



**Program in Placebo Studies  
& the Therapeutic Encounter**  
Beth Israel Deaconess Medical Center  
Harvard Medical School



# The Emperor's New Drugs: Medication and Placebo in the Treatment of Depression

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I have no affiliations, sponsorships, honoraria, monetary support or conflict of interest from any commercial source.



26<sup>th</sup> February 2008



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## Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration


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# THE TIMES

Tuesday February 20 2018 11:00am (UK) £10 (incl. VAT)

709

## Depression drugs don't work, says new study

• **17th world leaders' summit** (p. 10)

• **Baroness** (p. 12)

**Healthcare**

Millions of people taking common antidepressant drugs may be taking them for nothing, a new study says.

Scientists studying mental health patients in the United Kingdom found that 10% of patients were taking antidepressants but not responding to them.

The study, published in the journal *Journal of Clinical Pharmacy and Therapeutics*, found that 10% of patients taking antidepressants were not responding to them.

The study involved 1,000 patients taking antidepressants. The researchers found that 10% of patients were not responding to their medication.

The researchers say that the study highlights the need for better diagnostic tools to identify patients who do not respond to antidepressants.

The study was led by researchers at the University of Manchester.

The researchers say that the study highlights the need for better diagnostic tools to identify patients who do not respond to antidepressants.

of 17th world leaders' summit in London. The summit is a key event in the calendar of the British state, which is expected to be held in the capital city of London.

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## Cheers for head girl who escaped killer

Head girl who escaped killer who was shot dead in London last night.

### IN THE NEWS

#### Jersey, the island of secrets and whippers

Full coverage of the Jersey news and analysis. Jersey is a key part of the British state, which is expected to be held in the capital city of London.

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Full coverage of Nicolas Sarkozy's visit to the UK. Sarkozy is a key figure in the French political scene.

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Full coverage of Marks & Spencer's expansion into the Indian market. M&S is a key retail brand in the UK.

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Full coverage of the political scene. The political scene is a key part of the UK's governance.

Trends, triumphs and tragedies  
Unpicking the Oscars red carpet

62 **Current**



Rowan Williams  
Teenagers need space,  
not buzzers

Comment Page 34

Nancy Banks-Smith  
Portillo on Thatcher or  
How I Missed Becoming  
Leader By A Whisker

TV Review  
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66p  
Tuesday 23 Oct 11  
Published in London and  
Manchester  
guardian.co.uk

# the guardian

## Prozac, used by 40m people, does not work say scientists



Analysis of unseen trials and other data concludes it is no better than placebo

Small study by scientists

Prozac, the bestselling antidepressant used by an estimated 40 million people in the world, does not work, according to a new study published today.

The study, published in the journal *PLoS One*, says that the drug is no better than a placebo.

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## Obama camp claims smear over turban photograph

From Washington

Obama's camp has accused a group of conservative bloggers of spreading a false story that he had been wearing a turban during a campaign event.

The group, known as the "Obama Turban Club", claims that Obama was seen wearing a turban during a campaign event in New York City.

Obama's camp has denied the claim, saying that Obama was wearing a hat during the event.

The group has also accused Obama's camp of spreading a false story that Obama was wearing a turban during a campaign event.

Obama's camp has denied the claim, saying that Obama was wearing a hat during the event.

Comment on page 10





# THE INDEPENDENT



(Ireland, €1.90) 80p

Tuesday 26 February 2008

www.independent.co.uk

0203 778600



## THE FASHION OSCARS

Susannah Frankel's verdict on Hollywood's big night **Pages 6-7**

**PLUS BOYD TONKIN ON THE GENIUS OF CORMAC MCCARTHY** In Extra

# Antidepressant drugs don't work – official study



**PROZAC**



**SEROXAT**



**EFEXOR**

**75**

### Manufacturers 'withheld'

By Jeremy Lawrence  
Health Editor

They are among the highest-selling drugs of all time, the "big boys" that supposedly lift the mood of those

who suffer depression and are taken by millions of people in Britain every year. But one of the largest studies of modern antidepressant drugs has found that they have *no* clinically significant effect. In other words, they don't work. The finding will send shock waves

through the medical profession and patients and raises serious questions about the regulation of the multi-billion pharmaceutical industry, which will be accused of withholding data on the drugs. It also came as Alan Johnson, the

Health Secretary, announced that 1,600 prescriptions are to be withdrawn during the next three years to provide patients with access through the GP surgery to "alternative treatments" for depression, instead of drugs. In a £170m initiative. The

CONTINUED ON PAGE 1

## Health IN EXTRA

### Get in shape - without going to the gym



### PLUS My double-lung transplant



### The ten best beauty serums

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FEBRUARY 8, 2010

# Newsweek

## ANTIDEPRESSANTS DON'T WORK

THE DEBATE OVER  
THE NATION'S  
MOST POPULAR PILLS

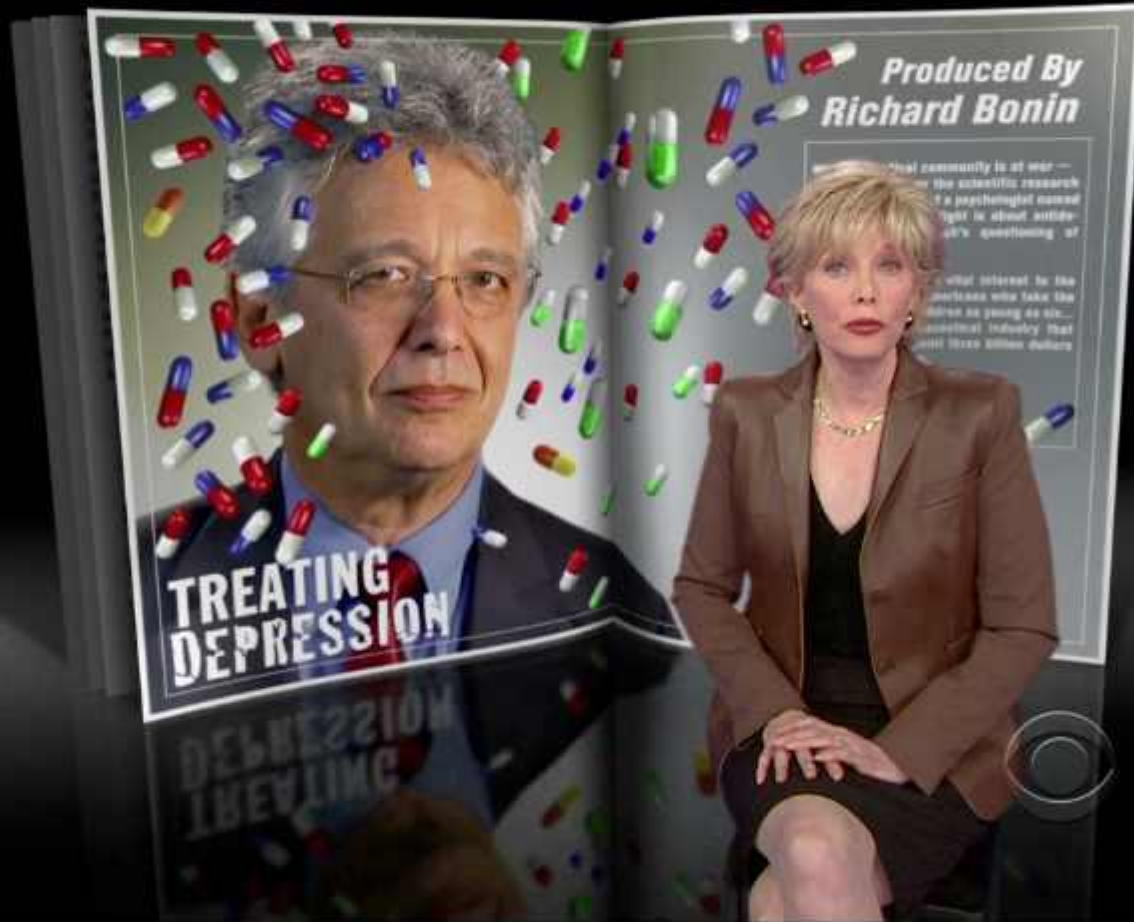
BY SHARON BEGLEY





# 60 MINUTES

February 19, 2012






MATT GROENING



How it happened

Meta-analysis of published  
antidepressant trials  
(Kirsch & Sapirstein, 1998)

