Treating Bipolar Spectrum Disorders:
First do no harm

Unipolar  BP NOS  Bipolar II  Bipolar I

Jim Phelps, MD
Samaritan Mental Health
Corvallis, OR
8 years inpatient/outpatient
6 years private outpatient
6 years residency program

Samaritan Mental Health in Corvallis
PsychEducation.org
(International Society for Bipolar Disorders)
30,000 ft.
Recurrent depression
Occasional easing, then severe again
4 or more AD's to date
Trazodone, benzo, z-drugs
• DSM-5 or NIMH:
  – Yes/no categories
  – How bipolar are you?

• Antidepressants
  – Efficacy
  – ISBD guidelines
  – 9 better options

• Mixed States
  – DSM evolution
  – Anxiety as a bipolar symptom?
  – Markers and management

• Toward sleep without medications
  – Social rhythm therapy
  – Dark therapy
  – Light management
Bipolarity Index

“How bipolar are you?”

**Medscape:** ... It's not a categorical yes or no ... but rather, "To what extent are you bipolar?“

**Dr. Sachs:** Yes, and we're not looking to replace the Diagnostic and Statistical Manual with it... it's just that we are able to approach it *more as a continuous issue, rather than as a black-and-white, yes-no.*
…*categories will remain somewhat arbitrary* because they will be imposed on *fully continuous, smooth distributions*.
…categories will remain somewhat arbitrary because they will be imposed on fully continuous, smooth distributions.

Ellen Liebenluft, M.D.
Chief, Section on Bipolar Spectrum Disorders

Categories and Dimensions, Brain and Behavior. JAMA Psychiatry, Jan. 2014
226 Genes or Loci Associated With Bipolar Disorder at <0.05

A2BP1, AA1A, ABLIM1, AC5S3, ADAMTS12, ADAMTS19, ADAMTS2, AGBL1, AGL1, AKAP12, ANK3, ANKFN1, ANK18, ANO3, ARHGEF3, ARL15, ASAP2, ASB18, ATXN1, AUTS2, B3GALT1, BAI3, BNC2, C10orf11, C14orf101, C21orf34, C6orf105, C8orf34, CA10, CACNA1C, CACNA2D3, CADM2, CAMTA1, CDH18, CDKL1, CGNL1, CHST11, CMIP, CMYA5, CNBD1, CNTN3, CNTN6, CNTNAP2, COL13A1, COLIA2, COL28A1, CREBBP, CSMD1, CNNA3, CYP4Z1, CYTSB, DCC, DGKB, DGKH, DGKL, DIS3L2, DLG2, DOCK2, DPP10, DTNA, DYSK1, ELMO1, ELOVL2, EML1, ENPP2, EYS, FAM107B, FAM171A1, FAM184A, FBN2, FBXL7, FBXO18, FGF12, FHOD3, FLJ30838, FLJ41278, FLJ46010, FOXN3, FOXP1, FRMD6, FRY, FUT9, FYB, GFRA1, GLI3, GNG2, GNPTAB, GOLSN, GPC5, GPC6, GPR1, GREM2, GRM1, GRM7, HHAT, HTR2A, IQGAP2, ISPD, ITGB1, ITIH5, ITPR2, KCND2, KCNMA1, KIAA1797, KIFAP3, KIRREL3, LAMC2, LASS6, LGMN, LHPP, LMBRI, LOC100129633, LOC100132891, LOC100288428, LOC100505875, LOC100506027, LOC100506072, LOC100506380, LOC100506403, LOC100507421, LOC400794, LOC642924, LOC643542, LRP2, LRR1C6A, LRR3C, LRRM4, LSAMP, MAD1L1, MAML3, MAN1C1, MAST4, ME1, MEF2C, MGC27382, MKL1, MMP7, MTHFD1L, MYBPC1, MYO5B, MYOM2, NALCN, NAV2, NCA1, NCOA2, NOS1AP, NPAS3, NSP1R, NRXN3, NT5DC1, NTRK3, ODZ4, OTUD7A, PAK7, PALLD, PAN3, PCGF5, PCNL2, PCSK2, PDE7B, PDZRN4, PHACTR1, PHF21A, PHF21B, PLA2R1, PLCB1, PLCG2, PLD1, PLEKHG1, POU2F1, PPFIBP1, PPP1R1C, PPP2R5E, PTGIS, PTPRR, PTPR, RALGAPA2, RBPMS, RFX2, RGS6, RGS7, RO1R, RPL1-210181, RP3-39BD13.1, SATB2, SEMA3C, SEMA5A, SEZ6L, SGCC, SGMS1, SHANK2, SIAH3, SIK3, SLC10A7, SLC2A13, SLIT3, SMG6, SNBP1, SNX29, SORCS2, SPTAS2L, SPTLC1, SRGAP3, ST7, STK24, STK4, SYN3, SYNE1, SYT14, tccag71213, TCF7L1, THSD4, THSD7A, TMEM110B, TRDN, TRPV3, TPAN18, TULP4, ULK4, VAT1L, VAV3, WDFY4, WDR72, ZCCHC17, ZNF236, ZNF385B

