Recognition of Childhood Onset Bipolar Disorders: An excess in the US and what we should do about it

Robert M. Post, MD
Editor: www.bipolarnews.org
(click on Child Network)

Maryland Psychiatric Society
PSYCHOPHARMACOLOGICAL UPDATE
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Potential Conflicts of Interest

Speaker for: (drug discussed)

Astra Zeneca……..(quetiapine, Seroquel),

Sunovion…… (lurasidone, Latuda),

Validus…….. (long acting CBZ, Equetro),

Takeda……. (vortioxetine, Trintellix), &

Pam Labs…… (l-methylfolate, Deplin)

Investigators in the Bipolar Collaborative Network (BCN):

4 sites in United States

1. **UCLA Los Angeles**
   - Lori Altshuler
   - Mark Frye
2. **UTSW Dallas**
   - Trisha Suppes
3. **Cincinnati**
   - Paul Keck
   - Sue McElroy
4. **NIMH Bethesda**
   - Gabriele Leverich
   - Robert Post

3 sites in Europe

1. **HC Rumke Group Utrecht**
   - Willem Nolen
   - Ralph Kupka
2. **Freiburg**
   - Jörg Walden
3. **Munich**
   - Heinz Grunze

In BCN, 956 patients were studied and treated longitudinally

More Familial Psychiatric Illness and Psychosocial Adversity in the U.S. Compared to Europe

In U.S. THERE WAS MORE:

I. GENETIC/FAMILIAL Risk:
- A. Grandparental Illness
- B. Parental Illness
- C. Sibling & Spouse
- D. Offspring Illness

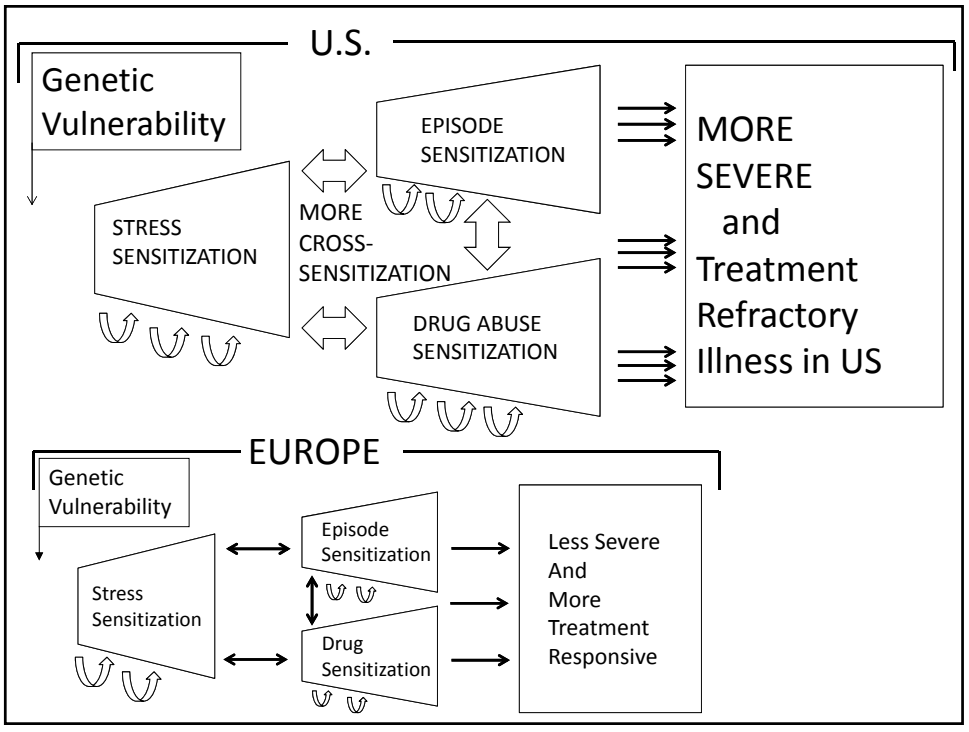
II. ENVIRONMENTAL Adversity
- A. Childhood Abuse
- B. Loss of Social Support
- C. Financial/Employment
- D. Health and Care Access

III. Adverse COURSE OF ILLNESS:
- A. Earlier Age of Illness
- B. More Episodes (> 20 and R.C.)
- C. More Anxiety Disorder
- D. More Substance Abuse
- E. More Medical Comorbidities

IV. Treatment NONRESPONDERS
- A. Fewer Well on entry
- B. Fewer long-term Responders (for ≥ 6 months) to naturalistic treatment

This equates to more recurrent stressors, episodes, and substance abuse in the US

- 1) Stressors, 2) mood episodes, and 3) bouts of substance abuse each shows sensitization effects (increased behavioral reactivity) upon their recurrence and cross- sensitization to the two others.
- Sensitization is mediated by memory-like epigenetic effects yielding long lasting alterations in gene transcription which further drive the downhill spiral of illness progression.



Avoiding Treatment Resistance

- I. Attempt primary prophylaxis in those at high risk
- II. Treat Prodromal syndromes
- III. Treat continuously (preventively) after 1st mania
- IV. Prevent illness recurrence and progression
- V. Treat anxiety and substance abuse comorbidities
- VI. Use intensive multi-modal treatment for Rx refractory patients
- VII. More medications with different mechanisms of action will be required

Two Thirds of Bipolar Disorder in the U.S. Begins in Childhood or Adolescence (< age 19)

	United States vs	Elsewhere
Post et al 2014 BCN	U.S **69.2%**.....	Netherlands/Germany **32.2%**
Perlis 2004; STEP-BD	**66%**.....	
Bellivier 2012 Pittsburgh Registry	**63%**.....	10 European Countries **25%**
Etain et al 2013 Metabolome data	**68%**.....	France **42%**
Holtzman et al 2015 Mean Age of Onset	Palo Alto **17.9** years..... +/- 8.4	Argentina **27.1 years** +/- 11.4

Early Onset is associated with Longer Delays to First Treatment.

- Both Early Onset and Treatment Delay are risk factors for poor outcome in adulthood.

