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:

$$Y = \beta_0 + \beta_1 T + \beta_2 M + \beta_3 (T * M) + \epsilon \quad (1)$$

$$M = \gamma_0 + \gamma_1 T + \epsilon^* \quad (2)$$

where M is potential mediator/moderator
$\epsilon \sim N(0, \sigma_Y^2)$
$\epsilon^* \sim N(0, \sigma_M^2)$
T is coded as ± 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 $T * M$ ($\beta_3 \neq 0$)
- Tx effect size for mediation

$$\delta = \frac{\beta_1 + \beta_2\gamma_1 + \beta_3\gamma_0}{\sqrt{\sigma_Y^2 + .5[(\beta_2 + .5\beta_3)^2\sigma_{M1}^2 + (\beta_2 - .5\beta_3)^2\sigma_{M2}^2]}} \quad (3)$$

  where σ_{M1}^2 and σ_{M2}^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 $T * M$ ($\beta_3 \neq 0$)
- Tx effect size for moderation:

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

- 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:

$$Y = \beta_0 + \beta_1 T + \beta_2 S + \beta_3 (T * S) + \beta_4 Me + \beta_5 (T * Me) + \epsilon \quad (5)$$

$$Me = \gamma_0 + \gamma_1 T + \gamma_2 S + \gamma_3 (T * S) + \epsilon^* \quad (6)$$

where S is site variable (coded as ± 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 ± 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 ($\gamma_1 \neq 0$) or moderated by S ($\gamma_3 \neq 0$)
- Analytic criteria:
  1. either a main effect of Me ($\beta_4 \neq 0$) or an interactive effect of $T * Me$ ($\beta_5 \neq 0$) 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:

$$\delta_{\text{tx}} = \frac{\beta_1 + \beta_3 S + \beta_4(\gamma_1 + \gamma_3 S) + \beta_5(\gamma_0 + \gamma_2 S)}{\sqrt{\sigma_Y^2 + .5[(\beta_4 + .5\beta_5)^2\sigma_{M1}^2 + (\beta_4 - .5\beta_5)^2\sigma_{M2}^2]}} \tag{7}$$

- Regarding the second analytic criterion, we can compare the original magnitude of moderation from (1), $\delta = \frac{\beta_1 + \beta_3(M = m)}{\sqrt{\sigma_Y^2}}$ with $\delta_{\text{mod}} = \frac{\beta_1 + \beta_3(S = s)}{\sqrt{\sigma_Y^2}}$, which is the magnitude of unexplained moderation from (5).
- Ideally, the difference between the δ_{mod}'s at each site should be negligible.

Brent et al. JAMA, 2008 [1]

- Original outcome: CGI score ≤ 2 & relative change in CDRS-R $\geq 50\%$
- 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.

	Sites		
TX	(1,3,4)	(2,5,6)	ALL
CBT-MED	0.428	0.544	0.485
MED	0.497	0.369	0.435
Δ	-0.069	0.175	0.050

- 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 ($\delta_{\text{mod}} = -0.131$ and $\delta_{\text{mod}} = 0.561$ in sites 1 and 2, respectively)

Result

1. After accounting for BHS, the effect sizes for CBT-MED were $\delta_{\text{tx}} = -0.225$ and $\delta_{\text{tx}} = 0.567$ in sites 1 and 2, respectively.
2. Suggests that 6-week change in hopelessness partially mediates the moderating effect of site on CBT-MED.

Conclusion

- 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.

Discussion

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 > 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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