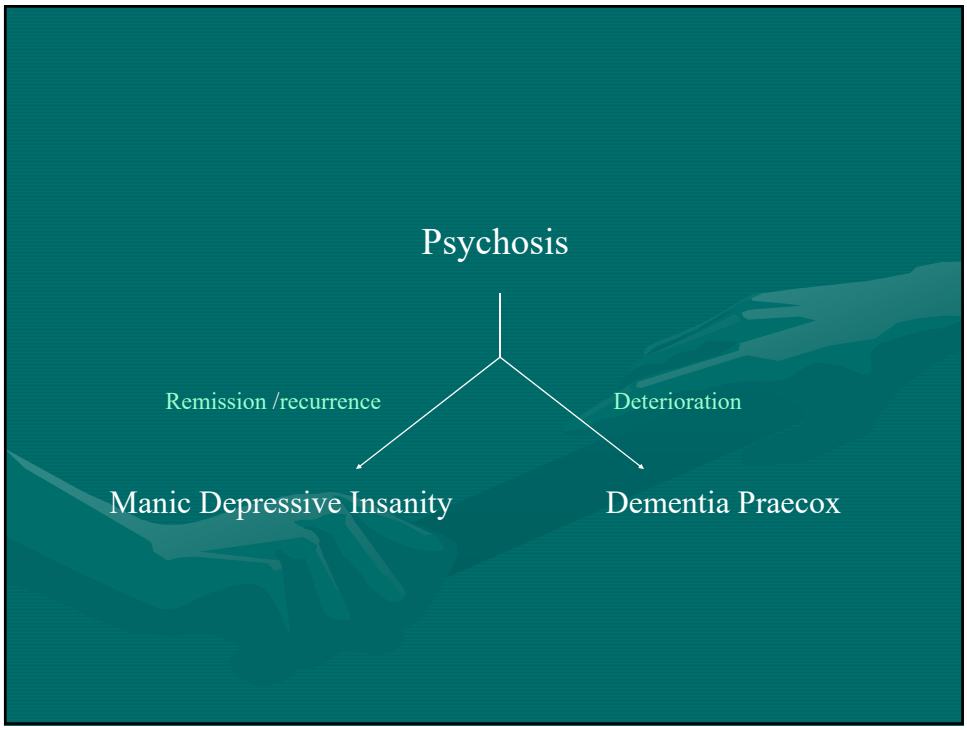
Bipolar Disorder: Comprehensive Update

Steven L Dubovsky, M.D.



It is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses [manic depressive insanity and dementia praecox], and this brings home the suspicion that our formulation of the problem may be incorrect.

Kraepelin, 1920

Secular Changes in Epidemiology of Mood Disorders in 20th Century

- Increasing incidence (new cases)
- Younger age of onset
- Increasing severity and complexity
- More violent bipolar adolescents

Why is the Prevalence of Mood Disorders Increasing?

- Assortive mating
  - Accumulation of genetic risk
- Anticipation
  - Accumulation of trinucleotide repeats
- Decreased modulation of arousal by families
- Increased exposure to overstimulation in media
- Increased treatment of younger patients with antidepressants and stimulants

Diagnostic Issues

Spectrum of Mania

Hyperthymia	Cyclothymia	Hypomania	Mania
Elevated activity Reduced sleep Optimistic	Mild mood swings	Symptoms last days No impaired functioning or psychosis No hospitalization	Psychosis Gross impairment

Categorical Bipolar Spectrum

Mania	Hypomania	Hypomanic symptoms lasting < 4 days	Hypomania without Impairment; elation/ Irritability + 3 symptoms for several days	Elation/irritability or hyperactivity + 3 symptoms	Recurrent psychosis with motility, confusion, anxiety or transcendence	Major depression lasting < 2 weeks recurring monthly
Bipolar I	Bipolar II	Brief hypomania	Subthreshold bipolar	Bipolar specifier	Cycloid psychosis	Recurrent brief depression

Bipolar Spectrum in the World Mental Health Inititative

- 61,392 adults in 11 countries
- Lifetime prevalence in U.S.
  - Bipolar I: 1.0
  - Bipolar II: 1.1
  - Subthreshold bipolar: 2.4
- Suicide attempts
  - Bipolar I: 25%
  - Bipolar II: 20%
  - Subthreshold bipolar: 10%
- Severe role impairment
  - Bipolar I: 57%
  - Bipolar II: 57%
  - Subthreshold bipolar: 46%
- Mental health specialty treatment
  - Bipolar I: 52%
  - Bipolar II: 60%
  - Subthreshold bipolar: 33%

KR Merikangas et al: Arch Gen Psychiatry 2011;68:241-251

Covert Bipolar Disorder in Depressed Patients

- Depressed patients in two primary care practices
  - DSM bipolar disorder: 26.6%
  - Subthreshold bipolar disorder: 31%
  - Number diagnosed by PCP: 0
  - 14% of bipolar patients took a mood stabilizer (all treated by a psychiatrist)
  - 56% of bipolar patients took antidepressants with no mood stabilizer
- Bipolarity specifier criteria
  - Episode of elevated or irritable mood or increased activity plus
    - 3 or more DSM Criterion B symptoms
  - International study of 5635 adults with a MDE
    - 16% had DSM-IV-TR bipolar I or II
    - Another 31% met bipolar specifier criteria
    - All DSM bipolar patients also met specifier criteria

Slide 3

Angst et al: Arch Gen Psychiatry 2011;68:791; Dubovsky et al: Postgraduate Medicine 2011;123:129

Bipolar Outcome of Depression

- Risk of bipolar conversion highest in 4 years after first depressive episode
  - Afterward conversion rate =1.25%/year
- Average time from first episode of major depression to bipolar diagnosis: 9 years
- Bipolar outcome in antidepressant-induced hypomania:
  - 60% of adults
    - Mania increases true bipolar risk
  - 100% of children and adolescents

Slide 1

Bipolar Outcome of Depression

- NIMH Collaborative Depression Study
  - 550 subjects with major depression
  - Mean follow-up 17.5 years
  - Bipolar conversion in 20%
    - 12% bipolar II
    - 8% bipolar I
  - Bipolar outcome predicted by
    - 3 or more subclinical manic symptoms
      - Especially decreased need for sleep, high energy, increased goal directed activity, grandiosity
      - Sensitivity 16%
      - Specificity 95%
      - Positive predictive value 42%
      - Negative predictive value 82%
      - Many patients without subthreshold hypomanic symptoms eventually developed mania or hypomania
    - Psychotic symptoms
    - Early onset
    - Bipolar family history

Slide 2

JG Fiedorowicz et al: Am J Psychiatry 2011;168:40-48

Bipolar Outcome of Depression

- National Health Insurance database in Taiwan from 1996-2007
  - Covers 99% of population
  - N=1,000,000
- Two cohorts with MDD
  - 2000 and 2003
- Four treatment groups
  - Easy to treat: no antidepressant or just one antidepressant
  - Intermediate: changed antidepressant once
  - Difficult to treat: changed antidepressant at least twice
- Diagnosis changed to bipolar disorder in 8-12% in average of 1.9-3 years
  - 26-27% of difficult to treat patients had diagnosis changed to bipolar
- Difficult to treat patients had highest likelihood of change to bipolar diagnosis
  - O.R. 1.88-4.94

Slide 3

L. Cheng-Ta et al: Br J Psychiatry 2012;200:45-51

Bipolar Outcome of Depression

- Predictors of bipolar outcome
  - Early onset of depression
  - Family bipolar history
  - Multiple past depressive episodes
  - Acute onset
  - Treatment resistance
  - Postpartum onset
  - Mood lability, mania or hypomania with antidepressants
  - Mixed mood symptoms
  - Psychotic symptoms in younger patient
  - Comorbid substance abuse
  - Lack of anhedonia
  - Looking better than one feels

Slide 4

JG Fiedorowicz et al: Am J Psychiatry 2011;168:40-48

Bipolar and Borderline

Borderline	Bipolar
Frantic efforts to avoid abandonment	Anxious attachment
Unstable relationships alternating between idealization and devaluation	Overstimulation alternating with withdrawal (next slide)
Unstable sense of self or self-image	Expansiveness, depression, fluctuating experience organized around mood states
Impulsivity that is self-damaging	Impulsivity: grandiose, hypersexual, destructive, self-destructive
Recurrent suicidal behavior or self-mutiliation	Suicide, parasuicide driven by depression or depletion of the self
Affective instability; mood reactivity	Unstable mood; intensely reactive mood
Chronic feelings of emptiness	Emptiness associated with depression or loss of overstimulation
Inappropriate anger; angry outbursts	Rage; irritability
Stress-related paranoia or dissociation	Fluctuating psychosis; dissociation
Splitting	Contradictory mental states driven by contradictory moods

Bipolar and Narcissistic Personality Disorder

Narcissistic	Bipolar
Grandiose self-importance	Grandiosity
Fantasies of success, brilliance	Grandiose schemes
Belief of being special and associating with special people/institutions	Grandiosity
Requires admiration	Attention-seeking; stimulation-seeking
Sense of entitlement	Grandiose pressure; irritability when schemes confronted
Interpersonal exploitation	Behavior driven by pressure of mood
Lacks empathy	Preoccupied by intense mood and internal state; attacks others' weaknesses
Envies others or feels that others are envious	Grandiosity; devaluation of others
Arrogant, haughty	Grandiose; elated; irritable

ADHD and Bipolar Disorder: Inattention

ADHD	Bipolar
Fails to pay attention	Racing and tangential thoughts
Difficulty sustaining attention	Attention driven by racing thoughts, affective themes and psychosis
Does not follow through	Direction of activity shifts with shifting mood
Difficulty organizing tasks	Disorganization, psychosis, excessive energy
Easily distracted	Distractibility

ADHD and Bipolar Disorder: Hyperactivity

ADHD	Bipolar
Fidgets or squirms	Increased energy and activity
Runs about or climbs excessively	Hyperactivity, thrill seeking
Difficulty engaging in leisure activities quietly	Increased energy, boredom
Often on the go	Increased energy, hyperactivity
Talks excessively	Increased speed and content of speech

ADHD and Bipolar Disorder: Impulsivity

ADHD	Bipolar
Blurts out answers	Rapid, pressured, impulsive speech
Difficulty awaiting turn	Hyperactivity, increased energy, impatience, impulsivity, grandiosity
Interrupts or intrudes on others	Impatience, impulsivity, pressured speech, expansiveness

Features of Bipolar Disorder not Seen in ADHD

- Depression
- Elation
- Suicidal thoughts
- Murderous rage
- Psychosis
- Decreased/increased sleep
- Hypersexuality
- Hyper focused attention, especially on people or ideas
- Affective family history

Nonspecific Effects of Stimulants

- Prolonged performance of repetitive tasks
- Decreased fatigue
- Increased alertness
- Maintenance of ability to perceive new events on radar screen
- Reduced impulsive responses on cognitive tests
- Improved short-term memory
- Faster reaction time
- Enhanced sustained attention
- Sedation in children and some bipolar individuals
- Elevated mood; antidepressant effect
- Paradoxical sedation in children and bipolar disorder
- Induction of psychosis

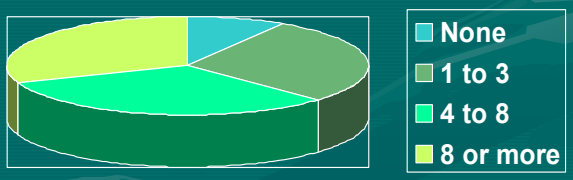
Prognosis

Prognosis in Bipolar Disorder

- 70% have a recurrence within 4 years of first episode
- Over 13 years prospective follow-up bipolar I patients were
  - Depressed 32% of the time
  - Manic 9% of the time
  - Experiencing mixed symptoms 6% of the time

LL Judd et al: Arch Gen Psychiatry 2002;59:530-537

Number of Episodes in 1-Year Prospective Follow-up



Post RM et al: J Clin Psychiatry 2003;64:680-690

STEP-BD Outcomes

- Recovery defined as 8 weeks of <2 symptoms
- 59% recovered
  - ½ of these were well 1 year later
  - 1/3 remained well for 2 years
- Probability of relapse into depression within 2 years of recovery 80%
- Risk of relapse into mania harder to assess due to N
- Residual symptoms increased relapse rate

Am J Psychiatry Feb 2006 p 217

Poor Long-Term Outcome in Bipolar Disorder

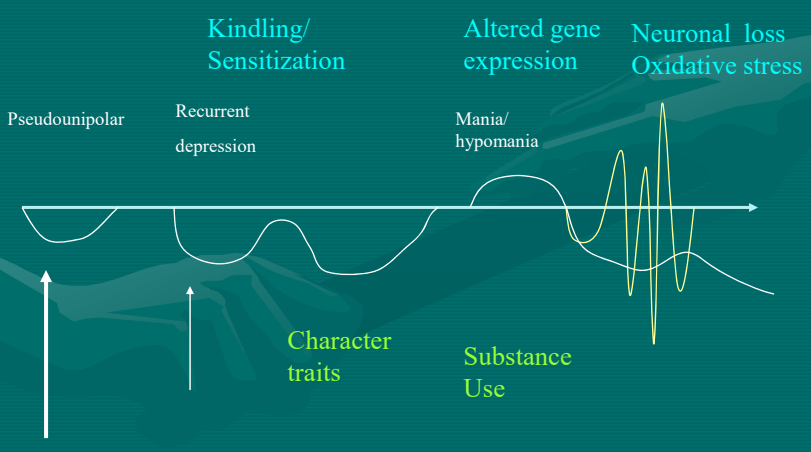
- 10-year naturalistic outcome of 367 bipolar patients who were euthymic for 6 months in 1989
- 167 took one medication; 200 took medication combinations
- Overall probability of remaining well for
  - 1 year: 91%
  - 2 years: 81%
  - 4 years: 57%
  - 10 years: 32%
- No difference in outcome between monotherapy and polytherapy
- The longer patients were well, the longer they remained well

APA 2003 G Laje et al: NYU

Disability in Bipolar Disorder

- More disability than
  - Cancer
  - Epilepsy
  - Alzheimer's disease
- Comorbidity common with
  - Anxiety disorders
  - Substance abuse
- Highest suicide rate

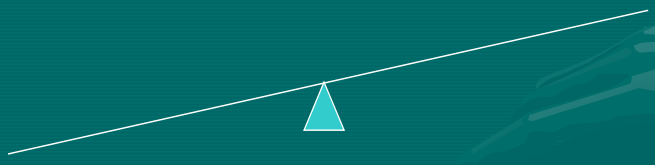
Evolution of Bipolar Mood Disorders



Pathophysiology

Downward affective regulation

Upward affective regulation



Depression
Low energy
Hypersomnia

Mania
Excessive energy
Fluctuation

Familial Overlap Between Bipolar Disorder and Schizophrenia

- Meta analysis of
  - 18 studies of rates of bipolar disorder in 8896 first degree relatives of 2084 schizophrenia probands
  - 19 studies of rates of schizophrenia in 7066 first degree relatives of 1312 bipolar probands
- In first degree relatives of *bipolar* probands versus controls
  - Risk of bipolar = 24.47
  - Risk of schizophrenia (using morbid risk estimate only) = 3.49
- In first degree relatives of *schizophrenia* probands versus controls
  - Risk of schizophrenia = 8.38
  - Risk of bipolar = 2.08

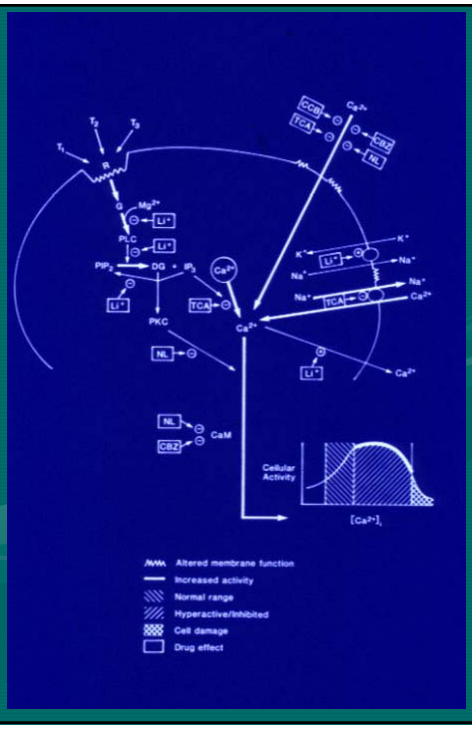
Van Snellenberg JX, de Condida T: Arch Gen Psychiatry 2009;66:748-755

