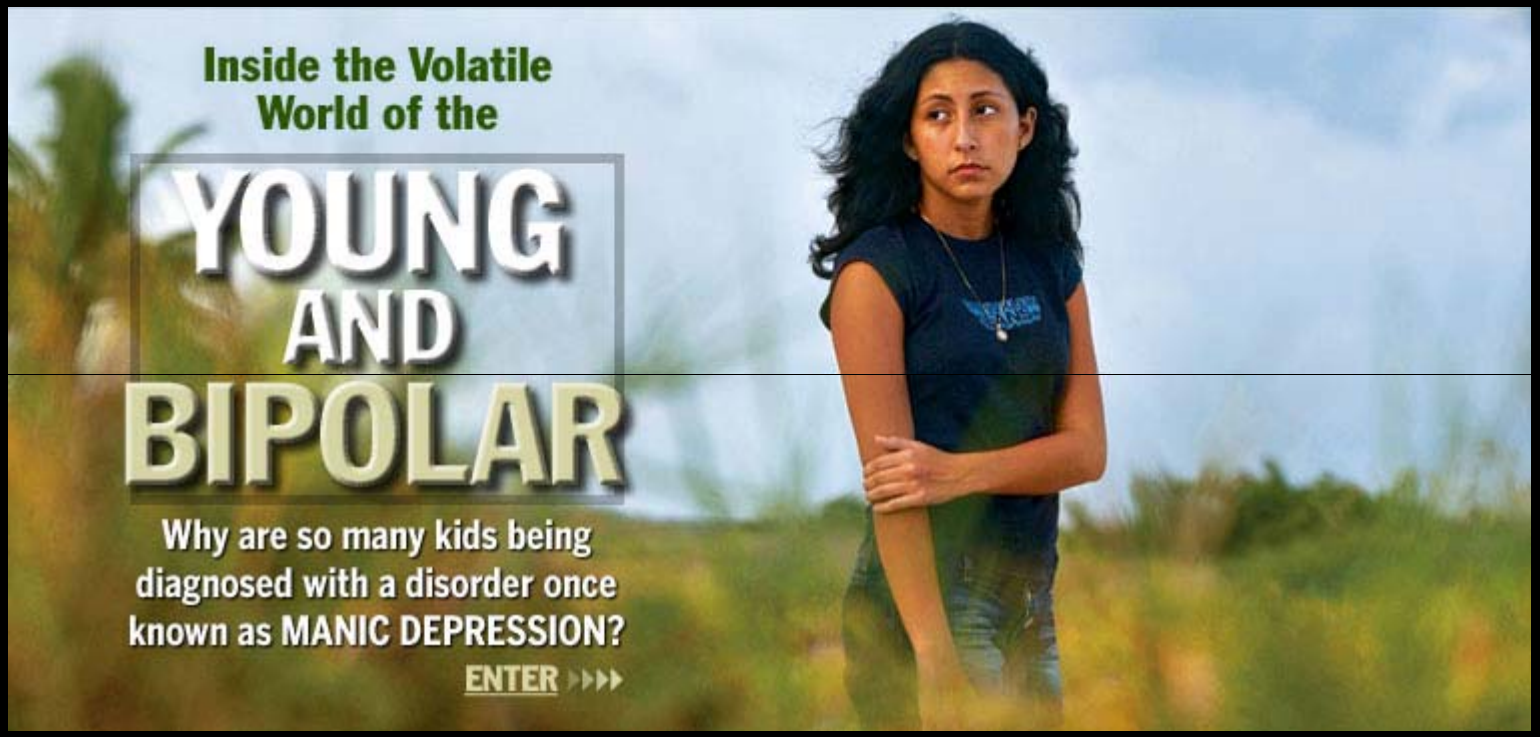

Inside the Volatile
World of the
YOUNG
AND
BIPOLAR
Why are so many kids being
diagnosed with a disorder once
known as MANIC DEPRESSION?
ENTER

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

Journal of the Academy of Child and Adolescent Psychiatry, 1997

Primary Authors: Jon McClellan MD and John Werry MD

Bipolar Disorder

Manic Phase

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

Bipolar Disorder

Depressed Phase

- Persistent Dysphoria
- Anhedonia
- Weight and
- Appetite Changes
- Insomnia or hypersomnia
- Psychomotor agitation or Retardation
- Lethargy
- Worthlessness or guilt
- Decreased Concentration
- Suicidal Ideation

