Our lethal and highly costly drug epidemic

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I have no conflicts of interest

Deadly medicines

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.

Deadly medicines

On average, every GP kills one of their patients every year.

The causes of most deaths are invisible for the doctor.

Gøtzsche PC. Deadly medicines and organised crime. London: Radcliffe Publishing, 2013.
Gøtzsche PC. [The many invisible drug deaths]. Ugeskr Læger 2016;178:990-1.

Our drug epidemic

8 mio daily doses in Denmark; 5.5 mio inhabitants

One of eight get at least 5 drugs every day

39% of those at least 65 years old

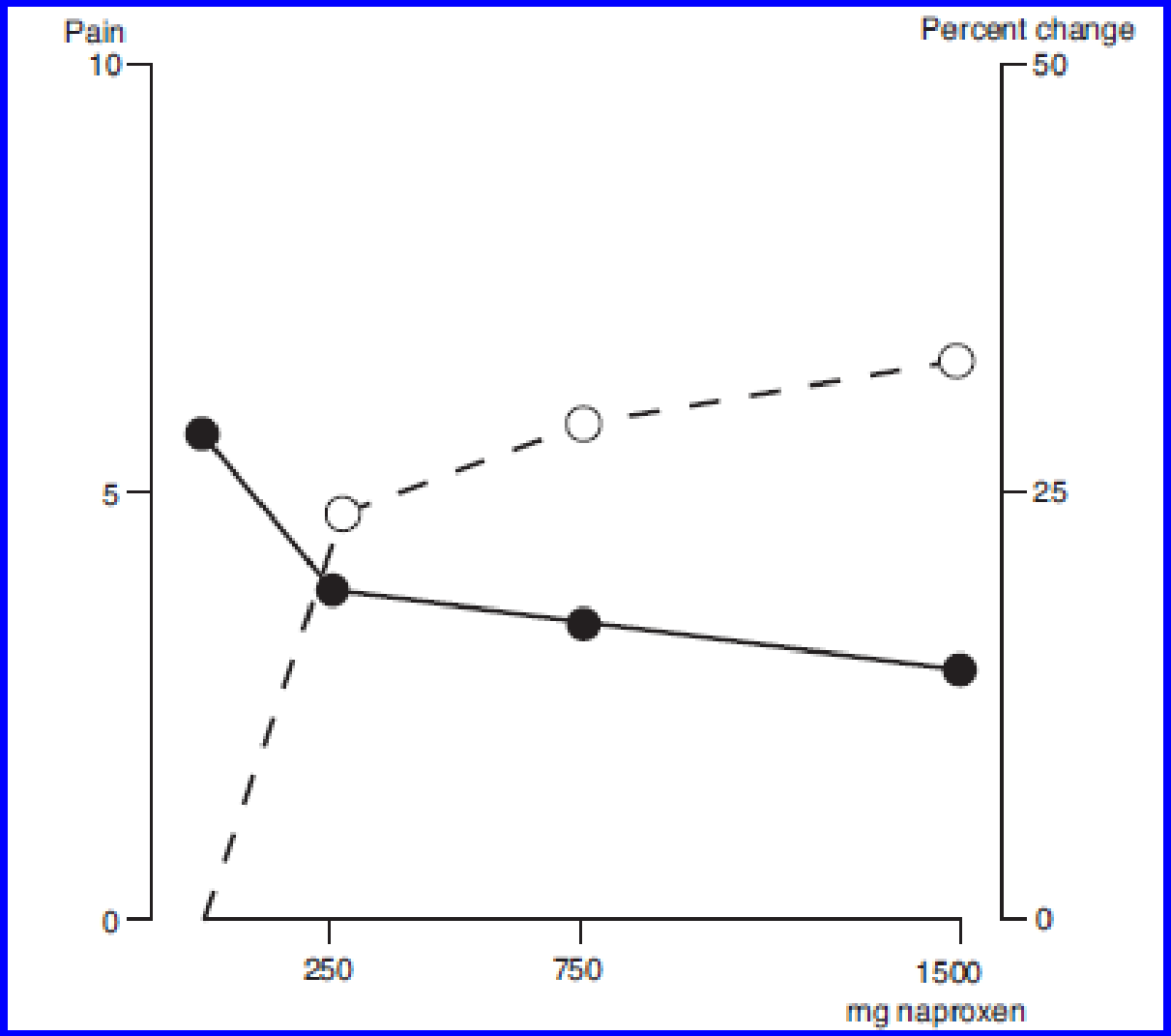
NSAIDs (arthritis drugs): one of eight get one every year

