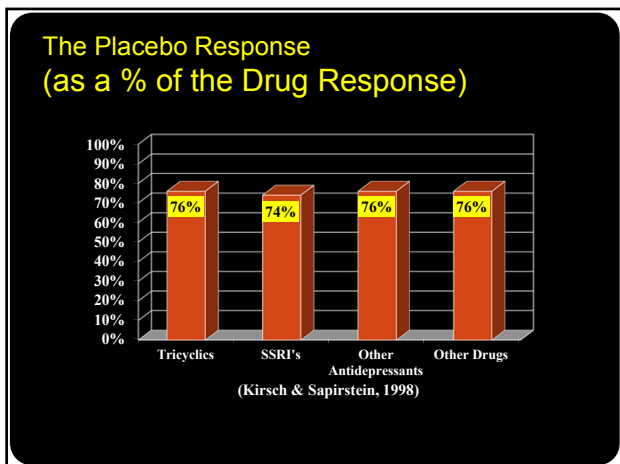
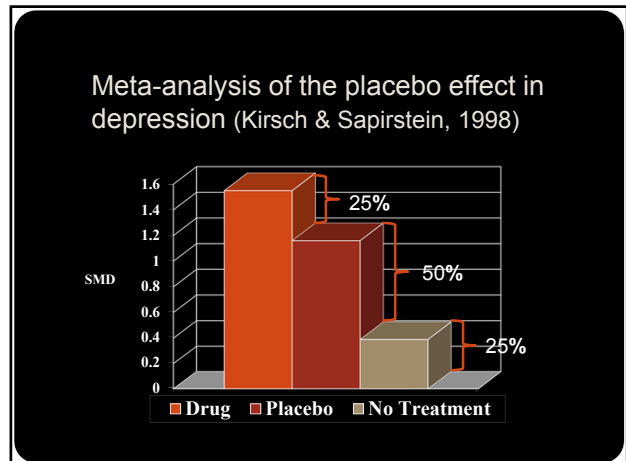


Program in Placebo Studies & the Therapeutic Encounter
Roth Israel Deaconess Medical Center
Harvard Medical School

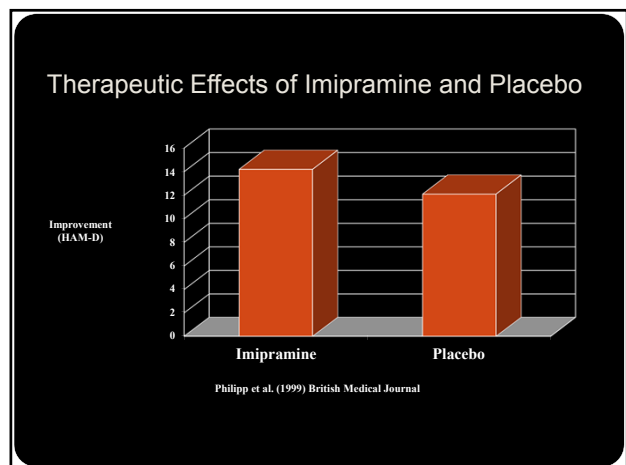
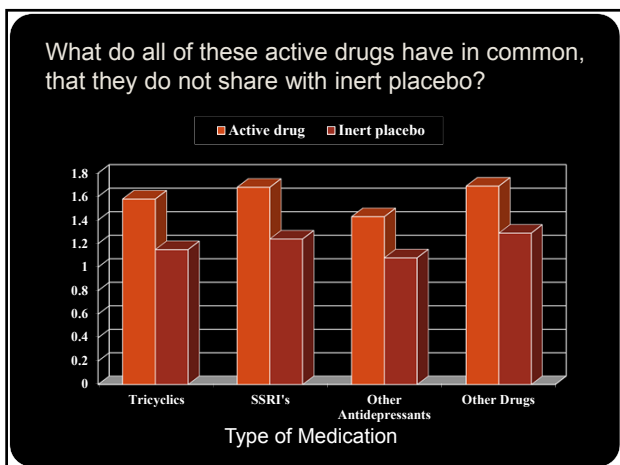
Placebo Therapy as an Ethical Alternative

