# Osmotic-release methylphenidate randomized controlled trial for adolescents with attention-deficit/hyperactivity disorders and substance use disorders:

## *A missing data sensitivity analysis*

Sterling McPherson, Ph.D.
Mary Rose Mamey, M.S.
Celestina Barbosa-Leiker, Ph.D.
Sean Murphy, Ph.D.
John Roll, Ph.D.

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# CONFLICT OF INTEREST AND FUNDING

- The authors have no conflicts of interest related to this project.


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PROGRAM OF EXCELLENCE IN ADDICTIONS RESEARCH

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# BACKGROUND AND AIM

- Treatment efficacy can vary as a function of how missing data are handled in substance use disorder randomized clinical trials (RCTs)[1,2]
- Bias can result from inappropriate handling[7-11]
- Substance use disorder RCTs often use sub-optimal methods[1,2]

# BACKGROUND AND AIM

- Missing at Random (MAR):
  - Missing values depend on observed values that are included in the analysis
- Missing Not at Random (MNAR):
  - Missing values depend on unobserved values

# BACKGROUND AND AIM

- *We compared 3 modeling strategies for handling of missing values (i.e., missing at random [MAR] model, 2 different missing not at random [MNAR] models; Diggle-Kenward and Wu-Carroll)*

# METHOD: A PARALLEL GROWTH EXAMPLE

- Data from a National Drug Abuse Treatment Clinical Trials Network study (N=303)[6]
- Evaluated the safety/efficacy of a 16-week RCT of OROS vs. placebo in adolescents (aged 13-18) with ADHD, also receiving cognitive behavioral therapy for their substance use disorder
- Two primary outcomes were clinician-reported ADHD symptoms and self-reported past 28 days of substance use (SU)