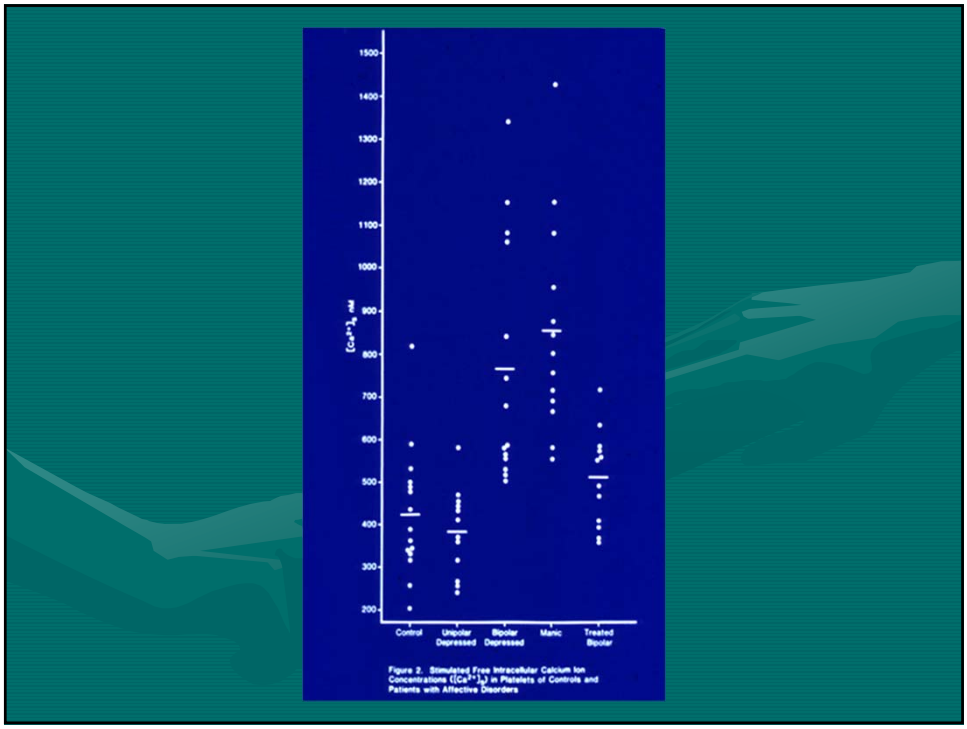
Susceptibility Genes for Bipolar and Schizophrenia

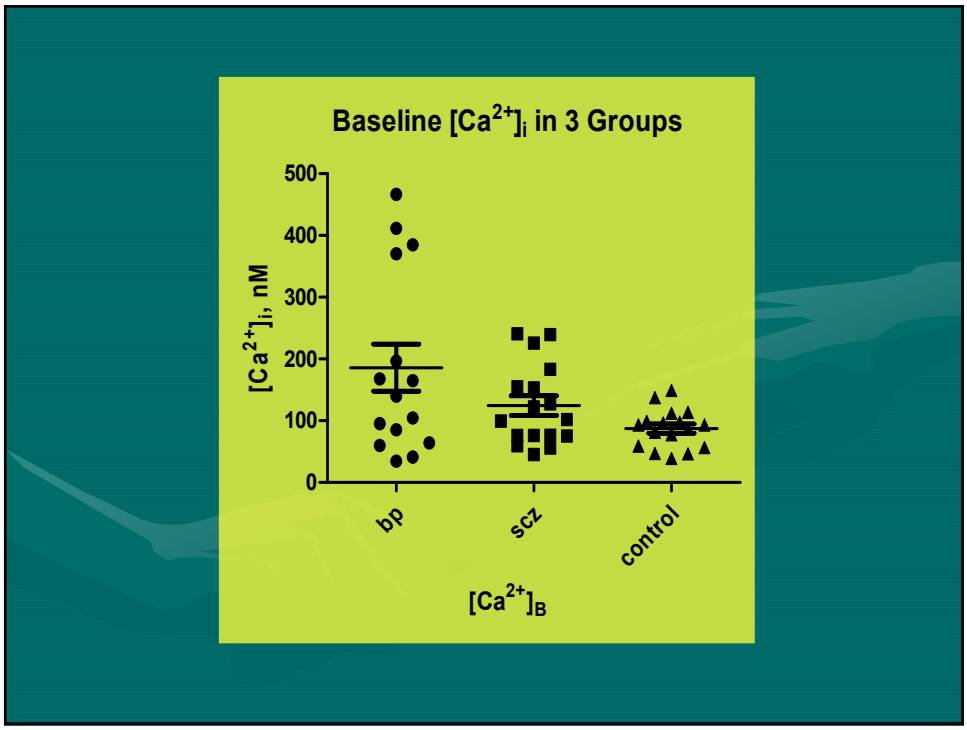
- DISC1 (disrupted in schizophrenia 1)
- COMT
- NRG1 (neuregulin 1)
- BDNF
- BRD1 (bromodomain containing 1)
- CLOCK (circadian locomotor output cycles kaput protein)
  - Increased frequency of bipolar recurrences
- CACN1 (calcium channel)
- SNAP91 (calcium signaling and Wnt pathway)
- ANK3

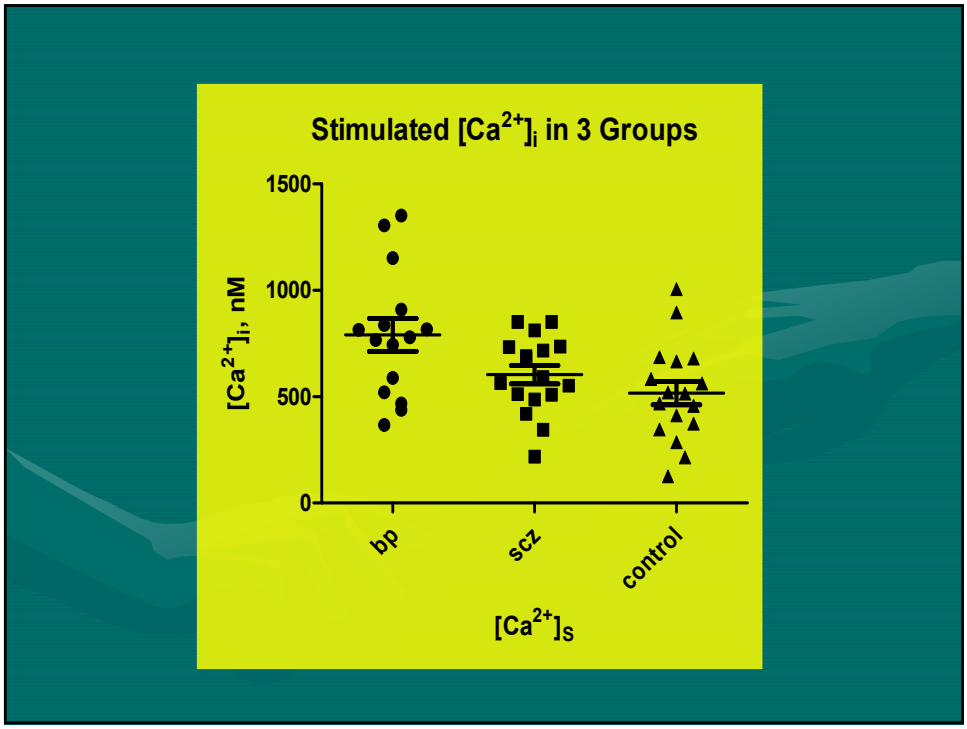
FS Goes et al: Transl Psychiatry 2012;2, e180; doi:10.1038/tp.2012.106

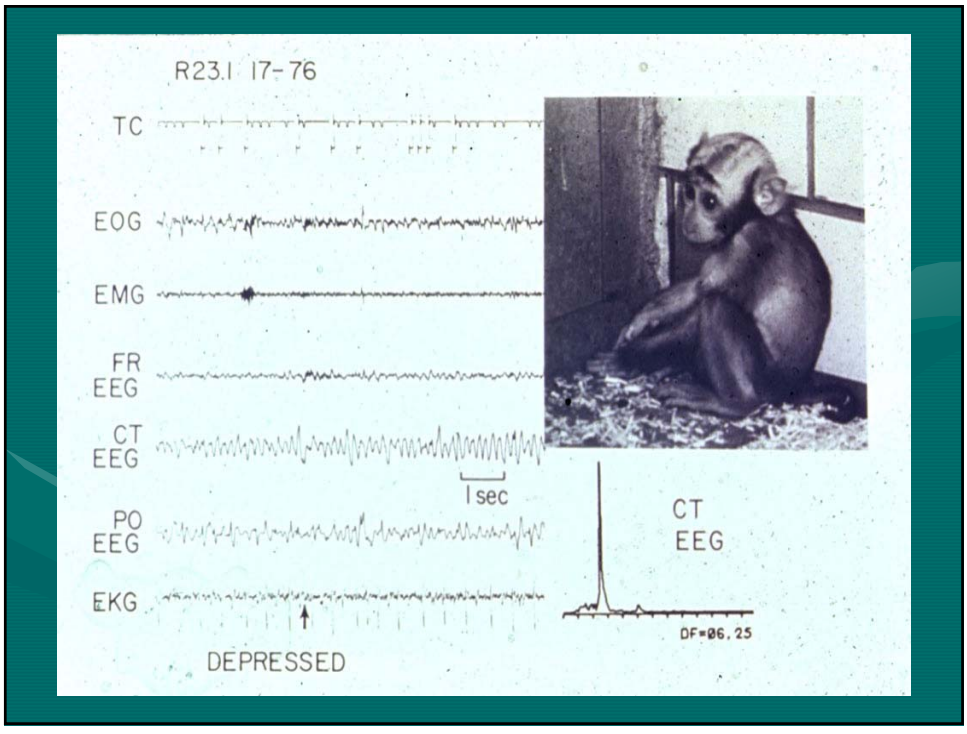
Kindling

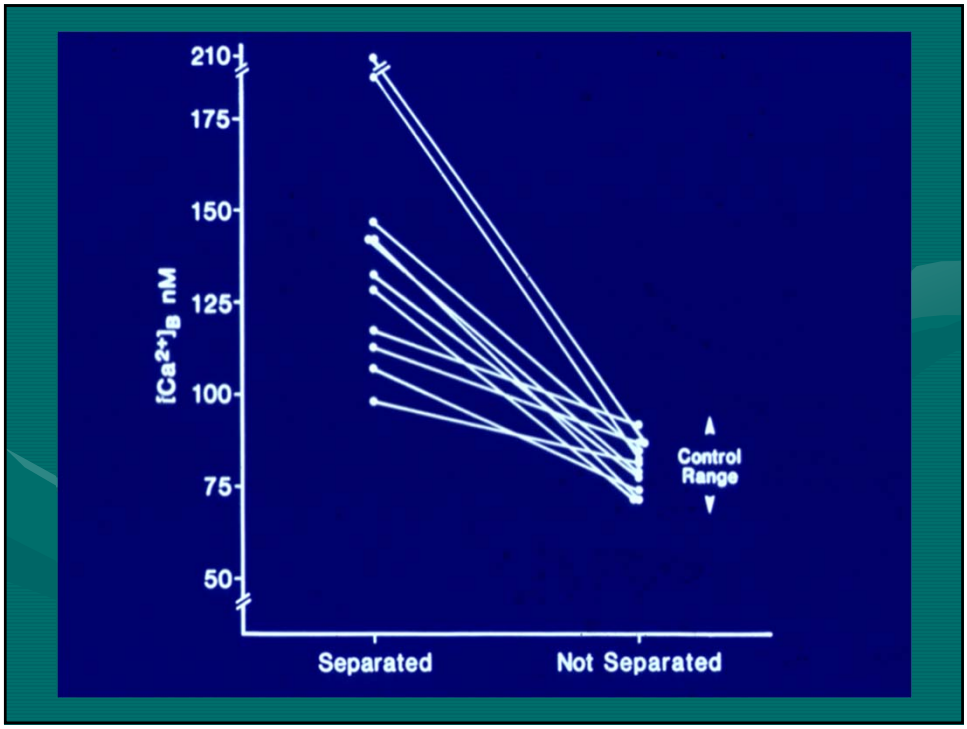

CCB
TCA
CBZ
NL
Ca2+
T1
T2
R
G
Mg2+
Li+
PLC
PIP2
DG
IP3
PKC
K+
Na+
Cellular Activity
[Ca2+]i
CaM
Altered membrane function
Increased activity
Normal range
Hyperactive/Inhibited
Cell damage
Drug effect


Control
Unipolar Depressed
Bipolar Depressed
Manic
Treated Bipolar


Baseline [Ca2+]i in 3 Groups
[Ca2+]i, nM
500
400
300
200
100
0
bp
scz
control
[Ca2+]B

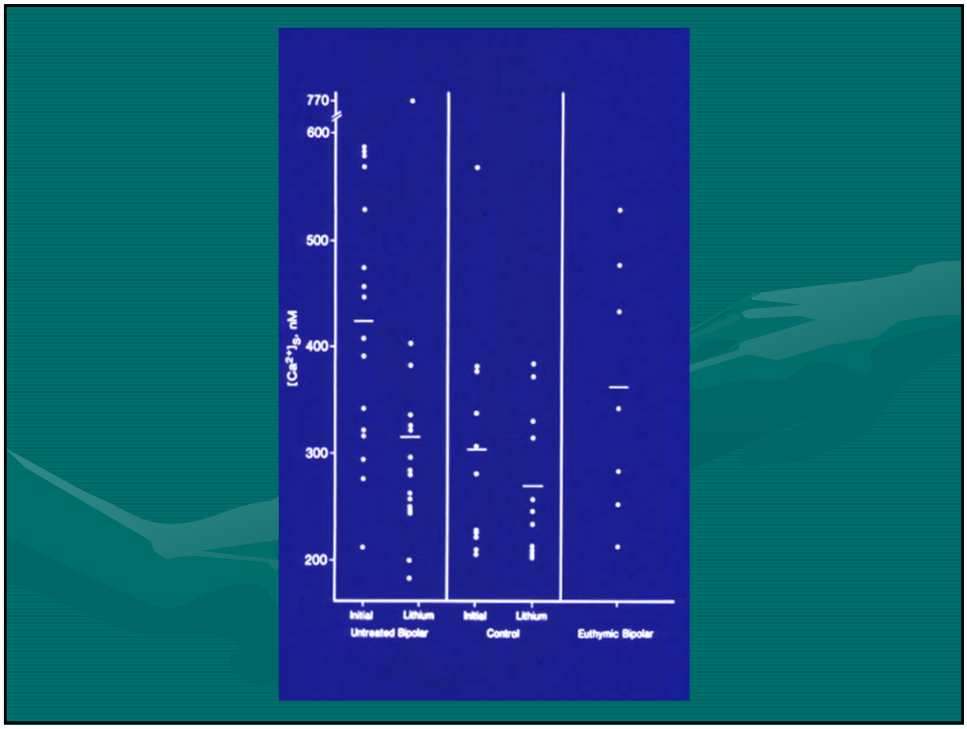

Stimulated $[Ca^{2+}]_i$ in 3 Groups
1500
1000
500
0
$[Ca^{2+}]_i$, nM
bp
scz
control
$[Ca^{2+}]_S$