SSRIs (antidepressants): 6 years of our lives

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

Gøtzsche PC. Deadly medicines and organised crime. London: Radcliffe Publishing, 2013.
Kantor et al. *JAMA*. 2015;314(17):1818

Deadly marketing of an NSAID



Doubling of the dose from 500 to 1000 mg doubled serious harms for no benefit.

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

Deadly marketing of an NSAID

Pfizer's marketing, very successful and completely untruthful:

Piroxicam is more effective than aspirin and has a lower rate of gastrointestinal side effects than many other NSAIDs.

The truth: Piroxicam has more fatal reactions and more fatal gastrointestinal side effects than other drugs.

Pfizer tried to prevent publication of this study in the BMJ.

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

Deadly marketing of COX-2 inhibitors

Merck concealed cases of myocardial infarction and deaths with rofecoxib, which were missing in reports of the pivotal trials.

Pfizer denied that celecoxib causes heart attacks at an FDA hearing in 2005, despite having unpublished evidence to the contrary, and still called the evidence “inconclusive” in 2009 in information to patients invited to take part in a trial.

By 2004, rofecoxib had likely killed 120,000 people worldwide and celecoxib 75,000.

(Gøtzsche PC. Deadly Medicines and Organised Crime, 2013)

"I'm going to prescribe something that works like aspirin but costs much, much more."

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.

