Bipolar Disorder: DSM-V Criteria & Diagnostic Features

- Review of Subtypes
- Diagnostic Criteria of Bipolar I Disorder
- Criteria of a Manic Episode
- Criteria of a Hypomanic Episode
- Criteria of a Depressive Episode
- Associated Diagnostic Features

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Bipolar Subtypes

- Bipolar I Disorder
  - Dx only requires 1 type of mood episode (manic)
  - Major depressive episode *not* required
- Bipolar II Disorder
  - Dx requires 2 types of mood episodes (depressive/hypomanic)
  - Absence of full manic episode
  - NOT just a "milder" version of Bipolar I; significant time in depressive episodes and fluctuating moods
- Cyclothymic Disorder
  - Dx similar to type II, except mood episode criteria not fully met
  - Timeframe: at least 2 years (or 1 year for children)
- Secondary Bipolar Disorders:
  - Drug/medication-induced
  - Secondary to other medical condition

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Bipolar I Diagnostic Criteria

- Required: At least one manic episode
- +/- hypomanic episode(s)
- +/- major depressive episode(s)
- +/- disorder specifier(s)
  - w/ rapid cycling
  - w/ psychotic features
  - w/ mixed features*
  - etc.

*Change from DSM IV. Replaces "mixed episode."

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Manic Episode Criteria

- Distinct period (> 1 week OR hospitalization) of abnormally and persistently elevated, expansive or irritable mood
- *plus* abnormally and persistently increased goal-directed activity
- *plus* 3 (or 4 if irritable mood) of DIG FAST
- *plus* marked impairment (social or occupational)

Note: cannot be due to substance or other medical condition

DIG FAST

Distractibility

Insomnia

Grandiosity

Flight of Ideas

Activities

Speech

Thoughtlessness

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Hypomanic (vs Manic) Episode Criteria

- Time: at least 4 days (instead of 1 week)
- Severity: episode observable by others but *not* severe enough to cause marked impairment or hospitalization

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Major Depressive Episode Criteria

- Five (or more) of SIG E CAPS for a period of 2 weeks or more (w/ at least one major symptom)
- *plus* clinically significant distress or impairment (social, occupational, etc.)

Note: cannot be due to substance or other medical condition

Depression: SIG E CAPS

Depressed mood*

Sleep (increased or decreased)

Interests*

Guilt

Energy

Concentration

Appetite

Psychomotor agitation/retardation

Suicidal ideation

*** = major symptom**

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Associated Diagnostic Features

- During manic episode, individuals often do not perceive that they are ill; may resist treatment
- Individuals may change dress, make-up and/or appearance
- Mood may shift very rapidly to anger or depression
- Some individuals may become hostile

Prevalence and Risk/Prognosis

9/17/14

Bipolar I

- 12- month prevalence- 0.6%
- Male to Female- 1.1:1
- Mean age of onset of first manic, hypomanic, or major depressive episode: 18 yo
- Onset occurs throughout the life-cycle
- Late-Onset (60s or 70s)

Bipolar I

- 90% of individuals with a single manic episode go on to have recurrent mood episodes
- 60% of manic episodes occur immediately before a major depressive episode
- 4+ mood episodes within 1 year = “with rapid cycling”

Bipolar I Risk/Prognosis

- More common in high-income countries than low-income countries (1.4 v 0.7%)
- Increased in separated, divorced, or widowed (not never married)
- 10-fold increase in adult relatives of individuals with Bipolar I or II
- Likely shares genetic origin with Schizophrenia (familial co-aggregation)

Bipolar I Risk/Prognosis

- After an individual has a manic episode with psychotic features subsequent episodes are more likely to include psychotic features
- Females more likely to experience rapid cycling, mixed states, depressive symptoms, alcohol use disorder, and have comorbid eating disorders
- Suicide risk is 15X that of general population

Bipolar II

- 12 month prevalence- 0.8%
- Average age of onset- mid 20s
- About 12% of people initially diagnosed with MDD turn out to have Bipolar II
- Number of Lifetime mood episodes > MDD or Bipolar I

Bipolar II

- *Individuals with Bipolar I are *more* likely to experience hypomania than those w Bipolar II
- Interval between mood episodes tends to decrease with age
- Also can indicate “with rapid cycling”
- Psychotic Symptoms do NOT occur in hypomanic episodes (definition)

Bipolar II

- Psychotic Symptoms are less frequent in the major depressive episodes of Bipolar II than Bipolar I
- 5-15% of individuals originally diagnosed with Bipolar II will have diagnosed changed to Bipolar I Disorder due to a manic episode

