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

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

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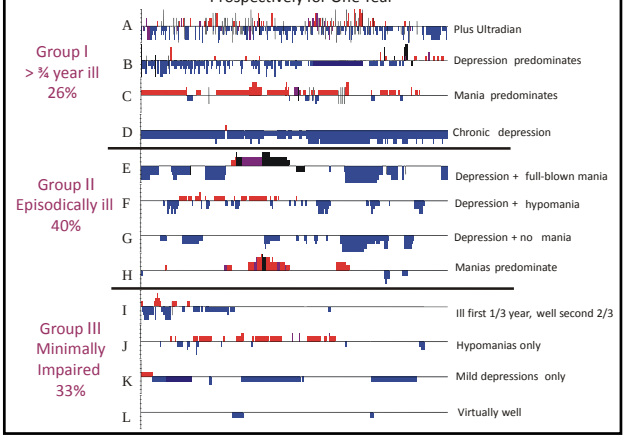
Objectives

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

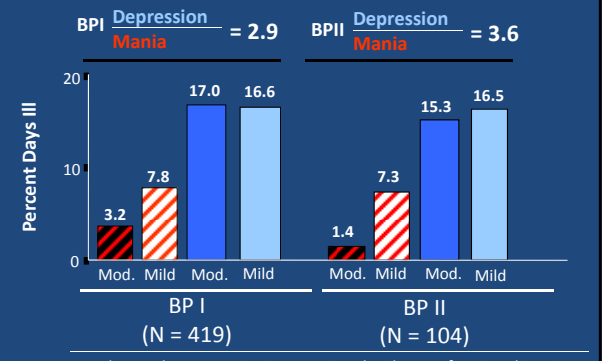
DISCUSS THE NEED FOR EARLY INTERVENTION, COMPLEX COMBINATION TREATMENT, AND LONG TERM PROPHYLAXIS

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



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



mod. ≥ moderate severity, i.e. associated with some functional impairmen

Kupka et al., 2004

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	***	***

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

Kupka et al 2003

	Rapid cyclers (N = 206)	Non-rapid cyclers (N = 333)
DSM-IV* (NIMH-LFA)	38.2% (61.6%)	61.8% (38.4%)
Total no. of Episodes	7.1 ± 3.4	1.4 ± 1.1**
Manic / hypomanic	5.8 ± 3.6	0.9 ± 0.9**
Depressive	1.3 ± 1.3	0.6 ± 0.7**
Total no. of classes of Medications used	4.6 ± 1.8	3.5 ± 1.8**

* DSM, ** = ? Kupka et al., 2003.

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

(L.R. = Logistic Regression Analysis); Kupka et al 2003

Pertinent Positives	Sign.	O.R.
More than 10 prior episodes	*	6.3
More than 20 prior episodes	*	5.5
Prior Hx of R.C.	***	4.3
Hx of Prior Drug Abuse	*	2.6
Abuse as Child	*	2.1

Pertinent Negatives

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

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

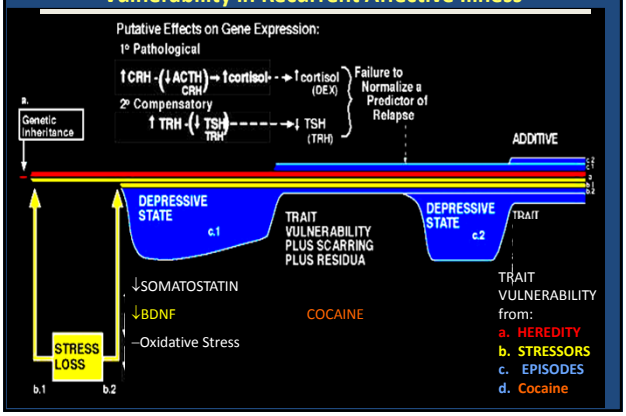
I. NATURALISTIC TREATMENT — Post 2004; Nolan 2005
II. MOOD STABILIZERS (M.S.)
- Lithium > 14 studies — (but see Baldessarini & Tondo 2000)
- Carbamazepine — McKeon 1992; Otusa 1993; Denicoff 1997
- Lamotrigine — Frye et al 2000; Obrocea 2002
- Valproate (Accelerating course), — Calabrese; Post 2012(t)