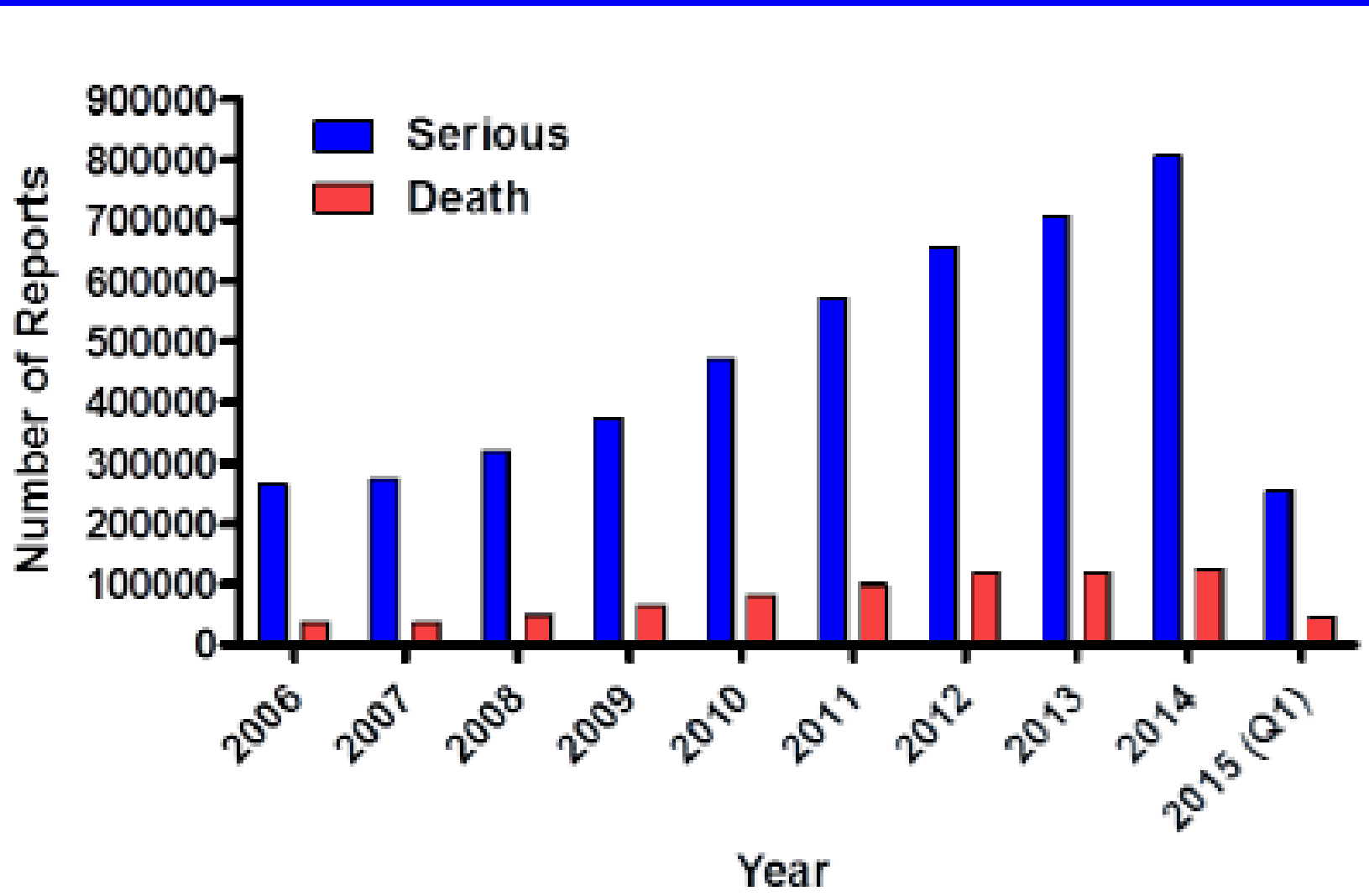
What FDA says is: We can't be 95 percent certain this drug will kill you, therefore we will assume it doesn't – and they let it on the market.

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 adverse events reports

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070461.htm



FDA's fake fixes

Warnings, precautions, contraindications, etc.

Warfarin is used when contraindicated.

Cisapride (Propulsid), black box warning in 1998 about contraindications. Prolongs the QT interval.

Contraindicated for users:

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

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 scale 0-52, i.e. no effect (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?

What does the poor blinding mean?

Effect in children and adolescents in two systematic reviews:

SMD = 0.25 (psychiatrists' evaluation) (Hamilton 1.9)

SMD = 0.05 (patients' evaluation) (Hamilton 0.4)

SMD = 0.29 (psychiatrists' evaluation)

SMD = 0.06 (patients' evaluation)

Effect in adults, old drugs like amitriptyline:

SMD = 0.25 (psychiatrists' evaluation)

SMD = 0.06 (patients' evaluation)