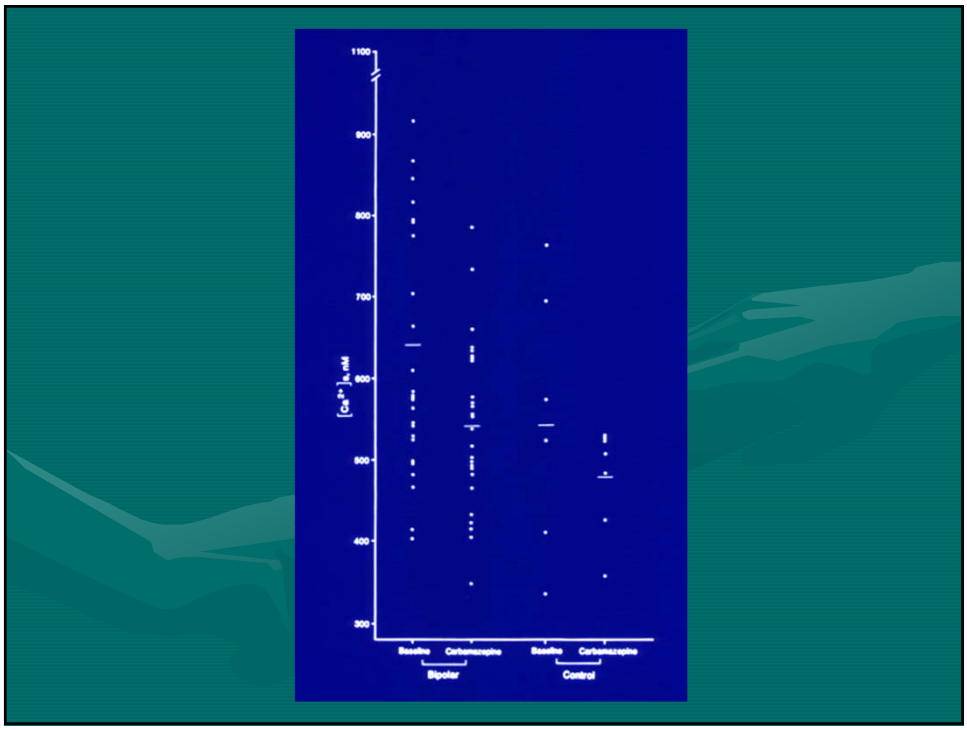

R23.I 17-76
TC
EOG
EMG
FR EEG
CT EEG
PO EEG
EKG
1 sec
CT EEG
DF=86.25
DEPRESSED

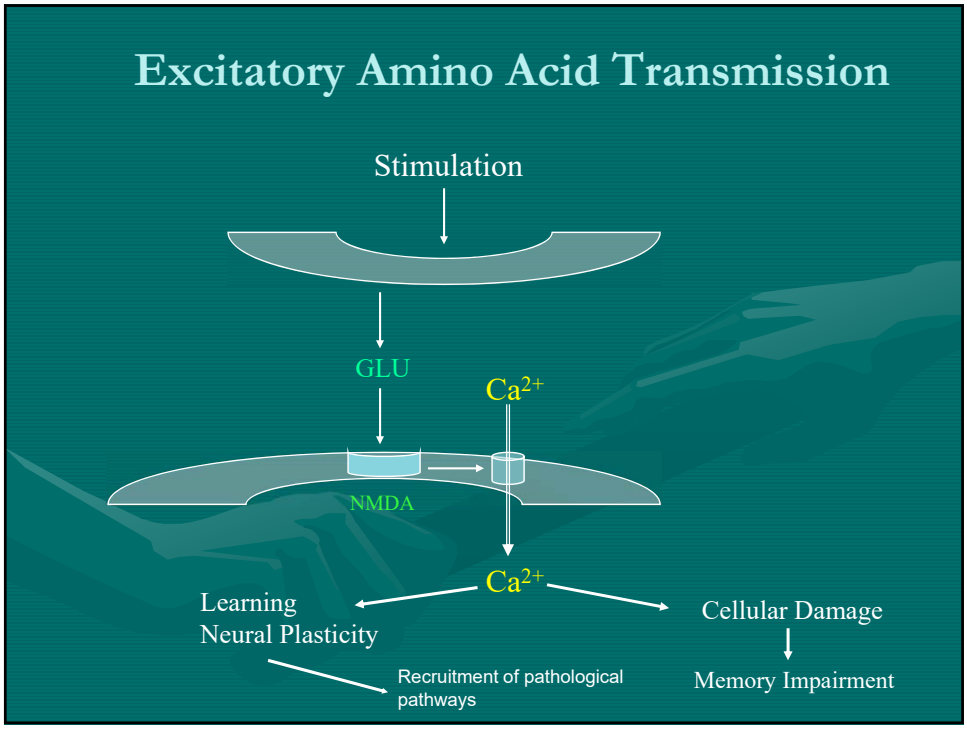


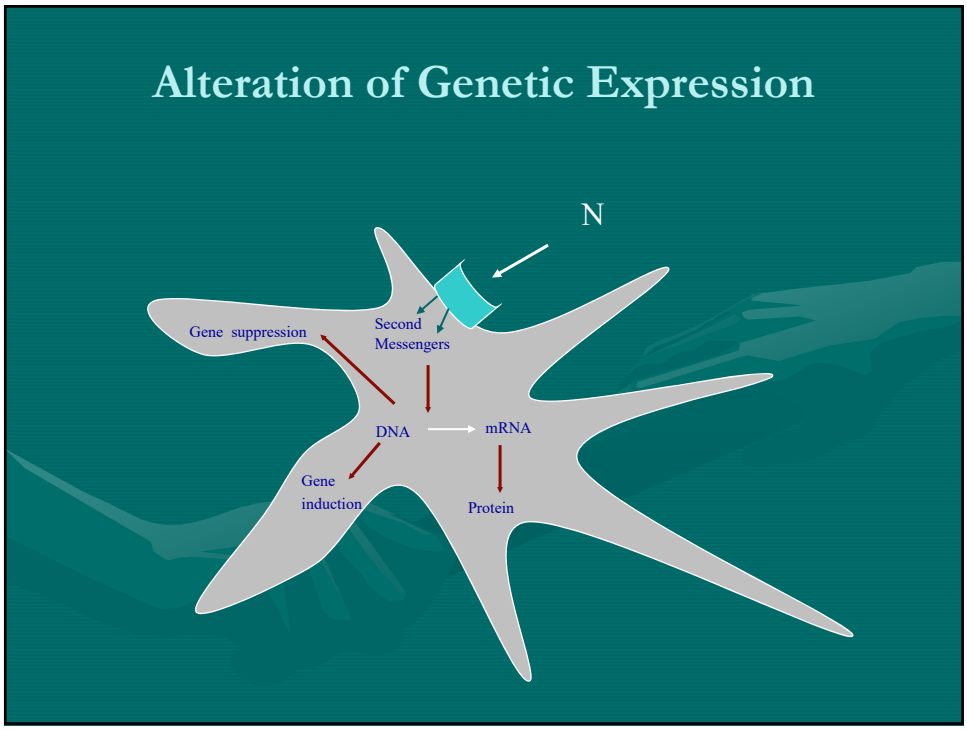
Incubation of Normal Platelets with Bipolar Plasma Ultrafiltrate

Condition	$[Ca^{2+}]_i$, nM
Control	88± 9
Ultrafiltrate	85±5


770
600
500
400
300
200
$[Ca^{2+}]_i$, nM
Initial
Lithium
Initial
Lithium
Untreated Bipolar
Control
Euthymic Bipolar


1100
900
800
700
600
500
400
300
$[Ca^{2+}]_i$, nM
Baseline
Carbamazepine
Baseline
Carbamazepine
Bipolar
Control

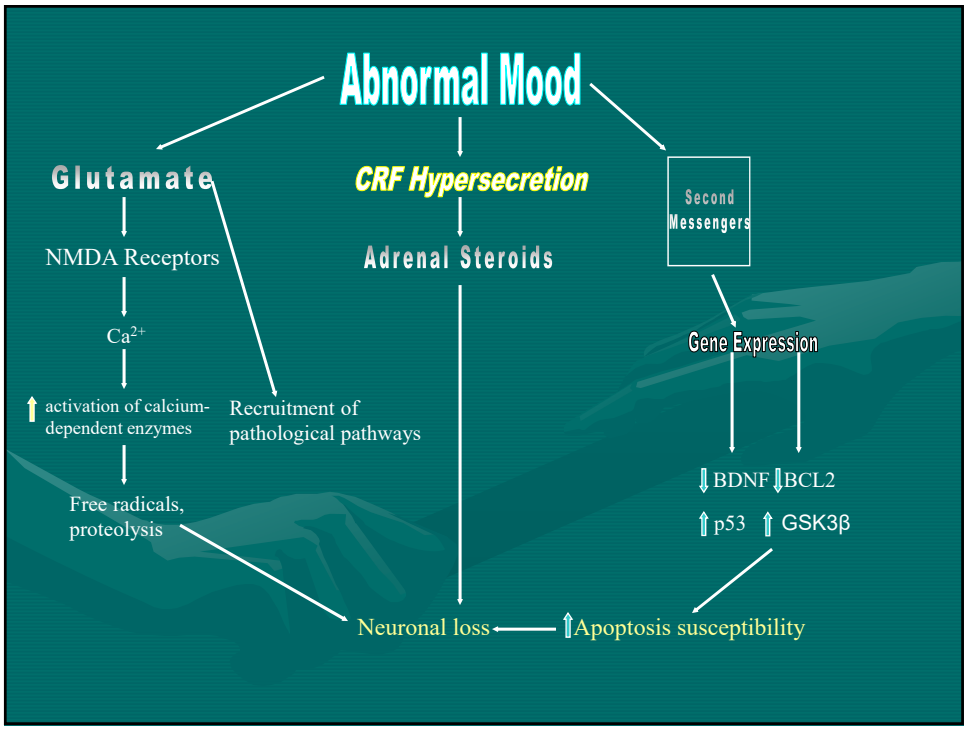

Excitatory Amino Acid Transmission
Stimulation
GLU
Ca2+
NMDA
Ca2+
Learning
Neural Plasticity
Recruitment of pathological pathways
Cellular Damage
Memory Impairment

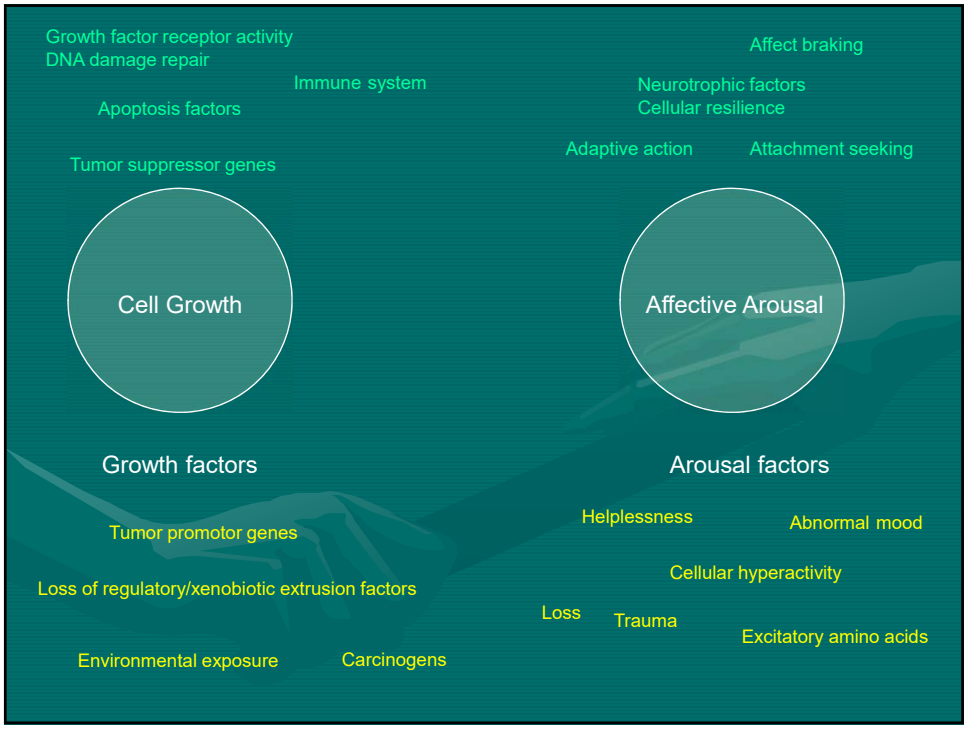

Alteration of Genetic Expression
N
Gene suppression
Second Messengers
DNA
mRNA
Gene induction
Protein

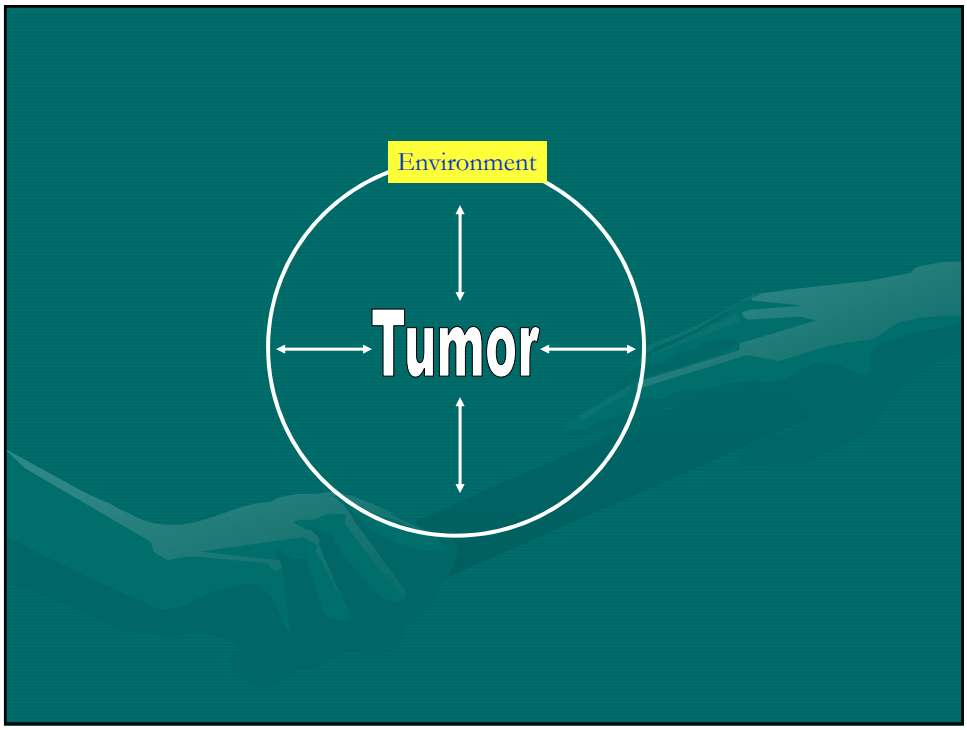
Altered Gene Expression in Bipolar Disorder

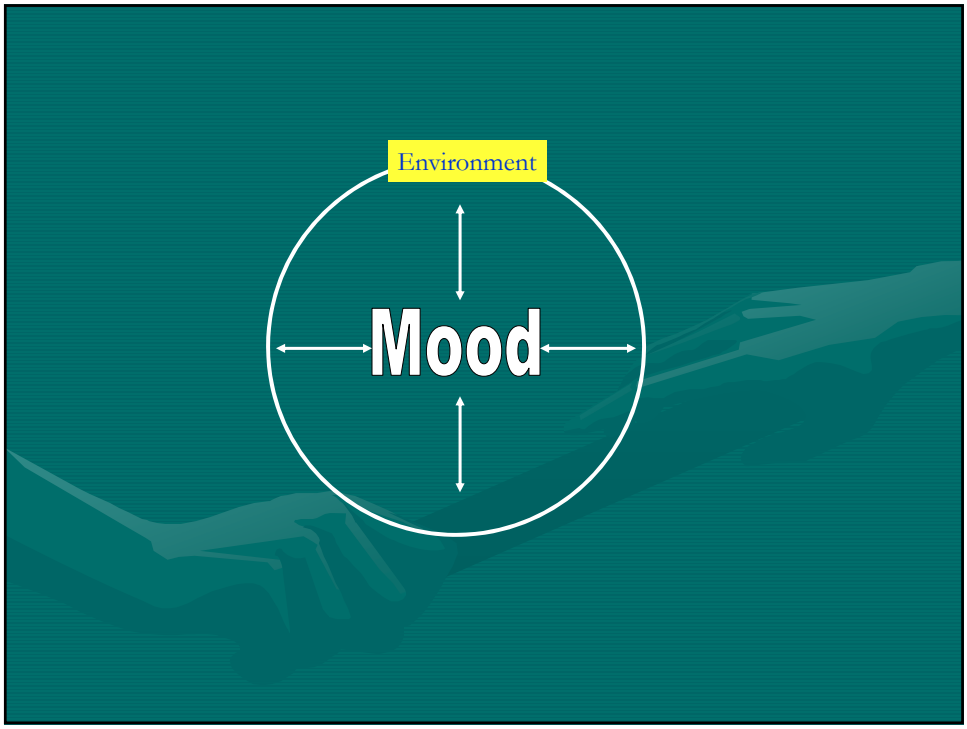
- Histone deacetylase
- Glucocorticoid receptor
- Cell adhesion molecule L1
- Mitogen activated protein kinase 6 (MAP6)
- Neuregulen-1 (NRG1)
- Immune response
- Mitochondrial genes
- BDNF