III. ATYPICAL ANTIPSYCHOTICS (A.A.)
- Olanzepine — Ketter 2006; Berk 2011
- Any A.A. — Post 2010

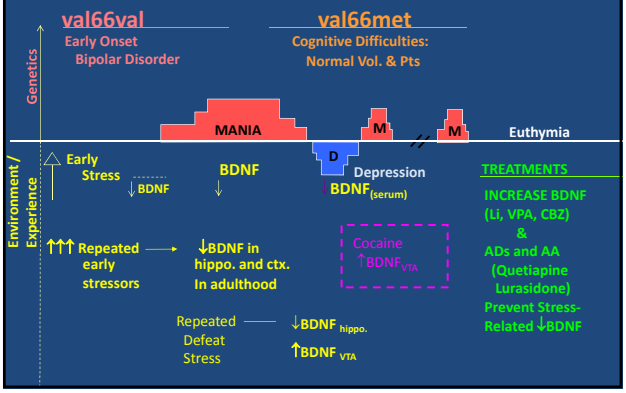
IV. ANTIDEPRESSANT AUGMENTATION OF A M.S.
- Venlafaxine — Post 2006
- AD — Ghaemi 2010; Post 2012(t)

V. BENZODIAZEPINES — Post 2012(t)
VI. COGNITIVE BEHAVIORAL THERAPY (CBT) — Scott, 2006

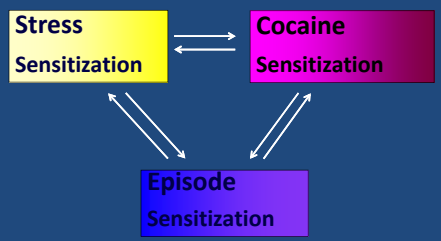
Accumulating Stress and Episode-Related Vulnerability in Recurrent Affective Illness



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



CROSS SENSITIZATION AMONG STRESSORS, DRUGS OF ABUSE, AND EPISODES



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

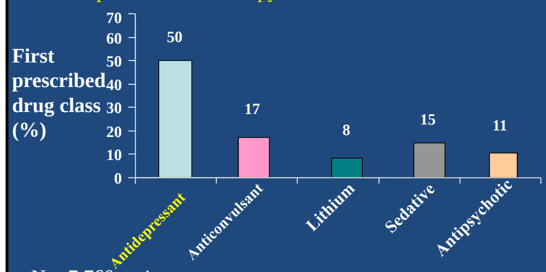
Possible Example: N acetylcysteine (NAC) may Ameliorate Overlearned Habits

NAC Reduces:

- **Addictions to: Cocaine, Heroin, Gambling, Alcohol, Marijuana, Nicotine.
- **Trichotillomania, OCD
- **Depression and Anxiety in Bipolar Disorder

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

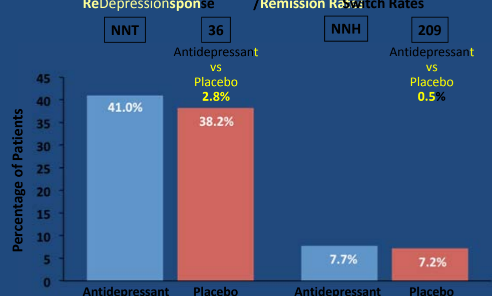
Antidepressant monotherapy twice as common as mood stabilizers



