

MARK W. WILSON, MD  
330 W58TH STREET, SUITE 313  
NEW YORK, NEW YORK 10019

*Mood Instability and Bipolar Spectrum Disorders in Youth: General*



From *The Bipolar Child*

- **General**
  - See separate handout for general information on bipolar disorder (not specific to youth)
  - History
    - Kraepelin, 1921: mania occurs (but rarely) in children and the onset of first episodes increased significantly after puberty
    - Early-onset mania generally unrecognized in the first part of the 20<sup>th</sup> century
    - Anthony and Scott, 1960: reported cases of manic-depressive psychosis in children
    - Carlson et al, 1977; Joyce, 1984; Loranger and Levine, 1978: found that 1/5 of adult cases retrospectively had evidence of the illness before age 19 (see below)
    - Carlson and Strober, 1978: reported bipolar disorder in six adolescents which was originally misdiagnosed as schizophrenia
    - McGlashan, 1988: mania in adolescence often presents with psychosis
    - Lish et al, 1994; Perlis et al, 2004: many adults with bipolar disorder describe the onset of mood disorder describe the onset of mood symptoms during childhood, presenting symptoms are most often depression and hyperactivity
  - Concept of *cyclotaxia*—genetic vulnerability to cyclical mood states
    - Absence of bipolar I or II
    - Elevated mood symptoms, key symptoms of which include
      - Elevated mood
      - Irritability
      - Rapid Mood fluctuations
    - Psychosocial dysfunction
  - Bipolar disorder not otherwise specified (BP NOS)/cyclothymia are most common (as opposed to bipolar I or II disorder)
    - Less marked symptomatology
    - Serious difficulties
    - At risk of developing more serious mood disorders
    - BP NOS appears to be the result of failure to meet episode duration criteria for syndromal mood episodes
    - Might be placebo responsive
  - Early symptom picture
    - Prodromal syndromes (that could evolve into bipolar disorder); Chang 2003
      - ADHD
        - 1 in 5 may develop bipolar disorder; often seen/diagnosed first
        - Adults with a history of ADHD have earlier onset of bipolar disorder
        - ADHD is a non-specific, heterogenous disorder which involves the same brain regions
      - Depression/irritability/brief euphoria
      - Temperament clues: mood reactivity, rejection sensitivity, decreased flexibility, increase activity
    - Symptom progression from the age of 5 through the age of 15 (Findling et al, 2001; Youngstrom et al, 2003)
      - Early years: pure manic hypomanic symptoms dominate early on, and, less so, mixed symptoms and even less so depressive symptoms
      - As progresses: decreasing pure manic and hypomanic symptoms and greatly increasing mixed symptoms and less so depressive symptoms
      - Severity of depression increases over time
      - Pure mania and hypomania plateau
  - Symptom progression from the age of 15 through the age of 65
    - Early years (ages 15-20): mixed episodes predominate with more or less equal risk of pure mania/hypomania or pure depression
    - Ages 25 on: risk of depressive episodes increase all the way through age 65; risk of mixed episodes decrease slowly over time; risk of pure manic episodes decrease much less slowly through age 65
  - Pediatric bipolar disorder and suicidality
    - Past
      - Suicidal ideation 57.4%
      - Suicide attempts 21.3%
    - Current
      - Suicidal ideation 50.4%
      - Suicide attempts 25.5%
- Geller, 2008, 8-year follow-up of children with bipolar I

- After 1 year about
  - 60% are better
  - 50% relapse
- Years 5 on, ~88% recovered
  - 73% relapse
- By young adulthood
  - 44% had manic episode
  - 20% had depressive episode
  - 35% had substance abuse disorders
- Distinguishing Bipolar Depression from Unipolar Depression in Youth: Preliminary Findings  
 Rasim Somer Diler, Tina R Goldstein, Danella Hafeman, John Merranko, Fangzi Liao, Benjamin I Goldstein, Heather Hower, Mary Kay Gill, Jeffrey Hunt, Shirley Yen, Martin B Keller, David Axelson, Michael Strober, Satish Iyengar, Neal D Ryan, Boris Birmaher  
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  - **OBJECTIVES:** To identify mood symptoms that distinguishes bipolar disorder (BP) depression versus unipolar depression in youth during an acute depressive episode.
  - **METHODS:** Youth with BP (N = 30) were compared with youth with unipolar depression (N = 59) during an acute depressive episode using the depression and mania items derived from the Schedule for Affective Disorders and Schizophrenia for Children (K-SADS)-Present Version. The results were adjusted for multiple comparisons, and any significant between-group differences in demographic, nonmood comorbid disorders, and psychiatric family history.
  - **RESULTS:** In comparison with unipolar depressed youth, BP depressed youth had significantly higher scores in several depressive symptoms and all subsyndromal manic symptoms, with the exception of increased goal-directed activity. Among the depressive symptoms, higher ratings of nonsuicidal physical self-injurious acts and mood reactivity, and lower ratings of aches/pains, were the symptoms that best discriminated BP from unipolar depressed youth. Subsyndromal manic symptoms, particularly motor hyperactivity, distractibility, and pressured speech, were higher in BP depressed youth and discriminated BP depressed from unipolar depressed youth.
  - **CONCLUSIONS:** The results of this study suggest that it is possible to differentiate BP depression from unipolar depression based on depressive symptoms, and in particular subsyndromal manic symptoms. If replicated, these results have important clinical and research implications.
- Other studies of symptom pictures over all (Geller, 2000, 2001, 2002, 2004 and 2006; Wilens et al, 2003; Bromet, 2005)
  - Symptoms occur 3-4 times-a-day, most days of the week
  - Symptoms severe enough to cause extreme disturbance in one domain or moderate disturbance in two or more domains
  - Most prevalent pattern for juvenile bipolar disorder is to be ill for over 3.2-3.6 years (fuller ranger 1-6 years) during which there are multiple episodes on a daily basis.
    - In some patients, long-term chronic symptoms and impairment come to represent their baseline functioning
    - 50-62% youth with subsyndromal bipolar disorder have a history of depression or dysthymia.
    - 67% of depressed youth with the triad of psychosis, psychomotor retardation and rapid onset of symptoms developed bipolar disorder (whereas 4% of youth who did not have this triad developed bipolar depression).
    - 10-20% of adults with bipolar disorder have a childhood history of hyperactivity
- Consensus (especially in very early onset) and other generalities
  - Chronic impairment
  - Cyclic disorder is follow life charting
  - Lack of clear, distinct episodes of affective states
  - Lack of clear inter-episode recovery
  - Mixed states can be blurry or flurry of symptoms of the can be distinct symptom syndromes/episodes occurring distinctly but simultaneously
  - Looking at 6 studies from 1995-2017 (De Crescenzo et al, 2017), with 2303 participants diagnosed with mood disorder, aged 3-18 y.o., rates of suicide attempts were as follows:
    - 31.5% of those with bipolar disorder
    - 20.5% of those with major depressive disorder
- Juvenile Bipolar Research Foundation Criteria for Core Phenotype of Pediatric Bipolar Disorder
  - severe nightmares
  - antagonizes siblings
  - excessively craves sweets and carbohydrates
  - wets the bed
  - sleeps hot
  - takes excessive risks
  - hoards food
  - has many ideas at once
  - interrupts or intrudes on others
  - experiences periods of self-doubt and poor self-esteem
  - deflects blame
  - Fear-of-Harm phenotype
    - extreme anxiety
    - hyper-perception of threat
    - defensive retaliatory behavior
- “Red Herring” symptoms (ones that may suggest bipolar disorder to some, but often isn’t)
  - Bizarre appearance: not at all specific unless when pattern of changes in appearance parallel mood episodes
  - Lack of insight: most don’t have insight
  - Irritability is the “dog’s breath” of psychiatry—can be present in any diagnosis
  - Aggression; not so much a “red herring” but relatively non-specific
    - Most impairing symptom

