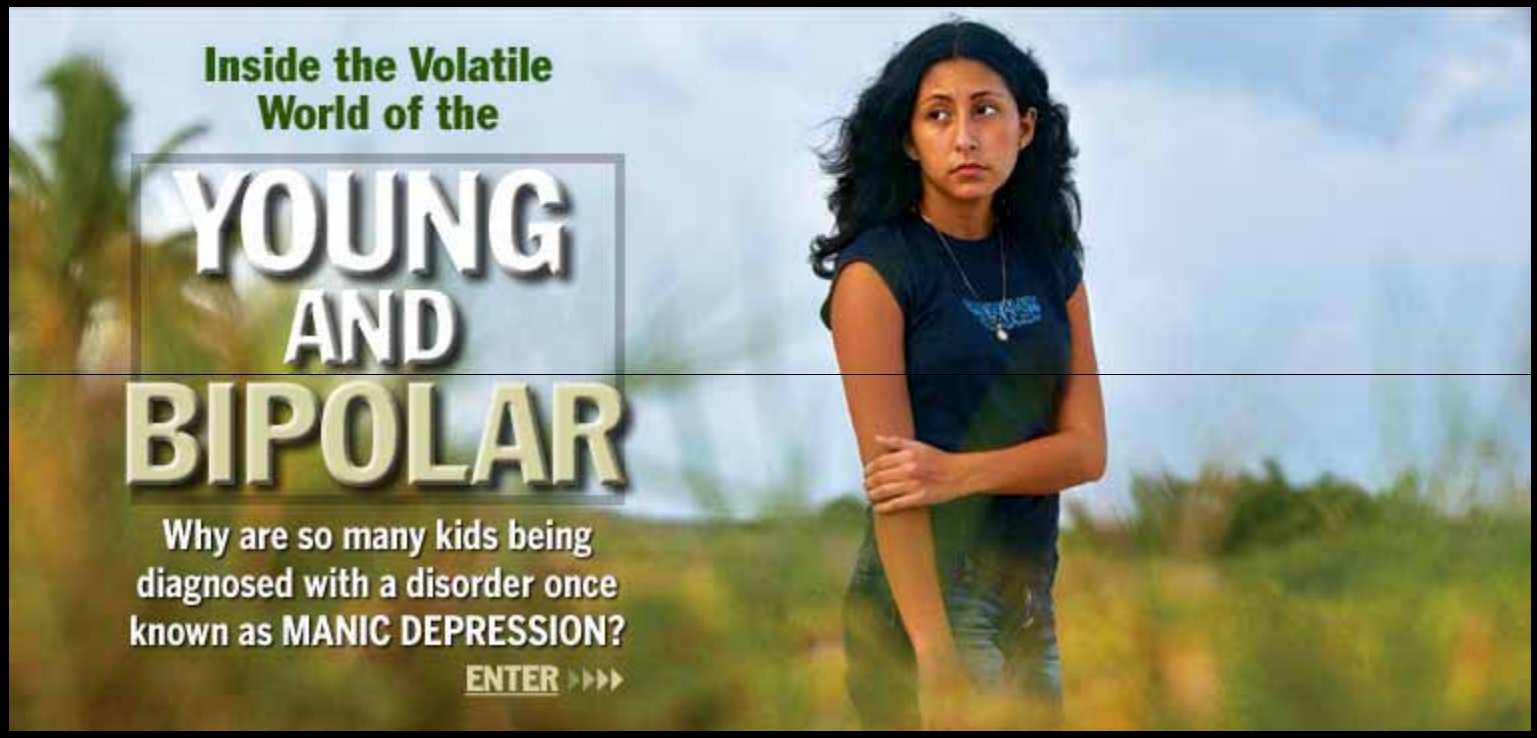

Inside the Volatile
World of the
YOUNG
AND
BIPOLAR
Why are so many kids being
diagnosed with a disorder once
known as MANIC DEPRESSION?
ENTER

Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder

- Originally Published 1997
- Revised, JAACAP, 2007, lead authors are
  - Jon McClellan, MD
  - Robert Findling, MD
  - Robert Kowatch, MD

Bipolar Disorder

Areas of Debate

- Bipolar Disorder in youth, especially Children, typically has a different pattern of illness than the classic adult syndrome
  - Is Juvenile Mania continuous with the adult onset form?
  - Can the adult treatment literature be extrapolated to children and adolescents?
  - How early can it be diagnosed?

