Antidepressants do more harm than good and should be avoided

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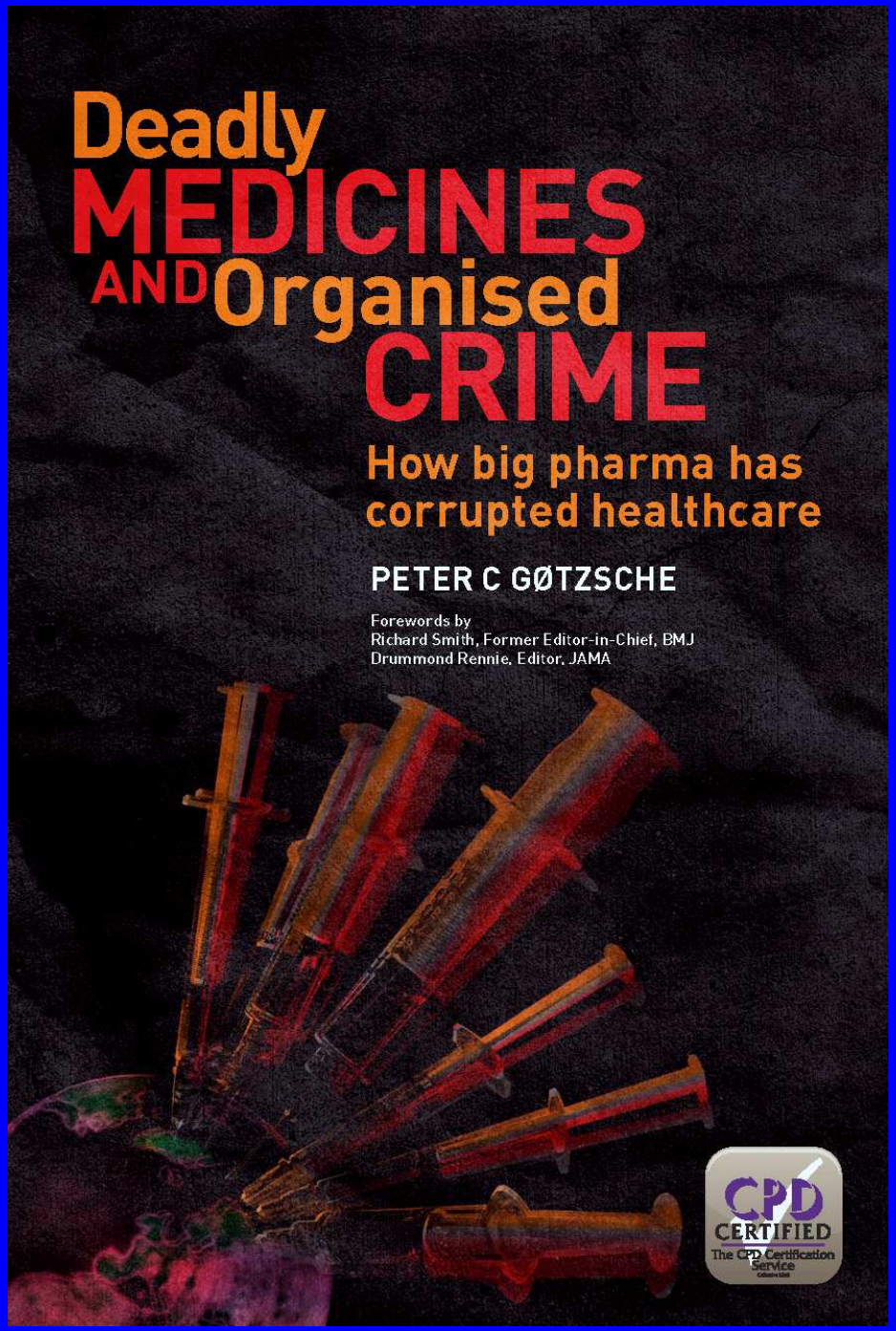
I have no conflicts of interest
The views presented are mine


Deadly
MEDICINES
AND Organised
CRIME
How big pharma has corrupted healthcare
PETER C GØTZSCHE
Forewords by
Richard Smith, Former Editor-in-Chief, BMJ
Drummond Rennie, Editor, JAMA
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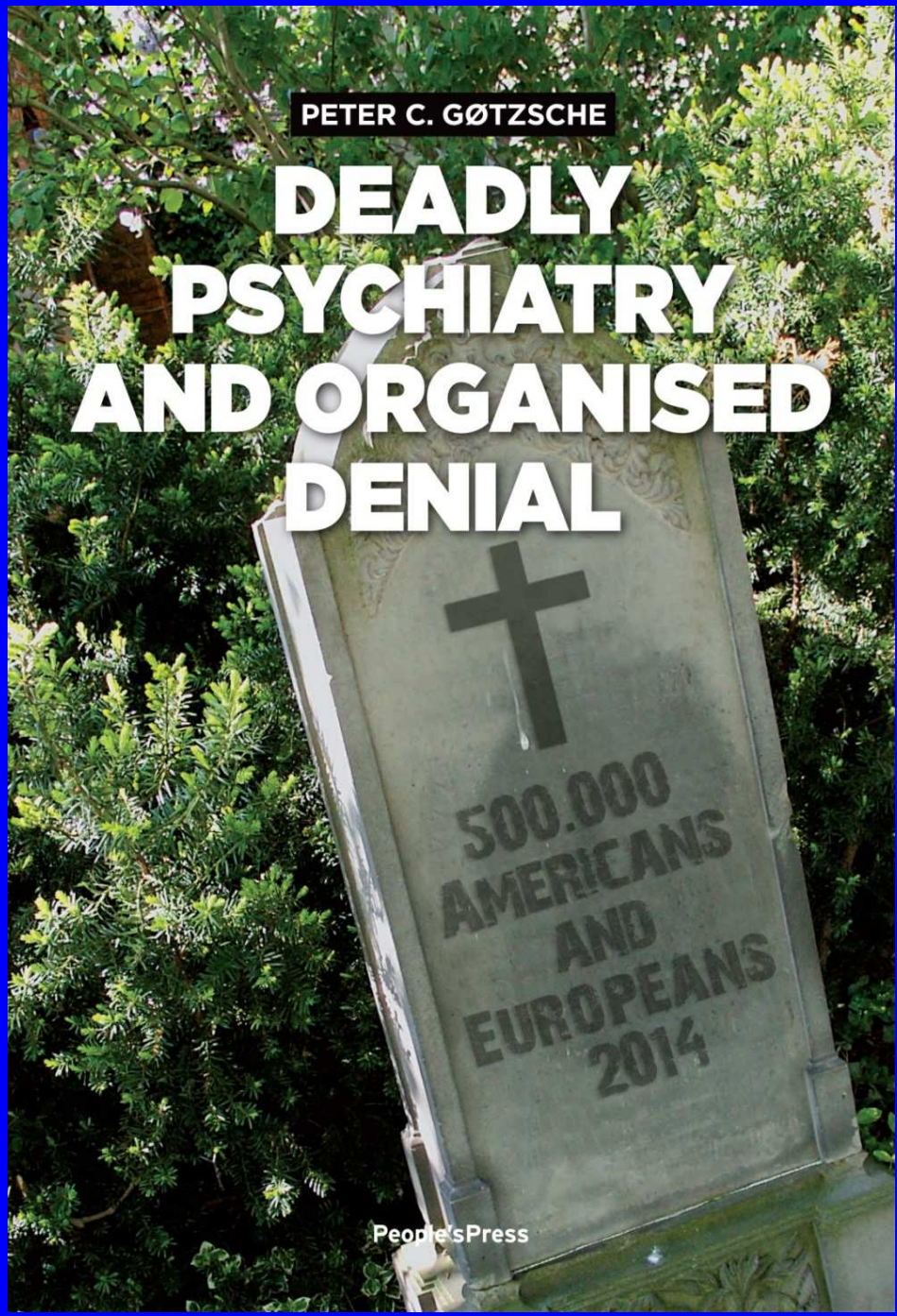
2013

2015


PETER C. GØTZSCHE
DEADLY
PSYCHIATRY
AND ORGANISED
DENIAL
500.000
AMERICANS
AND
EUROPEANS
2014
People'sPress

Depressing diagnosis of depression

US Centers for Disease Control and Prevention (2010):

- 9% of the adults are depressed according to DSM-IV criteria

You were depressed if you had had little interest or pleasure in doing things for more than 7 days over the past 14 days plus one additional symptom, which could be many things; for example:

- trouble falling asleep
- poor appetite or overeating
- being so fidgety or restless that you have been moving around a lot more than usual.

