Antidepressants and the Placebo Effect

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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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Depression drugs don’t work, says new study

Cheers for head girl who escaped killer
Prozac, used by 40m people, does not work say scientists

Analysis of unseen trials and other data concludes it is no better than placebo
Antidepressant drugs don’t work — official study

Manufacturers ‘withheld’
ANTIDEPRESSANTS DON’T WORK

THE DEBATE OVER THE NATION’S MOST POPULAR PILLS

BY SHARON BEGLEY

FEBRUARY 8, 2010
How it happened

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

- Published: 76%
- Not published: 12%

Not significant

Significant
Drug-Placebo Differences
(Kirsch et al., 2002, 2008)

HAM-D (range: 0-53)

Drug Placebo

10.13 8.34

1.8 points ($d = 0.32$)

82%

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

Severity of Depression
(Kirsch et al., 2008)
Drug-Placebo Differences

Severity of Depression

(Kirsch et al., 2008)
Severity of MDD in Clinical Practice

Zimmerman et al. (2002)

90% of clinically depressed patients do not benefit significantly from the drug.
The critics in 2008:

The patients were too depressed!

Drug-Placebo Differences

Severity of Depression

(Kirsch et al., 2008)
Independent Replication

(Fournier et al., 2010)

Clinical Significance (NICE)

- Mild: (8-13)
- Moderate: (14-18)
- Severe: (19-22)
- Very Severe: (23+)

SMD

-0.10  0.00  0.10  0.20  0.30  0.40  0.50  0.60  0.70  0.80  0.90  1.00
The Critics:

The NICE criteria are arbitrary as arbitrary as criteria for:

- Statistical significance: $p < .05$
- Response: $\geq 50\%$ symptom reduction
- Remission: $< 8$ point HAM-D score

What would a non-arbitrary criterion be?
HAM-D and CGI-Improvement (Leucht et al., 2013)

Mean Improvement HAM-D

Clinical Global Impression

Raw data
43 trials
N = 7131

-12
-6
-4
0
3
7
14
20

Very much worse
Much worse
Minimally worse
No change
Minimally improved
Much improved
Very much improved
Drug-Placebo Differences

Severity of Depression

(Kirsch et al., 2008)

HAM-D Improvement

CGI-I: “Minimally Improved”

CGI-I: “No Change”

0.07

1.86

4.28

0

1

2

3

4

5

6

7

8

9

10

Moderate

Severe

Very Severe
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)

Kirsch et al. (2002, 2008)
Fountoulakis and Möller (2010)
Fournier et al (2010)
Gibbons et al. (2012)
FDA (2011)
FDA (2015)

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)
Head to Head Comparisons

- SSRI: 62%
- NDRI: 59%
- Tricyclic: 65%
- Benzodiazepine: 62%

Response Rates
Tianeptine

- SSRI
  - Selective Serotonin Reuptake Inhibitor

- SSRE
  - Selective Serotonin Reuptake Enhancer
Head to Head Comparisons

Response Rates

SSRI: 62%
NDRI: 59%
Tricyclic: 65%
Benzodiazepine: 62%
SSRE: 63%
What do you call pills, the effects of which are independent of their chemical composition?
Benefits vs Risks

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

Flu-like aches and pains
Fever
Sweats
Chills
Runny nose
Sore eyes
Headache
Dizziness
Dis-equilibrium
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
SSRI withdrawal in newborn infants
(Levinson-Castiel et al., 2006)

Other drugs that produce NAS:
- morphine
- heroin
- cocaine

- Neonatal Abstinence Syndrome (NAS)
- High–pitched cry
- Sleep disturbance
- Tremors
- Gastrointestinal disturbance
- Hypertonicity
- Tachypnea

% Occurrence (N = 120)
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

• 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)

49% Increased relapse

Drug-Placebo

Placebo-Placebo 21%
NIMH Collaborative Research Program
18 month follow-up

Relapse

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>CBT</td>
<td>36%</td>
</tr>
<tr>
<td>Interpersonal psychotherapy</td>
<td>33%</td>
</tr>
<tr>
<td>Placebo</td>
<td>33%</td>
</tr>
<tr>
<td>Imipramine</td>
<td>50%</td>
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</tbody>
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Exercise (Babyak et al., 2000)

Adding an SSRI quadrupled the risk of relapse.
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?”
Treatments for Depression

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

Symptom Reduction (Blind Ratings)

- Antidepressant: 46%
- Acupuncture: 52%
Paradoxical Data

The Efficacy Paradox (Walach, 2001)

The Efficacy Paradox in Migraine

Meissner et al. (2013)

- Treatment vs Placebo
- Response Rate Differences

Medication: 0.19
Acupuncture: 0.13
The Efficacy Paradox in Migraine

Meissner et al. (2013)

Response Rates

- Medication: 0.41
- Acupuncture: 0.51

0.0 0.1 0.2 0.3 0.4 0.5 0.6
Response Rates

0 0.1 0.2 0.3 0.4 0.5 0.6
The Efficacy Paradox in Migraine

Meissner et al. (2013)
The Efficacy Paradox in Migraine

Meissner et al. (2013)

- Medication: 0.41
- Acupuncture: 0.51

Treatment Response Rates
The Efficacy Paradox in Migraine

Meissner et al. (2013)

Response Rates

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<th>Placebo</th>
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<table>
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<th>Real</th>
<th>Placebo</th>
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<td>0.51</td>
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<td></td>
<td>0.38</td>
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Treatment Effect
The Efficacy Paradox in Chronic Low Back Pain (Haake et al., 2007)

- Acupuncture (n=387)
- Sham acupuncture (n=387)
  - Superficial needling at non-acupuncture points
- Conventional therapy (n=388)
  - Drugs + physical therapy + exercise
The Efficacy Paradox in Chronic Low Back Pain (Haake et al., 2007)
Is sham acupuncture a sham?

Aspirin
  Mechanism not known until 1971

There’s something about needling
The placebo trap (Walach, 2001):

“The placebo trap is the idea that only specific effects over and above placebo effects are worth looking for, worth demonstrating, and worth achieving.

“This is only true for the small sector of research that has the aim of proving the efficacy of newly developed drugs.

“It is not true for all those complex interventions that do not rely on one mechanistic specific agent but intervene in a more complex fashion,

“stimulating organisms toward self-healing actions.”
Kaptchuck (2002):

“Should a patient with chronic neck pain who cannot take diazepam because of unacceptable side effects be denied acupuncture that may have an “enhanced placebo effect” because such an effect is “bogus”? “Who should decide?”
“Who should decide?” (Kaptchuk, 2002)

Guidelines for Treatment Choice:

When treatments are equally effective

Prescribe the safest

When treatments are equally effective

Let the patient decide
Don’t be afraid of the big bad placebo effect

Embrace it
We don’t have to prescribe placebos
But I wish we could
Placebo Approved by FDA
13 December 2015

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.
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.