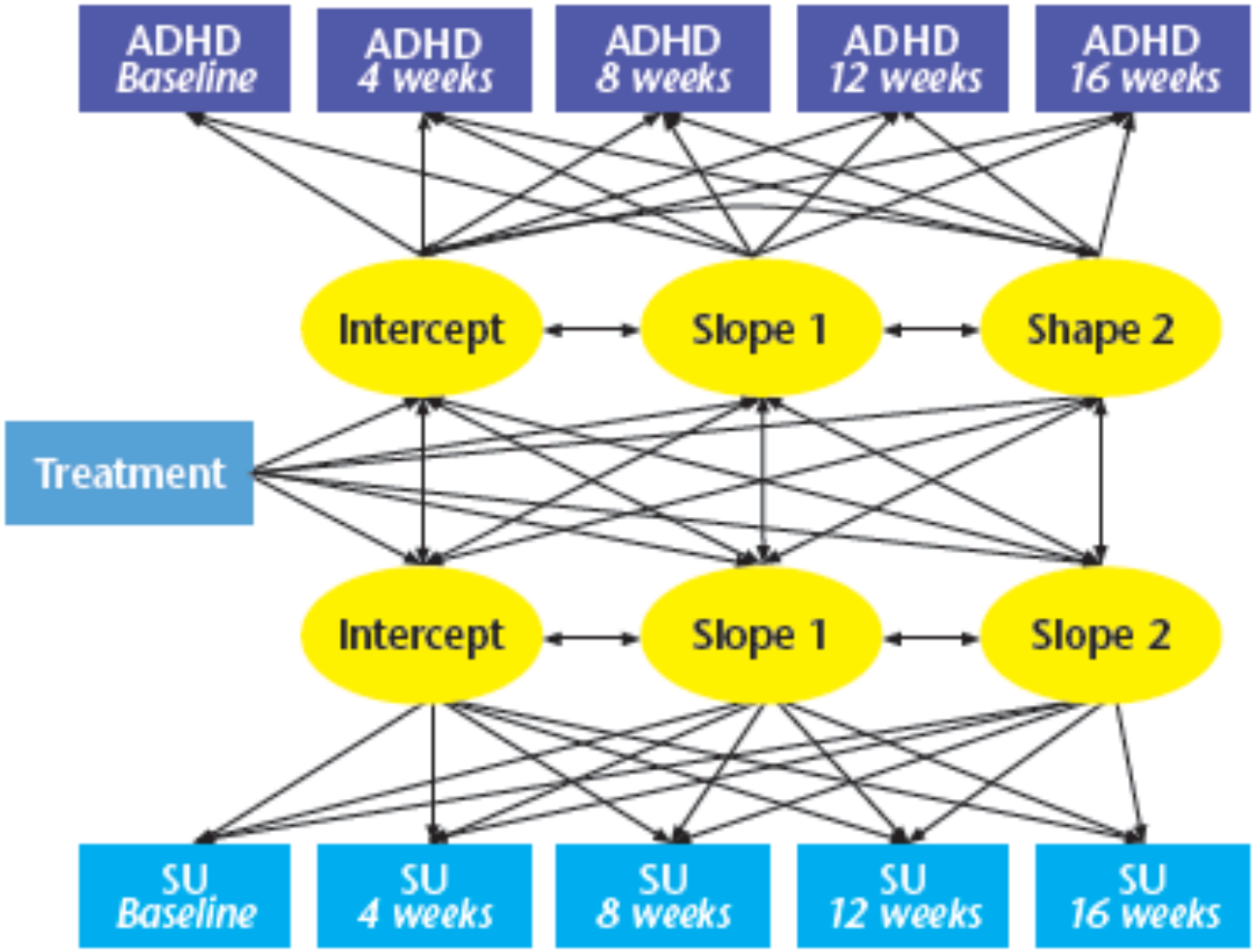
# METHOD: A PARALLEL GROWTH EXAMPLE

- Original RCT thoroughly evaluated missing data
  - MAR is most likely, but this dataset provides a unique example for demonstration purposes
- Out sensitivity analysis is intended to build on original analyses and demonstrate models for consideration when examining treatment for co-morbid populations

# METHOD: A PARALLEL GROWTH EXAMPLE

- Used latent growth modeling to compare methods of handling missing data:
  - 1) Latent growth model using maximum likelihood for missing data (i.e. MAR model)[3,7]