Bipolar Disorder

- Biphasic Disorder
  - Well Demarcated Episodes of Mania and Depression
  - Episodes represent significant departure from baseline functioning
- Peak Ages of Onset Between 15 – 30 years
  - Average age of Onset ~ 20 years of age

Bipolar Disorder

- Bipolar I Disorder: At least one episode of Mania
- Bipolar II Disorder: One or more episodes of Major Depression and Hypomania, no Manic episodes
- Cyclothymia: Numerous Hypomanic and Dysthymic Episodes Persisting for at least One Year (Two years for Adults)

- Mixed Episode: Symptoms of Mania and a Major Depressive Disorder, duration of at least 1 week
- Rapid Cycling: At Least 4 Episodes of Mood disturbance over a 12 month period

Bipolar Disorder

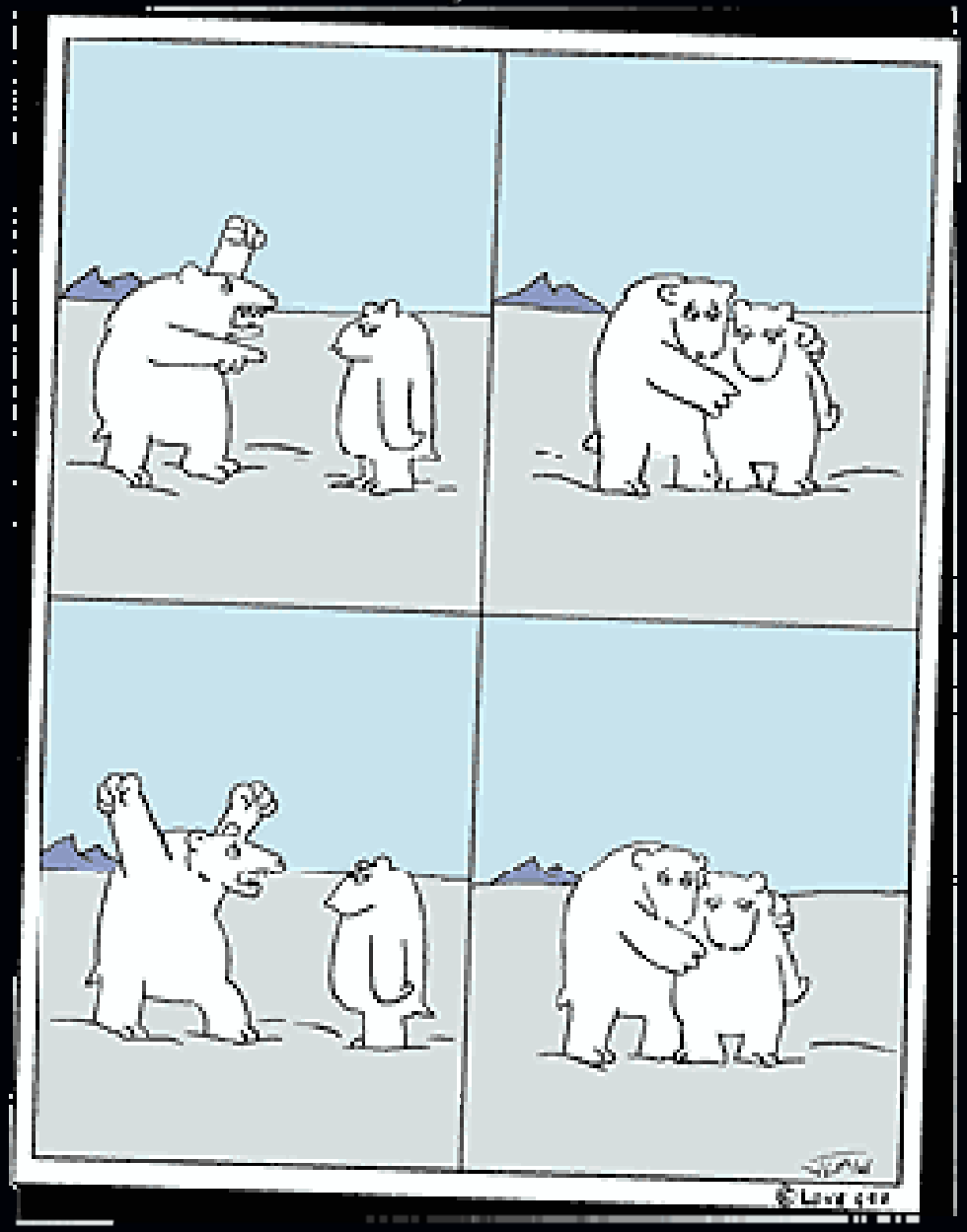
Manic Phase

- Persistently elevated mood (1 week or more)
- Pressured Speech
- Racing Thoughts
- Decreased Sleep
- Increased Energy
- Grandiosity
- Reckless or Dangerous Behavior

Pediatric Bipolar Disorder

- Presentation Most often Considered “Atypical”
  - Intense frequent outbursts of agitation, irritability
  - Moods labile and reactive
  - Course of illness varies from ultrarapid cycling to chronic baseline impairment
- High Rates of Comorbid Disruptive Behavioral Disorders, including ADHD
