

## Mood Instability and Bipolar Spectrum Disorders: Efficacy, Safety, and Treatment Guidelines

Non-medication treatments

- Social Rhythm Therapy/Stabilization Schedule (Ellen Frank, PhD)

Activity	Target time/Target met?						
	Mon	Tues	Wed	Thur	Fri	Sat	Sun
Out of bed							
First social contact							
AM beverage/breakfast							
First outside							
Start of work/activities							
Lunch							
Afternoon nap							
Dinner							
Exercise							
Evening snack							
Evening TV news, etc							
Other activities							
Return home							
<u>Bed time</u>							
Mood							

- CBT/psychotherapy
- Exercise

### ***Summary of Consensus Statements from The Bipolar Summit 2006***

*(consensus includes varying degrees of agreement/disagreement among clinicians)*

1. The clinical presentation of bipolar disorder in children and adolescents is different than that of adults
  2. Treatment for bipolar disorder in children and adolescents is the same as that for adults
  3. Twenty percent or greater of individuals presenting with depression have bipolar disorder
  4. Suicide rates are higher in bipolar disorder than in unipolar depression
  5. Bipolar disorder should always be part of a differential diagnosis for behavioral disorders in the elderly
  6. SSRIs should not be first-line treatment for depression in individuals with bipolar disorder
    - a. STEP-BD, 2007: Paxil and Wellbutrin were no more likely than placebo to treat bipolar depression
    - b. Gijnsman et al: review of 12 RCT's on the efficacy and safety of antidepressants in the short-term (10 week) treatment of bipolar depression—they were safe and effective, but long-term safety and efficacy was not determined
    - c. Leverich et al: Wellbutrin, Zoloft, and Effexor associated with substantial risk of switching to mania or hypomania—Effexor had the highest risk, Wellbutrin the lowest; there were more switches with bipolar I than II
  7. First-line treatment of acute mania in bipolar disorder should include an atypical antipsychotic
  8. Maintenance therapy for bipolar I disorder is best managed with combination therapy using a mood stabilizer (e.g., lithium, valproate, carbamazepine) and an atypical antipsychotic
  9. Patients with bipolar II disorder require maintenance pharmacotherapy
  10. Treatment of patients with psychotic mania in bipolar disorder should include an atypical antipsychotic
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## *General Treatment in Adults*

- General issues with medications
  - FDA-approved bipolar disorder treatments in adults
 

	Mania	Mixed	Depression	Maintenance
○ Abilify:	+	+	-	+
○ Zyprexa	+	+	- (Symbyax is +)	-
○ Seroquel	+	-	+	-
○ Risperdal	+ (youth too)	+	-	-
○ Geodon	+	+	-	-
○ Equetro (carbamazepine)	+	+	-	-
○ Depakote	+	-	-	-
○ Depakote ER	+	+	-	-
○ Lamictal	-	-	-	+
○ Lithium	+	-	-	+
○ Symbyax	-	-	+	-
○ Latuda	-	-	+	-
  - Lithium responders tend to have a significant excess of bipolar disorder in their family tree
  - Lamictal responders tend to have a significant excess of anxiety disorders, panic attacks, substance abuse, and alcohol addictions
  - Responders to antipsychotic mood stabilizers tend not to have an increased history of bipolar or anxiety disorders but do tend to have an excess of chronic psychiatric illnesses in their family trees
  - Suicidal Behavior During Lithium and Valproate Treatment: A Within-Individual 8-Year Prospective Study of 50,000 Patients With Bipolar Disorder (Song et al, 2017)
    - 51,535 folks with bipolar disorder followed from 2005-2013 for treatment with lithium and valproate
    - 10,648 suicide-related events occurred
      - The incidence rate was decreased by 14% during lithium treatment, but not during valproate treatment
  - BALANCE Study
    - Lithium vs. Depakote vs. Lithium+Depakote
    - 4 countries, 41 sites, 90% UK
    - Results
      - Lithium > Depakote
      - Lithium + Depakote > Lithium alone or Depakote alone
    - Issues with study
      - Depakote levels not noted
      - 1/4 - 1/3 used other meds too
      - High prevalence of manic episodes, low prevalence of depressive episodes
      - No patients with bipolar II
      - Open study
  - Neuroinflammation/oxidative stress a critical issue, which can be, in schizophrenia/schizoaffective disorder, neurodegenerative
    - Anti-inflammatory/anti-oxidant/neuroprotective approaches
      - Second generation atypical antipsychotics
      - Minocycline
      - Cox-2 inhibitors
      - Lithium
      - Omega-3 fatty acids
      - N-acetyl cysteine
      - Aspirin
      - ?Vitamin E
      - Exercise
      - SSRI's
      - Avoidance of pro-inflammation/pro-oxidative/inducers of apoptosis (cell death) factors
        - Haldol is pro-oxidative, so are other first generation anti-psychotic meds
        - Amphetamine
        - Cocaine
        - Cannabis
        - Lipid peroxidase products

## Acute mania in adults

- Yildiz et al, 2015 meta-analysis
  - In decreasing order of relative efficacy
    - Risperdal
    - Zyprexa=Vraylar
    - Lithium
    - Carbamazepine
    - Invega=Abilify
    - Saphris
    - Seroquel
    - Geodon=Depakote
    - Trileptal
    - Lamictal (~0, in mania)
- 2012 meta-analyses
  - One
    - Abilify, Saphris, Tegretol, cariprazine, Haldol, lithium, Zyprexa, paliperidone, Seroquel, Risperdal, tamoxifen, Depakote, and Geodon all > placebo
    - Large effect sizes for Tegretol, cariprazine, Haldol, Risperdal, and tamoxifen
  - Two
    - Antipsychotic medications more effective than mood stabilizers
    - Risperdal, Zyprexa and Haldol were particularly efficacious
    - Risperdal, Zyprexa, and Seroquel more tolerable than Haldol
- 2011 Meta-Analysis, Cipriani and colleagues
  - Haldol > Risperdal/Zyprexa > lithium/Depakote/Tegretol/Seroquel/Abilify/Saphris/Geodon > placebo
  - This study did not look at treatment of mania beyond 3 weeks (e.g., recurrence rates) nor safety/tolerability issues
- Kemp, 2011
  - Folks with improvement (with Zyprexa or Risperdal) of 25% or more by week 1 much more likely to achieve remission by week 3
  - Folks with improvement of 50% or more by week 1 much more likely to remain responders (and achieve remission) by week 3
- Corell et al, 2010
  - Depakote>carbamazepine>lithium
  - Risperdal>Haldol>Seroquel>Zyprexa>Geodon>Abilify
- Bowden, et al, 2005 (and in Goodwin and Jamison, 2007)
  - Response rates in adult mania
 

○ <b>Risperdal</b>	~58%	<b>Average dose 4.9 mg/day</b>	<b>279 patients</b>
○ <b>Zyprexa</b>	~54%	<b>Average dose 16 mg/day</b>	<b>304 patients</b>
○ <b>Lithium</b>	50%	<b>Average dose 1950 mg/day</b>	<b>134 patients</b>
○ <b>Carbamazepine</b>	50%	<b>Average dose 707 mg/day</b>	<b>223 patients</b>
○ Depakote	~45%	Average dose 1694 mg/day	255 patients
○ Seroquel	~45%	Average dose 575 mg/day	208 patients
○ Geodon	~45%	Average dose 121 mg/day	268 patients
○ Abilify	~42%	Average dose 28 mg/day	260 patients
○ Placebo	25%		1265 patients
- COLT youth mania study:
 

○ <b>Depakote</b>	~52%	<b>Significant</b>
○ Trileptal	~41%	Not significant
○ Lithium	~38-41%	Not significant
○ Topamax	~35%	Not significant
○ Depakote ER	~24%	Not significant
○ Placebo	~22-28%	
- **FDA-approved meds for Pediatric Bipolar I, mixed or manic episodes (studied for ~3 weeks)**
  - **Saphris** 10-17 yo (approved range)
  - **Abilify** 10-17
  - **Zyprexa** 13-17
  - **Seroquel** 10-17
  - **Risperdal** 10-17
  - **Lithium** 12-17 (not based on a study)
- Summary of second generation atypical antipsychotics in youth mania
  - **Abilify (hi)** ~64%
  - **Risperdal (hi)** ~63% (up to 68% in Geller, et al, 2012)
  - **Seroquel (lo)** ~62%