  - 2) Diggle and Kenward (1994) MNAR selection model, dropout is a function of previous and concurrent self-reported SU[8]
  - 3) Wu and Carroll (1988) MNAR selection model where dropout is a function of the random effects (i.e., intercept and linear slope growth factors)[9]

**Figure 1.** Parallel, piecewise latent growth curve model of substance use (SU) and attention-deficit/hyperactivity disorder (ADHD).



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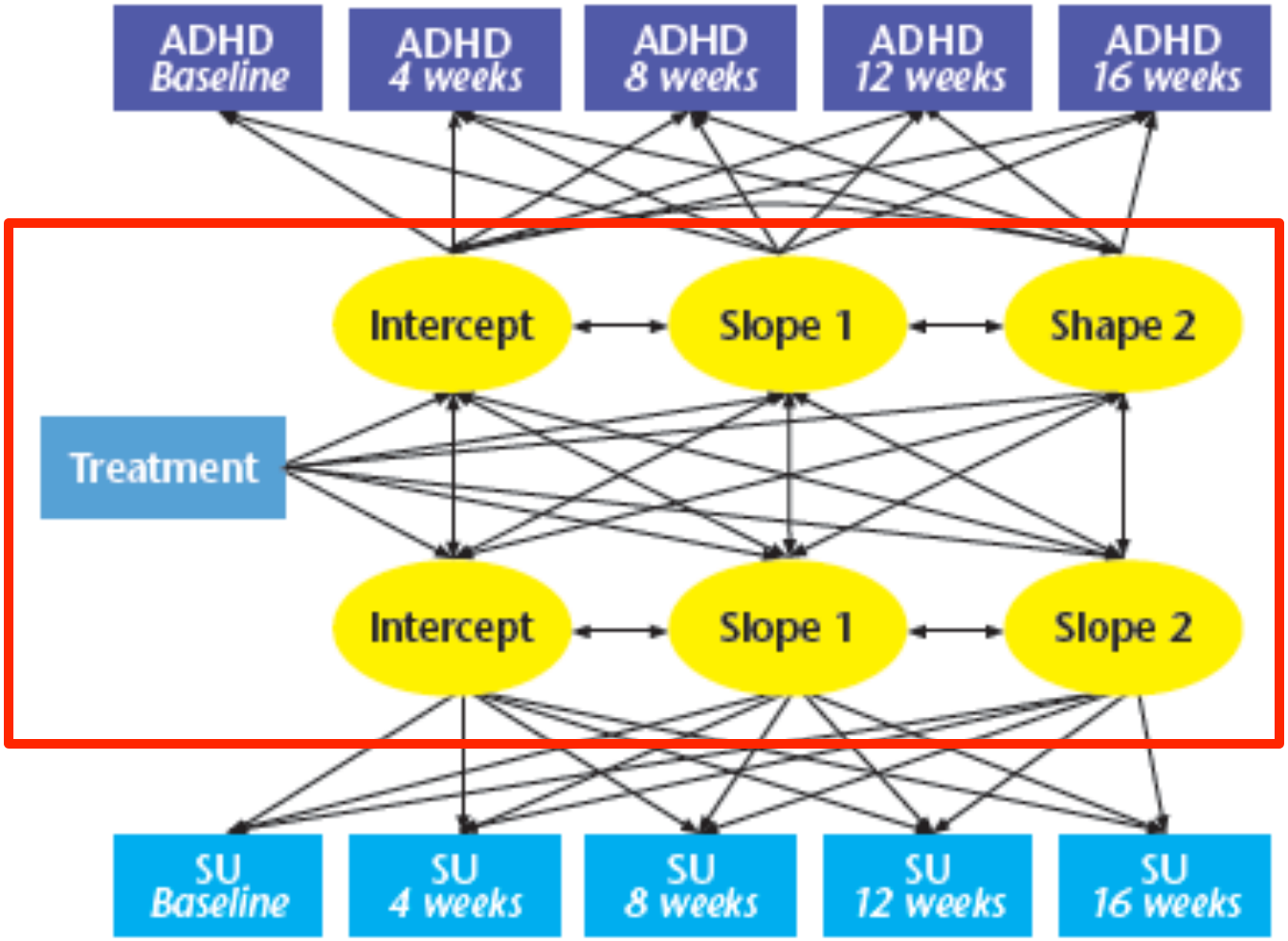