--- Treatment delay is a remedial risk factor---

DELAY FROM ONSET OF BIPOLAR ILLNESS TO FIRST TREATMENT INDEPENDENTLY RELATES* TO WORSE IllNESS AS AN ADULT including :

Greater DURATION and SEVERITY of DEPRESSION,

More EPISODES, and

More Ultradian CYCLING

* by linear regression (Post et al 2010)

The following slides show that

US Patients with Bipolar Disorder Are Much Sicker than the Europeans;

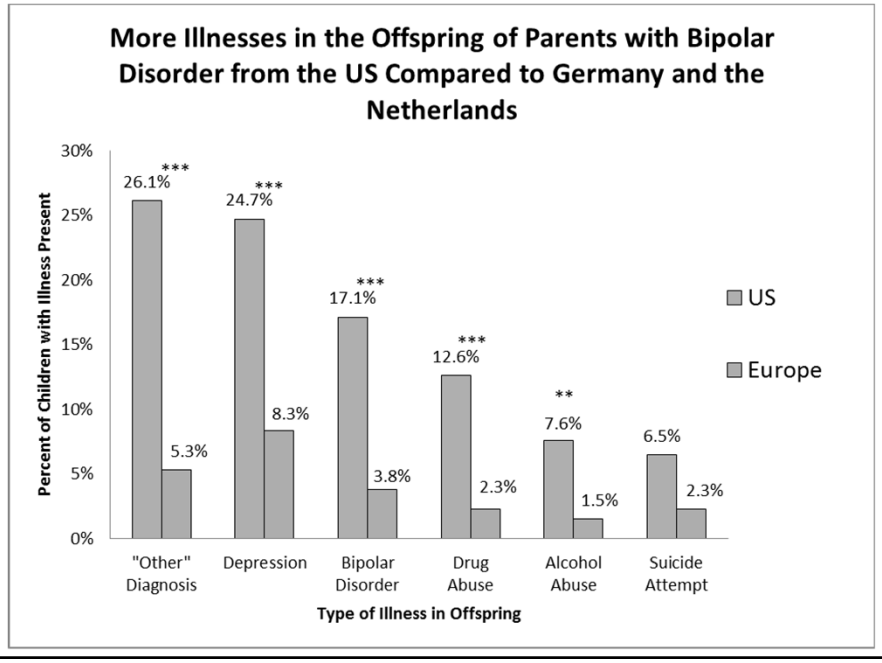
And so are there Offspring

US Patients with Bipolar Disorder Are More Ill Than The EUROPEANS

	US (N=676)	EUROPE (N=292)
ANXIETY DISORDER	46.6%***	28.1%
ALCOHOL ABUSE	33.1%***	14.7%
SUBSTANCE ABUSE	38.3%***	17.8%
RAPID CYCLING	74.1%***	41.5%
> 20 EPISODES	59.0%***	23.3%
Hospitalizations	Fewer**	More
PROSPECTIVE NON-RESPONDERS	51.7%***	31.1%

GREATER ILLNESS BURDEN IN OFFSPRING OF BIPOLAR PROBANDS FROM THE US vs EUROPE

Offsprings Dx :	US	Europe
• UP Depression	26.5%	8.9%
• Bipolar	17.8%	3.8%
• Suicide attempt.	6.0%	2.2%
• ETOH ABUSE	7.2%	1.4%
• SUBSTANCE Abuse	12.0%	2.1%
Other	24.9%	5.1%
• **Any Illness**	**36.3%**	**13.3%**



Banks et al , JAMA, 2006, concluded:

"**First, Americans** (55-64 years) **are much sicker (**medically***) than the English. Self reports are not deceiving us.."**

(* this includes: diabetes, hypertension, heart attack, stroke, lung disease, and cancer)

-- all confounders covaried --

It now looks like:

"**Children and their progenitors in the United States are much sicker (**psychiatrically**) than the Europeans"**

(Provisional- confounders not covaried)

EVEN GREATER ILLNESS BURDEN IN 74.2% of OFFSPRING OF A BIPOLAR PARENT IN A 7 YEAR PROSPECTIVE FOLLOW-UP STUDY in the US (AXELSON ET AL, 2015)

Offsprings Dx :	Axelson (BP)	US (BP)	Europe (BP)	US (Controls)
Depression	32.0%	26.5%	8.9%	4.9%
• Bipolar	22.5%	17.8%	3.8%	2.0%
• Suicide att'pt.		6.0%	2.2%	
• Alcohol Abuse		7.2%	1.4%	
• Substance Ab	19.9%	12.0%	2.1%	10.1%
Other (Anxiety)	39.9%	24.9%	5.1%	21.8%
• Any:	74.2%	36.3%	13.3%	46.8%

Remarkably, 46.8% THE OFFSPRING Of the COMMUNITY CONTROLS (Axelson et al, 2015) (ie, US PARENTS WITHOUT BIPOLAR DISORER) Have a Major Psychiatric Diagnosis on Follow up

4 Generations of Family Members of US Patients Are More Ill than the Europeans.

This includes:

IV. GRANDPARENTS

III. PARENTS

II. SIBLINGS & SPOUSES

I. OFFSPRING

(With few exceptions), EACH Generation of RELATIVES (I – IV) HAS MORE of Each of the Following Illnesses:

1.DEPRESSION

2.BIPOLAR DISORDER

3.SUICIDE ATTEMPTS

4.ALCOHOL ABUSE

5.SUBSTANCE ABUSE

6. "OTHER" ILLNESS

HEAT MAP:

Higher I.) FAMILY ILLNESS BURDEN and
II.) ADVERSITY IN CHILDHOOD
HAVE ADDITIVE EFFECTS ON EARLIER AGE OF ONSET OF BIPOLAR DISORDER

Average Age of Onset (years)

I.) Total Family Illness Burden	II.) Total Childhood Abuse 0	1	2	3
5	15	**12**	14	**5**
4	20	13	**12**	**9**
3	10	14	**12**	**9**
2	17	18	16	**12**
1	23	20	17	16
0	**26**	25	17	13

Mean age of onset is 26 years with no vulnerability factors; Onset is in childhood (<13 years) with high levels of both abuse and family illness burden

Other Early Onset Illnesses That Are More Severe Than Late Onset Illnesses

Include:

Huntington's Chorea

- Rheumatoid Arthritis
- Breast Cancer
- Diabetes
- Alzheimer's
- Multiple Sclerosis
- Schizophrenia
- Lupus
- Crohn's Disease

Question:
Is Childhood Onset Bipolar Disorder also in this group?

or

Is it just poorly recognized and treated?

IN EITHER EVENT CHILDHOOD ONSET BIPOLAR AND RELATED DISORDERS ARE A PUBLIC HEALTH CRISIS OF ENORMOUS PROPORTIONS AND CONSEQUENCES

PARENTS and GRANDPARENTS OF BIPOLAR PATIENTS in US versus EUROPE

HAVE MORE: DEPRESSION, BIPOLAR DISORDER, ALCOHOL ABUSE, SUBSTANCE ABUSE, and "OTHER" Illness

THIS FAMILIAL BURDEN BREEDS TRUE TO ILLNESSES IN THE PATIENT'S

SIBLINGS AND OFFSPRING

This MULTIGENERATIONAL POSITIVE FAMILY HX in the US IS ASSOCIATED with US PATIENTS with bipolar disorder having MORE:

CHILD ADVERSITY, EARLY ONSET BIPOLAR DISORDER, ANXIETY & SUBSTANCE ABUSE COMORBITIDY, MOOD EPISODES AND RAPID CYCLING

Each of these is associated with a poor long term prognosis

The Literature on Early Onset Bipolar Disorder and Treatment Delay Is Clear

I. Early Onset Bipolar Disorder Has a More Difficult Course

Carlson et al 2002
Carter et al 2003
Perlis et al 2004
Ernst & Goldberg 2004
DelBello et al 2007
Birmaher et al 2009 & 2014
Post et al 2010
Holtzman et al 2015

II. Early Onset Has a Longer Delay to First Treatment

III . A Longer Treatment Delay is Associated with a Worse Outcome in Adulthood

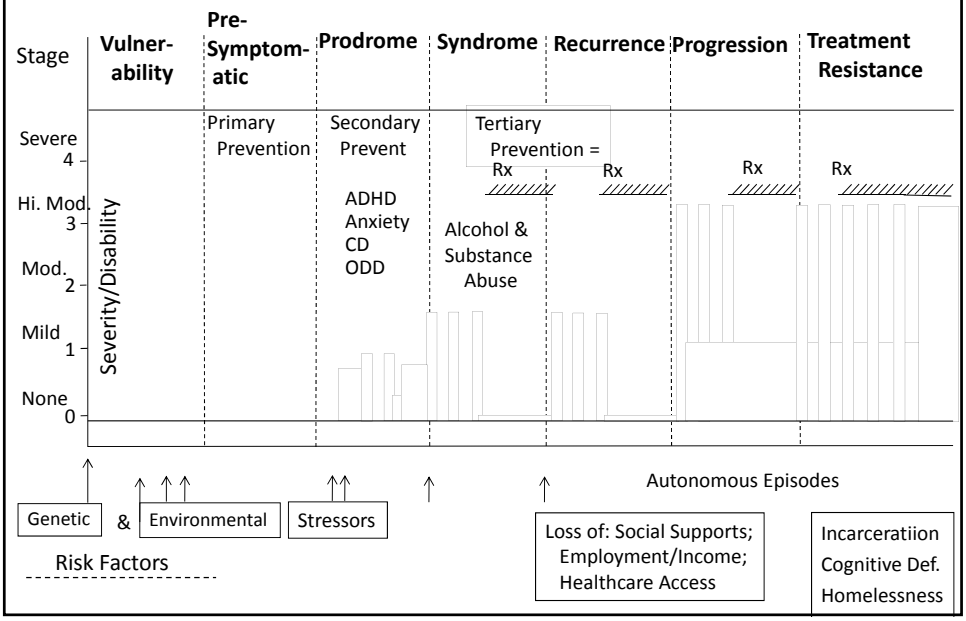
Suominen et al 2007
Morkin et al 2009
Post et al 2010*
*worse outcome independent of earlier age of onset

IV. Treatment Delay is a Remediable Risk Factor!

How will we address the epidemic of childhood onset psychiatric disorders in the US?

1. Ignore the data; find alternative explanations
2. Note the data, but play "ostrich"
3. Call for "more studies" …..OR
4. - Begin to actively address the problem with treatment studies that help generate new information and point to new directions for intervention.
   - Build on what works and discard what doesn't.
   - Combine science and practice.
   - A practical clinical trials network

Intervention Needed at Earlier Stages of Bipolar Illness Evolution



We Need to Be Alert to Childhood Onsets of Not Only Bipolar disorder, but also anxiety, depression, and externalizing disorders

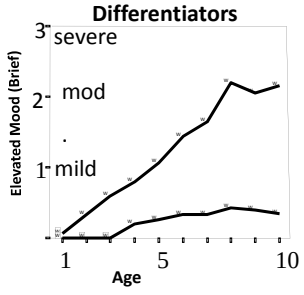
PEDIATRICIANS Need to Ask About Children's Psychological as well as Medical Health (Shonkoff and Gardner, 2012)

ADULT PSYCHIATRISTS Need to Ask about the Health of the ChIldren of their Patients with Bipolar Disorder and Depression (Post, et al 2017)

PARENTS Can take a proactive stance to assist clinicians in their child's evaluation. They can sign up for the Child Network at www.bipolarnews. org

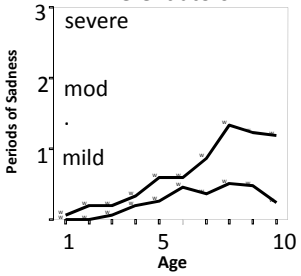
DISCRIMINATORS* OF PREPUBERTAL ONSET BIPOLAR DISORDER AND ADHD

EARLY, Persistent Differentiators



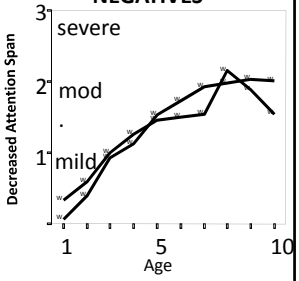
1) BRIEF (illustrated above)
Or 2) **EXTENDED MOOD ELEVATION**
3) DECREASED NEED FOR SLEEP
4) Greater Degrees of **Irritability**
5) Poorer **Frustration Tolerance**

LATER Differentiators



1) Periods of **SADNESS** (illustrated above)
2) **SUICIDAL** Thinking
3) Change in **Appetite**
4) **Physical** Complaints
5) Inappropriate **SEXUAL Behavior**

Pertinent NEGATIVES



1) Decreased **Attention** Span (see above)
2) **Hyperactivity**
3) **Impulsivity**
4) **Racing Thoughts**
5) Decreased **Self-Esteem**

•Based on Linear Mixed Model; Dysfunction For Each Symptom:

LACK OF TREATMENT AND APPROPRIATE TREATMENT IN THE US

- 2.2% of US children aged 13-18 have a bipolar spectrum diagnosis, yet Most Children Are Not in Treatment;

  Only 22% Are in Treatment (Merikangus et al, 2011)

