A Large-Scale Collaborative Synthesis of Prevention and Treatment Trials for Adolescent Depression: Methodologic, Scientific, and Policy Perspectives

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In Partnership with Substance Abuse and Mental Health Services Administration (SAMHSA)
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Irwin Sandler, Arizona State University
Gracelyn Cruden, Juned Siddique, Peter de Chavez, Northwestern University
Two Fundamental Challenges Guiding our Interests in Improving Behavioral Health for Children, Youth, and Families

1. How do you improve system performance to deliver effective programs for overall benefit?
   - Discovering what interventions work under what conditions: including Prevention
   - Implement Evidence-Based Programs in Ways that Address Local Needs
     We have numerous effective prevention programs but these are not often used in practice: IOM 2009

2. How do you improve system performance for the most vulnerable, especially when the system itself is poorly functioning?
   - Disparities ➔ Health Equities
   - Scientific Equity is needed first.

 Relevant to the Social Work Grand Challenge: The Coalition for the Promotion of Behavioral Health

“Social work is ideally positioned to design, deliver, and test programs aimed at preventing behavioral health problems.”
The Concept of “Scientific Equity”

--- “Equality in the amount of scientific knowledge that is produced to understand both the causes and solutions to health inequities”

-- Including the “…Application of knowledge to narrowing the health and health service gap between culturally and linguistically diverse minority populations in the US.”

While there is a substantial amount data to indicate that health inequities exist and that they must be addressed, we need specific additional research data to guide an effective strategy to achieve health equity.

Brown, Mohr, Gallo et al. (I 2013). JAIDS  Computational Future of HIV Prevention in Minority Populations

Five Key Principles and Concepts

• Collaborative Partnership Approach to Synthesis of Research Trials
  Collaborative Data Synthesis for Adolescent Depression Trials (CDSADT).
• Methods Development for Data Synthesis
  Integrative Data Analysis
• Treatment AND Prevention
  Impact on Populations
• Informing Science Policy
  Scientific Equity
• Knowledge Exchange around Community, Practice, Policy, and Research
  Implementation Science
Our Goals of Data Synthesis for Randomized Trials

Develop novel quantitative methods integrate findings across trials
Apply these methods to prevent and treat depression in adolescence
Building and testing the next generation of comprehensive intervention strategies.

• Is there Overall Benefit of One set of Interventions versus Control?
• Understand Who Benefits/Harmed in Which Contexts (Moderator), for How Long (Growth Modeling), How Benefit Occurs (Mediation) across What Outcomes?
• Which intervention(s) are better that others for which person (Comparative Effectiveness)?

How can we learn as much as we can from combining evidence from a family of similar randomized trials?

Why the need for multiple trials?

Single trials are almost always underpowered for interesting analyses. 4 times as many observations to achieve the same statistical power for a moderation analysis than it does for a main effect analysis.

Why you don’t need exact replication of interventions/dosage across trials?

Combining even a small number of trials nearly always produces higher precision than a single trial - Brown et al., 2013 Prevention Science.

Propose that we need

• Individual level data from multiple trials
• Ongoing Involvement of those who conducted the trials
Why Individual Level Data are Needed

Three ways to conduct a data synthesis

• Meta-analysis – Combine summaries of published statistical analyses from a family of randomized trials
  Requires retrieving reported summary analyses

• Integrative Data Analysis (IDA) -- Combine individual level data from a family of studies, e.g. trials
  Requires sharing of individual level data

• Parallel Data Analysis – Have each lab conduct equivalent statistical analyses on their own dataset, then combine the summary findings into a composite analysis.
  Requires shared analytic method.

Brown et al., 2013 Prevention Science
Meta-Analysis
Integrative Data Analysis

- Trial 1
- Trial 2
- Trial 3

Shared Datasets

Trials 1-3

Synthesized Findings
Parallel Data Analysis

Diagram:
- Shared Analytic Method
- Trial 1
  - New Analysis 1
- Trial 2
  - New Analysis 2
- Trial 3
  - New Analysis 3
- Synthesized Findings
A. Theoretical results strongly favor integrative data analysis and parallel data analysis over meta-analysis for moderation and mediation.

