LITHIUM: Wider Range of Effectiveness and Fewer Side Effects Than Assumed

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Editor: www.bipolarnews.org
(click on Child Network)

Ashville, North Carolina
PSYCHOPHARMACOLOGICAL UPDATE
September 30, 2018

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)

Lithium: Present at the Origin of the Universe

- Lithium appeared 20 minutes after the Big Bang,
  supranova → fusion of hydrogen

- Quarks contributed to baryons, yielding
  Lithium (Li), Helium (He), Beryllium (Be)

- Salt (Na+Cl-) emerged millions of years after the Big Bang
- _____
- Without lithium, animals develop abnormally
- Lithium should be considered an essential element—
  daily dose of 1000mg/day for 70kg human

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

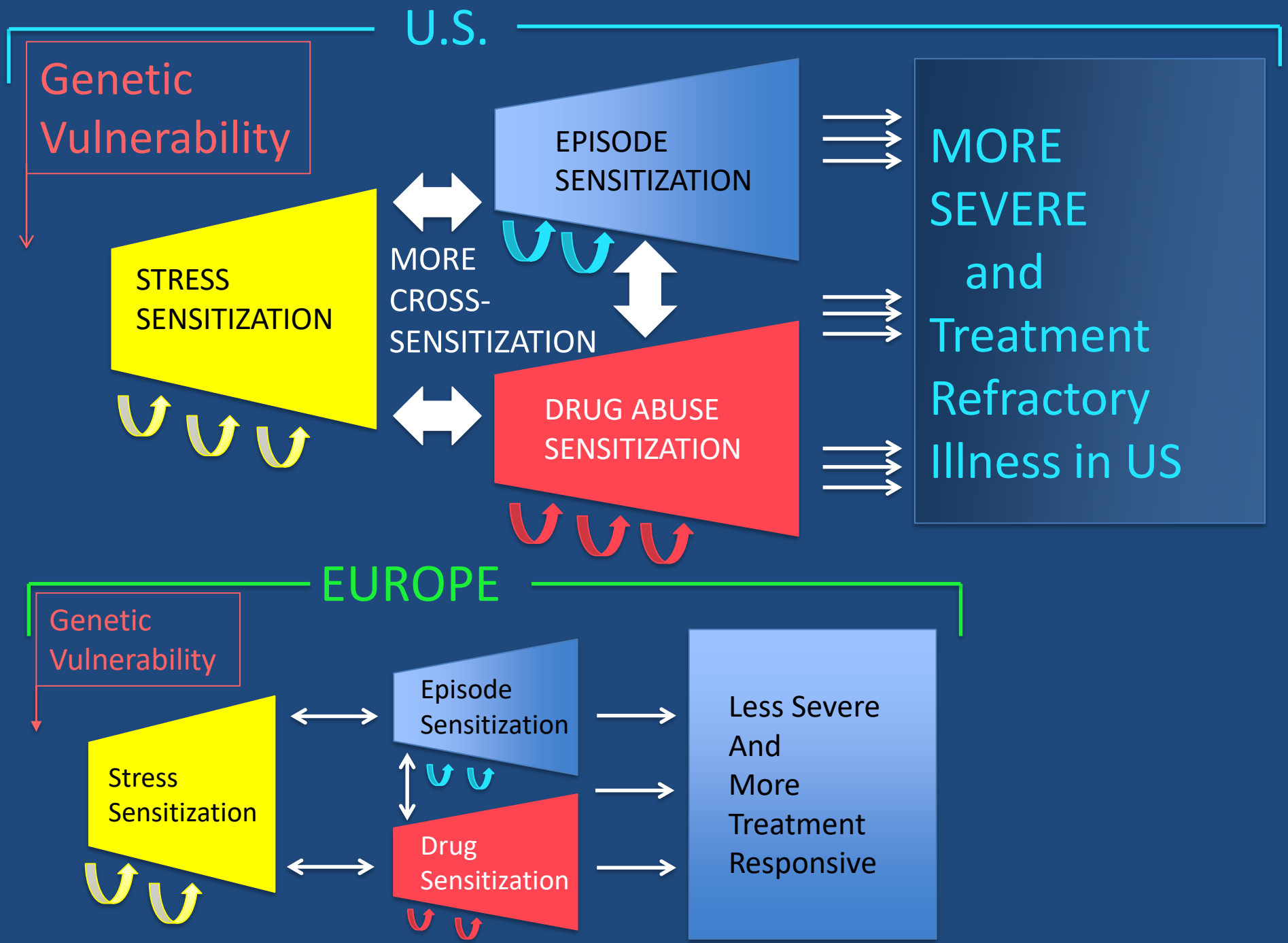
- A. Childhood Abuse
- B. Loss of Social Support
- C. Financial/Employment
- D. Health and Care Access

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


U.S.
Genetic Vulnerability
EPISODE SENSITIZATION
STRESS SENSITIZATION
MORE CROSS-SENSITIZATION
DRUG ABUSE SENSITIZATION
MORE SEVERE and Treatment Refractory Illness in US
EUROPE
Genetic Vulnerability
Episode Sensitization
Stress Sensitization
Drug Sensitization
Less Severe And More Treatment Responsive