Medicalising grief

Bereavement is a depressive disorder if it has lasted more than:

- 2 years (DSM-III from 1980)
- 2 months (DSM-IV from 1994)
- 2 weeks (DSM-V from 2013)
- 2 days perhaps in DSM-VI?

Why cannot the psychiatrists get enough?

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!

Cochrane review of depression in general practice:

- 58% responded on drug, 46% on placebo
- biased estimate: based on published trials in contrast to FDA analysis

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

Arrol CD007954

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

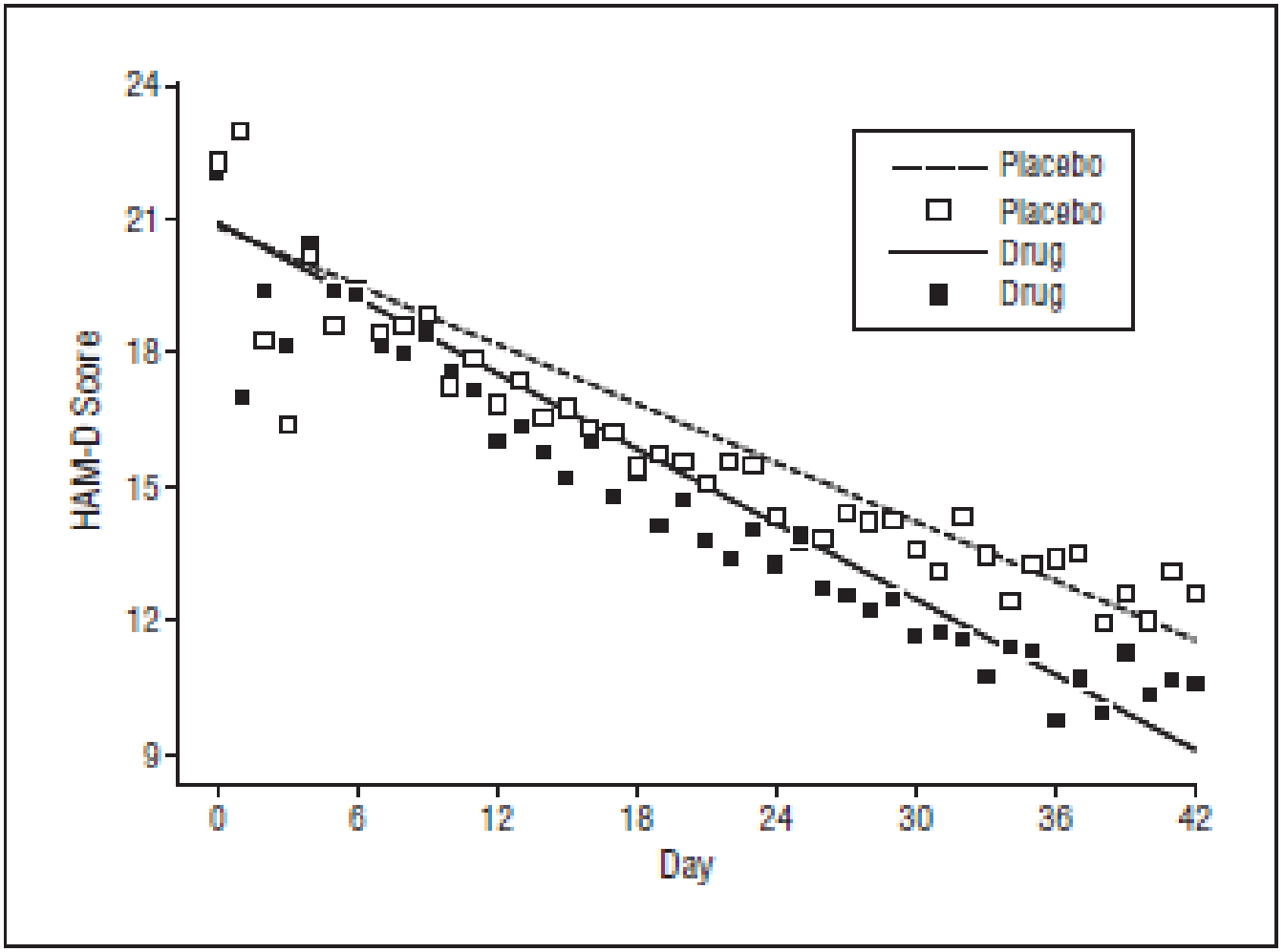


Figure. Observed vs estimated depression severity time trends for drug vs placebo in 37 adult and geriatric studies. HAM-D indicates Hamilton Depression Scale.

Sponsor-conducted RCTs of fluoxetine and venlafaxine.

OBS: Linear regression is wrong on these data

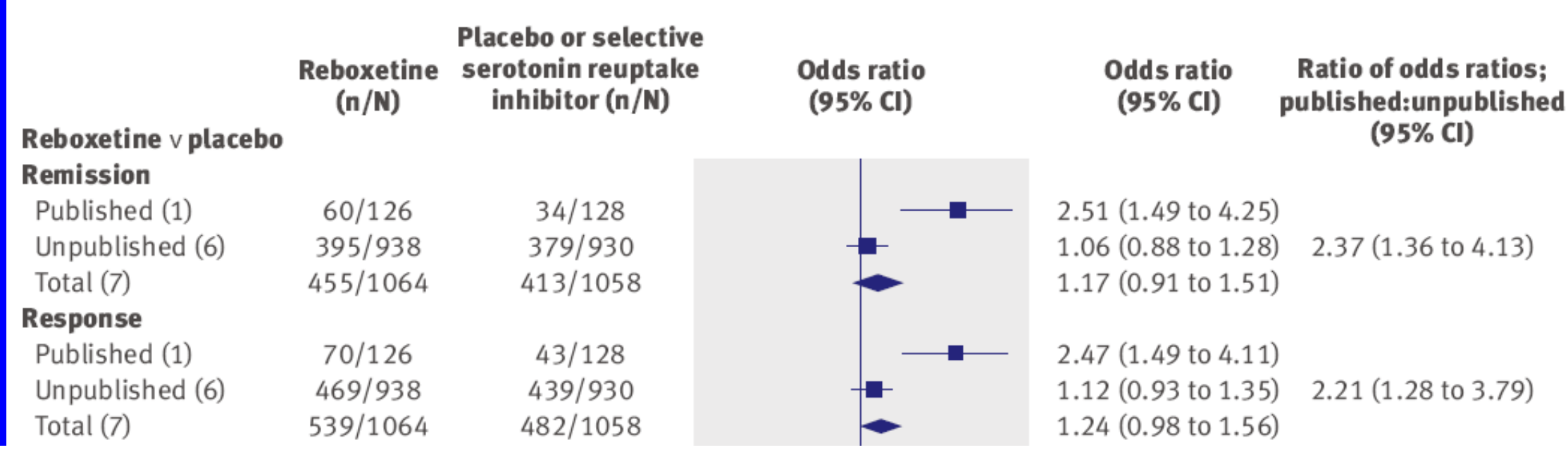
Gibbons et al,
Arch Gen Psychiatry.
Online March 5, 2012.

doi:10.1001/archgenpsychiatry.2011.2044

Don’t ever trust published trials!