Bipolar II Risk/Prognosis

- Childhood or Adolescent Onset of disorder may be associated with more severe lifetime course
- Risk for Bipolar II elevated in those with relatives who have Bipolar II (but not Bipolar I or MDD)
- Rapid-Cycling pattern associated with worse prognosis

Bipolar II Risk/Prognosis

- More education, fewer years of illness, and being married are independently associated with functional recovery
- Gender differences data are mixed, many suggesting a slightly higher prevalence in females
- Hypomanic episode following childbirth, 10-20%

Bipolar II Risk/Prognosis

- 32% report a lifetime history of a suicide attempt
- 6.5 fold higher risk of suicide among first-degree relatives of those with Bipolar II than Bipolar I
- 60% have 3+ co-occurring mental disorders (75% anxiety, 37% substance use, 14% eating disorder)

Cyclothymic Disorder

- Lifetime prevalence- 0.4-1.0%
- In mood disorder clinics- 3-5%
- Begins in adolescence or early adulthood
- 15%-50% of people diagnosed with Cyclothymic Disorder will eventually meet criteria for Bipolar Disorder
- More common in first-degree relatives of individuals with Bipolar I Disorder

Neurobiology of Bipolar Disorder

Dave Conklin

Morning Report

9/17/2014

Outline

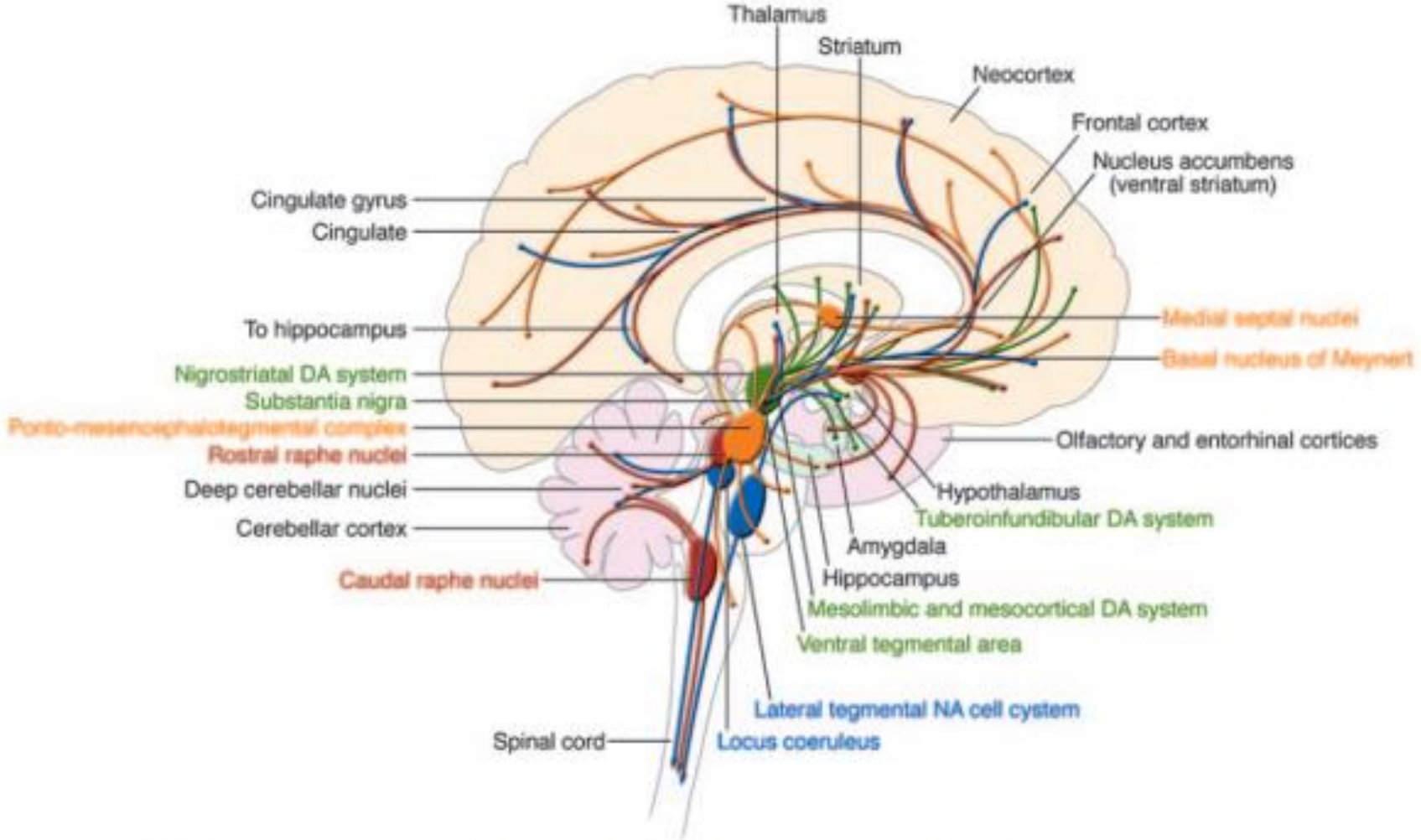
- Neurotransmitters
- Neuroimaging
- Tissue Studies
- Genetic Studies
- Molecular and Cellular Studies

