Mastering the Mysteries of Bipolar Disorder: Treatment

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Learning Objectives

1. Become with Bipolar Treatment guidelines
2. Appreciate the role of atypical antipsychotics in treating mania.
3. Be updated on treatments for bipolar depression
4. Recognize FDA-approved maintenance treatments for Bipolar Disorder

Pre-Test Question #1

1. The most current Bipolar Treatment guideline is which of the following?

A. APA Practice
B. TIMA Algorithms
C. WFSBP
D. CANMAT
E. Br Assoc Psychopharm

Pre-Test Question #2

2. The most prominent proponent of blood-letting for mania was which of the following?

A. Benjamin Rush
B. John Rush
C. Rush Limbaugh
D. Rush University Medical School
E. Pass Rush

Pre-Test Question #3

3. Which of the following is FDA-approved for the treatment of Bipolar Depression?

A. Aripiprazole
B. Risperidone
C. Lurasidone
D. Escitalopram
E. Modafinil

Pre-Test Question #4

4. The BALANCE study of bipolar maintenance found which of the following?

A. Lithium = valproate

B. Lithium > valproate

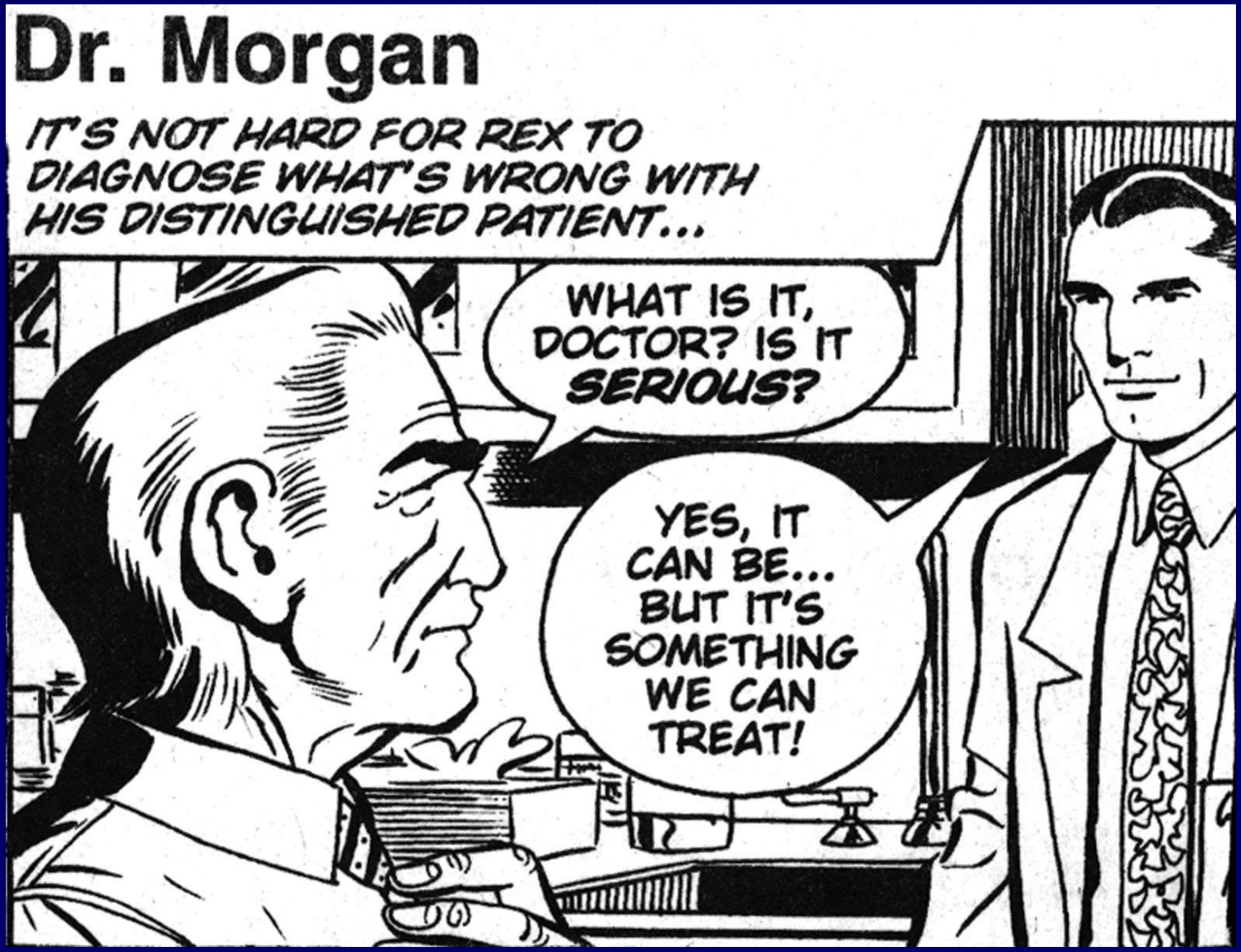
C. Valproate > lithium

Pre-Test Question #5

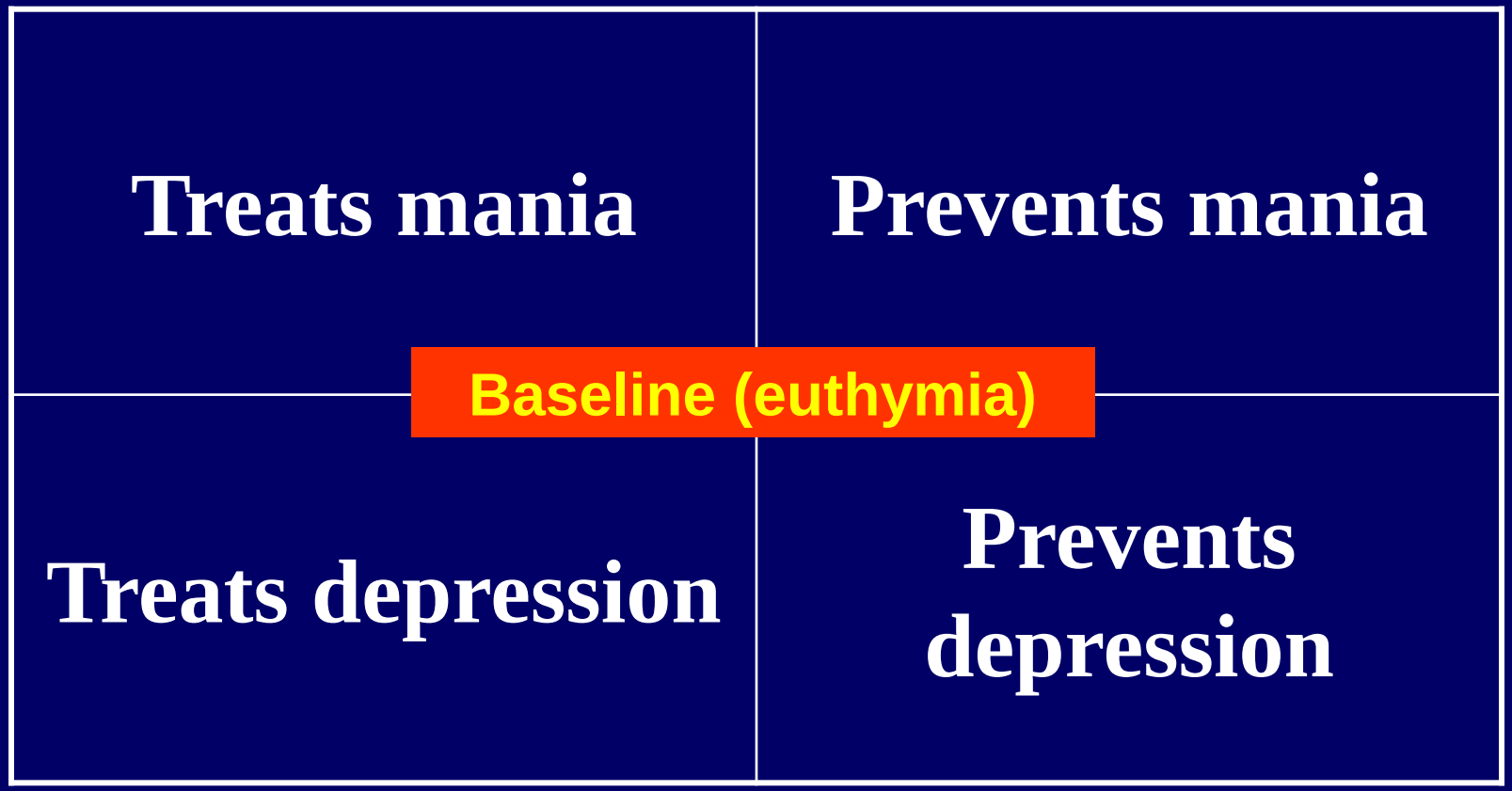
5. The first antipsychotic FDA-approved for the treatment of mania was which of the following?

A. Aripiprazole
B. Risperidone
C. Olanzapine
D. Chlorpromazine
E. Haloperidol

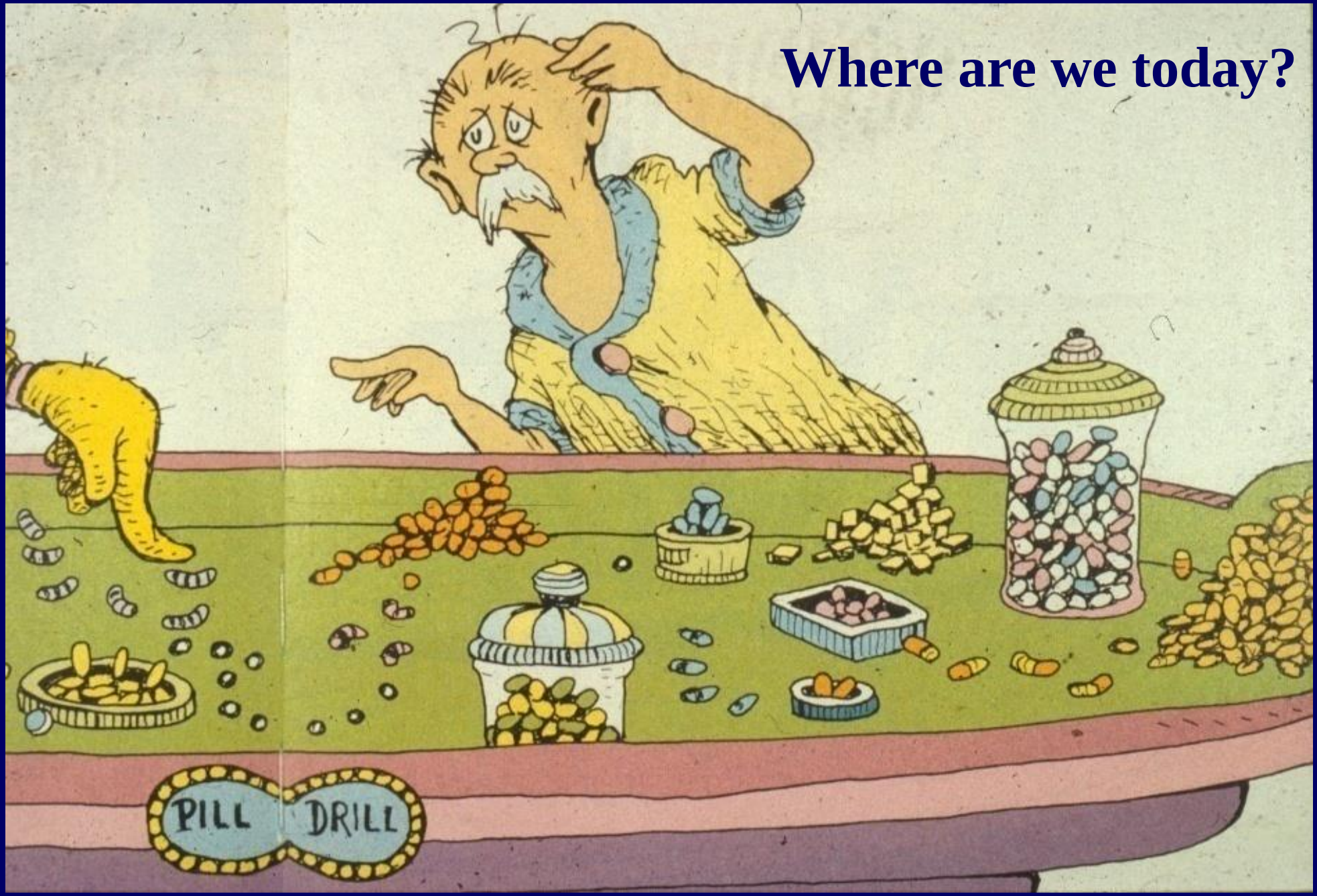
Dr. Morgan


IT'S NOT HARD FOR REX TO DIAGNOSE WHAT'S WRONG WITH HIS DISTINGUISHED PATIENT...
WHAT IS IT, DOCTOR? IS IT SERIOUS?
YES, IT CAN BE... BUT IT'S SOMETHING WE CAN TREAT!

Mood Stabilizer: 'Stabilization From Above vs. Below'



Adapted from Ketter TA, Calabrese J. J Clin Psychiatry. 2002;63:146-151.