- Analogous to “fever” or “pain” in it’s non-specificity
  - Most cases of bipolar disorder will have aggression, but non-specific nonetheless
  - “Polyanna” syndrome of over-optimism; if chronic and pervasive, may be character as opposed to hypomania/mania
- “Hallmark” or “handle” symptoms
  - Grandiosity and elevated self-esteem more specific but also present in ADHD, ODD, conduct disorder
  - Hypersexuality not specific to bipolar disorder but more likely to be part of it
  - Racing thoughts and pressured speech not fully specific to bipolar disorder but more likely to be part of it
  - Decreased need for sleep: up and about and active at night, not so tired in the day; this is opposed to the initial insomnia, as an example, of depression or anxiety more likely associated with lumbering rumination
- Mixed state model: prolonged mixed state
  - Look for coloring/colors of moods; bring the predominant mood(s)/symptom(s) to the foreground to help diagnosis type of episode
- Rapid cycling model: ultradian cycles
  - Kraepelin (1921) believe that very rapid cycling presentations are not mixed states: look for transitions of euthymia
  - Kraepelin did not believe irritable mania was mixed mania
  - Kraepelin believed that mixed episodes were transition periods between prototypical states
  - Episodes “have by no means permanently a uniform coloring. Manic patients may transitorily appear not only sad and despairing, but also quiet and inhibited...Sudden reversals lasting for hours or for whole days are extremely frequent” (Kraepelin); i.e., patients with depression don’t cry all the time, are not sad all the time, but do have a predominant mood state over time and as such is considered one episode
- Presume co-morbidity until proven otherwise; rule out:
  - More parsimonious diagnostic conceptualizations/misdiagnoses
  - Look especially at periods predating diagnosis of bipolar disorder and in periods of euthymia
  - Look especially for depression/anxiety disorders/ADHD/PTSD/ODD/conduct disorders, substance use disorders, etc
  - Abuse, family disarray
  - Family history of formal diagnoses and symptom clusters very important here
  - General co-morbidity pattern
    - ADHD 62%
    - ODD 53%
    - Psychosis 42%
    - Anxiety 27%
    - Conduct disorder 19%
    - Substance use disorder 12%
  - Treat bipolar disorder first and related impairment, then start working on co-morbid conditions and symptom clusters
- Heritability: Huge numbers of carriers of risk (e.g., cyclotaxia) genes
- Rates of diagnosis in children
  - Best estimate of rate of bipolar disorder in kids who come to outpatient treatment or research is 5-7%
  - More specialized research clinics have rates at 15-17%
  - In inpatient units rates at 30-40%
- None of the most commonly used tests have been validated for pediatric bipolar disorder
  - Personality and psychopathology tests have not been demonstrated to discriminate pediatric bipolar disorder
  - Tests have not been shown to retain validity for other constructs when used in context of pediatric bipolar disorder
  - CBCL “evidence” of bipolar disorder
    - 4-fold increased risk of pediatric bipolar disorder, but 4-fold risk relative to population that you are looking at; this means that 4-fold risk in school where rates are very low is not the same thing as 4-fold increased risk in folks in private practice or research clinic where the risk then is much, much higher
    - Young Mania Rating Scale (Y-MRS)—severity measure; designed for adults; not diagnostic
    - Mood Disorders Questionnaire (Y-MRS)
    - Child Mania Rating Scale
    - Short Form Parent General Behavior Inventory (SF-PGBI)
- Other diagnostic strategies not yet ready for clinical use
  - Functional MRI (fMRI)—expensive and findings not specific to bipolar disorder
  - Neuropsychological batteries—findings not specific; not validated against clinically meaningful comparison groups yet; MMPI-A or Personality Inventory for Children—conceptually promising, but not validated yet
  - Teacher report does not discriminate bipolar disorder from other disorders; low evidence of diagnosis from teachers does not mean lack of presence of diagnosis
- Critical for diagnosis is retrospective and prospective life charting (found on [www.cabf.org](http://www.cabf.org) and [www.dbsalliance.org](http://www.dbsalliance.org))
- **Risk of bipolar disorder in offspring (2010)**
  - **No parent with bipolar disorder (2,239,553 youth)**
    - **0.48%**
  - **1 parent with bipolar disorder (11,995 youth)**
    - **4.4% so 95.6% do NOT go on to develop bipolar disorder)**
  - **2 parents with bipolar disorder (83 youth)**
    - **24.9% (so 75% do NOT go on to develop bipolar disorder)**
- Risk/Risk factors for progression of pediatric depression to bipolar disorder (Wilens et al, 2003 and others listed below):
  - Pediatric depression 1-83% overall
    - Rates overall
      - 1% in a recent follow-up study of adolescents with major depression in a community sample
      - 10-50% in other studies
      - 20-50% of children with depression go on to develop bipolar disorder later in life
      - 83% in a Japanese study

- Geller 2001: adult diagnoses in those with youth histories of prepubertal depression vs. youth histories with no psychiatric diagnoses
  - Bipolar I or II or NOS 48% vs. 7% in controls; 33% of which bipolar I vs. 0% in controls
  - Major depression 36% vs. 14% in controls
  - Substance use disorder 31% vs. 11% in controls
  - With suicidality 22% vs. 4% in controls
- Relative differences between pediatric unipolar depression and pediatric bipolar depression, the latter of which is associated with:
  - More severe depression
  - More hopelessness
  - More suicidality
  - More comorbid conditions
  - Lower functioning
  - More psychiatric hospitalizations
- Predictors within the risk factor of depression (Geller; Akiskal; Luby and Mrakotsky; Masi; Kovacs; Rao et al; Strober and Carlson)
  - severity
  - earlier age of onset (NB: preschoolers with depression have higher family history of bipolar disorder)
  - rapid symptom onset
  - psychomotor retardation
  - self-reproach
  - psychotic features: 13% of children with major depression with psychotic features may go on to experience a mania (and thus meet criteria for bipolar disorder)
  - co-morbid ADHD
- Family history of mood disorders (also see handout on biology and genetics)
  - High heritability; family assessment is vital; rules of thumb:
    - Many parents of children go undiagnosed too; many have mood disorders; more than 80% of youth with bipolar disorder have at least one parent with a mood disorder; more than 50% of moms and more than 50% of dads have a mood disorder when looked at separately
    - Clear bipolar disorder in one parent increases risk of bipolar disorder in youth 5-fold (range 5-fold to 10-fold increased risk); this means ~5.4% (up to 10%) of offspring of a parent with clear bipolar disorder vs. 0.6~1% in general public
    - Clear bipolar disorder in grandparent, aunt, uncle increases risk 2.5-fold
    - “Fuzzy” bipolar disorder or clear mood history increase risk up to 2-fold
  - Sparks et al, 2014; offspring of parents with bipolar disorder
    - 8.3-fold increased rate of disruptive mood dysregulation disorder (DMDD)
    - 5.4-fold increased rate of disruptive mood dysregulation disorder (DMDD) when control for co-morbid parent diagnoses
  - Pittsburgh Bipolar Offspring Study (BIOS)
    - Increased rate of mood disorders and anxiety disorders for offspring of parents with bipolar disorder compared to controls
    - Risk of bipolar spectrum disorder 13.4 fold higher
    - Risk of depressive disorder 2.1 fold higher
  - Lapalme 1997, Delbello 2001, Chang et al, 2000, children of parent(s) with bipolar disorder:
    - ADHD in 25-30% vs. 5-7% in general population
      - 10% of youth with both ADHD and family history of bipolar disorder developed bipolar I by 1 year
      - 36% of youth with both ADHD and family history of bipolar disorder developed bipolar I by 3 years
    - Depression 15-20%
    - Bipolar disorder 13-20%
    - ODD 10%
    - Anxiety disorders (not including OCD) 5%
    - OCD 3%
    - Enuresis 3%
    - Tic disorder 3%
  - Lapalme 1997, Delbello 2001, Chang 2003
    - 2.7-fold increased risk of any psychiatric disorder
    - 4-fold increased risk of mood disorders
    - 50% with a psychiatric disorder
- Bodily concerns
- Diminished concentration
- Smaller ventral prefrontal cortical (VPFC) volumes (in youth with rapid cycling); current use of medication associated with larger
- Antidepressant-induced hypomania/mania
  - In retrospective study of patients with bipolar disorder (Papolos, 1999)
    - 65% of those treated with stimulants switched to mania, rapid cycling agitated states, or psychosis; many with violent or suicidal ideas
    - 85% of those treated with antidepressants of all classes.
  - High rates of onset of bipolar disorder and switching to mania when tricyclic antidepressants used in prepubertal depression (Geller, 1993)
  - Several studies have demonstrated the efficacy of antidepressants in pediatric bipolar depression with evidence of absence of long term detrimental effect on bipolar disorder. one study showed treatment of the depression with antidepressants **decreased** the risk fourfold; Del Bello et al, 2007, found the opposite;