(Brown et al., 2013 Prev Sci, Dagne et al., under review)

B. Empirical evidence also shows limitations in meta-analysis
## Meta-Analyses and “Overviews” of Meta-Analyses Provide Little Information on Moderation, Mediation, and Comparative Effectiveness

### Overview of 5 Meta-Analyses on Child Depression*

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<th>Types of Analysis (Number) Reported</th>
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From Meta-Analytic Summaries

From Original Trials

Can the potential benefits of Integrative Data Analysis be achieved?

Are Trials Similar Enough to Synthesize?

A. For Pharmacologic Treatment most trials have similar designs and interventions: Gibbons et al., 2012ab *JAMA Psychiatry*

B. For Behavioral Interventions: All Prevention Trials and Majority of Treatment Trials, Challenging Methodologic Problems with Integrative Data Analysis

Trials have different interventions: CB/IPT, Parenting, Child, Conjoint measures (harmonization), times of measurement (growth modeling), populations and contexts (comparability)

Do trialists actually share their data?

Pharmacologic Treatment: Gibbons et al., 2012ab *JAMA Psychiatry*
Prevention: *Prevention Science* Special Issue
Behavioral Prevention: . . . . .
Do Antidepressants Work for Youth?

- In Single Trials, only one medication has demonstrated effectiveness in youth – fluoxetine (Prozac)
- Meta-analysis of 27 pediatric trials (Bridge et al. 2007 *JAMA Psychiatry*)
  
  **On Depressive Symptoms**
  
  61% response to antidepressants vs
  
  50% response to placebo  (CI on gain 7%-15%)
  
  NNT = 10
Three Approaches to Synthesis of Trials beyond Meta-Analysis

• Repository of Trials –
  – Urge or require researchers to submit their trials so that others can obtain raw data
    Current NIMH Plan is to require all new trials funded by NIMH

• Access to All Trial Level Data through role as expert witness for US DoJ, Wyeth, Pfizer Pharmaceuticals (Gibbons)
  All Industry-Sponsored Fluoxetine trials in US

• Collaborative Synthesis – Partnership of trialists around data harmonization and analysis
  Our main approach
  Received one youth Venlafaxine trial, not permitted to report impact
Summary of Youth Synthesis Findings of Fluoxetine on Depressive Sx

- Slope of Depression over 6 Weeks
  Reduced 16 units on placebo, 21.6 units on fluoxetine.
- Response Rates (50% Reduction in Symptoms)
  6% for placebo, 30% for fluoxetine

No indication of variation in impact on depressive symptoms as a function of baseline level of symptoms (CDRS-R)

NIMH funded Collaborative Data Synthesis on Adolescent Depression Trials Study

**Specific Aims:**

1. Develop new statistical methods to synthesize research findings on **mediation (how)** and **moderation (for whom)** across related randomized trials.

2. Apply these methods to identify shared and unique mediational mechanisms, and moderators of intervention effects on depression in adolescents.

3. Identify key gaps in our understanding of intervention efficacy and mechanism that need to be addressed in the next generation of intervention trials.
Gathered Datasets

1. **Prevention Synthesis Dataset** has 19 prevention trials of 25 requested- approximately 76% shared

2. **Treatment Synthesis Dataset** has 14 treatment trials of 19 requested- approximately 74% shared

*This represents data from nearly 8,200 participants.*
Gathered collaborative group of stakeholders in adolescent depression prevention and treatment

Goals:

1. **Sharing methods developments**: Informing collaborators about synthesis methods issues being addressed; Making methods available to them

2. **Working on substantive questions**: Getting their input on prioritizing intervention mediator and moderators examined; Involving collaborators as manuscript co-authors; Disseminating findings to inform their work and trials.