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 Depression



Patients with bipolar I >> bipolar II. Response: ≥50% decrease in depression ,

SIDOR AND MACQUEEN, 2010

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

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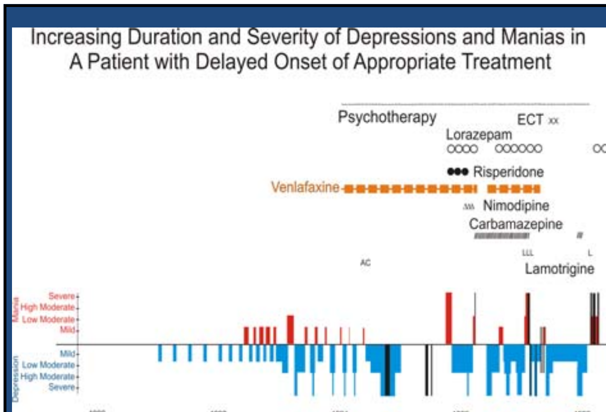
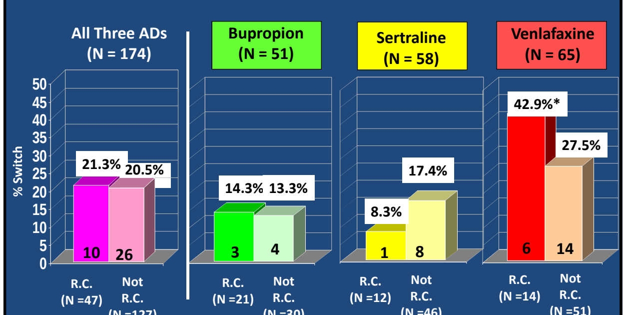
Increasing Duration and Severity of Depressions and Manias in A Patient with Delayed Onset of Appropriate Treatment



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 (≥6 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 Psychiat., 2011)

*by logistic regression.

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However, Continuation of Antidepressants (ADs) as Augmentation of Mood Stabilizers for Bipolar Depression (in the very small subgroup of 15% good responders for at least two months) May Prevent Depressive Recurrences Compared to AD Discontinuation

(Altshuler et al a,b; Joffe et al; Ghaemi et al)

However, in RAPID CYCLERS AD CONTINUATION INCREASES THE FREQUENCY OF DEPRESSIVE RECURRENCES

(N. Ghaemi et al 2010)

Correlates of Antidepressant –Related Switching into Hypo/Mania

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 > 5HT or DA
7. Substance abuse history

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)

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Lithium (Li) Plus Carbamazepine* (CBZ) Is More Effective† Than Monotherapy in Rapid Cycler Patients‡

Treatment Phase	Response Rate: Li Alone (N = 42)	CBZ Alone (N = 34)	Li + CBZ (N = 27)
No rapid cycling	41.2%	53.8%	50%
Rapid cycling	28%	19%	53%*

* Cochran's $Q = 5.429$, $df = 2$, $P = 0.066$.
† CGI rating of marked or moderate.
‡ History of rapid cycling at any time by retrospective LCM.

Low Response to Lithium plus Valproate in Rapid Cycling Bipolar Illness

# Enrolled	% Response: Intent to Treat
N =219	19%
# Completing 4 Weeks of Combination Tx Li + VPA	Observed Cases
N=189	25%

Calabrese et al. 2000

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.

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**

Combination Treatment: Safety and Tolerability Primary Considerations

- 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

Acute Mania		Acute Depression		Longer-Term	
Year	Drug	Year	Drug	Year	Drug
1970	Lithium	2003	Olanzapine+fluoxetine combination	1974	Lithium
1973	Chlorpromazine	2006	Quetiapine, XR (2008)	2003	Lamotrigine
1994	Divalproex, ER (2005)	2012	Lurasidone	2004	Olanzapine
2000	Olanzapine*			2005	Aripiprazole*
2003	Risperidone*			2008	Quetiapine, XR (adjunct)
2004	Quetiapine, XR (2008)*			2009	Risperidone LAI*
2004	Ziprasidone			2009	Ziprasidone (adjunct)
2004	Aripiprazole*				
2004	Carbamazepine ERC				
2009	Asenapine*				

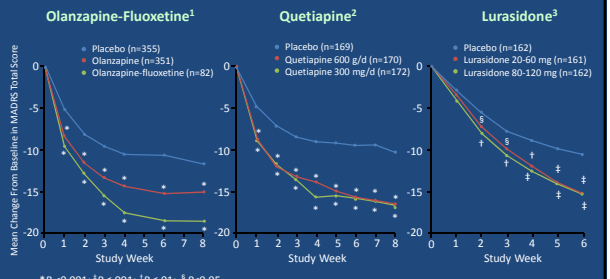
UNMET NEED

Unmet Need

*Adjunctive and monotherapy; LAI = Long-Acting Injectable formulation

Ketter TA (ed). Handbook of Diagnosis and Treatment of Bipolar Disorder, Am Psych Pub, Inc., Washington, DC, 2010.