Genomics Consortium Bipolar Group

Nurnburger et al. JAMA Psych, June 2014
Recurrent depression
Occasional easing, then severe again
4 or more AD’s to date
Trazodone, benzo, z-drugs
• DSM-5 or NIMH:
  – Yes/no categories
  – How bipolar are you?
  – (Why the Finches?)

• Antidepressants
  – Efficacy?
  – ISBD guidelines
  – 9 better options

• Mixed States
  – DSM evolution
  – Anxiety as a bipolar symptom?
  – Markers and management

• Toward sleep without medications
  – Social rhythm therapy
  – Dark therapy
  – Light management
The Depressing News About Antidepressants

Studies suggest that the popular drugs are no more effective than a placebo. In fact, they may be worse.
Antidepressant controversies in bipolar disorders

1. Do they work?

2. Cause switching; How often?

3. Mood destabilization
   a) Cause rapid cycling, mixed states
   b) Prevent stabilization?
   c) Cause “kindling”? “tardive dysphoria”?

4. Already on, and a mood stabilizer, and doing well – when to taper off? Leave on? How fast to taper?
Bipolar patients, on mood stabilizers, now depressed: add…. 

Sachs G et al, New England Journal of Medicine, April 2007
Bipolar patients, on mood stabilizers, now depressed:
add,….

bupropion or placebo
paroxetine

N = 179   N = 187

Sachs G et al, New England Journal of Medicine, April 2007
Bipolar patients, on mood stabilizers, now depressed: add….

Percent "Durable Recovery"

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<tr>
<th>Treatment</th>
<th>N</th>
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<td>bupropion</td>
<td>179</td>
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<tr>
<td>paroxetine</td>
<td></td>
</tr>
<tr>
<td>or placebo</td>
<td>187</td>
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Sachs G et al, New England Journal of Medicine, April 2007
Bipolar patients, on mood stabilizers, now depressed: antidepressants versus placebo

Sachs G et al, New England Journal of Medicine, April 2007
Antidepressants in Bipolar Disorder

(a) Depression

Prien et al. 1973(38)[a]
Prien et al. 1973(38)[b]
Quitkin et al. 1981(39)
Kane et al. 1982 (40)[a]
Kane et al. 1982 (40)[b]
Kane et al. 1982 (40)[c]
Kane et al. 1982 (40)[d]
Prien et al. 1984 (41)[a]
Prien et al. 1984 (41)[b]
Johnstone et al. 1990 (42)
Amsterdam et al. 2005 (43)
Ghaemi et al. 2005 (44)

Pooled RR
(0.73 [0.55–0.97])

RR [95% CI]
The International Society for Bipolar Disorders (ISBD)
Task Force Report on Antidepressant Use in Bipolar Disorders