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

Juvenile Bipolar Disorder

Definitions (Geller et al., 2000)

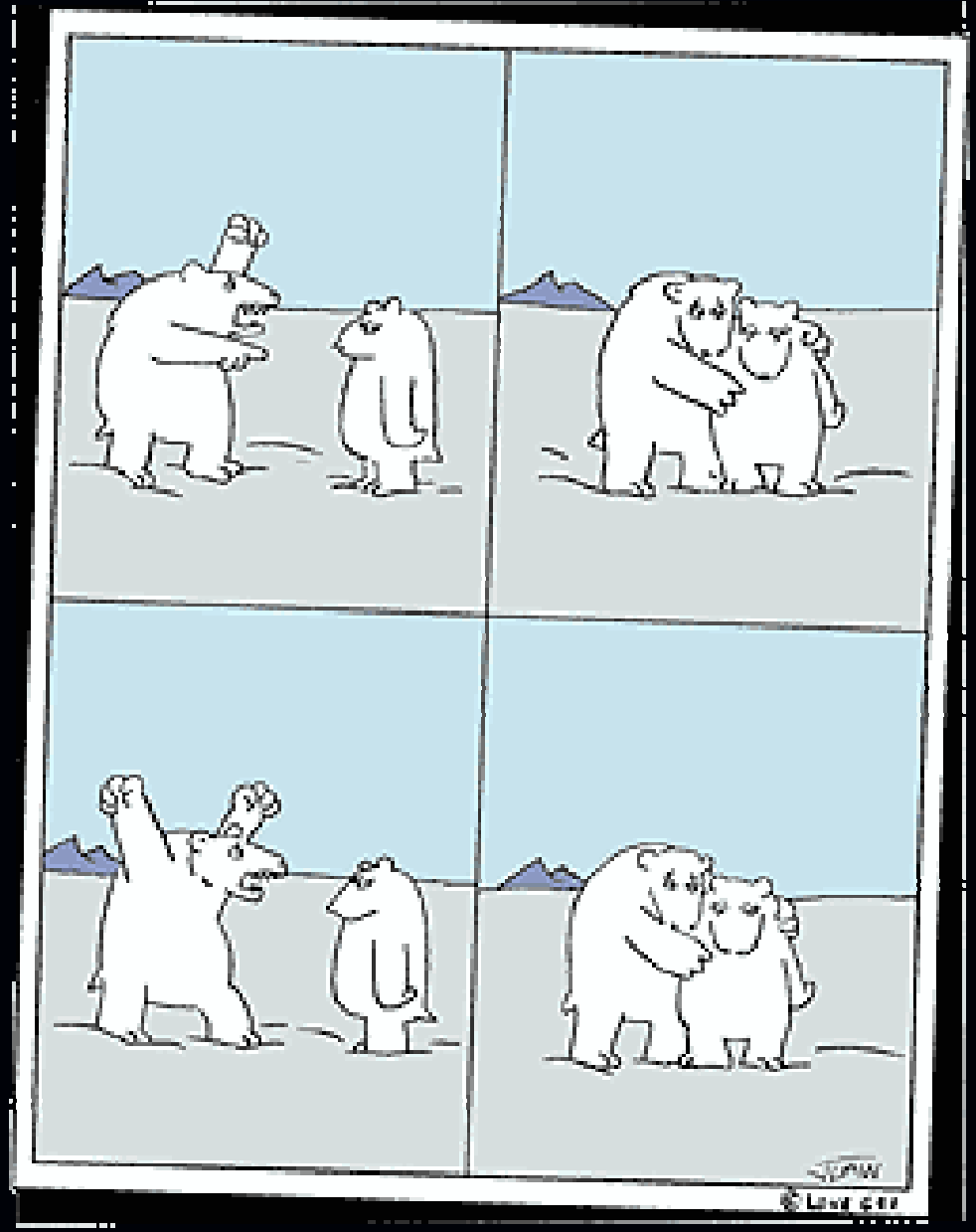
- Ultrarapid Cycling: Very brief frequent manic episodes lasting hours to days (< 4 days)

  5 – 364 cycles per year.