Avoiding Treatment Resistance

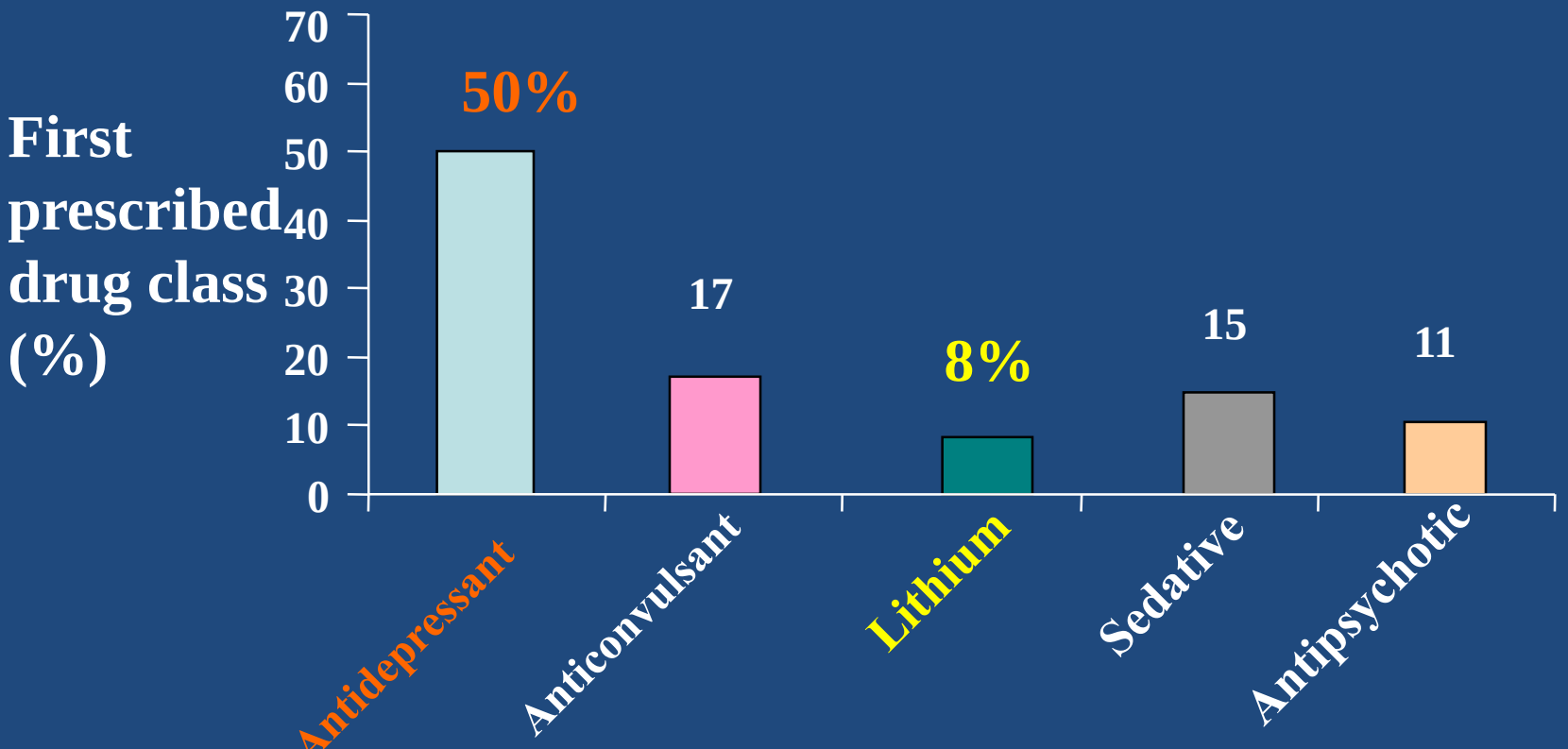
- I. Attempt primary prophylaxis in those at high risk
- II. Treat Prodromal syndromes
- III. Treat continuously (preventively) after 1st mania
- IV. Prevent illness recurrence and progression
- V. Treat anxiety and substance abuse comorbidities
- VI. Use intensive multi-modal treatment for Rx refractory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

Lithium is Under-Utilized in the Treatment of Bipolar Disorder

- This is particularly true in the US, were more anticonvulsant mood stabilizers, such as divalproex (valproate), and atypical antipsychotics are used, and, regrettably, antidepressants are the most widely prescribed drug class for newly diagnosed patients with bipolar disorder.

Initial Treatment of Bipolar Disorders in the United States 2002–2003: Not on Target

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.

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 Increases Every Kind of Stem Cell (Gallichio, 2011)

- **Bone marrow** (pluripotent hematopoietic stem cells)
- **Somatic induced pluripotent stem cells** (iPSCs) (lithium normalizes the increased excitability of iPSCs from bipolar patients)
- **Mesenchymal derived stem cells** (MSCs)
- **Brain Derived Neural Stem Cells** (NSCs)

Lithium Reduces Lesion Size in Animal Models of:

1. Stroke/ischemia (even AFTER the ligation of the middle cerebral artery)
1. Alzheimer's disease
2. Parkinson's disease
3. Tauopathies
4. Huntington's disease
5. AIDs encephalopathy

Lithium Reduces Rehospitalization in Unipolar Dep.

123,712 hosp. in Finland; mean follow up 7.7 years (1996-2012) in national registry. (J. TIIHONEN ET AL 2018)

LITHIUM LOWERED RISK OF RE-HOSPITALIZATION (HR 0.47)

Antidepressants didn't lower risk of re-hospitalization(HR 1.10)

Antipsychotics did not lower risk of rehospitalization (HR 1.16)
Except clozapine which did lower risk (HR 0.65)

LITHIUM RISK LOWEST WHEN USED WITHOUT AN AD (HR 0.33)

LITHIUM USED WITH A CONCOMITANT AD (HR 0.65)

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

Lithium: Once a day (od) is superior to b.i.d and t.i.d (Plenge, 1982)

<u>O.D. vs. 2-3x/day:</u>

<u>Increased convience/compliance</u>

- Decreased urinary volume
- Decreased number of sclerotic glomeruli
- Decreased fibrosis and atrophic granules

New Message: Treat Intensively and Continuously After a First Mania

AFTER A MANIC HOSPITALIZATION:

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 over the next year only if there are no further episodes

   (Yatham et al 2017

   and Demmo et al 2017)

