Bipolar Disorder: Depression, Rapid Cycling, and Comorbidities Require Complex Treatment

Robert M. Post, M.D.
Bipolar Collaborative Network, Bethesda, MD

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Objectives

REVIEW EVIDENCE OF THE PROGRESSIVE NATURE OF INADEQUATELY TREATED BIPOLAR DISORDER AND ITS NEUROBIOLOGICAL CONSEQUENCES

DISCUSS THE NEED FOR EARLY INTERVENTION, COMPLEX COMBINATION TREATMENT, AND LONG-TERM PROPHYLAXIS

REVIEW SOME PROMISING AND NOVEL APPROACHES TO TREATMENT OF ADDICTIONS WITH N-ACETYLCYSTEINE AND THERAPY IN THE RE-CONSOLIDATION WINDOW

Patterns of Illness Among 258 SFBN Patients Treated and Followed Prospectively for One Year

Predictors of Severity of Depression in Year of Prospective Follow-up

Variable

Significance

Univariate

Multivariate

Early Age of Onset of Depression

***

Ten or more prior Depressive Episodes

***

History of Limited Occupational Functioning

***

Mood state at Network Entry: Depressed

***

Three Times the Amount of Depression vs. Mania in Treated Bipolar I vs. Bipolar II Disorder

BP I (N = 419)

BP II (N = 104)

High Incidence of Rapid and Faster Cycling in Naturalistically Treated Outpatients with Bipolar Disorder (N = 674)

I. Non-Rapid Cycling

NRC = 58%

II. Rapid Cycling (≥ 4 episodes/yr)

RC = 42%

A. Ultra Rapid Cycling: URC = 26.8% (≥ episodes/month)

B. Ultra-Ultra Rapid Cycling: UURC = 19.7% (multiple switches in 24 hours; ≥ 4 days/wk)
Prospectively Assessed Rapid Cycling Rated for 1 Year in 539 Outpatients

<table>
<thead>
<tr>
<th></th>
<th>Rapid cyclers</th>
<th>Non-rapid cyclers</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-IV*</td>
<td>38.2% (61.6%)</td>
<td>61.8% (38.4%)</td>
</tr>
<tr>
<td>Total no. of Episodes</td>
<td>7.1 ± 3.4</td>
<td>1.4 ± 1.1**</td>
</tr>
<tr>
<td>Manic / hypomanic</td>
<td>5.8 ± 3.6</td>
<td>0.9 ± 0.9**</td>
</tr>
<tr>
<td>Depressive</td>
<td>1.3 ± 1.3</td>
<td>0.6 ± 0.7**</td>
</tr>
<tr>
<td>Total no. of classes of Medications used</td>
<td>4.6 ± 1.8</td>
<td>3.5 ± 1.8**</td>
</tr>
</tbody>
</table>

DSM-IV: *NIMH-LFA

Rapid cyclers (N = 206) Non-rapid cyclers (N = 333)

More Episodes and/or Rapid Cycling Is a Predictor of Poor Response to Treatments of Bipolar Illness

I. NATURALISTIC TREATMENT
   Post 2004; Nolan 2005

II. MOOD STABILIZERS (M.S.)
   - Lithium >14 studies (but see Baldessarini & Tondo 2000)
   - Carbamazepine: McKee 1992; Otaua 1993; Denicoff 1997
   - Valproate (Accelerating course): Cabre; Post 2012(t)

III. ATYPICAL ANTI PSYCHOTICS (A.A.)
   - Olanzepine: Scott 2006
   - Any A.A. Post 2010

IV. ANTIDEPRESSANT AUGMENTATION OF A M.S.
   - Venlafaxine: Post 2006
   - AD: Gharemi 2010; Post 2012(t)

V. BENZODIAZEPINES
   Post 2012(t)

VI. COGNITIVE BEHAVIORAL THERAPY (CBT)
   Scott, 2006

BDNF Is Involved in Onset, Course, and Treatment of Bipolar Disorder

BDNF is involved in:
Onset, Course, and Treatment of Bipolar Disorder

Risk Factors for Prospective Rapid Cycling vs. Non-Rapid Cycling in Bipolar Illness (N = 293)