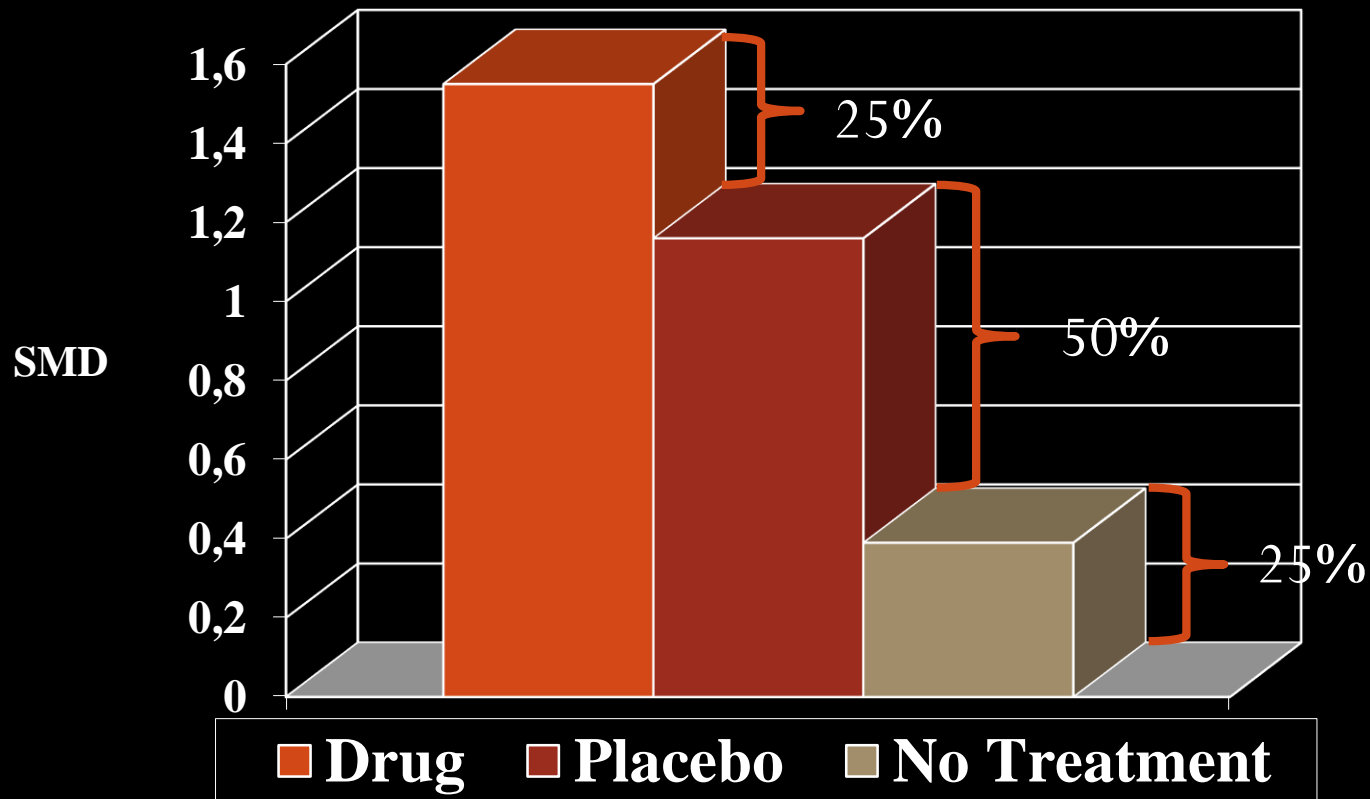


A cartoon illustration of a man in a blue suit and glasses standing at a podium on a stage. A banner above him reads "PLACEBOS ANONYMOUS". A speech bubble next to him says "I don't really have a problem." The stage is lit with a yellow spotlight, and there are green curtains on either side. In the foreground, the silhouettes of an audience are visible.

PLACEBOS  
ANONYMOUS

I don't really have a  
problem.

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



“Listening to Prozac but Hearing Placebo”  
(1998)

The Critics:

Your analysis is flawed

“It derives from a miniscule group of unrepresentative,  
inconsistently and erroneously selected articles” (Klein, 1998)



# Freedom of Information Act FDA Data

Fluoxetine

Paroxetine

Sertraline

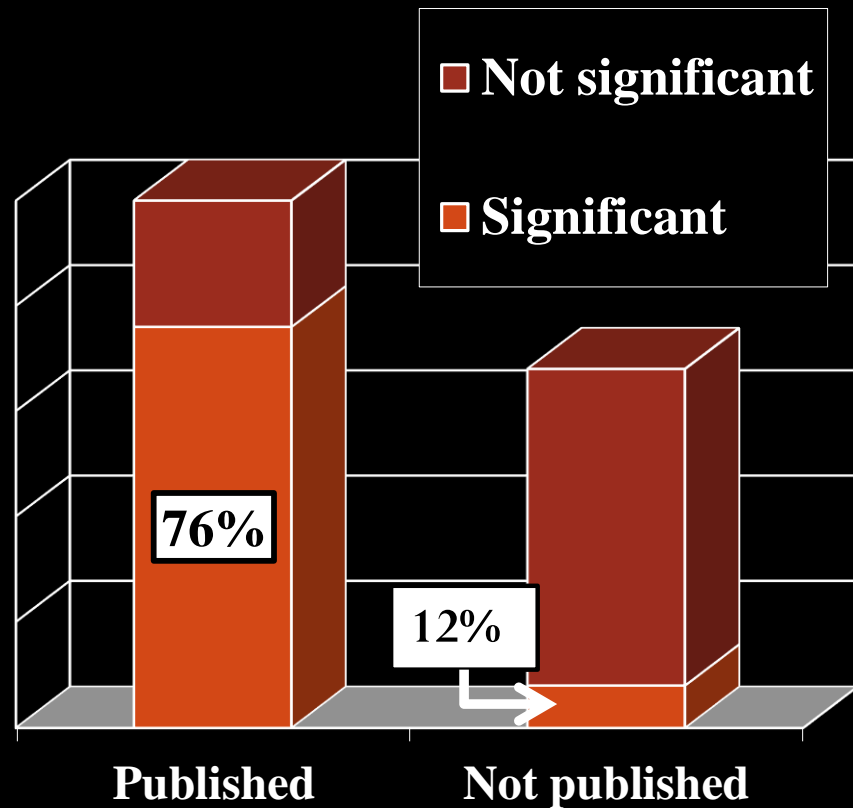
Venlafaxine

Nefazodone

Citalopram

# FDA data

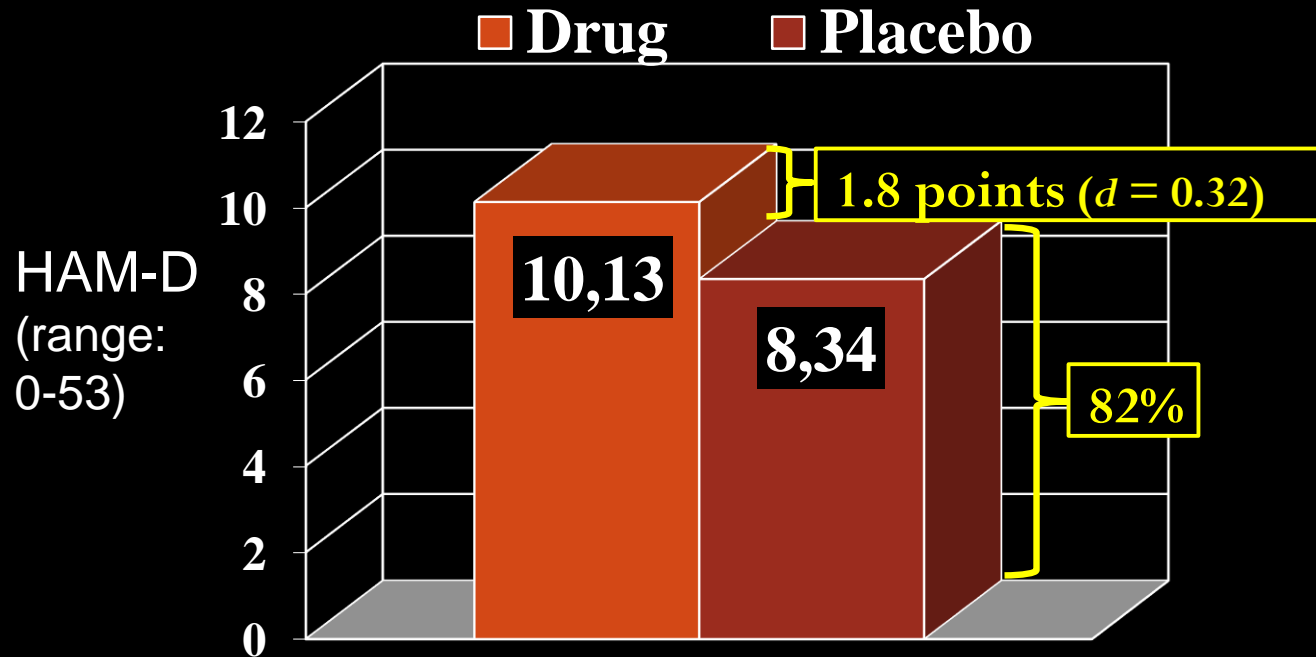
- The basis for drug approval
- Includes **all** “adequate and well-controlled” studies
- 40% not published



Melander (2003)

# Drug-Placebo Differences

(Kirsch et al., 2002, 2008)



**NICE Criteria for Clinical Significance:**  
**3 points ( $d = 0.50$ )**

# Statistical vs. Clinical Significance

- Statistical Significance
  - Is an effect real or just chance?
- Clinical Significance
  - How big is the effect?
- A study on 500,000 people finds that smiling increases life expectancy

