Using Mediated Moderation to Explain Treatment-by-Site Interaction in Multisite Clinical Trials

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Introduction

- In multisite clinical trials, the primary comparison is that between treatment and control.
- Despite efforts to make sites as homogenous as possible, inherent differences can add up and temper the true effect of treatment.
- The result is treatment-by-site interaction, which investigators must discern post-hoc.

Issues with interaction

- Difficulty in interpretation of the main effect of treatment.
- Statistical test for interaction typically has low power.

In the literature

- While studies acknowledge, rarely do they attempt to explain in detail.
Brent et al. *Switching to venlafaxine or another SSRI with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORDIA randomized control trial.* JAMA, 2008 [1]

- NIMH funded multisite study that sought to evaluate the efficacy of four treatment strategies in 334 depressed youths across 6 sites.

- Four treatment regimens:
  1. switch to a second, different SSRI
  2. switch to a different SSRI plus cognitive behavior therapy (CBT)
  3. switch to venlafaxine, or
  4. switch to venlafaxine plus CBT

- Study showed that CBT plus either medication showed a higher rate of response than medication alone.

- The effect of CBT-MED was heterogeneous across the sites.

- This led to: Spirito et al. *Sources of Site Differences in the Efficacy of a Multi-site Clinical Trial.* JCCP, 2009 [2]
Background

- The process of explaining site differences in clinical trials involves two phenomena: moderation and mediation [3, 4, 5, 6, 7, 8, 9, 10, 11].
- Mediation: how and why a treatment or intervention works
- Moderation: for whom and under what condition it works

MacArthur Approach (Kraemer et al. (2002 & 2008) [4, 10])

- provided a framework for characterizing meds/mods in RCTs
- introduced specific criteria for determining whether med/mod occurred and, if so, what variables were involved
- eligibility criteria: identified potential meds/mods
- analytical criteria: used statistical methods to determine if a variable functioned as a med/mod
- recommendations: 1) report effect sizes rather than p-values; 2) validate meds/mods in subsequent trials that are adequately powered
MacArthur Approach

Assumed the following linear models:

\[ Y = \beta_0 + \beta_1 T + \beta_2 M + \beta_3 (T \ast M) + \epsilon \] (1)

\[ M = \gamma_0 + \gamma_1 T + \epsilon^* \] (2)

where \( M \) is potential mediator/moderator
\( \epsilon \sim N(0, \sigma_Y^2) \)
\( \epsilon^* \sim N(0, \sigma_M^2) \)
\( T \) is coded as \( \pm 0.5 \)
\( M \) is centered at \( c \) (If \( T \) precedes \( M \), \( c = 0 \); otherwise, \( c \) is the mean of \( M \))
Mediation

- **Eligibility criteria:**
  1. T precedes M
  2. Association between M and T (\(\gamma_1 \neq 0\))

- **Analytic criteria:**
  1. Either a main effect of M (\(\beta_2 \neq 0\)) or an interactive effect of T \(\times\) M (\(\beta_3 \neq 0\))

- **Tx effect size for mediation**

\[
\delta = \frac{\beta_1 + \beta_2 \gamma_1 + \beta_3 \gamma_0}{\sqrt{\sigma_Y^2 + .5[(\beta_2 + .5\beta_3)^2\sigma_{M_1}^2 + (\beta_2 - .5\beta_3)^2\sigma_{M_2}^2]}}
\]  (3)

where \(\sigma_{M_1}^2\) and \(\sigma_{M_2}^2\) are the variances of the mediator in the treatment and control groups, respectively.

- **Validation:** design a new RCT in which Tx is augmented with M; show that new Tx is superior to old Tx
Moderation

- Eligibility criteria:
  1. $M$ precedes $T$
  2. $M$ and $T$ are independent ($\gamma_1 = 0$)

- Analytic criteria:
  1. an interactive effect of $T \times M$ ($\beta_3 \neq 0$)

- Tx effect size for moderation:

$$\delta = \frac{\beta_1 + \beta_3(M = m)}{\sqrt{\sigma_Y^2}}.$$ (4)

- Validation: design a new RCT in which $M$ is used as a stratification variable
Extension to Mediated Moderation

- While the aforementioned gives insight into how to deal with moderation and mediation separately, explaining site heterogeneity in multisite clinical trials involves dealing with both simultaneously.
- Main objective: pinpoint particular variables that mediate the moderation of treatment effect.