  - Mood problems common in children with behavioral disorders, but not part of diagnostic criteria
- Lots of Youth have significant emotional and behavioral dysregulation that is not well characterized by current DSM categories

SNAPSHOTS by Jason Lutz



bipolar bear.

Pediatric Bipolar Disorder

- Is Pediatric Bipolar Disorder Continuous with Classic Adult Onset Form?
  - Epidemiology and Age of Onset
  - Symptom Specificity and Course of Illness
  - Longitudinal Follow-Up
  - Family History

Bipolar Disorder
Epidemiology

- Lifetime prevalence of bipolar I disorder in the general population ranges from 0.4% to 1.6%, with an additional ~ 0.5% having bipolar II (APA, 2000)

- However, some studies of adults suggest rates as high as ~ 6 % when including subthreshold or “spectrum” cases (Judd and Akiskal, 2003)

  - ☞Prevalence in Adults also a topic of debate

Pediatric Bipolar Disorder

Historically Onset Below Age 10 was thought to be Rare?

Surveys of Adult Patients

- Kraeplin (1921): 0.4 % of 903 patients had onset below age 10 years
- Loranger and Levine, (1978): 0.5% (200 patients)
- Goodwin and Jamison, (1990): 0.3% (898 patients)

However, later surveys (Lish et al., 1994; Perlis et al., 2004) suggest symptoms commonly present first in childhood