*by 10 seconds*

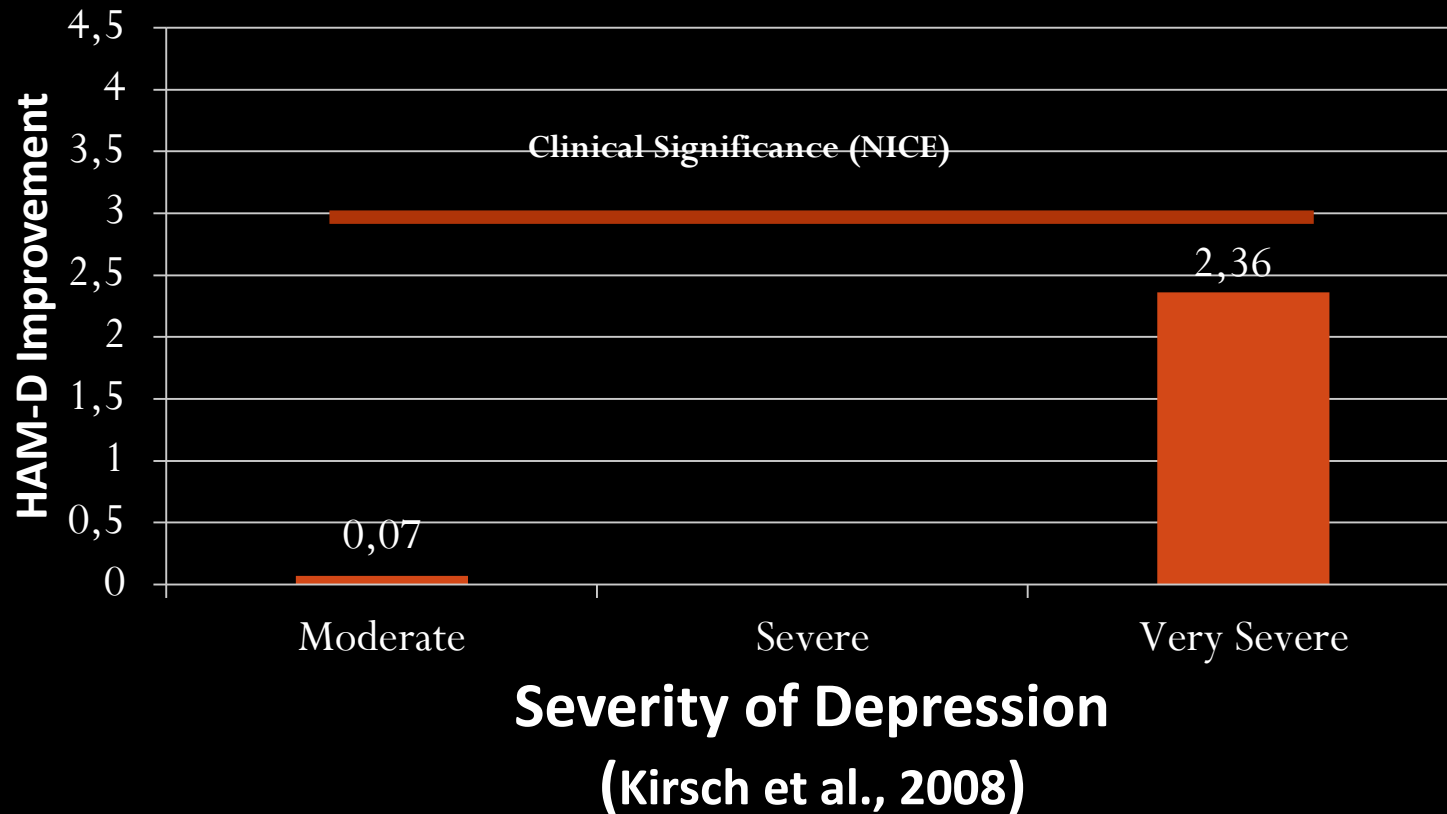


## The Critics in 2002:

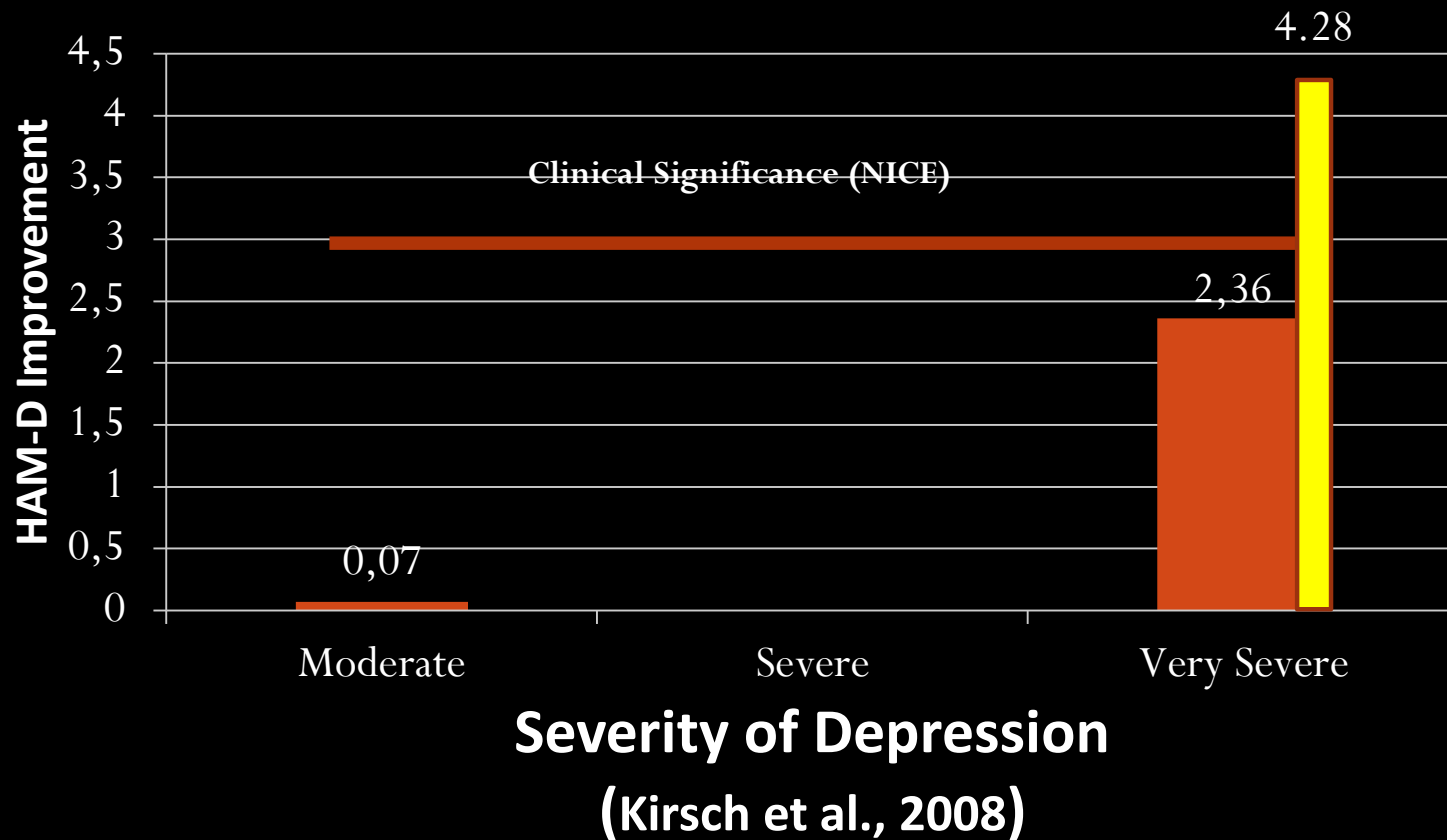


“The patients weren’t depressed enough”

# Drug-Placebo Differences



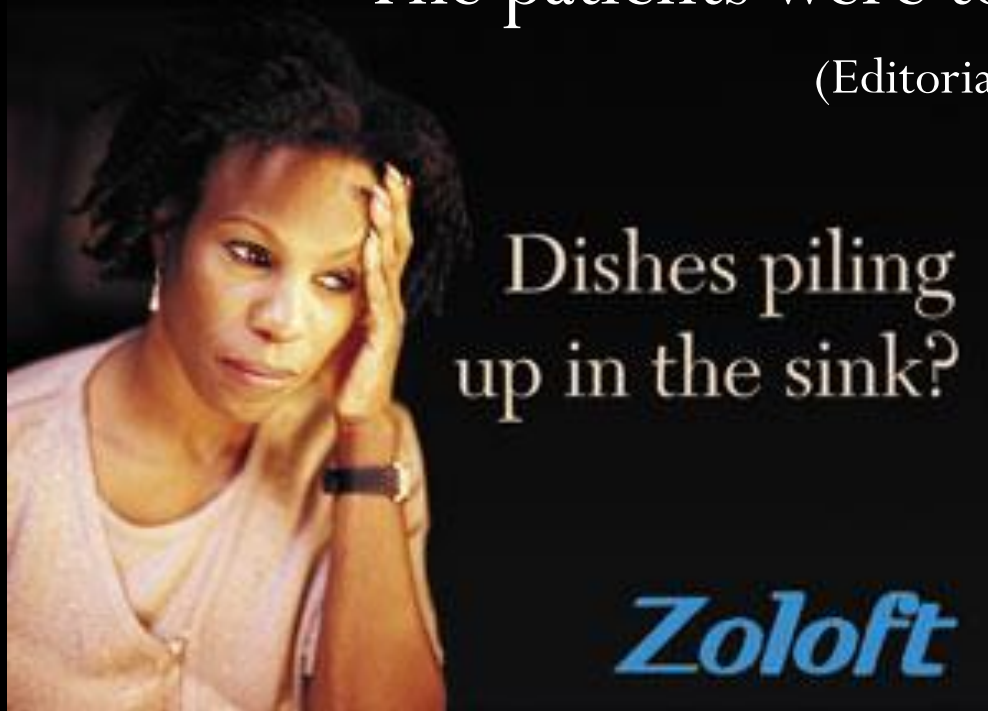
# Drug-Placebo Differences



The critics in 2008:

The patients were too depressed!

(Editorial, *Nature Reviews Drug Discovery*, 2008)

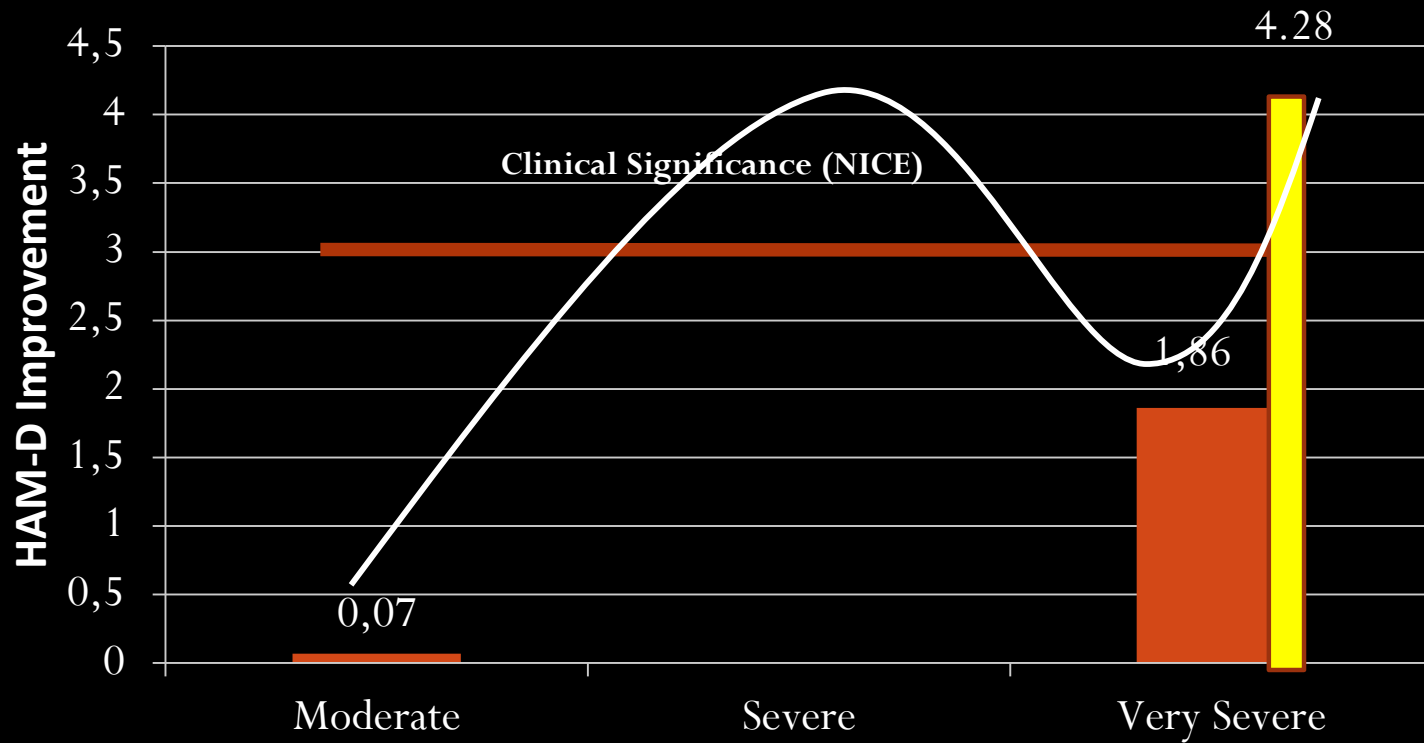
A black and white photograph of a woman with dark, curly hair, looking down with a sad expression. She is resting her head on her right hand. The image is part of a Zoloft advertisement. The text 'Dishes piling up in the sink?' is overlaid on the right side of the image, and the Zoloft logo is at the bottom right.