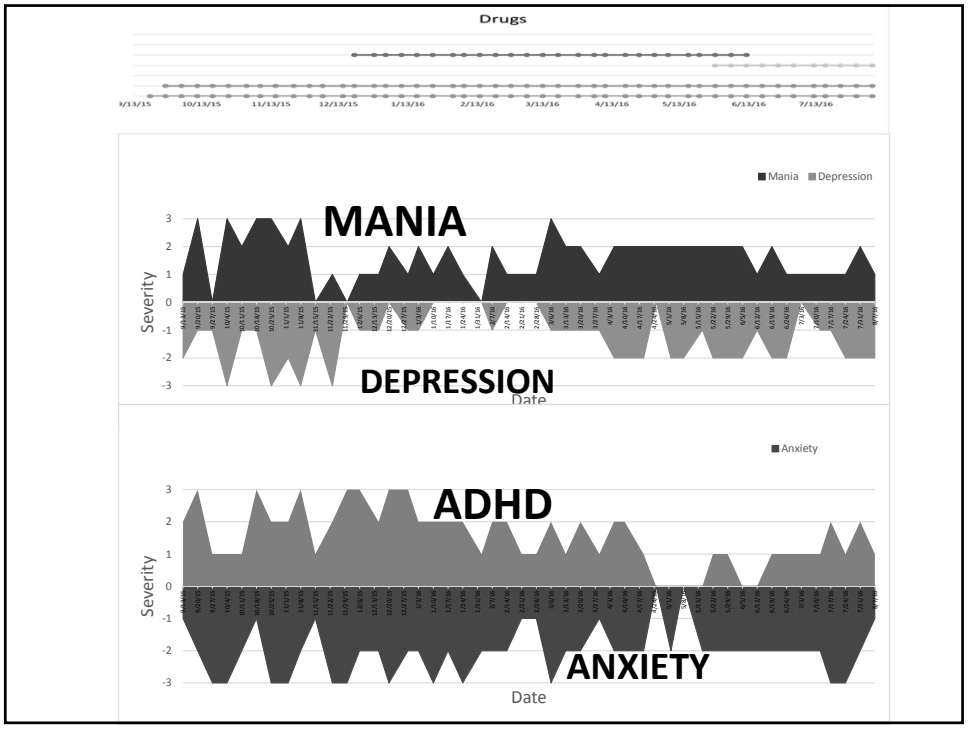
- In Carefully Diagnosed Children with BPD; 37% of the Children Treated in the Community Never Received Any Consensus Recommended Treatment (Li, MS, AA) During 8 Years of Follow Up. Those who received LITHIUM showed the most time in REMISSION. (Geller et al 2010)

CHILD MOOD DISORDER INITIATIVE

PARENTS CAN RATE THEIR CHILD (AGED 2 -12) ON SYMPTOMS OF ANXIETY, DEPRESSION, ADHD, OPPOSITIONAL BEHAVIOR, AND MANIA ON A WEEKLY BASIS ON A SECURE WEB SITE.

- INFORMED CONSENT AT www.bipolarnews.org (click on Child Network)

THE WEEKLY MOOD AND BEHAVIORAL RATINGS CAN BE **PRINTED OUT** TO PROVIDE PARENTS & CLINICIANS EASY VISUALIZATION OF SYMPTOM COURSE, NEED FOR TREATMENT, AND ITS EFFECTIVENESS



Very High Risk Children Because of Parental and Grandparental Illness Could Have:

A. Good Diet and Exercise Regimens

B. Family Psychoeducation

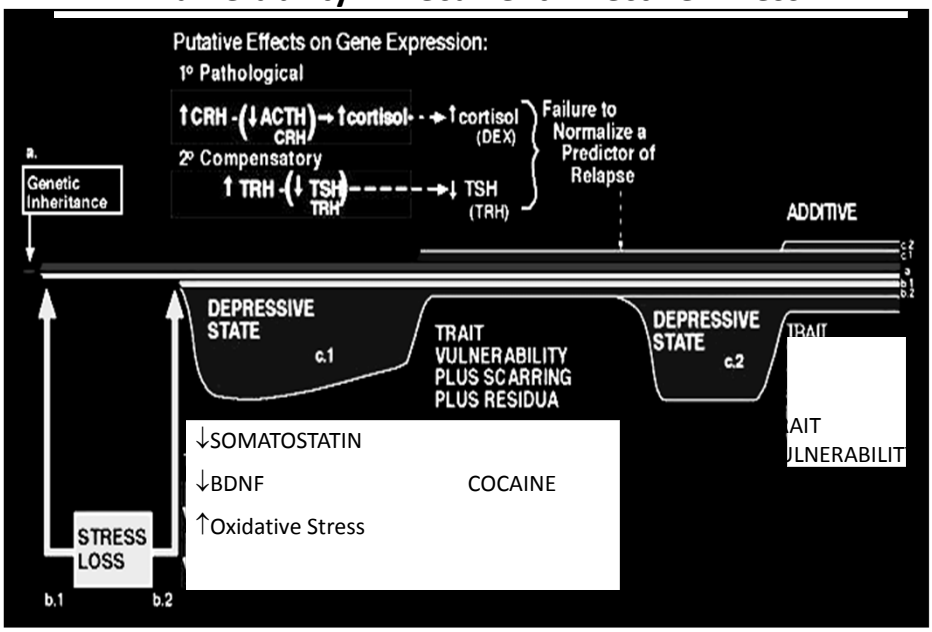
C. Coping Strategies/Cognitive Behavioral Therapy (CBT)

D. Mindfulness Training

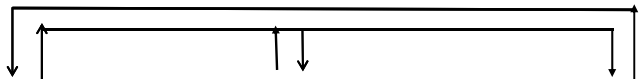
E. Mood Charting Longitudinally

F. Family Focused Therapy (FFT), especially for High Expressed Emotion

Prevent the Accumulation of Stress and Episode-Related Vulnerability in Recurrent Affective Illness



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



Stress Sensitization

- PSYCHOEDUCATION
- Social support
- Psychotherapy
- Stress Coping
- Family Rx

Substance Abuse Sensitization

- PSYCHOEDUCATION

Primary Prevention
•Rx of Risk factors

Tertiary Prevention
•Rx of Abused substances

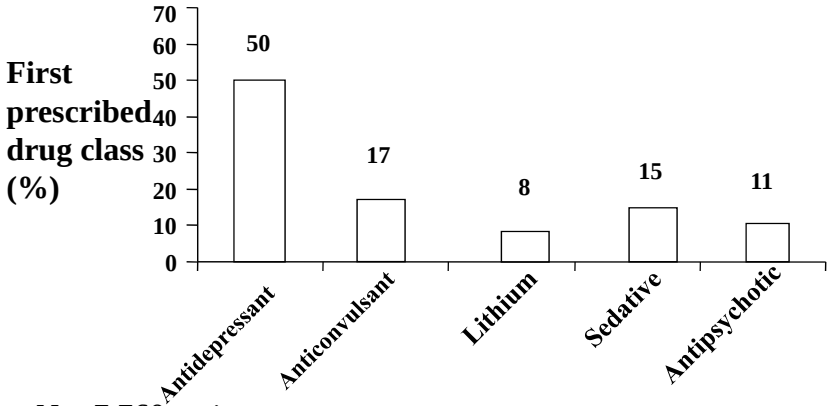
Episode Sensitization

- PSYCHOEDUCATION
- Early Initiation of Prophylaxis
- Combination treatment (Rx)
- Complex Rx of comorbidities
- Adjunctive Psycho Rx & Medications

Better Treatment of a Parent's Depression or Bipolar Disorder Results in Fewer Psychiatric Illnesses in the Offspring