Approved Agents for Bipolar Depression



*P <0.001; †P ≤.001; ‡P ≤.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.

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Efficacy of Lurasidone Monotherapy in Bipolar Depression

Lurasidone 2 doses vs Placebo for 6 weeks

	Placebo (N = 170)	(LUR 20-60mg) (N=166)	LUR (80-120mg) (N=169)
Responders:	**30%**	**53%*** **	**51%*** **
Remitters (MADRS ≤ 12)	**25%**	**42%****	**40%****

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

	Affinity: Highest	High	Moderate		Low		Very low	Negligible
TYPE	$5HT_7$		$5HT_{1A}$		$5HT_{2A}$	D_2	H1	Muscarinic
POSITIVE EFFECTS	AD effects in animals		AD & ↓ Anx.		AD	AA AM		
SIDE EFFECTS					Sex Dysf. Activating	Parkinsonism	Low sedation, Weight gain	Minimal Dry mouth, constipation

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 Pflug, 1971

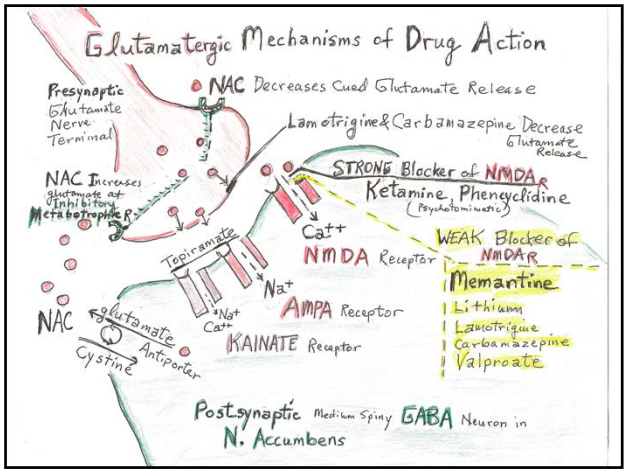
How to Sustain AD Effect in Long-term?

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)
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 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): $\bar{x} = 6.7$

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

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	$\bar{x}$ =18 months

Memantine in 72 Euthymic Bipolar Patients with COGNITIVE DYSFUNCTION

Losifescu et al., Biol. Psy. 2012 Vol 71,85, p. 59, Abstract #195

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

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)	Carbamazepine (C,B)	Topiramate (A,A0
	Carbamazepine (C,B)	Atypical Antipsy (A, A)	Lamotrigine (D,B)
	Lamotrigine B,A**	Benzodiazepine (E,D)	Carbamazepine (D,B)
			Gabapentin (D, C)

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

A=Double Blind Clinical Trial; D=Few Cases; **UTILITY IN BIPOLAR**
B=Large Case Experience; E=Ambiguous; **A = VERY LIKELY**
C=Much Open Study; F=Worse **B = LIKELY**
C = POSSIBLE
D = UNLIKELY

**=Studied in Bipolar Disorder

Treatments for Bipolar Comorbidities: Substance Use/Abuse Disorders

Alcohol		Cocaine	Nicotine
Abstinence		Topiramate (A,A)	Bupropion (A,A)
Naltrexone (A,A)	Withdrawal	Modafinil (A,A)	Nicotine (A,A) Patch
Acamprosate (A,B)	Benzodiazepine (A,A)	12 Step (A,A)	alpha7 agonist (A,B)
Disulfiram (A,D)	Carbamazepine (A,A)	Carbamazepine (C,C)	
Topiramate (A,A)	Valproate (B,B)	Disulfiram (A,D)	**Food/Bulimia**
12 Step (A,A)	Gabapentin (A,A)	N-acetylcysteine-A,A	Topiramate (A,A)
Valproate A,A**		Baclofen (A, but poor choice for bipolar = D	Zonisamide (A,A)
Lamotrigine (C,C)**			Dexamfedamine (A,C)