Dishes piling  
up in the sink?

**Zoloft**



# Drug-Placebo Differences

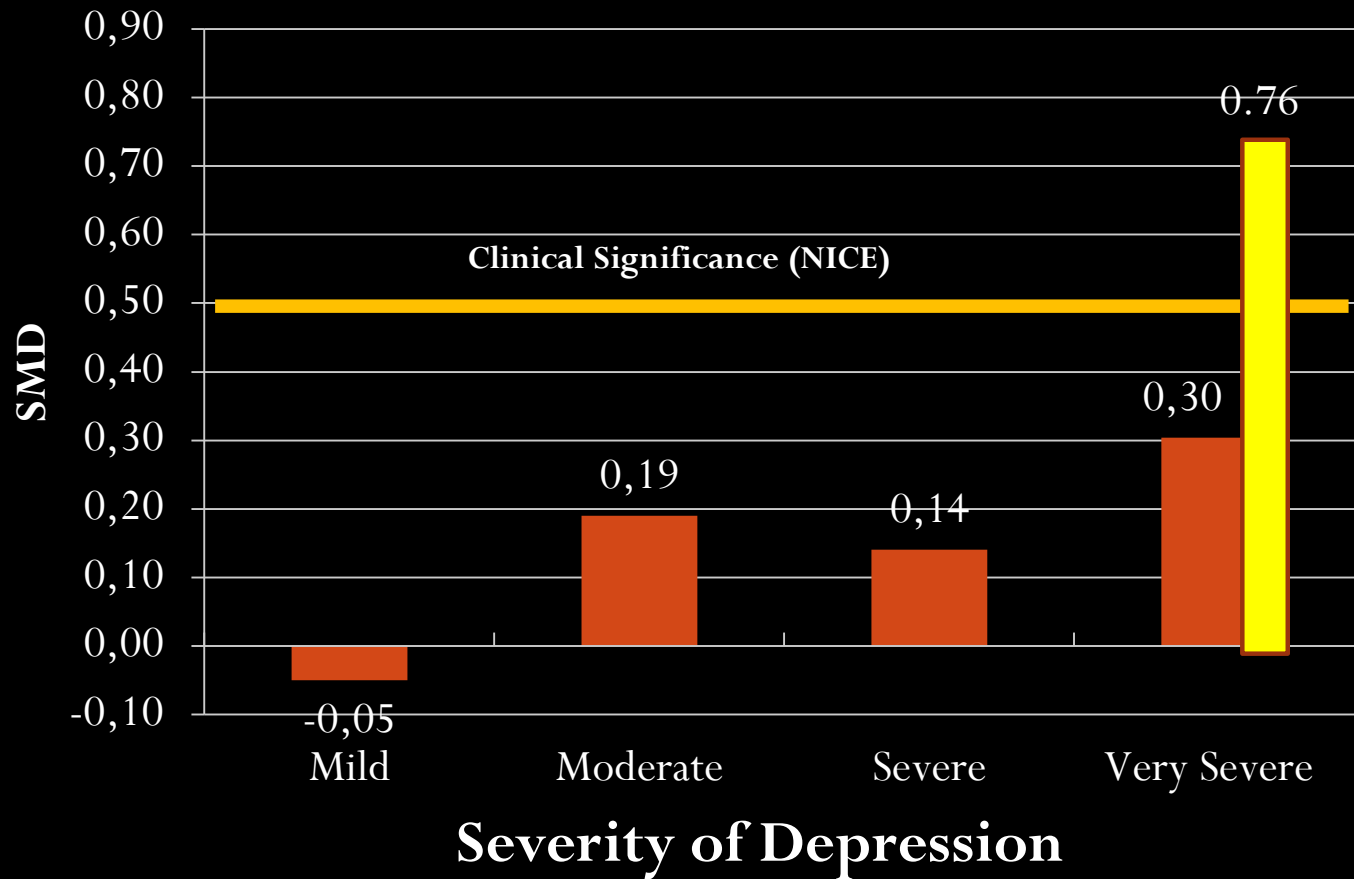


**Severity of Depression**

(Kirsch et al., 2008)

# Independent Replication

(Fournier et al., 2010)



## The Critics:

The NICE criteria are arbitrary

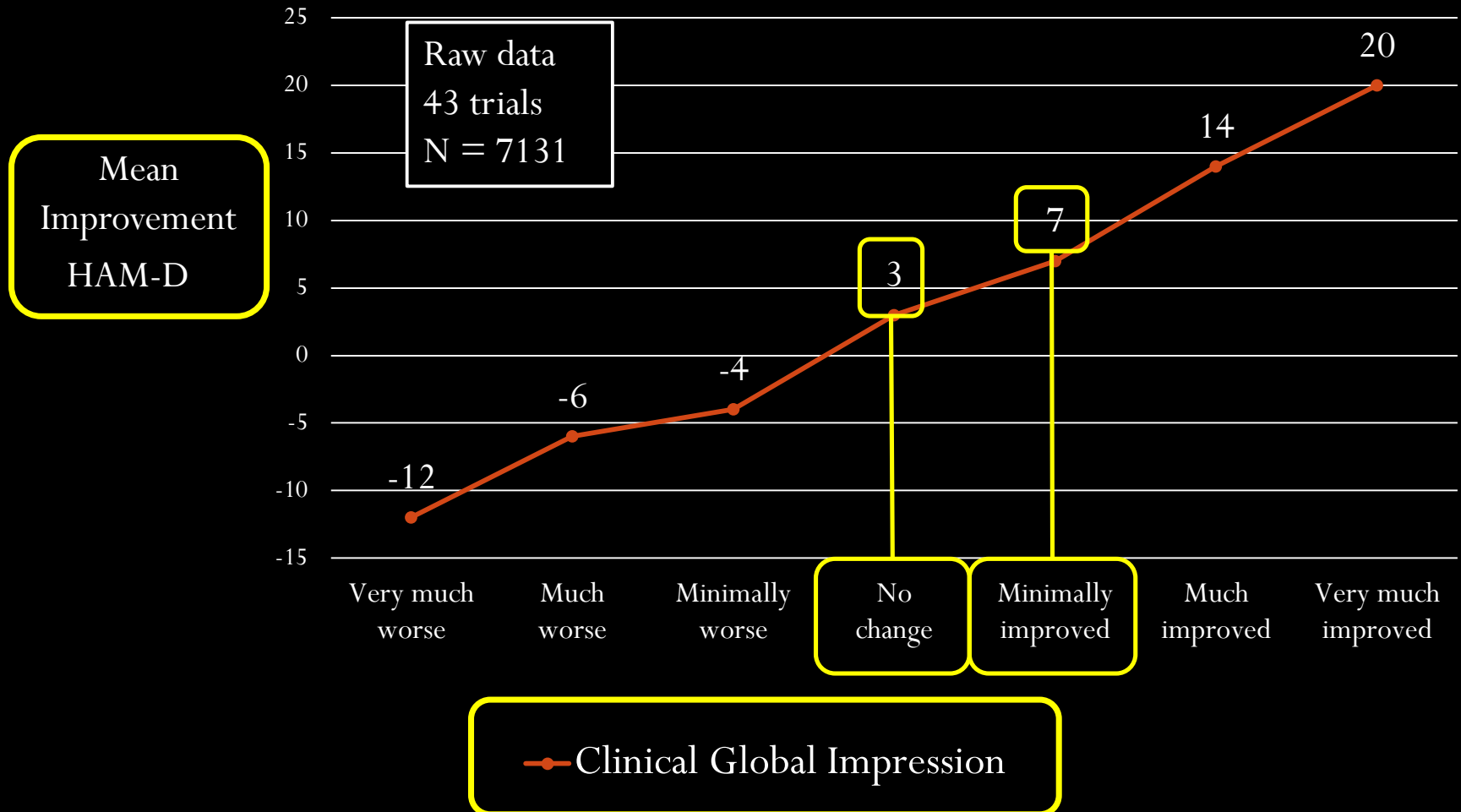
as arbitrary as criteria for:

- Statistical significance:  $p < .05$

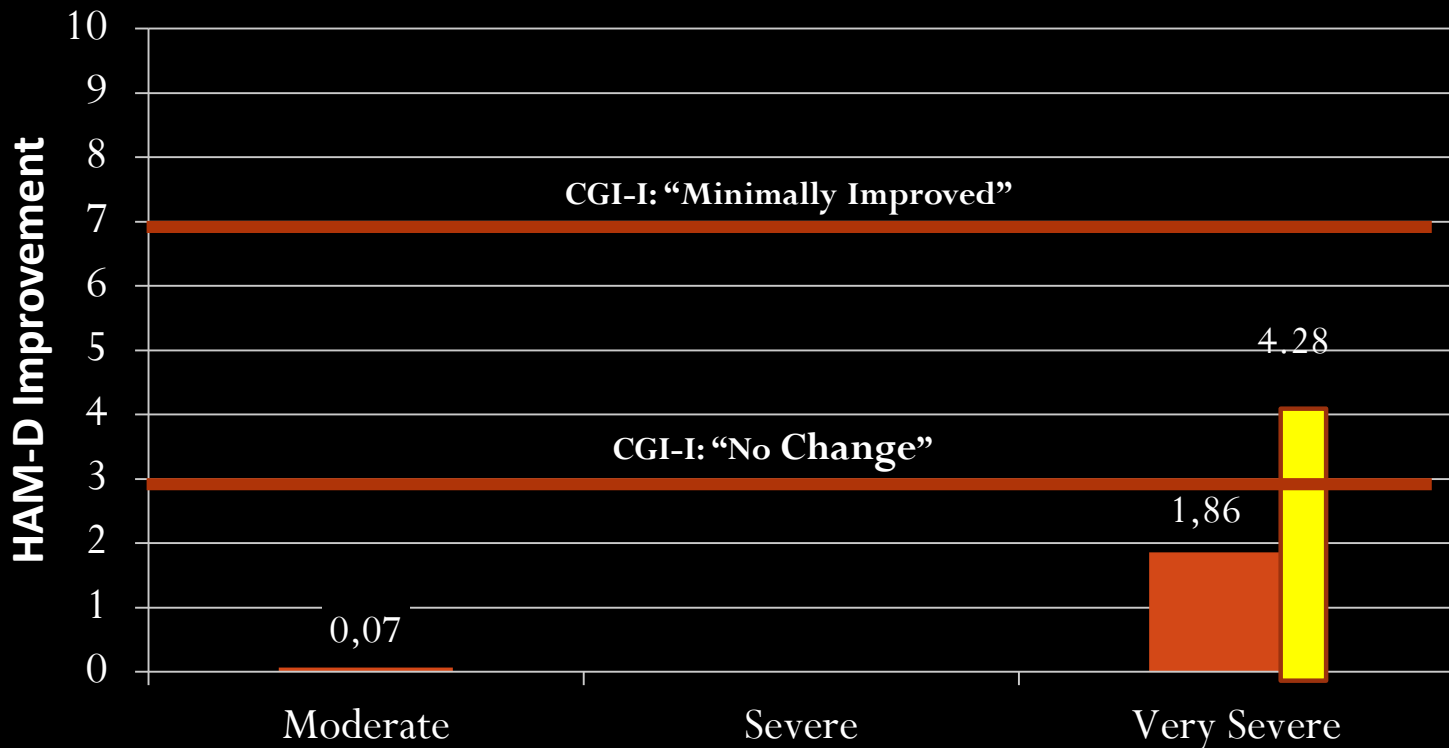
What would a non-arbitrary criterion be?