- **Geodon** ~60%
- **Cariprazine** 59.3-60.6 (youth; Calabrese, et al, 2015)
- **Risperdal (lo)** ~58%
- **Seroquel (hi)** ~56%
- Zyprexa ~45%
- Abilify (lo) ~45%
- Saphris 42-54% (youth; Findling, 2015)
- Placebo ~18-35%
- Combining the three summary studies immediately above for mania (adult and youth) (Me, 2016)
  - **Risperdal** ~58-68%
  - **Cariprazine** 59.3-60.6 (youth; Calabrese, et al, 2015)
  - **Carbamazepine** 50%
  - **Seroquel** ~45-62%
  - **Geodon** ~45-60%
  - **Zyprexa** ~45-54%
  - **Depakote** ~45-53%
  - **Abilify** ~42-64%
  - **Saphris** 42-54% (youth; Findling, 2015)
  - **Lithium** ~38-50%
  - Topamax 35%
  - Depakote ER ~24%
  - Placebo ~22-35%
- **Response rates for SGA's for mania in youth (2007-2009 data)**
  - 45-65%
- Medications for **MONOTHERAPY** ranked by “numbers needed to treat”
  - **I.**
    - **Lithium**
    - **Equetro (carbamazepine)**
    - **Risperdal**
      - **NNT, youth: 3 for response, 3-4 for remission (3-6 mg better)**
      - **NNH, weight, youth: 11-21**
  - **II.**
    - **Zyprexa**
      - **NNT, youth: 4 for response, 4 for remission**
      - **NNH, weight, youth: 3**
    - **Abilify**
      - **NNT, youth: 3-5 for response, 2-4 for remission (30 mg better)**
      - **NNH, weight, youth: n/a - 16**
    - **Haldol (unapproved)**
  - **III.**
    - **Seroquel**
      - **NNT, youth: 4-5 for response, 4 for remission (600 mg ~better)**
      - **NNH, weight, youth: 7-10**
  - **IV.**
    - Depakote
    - Geodon
  - **V.**
    - Saphris
- Medications for **ADJUNCTIVE** THERAPRY ranked by “numbers needed to treat”
  - **I.**
    - **Zyprexa**
    - **Depakote (unapproved)**
  - **II.**
    - **Risperdal**
    - **Haldol (unapproved)**
  - **III.**
    - **Abilify**
  - **IV.**
    - Seroquel
    - Saphris

## *Treatment Guidelines ADULT Mania (from U.S. and Other Countries)*

Scherk et al, 2007, analysis of studies on second generation (atypical) antipsychotic (SGA) medications in the monotherapy or polytherapy of acute mania

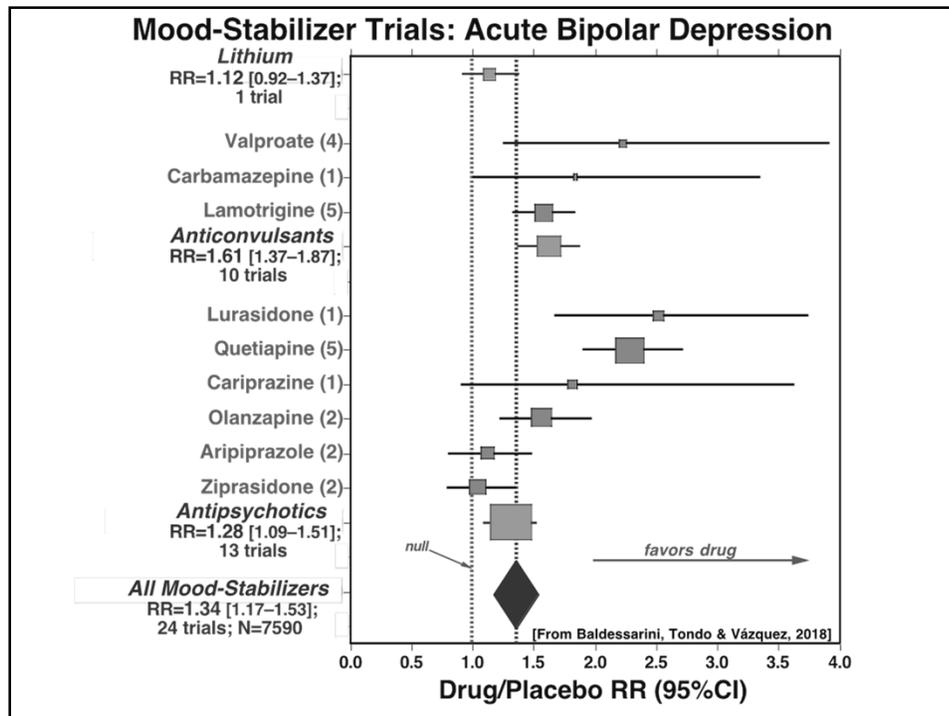
- o SGA monotherapy vs. placebo
  - o All effective (Seroquel a bit less)
  - o Drop-out due to adverse side effects equal between SGA's and placebo
  - o Less drop-out due to inefficacy than placebo
  - o Weight gain significant in Zyprexa and Seroquel vs. placebo
  - o Somnolence more with all SGA's than placebo
  - o Muscle side effects more with Abilify and Risperdal than placebo; akathisia more in Abilify and Geodon than placebo
- o SGA monotherapy vs. mood stabilizer (Depakote OR lithium)
  - o Zyprexa (only) more effective than Depakote (only)
  - o Trend towards higher efficacy in SGA's than Depakote or lithium, but not significant (except as above)
  - o No differences in drop-out rates
  - o Weight gain more with Zyprexa and Seroquel
  - o Somnolence more with Zyprexa and Seroquel
- o Mood stabilizer (Depakote OR Tegretol OR lithium) PLUS SGA vs. mood stabilizer PLUS placebo
  - o Add-on SGA's more effective than add-on placebo
  - o Specifically, add-on Zyprexa, Seroquel, and Risperdal more effective than add-on placebo; add-on Geodon not more effective
  - o Overall drop-out rate with add-on Zyprexa and Seroquel less than with add-on placebo
  - o Drop-out rates due to adverse side effects higher in add-on Zyprexa than with add-on placebo
  - o Drop-out rates due to inefficacy overall lower with add-on SGA's than with add-on placebo, specifically though with Zyprexa only
  - o More weight gain with add-on Zyprexa, Risperdal, or Seroquel
  - o More somnolence with add-on Zyprexa, Seroquel, or Geodon but not with Risperdal
  - o More muscle side effects with add-on Geodon but not with add-on Risperdal

### *Classical      Mixed      Rapid Cycling      Hypomania*

SGA = second generation (atypical) antipsychotic medication

- |  |  |   |   |  |
|--|--|---|---|--|
| <ol style="list-style-type: none"> <li>1. One of the following:           <ol style="list-style-type: none"> <li>a. Lithium (Li)</li> <li>b. Depakote (Dep)</li> <li>c. Zyprexa</li> <li>d. Risperdal</li> <li>e. Seroquel</li> <li>f. Abilify</li> <li>g. Geodon</li> <li>h. Lithium OR Depakote PLUS Zyprexa</li> <li>i. Lithium OR Depakote PLUS Risperdal</li> <li>j. Lithium OR Depkaote PLUS Seroquel</li> </ol> </li> <li>2. Next, one of the following:           <ol style="list-style-type: none"> <li>a. Lithium PLUS Depakote</li> <li>b. Tegretol (Teg)</li> <li>c. Trileptal</li> <li>d. ECT</li> </ol> </li> <li>3. Next: one of the following:           <ol style="list-style-type: none"> <li>a. Lithium PLUS Tegretol</li> <li>b. Haldol</li> <li>c. Thorazine</li> <li>d. Lithium or Depakote PLUS Haldol</li> <li>e. Clozapine</li> </ol> </li> <li>4. NOT RECOMMENDED:           <ol style="list-style-type: none"> <li>a. Neurontin alone</li> <li>b. Topamax alone</li> <li>c. Lamictal alone</li> <li>d. Verapamil alone</li> <li>e. Tiagabine alone</li> <li>f. Risperdal PLUS Tegretol</li> </ol> </li> </ol> | <ol style="list-style-type: none"> <li>a. Li</li> <li>b. Dep</li> <li>c. Teg</li> <li>d. SGA</li> <li>e. SGA added</li> <li>f. Li/Dep</li> </ol> | <ol style="list-style-type: none"> <li>a. Dep+SGA</li> <li>b. Li+SGA</li> <li>c. SGA</li> <li>d. Teg</li> <li>e. SGA+Teg</li> </ol> | <ol style="list-style-type: none"> <li>a. Li</li> <li>b. Dep</li> <li>c. Lam</li> <li>d. Teg</li> <li>e. Li+Dep or Teg</li> </ol> | <ol style="list-style-type: none"> <li>a. Dep</li> <li>b. SGA</li> <li>c. Dep+SGA</li> </ol> |
|--|--|---|---|--|