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

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

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

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

II. GAMBLING ADDICT.

III. TRICHOTILLOMANIA

IV. OCD (Augumentation of SSRI)

V. Stereotypy & Irritability in AUTISM***

VI. BP DEPRESSION

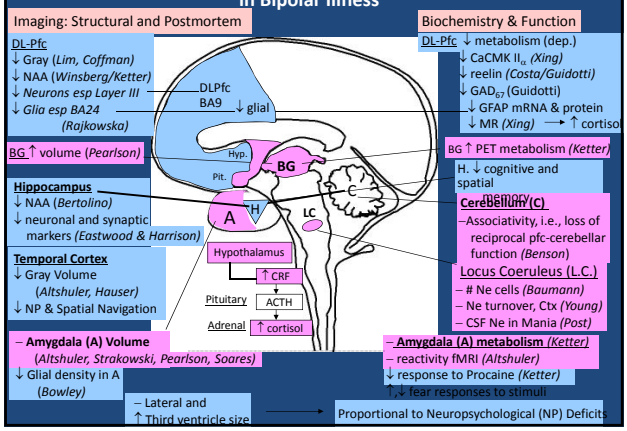
VII. UP DEPRESSION

VIII. Negative Sx SCHIZOPHRENIA

- 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

Convergence of Structural, Biochemical, & Functional Abnormalities in Bipolar Illness



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

One Schema for Treatment of Rapid Cyclers

Combination Treatment

Lithium + VPA	Lithium + CBZ/OXC	Lithium + LTG
(Dysphoric mania)	(Schizoaffective, BPII) (Substance abuse)	(Depressions predominates)

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)

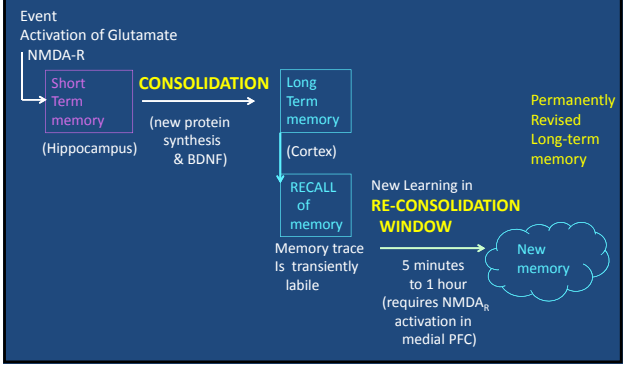
G. For Atypical Depression: MAOI

H. For Cocaine: TOPIRAMATE, MODAFINIL, NAC

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.

Altering Long-term Memories & Habits in the RECONSOLIDATION WINDOW



Extinction of Cocaine/Heroin Addiction by Opening the Reconsolidation Window

Xue et al., Science 2012

Day 1	Day 2			Days 4, 34, 184
Pretest:	Recall	Delay	Extinction Training	Post tests:
Cue ↑↑Craving ↑↑Blood Pressure	5-minute video of drug cues to achieve memory recall	10-minute delay	60-minute Extinction Training: 4 sessions, 3 cues/session	Cue: • Craving Gone • No Blood Pressure Increase • No spontaneous-, cued-, or stressor – induced relapse
	(Neutral video NOT effective)	(6-hour delay NOT effective)		

Disruption of Reconsolidation Erases Amygdala Fear Memory Trace in Humans

Agren et al Science 2012

Day 1
Fear Conditioning
16 shocks paired with visual cue

Day 2
Visual cue
Memory Recall

Extinction Training
8 cues ..... (No Shock)
10 Minute delay – ie Inside the Reconsolidation Window
6 Hour Delay -- ie (Outside Reconsolidat Window)

Day 3
Fear Renewal Cue in the fMRI

Day 5
Consolidation: Disrupted in 10 minute group NO RETURN OF FEAR
vs. 6 hour group FEAR RETURNS

Day 3 fMRI Results

Agren et al 2012

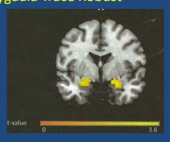
10 minute group:
Extinction WITHIN the Reconsolidation Window:
NO AMYGDALA SIGNAL:
"IT HAS BEEN ERASED"

6 hour group:
Extinction Outside of the Reconsolidation Window
Strong Amygdala Activation Persists &
Connectivity to other centers in the fear circuit (ACG, insula, hippo.)

