Lessons from LAMS: Longitudinal Assessment of Manic Symptoms

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Conflict of Interest/Funding

- **Royalties**
  - CFPSI: *MF-PEP and IF-PEP Workbooks*
  - Guilford Press:
    - *Raising a Moody Child: How to Cope with Depression and Bipolar Disorder*
    - *Psychotherapy for Children with Bipolar and Depressive Disorders*
  - APPI:
    - *Clinical Manual for Management of Bipolar Disorder in Children and Adolescents*
    - *Children’s Interview for Psychiatric Syndromes (ChIPS)*

- **Grant Support**: NIMH
Manic Symptoms and LAMS

- There is considerable debate over the meaning of symptoms associated with mania and their relationship to various bipolar spectrum disorders (BPSD).

- **Goal of LAMS:** investigate the rate, longitudinal course, diagnostic evolution, and risk factors associated with elevated symptoms of mania (ESM).
Presentation Objectives

Using LAMS data…

- Identify different **developmental trajectories** of children with baseline ESM
- Contrast features of youth with BP-I and BP-NOS
- Name **risk factors** for the development of BPSD in childhood
- Examine characteristics of DMDD
- Compare youth with BPSD and ADHD
- Examine patterns of **medication & service utilization**
LAMS Background

- LAMS Study was created to investigate bipolar disorder’s phenomenological hallmark, elevated symptoms of mania (ESM)
  - Few epidemiologic and no longitudinal studies of youth selected only for ESM
  - Many youth with ESM may not meet diagnostic criteria for BP-I or BP-II but still suffer from significant psychopathology and dysfunction

Horwitz, et al. (2010)
LAMS Background: Study Objectives

1. Document **rate of ESM** in 6-12 year old outpatients

2. Describe the **longitudinal course and diagnostic evolution** of ESM from childhood to adolescence in this cohort

3. Identify **childhood risk factors** that predict poor functional outcomes in adolescence among children who present with ESM at study entry

*Horwitz, et al. (2010)*
LAMS Methodology

- 2-phase prospective design
  - Large screening group
  - Smaller diagnostic assessment group
- Outpatient population, 6-12 years at 9 sites in 4 Midwestern cities
- PGBI-10M used to screen for ESM to create two groups:
  - **ESM+** (score ≥12): invited to enroll in longitudinal portion of study
  - **ESM–** (score ≤11): one matched control for every 10 consecutive ESM+ enrolled

Horwitz, et al. (2010)
LAMS Methodology

PGBI-10M items – in the past 2 weeks:

1. Has your child experienced periods of several days or more when, although he/she was feeling unusually happy and intensely energetic (clearly more than your child’s usual self), he/she was also physically restless, unable to sit still, and had to keep moving or jumping from one activity to another?

2. Have there been periods of several days or more when your child’s friends or other family members told you that your child seemed unusually happy or high – clearly different from his/her usual self or from a typical good mood?
LAMS Methodology

3. Has your child’s **mood or energy shifted rapidly** back and forth from happy to sad or high to low?

4. Has your child had periods of **extreme happiness and intense energy** lasting several days or more when he/she also felt much more **anxious** or tense (jittery, nervous, uptight) than usual (**other than related to the menstrual cycle**)?

5. Have there been **times of several days or more** when, although your child was feeling **unusually happy and intensely energetic** (clearly more than his/her usual self), he/she also had to struggle very hard to control inner feelings of **rage** or an urge to smash or destroy things?
LAMS Methodology

6. Has your child had periods of extreme happiness and intense energy (clearly more than his/her usual self) when, for days or more, it took him/her over an hour to get to sleep at night?

7. Have you found that your child’s feelings or energy are generally up or down, but rarely in the middle?

8. Has your child had periods lasting several days or more when he/she felt depressed or irritable, and then other periods of several days or more when he/she felt extremely high, elated, and overflowing with energy?
LAMS Methodology

9. Have there been periods when, although your child was feeling unusually happy and intensely energetic, almost everything got on his/her nerves and made him/her irritable or angry (other than related to the menstrual cycle)?

10. Has your child had times when his/her thoughts and ideas came so fast that he/she couldn’t get them all out, or they came so quickly that others complained that they couldn’t keep up with your child’s ideas?
Initial Screening Results

- Of 3,329 children/parents, 79% (2,622) were eligible and agreed to participate
- 66% male, 67% white
- Mean age=9.4 yrs (SD=2.0, range=6.0-12.9)
- 41% Medicaid, 53% private insurance, 6% both
- 42.9% ESM+, 57.1% ESM–
- ESM+ more likely to be Latino, younger, and supported by Medicaid
- No significant sex or race differences

Horwitz et al. (2010)
Initial Screening Results

PGBI-10M symptom endorsement: ESM+ vs ESM–

- All 10 items more frequently endorsed by ESM+
  - 4 endorsed most frequently by ESM+
    - Unusually happy and intensely energetic, but everything gets on nerves and makes angry
    - Mood/energy shifts rapidly from happy to sad or high to low
    - Feelings/energy are generally up or down but rarely in the middle
    - Days unusually happy and intensely energetic, yet also physically restless, shifting activities

Horwitz et al. (2010)
Initial Screening Results

- Items that best discriminated ESM+ and ESM–
  - Days more depressed/irritable, then days or more extremely high, elated, overflowing with energy
  - Unusually happy and intensely energetic, but everything gets on nerves and makes angry
  - Days or more of extreme happiness or energy, yet also anxious or tense
  - Days or more unusually happy and energetic, yet also struggles with rage or urge to smash/destroy

Horwitz et al. (2010)
Conclusions: Initial Screening Results

- 42.9% of participants were ESM+
  - Mania diagnosis has been reported in ~16% of outpatients 12 or younger\(^1\)
  - Manic symptoms may be more common in young outpatients than previously thought

- ESM+ and ESM– children appeared dissimilar

- Though the items best discriminating ESM+ and ESM– are specific to BD, the diagnostic evolution may not be homotypic

\(^1\) Wozniak et al. (1995).
Characteristics of ESM+ Children: Background

- Previous studies: ESM+ inpatients (who don’t meet BD diagnostic criteria) experience marked psychological dysfunction and psychopathology\(^1,2\)

- LAMS ?: Which ESM+ youth will develop BD?