## Bipolar depression in adults

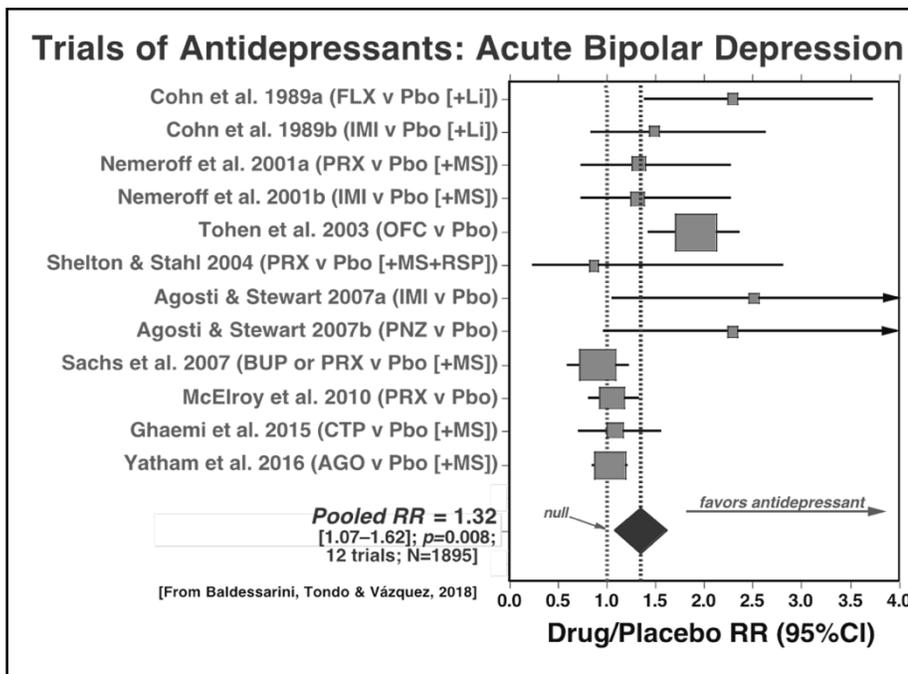
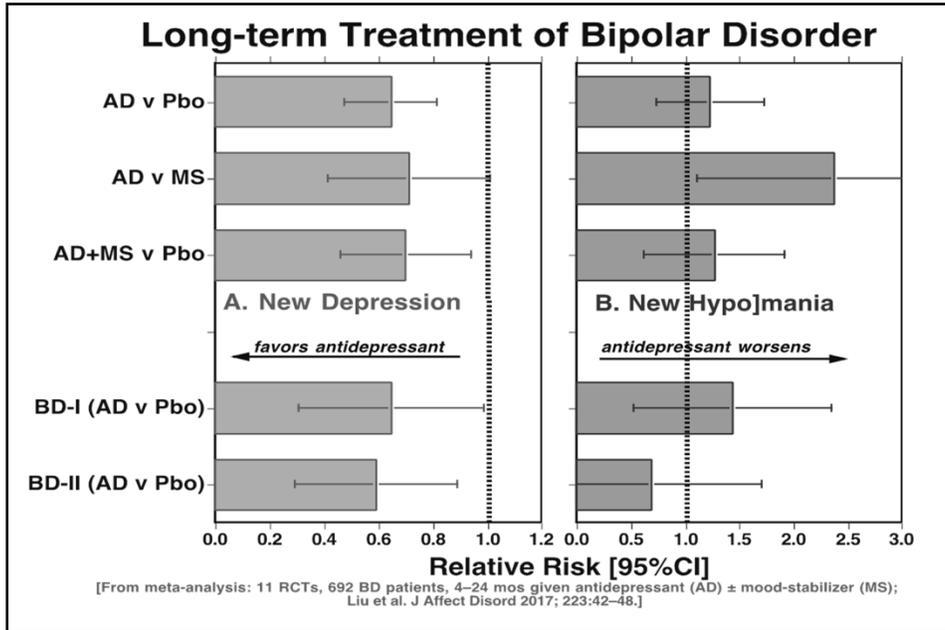


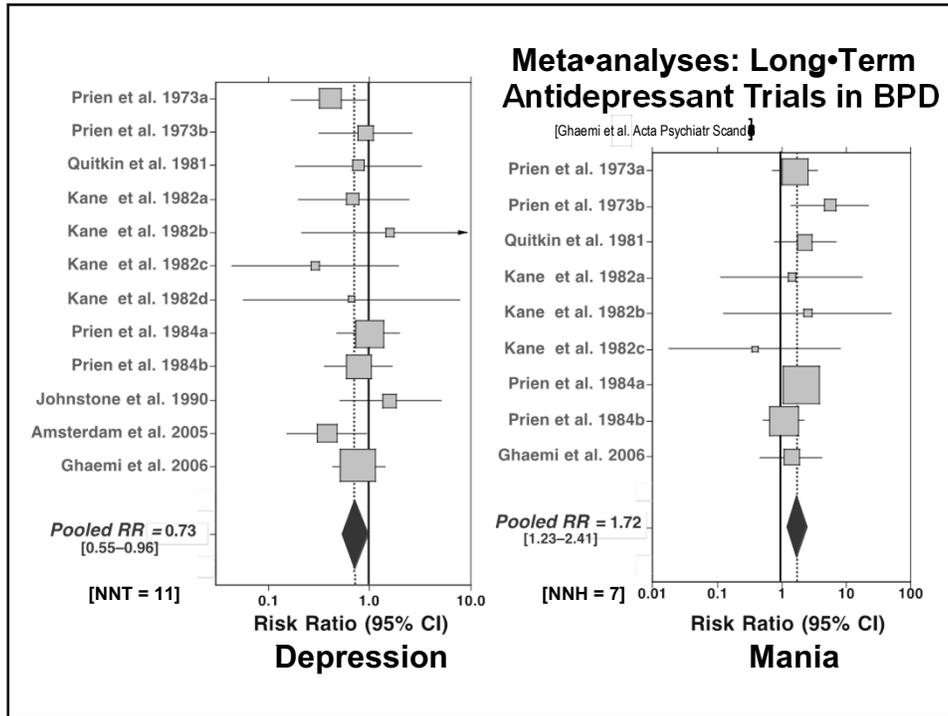
## Treatments for bipolar depression

Agent	FDA-Approved Indications
Older Antidepressants	None (UP only, widely assumed risky in BD)
Modern Antidepressants	None (UP only, widely assumed for any depr)
Dopamine agonists	None, but may help, esp. in BD-II
Lithium salts	Long-term: BD "recurrences" (depr not specified)
Divalproex	None (antimanic only)
Carbamazepine	None (antimanic only)
Lamotrigine	Long-term only (minimally antimanic)
Olanzapine-fluoxetine	Short-term, acute BP depression
Quetiapine	Short- & long term: BP depr & mania
Lurasidone	Short-term, acute BP depression

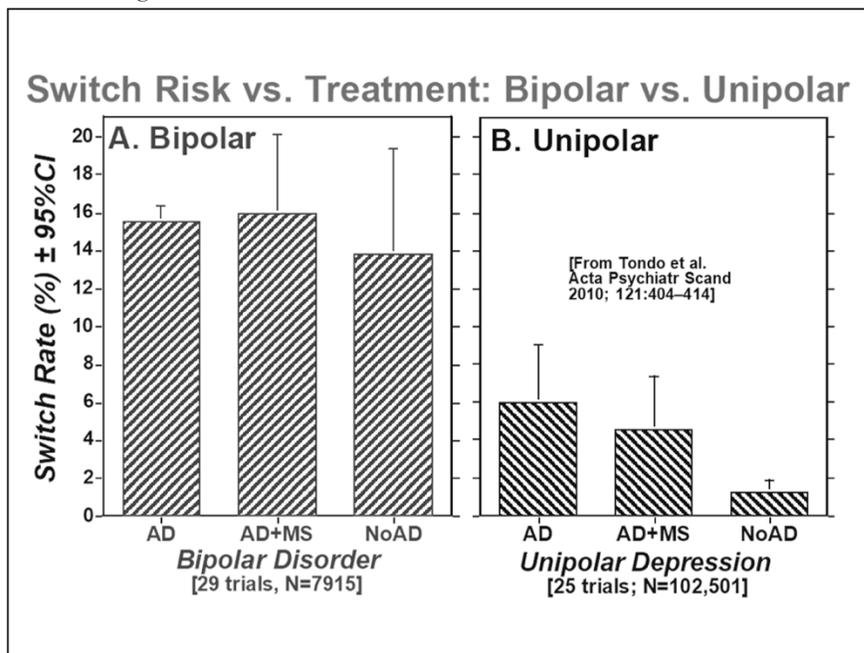
- Latuda
  - Cucchiari, 2012: Latuda in Bipolar I Depression
    - 485 patients, 6 week trial, with or without rapid cycling
    - Latuda 20-60 as effective as 80-120, both 50% more effective than placebo
  - From company, Latuda vs. placebo added to lithium or Depakote in Bipolar I depression, 340 patients, Latuda effective by week 3
- Mirapex vs. placebo + mood stabilizers
  - Burdick et al, 2012
    - Mirapex > placebo for cognitive dysfunction in bipolar disorder
  - Goldberg et al, 2004; 12 patients on Mirapex (avg dose 1.7 mg/d) and 10 on placebo

- 67% response rate with Mirapex
- 20% response rate with placebo
- Zarate et al, 2004; 10 patients on Mirapex (avg dose 1.7 mg/d) and 11 patients on placebo
  - 60% response rate with Mirapex
  - 9% response rate with placebo
- Modafinil/Armodafinil
  - Modafinil
    - Frye et al, 2007; adjunctive modafinil vs. placebo; 6 wks, 90 patients; effective
  - Armodafinil
    - Calabrese et al, 2010; adjunctive armodafinil vs. placebo; 8 wks, 257 patients
- Antidepressants in bipolar disorder in adults





- Pacchiarotti et al, 2013 (ISBD Task Force):
  - Evidence-based recommendations for the use of antidepressants in bipolar disorder cannot be made at this time
  - Recommends trials on Lamictal, lithium, Zyprexa, Seroquel, and Latuda before an antidepressant is used
  - If antidepressants are to be used in bipolar I, use only with a mood stabilizer
  - Better tolerated in bipolar II, but no evidence that they are effective in acute bipolar depression in bipolar II
  - Should be avoided in patients with current manic symptoms, agitation, and/or rapid cycling, mixed features, current mood instability, or a history of antidepressant-induced mania or hypomania
- Meta-analysis of antidepressant-associated mania/hypomania (Tondo, 2010):
  - 109 trials, 114,521 subjects
  - Overall mania risk: 12.5%
    - 13.8% with no mood stabilizer
    - 15.9% with mood stabilizer
  - TCA's had higher risk than SSRIs



Switch rates not much worse with AD, but mood stabilizers don't necessarily protect them from switch. These aren't from great RCT studies. Switch rates in UD are worse, but that's due to hidden bipolar disorder.

