

Pediatric Bipolar Disorder

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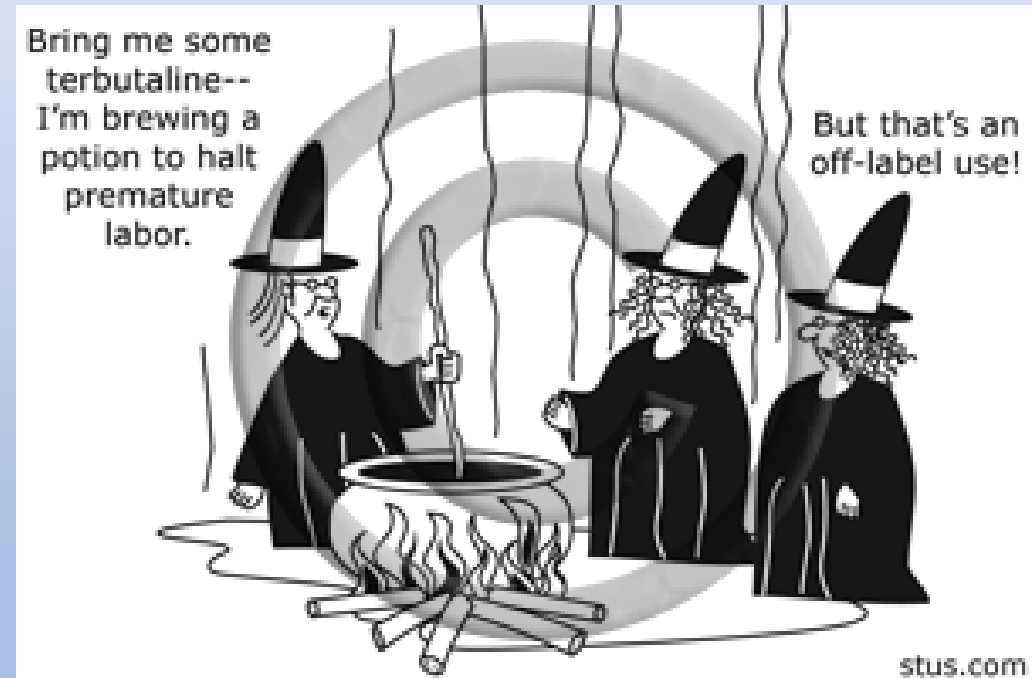
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Disclosure

The content of this presentation does not relate to any product of a commercial entity; therefore, I have no relationships to report.

I will be discussing off-label use of medications.



Objectives

- Discuss diagnostic criteria for bipolar disorder
- Outline some of the most common psychopharmacologic agents used in youth with Bipolar Disorder. This shall include, but not be limited to, dosages, indications for use, contraindications, red flags, and expected outcomes.
- Outline appropriate therapeutic interventions that can be utilized when treating youth with Bipolar Disorder. This shall include, but not be limited to psychoeducation, lifestyle interventions, and psychotherapy.

DSM-5 Definition of Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary)

B. 3 or more of the following:

1. Inflated self esteem or **grandiosity**
2. **Decreased need for sleep**
3. More talkative than usual or pressure to keep talking
4. Flight of ideas or **racing thoughts**
5. Distractibility
6. Increase in goal-directed activity
7. Increased risky behaviors (**hypersexuality**, unrestrained buying sprees)

Mania criteria

- Must cause marked impairment in social or occupational functioning or necessitate hospitalization
- Not attributable to the physiological effects of a substance or a medical condition
- Medication induced
 - Antidepressant-induced mania is called Bipolar if manic symptoms persist after offending drug is stopped
- Hypomanic Episode:
 - Lasts at least 4 consecutive days
 - NOT severe enough to cause marked impairment
 - Can NOT be associated with psychotic features

Making the diagnosis: Specific Screening questions

- Detailed history, get collateral info, use screening tools, assess suicide risk
- Distinct, spontaneous periods of mood changes associated with sleep disturbances and psychomotor activation
- Non specific: irritability, reckless behaviors, increased energy
- You have to assess the symptoms within the context for the individual child
- Sleep disturbance:
 - different from baseline sleep?
 - do sleep changes correlate with mood state?
 - How are parents learning about the child's sleep?