Data on 74% (3033/4098) of patients were unpublished

Eyding, IQWiG, BMJ 2010:c4737



	Reboxetine (n/N)	Placebo or selective serotonin reuptake inhibitor (n/N)	Odds ratio (95% CI)	Odds ratio (95% CI)	Ratio of odds ratios; published:unpublished (95% CI)
Reboxetine v placebo					
Remission					
Published (1)	60/126	34/128		2.51 (1.49 to 4.25)	
Unpublished (6)	395/938	379/930		1.06 (0.88 to 1.28)	2.37 (1.36 to 4.13)
Total (7)	455/1064	413/1058		1.17 (0.91 to 1.51)	
Response					
Published (1)	70/126	43/128		2.47 (1.49 to 4.11)	
Unpublished (6)	469/938	439/930		1.12 (0.93 to 1.35)	2.21 (1.28 to 3.79)
Total (7)	539/1064	482/1058		1.24 (0.98 to 1.56)	

Antidepressants, any benefits?

Considering benefits and harms together, the patients find the drugs useless:

- as many patients stop treatment on SSRIs as on placebo for any reason.
- after only 2 months, half the patients have stopped taking the drug.

And so did the psychiatrists and the drug regulators in the beginning:

- the first SSRI was fluoxetine, which the German drug regulator deemed "totally unsuitable for the treatment of depression".
- fluoxetine was approved in Sweden first, through bribery.

Barbui, CMAJ 2008;178:296; Serna, Eur Psychiatry 2010;25:206.

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

Virapen J. Side Effects: death. College Station: Virtualbookworm.com Publishing;2010.

Antidepressants, any benefits?

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.

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

Sexual disturbances

An FDA scientist found out that the companies had hidden sexual problems by blaming the patients rather than the drug, e.g. female anorgasmia was coded as 'Female Genital Disorder'

Eli Lilly: only 2% of the patients become sexually disturbed

Independent research: 59% of 1022 people with a normal sex life became sexually disturbed, with a low tolerance among 40% of the patients:
- decreased libido, 57% of patients
- delayed orgasm or ejaculation, 57%
- no orgasm or ejaculation, 46%
- erectile dysfunction or decreased vaginal lubrication ,31%

Some patients yawned during orgasm

Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press , 2015
Montejo et al., J Clin Psychiatry. 2001; 62(Suppl. 3):10–21.

Withdrawal symptoms

Not listed in table of side effects in UK package insert for citalopram but in the text:

“In clinical trials adverse events seen on treatment discontinuation occurred in approximately 40% of patients treated with citalopram.”

”recommended that the dose is gradually reduced over a period of at least one week”

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Withdrawal symptoms

The withdrawal symptoms were described in similar terms for benzodiazepines and SSRIs and were very similar for 37 of 42 identified symptoms.

However, they were not described as dependence for SSRIs.

To define similar problems as “dependence” for benzodiazepines and as “withdrawal reactions” for SSRIs is irrational.

For patients, the symptoms are just the same; it can be very hard for them to stop either type of drug.

Nielsen, Addiction 2012;107:900

Addiction to SSRIs

Until 2003, the UK drug regulator said that SSRIs are not addictive

In 2003, the WHO published a report that noted that three SSRIs (fluoxetine, paroxetine and sertraline) were among the top 30 highest-ranking drugs for which drug dependence had ever been reported.

In 2003, Glaxo quietly and in small print revised its previous estimate of the risk of withdrawal reactions in the prescribing instructions from 0.2% to 25%, a 100 times increase.

Medawar C, Hardon A. Medicines out of Control? Antidepressants and the conspiracy of goodwill. Netherlands: Aksant Academic Publishers; 2004.
Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press , 2015

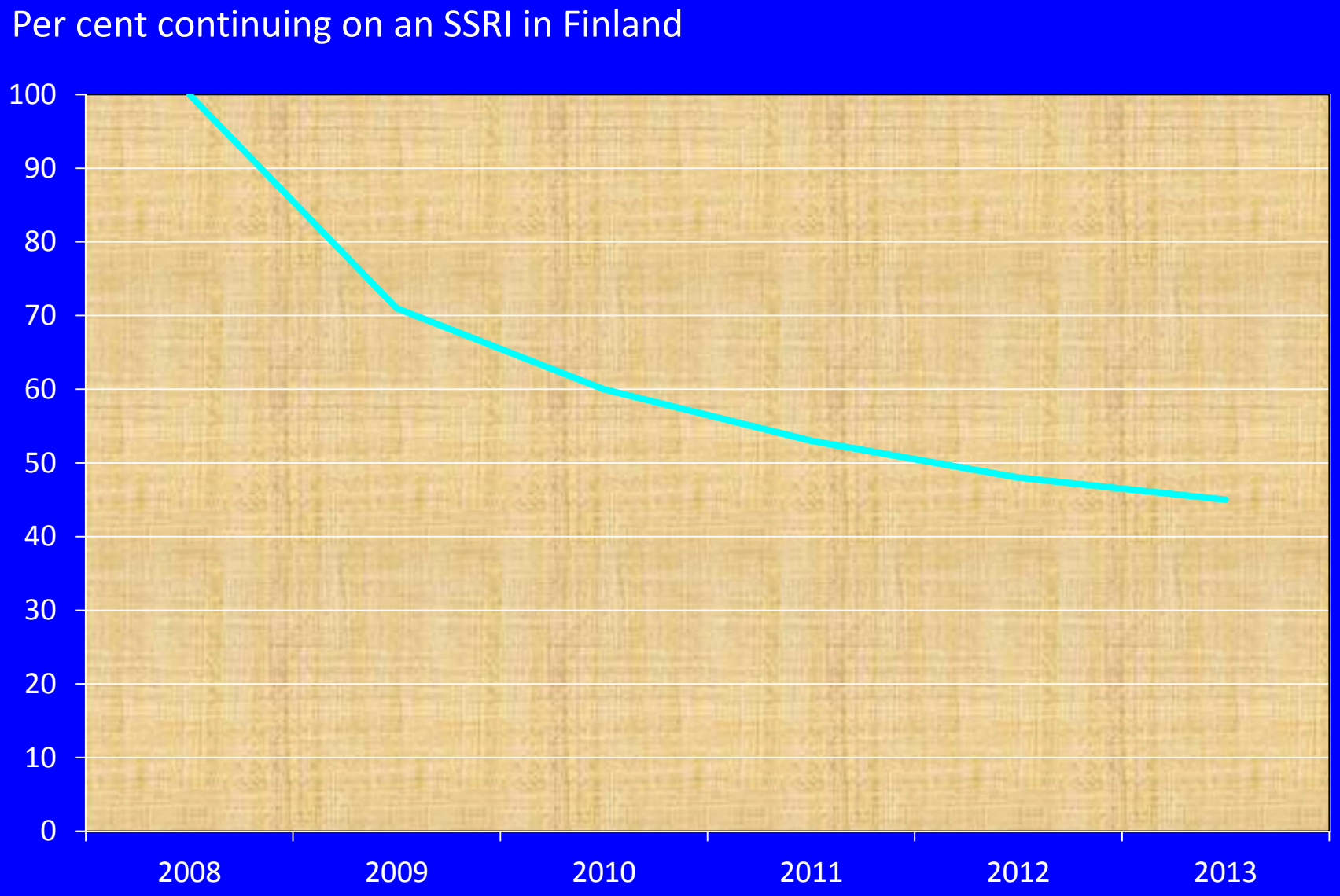
Withdrawal symptoms in patients with remitted depression during a 5-8 days placebo period 4 to 24 months after remission

	fluoxetine (n = 63)	sertraline (n = 63)	paroxetine (n = 59)
Worsened mood	22%	28%	45%
Irritability	17%	38%	35%
Agitation	16%	37%	31%
Hamilton increase ≥8	6%	30%	36%

Rosenbaum, Biol Psychiatry 1998;44:77-87

Study supported by Eli Lilly

People go on and on and on…



The chemical imbalance hoax

About half the patients (or more) have been told:

“You have a 'chemical imbalance’ in the brain, which we will need to fix.”
“This is like giving insulin to a patient with diabetes .”

If this were true, the number of disabled mentally ill would have gone down after we introduced antipsychotics and antidepressants,.

The number of people with psychiatric diagnoses and disability pension has skyrocketed.

The drugs CREATE a ’chemical imbalance’, which is why it is so difficult stopping them. In contrast to insulin, the drugs are totally unspecific and they make temporary problems chronic.