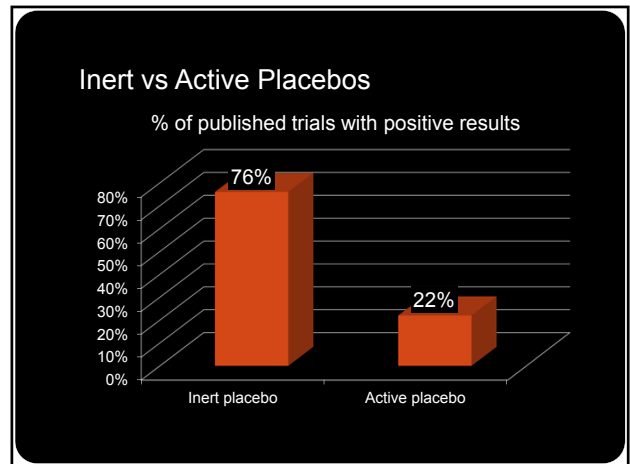
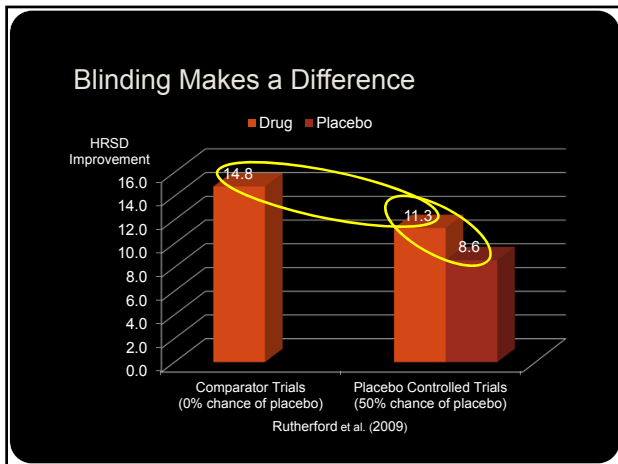
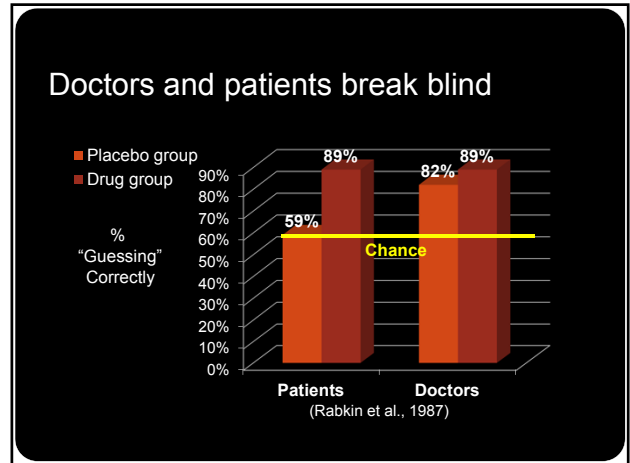
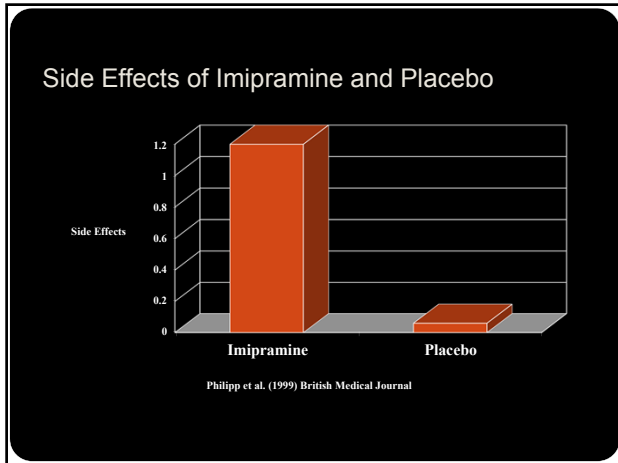
Irving Kirsch, PhD
Associate Director, Program in Placebo Studies
Harvard Medical School
Professor Emeritus of Psychology
Plymouth University, University of Connecticut, and University of Hull

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



- ### "Other Drugs"
- Lithium
 - Amylobarbitone
 - Barbiturate
 - Liothyronine
 - Synthetic thyroid hormone
 - Adinazolam
 - Benzodiazepine