- Symptoms most often depression and hyperactivity

Pediatric Bipolar Disorder
Epidemiology

Most epidemiological surveys of youth have not assessed the disorder

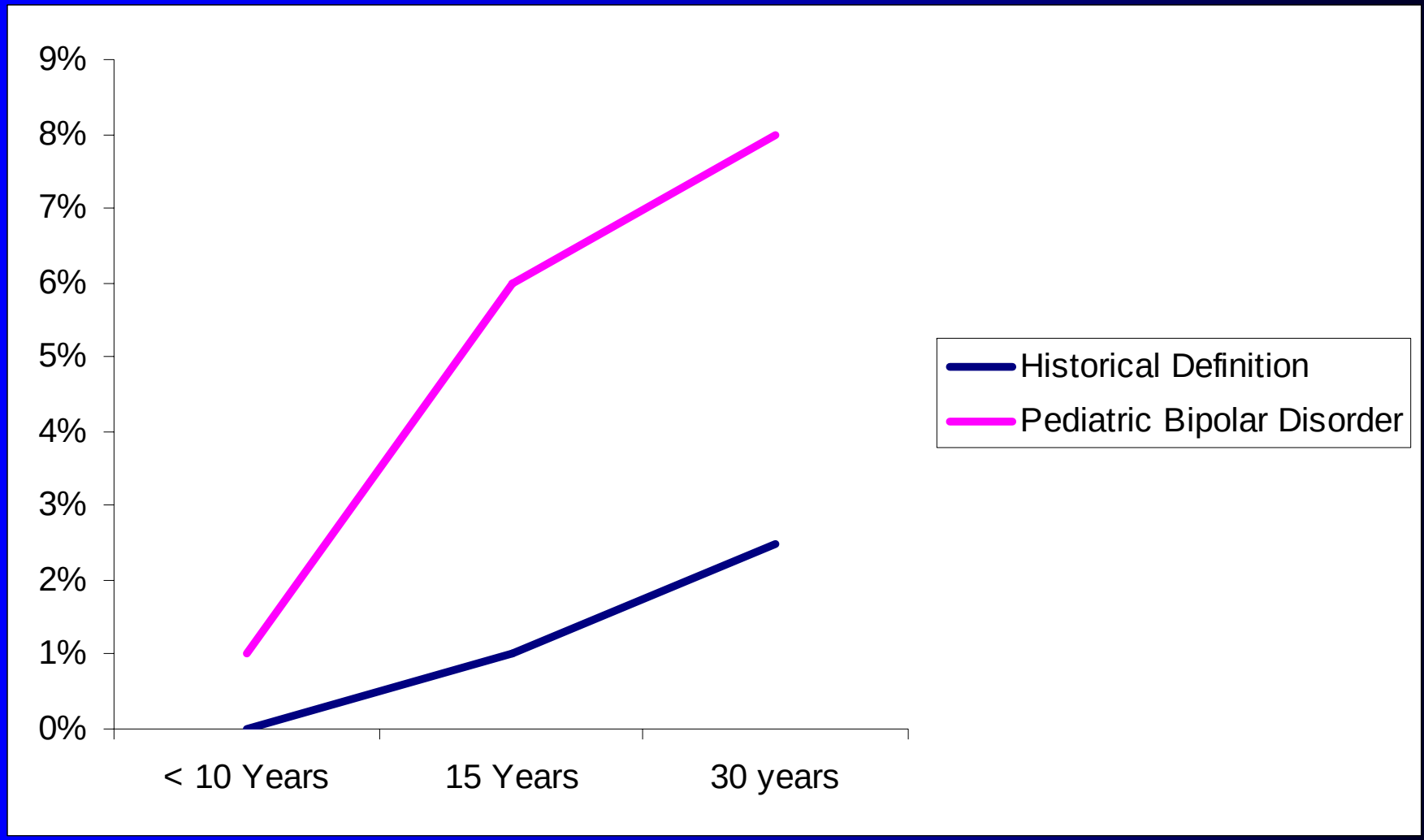
- Carlson and Kashani, 1988: Community Survey (14 - 16 yrs)
  - Lifetime prevalence of mania varied from 0.6% to 13.3% depending on severity and duration criteria.
- Great Smoky Mountains Study of Youth (Costello et al., 1996)
  - Predominantly rural sample
  - No cases of mania in 9, 11, or 13 year old youth
- Lewinsohn et al., 1995: School Survey (ages 14 - 18 yrs)
  - 1 % Lifetime Prevalence Rate (mostly Bipolar II)
  - 6 % Subthreshold Symptomatology

Pediatric Bipolar Disorder

Diagnosis of bipolar disorder in youth is now common

- Rates of hospitalization for pediatric bipolar disorder doubled from 1995 – 2000 (Harpaz-Rotem et al., 2005)
- Child & Adolescent Bipolar Foundation Survey:
  - 24% of the respondents' affected children (n = 854) were between the ages of 1 and 8 years (Hellander, 2002).
- Diagnosis being applied to preschoolers (Wilens et al., 2002)
- High rates specific to US populations (Soutullo et al., 2005)

Prevalence of Bipolar Disorder Across Age Span?



Pediatric Bipolar Disorder
Diagnostic Controversy

- Symptom and Course of Illness Specificity
  - Is all irritability manic?
  - What is grandiosity in child?
  - How do you define an episode?
  - How do you differentiate behavior problems from mood symptoms?

Juvenile Bipolar Disorder

Definitions (Geller et al., 2000)

- Ultrarapid Cycling: Very brief frequent manic episodes lasting hours to days (< 4 days)

  5 – 364 cycles per year.

- Ultradian Cycling: Repeated brief (minutes to hours) cycles that occur daily.

  > 365 cycles per year.