- **Symptom prevalence (in decreasing order of prevalence)**
  - Concurrent elation AND irritability (e.g., mixed mood) in 87.1% in Geller, 2002
  - Motor hyperactivity in 87-94% in most severe manic episode in Geller 2006
  - Rage attacks in 78-88.5%
    - 88.5% in Danielyan et al, 2007
    - in JAACAP, 5/06; ~18% in ADHD, ~4% in case controls
  - Irritable mood in 77-100%
    - 84.6% in Danielyan et al, 2007
    - 95.1-100% in Tillman and Geller, 2007
    - 77-85% in most severe manic episode in Geller 2006
    - 82% in JAACAP, 5/06; ~24% in ADHD, 4% in case controls
    - 94% in Wozniak, 2005
    - 97.9% in Geller, 2002; 71.6% in ADHD, 3.2% in case controls
    - often episodic though may appear continuous within the day, pulsating, volatile, extreme meltdowns or rages over trivial matters
    - often accompanied by aggressive or self-injurious behavior
  - Papolos, 2005: obsessive fear of harm to self or others (in bipolar children) associated with higher risk of harm to self and others as well as suicidal threats
  - Rapid mood swings in 77-90%
    - 77% in JAACAP, 5/06; ~18% in ADHD, ~2% in case controls
    - 90% in most severe manic episode in Geller 2006
  - Distractibility (change from baseline and in conjunction with a “manic” mood shift) in 74-98.6%
    - 95.1-98.6% (Tillman and Geller, 2007)
    - 74-85% in most severe manic episode in Geller 2006
    - 82% in JAACAP, 5/06; ~30% in ADHD, 10% in case controls
    - 84% in Kowatch, 2005
    - 93.6% in Geller, 2002; 96.3% in ADHD, 2.1% in case controls
  - Pressured/accelerated speech/ loud, intrusive, difficult to interrupt (change from baseline) in 72-97%
    - 95.1-99.3% (Tillman and Geller, 2007)
    - 72% in JAACAP, 5/06; ~54% in ADHD, 14% in case controls
    - 82-93% in most severe manic episode in Geller 2006
    - 82% in Kowatch, 2005
    - 97% in Geller, 2002; 81.5% in ADHD, 11.7% in case controls
  - History of marked sensitivity to sensory stimuli in infancy and early childhood in 70% in Papolos, 2002
  - Daredevil acts in 62.1-89.6%
    - 62.1-89.6% (Tillman and Geller, 2007)
    - 65.6% in Geller, 2002; 11.1% in ADHD, 0 in case controls
  - Uninhibited people seeking in 58.3-71.5%
    - 58.3-71.5% (Tillman and Geller, 2007)
    - 65.6% in Geller, 2002; 24.7% in ADHD, 3.2% in case controls
  - History of arousal disorders of sleep (night terrors, restless leg syndrome, bruxism) in 55% in Papolos, 2002
  - Flight of ideas (objectively) 52.4-80%
    - 52.4-90.3% (Tillman and Geller, 2007)
    - 66-80% in most severe manic episode in Geller 2006
    - 56% in Kowatch, 2005
  - Increased/unusual energy in 50-100%
    - 50% in Danielyan et al, 2007
    - 92.2-95.1% (Tillman and Geller, 2007)
    - 76% in JAACAP, 5/06; 84% in ADHD, 10% in case controls
    - 83-92% in most severe manic episode in Geller 2006
    - 89% in Kowatch, 2005
    - 100% in Geller, 2002; 95.1% in ADHD, 11.7% in case controls
  - Racing thoughts (subjectively) in 46.6-71%
    - 46.6-72.9% (Tillman and Geller, 2007)
    - 62% in JAACAP, 5/06; ~14% in ADHD, 4% in case controls
    - 65-76% in most severe manic episode in Geller 2006
    - 74% in Kowatch, 2005
    - 71% in Geller, 2002; 9.9% in ADHD, 0 in case controls
  - Rapid cycling in 46-87% (Geller, various studies: 75-87%)
    - ultrarapid cycling in 10-30%
    - ultradian cycling Symptoms occur 4 or more hours-a-day, total (not necessarily contiguous)
    - 78.6-98.6% (Tillman and Geller, 2007)
    - 77% in older Geller studies: an average of 3.7 cycles/day in youth (range 1.6-5.9)
    - 50% with no inter-episode recovery
    - More than twofold increase over adults
  - History of separation anxiety disorder in 42% in Papolos, 2002
  - Increase in goal-directed activity/psychomotor agitation in 39.8-67.4%
    - 39.8-67.4% (Tillman and Geller, 2007)
    - 58% in JAACAP, 5/06; ~18% in ADHD, 4% in case controls
    - 57-61% in most severe manic episode in Geller 2006
    - may draw copiously, build elaborate block towns, write novels
    - often with psychomotor agitation, change from baseline, pressured
  - Sharpened thinking 39.8-61.1% (Tillman and Geller, 2007)
  - Inflated self-esteem 38-78%
    - 38% in JAACAP, 5/06; ~7% in ADHD, 16% in case controls
    - 78% in Kowatch, 2005
  - Poor judgment in 32-90.3%
    - ~32% in JAACAP, 5/06; ~18% in ADHD, ~2% in case controls