Manic Grandiosity and Irritability

- Should:
 - Be Acute in onset
 - Be Markedly different from the individual's baseline
 - Impair the individual's ability to function in all realms
- Should NOT be:
 - In response to a situation
 - Temperamental traits
 - Negotiation strategies
 - Anger outbursts



Differential Diagnosis

- ADHD
- Substance Abuse/Dependence (get tox screens)
- Head Trauma
- Seizures
- Encephalopathy
- Prescribed Medication Mood Changes
- Trauma
- Parent Child Relationship Conflicts
- Developmental Disorders
- Temperamental Difficulties



Red Flags

- **Family history of Bipolar Disorder**
- Early Onset of Depression
- Treatment resistant Depression
- Antidepressant Coincident Mania
- Episodic Mood Lability
- Episodic Aggressive behavior
- **Psychotic features**
- **Sleep Disturbance**



Free, Brief Screening tools for Bipolar Disorder

- Depression

- Patient Health Questionnaire-9 (PHQ-9): 9 item,
 - www.phqscreeners.com
- Quick Inventory of Depressive Symptomatology-self report: (QIDS-SR-16)-16 item
 - <http://www.ids-qids.org>

- Mania

- The Young Mania Rating Scale (YMRS)- 11 item, clinician rating form
 - <https://projectteachny.org/rating-scales/>
- The Child Mania Rating Scale (CMRS): parent version, 21 item, age 5-17,
 - <https://projectteachny.org/rating-scales/>
- Mood Disorder Questionnaire (MDQ-15 item) at
 - <https://www.integration.samhsa.gov/clinical-practice/screening-tools>

Before starting Medication Consider:

- Evidence of efficacy
- Phase of illness
- Presence of confounding presentations/symptoms
- Agent's side effect spectrum and safety
- Patient's history of medication response
- Family History of treatment response to mood stabilizing medications.
- Preferences of the patient & family
- Cost



FDA approved Medications for Bipolar Disorder

Medication	Indication	Age
Lithium (Lithobid, Eskalith)	Mania/Maintenance	>12
Divalproex (Depakote)	Mania	adults
Carbamazepine (Tegretol)	Mania/Mixed	adults
Lamotrigine (Lamictal)	Maintenance	adults
Aripiprazole (Abilify)	Mania/Mixed/Maintenance	>10
Risperidone (Risperdal)	Mania	>10
Quetiapine (Seroquel)	Mania	>10
Olanzapine (Zyprexa)	Mania	>13
Olanzapine fluoxetine combo (Symbyax)	Bipolar 1 depression	>10
Asenapine (Saphris)	Mania	>10
Lurasidone (Latuda)	Bipolar depression	>10
Ziprasidone (Geodon)	Mania	adults
Cariprazine (Vraylar)	Mania/Mixed	adults

Lithium

- Used in acute mania and as prophylaxis for manic and depressive disorders
- shown to decrease the rate of suicide
- Metabolized by kidney
- Prior to tx: EKG (if patient is over 50), BMP (kidney function), TSH, BMI, pregnancy test
 - Regularly monitor: TSH, kidney function and lithium level
- Target level between 1.0 – 1.2 mEq/L (check at 5 days, then every 2-3 days until therapeutic)
 - Toxic: > 1.5
 - Lethal: > 2.0
- Dosing up to 1800 mg/day (acutely manic adults)
- Maintenance dose 900-1200 mg/day
- Efficacy: CoLT trials: Li more effective than PBO in pediatric mania

Lithium – Side effects

- Toxic level close to therapeutic level – risk of overdose
- Drug interactions (ibuprofen, some antibiotics, diuretics)
- Toxicity when dehydrated or when sick
- Potential kidney and thyroid problems
- Polydipsia and polyuria, nephrogenic DI
- Can make acne and psoriasis worse
- Tremor, GI disturbance (diarrhea/nausea), weight gain, sedation
- Toxicity: sedation, slurred speech, clumsiness, nausea / vomiting, stomach pain, diarrhea, coarse tremor, convulsions, death
- Need to make sure that the family will control the meds - keep locked away from small children and suicidal people
- Teratogenic effects – **Epstein's anomaly**

Valproate/Divalproex (Depakote)

- Uses: bipolar disorder, aggression, impulsivity, and migraine prophylaxis.
- Metabolized by the liver
- Prior to tx: CBC (platelet counts), Liver Function tests, pregnancy test, and BMI
- Target level: between 80 – 120 ug/mL
 - Usually check level after 4-5 days
 - Dosing: roughly 10 x body weight in lbs (usually start at half that dose) 1200-1500 mg/d in adults
- Side effects:
 - weight gain, hair loss, low platelets,
 - Polycystic ovary disease, pancreatitis, liver toxicity,
 - Teratogenic (neural tube defects)
 - Drug interactions (lamotrigine)