3. Randomization to

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

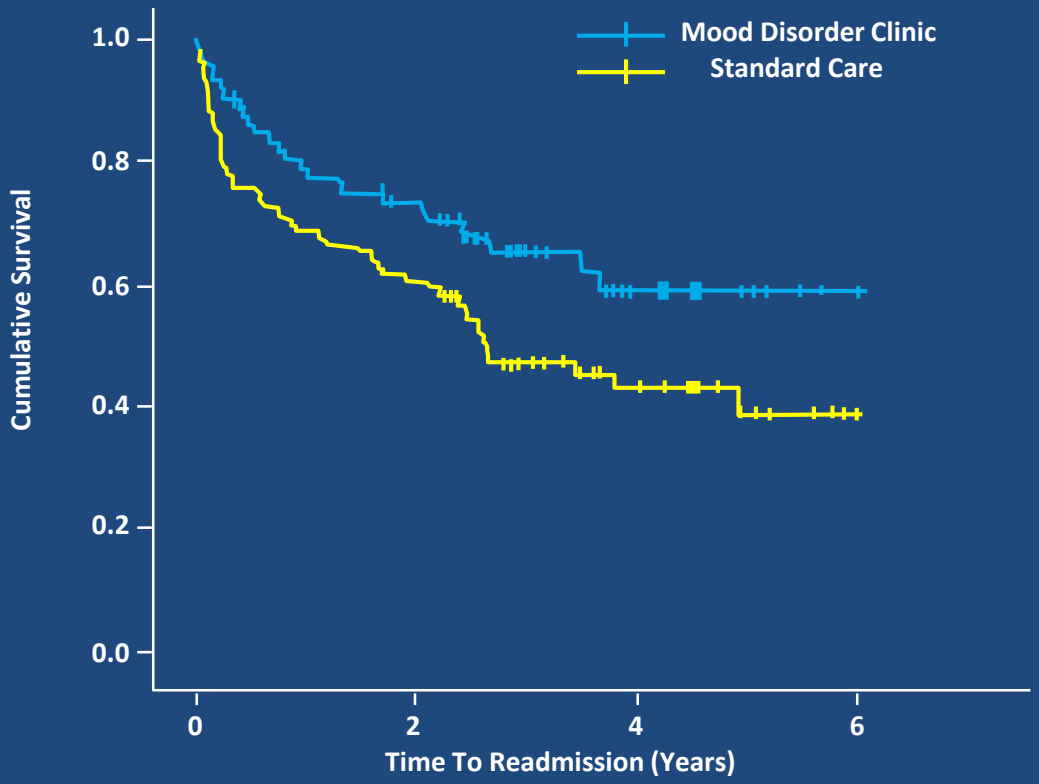
   (Berk et al 2017)

After a First Mania, One Year of Lithium Beats One Year of Quetiapine for:

1) Less mania
2) Better functioning
3) Better cognition
4) Better quality of life
5) Less depression
6) Less white matter reduction
7) More neuroprotective markers on MRS
8) More normalization of connectivity

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.

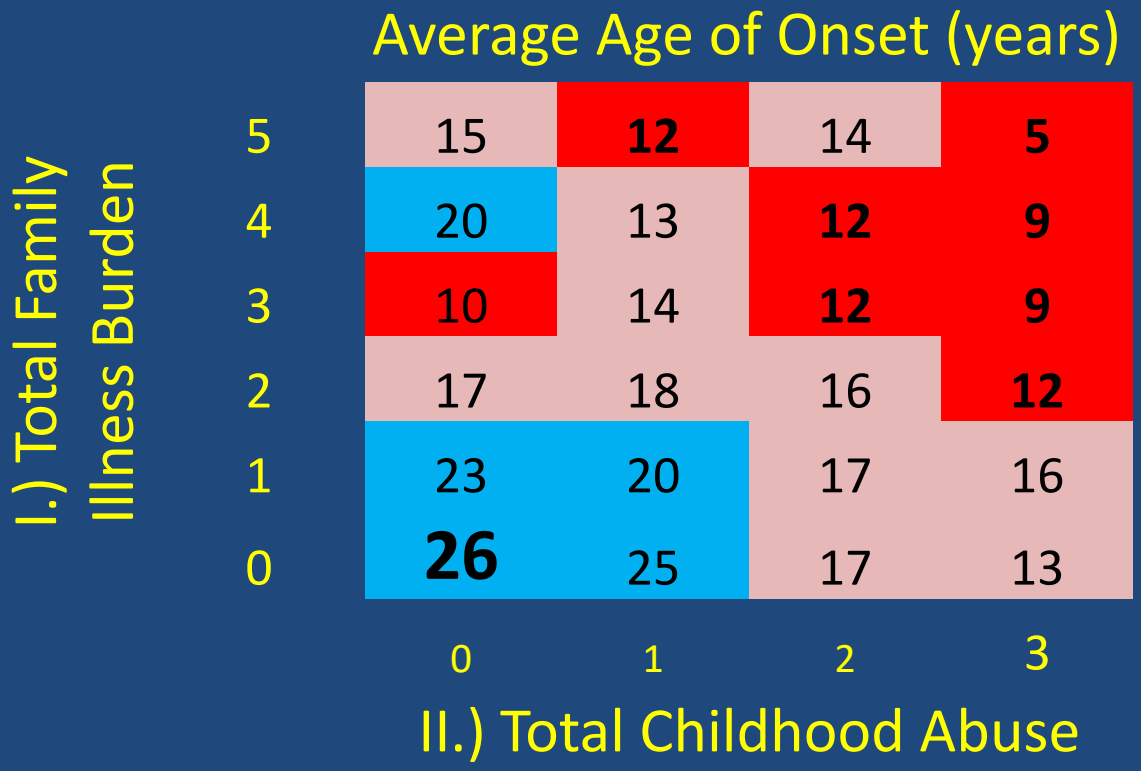
Early Expert Intervention and Patient Education Changes the Long Term Course of Illness

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

HEAT MAP:

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



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

Early Onset is associated with Longer Delays to First Treatment.