- Implications of a BD diagnosis (whether correct or incorrect) make this question very important

Goals:
- Delineate relationship between ESM and BD
- Define characteristics of children with ESM

Characteristics of ESM+ Children:  
Method

- Of 1,124 ESM+ children in the screening group, 621 (55%) participated in the longitudinal study
- 86 ESM– (demographically matched) children enrolled in longitudinal study
- Visits every 6 months, full annual evals

Findling et al. (2010)
Instruments

- Demographic info (including insurance type)
- Diagnoses (K-SADS-PL-W)
  - Filtered ratings: KMRS, KDRS
  - BP-NOS criteria same as in COBY study
- Unfiltered ratings (PGBI-10M, YMRS, CDSR-R, CASI-4R, SCARED-P)
- Medication history
- Functional assessment (CGAS)
- Family history (Family History Screen-FHS)
- Service use (SACA)

Characteristics of ESM+/ESM- Children: Demographics & Rate of Diagnoses

Demographics: ESM+ compared to ESM-
- ↓ living in intact families
- ↓ functioning (CGAS scores)
- ≈ age, sex, race, ethnicity, insurance status
- ≈ use of special education, number of prior psychiatric hospitalizations

Psychiatric diagnoses
- None: 9 ESM+ (1.4%) < 5 ESM– (5.8%)
- Mean number of diagnoses: 2.5 (SD 1.3)
  - ESM+: 2.6 (SD 1.3) > ESM–: 2.0 (SD 1.2)

Findling et al. (2010)
Characteristics of ESM+/ESM- Children: *Diagnoses and Rating Scales*

- ↑ mood/BPSD diagnoses
- ↑ scores: baseline YMRS, PGBI-10M, CDRS-R
- ↑ disruptive behavior scores: CASI-4R ODD, CD, ADHD subscale scores
- ↑ SCARED-P scores
- ↓ PDD diagnoses
- ≈ diagnoses: depression, psychosis, anxiety, adjustment, and ADHD

Findling et al. (2010)
Characteristics of ESM+/ESM- Children: *Psychotropic Medication Exposure*

- Overall: 63% prescribed ≥1 psychotropic medication
- ≈ current, past overall prescription rates
- ≈ prescription rates for specific medication categories (lithium, anticonvulsants, antidepressants, antipsychotics, stimulants, α₂ agonists)

*Findling et al. (2010)*
Characteristics of ESM+ Children: with and without BD

**ESM+ with BD (n=155, 25%)**
- ↑ psychiatric hospitalizations
- ↑ age
- ↓ functioning
- ↑ biological mothers and fathers with elevated mood
- ↑ rate of currently prescribed antipsychotics, mood stabilizers, and anticonvulsants
- ↑ scores on all unfiltered mood symptom ratings

**ESM+ without BD (n=466, 75%)**
- ↑ current disruptive behavior disorders (CD, ODD, disruptive behavior NOS)

Findling et al. (2010)
ESM+ Conclusions

- ESM are common in outpt psychiatric settings
- ESM are associated with substantially increased rates of BDs → may be a useful screening aid
- ESM also associated with other diagnoses; may be a marker of severe pathology rather than BD
- ≈ ¼ of ESM+ met diagnosis for a BPSD
  - BP-NOS > BP-I > CYC > BP-II
  - ESM+ had ↑ depressive, ADHD and anxiety Sx

Findling et al. (2010)
Characteristics of Children with ESM: Conclusions

- ESM+ w/o BD
  - *Greater* rate of disruptive behavior disorders (DBD) suggests 2 ESM+ profiles
    1. Having a BPSD
    2. Having a DBD and some mood symptoms

- Further longitudinal data are required to examine which factors are associated with evolution from ESM to BPSD, risk and protective factors associated with long-term outcomes in the population

*Findling et al. (2010)*
Course of ESM: Background

- Children assessed at two time points: screening (SCR) and baseline (BL), 3-6 weeks later
- Study sought to describe diagnostic differences among the following groups:
  - Persistent ESM+
  - Progressed to ESM+
  - Remitted ESM+
  - Persistent ESM–

Frazier et al. (2011).
Course of ESM: Methods

Sample
- 383 (55%) Persistent ESM+
- 11 (2%) Progressed to ESM+
- 225 (33%) Remitted ESM+
- 73 (11%) Persistent ESM–

- No differences in age, sex, or insurance status
  - Race and ethnicity differences were small, largely accounted for by Progressed to ESM+

- BL YMRS and CDRS-R scores ↓ in Persistent ESM– group; ↑ in Persistent ESM+ group