Other Anticonvulsants

- **Carbamazepine**- not good efficacy data
- **Oxcarbazepine** – negative study, no good efficacy data
- **Topiramate** – no good efficacy data; weight loss can be helpful,
 - few serious side effects (glaucoma),
 - cognitive side effects,
 - hypochloremic non-anion gap metabolic acidosis,
 - kidney stones
- **Lamotrigine**- effective in bipolar depression/maintenance, not for mania

Antipsychotics

- Typical (First Generation Antipsychotics or FGAs)
 - Chlorpromazine Fluphenazine
 - Haloperidol Loxapine
 - Molindone Perphenazine
 - Pimozide Thioridazine
 - Thiothixene Trifluoperazine
- Atypical (second generation antipsychotics or SGAs)
 - Clozapine (Clozaril) Olanzapine (Zyprexa)
 - Quetiapine (Seroquel) Risperidone (Risperdal)
 - Ziprasidone (Geodon) Aripiprazole (Abilify)
 - Paliperidone (Invega)

DBPC trials of Atypical Antipsychotics in Manic Youth

	N	Dose	Week	NNT Res	NNH >7%wt ↑
Risperidone*	50/61/58	0.5-2.5mg	3	3	11
	1:1:1	3-6mg		3	21
Olanzapine*	107/54	2.5-20	3	4	3
	2:1	≈9mg			
Aripiprazole*	98/99/99	10mg	4	5	N/A
	1:1:1	30mg		3	16
Ziprasidone	149/88	80-160 mg	4	4	33
	2:1	120 mg			
Quetiapine*	93/95/89	400 mg	3	4	7
	1:1:1	600 mg		5	10
Asenapine*	104/99/99/1	5 mg	3	7	9
	01	10 mg		4	13
	1:1:1:1	20 mg		4	14

*FDA approved in U.S. for Mania;
Correll et al, Bipolar Disorders, 2010; Findling et al JAACAP 2015

Antipsychotic Effects and Side Effects

- Dopamine (Blocks D2). Decreases the “positive” symptoms of schizophrenia.
 - More D2=more potent.
 - Also causes extrapyramidal effects (EPS: Parkinsonism, dystonia, restlessness)
 - More likely to cause EPS in kids than in adults
- Serotonin (Blocks many 5-HT receptors) Cardinal feature of atypicals.
 - Reduces “negative” symptoms (apathy/amotivation).
 - Decreases EPS
 - Significant weight gain (5-HT) (More weight gain than in adults)
- Metabolic Syndrome (wt gain, ↑cholesterol, diabetes)-more likely with atypicals
- Other side effects: seizures (clozapine), agranulocytosis (clozapine) ↑prolactin, anticholinergic side effects, cardiac (QT prolongation)
- Tardive Dyskinesia (greater risk with typicals vs atypicals)
- Neuroleptic Malignant Syndrome – rare, life-threatening
 - (fever, rigidity, mental status changes, autonomic dysfunction)

Antipsychotic Induced Weight gain/metabolic changes

SATIETY Study

Drug	Weight gain	Cholesterol increase	Triglyceride Increase
Olanzapine	+ 8.5 kg	15.6 mg/dl	24.3 mg/dl
Quetiapine	+ 6.1 kg	9.1 mg /dl	37 mg/dl
Risperidone	+ 5.3 kg		9.7 mg/dl
Aripiprazole	+ 4.4 kg		
Comparison	+ 0.2 kg		

Recommended monitoring

Parameter	Baseline	1 Mo.	2 Mo.	3 Mo.	6 Mo.	Q year
Waist Circumference	x	x	x	x	x	x
Body Mass Index	x	x	x	x	x	x
Hgb A1C	x			x		x
Fasting Glucose	x			x		x
Fasting Lipid Panel	x			x		x

Interventions for Weight Gain

Psychosocial Interventions

- Psychoeducation focused on:
 - nutritional counseling
 - caloric expenditure
 - portion control
- Behavioral self-management including:
 - motivational enhancement
 - goal setting
 - regular weigh-ins
- Self-monitoring of daily food and activity levels
- Dietary and physical activity modifications

Pharmacologic

- Try to reduce or stop wt gain inducing medication,
- switch to med with a lower propensity to cause wt gain
- A review of the literature suggests that Metformin
 - Can help with modest weight loss
 - Can help lower cholesterol and Hgb A1C
 - Start 250 BID, Then 500 BID, Then 1000 BID