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

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

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%**

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%

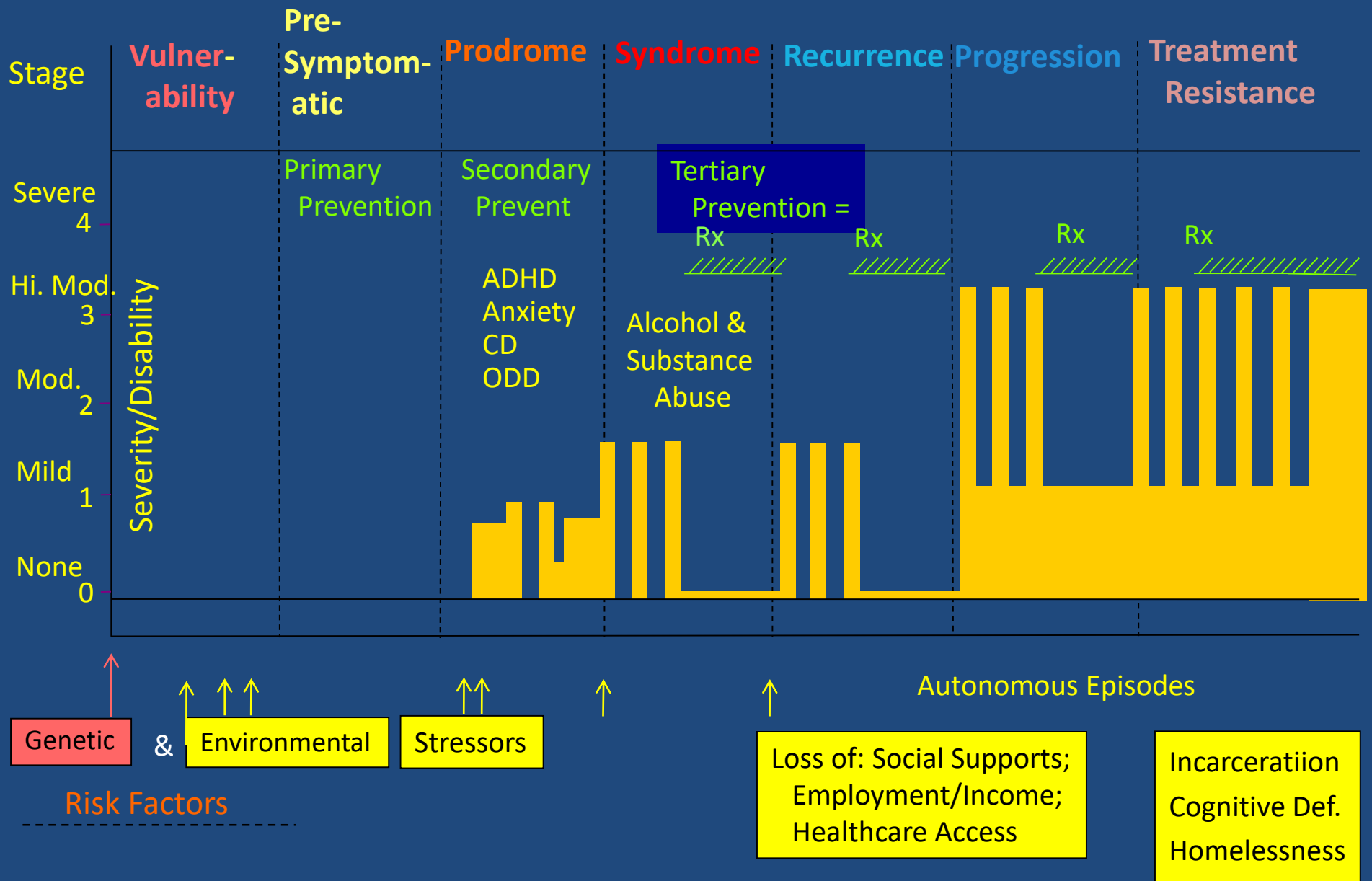
Remarkably, 46.8% THE OFFSPRING Of the COMMUNITY CONTROLS (Axelson et al, 2015) (ie, US PARENTS WITHOUT BIPOLAR DISORER) Have a Major Psychiatric Diagnosis on Follow up

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



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

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)

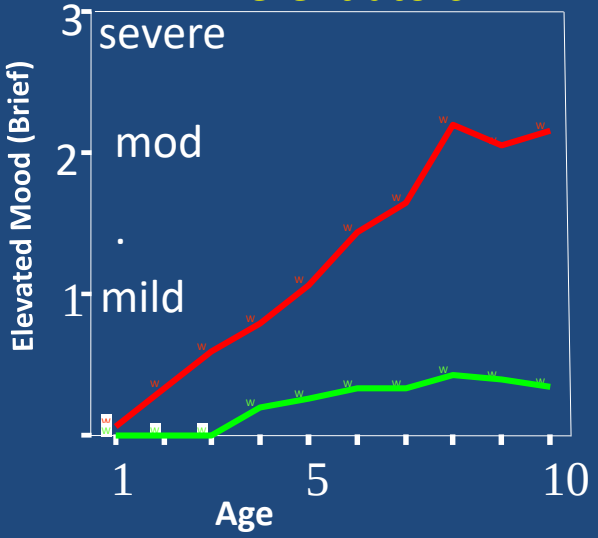
ADULT PSYCHIATRISTS Need to Ask about the Health of the ChIldren of their Patients with Bipolar Disorder and Depression (Post, et al 2017)

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

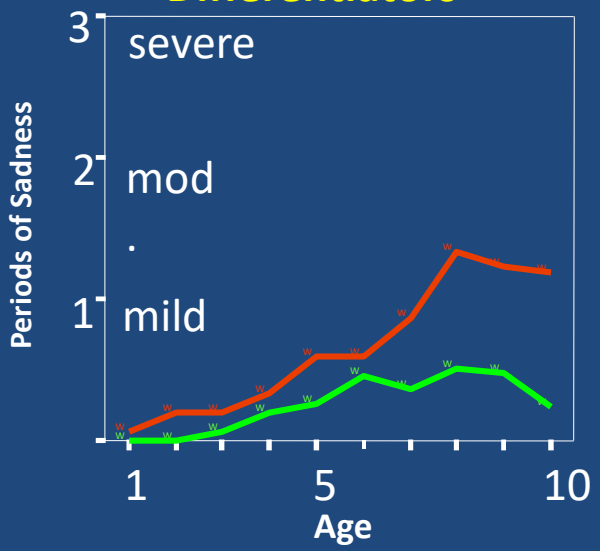
BIPOLAR DISORDER AND ADHD

EARLY, Persistent Differentiators



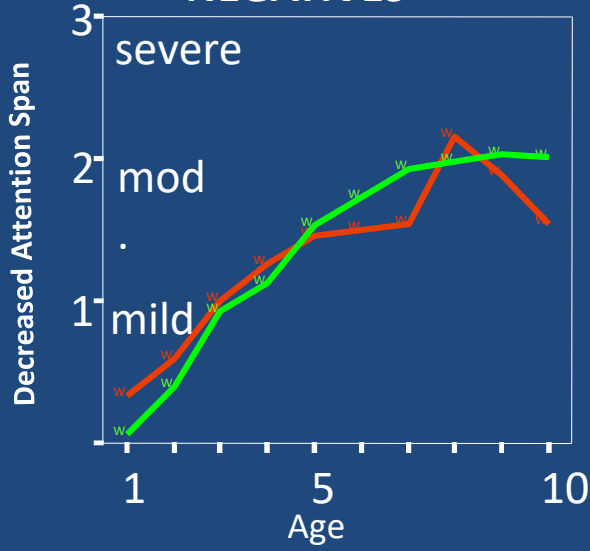
1) BRIEF (illustrated above)
Or 2) **EXTENDED MOOD ELEVATION**
3) DECREASED NEED FOR SLEEP
4) Greater Degrees of **Irritability**
5) Poorer **Frustration Tolerance**

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:

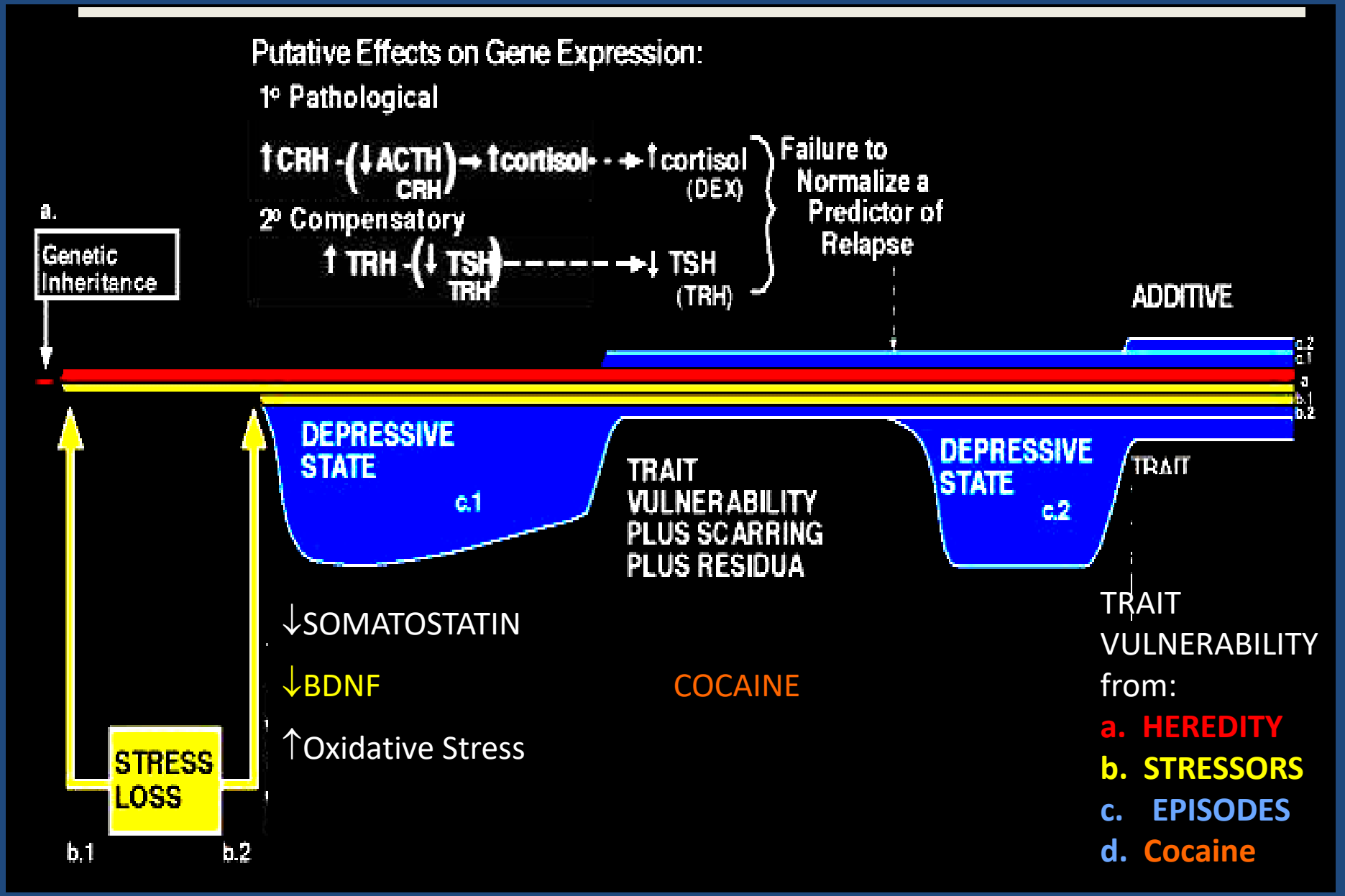
LACK OF TREATMENT AND APPROPRIATE TREATMENT IN THE US

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

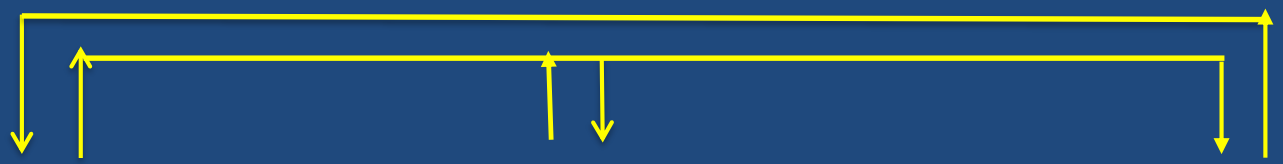
  Only 22% Are in Treatment (Merikangus et al, 2011)

- 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)

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

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

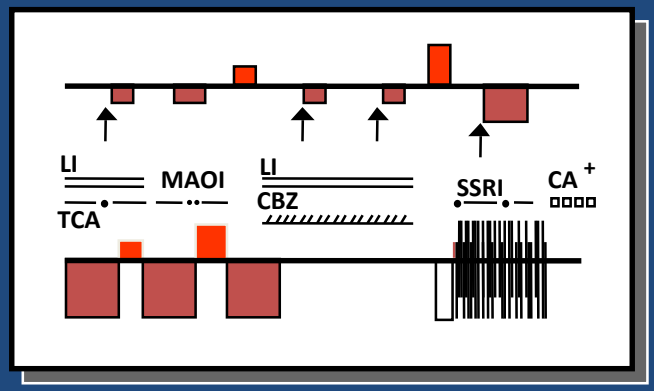
(Weissman et al 2006)

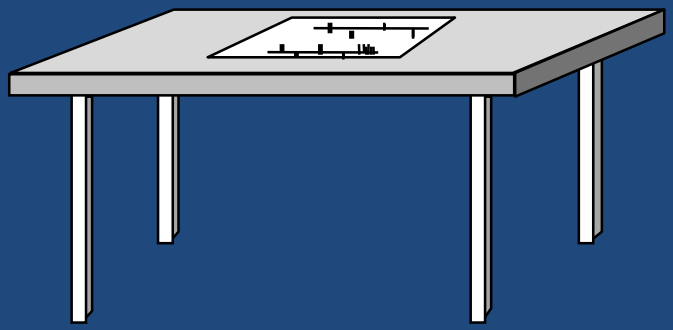
In Refractory Bipolar Disorder:

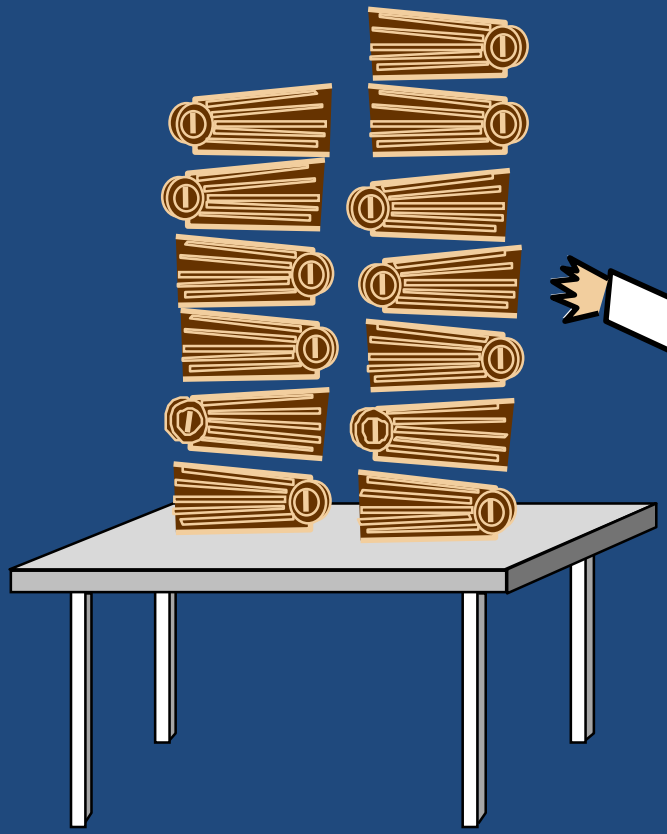
- Be carefully therapeutically aggressive and innovative.
- Test what really works in an individual patient*.
- Your patient's Response/Nonresponse/SE's trumps all guidelines, FDA approval, and academic pronouncements.

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

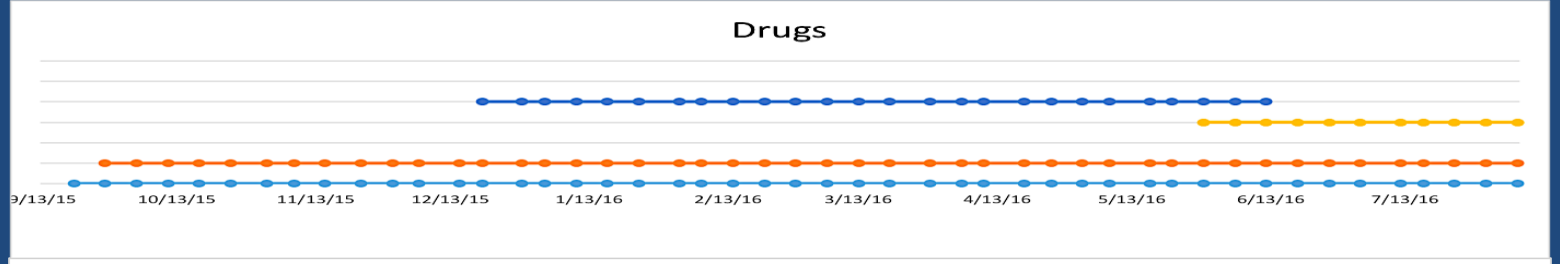
A Life Chart Picture is Worth 100,000 Words







Personal calendar available: www. bipolarnews.org


Drugs
9/13/15
10/13/15
11/13/15
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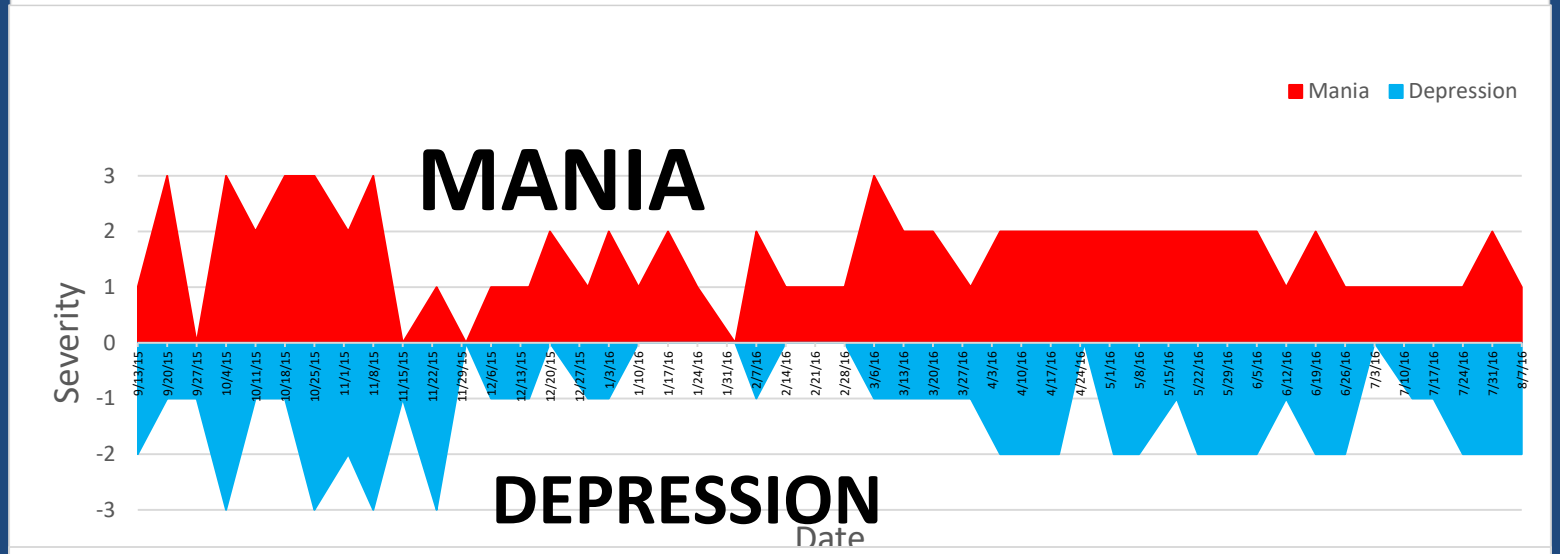
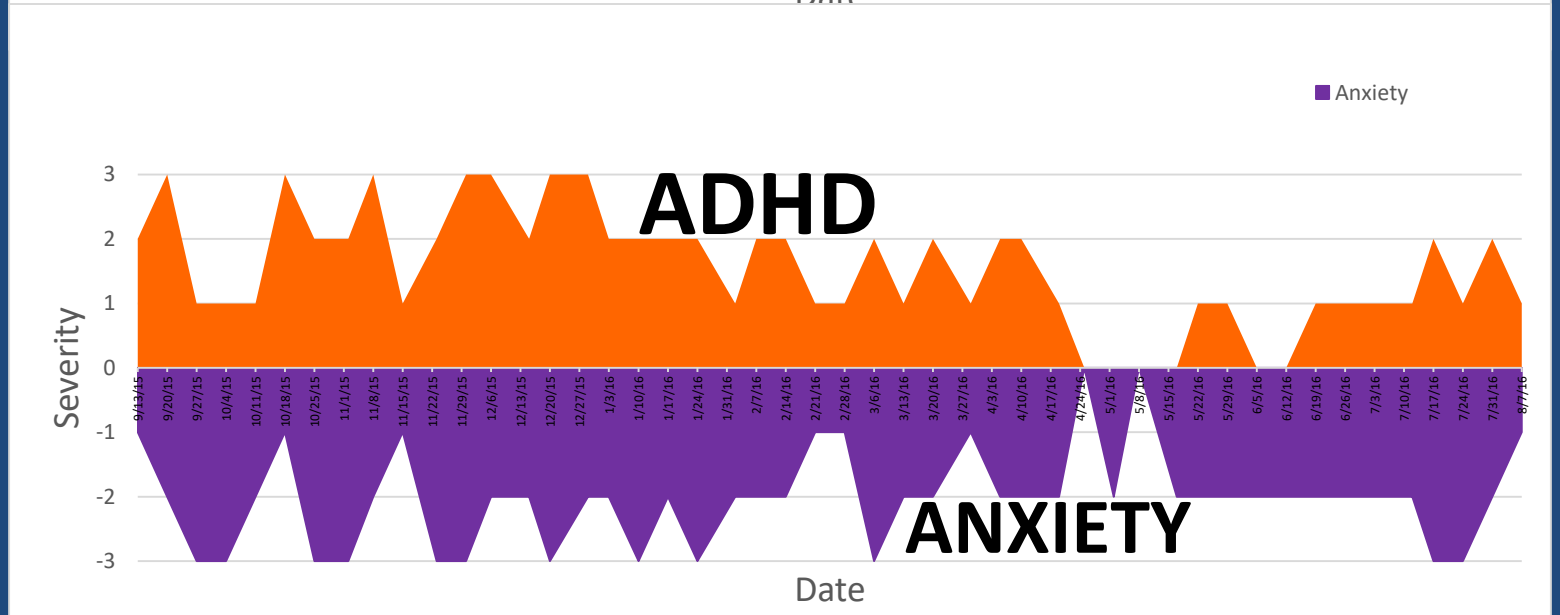
7/13/16