Table 1

*Piecewise, Parallel Growth Model of Substance Use (SU) and Attention-Deficit/Hyperactivity Disorder Across 16-Weeks: Missing at Random Model*

| *Outcomes* | *Unstandardized Estimate* | *Standard Error* | *p-value* |
|---|---|---|---|
| ADHD Intercept | - 1.216 | - 1.196 | 0.232 |
| SU Intercept | -0.856 | 1.087 | 0.431 |
| ADHD Slope 1 | 0.705 | 1.417 | 0.619 |
| ADHD Slope 2 | 0.284 | 0.405 | 0.483 |
| SU Slope 1 | 0.123 | 1.006 | 0.903 |
| SU Shape 2 | - 0.125 | 0.345 | 0.717 |

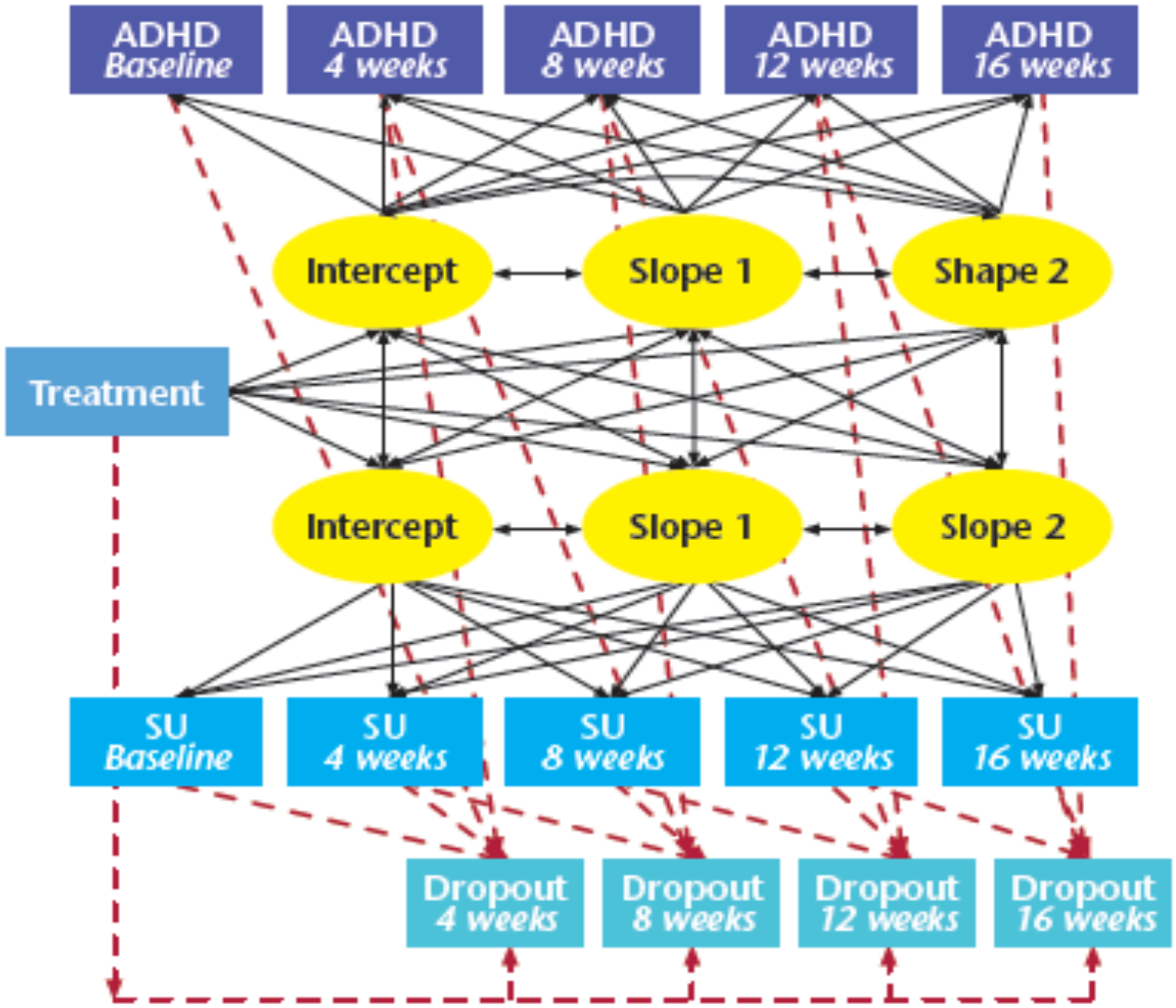
Unstandardized estimates represent the beta coefficient of the indicated random effect regressed onto treatment (osmotic-release methylphenidate + CBT = 1; 0 = placebo + CBT). *p < .05.

# RESULTS: PARALLEL GROWTH MODEL

- MAR model: No significant treatment effect on ADHD or SU, small effect sizes for both ADHD and SU (*d*=0.16, 0.10, respectively)

**Figure 2.** Parallel, piecewise Diggle-Kenward latent growth curve model of substance use (SU) and attention-deficit/hyperactivity disorder (ADHD).

Note: Dashed lines represent parameters associated with the dropout indicators.