Mood stabilizers vs Antipsychotics in bipolar disorder

- 6 wk DB-RCT of outpts w/ mania (8-18 yrs, N=66), (Pavaluri et al 2010)
Risperidone more effective than DVX:
 - Remission: 62.5% (risperidone) & 33.3% (DVX)
- Treatment of Emerging Age Mania (TEAM) study
 - Response: Risperidone 68.5%, Li 35.6%, DVX 24.0%.
- Atypical antipsychotics seem to be more effective for acute mania, but cause more side effects (weight gain/metabolic)

Pharmacotherapy of Bipolar Depression

- Selective serotonin reuptake inhibitors (SSRIs)
 - Most effective treatment for acute bipolar depression BUT
 - May have mood destabilizing effects
- SSRI-Induced Mania
 - Rates as high as 50% of children with bipolar d/o
 - May account for reports of increased suicidality in children on SSRIs
 - Risk factors:
 - Bipolar family history
 - Psychomotor retardation
 - Atypical depression (hypersomnia, wt gain, reactive mood)
 - Acute onset of depression

Atypical Antipsychotics for Bipolar Depression

- **Olanzapine-Fluoxetine Combo**

- Superior to PBO in teens (Detke et al *JAACAP* 2015)
- Half of patients gained $> 7\%$ of their body weight

- **Lurasidone-** Superior to PBO in teens with bipolar depression (DelBello et al *JAACAP* 2017)

- Negative study with Quetiapine XR



Longer Term (Maintenance) Treatment

- **Aripiprazole**

- More effective than placebo in a 30-week randomized Placebo-Controlled Study: Both 10mg/day and 30mg/day were more effective than PBO but more side effects at 30 mg dose.

- **Lamotrigine**

- Lamotrigine withdrawal study-lamotrigine was effective in maintaining remission for teens(13-17y.o., but not for younger kids)

Youth At-Risk for Bipolar Disorder

- Family Focused Therapy
- Mindfulness-based Cognitive Therapy
- Omega-3 fatty acids
- Possibly lamotrigine
- Second generation antipsychotics
- Antidepressants risky:
 - 57% of at risk youth (depressed/anxious, with a bipolar I parent) treated with an antidepressant had an adverse event (leading to discontinuation)
 - Greatest risk of an adverse event in younger patients
 - Strawn et al 2014

Consider ECT in adolescents

- Treatment of choice for adults with bipolar disorder and
 - Pregnancy
 - Catatonia
 - Neuroleptic malignant syndrome
 - Other medical condition in which more standard medication regimens are contraindicated
 - Need for rapid, definitive response
- Consider ECT in teens with Bipolar I disorder if
 - Severe Mania or depression
 - Nonresponsive or unable to take standard medication
 - Need for a rapid definitive response
 - Risks of other treatments outweigh the risks of ECT
 - History of previous good response

Don't forget therapy!

- Therapy can improve medication compliance, prevent relapse, help kids cope with developmental impact of illness
- Focus of therapy:
 - Psychoeducation
 - Relapse prevention
 - Individual psychotherapy
 - CBT
 - DBT
 - ACT
 - Social and family functioning
 - Academic and occupational functioning

Educate patients re: Sleep Hygiene

- Stick to a schedule
- Establish a bedtime routine
- Don't eat or drink a lot before bed
- Avoid caffeine and nicotine
- Exercise
- Keep your room cool
- Sleep primarily at night
- Keep it dark, quiet, and no screens
- Use your bed only for sleep
- Soak and sack out
- Don't rely on sleeping pills
- Don't catastrophize



Take home points!

- Make sure it's truly Bipolar, consider comorbid diagnoses
- Get them to take their medications
 - For acute mania: start with SGA - (better efficacy than mood stabilizers)
 - For Maintenance: Lithium, Lamotrigine, Aripiprazole
 - Augmentation of mood stabilizer/SGA: lamotrigine
 - For Bipolar Depression: Lurasidone, olanzapine-fluoxetine combo
 - Be cautious with antidepressants (high risk of adverse effects/hypomania)
 - In hi risk anxious/depressed kids (with bipolar parent), avoid antidepressants, esp in younger kids
 - Consider ECT
- Refer for therapy to help with medication compliance, relapse prevention, and to improve functioning

Text Book & Online Resources

- Child & Adolescent Clinical Psychopharmacology 4th edition, Wayne Green, Lippincott Williams & Wilkins 2006.
- Straight Talk about Psychiatric Medicines for Kids, 3rd Edition Timothy E. Wilens, M.D., The Guilford Press, 2008
- Essential Psychopharmacology 5th edition, Steven M. Stahl, Cambridge University Press, 2013
- American Academy of Child & Adolescent Psychiatry: www.aacap.org
- American Psychiatric Association: www.psych.org
- National Institute of Mental Health: www.nih.nimh.org

Thank You!