Psychotropics - The Other Side of Antidepressant Medication Dogma

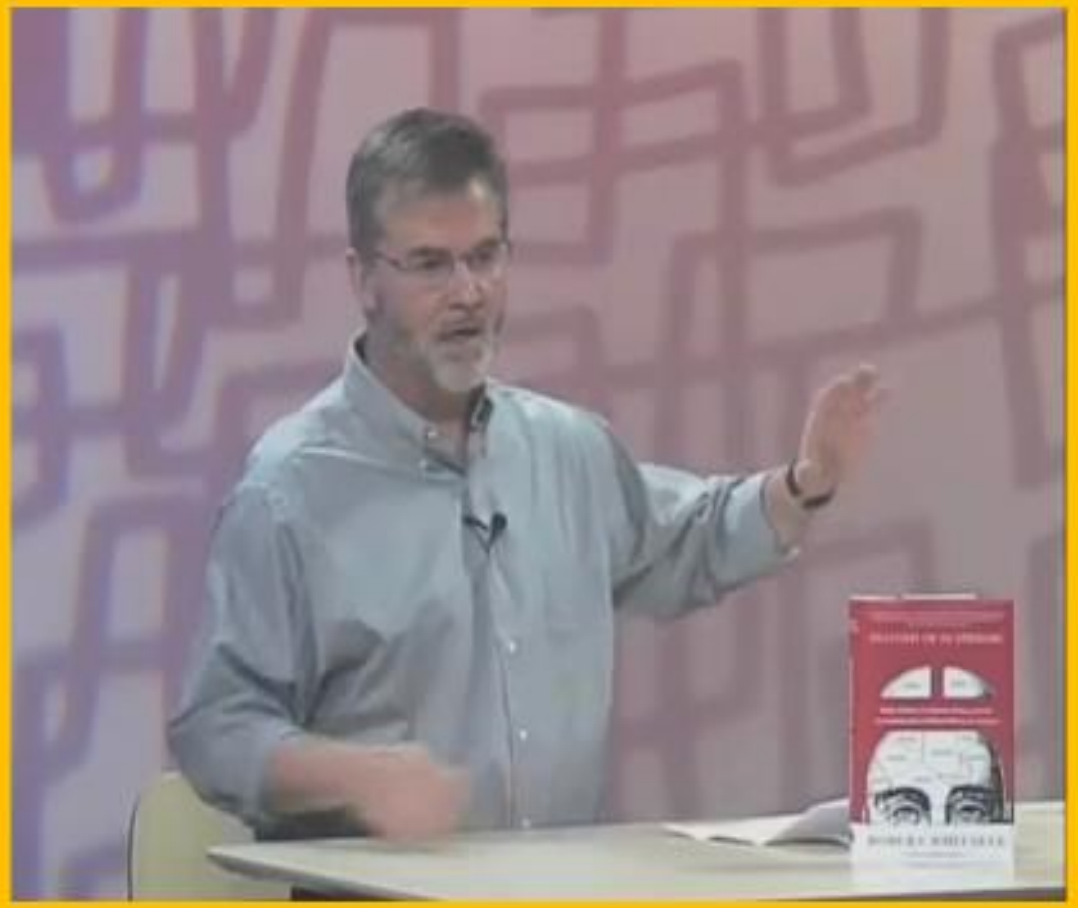
Jeffrey E. Hansen, Ph.D.

Psychotropics - The Other Side of Antidepressant Medication Dogma

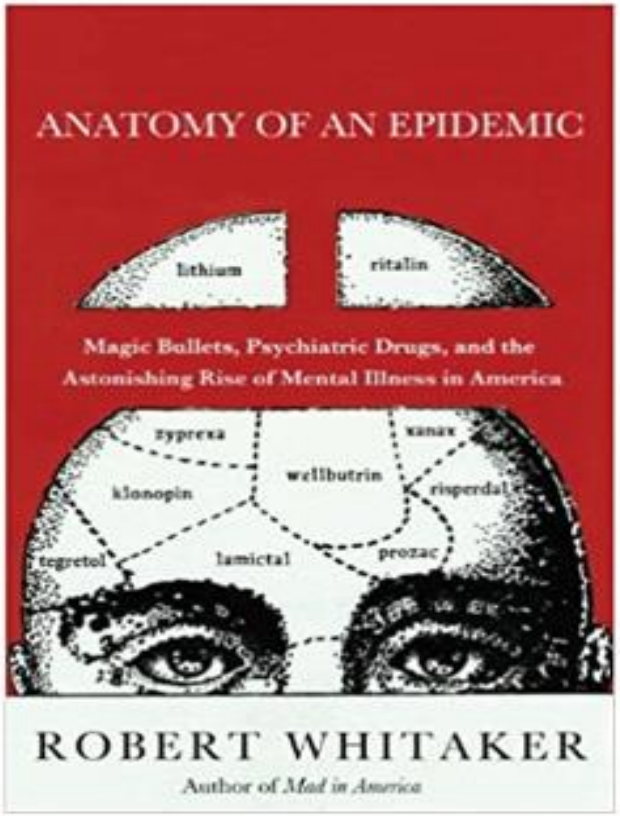
We are at a time when it is a good thing to evaluate the efficacy of psychotropic medications. This PowerPoint summarizes the work of Robert Whitaker, medical journalist, Dr. Peter Gøtzsche, Danish physician and Dr. Irving Kirsch, Harvard psychology professor, who have written and spoken about the need to re-think how we are treating mental illness, in particular, the use of psychotropics with emphasis on antidepressants. Although they acknowledge that psychotropics have a use, they suggest that these medications should be used more judiciously and, in many cases, there is reason to be concerned that long-term use can have a significant and concerning downside.

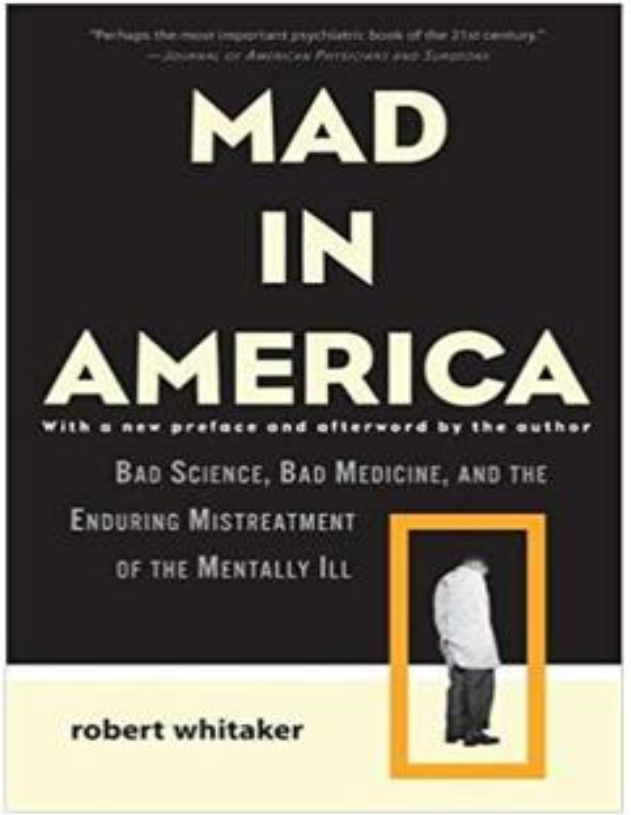
Please note that I am not a prescriber, and I am not advising you to take or not take these medications. Rather, I am offering some of the research on the mechanisms and outcomes of their use to help you form your own opinion.

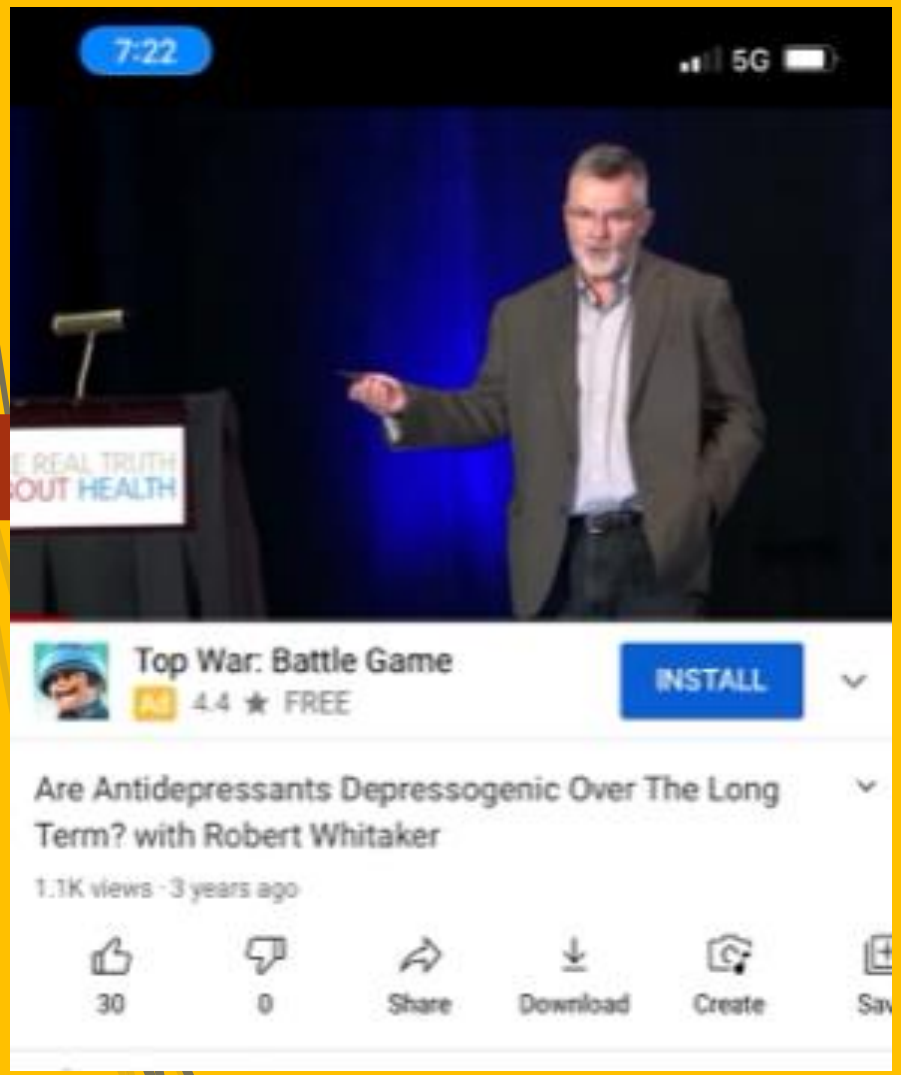
This PowerPoint summarizes the courageous and brilliant work of journalist Robert Whitaker, Danish physician Dr. Peter Gotzsche and psychology professor Dr. Irving Kirsch who are leading the way in investigating the other side of dogma of psychotropics



Robert Whitaker is an American journalist and author who has won numerous awards as a journalist covering medicine and science, including the George Polk Award for Medical Writing and a National Association for Science Writers' Award for best magazine article. In 1998, he co-wrote a series on psychiatric research for the Boston Globe that was a finalist for the Pulitzer Prize for Public Service. His first book, *Mad in America,* was named by *Discover* magazine as one of the best science books of 2002. *Anatomy of an Epidemic* won the 2010 Investigative Reporters and Editors book award for best investigative journalism. He is the publisher of madinamerica.com.


ANATOMY OF AN EPIDEMIC
lithium
ritalin
Magic Bullets, Psychiatric Drugs, and the Astonishing Rise of Mental Illness in America
zyprexa
xanax
wellbutrin
klonopin
risperdal
tegretol
lamictal
prozac
ROBERT WHITAKER
Author of Mad in America


MAD IN AMERICA
With a new preface and afterword by the author
Bad Science, Bad Medicine, and the Enduring Mistreatment of the Mentally Ill
robert whitaker



The content of the following slides are largely from Robert Whitaker's excellent YouTube videos:

Robert Whitaker
https://youtu.be/5VBXWdhabuQ
https://youtu.be/FY-5npruTGc
https://youtu.be/esfwU1d2-Yg
https://youtu.be/TEpjyKCPTEE

Robert Whitaker's website:
https://madinamerica.com

How The Public Came to Believe in the Low Serotonin Theory of Depression

1980: DSM III is published. The APA adopts a disease model for categorizing mental disorders.

1981: "Researchers believe clinical depression is caused by a chemical imbalance in the brain." University of Chicago psychiatrist Herbert Meltzer, in interview with Associated Press.

1984. "There are many hints that mental illness is due to chemical imbalances in the brain and that treatment involves correcting these chemical imbalances." Nancy Andreasen, in her book, *The Broken Brain*.

1987. The FDA approves Prozac for marketing. Eli Lilly markets Prozac as a selective serotonin reuptake inhibitor (SSRI).

1988. Antidepressants "restore the chemical imbalance scientists have linked to many depressions." John Talbott, former president of the American Psychiatric Association (APA), in interview with the *St. Petersburg Times*.

2001: "We now know that mental illnesses--such as depression or schizophrenia--are not 'moral weaknesses' or 'imagined' but real diseases caused by abnormalities of brain structure and imbalances of chemicals in the brain." -- APA President Richard Harding, in article in *Family Circle* magazine.

2001: Antidepressants "restore brain chemistry to normal." Future APA President Nada Stotland, in *Family Circle* magazine.

2005: The APA reports that "75% of consumers believe that mental illnesses are usually caused by a chemical imbalance in the brain." -- APA press release.

2005: A psychiatrist is a "specialist specifically trained to diagnose and treat chemical imbalances."--APA press release.

2005: "Antidepressants may be prescribed to correct imbalances in the levels of chemicals in the brain." APA's "Let's Talk Facts About Depression" brochure.

2014

Websites:

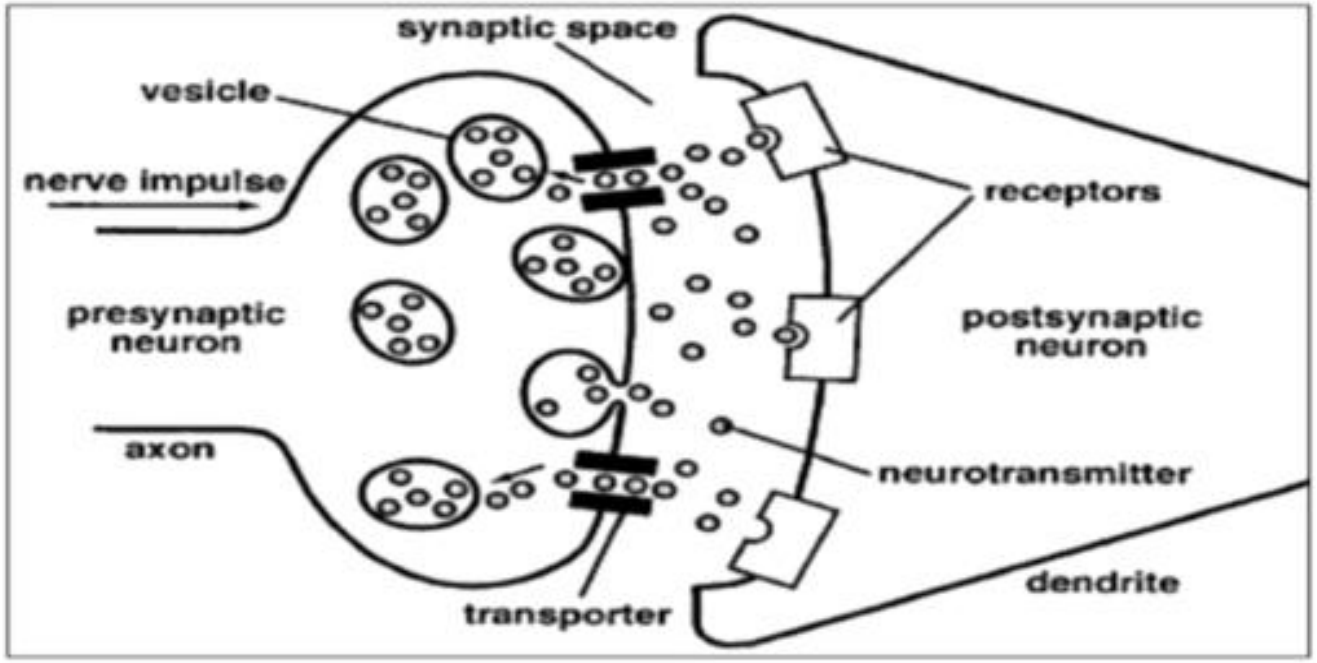
"Antidepressant medications work to restore proper chemical balance in the brain." -- Balanced Mind Parent Network

"Depression is caused by a chemical imbalance in the brain." -- Depression and Bipolar Support Alliance.

"Research has shown that imbalance in neurotransmitters like serotonin, dopamine and norepinephrine can be corrected with antidepressants." --National Alliance on Mental Illness.

