDA trials: 10 per 10,000 (22 suicides in 22,062 patients on drug)

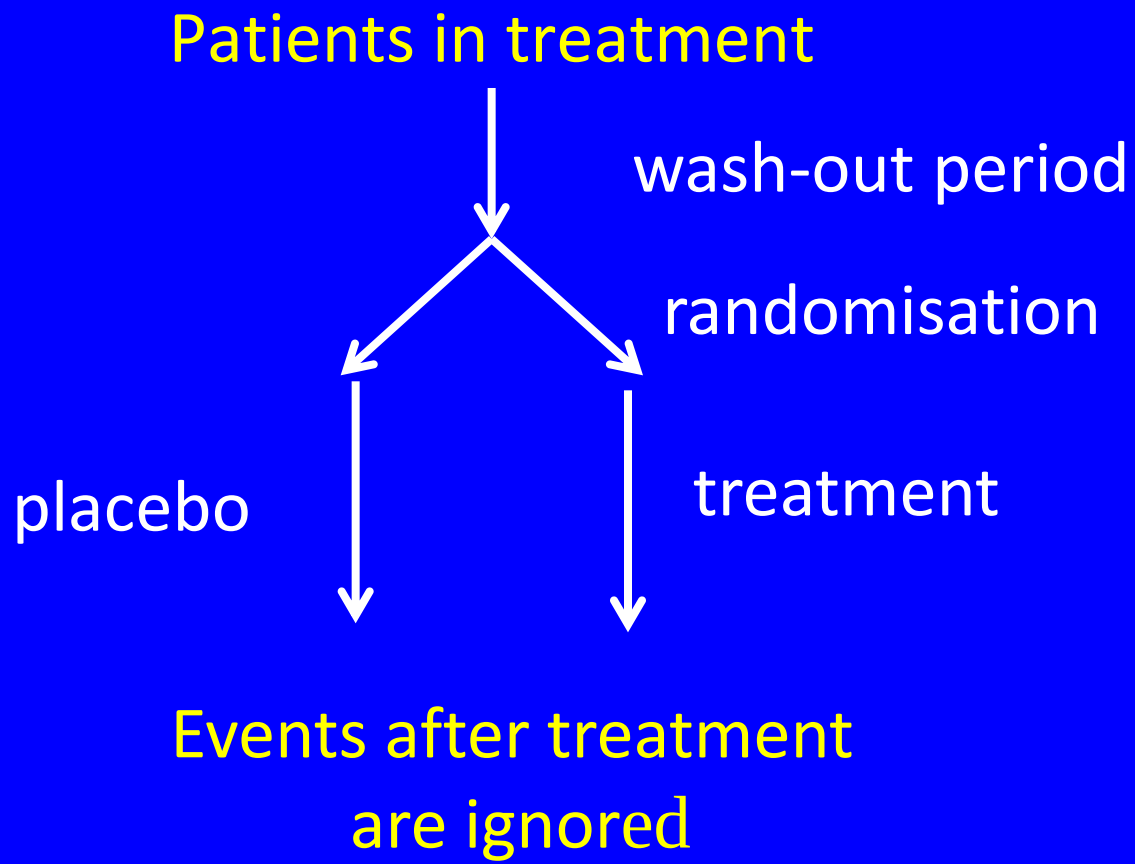
There should have been 15 times more suicides in the FDA analysis ,
an error of 1,400%

Only events occurring within 24 hours after stopping drug were included.

People with agitation/akathisia were put on benzodiazepines. Many other flaws

Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press , 2015

# Two flaws in antidepressant trials



# Example: sertraline studies in adults, suicides and suicide attempts

| | | sertraline | | placebo | | |
|---|---|---|---|---|---|---|
| | Follow-up | n | N | n | N | RR [95% CI] |
| FDA 2006 | 24 h | 7 | 6950 | 7 | 6047 | 0.87 [0.31, 2.48] |
| Pfizer 2009 | 24 h | 5 | 6561 | 8 | 5480 | 0.52 [0.17, 1.59] |
| Pfizer 2009 | 30 days | 25 | 10917 | 14 | 9006 | 1.47 [0.77, 2.83] |
| Gunnell 2005 (MHRA) | >24 h | 24 | 7169 | 8 | 5108 | 2.14 [0.96, 4.75] |

FDA: suicide, suicide attempt or self harm (Laughren, see ref. in other slides)

Pfizer: the same definitions (Vanderburg, J Clin Psychiatry 2009;70:674)