Frazier et al. (2011).
### Course of ESM & BPSD Diagnostic Rates

#### Diagnostic Rates by Elevated Symptoms of Mania (ESM) Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Persistent ESM+ (n=383), %</th>
<th>Progressed to ESM+ (n=11), %</th>
<th>Remitted ESM+ (n=225), %</th>
<th>Persistent ESM– (n=73), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any BPSD</td>
<td>162</td>
<td>33.4*</td>
<td>27.3</td>
<td>12.0</td>
<td>5.5</td>
</tr>
<tr>
<td>BP-I</td>
<td>71</td>
<td>15.4</td>
<td>27.3</td>
<td>3.1</td>
<td>2.7</td>
</tr>
<tr>
<td>BI-II</td>
<td>3</td>
<td>0.8</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>CYC</td>
<td>11</td>
<td>2.6</td>
<td>0</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>BP-NOS</td>
<td>77</td>
<td>14.6</td>
<td>0</td>
<td>8.4</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*Persistent ESM+ vs All Others, Relative Risk, 3.04, p,.001

Frazier et al. (2011).
Course of ESM & BPSD Diagnoses:
Persistent ESM+:

- 3x ↑ rate of BPSD dx

- Compared to Persistent ESM– group
  RR= 6.10; 95% CI, 2.33-19.14

- Compared to Remitted ESM+ group
  RR= 2.79, 95% CI, 1.89-4.20

Frazier et al. (2011).
Course of ESM: PGBI-10M Scores

- BL PGBI-10M administration improved prediction of BPSD diagnosis substantially over using only SCR administration ($\Delta R^2 = 0.10, \Delta X^2_1 = 50.06, \ P < .001$)
- Maintained when time between SCR and BL was included in model ($\Delta R^2 = 0.10, \Delta X^2_1 = 46.95, \ P < .001$)

Frazier et al. (2011).
Course of ESM: Conclusions

- Persistent or increasing levels of ESM are strongly associated with BPSD diagnoses.
- Persistent ESM+ did not increase odds of having other diagnoses or suicidal ideation/behavior.
- Persistently elevated PGBI-10M scores (≥20) appear to predict BPSD fairly specifically.
  - However, only a minority of individuals with moderate levels of persistent ESM+ met criteria for a BPSD diagnosis (moderate ESM+ levels can occur in individuals with other common disorders, such as ADHD).
- Findings support repeated administration of PGBI-10M.

Frazier et al. (2011).
24-Month ESM Trajectory: Hierarchical Linear Modeling

- C1: High and rising (8.3%)
- C2: Unstable (6.0%)
- C3: High and falling (38.5%)
- C4: Low and falling (47.2%)

Findling et al. (under review).
BP-NOS Phenomenology: Background

- As the previous data have demonstrated, BP-I is relatively rare in youth.
- “Subsyndromal” (eg, BP-NOS) episodic mood disturbances are as common as BP-I.
- BP-NOS may also lead to negative outcomes.
- COBY: operationalized criteria for BP-NOS.

Hafeman et al. (in press).
BP-NOS: COBY & LAMS Criteria

1. Elated mood + 2 associated manic symptoms
2. Change in level of functioning
3. Symptoms present for ≥ 4 hrs within 24-hrs
4. ≥ 4 episodes of 4 hours’ duration (can be on separate days or consecutive)
BP-NOS Phenomenology: Background

- Is BP-NOS really part of a BP spectrum or is it something else?
  - *Clinical samples*: high rate of progression from BP-NOS to BP-I or BP-II
  - *Epidemiologic samples*: much lower degree of progression

- COBY: Summary of findings
  - BP-NOS: large degree of functional impairment and family history of BD. Manic episodes did not significantly differ from BP-I, BP-II.

BP-NOS Phenomenology: Background

Research question:

- Data from a clinical sample supports a spectrum of disorder
- Will this hold true with a more broadly defined population of youth with non-specific (and sometimes non-episodic) manic-type symptoms?
- LAMS BL: ≈ ¼ fit criteria for BPSD (BP-I, BP-II, CYC, BP-NOS)

Hafeman et al. (in press)
BP-NOS Phenomenology: Hypotheses

- BP-NOS ≈ BP-I < BPSD–: overall functioning
- BP-NOS ≈ BP-I: comorbidity
- BP-NOS ≈ BP-I: ↑ parental hx of mania
- BP-NOS and BP-I:
  - Qualitative differences in phenomenology of manic symptomatology

Hafeman et al. (in press)
BP-NOS Phenomenology: Demographics

- Of 707 total participants at intake:
  - BP-I: 71
  - BP-II: 3
  - BP-NOS: 88
    (11 also satisfied criteria for CYC)
  - 545 did not meet criteria for BPSD

- BPSD (n=704, BP-II excluded)
  - Slightly older than BPSD-

Hafeman et al. (in press)
BP-NOS Phenomenology: *Reasons for BP-NOS Diagnosis*

- Insufficient duration
  - 98%: episodes < 7 days

- Insufficient threshold of symptom severity
  - Mild: 81% met criteria for manic/hypomanic episode
  - Moderate: 24% met criteria

- Small minority (7%) met both duration and sx criteria for hypomania, but did not have MDE (one child did, but had marked impairment during hypomania)

_Hafeman et al. (in press)_
BP-NOS Phenomenology: Symptom Severity and Overall Functioning

- **BP-NOS ≈ BP-I > BPSD**–
  - Current mood symptoms
  - Current global impairment

- **BP-I > BP-NOS > BPSD**–
  - Worst mood symptoms
  - Worst global impairment

_Hafeman et al. (in press)_
BP-NOS Phenomenology: Comorbidity

- **Total sample:**
  - ADHD, 67%
  - Disruptive behavior disorders, 37%
  - Anxiety 29%
  - PDD 6%

- BP-NOS ≈ BP-I > BPSD‒: Conduct d/o
- BP-NOS ≈ BPSD‒ > BP-I: ODD

Hafeman et al. (in press)
BP-NOS Phenomenology: Depressive, Suicidal & Psychotic Symptoms