Pertinent Positives

<table>
<thead>
<tr>
<th>Positive</th>
<th>Sign.</th>
<th>O.R.</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 10 prior episodes</td>
<td>*</td>
<td>6.3</td>
</tr>
<tr>
<td>More than 20 prior episodes</td>
<td>*</td>
<td>5.5</td>
</tr>
<tr>
<td>Prior Hx of R.C.</td>
<td>***</td>
<td>4.1</td>
</tr>
<tr>
<td>Hx of Prior Drug Abuse</td>
<td>*</td>
<td>2.6</td>
</tr>
<tr>
<td>Abuse as Child</td>
<td>*</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Pertinent Negatives

Gender
BPII
Antidepressant Exposure
Hypothyroidism
Age Onset or Duration of Illness
Parental Hx of Affective Illness

Accumulating Stress and Episode-Related Vulnerability in Recurrent Affective Illness

CROSS SENSITIZATION AMONG STRESSORS, DRUGS OF ABUSE, AND EPISODES

Stress Sensitization
Cocaine Sensitization

Repetition of Each Increases Responsivity to Itself and the Others
Convergent Mechanisms of Stress, Episode, and Cocaine Sensitization Suggest that a Single Therapy Could Improve All Three

Possible Example: N acetylcysteine (NAC) may Ameliorate Overlearned Habits

NAC Reduces:
**Addictions to:**
- Cocaine, Heroin, Gambling, Alcohol, Marijuana, Nicotine.

**Trichotillomania, OCD**

**Depression and Anxiety in Bipolar Disorder**

Meta-analysis: Antidepressants Are Ineffective in Acute Bipolar Depression

- ReDepression Rate
- Remission Rate


Increased Switch Rate on Venlafaxine Largely Attributable to High Switch Rate in Rapid Cyclers

More Prior Antidepressant Trials Related to Poor Long-Term Prospective Outcome

RESPONSE (26 months) to Naturalistic Treatment assessed in 139 outpatients with bipolar I disorder

- Treatment NON-Response independently* linked to:
  - Anxiety disorder comorbidity
  - More prior depressive episodes
  - More prior antidepressant trials

(Post et al J Clin Psychiatr., 2011)

*by logistic regression.
Correlates of Antidepressant—Related Switching into Hypomania

1. Younger Age
2. BPI more than BPII subtype
3. Rapid Cycling (>4 episodes) in past year
4. "Mixed Depression", i.e., activated, speeded up, Racing Thoughts
5. TCAs > 2nd Generation ADs
6. NE Active > SHT or DA
7. Substance abuse history

Correlates of Response to Mood Stabilizers

<table>
<thead>
<tr>
<th>Drug: LITHIUM</th>
<th>CARBAMAZEPINE</th>
<th>VALPROATE</th>
<th>LAMOTRIGINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPI</td>
<td>BPI</td>
<td>BPI or II</td>
<td>BPI &amp; II</td>
</tr>
</tbody>
</table>

Candidates

● Substance Abuse:
● Anxiety:
● Manic:
● Single:
● Fewer:
● Discrete:

Mood swings:

● Epidemic:
● Well intervals:

Positive:

● Bipolar Illness:
● Type of Response:

Negative:

● Anxiety:
● Euphoric:

History:

● Bipolar Illness:
● Other:

Others:

● Medical:
● Morbidity:

+ LITHIUM + CARBAMAZEPINE

Low Response to Lithium plus Valproate in Rapid Cycling Bipolar Illness

<table>
<thead>
<tr>
<th>Low Response Rate</th>
<th># Enrolled</th>
<th>Intent to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li Alone (N=42)</td>
<td>41.2%</td>
<td>19%</td>
</tr>
<tr>
<td>CBZ Alone (N=34)</td>
<td>53.8%</td>
<td></td>
</tr>
<tr>
<td>Li + CBZ (N=27)</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

Calebrese et al. 2000

Lithium (Li) Plus Carbamazepine (CBZ) Is More Effective than Monotherapy in Rapid Cycling Bipolar Illness

<table>
<thead>
<tr>
<th>Treatment Phase</th>
<th>Li Alone (N=42)</th>
<th>CBZ Alone (N=34)</th>
<th>Li + CBZ (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rapid cycling</td>
<td>41.2%</td>
<td>53.8%</td>
<td>50%</td>
</tr>
<tr>
<td>Rapid cycling</td>
<td>28%</td>
<td>19%</td>
<td>53%*</td>
</tr>
</tbody>
</table>

* Cochran’s Q = 5.429, df=2, P = 0.066.