Reviewing the Science:
Investigating the Low-Serotonin Theory of Depression

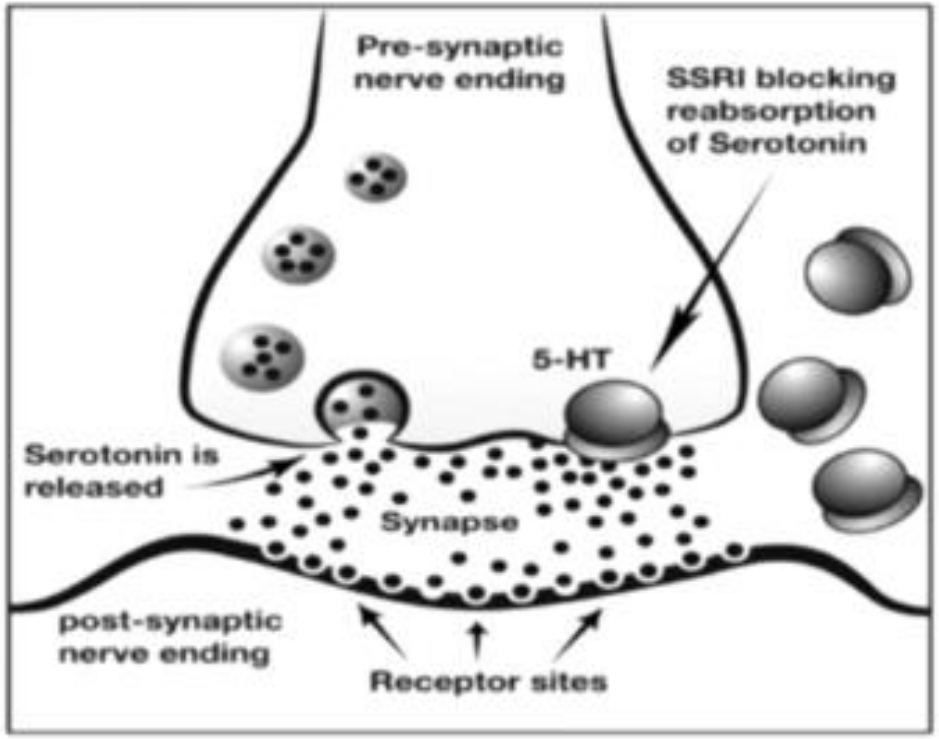
Transmission of neuronal messages



The Scientific Origins of the Theory

The chemical imbalance theory of depression arose in 1965, after researchers discovered that monoamine oxidase inhibitors and tricyclic antidepressants both blocked the normal removal of norepinephrine and serotonin from the synaptic cleft between neurons. This theoretically increased serotonergic levels in the synaptic cleft, and thus researchers hypothesized that perhaps one or more of these neurotransmitters was abnormally low in depressed patients.

Focus on Serotonin as the Key Neurotransmitter in the SSRI Era



But Do People With Depression Have Low Serotonin?

"Elevations or decrements in the functioning of serotonergic systems per se are not likely to be associated with depression."

--NIMH, 1984.

APA's *Textbook of Psychiatry,* 1999

"The monoamine hypothesis, which was first proposed in 1965, holds that monamines such as norepinephrine and 5-HT (serotonin) are deficient in depression and that the action of antidepressants depends on increasing the synaptic availability of these monoamines. The monoamine hypothesis was based on observations that antidepressants block reuptake inhibition on norepinephrine, 5-HT, and/or dopamine. However, inferring neurotransmitter pathophysiology from an observed action of a class of medications on neurotransmitter availability is similar to concluding that because aspirin causes gastrointestinal bleeding, headaches are caused by too much blood loss and the therapeutic action of aspiring in headaches involves blood loss. Additional experience has not confirmed the monoamine depletion hypothesis."

"There is no clear and convincing evidence that monoamine deficiency accounts for depression; that is, there is no real monamine deficit."

--Stephen Stahl, *Essential Psychopharmacology*, 2000

"After more than a decade of PET studies, monamine depletion studies, and genetic association analyses examining polymorphisms in monaminergic genes, there is little evidence to implicate true deficits in serotonergic, noradrenergic, or dopaminergic neurotransmission in the pathophysiology of depression. This is not surprising, as there is no a priori reason that the mechanism of action of a treatment is the opposite of disease pathophysiology."

Eric Nestler, "Linking Molecules to Mood," 2010.

"I don't think there's any convincing body of data that anybody has ever found that depression is associated, to a significant extent, with loss of serotonin."

--Alan Frazer, University of Texas Health Science Center, 2012

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.

The Bottom Line

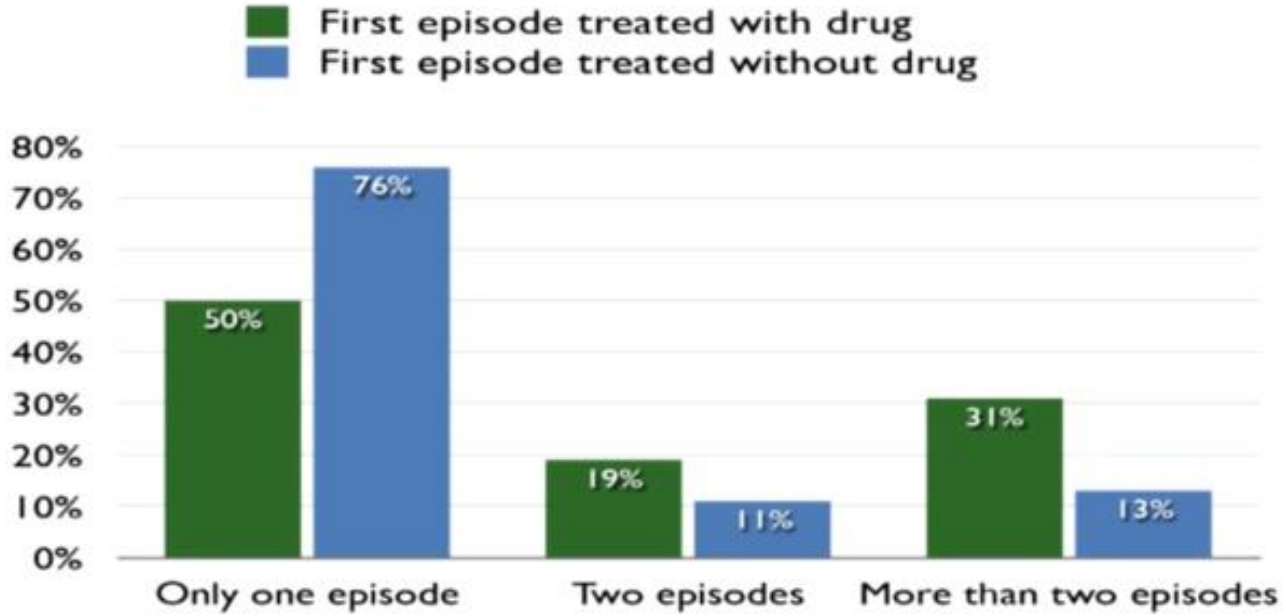
- Research into the chemical imbalance hypothesis of mental disorders found that prior to being medicated, people diagnosed with depression, schizophrenia and other mental disorders did not have a characteristic "chemical imbalance."

- However, once a person takes a psychiatric medication, the brain goes through a series of compensatory adaptions, which are designed to help restore a "homeostatic equilibrium" in brain function.

- This adaptive process causes the very abnormality in brain function hypothesized to cause the mental disorder in the first place.

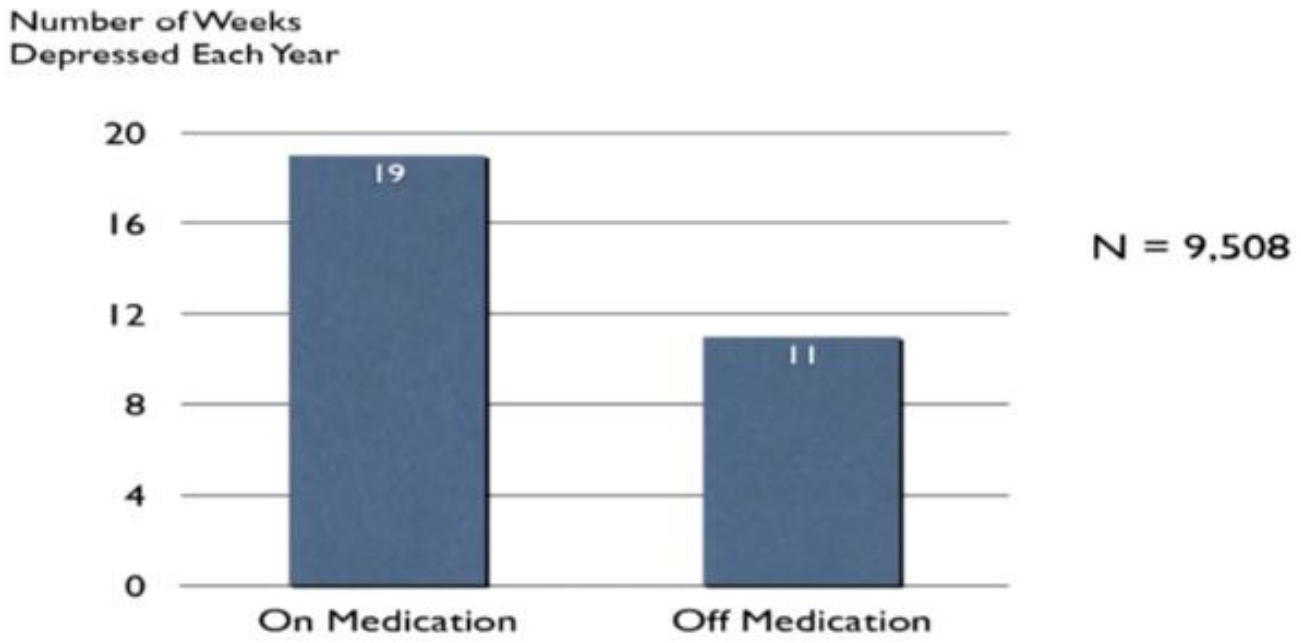
Depression in the Netherlands

(Over the course of ten years)



Source: E. Weel-Baumgarten, "Treatment of depression related to recurrence," *J Clin Psychiatry & Therapeutics* 25 (2000):61-66

Five-Year Outcomes in Canada



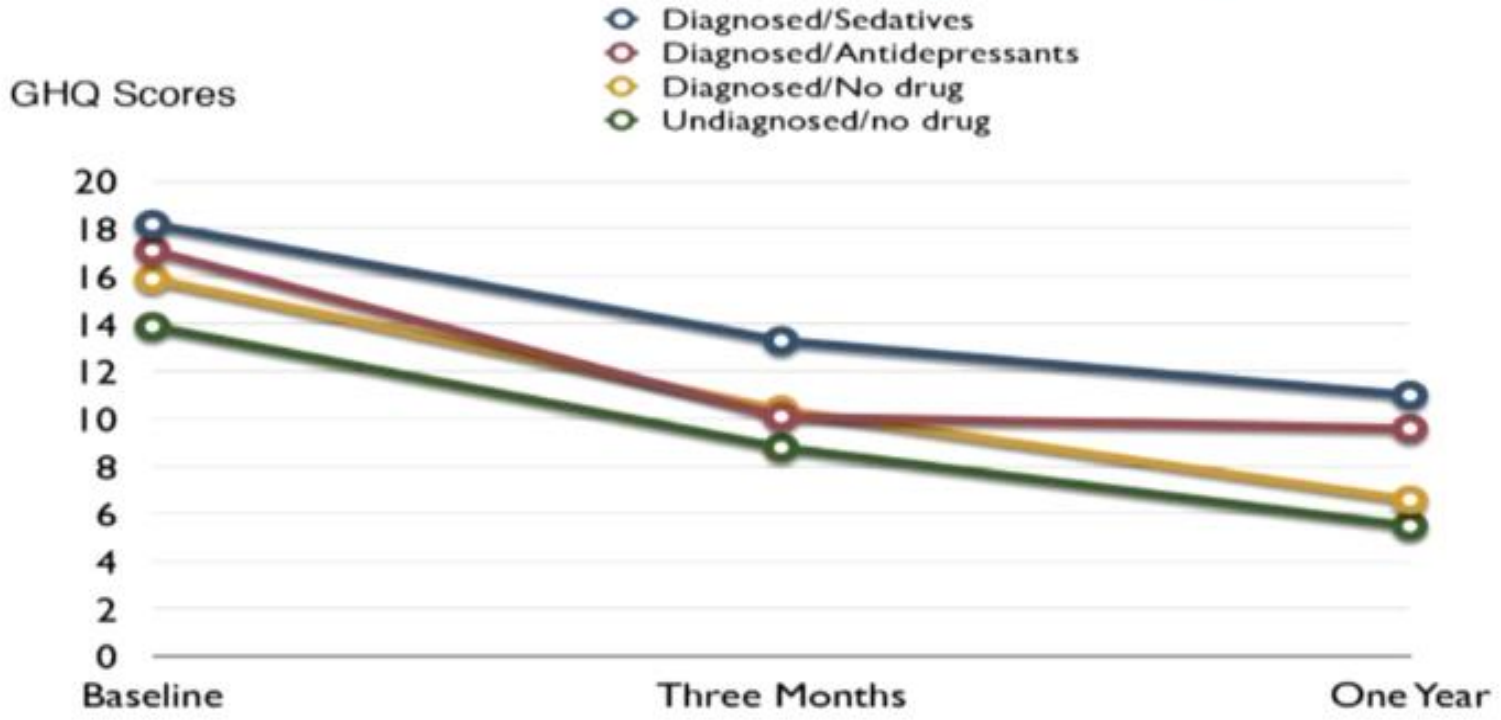
Source: S. Patten, "The Impact of antidepressant treatment on population health." *Population Health Metrics* 2 (2004): 9.

One possible interpretation of results:

These findings are consistent with Giovanni Fava's hypothesis that "antidepressant treatment may lead to a deterioration in the long-term course of mood disorders."

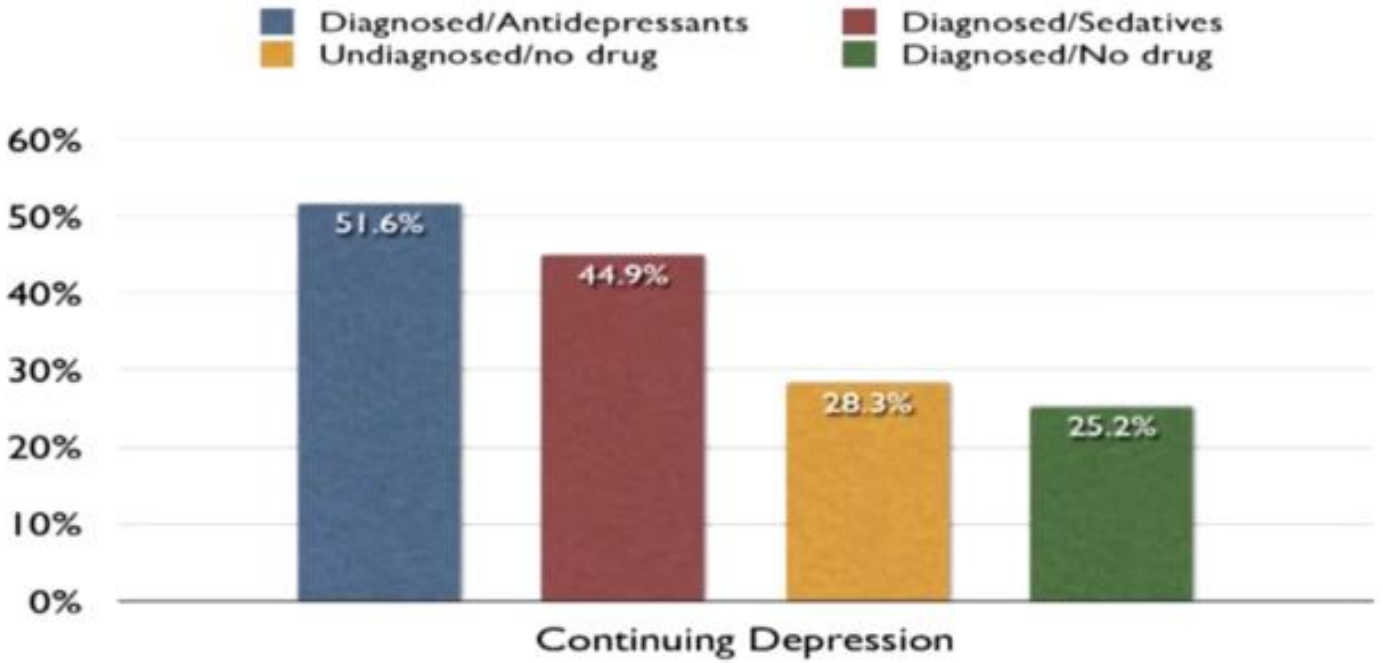
--Scott Patten

WHO Screening Study for Depression



Source: D. Goldberg. "The effects of detection and treatment of major depression in primary care." *British Journal of General Practice* 48 (1998):1840-44.

One-Year Outcomes in WHO Screening Study for Depression

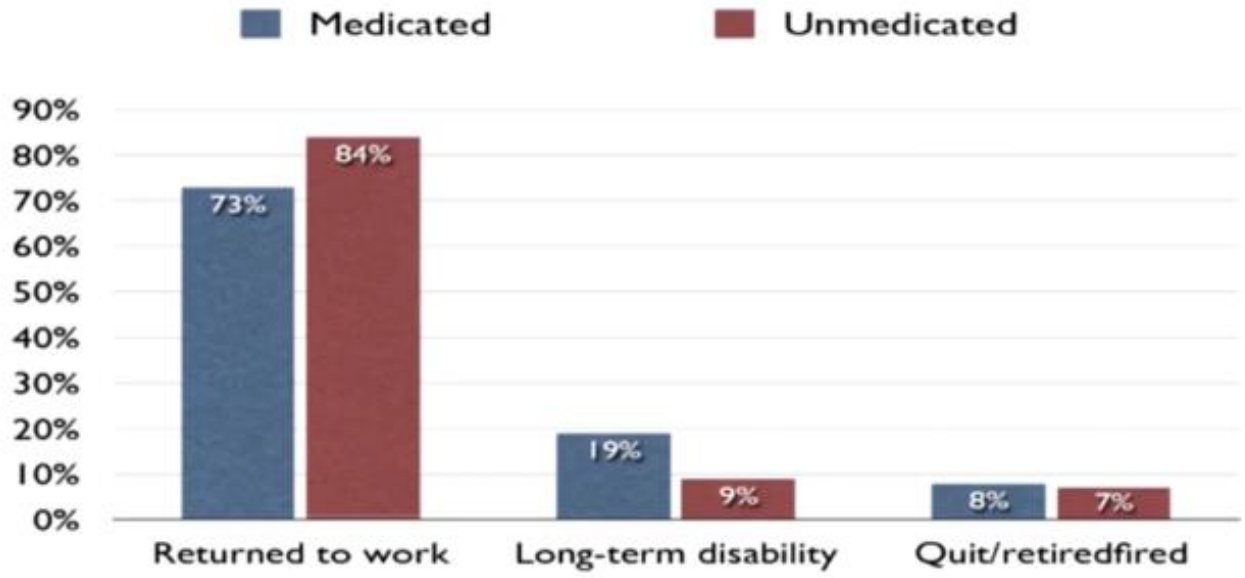


Source: D. Goldberg. "The effects of detection and treatment of major depression in primary care." *British Journal of General Practice* 48 (1998):1840-44.