- **Total sample:**
  - Suicidal ideation 19%
  - Suicidal behavior or attempts 2%
  - Lifetime depressive episode 15%
  - Psychotic features 7%

- **BP-I > BP-NOS ≈ BPSD–:** suicidal ideation
- **BP-I > BPSD-:** suicidal behavior/attempts
- **BP-I > BP-NOS > BPSD-:** psychotic features

Hafeman et al. (in press)
BP-NOS Phenomenology: Treatment History

- **Total sample:**
  - Ever hospitalized 9%
  - Ever medicated 63%
    - Stimulants 57% (BP-I > BPSD-)
    - Antipsychotics 27%
    - Antidepressants 20% (BP-I ≈ BP-NOS ≈ BPSD-)
    - Alpha 2 agonists 15%
    - Mood stabilizers 13%
- BP-I > BP-NOS > BPSD–: antipsychotics, mood stabilizers
- BP-I > BP-NOS ≈ BPSD–: ever hospitalized, ever medicated, alpha 2 agonist

Hafeman et al. (in press)
BP-NOS Phenomenology: Family History

- **Total sample**: Parental history of...
  - Depression 63%
  - Anxiety 53%
  - Substance dependence 46%
  - Conduct disorder 40%
  - ADHD 27%
  - Suicide attempt 24%
  - Mania 20%
  - Psychosis 11%

- BP-NOS ≈ BP-I > BPSD–: Mania
- BP-NOS > BPSD–: CD, psychosis

_Hafeman et al. (in press)_)
BP-NOS Phenomenology: 
Manic Symptoms--BP-I > BP-NOS
(Most Severe Lifetime Episode)

- Irritability: 92% vs 73%
- Distractibility: 82% vs 64%
- Racing thoughts: 76% vs 64%
- Poor judgment: 72% vs 51%
- ↓ need for sleep: 66% vs 41%
- Flight of ideas: 61% vs 46%

Hafeman et al. (in press)
BP-NOS Phenomenology:

**Manic Symptoms--BP-I ≈ BP-NOS (Most Severe Lifetime Episode)**

- Elated mood: 83% vs 78%
- Energetic: 87% vs 84%
- ↑ Goal directed activity: 58% vs 43%
- Grandiosity: 54% vs 38%
- Pressured speech: 86% vs 73%
- Inappropriate laughing: 70% vs 57%
- Uninhibited, gregarious behavior: 35% vs 28%
- ↑ productivity: 37% vs 30%
- ↑ creativity: 36% vs 22%

*Hafeman et al. (in press)*
BP-NOS Phenomenology: *Manic Symptoms*--*BP-I* \(\leq\) *BP-NOS* (Most Severe Lifetime Episode)

- **BP-NOS > BP-I (NS)**
  - Psychomotor agitation: 78% vs 69%
  - Motor hyperactivity: 77% vs 73%
  - Mood lability: 85% vs 80%

- **BP-NOS = BP-I**
  - Hypersexuality 20%

*Hafeman et al. (in press)*
BP-NOS Phenomenology: Conclusions

- BP-NOS and BP-I share many similarities that BPSD– participants do not
- BPSD > BPSD–:
  - baseline impairment
  - parental history of mania
  - CD
- Gradient of severity: BP-I > BP-NOS > BPSD–
  - Most severe past functioning (CGAS, KMRS, presence of psychotic features)
- BP-I > BP-NOS:
  - suicidal ideation
  - suicidal behavior
  - history of hospitalization

Hafeman et al. (in press)
BP-NOS Phenomenology: Conclusions

BP-NOS ≈ BP-I:
- Age of onset
- Duration of BPSD
- Manic symptomatology

Data support notion of bipolar spectrum
- Similarities suggest common elements
- Severity differs across the spectrum
- BP-NOS associated with significant impairment and warrants treatment

Hafeman et al. (in press)
What Predicts BPSD?: Background

Family History

- 1 or 2 parents with BPSD: well-established risk factor
- ~1/2 offspring of parents with BD develop at least one psychiatric disorder (BD 14-50%)
- Those who convert from MDD to BD are six times more likely to have a family history of major affective disorder

Fristad et al. (2012)
What Predicts BPSD?: Background

Family Environment

- Hostile family climate, ↑ expressed emotion (EE), impairment in family relations, ↓ warmth, ↓ functioning, conflict:

  associated with ↑ BPSD relapse, severity, suicidality, and ↓ medication treatment response

Stressful Life Events (SLEs)

- Associated with relapse, onset, and time to recovery

Fristad et al. (2012). 1: Belardinelli et al. (2008)
What Predicts BPSD?: Hypotheses

**Purpose:** Examine relative contributions of family history, family environment and SLEs in predicting which youth seeking outpatient care will have a BPSD dx

**Hypotheses:**

1. History of manic symptoms in biological parents will be a robust predictor of BPSD, even after accounting for current parent-reported manic symptoms in the child

2. SLEs and family environment each will provide a small but meaningful increase in predicting BPSD after accounting for current symptoms and family history

_Fristad et al. (2012)_
What Predicts BPSD?: Method

Instruments
Family history: Family History Screen (FHS)
Family environment: Parent Stress Survey (PSS)
Stressful Life Events (SLE): SLE Scale (SLES)

Sample
629 of 707 participants had complete data
- 23.5% BPSD: 10.2% BP-I, 0.5% BP-II, 1.6% CYC, 11.3% BP-NOS
- BPSD > BPSD-: ↑ age, girls,
- BPSD ≈ BPSD-: race, ethnicity, insurance

Fristad et al. (2012)
What Predicts BPSD?: Results

- BPSD > BPSD-:
  - mania symptom levels at SCR and BL
  - % biological parents with a history of mania
  - parenting stress
  - SLEs