○

## Antidepressant Switch Risks: Bipolar & Unipolar Depression

AD Type	Trials (n)	Subjects (N)	New Hypo[mania] Rate (%) [95%CI]
Various	22	3878	22.1 [21.6–22.5]
TCA's	46	10,187	12.7 [12.4–12.9]
SRI's	18	38,187	8.71 [8.59–8.83]
SNRI's	6	1361	7.77 [7.22–8.33]
Bupropion	3	69	7.63 [6.04–9.21]
MAOI's	14	2179	4.58 [4.38–4.77]
All ADs	111	56,212	12.5 [12.4–12.6]
No ADs	45	58,309	7.46 [7.36–7.56]

From Tondo, Vazquez & Baldessarini Acta Psychiatr Scand 2012; 121:404–414.  
Relative risk with/ without antidepressants: 1.68. For bipolar disorder patients only, switching risk was 15.5% vs. 13.8% with vs. without antidepressant treatment.

- Effexor is more like TCA's despite data. Data on MAOI's is not based on huge numbers.

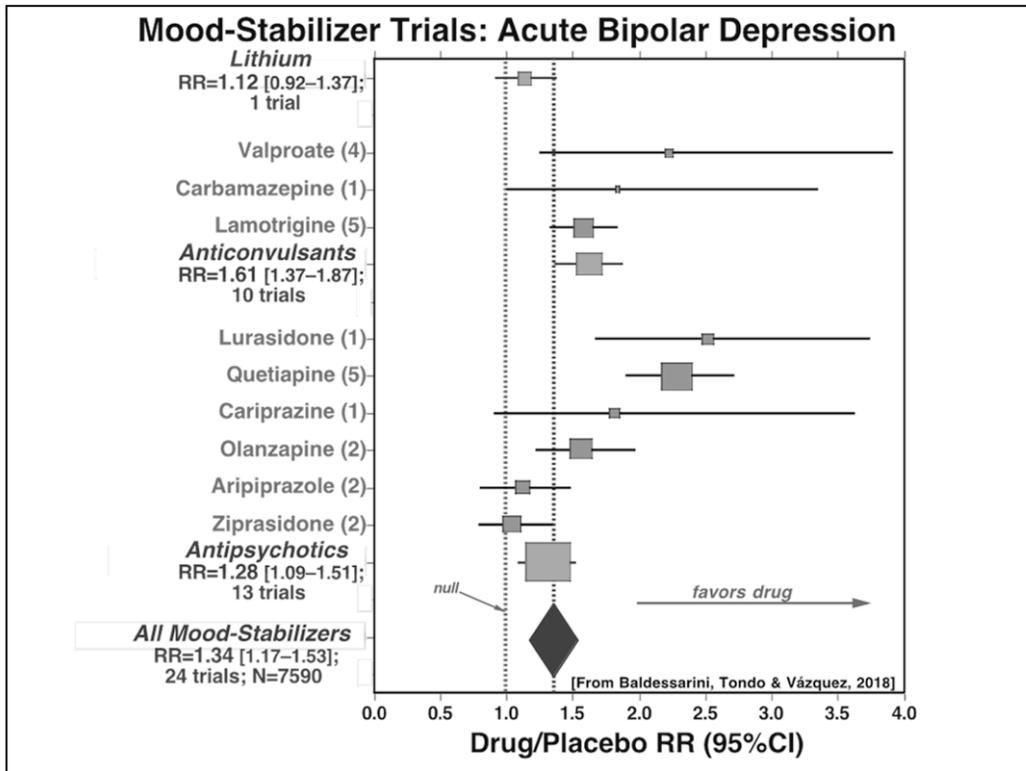
### Elevated Switch-Risk with Antidepressants

- Family history of probable BD
- Onset before age 25 years
- Depressive first-lifetime episode
- Multiple recurrences (≥4/past 10 years)
- Hyperthymic, cyclothymic, irritable temperament traits
- D-M-I > M-D-I episode-sequencing
- Undiagnosed BD-II vs. MDD
- Prior postpartum mood or psychotic illness
- Multiple hospitalizations
- Comorbid substance abuse
- Current agitation, dysphoric, mixed, or psychotic features
- Psychomotor retardation, hypersomnia, hyperphagia in depression
- Mild hypothyroidism
- Serotonin transporter short-allele
- Highly responsive to antidepressant treatment
- Treatment-associated excessive mood-elevation
- Tricyclics & venlafaxine: higher risk
- Lack of mood-stabilizer

Adapted from Tondo et al. Acta Psychiatr Scand 2013; 127:355–364; Tondo Intl BPD Symposium, Seville, March 2013. Several such features were found in 15.3% of depressed patients.

- Prozac vs. Lithium for bipolar II disorder (Amsterdam et al, 2010): Prozac (10-40 mg/day) vs. lithium (300-1200 mg/day) monotherapy in bipolar II, 50 weeks (after recovery from bipolar depression)
  - Mean time to relapse
    - 250 days for Prozac
    - 156 days for lithium
    - 187 days for placebo
  - No differences in hypomanic symptoms
- Goldberg, 2007: antidepressants did not hasten recovery from mixed depression in bipolar disorder (part of STEP-BD study)
- STEP-BD (Sachs et al, 2007); 366 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
- Antidepressant Use in Bipolar Disorder, ISBD Task Force Recommendations (2013)
  - Adjunctive antidepressants for acute bipolar depression
    - Permissible if history of positive antidepressant response
    - Avoid in presence of 2+ core manic symptoms, psychomotor agitation, or rapid cycling
  - Antidepressant monotherapy for acute bipolar depression

- Avoid in bipolar I disorder
- Avoid in bipolar II disorder in the presence of 2+ core manic symptoms
- Adjunctive antidepressants for bipolar maintenance
  - Permissible if patient relapses into depressive episode after stopping antidepressant therapy
- Antidepressant-Induced Switching
- Monitor patients and discontinue antidepressants
- Discourage antidepressants if there is a history of antidepressant-emergent manic, hypomania or mixed states
- Avoid if there is high mood instability or history of rapid cycling
- Antidepressant Use in Mixed States
- Avoid
- Discontinue if mixed states emerge
- Antidepressant Classes and Increased Risks of Switching
- SNRI's and TCA's have higher risk; permissible if closely monitored. Exception in SNRI's: Effexor XR is as likely a TCA's



lithium—data is not great long term. Likely helpful long term. Depakote data is good.

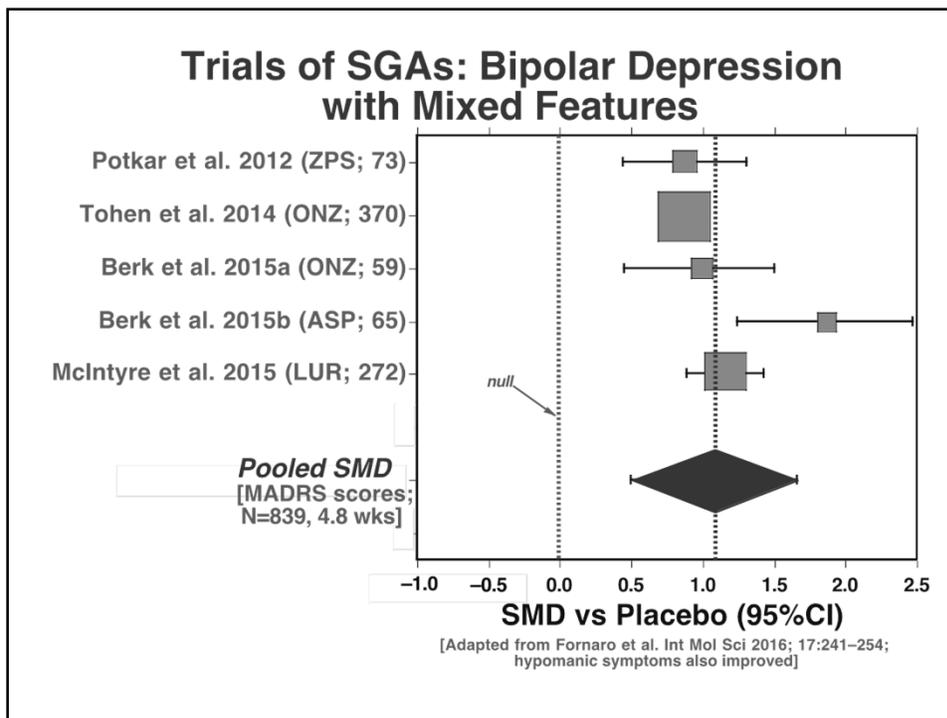
- Abil/Geo not so helpful. Lat/QTP/OLA+proz most helpful, BUT still early.

- Lithium

- 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%

- Lamictal

- 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



Modest benefit; long term risks.

