What have Observational Studies taught us about the Emergence and Course of Bipolar Disorder (BP) Among Youth?
Disclosures

- National Institute of Mental Health (NIMH) grants
- Up to Date
- Royalties for Books
  - Up to Date reviews- “Phenomenology and Treatment of Pediatric Bipolar Disorder” 2014
  - American Psychiatric Association Publishing: “Major Depressive Disorder” 2015
The Pittsburgh Bipolar Offspring Study (BIOS)

- Recruited parents who have BP-I or II and child/adolescent offspring (ages 6-18)
- Demographically match community control parents with child/adolescent offspring
- Assess participants longitudinally (every 2 years) using diagnostic/dimensional
- Assessments are **blind** to parental diagnosis
Parents with BP vs. Community Controls

Psychiatric Disorders at Intake

Birmaher et al., AGP, 2009
School age Offspring - Demographics

- Total Sample: 639
  - Offspring of parents with BP: 388
  - Offspring of controls: 251
- ~ 12 years
- ~ 50% females
- ~ 80% Caucasian
- ~ 65% Tanner Stage: I-III
- ~ 50% living with both biological parents
Offspring with BP vs. Community Controls

Lifetime Disorders (intake + follow-up)

- High-Risk Offspring % (n= 388)
- Comparison Offspring % (n=251)
Onset of depression and non-mood disorders relative to onset of Bipolar Spectrum Disorders

Axelson et al., AJP, 2015
Cumulative rate of bipolar spectrum disorders by Age

Axelson et al., Am J of Psychiatry, 2015
Children’s Affective Lability Scale (CALS) Scores at Intake

- BP offspring of BP parents (n=41)
- Non-BP offspring of BP parents (n=257)
- Controls (n=192)

Birmaher et al., Bipolar Disorders, 2013
Dimensional Predictors of Bipolar Spectrum Disorders in At-Risk Youths

Hafeman et al., American Journal of Psychiatry, 2016
Model: Bipolar Disorder Prodrome

Non-Specific Symptoms (e.g. anxiety, depression, mood lability)

Specific Prodrome (e.g. hypomanic symptoms)

Bipolar Spectrum Disorder

How likely is it that an individual child or adolescent with an affected parent will develop BPSD?

We looked at a time window of 5 years

Variables included in the calculator:

- Depression
- Subsyndromal symptoms of mania, anxiety
- General psychosocial functioning,
- Parental age of mood disorder onset (AUC=0.76)

AUC= 0.76 (comparable to risk calculators used clinically in other areas of medicine)

Relevant for clinical and research purposes

Hafeman et al., submitted
This risk assessment tool uses data from the Pittsburgh Bipolar Offspring Study (BIOS) to predict the likelihood that your patient (ages 8-17) will develop bipolar spectrum disorder in the next 5 years, if they have a parent with bipolar disorder. To find your patient’s score, enter the information in the calculator below.

Current age:  
Child Affective Lability Scale (child-report):  
Mood and Feelings Questionnaire (child-report):  
Screen for Anxiety Related Disorders (child-report):  
Modified KSADS Mania Rating Scale:  
Modified KSADS Depression Rating Scale:  
Age of Parental Mood Disorder Onset:  

Click HERE to calculate the likelihood that your patient will develop bipolar spectrum disorder in the next 5 years.

Hafeman et al., submitted
Course and Outcome of Bipolar Youth (COBY)

- Multicenter Study (Universities of Brown, UCLA, and UPMC)

- Children and adolescents with Bipolar Disorder - I, II and NOS

- Interviews with youth and parents about: mood, behavior, life events, treatment, cognition, school and family functioning, medical problems (including inflammatory markers)

- Follow-up every 6 months
Course and Outcome of Bipolar Youth (COBY) (Brown University, UCLA, and UPMC)

Axelson et al., AGP, 2006, Birmaher et al., AJP, 2009
After the Index episode about 80% recovered (Fig 1). Of those who recovered about 60% had recurrences in a period of 4 years (Fig 2).

Birmaher et al., *Am J Psychiatry*, 2009
Percentage of time during the follow-up Euthymic (well) or with mood symptoms during 4 years follow-up

BP-I
BP-II
BP-NOS

4 years follow-up

~40% Euthymic

~40% Subclinical

~20% Syndromal

Most mixed, rapid cycling and depression

Birmaher et al., *Am J Psychiatry*, 2009
Percentage of time spent with mood symptoms between youth with BP-I (Birmaher et al., 2009) vs. adults with BP-I (Judd et al., 2002)
Tom a 13 y.o boy with:
P is a ___ year old boy with:

- Chronic ODD and severe ADHD symptoms that responded to stimulants,
  However, above and beyond the symptoms of ADHD/ODD, he also has:

- Episodes that last up to 2 weeks:
  - Increase energy, silliness, talkativeness, intrusiveness, hypersexual behaviors, more angry and irritable if interrupted, sleeps 2-3 hours per night for 3-4 days in a row, “superpowers” to save the world, many ideas which he constantly writes in note books
Decent Leather Jacket