Pediatric Bipolar Disorder

Prepubertal and Early Adolescent Bipolar Disorder Phenotype (PEA-BP)

- 10% Ultrarapid cycling & 77% Ultradian cycling
  - None Met DSM – IV criteria for Rapid Cycling
  - 3.7 ± 2.1 cycles per day
- Average age of onset: 7.3 ± 3.5 years
- Average duration of episode: 3.6 ± 2.5 years
- High rate (87%) of comorbid ADHD
- PEA-BP appears reliable and stable at 6 months, 1, 2 and 4 years
  - A low rate of recovery over a four-year period
  - Community Treatment (including mood stabilizers) did not appear to impact outcome

Geller et al., 2000, 2002, 2004

Pediatric Bipolar Disorder

- 20 % of Children with ADHD (n = 206) met DSM-III-R Criteria for mania
  - Predominately mixed episodes, with irritability and explosiveness
- Average age of onset: 4.4 ± 3.1 years
- Average duration of Illness: 3.0 ± 2.1 years
- High rates (98%) of comorbid ADHD
  - Also conduct disorder, anxiety and substance abuse
- Chronic vs Cyclical Course
  - 23 % "mania always present" (i.e., represents baseline state of functioning)

Biederman et al., 2004, Wozniak et al. 1995

Pediatric Bipolar Disorder

Bipolar Disorder in Very Young Children

- Wilens et al., (2002): 26% of preschoolers with ADHD have bipolar disorder, a rate significantly higher than found in their comparison school age sample


That wasn't chicken.

Pediatric Bipolar Disorder

Symptom Specificity

- DSM manic symptoms
  - grandiosity, psychomotor agitation, and reckless behavior
- Common Symptoms of Childhood Disorders
  - hyperactivity, irritability, dangerous play, and inappropriate sexualized activity
- Common Normal Childhood Phenomena
  - boasting, imaginary play, overactivity, and youthful indiscretions

⇨ "Manic" symptoms may be nonspecific markers for emotionality and severity (Thuppal et al., 2002; Carlson et al., 1998; Hazell et al., 2003)

Pediatric Bipolar Disorder

Symptom Specificity

- Geller (2002) required elation and grandiosity as part of diagnostic criteria

However, Definitions may lack Development Context

- Elation
  - ✓ excessive silliness and giggling
- Grandiosity
  - ✓ saying it is not wrong to steal after getting caught
  - ✓ believing he/she can grow up to be a famous athlete even though he/she is not good at sports
  - ✓ Telling peers how to do homework when he/she fails to do it themselves

Pediatric Bipolar Disorder Specificity of Symptoms

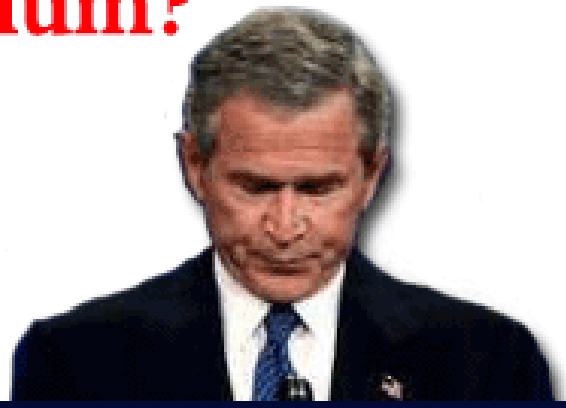
Mania	ADHD
Irritability	Grumpy
Increased Energy	Hyperactive
Pressured Speech	Talking Fast
Reckless Behavior	Reckless Behavior
Grandiosity	Bragging
Distractibility	Distractibility
Decreased Sleep	Restless Sleeper


pLLice
freeze

Pediatric Bipolar Disorder Specificity of Symptoms

Mania	Borderline/PTSD
Mood Swings	Affective Instability
Paranoia	Hypervigilance
Irritability	Behavioral Dyscontrol
Reckless Behavior	Sleep Problems
Distractibility	Dissociative Symptoms
Decreased Sleep	(Psychotic-like Symptoms)

Lithium?



Miami

Ritalin?

St. Louis

Ask your doctor about which Bush may be right for you

Serious side effects may occur, including loss of appetite for reality and (if taken in conjunction with military enlistment) death. Side effects are similar to those experienced by citizens with placebo leaders and crazed dictators. Not to be taken while binge drinking or operating heavy machinery, such as an army.