Whitaker R. Anatomy of an Epidemic. New York: Broadway Paperbacks; 2010 and various surveys.

A Paradigm for Understanding Psychotropic Drugs

Stephen Hyman, former director of the NIMH, 1996:

- Psychiatric medications "create perturbations in neurotransmitter functions."

- In response, the brain goes through a series of compensatory adaptations in order "to maintain their equilibrium in the face of alterations in the environment or changes in the internal milieu."

- The "chronic administration" of the drugs then cause "substantial and long-lasting alterations in neural function."

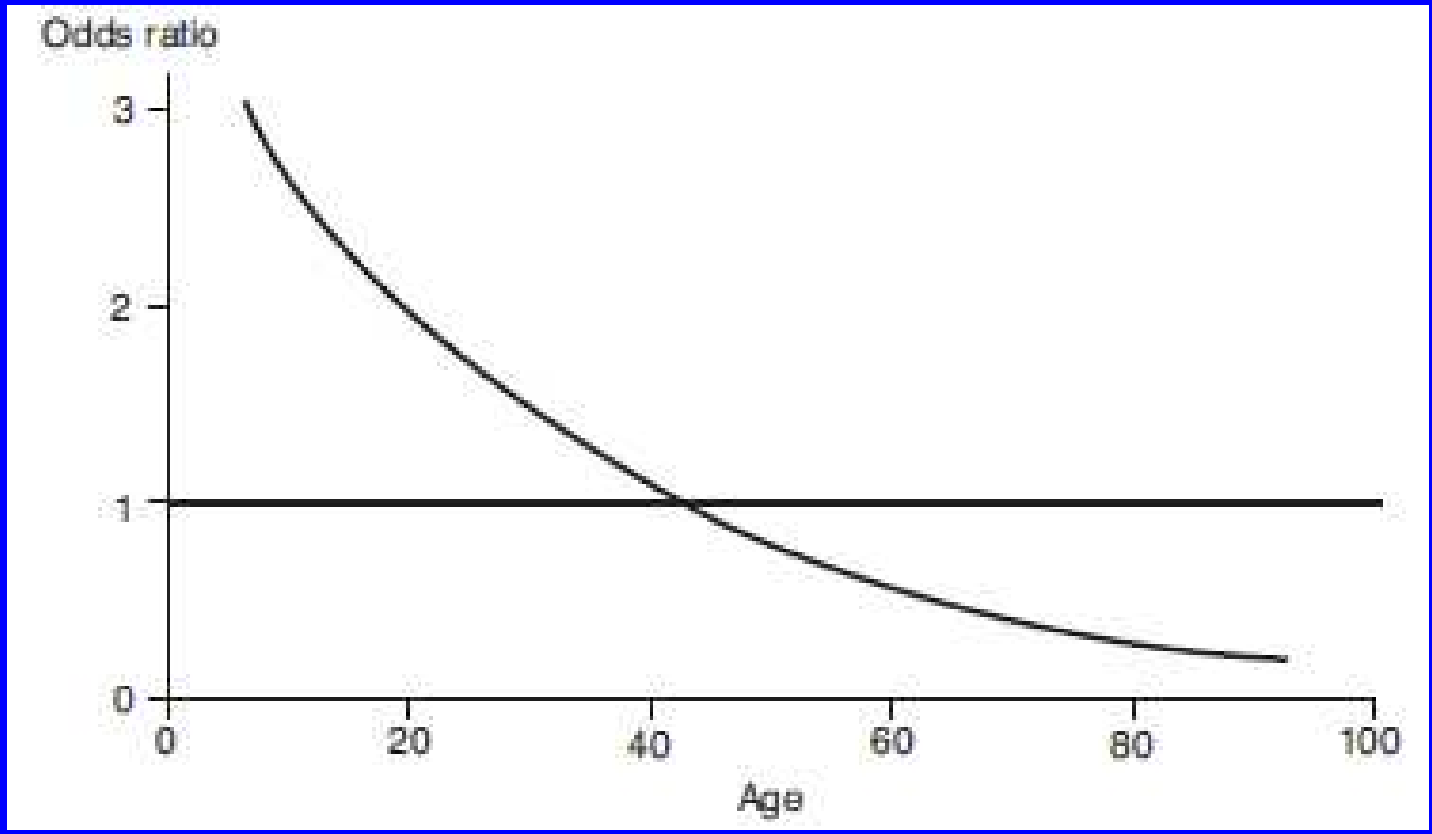
- After a few weeks, the person's brain is now functioning in a manner that is "qualitatively as well as quantitatively different from the normal state."

Source: Hyman, S. "Initiation and adaptation: A paradigm for understanding psychotropic drug action." *Am J Psychiatry* 153 (1996):151-61.

Slide from Whitaker, author of *Mad in America* and *Anatomy of an Epidemic*

Antidepressants and suicide

FDA analysis: Antidepressants increase suicidal behaviour till age 40



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

Antidepressants and suicide

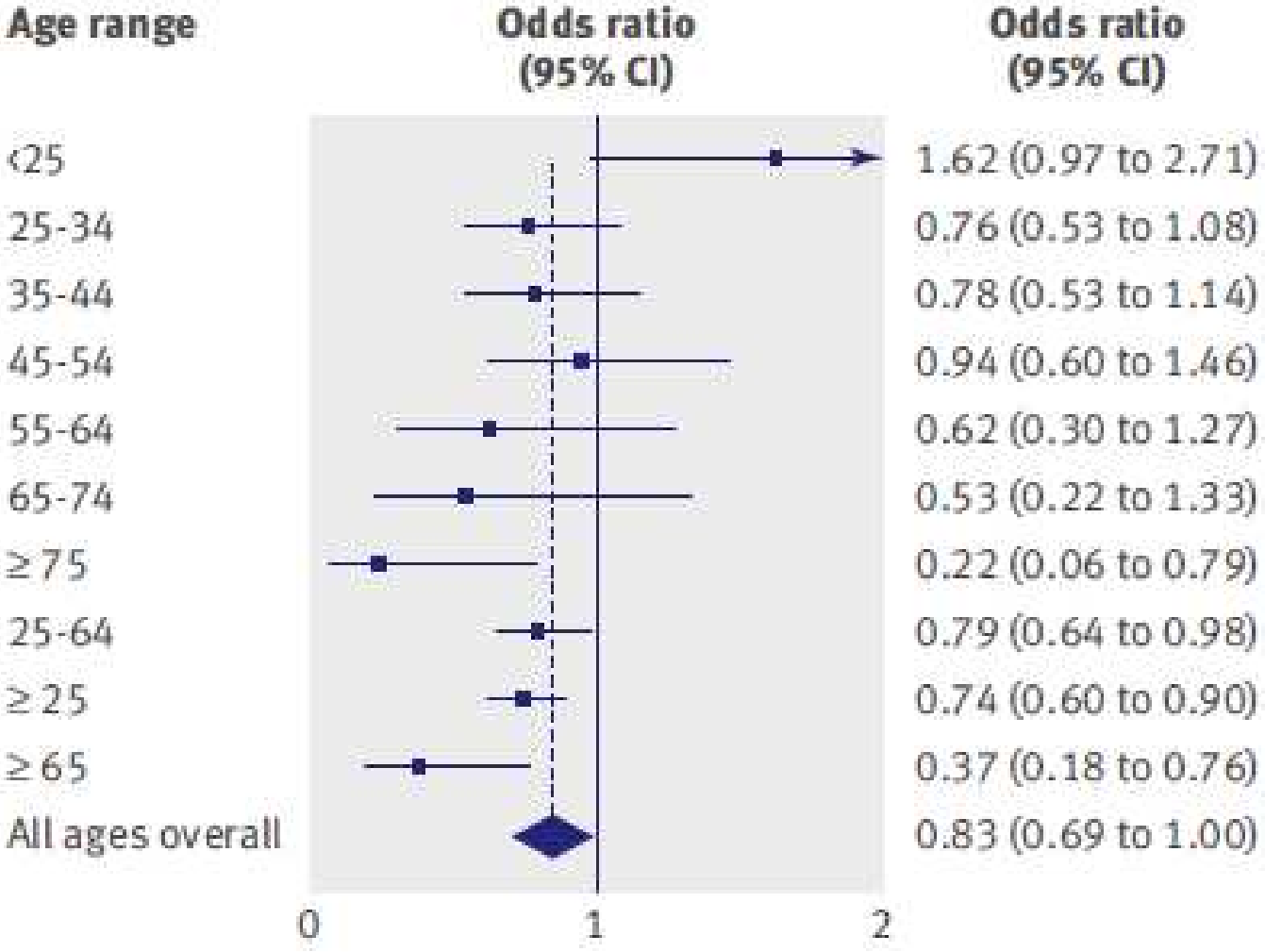


Fig 2 | Odds of suicidality (ideation or worse) for active drug relative to placebo by age in adults with psychiatric disorders

When the FDA published their findings, they looked much better for the drug companies

Stone et al., BMJ 2009;339:b2880

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

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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.