"Patients not given drugs had milder illnesses but did significantly better than those receiving drugs, both in terms of symptoms lost and their diagnostic status." This was so "even after adjustment for initial scores on each instrument."

--D. Goldberg

Canadian Study of Risk of Long-term Disability for Depressed Workers

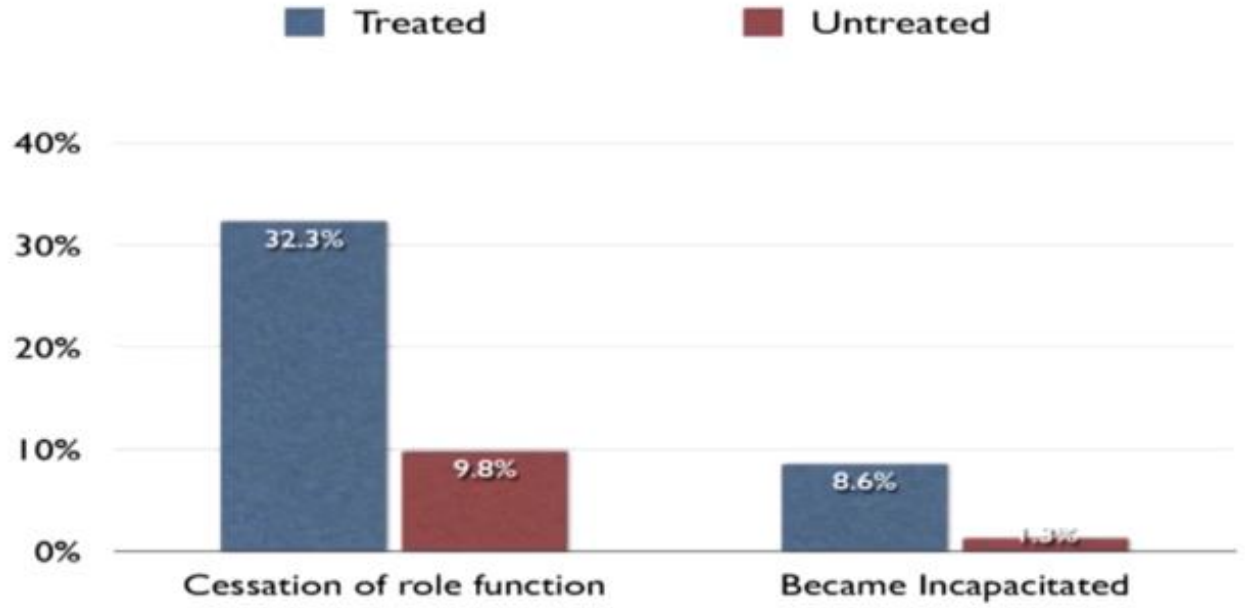


Source: C Dewa. "Pattern of antidepressant use and duration of depression-related absence from work." *British Journal of Psychiatry* 183 (2003):507-13.

"Does the lack of antidepressant use reflect a resistance to adopting a sick role and consequently a more rapid return to work?"

--Carolyn Dewa

NIMH's Study of Untreated Depression

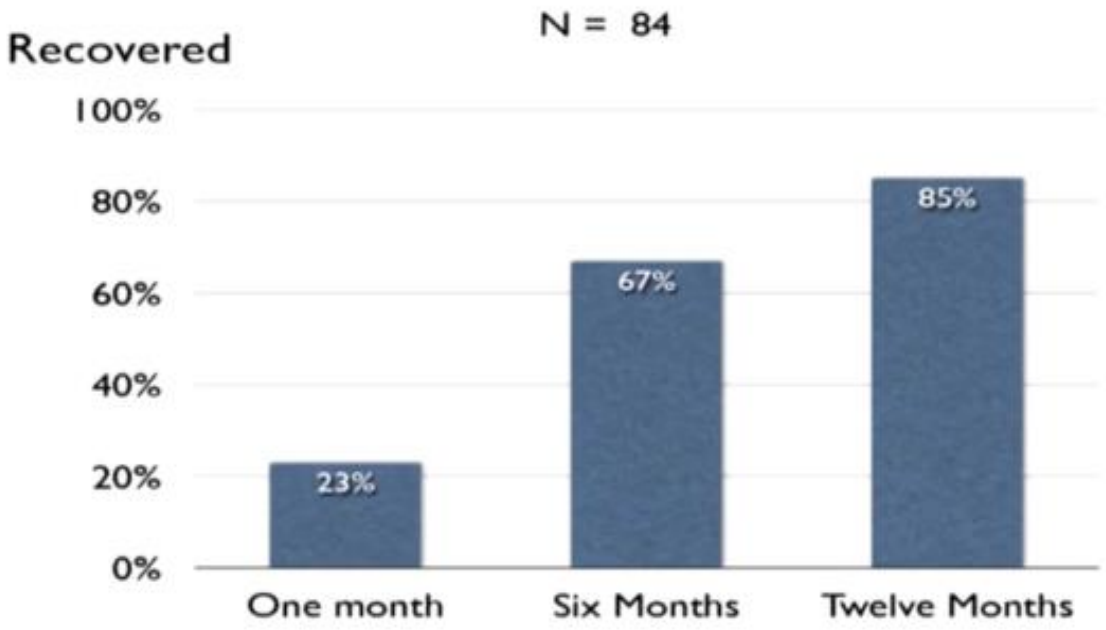


Source: W. Coryell. "Characteristics and significance of untreated major depressive disorder." *American Journal of Psychiatry* 152 (1995):1124-29.

"The untreated individuals described here had milder and shorter-lived illnesses [than those who were treated], and, despite the absence of treatment, did not show significant changes in socioeconomic status."

--William Coryell

One-Year Recovery Rates in NIMH-Funded Study of Unmedicated Depression



Source: M. Posternak, "The naturalistic course of unipolar major depression in the absence of somatic therapy." *Journal of Nervous and Mental Disease* 194 (2006):324-349.

"If as many as 85% of depressed individuals who go without somatic treatment spontaneously recover within one year, it would be extremely difficult for any intervention to demonstrate a superior result to this."

--Michael Posternak

"The untreated individuals described here had milder and shorter-lived illnesses [than those who were treated], and, despite the absence of treatment, did not show significant changes in socioeconomic status."

--William Coryell

Antidepressants Lessen the Long-Term Benefits of Exercise

Treatment during first 16 weeks	Percentage of patients in remission at end of 16 weeks	Percentage of patents who relapsed in following six months	Percentage of all patients depressed at end of ten months
Zoloft alone	69%	38%	52%
Zoloft plus exercise	66%	31%	55%
Exercise alone	60%	8%	30%

Source: Babyak, M. "Exercise treatment for major depression." *Psychosomatic Medicine* 62 (2000):633-8.

A Biological Explanation for Why Antidepressants May Be Depressogenic Agents Over the Long-Term

The Problem

- Over time, antidepressants induce brain changes that "are the opposite of what the the medication originally produced." Rather than raise serotonin levels, the drugs over the long-term impair serotonergic pathways in the brain.

Animal Evidence

- In studies with rats, long-term treatment with an SSRI led to markedly reduced serotonin in "nine areas of the brain." In addition, treatment with an SSRI leads to a reduced density of receptors for serotonin in the brain.

- In experiments with animals, such impairments in serotonergic functions are "associated with increased depressive and anxious behaviors."

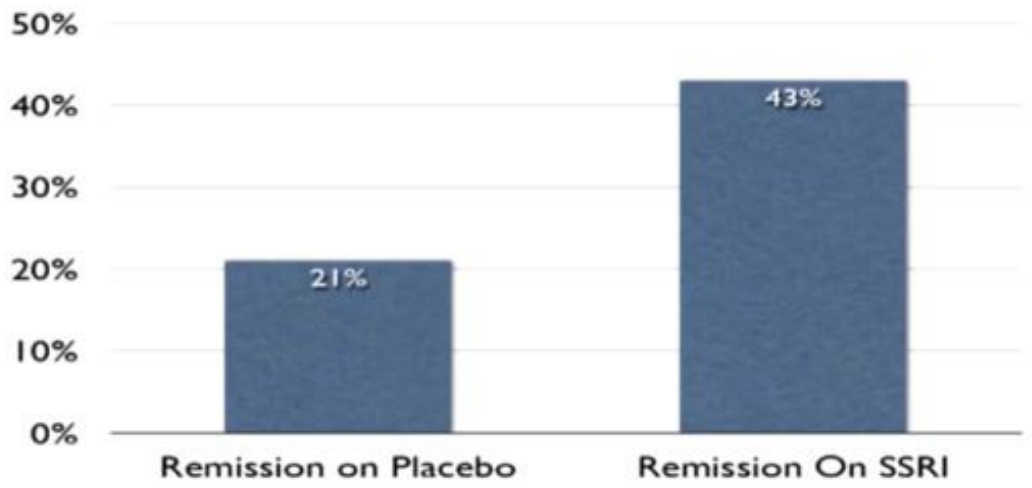
Source: El-Mallakh, R. "Tardive dysphoria: The role of long-term antidepressant use in inducing chronic depression. *Medical Hypotheses* 76 (2011): 769-773.

"When we prolong treatment over 6-9 months, we may recruit processes that oppose the initial acute effects of antidepressant drugs (loss of clinical effects) . . . We may also propel the illness to a malignant and treatment-unresponsive course that may take the form of resistance or episode acceleration. When drug treatment ends, these processes may be unopposed and yield withdrawal symptoms and increased vulnerability to relapse. Such processes are not necessarily reversible."

Giovanni Fava, 2011

Source: G. Fava. "The mechanisms of tolerance in antidepressant action." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 35 (2011): 1593-1602.

Three-Month Risk of Relapse After Initial Remission: Placebo vs. SSRI-Withdrawn Patients

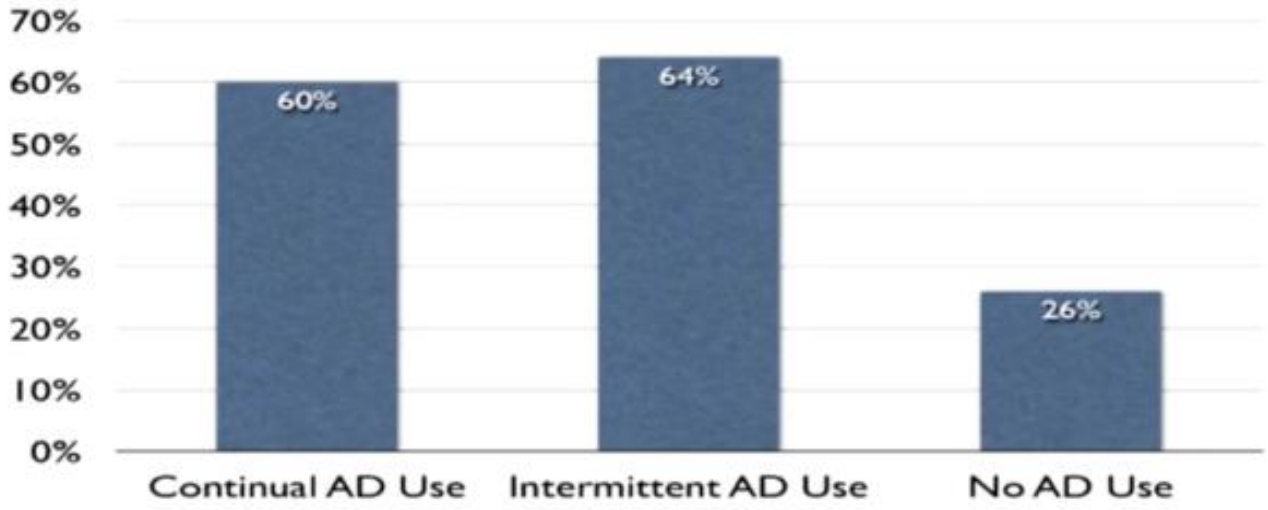


P. Andrews: "Primum non nocere: an evolutionary analysis of whether antidepressants do more harm than good." Frontiers in Psychology 3 (2012): 1-18.

"The more antidepressants perturb monamine levels in the brain, the more the brain appears to push back, which increases the risk of relapse when the drug is discontinued . . . antidepressant use appears to increase [biological] susceptibility to depression."

--Paul Andrews, 2012

Two-Year Relapse Rates for Remitted Patients in the Netherlands



Source: C. Bockting. "Continuation and maintenance use of antidepressants in recurrent depression." *Psychotherapy and Psychosomatics* 77 (2008): 17-26.

Are Antidepressants Depressogenic Over the Long-Term?

"Antidepressant drugs in depression might be beneficial in the short term, but worsen the progression of the disease in the long term, by increasing the biochemical vulnerability to depression . . . Use of antidepressant drugs may propel the illness to a more malignant and treatment unresponsive course."

--Giovanni Fava, *Psychotherapy and Psychosomatics*, 1995

"Even when a diagnosis of Major Depressive Disorder has been made, spontaneous recovery should be considered for a number of cases in general practice and watchful waiting could prove worthwhile."

--E.M. van Weel-Baumgarten, 2000

The Critical Question

How do psychiatric medications affect the long-term course of mental disorders? Do they increase the likelihood that people diagnosed with a major mental disorder will do well over the long-term? Or do they increase the likelihood that people so diagnosed will have a poor long-term outcome?

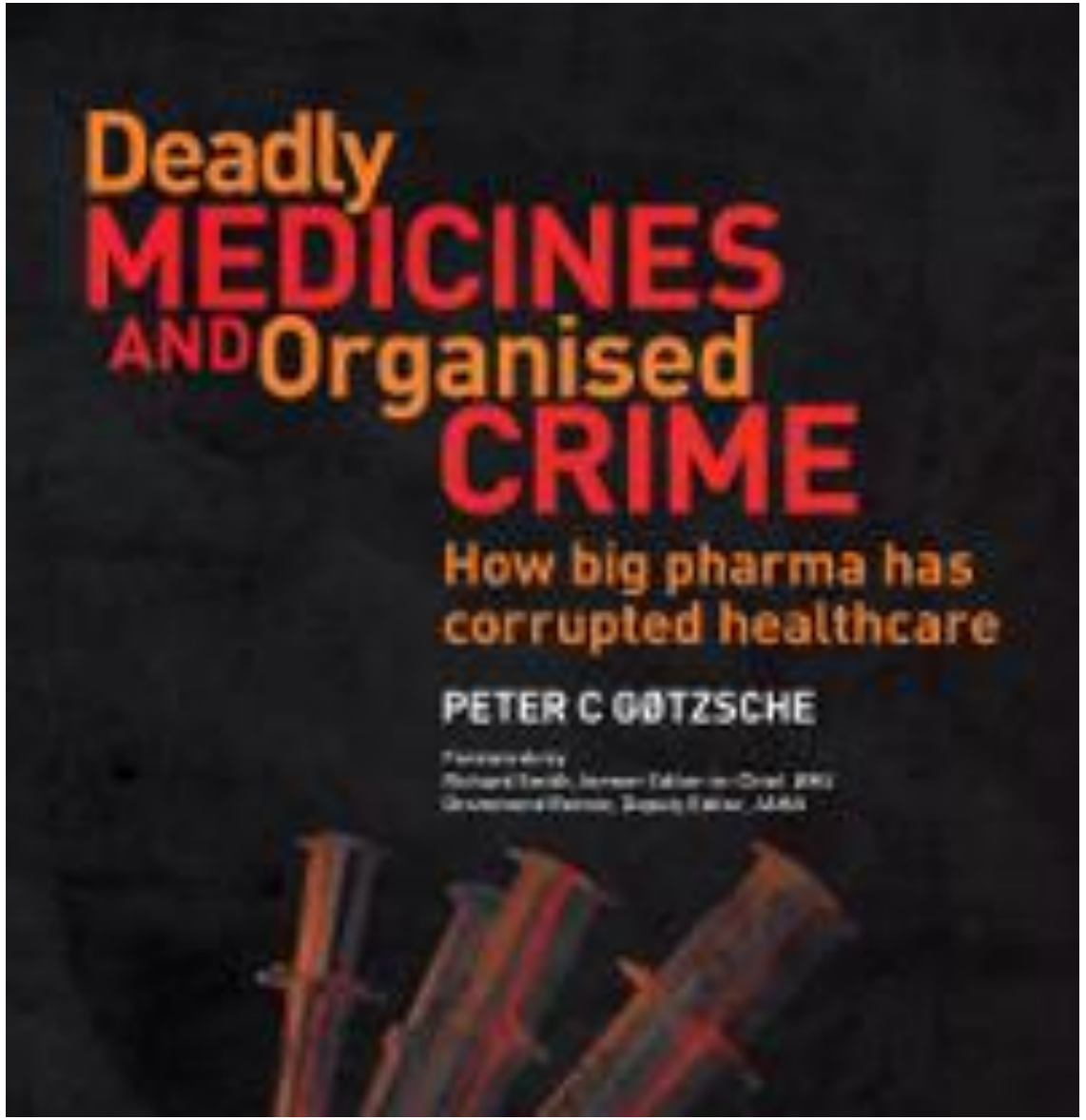
The content of the following slides are largely from Dr. Peter Gøtzsche excellent YouTube videos:

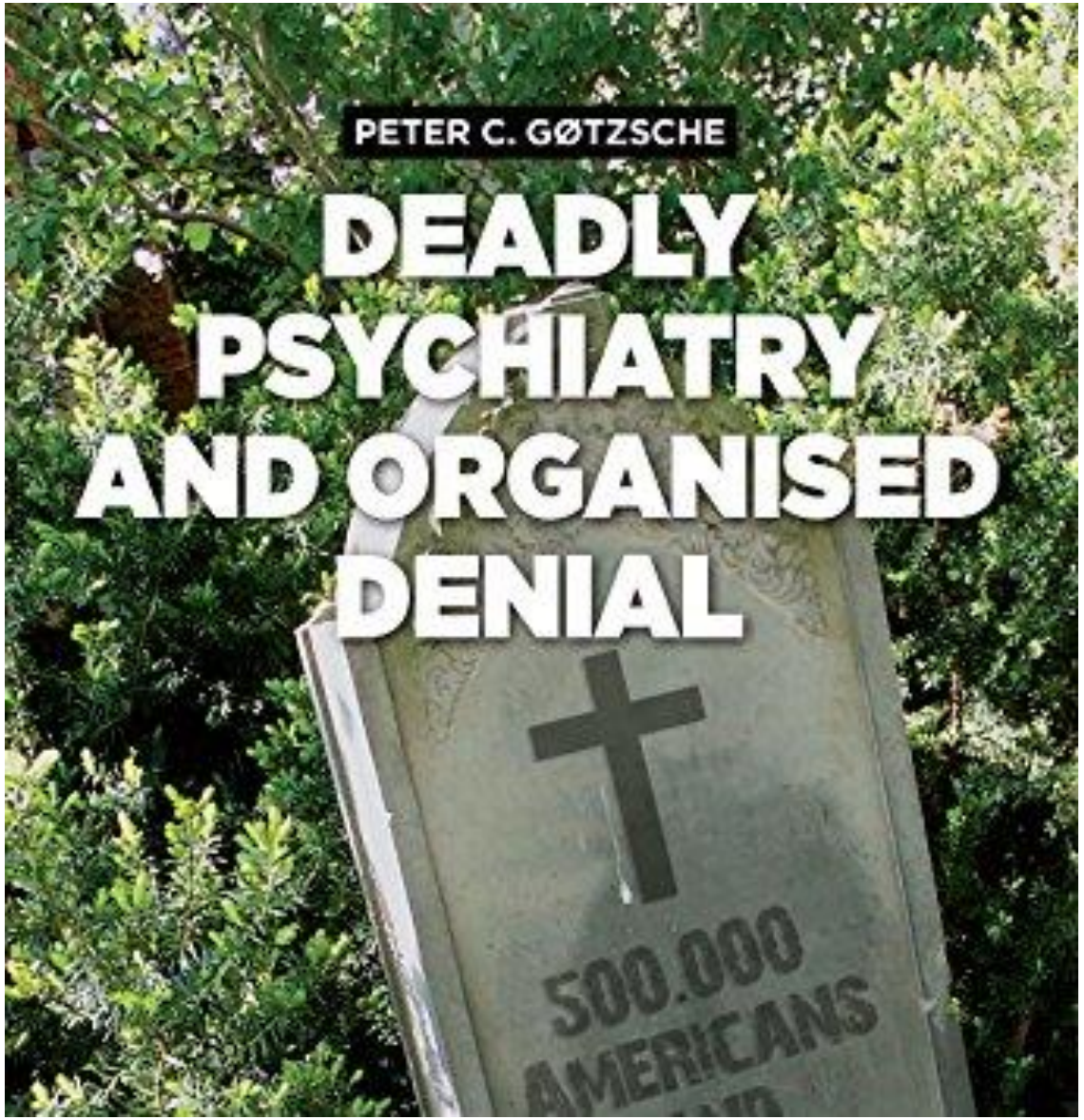
Dr. Peter Gøtzsche
https://www.youtube.com/watch?v=LQx4waMijd8
https://www.youtube.com/watch?v=_9cfjKOmPF8
https://www.youtube.com/watch?v=RyHQRxQGBhI
https://www.youtube.com/watch?v=KpDzB8uYHgY

Dr. Peter Gotzsche website:
https://www.deadlymedicines.dk/about/

- Professor Peter C Gøtzsche graduated as a Master of Science in biology; worked with clinical trials and regulatory affairs in the drug industry 197and chemistry in 1974 and as a physician 1984. He is a specialist in internal medicine5-1983, and at hospitals in Copenhagen 1984-95. With about 80 others, he co-founded the Cochrane Collaboration in 1993 (the founder is Sir Iain Chalmers) and established the Nordic Cochrane Centre the same year. He became professor of Clinical Research Design and Analysis in 2010 at the University of Copenhagen and has been a member of the Cochrane Governing Board twice. Founded the Institute for Scientific Freedom in 2019.

- Peter has published more than 75 papers in “the big five” (BMJ, Lancet, JAMA, Annals of Internal Medicine and New England Journal of Medicine) and his scientific works have been cited about 50,000 times (his H-index is 70 according to Web of Science, April 2019, which means that 70 papers have been cited at least 70 times). Peter is author of several books. The most recent ones are:


Deadly
MEDICINES
AND Organised
CRIME
How big pharma has corrupted healthcare
PETER C GØTZSCHE


PETER C. GØTZSCHE
DEADLY PSYCHIATRY AND ORGANISED DENIAL
500.000
AMERICANS

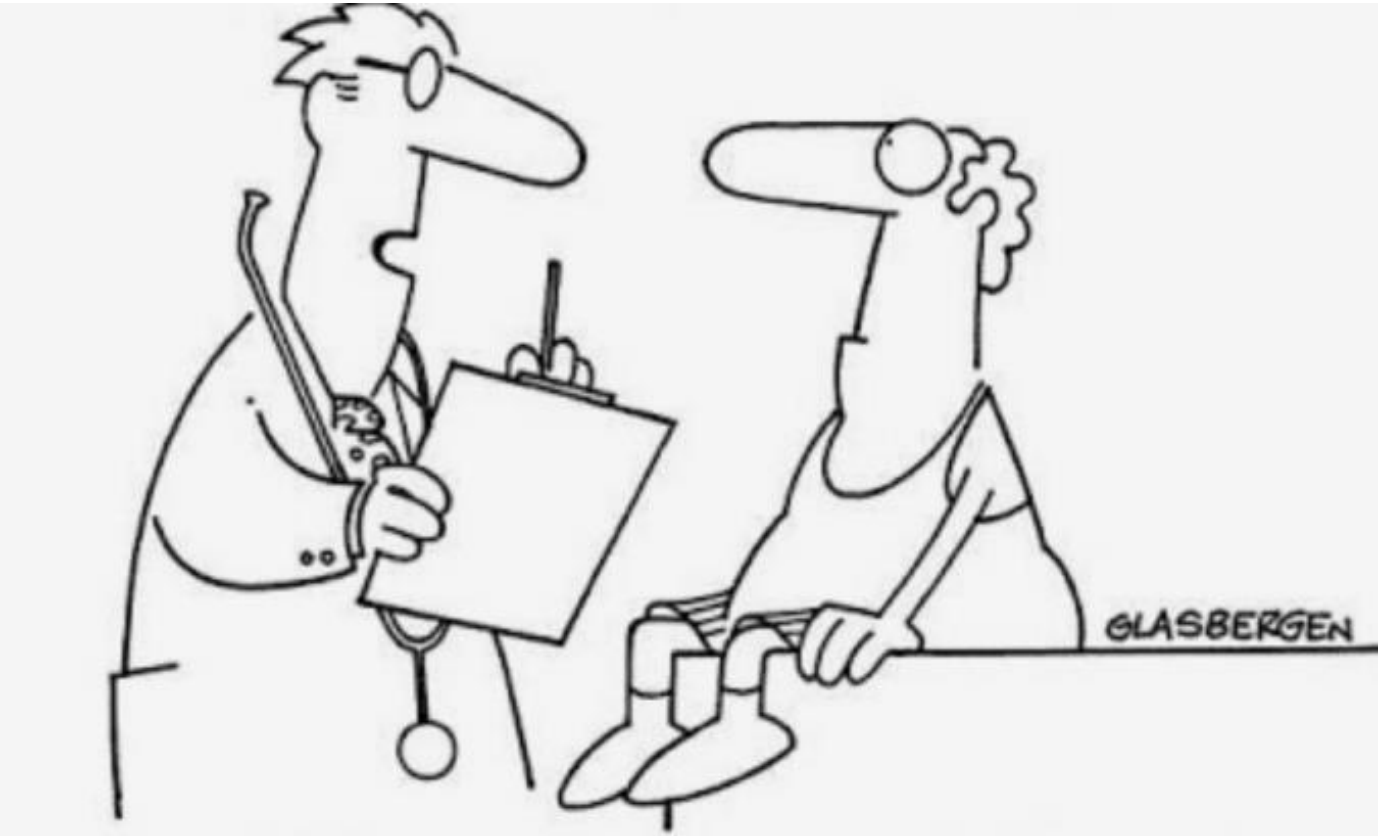
Depressing diagnosis of depression

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.



"We can't find anything wrong with you, so we're going to treat you for Symptom Deficit Disorder."

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!

But this estimate is seriously biased.

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?

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

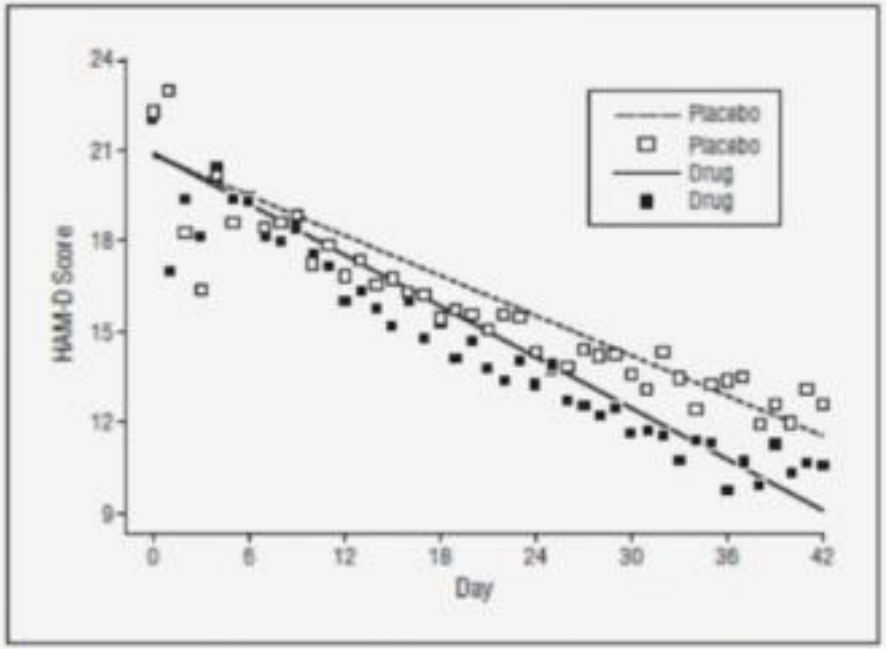


Figure. Observed vs estimated depression severity time trends for drug vs placebo in 37 adult and geriatric studies. HAM-D indicates Hamilton Depression Scale.

Sponsor-conducted RCTs of fluoxetine and venlafaxine.
Highly biased.

OBS: Linear regression is wrong on these data

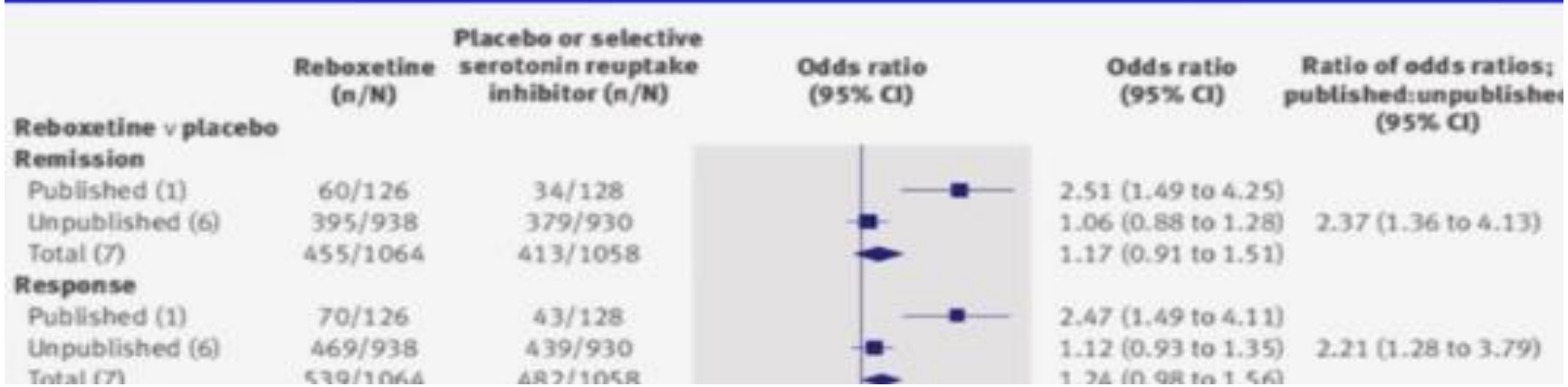
Gibbons et al,
Arch Gen Psychiatry.
Online March 5, 2012.

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 v placebo	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)
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)	

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"

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

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.

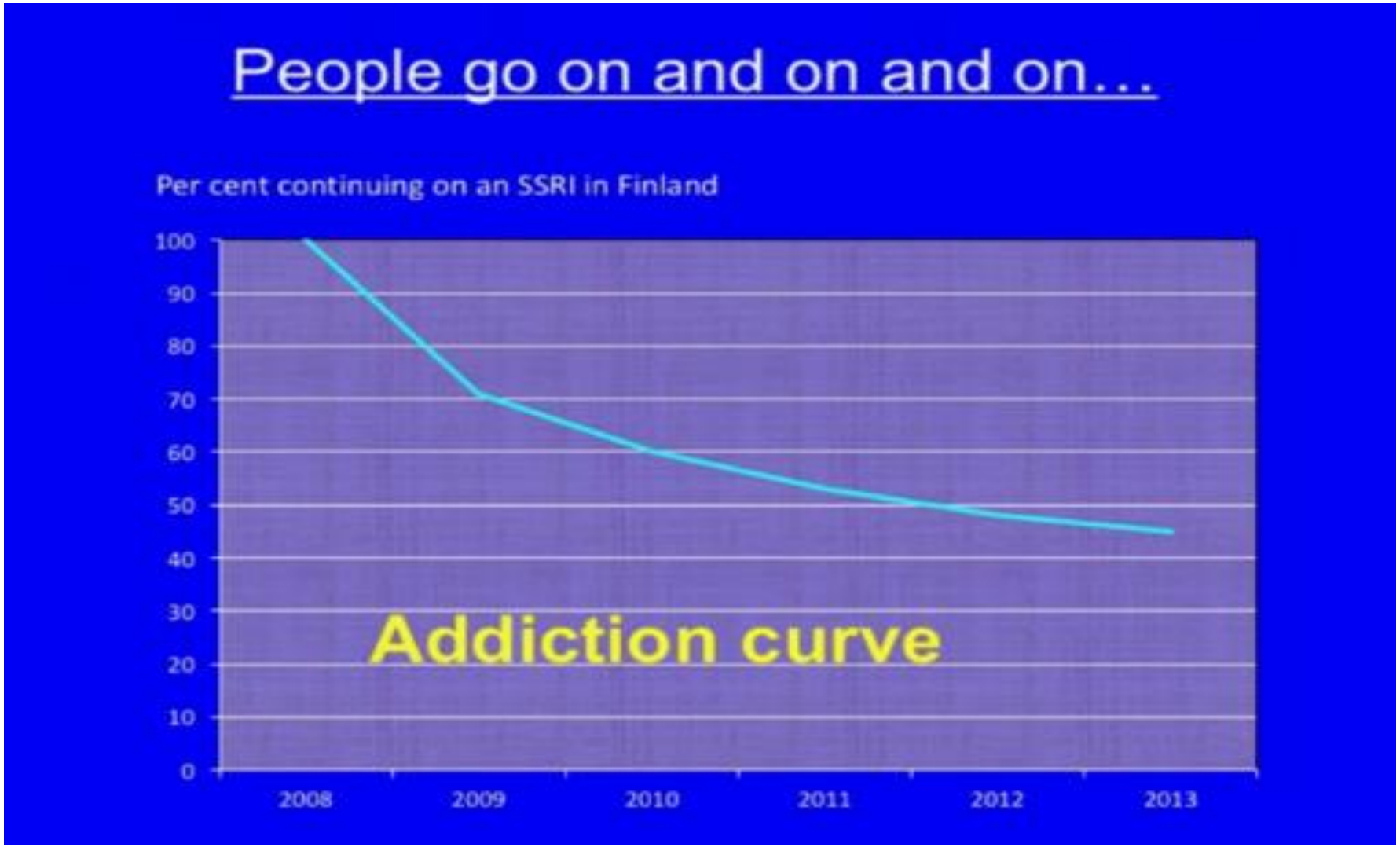
Medawar C, Hardon A. Medicines out of Control? Antidepressants and the conspiracy of goodwill. Netherlands: Aksant Academic Publishers; 2004.
Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press , 2015

