Estimating drug effects in the presence of placebo response: Causal inference using growth mixture modeling

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Presentation at Inserm Atelier de formation 205, Saint-Raphael, June 4, 2010
How many of those who respond to the drug would have responded to placebo?
Overview


1. An antidepressant trial with a drug and a placebo group
2. Limitations of conventional assessment of drug effects
3. A new approach to assessing drug effects
5. Analysis of the antidepressant trial data
   - Using a simple growth mixture model
   - Using a fuller growth mixture model
10-week double-blind clinical trial with a 1 week single-blind washout period (McGrath et al., 2000)

Fluoxetine and imipramine ($n = 102$) versus placebo ($n = 52$)

28-item Hamilton Depression rating scale

Evidence of placebo response
Antidepressant trial ($n = 154$)
Limitations of conventional assessment of drug effects

- **End-point analysis:** Response if $\geq 50\%$ drop
  - LOCF
  - Irrelevant time-specific variation, trend ignored
- **ITT analysis:** Causal effect of randomization, not of drug
  - Some of the drug responders may have responded to placebo as well
  - Some of the drug non-responders may have responded to placebo
Background: The causal inference model with non-compliance (Angrist, Imbens & Rubin, 1996, JASA)

Consider $Y_i(X_i, D_i(X_i))$, where $Y_i$ is the outcome for individual $i$, $X_i$ is the treatment status, and $D_i$ indicates whether or not the individual takes up treatment. Using the idea of potential outcomes, AIR considers 4 classes of subjects:

- **Never takers** ($D_i(1) = 0, D_i(0) = 0$): subjects who would not take up treatment if randomized to either treatment or control (causal effect $= 0$ under the exclusion restriction)

- **Compliers** ($D_i(1) = 1, D_i(0) = 0$): subjects who would take up treatment if randomized to treatment and otherwise not (causal effect $= Y_i(1,1) - Y_i(0,0)$)

- **Defiers** ($D_i(1) = 0, D_i(0) = 1$): subjects who would do the opposite of their treatment assignment (causal effect $= -(Y_i(1,1) - Y_i(0,0))$)

- **Always takers** ($D_i(1) = 1, D_i(0) = 1$): subjects who would take up treatment whether randomized to treatment or control (causal effect $= 0$ under exclusion restriction)
A new drug assessment approach: Four classes of subjects, probabilities, and means for placebo (0) and drug (1) groups

<table>
<thead>
<tr>
<th>Placebo Group</th>
<th>Non-Responder</th>
<th>Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Responder</td>
<td>Never Responder</td>
<td>Drug Only Responder</td>
</tr>
<tr>
<td></td>
<td>$\pi_n$, $\mu_{n0}$, $\mu_{n1}$</td>
<td>$\pi_d$, $\mu_{d0}$, $\mu_{d1}$</td>
</tr>
<tr>
<td>Responder</td>
<td>Placebo Only Responder</td>
<td>Always Responder</td>
</tr>
<tr>
<td></td>
<td>$\pi_p$, $\mu_{p0}$, $\mu_{p1}$</td>
<td>$\pi_a$, $\mu_{a0}$, $\mu_{a1}$</td>
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</tbody>
</table>

The 4 classes are principal strata in the sense of Frangakis & Rubin (2002), Biometrics: Principal stratum membership is not influenced by treatment and ”can be used as any pre-treatment covariate”.

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Alternative growth mixture models for clinical trial data

Drug effects in the presence of placebo response
A special case of the general latent variable modeling framework in Mplus (www.statmodel.com)

- Maximum-likelihood estimation using EM in combination with FS and QN
- Number of classes informed by BIC and bootstrapped likelihood-ratio test
A simpler model alternative: The AIR 3-class moment estimator applied to drug and placebo response

The hypothesized 4-class mixture model has the following outcome means for the placebo and drug groups at a certain time point:

\[
\mu_0 = \pi_n \mu_{n0} + \pi_d \mu_{d0} + \pi_p \mu_{p0} + \pi_a \mu_{a0},
\]

\[
\mu_1 = \pi_n \mu_{n1} + \pi_d \mu_{d1} + \pi_p \mu_{p1} + \pi_a \mu_{a1},
\]

ITT effect: \( \mu_1 - \mu_0 \) (drug minus placebo).
AIR assumes monotonicity, i.e. no ”defier”, i.e. no Placebo Only Responders, \( \pi_p = 0 \) (i.e only 3 classes), and exclusion restriction, \( \mu_{n0} = \mu_{n1}, \mu_{a0} = \mu_{a1} \), so that (2) minus (1):

\[
\mu_1 - \mu_0 = \pi_d (\mu_{d1} - \mu_{d0})
\]

identifying the average causal effect of the drug in the Drug Only Responder class as

\[
\mu_{d1} - \mu_{d0} = (\mu_1 - \mu_0)/\pi_d.
\]
A simpler growth mixture model: 3-class model with only two sets of means

- Exclusion restriction: $\mu_{n0} = \mu_{n1}, \mu_{a0} = \mu_{a1}$
- Add the assumption of one mean for responders and one mean for non-responders: $\mu_{n0} = \mu_{d0}, \mu_{d1} = \mu_{a1}$

This results in only non-responder and responder means, assuming:

1. A non-responder mean is the same if the subject is
   - in the placebo group and in the Never Responder class,
   - in the placebo group and in the Drug Only Responder class,
   - in the drug group and in the Never Responder class.

2. A responder mean is the same if the subject is
   - in the drug group and in the Drug Only Responder class,
   - in the drug group and in the Always Responder class,
   - in the placebo group and in the Always Responder class.
Estimated mean curves for the simple model: 3-classes, 2 sets of means
Estimated mean curves for the full model: 4-classes, 8 sets of means
Comparing the simple and the full model

<table>
<thead>
<tr>
<th>Model</th>
<th>LL</th>
<th>#par.</th>
<th>BIC</th>
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</thead>
<tbody>
<tr>
<td>Simple model:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3 classes,</td>
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<td></td>
</tr>
<tr>
<td>2 sets of means</td>
<td>-4688</td>
<td>37</td>
<td>9562</td>
</tr>
<tr>
<td>Full model:</td>
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<tr>
<td>4 classes,</td>
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<tr>
<td>8 sets of means</td>
<td>-4652</td>
<td>58</td>
<td>9597</td>
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Prevalence of four types of subjects under simple and full model. Drug Only Responder tx effect is 14 vs 18

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<tbody>
<tr>
<td>Non-Responder</td>
<td>Never Responder</td>
<td>26%</td>
<td>Drug Only Responder</td>
</tr>
<tr>
<td></td>
<td>Placebo Only Responder</td>
<td>0%</td>
<td>Always Responder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26%</td>
<td></td>
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</tbody>
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<td>Drug Only Responder</td>
</tr>
<tr>
<td></td>
<td>Placebo Only Responder</td>
<td>4%</td>
<td>Always Responder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32%</td>
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