# HAM-D and CGI-Improvement

(Leucht et al., 2013; Moncrieff & Kirsch, 2015)



# Drug-Placebo Differences



**Severity of Depression**

(Kirsch et al., 2008)



# The critics' last resort:

"Antidepressants work...everybody knows they work" (Nutt, 2008)



"Millions of content patients can't be that wrong" (Werner, 2008)

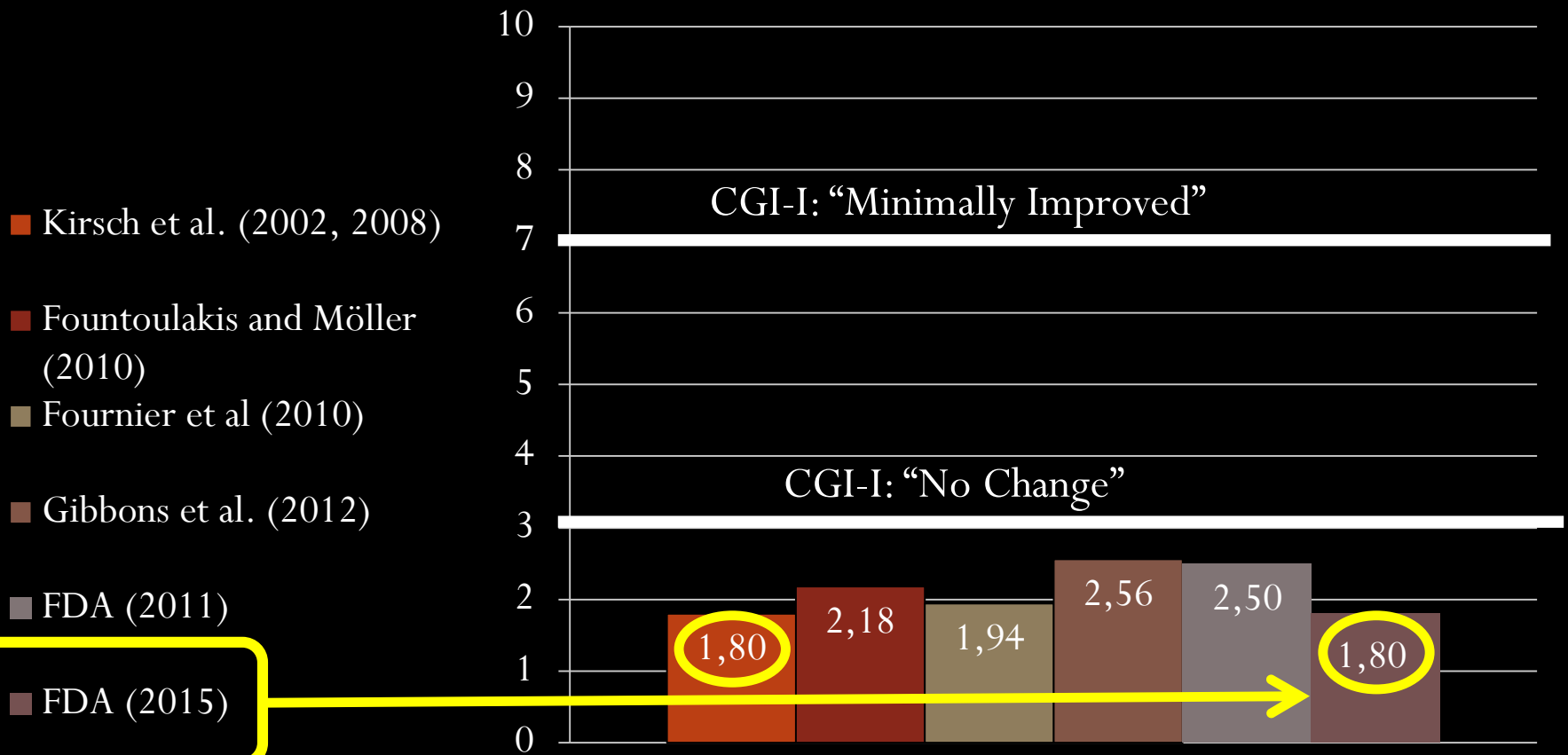
# History of Medicine

Treatments that have worked for millions:

- Bloodletting
  - Lizard's blood
  - Crocodile dung
  - Pig's teeth
  - Putrid meat
  - Fly specks
  - Frog's sperm
  - Powdered stone
  - Human sweat
  - Worms
  - Spiders
  - Furs
  - Feathers
- Honigfeld 1964

# Everyone gets the same results

## Drug-Placebo Differences (HAM-D)



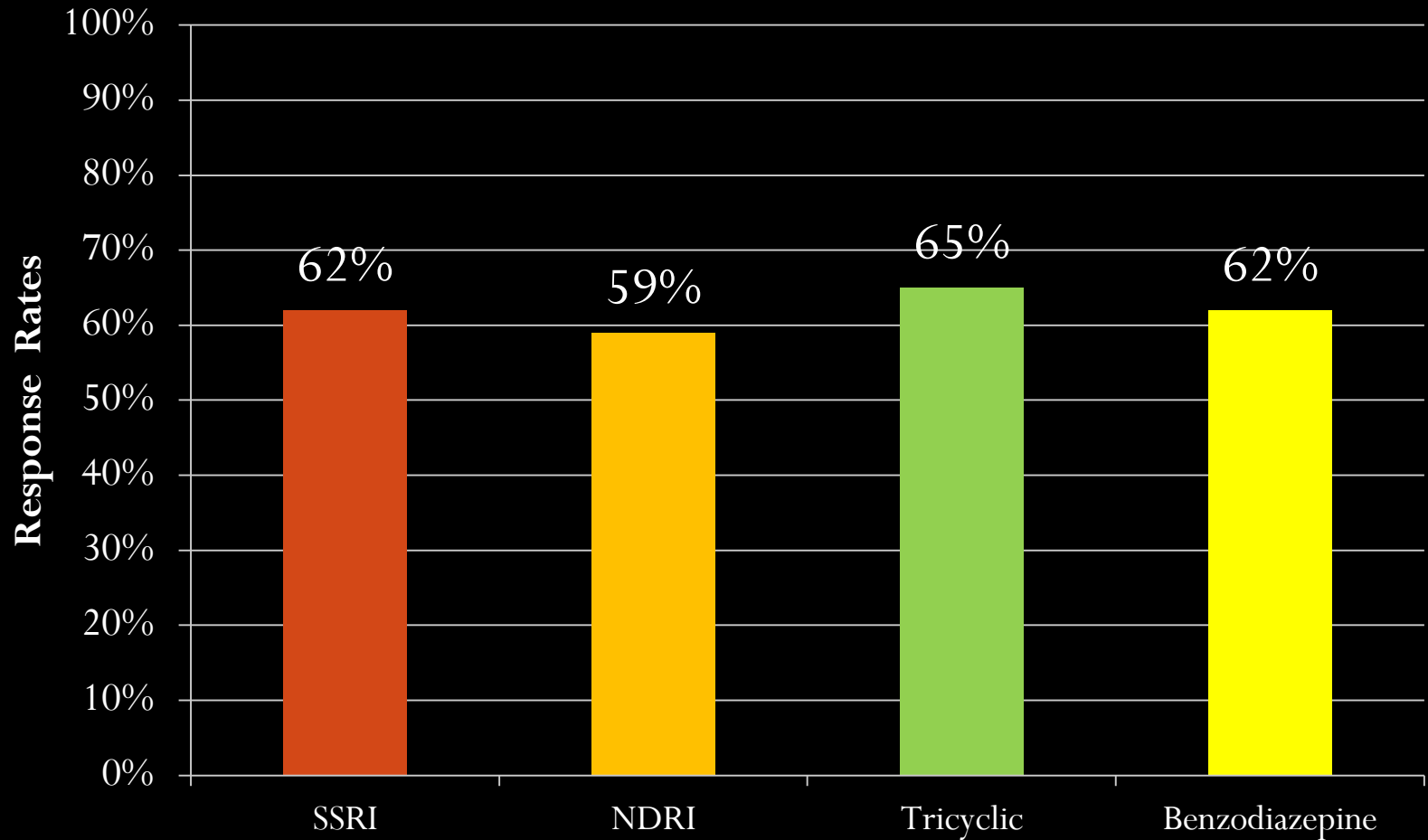
Patient level data - 23,295 patients - 92 trials