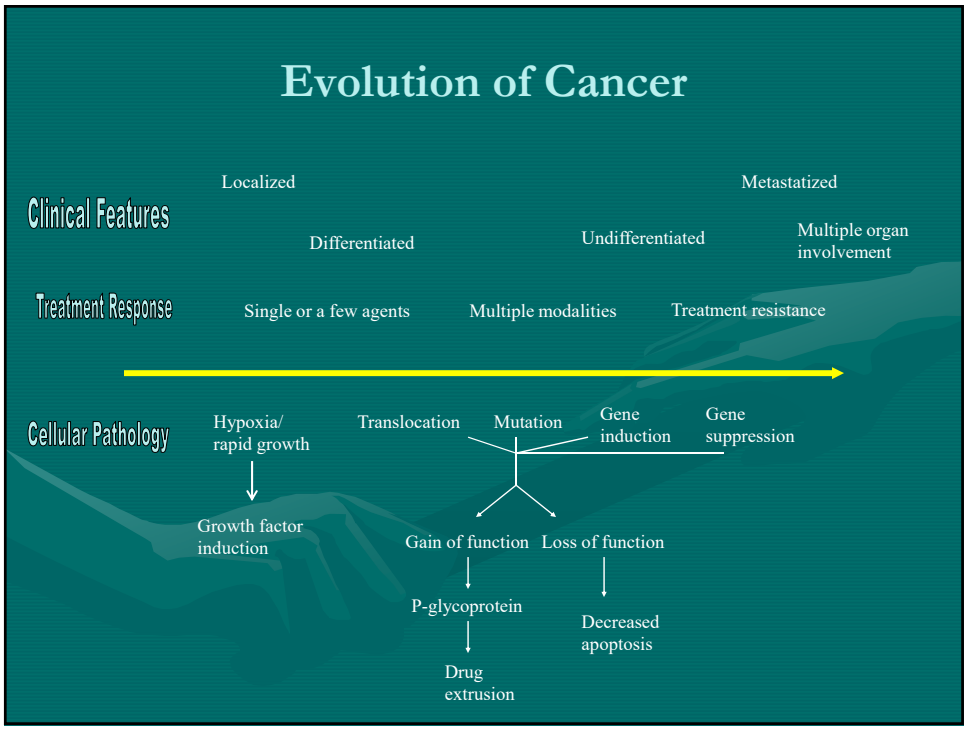
K Munkholm et al: Bipolar Disorders 2012;14:684



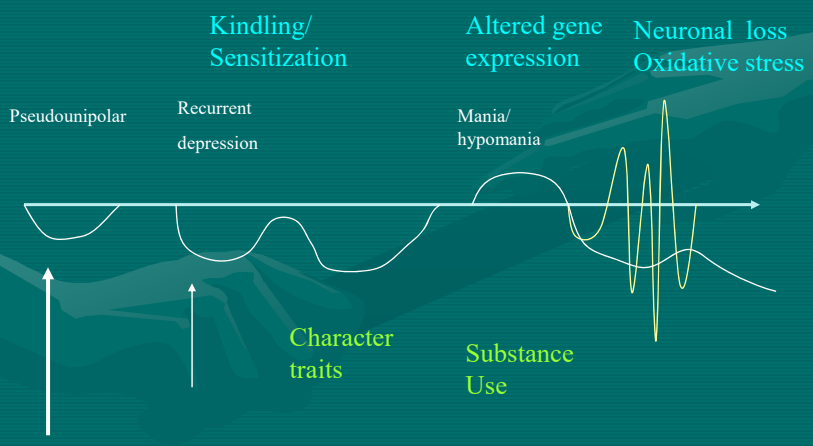

Growth factor receptor activity
DNA damage repair
Immune system
Apoptosis factors
Tumor suppressor genes
Cell Growth
Growth factors
Tumor promotor genes
Loss of regulatory/xenobiotic extrusion factors
Environmental exposure
Carcinogens
Affect braking
Neurotrophic factors
Cellular resilience
Adaptive action
Attachment seeking
Affective Arousal
Arousal factors
Helplessness
Abnormal mood
Cellular hyperactivity
Loss
Trauma
Excitatory amino acids


Environment
Tumor


Environment
Mood


Evolution of Cancer
Clinical Features
Localized
Metastatized
Differentiated
Undifferentiated
Multiple organ involvement
Treatment Response
Single or a few agents
Multiple modalities
Treatment resistance
Cellular Pathology
Hypoxia/ rapid growth
Translocation
Mutation
Gene induction
Gene suppression
Growth factor induction
Gain of function
Loss of function
P-glycoprotein
Decreased apoptosis
Drug extrusion

Evolution of Mood Disorders



Treatment of Mania

Olanzapine

- Antimanic drug in 3-4 week placebo controlled studies
  - "Mood stabilizer" designation derived from acute improvement of depression mixed with mania
- Random assignment of patients with pure or mixed mania to 17 mg olanzapine or 1400 mg divalproex
  - Decreases in YMRS
    - Divalproex: 28→18
    - Olanzapine: 27→14
    - Final score ≤ 12 in 47% olanzapine, 34% divalproex
  - Reduction in depression scores not significant
  - Higher chronic doses may destabilize mood

Tohen M et al: Am J Psychiatry 2002;159:1011-1017

Meta Analysis of Acute Antimanic Drugs

- 68 industry sponsored 3-week randomized treatment trials
  - 16,073 patients
  - 17 trials were add-ons of antipsychotic to lithium or valproate
- Main outcome variable: Change in YMRS score
- Acceptability: measured by treatment discontinuation
- All treatments were > placebo except
  - Lamotrigine
  - Gabapentin
  - Topiramate

Slide 1

A Cipriani et al: Lancet 2011;378:1306-1315

Meta Analysis of Acute Antimanic Drugs

- Haloperidol (10 mg average) had significantly more efficacy than other drugs in the most studies
- Fewest dropouts with olanzapine, risperidone, quetiapine
- Combining YMRS decreases and dropouts, best results in 3 weeks were with
  - Risperidone
  - Olanzapine
  - Haloperidol
  - Quetiapine
  - Carbamazepine
  - Aripiprazole
  - Valproate
  - Lithium
  - Ziprasidone
  - Asenapine
- Antipsychotic drugs generally work faster than mood stabilizers for mania

Slide 2

A Cipriani et al: Lancet 2011;378:1306-1315

Meta-Analysis of Antipsychotic Treatment of Mania

- Individual patient data meta-analysis of RCTs of olanzapine for mania/mixed episode
  - Avoids errors in aggregate data analysis
  - 5 studies of 939 patients
  - All industry sponsored
- Mean square YMRS differences at 3 weeks between placebo and olanzapine
  - Baseline YMRS 20-25: 2.56
  - Baseline YMRS 25-35: 4.74
  - Baseline YMRS 35-60: 8.01

Slide 1

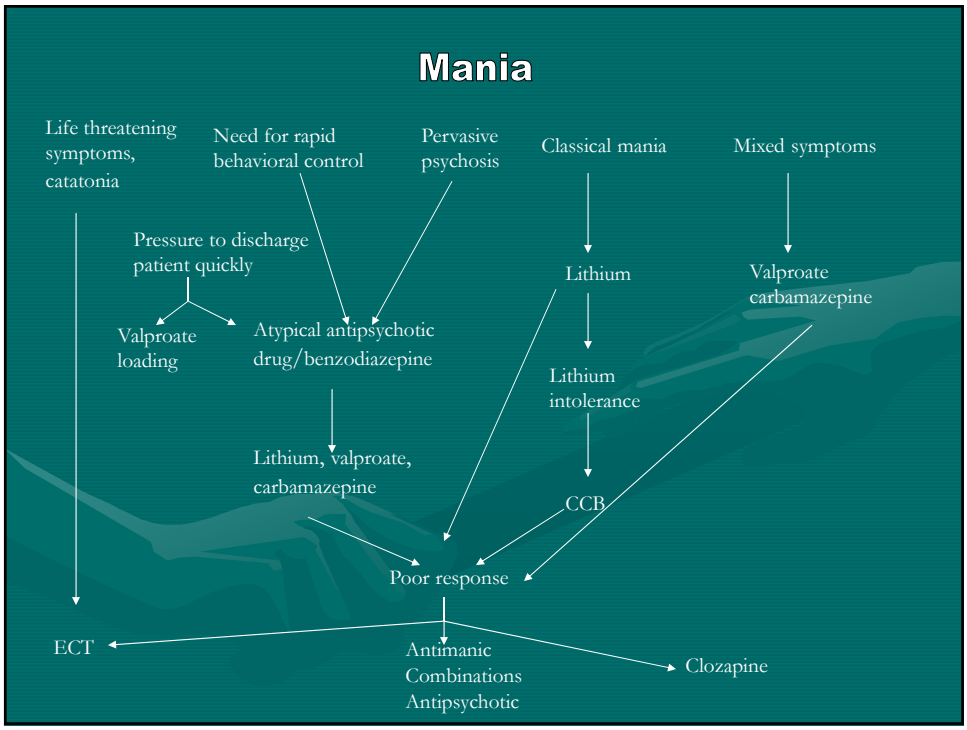
MT Samara: Lancet Psychiatry 2017;4:859

Meta-Analysis of Antipsychotic Treatment of Mania

- For a 50% YMRS improvement
  - Baseline YMRS 20: NNT=7
  - Baseline YMRS 30: NNT=5
  - Baseline YMRS 45: NNT=4
- Conclusions
  - Antipsychotic more effective for mania of greater severity
  - Adverse effects the same at all levels of severity
  - Risk/benefit analysis may not favor antipsychotic for milder mania
  - Same may be true of maintenance treatment if symptoms not severe

Slide 2

MT Samara: Lancet Psychiatry 2017;4:859



Valproate Levels

- Response may be correlated with serum level or with rise in serum level
- Pooled data from three 21-day industry sponsored RCTs of valproate ER
  - 374 inpatients
  - Primary outcome measure: change in YMRS
- Valproate significantly > placebo beginning at 71-85 µg/mL
- Levels >74 better than < 55
- Effect size at highest levels corresponds to 12 point reduction on YMRS
- Aim for levels >90
  - Generally well tolerated in industry sponsored mania trials

Allen M et al: Am J Psychiatry 2007;163:72

Valproate Effect Size as Function of Serum Level

Allen M et al: Am J Psychiatry 2007;163:72

How Long To Continue Antipsychotic Drug?

- Industry sponsored studies do not compare different durations of antipsychotic treatment
- 52 week DBPC study of 159 patients remitted from mania for 2 weeks with treatment with risperidone (1-6 mg) or olanzapine (5-25 mg) plus lithium or valproate
- Patients randomized to discontinue antipsychotic (placebo substitution)
  - Over first 2 weeks
  - After 6 months
  - After 12 months
- Mood stabilizer continued

Slide 1

LN Yatham et al: Mol Psychiatry 2015; doi:10.1038/mp.2015.158

How Long To Continue Antipsychotic Drug?

- Time to relapse of any mood episode significantly longer with 6-month versus immediate antipsychotic withdrawal
- Time to relapse in 12-month group=6-month group
  - More adverse effects
  - More weight gain
- Benefit for manic>depressive relapse
- No evidence of increased benefit from continuing antipsychotic drug after 6 months
- Continued antipsychotic use could increase risk of depressive relapse

Slide 2

LN Yatham et al: Mol Psychiatry 2015; doi:10.1038/mp.2015.158

Blue Blocking Glasses for Mania

- Dark therapy: attempt to synchronize circadian rhythms in mania by putting patient in completely dark room for 14 hrs./night
  - Problems: compliance, sensory deprivation
- Blue light is the primary signal of daylight
- Intrinsically photo-responsive retinal ganglion cells (ipRGCs)
  - Sensitive to blue light
  - Detect light/dark status of environment
  - Connect to limbic system, striatum, brain stem
  - Involved in affect and cognition
  - Affect circadian rhythms
- Blocking blue light produces virtual darkness in brain
- Orange glasses block blue light

Slide 1

TEG Henriksen et al: Bipolar Disorders 2016;18:221

Blue Blocking Glasses for Mania

- Multi-center Norwegian trial of blue blocking glasses in mania
  - 24 manic patients
  - 7-day observation followed by 7-day trial of blue blocking (BB) or clear glasses
    - 6 PM-8AM
  - Patients already treated with valproate, lithium, carbamazepine, and/or lamotrigine
    - Most patients also took a benzodiazepine
      - 1 patient took mirtazapine, lithium and lamotrigine
  - Initial YMRS 23-27
  - Mean YMRS decrease after 7 days
    - BB glasses: 14
    - Control: 1.7
    - ES=1.86

Slide 2

TEG Henriksen et al: Bipolar Disorders 2016;18:221

Blue Blocking Glasses for Mania

- BB Study (cont)
  - 2 patients developed transient depression
    - Ameliorated by decreasing BB time by 2 hours
  - Activity significantly decreased in BB group
  - No significant change in sleep
  - Psychotic patients tolerated glasses
- Effect may be mediated by direct effect on ipRGC moderation of mood and cognition rather than improved sleep or change in melatonin secretion

Slide 3

TEG Henriksen et al: Bipolar Disorders 2016;18:221

Mood Stabilizers

Evidence Based Review of Mood Stabilizer Studies

- Review of all bipolar treatment pharmacologic treatment studies through June 2002
- Results categorized as positive or negative
- Criteria for efficacy as mood stabilizer: 2 positive trials
  - Placebo controlled: active agent > placebo at $p<0.05$
  - ABA: 50% relapse with placebo substitution
  - Active drug: > comparison drug at $p<0.05$
- 81 class A monotherapy trials

Slide 1 of 2

Bauer MS, Mitchner L: Am J Psychiatry 2004;161:3-18

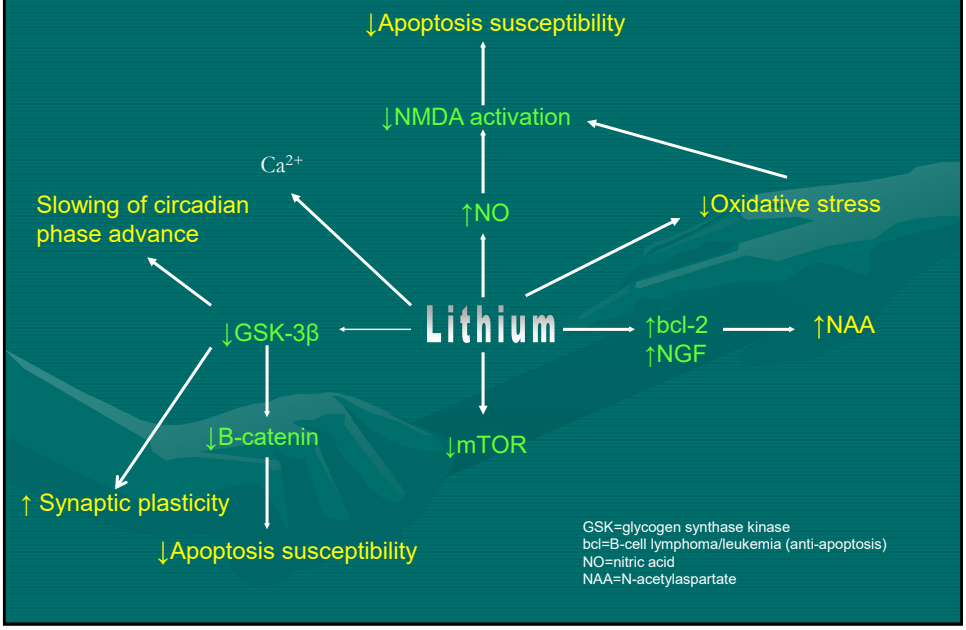
Evidence Based Review of Mood Stabilizer Studies