“Listening to Prozac but Hearing Placebo”

(1998)

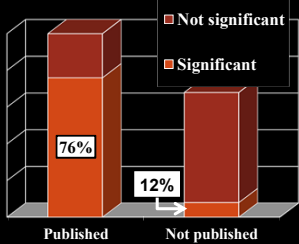
The Critics:
 Your analysis is flawed
 “It derives from a miniscule group of unrepresentative, inconsistently and erroneously selected articles” (Klein, 1998)

Freedom of Information Act FDA Data

- Fluoxetine
- Paroxetine
- Sertraline
- Venlafaxine
- Nefazodone
- Citalopram

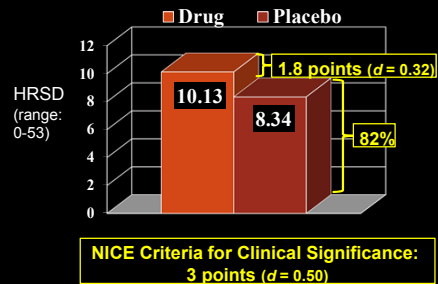
FDA data

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



Drug-Placebo Differences

(Kirsch et al., 2002, 2008)



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

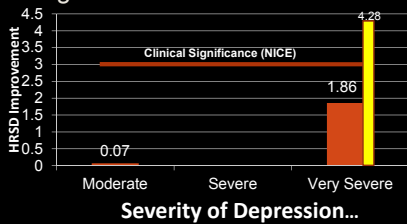
by 10 seconds

The Critics in 2002:



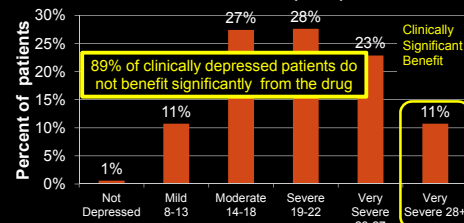
"The patients weren't depressed enough"

Drug-Placebo Differences




Severity of MDD in Clinical Practice

Zimmerman et al. (2002)


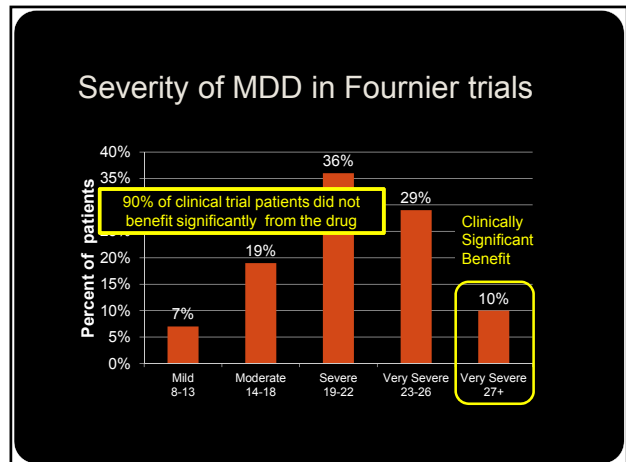
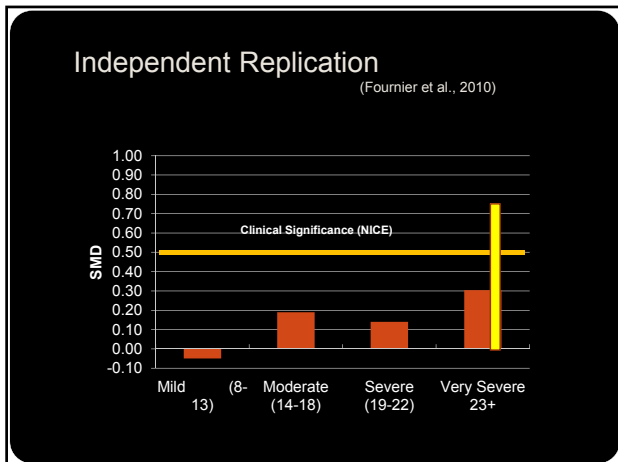
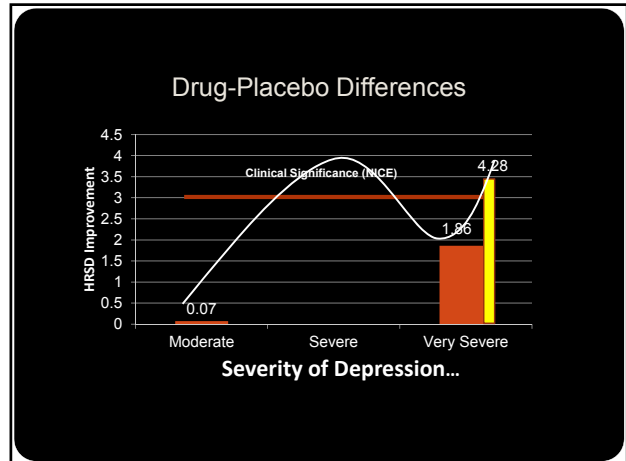