- Differentiating features:
  - BL PGBI-10M ($\Delta \chi^2=46.54, p<0.001, \Delta R^2=0.105$)
  - SCR PGBI-10M ($\Delta \chi^2=16.10, p<0.001, \Delta R^2=0.038$)
  - Biological parent’s history of mania ($\Delta \chi^2=11.21, p=0.001, \Delta R^2=0.024$)
  - Parenting stress ($\Delta \chi^2=5.81, p=0.016, \Delta R^2=0.012$)

Fristad et al. (2012)
What Predicts BPSD?: Risk Factors

- ESM at SCR and BL
- Parental history of mania significantly increased prediction of BPSD (marginal increase, .024, in variance, not meeting a priori criteria for meaningful increment)
- PSS and SLES did not provide meaningful increments in variance
- Some small age/sex differences: PSS a predictor for girls, not boys; older, not younger children

Fristad et al. (2012)
What Predicts BPSD?: Conclusions

- Likelihood of BPSD increases as risk factors (PGBI-10M scores, parental history of mania, parental stress and SLEs) are added
  - Rates nearly double with two risk factors
    BL + SCR PGBI-10M or SCR + PHM
  - *No combination of risk factors elevated risk over 50%*

- SLEs not a robust predictor of BPSD except when other 3 risk factors were low, 2% $\rightarrow$ 8% (but still less than study base rate of 24%)

- BL PGBI-10M scores more discriminating than SCR scores

*Fristad et al. (2012)*
DMDD: Examination of the New Diagnosis in the LAMS sample

- Irritable mood/temper outbursts:
  - Common in outpts
  - Core features of DMDD

- Criteria:
  - Frequent, severe, recurrent temper outbursts
  - Chronically irritable and/or angry mood
  - Both must be present for one year or longer
  - Impairment > 1 setting
  - Exclusion: Elevated mood+manic sxs > 1 day
  - Exclusion: Sxs occur during psychosis/mood d/o or are clearly accounted for by another disorder

Axelson et al. (2012)
DMDD in LAMS: Method

- Four domains examined:
  - Clinical phenomenology
  - Delimitation from other diagnoses
  - Longitudinal stability
  - Association with parental psychiatric disorders

- 707 youth—data from baseline, 12 and 24 mos

- Retrospective dx of DMDD from KSADS-PL-W
  - Loses temper: Severe temper outbursts 2-5x/wk
  - Easily annoyed or angered daily or almost daily AND angry or resentful daily or almost daily
  - ≥6 Mos

Axelson et al. (2012)
DMDD in LAMS: Results at Baseline

- 26% met operational DMDD
  - 52% severe, recurrent temper outbursts
  - 35% chronic irritability

- 96% of DMDD (vs 40%, BPSD) had ODD/CD

- 77% of DMDD (vs 34%, BPSD) had ADHD+ODD/CD

- ODD: 58% DMDD+

- CD: 61% DMDD+

- BPSD: 44% would meet DMDD criteria

Axelson et al. (2012)
DMDD in LAMS: Results at Baseline

- DMDD > no DMDD: ↑ ODD, CD (logistic regression) (univariate analyses: elimination, dysthymia, ADHD)
- DMDD ≈ no DMDD: BPSD, depression, anxiety, ADHD, comorbidity, symptom severity, functional impairment

Axelson et al. (2012)
DMDD in LAMS: Results at Follow-Up

- 40% met DMDD at ≥ 1 time: BL, 1 or 2 year follow-up
- DMDD Persistence: 19% at all 3 assessments (29%, 2 assessments; 52%, only 1 assessment)
- ADHD Persistence: 61% at all 3 assessments (21%, 2 assessments; 18%, only 1 assessment)
- DMDD at intake: not associated with new onset of mood or anxiety disorders or parental psychiatric history

Axelson et al. (2012)
DMDD in LAMS: Conclusions

- DMDD symptoms are common in outpatients
- DMDD is not delimited from ODD, CD
- DMDD had limited diagnostic stability
- DMDD not associated with current, future-onset or parental history of mood/anxiety disorders
- Findings raise concerns about diagnostic utility of DMDD in clinical populations
BPSD and ADHD: Comparison and Comorbidity in LAMS

- Cross-sectionally, many BPSD and ADHD symptoms are the same
- Some research groups report
  - ADHD is associated with earlier onset of BPSD
  - Both chronic and episodic courses have been linked to comorbid BPSD and ADHD
- Comorbidity of ADHD w/ BPSD: 11-98%
- Biederman et al:
  - 11% of ADHD also have BPSD
  - 21% at 4-year follow-up
- MTA: 8-year follow-up, rates low (1.8% mania, hypomania or psychosis) and unchanging

Arnold et al. (2011)
BPSD and ADHD: 
Comparison and Comorbidity in LAMS

- Comorbidity associated with:
  - Greater functional impairment
  - Younger age of onset

- ADHD → BPSD: two diagnoses or one?