- Seroquel
  - Hirschfeld et al, 2006
    - 542 patients, bipolar I and II; 8 weeks; Seroquel 300 vs. 600 vs. placebo
    - Significant reduction of anxiety symptoms in bipolar I but not bipolar II
  - Calabrese, 2005 and Thase, 2006: Seroquel in acute bipolar depression
    - 978 patients, Seroquel 300 vs. 600 vs. placebo
    - Seroquel 300 = 600, both of which were better than placebo
- Treatments Compared (Taylor et al, 2014)
  - 29 studies with over 8000 patients analyzed
  - Efficacy
    - \*Symbyax (statistically significant)
    - \*Zyprexa (statistically significant)
    - Seroquel
    - Latuda
    - Depakote
    - Lithium
    - Lamictal
  - Most optimal balance of efficacy and safety from manic switch
    - \*Symbyax
    - \*Seroquel
    - Zyprexa
    - Latuda
    - Depakote
    - SSRI's
  - Evidence of lack of efficacy (though few studies looked at these agents)
    - Geodon
    - Abilify
    - Risperdal

- Medications ranked by “numbers needed to treat” for the treatment of acute depression
  - **I.**
    - **Symbyax**
      - **NNT 4 for response, 5 for remission**
      - **NNH 6 for wgt gain, 12 for sedation; also: diarrhea**
    - **Lamictal (in one study for bipolar II, rapid cycling)**
      - **NNT 4 (vs 13 in bipolar I)**
    - **Latuda**
      - **NNT 5 for response**
      - **NNH 15 for akathisia, 17 for nausea, 25 for sedation, -493 for clinically significant weight gain (less than placebo)**
  - **II.**
    - **Seroquel**
      - **NNT 6 for response**
      - **NNH 6 for sedation, 19 for clinically significant weight gain**
  - **III.**
    - **Latuda added to mood stabilizer**
      - **NNT 7 for response**
      - **NNH 16 for nausea, 19 for sedation, 30 for akathisia, -51 for clinically significant weight gain (less than placebo)**
    - Lamictal (unapproved)
      - NNT 12 for response (see above)
      - NNH 42 for sedation, -34 for weight gain (less than placebo)
    - Zyprexa (unapproved)
      - NNT 12 for response
      - NNH 6 for clinically significant weight gain and 7 for sedation
  - **IV**
    - Nuvigil response rate 46% vs. 34% placebo in one study)
      - NNT 9 for response
      - NNH -37 for clinically significant weight gain (less than placebo)
    - Lithium
      - NNT 15 for response
      - NNH 20 for sedation, -112 for clinically significant weight gain (less than placebo)
  - **V**
    - Antidepressants
      - NNT 36 for response (very similar rate to placebo; meta-analysis, mostly bipolar I depression)
      - NNH 209 for switch (very low)
        - Placebo: 4.2%
        - SSRI: 3.7%
        - TCA: 11.2%
      - In addition:
        - Goldberg et al, 2007: no benefit of antidepressants for bipolar depression with manic symptoms
        - Sachs et al, 2007: no advantage or disadvantage to adding antidepressants to mood stabilizers for bipolar depression
        - Baseline score on Young Mania Rating Score predicts antidepressant-induced switches (higher scores associated with higher risk of switching)
        - Less antidepressant associated switching when bipolar depression is preceded by euthymia (normal mood) vs. mania
  - 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

### **Adult Bipolar Depression**

- See above
- Other possible treatments
  - Mirapex monotherapy
  - Amantadine
  - Bromocriptine
  - Riluzole
  - Memantine

- Comparison in specific symptom reduction of Seroquel vs. Zyprexa+Prozac vs. Zyprexa:

	Seroquel 600 mg	Seroquel 300 mg	Zyprexa + Prozac	Zyprexa alone
○ Apparent sadness	15%	17%	21%	2%

○ Reported sadness	17%	19%	20%	6-7%
○ Inability to feel	17%	15%	20%	0%
○ Pessimistic thoughts	25%	21%	22%	2.5%
○ Suicidal thoughts	28%	26%	18%	7%

Effects sizes (overall efficacy with 0.2 as small, 0.5 as medium and 0.8 as large)

- **Seroquel 600 mg (in bipolar I): 1.09**
- **Seroquel 300 mg (in bipolar I): 0.91**
- **Zyprexa+Prozac (in bipolar I) 0.68**
- Seroquel 600 mg (in bipolar II): 0.39
- Zyprexa alone (in bipolar I): 0.32
- Seroquel 300 mg (in bipolar II): 0.28

### **Clinical Confidence Treatment Options for Adult Bipolar Depression**

- Level I (substantial confidence, based on evidence from randomized trials)
  - Lamictal (two studies)
  - Lithium (one)
  - Seroquel (one)
  - Zyprexa (one)
  - Mirapex (two)
- Level II (moderate confidence, based on evidence from open trials or large naturalistic databases)
  - Depakote (one)
  - Tegretol (one)
- Level III (low confidence, based on evidence from case series or small open trials)
  - Transcranial magnetic stimulation (one)
  - Methylphenidate (Ritalin; one)
  - Omega-3 fatty acids (one)
  - Myo-inositol (one)
  - Riluzole (one)

### **Treatment Guidelines ADULT Bipolar Depression**

- If taking lithium OR other antimanic OR no antimanic with a history of severe and/or recent mania
  - Antimanic AND Lamictal
- If NOT taking antimanic without a history of severe and/or recent mania
  - Lamictal
- Next: replacement with:
  - Seroquel, or
  - Zyprexa PLUS Prozac
- Next: combination of two or more of the following:
  - Lithium
  - Lamictal
  - Seroquel
  - Zyprexa PLUS Prozac
- Next: one of the following combinations
  - Two or more of: Lithium, Lamictal, Seroquel, Zyprexa PLUS Prozac, Depakote, OR
  - Tegretol PLUS SSRI, OR
  - Wellbutrin, OR
  - Effexor, OR
  - ECT
- Next: monotherapy or combination therapy with one or more of the following, with or without combination with medications in any of the steps above (unless certain combinations are contraindicated)
  - MAOI
  - Tricyclic antidepressant
  - Mirapex
  - Other second generation atypical antidepressants
  - Trileptal
  - Other combinations not tried in the previous stages above
  - Inositol
  - Stimulants
  - Thyroid
- Treatment guidelines from other countries:
  - Li
  - SSRI+Li
  - SSRI+Li+Lamictal
  - Dep
  - Teg
  - SGA
  - Lamictal
  - Lamictal+SSRI

- Li+Dep+SGA

- **Maintenance Treatment in adults**

- Lindstrom et al, 2017; maintenance treatment for 6 mo up to 2 yrs

- Seroquel
  - Mania 0.39-fold less risk
  - Depression 0.38
  - Any 0.38
- Geodon
  - Mania No data
  - Depression No data
  - Any 0.62
- Abilify
  - Mania 0.46
  - Depression 0.76 (non-significant)
  - Any 0.65
- Zyprexa
  - Mania 0.51 (non-significant)
  - Depression 0.44
  - Any 0.49
- Risperdal
  - Mania 0.38 (non-significant)
  - Depression 0.66 (non-significant)
  - Any 0.5

- Medications for **MONOTHERAPY** ranked by “numbers needed to treat”

- **I.**
  - **Zyprexa**
- **II.**
  - **Risperdal**
  - **Seroquel (unapproved)**
- **III.**
  - **Abilify**
- IV.
  - Lithium
- V.
  - Depakote (unapproved)
- VI.
  - Lamictal

- Medications for **ADJUNCTIVE** THERAPY ranked by “numbers needed to treat”

- **I.**
  - **Seroquel**
- **II.**
  - **?Risperdal**
- **III.**
  - **Geodon**
- IV.
  - Abilify

- Medications for ranked by “numbers needed to treat” **FOR EPISODE PREVENTION**

- **I.**
  - **Zyprexa**
- **II.**
  - **Risperdal**
  - **Seroquel (unapproved)**
  - **Seroquel plus lithium/Depakote**
- **III.**
  - **Abilify**
- IV.
  - Lithium
- V.
  - Depakote (unapproved)
  - Geodon plus lithium/Depakote
- VI.
  - Lamictal
- VII.

- Abilify plus lithium/Depakote
- Medications for ranked by “numbers needed to treat” **FOR MANIA PREVENTION**
  - **I.**
    - **Risperdal**
  - **II.**
    - **Zyprexa**
  - **III.**
    - **Abilify**
    - **Seroquel (unapproved)**
  - **IV.**
    - Lithium
    - Seroquel plus lithium/Depakote
  - **V.**
    - Geodon plus lithium/Depakote
  - **VI.**
    - Abilify plus lithium/Depakote
- Medications for ranked by “numbers needed to treat” **FOR DEPRESSION PREVENTION**
  - **I.**
    - **Seroquel plus lithium/Depakote**
  - **II.**
    - **Seroquel (unapproved)**
  - **III.**
    - **Depakote**
  - **IV.**
    - Zyprexa
  - **V.**
    - Lamictal
  - **VI.**
    - ?Risperdal/Risperdal plus lithium/Depakote
- How long to treat
  - Consider tapering antipsychotic if in remission for 12-24 months
  - If patient has been hospitalized and/or psychotic, consider longer duration
  - If less severe or in patients for whom diagnosis is not clear, could consider briefer treatment

General Treatment in Youth

Mania

**Controlled Studies of FDA Approved Drugs for Acute Mania**

(G. Carlson, AACAP; 2018)

