“Man is most nearly himself when he achieves the seriousness of a child at play.”

Heraclitus, philosopher (c. 535-475 BC)
IS THERE SOMETHING ELSE IN THE PILLS WE PRESCRIBE?:
PLACEBOS AND PLACEBO EFFECTS IN CHILD AND ADOLESCENT PSYCHIATRY

Dr. Mark Sinyor
MSc., MD, FRCPCH

LEARNING OBJECTIVES
By the end of this presentation you will:
• understand the putative mechanism of the placebo effect and its role in psychiatric research
• be aware of issues specific to placebos in children and adolescents
• be able to discuss the implications for clinical practice

EXPECTATIONS AND WINE

<table>
<thead>
<tr>
<th>Wine 1</th>
<th>Wine 2</th>
<th>Wine 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>$5</td>
<td>$45</td>
<td>$35</td>
</tr>
<tr>
<td><strong>p&lt;.01</strong></td>
<td><strong>p&lt;.01</strong></td>
<td></td>
</tr>
</tbody>
</table>


FEATURES OF CLINIC VISIT FOR TONSILLITIS IN EXPERIMENTAL AND CONTROL PATIENTS

<table>
<thead>
<tr>
<th>EXPERIMENTAL (N=50)</th>
<th>CONTROL (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor’s Demeanor</td>
<td>WARM</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>EXTENSIVE</td>
</tr>
<tr>
<td>Prognosis</td>
<td>POSITIVE</td>
</tr>
<tr>
<td>Visit Length (mean)</td>
<td>10 MINUTES</td>
</tr>
</tbody>
</table>

Adapted from Olsson, Olsson and Tibblin, 1989

With Permission from Walter Brown, 2011

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Tonsillitis Symptoms 2 Days After Clinic Visit

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>48</td>
</tr>
<tr>
<td>Patients with 18-hour improvement</td>
<td>17</td>
</tr>
<tr>
<td>Total patients with 18-hour improvement</td>
<td>18</td>
</tr>
</tbody>
</table>

Olsson, Olsson & Tibblin, 1989

Practitioner Empathy and the Duration of the Common Cold

<table>
<thead>
<tr>
<th>Group Cold Outcome Differences Based on Perfect CARE Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pill Label</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Placebo Placebo</td>
</tr>
<tr>
<td>Maxalt or placebo</td>
</tr>
<tr>
<td>Maxalt</td>
</tr>
<tr>
<td>Maxalt or placebo</td>
</tr>
<tr>
<td>Maxalt</td>
</tr>
</tbody>
</table>

Total number of attacks: 459


Effect on IBS of Observation, Placebo Acupuncture and Placebo Acupuncture Plus Practitioner Warmth and Attention


Mechanism of Placebo Effect

- theory: interplay between unconscious conditioning and conscious expectations
- dopamine and endogenous opioids


Marcinkiewicz, S. et al. (2006) Expectation and the placebo effect in Parkinson’s disease patients with subthalamic nucleus deep brain stimulation. Mov. Disord. 21, 1457-1461


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Amygdala activation during nocebo and correlation to pain ratings.

© The Author 2014. Published by Oxford University Press.

~50% prescribed placebos
most common “placebos”: analgesics, vitamins
less common: antibiotics, sedatives
rare: sugar pills
62% said prescribing placebo is ethical

CANADIAN DATA

PLACEBOS / PLACEBO EFFECTS IN CHILDREN AND ADOLESCENTS

PLACEBOS IN CHILDREN AND ADOLESCENTS
- high in:
  - migraine
  - epilepsy
  - pain
  - functional GI disorders

IMPORTANT MEDIATORS OF THE PLACEBO EFFECT IN C&A
- design features playing a role:
  - frequency of contact with trial staff
  - poor patient screening
- predictors of response:
  - females
  - younger age
  - shorter duration of illness
  - lower baseline severity**
ADHD – A GOOD TEST CASES

PLACEBO EFFECTS IN ADHD

- less placebo responsive than mood & anxiety disorders
- nevertheless, a nice case study of different options for why placebos might work

ADHD

- placebo response generally ~20-30%
  - Newcorn meta-analysis: 731 placebo-treated patients
    - 33% were at least "minimally responsive" ≥ 25% ↓ symptoms
    - 21% were "robust responders" ≥ 40% ↓ symptoms

predictors of placebo response:
  - inattentive subtype (2.3x more likely)
  - lack of previous stimulant experience (1.6x more likely)


PUTATIVE MECHANISMS OF PLACEBO EFFECTS IN ADHD

1. expectancy effects
   - no support from balanced placebo design studies
2. a caregiver perception – "placebo by proxy"
   - effect size compared to placebo = 0.92 for subjective (teacher) measures and = 0.72 for objective measures (e.g. work completion)
   - similar findings in parents
   - tend to attribute positive behaviour to meds
   - poor agreement between guessed and actual medication status


PUTATIVE MECHANISMS OF PLACEBO EFFECTS IN ADHD

Table 1. Means and Standard Deviations (in Parentheses) by Condition and Rigidity Status for the Parent-Teacher Interaction Questionnaire (PTI) Scales

<table>
<thead>
<tr>
<th>Sugar</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>High rigidity</td>
<td>Low rigidity</td>
</tr>
<tr>
<td>N = 10</td>
<td>N = 10</td>
</tr>
<tr>
<td>Methylen phospho (MPh)</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>4.65 (0.97)</td>
</tr>
<tr>
<td>Affect</td>
<td>7.65 (1.3)</td>
</tr>
<tr>
<td>Effect</td>
<td>6.27 (1.2)</td>
</tr>
</tbody>
</table>