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…



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

Antidepressants and suicide

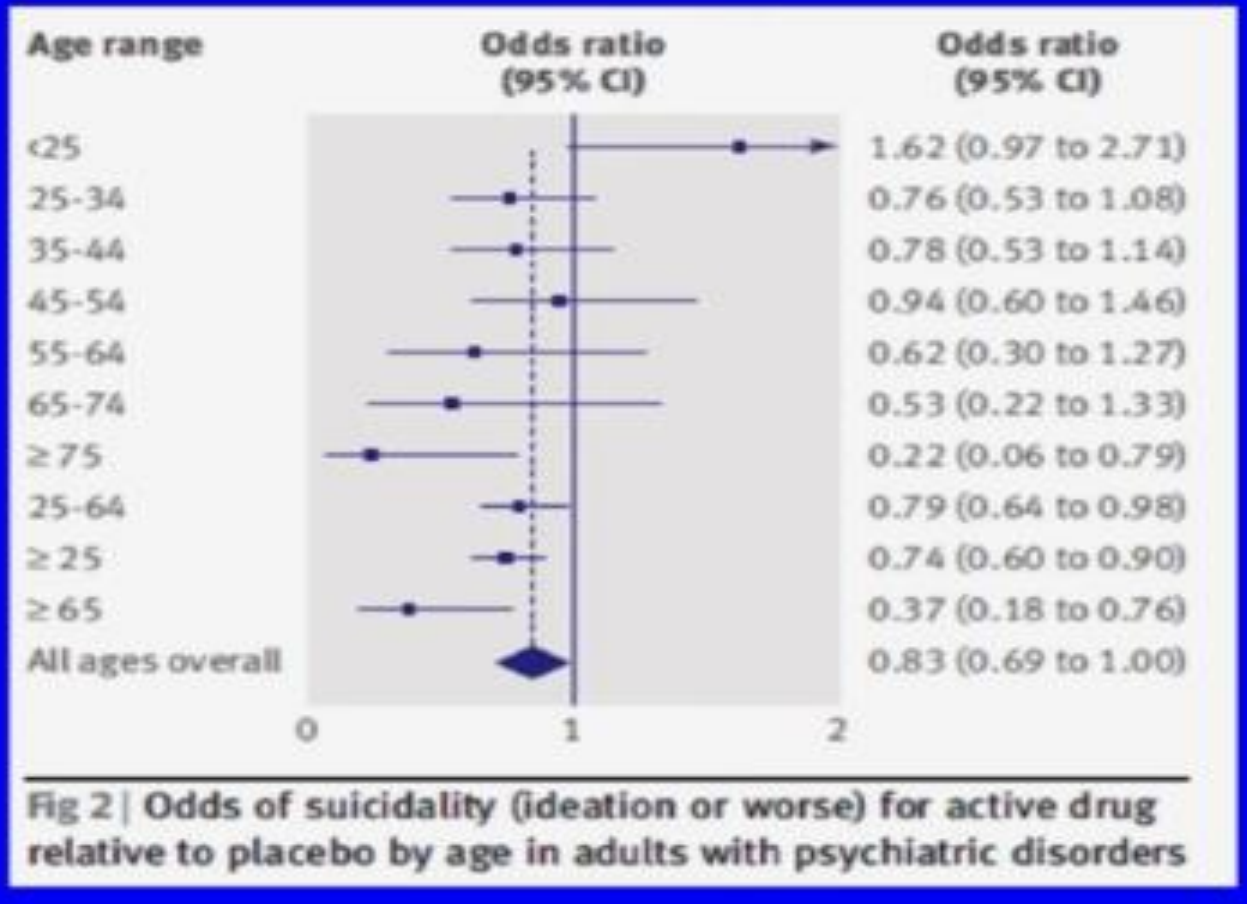


Fig 2 | **Odds of suicidality (ideation or worse) for active drug relative to placebo by age in adults with psychiatric disorders**

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

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

Suicide risk is adult healthy volunteers

13 placebo controlled trials in adult healthy volunteers

Harms related to suicidality, hostility, activation events, psychotic events and mood disturbances:

OR 1.85 (95% CI 1.11 to 3.08).

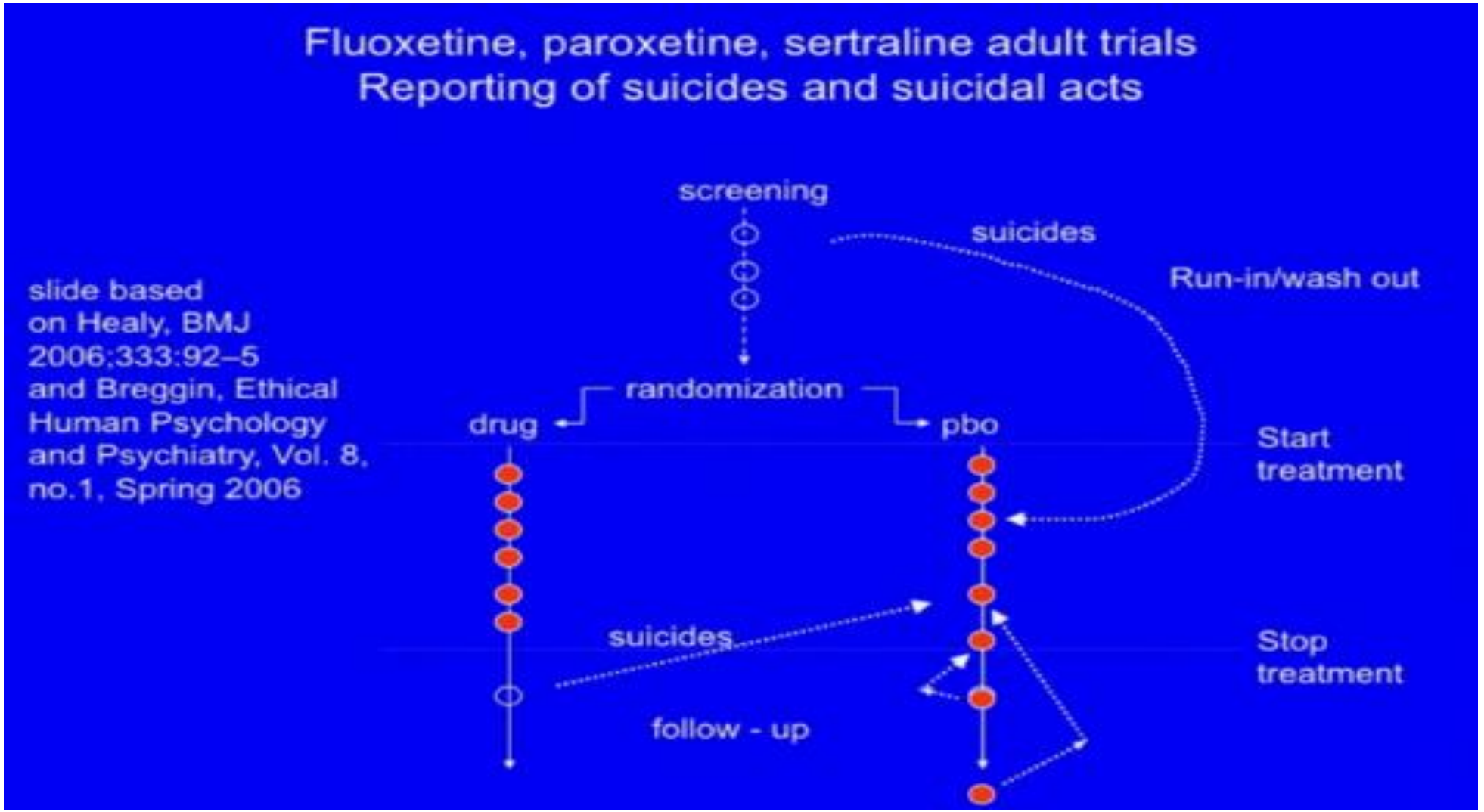
NNH 16 (95% CI 8 to 100).

We underestimated the harms of antidepressants.

We only had access to the published articles for 11 of our 13 trials.

Bielefeldt, Danborg and Gøtzsche. J R Soc Med 2016;;109:391-82.

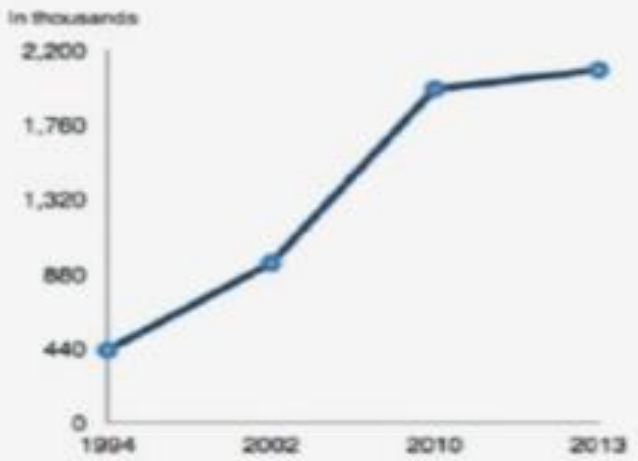
Fluoxetine, paroxetine, sertraline adult trials
Reporting of suicides and suicidal acts



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

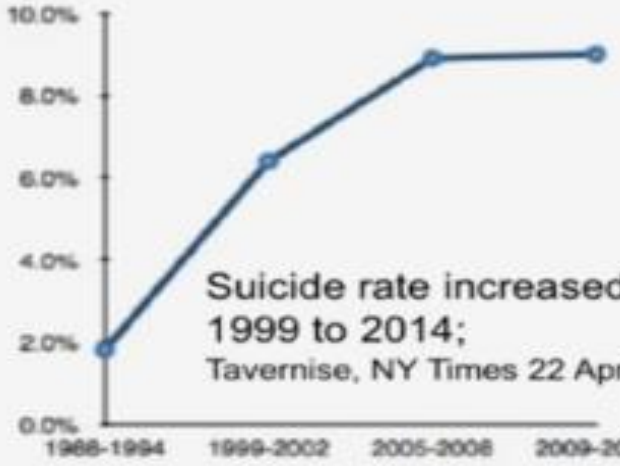
United States, 1988-2013

Number on government disability due to mood disorders



Source: R. Rosenheck, "The growth of psychopharmacology in the 1990s," *Int J of Law and Psychiatry* 28 (2005):467-83. U.S. Social Security Administration, Annual Statistical Report on the Social Security Disability Insurance Program, and SSI Annual Statistical Report, 2010-2013.

Percent of population who used antidepressants in past month



Suicide rate increased 24% 1999 to 2014;
Tavernise, NY Times 22 April 2016

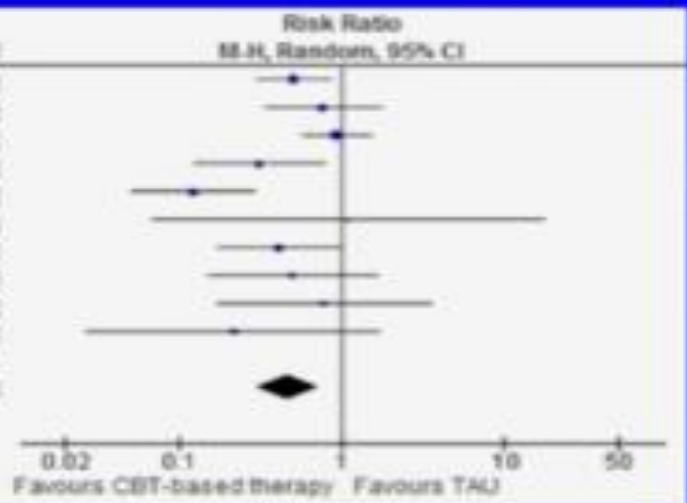
Source: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, "Health, United States, 2014."

Slide from Whitaker 2016

Cognitive behavioural therapy halves suicide attempts in people with previous such attempts

Study or Subgroup	CBT-based therapy Events	Total	TAU Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brown 2005	13	45	23	40	16.1%	0.50 [0.30, 0.85]
Dubois 1999	8	43	10	41	12.2%	0.76 [0.33, 1.74]
Gibbons 1978	27	200	29	200	16.6%	0.93 [0.57, 1.51]
Guthrie 2001	5	58	17	61	11.0%	0.31 [0.12, 0.78]
Oysin-Maillart 2017	5	60	41	60	11.8%	0.12 [0.05, 0.29]
Husain 2014	1	102	1	111	2.4%	1.09 [0.07, 17.17]
Rudd 2014	6	59	14	57	11.5%	0.41 [0.17, 1.00]
Salkovskis 1990	3	12	4	8	8.4%	0.50 [0.15, 1.66]
Stewart 2009	4	23	2	9	6.2%	0.78 [0.17, 3.55]
Wei 2013	1	25	5	27	3.8%	0.22 [0.03, 1.72]
Total (95% CI)		627		614	100.0%	0.47 [0.30, 0.73]
Total events	73		146			

Heterogeneity: Tau² = 0.26; Chi² = 20.73, df = 9 (P = 0.01); I² = 57%
Test for overall effect: Z = 3.32 (P = 0.0009)



Gøtzsche & Gøtzsche, J R Soc Med submitted

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)

Antidepressants, suicide and falls

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

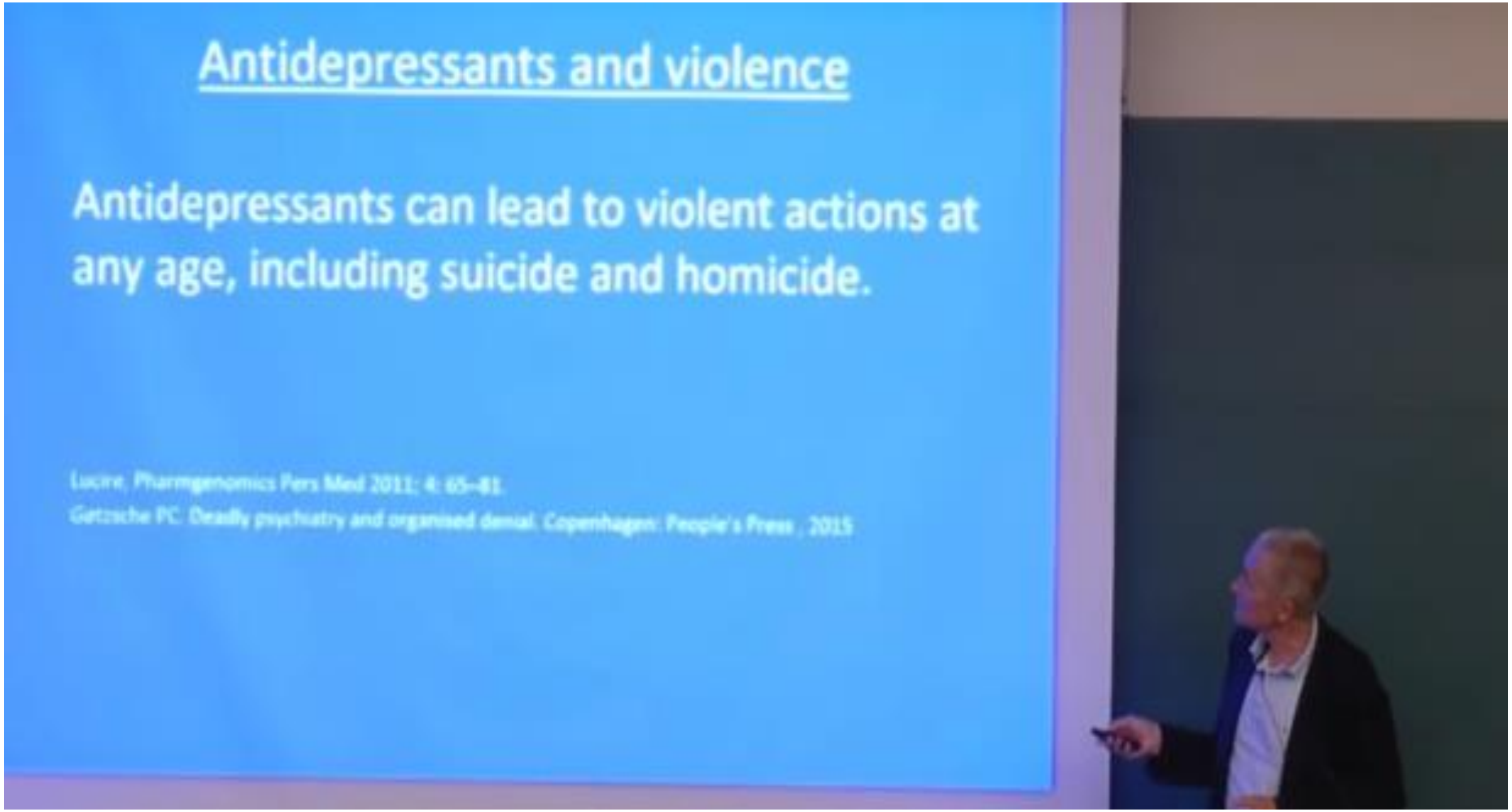
A controlled cohort study of depressed people over 65 years of age showed that SSRIs lead to falls. For every 28 people treated for 1 year with an SSRI, there was one additional death, compared to no treatment.