- Hypotheses:
  1) BPSD+ADHD vs BPSD-ADHD: ↓ age of mood sx onset
  2 + 3 + 4) BPSD+ADHD:
     ↑ severe BPSD sx, ↓ global fx, ↑ comorbidities than BPSD only
     ↑ severe ADHD sx and ↓ global fx, ↑ comorbidities than ADHD only

Arnold et al. (2011)
BPSD and ADHD: Comparison and Comorbidity in LAMS

- Children’s diagnoses:
  - *Note: “Alone” means ADHD or BPSD, not both, but other comorbidities could be present*
  - ADHD Alone: 60%
  - BPSD Alone: 6%
  - BPSD+ADHD: 17% (17.5% expected by chance)
  - Neither: 18%

- **Hypothesis 1: Age of mood sx onset**
  - BPSD Alone: 6.9 yrs vs BPSD+ADHD: 6.7 yrs
  - However, BPSD+ADHD group were younger at
    - LAMS visit (9.6 yrs vs 10.5 yrs)
    - 1st outpt clinic visit (5.5 yrs vs 6.8 yrs)

Arnold et al. (2011)
Hypothesis 2: BPSD+ADHD more severe ADHD sx than ADHD Alone and more severe BPSD sx than BPSD Alone

**ADHD Sx:**
- PARENTS: True (CASI-4R Inattentive, Hyperactive-Impulsive, Combined)
- TEACHERS: False (CASI-R-same)

**BPSD Sx:**
- PARENTS: False (PBGI-10M, YMRS, CASI-4R Mania)
- TEACHERS: True (CASI-R Mania)
BPSD and ADHD: Comparison and Comorbidity in LAMS

- **Hypothesis 3:** BPSD+ADHD > ADHD Alone or BPSD Alone: global impairment
  - C-GAS: SUPPORTED
    - BPSD+ADHD: 50.0
    - ADHD Alone: 55.2
    - BPSD Alone: 54.5

- **Hypothesis 4:** BPSD+ADHD > ADHD Alone or BPSD Alone: Comorbidities
  - # of Other Diagnoses, % w/ 2+: SUPPORTED
    - BPSD+ADHD: 3.27, 71%
    - ADHD Alone: 2.57, 46%
    - BPSD Alone: 1.87, 22%

Arnold et al. (2011)
BPSD and ADHD: Comparison and Comorbidity in LAMS

- ANOVAs were repeated with four covariates:
  - +/- disruptive behavior disorders
  - Age
  - Sex
  - Medicaid status (proxy for SES)
- Results remained the same (except for teacher-reported ODD/CD sxs)
- ADHD Alone:BPSD Alone 2:1 comorbid ratio
- Hospitalization:
  - 22%, BPSD+ADHD, 22% BPSD, 5% ADHD

Arnold et al. (2011)
BPSD & ADHD: Family History Comparison

- Family hx of mania higher in relatives of youth w/ BPSD+ADHD vs BPSD alone
- Many, but not all studies report offspring of parents with BPSD have higher rates of ADHD, ODD
- Molecular genetics studies do not disclose overlapping genes

**Hypotheses**: Higher rates of parental bipolar and ADHD symptoms will be found in children with:
1) BPSD or ADHD > children with neither BPSD or ADHD
2) BPSD+ADHD > BPSD Alone or ADHD Alone

Arnold et al. (2012)
BPSD & ADHD: Family History Comparison

- PHM=Parental History of Mania
  - Extreme elevated mood + 3 supporting sxss
    (more talkative, inflated self-esteem, decreased need for sleep, racing thoughts, more distractible than usual, more restless, excessive involvement in pleasurable activities) OR
  - Extreme irritable mood + 4 supporting sxss

- PHA=Parental History of ADHD
  - In grade school, did the parent fidget, leave their seat when they weren’t supposed to, not finish their schoolwork, or not pay attention to the teacher?

Arnold et al. (2012)
Fig. 1. Percent of each child diagnostic group with parental manic or ADHD symptoms.
BPSD & ADHD: Family History Comparison

- **Parental Manic Sxs**: omnibus $^2 p<.001$ (E/M/F)
  BPSD+ADHD $\approx$ BPSD $> ADHD \approx$ Other/no dx
  Either/Mother/Father (F:combined vs ADHD, $p<.08$)

- **Parental ADHD Sxs**: omnibus $^2 p<.04$ (E)
  BPSD+ADHD $\approx$ ADHD dx
  ADHD Alone $> BPSD$ Alone, Either/Father

Arnold et al. (2012)
Does BPSD or ADHD Dx or Parental History of Mania or ADHD Predict Mood and ADHD Scale Scores?: Hierarchical Regression

- YMRS = BPSD Dx
- PGBI-10M = BPSD Dx + PHM + ADHD Dx
- CASI-4R (Prt-M) = BPSD Dx + PHM + ADHD Dx
- CASI-4R (Tchr-M) = ADHD Dx
- CASI-4R (Prt-A) = ADHD Dx + BPSD Dx + PHM + BPSD X PHM (negative)
- CASI-4R (Tchr-A) = ADHD Dx + PHA

Arnold et al. (2012)
BPSD & ADHD: Family History Comparison

Conclusions

- **TOP-DOWN ANALYSES**
  - Parental manic symptoms associated ONLY with child BPSD, not child ADHD
  - Tendency toward parental ADHD symptoms associated with child ADHD, not child BPSD

- **BOTTOM-UP ANALYSES**
  - Child manic sx severity: predicted by parental manic sx (true-parents; false-teachers)
  - Child ADHD sx severity: predicted by parental ADHD sx (true-teachers; false-parents)

Arnold et al. (2012)
BPSD & ADHD: Family History Comparison
Clinical Implications

- Offspring of BPSD parents do not have higher rates of ADHD compared to offspring of parents with non-BPSD psychopathology.

- There may be shared components of BPSD + ADHD, but not a linkage at the global diagnostic level.

- Comorbidity not more than expected by chance.

- Teacher data: not useful for diagnosing child mania (convergence with other research findings- Carlson/Youngstrom).