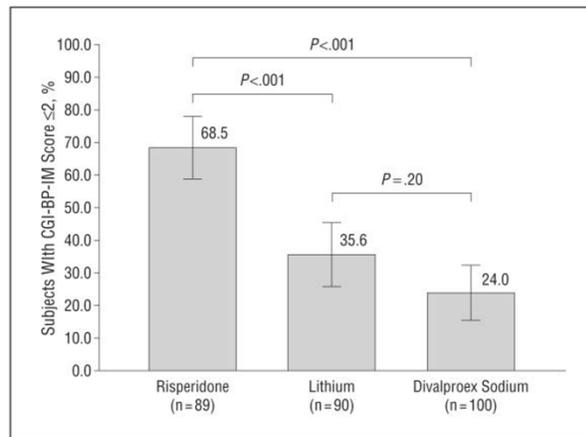
Drug	<u>Age &gt; 18</u>	<u>Age &lt; 18</u>
Lithium	+	Approved > 12
Divalproex	+	FDA study (-); another ( <u>+</u> )
Olanzapine	+	Approved > 13
Carbamazepine ER	+	Trial suspended
Risperidone	+	Approved >10
Quetiapine	+	Approved >10
Ziprasidone	+	Positive; no FDA approval kids
Aripiprazole	+	Approved >10
<u>Topiramate</u>	Negative	Negative
<u>Oxcarbamazepine</u>	Not studied	Negative
<u>Asenapine</u>	+	Approved > 10

**Antipsychotic and Mood Stabilizer Efficacy in Pediatric and Adult Patients with Bipolar I Mania**

(Correll, C. et al; Bipolar Disorders 2010; 12; 116-141)

<u>Medication</u>	<u>Effect Size</u> <u>Child (95% CI)</u>	<u>vs.</u>	<u>Adult</u>
Divalproex-IR/ER	0.28 (0.01-0.54)		0.61
Lithium	0.31 (-0.12-0.73)		0.50
Oxcarbazepine	0.11 (-0.26-0.49)		N/A
<u>Topiramate</u>	0.51 (0.03-1.14)		0.05
<b><u>Weighted MS</u></b>	<b><u>0.24 (0.06-0.41)</u></b>		<b><u>0.46</u></b>
Aripiprazole	0.69 (0.44-0.94)		0.36
Olanzapine	0.75 (0.41-1.08)		0.48
Quetiapine	0.60 (0.35-0.86)		0.52
Risperidone	0.81 (0.48-1.14)		0.71
Ziprasidone	0.48 (0.21-0.76)		0.42
<b><u>Weighted SGAs</u></b>	<b><u>0.65 (0.53-0.78)</u></b>		<b><u>0.48</u></b>

# The Treatment of Early Age Mania (TEAM) study



Geller B et al. Arch Gen Psychiatry. 2012

- Individual agents
  - Lithium
    - 38-42% response rate vs. 28-29% placebo
    - NNT 11
    - Effect size 0.31 (-0.12-0.73)
  - Depakote ER
    - 26% response rate vs. 24% placebo
    - NNT 100
    - Effect size 0.28 (0.01-0.54)
  - Trileptal
    - 43% response rate vs. 26% placebo
    - NNT, children 4
    - NNT, teens 33
    - Effect size 0.11 (-0.26-0.49)
  - Topamax
    - 35% response rate vs. 22% placebo
    - NNT 8
    - Effect size 0.51 (0.03-1.04)
  - Risperdal
    - NNT 3
    - NNH, wgt 12
    - Effect size 0.81 (0.48-1.14)
  - Zyprexa
    - NNT 4
    - NNH, wgt 4
    - Effect size 0.75 (0.41-1.08)
  - Abilify
    - 58.7-64.8% response rates (10 mg-30 mg/day, at 30 weeks, Findling et al, 2013) vs. 29.7% placebo
    - NNT 3-5
    - NNH, wgt 20
    - Effect size 0.69 (0.44-0.94)
  - Geodon
    - NNT 4
    - NNH, wgt 17

- Effect size 0.48 (0.21-0.76)
- Seroquel
  - NNT 4-5
  - NNH, wgt 6
  - Effect size 0.6 (0.35-0.86)
- Saphris
  - NNT 4 (7 with 5 mg/day)
  - NNH, wgt 17
- Iloperidone
  - NNH, wgt 12
- Paliperidone
  - NNH, wgt 25
- Latuda
  - NNH, wgt 50
  - If pediatric bipolar I mania not classic/formal, consider
- 5/6/2018 Conference (Wagner): treatment duration
  - 4-6 weeks per each treatment trial (assuming tolerability)
  - therapeutic blood levels and/or adequate dose
  - consider tapering med after sustained remission of at least 12-24 consecutive months
- Geller et al, 2012/Vitello et al, 2012; TEAM Study (Risperdal vs Lithium vs Depakote in bipolar I mania/mixed episodes, 279 youth, 6-15)
  - Response rates at 8 weeks:
    - Risperdal (avg dose 2.6) 68.5%
    - Lithium (avg bld level 1.1) 35.6%
    - Depakote (avg bld level 114) 24%
  - For non-responders and partial responders:
    - Non-responders (89) were switched; response rates according to what they were switched to:
      - Risperdal switch 47.6%
      - Lithium switch 12.8%
      - Depakote switch 17.2%
    - Partial responders (65) were augmented with 1 of the other agents that they were not on; response rates according to what med was added on:
      - Risperdal add-on 53.3%
      - Lithium add-on 26.7%
      - Depakote add-on 0%
- Treatment of Early Age Mania (6-15), 279 kids, lithium (avg level 1.09) vs. Depakote (avg level 113.6) vs. Risperdal (avg dose 2.57 mg); 2012; see above
  - 68.5% response rate Risperdal (and depressive symptoms also improved faster and better)
  - 35.6% response rate lithium
  - 24% response rate Depakote
- Second Generation Antipsychotics in youth mania
  - Abilify: 45-63% response rates
  - Risperdal: 58-62% response rates
  - Seroquel: 57-62% response rates
  - Geodon: 60% response rate
  - Zyprexa: 45% response rate
  - Placebo 20-35% response rates
- Corell et al, 2010; mania
  - Topamax>lithium>Depakote>Trileptal
  - Risperdal>Zyprexa>Abilify>Seroquel>Geodon
- Controlled trials for youth mania
  - Lithium 3 studies (Geller 1998, Findling 2005, Kafantaris 2005)
  - Depakote 3 studies (Delbello 2002, Findling 2005, Delbello 2006)
  - Carbamazepine 0 studies
  - SGA's 6 studies (Delbello 2002, Tohen 2006, Delbello 2006, plus 3 more above)

### **Treatment Guidelines YOUTH Mania Without Psychosis**

- First: Lithium OR Depakote OR Tegretol OR SGA (Risperdal or Zyprexa or Seroquel...)
- Next: switch agent from selection in (A), OR Lithium OR Depakote OR Tegretol PLUS SGA
- Next: switch agent from selection in (A), OR Switch combination
- Next: two mood stabilizers and an SGA
- Next: Trileptal OR Abilify OR Geodon OR combination
- Next: Clozaril OR ECT

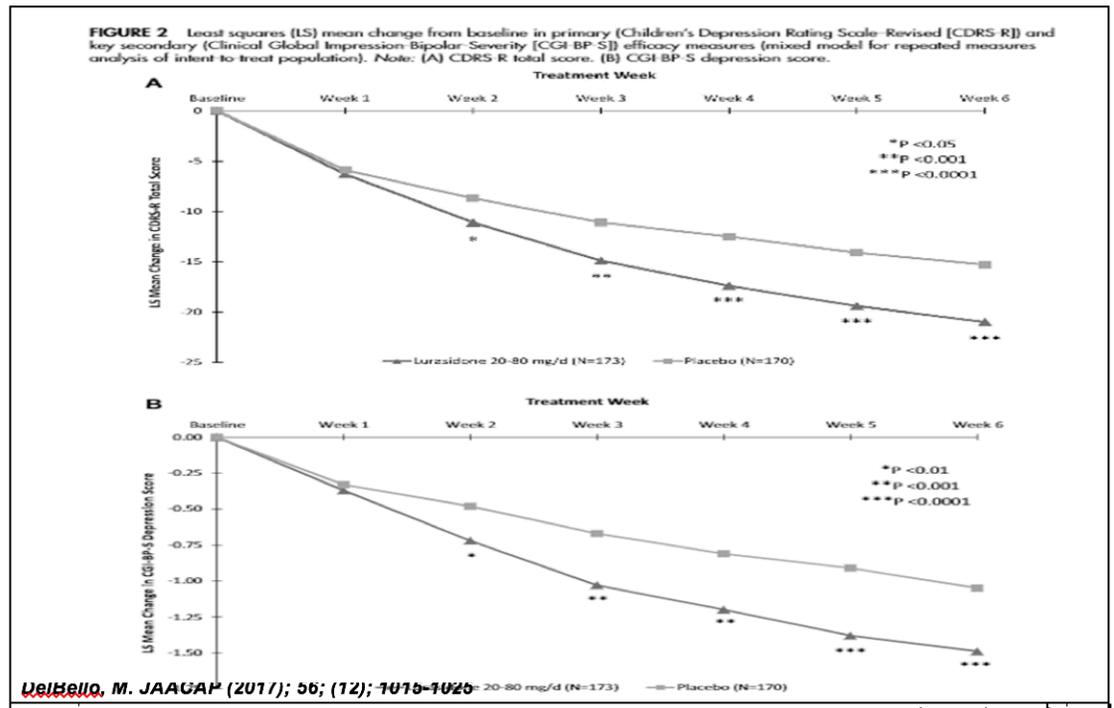
### **Treatment Guidelines YOUTH Mania WITH Psychosis**