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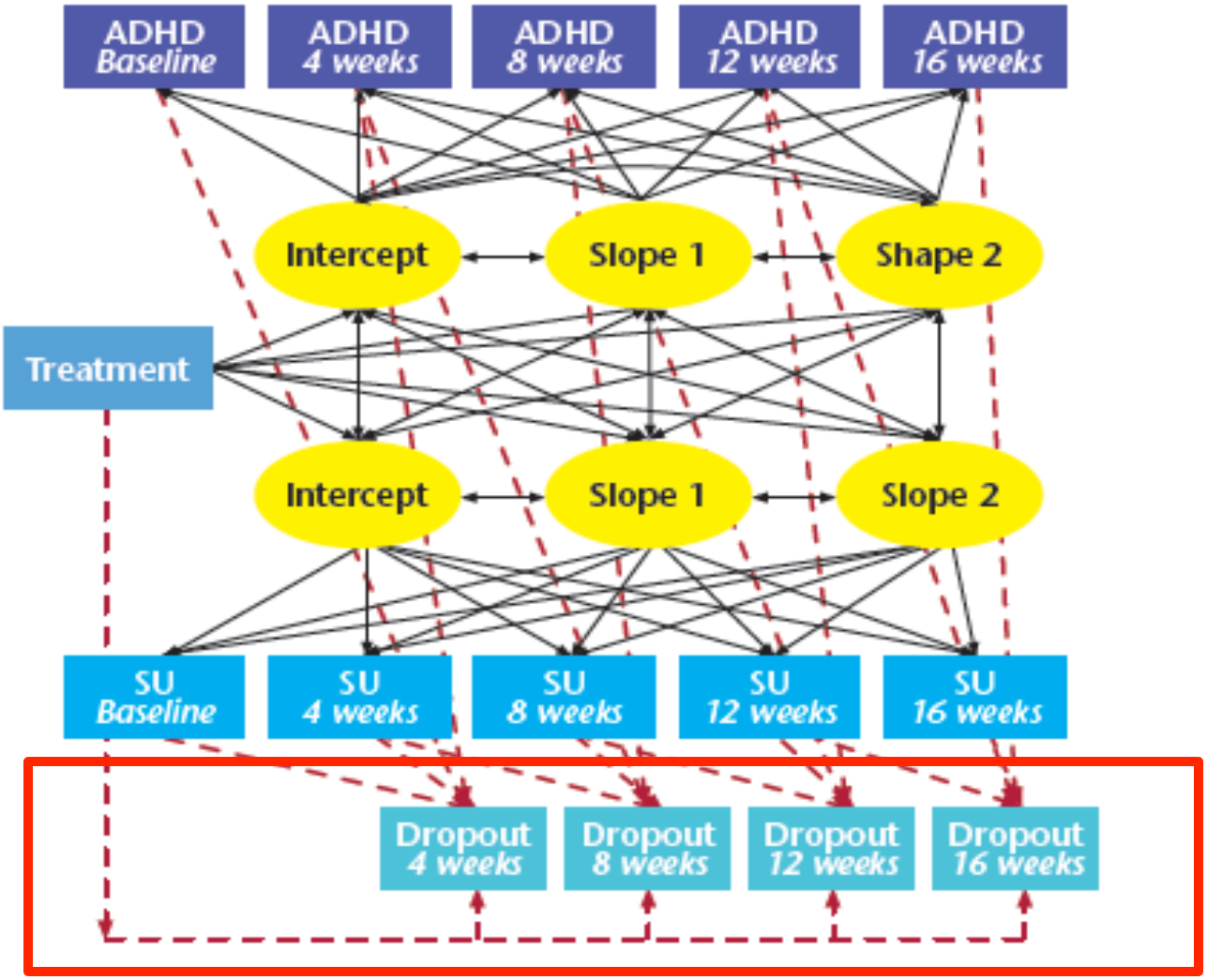


Table 2

*Piecewise, Parallel Growth Model of Substance Use (SU) and Attention-Deficit/Hyperactivity Disorder Across 16-Weeks: Missing Not at Random (Diggle-Kenward) Model*

| *Outcomes* | *Unstandardized Estimate* | *Standard Error* | *p-value* |
|---|---|---|---|
| ADHD Intercept | - 1.214 | 1.017 | 0.233 |
| SU Intercept | - 0.870 | 1.088 | 0.424 |
| ADHD Slope 1 | 0.540 | 1.449 | 0.709 |
| ADHD Shape 2 | 0.277 | 0.409 | 0.499 |
| SU Slope 1 | 0.298 | 1.017 | 0.769 |
| SU Slope 2 | - 0.144 | 0.342 | 0.673 |
| Dropout | - 0.375 | 0.248 | 0.130 |