1. Cutoff of marked or moderate.
2. History of rapid cycling at any time by retrospective DSM.
Combinations Are More Effective Than Monotherapy in Bipolar Disorder Prophylaxis

**Lithium plus carbamazepine (CBZ)**
- Denicoff et al

**Lithium plus valproate (VPA)**
- Calabrese et al. (Adults)
- Finding et al. (Children)
- Geddes et al. 2010, BALANCE

**VPA plus lamotrigine (LTG)**
- Bowden et al.
- (better than VPA Alone)

Atypical Antipsychotics as Adjuncts to Lithium or Valproate
- (better than Li or VPA Alone)

### Combination Treatment: Safety and Tolerability

- **Titrate new drug toward efficacy and side effect tolerability**
  (not by blood levels)
- **Maximize one regimen (if signs of improvement) before switching to another**
- **Augmentation** saves time over substitution

### Rationales for Complex Combination Treatment

- **Necessary in Other Chronic Medical Conditions**
  (AIDs, TB, CHF, Cancer, Epilepsy)
- **Differential Targeting of Multiple Systems, Symptoms, and Comorbidities**
- **Failure of Mono or Dual Therapy**
- **Avoidance of Side Effects**
- **Wish to Treat to Full Remission and Prevent Loss of Efficacy**

### Approved Agents for Bipolar Depression

**Olanzapine-Fluoxetine**
- Placebo (n=166)
- Olanzapine (n=83)
- Olanzapine-Fluoxetine (n=121)

**Quetiapine**
- Placebo (n=168)
- Quetiapine 400mg/d (n=172)
- Quetiapine 800mg/d (n=157)

**Lurasidone**
- Placebo (n=166)
- Lurasidone 20mg/d (n=162)
- Lurasidone 40mg/d (n=161)

**Efficacy of Lurasidone Monotherapy in Bipolar Depression**

Lurasidone 2 doses vs Placebo for 6 weeks

<table>
<thead>
<tr>
<th>Lurasidone &amp; Placebo</th>
<th>LUR 20-60mg</th>
<th>LUR 80mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong> (N=170)</td>
<td>(N=166)</td>
<td>(N=169)</td>
</tr>
<tr>
<td>Responders:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td>53%***</td>
<td>51%***</td>
</tr>
<tr>
<td>Remitters (MADRS ≤ 12)</td>
<td>25%</td>
<td>42%**</td>
</tr>
</tbody>
</table>

Also significant improvement on both doses in:
- MADRS, CGI-BP Severity, Anxiety and Social and Occupational Functioning
Recepter Binding Affinities of Lurasidone: Linkage to Efficacy and Tolerability

<table>
<thead>
<tr>
<th>TYPE</th>
<th>POSITIVE EFFECTS</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHT7</td>
<td>Highest</td>
<td>Low sedation, Weight gain</td>
</tr>
<tr>
<td>SHT6</td>
<td>High</td>
<td>Minimal</td>
</tr>
<tr>
<td>SH3A</td>
<td>Moderate</td>
<td>Dry mouth, constipation</td>
</tr>
<tr>
<td>D2</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>H1</td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>Negligible</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rapid Onset AD Effects in Bipolar Depression

1. KETAMINE 0.5mg I.V. (40 minutes) Zarate et al 2011
2. SCOPOLAMINE I.V. (4ug/kg) Zarate et al 2012
3. TRH (intratheal, I.V., subcut.) Marangell et al 1997
4. SLEEP DEPRIVATION, one night (last half) Tolle and Pfug, 1971

How to Sustain AD Effect in Long-term?

Attempts to Sustain Rapid-Onset AD Effects

KETAMINE
1. Multiple infusions (x5) Successful short term
2. Riluzole follow on – Not successful x2
3. Hypothetical: Memantine, Lithium – to be tested (TBT)

SCOPOLAMINE
1. Hypothetical: Quetiapine potent blocker muscarinic R (TBT)

SLEEP DEPRIVATION for One Night
1. Lithium – Successful
2. Phase Advance – Successful
3. Phase Advance & high intensity light – Successful
4. Phase advance with Agomelatine. Hypothetical (TBT)

NMDA Receptor Blocker Differences

Serra et al 2012

I. POTENT BLOCKERS of glutamate NMDA receptors with high % trapping:
   - KETAMINE, Phencyclidine (PCP), MK801 (Potentially Psychomimetic)
   - MEMANTINE