Some trials had run-in periods on active drug.

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

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Ecological studies of suicide

Many studies have claimed that when sales went down, suicides went up, and that this association is causal, e.g studies by:

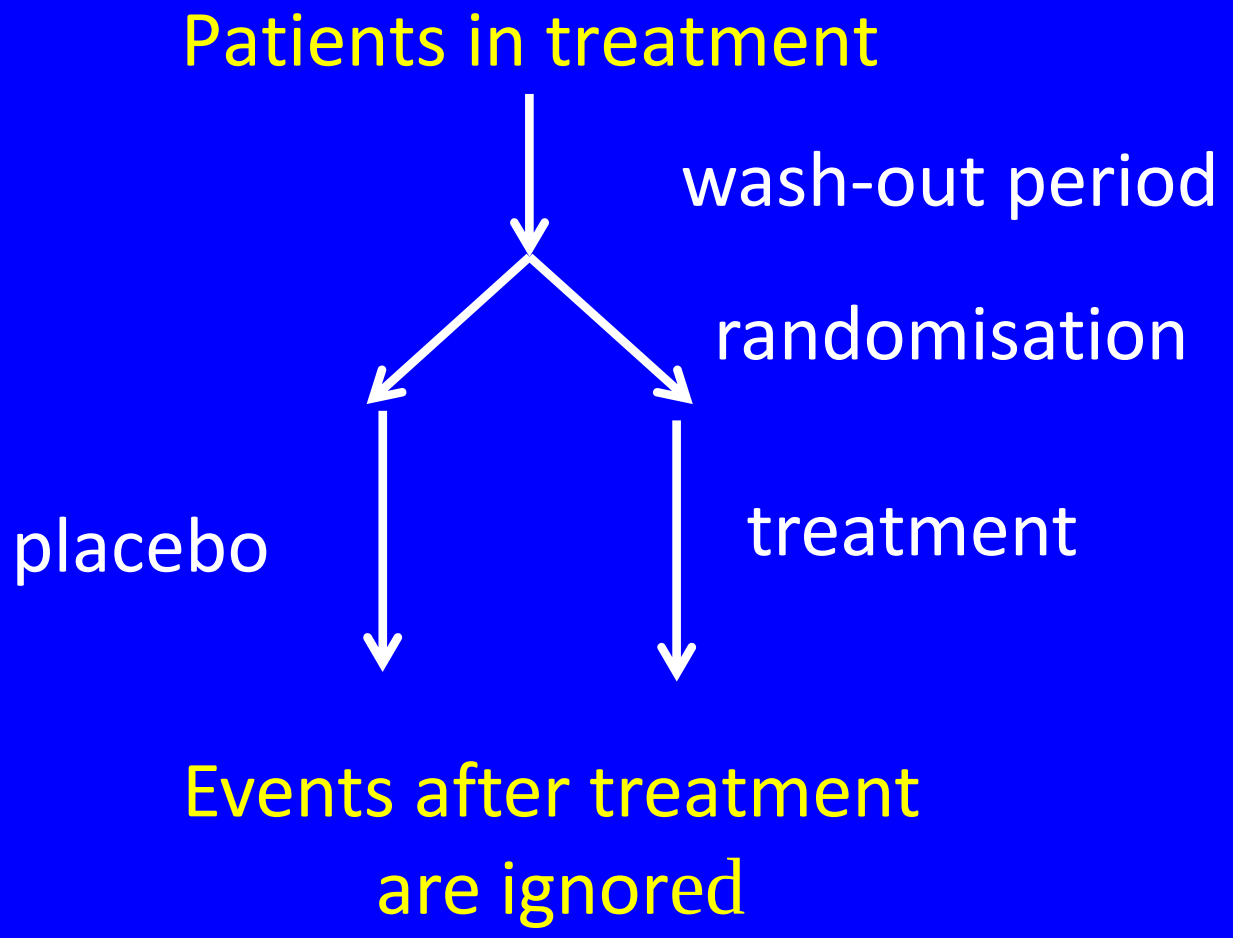
Robert Gibbons, Göran Isacsson, Christine Lu (BMJ 2014;348:g3596)

These studies have numerous flaws. No sound studies have found this.

Claims often based on the 2004 FDA black box warning in 2004 against suicide risk with SSRIs in children and in 2007 in adolescents:

"We briefly summarize here five readily available, online data sources that provide more direct and valid measures of youth suicidal behavior, and we discuss problems with the proxy that Lu's study used [poisonings by psychotropics] ... Lu's study findings are roundly unsupported by national data" (Miller BMJ 2014;348:g3596)

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]

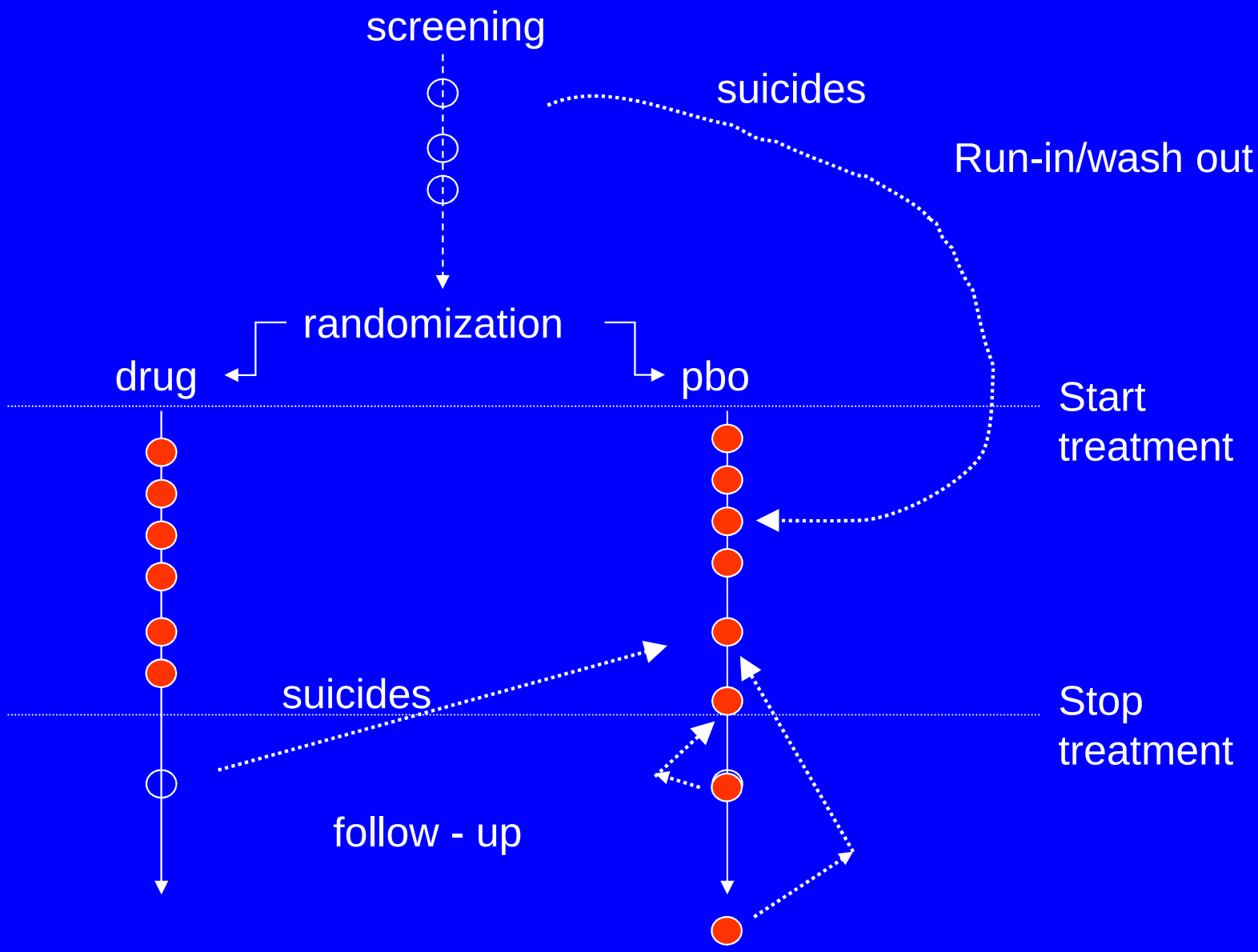
FDA: suicide, suicide attempt or self harm (Laughren, see ref. in other slides)

