Sequential Parallel Comparison Design for Trials with High Placebo Response

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Placebo response

“If I don’t think it’s going to work, will it still work?”
Increased placebo response over time

Data from 86 major depressive disorder trials submitted to FDA during 1986 to 2008 (Khin et al., 2011)

+ US trials
- Non US trials
Diminished treatment effect over time

[Graph showing treatment effect over time with markers for US and non-US trials]
Rising placebo response RCTs and failed trials

Undurraga and Baldessarini 2012
Placebo response

- In many studies in depression and schizophrenia considered by FDA over 12 year period, 1987 through 1999, in which investigational drug could not be distinguished from placebo also included an active standard drug that could not be distinguish from placebo (Laughren, 2001).
Placebo response

**Yellow pills**
make the most effective antidepressants, like little doses of pharmaceutical sunshine

**Red pills**
can give you a more stimulating kick

**More is better**
Placebos taken four times a day deliver greater relief than those taken twice daily.

**More $ is better**
Partial List of Illnesses Cited as Having Significant Placebo Responses
Organized by FDA Center for Drug Evaluation and Research Review Divisions

Anesthesia, Analgesic and Rheumatology
- Arthritis
- Pain
- Psoriatic arthritis
- Rheumatic diseases

Anti-viral
- Herpes simplex

Cardiovascular and Renal
- Heart failure, congestive
- Hypertension

Ear, Nose and Throat
- Tinnitus

Gastroenterology
- Crohn’s disease
- Dyspepsia and gastric motility
- Gastric and duodenal ulcers
- GERD
- Irritable bowel syndrome

Gastroenterology (cont.)
- Nausea
- Obesity
- Reflux esophagitis
- Ulcerative colitis

Neurology
- Alzheimer’s Disease
- Autism
- Epilepsy
- Headache
- Migraine
- Multiple Sclerosis
- Parkinson’s disease
- Restless leg syndrome

Psychiatry
- ADHD
- Anxiety disorders
- Binge eating disorder
- Bipolar mania

Psychiatry (cont.)
- Chronic Fatigue syndrome
- Depression
- Insomnia
- Panic disorders
- Schizophrenia
- Social Phobia

Pulmonary and Allergy
- Allergies
- Asthma
- Cough
- Cystic Fibrosis
- Food allergy

Reproductive and Urologic
- Benign prostatic enlargement
- Erectile dysfunction
- Premenstrual dysphoric disorder
- Sexual dysfunction, women
- Vulvar vestibulitis
- Urinary incontinence
Design options to lower placebo response
Option 1. Parallel single stage design
Option 2: The Placebo Lead-in

Use placebo lead-in (run-in) to eliminate placebo responders
Advantages of Placebo Lead-In

Advantages

- Possible increase in power from larger effect size in placebo non-responders
Impact of the placebo lead-in duration on the placebo response in 86 major depressive disorder trials

30 trials without placebo lead-in had an average HAMD total -9.24 and SD 1.87, but 56 MDD trials with placebo lead-in had an average HAMD total -7.6 and SD 1.83.
Disadvantages of Placebo Lead-In

Disadvantages

• Longer trial duration
• **Might fail to eliminate placebo responders**

Analysis has shown that placebo lead-in periods (at least those that are single blind) rarely deliver their theoretical benefit. Trivedi and Rush (1994) reported that meta-analyses of 101 antidepressant studies “reveal that a placebo lead-in does NOT

(1) lower the placebo response rate,
(2) **increase the drug-placebo difference**, or
(3) affect the drug response rate post-randomization...”.