<table>
<thead>
<tr>
<th>Acute treatment</th>
<th>1. Adjunctive antidepressants may be used for an acute bipolar I or II depressive episode when there is a history of previous positive response to antidepressants.</th>
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<td>2. Adjunctive antidepressants should be avoided for an acute bipolar I or II depressive episode with two or more concomitant core manic symptoms in the presence of psychomotor agitation or rapid cycling.</td>
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<td>Maintenance treatment</td>
<td>3. Maintenance treatment with adjunctive antidepressants may be considered if a patient relapses into a depressive episode after stopping antidepressant therapy.</td>
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<td>Monotherapy</td>
<td>4. Antidepressant monotherapy should be avoided in bipolar I disorder.</td>
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<tr>
<td></td>
<td>5. Antidepressant monotherapy should be avoided in bipolar I and II depression with two or more concomitant core manic symptoms.</td>
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<td>Switch to mania, hypomania, or mixed states and rapid cycling</td>
<td>6. Bipolar patients starting antidepressants should be closely monitored for signs of hypomania or mania and increased psychomotor agitation, in which case antidepressants should be discontinued.</td>
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<td>7. The use of antidepressants should be discouraged if there is a history of past mania, hypomania, or mixed episodes emerging during antidepressant treatment.</td>
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<td>8. Antidepressant use should be avoided in bipolar patients with a high mood instability (i.e., a high number of episodes) or with a history of rapid cycling.</td>
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<td>Use in mixed states</td>
<td>9. Antidepressants should be avoided during manic and depressive episodes with mixed features.</td>
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<td>10. Antidepressants should be avoided in bipolar patients with predominantly mixed states.</td>
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<td></td>
<td>11. Previously prescribed antidepressants should be discontinued in patients currently experiencing mixed states.</td>
</tr>
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<td>Drug class</td>
<td>12. Adjunctive treatment with norepinephrine-serotonin reuptake inhibitors or tri- and tetracyclics should be considered only after other antidepressants have been tried, and should be closely monitored because of an increased risk of mood switch or destabilization.</td>
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<td><strong>Acute</strong></td>
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9 alternatives to antidepressants
equal or better evidence for efficacy
don’t make bipolar disorders worse

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Chronotherapy: Unipolar

Gorgulu and Caliyurt. Brain Res Bull. 2009 Sep
Chronotherapeutic Augmentation Treatment: input TSD (1) + light (3) + phase advance (3)


Li+/SER outpt.

Li+/SER CAT
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Fish Oil

1 gram EPA
\[\geq 60\% \ast \text{ EPA}\]

\ast (\text{EPA / EPA} + \text{DHA})

N-acetyl cysteine

1 gram bid

Google NAC bipolar
(Psycheducation.org)
9 alternatives to antidepressants
equal or better evidence for efficacy
don’t make bipolar disorders worse

| Not Pills               | “Natural”                        | Pharmaceutical |
|-------------------------|----------------------------------|----------------|---|
| Psychotherapies         | Fish oil                         |                |
| Exercise                | N-acetylcysteine                 |                |
| Chronotherapies         | Optimize thyroid (supraphysiologic) |                |
supraphysiologic thyroid

B. Women (n = 32)

Placebo (n = 15)
Levothyroxine (n = 17)

Mean HDRS Score

0 1 2 3 4 5 6
Weeks of Double-Blind Treatment

300 mcg of T4

thyroid

- augmentation (T4)
- optimize (TSH ~ 1.0)
# 9 alternatives to antidepressants

- equal or better evidence for efficacy
- don’t make bipolar disorders worse

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<td>Year</td>
<td>Organization</td>
<td>Lithium</td>
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<td>2003</td>
<td>British Ass’n Psychopharmacology</td>
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<td>NICE (European)</td>
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TMAP: Texas Medical Algorithm Project  
NICE: National Institute for Health and Clinical Excellence  
CANMAT: Canadian Network for Mood/Anxiety Treatment  

Adapted from Malhi et al.  
Bipolar Disorders, 2009 June
Recurrent depression
Occasional easing, then severe again
4 or more AD’s to date
Trazodone, benzo, z-drugs
International Society for Bipolar Disorders
Committee on Diagnosis, 2008