Pediatric Bipolar Disorder

Long Term Follow-up

- Lewinsohn et al. (2000)
  - DSM-IV-defined bipolar disorder during later adolescence predicted continuity of the disorder at age 24 years
  - Subsyndromal cases (e.g., bipolar disorder NOS): increase in psychopathology and adverse outcomes as young adults (including borderline and/or antisocial traits)
    - ☞No Increase in bipolar disorder in the spectrum cases
- Hazell et al. (2003) (6-year follow-up study)
  - Manic symptoms in boys with ADHD did not persist or evolve into DSM-IV-defined bipolar disorder
- Atypical presentations persist (Geller et al., 2004; Biederman et al., 2004), but so far do not appear to evolve into the classic form

Pediatric Bipolar Disorder?

ADHD versus Bipolar Disorder?

- Manuzza et al., 1993: 91 males with ADD (mean age 18.3 years, mean f/u 16 years) vs. 100 controls:
  - Increased Rates of ADHD, Antisocial Personality Disorder and Drug Abuse
  - No cases of Bipolar Disorder
- Weiss et al., 1985: 63 youth with ADD vs. 41 controls (ages 21 - 33 years):
  - Increased rates of ADD symptoms/Antisocial Personality Disorder
  - No Increase in Mood Disorders

Pediatric Bipolar Disorder?

ADHD versus Bipolar Disorder?

- NIMH Multimodal Treatment Study of ADHD (MTA Study)
  - 579 children with ADHD (ages 7 to 9 years) at 6 sites
  - No cases of bipolar disorder

- For “bipolar disorder nos”, boys with ADHD plus manic-like symptoms appear to respond as well as those without manic symptoms to methylphenidate
  - ☞Stimulant treatment did not precipitate progression into bipolar disorder (Carlson et al., 2000; Carlson and Kelly, 2003; Galanter et al., 2003)

Pediatric Bipolar Disorder

Family History

- The heritability of early-onset bipolar disorder appears to be high (Faraone and Tsuang, 2003)
  - Supports a link between juvenile and more typical later-onset forms

However, studies have used broader definitions in both youth and adults

  - e.g., rates in control samples much higher than expected in some family studies

Pediatric Bipolar Mania

Is it the same illness as the Classic Adult Illness?

Limited Evidence Suggests

- ✓ Different Pattern of Illness
- ✓ Different Age of Onset
- ✓ Few Longitudinal Studies have not demonstrated juvenile form progresses into the adult-onset form

- ☞ Therefore, cannot readily extrapolate adult treatment literature to juvenile mania


H E A L T H
Are We Giving Kids Too Many Drugs?
A medicated generation is growing up with quick fixes for mood and behavior. Here are the benefits — and the risks . Read The Cover Story >>


TIME
ARE WE GIVING KIDS TOO MANY DRUGS?

Rx

Bipolar Disorder

FDA Approved Agents (for adults)

- Acute Mania: Lithium, Valproate, Olanzapine, Risperidone, Quetiapine, Aripiprazole, Ziprasidone
- Maintenance Therapy: Lithium, Lamotrigine
- Bipolar Depression: OLAN/FLU Combination

Pediatric Bipolar Disorder Psychopharmacology

- The effective of mood stabilizers and atypical antipsychotic agents well established in adults
- The adult treatment literature may not apply to the juvenile form
- Treatment response does not equal diagnosis
- In youth, Polypharmacy is common, with some youth taking five or more drugs (Duffy et al., 2005).
  - Diagnosis associated with substantial increased use of psychotropics in preschoolers (Zito et al., 2000)

Early Onset Bipolar Disorder Pharmacology

Child and Adolescent Bipolar Foundation Survey of children and adolescents diagnosed with bipolar disorder

- Anticonvulsants and Atypical Antipsychotics are agents most often used
- Polypharmacy is common