Take Home Points

- Neurotransmitters are not the answer!
- Synapses and neural plasticity in affective and cognitive circuits appear important.
- A multifactorial disease resulting from genetic profiles (protective and risk genes) as well as environmental influences (chronic stressors and trauma)

Neuroplasticity

- Changes in neural pathways and synapses which are due to changes in behavior, environment, neural processes, thinking, emotions, and injury
- Cellular and molecular
- Cortical re-mapping
- Changes in physical structure and functional organization
- Alteration in number and location of synapses



Nuclei as well as their projections are color coded: yellow, cholinergic; green, dopaminergic; blue, noradrenergic; red, serotonergic.

Neurotransmitters:

Noradrenergic System:

- Elevated NE in CSF in mania compared to depression

Serotonergic:

- No alteration in CSF 5-HIAA relative to depression
- No change in receptors relative to depression

Dopaminergic System:

- No evidence to demonstrate differences between unipolar and bipolar depression

Cholinergic:

- Some evidence that cholinergic tone is disrupted in mania
- Physostigmine increases tone in mania
- Pilocarpine requirements increased but normalized after Li.

Neuroimaging

- Reduced activity in R prefrontal cortex during mania
  - Poor impulse control, risk taking, distractibility, poor attention, and delusions
- Decreased gray matter volume , increased ventricular size, and decreased frontal cortical volume.
  - Decreased volume in ACG
  - Decreased gray matter in L dorsal lateral PFC, ventral PFC, and orbital PFC
- Increased white matter hyperintensities
  - Not novel to BPAD
- Decreased N-acetyl-aspartate (a neurochemical produced by mitochondrial but is a marker of mature neurons)
  - In hipocampus, DL-PFC, orbito frontal cortex, and basal ganglia
- Evidence of mitochondrial dysfunction and their role in apoptosis, intracellular calcium regulation, and synaptic plasticity

Post-Mortem Tissues

- Various studies have shown differential neuronal densities and morphologies that to be layer and cell type specific.
- Decreased GAP-43 a neuroplasticity marker is reduced is BPAD in cingulate cortex and hippocampus
- Decreased density of glial cells in frontal cortical areas
- Reduced number of oligodendrocytes and the expression of genes that are related to oligodendrocyte differentiation and myleing productioninthe DL-PFC