Arnold et al. (2012)
Clinical Characteristics of Children Receiving Antipsychotic Medications

- Concern has been raised about the significant increase in antipsychotic use in children. Many may be receiving for indications without regulatory approval or scientific evidence.
  - In particular, may be used for ADHD.
  - Also, may be used for broadly defined BPSD.
- Antipsychotics have clear risks associated.
- Many concerns stem from administrative database analyses:
  - Large samples +
  - Accuracy of dxs?

Findling et al. (2011)
Clinical Characteristics of Children Receiving Antipsychotic Medications

- Study Aims:
  1) Compare demographic and diagnostic features of youth prescribed APs vs other psychotropics (OPs)
  2) Do children with ADHD Only get prescribed APs?

- 63% (N=443) prescribed medications at BL (all but 6, prior to screening visit)
  - 35% of these, APs (n=157)
  - 65% of these, OPs (n=286)

Findling et al. (2011)
Clinical Characteristics of Children Receiving Antipsychotic Medications

- AP > OP in youth who were/had:
  - White
  - Non-Medicaid insurance
  - Previous psychiatric hospitalization
  - ↓ C-GAS scores
  - Dx of psychosis or BPSD (and BP1)
  - ↑ scale scores on: PGBI-10M, YMRS, CASI-4R ODD and CD, IDA Outward Irritability

Findling et al. (2011)
Clinical Characteristics of Children Receiving Antipsychotic Medications

- **AP ≈ OP**
  - Age
  - ESM at Screen
  - # of current dx at BL
  - Dx of DBD, PDD, Tourette/Tic, depression, anxiety, > 1 BL Dx
  - CDRS-R, CASI-4R ADHD (I, H, Comb) scores

- **AP < OP**
  - ADHD

Findling et al. (2011)
Clinical Characteristics of Children Receiving Antipsychotic Medications

- AP=White + Previous inpt + psychotic or BPSD Dx + Site (more at Case Western, Cincinnati)

- ADHD: 70% (n=252) OPs; 30% (n=109) APs

- ADHD w/ APs= # of current dxs + C-GAS + BPSD + any other comorbid dx + DBD + YMRS + PGBI-10M + CASI-4R ODD + CASI-4R CD + IDA

Findling et al. (2011)
Clinical Characteristics of 13 Children with ADHD Alone Prescribed APs

- ADHD Alone: n=62; 13 (21%) were on APs
- 12 of 13 had prior stimulant trials
- 1 of 13 had persistent ESM scores > 12
- Past dxs:
  - D-NOS
  - Transient tic disorder, MDD + Anx-NOS
- Current dxs:
  - 4 of 13 ESM+
  - 3 of 13 elevated CASI-4R ODD/CD scores
  - 4 of 13 elevated IDA scores
  - 8 of 13 had ≥ 1 of the above
  - 5 prescribed for ?? reasons (<1% total sample)

Findling et al. (2011)
Polypharmacy Patterns in LAMS

- Medication overutilization has been suggested in some research, particularly in vulnerable populations (e.g., young children, Medicaid, foster children)

- **Study Aim**: Examine demographic and clinical characteristics related to polypharmacy in LAMS outpts

- **Hypotheses**: Diagnosis and severity will increase odds of polypharmacy

- **Data Analysis**: No post-hoc corrections to increase possibility of detecting harm

Kowatch et al., (in press)
Polypharmacy Patterns in LAMS

- N=698 w/ relevant data
  - No medication, n=262 (38%)
  - One medication, n=235 (34%)
  - Two medications, n=131 (19%)
  - Three or more meds, n=70 (10%)

- Those on ≥ 2 meds:
  - ↓ C-GAS, ↑ PGBI-10M, YRMS, CDRS-R scores
  - ↑ bipolar or PDD dxs
  - ↑ comorbid dxs
  - ↑ special education, inpt tx
  - ↑ maternal and paternal + family hx

Combined, 29%

Kowatch et al., (in press)
Polypharmacy Patterns in LAMS

- Predictors of ≥ 2 meds: $R^2 = 0.30$
  - Site (Pittsburgh, lowest), 0.04
  - White, 0.07
  - Diagnosis (bipolar, PDD, ADHD, psychosis-hx), 0.09
  - Severity (inpt tx, special ed), 0.05
  - Provider (psychiatrist, psychologist, total N), 0.05

- Significant incremental predictors in final model
  * White, OR=3.1
  * ADHD, OR=2.5
  * Bipolar, OR=1.8
  * Inpt tx, OR=3.4
  * Psychiatrist, OR=2.3
  * Psychologist, OR=1.1
  * Total N professionals, OR=1.4

Kowatch et al., (in press)
Polypharmacy Patterns in LAMS

- Results similar for
  - Antipsychotics
  - Mood stabilizers
  - Antidepressants
  - Stimulants

- Results different from previous claims-based studies (Zito et al, 2008a, b; Olfson et al, 2010; Constantine et al, 2010) but are similar to recent study of 10,123 adolescents in the National Comorbidity Survey Adolescent Supplement (Merikangas et al, 2013)
Mental Health Service Use in LAMS

- Mental illness causes significant impairment for 3-18% of youth
- Many receive either no services or school-based services only
- Little is known about services on a per-dx basis

**Study Aim:** Describe service utilization based on demographics and diagnoses

**Hypotheses:** More service utilization for
- Males, ↑ age, White, private insurance
- Major mental illness, comorbid dx, ↓ C-GAS

Mendenhall et al. (2011)
### Treatment modality

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>N</th>
<th>%</th>
<th>M</th>
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<td><strong>Intensive-restrictive services</strong></td>
<td>82</td>
<td>12</td>
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<td>Residential placement, partial hospitalization, or day treatment program</td>
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<td>6</td>
<td>7.7</td>
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<td><strong>Inpatient hospitalization</strong></td>
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<td>9</td>
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<td><strong>Outpatient services</strong></td>
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<td>98</td>
<td>6.3</td>
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**Type of professional**