The critics in 2008:

The patients were too depressed!
 (Editorial, *Nature Reviews Drug Discovery*, 2008)



Dishes piling up in the sink?

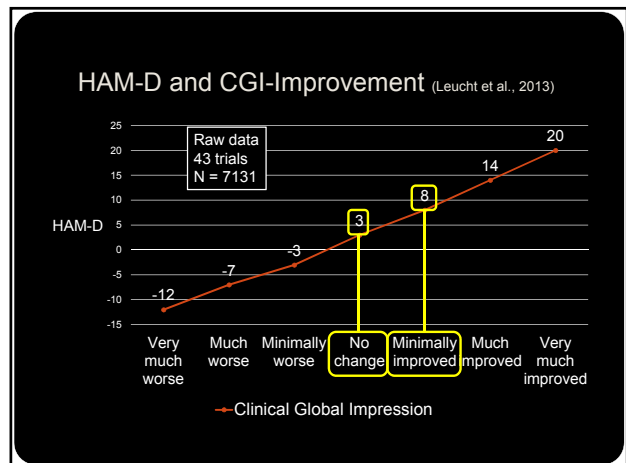
The Critics:

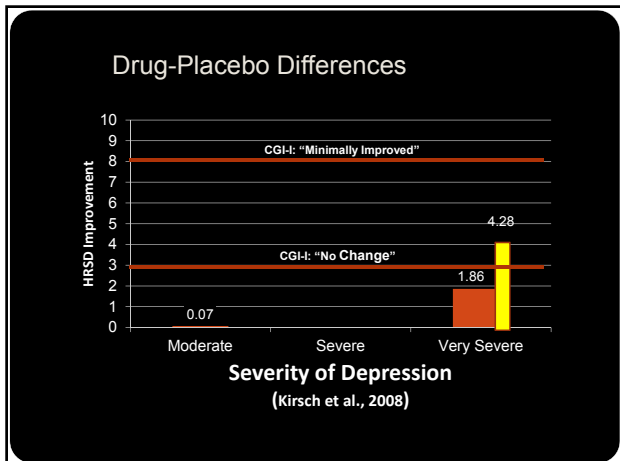
The NICE criteria are arbitrary

as arbitrary as criteria for:

- Statistical significance: $p < .05$
- Response: 50% symptom reduction
- Remission: < 8 HRSD

• What would a non-arbitrary criterion be?





The critics' last resort:

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

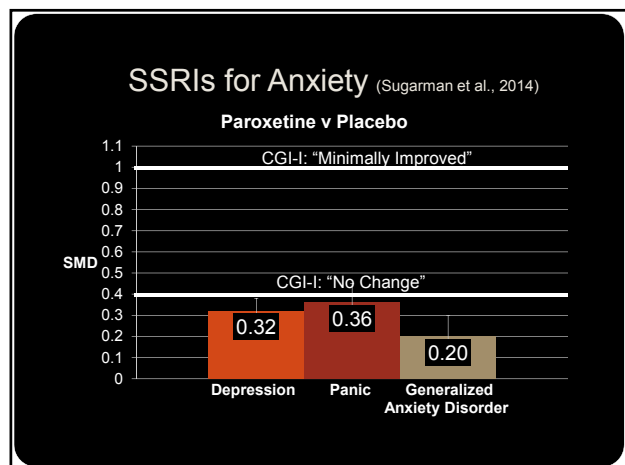
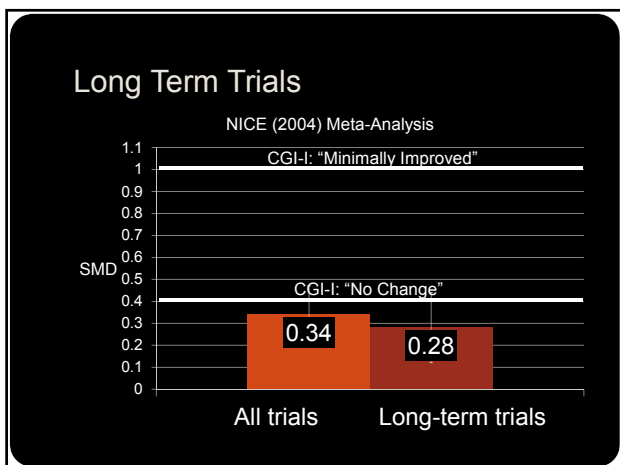
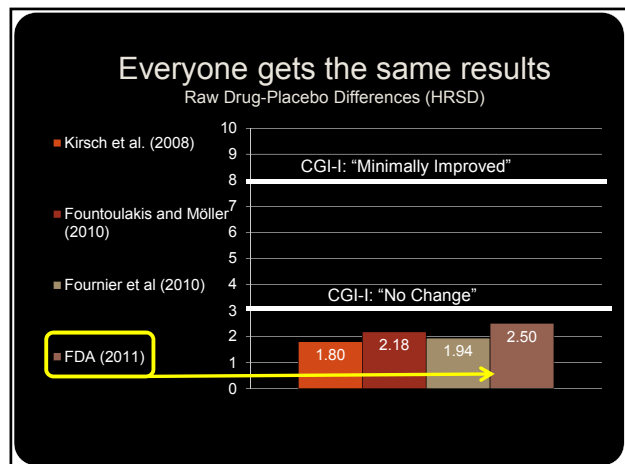
"Clinical practice plus millions of content patients can't be that wrong" (Werner, 2008)

History of Medicine

Treatments that have worked for millions:

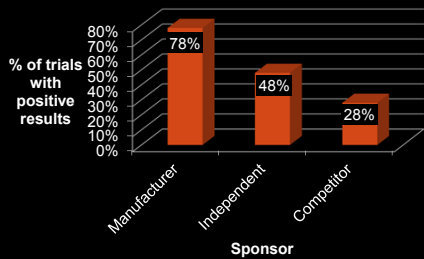
- Bloodletting
- Lizard's blood
- Crocodile dung
- Pig's teeth
- Putrid meat
- Fly specs
- Frog's sperm
- Powdered stone
- Human sweat
- Worms
- Spiders
- Furs
- Feathers

Honigfeld 1964



FDA Trials Biased Toward Drug

- Industry funded



Kelly et al. (2006)

Trials Biased Toward Drug

- Industry funded
- Placebo responders screened out

Trials Biased Toward Drug

- Industry funded
- Placebo responders screened out
- Patients unlikely to show a drug effect screened out
 - Mildly and moderately depressed
 - Chronically depressed
 - Previous non-responders
 - Co-morbid conditions
 - Suicidal

STAR*D

78% of patients would have been excluded

Barber et al. (2012)

16 Week trial

Sertraline, placebo, psychotherapy

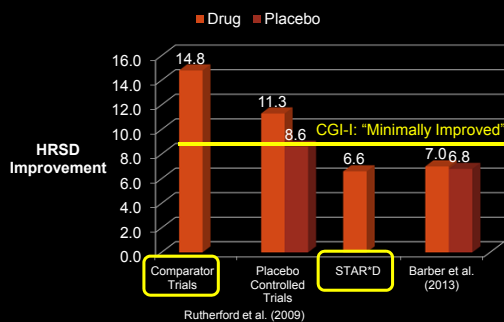
Patients:

- Economically disadvantaged
- 52% minority
- Highly comorbid
- Chronic
- Recurrently depressed

Non-responders switched at week 8:

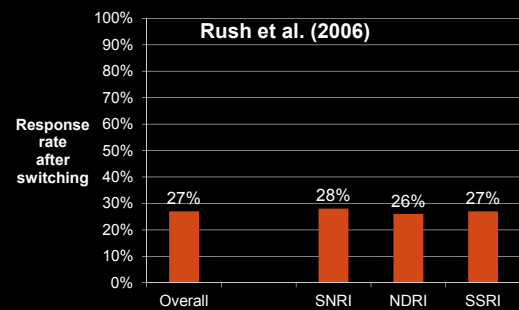
- Sertraline patients switched to venlafaxine
- Placebo patients switched to different placebo

The Impact of Exclusion Criteria



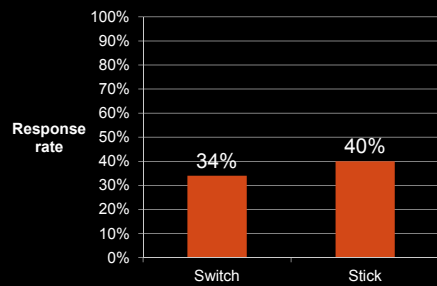
STAR*D trial

Switching unresponsive patients



Switching antidepressants

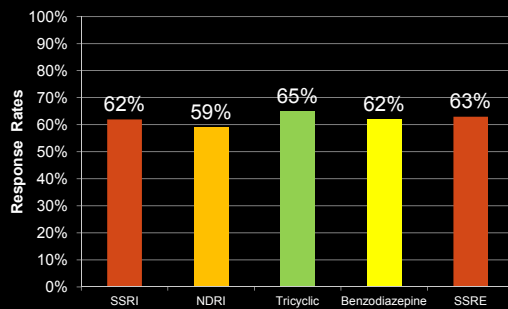
(Bschor & Baethge, 2010)



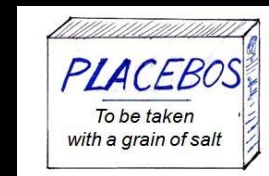
Tianeptine

- **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 did these drugs get approved?

FDA Approval Criterion

- Two clinical trials showing significant difference between drug and placebo
- No limit on the number of trials conducted
- 50% of trials are negative
- Negative trials don't count
- Clinical significance not considered

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 18, 2011

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for vilazodone tablets as a treatment for major depressive disorder (MDD).

“Although these trials were either failed or negative on the primary endpoint, the two fixed dose trials did reveal findings on the MADRS, a secondary endpoint, that were at least suggestive of efficacy.”

Other drugs that cause neonatal abstinence syndrome:

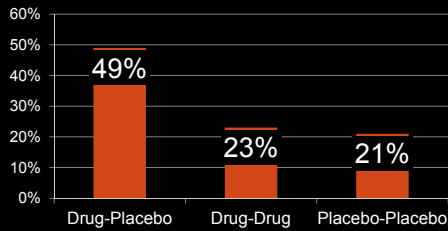
- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine
- Morphine
- Heroin

Health Risks

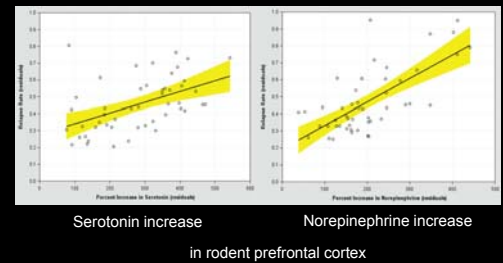
- Children & Young Adults
 - Suicidal behaviour
- Elderly
 - Stroke
 - Death from all causes
- Pregnant women
 - Miscarriage
 - Babies born with
 - birth defects, persistent pulmonary hypertension, autism, neonatal abstinence syndrome (30%)
- Everyone
 - Diabetes
 - **Relapse**

Continuation and Discontinuation Trials

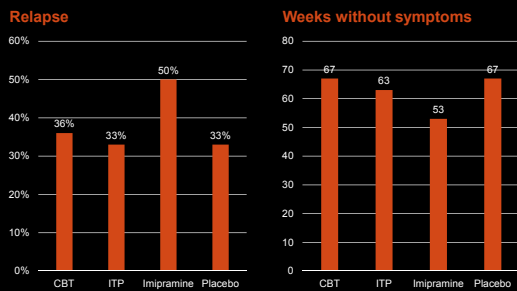
(Andrews et al., 2010, 1912; Williams et al., 2009)