- Lithium OR Depakote OR Tegretol PLUS SGA
- Next: Different combinations
- Next: Trileptal, Geodon, Abilify
- Next: Clozaril or Abilify

- **Bipolar depression in youth**
  - Atypical antipsychotics
    - Seroquel
      - Seroquel immediate release not superior to placebo, Delbello et al, 2009
      - Seroquel XR not superior to placebo, Findling et al, 2014
    - Symbyx
      - Successful in youth 10-17, Detke et al, 2015
        - More symptom reduction than placebo
        - Higher rates of response and shorter time to remission than placebo
        - Weight gain 8-9 pounds, compared to 1.1 pound with placebo
    - Latuda

**Efficacy and Safety of Lurasidone in Children and Adolescents with Bipolar 1 Depression: A Double Blind, Placebo Controlled Study**  
 (DelBello, M., et al. *JAACAP*; 56 (12); 2017; 1015-1025)

- ▶ **Method:** Patients age 10-17 were randomized to 6 weeks of double blind treatment of flexibly dosed lurasidone 20-80 mg.
- ▶ Primary endpoint was change of CDRS-R from baseline to endpoint.
- ▶ **Results:** N=347 patients were randomized; mean age 14 years. Mean dose 33.6 mg.
- ▶ At week 6, treatment with lurasidone was associated with statistically significant reduction in CDRS-R score ( $p < 0.001$ , ES 0.45) compared to placebo.
- ▶ Lurasidone was generally well tolerated; most common adverse effects were nausea and somnolence.
- ▶ **Conclusion:** Monotherapy with lurasidone significantly decreased bipolar depression symptoms in children and adolescents.



- Successful in youth 10-17, Delbello et al, 2017
  - 20-80 mg/day (avg 32.6 mg/day)
  - Response rates significantly better, but not remission rates
  - Common side effects
    - Nausea
    - Somnolence
    - Increased weight (rate of significant weight gain NOT more than placebo)
    - Insomnia
    - Akathisia
    - Elevated prolactin

- FDA-approved for bipolar depression in youth, 2018
- Lithium
  - CoLT I/II trials (Findling et al, 2013)
    - I: open label trial in 7-17 yo's with bipolar I, mixed or manic state
      - Average reduction in depressive symptoms of 15.5 pts
    - II: open label/double blind study, followed by blinded discontinuation phase
      - Responders randomized to lithium or placebo and monitored
        - 29% on lithium had a recurrence of symptoms; avg inc in symptoms 1.7
        - 71% on placebo had a recurrence; avg inc in symptoms 5.2
  - TEAM study (Salpekar et al, 2015) compared lithium to risperidone and Depakote
    - 69.2% of study completers on risperidone were "much or very much improved" for CGI for depression
    - 61.3% of those on lithium
    - 46.1% of those on Depakote
  - Open label study of 27 youth with bipolar depression (Patel et al, 2006); lithium dose to 1-1.2 level
    - 48% responders
    - 30% remitted
    - Average reduction in symptoms 15.5
- Lamictal
  - Open label study of 20 youth (Chang et al, 2006)
    - Avg dose 132 mg/day
    - 63% responders
    - 58% remitted
    - Side effects
      - Headache
      - Fatigue
      - Nausea
    - Open-label add-on study, followed by blinded discontinuation phase in youth with bipolar disorder (Findling et al, 2015)
      - Avg depression score dropped 6 points
      - 62% of youth depressed at baseline responded

### ***Treatment Guidelines YOUTH Bipolar Depression***

- Lithium
- Next: addition of or replacement with SSRI OR Wellbutrin if mood stabilized
- Next: addition of or replacement with Lamictal
- Antidepressant-Induced Switching Rates from Various Studies
  - Antidepressants other than TCA's
    - 3%
  - SSRIs
    - 7% (Prozac)
    - 7% (Zoloft)
    - 3.7%
    - 1% (Paxil)
    - 0% (Paxil)
  - Effexor
    - 15%
    - 13%
    - 0.4% (in unipolar depression study)
  - Wellbutrin
    - 11%
    - 4%
  - TCA's
    - 50% (DMI)
    - 11.2%
    - 10%
    - 7.7% (IMI)
    - 7%
  - MAOIs
  - Placebo
    - 4.7%
    - 4.2%
    - 2.3%

## **MAINTENANCE TREATMENT**

### **Time to Intervention for Any Mood Episode in Youth**

- Lithium: 16.3 weeks before 50% of clients require intervention  
Preventative effect plateaus at ~30 weeks where 70% of clients required intervention  
From 30 weeks through >70 weeks, just under 30% did NOT require intervention
- Depakote: 16.0 weeks before 50% of clients require intervention  
Preventative effect plateaus at ~55 weeks where >80% of clients required intervention  
From ~55 weeks through >70 weeks, just under 20% did NOT require intervention

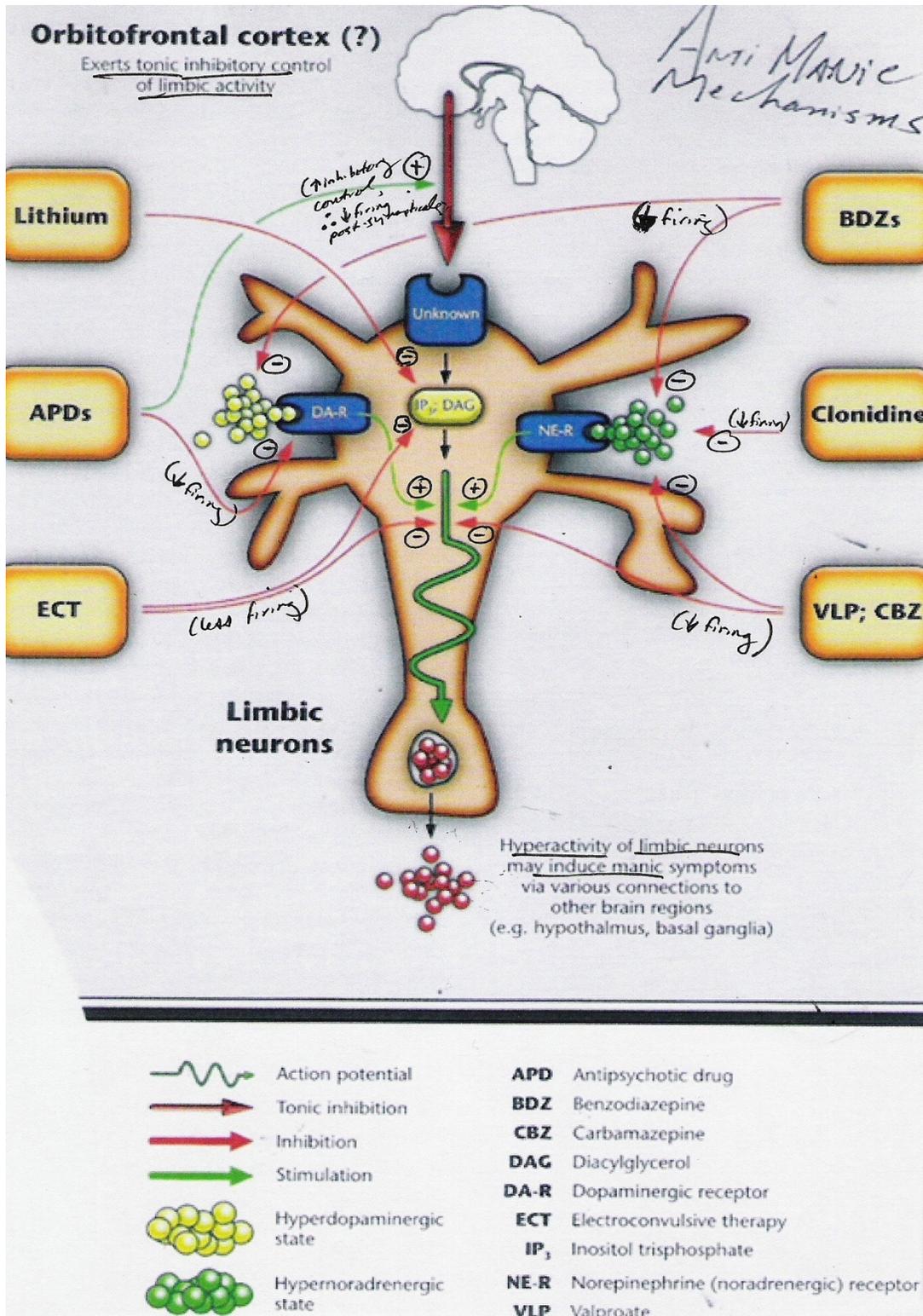
### **Treatment Guidelines YOUTH Maintenance Treatment**