Spielmans et al, Psychother Psychosom 2014;83:158–64

Hetrick et al, Cochrane Database Syst Rev 2012;11:CD004851

Greenberg et al, J Consult Clin Psychol 1992;60:664-9

One week later, placebo equals active drug

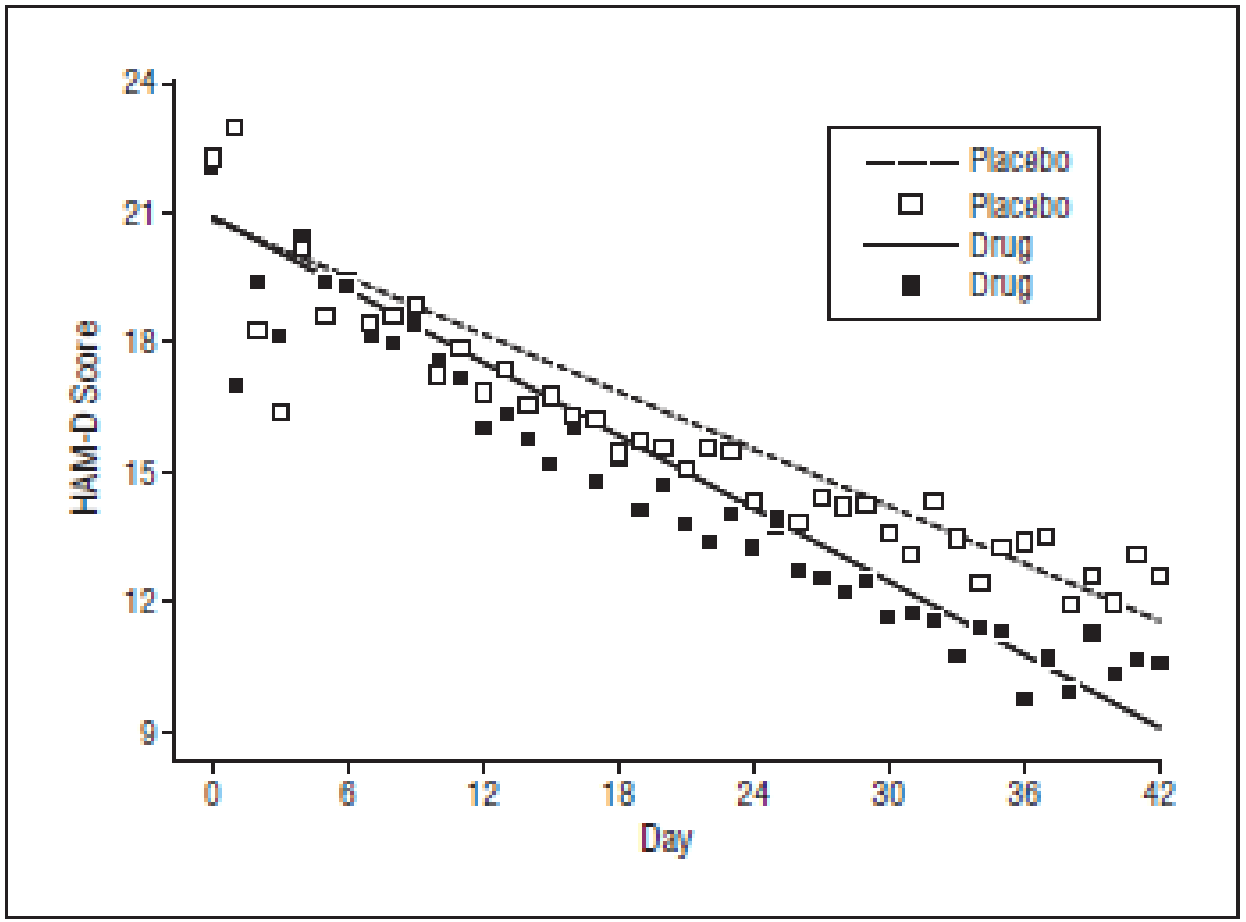


Figure. Observed vs estimated depression severity time trends for drug vs placebo in 37 adult and geriatric studies. HAM-D indicates Hamilton Depression Scale.

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

Suicide risk is far worse than what the FDA found

Suicides in the trials:

5 suicides in 52,960 patients on antidepressants in 2006 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 are likely to have been 15 times more suicides than reported 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

Antidepressants and suicide

Suicide risk is far worse than what the FDA found

Many suicidal events had been coded as something else, and the companies knew that the FDA would not check them when the FDA asked for their data.

Only people at very low risk of committing suicide were recruited for the trials.

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

Antidepressants, suicide and falls

Middle-aged people who were completely normal have also committed suicide (or homicide) on antidepressants.

A controlled cohort study of depressed people over 65 years of age showed that SSRIs lead to falls. For every 28 people treated for 1 year with an SSRI, there was one additional death, compared to no treatment.

It is doubtful whether these drugs are safe at any age.