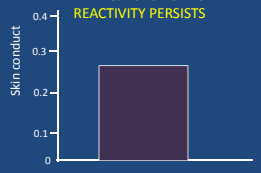
Memory TRACE Of Conditioned Fear REMOVED

Agren et al., Science 2012

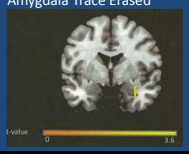
6 hours Extinction Training (Outside Reconsolidation Window)
Amygdala Trace Robust



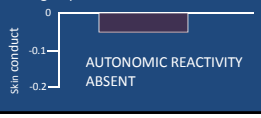
Day 5: 6 hour group FEAR & AUTONOMIC REACTIVITY PERSISTS



At 10 minutes: Extinction Training Amygdala Trace Erased

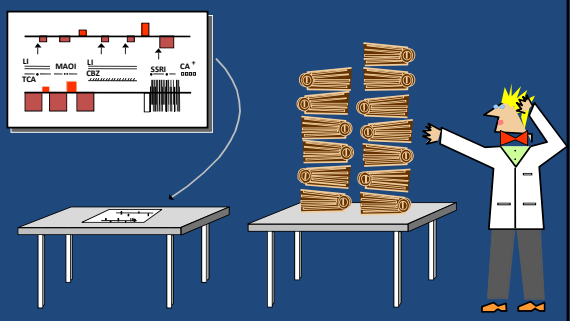


10 minute group: No Return of Fear



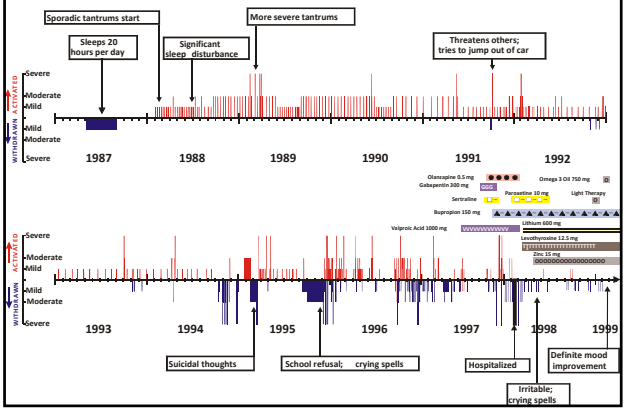
AUTONOMIC REACTIVITY ABSENT

A Life Chart Picture is Worth 100,000 Words



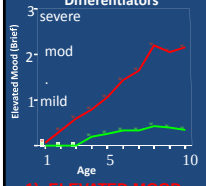
Personal calendar available: www. bipolarnews.org

KIDDIE LIFE CHART (K-LCM™) OF A TWELVE YEAR-OLD WITH AFFECTIVE DYSFUNCTION FROM THE FIRST YEARS OF LIFE



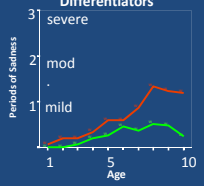
DISCRIMINATORS* OF PREPUBERTAL ONSET BIPOLAR DISORDER AND ADHD

EARLY, Persistent Differentiators



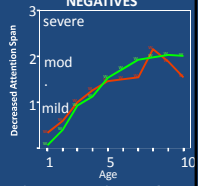
1) **ELEVATED MOOD-BRIEF** (Illustrated above)
2) **EXTENDED**
3) **Decreased** Need for **SLEEP**
4) Greater Degrees of **Irritability**
5) Poor **Frustration Tolerance**

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:

Early Onset Bipolar Illness is Associated with a Poor Prognosis as Adults

	Retrospective STEP	Retrospective BCN	Pro-spective
MORE RECURRENCES	***	***	
Depressions	****		
Manias	**		
LESS EUTHYMIA	***	**	***
More Days Depressed			**
More Days Manic			**
More Wks Irritable	***		
Dysphoric Mania		***	
Rapid Cycling (Lifetime & Current)		***	
Ultradian Cycling			***
INCREASED SUICIDE ATTEMPTS		***	
MORE COMORBIDITIES:			
ANXIETY DISORDERS	****	****	
SUBSTANCE ABUSE: Alcohol	****	(*	
Drug Abuse	***	)	