II. MEMANTINE, a low affinity, non-competitive NMDA receptor blocker with lesser trapping:
   - Block is voltage/use dependent, & memantine blocks extrasynaptic (excitotoxic) receptors,
   - & thus maintains normal synaptic function

Sustained Mood-Stabilizing Effects upon Memantine Augmentation

Koukopoulos et al. (2012) J Affect Dis, 136, 163-166

40 treatment resistant bipolar patients
memantine 10-30 mg/day open, add on CGI-BP at 6 & 12 months
At Baseline: (marked ill to very severely ill): x = 6.7

72.5% Much or Very Much Improved on CGI-BP
68.4% of Rapid Cyclers reached Remission
At 6 & 12 months of memantine Rx

www.ohsubrains.com/pins
Memantine vs. Naturalistic Treatment in Two Separate Populations of Bipolar Patients

Koukopoulos et al
MEMANTINE Rx (10-30 mg)
Post, Nolen et al
NATURALISTIC Rx (3 ± 3 drugs)

Higher RESPONSE Rate:
72.5% 45.5%

More SEVERELY ILL at baseline CGI-BP
6.7 4.7

Shorter Time to achieve Response
6 months x = 18 months

Higher RESPONSE Rate:
72.5% 45.5%

More SEVERELY ILL at baseline CGI-BP
6.7 4.7

Shorter Time to achieve Response
6 months x = 18 months

Memantine in 72 Euthymic Bipolar Patients with COGNITIVE DYSFUNCTION

12 week randomized memantine vs placebo

Significant Improvement in:
Spatial and working memory
Verbal and episodic memory

↑ NAA in left hippocampus
↑ Choline in right hippocampus

Potential Treatments for Comorbidities:

Anxiety Disorders

<table>
<thead>
<tr>
<th>Social Phobia</th>
<th>Panic/Agrophobia</th>
<th>PTSD</th>
<th>OCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin (A,A)</td>
<td>Gabapentin (A,A)</td>
<td>SSRI’s (A,B)</td>
<td>Topiramate (C,A)</td>
</tr>
<tr>
<td>Clonazepam (A,A)</td>
<td>Clonazepam (A,A)</td>
<td>Lamotrigine B, A**</td>
<td>Clozapine (B,C)</td>
</tr>
<tr>
<td>Antidepressants (A,B)</td>
<td>Antidepressants (A,B)</td>
<td>Carbamazepine (C,B)</td>
<td>Atypical Antipsy (A, B)</td>
</tr>
<tr>
<td>Valproate (B,A)</td>
<td>Carbamazepine (C,B)</td>
<td>Lamotrigine B (D,B)</td>
<td>Benzodiazepine (E,D)</td>
</tr>
<tr>
<td>Lamotrigine B, A**</td>
<td>Carbamazepine (C,B)</td>
<td>Gabapentin (D, C)</td>
<td></td>
</tr>
</tbody>
</table>

Level of Evidence in Primary Disorder = First Letter; Utility in Bipolar = Second Letter

A=Double Blind Clinical Trial; B=Large Case Experience; C=Much Open Study; D=Few Cases; E=Ambiguous; F=Worse

UTILITY IN Bipolar
A = VERY LIKELY
B = LIKELY
C = POSSIBLE
D = UNLIKELY

**= Studied in Bipolar Disorder

Treatments for Bipolar Comorbidities: Substance Use/Abuse Disorders

Alcohol

<table>
<thead>
<tr>
<th>Abstinence</th>
<th>Naltrexone (A,A)</th>
<th>Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate (A,A)</td>
<td>Benzodiazepine (B,C)</td>
<td>Modafinil (A,A)</td>
</tr>
<tr>
<td>Disulfiram (A,D)</td>
<td>Carbamazepine (A,B)</td>
<td>Valproate (B,B)</td>
</tr>
<tr>
<td>Topiramate (A,A)</td>
<td>Carbamazepine (C,B)</td>
<td>Gabapentin (A,A)</td>
</tr>
<tr>
<td>12 Step (A,A)</td>
<td>Lamotrigine (C,C)</td>
<td>Baclofen (A, but poor choice for bipolar = D)</td>
</tr>
<tr>
<td>Valproate A,A**</td>
<td>Lamotrigine (C,C)**</td>
<td></td>
</tr>
</tbody>
</table>