Genetic Studies

- High concordance rate as evidenced by family and MZT studies

- Risk genes interact with PKC and glycogen synthase kinase-3β

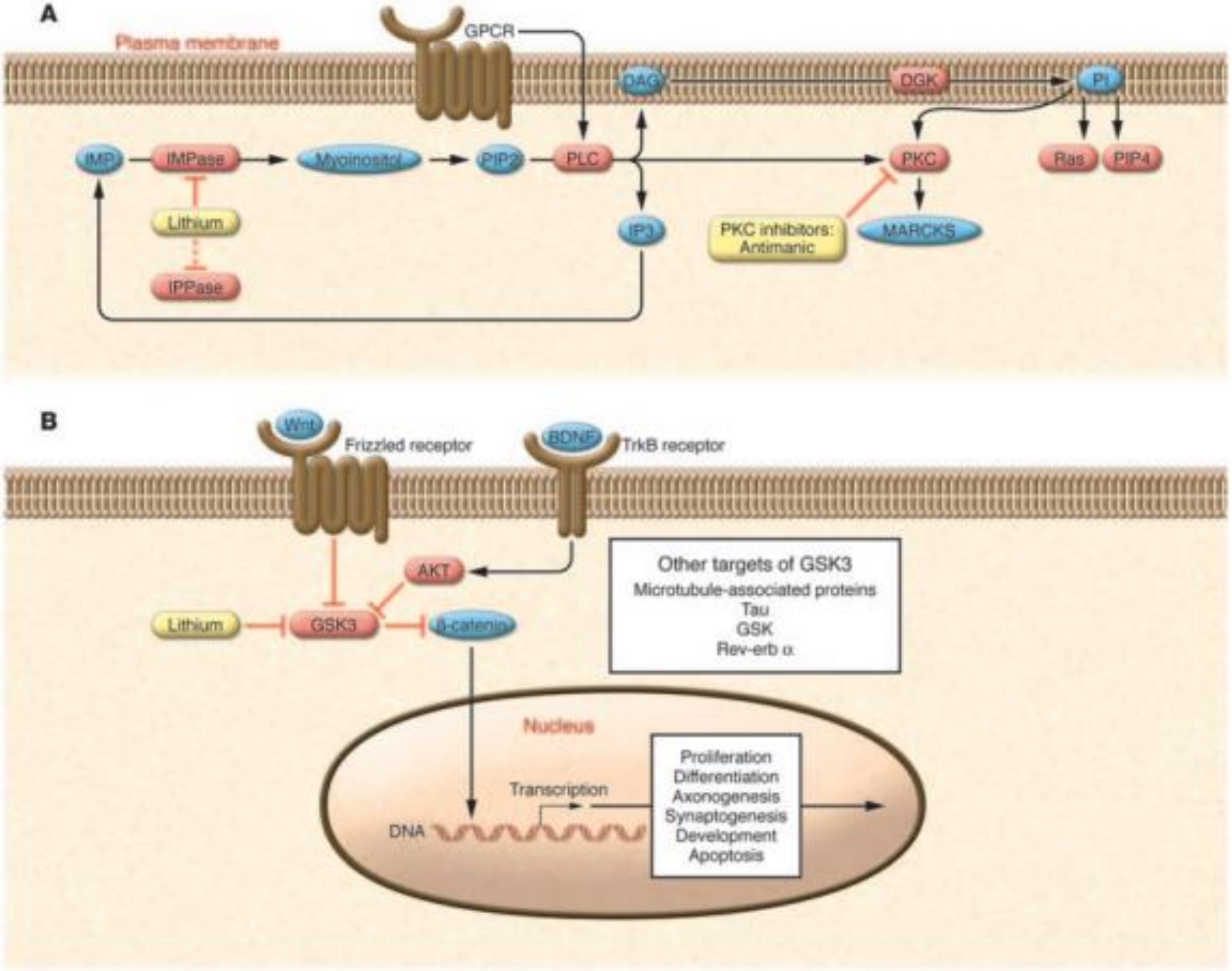
Molecular and Pharmacologic Studies:

Li

- GSK - 3β
  - Antagonizes Wnt and insulin
  - Demonstrated to modulate neuroplasticity via Wnt
- Inositol Monophosphatase (IMPase) Inhibition
  - Inhibits PIP2/IP3 signaling
  - PKC Inhibition
- Chronic Li induces prominent neuroprotective and neurotrophic factors in rodents:
  - Bcl-2 is anti-apoptotic and stimulates axonal regeneration
  - BDNF
  - Increases NAA (a marker of neuroviability

Valproic Acid:

- Acts on high frequency sodium channel firing and GABA
- A histone deacetylase inhibitor
  - Acetylates lysine on histones to affect/activate transcription
  - Epigenomic state of target genes has been reversed by VPA in rats


A
Plasma membrane
GPCR
DAG
DGK
PI
IMP
IMPase
Myoinositol
PIP2
PLC
PKC
Ras
PIP4
Lithium
IP3
PKC inhibitors:
Antimanic
MARCKS
IPPase
B
Wnt
Frizzled receptor
BDNF
TrkB receptor
AKT
Other targets of GSK3
Microtubule-associated proteins
Tau
GSK
Rev-erb α
Lithium
GSK3
β-catenin
Nucleus
Transcription
DNA
Proliferation
Differentiation
Axonogenesis
Synaptogenesis
Development
Apoptosis

Take Home Points

- Neurotransmitters are not the answer!
- Synapses and neural plasticity in affective and cognitive circuits appear important.
- A multifactorial disease resulting from genetic profiles (protective and risk genes) as well as environmental influences (chronic stressors and trauma)