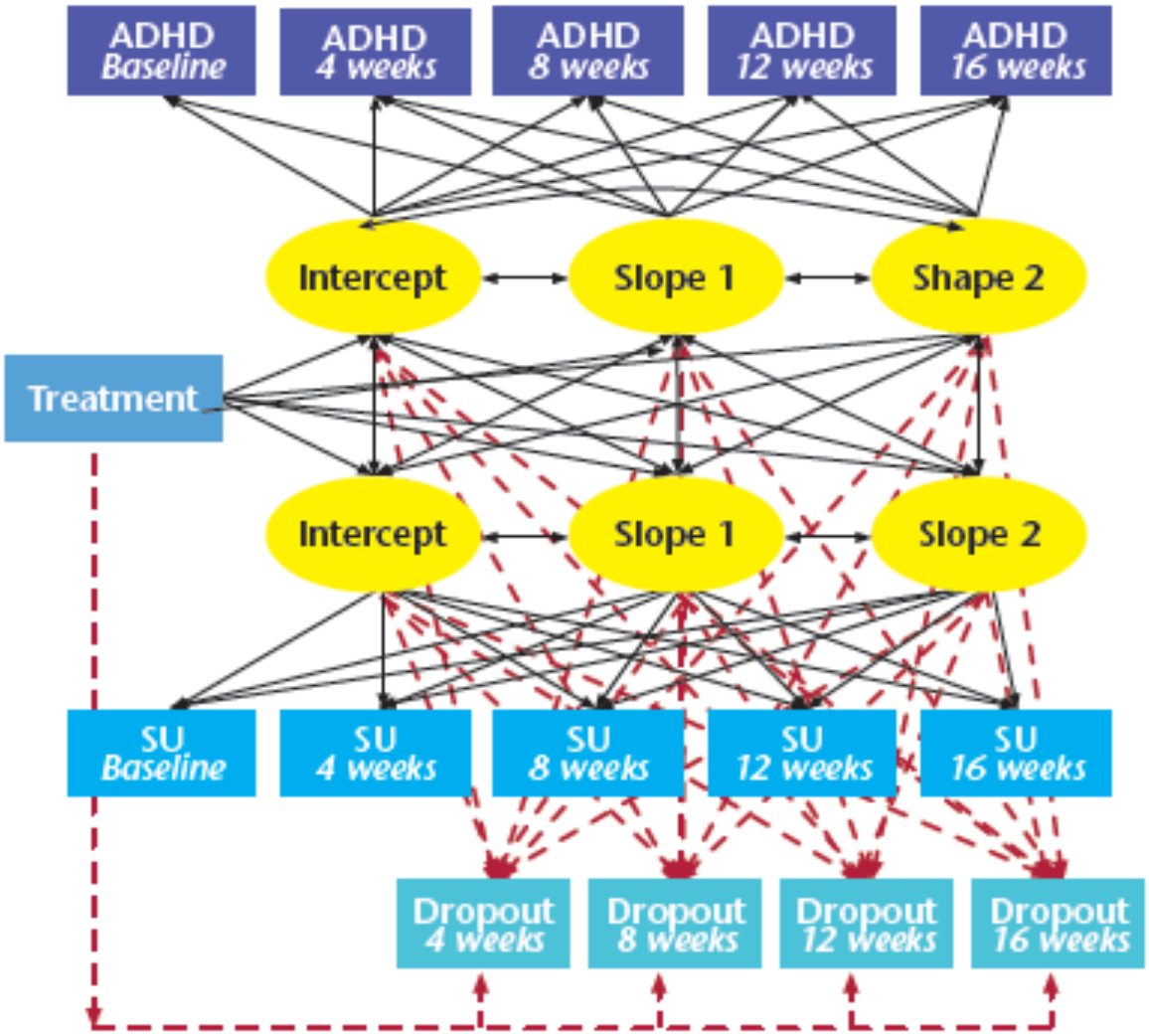
Unstandardized estimates represent the beta coefficient of the indicated random effect regressed onto treatment (osmotic-release methylphenidate + CBT = 1; 0 = placebo + CBT). *p < .05.

# RESULTS: PARALLEL GROWTH MODEL

- MNAR DK model: No significant treatment effects with similar effect sizes of ADHD (*d*=0.03) and SU (*d*=0.11)

**Figure 3.** Parallel, piecewise Wu-Carroll latent growth curve model of substance use (SU) and attention-deficit/hyperactivity disorder (ADHD).

Note: Dashed lines represent parameters associated with the dropout indicators.