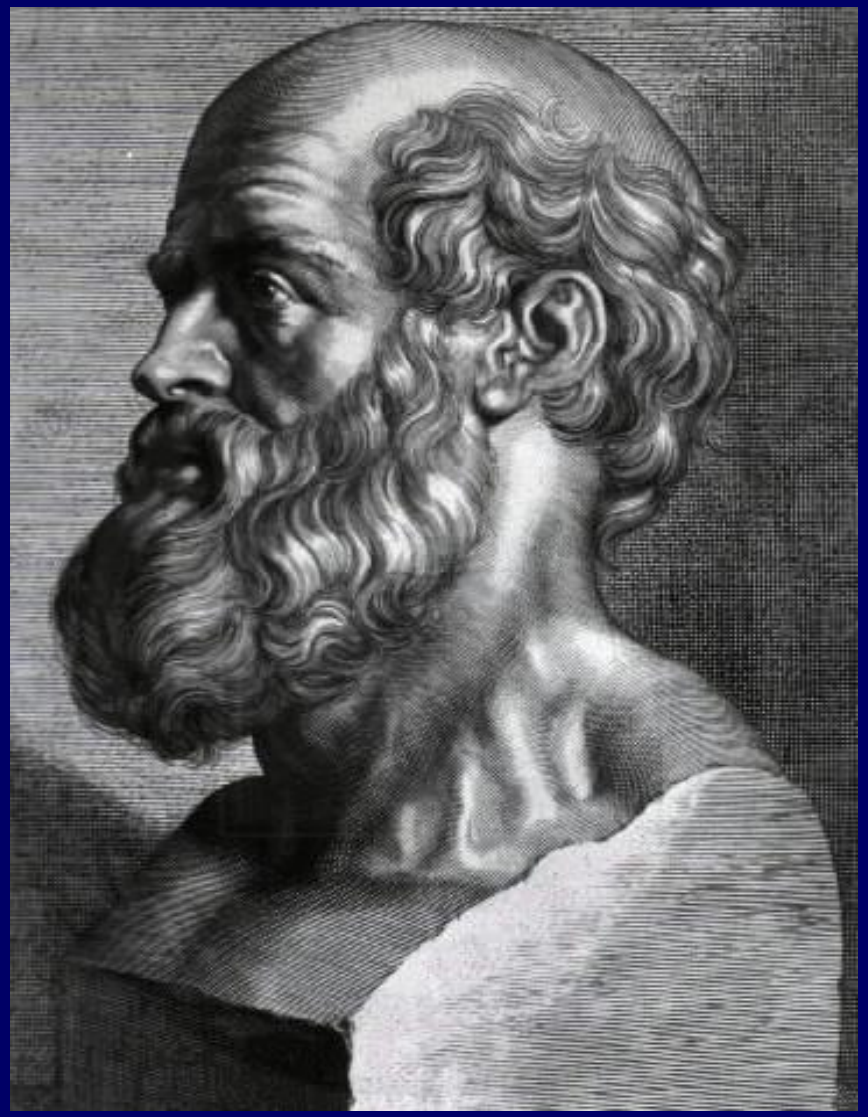

Where are we today?
PILL
DRILL

Choice of Medication(s)

- Phase of illness
- Prior response and tolerability (including family)
- Medical and psychiatric comorbidities
- Side effects
- Drug interactions
- Patient and physician preferences

“Keep watch also on the faults of the patients, which often make them lie about things prescribed.”

Hippocrates
(460 BC-377 BC)



Polypharmacy is Not a Bad Word

- Monotherapy is the exception
- Combination therapy can be effective
- Increased risk of side effects and drug interactions

Bipolar Guidelines Abound

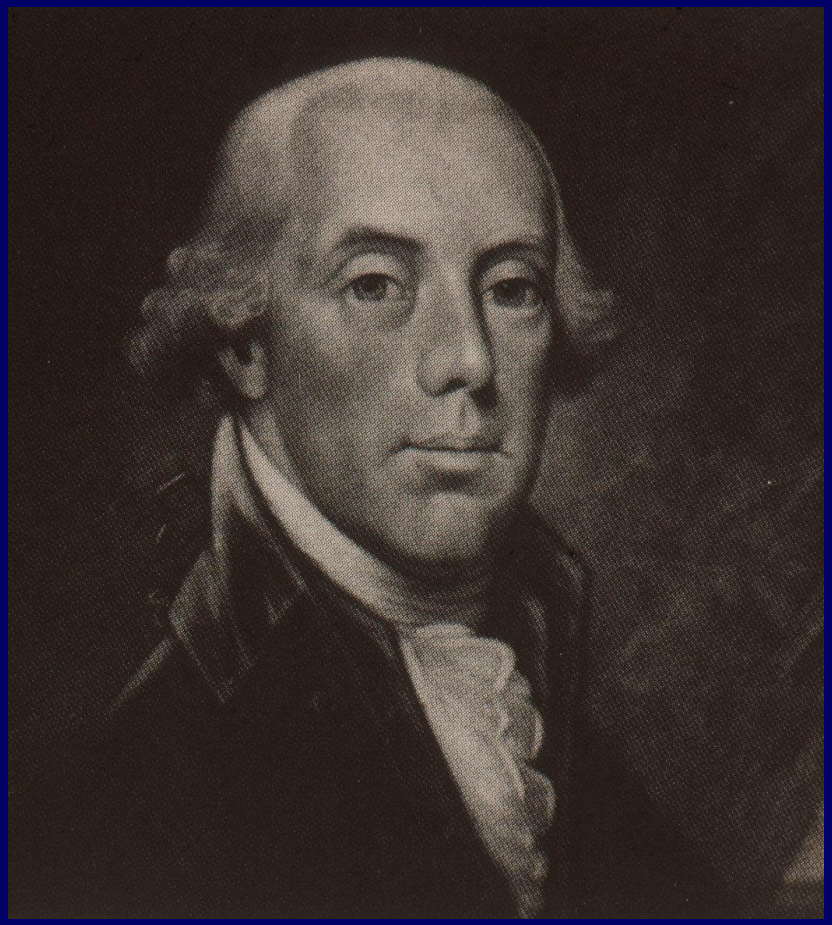
• APA Practice Guidelines	2002 (ancient)
• Expert Consensus Guidelines	2004
• TIMA Algorithms	2005
• Br Assoc Psychopharmacol	2003, 2009
• WFSBP Guidelines	2004, 2009, 2010
• CANMAT Guidelines	2005, 2006, 2009, 2013 (best)

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT Bipolar guidelines: 2013

Yatham LN et al.,

Bipolar Disorders 2013;15:1-44

Acute Mania



“Many mad people, who have attempted to destroy themselves by cutting their throats... have been cured by the profuse haemorrhages.”