$100

Candy Maker

Luxury Yummy Sustains

Leop Shorts

Wimbledon Shirts

Jeeves

Huck

Caressing

Guess

Fezki

Mark

Ice Cold

Private Air

One of Day

Fingertip Door Clock

Her Guns

Leo Soren

Fleece Yoga Mat

Pool Blocks

In Box

Checklist

Toys

Delight

Third Will Surf Trip

Wireless 3D Viewer

$25 - 100

Star War Monkey

Diamond Shaped Cut

Sword Okinawa

Real Color Microwave

Ej81 Alarm Clock

Ninja Mug

90's/10's and Camones

nP47 Water Gun

Yelling Pokey Toy

Legs From Oliy

Surf Light V.G.E.
P is a ___ year old boy with: (Cont’)

- Episodes up to one week:
  - Feeling down, sad, irritable, numerous fights at school, low motivation, isolation, worse concentration, does like to play videogames, sleeps more, cries, and complains that has a "voice" telling him to hurt himself and others (it may be my imaginations but "it seems very real").
Other Outcomes:

- Increased service utilization
- Polypharmacy
- Family conflicts
- Academic difficulties
- Exposure to negative events
- Psychosis
Suicidal Attempts

- **At baseline:** 33% (133/405)
- **New cases at follow-up:** 18% (76/413) made at least 1 suicide attempt – 31 had multiple attempts
- **Predictors 8-weeks before a suicide attempt:** more persistent depression, substance abuse, mixed mood symptoms.

Goldstein Tina et al., *Bipolar Disord*. 2005; Jama *Psychiatry*. 2012
Substance Abuse

- At baseline: 16% (40/249)
- New cases at follow-Up: 32% (n=54/117)
- Cannabis followed by alcohol
- ≥2 substances: 76%

Predictors

- Lifetime alcohol experimentation
- Lifetime ODD, panic disorder,
- More severe manic symptoms 12 weeks before SUD
- No use of antidepressants or lithium
- Family history of SUD and low family cohesiveness

Goldstein B et al., Bipolar Disord, 2008; JAACAP 2013
Prior analyses included all subjects together

However, we were also interested to evaluate whether there are subgroups with different course patterns over time
Latent class growth analyses based on % time euthymic for subjects with least 4 years of follow-up (n=367)

Birmaher et al., AJP, 2015
Risk Calculator-Preliminary Findings

- In 5 years, about 50% of youth with BP-NOS converted into BP-I/II

**Individualized** risk factors (AUC:0.75)
- Elevated manic or anxiety symptoms
- Family History of mania
- Younger age of BP-NOS onset
- Female
- White

**Protective factors:**
- Higher socioeconomic status
- Living with both parents
Thank You

- All Families for their participation

- **Course and Outcome of Bipolar Youth (COBY) Study**
  - *Pittsburgh*: David Axelson, Katie Aronson, Boris Birmaher (PI), Renee Clark, Josh Feldmiller, Mary Kay Gill, Ben Goldstein, Tina Goldstein, Heather Kumar, Fangzi Liao, John Merranko, Sharon Nau, Neal Ryan, Raeanne Sylvester, Vicky Tzanakos
  - *Brown*: Daniel Dickstein, Kerry Gagnon, Heather Hower, Jeff Hunt, Matthew Killam, Martin Keller (PI), Claire Walker, Shirley Yen
  - *UCLA*: Michael Strober (PI)

- **The Pittsburgh Bipolar Offspring Study (BIOS):** David Axelson, Boris Birmaher (PI), David Brent, Renee Clark, Nicholas Curcio, Ronna Currie, Rasim Diler, Tina Goldstein, Danella Hafeman, Mary Beth Hickey, David Kupfer, Cecile Ladouceur, John Merranko, Kelly Monk, Mary Phillips, Brian Rooks, Dara Sakolsky, Rita Scholle, Lindsay Virgin

- **Longitudinal Assessment of Manic Symptoms (LAMS) Study:** David Axelson, Boris, Birmaher, Rasim Diler, Mary Kay Gill, C.H. Jaquette, Dawn Rice, Leslie Wehman

- **Ways for Adolescents to Validate Emotions (WAVE) Study:** Rachel Fersch-Podrat, Nina Hotkowski, Tina Goldstein (PI), Matt Garcia, Megan Krantz, Jessica Levenson, Dawn Rice, Sue Wassick, Tim Winbush, Christine Hoover, Stacy Simon, Barbara Pane

- **Children and Adolescents Bipolar Services (CABS) (Outpatient and Inpatient):** Boris Birmaher, Donna Barham, Rasim Diler, Rachael Fersch-Podrat, Tina Goldstein, Christine Hoover, Nina Hotkowski, Aaron Jennings, Nicole Kroll, Dara Sakolsky, Kathy Scheuble, Amy Schlonski, Jessica Singer, Susan Wassick, Tim Winbush

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