- Conclusions
  - Not enough data to evaluate efficacy of any drug in reducing frequency or severity of one kind of episode while not increasing frequency or severity of another kind of episode
  - Only lithium fulfills all 4 mood stabilizer criteria whether or not equivalence trials are included:
    - Treats mania
    - Treats bipolar depression
    - Prophylaxis of mania
    - Prophylaxis of bipolar depression

Slide 2 of 2

Bauer MS, Mitchner L: Am J Psychiatry 2004;161:3-18

Lithium Intracellular Actions



Lithium and Kidney Disease

- Danish data base study of 1.8 million people over 17 years
  - 10,591 with first mania/bipolar diagnosis during study
- Risk of chronic kidney disease (CKD) increased in bipolar disorder independent of treatment
- In bipolar disorder
  - Chronic lithium treatment (≥60 prescriptions) associated with increased possible and definite laboratory CKD but not renal failure (dialysis or transplant)
    - Could be result of more careful monitoring

Slide 1

L.V Kessing et al. JAMA Psychiatry doi:10.1001/jamapsychiatry.2015.1834

Lithium and Kidney Disease

- Chronic anticonvulsant treatment associated with increased laboratory CKD
  - Greater risk of renal failure with more prescriptions
  - Could be result of patients with pre-existing renal disease given anticonvulsants with natural history of progression of CKD
- Conclusions
  - Renal function should be monitored in all bipolar disorder patients
  - Mild increases in renal function tests with lithium may not progress to renal failure
  - Authors' recommendation that levels of 0.6-0.8 have lower risk of CKD not justified
    - No lithium levels reported in study

Slide 2

Lithium in Women

- Greater risk of hypothyroidism
- Decreased serum levels premenstrually
  - May result in premenstrual relapse

Summary of CCB Studies

- Verapamil best studied
  - Most trials demonstrate superiority to placebo and equivalence to lithium or clonidine for mania
  - Case reports suggest mood stabilizing effects
  - Equal to placebo for mania in one study
    - 9-13 day trial
    - Inadequate lithium dose
    - Dosing not frequent enough
  - Advantages of verapamil:
    - Well tolerated
    - No blood tests, sedation, weight gain
  - Disadvantages of verapamil:
    - Not useful in treatment resistant bipolar disorder
    - Extensive first pass metabolism requires high doses and frequent administration
    - Neurotoxic interactions with carbamazepine

Slide 1

Summary of CCB Studies

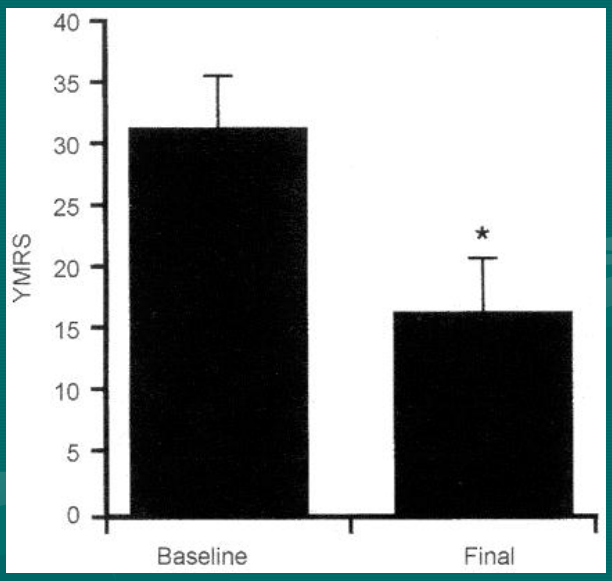
- Nimodipine
  - Positive studies in mania and refractory, complex mood cycling
    - Equivalent to lithium in one mood stabilizing study
  - Requires high doses and very frequent administration
- Isradipine
  - Structurally related to nimodipine
  - Binds to different receptor although a DHP
  - Seems to have potential as mood stabilizer
    - Recent positive study

Slide 2

PKC Inhibitor

- Tamoxifen is estrogen receptor antagonist and PKC inhibitor at similar doses
- Open trial suggested antimanic effect
  - Small N
- Recent double-blind study
  - NNT for response 2.5
- Not a practical long-term treatment
  - Induces menopause
  - Risk of uterine cancer
  - Could cause rebound estrogen receptor up-regulation

Manji H et al: Br J Psychiatry 2001;178 Suppl 41:s107-s119



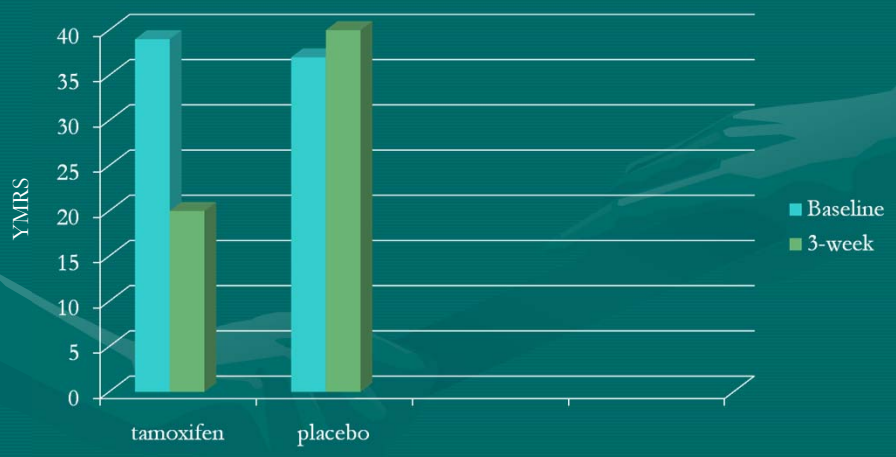
Open Tamoxifen Trial in Mania

Double-Blind Tamoxifen Trial

- Three week trial in 66 treatment refractory hospitalized manic patients
- All patients hospitalized
- Low dropout rate
- YMRS and CGI-Bipolar decreased with tamoxifen, increased with placebo
- Response rate 44% with tamoxifen, 4% with placebo

A Yildiz : Arch Gen Psychiatry 2008;65:255-263

Controlled Tamoxifen Trial



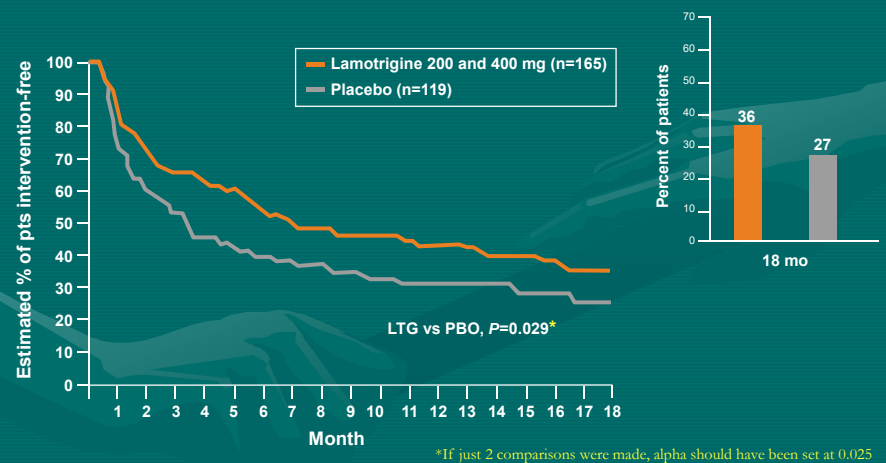
Yildiz A et al: Arch Gen Psychiatry 2008;65:255-263

Lamotrigine Maintenance in Bipolar Depression

- 349 recently depressed bipolar I patients switched over 6 weeks to lamotrigine over 8-16 week open-label phase
- 175 patients who stabilized were randomized for 18 months to
  - Lamotrigine 50, 200, 400 mg/day
  - Lithium 0.8-1.1 mM
  - Placebo
- Lamotrigine significantly > placebo for lengthening time to recurrence of depressive symptoms; no increase in mania
- Lithium significantly > placebo for increasing time to manic recurrence; no increase in depression

L Gyulai, M Frye: GSK, UCLA; Bowden et al 2003

Lamotrigine Time to New Intervention for Bipolar Depression

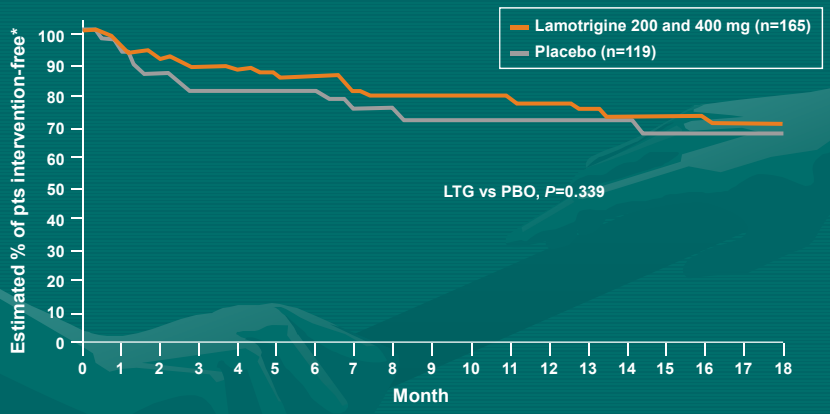


*If just 2 comparisons were made, alpha should have been set at 0.025
If more comparisons, alpha should be lower

Calabrese JR et al. *J Clin Psychiatry 1999;60:79-88*

Lamotrigine Time to Intervention for a Manic Episode

Currently or Recently Depressed Patients



Note: the study was not designed to demonstrate a difference in time to intervention for a manic episode.
* Some patients considered intervention-free for manic episodes could have had intervention for depressive episodes.

Bowden et al. Arch Gen Psychiatry. 2003:60:392-400

Open Studies of Gabapentin

Investigators	Target symptoms	Scale used	N	Response rate %
Altshuler et al, 1999	Hypomania/mania	CGI-BP	18	78
Ghaemi et al, 2001	Mania	CGI-BP	21	43
Ghaemi et al, 1998	Mania and depression	CGI-I	50	30
Knoll et al, 1998	Mania and depression	CGI-I	12	75
Young et al, 1997	Depression	HDRS	15	53

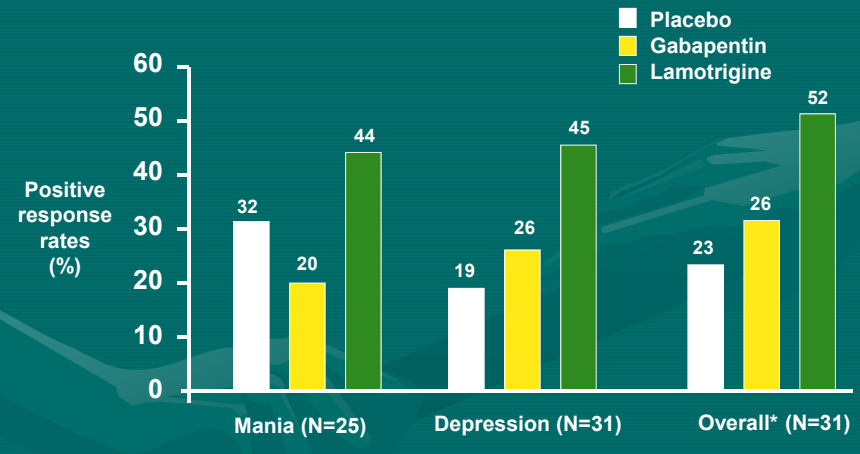
CGI-BP = Clinical Global Depression for Bipolar Disorder; CGI-I = Clinical Global Impression of Improvement Scale; HDRS = Hamilton Depression Rating Scale.

Adjunctive Gabapentin in Bipolar Disorder: A Placebo-Controlled Trial

*Placebo>gabapentin
** p=NS

Pande AC, et al. *Bipolar Disord.* 2000;2(3pt 2):249-255.

Double Blind Comparison of 6-Week Crossover Trials of Placebo, Gabapentin, Lamotrigine in Refractory Bipolar Disorder

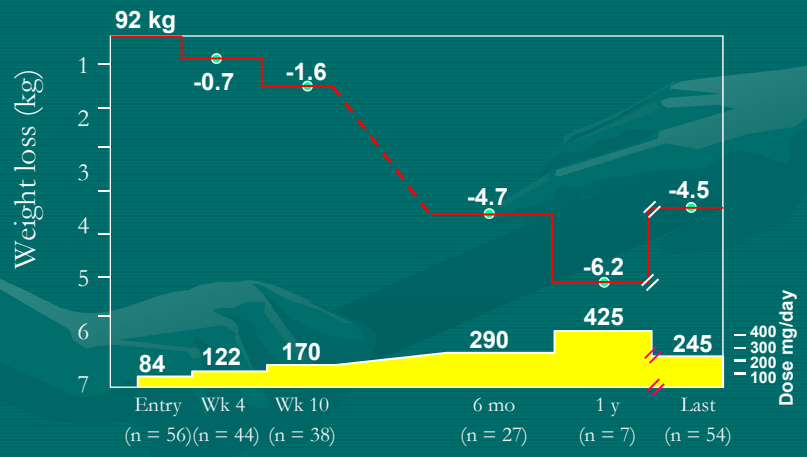


Lamotrigine>gabapentin=placebo

Frye MA, et al. *J Clin Psychopharmacol.* 2000;20:607-614.

Weight Loss with Topiramate with Duration of Treatment

Stanley Foundation Bipolar Outcome Network



McElroy S, et al. *Biol Psychiatry.* 2000;47:1025–33.

Zonisamide

- Open label trial beneficial in 21 bipolar patients
- Controlled study negative
- 16-week randomized, double-blind, placebo controlled trial of zonisamide (mean dose 427 mg) in 51 of 60 patients followed by 16-week single-blind extension
  - All received dietary counseling
  - In the double-blind phase, the zonisamide group lost 5.9 kg, versus 0.9 kg for the placebo group ($p < 0.001$)
  - Considering just the patients who completed this phase, zonisamide patients lost 6.4 kg and placebo patients lost 1.1 kg ($p < 0.001$)
  - 10/19 zonisamide patients and none of 17 placebo patients had lost at least 10% of their body weight by week 32 ($p < 0.001$)

Gadde et al 2003

Levetiracetam

- N-type calcium channel blocker anticonvulsant
  - Does not alters $[Ca^{2+}]_i$
- Approved as adjunctive therapy for refractory complex seizures
- Reduced mania in 7/10 manic patients over 4 weeks when added to haloperidol
- No difference from placebo in 6-week DBPC study of bipolar depression

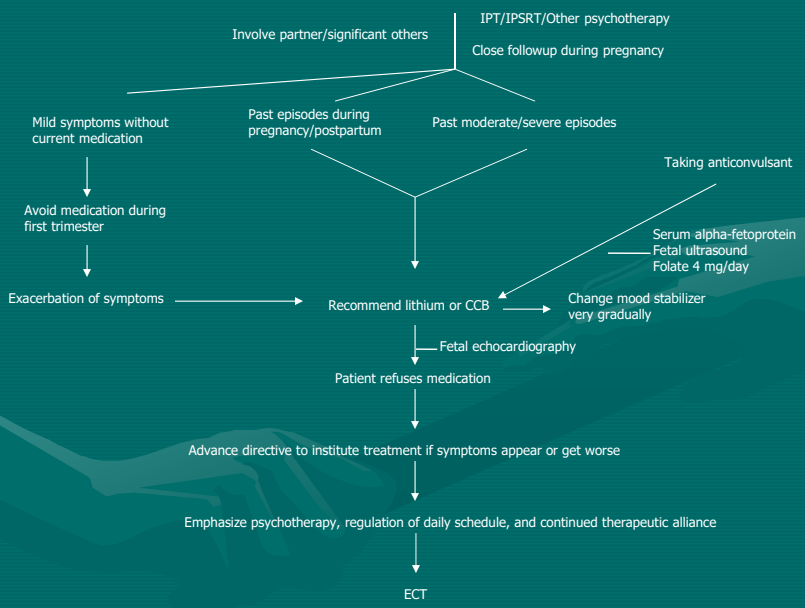
Grunze and Walden 2002; A Saricicek et al: J Clin Psychiatry 2011;72:744-780