Benjamin Rush, Remedies for Mania, 1812

Blood-letting for Mania

- It should be copious on the first attack

  – 20 to 40 ounces
- The effects are wonderful in calming mad people
- The quantity drawn should be greater than for any other organic disease

Benjamin Rush, 1812

William A Hammond, MD (1828-1900)

- **Lithium bromide for acute mania**

- **60 grains or more every 2 to 3 hours "til sleep be produced."**

A Treatise on Diseases of the Nervous System

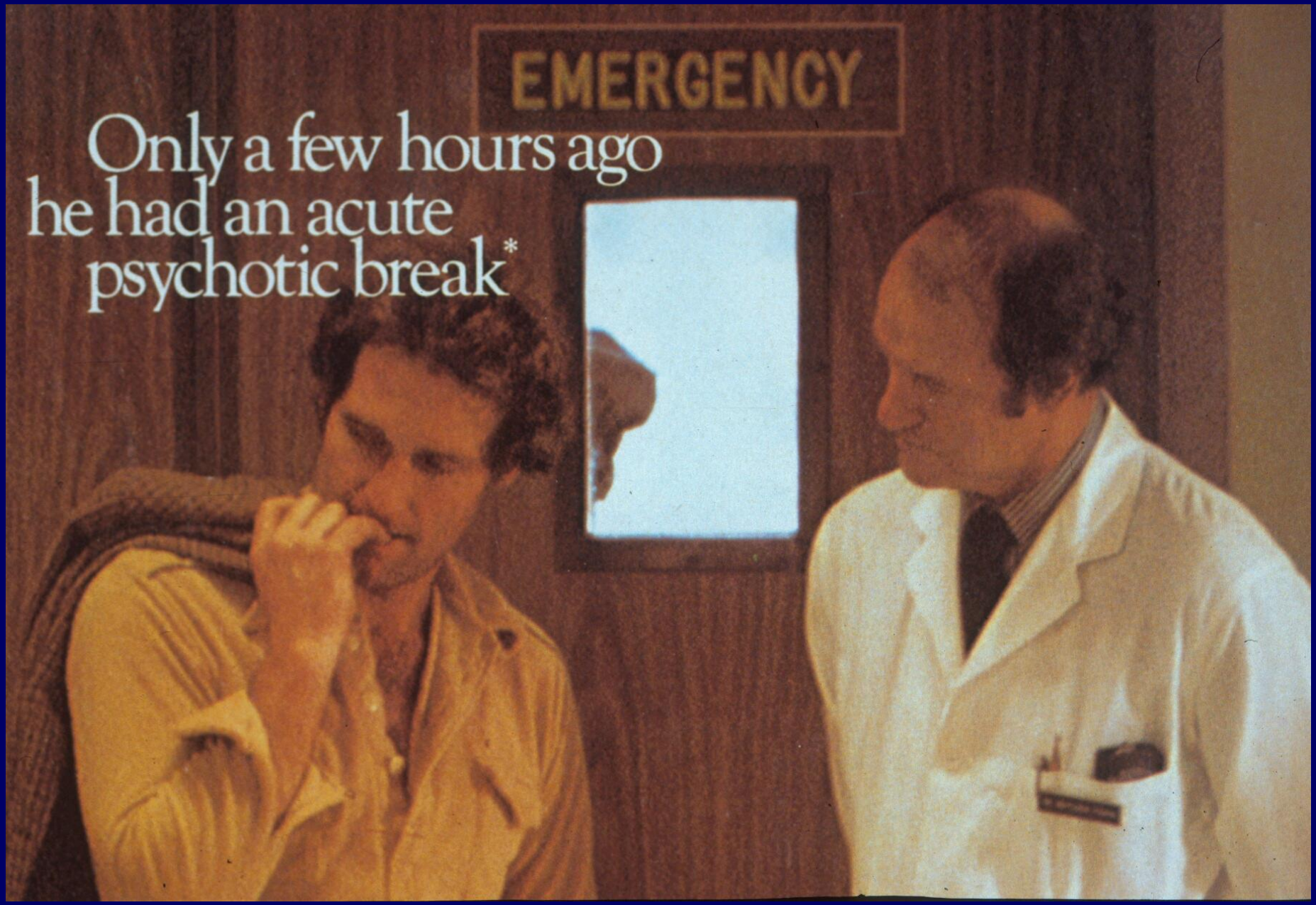
1871

Acute Mania: FDA-Approved

- 1970 Lithium***
- 1973 Chlorpromazine
- 1995 Divalproex

- 2000 Olanzapine**
- 2003 Risperidone*
- 2004 Quetiapine*
- 2004 Ziprasidone
- 2004 Aripiprazole*
- 2004 Carbamazepine ER
- 2005 Divalproex ER
- 2009 Asenapine

*Also pediatric (10-17) mania (RIS 2007, ARI 2008, QTP 2009)
**Also adolescent (13-17) mania (OLZ 2009)
***Also pediatric (12-17)


EMERGENCY
Only a few hours ago
he had an acute
psychotic break*

All Antipsychotic Drugs Are Antimanic

Name one that isn't!

(But not all are FDA-Approved for Mania)

FDA-Approved Atypical Antipsychotics for Mania

- Aripiprazole*
- Olanzapine*
- Quetiapine*
- Risperidone*
- Ziprasidone**
- Asenapine*