Level of Evidence (A-E) in Primary Syndrome; UTILITY = in Bipolar Patients

Nicotine

<table>
<thead>
<tr>
<th>Nicotine</th>
<th>Bupropion (A,A)</th>
<th>Nicotine (A,A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate (A,A)</td>
<td>Patch alpha7 agonist (A,B)</td>
<td></td>
</tr>
<tr>
<td>Modafinil (A,A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate (B,B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin (A,A)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Food/Bulimia

<table>
<thead>
<tr>
<th>Food/Bulimia</th>
<th>N-acetylcysteine-A, A</th>
<th>Topiramate (A,A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine (A,A)</td>
<td>Baclofen (A, but poor choice for bipolar = D)</td>
<td></td>
</tr>
<tr>
<td>Topiramate (A,A)</td>
<td>Zonisamide (A,A)</td>
<td></td>
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</tbody>
</table>

The amygdala and hippocampus are the substrates for conscious REPRESENTATIONAL memory

The striatum is the substrate for automatic, unconscious HABIT memory

Hyperactive Cued Glutamate Release from Cortical Neurons onto N. Accumbens GABAergic Neurons May Be the Basis of Multiple Addictions and Habits

N-acetylcysteine Increases Glial Glutamate Transporters, Dampens Conditioned Glutamate Release and Is Effective in Many Habits & Addictions

www.ohsubrains.com/pins
N-acetylcysteine (NAC)*: Spectrum of Efficacy in Repetitive Habit Disorders

I. DRUG ADDICTION
Cocaine
Heroin
Alcohol
Marijuana
Nicotine**

II. GAMBLING ADDICTION
• NAC: typical dosing versus placebo:
  - 1 cap (500mg) BID for 1 week,
  - then 2 caps (1000 mg) BID thereafter
** 1,500mg BID
*** max daily dose = 2,700mg

Options for Bipolar Depression

• Lithium
• Anticonvulsants: (divalproex, carbamazepine, lamotrigine)
• Second-Generation Antipsychotics:
  (quetiapine**, olanzapine+fluoxetine combination**, lurasidone)**
• Adjunctive medications: (ADs, pramipexole, T3
  modafinil/, folate, Vit. D3, N-acetylcysteine, etc)
• Adjunctive psychotherapy
• ECT, rTMS, sleep deprivation+phase advance
  ** Only AAs are FDA approved

In Refractory Bipolar Depression:

• Be carefully therapeutically aggressive
  and clinically innovative.
• Test what really works in your Individual Patient.
• Your Patient’s Response/Nonresponse/SE’s trumps
  all guidelines, FDA approval, and academic pronouncements.

One Schema for Treatment of Rapid Cyclers

Combination Treatment

<table>
<thead>
<tr>
<th>Lithium + VPA</th>
<th>Lithium + CRZ/OXC</th>
<th>Lithium + LTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Depressive state)</td>
<td>(Schizoaffective, BPI)</td>
<td>(Depressions predominates)</td>
</tr>
</tbody>
</table>

Adjuncts

A. For Agitation/Insomnia: CLONAZEPAM, LORAZEPAM, OR GABAPENTIN
B. For Psychosis: ATYPICAL ANTIPSYCHOTICS
C. For Persistent Cycling: THIRD MOOD STABILIZER
D. For Weight Loss: TOPIRAMATE, ZONISAMIDE, Bupropion + Naltrexone
E. For Alcoholism: TOPIRAMATE, NAC
F. For Ultradian Cycling: NIMODIPINE (dihydropyridine Ca++ blocker)
G. For Atypical Depression: MAOI
H. For Cocaine: TOPIRAMATE, MODAFINIL, NAC

Altering Long-term Memories & Habits in the RECONSOLIDATION WINDOW

Event
Activation of Glutamate
NMDA-R

Short Term
memory
(Hippocampus)

CONSOLIDATION
(new protein synthesis & BDNF)

Long Term
memory
(Cortex)

RECALL of memory
Memory trace is transiently table

New Learning in Re-consolidation Window

5 minutes to 1 hour
(requires NMDAR activation in medial PFC)

Permanently Revised long-term memory
Extinction of Cocaine/Heroin Addiction by Opening the Reconsolidation Window

Xue et al., Science 2012

Day 1

Pretest: Cue

Delay

10-minute delay

Recall

5-minute video of drug cues to achieve memory recall

Extinction Training

60-minute Extinction Training: 4 sessions, 3 cues/session

Post test:

Cue:

• Craving Gone

• No Blood Pressure Increase

• No spontaneous, cue-, or stressor-induced relapse

(16-hour delay NOT effective)

(Neutral video NOT effective)

Day 2

Day 4, 34, 184

Extinction

Delay

LI

SSRI

CA+

Extinction

Day 5

Fear Renewal
Cue in the
fMRI

Day 3 fMRI Results

Agren et al 2012

10 minute group:
Extinction WITHIN the
Reconsolidation
Window:
NO AMYGDALA
SIGNAL:
“IT HAS BEEN ERASED”

6 hour group:
Extinction Outside of the
Reconsolidation
Window

Strong Amygdala
Activation Persists &
Connectivity to other
centers in the fear circuit
(ACG, insula, hippo.)

Disruption of Reconsolidation Erases
Amygdala Fear Memory Trace in Humans

Agren et al Science 2012

Day 1

Fear Conditioning

Extinction Training

16 shocks paired with visual cue

Visual cue

Memory Recall

Day 2

Extinction Training

8 cues … (No Shock)

Extinction Window

Memory Recall

10 minute group:
NO RETURN OF FEAR

Day 3

Fear Renewal
Cue in the
fMRI

Consolidation:

Disrupted in
10 minute group

6 hour group:
FEAR RETURNS

Day 4, 34, 184

Extinction

Delay

LI

SSRI

CA+

Extinction

Day 5:
Extinction Training

(Outside Reconsolidation Window)

Amygdala Trace Robust

At 10 minutes Extinction Training
Amygdala Trace Erased

Memory TRACE Of Conditioned Fear REMOVED

Agren et al., Science 2012

Day 5: 6 hour group
FEAR & AUTONOMIC
REACTIVITY PERSISTS

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FEAR & AUTONOMIC
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Day 5: 6 hour group
FEA...
Early Onset Bipolar Illness is Associated with a Poor Prognosis as Adults

- More Recurrences
  - Mania
  - Depression
- Less Euthymia
- More Days Depressed
- More Days Manic
- More Wks Irritable
- Dysphoric Mania
- Rapid Cycles (Lifetime & Current)
- Ultradyn Cycles
- INCREASED SUICIDE ATTEMPTS
- MORE COMORBIDITIES:
  - Anxiety Disorders
  - Substance Abuse: Alcohol
  - Drug Abuse

Two Thirds of Bipolar Disorder in Adults in the US Begins in Childhood or Adolescence

- Early Onset Bipolar Disorder is Associated with 10 to 15 YEARS DELAY to First Treatment (Post et al 2010)
- Duration of DELAY to First Treatment is an Independent Predictor of a Poor Outcome in Adulthood
- Most Children with Bipolar Disorder Are Not in Treatment (Merikangus et al, 2011); only 22% are
- In Carefully Diagnosed Children with BPD; 37% Treated in the Community Never Received Any Consensus Recommended Treatment (Li, MS, AA) During 8 Years of Follow Up (Geller et al 2010)

Two thirds of bipolar disorders in adults in the US begins in childhood or adolescence. Early age of onset increases the risk of more recurrences and decreases the risk of euthymia. More children with bipolar disorder are not in treatment compared to adults. Early onset is associated with longer delay to first treatment and poorer outcomes.

Investigators in the Bipolar Collaborative Network (BCN)

- United States
  - UCLA
  - Los Angeles
  - 3. Cincinnati
  - Paul Keck
  - Sue McElroy
  - UT SW
  - Dallas
  - Trisha Suppes
  - NIMH
  - Bethesda
  - 4. Munich
  - Gabriele Leverich
  - Robert Post
  - 2. Freiburg
  - Jörg Walden
  - 3. Munich
  - Heinz Grunze

- Europe
  - HC Rumke Group Utrecht
  - Willem Nolen
  - Ralph Kopka

More Vulnerability Factors and Illness Adversity in the U.S. Compared to Europe:

- In U.S. More:
  - GENETIC Risk Factors:
    - Parental and Grandparental Psychiatric Illness
    - Assortative Mating
  - III. ADVERSE COURSE OF ILLNESS:
    - Earlier Age of Illness
    - More Episodes (> 20 and R.C.)
    - More Anxiety Disorder
    - More Substance Abuse
    - More Medical Comorbidities
- II. ENVIRONMENTAL Adversity
  - Childhood Abuse
  - Loss of Social Support
  - Financial/Employment
  - Health and Care Access
- IV. Treatment NONRESPONDERS
  - Fewer Well on entry
  - Fewer long-term Responders (for > 6 months) to naturalistic treatment
Bipolar Disorder in US Compared to the Netherlands and Germany

