Understanding Placebo Response in Psychiatry: The Good, The Bad, and The Ugly

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Outline

• Why we care about placebo response:
  – the good
  – the bad, and
  – some really ugly implications
• Future directions for research
• Practical recommendations for practice

Definitions

• Placebo: Substance that has no inherent power to produce a pharmacologic effect (Origin: from Greek, meaning to please); the term sham is used for the equivalent of a placebo for a device or procedure
• Placebo response: Change in symptoms among participants randomized to placebo
• Nocebo: A placebo with a negative effect or side effect

The Good:
A Placebo Response is a Fundamental Component of Helping Relationships

A Model of Placebo Response in Antidepressant Clinical Trials


Placebo: The Major Reason People Get Better in Modern Antidepressant Trials

Placebo Accounted for 70+% of Benefit of Bupropion and SSRIs in Standard RCTs

- Placebo accounted for 70+% of the benefit of Bupropion and SSRIs in standard RCTs.
- Pooled data from 9 trials: SSRI (sertraline N = 358), fluoxetine (N = 348), paroxetine (N = 52).
- BUP = bupropion; HAM-D = Hamilton Rating Scale for Depression; PBO = placebo; RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor.


Placebo Amplifies the Natural History (Spontaneous Remission)

- Acute depressive episodes often spontaneously remit – 30% untreated depressed patients recover in 10 weeks and up to 60% by 6 months.
- Wait-list controls: 10 studies (N = 340), improve 4 HAM-D points on average, 10% response rate.
- Placebo response rates higher among more acute and less severe patients.
- Placebo response lower among older depressed patients with elevated urinary free cortisol levels.


A Placebo is So Much More Than a Pill

- Patients prescribed a medication receive a pill/capsule PLUS:
  - A coherent narrative about their illness and a time-honored/tested approach to relief
  - This can restore morale/hope and create an expectation for symptom relief
  - Prescription is accompanied by regular visits with a health care professional who is empathic and offers helpful advice and
  - Regularly monitors progress and makes changes
  - In clinical trials, the more visits and the longer the visits, the higher the likelihood of a placebo response


Therapeutic Contact Moderates Placebo Response in RCTs

- 3 less visits
- Mean visits
- 3 more visits


Is a Placebo Still Useful If You Know It’s a Placebo?

- Placebos without Deception: A Randomized Controlled Trial in Irritable Bowel Syndrome
  - Effective as the leading homeopathic remedy

Open-Label Administration of Placebo in Irritable Bowel Syndrome


N = 80

No Treatment Control
N = 43
Open-Label Placebo
N = 37

No Treatment Control Completers
N = 39
Open-Label Placebo Completers
N = 31

Several Surveys Suggest That Physicians Want to Utilize Placebos


“A Placebo Effects”


The Good: Placebo Responses Can be Helpful via Classical Conditioning


Placebos Mitigate the Impact of Pain via Impact on Opiate Circuitry
The Bad: Placebo Responses are Not Always Beneficial

- Placebos are notorious for eliciting the same side effects as the matched drug (just less frequent and less severe)
- Under some circumstances, the very idea of taking a placebo can cause outcomes to worsen
- Recent work in pain studies suggests that a nocebo effect is associated with a failure to elicit the expected effect on opiate receptors

Nocebo: The Bad

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Relapses Resulting from a Switch from Open-Label to Double-Blind Therapy

- Doubt about the Treatment Adversely Affected Drug and Placebo Equally

- Nocebo Effect Mediated by Failure to Engage Endogenous Opiate System

- Placebo: The Ugly

- High placebo response rather than low medication response causes failed trials
- Compared to other drugs, developing CNS agents...
  - are less successful (8.1% CNS drug candidates reach marketplace vs 15% for all drugs),
  - take longer (CNS drugs spend > 2 years longer in human testing compared to other drugs),
  - and are more expensive ($800 million per new agent approved)

CNS = central nervous system.