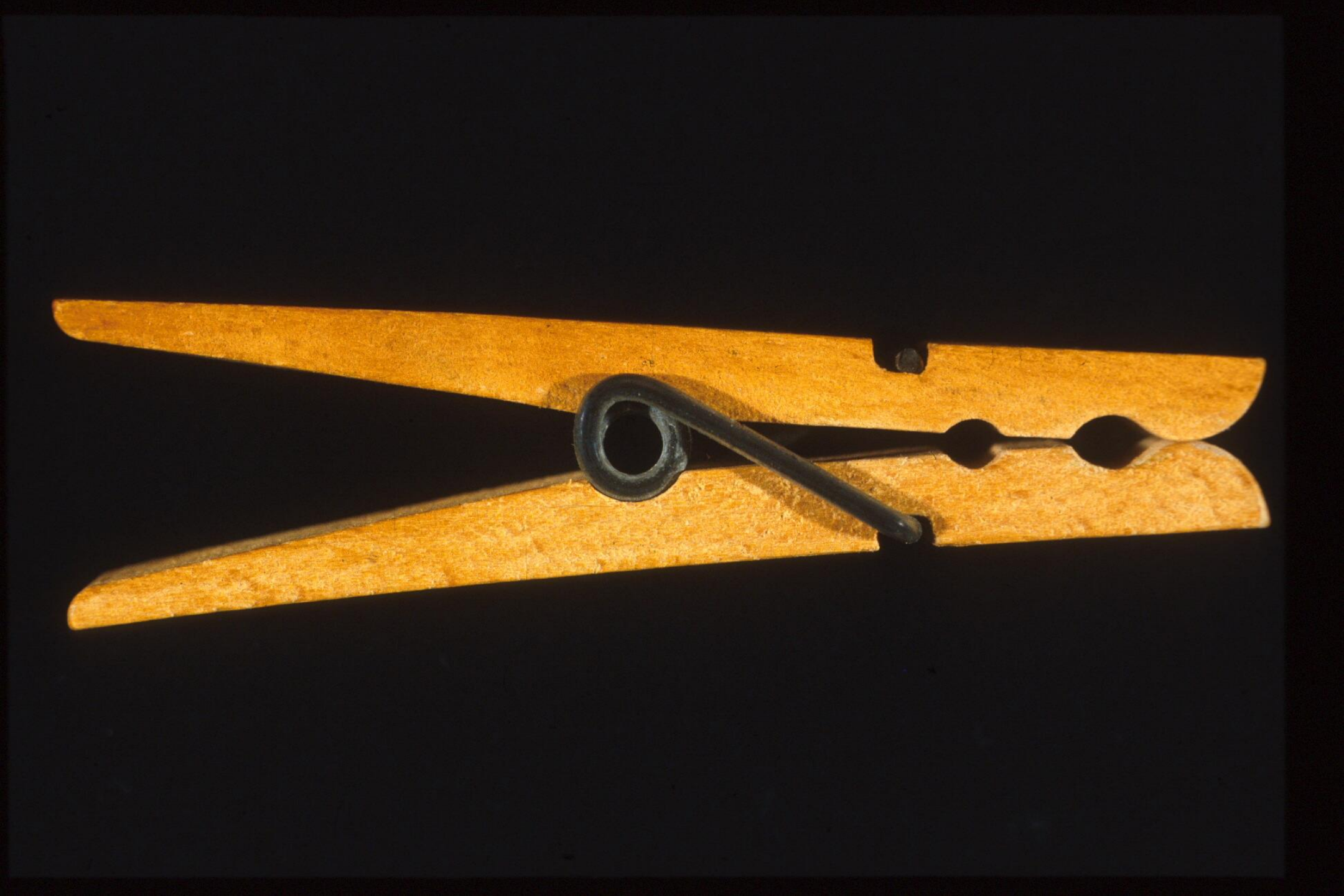
*FDA approved-monotherapy and add-on

**FDA approved-monotherapy only

Multi-Treatments Meta-Analysis of Antimanic Drugs in Acute Mania

- 68 randomized controlled trials (n=16,073)
- Antipsychotics significantly more effective than mood stabilizers
- Best options for manic episodes: risperidone, olanzapine, haloperidol

Cipriani A et al., Lancet 2011;378:1306-1315 (Oct 8)



Clozapine for Bipolar Disorder

- The ace in the hole

- Open label reports of benefit for mania, maintenance, and possibly depression
- Still no double-blind studies (2014)

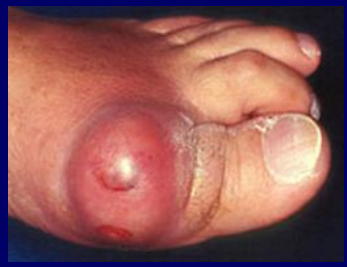
Real-World Effectiveness of Clozapine in Bipolar Disorder: A 2-Year Mirror Image Study (1996-2007)

- **Significant and clinically relevant reduction in:**
  - **Number of bed-days**
  - **Psychiatric admissions**
  - **Psychotropic co-medications**
  - **Hospital contact for self-harm/overdose**
- **Adverse events "relatively low"**

Nielsen J et al., Bipolar Disorders 2012;14:863-869

Or Maybe a Taste of Adjunctive Allopurinol (an adenosine agonist) for Acute Mania

- 8-week, db, n=41, Li + HAL and ALLO 300 mg or PBO ALLO > PBO (p= 0.008)
- 4-week, db, n=180, Li + ALLO 600 mg; ALLO > PBO (p= 0.003)
- 4-week, db, n=57, VPA + ALLO or PBO ALLO > PBO



Akhondzadeh S et al., Bipolar Disord 2006;8:485-489;
Machado-Vieira R et al., J Clin Psychiatry 2008;69:1237-1235
Janagard L et al., Euro Neuropsychopharmacol 2014;24:1210-1221

Or Maybe Not for Acute Mania

- 6-week, db, PBO controlled, n=180
- Add-on to mood stabilizers and/or antipsychotics
- ALLO was no better than PBO

Weiser M et al., Bipolar Disorders 2014;16:441-447

Tamoxifen for Acute Mania

3-week, double-blind, placebo-controlled, n=66

- Relatively selective protein kinase C inhibitor and selective estrogen receptor modulator
- Dose: Start 40 mg/day, max 80 mg/day
- Tamoxifen > placebo on ↓ YMRS, response (44% vs. 5%), remission (28% vs. 0%)

Response ≥ 50% ↓YMRS; Remission YMRS ≤12

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

No patient achieved response or remission prior to day 21

Adjunctive Tamoxifen for Acute Mania
6-week, double-blind, placebo-controlled, n=40

- Lithium + PBO or lithium + tamoxifen 80 mg
- YMRS primary outcome measure
- Tamoxifen > PBO at weeks 1, 3, 6
- Remission at week 6: 90% vs. 55% PBO
- Well tolerated, some fatigue

Amrollahi Z et al. J Affective Dis 2011;119:327-331

For a current review, see Armani F et al., Psychopharmacology 2014;231:639-649

“Harry’s mood stabilized in ’78, and it hasn’t budged since.”