Greater Stressors Environmental

Greater Illness Burden and Treatment Resistance in US than in Europe

More Cross Sensitization

More Drug & Alcohol Sensitization

More Affective Disorders

Greater Episode Sensitization

Each Type of Sensitization and Cross-Sensitization Can Be Prevented with Appropriate Treatment Interventions

Stress Sensitization

Substance Abuse Sensitization

Episode Sensitization

• Psychoeducation
  - Primary Prevention
  - Tertiary Prevention

• Social Support

• Psychotherapy

• Stress Coping

• Family Rx

More Episodes and/or Rapid Cycling Is a Predictor of Poor Response to Treatment of Bipolar Illness

I. Naturalistic Treatment Post 2004; Nolan 2005

II. Mood Stabilizers (M.S.)
  - Lithium >14 studies (but see Baldessarini & Tondo 2000)
  - Carbamazepine
  - Lamotrigine
  - Valproate (Accelerating course) Calabrese; Post 2012(t)

III. Atypical Antipsychotics (A.A.)
  - Olanzapine Ketter 2006; Berk 2011

IV. Antidepressant Augmentation of a M.S.
  - Venlafaxine Post 2006
  - AD Ghaemi 2010; Post 2012(t)

V. Benzodiazepines Post 2012(t)

VI. Cognitive Behavioral Therapy (CBT) Scott, 2006

Lithium: Under-utilized in the U.S.

I. Lithium (Li) is superior to Valproate clinically
  - A. Significant prophylaxis of depressive episodes
  - B. Antisuicidal effects occur:
    1. At therapeutic levels in mood disorders
    2. In trace levels in water (in studies in Texas, Austria, Japan)

II. Li increases ratio of cell survival (BDNF and BCl-2) to cell death factors (BAX and P-53)
  - A. Li increases hippocampal volume
  - B. Li increases prefrontal grey matter
  - C. Decreases incidence of Alzheimer's (preliminary data)
  - D. Prevents progression from mild cognitive impairment (MCI) to dementia in normal elderly women (150 mg/day)

Stages of Bipolar Illness Evolution

- Manic and Depressive Episodes
  - Decrease BDNF & Increase Oxidative Stress and Are Associated with
    Decreased Prefrontal Cortex Structure and Function & Increased Amygdala Function

- An Increased Number of Depressions Is Associated with:
  - Greater Cognitive Dysfunction
  - More Disability
  - Treatment Refractoriness
  - Late Life Dementia
  - Medical Comorbidities
  - Loss of Short Telomeres

Affective Episodes Likely Alter the Brain: Long Term Prevention Must Be the Primary Goal
Efficacy of Family Focused Therapy (FFT) for High Risk Children
D. Miklowitz, K. Chang et al 2012

40 youth (x age = 12 ± 3 yrs; range 9-17)
First degree relative with Bipolar Disorder
Early symptoms: BPNOS; MDD; or Cyclothymia
12 sessions FFT vs Education Control (1-2)

Results:
- FFT: More RAPID RECOVERY
- More weeks in REMISSION
- Lower rise in YMRS over 1yr
- Effects greatest in high expressed emotion families

RECOMMEND FFT FOR AT-RISK PRODROMAL CHILDREN

Early Recognition and
Concerted Prophylactic Treatment
Hopefully Can Convert the Recurrent Affective Disorders into More Benign Illnesses

For Bipolar Disorder:

“An Ounce of Prevention, Is Worth a Pound of Cure”
(Or Many Pounds of Pharmacotherapy)

Specialty Clinic Superior to TAU
Lars Kessing et al Brit J. Psy. 2013

Two years of Specialty Clinic Rx led to fewer relapses over the next 6 years in those with a first hospitalization for mania
(Clinic offered psychoeducation, cognitive behavior therapy, monitoring and early detection strategies)

Summary/Conclusions:

Rapid cycling, depression, and comorbidities are common and highly treatment resistant.
Treatment requires multimodal complex combination therapy.
Antidepressants should be avoided (F-A-L-A-P).
Treatment resistance, cognitive dysfunction, and medical comorbidities increase as a function of number of episodes.
A new mantra for patients and clinicians:
“Prevent episodes, protect the body and the brain”