1. Family History

   BP relative

2. Age of Onset

   18 – 25; < 18

3. Course of Illness:

   - Number of episodes: >10 (many)
   - Duration of episodes: 3 mos (short)
   - Markers: (psychosis, post-partum; season)
   - Atypical symptoms: (↑ eat, ↑ sleep; leaden, rejection)

4. Response to Rx

   AD-induced hypo/mania
   AD loss of response, > 3 AD’s

- Statistically associated with bipolar disorder
  - family history
  - outcome
- ↑ the probability that depression has “bipolarity”
9 alternatives to antidepressants equal or better evidence for efficacy don’t make bipolar disorders worse

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9 alternatives to antidepressants, equal or better evidence for efficacy
do not make bipolar disorders worse

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**2a: gradually taper AD**
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"2b"
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*Low dose ≤0.8 level*
quetiapine

MADRS Total Score

Lurasidone/Latuda

• DSM-5 or NIMH:
  – Yes/no categories
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Recurrent depression
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Trazodone, benzo, z-drugs

General hyperarousal
Inner tension
Irritability / impatience

“Frantically anxious”
Anxiety -- a *Bipolar* Symptom?
The evolution of psychiatric diagnosis: Mixed States
DSM-3, 1980
DSM-4, 1994

Diagram showing a point labeled "Mixed State" on a graph with axes labeled 'Mania' and 'Depression'.
DSM-5

Mania

"Mixed State"

Depression
Anxiety -- a *Bipolar* Symptom?

Bipolar Mixed States

General hyperarousal
Inner tension
Irritability /impatience
Agitation

“Frantically anxious”
Bipolar Mixed States

General hyperarousal
Inner tension
Irritability /impatience
Agitation
“Frantically anxious”

“...[anxiety is] a core symptom of mixed episodes.”

“some but not all agitated depressed states are bipolar.”

Bipolar Mixed States

General hyperarousal
Inner tension
Irritability /impatience
Agitation
“Frantically anxious”

“could occur pharmacologically” (antidepressants)

“some but not all agitated depressed states are bipolar.”

“...[anxiety is] a core symptom of mixed episodes.”
Marker

trazodone, benzodiazepines, Z-drugs ... + AD
Rx: taper the AD
trazodone, benzodiazepines, Z-drugs
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Light is an antidepressant
“Dark Therapy”

Wehr et al. Biol Psych, 1998
“Dark Therapy”

Wehr et al. Biol Psych, 1998
“Dark Therapy”

14 hrs

Wehr et al. Biol Psych, 1998
“Dark Therapy”

10 hrs:
10 pm to 8 am

Wehr et al. Biol Psych, 1998
“Dark Therapy”

10 hrs:
10 pm to 8 am

Wehr et al. Biol Psych, 1998
Wirz-Justice et al. Biol Psych, 1999
Barbini et al, Bipolar Disorders, 2005
Evidence for a novel circadian photoreceptor.

Glickman, Brainard et al. *J Neurosci.*, 2001
Physiologic Evidence

Kayumov et al. J Clin Endocrinol Metabolism, 2005
Virtual Darkness as Treatment

- 20-pt case series, initial or middle insomnia (BP)
  50% response: shorter latency

- 20-pt randomized trial, initial or middle insomnia
  Burkhart and Phelps. *Chronobiology Internat*, 2009
“Chronotherapeutic suite”

Education: biological clock
(website: dark therapy, light therapy)

- no-blue nightlight, $25
  (lowbluelights.com)
- amber lenses, $7
  (website: Light and Darkness)
- light box, $65-$143
  Lightphoria, Uplift
- dawn simulator, $25
  (website: Light Therapy)
• DSM-5 or NIMH:
  – Yes/no categories
  – How bipolar are you?

• Antidepressants
  – Efficacy
  – ISBD guidelines
  – 9 better options

• Mixed States
  – DSM evolution
  – Anxiety as a bipolar symptom?
  – Markers and management

• Toward sleep without medications
  – Social rhythm therapy
  – Dark therapy
  – Light management