Bipolar Depression

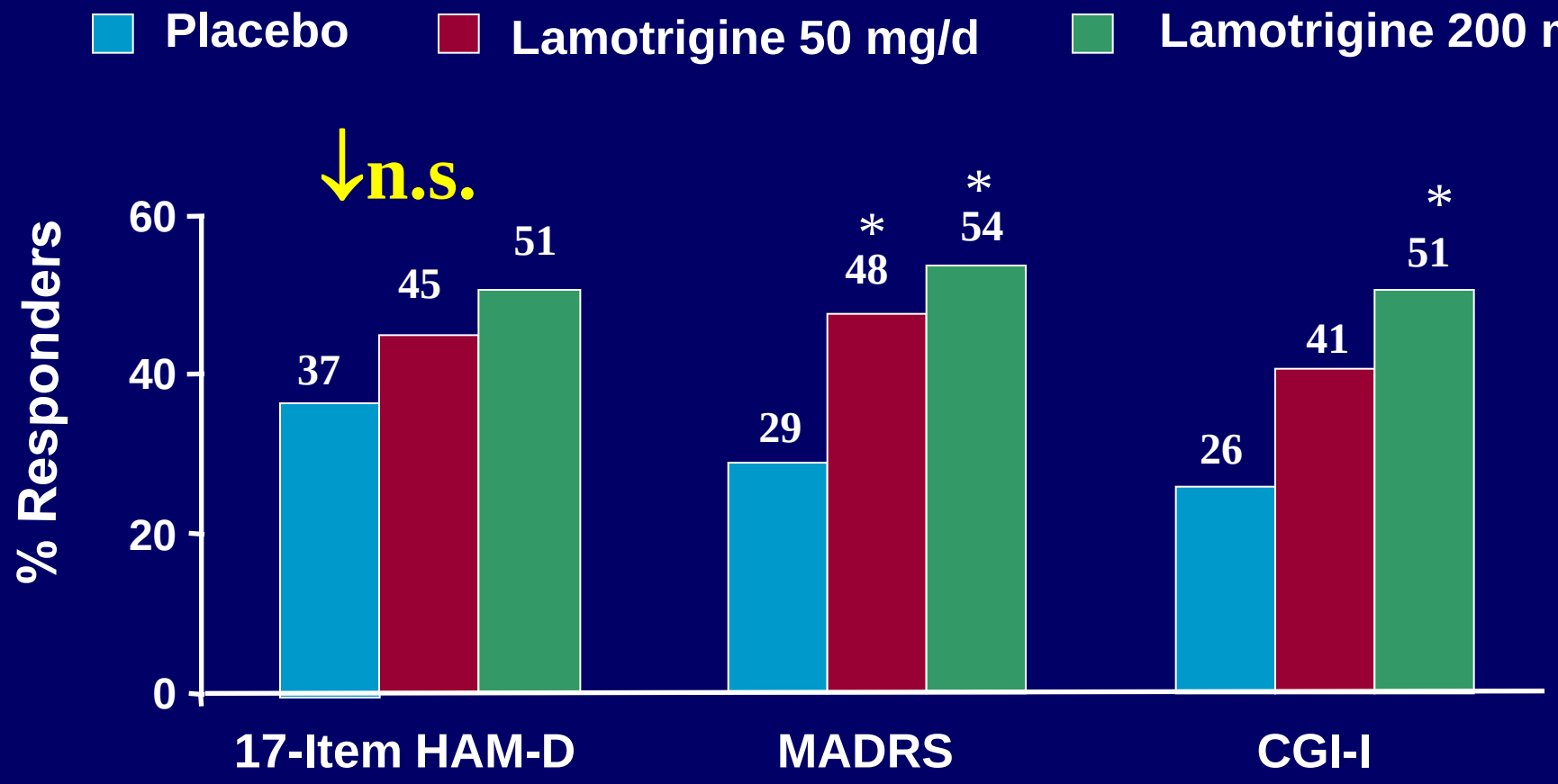
“I have known many a lifeless and unhallowed hour … long intervals of darkness, interrupted by short returns of peace and joy.”

Memoir of the Early Life of William Cowper, Esq. (1816)

Bipolar Depression: FDA Approval

- **Lurasidone**
  - **-2013 for bipolar I depression**
- **Quetiapine**
  - **-2006 for bipolar I and II depression**
- **Olanzapine/fluoxetine combination**
  - **-2003 for bipolar I depression**

Lamotrigine Monotherapy for Bipolar I Depression (7 weeks, n=192)



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

*p<0.05

Lamotrigine for Bipolar Depression (5 multicenter, placebo-controlled studies)

- **Lamotrigine did not separate from placebo on the primary endpoint of any of the 5 studies***

***Geddes et al., NCDEU Annual Meeting poster I-64, June 2007**
Also see Calabrese et al. Bipolar Disorders 2008;10:323-333

The great tragedy of Science-
the slaying of a beautiful hypothesis by an ugly fact

Thomas Huxley (1825-1895)

Lamotrigine for Bipolar Depression (5 multicenter, placebo-controlled studies)

- Lamotrigine did not separate from placebo on the primary endpoint of any of the 5 studies
- But, a meta-analysis found "consistent evidence of a mild to modest, but clinically worthwhile benefit for lamotrigine that is unlikely to be due to chance."*

*Geddes et al., NCDEU Annual Meeting poster I-64, June 2007
Also see Calabrese et al. Bipolar Disorders 2008;10:323-333

Lamotrigine Add-On to Lithium for Bipolar Depression

(8-week, double-blind, placebo-controlled, n=124)

- **Dose: maximum 200 mg/day**
- **LTG > PBO on MADRS change (p=.024)**

  MADRS response (51.6% vs. 31.7%) (p=.030)
- **No remission data**
- **Well tolerated (1 severe rash—on placebo)**

Van der Loos et al. J Clin Psychiatry 2009;70:223-231

Quetiapine vs Lithium and Placebo for Bipolar I/II Depression (EMBOLDEN I) (8-week, double-blind,, n=794)

- ↓ MADRS: QTP 300 mg = QTP 600 mg
  > Lithium (0.6-1.2 meq/l) = placebo

- Remission at week 8 (MADRS ≤ 12)

QTP 300 mg	69.8%	(p<0.01)	(NNT=7)
QTP 600 mg	70.3%	(p<0.01)	(NNT=7)
Lithium	62.5%	(n.s.)	(NNT=13)
Placebo	55.0%		

Young et al. J Clin Psychiatry 2010;71:150-162

Quetiapine vs Paroxetine and Placebo Monotherapy for Bipolar I/II Depression (EMBOLDEN II)
(8-week, double-blind,, n=740)

- ↓ MADRS: QTP 300 mg = QTP 600 mg
  >Paroxetine = placebo

- Remission at week 8 (MADRS ≤ 12)

QTP 600 mg	68.5%	(p<0.05)	(NNT=8)
QTP 300 mg	64.6%	(n.s.)	(NNT=11)
Paroxetine	56.8%	(n.s.)	(NNT=71)
Placebo	55.4%		

McElroy et al. J Clin Psychiatry 2010;71:163-174

Lurasidone Enters the Bipolar Depression Arena

- Potent D2, 5-HT2A, 5-HT7 antagonist
- Moderate affinity for α2C, antagonist α2A
- Partial agonist at 5-HT1A
- Little or no affinity for histamine H1 and muscarinic M1 receptors

Package insert 2013,
Kane J, J Clin Psychiatry 2011;72(suppl 1):24-28

Lurasidone for Bipolar I Depression

- **FDA-approved July 2013 as monotherapy and adjunctive therapy**

- **Monotherapy: 6-week, db, PBO-controlled, LUR 20-60 mg or 80-120 mg, n=485****