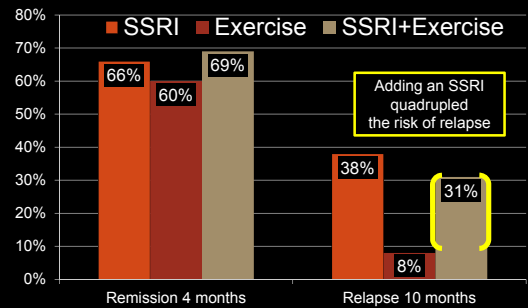
Monoamine increase and the risk of relapse (Andrews et al., 2011, 2012)



NIMH Collaborative Research Program 18 month follow-up



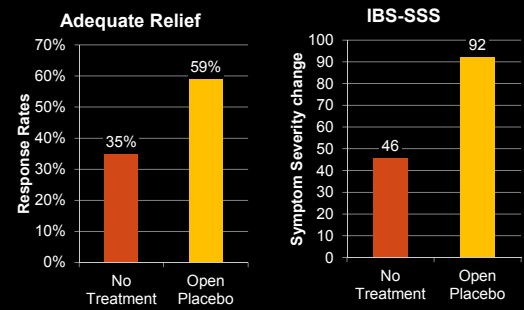
Exercise (Babyak et al., 2000)



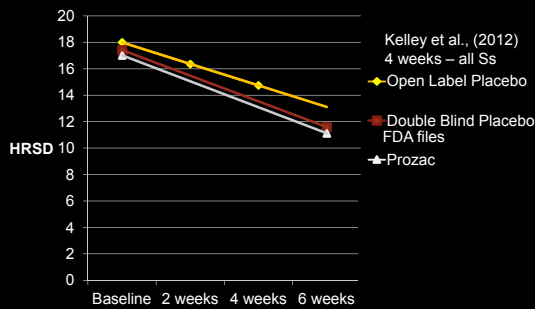
Placebos Without Deception (Kaptchuk et al., 2010)

- Advertisement :“A novel mind-body management study of IBS”
- Telephone screening: “placebo (inert) pills, which are like sugar pills”
- Meeting with physician:
 - 1) the placebo effect is powerful
 - 2) the body can automatically respond to taking placebo pills like Pavlov’s dogs who salivated when they heard a bell
 - 3) a positive attitude helps but is not necessary
 - 4) taking the pills faithfully is critical
- Randomization
 - “placebo pills: take 2 pills twice daily”
 - No treatment control

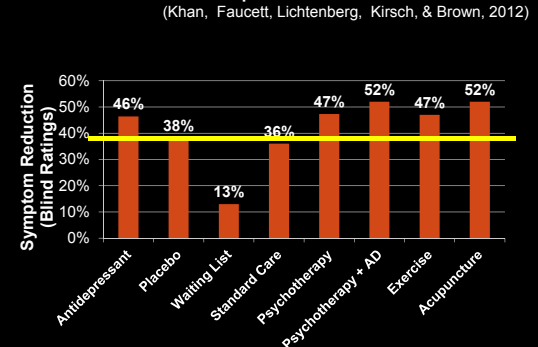
Placebos Without Deception



Open label placebo for mild-moderate depression (Kelley et al., 2012)



Treatments for Depression (Khan, Fauceit, Lichtenberg, Kirsch, & Brown, 2012)



Guidelines for Treatment Choice

- When treatments are equally effective
Prescribe the safest
- When treatments are equally safe
Prescribe what the patient prefers

75% prefer psychotherapy
(McHugh et al., 2013, Meta-analysis of 34 patient choice studies)

THE EMPEROR'S NEW DRUGS

Exploding the Antidepressant Myth



IRVING KIRSCH, Ph.D.

Thanks my collaborators:

- Ted J. Kaptchuk
- John M. Kelley
- Anthony J. Lembo
- Kathryn T. Hall
- Jian Kong
- Randy Gollub
- Guy Sapirstein
- Thomas J. Moore
- Blair T. Johnson
- Tania B. Huedo-Medina
- Alan Scoboria
- Brett J. Deacon
- Arif Khan
- Walter A. Brown
- James Faucett
- Pesach Lichtenberg
- Joanna Moncrief

With additional data supplied by:

- Robert J. DeRubeis
- Steven D. Hollon
- Jay C. Fournier
- Bret R. Rutherford