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

  > 365 cycles per year.

SNAPSHOTS by Jason Lutes



Bipolar bear.

Early Onset Bipolar Disorder
Epidemiology

- Approximately 20% of All Bipolar Patients Have Onset Prior to Age 20 years.
- Lewinsohn et al., 1995: School Survey (ages 14 - 18 yrs)
  - 1 % Lifetime Prevalence Rate (mostly Bipolar II)
  - 6 % Subthreshold Symptomatology (at age 24 years these youth had increased psychopathology, but not bipolar)
- 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.
- Lifetime Estimated Prevalence Rate = 0.8% in General Population (APA, 1994).

Early Onset Bipolar Disorder

Onset Below Age 10 is 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)

Early Onset Bipolar Disorder

Onset Below Age 12 is Not Rare?

- Weller et al., (1986): 38/157 cases diagnosed with mania in reports of severely mentally ill children.
- Wozniak et al., (1995): 43/262 referred children (<=12 yrs old), met DSM-III-R criteria for mania .

  16 - 24% of clinically referred children have mania?
- Geller et al., (1994): 25/79 children with major depression developed mania (80% prior to age 13 yrs)
- Geller et al., (2000): PEA-BP appears to be a homogeneous subtype in 93 consecutively ascertained outpatients

Juvenile Bipolar Disorder

⇨ Geller and Luby (1997):

Prevalence of bipolar disorder in youth may be the same as that in adults

Early Onset Bipolar Disorder

Diagnostic Issues

Childhood Onset

- Irritability and Mixed Symptoms are more Common than Euphoria
- Changes in Mood, Psychomotor Functioning, and Behavior are often Labile and Erratic
- Chronic vs. Episodic vs. Rapid Cycling Course?
- High Rates of Comorbid Behavior Disorders

Juvenile Bipolar Disorder

Childhood Mania

- 20 % of Children with ADHD (n = 206) met DSM-III-R Criteria for mania
- Average age of onset: 4.4 ± 3.1 years
- Average duration of Illness: 3.0 ± 2.1 years
- High rate (98%) of comorbid ADHD
- Chronic vs Cyclical Course
  - 23 % “mania always present”

Wozniak et al., 1995

Juvenile Bipolar Disorder

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

- 10% Ultrarapid cycling & 77% Ultradian cycling
- Average age of onset: 7.3 ± 3.5 years
- Average duration of episode: 3.6 ± 2.5 years
- High rate (87%) of comorbid ADHD

Geller et al., 2000 J Child Adolesc Psychopharmacol

Juvenile Bipolar Disorder

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

PEA-BP appears reliable and stable at 6 months, 1 and 2 years

- 3.7 ± 2.1 cycles per day
- A low rate of recovery over a two-year period
- Treatment (including mood stablizers) did not appear to impact outcome

Geller et al., 2000, 2002

Juvenile 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.

- In a survey of members of the Child & Adolescent Bipolar Foundation, 24 percent of the youth (n = 854) were between the ages of 1 and 8 years (Hellander, 2002).

Early Onset Bipolar Disorder

Diagnostic Issues

Adolescent Onset

- Psychotic Symptoms
- Markedly Labile Moods with Mixed Symptoms
- Severe Deterioration in Behavior
- Early Course More Chronic, and Refractory to Treatment
- High Rate of Misdiagnosis as Schizophrenia

Early Onset Bipolar Disorder

Associated Features

- High Rates of Comorbid ADHD/Conduct Disorder; Substance Abuse in Adolescents
- Premorbid Histories Include:
  - Disruptive Behavior Disorders
  - Depression
  - Anxiety
- Increased Family History of Bipolar Disorder
- Increased Suicide Risk

Early Onset Bipolar Disorder
Course and Prognosis

- Adolescents: Early Course often prolonged and treatment refractory
  - Long-term prognosis appears similar to adults
  - 50% functioning impairment below their premorbid state.
- Children: Course may be more chronic and severe, but studies are lacking
- > 90% of Adolescents Noncompliant with Lithium relapsed over an 18 month period (37.5% on Lithium relapsed) (Strober et al., 1990)
- 20 % of Adolescents Made a Least One Significant Suicide Attempt over a 5 year period (Strober et al., 1995).