The Ugly: Companies Bailing Out

AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Sanofi-Aventis, and Novartis have essentially stopped psychiatric medication Research & Development

“Psychopharmacology in crisis”
“Vanishing clinical psychopharmacology”

High Placebo Responses Have Reduced Public Trust and Confidence in Our Therapeutics

Mean Placebo Response 30%

The Placebo Response “Epidemic”:
The Really, Really Ugly

Effect Sizes of Placebo and Drug–Placebo Differences over Time

Temporal Trends with Increasing Placebo Response Seen across Indications in Psychiatry
Temporal Increase in Placebo Response Rates in RCTs of Schizophrenia

The Bad:
Some Evidence Suggests “True Drug Effects” Only for the Most Severely Symptomatic Patients

Mean Drug–Placebo Differences as a Function of Initial Severity

Meta-analysis: Pretreatment Severity and Response to ADMS and PBO

Why are These Observations So Controversial?

- The percentage of persons treated with ADMS in the United States increased from 5.8% to 10.1% between 1996 to 2005; 11% to 13% of US adults now take ADMS
- Increasing use of ADMS corresponded to decreasing rates of counseling and psychotherapy
- ADMS are about twice as likely to be prescribed by primary care providers than psychiatrists; patients give primary care treatment lower marks for “consumer satisfaction”

Small Effects in Grouped Data Obscure Larger Effects in Subsets of Patients

- Study of escitalopram data set using studies permitting 20 mg/day dose
- Latent class analysis applied to placebo and escitalopram arms of the trials
- Outcomes in both sub-samples were consistent with 2 classes of response
- A small overall effect corresponded to large and clinically meaningful differences in the proportions who benefit – and don’t benefit – from therapy
Latent Class Analysis of Severe Depression: Placebo Group

Latent Class Analysis: Escitalopram Group

Design Alternatives to Reduce Placebo Response

- Limit number of study arms: simple 2-arm placebo-controlled studies have the lowest expectations of benefit and the greatest chances of success
- Longer double-blind placebo lead-in
- Variable length, double-blind placebo lead-in
- Sequential parallel group design
- Concealed focus on subset of participants with higher severity scores
- Psychotherapy lead-in

Psychotherapy Lead-in: Rationale

- Provides an accepted intervention for the first x weeks (4, 6, 8, 12?) to address concerns about duration of placebo exposure
- Addition of placebo to psychotherapy does not appreciably increase response rate
- Outcome of 12- to 16-week courses of focused psychotherapy can be predicted with 80+% accuracy after 6 to 8 weeks
- Reduces attrition and improves satisfaction with care

Non-inferiority Designs: Pros and Cons

- **Pros**: More acceptable to “real” patients, fewer ethical concerns, better comparative data on novel compounds
- **Cons**: Require extremely large samples (> 3 × that of a placebo-controlled design), absence of placebo raises expectations of benefit, interpretability problems

Interpretive Issues with Non-inferiority Trials

- The inherent bias in a non-inferiority trial favors conclusion of non-inferiority
- Inclusion criteria, dosing, small Ns, reliability of assessment, nonadherence, early attrition, and unblinding all can contribute to biased non-inferiority trials
- Interpretation problematic if active comparator inconsistently separates from placebo
Sequential Parallel Comparison Design

Phase 1
- Randomize
- D = Drug; P = Placebo; R = Responder; NR = Non-Responders.

Phase 2
- Randomize

Summary
- Placebo response is a fundamental part of the therapeutic process
- A placebo response includes spontaneous remission, regression to the mean, nonspecific benefit from clinical support, and – for some indications – classical conditioning
- It is not ethical to use placebos as part of standard (non-research) care
- Nevertheless, contributions of expectancy and therapeutic contact can be capitalized upon to improve outcomes in everyday patient care
- You can improve outcomes in practice by delivering more of the characteristics that amplify placebo response