Mania
Depression
MANIA
DEPRESSION
Severity
Date


Anxiety
ADHD
ANXIETY
Severity
Date

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:

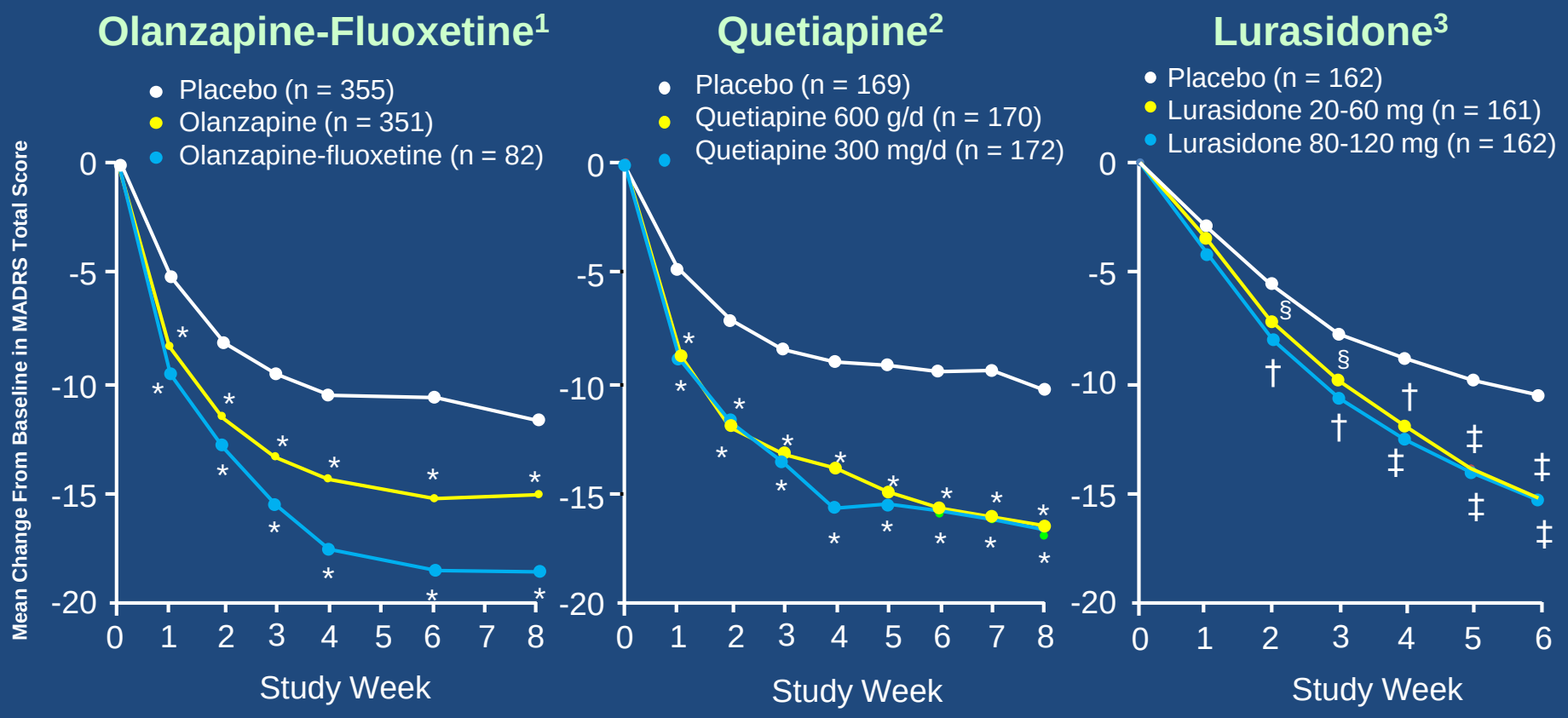
"An Ounce of Prevention, Is Worth a Pound of Cure".....or

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

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)

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

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

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.