Adverse Effects

Risks of Mood Stabilizers During Pregnancy

Lithium	Ebstein's anomaly (risk increased 10-400 times, or 1/50-1/2000) Floppy infant Neonatal lithium toxicity in baby and mother if dose not reduced Neonatal goiter
Anticonvulsants (lamotrigine may be somewhat safer)	Neural tube defects Congenital heart disease Mental/growth retardation Urogenital defects Neonatal hypoglycemia/hepatoxicity with valproate Fetal valproate syndrome (facial dysmorphology, limb/heart defects Risk 7-10% IQ 9 points lower at age 3 in children exposed to carbamazepine, lamotrigine, phenytoin or valproate in third trimester Increased risk with polytherapy and higher dose
Antipsychotic drugs	Low birth rate with atypicals No teratogenicity with neuroleptics except possible malformations with aliphtic phenothiazines during weeks 4-10 Trifluoperazine, perphenazine may be safest Neonatal EPS, jaundice, intestinal obstruction rare Neuropsychological impairment at age 6 months Behavioral teratogenicity in animals
Calcium channel blockers	None demonstrated
ECT	None

Bipolar Patient And Pregnancy



PCOS and Valproate

- Valproate
  - Study of 238 epileptic women taking CBZ and/or VALP
    - Polycystic ovaries on ultrasound in
      - 43% on VALP
      - 50% on VALP + CBZ
      - 80% of women who began VALP before age 20
    - Elevated testosterone in 17-38% on VALP without or with CBZ

Slide 1

Isojarvi et al: NEJM 1993;319:1383-1388

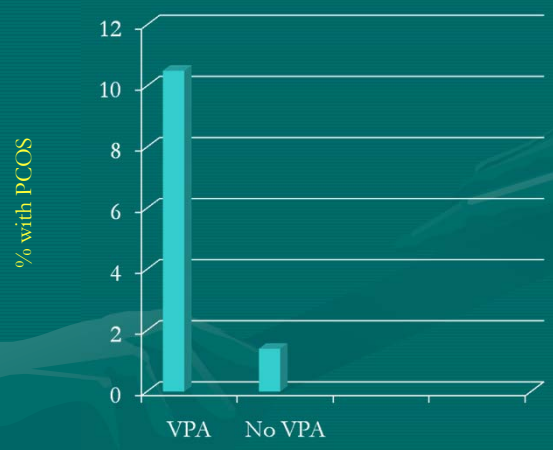
PCOS and Valproate

- Valproate
  - 65 women taking VALP and/or CBZ
    - 50% gained mean of 21 kg
    - 64% had polycystic ovaries and/or hyperandrogenism
    - Elevated insulin
  - Valproate promotes anovulatory cycles and obesity
    - Increases risk of polycystic ovaries
- PCOS
  - Polycystic ovaries
  - Menstrual abnormalities
  - Hyperandrogenism
  - Obesity, insulin resistance, diabetes risk, hypertension

Slide 2

Isojarvi et al: Ann Neurol 1996;39:579-584

PCOS in STEP-BD



Other Anticonvulsants and Gender

- Carbamazepine
  - CYP 3A4 and 2C 19 induction reduces estrogen levels in women taking oral contraceptives
  - Increased risk of OC failure
  - Teratogenicity risk if pregnancy occurs
- Oxcarbazepine
  - 2C 19 inducer
  - Similar pregnancy risk

Slide 3

Maintenance Antipsychotics

Atypical Antipsychotics

- Effect of mood stabilizing medications usually not immediate
- All antipsychotic drugs are rapidly effective for mania
  - Benzodiazepines, barbiturates and ECT are effective acutely for mania
- Maintenance studies of atypical antipsychotics limited by
  - Sample enrichment
    - Recently manic now stable patients who responded to open treatment
      - Usually mood stabilizer + atypical or placebo
  - Only patients studied are
    - Bipolar I
    - Willing to enroll in long-term study
  - Only outcome measures are symptom rating scale scores
  - "Remission" defined as YMRS ≤ 12 (i.e., patients 1/3 as manic)
- Conclusion: Atypicals are first choice for acute treatment of mania, later choice for maintenance

Olanzapine Add-On Maintenance Study

- 344 patients with remission of pure or mixed mania after 6 weeks treatment with lithium or valproate + olanzapine or placebo after poor response with 2 weeks of monotherapy with mood stabilizer
  - Patients had received therapeutic level of lithium or valproate for mean of 67 days prior to study
- 160 patients had lithium or valproate plus olanzapine
  - 61 excluded; 58 because no remission
  - 99 had syndromic remission
    - These patients were randomly assigned to
      - Lithium or valproate plus placebo
      - Lithium or valproate plus olanzapine
    - 18 month trial
- Patients stayed on olanzapine longer than placebo
- Time to relapse of some symptoms but not actual episode longer with olanzapine add-on
  - Primarily for hypomanic symptoms like irritability, thought disorder, aggression

Tohen M et al: Br J Psychiatry 2004;184:337-345

Slide 1

Olanzapine Add-On Maintenance Study

- Weaknesses
  - Study enriched by eliminating almost 40% of acutely treated olanzapine patients
  - Fewer symptomatic relapses explained by sedative and antipsychotic effects
    - No change in syndromic relapse
  - Assumptions for powering study were wrong (dropout rate too high)
  - The positive finding was that almost 70% of patients did not complete olanzapine trial, mainly for lack of efficacy
  - Mean mood stabilizer levels low
    - Lithium: 0.75
    - Valproate: 67
  - Mean weight gain with addition of olanzapine 5-6 kg

Tohen M et al: Br J Psychiatry 2004;184:337-345

Slide 2

Olanzapine Monotherapy Continuation Study

- Industry sponsored multicenter study of 543 patients with bipolar I manic or mixed episode
  - Open-label olanzapine + lithium for 6 weeks
  - 431 patients had YMRS ≤ 12 and HRSD ≤ 8
  - "Remitted" patients randomized to olanzapine 5-20 mg/day or lithium 0.6-1.2 mM for 52 weeks
  - Olanzapine significantly > lithium for
    - Completing trial: 47%% versus 33%
    - Manic relapse: 14% versus 28%
  - Equal rates of relapse to affective episode (30% and 39%) and relapse into depressive episode (16% and 15%)
  - Significantly more weight gain with olanzapine: 1.8 kg versus -1.4 kg

Tohen et al: Am J Psychiatry 2006;163:247

Quetiapine Add-On Maintenance Study

- Industry sponsored multicenter study
- Bipolar I
  - Acute episode within past 26 weeks
  - Substance abuse, medical illness excluded
  - Psychotic symptoms not discussed
- Open label phase: 12-36 weeks
  - Open treatment with lithium or valproate
    - No further adjustment after randomization
  - Open combination of mood stabilizer with quetiapine
  - Patients had to be stable for 12 weeks on quetiapine + mood stabilizer
    - YMRS and MADRS ≤ 12

Slide 1

E. Vieta et al: J. Affective Disord. 2008;109:251-263

Quetiapine Add-On Maintenance Study

- Randomized phase: up to 2 years
  - "Stabilized patients"
  - Hospitalization, ECT, suicide attempt, substance abuse were exclusions
  - Random assignment to quetiapine (mean dose 446 mg) or placebo + lithium or valproate
  - No adjustment of mood stabilizer
  - Hypnotic and lorazepam OK

Slide 2

E. Vieta et al: J. Affective Disord. 2008;109:251-263

Quetiapine Add-On Maintenance Study

Open label: 1461

Double blind: 703

Quetiapine: 336

Placebo: 367

Completed: 213
"Recurrence:" 62

Completed: 134
"Recurrence:" 179

who received adjunctive lorazepam/hypnotic: not reported
well: not known

Slide 3

E. Vieta et al: J. Affective Disord. 2008;109:251-263

Quetiapine Conclusions

- 50% of stable bipolar I patients cannot remain well on quetiapine for 12 weeks
- Effects of sedation and sleep not controlled
  - Was mood improved without sedative/sleep effects?
- Bipolar I patients who do not deteriorate on open label quetiapine are more likely not to deteriorate in double-blind treatment
- Not known if patients without major recurrence are well
- Metabolic side effects more common with quetiapine
- Results cannot be extrapolated to
  - Bipolar II, cyclothymia, etc
  - Bipolar with substance abuse or suicidality
  - Patients who are not stable to begin with
  - Patients who have not responded to quetiapine to begin with
  - Patients treated with mood stabilizer combinations

E. Vieta et al: J. Affective Disord. 2008;109:251-263

Clozapine in Bipolar Disorder

- Weak antidepressant
- Dysphoric mania
- Case series suggest mood stabilizing action
  - Less likely to induce mania than other atypical antipsychotics
  - Better at preventing manic than depressive recurrences
  - Most useful combined with mood stabilizers

Slide 1

Clozapine in Bipolar Disorder

- Clozapine vs no clozapine added to usual treatment in refractory bipolar or schizomanic disorder
  - Patients already taking mean of 4 drugs
  - 82% vs 57% had 30% improvement at 6 months
  - More potent for mania and cycling than depression
  - Mean dose 355 mg/day

Slide 2

Suppes et al: Am J Psychiatry 1999;156:1164

Bipolar Depression

Do Antidepressants Aggravate Bipolar Disorder?

- Natural course of illness
- Antidepressants may be administered in response to deteriorating course
- Not known how long it should take for antidepressants to induce mood cycling
- Incidence of mania in antidepressant trials of unipolar depression depends on ability of investigator to exclude bipolar patients
  - Lower rates in more recent studies with better diagnoses
- "Minor cycling" (hypomania and minor depression with < 8 weeks of euthymia) and subsyndromal symptoms constitute > 1/3 of affective episodes but are not recorded in studies

Solomon DA: APA Meeting, Washington DC May 2008 p 142

Antidepressants and Bipolar Disorder-Acute Study

- 184 patients in Stanley Foundation network randomized to 10 weeks of mood stabilizer + sertraline, bupropion or venlafaxine
  - All patients had depression during treatment with mood stabilizers
    - Average of 1.96 mood stabilizers
  - Responders continued treatment for 1 year
  - Non-responders re-randomized
  - Life charts available for 159 patients
- Total of 228 antidepressant trials
- 49% had acute response
  - Response rate in absence of switch 33%
- 9% switched into mania or hypomania interfering with function
- Another 9% had hypomania without dysfunction

Post R. et al: Bipolar Disorders 2003;5:396-406; Leverich et al 2006

Antidepressants and Bipolar Disorder- Continuation Study

- Report of the 87 one-year antidepressant continuation trials from acute Stanley Foundation study
  - 38% of the 228 acute trials
- "Overall rate of adherence was high…"
- Switch to mania or sustained (≥7 days) hypomania in 37%
- Response rate in absence of switch
  - 43% of those who got to continuation phase
  - 16% of the original intent-to-treat acute sample
- No difference between antidepressants in response rates or switch rates
  - Higher ratio of full to sub-threshold (1-7 days) hypomania in venlafaxine (195 mg)>sertraline (192 mg)>bupropion (286 mg)
    - *Not statistically significant*
- Deterioration of mood more frequent in patients with mixed symptoms

GS Leverich et al: Am J Psychiatry 2006;163:232-239

Antidepressants in STEP-BD

- Initial open trial
  - 2689 of 4366 patients had >1 depressive episode
  - 366 eligible to enroll in antidepressant trial and consented
  - 35% of enrolled patients completed 4 months of treatment
- Six-month controlled trial: 163 patients randomized to mood stabilizer + placebo or antidepressant
  - Lithium; valproate; lithium + valproate; carbamazepine
  - Bupropion (median 300 mg) or paroxetine (median 30 mg)
- 24%-27% had "euthymia" for 8 weeks
  - No difference between placebo and antidepressant addition
- Conclusions:
  - Antidepressants no > placebo for bipolar depression
  - If antidepressants don't help, they may not make patient worse

Sachs G et al: NEJM 2007;356:1711-1722

More From STEP-BD

- Prospective 1-year data from 1742 patients
  - 1/3 had rapid cycling in previous year
  - 1191 completed one year of treatment
- During treatment
  - 60% took antidepressants
    - 43% with a mood stabilizer
    - 43% with a mood stabilizer and atypical antipsychotic
    - 6% took antidepressant alone
- Compared with no antidepressant and controlling for depression severity, ORs with antidepressant for:
  - Rapid cycling: 3.8
  - 2-3 episodes: 2.0
  - 1 episode: 1.7
- More stable patients had
  - Less prior rapid cycling
  - Less antidepressant use
  - More severe symptoms

Schneck CP et al: Am J Psychiatry 2008;165:370-377

Randomized Fluoxetine vs Lithium Trial

- 148 bipolar II outpatients with current MDE treated openly with 20-80 mg/day fluoxetine
- 83 completed open-label treatment and had HDRS score ≤ 8
- 81 randomly assigned for 50 weeks to
  - Fluoxetine monotherapy (N=28)
    - 11 completed treatment
  - Lithium monotherapy (level 0.5-1.5; N=26)
    - 5 completed treatment
  - Placebo (N=27)
    - 7 completed treatment

Slide 1

JD Amsterdam, J Shults: Am J Psychiatry 2010;167:792

Randomized Fluoxetine vs Lithium Trial

- Overall attrition was 75%
- Mean time to relapse of depression
  - Fluoxetine: 250 days
  - Lithium: 156 days
    - Relapse hazard: 2.5 versus fluoxetine
  - Placebo: 187 days
- Risk of hypomania
  - Symptoms 3 times as high with fluoxetine versus lithium
  - Syndromal hypomania
    - Fluoxetine: 50%
    - Lithium or placebo: 34%
  - Insomnia was sometimes attributed to depression and sometimes to hypomania, possibly artificially lowering hypomania rate
- Enriched sample and small number of completers suggest that a few patients with bipolar depression may do reasonably well with antidepressant monotherapy but most do not

Slide 2

JD Amsterdam, J Shults: Am J Psychiatry 2010;167:792; Suppes T: Am J Psychiatry 2010;167:738

Antidepressant Discontinuation Study

- Of 1078 subjects in Stanley Foundation Network
  - 549 received an antidepressant for depression
  - 189 took an antidepressant for at least 2 months
    - 84 of these (44% of 189) responded
  - All patients were also taking mood stabilizers
  - Only outcome measure: open CGI
- Of the 84 antidepressant responders
  - Risk of relapse of depression four times greater in the 43 patients who discontinued antidepressant in mean of 74 days after response than the 41 who continued antidepressant for mean of 484 days

Slide 1

L. Altshuler et al: Am J Psychiatry 2003;160:1252-1262

Antidepressant Discontinuation Study

- Limitations
  - Only 189/549 (15%) of bipolar depressed patients were able to continue an antidepressant for 8 weeks
  - Overall antidepressant response rate (44%) lower than response rate in unipolar depression antidepressant trials
  - Hypomania and subsyndromal cycling were not considered
  - No symptom or diagnostic scales were used to measure relapse
  - Antidepressants were discontinued quickly
- Actual conclusions
  - Bipolar depressed patients who do well on antidepressant + mood stabilizer for 6 months may be able to continue the antidepressant for another 6 months
  - Rapid antidepressant discontinuation may lead to rebound depression

Slide 2

L. Altshuler et al: Am J Psychiatry 2003;160:1252-1262

Long-Term Antidepressant Trial

- 70 patients who recovered from bipolar depressive episode on mood stabilizer + antidepressant randomized to
  - Continue antidepressant (N=31)
  - Discontinue antidepressant (N=39)
- 3-year follow-up
- No difference between groups in recurrence of depression
- Nonsigificant increase in mania in antidepressant group
- Long-term continuation of antidepressant did not prevent depressive relapse but did not make patients markedly worse

Ghaemi SN et al: NCDEU annual meeting May 2007; Boca Raton, FL

Ketamine

- 15 unresponsive inpatients with bipolar I or bipolar II depression
- Maintained on lithium or valproate
- Ketamine > placebo for depression with effect size
  - 0.85-0.89 over 40-230 minutes
  - 0.68-0.70 1 day after infusion
  - 0.94-2.09 for suicidal thoughts
- Relapse after 4.5 days

C.A. Zarate et al: Biol Psychiatry 2012;71:939-946

Who Gets Worse on Antidepressants?