Initial Treatment of Bipolar Disorders in the United States 2002–2003

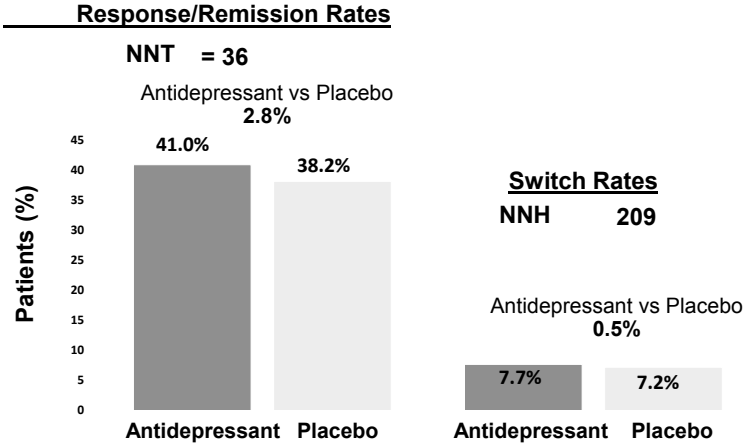
Antidepressant monotherapy twice as common as mood stabilizers



N = 7,760 patients with bipolar disorder; 69% BP I, 16% BP II, 14% BP NOS

Baldessarini R, et al. *Psychiatr Serv*. 2007;58(1):85-91.

Meta-Analysis: Antidepressants Are INEFFECTIVE in Acute Bipolar Disorder



Patients with bipolar I >> bipolar II. Response: ≥50% decrease in depression, SIDOR AND MACQUEEN, 2010 ratings.

NNH = number needed to harm; NNT = number needed to treat.

Sidor MM, MacQueen GM. *J Clin Psychiatry.* 2011;72:156-167.

Depression is three times more prevalent than mania in naturalistically treated patients with bipolar disorder.

(Judd et al 2002; Kupka et al 2007)

More than 2/3 of the patients were being treated with adjunctive antidepressants.

If antidepressants were highly effective in bipolar disorder, there would be a lot less time depressed.

Correlates of Antidepressant–Related Switching into Hypo/Mania

1. Younger Age (Martin et al)
2. BPI more than BPII subtype (Altshuler et al)
3. Rapid Cycling (> 4 episodes) in past year (Post et al)
4. "Mixed Depression", i.e.
   Activated, Speeded up, Racing Thoughts (Frye et al)
5. TCAs > 2nd Generation ADs
6. NE Active > 5HT or DA (Post et al; Vieta et al)
7. Substance abuse history (Goldberg et al)

New Message: Treat Intensively and Continuously After a First Mania

AFTER A FIRST MANIA:

1. Randomization to **2 years of expert specialty clinic* leads to fewer relapses than with treatment as usual over the next 6 years!**
(*includes illness education, psychotherapy, drug Rx, mood monitoring)

(Kessing et al 2013)

2. **Cognition declines --**

And recovers only if there are no further episodes (Yatham et al 2017)

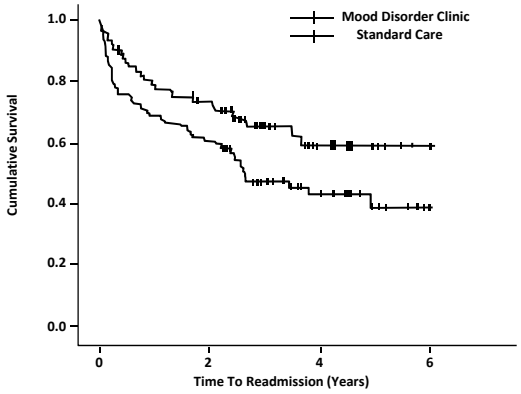
3. Randomization to

1 year of lithium is superior to quetiapine on all measures:
(ie. mania, depression, functioning, cognition, brain imaging)

(Berk et al 2017)

Randomized Specialty Bipolar Clinic vs Treatment As Usual (TAU)

- Specialty clinic for 2 years vs TAU showed markedly decreased relapses and enhanced compliance.
- Differences persisted and grew stronger over 6 years



Kessing, LV et al. *BJP.* 2013;2012:212-219.

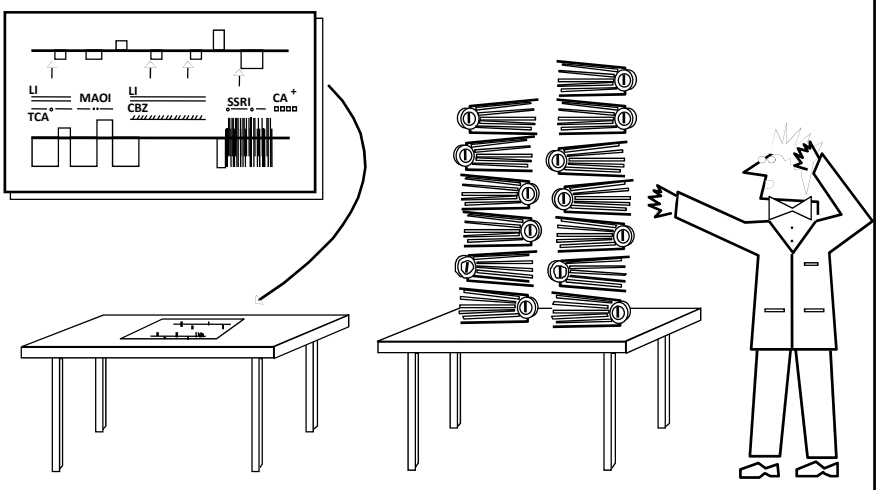
Early Expert Intervention and Patient Education Changes the Long Term Course of Illness

In Refractory Bipolar Disorder:

- Be carefully therapeutically aggressive and innovative.
- Test what really works in an individual patient*.
- Your patient's Response/Nonresponse/SE's trumps all guidelines, FDA approval, and academic pronouncements.

*Personal Calendar and Child Network weekly ratings available at: "bipolarnews.org"

A Life Chart Picture is Worth 100,000 Words



Personal calendar available: www. bipolarnews.org

More Prior Episodes or Rapid Cycling Predicts Poor Response to Almost All Treatments

I.	NATURALISTIC TREATMENT	Post 2004; Nolan 2005
II.	MOOD STABILIZERS (M.S.)	
	- Lithium	> 14 studies (except Baldessarini & Tondo 2000)
	- Carbamazepine	McKeon 1992; Otusa 1993; Denicoff 1997
	- Lamotrigine	Frye et al 2000; Obrocea 2002
	- Valproate (Accelerating course),	Calabrese; Post 2012(t)
III.	ATYPICAL ANTIPSYCHOTICS (A.A.)	
	- Olanzepine	Ketter 2006; Berk 2011
	- Any A.A.	Post 2010
IV.	ANTIDEPRESSANT AUGMENTATION OF A M.S.	
	- Venlafaxine	Post 2006
	- Any AD	Ghaemi 2010; Post 2012(t)
V.	BENZODIAZEPINES	Post 2012(t)
VI.	COGNITIVE BEHAVIORAL THERAPY (CBT)	Scott, 2006