  14 % (n = 854) on 5 or more drugs

Hellander et al., 2002

Pediatric Psychopharmacology Lithium

- Few Positive Small Controlled Trials for Youth with “manic-like” symptoms (Delong and Neiman, 1983; McKnew et al., 1981)
- Helpful for Bipolar Disorder plus Substance Abuse in Adolescents (Geller et al., 1998)
- Large Open Label Trial (Kafantaris et al., 2003) (n = 100) had a 63% response rate in adolescents with Bipolar I
- Lithium FDA Approved for Youth 12 years of age or older with Bipolar

Pediatric Psychopharmacology Valproate

- ✓ FDA Approved for Acute Mania in Adults
- ✓ May work better for rapid cycling or mixed episodes
- ✓ No Controlled Trials for Juveniles

- Dosing
  - Therapeutic Blood Levels 50 - 120 ug/ml
- Potential Side-Effects
  - Hepatic
  - Hematologic
  - PolyCystic Ovary Disease
  - Drug-Drug Interactions (e.g., BCP)

Pediatric Psychopharmacology Other Anticonvulants

- Lamotrigine
  - Effective In Adult Studies of Bipolar Depression
  - Rash is greatest Concern
- Oxcarbazepine
  - Few Adult Studies Show Efficacy
  - Negative Trial in Youth
- Carbamazepine
  - Adult Studies Not as Robust as for VPA
- Gabapentin
  - Large Controlled Trial in Adults was negative

Psychopharmacology of Early Onset Bipolar Disorders Atypical Antipsychotics

- Case Reports and Adult Studies Suggest that Atypical antipsychotics may be used as first line agents for youth with manic and mixed manic episodes
- Delbello et al., 2002: Double blind trial found quetiapine plus valproate superior to valproate alone for adolescent mania
- Youth may be at greater risk for problems with weight gain with atypical agents

Antipsychotics
Side-Effects

- Youth appear to have the same spectrum of adverse events noted in adults
- With Atypical Agents, Metabolic Side Effects are the greatest Concern
  - Youth appear to be at great risk for Weight Gain than Adults
- Long-term Safety Monitoring is Needed:
  - ADA Guidelines for Metabolic Syndrome
    - ✓Weight/BMI
    - ✓Fasting Glucose
    - ✓Triglycerides/Lipids
    - ✓Blood Pressure
  - Abnormal Movements
  - Other Drug Specific Monitoring (e.g., ECG's with ziprasidone, liver functions, especially with weight gain)

Early Onset Bipolar Disorder Psychopharmacology

Combined Therapies

- Combinations of mood stabilizers may be helpful and appear well tolerated in youth (Findling et al., 2003; Kowatch et al., 2003).
- Kafantaris et al., (2001) found lower relapse rates when antipsychotic agents were maintained for at least four weeks, in combination with lithium
- Justification for polypharmacy better supported for classic bipolar versus bipolar nos.

Early Onset Bipolar Disorder Antidepressants

- All Antidepressants have the potential risk of Inducing Mania
  - Antidepressants should only added to stable mood stabilizer regimens
  - SSRI's may cause irritability, dysinhibition, or hypomania, thus worsening aggression
  - FDA warnings regarding risk for increased suicidality in youth with Paroxetine
- ⇨ Lamotrigine Effective in Adult Studies of Bipolar Depression, may be a better alternative

Early Onset Bipolar Disorder Stimulants

- Despite concerns to the contrary, methylphenidate has been found to be helpful in boys with ADHD plus “manic-like” symptoms (Carlson et al., 2002; Galanter et al., 2003)
- For clearly defined bipolar disorder, stimulants are generally avoided until mood symptoms are well controlled with mood stabilizers

Early Onset Bipolar Disorder Treatment Strategies

- Psychosocial Treatments as an adjunct to Medications
  - Parent/Family Psychoeducation
  - Relapse Prevention
  - CBT or IPT for Depression
  - Interpersonal and Social Rhythm Therapy
  - Family Focused Therapy
  - Community Support Programs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Bipolar Disorder Research at Children's Hospital

- Social Rhythm Therapy for Adolescents
  - Stefanie Hlastala Ph.D. 206 – 368 – 4813
- Lithium For the Treatment of Pediatric Mania
  - NICHD multi-center trial
  - Recruitment to begin by ~ 3/07
- Contact
  - Jon McClellan MD 253 - 756- 2319
  - Leslie Pierson 206 - 713 - 3717