- 176 bipolar depressed outpatients on mood stabilizer + bupropion, sertraline or venlafaxine
  - 10 week trial with 8 week follow-up
  - 85 patients responded
  - 45 did not respond but no hypomania
  - 46 developed mania or hypomania
- Patients with treatment-emergent mania/hypomania had more
  - Motor/verbal activation
  - Rapid, pressured speech
  - Racing, tangential thoughts, distractibility
- In 1380 bipolar depressed patients in STEP-BD
  - 2/3 had concomitant manic symptoms, especially
    - Distractibility
    - Flight of ideas/racing thoughts
    - Psychomotor agitation

Frye MA et al: Am J Psychiatry 2009;166:172; Goldberg JF et al: Am J Psychiatry 2009;166:173-181

Antidepressant-Antipsychotic Combination for Bipolar Depression

- 833 patients with bipolar depression (duration 63-82 days) randomized for 8 weeks to
  - Placebo (N=377)
  - Olanzapine 5-20 mg (N=370)
  - Olanzapine + fluoxetine (6/25, 6/50 or 12/50; N=86)
- Half the active treatment patients and 2/3 of placebo patients dropped out
- Both active treatments > placebo
  - Effect size 0.32 for olanzapine, 0.68 for olanzapine/ fluoxetine

Slide 1

Tohen M et al: Arch Gen Psychiatry 2003;60:1079-1088

Antidepressant-Antipsychotic Combination for Bipolar Depression

- No increase in mania scores over 8 weeks
- 19% taking olanzapine had > 7% weight gain
- Conclusions
  - Fluoxetine 50 mg plus olanzapine is about as effective acutely in bipolar depression as 20 mg of fluoxetine in unipolar depression
  - Not clear if fluoxetine alone would work as well
  - "Remitted" patients were not well
  - Absence of increased mania in 2 months does not prove that olanzapine will prevent long-term destabilization of mood by fluoxetine

Slide 2

Tohen M et al: Arch Gen Psychiatry 2003;60:1079-1088

Quetiapine in Bipolar Depression

- Manufacturer sponsored the
  - Studies
  - Manuscript preparation
- 8 week DBPC study of bipolar depression with YMRS<12
- Exclusion criteria
  - Duration <4 weeks or >1 year
  - Other axis I disorder
  - History of nonresponse to 2 or more antidepressants
  - Substance dependence within a year
  - Suicide/homicide risk
- Primary outcome measure: change in MADRS scores
- Randomly assigned to
  - quetiapine 300 mg
  - quetiapine 600 mg
  - placebo
- LOCF

Calabrese JR et al: Am J Psychiatry 2006;162:1351-60

BOLDER I

838 Screened

542 Randomized to one bedtime dose
(360 bipolar I)

511 had at least 1 dose and 1 assessment

Quetiapine 600 mg	Quetiapine 300 mg	Placebo
N=180	N=181	N=181
Baseline MADRS 30	Baseline MADRS 30	Baseline MADRS 31
82 dropped out	60 dropped out	74 dropped out
98 completed	121 completed	107 completed
MADRS change -17	MADRS change -16	MADRS change -10

Calabrese JR et al: Am J Psychiatry 2006;162:1351-60

BOLDER II

788 Screened

506 Received at least 1 dose
338 Bipolar I
30% DSMIV RC

467 had at least one post-baseline measure*

Quetiapine 600 mg	Quetiapine 300 mg	Placebo
Baseline MADRS 30 Baseline SDS 18	Baseline MADRS 31 Baseline SDS 19	Baseline MADRS 30 Baseline SDS 18
53% completed	59% completed	66% completed
MADRS change -16 52% remission SDS change -7.9	MADRS change -17 52% remission SDS change -7.3	MADRS change -12 37% remission SDS change -6.0

*No correction for multiple tests

Thase M et al: J Clin Psychopharmacol 2006;26:600

Sedation in Quetiapine Studies

- Somnolence only reported as adverse event, no questioning about sedation
- Somnolence reported by
  - 57% on quetiapine
  - 14% on placebo
- MADRS decrease for all *quetiapine* patients with somnolence -18.8
- MADRS decrease for all *placebo* patients with somnolence -18.9
- Similar MADRS decrease for quetiapine patients with and without somnolence, but no control of effect of somnolence on significance of MADRS score reduction

Quetiapine in Bipolar Depression

- Conclusions
  - 40% of ideal patients do not stay on quetiapine for 8 weeks
  - Quetiapine 300 mg=quetiapine 600 mg > placebo for reduction of MADRS
    - Difference only significant in bipolar I
  - Substantial impact of sedation on improvement
  - Response/remission defined only by a depression rating scale score
    - Statistically significant differences not clinically overwhelming
  - >70% of bipolar depressed patients would be excluded from this study
  - Impact on long-term mania/cycling/recurrence risk unknown

Lurasidone Add-On for Bipolar Depression

- 672 patients with bipolar I disorder with major depressive episode of 1-12 months duration screened
  - Mean age 41-43
  - Duration of illness 13 years
  - 324 excluded
  - 183 assigned to flexible dose lurasidone (mean dose 66 mg) + valproate (71-75 µg/mL) or lithium (0.67-0.74 mM)
    - 143 completed
  - 165 assigned to placebo + valproate or lithium
    - 136 completed
  - Duration of treatment with mood stabilizer not stated
- 6-week study
- Exclusions
  - Suicidality
  - Hospitalization for mania within 60 days
  - Substance abuse within 3 months or dependence within 1 year
  - Nonresponse to 3 or more antidepressants with or without mood stabilizer during current episode

Slide 1

A. Loebel et al: Am J Psychiatry 2014;171:169-177

Lurasidone Add-On for Bipolar Depression

- Changes with treatment
  - MADRS
    - Lurasidone: -17.1
      - Final score 13.5
    - Placebo: -13.5
      - Final score 17.3
    - Effect size 0.34
  - CGI depression severity
    - Lurasidone: -1.96
      - Final 2.54
    - Placebo: -1.51
      - Final 3.09
    - Effect size 0.38

Slide 2

A. Loebel et al: Am J Psychiatry 2014;171:169-177

Lurasidone for Bipolar Depression

- 6-week study
- Lurasidone or placebo added to lithium or valproate
- Lurasidone > placebo for MADRS reduction
  - -17.1 versus -13.5
    - Effect size 0.34
  - -16 versus -12 in BOLDER studies
- Lurasidone > placebo for CGI-BP severity reduction
  - -1.96 versus -1.51
    - Effect size 0.36
- Effect sizes small

A Loebel et al: Am J Psychiatry 2014;171:169

Lurasidone Conclusions

- Brief studies
- Real-life patients excluded
  - 50% failed screening
- Effect sizes small
- Lurasidone well-tolerated

Cariprazine Monotherapy for Bipolar I Depression

- D2/3 and 5HT1A partial agonist
- Industry sponsored 8-week RCT
- 1013 patients screened
  - Mean age 40-44
  - Duration of current episode: 3-4 months
    - Baseline MADRS 30-31
- 584 randomized to placebo or cariprazine 0.75, 1.5 or 3 mg
- 73% completed study
- MADRS changes:
  - Placebo: -11
  - 0.75 mg: -13; ES 0.20
  - 1.5 mg: -15; ES 0.42
  - 3.0 mg: -14; ES 0.26
- Final MADRS scores
  - Placebo: 20
  - Cariprazine: 16-18

S. Durgam et al. Am J Psychiatry doi: 10.1176/appi.ajp.2015.15020164

Cariprazine 6-Week Study

- Inclusion criteria
  - Bipolar 1 MDE ≥1 and <12 months duration (mean 4 months)
  - <12 on YMRS
- Exclusion criteria
  - Psychiatric or medical comorbidity
  - Substance abuse
  - Suicidal
  - Personality disorder
- 782 patients screened; 488 randomized
  - Mean age 42-44
  - Mean baseline MADRS 30-31
- Mean MADRS reduction
  - Placebo -12.6
  - Cariprazine 1.5 mg -15.1 (ES 0.28)
  - Cariprazine 3 mg -15.6 (ES 0.34)
- Other studies report same results

W Earley et al: AJP 2019;176:439

Noontime Artificial Bright Light for Bipolar Depression

- 43 patients with moderate bipolar depression
  - Stable doses of mood stabilizers
  - No manic symptoms
- 6-week random assignment to bright light 7000 lux vs 50 lux (control)
  - Median length of treatment 46 minutes
- Most improvement at 4-6 weeks
  - 68% remission with active light
  - 22% remission with control

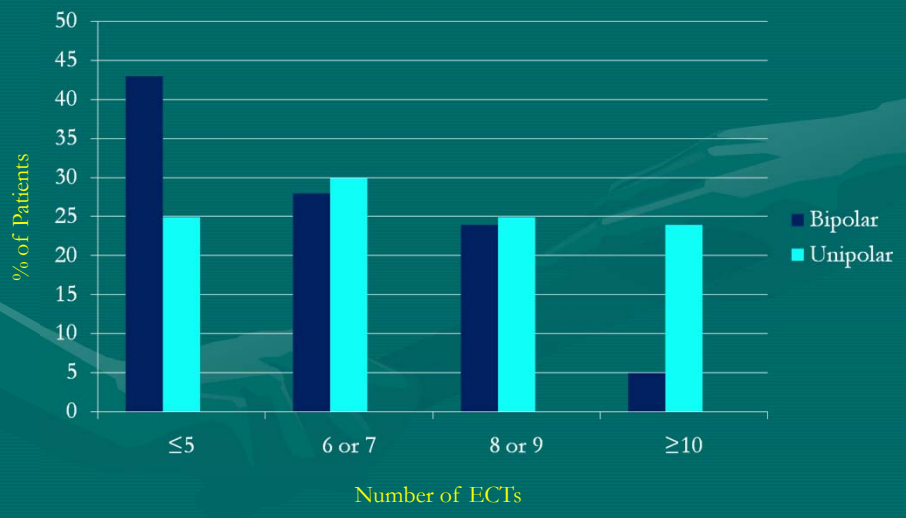
DT Sik et al: Am J Psychiatry doi:http://dx.doi.org/10.1176/appi.ajp.2017.16101200

ECT in Bipolar Illness

- More effective than lithium for mania
  - 80% efficacy
- ?BL>UL
  - Close electrode placement in UL may influence results
- ?Lower stimulus intensity than unipolar
- Fewer treatments for uncomplicated illness

Slide 1 of 2

Average # ECTs Needed by 333 Patients



Sackeim HJ, Prudic J: J ECT 2005;21:195

ECT in Bipolar Illness

- Use in rapid cycling unclear
- Interactions with lithium, anticonvulsants, benzodiazepines
- Maintenance ECT or medications necessary
- rTMS may not be as effective in bipolar disorder

Slide 2 of 2

DBS in Bipolar Depression

- 10 patients with treatment resistant MDD, 7 with treatment resistant bipolar depression
  - All but 2 taking medications
    - Mean # of medications: 3
- Subcallosal cingulate DBS
- 4 week single blind sham stimulation
- 24 weeks open stimulation
- Attempt at single blind sham substitution
  - 3/3 patients relapsed, this phase discontinued
- 2 years open treatment
- Equal response in unipolar and bipolar
- Neurological A/Es rare
- 2 suicide attempts

PE Holtzheimer et al: Arch Gen Psychiatry doi:10.1001/archgenpsychiatry.2011.1456

Thyroid Hormone in Refractory Bipolar Illness

- Up to 2/3 of rapid cyclers are subclinically hypothyroid
- Bauer and Whybrow, 1990:
  - 11 rapid cyclers
  - 8 were hypothyorid
  - Thyroxin 0.15-0.4 mg/day
  - 10 had decreased mania and depression over 78-370 days; 3/4 relapsed on placebo
  - All became hyperthyroid

Risks of Excessive Thyroid Replacement

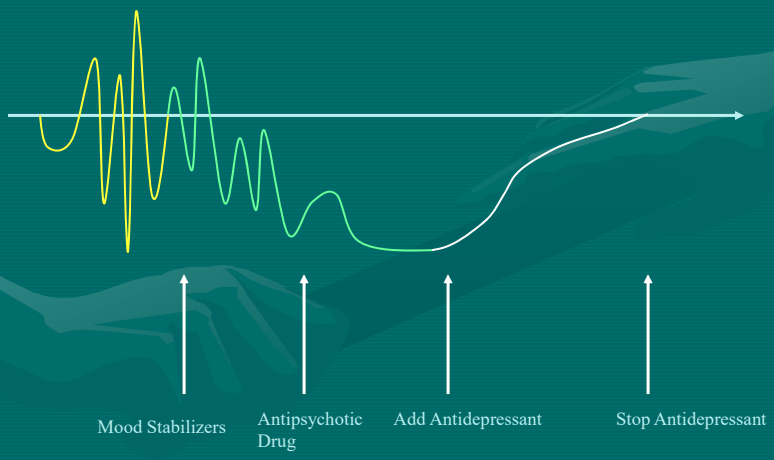
- Atrial fibrillation
- Congestive heart failure
- Osteoporosis
- Hypothyroidism
- Anxiety

Principles of Bipolar Maintenance

- Try mood stabilizer combinations first
- Address sleep and circadian rhythms
- Adjust all treatments until patients are well functionally as well as symptomatically
- There is no "therapeutic level" for valproate or carbamazepine; best results acutely occur with levels > 94 mcg/mL
- Anticonvulsant level obtained when patient is well is the therapeutic level for that patient
- Optimize lithium level to around 1 mM if possible
- Add antipsychotic drug when mood stabilizers are not fully effective
  - Especially for psychotic symptoms
- Maintenance ECT an option

Allen MH: Am J Psychiatry 2006;163:272-275

Treatment of Bipolar Depression and Mixed/Cycling States

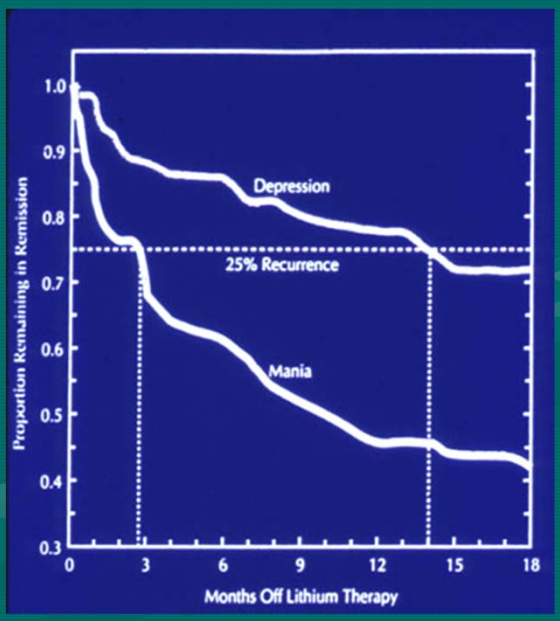


Antidepressants in Bipolar Depression

- Lamotrigine
- Gabapentin
- Artificial bright light
- Atypical antipsychotic drug
- Stimulant
- Antidepressant
  - Tranylcypromine or other MAOI
  - Short acting SSRI
  - Bupropion
- Pramipexole
- Modafinil

Principles in the Treatment of Mixed and Rapidly Cycling Bipolar Disorder

- Keep a mood chart
- Treat substance abuse
- Involve family members
- Address desire for immediate relief of depression
  - Review use of antidepressants



Psychotherapy in Bipolar Disorder

- Not fully effective by itself
- Increases effectiveness of medications
- Only structured psychotherapies have been studied

Randomized Psychotherapy Trial

- 244 bipolar depressed patients taking mood stabilizers with or without antidepressants randomly assigned to
  - Average 2.2 individual education sessions over 6 weeks
  - Planned 30 sessions over average of 7 months of
    - CBT (13 sessions)
    - IPSRT (17 sessions)
    - FFT (12 sessions)