For Bipolar Disorder:

"An Ounce of Prevention, Is Worth a Pound of Cure".....or

"A Few Hundred mgs of Prevention Is Worth 20 Kilograms of Acute Treatment"

Assets of Lithium: Beyond its Antimanic Effects

Lithium:

- Prevents unipolar and bipolar depressions
- Increases hippocampal and cortical volume
- Reduces dementia diagnosis in old age
- (150mg/day slows progression over 1 year of MCI)
- Has anti-suicide effects
  (at clinical doses and at miniscule doses in water supply)
- Increases and normalizes length of telomeres
- Reduces incidence of some neurological disorders; cancers

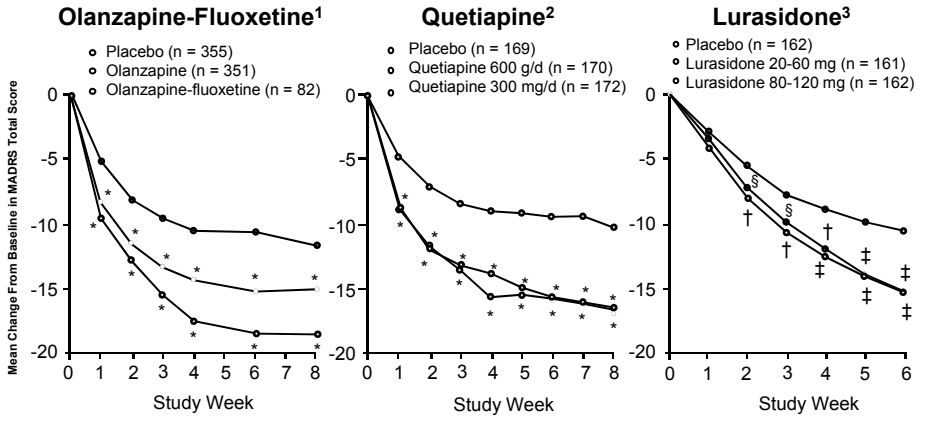
Lithium side effects have been over-estimated, and most can be avoided or dealt with

- LITHIUM CAN CAUSE CREATININE CREEP:
- Loss of renal function does not start for 15-30 years
- Is not associated with end-stage renal damage
- End-stage renal damage is more common with anticonvulsants
- Avoiding episodes of lithium toxicity may prevent damage

- LITHIUM CAUSES THYROID DYSFUNCTION
- This can readily be treated with thyroid replacement

- LOWER DOSES OF LITHIUM WILL AVOID MOST OTHER EFFECTS

Approved Agents for Bipolar Depression: AAs Work, (ADs Do Not)



*$P<0.001$; ‡$P\leq0.001$; †$P\leq0.01$; §$P<0.05$.

1. Tohen M et al. *Arch Gen Psychiatry*. 2003;60:1079-1088. 2. Calabrese JR et al. *Am J Psychiatry*. 2005;162:1351-1360. 3. Loebel A et al. *Am J Psychiatry*. 2014;171:160-168

Correlates of Response to Mood Stabilizers

Drug:	LITHIUM	CARBAMAZEPINE	VALPROATE	LAMOTRIGINE
Subtype:	BPI	BPII	BPI or II	BPI & II
Comorbid ● Substance Abuse:	None	Alcohol & Substance Use	Alcohol	
● Anx. Dx	No Anxiety	Anxiety (PTSD)	Anxiety (PTSD)	Anxiety (PTSD)
Manic Affect	Euphoric > Dysphoric	Dysphoric = Eurphoric	Dysphoric = Eurphoric	N.A.
Mood Incongruent Delusions	None	Yes, SA	±	±
Discrete Episodes	Episodic; Well Intervals	±	±	Cyclic, Continuous
Fewer Prior Episodes or ↓ Rapid Cycling	Yes	Yes	(± Yes)	Yes
Family Hx Positive	Bipolar Illness, Li Response	Negative for Bipolar Illness	?	Anxiety Disorders! & Substance Abuse
Single Nucleotide Polymorphism	5HT-T_{ss}			
Others	Antisuicide, Medical Morbidity	Paroxysmal Pain Syndromes	Migraine	For Prevention Not For acute Rx; slow titration required (serious rash)

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) Findling et al. (Children) Geddes et al. 2010, BALANCE
VPA plus lamotrigine (LTG) (better than VPA Alone)	Bowden et al.
Atypical Antipsychotics as Adjuncts to Lithium or Valproate (better than Li or VPA Alone)	Most AAs are FDA-Approved as Adjuncts to M.S.
Quetiapine plus lamotrigine	Geddes et al

Rationales for Complex Combination Therapy

- **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**

One Schema for Treatment of Rapid Cyclers

Start with Combination Treatment:

I. Lithium + VPA; (Dysphoric mania)	II. Lithium + CBZ/OXC; or (Schizoaffective, BPII) (Substance abuse)	III. Lithium + LTG (Depressions predominates)

Plus Adjuncts For:

A. **Agitation/Insomnia:** CLONAZEPAM, LORAZEPAM, OR GABAPENTIN

B. **Psychosis:** ATYPICAL ANTIPSYCHOTICS

C. **Persistent Cycling:** THIRD MOOD STABILIZER

D. **Weight Loss:** TOPIRAMATE, ZONISAMIDE, BUPROPION + NALTREXONE

E. **Alcoholism:** TOPIRAMATE, ZONISAMIDE, GABAPENTIN, NAC

F. **Ultradian Cycling:** NIMODIPINE (dihydropyridine Ca++ blocker)

G. **Atypical Depression:** BUPROPION, MAOI

H. **Cocaine:** TOPIRAMATE, MODAFINIL, NAC

Possible Treatment Sequences for Bipolar Depression As A Function of Family History, Presentation, and Comorbidities

II. FAMILY Hx: No BP
A. Carbamazepine (CBZ)

Targets:
1) BP II ++
2) Anxiety and Substance Abuse ++
3) Mood Incongruent Delusions ++
4) Continuous Cycling ++

Then begin A. through L. (as above)

I.FAMILY Hx POSITIVE UP OR BP
A. LITHIUM

III. Valproate VPA +/- Family Hx

Targets
1) Dysphoric Mania ++
2) Anxiety ++
3) Alcohol Abuse ++
4) Migraine +++

Then to A. through L. (as above)
(But at Step B. halve dose of LTG as VPA doubles LTE blood levels)

IV. Family Hx: Anxiety
A. Lamotrigine (LTG)

Targets:
1) BP II ++
2) Anxiety ++
3) Continuous Cycling

Then add A. Lithium and C. through L.