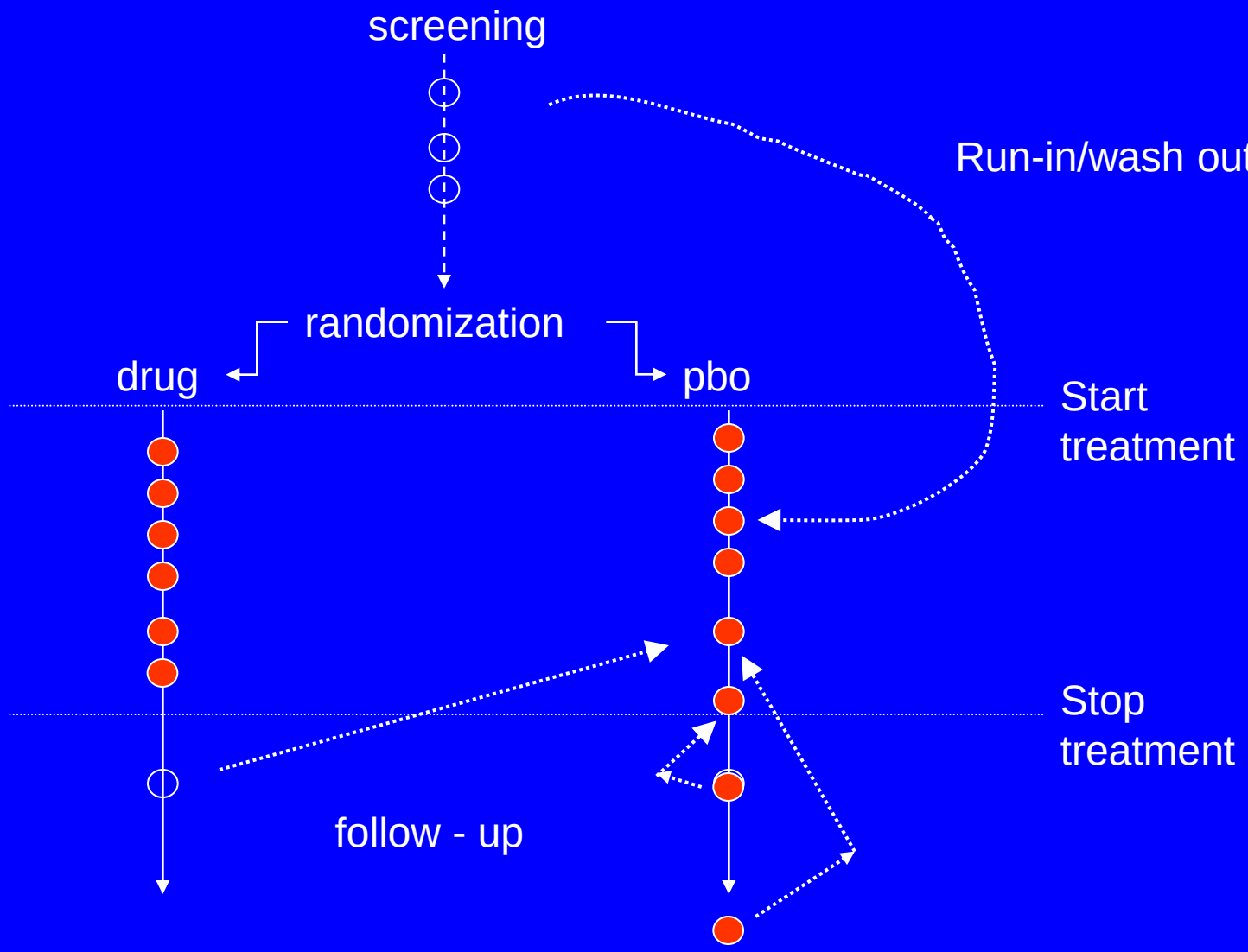
Gunnell: suicide or non-fatal self harm (BMJ 2005;330: 19 Feb)