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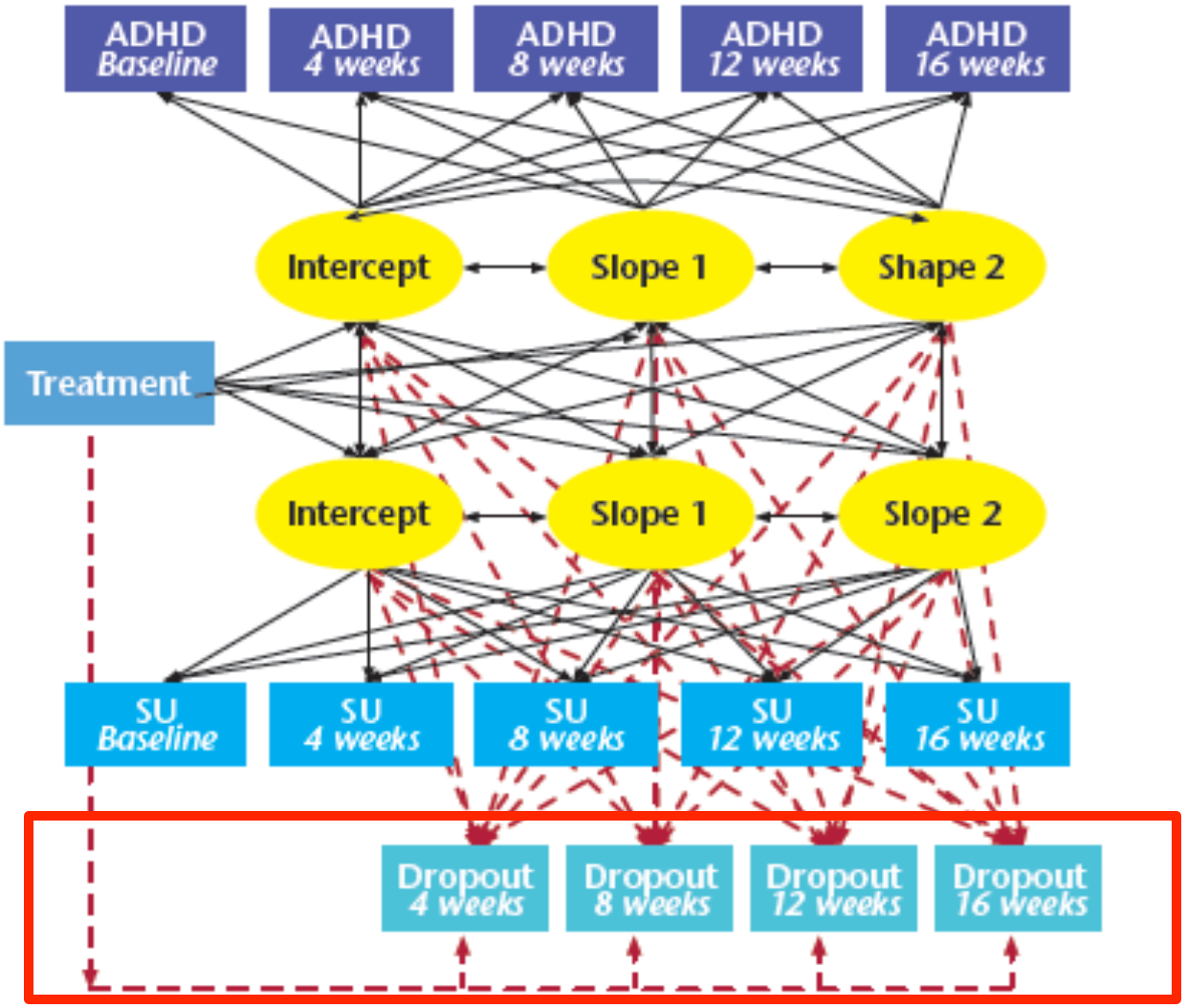

Table 3

*Piecewise, Parallel Growth Model of Substance Use (SU) and Attention-Deficit/Hyperactivity Disorder Across 16-Weeks: Missing Not at Random (Wu-Carroll) Model*

| *Outcomes* | *Unstandardized Estimate* | *Standard Error* | *p-value* |
|---|---|---|---|
| ADHD Intercept | -1.355 | 1.198 | 0.258 |
| SU Intercept | -3.745 | 2.532 | 0.139 |
| ADHD Slope 1 | 0.760 | 1.688 | 0.653 |
| ADHD Shape 2 | 0.333 | 1.172 | 0.776 |
| SU Slope 1 | 6.431 | 0.834 | <0.001* |
| SU Slope 2 | - 1.947 | 1.429 | 0.173 |
| Dropout | 4.572 | 4.541 | 0.314 |

Unstandardized estimates represent the beta coefficient of the indicated random effect regressed onto treatment (osmotic-release methylphenidate + CBT = 1; 0 = placebo + CBT). *p < .05.

# RESULTS: PARALLEL GROWTH MODEL

- The MNAR WC model evidenced a significant effect of OROS relative to placebo on SU, and the effect sizes for both ADHD (*d*=2.11) and SU (*d*=1.09) were larger than reported in the other models

# CONCLUSIONS

- Consider whether or not the additional assumptions associated with each MNAR and MAR model are reasonable [3-5,10]
- Observing how treatment effects vary across missing data methods should move research teams to explore missing data patterns and mechanism(s)[11]

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# Thank You!

smcpherson05@wsu.edu

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WASHINGTON STATE UNIVERSITY