FDA 2007: admitted indirectly that *SSRIs can cause suicide at all ages.*

ADHD

It’s just a name, not a biological entity

The diagnosis arises primarily from teacher complaints

Many of us could get this diagnosis

11% of school-age children in the United States “have it”

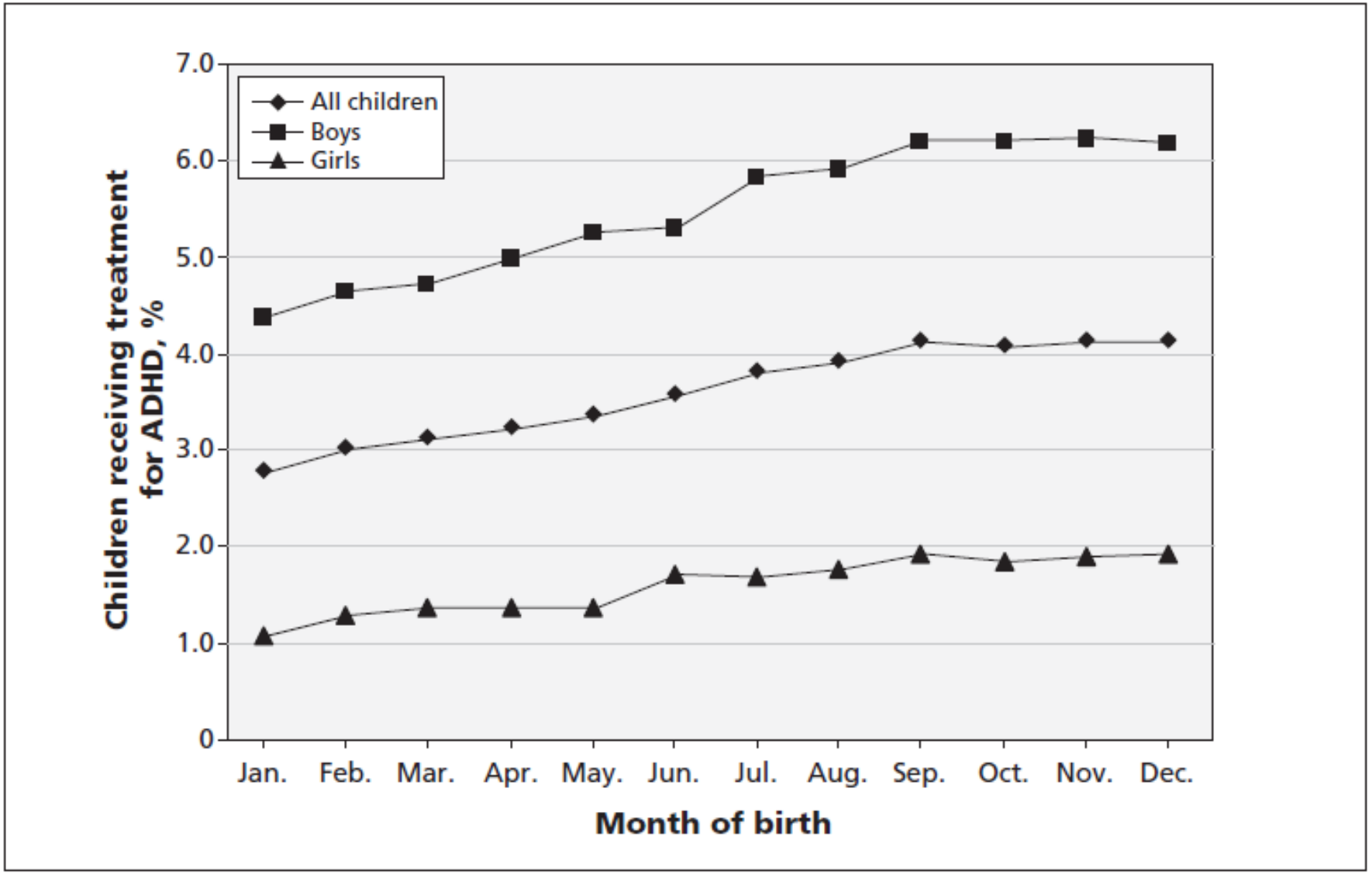


Figure 1: Percentage of children aged 6 to 12 years receiving pharmacologic treatment for ADHD, by month of birth. ADHD = attention-deficit/hyperactivity disorder.