- 72-85% in most severe manic episode in Geller 2006
  - 69% in Kowatch, 2005
  - 90.3% in Geller, 2002; 44.4% in ADHD, 3.2% in case controls
- Euphoric, expansive mood in 30.8-97.2%
  - 30.8% in Danielyan et al, 2007
  - 92.2-97.2 (Tillman and Geller, 2007)
  - 51% (Wozniak, 2005)
  - 60-70% in JAACAP, 5/06; ~16-22% in ADHD, ~4-6% in case controls
  - 82-92% in most severe manic episode in Geller 2006
  - 70% in Kowatch, 2005
  - 89.3% in Geller, 2002; 13.6% in ADHD, 0 in case controls
  - normal elation: happy, silly, giddy; mood appropriate to context, expected by adults, non-impairing
- Sleep disturbance/decreased need for sleep (by 2 hours or more per night for age without evidence of daytime fatigue) in 30-76%
  - 65.4% in Danielyan et al, 2007
  - 30% (JAACAP, 5/06); ~17% in ADHD, 4% in case control
  - 72% in Kowatch, 2005
  - 39.8% (Geller, 2002); 6.2% in ADHD, 1.1 in case controls
  - <50% (Geller, 1999)
  - <50% (Biederman et al, 1998)
  - 62-76% in most severe manic episode (Geller 2006)
- Disinhibited behavior in 30% in JAACAP, 5/06; ~4% in ADHD, ~2% in case controls
- Psychiatric hospitalization in 28.8-66.1% (Geller, 2006)
  - 28.8% for bipolar NOS
  - 53.3-66.1% for bipolar I or II
- Hypersexual (pleasure seeking) in 24-66.7%
  - 39.8-66.7% (Tillman and Geller, 2007)
  - 24-49% in most severe manic episode in Geller 2006
  - 29% in JAACAP, 5/06; ~4% in ADHD, 0% in case controls
  - 38% in Kowatch, 2005
  - 43% in Geller, 2002; 6.2% in ADHD, 0 in case controls
- Wetting in 22% (vs. 6% in controls)
- Suicidal ideation and behaviors in 20.9-93.3 (Geller, 2002, 2006)
  - Overall:
    - 26.2-61.1% (Tillman and Geller, 2007)
    - 24.7% (2002)
  - Ideation (2006): 71.9-93.3%
  - Attempt (2006): 20.9-43.3%
  - Papolos, 2005: obsessive fear of harm to self or others (in bipolar children) associated with higher risk of harm to self and others as well as suicidal threats.
- Grandiosity in 20-95.1%
  - 87.4-95.1% (Tillman and Geller, 2007)
  - 20% in JAACAP, 5/06; ~7% in ADHD, 2% in case controls
  - 86% in Geller, 2002; 4.9% in ADHD, 1.1 in case controls
  - e.g., teaches the class, asks principal to fire teacher, believes is a superhero
  - normal grandiosity: play, context appropriate, developmentally expected
- Mixed episodes in 20-85%
  - Dilsaver, 2005: 82% mixed; most common presentation of bipolar disorder in their sample.
  - Geller, 2002: 54.8%
- Silliness, laughing in 19.2-91%
  - 19.2% in Danielyan et al, 2007
  - 69.9-91% (Tillman and Geller, 2007)
  - 63.4% in Geller, 2002; 23.5% in ADHD, 0 in case controls
- Soiling in 15% (vs. 3% in controls)
- Psychosis in 10-84%
  - 61.2-84% (Tillman and Geller, 2007)
  - 10-38%
    - 10% with visual hallucinations (JAACAP, 5/06); 0% in ADHD, 0% in case controls
    - 18% with auditory hallucinations (JAACAP, 5/06); 0% in ADHD, 0% in case controls
    - 38% with delusions (JAACAP, 5/06); 0% in ADHD, 0% in case controls
  - 17.6-34.5% (Geller, 2006)
  - 60% (Geller 2002)
- **Childhood Bipolar Questionnaire (with critical questions highlighted)**
  - Oppositional/Poor Frustration Tolerance
    - Intolerant of delays
    - Relentlessly pursues needs/demanding of others
    - Willful, refuses to subordinate to others
    - Argues with adults
    - Bossy towards others
    - Defies or refuses to comply with rules
    - Blames others for his/her mistakes
    - Easily angered in response to limit setting
  - **Protracted, explosive temper tantrums**
  - Attention/Executive Functions Deficits
    - Easily distracted by extraneous stimuli
    - Easily distracted during repetitive chores
    - Demonstrates inability to concentrate at school

- Poor handwriting
- Difficulty organizing tasks
- Difficulty making transitions
- Difficulty estimating time
- Auditory processing/short-term memory deficit
- Depression
  - Complains of being bored
  - **Periods of low energy or withdrawal**
  - **Decreased initiative**
  - **Periods of self doubt/poor self-esteem**
  - **Easily criticized and/or rejected**
  - **Easily humiliated or shamed**
  - Made clear threats of suicide
- Sensory Sensitivity
  - Extremely sensitive to textures of clothes
  - Extreme sensitivity to sound
  - **Body temperature extremes**
  - **Concern with dirt, germs, contamination**
- Aggression
  - Difficulty maintaining friendships
  - **Aggressive behavior towards others**
  - Destroyed property intentionally
  - Makes moderate threats to others or self
  - Makes clear threats of violence to others/self
  - Made clear threats of suicide
  - Fascinated with gore, blood, violent imagery
- Sleep Cycle Problems
  - Difficulty rising in the morning
  - Hyperactive and easily excited in the evening
  - Difficulty settling at night
  - **Difficulty getting to sleep**
  - Sleeps fitfully and/or awakens in the night
  - **Has night terrors and/or nightmares**
- Grandiose/Hypersexual
  - Exaggerated ideas about self or abilities
  - Tells tall tales/embellishes or exaggerates
  - Precocious sexual curiosity
  - Inappropriate sexual behaviors
  - **Lies to avoid consequences of actions**
- Mania
  - Excitable with periods of high energy, frenetic activity
  - **Has many ideas at once**
  - **Interrupts or intrudes on others**
  - Periods of excessive rapid speech
  - **Displays abrupt, rapid mood swings**
  - **Elated or silly/giddy mood states**
- Fear of Harm/Anxiety
  - Excessive distress when separated
  - Excessive anxiety or worry
- Temperamental features (Papolos, 2002)
  - Hyperactivity/impulsivity
  - Easy arousability
  - Prominent switches in energy and activity in diurnal pattern
  - Separation anxiety in childhood
  - Periodic sweet and carbohydrate cravings with episodic bingeing
  - Predisposition for sleep/wake reversals
  - Seasonal variation in symptoms
  - Deficit in capacity to modify expression of aggressive behaviors
  - Deficits in social cognition, response flexibility
    - Pragmatic judgment of language
    - Facial expression recognition; in one study, misinterpreted sad, happy, and fearful child faces, but not adult faces, as angry (compared to children with anxiety disorders or no disorders).
    - Poorer performance on face-emotion recognition task
- Overlap with ADHD
  - Dr. Charles Popper: “all of the features of ADHD can be seen in mood disorders at times, so ADHD is a diagnosis reached only after ruling out a mood disorder.”
  - Symptoms that do **NOT** overlap with ADHD:
    - **Elated mood**—87-89% in bipolar disorder, 5-13% in ADHD
    - **Grandiosity**—85-86% in bipolar disorder, 5-7% in ADHD
    - **Flight of ideas/racing thoughts**—67-71% in bipolar disorder, 10% in ADHD
    - **Psychosis**: 60% in bipolar disorder, 0% in ADHD