Effect of parent guessing a medication vs. placebo - Cohen’s d effect sizes range: 0.48 to 0.89
**Putative Mechanisms of Placebo Effects in ADHD**

1. **expectancy effects**
2. Δ caregiver perception – “placebo by proxy”
3. Δ caregivers behaviour towards child → Δ child behaviour
   - actually a component of behavioural treatments
   - in sugar experiment mothers believing their children got sugar: stayed closer to children, talked to them more, criticized them more often
4. **classical conditioning / conditioned response**
   - theory, no evidence to date
   - “suggestibility” may play a more important role in kids

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**Open Label Placebos in ADHD**

- **Excerpt from parent script**
  
  You are being asked to allow your child to participate in a study to examine if children with ADHD can be maintained on a lower dose of stimulant medication with the same level of symptom control and a lowered risk of medication side effects. This may be possible by taking an additional capsule. This capsule is a placebo (a pill containing no active drug or medication), which we think may act as a ‘Dose Extender’.

- **Excerpt from child script**
  
  You are coming to see the doctors today because you have an attention problem called ADHD, and you have been taking a kind of medicine called a stimulant to help your attention problem. The doctors want to know if it may help you to take a lower dose of your stimulant medicine along with something called a ‘Dose Extender’ or placebo. A placebo is completely harmless. It can sometimes help ADHD and other medical problems.

  [Pour out a few placebos in hand] This little capsule is a placebo. Placebos have been used a lot in treating people. It is called ‘Dose Extender’. As you can see, it’s different from ___ (give name of prescribed stimulant). Dose Extender is something new. It has no drug in it. I can promise you that it won’t hurt you at all. It has no real side effects. But it may help you to help yourself. It may work well with your ___ kind of like a booster to the dose of ___. That’s why it’s called a Dose Extender.”

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**Mood and Anxiety Disorders**

- **placebo response:**
  - MDD 49.6% (range: 17–90%)
  - OCD 31% (range: 4–41%)
  - other anxiety 39.6% (range: 9–53%)
  - schizophrenia 35% (single study)

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**MDD – EXPECTANCY EFFECTS**
- medication response similar in adults and children but placebo response higher in C&A
- meta-analysis comparing 9 open, 4 active comparator, and 18 placebo-controlled
- odds of medication response were not different between comparator vs. placebo-controlled
- expectancy less important in child/adolescent depression


**BRIDGE ET AL. META-ANALYSIS (MDD)**
- 2,862 patients (aged 6-18) with MDD
  - response defined as CGI-I ≤ 2
  - 59% responded to active drug
  - 46% responder to placebo


**BRIDGE ET AL. META-ANALYSIS (MDD)**
- placebo response =
  - 54.3% in children (<12-13) vs.
  - 44.9% in adolescents
  - (p=0.02, one study excluded)
- other studies have shown the reverse...
- placebo response explained more of variance in efficacy (drug-placebo separation/NNT) than did response to active medication

**Bridge et al. Meta-analysis (MDD)**

**Important Mediators of the Placebo Effect in C&A**
- Design features playing a role:
  - Frequency of contact with trial staff
  - Poor patient screening
- Predictors of response:
  - Females
  - Younger age
  - Shorter duration of illness
  - Lower baseline severity
  - (Best drug-placebo separation = TADS study – one of the few trials of moderate to severe depression)

**Question**
- Is Major Depressive Disorder:
  A. Syndrome with essentially 1 underlying phenomenology with some variability?
  B. Several different biological endophenotypes masquerading as 1 disorder?

**What is Depression?**
- "Medical" Depression
- "True" MDD
- Major depression covers a heterogeneous population of disorders
  - 25-50% of people with MDD - were later reclassified as other psychiatric/medical disorder
  - Pt's with more depressive symptoms = more stable diagnoses over time
NOT A NEW IDEA

- Her-2/neu receptor +/- breast cancers
- Hodgkin’s vs. non-Hodgkin’s lymphoma
- Grave’s disease vs. thyroiditis
- Crohn’s vs. ulcerative colitis
- etc.
- melancholic vs. atypical depression (vs. seasonal affective disorder)

“MAJOR RESPIRATORY DISORDER”

- dyspnea
- cough
- fatigue
- abnormal chest X-ray

- cancer, emphysema, asthma, TB

- imagine an RCT examining a drug for this
  - results would depend on relative proportions of disorders
  - placebo would have the advantage
  - non-specific relievers would have the broadest effect

AUTISM
Relationship Between Baseline Composite Predictor Measures Dichotomized at the Median and Response to Treatment at Week 12

The arrows, the relative risk (RR), and the corresponding 95% CI pertain to the placebo group and are interpreted as the likelihood of response if the participant entered the study with a composite score below the median value of Disruptive Behavior (A), Mood/Autism (B), and Caregiver Strain (C). Response to citalopram hydrobromide was not affected by the baseline predictor composite score.

Figure Legend:

Learning Objectives

By the end of this presentation you will:

- understand the putative mechanism of the placebo effect and its role in psychiatric research
  - biological underpinnings include dopamine and endogenous opioids
  - psychological factors include conscious expectations & conditioned (unconscious) responses
- be aware of issues specific to placebos in children and adolescents
  - rates of placebo effects are high across disorders
  - likely involve “placebo by proxy”; changes in caregiver behaviour and suggestibility (expectations less important)
  - trial design features influence outcomes and need to be carefully thought out
- be able to discuss the implications for clinical practice
  - the deceptive use of placebos is usually unethical in adults and debatable in children but frequently done anyway in medicine
  - we should still aim to maximize placebo effects while giving gold standard care

Is It Ethical To Give Placebos To Kids?

- santa claus/tooth fairy
- phone call from superman?
- stuffed animal for protection
- "monster spray"