Morrow, CMAJ 2012;184:755; study of 1 million children

ADHD trials in children

- Highly biased, ”enriched design”
- Harms vastly underreported
- inbreeding: 21 trials (49%) came from Harvard Medical School or Massachusetts General Hospital, both in Boston
- Joseph Biederman was the great fertilizer, co-authoring no less than 13 of the papers (30%)
- personal payments from big pharma were not disclosed
- the children don’t like the drugs

Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People’s Pres

ADHD drugs, acute effects

ADHD drugs work like amphetamine and cocaine

The major acute effect of stimulants appears to be an improvement in classroom manageability rather than academic performance

Reductions in social interactions and curiosity

Moll, J Child and Adolescent Psychopharmacology 11 (2001): 15-24

Methylphenidate in children

Cochrane review 2015 (683 pages)

- 185 trials (12,245 patients), mean duration 2.5 months
- All trials were at high risk of bias
- Teacher-rated ADHD symptoms, mean diff. 9.6 on ADHD rating scale (0-72; minimally relevant diff. is 6.6)
- Very low-quality evidence
- Trials are not adequately blinded
- Trials with ”active” placebo are needed

ADHD drugs, long-term effects

Stimulants do not produce lasting improvements in:

- aggressivity
- conduct disorder
- criminality
- substance abuse
- education achievement
- job functioning
- marital relationships
- or long-term adjustment

Moll, J Child and Adolescent Psychopharmacology 11 (2001): 15-24
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ADHD drugs, long-term effects

Long-lasting brain damage in animal studies:

- anxiety
- depression
- loss of sexual interest
- less tolerance to stress
- decreased sensitivity to rewards

And the children lose height and weight, etc.