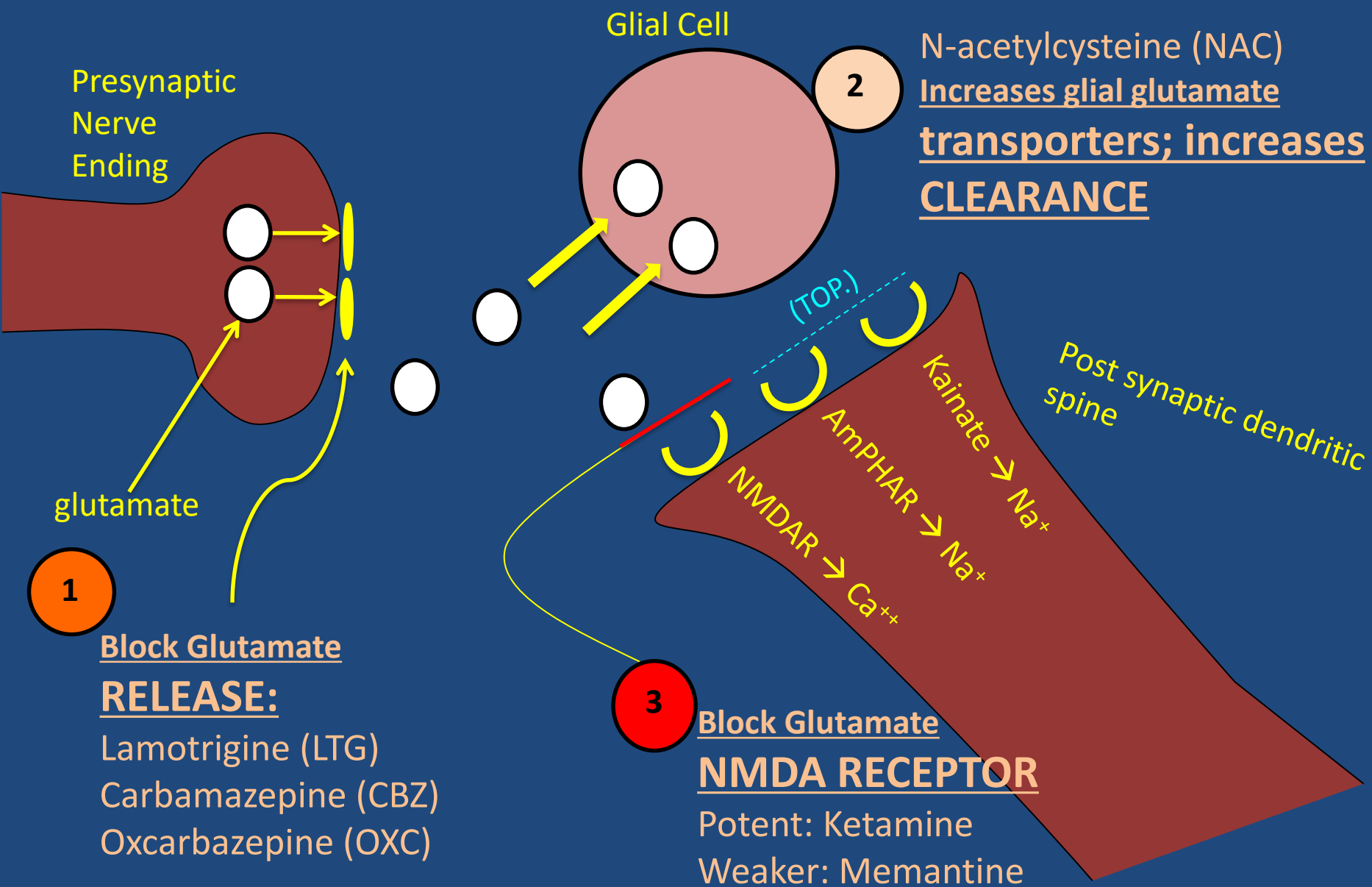
**Trichotillomania, OCD, PTSD

**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



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

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
Pain

Topiramate:
Alcohol
Cocaine
Bulimia
Anger Attacks
Migraine

Zonisamide:
Alcohol
Bulimia

Modafinil:
Cocaine
ADHD
Narcolepsy

Results of 10 Randomized Trials of Family Focused Therapy (FFT) for Patients with Bipolar Disorder (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 risk
  - 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)

Attempting 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

A Bottom Line Is: We Should Use Lithium More Often

- And we should use lithium earlier:

(Earlier initiation of lithium is more effective than starting after many episodes; in 9 of 10 studies) and, most recently Kessing et al 2014.

- 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.

Chronic treatment with lithium:

- Prevents manias and depressions
- Reduces suicide rate
- Reduces medical comorbidities
- Increases telomere length
- Increases longevity
- Prevents cognitive deterioration
- Decreases incidence of dementia in old age

Tell Patients about Lithium' Wide Range of Assets

Clinically in Bipolar Disorder

Decreases:

- Depression; Mania
- Suicide
- Progression to dementia
- UP Depression (AD potentiation)

Increases:

- Telomere length
- Physical health
- Hippocampal & cortex volume

- Low dose:
- 150mg protects MCI
- Li in water decreases suicides

Basic in laboratory animals

Decreases:

- Cell death factors BAX and P53
- Apoptosis
- Inflammation
- Lesion size in models of: HC, Alzheimer's, stroke AIDs, trauma

Increases:

- Neuroprotective Factors BDNF and BCL-2
- Neuronal stem cells

Conclusions

- Bipolar disorder is a progressive, relatively treatment resistant illness: prophylactic Rx after a first mania
- Lithium should be used more often because of its multiple benefits
- Treatment may require complex combination therapy: "More medications, FEWER effects"
- 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"

CONCLUSIONS:

Treat Aggressively from the FIRST EPISODE Onward

The goal is achieving and maintaining REMISSION

Complex COMBINATION treatment may be required

Re-think about using LITHIUM more often

Treatment resistance and cognitive dysfunction increase with increasing numbers of episodes

The new mantra is:

"PREVENT EPISODES, PROTECT THE BRAIN AND BODY"