• The number of patients recruited is larger than the $n$ of the trial
Option 3: The Sequential Parallel Comparison Design (SPCD)
Option 3: The Sequential Parallel Comparison Design

- Sequential Parallel Comparison Design (SPCD) is a clinical trial methodology developed in 2003 in Massachusetts General Hospital (Fava et al., 2003)
  - after parallel first stage, re-study the patients who do not respond to placebo
  - Unlike a placebo lead-in, all patients are utilized
    - and, some patients are utilized twice

- Massachusetts General Hospital holds a portfolio of patents related to SPCD, licensed by PPD.
The Sequential Parallel Comparison Design

SPCD is sometimes referred to as

• Sequential Parallel Design (SPD)

• Sequential Parallel Design with Re-Randomization or SPD - ReR (Chen et al., 2011)

• Doubly Randomized Delayed-Start Design (Liu et al., 2012)
SPCD: defining the outcome

Let \( q_1 \) and \( p_1 \) be placebo and drug response rates in Stage 1.
Let \( q_2 \) and \( p_2 \) be placebo and drug response rates in Stage 2, that is, **among placebo non-responders**
SPCD: Hypothesis testing

- Parallel single stage trial: population = all comers
  \[ H_0: p_1 = q_1 \]

- Placebo lead-in: population = placebo non-responders
  \[ H_0: p_2 = q_2 \]

- SPCD all comers placebo non-responders
  \[ H_0: p_1 = q_1 \cap p_2 = q_2 \]
  \[ H_1: p_1 > q_1 \text{ OR } p_2 > q_2 \]
Advantages of the SPCD

**Advantages**

- Unlike placebo lead-in, no eligible patients are recruited and then not used
- **Increase in power** for any given sample size
  - From potentially larger effect size in placebo non-responders
  - From reuse of patients
- More responses are observed compared to parallel design or placebo lead-in
- For any given power, overall trial duration is typically shorter because sample size is smaller
Disadvantages of the SPCD

Disadvantages

• Longer trial duration for individual subjects compared to the parallel design and placebo lead-in (because lead-in phase is usually shorter than full follow-up for response)

• Some controversy regarding hypothesis being tested. However,
  - Use of placebo non-responders (as in placebo lead-in) is well accepted for Phase 3 by FDA
  - 9 completed SPCD MDD trials and 9 ongoing trials, including completed and ongoing pivotal trials
SPCD data analysis

Linear combination test (Fava et al., 2003)

\[
\hat{\theta}_1 = \hat{p}_1 - \hat{q}_1 \\
\hat{\theta}_2 = \hat{p}_2 - \hat{q}_2 \\
T = \frac{w\hat{\theta}_1 + (1-w)\hat{\theta}_2}{\sqrt{w^2\text{Var}(\hat{\theta}_1) + (1-w)^2\text{Var}(\hat{\theta}_1)}}
\]

Since \( \text{cov}(\hat{\theta}_1, \hat{\theta}_2) \) asymptotically, \( T \sim N(0,1) \)
SPCD data analysis

1. Linear combination test (Fava et al., 2003)

\[ T = \frac{w\hat{\theta}_1 + (1-w)\hat{\theta}_2}{\sqrt{w^2\text{Var}(\hat{\theta}_1) + (1-w)^2\text{Var}(\hat{\theta}_1)}} \]

2. Score test (Ivanova, Qaqish, Shoenfeld, 2011), binary outcome

\[ r = \left( \frac{p_2 - q_2}{p_1 - q_1} \right) \]

3. Weighted combination of Z-scores (Liu et al., 2012)

\[ T = \sqrt{wZ_1} + \sqrt{1-w}Z_2 \]

where \( Z_1 \) is the test statistic for stage 1 and \( Z_2 \) is for stage 2
Ziprasidone (max 160 mg/day) vs. placebo for depression

\[ n = 120 \]

<table>
<thead>
<tr>
<th></th>
<th>Drug</th>
<th>Placebo</th>
<th>Difference</th>
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</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>44.8%</td>
<td>31.9%</td>
<td>12.9%</td>
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<tr>
<td>Stage 2</td>
<td>23.8%</td>
<td>28.0%</td>
<td>-4.2%</td>
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</tbody>
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Conventional Design p-value = 0.19 (response rates of Stage 1, using 50:50 randomization)

SPCD p-value = 0.42

*Response to placebo greater than response to drug. This was the first SPCD trial and, unlike others, used a single criterion to identify placebo non-responders to enter Stage 2.*

Note: All p-values are two-sided. SPCD p-values are obtained using the score test with an “r” = 1 (Ivanova et al., 2011). Single stage p-values are obtained using the Fisher’s exact test.
L-methylfolate (7.5 mg/day) vs. placebo for SSRI-resistant major depression

$n = 148$

Funded by Pamlab, Inc.