# FLUOXETINE – PAROXETINE - SERTRALINE ADULT TRIALS

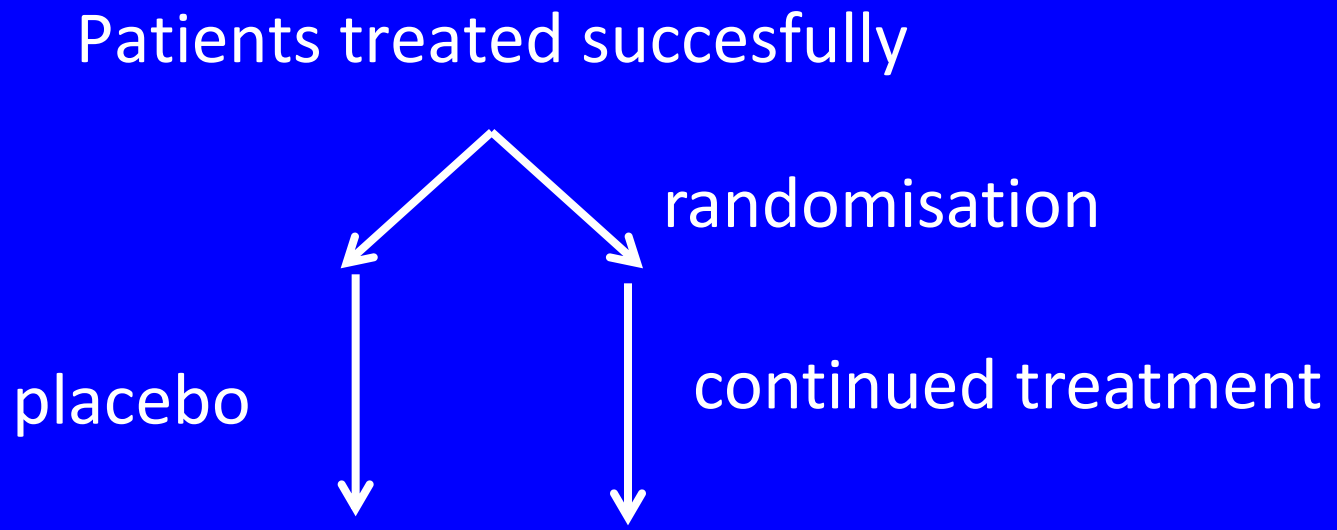
## Reporting of suicidal acts

Healy
BMJ
2006;
333:92–5

slide
from
Healy



# The fatal flaw in maintenance studies




Withdrawal symptoms in the placebo group
are interpreted as disease symptoms

# Do small effects exist?

## Money doesn't smell

## Anticholinergic drugs for "overactive bladder"

"Around 16% of adults have symptoms of overactive bladder"

61 trials (11,956 patients)

Cure or improvement: RR 1.39, 95%CI 1.28 to 1.51

**Authors' conclusions**

The use of anticholinergic drugs by people with overactive bladder syndrome results in statistically significant improvements in symptoms.

(Nabi, Cochrane review, CD003781)

# Anticholinergic drugs for urinary incontinence

## So what was the effect, really?

Number of leakage episodes per 24 hours in the largest study:

3.2 on drug and 3.3 on placebo

Number of pees (called micturitions in doctor's language) in the two studies that reported on this:

10 on drug and 11 on placebo.

It doesn't take much unblinding to get such results

(Nabi, Cochrane review, CD003781)

# Anticholinergic drugs for urinary incontinence

## What about the harms?

Frequent and disturbing side effects:
dry mouth, blurred vision, constipation and confusion.

Others are, for example:
dry eyes, dry nose, headache and gas.

Serious harms that require you call your doctor immediately:
difficulty urinating, rash, hives, itching and difficulty breathing or swallowing.

(Nabi, Cochrane review, CD003781)

# Do small effects exist?

## Cholinesterase inhibitors for Alzheimer's disease

“first line pharmacotherapy for mild to moderate Alzheimer's disease”

13 trials (7,298 patients)

Improvements in cognitive function, -2.7 points (95%CI -3.0 to -2.3), p<0.00001), in the midrange of the 70 point ADAS-Cog Scale.

Study clinicians rated global clinical state more positively in treated patients. Benefits of treatment were also seen on measures of activities of daily living and behaviour. None of these treatment effects are large.

**Authors' conclusions**

The three cholinesterase inhibitors are efficacious for mild to moderate Alzheimer’s disease

(Birks, Cochrane review, CD005593)

# Do small effects exist?

## Cholinesterase inhibitors for Alzheimer's disease

“Although many types of adverse event were reported, nausea, vomiting, diarrhoea, were significantly more frequent in the ChEI groups than in placebo.”

“More patients leave ChEI treatment groups, 29%, on account of adverse events than leave the placebo groups (18%).”

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The most common side effects of ARICEPT (donepezil) are:

Nausea, diarrhea, not sleeping well, vomiting, muscle cramps, feeling tired, not wanting to eat.

Just what we need for old people, isnt’ it?

(Birks, Cochrane review, CD005593)

# Do small effects exist?

## Cholinesterase inhibitors for Alzheimer's disease

The biggest trial, 565 patients, long-term (Courtney, Lancet 2004:363:2105)

Was excluded from the Cochrane review.

Outcomes after three years were similar with respect to institutionalisation, progression of disability, and behavioural and psychological symptoms.

Cognition: difference of 0.8 on scale 0-30 (MMSE)

Functionality: difference of 1.0 on scale 0-60 (BADSL)

**Interpretation** Donepezil is not cost effective, with benefits below minimally relevant thresholds. More effective treatments than cholinesterase inhibitors are needed for Alzheimer's disease.