3. **Accurate representation of trials**: Presenting trial level codings, summaries and hearing collaborators’ input

4. **Recommendations for the next generation of trials**: Work with collaborators to develop useful guidelines for future trials
CDSADT Collaborators

**Funding: National Institute of Mental Health R01-MH040859; Amy Goldstein- Project Officer**

**Study Team**
Hendricks Brown (PI)
George Howe (Co-I)
Tatiana Perrino (Co-I)
Hilda Pantin (Co-I)
Ahnalee Brincks
Gracelyn Cruden
Getachew Dagne
Peter De Chavez
Ophelia Hernandez
Shi Huang
Lei Liu
Juned Siddique

**Scientific Advisory Board**
David Brent
Guillermo Bernal
Graham Emslie
Velma Murry

**Other Partners**
Anne Sperling- NIMH

**Advocates**
David Shern, Mental Health America

**Individual Study Investigators**
William Beardslee
Guillermo Bernal
David Brent
Steve Brunwasser
Greg Clarke
Bruce Compas
Guy Diamond
Tom Dishion
Graham Emslie
Judy Garber
Jane Gillham
Tracy Gladstone
Nancy Gonzales
John March
Ann Mauricio
Laura Mufson
Velma Murry
Hilda Pantin
Guillermo Prado
Cleve Redmond
Irwin Sandler
Richard Spoth
Beth Stormshak
Jose Szapocznik
Jenn-Yun Tein
Ben Van Voorhees
Sharlene Wolchik
Jamie Young

**Northwestern Medicine**

Michael M. Davis Lecture Series SSA 24
Collaborative Data Sharing Model

- **Weekly research meetings**
- **Quarterly Collaborators Meeting**
- **Annual Face-to-Face Special Meetings**

Described in:
Key Elements

Data Use Agreements, Human Subjects Protection
Send/Receive the Data, Document, and Organize
Understand trial intricacies
Check Coding Decisions around Harmonization and Trial-Level Variables
Prioritize synthesis work around critical questions
Co-author papers
Why would Collaborators do all this for 5 years (and longer)?

• General Community-Based Participatory Research (CBPR)
  – Trust, Respect, Equal Voice

• Mutual Self-Interest – Saul Alinsky,
  – Front seat to next generation trials
  – Help their own analyses
Our Participatory Research Approach Differs from the Coming NIMH Policy on Depositing Trial Data in a Repository for others to analyze

- NIMH policy to make data widely available for others to analyze as quickly as possible

- We don’t provide results for any single trial, not competing
  Imputed data on unmeasured outcomes provided back to individual investigators for their own analysis

- Coding decisions are continually reviewed for accuracy by trialists
  A great deal of Tacit Knowledge about these trials remains in the hands of the investigators
We all make mistakes in research

Although association preferences documented in our study theoretically could be a consequence of either mating or shoaling preferences in the different female groups investigated (should we cite the crappy Gabor paper here?), shoaling preferences are unlikely drivers of the documented patterns both because of evidence from previous research and inconsistencies with a priori predictions. Our methods closely followed those of published mate choice experiments in this system (Tobler et al. 2009a,b; Plath et al. 2013).

Culumber ZW et al., Variation in Melanism and Female Preference in Proximate but Ecologically Distinct Environments. Ethology

- Volume 120, Issue 11, 1090–1100, November 2014 (Wiley Online Library)
• Data Synthesis involving Individual Level Data

Integrative Data Analysis –
Consort Diagram on Prevention Trials:
Inclusion/Exclusion: Population, Intervention, Trial

Original trials requested (n= 24)

Excluded (n= 6)
° Not meeting inclusion criteria (n= 0)
° Declined to participate (n= 5)
Data not ready (n= 1)

Original requests (18)

19 Included Trials

Additional trials requested to aid harmonization (n= 1)

Trials in dataset: 19
Participants in dataset: 5558
° Excluded from analysis (n=0)

Analysis

Population: 11 – 17, non-clinical
Intervention: Prevent internalizing or externalizing if family involved
Design: Quality randomized trial with long term follow-up
Excluded: Teacher-delivered intervention
Trial List

• Familias Unidas 1  (Hispanic)
• Familias Unidas II  (Hispanic)
• Familias Unidas DJJ  (Hispanic)
• Familias Unidas CDC  (Hispanic)
• Family Talk
• Family Bereavement
• New Beginnings Program
• Bridges  (Hispanic)
• Project Alliance I
• Project Alliance II
• K-IPT
• NARSAD
• IPT-AST
• ADEPT
• PODS
• Penn Resiliency Program I
• Penn Resiliency Program II
• CATCH-IT  (Internet)
• Preparing for the Drug-Free Years
First Set of Research Questions on Prevention Trials