Treat Anxiety and Substance Abuse Comorbidities

(Note, Almost all of these treatments are off label)

Potential Treatments for Comorbidities:

Anxiety Disorders

Social Phobia	Panic/ Agrophobia	PTSD	OCD
Gabapentin (A,**A**)	Gabapentin (A,**A**)	SSRI's (A,**B**)	SSRI's (A,B)
Clonazepam (A,**A**)	Clonazepam (A,**A**)	Topiramate (C, A)	Atypicals (A,A)
Antidepressants (A,**B**)	Antidepressants (A,**B**)	Lamotrigine B, A****	N-acetylcysteine(A,A)
	Valproate (B,**A**)	N-acetylcysteine (AA)	Topiramate (A,A)
	Carbamazepine (C,**B**)	Carbamazepine (C,**B**)	Lamotrigine (D,B)
	Lamotrigine B,A****	Atypical Antipsy (A, A)	Carbamazepine (D,B)
		Benzodiazepine (E,D)	Gabapentin (D, C)

(Evidence in Primary Disorder = First Letter; **Utility in Bipolar = Second Letter)**

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

** **= Studied in Bipolar Disorder

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

Convergent Mechanisms of Cross Sensitization to Stressors, Episodes, and Cocaine Suggest that a Single Therapy Could Improve All Three

N-acetylcysteine (NAC) as a possible example

NAC Reduces:

**Addictions to:
Cocaine, Gambling, Alcohol, Marijuana, Nicotine.

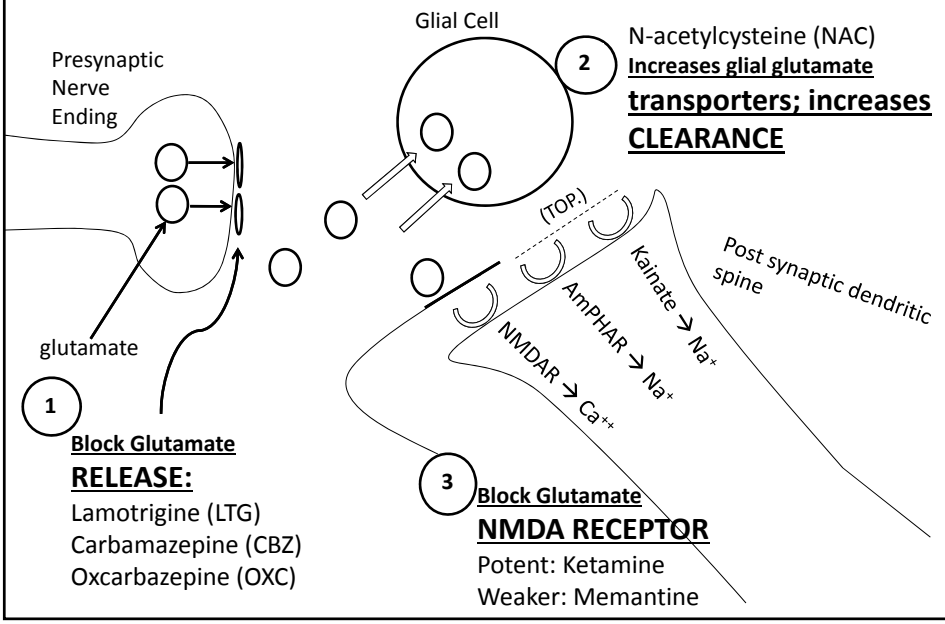
**Trichotillomania, OCD, PTSD

**Depression and Anxiety in Bipolar Disorder

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

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

Decreasing Glutamate-Induced Neuronal Hyperactivity that Drives Habits and Addictions



Non-Antidepressants that are effective in bipolar depression: What are the mechanistic differences?

Effective in Acute Depression:

- Somatic treatments
  - ECT, rTMS, VNS
- Ketamine,
  Sleep deprivation
  Modafinil
- Pramipexole
- Atypicals
  - olanzepine/fluoxetine
  - quetiapine
  - lurasidon

Prevent Depressive Recurrences:

- Lithium
- Lamotrigine
- Quetiapine
- Cognitive Behavioral/ Family Focused Therapy
- Psychoeducation

Most also increase BDNF, but not through the adenylate cyclase, PKA path like the ADs

Treatments for Bipolar Comorbidities: Substance Use/Abuse Disorders

Alcohol

Abstinence

- Naltrexone (A,A)
- Acamprosate (A,B)
- Disulfiram (A,D)
- Topiramate (A,A)
- 12 Step (A,A)
- Valproate A,A**
- NAC (A,A)
- Lamotrigine (C,C)**

Withdrawal

- Benzodiazepine (A,A)
- Carbamazepine (A,A)
- Valproate (B,B)
- Gabapentin (A,A)

Cocaine

- Topiramate (A,A)
- Modafinil (A,A)
- 12 Step (A,A)
- Carbamazepine (C,C)
- Disulfiram (A,D)
- N-acetylcysteine-A,A
- Baclofen (A, but poor choice for bipolar = D

Nicotine

- Bupropion (A,A)
- Nicotine P.(A,A)
- alpha7 agonist (A,B)
- NAC (A,A)

Food/Bulimia

- Topiramate (A,A)
- Zonisamide (A,A)
- Dexamfedamine (A,C)

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

SYMPTOM TARGETED SEQUENTIAL APPRAOCHES TO SEVERE PTSD +/- TBI
(1. - 6. from D. Bakish, 2014, see bipolarnews.org)

Symptom Target	Medications
1. Insomnia	Levetiracetam (Keppra) (150-500-1000mg) Trazodone (50-150mg)
2. Arousal / Depression	Desvenlafaxine (Pristiq)**
3. Substance Abuse Anger Attacks	Topiramate (Topamax) (100-400mg)
4. Depression & Cognitive Impairment	Buproprion (Wellbutrin)
5. Irritability, Flashbacks	Lamotrigine (Lamictal) (slow ↑ to avoid rash)
6. Mood Instability	Lithium
7. Irritability, Depression, Anxiety, Substance Abuse	N – Acetylcysteine (NAC) (1000mg BID)
8. Nightmares	Prazosin ** (slow ↑ to avoid hypotension)
9. Refractory PTSD	I.V. Ketamine

N-acetylcysteine (NAC)*: Efficacy in Repetitive Habit Disorders

I. DRUG ADDICTION
- Cocaine
- Alcohol
- Marijuana
- Nicotine**

II. GAMBLING ADDICTION.

III. TRICHOTILLOMANIA

IV. OCD (Augumentation of SSRI)

V. Stereotypy & Irritability in AUTISM***

VI. BP DEPRESSION

VII. UP DEPRESSION?

VIII. Negative Sx SCHIZOPHRENIA

IX. PTSD

* Typical dosing versus placebo: NAC 500mg B.i.d. for 1 week, then 2 caps (1000 mg) BID thereafter