EARLY AGE OF ONSET OF BIPOLAR DISORDER AGGREGATES IN FAMILIES, Suggesting a heritable trait

Lin et al., Am. J. Psychiatry, 2006

Clinical Correlates of Early – Onset Bipolar Disorder		
Age of Onset:	(<21) vs	(>21 yrs)
Higher Risks of:		
Drug Abuse	32%	15%
Alcohol Abuse	45%	29%
Rapid Cycling	52%	27%
Suicide Attempts	38%	21%

Familial Aggregation of Early – Onset Bipolar Disorder
SIBLINGS of Probands with Early Onset Are:
4 x More Likely to Have Early Onset
10 x ↑ Risk of Drug Abuse **
2 x ↑ Risk of Alcohol Abuse
3 x ↑ Risk of Suicide Attempt

** Early Age of Onset and Risk of Drug Abuse in Siblings; Association Survived Controlling for Age of Onset in Siblings and ± Drug Abuse in the Probands

" . . . THE FINDINGS SUGGEST AGE AT ONSET (OF BIPOLAR DISORDER) AND DRUG ABUSE MAY SHARE A COMMON GENETIC ETIOLOGY . . ."
Lin et al., 2006

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

(Perlis et al 2004; Post et al 2014)

- 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)

Investigators in the Bipolar Collaborative Network (BCN)

United States

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

Europe

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

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

In U.S. More:

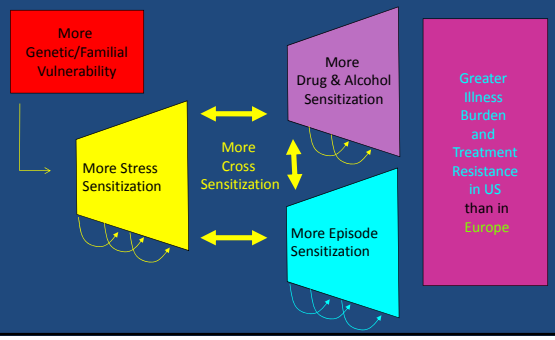
I. GENETIC Risk Factors:
- A. Parental and Grandparental Psychiatric Illness
- B. Assortative Mating

II. ENVIRONMENTAL Adversity
- A. Childhood Abuse (Verbal, Physical, Sexual)
- 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

Bipolar Disorder in US Compared to the Netherlands and Germany



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

Stress Sensitization	Substance Abuse Sensitization	Episode Sensitization
• PSYCHOEDUCATION	• PSYCHOEDUCATION	• PSYCHOEDUCATION
• Social support	Primary Prevention •Rx of Risk factors	• Early Initiation of Prophylaxis
• Psychotherapy	Tertiary Prevention •Rx of Abused substances	• Combination treatment (Rx)
• Stress Coping		• Complex Rx of comorbidities
• Family Rx		• Adjunctive Psycho Rx & Medications

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)
- Carbanzepine — 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
- 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)

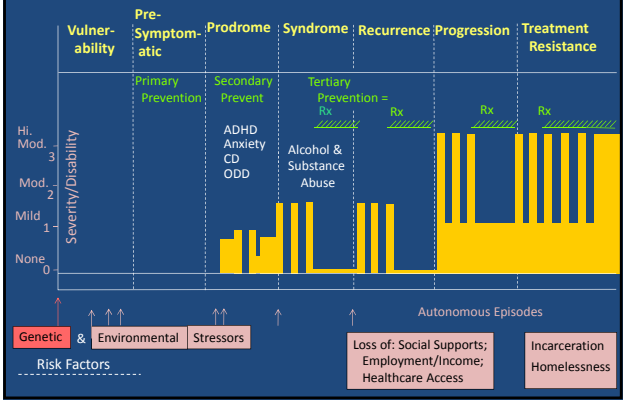
D. Prevents progression from mild cognitive impairment (MCI) to dementia in normal elderly women (150 mg/day)

- 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
  - Load of Short Telomeres

AFFECTIVE EPISODES LIKELY ALTER THE BRAIN;
LONG TERM PREVENTION MUST BE THE PRIMARY GOAL

Stages of Bipolar Illness Evolution



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 1 yr
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"