“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 antidepressant you take





# Tianeptine

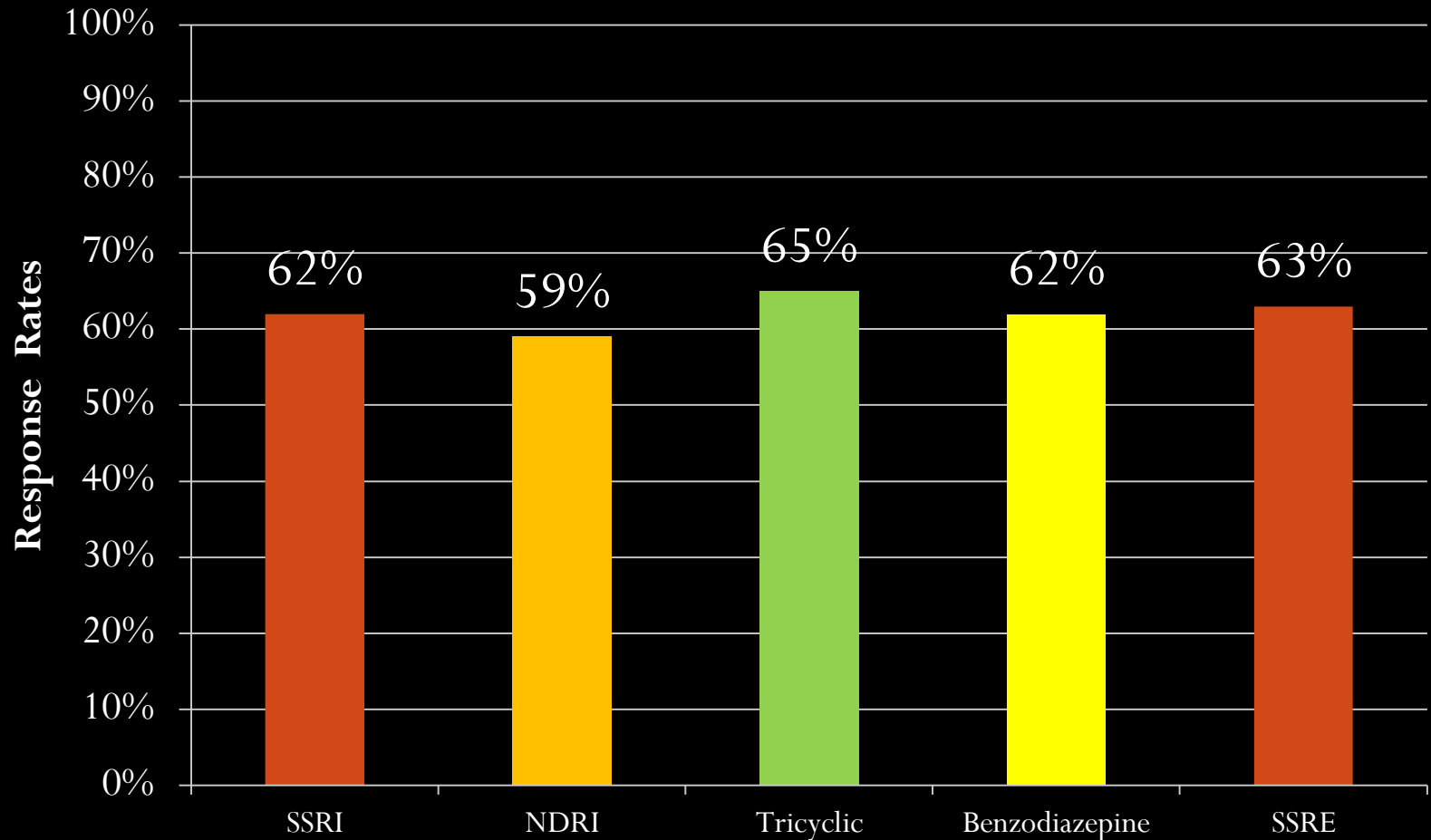
- **SSRI**

- **S**elective **S**erotonin **R**euptake **I**nhibitor

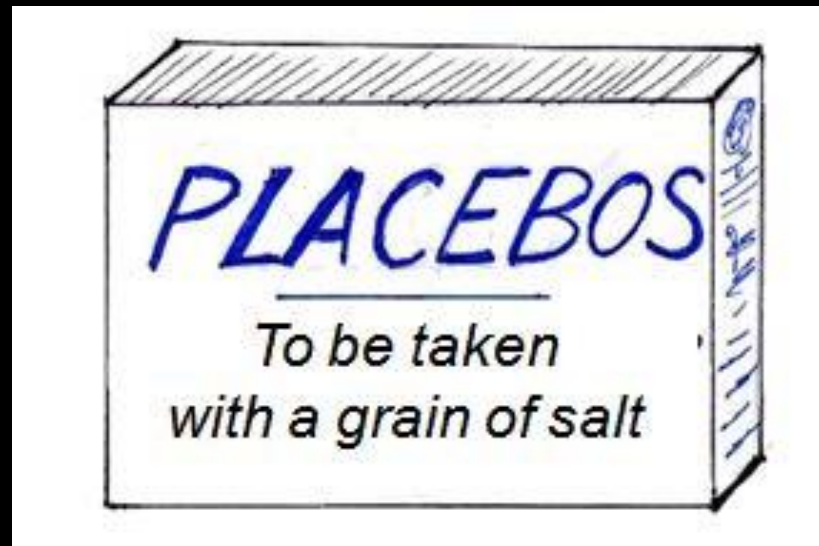
- **SSRE**

- **S**elective **S**erotonin **R**euptake *E*nhancer

# Head to Head Comparisons



What do you call pills,  
the effects of which are independent  
of their chemical composition?



How Should Depression be Treated?

Prescribe Antidepressants as Active  
Placebos?

## Benefits vs Risks

- **Side Effects**
  - Sexual dysfunction (75% on SSRIs)
  - Weight gain (25%)
  - Insomnia (20%)
  - Diarrhea (15%)
  - Nausea (15%)
  - Anorexia
  - Bleeding
  - Forgetfulness
  - Seizures...

# Antidepressant Discontinuation Syndrome

## ANTIDEPRESSANT WITHDRAWAL IS HELL !

Flu-like aches  
and pains  
Fever  
Sweats  
Chills  
Runny nose  
Sore eyes  
Headache  
Dizziness  
Disequilibrium  
Motion sickness  
Spinning, swaying, lightheaded  
Unsteady gait, poor coordination  
Hung over or waterlogged feeling  
twitches  
Slurred speech  
Blurred vision  
Feeling of restless legs  
Drooling or excessive saliva  
Muscle cramps, stiffness,  
Uncontrollable twitching of mouth  
Tremor  
Abnormal smells or tastes  
Abnormal visual sensations  
Numbness, burning, or tingling  
Ringing or other noises in the ears  
Electric zap-like sensations in the brain  
Electric shock-like sensations in the body



Impulsivity  
Self-harm  
Panic attacks (racing heart, breathless)  
Agitation (restlessness, hyperactivity)  
Trembling, jittery, or shaking  
Confusion or cognitive difficulties  
Homicidal thoughts or urges  
Elevated mood (feeling high)  
Crying spells  
Chest pain  
Irritability  
Mood swings  
Nightmares  
Aggressiveness  
Manic-like reactions  
Auditory hallucinations  
Visual hallucinations  
Dissociation  
Feeling detached or unreal  
Excessive or intense dreaming  
Electric shock-like sensations in the body

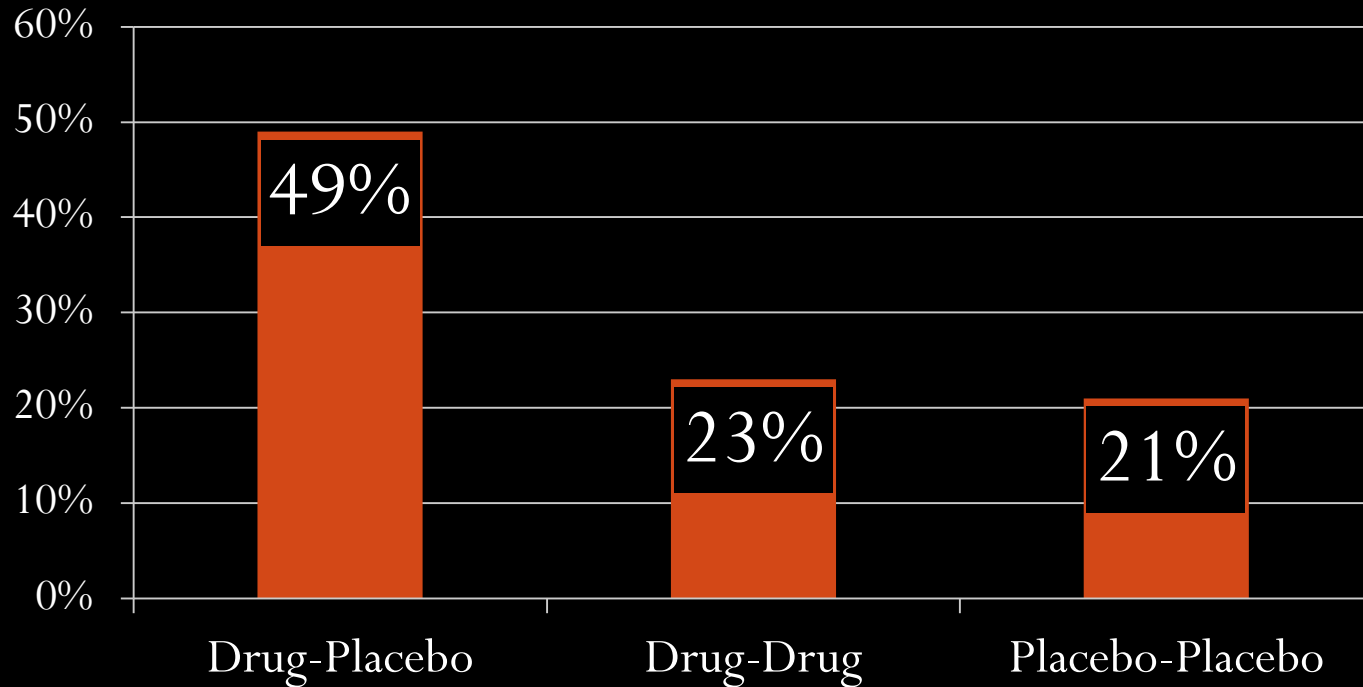
# Health Risks

- Children & Young Adults
  - Suicidal behaviour
  - Violent crime
- Elderly
  - Stroke
  - Death from all causes
- Pregnant women
  - Miscarriage
  - Babies born with
    - birth defects, persistent pulmonary hypertension, autism, neonatal abstinence syndrome (30%)
- Everyone
  - Diabetes
  - **Relapse**