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<thead>
<tr>
<th></th>
<th>Drug</th>
<th>Placebo</th>
<th>Difference</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>19.4%</td>
<td>28.5%</td>
<td>-9.1%</td>
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<tr>
<td>Stage 2</td>
<td>17.1%</td>
<td>9.1%</td>
<td>8.0%</td>
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Conventional Design p-value = 0.12 * (response rates of Stage 1, using 50:50 randomization)

SPCD p-value = 0.96

* Response to placebo greater than response to drug. Therefore, the Conventional Design p-value of 0.12 quantifies the advantage of placebo over the active drug in Stage 1.
**ADAPT-A: Aripiprazole Augmentation of SSRIs for major depression with inadequate antidepressant therapy response**

\[ n = 221 \]

Funded by Bristol-Myers Squibb

<table>
<thead>
<tr>
<th>Stage</th>
<th>Drug</th>
<th>Placebo</th>
<th>Difference</th>
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<tr>
<td>Stage 1</td>
<td>18.5%</td>
<td>17.4%</td>
<td>1.1%</td>
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<tr>
<td>Stage 2</td>
<td>18.0%</td>
<td>7.9%</td>
<td>10.1%</td>
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Conventional Design p-value = 0.86 (response rates of Stage 1, using 50:50 randomization)

SPCD p-value = 0.19
L-Methylfolate (15 mg/day) Augmentation of SSRIs vs. placebo for SSRI-resistant major depression

\[ n = 75 \]

Funded by Pamlab, Inc.

<table>
<thead>
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<th>Stage</th>
<th>Drug</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>36.8%</td>
<td>19.6%</td>
<td>17.2%</td>
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<tr>
<td>Stage 2</td>
<td>27.7%</td>
<td>9.5%</td>
<td>18.2%</td>
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</table>

Conventional Design p-value = 0.12 (response rates of Stage 1, using 50:50 randomization)

SPCD p-value = 0.03

Stage 1 p-value = 0.21
Stage 2 p-value = 0.22

\[ n = 19 \text{ (25%)} : n = 56 \text{ (75%)} \]

Drug : Placebo

\[ \approx 1 \times 1 \]
Example of a Dose-Finding Study with SPCD: Alkermes' Phase 2 Study of ALKS 5461 in Depression

• ALKS 5461, a novel opioid modulator, in patients with major depressive disorder and inadequate response to standard therapies

• Primary Endpoint
  - Hamilton Depression Rating Scale (HAM-D17)

• Secondary Endpoints
  - Montgomery-Åsberg Depression Rating Scale (MADRS)
  - Clinical Global Impression (CGI-S)
Alkermes' Phase 2 Study of ALKS 5461 in Depression

- **Total**: $n = 142$
- **Randomized**: $n = 99$
  - **Placebo**: $n = 22$
  - **Low Dose**: $n = 21$
  - **High Dose**: $n = 22$
  - **No Response**: $n = 20$

4 wk trt 1 wk taper
### Alkermes’ Phase 2 Study of ALKS 5461 in Depression

<table>
<thead>
<tr>
<th>Response rate</th>
<th>Low+High dose</th>
<th>Placebo</th>
<th>Difference</th>
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</thead>
<tbody>
<tr>
<td>SPCD Stage 1</td>
<td>41.9%</td>
<td>25.3%</td>
<td>16.6%</td>
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<tr>
<td>SPCD Stage 2</td>
<td>37.8%</td>
<td>5.0%</td>
<td>32.8%</td>
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Stage 1 p-value = 0.122  
Stage 2 p-value = 0.006  
SPCD p-value = 0.001
A Two-way Enriched Design (TED)
(Ivanova and Tamura, 2011)
Sequential Enriched Design (SED) (Chen and Tamura, 2014)
References


Laughren TP. The scientific and ethical basis for placebo-controlled trials in depression and schizophrenia: an FDA perspective. European Psychiatry 2001; 16:418-423.


Silberman, S. Placebos are getting more effective. Drugmakers are desperate to know why. Wired Magazine 2009, http://www.wired.com/wired/issue/17-09