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

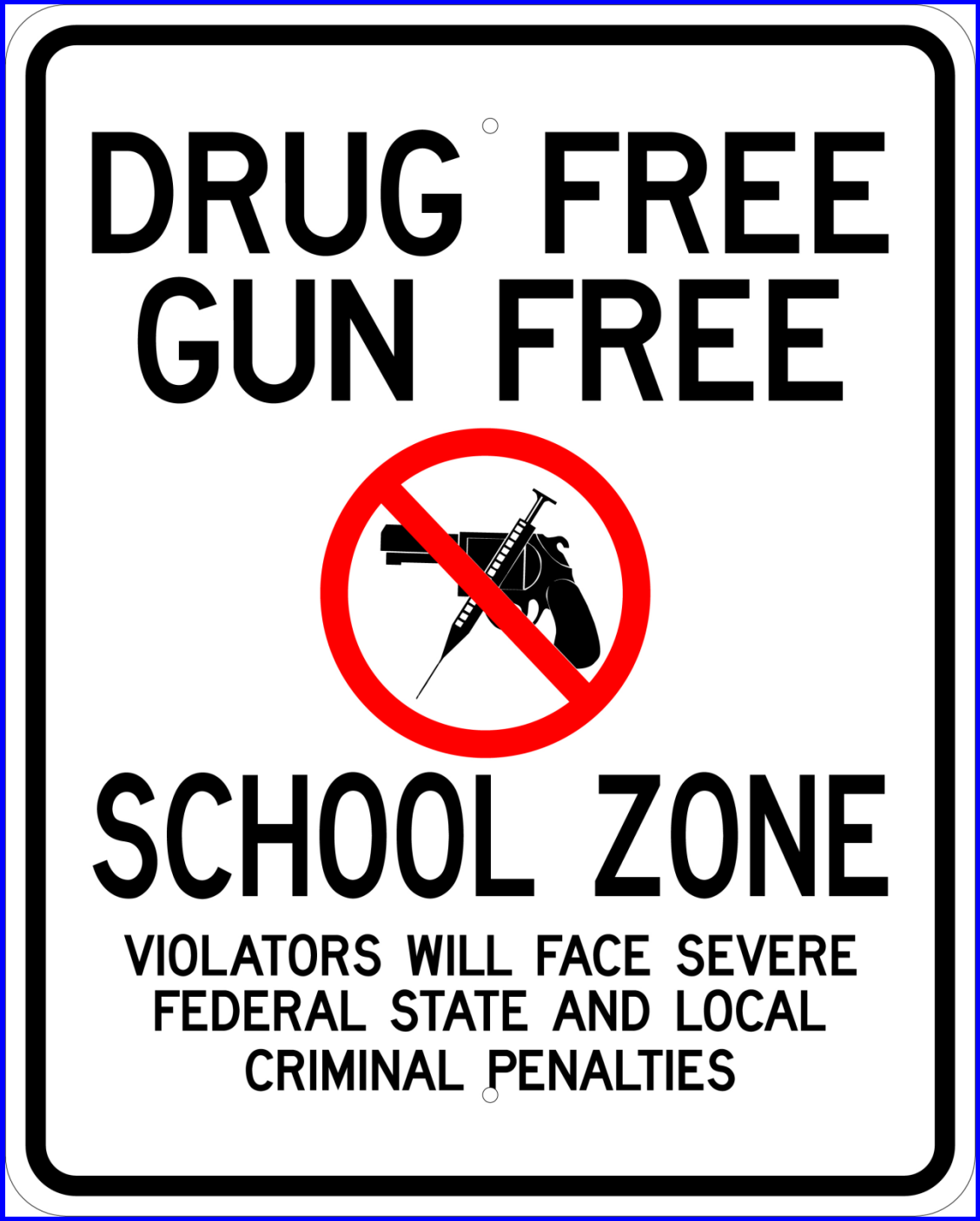
”The drug has demasked the disease”

Adverse drug effects are often mistaken for a worsening of the “disease,” or for demasking of an additional “disease.”

The children are often given additional diagnoses, e.g. depression, OCD or bipolar, and additional drugs, leading to chronicity.

It is bad medicine to come up with additional diagnoses when a person is under influence of a brain-active chemical, as the symptoms are most likely drug-induced.

Joseph Biederman from Harvard and his co-workers nonetheless made a diagnosis of bipolar in 23% of 128 children with ADHD.



Drug free schools in America?

They don’t exist

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. FDA: minimally relevant clinical change is 4 points.

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%).”

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?

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.

Manipulated factorial trial

TORCH trial in COPD, NEJM, 22 Feb 2007

6184 patients randomised to 4 groups:

placebo, salmeterol, fluticasone, both drugs

Abstract ”The hazard ratio for death in the combination-therapy group, as compared with the placebo group, was 0.825 (95% confidence interval [CI], 0.681 to 1.002; P = 0.052, adjusted for the interim analyses)”.

Factorial analysis Effect of fluticasone, rate ratio 1.00 (95% CI 0.89–1.13;

P = 0.99).

(Suissa, Eur Resp J 2008;31:927)

(Gøtzsche PC. J R Soc Med 2014;107:256-7).

Doctors on industry payroll

About 20,000 doctors in Denmark

Table 8.1 Roles of Danish doctors with permission to work for the drug industry. Data from 2010

Investigator	1626
Advisory Board member or consultant	1160
Lecturer	950
Stock ownership	175
Author	36
Other	89
Total	**4036**

Conclusions

We need:

- Truly independent evaluation of drugs.
- Truly blinded placebo trials.
- Blinding during data analysis and writing of papers.
- Large, long-term trials before marketing approval that can capture rare but devastating harms.
- To get the industry out of medical education
- A major culture change in health research (the data are generated by patients and belong to us all)
- Access to trial protocols, clinical study reports and raw data.