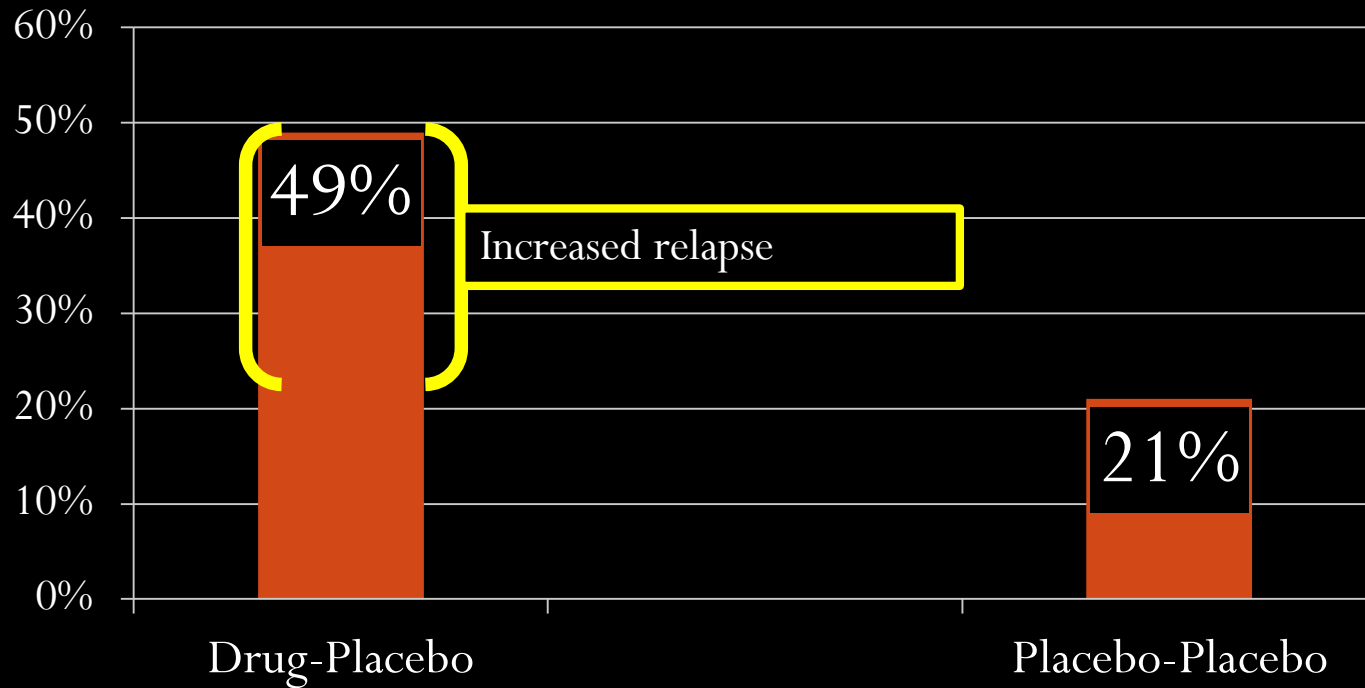
# Continuation and Discontinuation Trials

(Andrews et al., 2010, 1912; Williams et al., 2009)

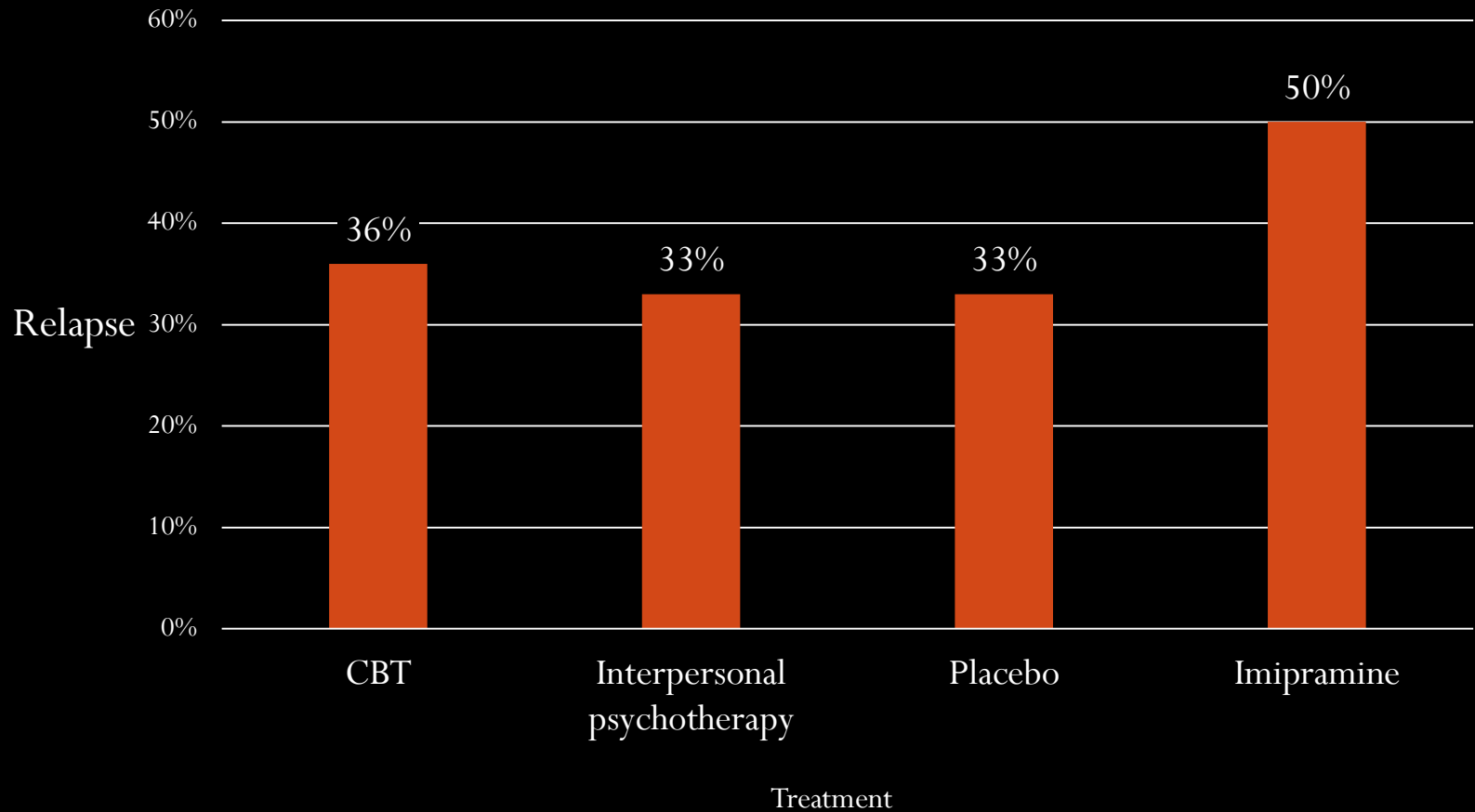


# Continuation and Discontinuation Trials

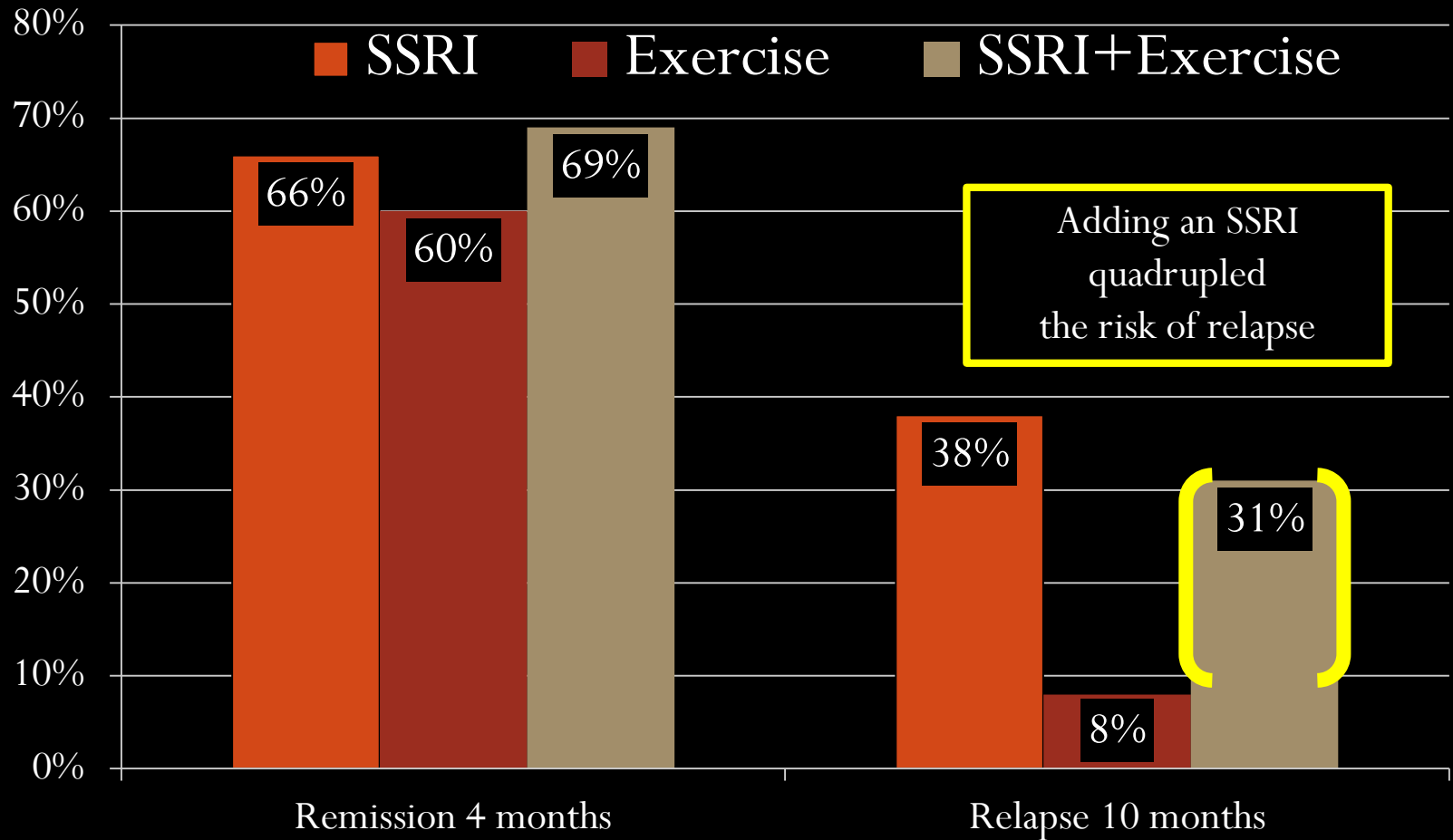
(Andrews et al., 2010, 1912; Williams et al., 2009)



# NIMH Collaborative Research Program 18 month follow-up



# Exercise (Babyak et al., 2000)



# Is exercise a placebo?

## Side Effects

### **Antidepressants**

- Sexual dysfunction
- Insomnia
- Weight gain
- Diarrhea
- Nausea
- Anorexia
- Bleeding
- Forgetfulness
- Seizures...