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 suicides and suicidal acts

slide based on Healy, BMJ 2006;333:92–5 and Breggin, Ethical Human Psychology and Psychiatry, Vol. 8, no.1, Spring 2006



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.*

”Keep out of reach of children” – why not out of reach of everyone?

Coupland et al, BMJ 2011;343:d4551.

Antidepressants and violence

Antidepressants can lead to violent actions at any age, including suicide and homicide.

Lucire, Pharmgenomics Pers Med 2011; 4: 65–81.

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

Violence reported to the FDA

Adverse drug events submitted to the FDA between 2004 and 2009

1937 cases of violence

387 of which were homicide.

The violence was particularly often reported for psychotropic drugs

- antidepressants
- sedatives/hypnotics
- ADHD drugs

Moore et al, PLoS One 2010; 5: e15337.

Antidepressants and homicide

Antidepressants can lead to suicide and homicide at any age
10 People with CYTP450 mutations

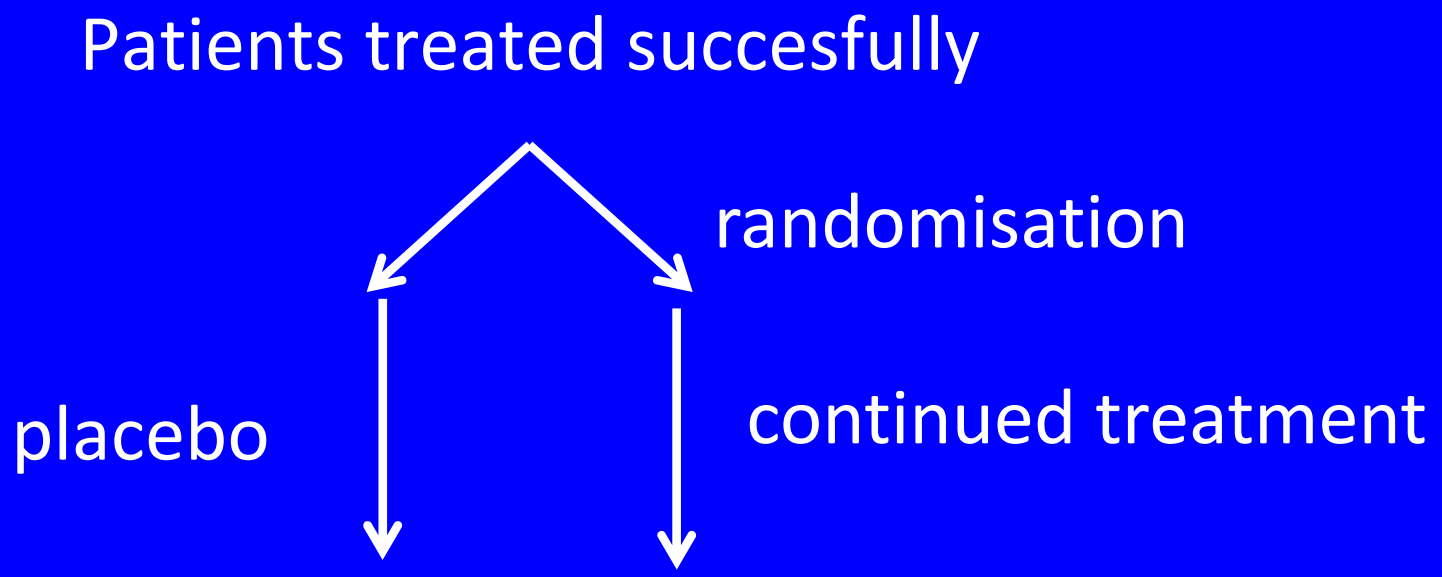
Gender, age	Drug	Indication	Event
Female, 35	nortriptyline	Distress due to husband's drinking	Killed teenage daughter in toxic delirium after 3 days
Male, 18	fluoxetine	Sister was comatose after a car crash	Violent akathisia for 14 days; killed father 4 days after he ran out of pills
Male, 35	paroxetine	Distressed by "on and off" relationship with mother of his child	Stabbed former partner 30+ times after 11 weeks of akathisia on paroxetine
Male, 46	paroxetine	Anxiety about not making enough money to support family	Killed son in a manic-shift akathisia/ delirium after 42 days on paroxetine and 20 days after dose increase

Lucire, Pharmgenomics Pers Med 2011; 4: 65–81.
Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press , 2015

Gender, age	Drug	Indication	Event
Male, 16	fluoxetine	Depressed, struggling at school, and girlfriend left	Killed therapist in hospital after 11 weeks
Male, 50	venlafaxine	Distress over divorce	Shot a stranger 4 days after stopping drug
Male, 24	sertraline, escitalopram	Anxiety and illicit substance use	Nearly killed partner
Female, 26	Several SSRIs	Difficulties with in-laws	Two attempts to kill two children
Female, 52	Several SSRIs	Harassment at work	Tried to kill two children
Female, 25	citalopram, venlafaxine	Marital distress	Jumped in front of train with child

All 10 people were able to stop taking antidepressants and return to their previously normal personalities

The fatal flaw in maintenance studies



Withdrawal symptoms in the placebo group
are interpreted as disease symptoms

Why few patients benefit from the drugs and many are harmed by them

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Director of the Nordic Cochrane Centre
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I have no conflicts of interest
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Evergreening and industry bias escitalopram verus citalopram