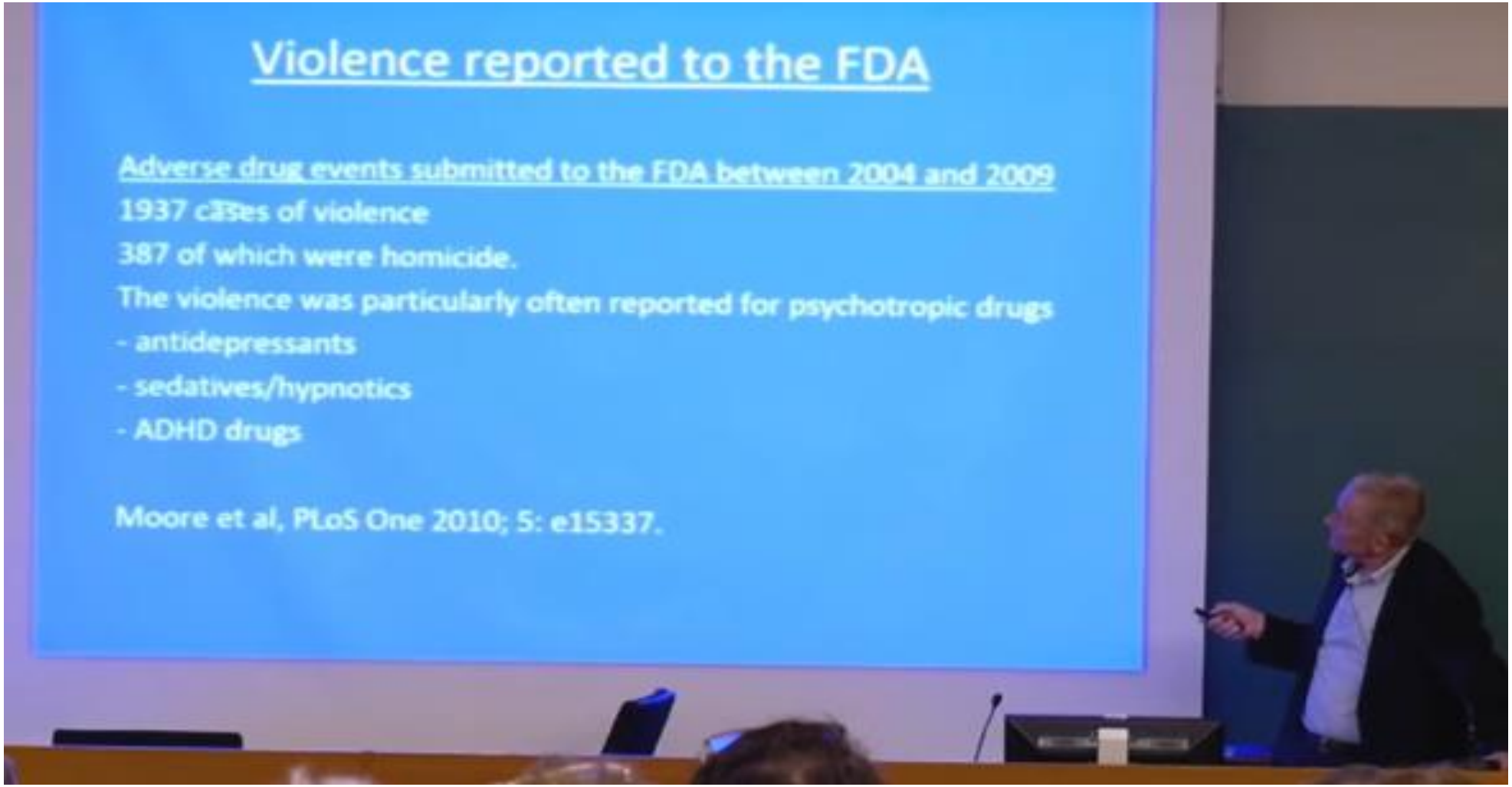
It is doubtful whether these drugs are safe at any age.

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.

The following slides are largely form Dr. Irving Kirsch's excellent YouTube videos:

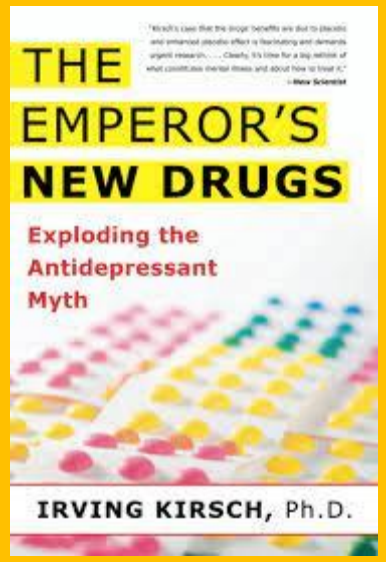
https://www.youtube.com/watch?v=UC5RZRG7-QQ

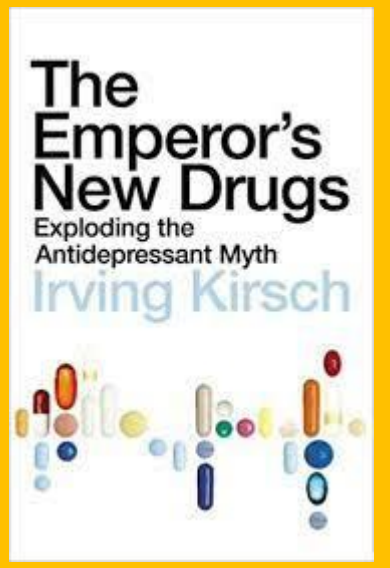
https://www.youtube.com/watch?v=Zihdr36WVi4

https://www.youtube.com/watch?v=NuyHi7ljWF4

Dr. Kirsch's website: https://connects.catalyst.harvard.edu/Profiles/display/Person/96221

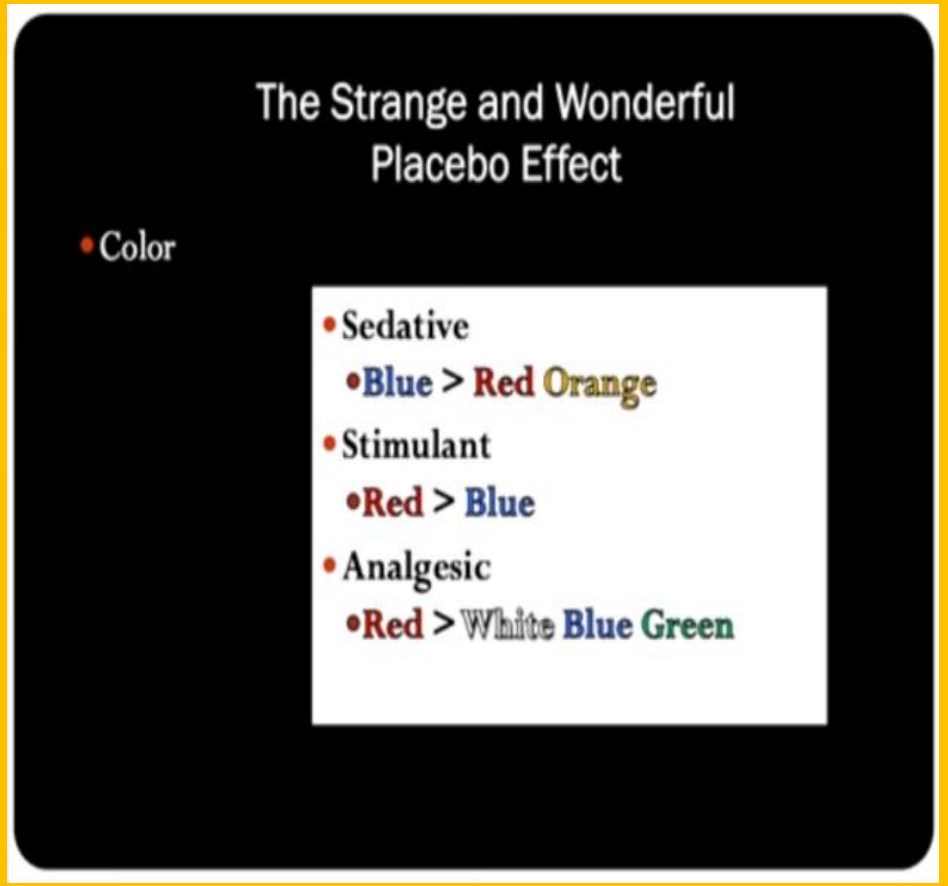
Dr. Irving Kirsch





Irving Kirsch (born March 7, 1943) is Associate Director of the Program in Placebo Studies and a lecturer in medicine at the Harvard Medical School and Beth Israel Deaconess Medical Center.[1] He is also professor emeritus of psychology at the Universities of Hull and Plymouth in the United Kingdom, and the University of Connecticut in the United States.[2][3] Kirsch is a leading researcher within the field of placebo studies who is noted for his work on placebo effects, antidepressants, expectancy, and hypnosis. He is the originator of response expectancy theory, and his analyses of clinical trials of antidepressants have influenced official treatment guidelines in the United Kingdom. He is the author of the 2009 book, *The Emperor's New Drugs*.

Color of the placebo makes a difference in its effect:



The Strange and Wonderful Placebo Effect

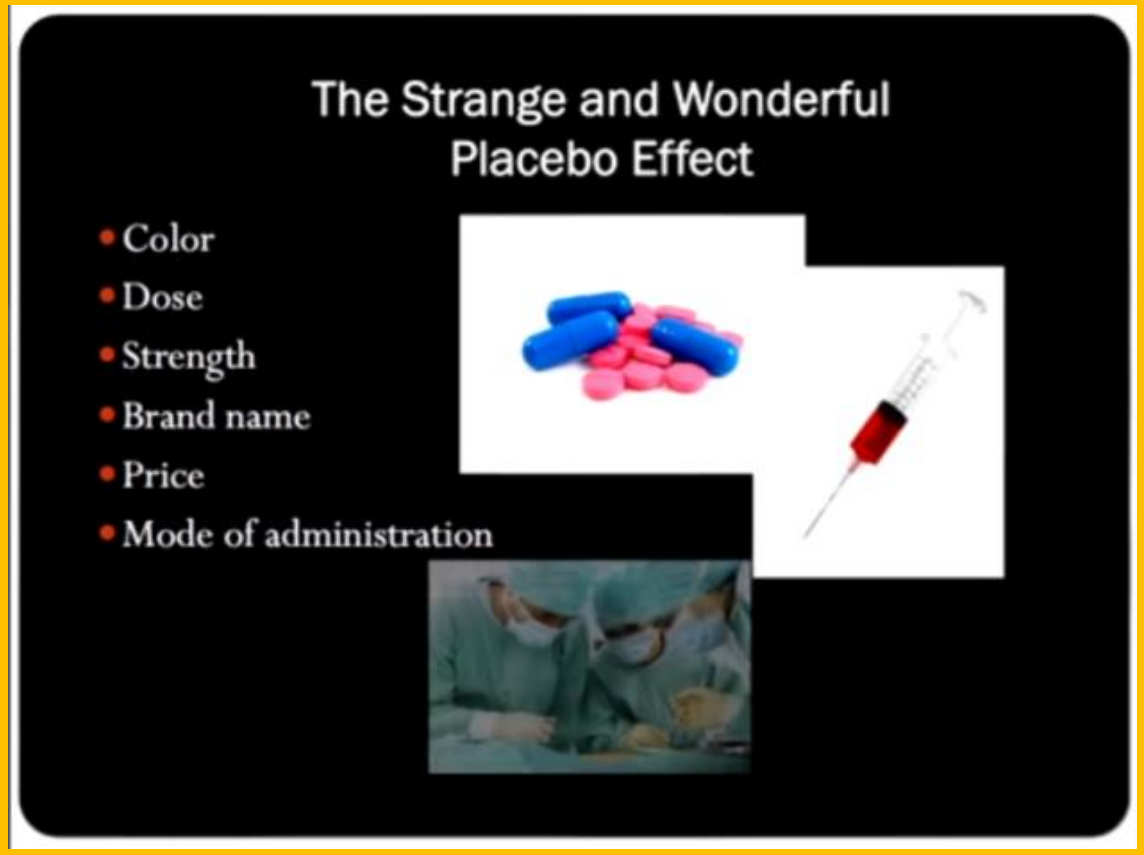
- Color
- Dose

Color, dose and strength together of the placebo make even more difference in its effect:

Color, dose, strength, and brand name together of the placebo make even more difference in its effect:

And the price you pay makes you like the placebo even more:

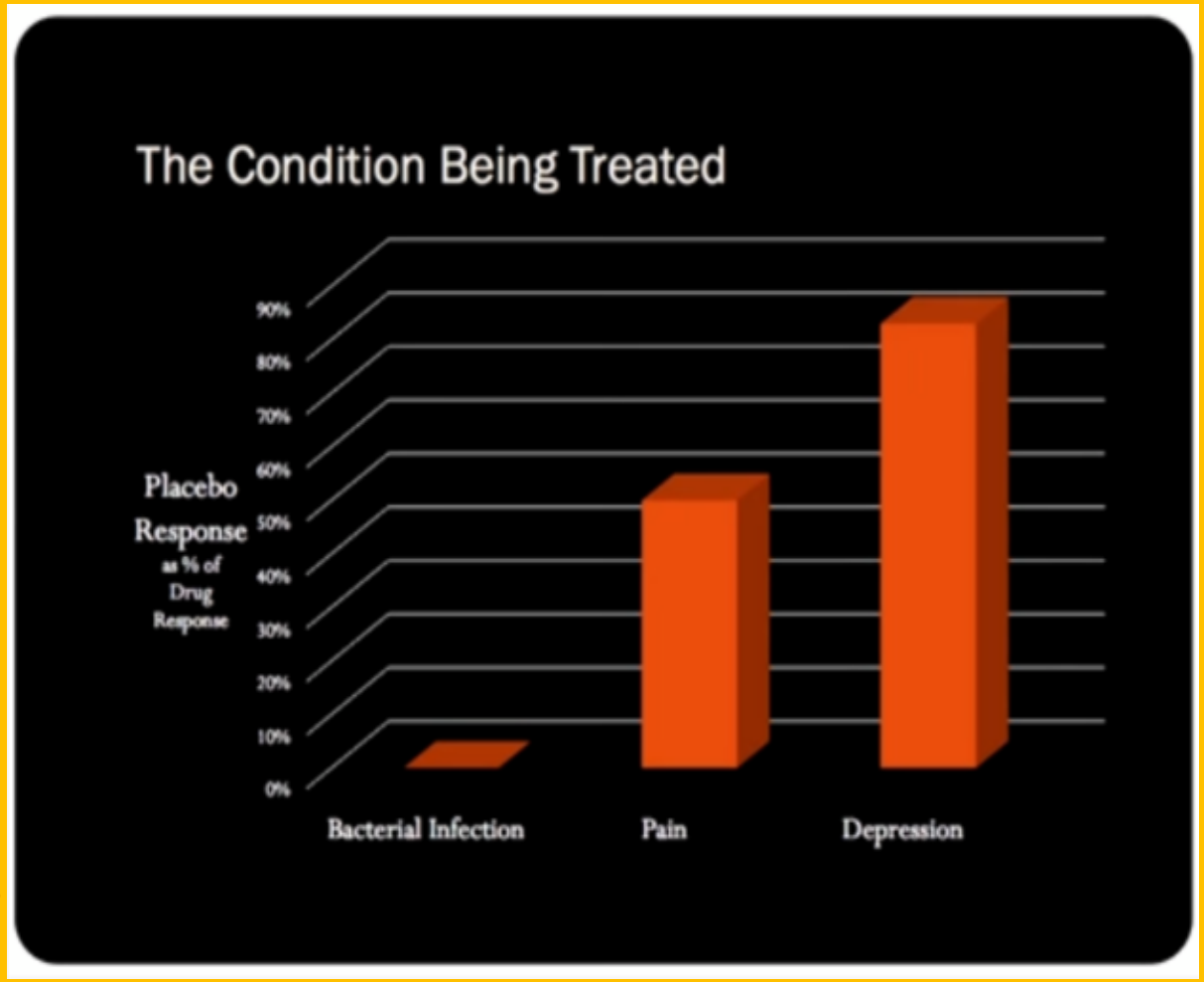
Let's not leave out the mode of administration to make you like the placebo even more. The more invasive, the better!