Slide 1

Miklowitz D et al: Arch Gen Psychiatry 2007;64:419

Randomized Psychotherapy Trial

- 59% completed trial
- One-year recovery
  - Experimental therapies: 64%
  - Control therapy: 52%
  - Recovery HR for experimental therapies 1.47; 95% CI 1.08-2.0
- Recovery faster for experimental therapies
  - No difference between IPSRT, FFT and CBT
- Patients in experimental therapy 1.6 times as likely to be well in any month

Slide 2

Miklowitz D et al: Arch Gen Psychiatry 2007;64:419

Common Features of the Effective Bipolar Therapies

- Stable therapeutic relationship
- Involves the family
- Trained therapist
- Address sleep-wake and other rhythms
- Deal with nonadherence
- Identify and treat early symptoms of relapse

Miklowitz D et al: Arch Gen Psychiatry 2007;64:419

Childhood Bipolar Disorder

Early Onset Bipolar Disorder

- More lifetime episodes
- More irritability, less euphoria
- More psychosis and rapid cycling
- Less euthymia
- More suicide attempts and violence
- More comorbidity
  - Especially anxiety, substance abuse, externalizing disorders, ADHD
- Lower medication response

MA Potter et al: J Child Adolesc Psychiatry 2009;19:529

Clues to Bipolarity in Children

- Mood swings
- Early onset depression
- Highly recurrent depression
- Lethargy
- Profound, vengeful aggression
- Intrusiveness
- Decreased need for sleep
- Difficulty getting out of bed in the morning
- Rapid speech
- Grandiose defiance

Slide 1

Clues to Bipolarity in Children

- Overstimulation in interactions
  - Escalating anger and confrontation in response to limit setting
  - Overstimulation decreases when child left alone
- Dramatic thrill seeking
  - No fear of consequences
  - Challenging death
- Abrupt onset or fluctuation of symptoms
- Psychosis, especially hallucinations
- Mood disorder in 3 consecutive generations

Slide 2

Severe Mood Dysregulation

- Now called disruptive mood dysregulation disorder
- Baseline chronic, non-episodic negative mood (anger/sadness) between outbursts with
  - Hyperarousal manifested by
    - Pressured speech
    - Agitation
    - Insomnia
    - Flight of ideas/racing thoughts
    - Distractibility
    - Intrusiveness
- Frequent increased reactivity to negative events and circumstances with
  - Temper tantrums
  - Rages
  - Aggression toward people/property

Slide 1

E Liebenluft: Am J Psychiatry 2011;168:129; A Stringaris et al: J Am Acad Child Adolesc Psychiatry 2010;49:397

Severe Mood Dysregulation

- In NIMH sample of 146 youths with SMD
  - 85% met criteria for ODD
  - 86% met criteria for ADHD
  - 58% met criteria for an anxiety disorder
  - 16% met criteria for MDD
- Lifetime prevalence thought to be 3.3% in age 9-19
- Lower bipolar family history than childhood bipolar disorder
- Difficulty processing social cues, inhibiting behavior, adapting behavior to changing circumstances
- Attentional deficits

Slide 2

E Liebenluft: Am J Psychiatry 2011;168:129; A Stringaris et al: J Am Acad Child Adolesc Psychiatry 2010;49:397

Severe Mood Dysregulation

- Comparison of 84 children with SMD and 93 with bipolar I/II with one clear manic/hypomanic episode with elevated or expansive mood but not irritability alone
  - Mean age 12-13
  - Comorbid diagnoses
    - ADHD: 45-82%
      - More common in SMD
    - ODD: 26-79%
      - More common in SMD
- 29-month follow-up
  - Rate of hypomania/mania
    - Bipolar: 62%
    - SMD: 1%
- Possible treatments
  - SSRIs
  - Stimulants
  - Valproate

Slide 3

E Liebenluft: Am J Psychiatry 2011;168:129 ; A Stringaris et al: J Am Acad Child Adolesc Psychiatry 2010;49:397

Severe Mood Dysregulation in DSM-5

- Disruptive mood dysregulation disorder
- Hyperarousal left out of diagnostic criteria
  - Data from SMD studies cannot be extrapolated
- Classified with depressive rather than bipolar disorders

Risks of Antidepressants and Stimulants in Bipolar Children

- Dysphoric mania/hypomania
  - Often with more impulsivity, irritability and psychosis
  - Elation rare
- Increased mood swings
  - Antidepressant works for a while and then "wears off"
  - Fewer well times
- Mixed states
- Cycling into more persistent depression
- Escalating defiance
- Treatment resistance

Slide 1 of 2

Risks of Antidepressants and Stimulants in Bipolar Children

- One study suggested no adverse effect of stimulants in children with bipolar disorder + ADHD treated with mood stabilizers
  - Not a randomized controlled trial
- It may take longer for mania to develop with stimulant than with antidepressant
- Bipolar disorder is diagnosed earlier in children who have taken antidepressants
  - Antidepressants bring out bipolar disorder
  - Antidepressants used earlier because depression is more severe
- Private insurance database examined new diagnosis of mania over mean of 41 weeks in 7 million enrollees
  - 5.4% developed mania
  - Hazard ratio for mania 2.1-3.9 with antidepressant
  - Younger age predicted greater risk of antidepressant-induced mania
    - Prepubertal children at highest risk (number needed to harm = 10, versus 23 for older patients)
  - No data on misdiagnosis of bipolar disorder after 41 weeks

Carlson GA et al: J Child Adolesc Psychopharmacol 2000;10:175-184; Martin A et al: Archives of Pediatrics and Adolescent Medicine 2004;158:773-780; Cicero D et al: Psychiatry 2003;66:317-322; Reichart CG, Nolen WA: J Affective Disord 2004;78:81-84

Slide 2 of 2

Treatment of Childhood Bipolar Disorder: General Principles

- Untreated bipolar disorder gets worse with time
  - Kindling and sensitization
  - Increasing complexity of illness
  - More opportunities to "bipolarize" family and peers

Slide 1

Treatment of Childhood Bipolar Disorder: General Principles

- Early treatment prevents later deterioration
- Rapid withdrawal of effective treatment leads to illness rebound
- Psychosocial treatments help but do not cure the mood disorder
- Medications and psychotherapy should usually be combined
  - Involve the family

Slide 2

Principles of Medication Use in Children

- Children are hypermetabolic compared to adults
  - More frequent dosing
  - Higher than expected mg/kg doses
- Frequent dosing increases noncompliance
  - Administering medications in school often not practical
- Higher lithium levels may be necessary in some younger bipolar patients
  - Discussed later

Mood Stabilizer Use in Children

- Phenomenology and Course of Pediatric Bipolar Disorders Study enrolled 115 patients with first manic or mixed episode
  - Over 8 years, 63% received lithium, anticonvulsant or antipsychotic
    - Antimanic drugs used much more frequently in psychiatric versus pediatric practice
  - Other medications received
    - Stimulant: 76%
    - Antidepressant: 64%
    - Beta blocker: 30%
  - 70% were taking two or more medications
  - Earlier recovery over 8 years predicted by
    - Greater % of weeks on lithium
    - Less time in group therapy
      - Overstimulation versus sicker patients assigned to group therapy
- Academy practice parameter recommends lithium or valproate and/or atypical antipsychotic
  - Antipsychotics are used four times as frequently, especially for mania
  - No controlled maintenance studies in pediatric patients
  - Antipsychotics may be more useful for recurrence of psychotic versus nonpsychotic mania

B Geller et al: NCDEU, Hollywood, Fla, June 2009; MP Potter et al J Child Adolesc Psychopharmacol 2009;19-529

Mood Stabilizing Medications in Children

- Lithium
  - Best studied thymoleptic
  - Dosing discussed next
  - Side effects and blood tests can be troublesome
    - Hypothyroidism in >1/3 of patients
    - Cognitive side effects in 50%
- Carbamazepine
  - Sometimes makes adolescents more aggressive
  - 3-4 times/day dosing necessary
- Valproate (divalproex)
  - Follow risk of polycystic ovaries and androgen excess in girls

DBPC Study of Lithium

- 81 bipolar disorder outpatients randomized for 8 weeks to lithium or placebo
  - Mean age 11-12
  - 50% manic, 50% mixed episode
  - Baseline YMRS 30
  - 64% comorbid ADHD
  - Mean lithium dose
    - <30 kg: 956 mg/kg
    - ≥30 kg: 1583 mg/kg
    - No dosing schedule or blood levels reported
    - Concomitant stimulants allowed after 4 weeks

Slide 1

RL Findling et al: Pediatrics; 2015;135:885

DBPC Study of Lithium

- 1 month to statistical separation from placebo
- Final YMRS
  - Lithium: 18
  - Placebo: 22
- Adjusted ES: 0.53
- Side effects
  - weight gain < placebo
  - Mean TSH increase: 3
    - 53% had increase
- Factors affecting outcomes
  - Outpatients without significant complications
    - Moderate baseline mania limits demonstration of decrease
  - No adjustment by blood level
  - Immediate release preparation, presumably with once daily dosing

Slide 2

RL Findling et al: Pediatrics; 2015;135:885

Lithium Dosing in Children

- Usual recommended level around 1mM (27 mg/kg)
- Measurement of brain lithium concentrations using Li-7 magnetic spectroscopy
  - 9 bipolar children and adolescents mean age 13
  - 18 adults mean age 37
  - Brain/serum lithium levels
    - Adults: 0.92
    - Children/adolescents: 0.58
  - Suggests decreased entry or increased efflux of lithium from brain
- More frequent dosing may be necessary due to rapid elimination

Moore et al 2002

Experimental Mood Stabilizers in Children

- Oxcarbazepine
  - No research in bipolar children
  - Epileptic children need higher than predicted mg/kg dose to achieve therapeutic level
- Verapamil
  - Well tolerated
  - No blood tests
  - Frequent dosing necessary
  - Case series only
- Nimodipine
  - Well tolerated
  - Expensive and requires very frequent dosing
  - No studies in children
- Atypical antipsychotic medications
  - Clearly effective for mania in adults
  - Sometimes useful as maintenance treatment
  - Aripiprazole and risperidone FDA approved
  - Rapid development of diabetes reported in adolescents taking olanzapine

Treatment of Comorbid ADHD

- Lower response rate than uncomplicated ADHD
- Some studies suggest mixed amphetamine salts or methylphenidate were effective and safe if adequate mood stabilization
- AACAP guidelines suggest stimulant + mood stabilizer
  - Determine if adequate mood stabilization improves attention
    - Residual inattention could reflect incomplete remission or medication side effect

ADHD Treatment Alternatives in Bipolar Disorder

- α2 agonists
  - Clonidine
  - Guanfacine
  - Improvement of cognition and hyperactivity
    - Effect size 0.4-0.9 for total ADHD scores
      - 0.04-0.16 mg/kg guanfacine
  - Irritability responds better to stimulants
  - Two-year open study found sustained improvement with guanfacine monotherapy
    - Dropout rate 77%!
- Atomoxetine
  - Possible antidepressant effects
- Cholinesterase inhibitors
  - Minimal research
  - Possible additive mood stabilizer effect

FR Sallee et al: J Child Adolesc Psychopharmacol 2009;19:215

Overstimulated Bipolar Child Dilemma

Limit Setting

- Discussion about reasons for limits is overstimulating
- Activation will decrease if child can be alone
- Overstimulated child resists being isolated
- It may be necessary to forcibly isolate the child

Psychosocial Treatments

- Treat the family
  - Mood disorders run in family
  - High expressed emotion makes mood disorder worse
  - Teach family how to limit or discontinue overstimulating interactions
- Social rhythms therapy

Slide 1

Psychosocial Treatments

- Address organization of pathological traits around abnormal mood
  - Make others dislike or leave you before they decide to do it on their own
  - Bring on abnormal mood (e.g., with drug use) rather than experience mood swings passively
  - Self-concept of an unstable, unreliable, unlikable person

Slide 2

Dealing with Trauma

- Bipolar children have high rates of trauma and overstimulation
  - Bipolar family
  - Provocative child
- Discussing trauma may increase affective load
- First goal is to help patient manage mood disorder
- Consider exposure only when mood stabilized

Scope of Nonadherence

- General medical disorders: 25%
- Bipolar disorder: 20-65%
- Patient report may be more accurate than blood levels
- Accounts for significant portion of efficacy-effectiveness gap
  - 2/3 respond in clinical trials
  - 1/3 have similar improvement in practice
- Nonadherence causes
  - Relapse
  - Hospitalization
  - Impairment
  - Higher cost of care
  - Suicide

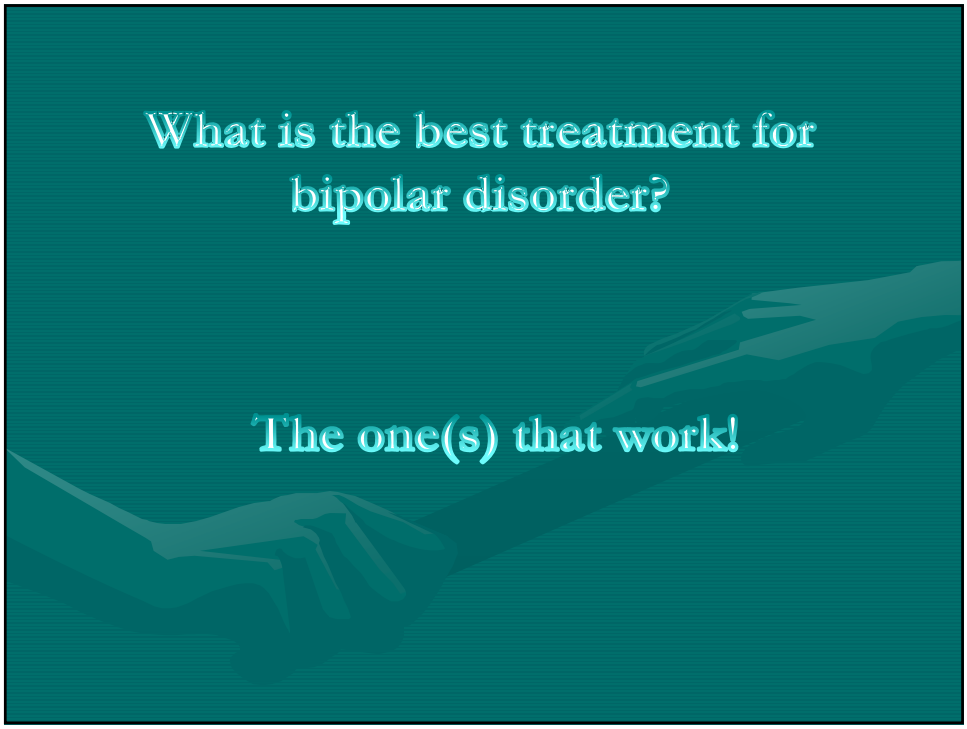
Clinician Nonadherence

- Treatment of 2644 bipolar I Medicaid patients from 1994-2000 for
  - Guideline-recommended care: mood stabilizer + psychotherapy
  - Guideline-discouraged care: Antidepressant without mood stabilizer
  - 1/3 received appropriate care by these measures
  - Bipolar diagnosis associated with prescription of less psychotherapy
- Bipolar patients with SUDs are more likely to get benzodiazepines and to take higher doses than those without SUDs
- Hospitalized bipolar I patients discharged on guideline recommended treatment
  - With psychosis: 1/3
  - Without psychosis: 1/6
- Clinicians who are more familiar with guidelines adhere less to them

AB Busch et al: Psychiatric Services 2007;58:848-854; RE Clark et al: J Clin Psychiatry 2004;65:151-155
PZ Lim et al: Bipolar Disorders 2001;3:165-173EB Dennehy et al: Psychol Med 2005;35:1695-1706

Minimizing Deterioration in View of Limited Data

- Single mood stabilizer for uncomplicated bipolar disorder
- Mood stabilizer combinations for complex or later stage bipolar disorder
- Slow adjustment of all treatments to reduce rebound and excessively rapid control of mixed hypomania
- Intermittent use of antidepressants may be safer than chronic use for bipolar depression
  - Opposite of unipolar depression
- Treat substance abuse
- Integrate psychosocial treatment with pharmacotherapy
  - IPSRT, other conjoint/family therapies
  - Sensitivity to loss
  - Desire to achieve sense of control by making things worse
- Residual symptoms predict later major relapse
- Preventing recurrence has higher priority than immediately treating depressive recurrence


What is the best treatment for bipolar disorder?
The one(s) that work!