- **Hypersexuality**—43-45% in bipolar disorder, 6-8% in ADHD
- **Decreased need for sleep**—43% in bipolar disorder, 5-6% in ADHD
- **Suicidality**—25% in bipolar disorder, 0% in ADHD
- Symptoms that partially overlap with ADHD:
  - Daredevil acts
  - Silliness
  - Uninhibited people seeking
- Symptoms that fully overlap with ADHD:
  - Irritable mood—98% in early onset bipolar disorder (EOBD), 72% in ADHD
  - Accelerated speech—97% in EOBD, 81% in ADHD
  - Distractibility—93% in EOBD, 96% in ADHD
  - Increased energy—100% in EOBD, 95% in ADHD
- Distinctions
  - ADHD
    - Destructiveness
      - often break things carelessly while playing
      - usually calm down in 20-30 minutes
      - triggered by sensory and emotional overstimulation
    - Misbehavior
      - often accidental
      - usually caused by oblivious inattention
    - Risky behavior
      - may engage in behavior that can lead to harmful consequences without being aware of the danger
    - Arousal
      - tend to arouse quickly and attain alertness in minutes
    - Sleep
      - Delayed sleep phase
  - Bipolar
    - Destructiveness
      - tends to occur in anger
      - severe temper tantrums during which they release manic quantities of physical and emotional energy, sometimes with violence and physical property destruction
      - may exhibit sadistic impulses
      - may continue to feel and act angry for up to four hours
      - may be regressed with disorganized thinking, language, and body position
      - may lose memory of the tantrum
      - triggered often by limit setting
      - often show dysphoria (depression) as predominant symptom
      - irritability is prominent, especially in the morning on arousal
    - Misbehavior
      - intentionally provoke or misbehave
      - “the bully on the playground”
    - Risky behavior
      - risk seeking
    - Arousal
      - slow arousal
      - several hours of irritability or dysphoria
      - several hours of fuzzy thinking or “cobwebs”
      - somatic complaints such as stomachaches and headaches upon waking up in the AM
    - Sleep
      - delayed sleep phase
      - severe nightmares or night terrors, often with themes of gore and bodily mutilation
    - Other
      - often show giftedness in certain cognitive functions, especially verbal and artistic skills, perhaps with verbal precocity and punning by age two to three years
      - strong early sexual interest and behavior
      - may exhibit gross distortions in the perception of reality or in the interpretation of emotional events—youth with ADHD usually do not
      - lithium treatment generally improves bipolar disorder but has little effect on ADHD
      - The continuous performance test (CPT) may help distinguish ADHD from bipolar disorder; those with ADHD will show improvements on the CPT after stimulant treatment whereas those with bipolar disorder may show worsening.
      - 9.5% of adults with bipolar disorder can be retrospectively diagnosable with ADHD in childhood (Nierenberg, 2005)
      - Note that some evidence (Carlson et al, 1992; Beiderman et al, 1999; Kowatch et al, 2003; Galanter et al, 2003; Carlson and Kelly, 2003; Scheffer et al, 2005; another study in 2006) suggests that youth with bipolar disorder and ADHD can safely treated with stimulant medications if their mood is stabilized
      - Tillman et al, 2006: blindly rated, 6 year, 7.7-11.7 yo age range, prospective study of 81 children diagnosed with ADHD (only): 28.5% switched from ADHD to prepubertal and early onset bipolar I disorder; risk factors included
        - More severe functioning at baseline

- Recurrent depression in father
  - Less stimulant use (!)
  - (Not correlated with antidepressant use)
- Bipolar children with depression, compared to children with unipolar depression, have more
  - Irritability
  - greater suicidality
  - anhedonia (lack of pleasure)
  - diurnal variation (change in symptom severity dependent on time of day)
  - hopelessness
  - psychomotor retardation (slowing of body movements)
  - delusions
  - co-morbid diagnoses.
- Comparison with OCD (Joshi et al, 2006)
  - Youth
    - Primary OCD—130 youth
      - OCD without bipolar—111 youth
      - OCD PLUS bipolar—19 youth
    - Primary Bipolar—94 youth
      - Bipolar without OCD—76 youth
      - Bipolar PLUS OCD—18 youth
  - Results
    - Bipolar PLUS OCD vs bipolar without OCD
      - More pressured speech
      - More flight of ideas
    - OCD PLUS bipolar vs. OCD without bipolar
      - More frequent obsessions and compulsions of hoarding/saving
      - Increased compulsions of rituals involving another person
      - Increased sociability
      - Worse impact on functioning
      - More frequent hospitalization
- Proposed diagnostic criteria for juvenile bipolar disorder; must meet criteria A-D for diagnosis
  - A.
    - Episodic and abrupt transitions in mood states accompanied by rapid alternations in levels of
      - Arousal
      - Emotional excitability
      - Sensory sensitivity
      - Motor activity
    - Variable mood states characterized by the following features:
      - Manic/hypomanic
        - Either one, the other, or both
          - Silly-goofy-giddy (and/or mirthful, elated, euphoric, overly optimistic, self-aggrandizing, grandiose)
          - Angry/irritable
        - 3 of the following symptoms and behaviors (4 if irritable mood only)
          - More talkative than usual
          - Pressured speech
          - Flight of ideas
          - Subjective experience of thoughts racing
          - Distractibility
          - Diminished need for sleep
          - Increase in goal-directed activity
          - Heightened interest, enjoyment, and enthusiasm for usual activities
          - Excessive involvement in pleasurable activities that have a high potential for painful consequences
          - Overestimation of resources and capacities
          - Overvaluation of self and others
          - More argumentative than usual
          - Overbearing
          - Bossy
          - In pursuit of personal needs or agenda
      - Depressive episodes are associated with
        - Either one, the other or both:
          - Dysphoric/sad/withdrawn/pessimistic/self-critical/irritable or anxious/fearful or both
          - Loss of interest and pleasure, increased boredom in previously enjoyed activities often resulting in expressions of boredom and excessive stimulus-seeking behaviors
        - 4 or more of the following
          - Decreased sense of self-esteem
          - Slowed speech
          - Paucity of thought
          - Increased need for sleep or disrupted sleep
          - Loss or increase in appetite

- Decrease or loss of energy
    - Difficulty sustaining attention
    - Diminished ability to concentrate or indecisiveness
    - Psychomotor retardation (slowed body movements)
    - Loss of initiative and motivation
    - Underestimate of resources and capabilities
    - Devaluation of self and others
    - Negative interpretation of events and misattribution of other's behaviors
    - Recurrent thoughts of death
    - Recurrent suicidal ideation
  - Mixed episodes
    - Overlapping features of manic/hypomanic, angry, depressed and/or anxiety states
    - Associated symptoms of manic/hypomanic and depressive mood states
    - May include
      - Irritability
      - Agitation
      - Insomnia
      - Appetite dysregulation
      - Poor control over aggressive impulses
        - Aggression directed at self or others
      - Psychotic features
- B.
  - Poor modulation of drives
    - Regulatory disturbance is associated with excessive aggressive/fight-based behaviors
      - Critical
      - Sarcastic
      - Demanding
      - Oppositional
      - Overbearing
      - Bossy
      - Easily enraged
      - Prone to violent outbursts
      - Self-directed aggression
        - Head-banging
        - Skin picking
        - Cutting
        - Suicide behaviors
    - Premature and intense sexual feelings and behaviors
      - Precocious curiosity about sex
      - Premature expression of sexual impulses
      - Inappropriate public displays
    - Appetite dysregulation
      - Excessive craving for carbohydrates and sweets
      - Binge eating
      - Purging
      - Anorexia
    - Poor control over acquisitive impulses
      - Relentless pursuit of needs
      - Buying excessively
      - Hoarding
  - Episodic and abrupt transitions in mood states and poor modulation of drives
    - Are currently present most days
    - Have been present for at least the past 12 months
    - No symptom-free periods exceeding 2 months in duration
    - Cause functional impairment in 1 or more settings
- C.
  - Four or more of the following disturbances have been present during the same 12-month period
    - Excessive anger and oppositional/aggressive responses to situations that elicit frustration, compared to peers
      - Difficulties in the postponement of immediate gratification when parents set limits; in particular
        - when answered "no" to expressed wishes
        - when having to wait his/her turn
        - when there are changes in planned activities or routines
      - Results in maladaptive responses
        - Seeming not to listen in a purposeful manner
        - Display of disruptive, intrusive, or overbearing behaviors
        - Temper tantrums
        - Aggressive attacks
        - Sullen withdrawal and expressions of remorse after tantrums and attacks
    - Poor self-esteem regulation
      - Overly optimistic at times
      - Defiant