- **Adjunctive to Li or Valproate: 6-week, db, PBO-controlled, LUR 20-120 mg, n=340***

Package insert July 2013

***Loebel A et al., Am J Psychiatry 2014;171:169-177**
****Loebel A et al., Am J Psychiatry 2014;171:160-168**

Lurasidone for Bipolar I Depression

- Start 20 mg/day, max 120 mg/day
- Take with food ≥ 350 calories for best absorption
- Don’t use with strong 3A4 inhibitors or inducers
- Expensive without good insurance

Lurasidone for Bipolar I Depression
24-week, open-label extension, n=817

- 39% monotherapy, 61% adjunctive
- Improvement sustained
- Mania: mono 1.3%, adjunct 3.8%
- Weight gain ≥ 7%: mono 5.6-13%
  adjunct 13.7-16.1%

Silva R et al., 2014 APA Annual Meeting

Looks promising, but lacks details and peer review

Aripiprazole Monotherapy for Acute Bipolar I Depression

- Two identical 8-week, double-blind, placebo-controlled studies (total n=749)
- Flexible dose: start 10 mg (range 5-30 mg)
- Primary endpoint: MADRS (LOCF)
  No significant difference in either study

Thase et al., J Clin Psychopharmacology 2008;28:13-20

Ziprasidone Monotherapy for Acute Bipolar I Depression

- Two similar 6-week, double-blind, placebo-controlled studies (total n=928)
- Flexible dose: Study 1- 40-80 mg/day or 120-160 mg/day; study 2- 40-160 mg/day*
- Primary endpoint: MADRS (MMRM)

No significant difference in either study!

Sachs et al. NCDEU Poster II-13, 49th Annual Meeting, June 29-July2, 2009
*Sachs et al. J Clin Psychiatry 2011 May 3 (Epub ahead of print)

The Moral of the Antipsychotics for Bipolar Depression Story

In clinical trials, some winners and some losers

Divalproex for Acute Bipolar Depression (Systematic Review and Meta-Analysis)

- 4 small double-blind studies (2 unpublished)
- Total sample size: n=142
- Response: DVPX 39.3%, PBO 17.5%
- Remission: DVPX 40.6%, PBO 24.3%
- Conclusion: Preliminary evidence suggests that it works

Bond et al. J Affect Dis 2010;124:228-234

Acute Bipolar Depression Meta-analyses of PBO-controlled, Monotherapy Trials

- "This body of evidence provides some encouraging leads, but does not establish consistent and unambiguous evidence of high levels of efficacy."
- Quetiapine possible exception, however "only modest effect sizes, and may be risky for long-term use"

Selle V et al., Pharmacopsychiatry 2014;47:43-52

“Would the gentleman prefer an antidepressant?”

Antidepressants for Bipolar Depression

Useful adjuncts

or

Ultimate evils?

CANMAT Guideline, Update 2013, for Bipolar Depression

- The role of antidepressants "remains one of the most controversial areas in psychiatry"
- SSRIs and bupropion could be first-line with a mood stabilizer short-term (not paroxetine*)
- Avoid TCAs, venlafaxine: ↑ risk of manic switch

*Less effective

Pharmacotherapy of Bipolar II Depression: A Review

- MEDLINE Jan 1950 to Jan 2009, 21 trials
- Quetiapine: "Compelling evidence"
- Lithium, antidepressants, pramipexole: "Prelininary support"
- Lamotrigine: "Mixed support"

Swartz HA, Thase ME. J Clin Psychiatry 2011;72:356-366

ISBD Task Force Report on Antidepressant Use in Bipolar Disorders

- **"There is striking incongruity between the wide use of and the weak evidence base for the efficacy and safety of antidepressant drugs in bipolar disorder."**

Am J Psychiatry 2013 (Nov);170:1249-1262 (67 authors)

ISBD Task Force Report on Antidepressant Use in Bipolar Disorders

- **"Because of limited data, the task force could not make broad statements endorsing antidepressant use but acknowledged that individual bipolar patients may benefit from antidepressants."**

Am j Psychiatry 2013 (Nov);170:1249-1262 (67 authors)

ISBD Task Force Report on Antidepressant Use in Bipolar Disorders

- **SSRIs and bupropion may have lower rates of manic switch than TCAs, tetracyclics, and NE/5-HT uptake inhibitors**

Am j Psychiatry 2013 (Nov);170:1249-1262 (67 authors)

“I’m taking you off the antidepressant”

Do Antidepressants Cause Mania/Hypomania?

Do Antidepressants Cause Mania/Hypomania?

Maybe

“Now that I’ve swung back to depression, I’m truly sorry for what I did while I was manic.”

Do Antidepressants Cause Rapid Cycling?

Do Antidepressants Cause Rapid Cycling?

Maybe

Odds and Ends

Adjunctive Modafinil for Bipolar I or II Depression (6-week, double-blind, n=85)

- Dose: 100 mg x 1-w, then 100 mg bid (mean 174 mg/day)
- Reponse (↓ IDS ≥50%): MOD 43.9% (P=0.038)
  PBO 22.7%
- Remission (IDS<12): MOD 39% (P=0.033)
  PBO 18%

Frye et al. Am J Psychiatry 2007;164:1242-1249

Adjunctive Armodafinil for Bipolar I Depression (8-week, double-blind, n=247)