1. Are there intervention main effects of Prevention Programs on the adolescent depressive symptoms outcome?

2. Are there differential intervention benefits by adolescents’
   • gender
   • age
   • Race/Ethnicity
   • baseline level of depressive symptoms

3. Are there differential intervention benefits by intervention:
   • focus (i.e., depression-focus vs. non-depression focus as primary outcome)
   • target (i.e., child alone, parent alone, child and parent together/conjointly)
Data

- 5,558 adolescents across 19 prevention trials w/ inclusion/exclusion criteria.
- 25 distinct, active intervention arms and 19 control conditions in these 19 trials.
- 33,045 assessments of depression over 19 trials through 6 years follow-up.
Methodologic Challenges

Trials Use **Different Measures** to Assess Depressive Symptoms

Trials Use **Different Time Points** to Assess Outcomes across Time
## Depressive Symptom Measures by Trial

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<th>Youth Self-Report</th>
<th>Behavior Problem Checklist</th>
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Participant Retention through 24 months

Trial Size at Baseline (N) and Follow-Up Percents T1-T5

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<td>86 %</td>
<td>86 %</td>
<td>83 %</td>
<td>39 %</td>
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<td>86 %</td>
<td>83 %</td>
<td>88 %</td>
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<td>93 %</td>
<td>88 %</td>
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<tr>
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<td>93 %</td>
<td>88 %</td>
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<tr>
<td>12</td>
<td>581</td>
<td>88 %</td>
<td>85 %</td>
<td>86 %</td>
<td>78 %</td>
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<tr>
<td>10</td>
<td>94</td>
<td>87 %</td>
<td>87 %</td>
<td>94 %</td>
<td>86 %</td>
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<tr>
<td>8</td>
<td>542</td>
<td>57 %</td>
<td>91 %</td>
<td>86 %</td>
<td>88 %</td>
<td>81 %</td>
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<td>6</td>
<td>242</td>
<td>97 %</td>
<td>96 %</td>
<td>86 %</td>
<td>88 %</td>
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<tr>
<td>3</td>
<td>257</td>
<td>99 %</td>
<td>98 %</td>
<td>97 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Amount of Missing Data is “Exceptionally” Large

- 75% of the outcome measures (e.g., CDI) are missing across the 19 trials.
- 43% of the trials are missing **ALL** outcome measures across one of the 6 time windows.
- Missing by Design (Missing at Random)
- Approaches for this Paper
  - Use a Single Factor Model for Internalizing/Depressive Symptoms
  - Use Growth Curves to Fill in Across Time
  - Full Information Maximum Likelihood to Handle Missing Variables
Measurement Model Across Time
Testing for No Treatment Effect at Baseline

Model Fit:
- LL = -26889.948
- BIC = 54207.106
- CFI = .964
- SRMR = .011
Handling Time of Measurement Using Growth Modeling

• A few trials have very long follow-ups, only a few have data beyond 2 years of randomization so these times are dropped

• Trials have varying numbers and timing of assessments post randomization.
Modeling Change through Growth Trajectories

Need a Flexible Model

Alternative Growth Patterns

- Slope Increases over Time
- Slope Decreases over Time
- Temporary Gain Offset by Worsening over Time

Transform

Time
Transforming the Time Scale

Empirically Determined Growth Model: Rapidly Increases then Slowly Increases, Gain is Permanent over 2 Years

\[ Y = 1 - \frac{2}{(2 + \text{Month})} \]

Intercept and “Slope” on this Transformed Scale
Longitudinal Intervention Model
(Second-Order Growth Model)
Summaries of Analysis Levels

• Individual Level Factors
  – Time of measurement, which measures observed
  – Age, Gender, Intervention Status
• Arm-Level Factors
  – What type of intervention is delivered
  – How it is delivered
• Trial-Level Factors
  – Mean values for Intervention and “Slope”
Overall Treatment Effects: Significant Reduction in Symptoms over a Two-Year Period

15% Faster Reduction Prevention Versus Control
Overall Effect: Interventions Reduce Symptoms Significantly Faster than does Control Condition

\[
Y = \text{Slope}_{\text{intervention}} - \text{Slope}_{\text{control}}
\]

\[B = -0.416, \ SE = 0.178, \ p = 0.02\]