Literature

- Muller et al. [12] described the methodologies of “mediated moderation”
  
  1. When an underlying mediation process is responsible for the overall moderation that exists; and by accounting for that process, the magnitude of moderation is reduced.
**Proposed Method**

- Assume the following linear models:

\[
Y = \beta_0 + \beta_1 T + \beta_2 S + \beta_3 (T \ast S) + \beta_4 Me + \beta_5 (T \ast Me) + \epsilon
\]  

(5)

\[
Me = \gamma_0 + \gamma_1 T + \gamma_2 S + \gamma_3 (T \ast S) + \epsilon^*
\]  

(6)

where \( S \) is site variable (coded as \( \pm 0.5 \))

- \( Me \) is the potential mediator

\[
\epsilon \sim N(0, \sigma_Y^2)
\]

\[
\epsilon^* \sim N(0, \sigma_M^2)
\]

\( T \) is coded as \( \pm 0.5 \)
Proposed Method (cont’d)

Eligibility criteria:
1. S should moderate the effect of T in a linear model such as (1); this is a given in the context of a multisite RCT
2. T (and as a consequence, S) must temporally precede Me
3. T should be predictive of Me, either alone (γ_1 ≠ 0) or moderated by S (γ_3 ≠ 0)

Analytic criteria:
1. either a main effect of Me (β_4 ≠ 0) or an interactive effect of T * Me (β_5 ≠ 0) demonstrated in (5)
2. evidence of a reduction in the magnitude of site moderation in (5) after accounting for the mediator variable
Proposed Method (cont’d)

- **Tx effect size for mediated moderation:**

\[
\delta_{tx} = \frac{\beta_1 + \beta_3 S + \beta_4(\gamma_1 + \gamma_3 S) + \beta_5(\gamma_0 + \gamma_2 S)}{\sqrt{\sigma^2_Y + .5[(\beta_4 + .5\beta_5)^2\sigma^2_{M1} + (\beta_4 - .5\beta_5)^2\sigma^2_{M2}]}}
\]  

(7)

- Regarding the second analytic criterion, we can compare the original magnitude of moderation from (1), \( \delta = \frac{\beta_1 + \beta_3(M = m)}{\sqrt{\sigma^2_Y}} \) with \( \delta_{mod} = \frac{\beta_1 + \beta_3(S = s)}{\sqrt{\sigma^2_Y}} \), which is the magnitude of unexplained moderation from (5).

- Ideally, the difference between the \( \delta_{mod} \)’s at each site should be negligible.
Brent et al. JAMA, 2008 [1]

- Original outcome: CGI score ≤ 2 & relative change in CDRS-R ≥ 50%
- Study showed that CBT plus either med showed a higher rate of response than med alone.
- The effect of CBT-MED was heterogeneous across the 6 sites.
- Our proposed method deals with a continuous outcome and only 2 sites
- So...our new outcome is relative change in CDRS-R; the 6 sites were collapsed into 2.

<table>
<thead>
<tr>
<th>Sites</th>
<th>(1,3,4)</th>
<th>(2,5,6)</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT-MED</td>
<td>0.428</td>
<td>0.544</td>
<td>0.485</td>
</tr>
<tr>
<td>MED</td>
<td>0.497</td>
<td>0.369</td>
<td>0.435</td>
</tr>
<tr>
<td>Δ</td>
<td>-0.069</td>
<td>0.175</td>
<td>0.050</td>
</tr>
</tbody>
</table>
Overall site moderation was established by (1)

Estimated CBT-MED effect sizes were $\delta = -0.213$ in site 1 and $\delta = 0.539$ in site 2; CBT-MED had a small, negative effect in one site while having a moderate, positive effect in the other site.

Potential mediators (all measured as 6-week relative change):

1. severity of depression (BDI)
2. hopelessness (BHS)
3. parent-child conflict (CBQA)
4. drug use (DUSI)
5. social adjustment (SAS)
6. anxiety (SCARED)
7. suicidality (SIQ)

Eligibility and analytic criteria were individually applied to each variable to see if there was mediation of site moderation.

Only BHS met criteria.
Eligibility criteria

1. CBT-MED temporally preceded BHS
2. CBT-MED was predictive of BHS (moderated by site)

Analytic criteria

1. A main effect of BHS was demonstrated in (5)
2. There was a reduction in the magnitude of site moderation after accounting for BHS ($\delta_{mod} = -0.131$ and $\delta_{mod} = 0.561$ in sites 1 and 2, respectively)

Result

1. After accounting for BHS, the effect sizes for CBT-MED were $\delta_{tx} = -0.225$ and $\delta_{tx} = 0.567$ in sites 1 and 2, respectively.
2. Suggests that 6-week change in hopelessness partially mediates the moderating effect of site on CBT-MED.
Finding statistical methodology to explain tx-by-site interactions in multisite RCTs is critical.

Mediated moderation serves as a starting point to address the issue.
Limitations / Future Work

- Only for single mediators; variables may work in combination.
- Only for continuous outcomes and only 2 sites; already extended to dichotomous outcome at $\geq 2$ sites (future manuscript).
- Only two treatments; possible implications in CER.
- Mediator assumed to be Gaussian.
- Following the MacArthur “validation” approach: enhance the CBT-MED tx to address aspects of hopelessness and compare to original CBT-MED in subsequent RCT.
- Individual v. site level mediators
- Multiple comparisons
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