- Arrogant
  - Filled with bravado
  - Prone to self-aggrandizement
  - Exaggeration of abilities
  - Feelings of omnipotence
- Overly pessimistic at times
  - Self-critical
  - Overly sensitive to criticism or rejection
  - Often responding to criticism with intense feelings of shame and humiliation
  - Insecurity
  - Worthlessness
- Capable of rapid and intense idealization and devaluation of self and others
- Sleep/wake cycle disturbances; at least one of the following
  - Sleep discontinuity
    - Initial insomnia
    - Middle insomnia
    - Late insomnia (early morning awakenings)
    - Hypersomnia (oversleeping)
  - Sleep arousal disorders
    - Sleep inertia (in the morning)
    - Night terrors
    - Nightmares—often containing images of gore and mutilation, and themes of pursuit, bodily threat and parental abandonment
    - Sleep walking
    - Confusional arousals
    - Bruxism (teeth grinding)
    - Enuresis (bed wetting)
  - Sleep/wake reversals
    - Tendency towards periodic lengthening or shortening of sleep duration, often dependent on circadian and circannual (annual/seasonal) changes in light/dark and temperature cycles as well as the availability of regular social time givers
- Low threshold for anxiety
  - Tendency to react with excessive anxiety and fearfulness in response to novel or stressful situations
    - Transitions of context
    - Loss
    - Separation
    - Anticipation of loss
    - Separation from attachment objects
    - Loss of social status
  - Anxiety arising from fear of harm to self in the form of
    - Anger
    - Rejection
    - Criticism
    - Ostracism
    - Fear that will harm others or self
  - Can predispose to behavioral inhibition or flight-based behaviors such as
    - Separation anxiety disorder
    - Social phobia
    - Panic disorder
    - OCD
    - PTSD
- Disturbance in the capacity to habituate to sensory stimuli often when exposed to novel, repetitive, or monotonous sensory stimulation
  - Tendency to overreact to environmental sensory stimulation
  - Tendency to become overaroused, easily excited, irritated, angry, anxious, or fearful when exposed to
    - novel sensory experiences such as crowds, vacuum cleaners, ticking clocks, thunder and lightning
    - dissonant sensations such as shirt tags, fit of clothes or shoes, perceived foul odors
- Executive function deficits/mental inflexibility; difficulties in/with 1 or more of the following
  - Shifting cognitive set
  - Planning ahead
  - Planning strategically as seen in unrealistic estimate of energy resources and time requirements for the accomplishment of tasks (e.g., difficulty adjusting to changes in plans for the day such as planned trips and changes in venue)
  - Giving up an idea or desire, no matter how unrealistic or unfeasible
  - Starting and completing school assignments without a great deal of prompting, often getting caught up in small details of a project and missing the big picture
  - Working memory
  - Making transitions from one context to another
  - Organizational skills
  - Distractibility

- Excessive daydreaming
      - Written expression
    - Emotional inflexibility
      - Impulsive, acts before thinking
      - Overreacts to small events
      - Rapidly shifts emotional states
      - Can demonstrate sudden anger, resentment, and/or rage for longer than 15 minutes that is unresponsive to reason, discussion, or soothing
      - Can become progressively unrestrained or silly
      - Does not appear to gain pleasure from mastering a skill
    - Inflexibility of motor activity
      - Initiation of movement directed at the accomplishment of motor tasks is effortful
        - Has difficulty starting activities in the morning
        - Requires help initiating any activity
      - Is often restless and fidgety
      - Handwriting is poor
      - Trouble initiating and completing written assignments
    - Family history
      - Recurrent mood disorder and/or
      - Alcoholism and/or
      - Bipolar spectrum disorders
  - D.
    - Symptoms are not due to a general medical condition (e.g., hypothyroidism)
    - Episodes are defined by DSM-IV symptom criteria but NOT by DSM-IV duration criteria; manic/hypomanic or mixed episode(s) required for diagnosis
- Course/Prognosis:
  - Risks of depression (unipolar or bipolar) in youth
    - Number 1 cause of disability-adjusted years lost in teens (unipolar depression) (WHO, 2014)
    - Self-harm/suicide 3<sup>rd</sup> leading cause of death (below road injury and HIV/AIDS) in teens (WHO, 2014)
  - Overall, long-term prognosis
    - COBY Study
      - 4 years of follow-up
      - 82% remit
      - 63% of those that remit have a recurrence
      - Symptomatic 60% of time (20% syndromal, 40% subsyndromal)
      - In more recent analysis of youths over 93 months of follow-up
        - Trajectories
          - 24% were predominantly euthymic (euthymic ~84% of time)
          - 35% were moderately euthymic (euthymic ~47% of time)
          - 19% with ill but improving course (euthymic ~43% of time)
          - 22% with predominantly ill course (euthymic ~12% of time)
        - 43% were euthymic most of the 93 months
        - Youth with predominantly ill course were more likely to also have other diagnoses like ADHD, anxiety disorders
    - Other studies
      - 70-100% recover from their initial episode
      - Up to 80% experience a recurrence within 2-5 years
      - 40% of youth with bipolar disorder, not otherwise specified convert to bipolar I or bipolar II
    - Similar to adults in Carlson et al, 1977; McGlashan et al, 1988; Werry et al, 1991; McClellan et al, 1993
    - Worse than in adults in Carter et al, 2003
    - Life and family stress worsens mood symptoms in youth
    - Overall recovery rates (most define it as recovery from episode at the time of the study)
 

	# youth	Outpt/Inpt	Length study	Recovery
○ Strober 1995	54	O	5 yrs	98%
○ Srinath 1998	30	O	4-5 yrs	100%
○ Lewinsohn 2000	17	Epidemiologic	7 yrs	88%
○ Geller 2004	86	O	4 yrs	87%
○ Jairam 2004	25	O	4.3 yrs	100%
○ Birmaher 2006	263	O (16% I)	2 yrs	70%
○ DelBello 2007	71	I	1 yr	85%/39%/39%
○ Strober 1995	54		5 yrs	
  - Recovery by initial mood episode:
    - 90% if manic episode
    - 80% if mixed episode
    - 60% if rapid cycling
    - 43% if depression
  - Relapse after recovery by initial mood episode
    - 38% if depression
    - 40% if mixed
    - 42% if manic

- 60% if rapid cycling
- ADHD associated with decreased response rate to lithium
- Geller, 2004 study, 86 youth ages 7-16 years, 48 months
  - % recovered      % relapsed after recovery
  - By 6 months      14                      16.7
  - By 12 months     36                      29
  - By 18 months     55.6                    39.6
  - By 24 months     65.1                    55.4
  - By 36 months     77.9                    53.7
  - By 48 months     87.2                    64
  - Overall over the 4 year period
    - 47% of weeks with depression
    - Number of weeks with depression 99
    - Relapse into depression averaged 1.1 times-a-year
  - Further breakdown by age of onset
    - By 6 months
      - 14.6% in prepubertal onset
      - 51% in late teen onset
      - 70% in adult onset
    - By 12 months
      - 37.1% in prepubertal onset
      - 62% in late teen onset
      - 83% in adult onset
    - By 18 months
      - 56.2% in prepubertal onset
      - First 12-18 months in prepubertal onset:
        - 50% in full remission
        - 20% functionally remitted
        - 7% with stable normal mood
    - By 24 months
      - 56.2-65.2% in prepubertal onset
      - 75% in teen onset
      - 86% in adult onset
    - By 4 years
      - 87% in pediatric onset without psychotic symptoms
      - 50% in pediatric onset if with psychotic symptoms
- Jairam, 2004 study; 25 youths, ages 9-16 yo, with bipolar I, manic episode, followed over 4-5 years
  - Outcome:
    - One youth committed suicide during depressive episode
    - One youth dropped out of study
    - Of the remaining 23 youth
      - 100% recovered from episode that brought youth to evaluation
      - 64% relapsed an average of 18 months later; of those that relapsed, 72% were on medication
        - 58% relapsed into mania
        - 23% relapsed into depression
        - 16% relapsed into mixed episode
        - 3% relapsed into hypomania
- Birmaher 2006, 263 youths over 2 years