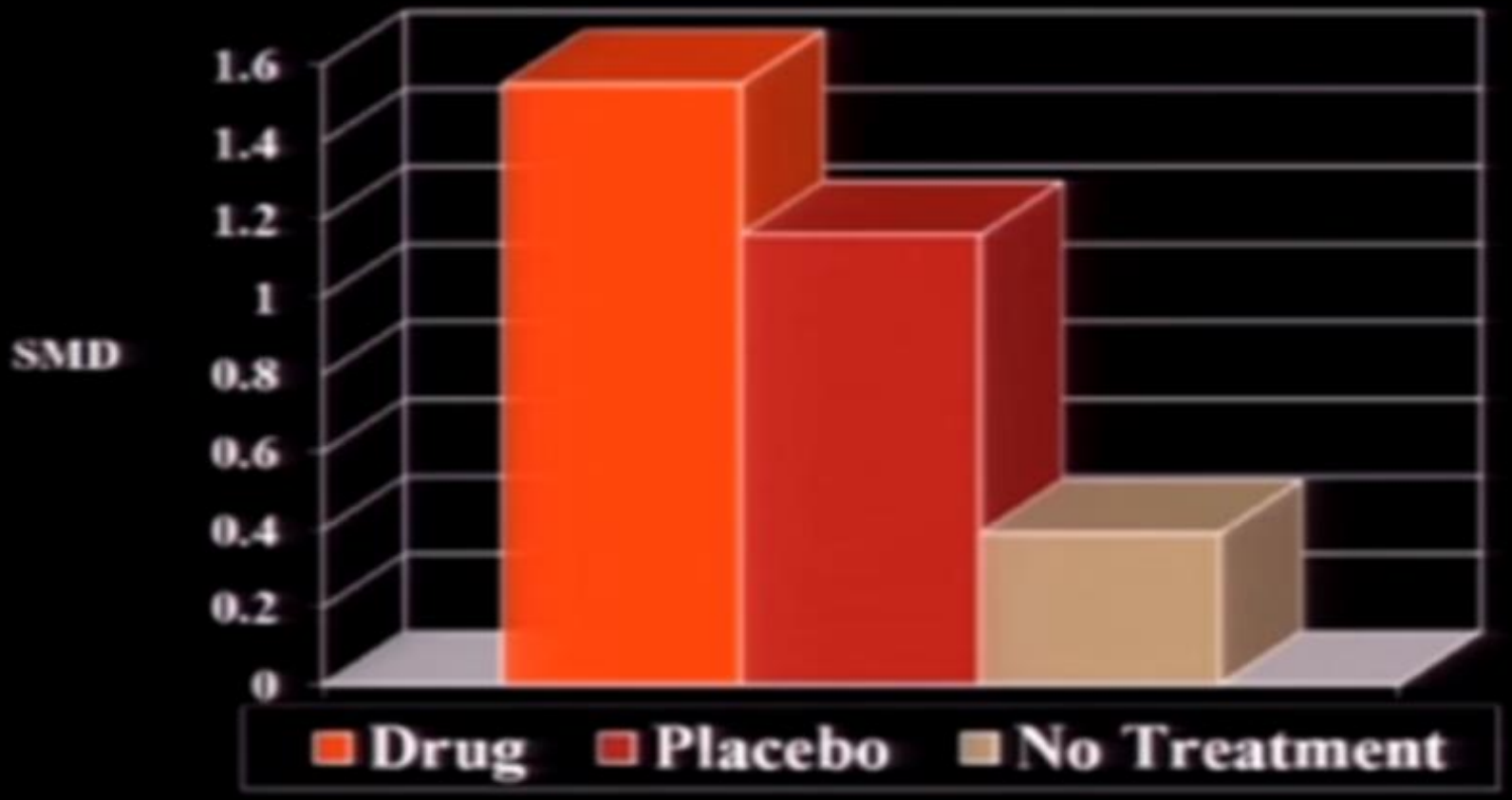
Placebo Surgery

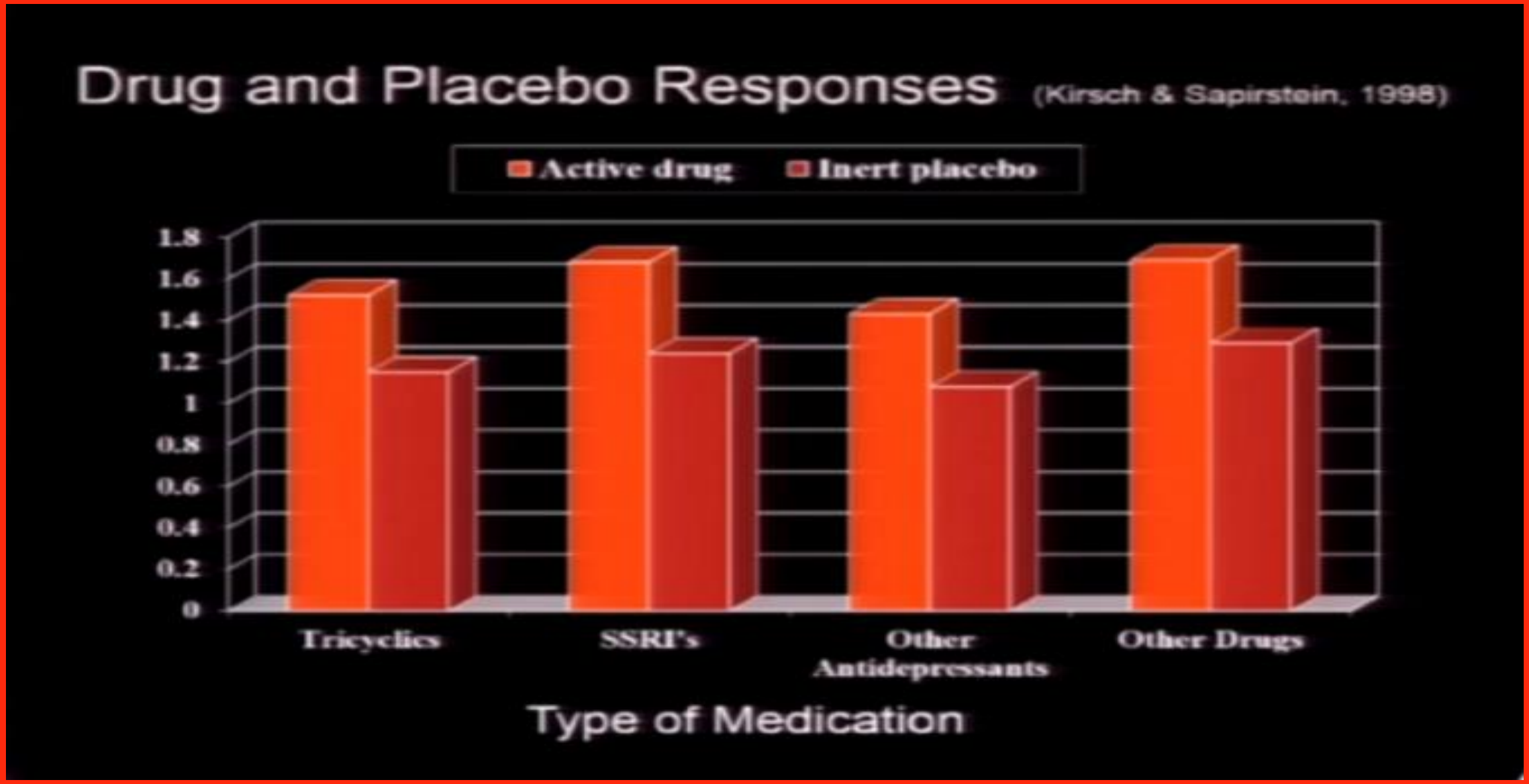
- Mammary ligation for angina
  - *Real surgery: 73% improvement*
  - *Sham surgery: 83% improvement*
- Arthroscopic surgery for osteoarthritis of the knee
  - *2 Weeks: Placebo > real surgery*
  - *1 year: Placebo > real surgery*
  - *2 years: No difference*

Pain and depression are very responsive to placebo but bilateral infection, not at all.



Meta-analysis of the placebo effect in depression (Kirsch & Sapirstein, 1998)

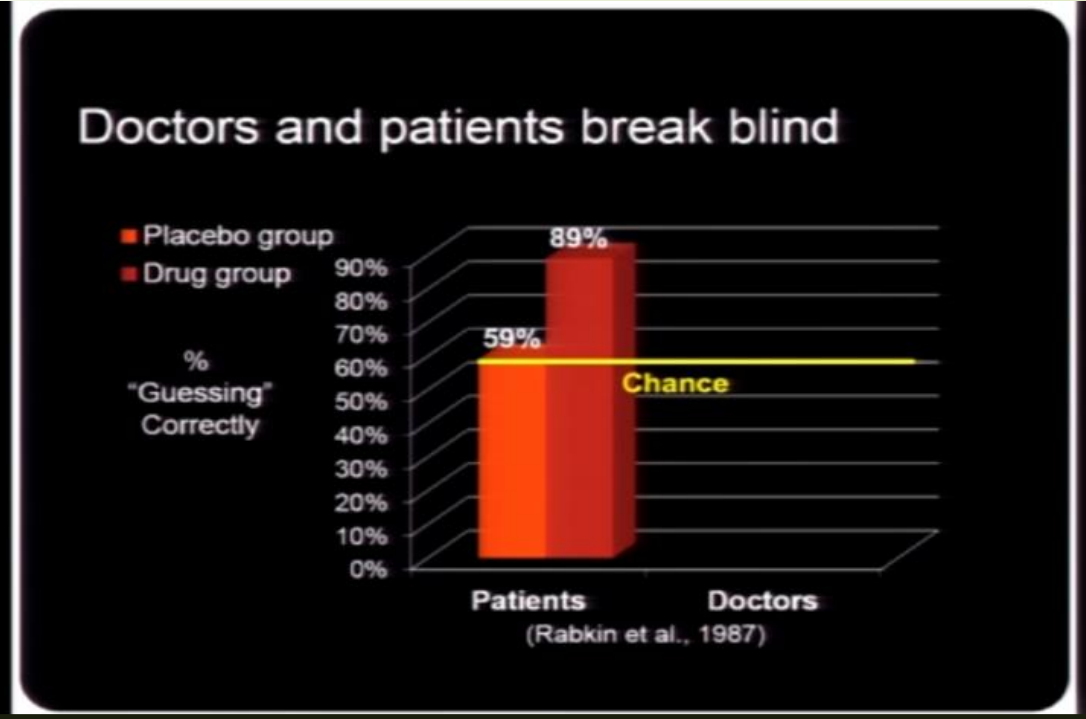



Drug and Placebo Responses
(Kirsch & Sapirstein, 1998)
Active drug
Inert placebo
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Tricyclics
SSRI's
Other Antidepressants
Other Drugs
Type of Medication

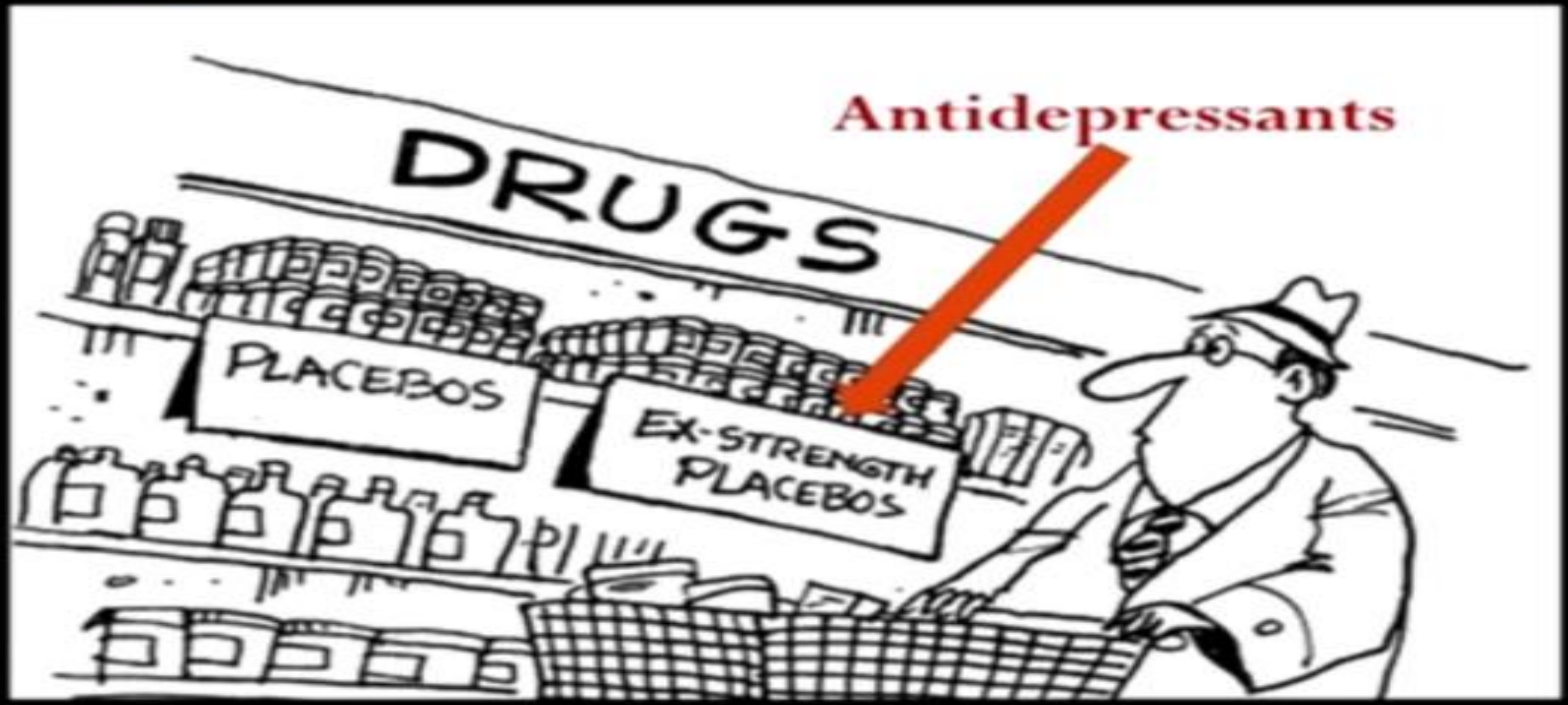

SIDE
EFFECTS


Why are Side Effects Important?
INFORMED CONSENT

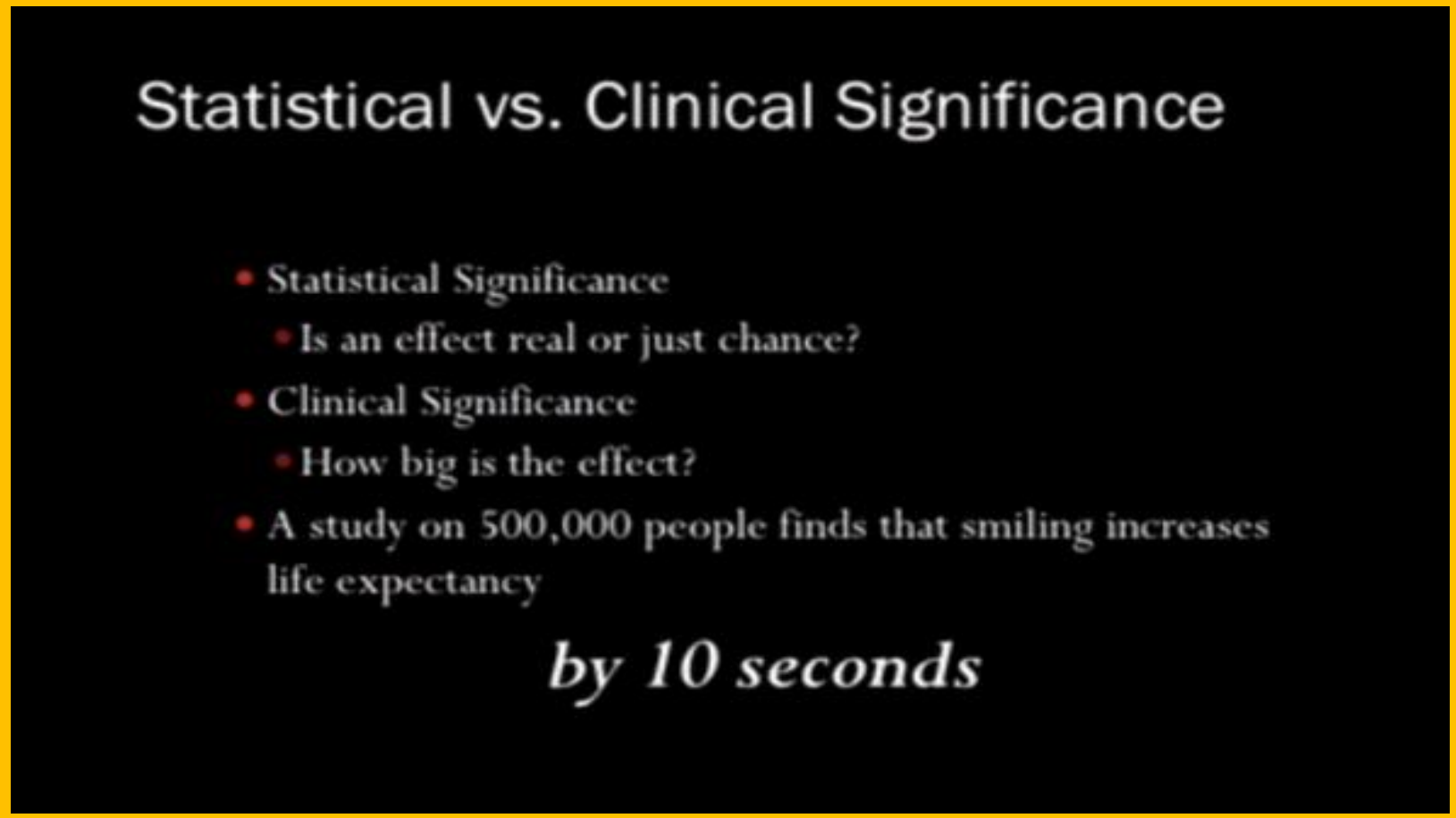
Many outcome studies are flawed because patients typically know the side effects of the medication and can guess correctly if they have the true medication, but controls are only 50% accurate in guessing.