Treatment of Bipolar Spectrum Disorders

Team 1: Gabriella Cozzi, Aaron Yengo-Kahn
09/19/2014

Outline

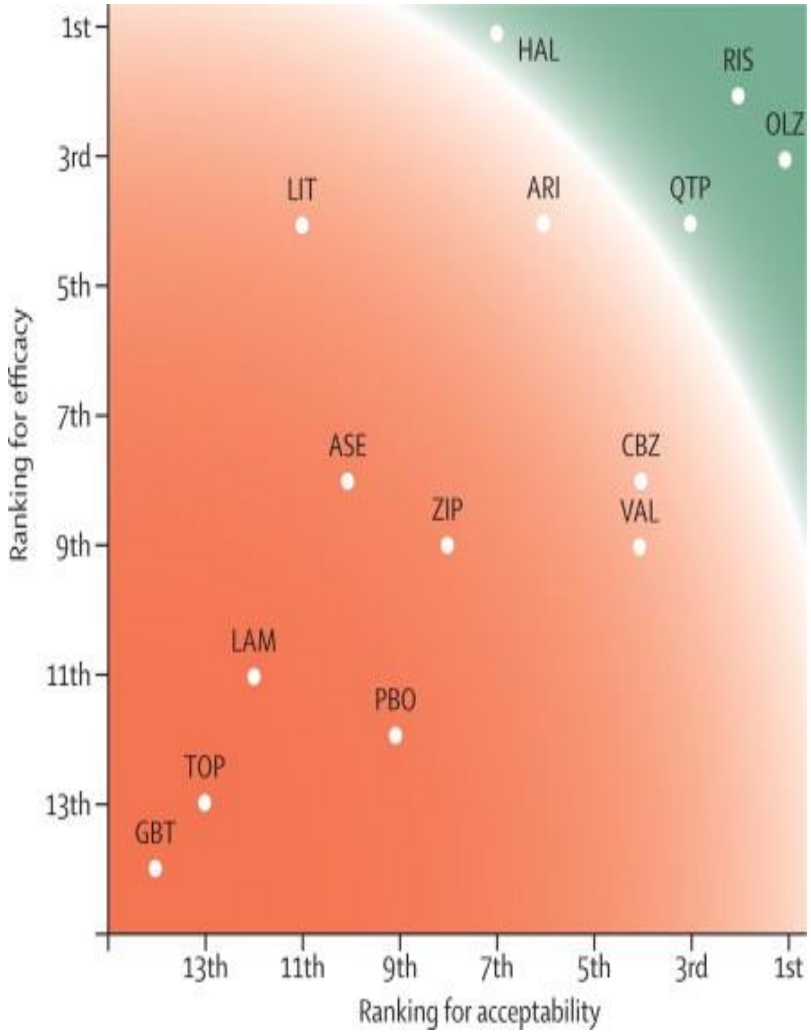
- Pharmacotherapy for acute mania
- Pharmacotherapy for acute bipolar depression
- Maintenance treatment for Bipolar I Disorder
- Physical treatments Bipolar spectrum

“Need more lemon pledge…”

Treatment of Acute Mania and Hypomania

- goal: remission, defined as improvement of mood symptoms to the point where only 1-2 exist in mild intensity
  - for mania w/ psychotic features, resolution of psychosis is required.
- lithium
- antipsychotics
  - typical: haloperidol
  - atypical: olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone
- anticonvulsants
  - valproate
  - carbamazepine