### **Exercise**

- Enhanced libido
- Better sleep
- Decreased body fat
- Improved muscle tone
- Longer life
- Increased strength and endurance
- Improved cholesterol levels...

# Should we prescribe placebos?



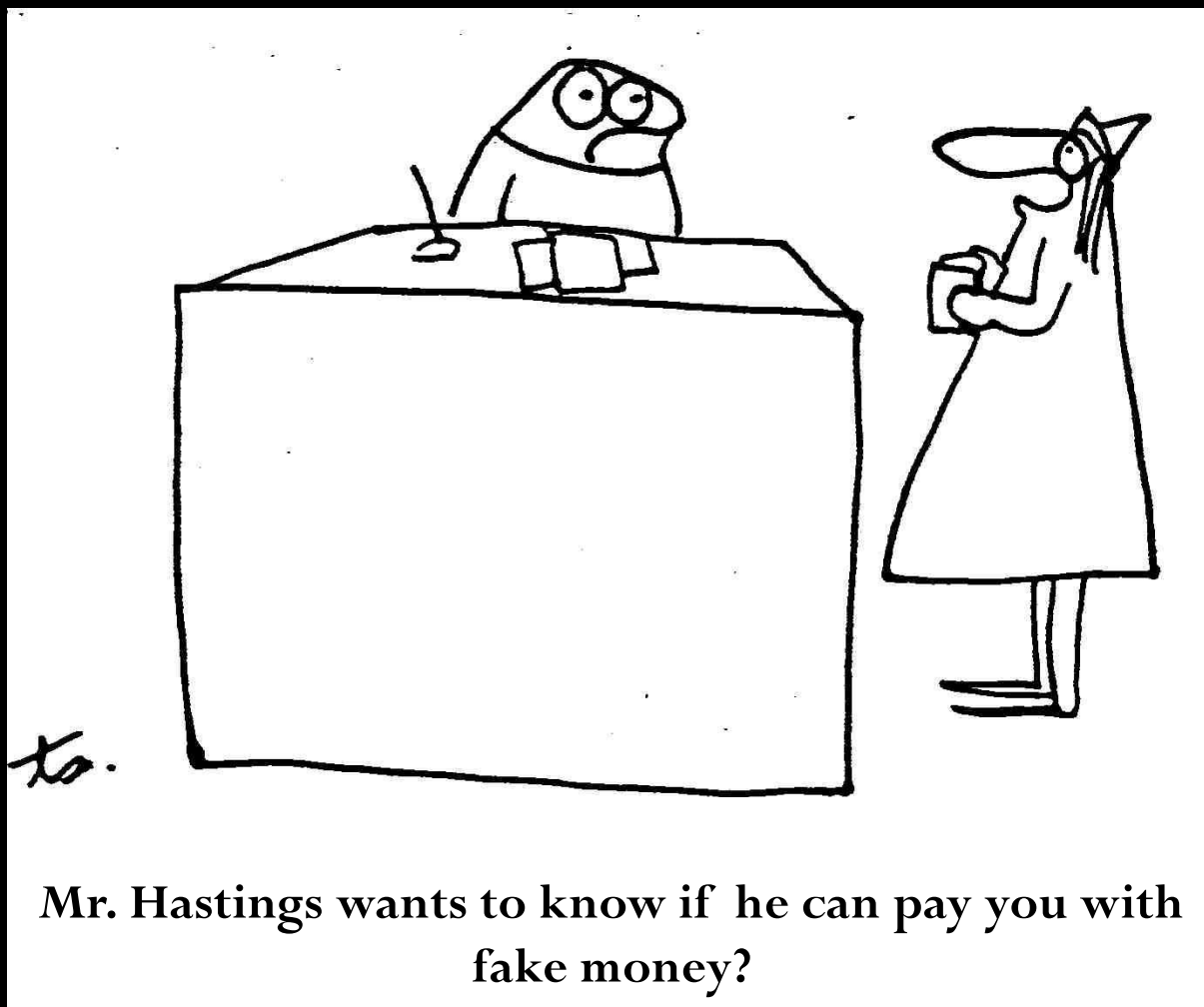
**“But if I know it’s a placebo, will it still work?”**



“Take this placebo twice a day.”  
“If it doesn’t work, I’ll give you a stronger one.”

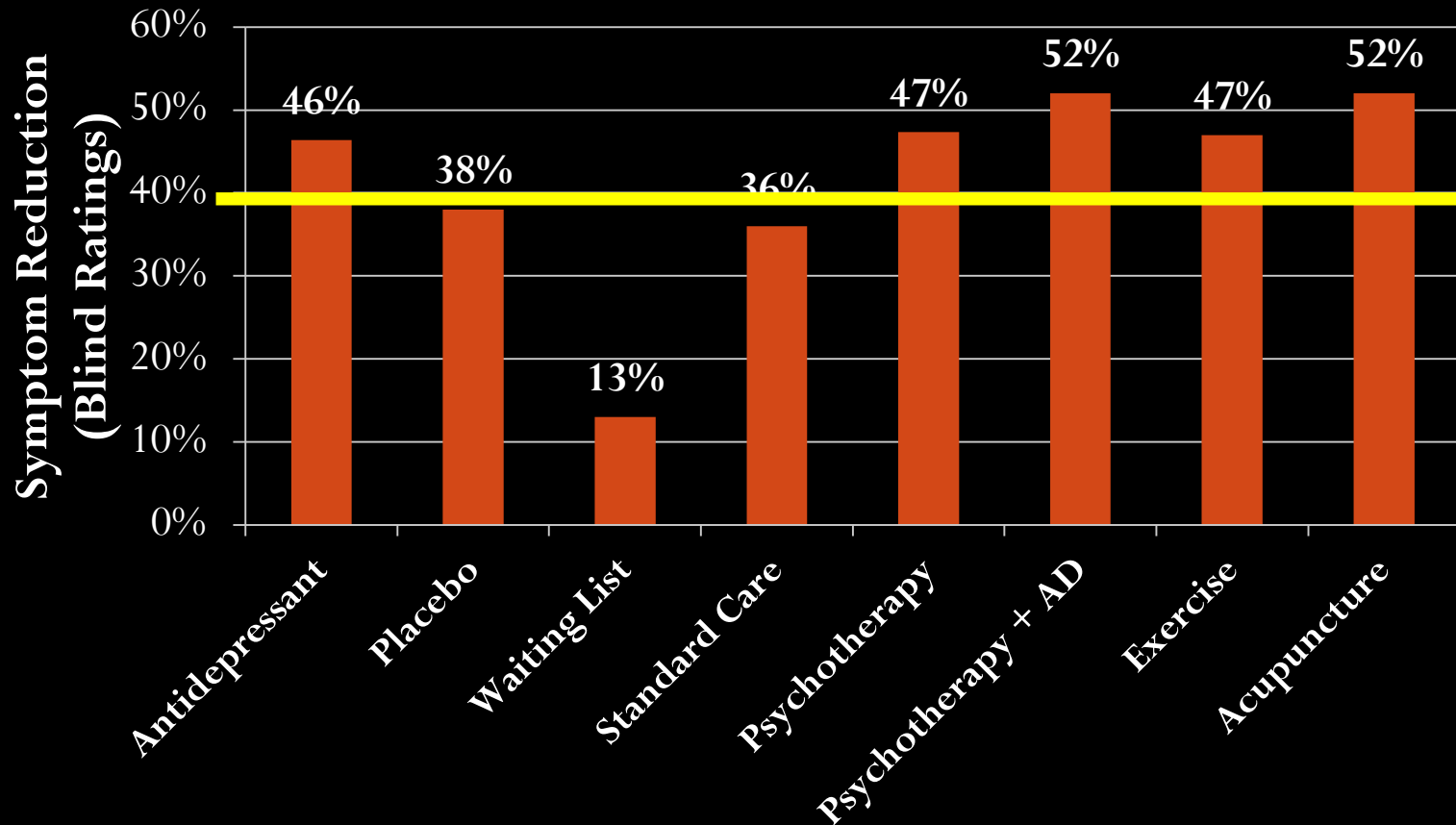


Should we prescribe open placebos for depression?



# Treatments for Depression

(Khan, Faucett, Lichtenberg, Kirsch, & Brown, 2012)



# Advantages of psychotherapy over ADM

- Better long-term effectiveness
- Safer
- Preferred

Meta-analysis of 34 patient choice studies  
(McHugh et al., 2013)

75% prefer psychotherapy

We can't prescribe placebos yet  
But I wish we could



# THE DEPENDENT

## Placebo Approved by FDA

13 December 2016

After decades of testing in tandem with SSRIs, placebo gained approval for prescription use from a regulatory agency.

The FDA has approved placebo in doses ranging from 1 to 40,000 mg.

Eleven major drug companies have developed placebo tablets.

# Investigational New Drug approval for placebo



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 126556

**STUDY MAY PROCEED**

Anthony Lembo, M.D.  
Beth Israel Deaconess Medical Center  
330 Brookline Avenue  
Boston, MA 02215

Dear Dr. Lembo:

Please refer to your **Investigational New Drug Application (IND)** submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for **microcrystalline cellulose**.

We have completed our 30-day, safety review of your application and have concluded that you may proceed with your proposed clinical investigation for irritable bowel syndrome (IBS).

# Prevaricain®

A genuine placebo medication

- **Tested:** in more clinical trials than any other treatment.
- **Powerful:** the standard by which all other medications are judged.
- **Effective:** used in the treatment of thousands of ailments.
- **Safe:** it can be given to infants, the elderly, and pregnant women.
- **Warning:** no serious side effects or health risks.

If it's a placebo, you can believe in it!

# THE EMPEROR'S NEW DRUGS

**Exploding the  
Antidepressant  
Myth**



**IRVING KIRSCH, Ph.D.**