- Lithium
- Next: Lamictal OR Zyprexa

## **COMBINATION TREATMENT**

- Saxena, 2006: safe and effective in the treatment of aggression in kids with bipolar disorder whose symptoms were not fully controlled by mood stabilizers.
- Pavuluri et al, 2006: one-year open-label trial of Risperdal augmentation in lithium nonresponder youth with preschool-onset bipolar disorder: 38 youth ages 4-17 (mean age 11); all received lithium monotherapy initially; patients who failed lithium after 8 weeks and those who relapsed after an initial response were given Risperdal augmentation for up to 11 months; results:
  - 17/38 on lithium monotherapy responded
  - 21/38 did not:
  - Risperdal augmentation → 86% response
- Pae, 2005: 6 month treatment with adjunctive Seroquel for mania; safe and effective.
- Findling et al, 2003: lithium PLUS Depakote in 90 patients, open-label, ages 5-17, treated up to 20 weeks: effective; 47% remission by 8 weeks
- Kowatch et al, 2003: combination treatment in 6-month semi-naturalistic study of 35 prepubertal youth (average age 11) after a 6-8 week acute treatment with one mood stabilizer (58% of those in this 6-8 week period needed additional treatment with stimulants, antipsychotics, or antidepressants): 80% response rate with two mood stabilizers
- Mullen, 2003: evidence of safety and efficacy in the adjunctive treatment of mania
- DelBello, 2002: 26 youth patients aged 10.5-17.5 yo (average 14), addition of Topamax 25-200 mg (average 100 mg) to mood stabilizer treatment; response rate 73% for mania, 62% overall
- Open label use as adjuvant to Depakote found to be safe and effective.
- Vieta, 2002: efficacy as add-on therapy to other mood stabilizers for rapid cycling bipolar disorder.
- Ghaemi, 2001: open-label prospective study of 40 patients rapid cycling bipolar I with or without adjunctive
- Chang and Ketter, 2000: Zyprexa at 2.5-5 mg/day as adjunctive in three acutely manic prepubertal children also treated with mood stabilizers; marked improvement evident in 3-5 days
- Garfinkel et al, 1985: lithium PLUS Tegretol in 19 treatment-resistant adolescents with acute or mixed mania; 100% positive response
- Adults: some evidence with
  - Lithium plus Depakote
  - Lithium plus carbamazepine
  - Symbyax (Zyprexa plus Prozac)

General/Other



Summary of Response/Remission Rates

	<u>Bipolar Depression</u>	<u>Rapid Cycling</u>	<u>Mania</u>	<u>Hypomania</u>	<u>Prevention</u>
MS PLUS MAOI	63-70% response, small Study (Nolan, 2007)				
MS PLUS Mirapex	60-67%	+?	+?	+?	+?
Seroquel	58% v. 36% placebo+ 53% v. 28% plac remission		61-72% v. ~40% placebo by 84 days; begins in 4-21 d 70-87% in youth (open)	+	+
MS PLUS Zyprexa	+	+?	68% v. 45% MS alone	+	70% in remn by 500 d
MS PLUS Seroquel	+	+	54% v. 33% MS alone 46% v. 26% MS alone remission	+	+
MS PLUS Risperdal	+	+?	53-59% v. 30-41% MS Alone	+	+
Lamictal 200 mg	54-60% 85% in youth (open)  Recent evidence in Bip II Depn Jae Seung Chang, 2011	60%+	Minimal	+	+ depression>mania 60-95% remission in youth (open label)
MS PLUS Zoloft	53%; 7% switch rate 36% remission				
MS PLUS Effexor	51%; 15% switch 34% remission				
Prozac PLUS Zyprexa	49-67%	+?	+?	+?	+?
MS PLUS Wellbutrin	49%; 4% switch rate 41% remission 27% response per STEP-BD				
Lamictal 50 mg	48%	+?	Minimal	+?	+ depression>mania
Geodon	+?	?	40-50% v. 19-35% placebo	+?	+?
Lithium PLUS Paxil	46% See STEP-BD below	?	?	?	+?
Lithium PLUS Imipramine	39%	?	?	?	+?
Lithium	35-68% 48% in youth 30% remission in youth	59%	52-75.5% by 84 days + 42% in youth 28-68% under 12 28-80% adols 26% remission in youth		65%, mania>depression 40% in remn by 500 d Risk relapse 40% v. 61% with placebo Risk relapse 27-28% v. 42-57% with Tegretol 44% no relapse in rapid cycling in 20 mo Risk relapse youth 28-53% v. 92-100% when non-compliant
MS PLUS LAMICTAL	31-36% in small study (Nolan, 2007)				
Depakote	30-35% overall 38-82% in subgroups 33% in youth	+	42-50% v. 27% placebo 41-94% in youth (open) 34% remission; begins in 62 53% remission in youth (open) 2007 study in youth negative	+	40% remission by 500 d 41-49% no relapse in rapid cycling in 20 mo
Tegretol	34.3%	+	42-61% v. 22% placebo 38% in youth	+	+ 82% in youth 1 y (open)

Zyprexa	33%	+?	49-65% v. 24-43% placebo 63% youth (open) 35-47% v. 11% placebo remission; begins in 14 d 30% youth remission (open)	+	+
MS PLUS Antidepressant STEP-BD	32.4% V. 38% placebo 23.5% v. 27.3% placebo durable recovery 10.1% v. 10.7% placebo affective switch (e.g., mania)				
Risperdal	+	+?	43-73% v. 24-36% placebo 53-74% in youth	+	+
Abilify	+?	+?	40-53% v. 19-32% placebo 67-71% in youth (open)	+	25% relapse 26 wk v. 43% relapse placebo
Allpurinol			+		
Saphris			+		
Invega			+		

MS = mood stabilizer (lithium, carbamazepine (Tegretol, Equetro), valproic acid (Depakote))

- Weight
  - Pharmacologic weight loss vs. placebo, in decreasing order of efficacy
    - Metformin
      - Prevention (Baptista et al, 2006; Wang et al, 2012; Wu et al, 2008)
      - Intervention (Arman et al; Baptista et al; Carrizo et al; Chen et al; Jarskog et al; Klein et al; Wu et al; Wu et al)
    - Topamax= d-fenfluramine = sibutramine
    - Reboxetine
    - (amantadine)
    - (nizatidine)
  - 40-50% of youth do not have their symptoms controlled with one mood stabilizer (Geller et al, 1998; Kowatch et al, 2000)
  - Bhangoo, 2003; in a review of medication treatment in youths with bipolar disorder:
    - Average number of medications is 3.4 (range 1-5)
    - Average number of medication trials is 6.32 (range 2-8)
    - 98% used a mood stabilizer or anticonvulsant mood stabilizer, of which
      - Depakote 79%
      - Lithium 51%
      - Neurontin 29%
    - 71% had had a trial of an antipsychotic/antimanic agent, of which
      - Risperdal 58%
      - Zyprexa 35%
      - Seroquel 26%
  - Weight gain from medications (though not in terms of BMI and so not adjusted for normative developmental weight gain)
    - Mood stabilizers, including Topamax: ~2.5 lb (-2 - 6.6 lb)
    - Mood stabilizers, excluding Topamax: ~4 lb (1 - 6.6 lb)
    - Two mood stabilizers: ~4.4 lb (2.2 - 6.6 lb)
    - Second generation antipsychotic (SGA): ~6.8 lb (up to 9 lb)
    - SGA plus mood stabilizer, excluding Topamax: ~12 lb (up to 16 lb)
- Stimulants in youth bipolar disorder
  - Not harmful (Galanter, 2003, 2006; Carlson, et al, 1998, 1999)
  - Helpful (Carlson, et al, 1992; Schaffer, et al, 2005; Findling, et al, 2008)
  - Mood stabilizers work better when ADHD treated first (Blader, et al, 2012; Aman, et al, 2014)
  - Conversion from ADHD to severe mood dysregulation is less common in youth than adults (Tillman, Geller, 2008)

Placebo-controlled trial of valproic Acid versus risperidone in children 3-7 years of age with bipolar I disorder

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**OBJECTIVE:** The objective of this study was to determine the efficacy and safety of valproic acid versus risperidone in children, 3-7 years of age, with bipolar I disorder (BPD), during a mixed or manic episode.

**METHODS:** Forty-six children with Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) diagnosis of bipolar disorder, manic, hypomanic, or mixed episode, were recruited over a 6 year period from two academic outpatient programs for a double-blinded, placebo-controlled trial in which subjects were randomized in a 2:2:1 ratio to risperidone solution, valproic acid, or placebo.

**RESULTS:** After 6 weeks of treatment, the least-mean Young Mania Rating Scale (YMRS) total scores change, adjusted for baseline YMRS scores, from baseline by treatment group was: Valproic acid 10.0±2.46 (p=0.50); risperidone 18.82±1.55 (p=0.008); and placebo 4.29±3.56 (F=3.93, p=0.02). The mixed

models for repeated measure (MMRM) analysis found a significant difference for risperidone-treated subjects versus placebo treated subjects ( $p=0.008$ ) but not for valproic acid-treated subjects versus placebo-treated subjects ( $p=0.50$ ). Treatment with risperidone over 6 weeks led to increased prolactin levels, liver functions, metabolic measures, and weight/body mass index (BMI). Treatment with valproic acid led to increases in weight/BMI and decreases in total red blood cells (RBC), hemoglobin, and hematocrit.

**CONCLUSIONS:** In this small sample of preschool children with BPD, risperidone demonstrated clear efficacy versus placebo, whereas valproic acid did not. The laboratory and weight findings suggest that younger children with BPD are more sensitive to the effects of both of these psychotropics, and that, therefore, frequent laboratory and weight monitoring are warranted.