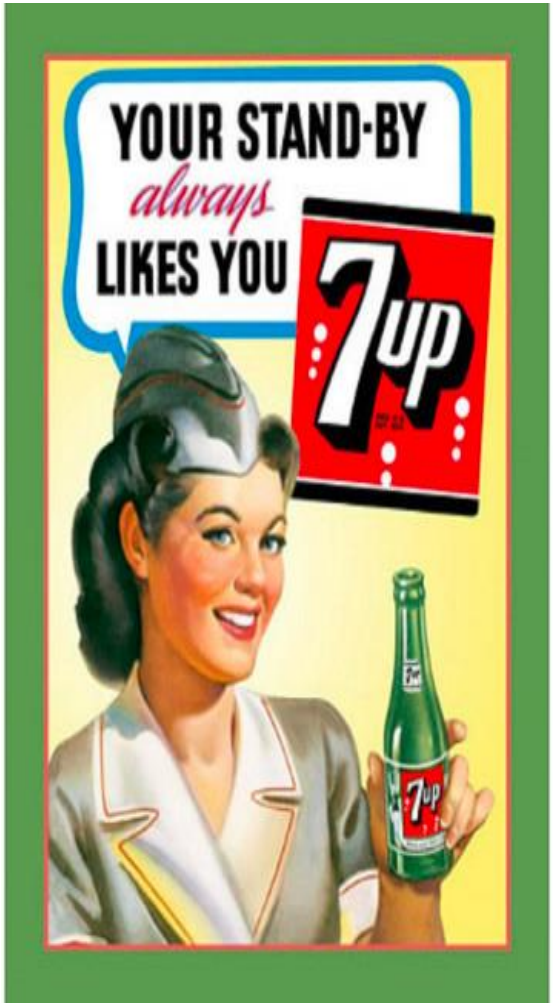
Treatment of Acute Mania



Cipriani et al., Lancet 2011

Lithium

- efficacy for acute mania, acute bipolar depression, maintenance
- reduces risk of suicide
- target 12-hour serum level of 0.8 to 1.2 mEq/L
- s/e: GI upset, tremor, weight gain, alopecia, acne, nephrogenic diabetes insipidus, hypercalcemia
- toxicity: n/v/d, cardiac arrhythmia, ataxia, confusion, seizure
    - renally excreted- try to avoid NSAIDS, diuretics, inc toxicity w/dehydration
    - 0.05-0.1% risk of Epstein's anomaly



Treatment of Acute Bipolar Depression

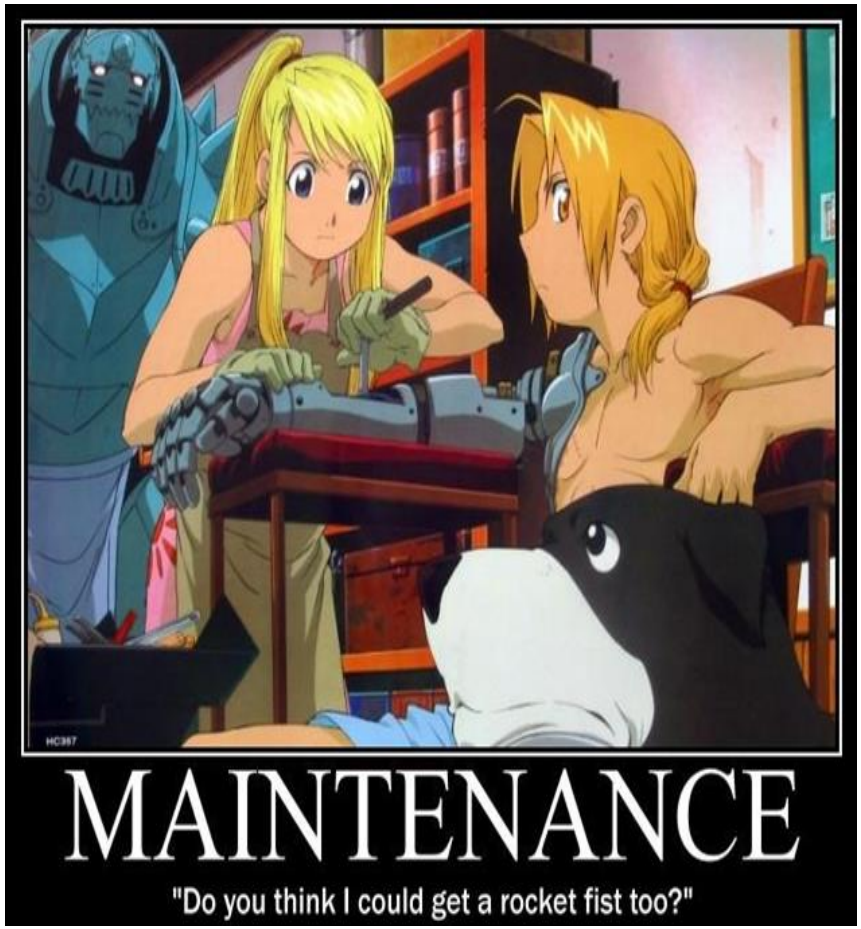
- lithium
  - onset of effect in 6-8 weeks
- lamotrigine
  - slow titration due to risk of Stevens-Johnson Syndrome, i.e., toxic epidermal necrolysis
  - first line treatment for pregnant patients
  - lithium + lamotrigine is better than lithium monotherapy
- quetiapine, olanzapine, lurasidone

Treatment of Acute Bipolar Depression

- antidepressant + mood stabilizer
  - works for pt. with a history of good response to antidepressant or patient who have never been on antidepressant.
  - avoid antidepressants in pt. with history of poor response to antidepressant, mixed episode, rapid cycling, substance use, or SI
  - use mood stabilizers (lithium, carbamazepine, valproate) or 2nd gen. antipsychotics (quetiapine, olanzapine)
    - fluoxetine + olanzapine