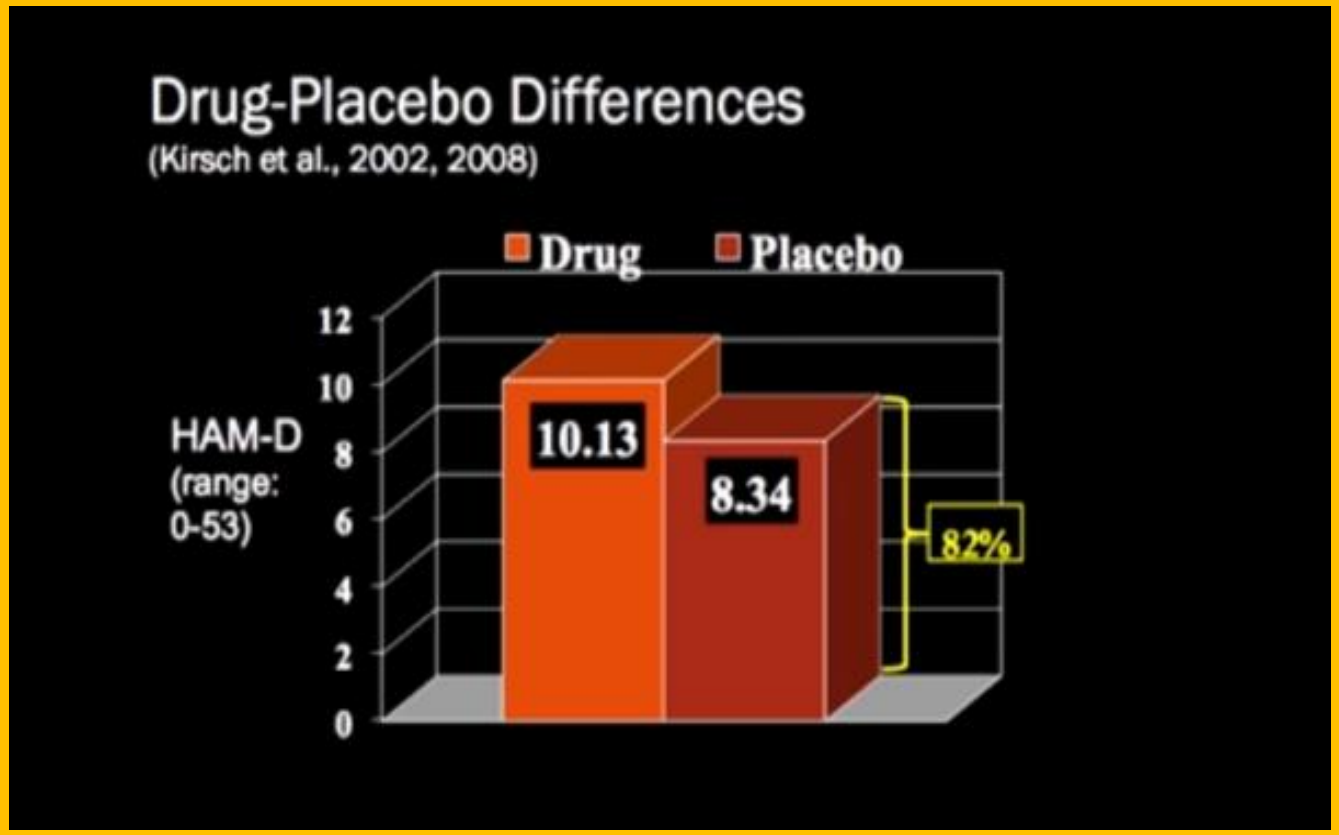
Drug-placebo differences in clinical trials



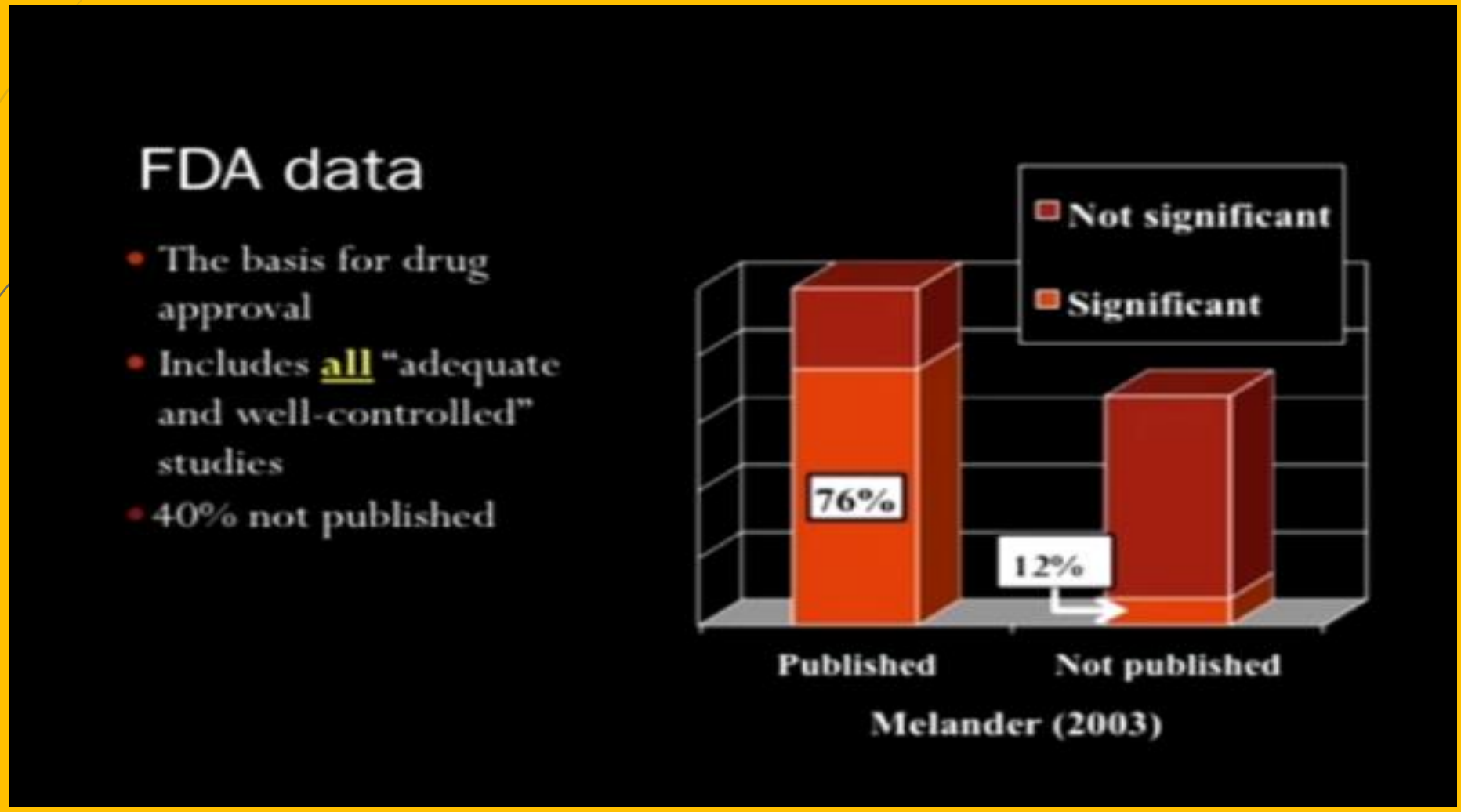
Many studies show a statistical difference with antidepressants but little to no clinical difference.



Most studies use the Hamilton Scale to measure the impact of the medication and drug-placebo trials typically find a statistical difference of only about two points, but any meaningful clinical difference requires a score of about 7 to be clinically meaningful.



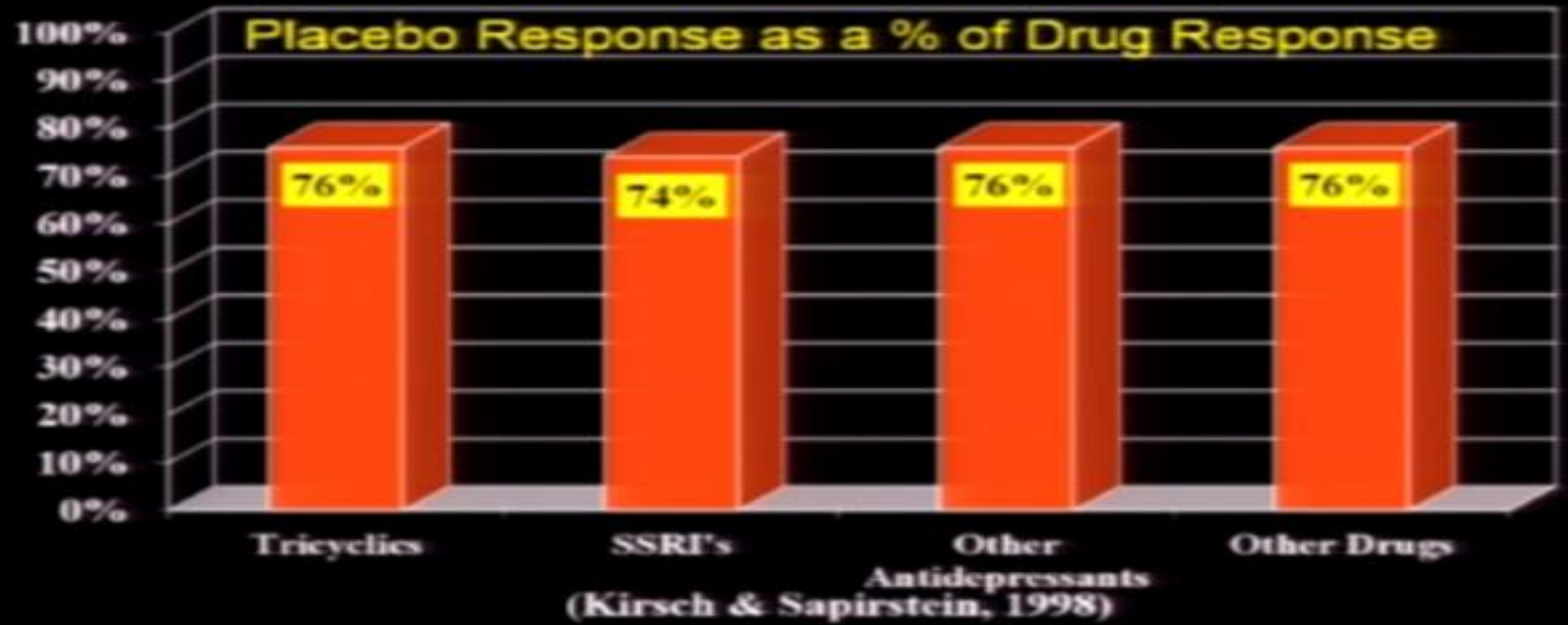
The FDA only requires only a few studies that show statistical efficacy (not clinical) to get the drug approved and the failed do not need to be reported so failed trials get buried. Under the Freedom of Information Act, we can acquire the failed studies. Not so surprising, the published studies on antidepressants show a 76% statistical response rate, but the ones not published show only a 12% statistical response rate.



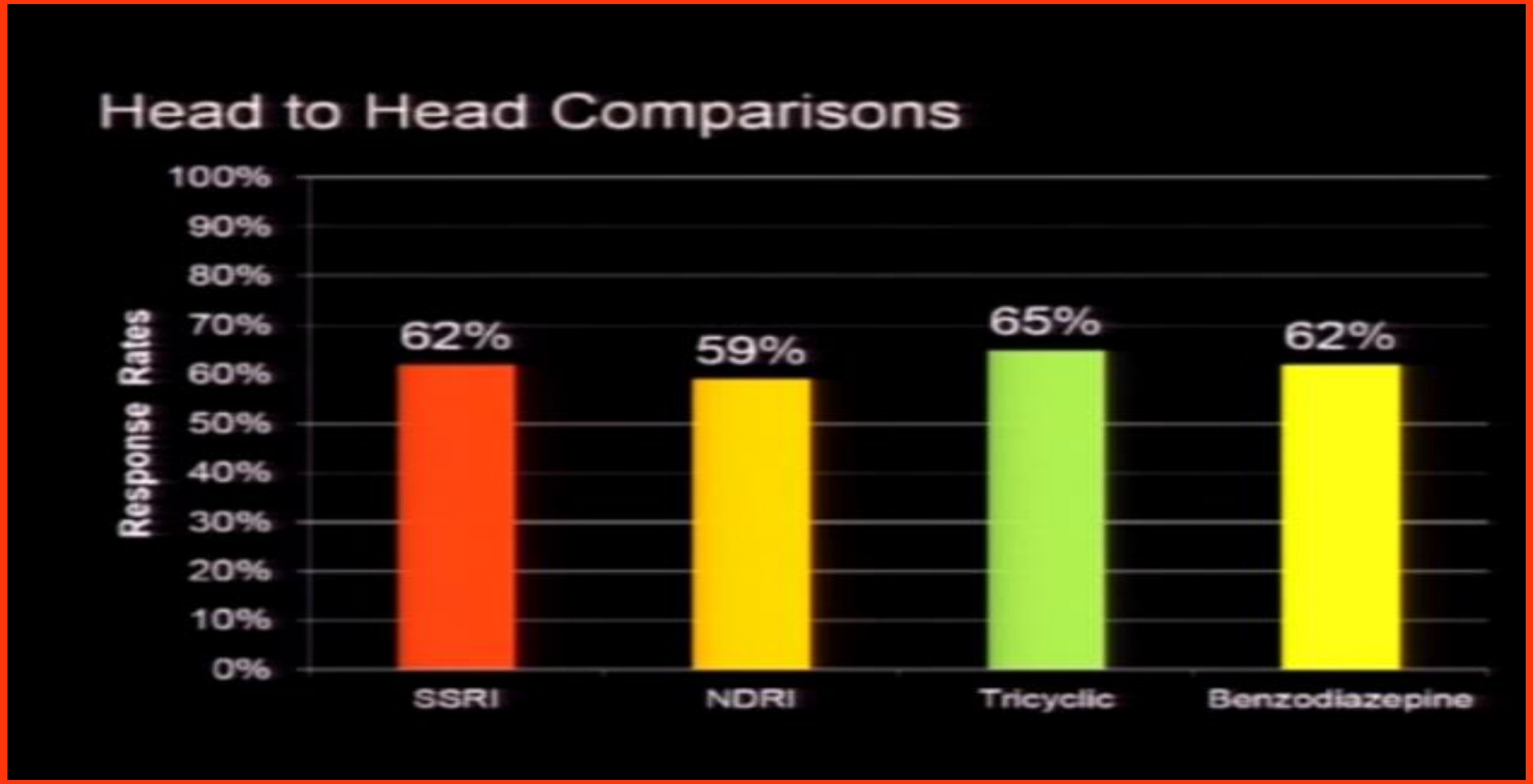
"We all agree...The difference in improvement between drug and placebo is rather small."

(Tom Laughren, MD
Director, FDA Division of Psychiatry Products)

It doesn't matter which AD you take



(Kirsch & Sapirstein, 1998)

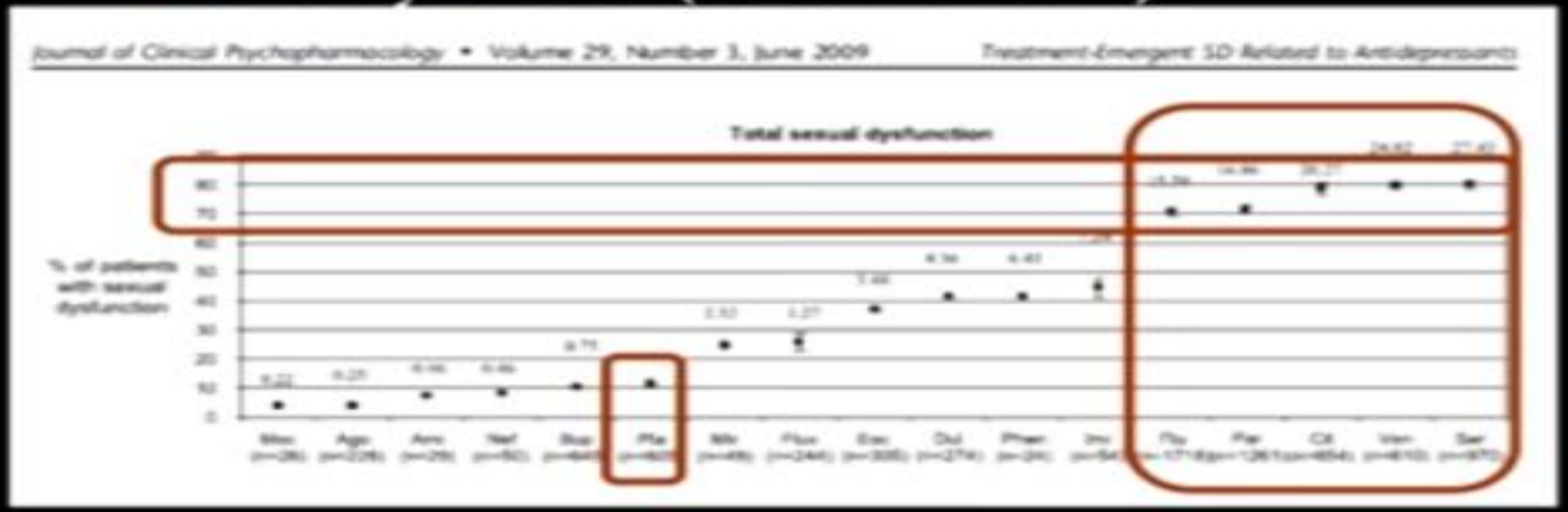

Head to Head Comparisons
Response Rates
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
62%
59%
65%
62%
SSRI
NDRI
Tricyclic
Benzodiazepine

Benefits vs Risks

- **Side Effects**
  - Sexual dysfunction (70-80% on SSRIs)
  - Weight gain (25%)
  - Insomnia (20%)
  - Diarrhea (15%)
  - Nausea (15%)
  - Anorexia
  - Bleeding
  - Forgetfulness
  - Seizures…

Benefits vs Risks

- Side Effects
  - Sexual dysfunction (70-80% on SSRIs)



Antidepressant
Discontinuation
Syndrome

The Hippocratic Oath

In order for a treatment to do no harm, it must improve on natural recovery rates.

In Conclusion

- To restate my opening comment, I am not recommending that you or your child take or not take any medication. Rather, I suggest that you apprise yourself of the outcome research as best you can before you take any psychotropic medication. Empower yourself to ask your prescriber about any concerns you might have to include the content of this PowerPoint. Robert Whitaker, Dr. Peter C Gøtzsche, and Dr. Irving Kirsch have done us a great service in offering the other side of medication dogma and I believe that we owe them much gratitude for their courage in challenging us on the need for thoughtful consideration before we embark down the medication highway.