	Bipolar I	Bipolar II	Bipolar NOS
○ Recovery rates	68%	79%	66%
○ Time to recovery	52 weeks	42 weeks	140 weeks
○ Rate of recurrence	58%	87%	46%
○ Time to recurrence	45 weeks	16 weeks	46 weeks

- 48-50% with at least one syndromal recurrence, particularly depressive episodes
- 60% of time, subjects have syndromal or subsyndromal symptoms with numerous changes in symptoms and shifts in polarity
  - Percentage of diagnostic conversion to bipolar I or II
    - 21% of those with bipolar II converted to bipolar I
    - 20% of those with bipolar NOS converted to bipolar I
    - 10% of those with bipolar NOS converted to bipolar II
  - Predictors of more time spent with syndromal mood symptoms
    - Bipolar I diagnosis
    - Psychosis
    - Female
  - Predictors of more time spent with subsyndromal mood symptoms
    - Bipolar NOS diagnosis
    - Younger onset
  - Predictors of poor recovery
    - Prepubertal onset
    - Bipolar NOS diagnosis

- Longer duration of episode
  - Predictors of recurrence
    - Bipolar II diagnosis
- In another study by Birmaher of 405 children with bipolar I, II, and NOS from 4 centers were followed for 2.5 years; 60% bipolar I, 7% bipolar II, 33% bipolar NOS; consequences:
  - School failure
  - Entanglement with the legal system
  - Hypersexuality/pregnancy
  - Low self-esteem
  - Family tension/chaos/impairment—loss of job time, divorce
  - Poor peer relationships
  - Increased rate of suicide attempts and completions
  - Twofold increased standardized mortality rate from medical causes
  - ~40% attempted suicide
  - 60% of bipolar I and II patients were admitted to a hospital
- Del Bello et al, 2007, 71 inpatient adolescents post-hospitalization, 1 year:
- **Functional** (full) recovery
  - **~41% by 48 weeks overall**
  - Time
    - 17 weeks for role performance
    - 20 weeks for recreational enjoyment
    - 24 weeks for interpersonal relationships
  - Prognostic factors
    - Less likely if have ADHD or other disruptive behavior disorder(s)
    - More likely in the area of interpersonal relationships if absence of stimulants
    - More likely to respond to recover in the area of recreational enjoyment if early onset
- **Symptomatic** recovery (~no symptoms but only partial functional recovery)
  - ~56% by ~43 weeks in boys
  - **~42% by ~43 weeks overall**
  - ~32% by ~43 weeks in girls
- **Syndromic** recovery (no longer meets formal criteria for disorder despite persistent symptoms and only partial functional recovery)
  - ~95% by ~41 weeks if medication compliant OR if no ADHD (OR both)
  - ~90% by ~43 weeks if no anxiety disorder
  - **~87% by ~43 weeks overall (AVERAGE 27 WEEKS)** OR if no disruptive behavior disorder
    - **52% of these had at least one syndromic recurrence 17 weeks post-recovery**
  - ~85% by ~43 weeks if + disruptive behavior disorder other than ADHD
  - ~81% by ~43 weeks if non medication compliant
  - ~80% by 40 weeks if + anxiety disorder
  - ~76% by ~42 weeks if + ADHD
  - In the year following hospitalization, time spent with syndromal symptoms or subsyndromal symptoms
    - 38% of time experiencing syndromic symptoms
    - 46% of time experiencing subsyndromal symptoms
  - Antidepressants associated with shorter time for syndromic recurrences
- Remission rates broken down by age of onset
  - < 12 yo: 41% by 6 months and 46% by 12 months
  - 13-17 yo: 56% by 6 months and 73.5% by 12 months
  - 15-29 yo: 62% by 6 months and 69% by 12 months
  - 30+ yo: 83% by 6 months and 84.4% by 12 months
- For each year of illness, youths have a 10% lower likelihood of recovery
- Adherence to medication tripled chance of recovery
- Poor adherence to medications strikingly low when alcohol or substance use is present
- Recurrence rates by 170 weeks ~45% in those with no substance abuse, 100% in those with substance abuse
  - 50-55.2% by two years in one study
    - In 6 months
      - 15.4% in prepubertal onset
      - 16% in late teen onset
      - 23.5% in adult onset
    - By one year
      - 27.3-38% in prepubertal onset
      - 25% in late teen onset
      - 36% in adult onset
    - By 18 months
      - 40% in prepubertal onset
    - By two years
      - 55.2% in prepubertal onset
      - 50% in late teen onset
      - 55% in adult onset
  - 64% by four years (Jairam, 2004)
  - 67% (Indian study)
- Studied over a four-year period:
  - spent 67% of weeks meeting bipolar diagnosis

- 57% of total weeks with mania or hypomania
  - 47% of total weeks with major depression or minor depression
  - In one study, relapses were usually into mania.
  - Higher frequency of suicidal ideation and attempts
- Other studies
- Indian study:
  - Rapid cycling in 8-14%
  - Very low rates of comorbid conditions and suicide/suicide attempts
  - Absence of alcohol and substance abuse
- Higher likelihood (81%) of multiple diagnoses
  - Disruptive behavior disorders; 74.4% with any disruptive behavior disorder (including ADHD)
    - ADHD
      - Consoletti et al, 2007: ADHD especially in adolescents is associated with more treatment resistance for bipolar disorder
      - Perugi et al, 2006: 37.8%
      - Geller, 2006: 43.3-62.1% (range is 43.3-98% (less with teenagers)
      - Nierenberg et al, 2005 and Faraone et al, 1997:
        - Children with child-onset mania: >90% have ADHD
        - Adolescents with child-onset mania: >80% have ADHD
        - Adolescents with adolescent-onset mania: <60% have ADHD
        - Adults with mania: <10% have ADHD
      - Galanter et al, 2003 (MTA): presence or absence of mania did NOT predict methylphenidate response nor side effects
      - Wilens et al, 2003:
        - Adults with bipolar disorder and ADHD have more than 2-fold more mood symptoms than those without ADHD (Wilens et al, 2003)
        - Wellbutrin for ADHD in adults with bipolar disorder; treat ADHD symptoms AND reduced symptoms of mania.
      - Carlson and Mick, 2003: stimulants for ADHD in inpatient youth with bipolar disorder reduced disruptive behavior and did NOT exacerbate mania or mood lability
      - Carlson et al, 2000: longitudinal analysis of children aged 6-12 yo, 58 children of which had ADHD and 17 of which had ADHD and mood symptoms (depression, bipolar disorder); when followed up at age 21-23:
        - Response to stimulants similar between those who went on to develop bipolar disorder and those who did not
        - Stimulant use not related to development of bipolar disorder
      - Scheffer et al: 6-17 yo youth with bipolar spectrum disorders and ADHD, treated with Depakote plus Adderall (5 mg twice-a-day) vs. Depakote plus placebo; Adderall effective in the treatment of ADHD
      - Biederman et al, 1999: ADHD symptoms improve with stabilization of mood; ADHD symptoms are worse during a manic relapse
    - Oppositional defiant disorder
      - Geller, 2006: 23.3-40.8 (range is 23.3-76.3%)
    - Conduct disorder:
      - Geller, 2006: 11.8-13.3% (range 5.6-37%)
  - Anxiety disorders in up to 90% with anxiety
    - Geller, 2006: 37.1-60%
    - Dickstein, 2005: 46.9-77.4% with co-morbid anxiety disorder
    - Masi, 2001: 78% with co-morbid anxiety disorder
    - Biederman, 1997; Birmaher, 2002: 19-52% of kids with panic disorder have co-morbid bipolar disorder
    - 56% of children and adolescents with bipolar disorder have multiple anxiety disorders.
    - 52% of children and adolescents with panic disorder have bipolar disorder
    - When present in bipolar youth with family histories of bipolar disorder in one or more parents (Simeonova et al, 2006), degree of anxiety symptoms correlated inversely with hippocampal volume
    - Hypersensitivity to carbon dioxide provocation of anxiety
  - Substance use disorders in 0-40%
    - Nearly 9-fold greater risk in adolescent-onset bipolar disorder vs. child-onset
  - Wetting in 21.5% (versus 22.2% in ADHD and 6.4% in controls); this % is in kids NOT receiving lithium.
  - Soiling in 15% (versus 3.2% in controls)
  - Pervasive development disorder
    - Essential characteristics include impairments in
      - Social interaction
      - Imaginative activity
      - Verbal and non-verbal communication skills
        - Poor social and reciprocal language
        - Fail to catch the subtleties of conversation, such as humor or irony
        - Language does not mold and modify according to responses and cues from the person with whom they are conversing
      - Interests and activities (limited and repetitive)
    - Connection with bipolar disorder (DeLong, 1988)
      - <50% of children with autism spectrum disorders have a first- or second-degree family member with bipolar disorder; the incidence was 4.2%, the higher incidence was in Asperger's syndrome
      - 10-35% of youth with autistic spectrum disorder may also have bipolar disorder