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

Early Onset Bipolar Disorder Specificity of Symptoms

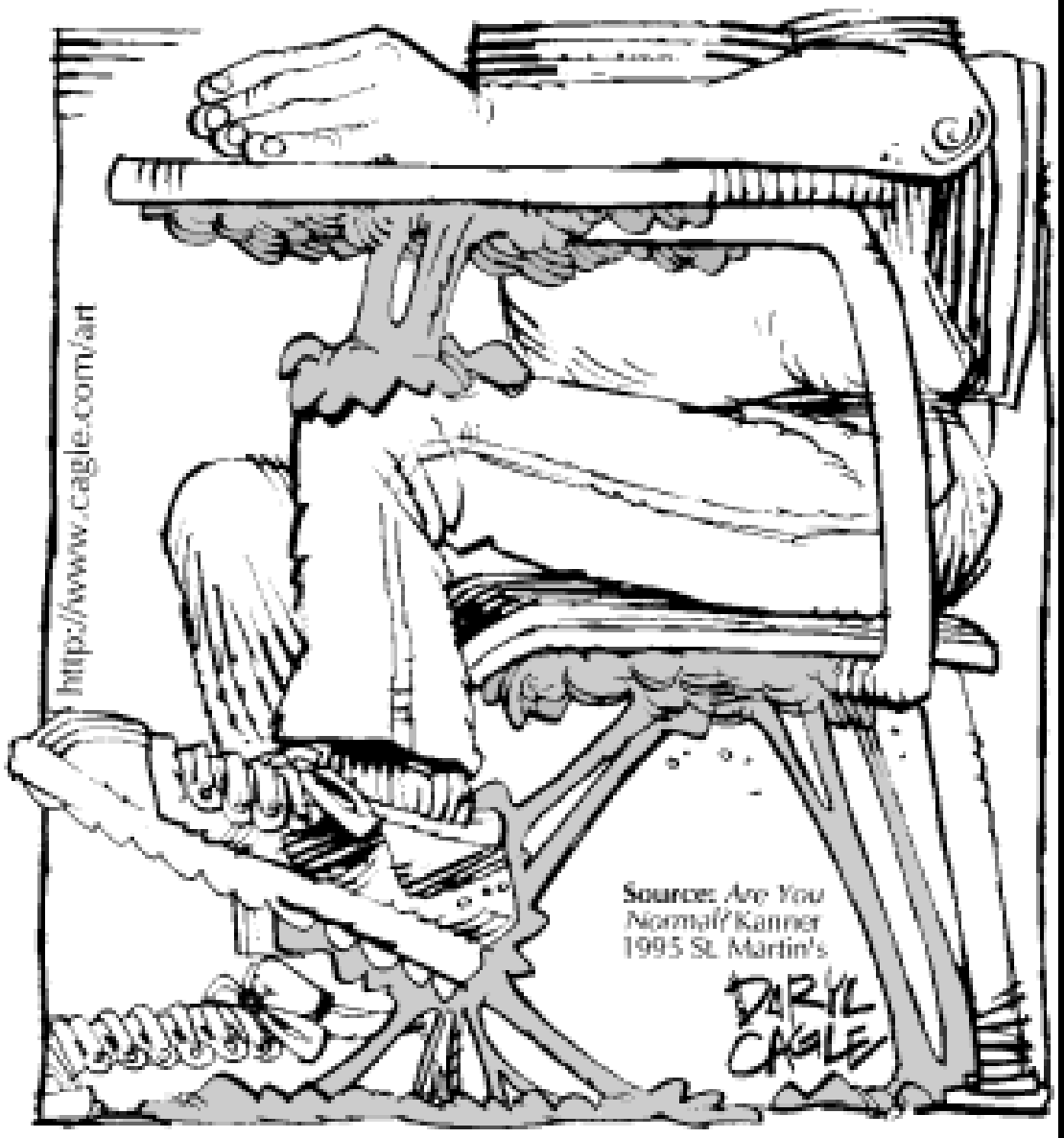
Mania	ADHD
Irritability	Grumpy
Increased Energy	Hyperactive
Pressured Speech	Talking Fast
Reckless Behavior	Reckless Behavior
Grandiosity	Bragging
Distractibility	Distractibility
Decreased Sleep	Restless Sleeper

Early Onset 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)

TRUE!

by Daryl Cagle



Kids are seven times more likely than adults to plant their gum in and under furniture.