Maintenance Treatment: Pharmacotherapy

- Following remission of a bipolar mood episode, pts maintenance treatment required to delay or prevent another episode.
- First line
  - lithium
  - anticonvulsants (valproate, lamotrigine)
  - risperidone IM for noncompliant pts
- Second line
  - antipsychotics (quetiapine, olanzapine, aripiprazole)



Maintenance Treatment: Psychotherapy

- Pharmacotherapy + psychotherapy is more efficacious than pharmacotherapy alone
- Options (in order of preference):
  - Psychoeducation
  - Cognitive-behavioral therapy
  - Marital and family therapy
  - Interpersonal and social rhythm therapy
- ideally, pts euthymic before starting psychotherapy

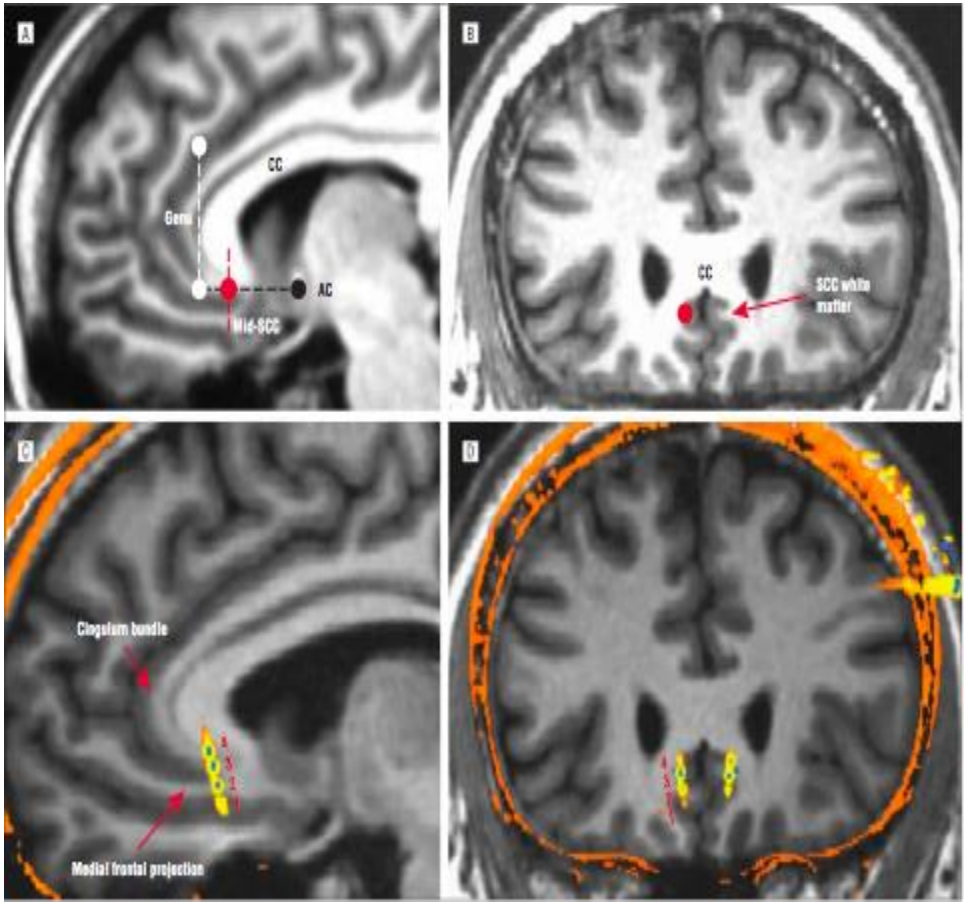
ECT

- 80% of acutely manic pts respond to ECT
- RCT comparing lithium and ECT for treatment of acute mania suggests ECT has slight advantage
  - Retrospective studies suggest significant advantage vs lithium
- considered appropriate second line treatment for pharmacotherapy resistant pts
- ECT also effective as prophylactic maintenance treatment, especially in those with recurrent mood episodes despite pharmacotherapy

Loo et al. J Aff Disorder 2011

Deep Brain Stimulation

- Shown to be safe and effective for treatment resistant depression in bipolar II disorder
- Target: subcallosal cingulate white matter



DBS - Results

- **Acute Stimulation**
  - 12 patients had intra-op testing
  - 8 spontaneously described acute positive effects

- **After 2 Years**
  - ***7*** individuals in remission (58%)
  - ***11*** in response (92%)
  - out of 12 individuals left in the study (3BP)
  - *No mania or hypomania occurred*