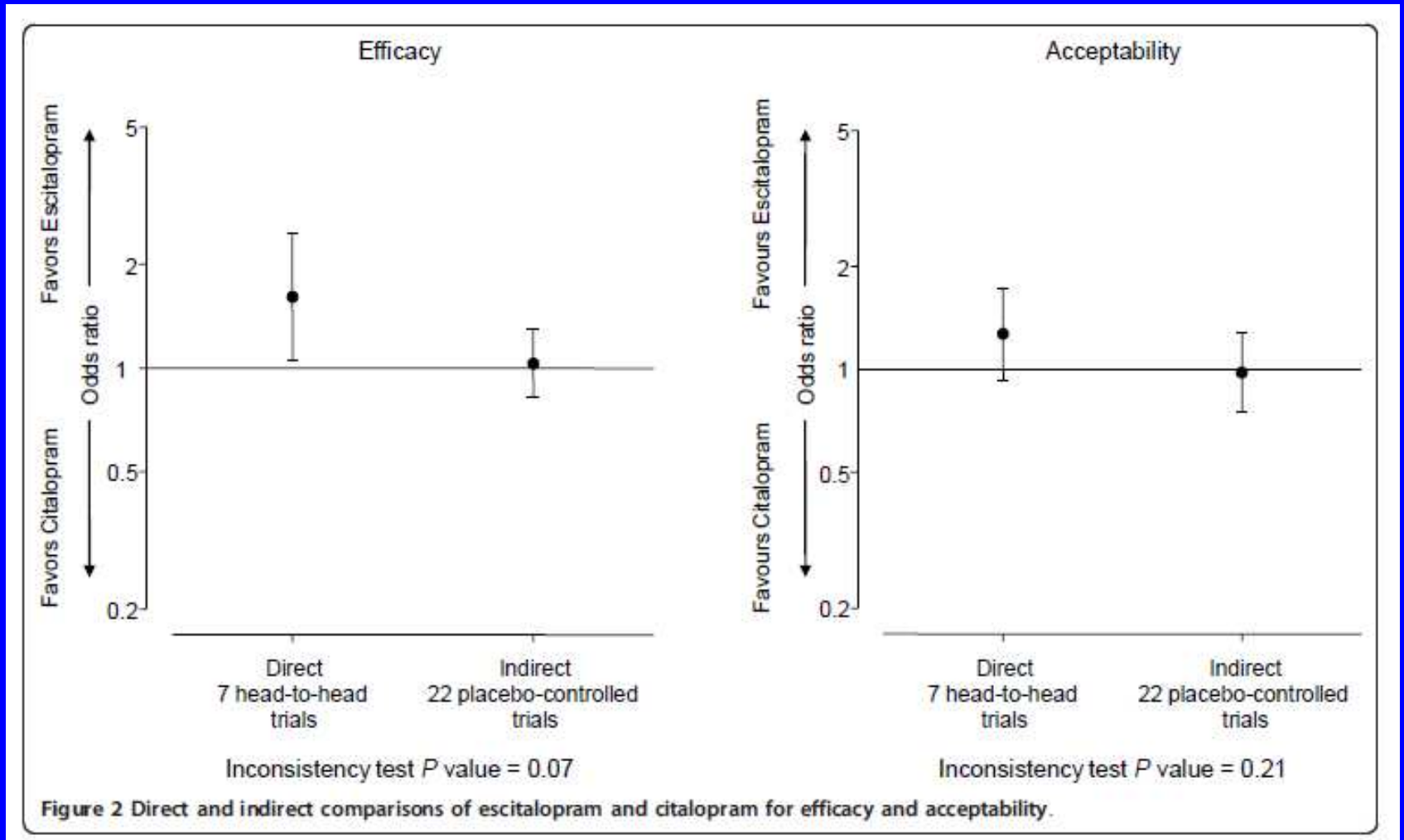


Figure 2 Direct and indirect comparisons of escitalopram and citalopram for efficacy and acceptability.

Alkhafaji et al., BMC Medicine 2012, 10:142

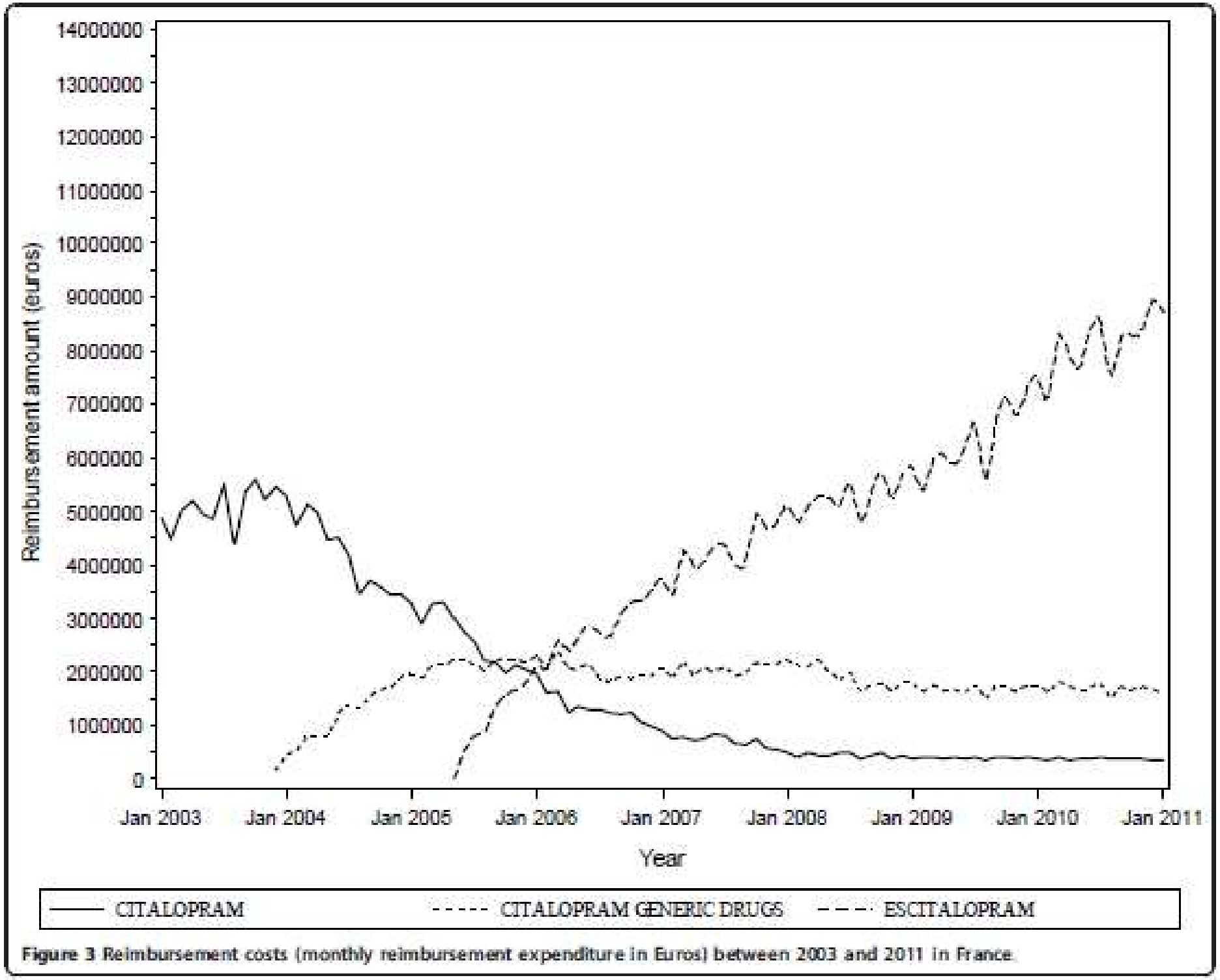


Figure 3 Reimbursement costs (monthly reimbursement expenditure in Euros) between 2003 and 2011 in France.