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<td>Psychologist, social worker, counselor, or therapist</td>
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<td>81</td>
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**Type of service**

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<td>Acupuncturist or chiropractor</td>
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<td>Self-help group or respite care</td>
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<td><strong>Outpatient and school services</strong></td>
<td>351</td>
<td>50</td>
<td>5.6</td>
<td>2.2</td>
</tr>
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</table>
Mental Health Service Use in LAMS: Type X Diagnostic Groups

- **Hospitalization:**
  BPSD 22% > Depression 14% > DBD 4%

- **Inpt, past year:**
  BPSD 14% > Depression 5% > DBD 1%

- **Psychotx only:**
  BPSD 20% < Depression 28% < DBD 39%

- **Medication only:**
  BPSD 19% ≈ Depression 12% ≈ DBD 15%

- **Meds + Psychotx:**
  BPSD 57% ≈ Depression 56% > DBD 36%

Mendenhall et al. (2011)
Mental Health Service Use in LAMS: Additional Characteristics

- Comorbid Dxs –did not impact usage
- BPSD w/ ↓ C-GAS:
  - ↓ likely to receive Meds Only
    12% vs 24%
  - ↑ likely to have ≥ 2 current services
    41% vs 26%
  - ↑ likely to have lifetime intensive + outpt
    29% vs 15%

Mendenhall et al. (2011).
Mental Health Service Use in LAMS: Characteristics of Inpatient Care

- If ever hospitalized (n=65, 9%), M=2.3
  - Median LOS=5 days

- **Meds only during inpt: 11%**
  - 0% benefit “a lot” 57% benefit “some”

- **Psychotx only during inpt: 28%**
  - 17% benefit “a lot” 78% benefit “some”

- **Combination tx during inpt: 14%**
  - 33% benefit “a lot” 56% benefit “some”
Mental Health Service Use in LAMS: Characteristics of Outpatient Care

- If currently treated (n=689, 97%), $M=1.2$
  - Meds only: 27%
    - 37% benefit “a lot” 46% benefit “some”
  - Psychotx only: 35%
    - 18% benefit “a lot” 49% benefit “some”
  - Combination tx: 15%
    - 34% benefit “a lot” 51% benefit “some”

Mendenhall et al. (2011).
Mental Health Service Use in LAMS: Clinical Implications

- Although multimodal tx is considered most effective for many disorders, < 50% received this
  - Clinician and consumer education re: multimodal treatment is warranted
- Frequency of inpt treatment points to the importance of early prevention/detection/intervention

Mendenhall et al. (2011).
Parents’ Perceptions of Treatment Benefits: Voting with Their Feet

- Only half of children with MH Dxs receive services
  - Of these, many txs are inadequate
  - Many receive evaluation only or
    - Prematurely terminate
    - Do not adhere to tx recommendations
    - Do not receive efficacious treatment

- Parental engagement (Olin et al) is based on
  - Beliefs and expectations
  - Social norms
  - Attitudes
  - Self-efficacy

- Structural barriers also exist

*Horwitz et al. (2012)*
Parents’ Perceptions of Treatment Benefits: Voting with Their Feet

- **Study Aims:**
  1) Examine family and child characteristics related to perceived benefits of outpatient MH services
  2) Determine if perception of benefit post-initial appt predicts continued use of MH services 6 mos later

- N=573
  - 29% benefit “a lot”
  - 52% benefit “some”
  - 19% benefit “none”

*Horwitz et al. (2012)*
Characteristics of Parents/Families Who Report “A Lot” of Benefit: Multivariate Analyses

- **Treatment (compared to therapy only)** $p = .003$
  - Multi-modal: $OR = 2.43$
  - Meds only: $OR = 1.99$

- **C-GAS Score (per 5-point increase)** $OR = 1.17$, $p = .01$

- **Study Site (compared to Cleveland)**, $p < .001$
  - Cincinnati $OR = 0.28$
  - Columbus $OR = 0.70$
  - Pittsburgh $OR = 0.41$

- **No comorbidity**, $OR = 1.91$, $p = .04$

- **Both biological parents in home**, $OR = 1.61$, $p = .03$

- **No immediate family member inpt tx**, $OR = 1.80$, $p = .02$

*Horwitz et al. (2012)*
Parents’ Perceptions of Treatment Benefits: Voting with Their Feet

- Variables that did NOT matter
  - Parental education, parental diagnoses, parental burden, parental stress, immediate family member prescribed meds

- 6-month follow-up: 76% continued to receive services

- More likely to continue if:
  - Live with both bio parents, 83% vs 73%
  - Private insurance, 81% vs 71%
  - Fewer parental MH problems, 4.5 vs 5.5
  - No immediate family member-inpt 79% vs 70%

Horwitz et al. (2012)
Parents’ Perceptions of Treatment Benefits: Voting with Their Feet

- Likelihood of Tx at 6 mos if BL perceived benefit is
  - A lot: 83%
  - Some: 78%
  - None: 60%
  - A lot vs None OR=1.91
- Living w both biological parents, OR=1.59
- Race, ethnicity, study site: NS

*Horwitz et al. (2012)*
References


OATS, 2011-2014, Two NIMH R34s

- OATS=Omega3 and Therapy Study
- Kayden Healy or Eli Nader, 614-293-4908
- N=60 MDD, Dysthymic Disorder, D-NOS
- N=60 BP-NOS/Cyclyothymic Disorder
- 12 week trial
- 7-14 years
- No meds/psychotherapy in previous month except stable stimulants, sleeping aids

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Wexner Medical Center