** 1,500mg BID

*** max daily dose = 2,700mg

NMDA Receptor Blocker Differences

Serra et al 2012

I. A POTENT BLOCKER of glutamate NMDA receptors with high % trapping is
   i.v. KETAMINE: 0.5mg/kg over 40 min., rapid onset antidepressant effects

versus

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 with 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
At Baseline: (markedly to severely ill): CGI = 6.7

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

Novel Approaches to Treatment Resistance

1. Ketamine, i.v. – repeated vs. nasal, oral
2. Memantine (Namenda) potentiates lamotrigine [A. Anand] and stabilizes rapid cycles [Koukopoulos]
3. rTMS with therapy during stimulation enhances new learning with experience – dependent neuroplasticity
4. Right unilateral high intensity brief pulse ECT with intensive continuation (weekly for 6 weeks; then q. 2 weeks)
   [Nordenskjold et al, ECT, 2013]
5. Supraphysiological T4 100mg/day; weekly increases to 300mg/day
   [Mike Bauer]
6. Nimodipine blocks CACNAIC gene; with lithium augmentation or as an alternative [Choudhry et al 2010]
7. Anti-inflammatories and minocycline
   (if CRP, IL-1, IL-6, or TNF-alpha is elevated)

Drugs Targeting Multiple Comorbidities

NAC: (N –acetyl-cysteine) Cocaine, Alcohol, Gambling, Smoking, Marijuana, OCD (+SSRI)

VPA: (Valproate) Migraine, Anxiety Alcohol

Gabapentin: Anxiety Social Phobia Alcohol

Topiramate: Alcohol Cocaine Bulimia Anger Attacks

Zonisamide: Alcohol Bulimia

Modafinil: Cocaine ADHD Narcolepsy

Results of Ten Randomized Trials of Family Focused Therapy (FFT) plus Medications for Patients with BD (Miklowitz et al, 2017)

- Total 1,140 patients (adjunctive to medications)
  - Five trials with bipolar adults
  - Two with bipolar adolescents
  - Three with youth at high
  - Comparisons included brief psychoeducation or equally intensive individual therapy
- Patients in FFT had greater benefits over 1-2 years in:
  - Depression stabilization (Cohen's d = 0.49 to 0.56)
  - Recurrence risk (RR= 0.79)
  - Psychosocial functioning/Quality of Life (d = .96)

How's that?

Even good psychotherapy beats antidepressants for bipolar depression.

Summary/Conclusions

- Bipolar depression is relatively treatment resistant: evidence-based treatments should be used first, earlier, and more persistently
- Treatment requires multimodal complex combination therapy: "More medications, FEWER SIDE EFFECTS"
- Antidepressants should be avoided (F-A-L-A-P)
- Treatment resistance, cognitive dysfunction, and medical comorbidities increase as a function of number of prior episodes
- Patients need a new mantra:
  - "Prevent episodes, protect the brain and body"

Must Attempt to Stop Illness Progression

WHAT PROGRESSES?

1. Episodes come faster and more automatically
2. Stressors accumulate and sensitize
3. Substance abuse increases and sensitizes
   - 1,2,3; have long term epigenetic mechanisms
   - 1,2,3; each shortens telomeres
4. Cognitive dysfunction as function of number of episodes;
   - 4 lifetime depressions doubles risk of dementia in old age
5. Medical comorbidities
6. Loss of brain volume (prefrontal cortex)
7. Premature loss of years of life expectancy

New Principles: Treatment After First Manic Episode

I. Treat to remission (multiple medications often needed)

II. Start prophylactic treatment after first mania

- A. Kessing: 2 yrs. Expert clinic → fewer recurrences over next 6 years
- B. Yatham: cognitive defects improve with no further episodes
- C. Berk: 1 year of lithium superior to 1 year of quetiapine (on all measures)

III. Treat comorbidities and residual mood symptoms until remission achieved.

IV. Teach patients and families about the illness

- A. Need for treatment; mood charting; recognizing early symptoms
- B. Start pharmacotherapy and psychotherapy (especially if abused)
- C. Establish an E.W.S (early warning system) and fire drill (for crisis intervention)

V. Maintain full dose prophylaxis

GOAL: moderate the early course of illness to prevent the development of treatment resistance

The Bottom Line Is:
We should use lithium more

- And we should use lithium earlier:
- Later initiation of lithium is not as effective as after fewer episodes (8 of 9 studies)

- Starting lithium after the first manic episode is associated with a better outcome than starting quetiapine (Berk et al 2017), and it may have neuroprotective and cognitive protective effects.

Study Preventive Strategies for those at Very High Risk as a Function of the Risks of the Treatment Intervention

Prevention Type I, II, III:

I Primary	II Secondary	III Tertiary
Good Diet	Psychotherapy	Lithium (Li)
Exercise	N-acetylcysteine	Li + VPA
Omega-3-	Omega-3-	+ LTG
Fatty Acids	Fatty Acids	+ OXC/CBZ
Mindfulness	Minocycline	AA + CBZ
----------	E-M power	VPA
NO RISK	----------	OXC/CBZ
	LOW RISK Rx	LTG

		HIGHER RISK Rx

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 with FFT

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

RECOMMEND FFT FOR AT-RISK PRODROMAL CHILDREN

Potential Safe Early Interventions for At Risk and Prodromal Children

I. At Risk (US > Europe)
1) Parental and Grandparental psychiatric history
2) Child Adversity
3) Prodromal Symptoms and Syndromes

II. Well Interval
Especially
If At Risk

Exercise
Diet
Sleep
Mindfulness/ meditation

Parent Education & Close Observation of Child.
(If maltreated: O – 3 – F.A. NAC)

III. Prodrome
A. Syndromes
ADD
Anxiety
Depression
ODD
DMDD
Rx of Each Syndrome

Sub threshold Bipolar
B. Symptoms
Insomnia,
Cyclothymia,
BP-NOS
Melatonin
O – 3 – F.A.
Vitamin D3
Folate

Family Focused Therapy (FFT), Psycho-Education (PE), Cognitive- Behavioral Therapy (CBT), Mindfulness/Meditation, Mood Charting: Child Network (see www.bipolarnews.org click on Child Network)

IV. Full Syndrome
Hypomania/ Mania

Routine
Pharmacotherapy
to achieve remission
(i.e. Lithium,
Mood stabilizing,
anticonvulsant, and
atypical antipsychotic)

FFT; CBT
DBT for Adolescents
Illness Education

McGorry et al in Australia overcame stigma and political resistance to initiate widespread studies of identifying and treating prodromal schizophrenia.

It is time for physicians, advocacy groups, private foundations, and the NIMH to begin to address the epidemic of childhood onset psychiatric illness in the US in an equally innovative and productive way.

Your Earlier Recognition and

Concerted Prophylactic Treatment

Can Convert Bipolar Disorder into a

More Benign Illness