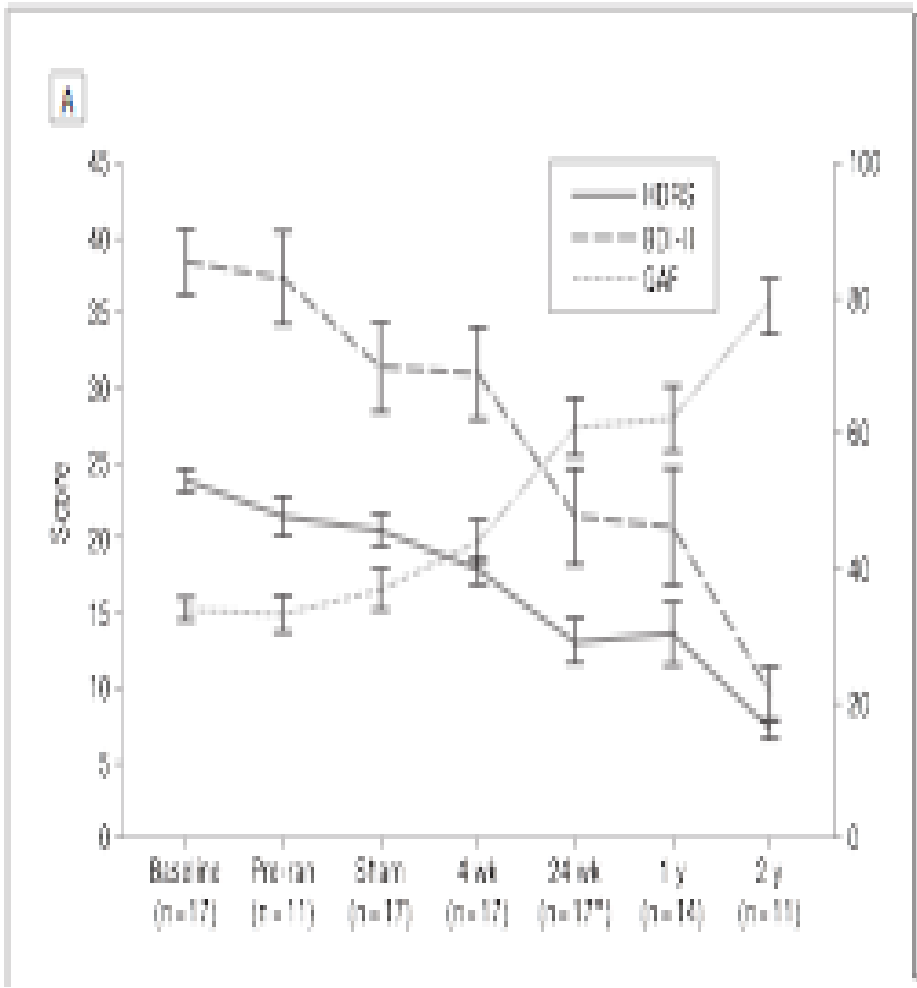


Table 2. Depression Severity and Function Over Time

Study Phase	Mean (SE) HDRS	BDI-II	GAF
Baseline (17 patients: 10 MDD, 7 BP)	23.9 (0.7)	38.4 (2.1)	33.9 (1.7)
Postoperative[a] (11 patients: 7 MDD, 4 BP)	21.5 (1.3)	37.3 (3.1)	33.2 (2.7)
4-wk sham stimulation (17 patients: 10 MDD, 7 BP)	20.5 (1.7)	31.4 (3.0)	36.9 (3.0)
4-wk active stimulation (17 patients: 10 MDD, 7 BP)	17.9 (0.9)	31.0 (3.1)	43.9 (3.4)
24-wk active stimulation (16 patients: 10 MDD, 6 BP)	13.1 (1.5)	21.4 (3.3)	60.8 (4.2)
1-y active stimulation (14 patients: 9 MDD, 5 BP)	13.6 (2.1)	20.8 (3.9)	62.2 (5.0)
2-y active stimulation (11 patients: 8 MDD, 3 BP)	7.3 (0.7)	9.5 (1.8)	78.7 (4.1)
P value[b]	<.001	<.001	<.001

"Significant improvement in all measures occurred, and there did not appear to be any large, clinically meaningful, or statistically significant differences between the MDD and BP groups" Holtzheimer et al. Arch Gen Psych. 2012.

DBS - Of Interest Notes

- 3 patients had stimulation turned off and restarted
- These patients experienced rebound depression, distress, suicidal ideation in 3/3