*More negative values = desired effect

Michael M. Davis Lecture Series SSA
Moderated Effect: Depression Focused Interventions Have Stronger Reduction in Symptoms than do Non-Depression Focused Interventions

\[ Y = \text{Slope}_{\text{intervention}} - \text{Slope}_{\text{control}} \]

\[ B = -0.967 (0.408), \quad p = 0.018 \]
Depression vs. Non-Depression Intervention Focus

![Graph: Trajectory of Internalizing vs. Time (log)]

Control: Non-depression target
Tx: Non-depression target
Control: Depression target
Tx: Depression target

1.187(0.593) p = 0.045
Intervention vs Control for Trials that are Depression Focused and Those that are Not

**Depression-Focused Intervention**
- N=14
- \(-1.187(0.593)\) \(p = 0.045\)

**Non-Depression-Focused Intervention**
- N=11
- \(B = -0.064, SE = 0.340, p = 0.850\)

*More negative values = desired effect*
Variation in Growth Trajectories and Differential Impact on Initially Higher Internalizing and Lower Internalizing

Latent Class Trajectories

Control

Intervention

Control

Intervention

37%

63%
Intervention Impact on African American and Hispanic Youth
Intervention Effect on African Americans and for Hispanics/Latinos in trials not designed specifically for Hispanics

Overall
African Americans (n = 491)
Hispanics/Latinos (n = 286)

Effects and Confidence Bounds by Select Race and Ethnic Groups

Slope of Symptom Change

Effects and Confidence Bounds
Select Race and Ethnic Group

Overall
African American
Hispanic

Slope of Symptom Change

-3  -2  -1  0  1
Impact of a Hispanic-Focused Interventions on Hispanic Youth: 3 Familias Unidas Trials Demonstrate Significant Benefit on Depressive Sx When Hypothesized Mediator of Family Communication is Poor

Perrino, Pantin et al. 2014 *Prevention Science*
There are few trials specifically designed for African Americans or Hispanics

• Health (and Health Service ) Disparities

• Health Equity

• Scientific Equity
What Evidence is Available to Show Whether Prevention Programs/Strategies Work for Hispanics?

<table>
<thead>
<tr>
<th>Race/Ethnic Group</th>
<th>In 19 Preventive Trials</th>
<th>In NIMH, NIDA, NIAAA Funded Trials Specific to this Population</th>
<th>Percent in US Population of Youth 10-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>491 (9%)</td>
<td>8 (4%)</td>
<td>17%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>286 (5%) general + 1415 (25%) Hispanic specific</td>
<td>16 (9%)</td>
<td>21%</td>
</tr>
<tr>
<td>Other</td>
<td>4,781 (61%)</td>
<td>159 (87%)</td>
<td>62%</td>
</tr>
<tr>
<td>Total</td>
<td>5,558</td>
<td>183</td>
<td>100%</td>
</tr>
</tbody>
</table>
Child-Focused Preventive Interventions Have Stronger Effects on Depressive Sx Compared to Non-Child Focused

\[ Y = \text{Slope}_{\text{intervention}} - \text{Slope}_{\text{control}} \]

\[ B = -0.861, \ SE = 0.412, \ p = 0.04 \]

*More negative values = desired effect*
Summary & Conclusions

• **Collaborative Data Synthesis is Viable and Successful**
  - Methodology
  - Partnership that redefines relationship between researchers, policy makers, advocates, practitioners

**Early Findings**
- Prevention Effective and Sustained Over 2 Years.
- Significant Impact for both lower and higher depressive symptoms
- Interventions deliberately focusing on depression have much stronger impact
- Important moderators and mediators
  - Child focused interventions stronger overall effect
  - Family-based interventions not effective for everyone BUT
    They are successful when parent-child communication is poor

**Policy Implications**
- Prevention, Integrated with Treatment for Population-Level Impact
- Multiple prevention interventions to match youth and family needs

• **Scientific Equity is far from being Achieved**
  - Hispanic-Focuses Interventions targeting Poor Family Communication Improve Internalizing and Externalizing
  - No Clear Evidence that African-American or Hispanic Youth Gain from Interventions Not Specific to these Populations
To Address Policy Needs, it Requires an Integration/Alignment of Research, Practice, Policy, Advocacy, and Methodology
CDSADT Publications