- Asperger's disorder
  - Range 1.9-3.3%; though one report noted 11%
- Adult patients with bipolar disorder often have antecedent youth diagnoses of:
  - ADHD
  - ODD
  - Conduct disorder
  - Separation or overanxious disorder
  - Enuresis (bed wetting)
- **Treatment of bipolar disorder**
  - Biederman, 2000, retrospective chart review, 59 youth with bipolar disorder
    - Depression
      - 42 youth had symptoms of depression at follow-up visits
      - 7 times more likely to improve on SSRI than no medication
      - No significant improvement with tricyclic antidepressants, mood stabilizers, stimulants, and neuroleptics
    - Mania
      - 3 times more likely to develop manic symptoms than on no medication
      - Improvement with mood stabilizer and SSRI
      - Not induced by stimulants
  - Case report of 17 yo with bipolar disorder stable on Depakote and Zyprexa, developed depression, received Cymbalta 20 mg twice-a-day, developed symptoms of mania and ultrarapid cycling; resolved with cessation of Cymbalta and increase in Depakote
  - STEP-BD (Sachs et al, 2007); 336 adults with bipolar I or II, depression; 179 were randomized to treatment of Paxil or Wellbutrin added to mood stabilizer; 187 were randomized to treatment of placebo added to mood stabilizer; 26 weeks
    - Durable recovery (8 consecutive weeks of euthymia)
      - 24% with antidepressant add-on
      - 27% with placebo add-on
    - Rates of mood episode switch
      - 10% with antidepressant add-on
      - 11% with placebo add-on
    - Antidepressants did not add any benefit for bipolar depression over 26 weeks
  - Patel 2006: open-label lithium for adolescent bipolar depression, 27 youth, bipolar I, depressed, lithium level 1.0-1.2 for 6 weeks
    - Response rate 48%
    - Remission rate 30%
  - Chang 2006: open-label Lamictal for adolescent bipolar depression, 20 youth, bipolar I, II, or NOS; mean dose 132 mg/d, monotherapy in 13 or adjunctive treatment in 7, 8 weeks (but keep in mind dosing starts very low and goes very slow due to rash risks)
    - Response rate 63-84%, depending on how define response
    - Remission rate 58%
    - Side effects: headache, fatigue, nausea, sweating, difficulty sleeping
  - Adjunctive psychoeducation (3 sessions in 6 weeks) vs. intensive psychotherapy (30 sessions in 9 months—either family-focused or interpersonal or cognitive behavioral, or social rhythm therapy) for 293 adults with bipolar I or II, depressed
    - Year-end recovery rate 52% with psychoeducation
    - Year-end recovery rate 64% with intensive psychotherapy
  - Other issues of pediatric bipolar disorder
    - 42-56% response rate to lithium and Depakote; 60-84% response rate to atypical antipsychotic medications
    - Compared to adults, respond more slowly and less well to lithium
    - Compared to adults, respond more slowly and less well to valproic acid and other AED mood stabilizers
    - Polypharmacy is often necessary
    - Compared to adults, even more weight gain on all mood stabilizing agents than adults
    - Higher incidence of life-threatening rash with Lamictal in children vs adults
    - Atypical antipsychotics may have faster onset
    - Stimulants—evidence of safety of stimulants in youth with bipolar disorder (Tilman and Geller, 2006; Galanter et al, 2003; Carlson et al, 2000, 2003)
    - SSRI's—evidence of efficacy but clear increased risk of switch to mania and suicidal ideation

#### Notes on talk on irritability

Grandiosity and inflated self esteem are cardinal symptoms of bipolar disorder

Explosive or severe/explosive irritability vs cranky irritable is low in adhd espec if no mood; in adhd irrit is heterog and varying in level of imprmt  
Low frustration tolerance itself is not associated with mood disorders

Explosive irrit is higher in mood+adhd and more severe explosive irrit is more likely bipolar do---so the point is that irrit in gen not specific to bip, the more explosive, though, the more likely to be bipolar

Those with explosive irrit with dx bip—more likely to have elated mood, grandiose, dec need for sleep, etc—

So the point here is also that explosive irrit itself is not even specific to bip but it is if in combo with other cardinal sx of bip

Family members of Kids with explos irrit and cardinal s/s bip are more likely to have explosive irrit and cardinal s/s bip  
Similar to depression

If kids with low level irrit—family members no more likely to have mood/bip disorders

So some adhd with minimal irrit

Adhd with low frust tol and irrit—likely to have odd

Adhd with more explos irrit and cardinal s/s—more likely to have mood disorder dep or bip

Adhd and comorbid conditions and risk of dx's in family members

Kids with psychosis more freq families with psychosis

Bip kids—more freq bip in families; same with depression

Adhd—no more likely freq bip in families or psychotic or dep

This is when use dsm iv

Risk of bip I in sibs is 5-6 fold higher in kids with bip 1

Severe mood dysregulation—

Bip kids—severe chronic irrit and mood dysregulation

Relatives of kids with

Relatives of sev mood dysreg—dep,manxiety sub use—didn't assess adhd---no bip vs relatives of explosive irritability/bip—inc bip mood, anx sub anx

So severe mood dysreg can often be adhd plus odd—but this can be fleeting dx—remits in 98%--this though is less persistant than adhd and odd. 67% met criteria for other dx's add, odd, cd

Research:

Smd vs. add/odd vs bip I kids—2/3 of which have narrow or irritable bip

Results: no diff in psychosis, deprn

Irrit bip looked like bip—inc in family of bip

Smd looked like adhd/odd—no increased risk of family bip

Adhd risk same in all groups

So: specific type of irritability is very important: looking at severity and explosiveness almost always associated with mania—less explosive or severe not assoc with irrit. Stil, it is just a screen

Prog of kids with ocd and bip is extremely poor