Fraud

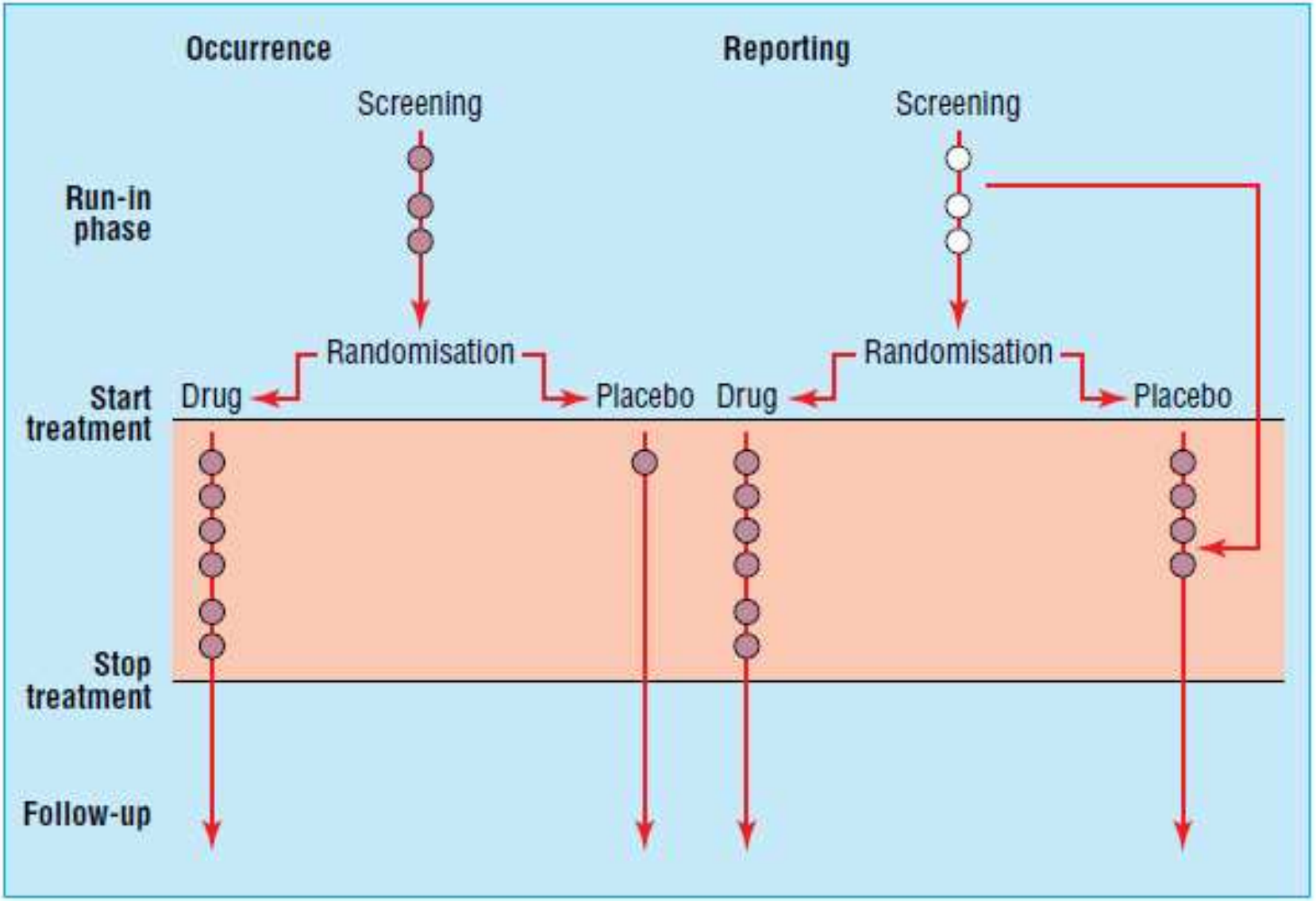


Fig 1 Time of occurrence and reporting of suicidal acts in adult trials of paroxetine, fluoxetine, and sertraline

Suicides and attempts were also added to placebo after stopping active treatment

Healy, BMJ 2006; 333:92–5

Antidepressants, any harms?

UK labelling for citalopram, 52 pages (rare events omitted)

≥10%	≥1%	≥0.1%	Rate unknown
Dry mouth, Nausea	Appetite and weight decreased, diarrhoea, constipation, vomiting, dyspepsia abdominal pain, flatulence	Increased weight and appetite	Thrombocytopenia, Liver function test abnormal
Somnolence, insomnia	Fatigue, dizziness, paraesthesia	Syncope, bradycardia, tachycardia	QT prolongation, orthostatic hypotension
Sweating Increased	Tremor, increased salivations rhinitis	Purpura	Inappropriate ADH secretion
Headache, asthenia, yawning	Agitation, anxiety, nervousness, confusional state, migraine,palpitation, taste perversion, impaired concentration, amnesia, apathy	Aggression, mania depersonalization, hallucination	Panic attack, restlessness, suicide ideation and behaviour, convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder, bruxism

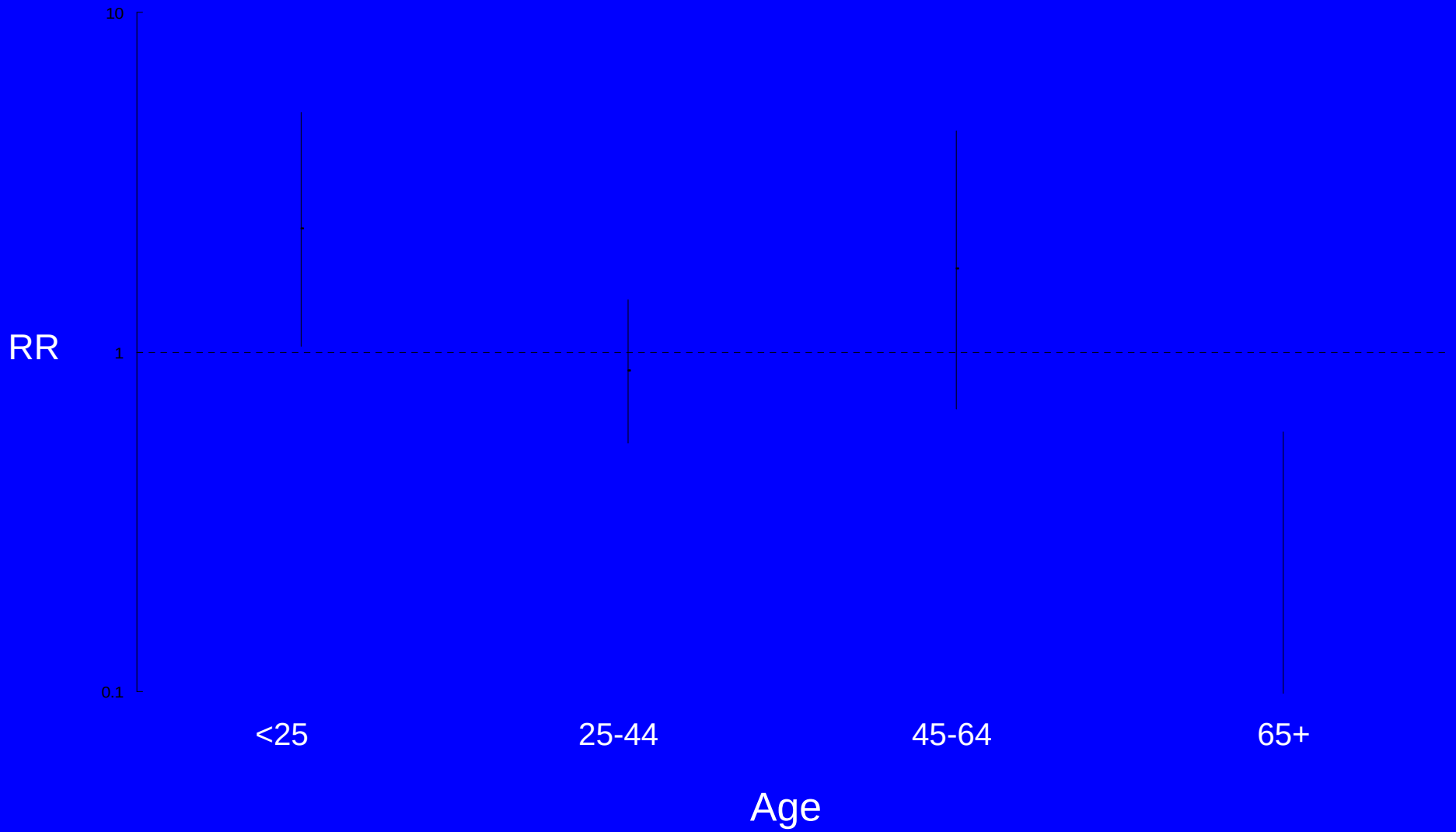
Antidepressants, any harms?

UK labelling for citalopram

≥1%	≥0.1%	Rate unknown
Libido decreased, impotence, ejaculation disorder and failure, abnormal orgasm (female)	Mydriasis (which may lead to acute narrow angle glaucoma)	Visual disturbance, bone fractures
Pruritus	Oedema, urticaria, alopecia, rash	Gastrointestinal haemorrhage (including rectal haemorrhage)
Tinnitus	Urinary retention, Female: menorrhagia	Female: Metrorrhagia Male: Priapism, galactorrhoea
Myalgia, arthralgia		Hypersensitivity, anaphylactic reaction, ecchymosis, angioedemas

Relative Risk of Suicidal Behavior for Antidepressants, by Age

Adults with psychiatric disorders



Stone M, Jones ML. Clinical review: relationship between antidepressant drugs and suicidality in adults. FDA, November 17, 2006:table 18.