Early Onset Bipolar Disorder
Diagnostic Controversy

- Diagnostic Nosology

  Criterion Describe Recognized Disorder, or

  Criterion Are the Disorder?
- Symptom Specificity
- Premorbid State versus Disorder
- Duration and Severity Criteria
  - Duration Criteria not included in DSM-III-R
- Lack of Follow-up Studies
  - No Follow-up Studies for Childhood Onset
- Lack of “Gold Standard”


Fuck you

Early Onset Bipolar Disorder Treatment Strategies

- Psychopharmacology
  - 4 – 6 week trial of First Line Antimanic Agent
  - Second Trial or Agent may be needed for Refractory Cases
  - Antidepressants may initiate cycling into mania, should only be used as adjunct to mood stabilizers
- Psychosocial Interventions
  - Psychoeducational/Cognitive-Behavioral/Interpersonal Therapy Strategies
- Electroconvulsive Therapy

Early Onset Bipolar Disorder Psychopharmacology

- First Line Mood Stabilizers
  - Lithium
  - Valproate
  - Atypical Antipsychotics
- Second Line Agents
  - Carbamazepine/ oxcarbazepine
  - Lamotrigine (Effective for Bipolar Depression)
  - Clozapine
- Adjunctive Agents
  - Benzodiazepines
  - Antidepressants
  - Stimulants (for comorbid ADHD)

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

Early Onset Bipolar Disorder Pharmacology

- Kowatch et al., (2000): Open label trial (n = 40) found positive effects for valproate, lithium and carbamazepine
  - Response rates for the three agents were 53, 38 and 38 percent, respectively
- Geller et al., (2002) noted that treatment (including mood stabilizers and antipsychotics) did not influence outcome over a 24 month period
- Biederman et al., (1999) noted that mood stabilizers appeared helpful, whereas atypical antipsychotics, stimulants and antidepressants were not
- ☞ Juvenile mania may be more difficult to treat. Controlled trials are needed.

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 Lithium

Dosing

- Serum Levels ranging from 0.6 – 1.2 mEq/L

Side Effects

- ☹ Nausea, Vomiting, Diarrhea
- ☹ Weight Gain, Acne, Enuresis
- ☹ Tremors
- ☹ Hypothyroidism
- ☹ Renal Problems

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
- 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

- Olanzapine FDA approved for Acute Mania
- 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

Pediatric Psychopharmacology Olanzapine

Dosing

- 2.5 - 20 mg/day

Side Effects

- Weight Gain
  - Risk for Diabetes and Hyperlipidemia
- Sedation
- Reports of Elevated Liver Enzymes associated with Weight Gain

Pediatric Psychopharmacology Risperidone

Dosing

- 0.5 - 6.0 mg/day

Side Effects

- Weight Gain
  - Risk for Diabetes and Hyperlipidemia
- Extrapyramidal Side-Effects
  - Tardive Dyskinesia
  - Neuroleptic Malignant Syndrome
- Reports of Elevated Liver Enzymes associated with Weight Gain

Pediatric Psychopharmacology Other Antipsychotics

- Quetiapine
  - 25 - 800 mg/day
  - Perhaps less weight gain than other agents
- Ziprasidone
  - 20 – 160 mg
  - Prolongs QTc interval
  - Activation, may initiate mania in some patients
- Aripiprazole
  - 10 – 30 mg/day
  - Unique Mechanism of Action:

    Partial D_2 & 5 HT_{1a} agonist: 5 HT_{2a} antagonist

Pediatric Psychopharmacology Clozapine

- Very Effective Atypical Antipsychotic, but Side Effect Profile makes is second line drug

Side Effects

- Drooling
- Weight Gain
- Hypotension
- 5 % Risk of Seizures
- 1 % Risk of Agranulocytosis

➔Extensive Monitoring Protocol

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