Marcia Angell, former Editor-in-Chief, NEJM

"It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine"

(Marcovitch, PLoS Med 2010, e1000355)

Missing deaths in published papers

Trials of olanzapine, aripiprazole, ziprasidone, atomoxetine, duloxetine and sertraline.

Online trial registries compared with first associated standalone journal articles (N = 142). No clear or consistent pattern on serious adverse events reporting criteria.

62% of deaths and 53% of suicides were not reported in journal articles.

Hughes, BMJ Open 2014;4:e005535.

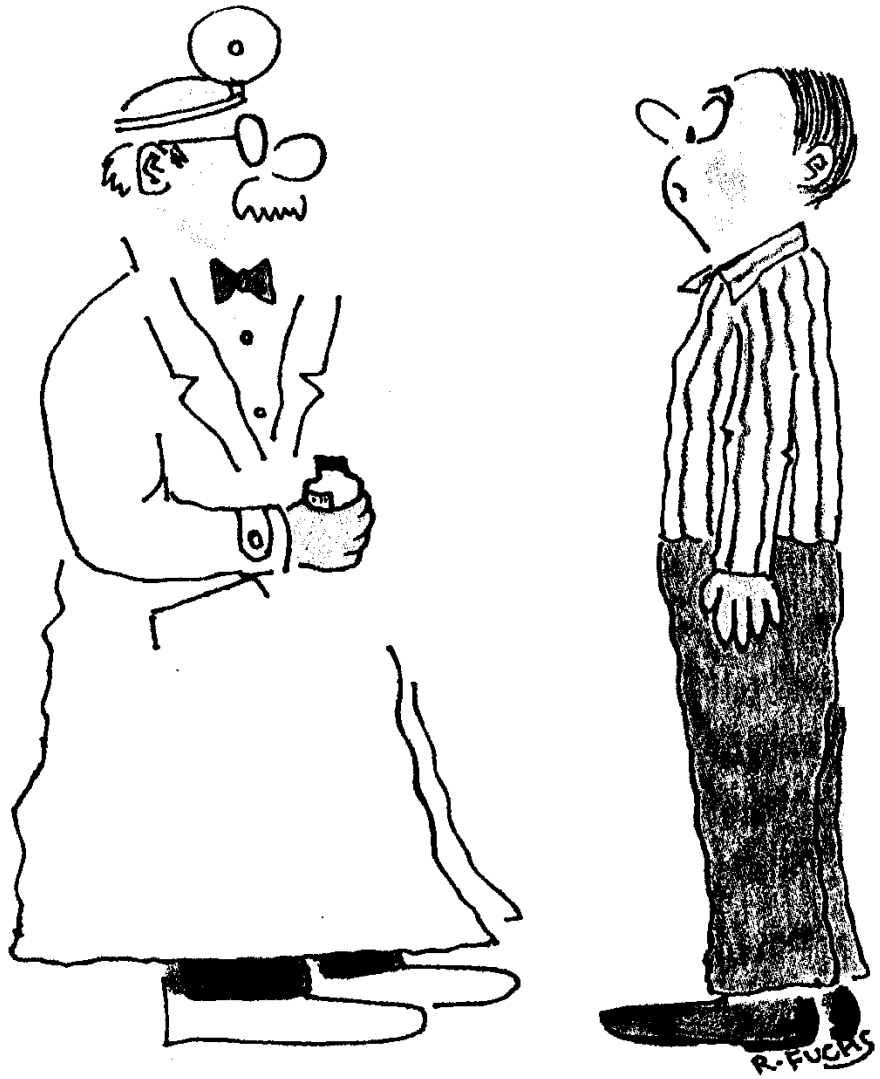
Suggestions for patients

Read the package insert on the Internet

Use drugs as little as possible

When you think you are getting old, it could be side effects

Try to taper off your drugs, one by one. You may get a new life.



"Take one of these tablets tonight, Mr Tate, and one more if you wake up tomorrow morning"