- **Dose: 150 mg/d or placebo**
- **Primary efficacy: IDS-C_{30} change**

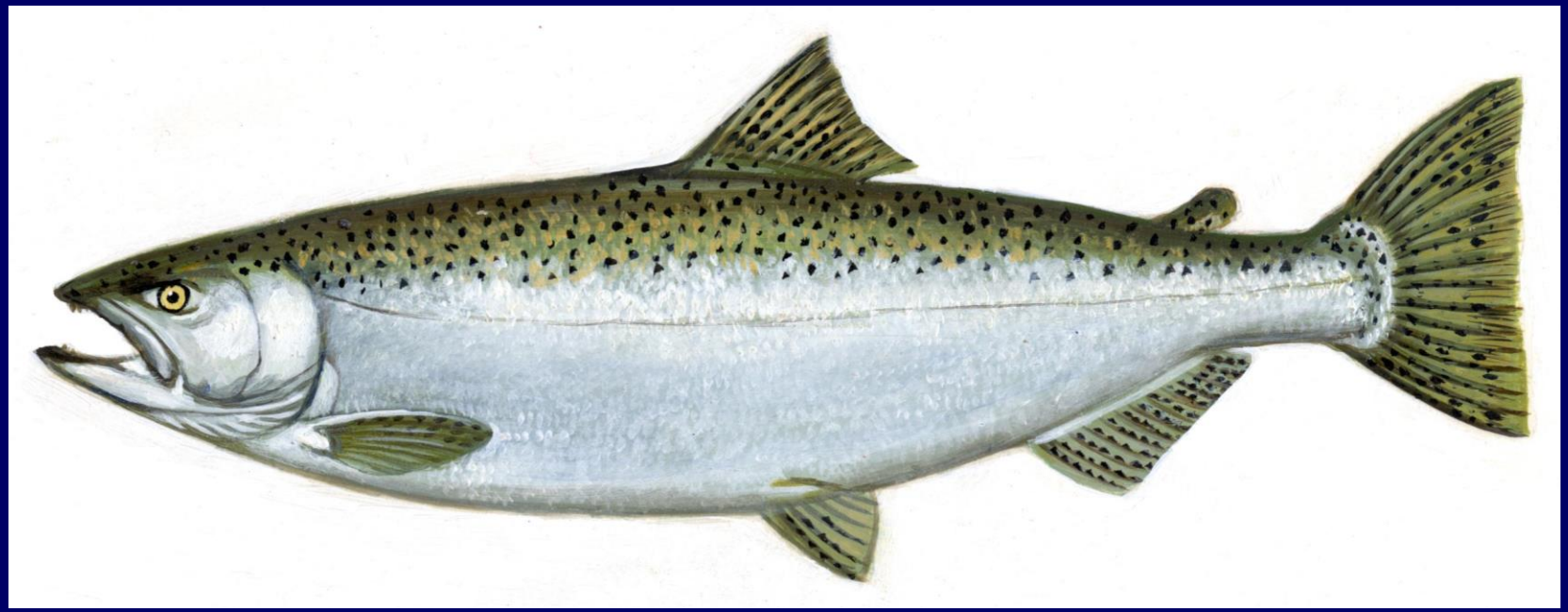
  ARM: -15.8

  PBO: -12.8

  (ANOVA: p=.044)
- **Secondary efficacy: No sig. diff on response, remission, QIDS-SR, MADRS, etc.**
- **Further studies needed**

Calabrese et al. J Clin Psychiatry 2010;71:1363-1370

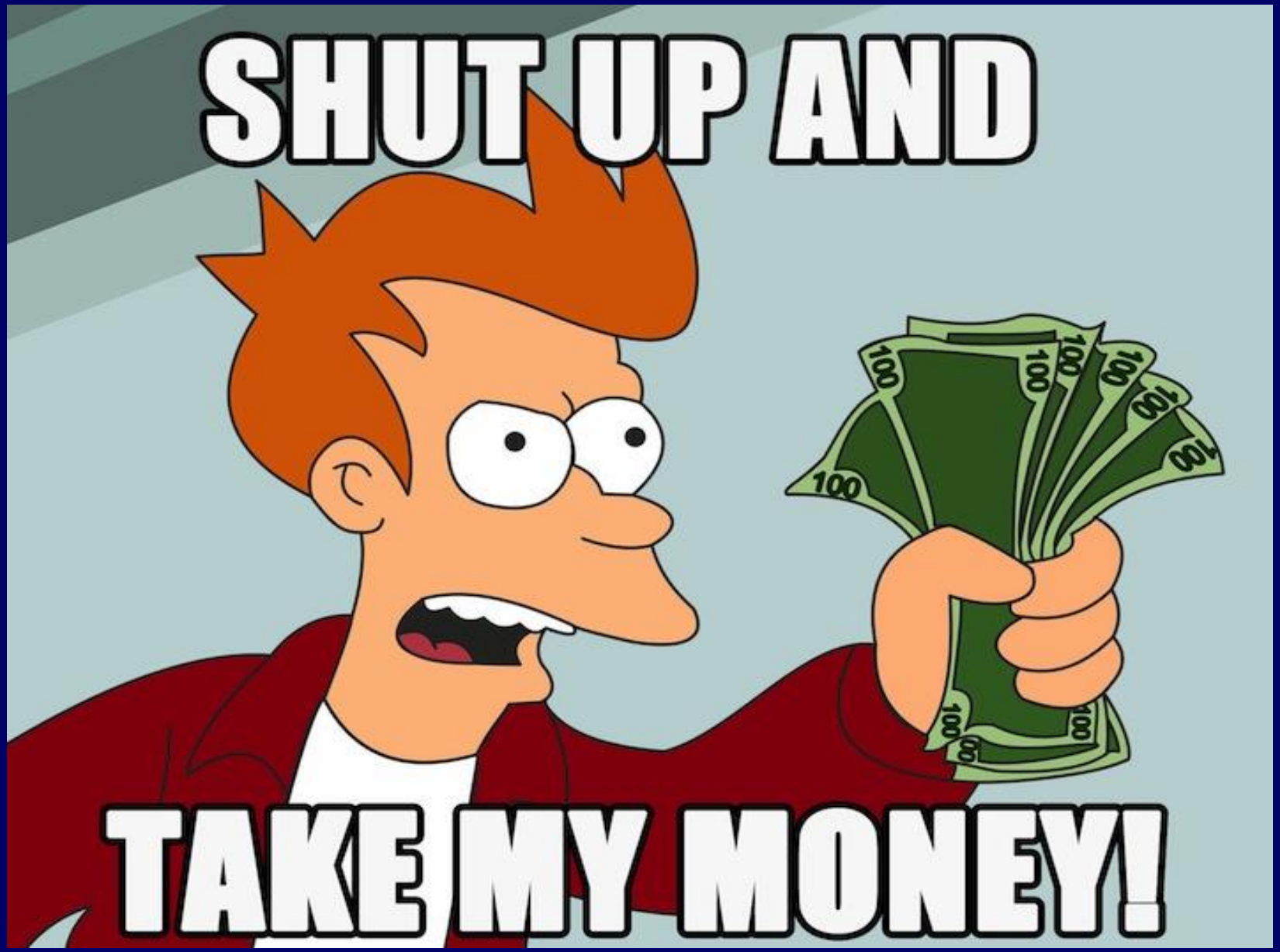
Omega-3 Fatty Acid Augmentation For Bipolar Depression



Omega-3 for Bipolar Disorder Meta-analysis

- Strong evidence that bipolar depression may be improved with adjunctive use
- Adjunctive use in mania not supported
- Well tolerated
- Controversy remains over best preparation and dose

Sarris J et al., J Clin Psychiatry 2012;73:81-86


SHUT UP AND
TAKE MY MONEY!

N-Acetyl Cysteine (NAC) for Bipolar Depression (and much more)

- Glutathione: Brain's major antioxidant, free-radical scavenger
- NAC: A glutathione precursor and dopamine modulator
- Preliminary promise for bipolar, addiction, cannabis, nicotine, OCD, schizophrenia, autism
- Most all the work by the Michael Berk group

Brek M, Trends in Pharmaceutical Sciences 2013;34:167-177

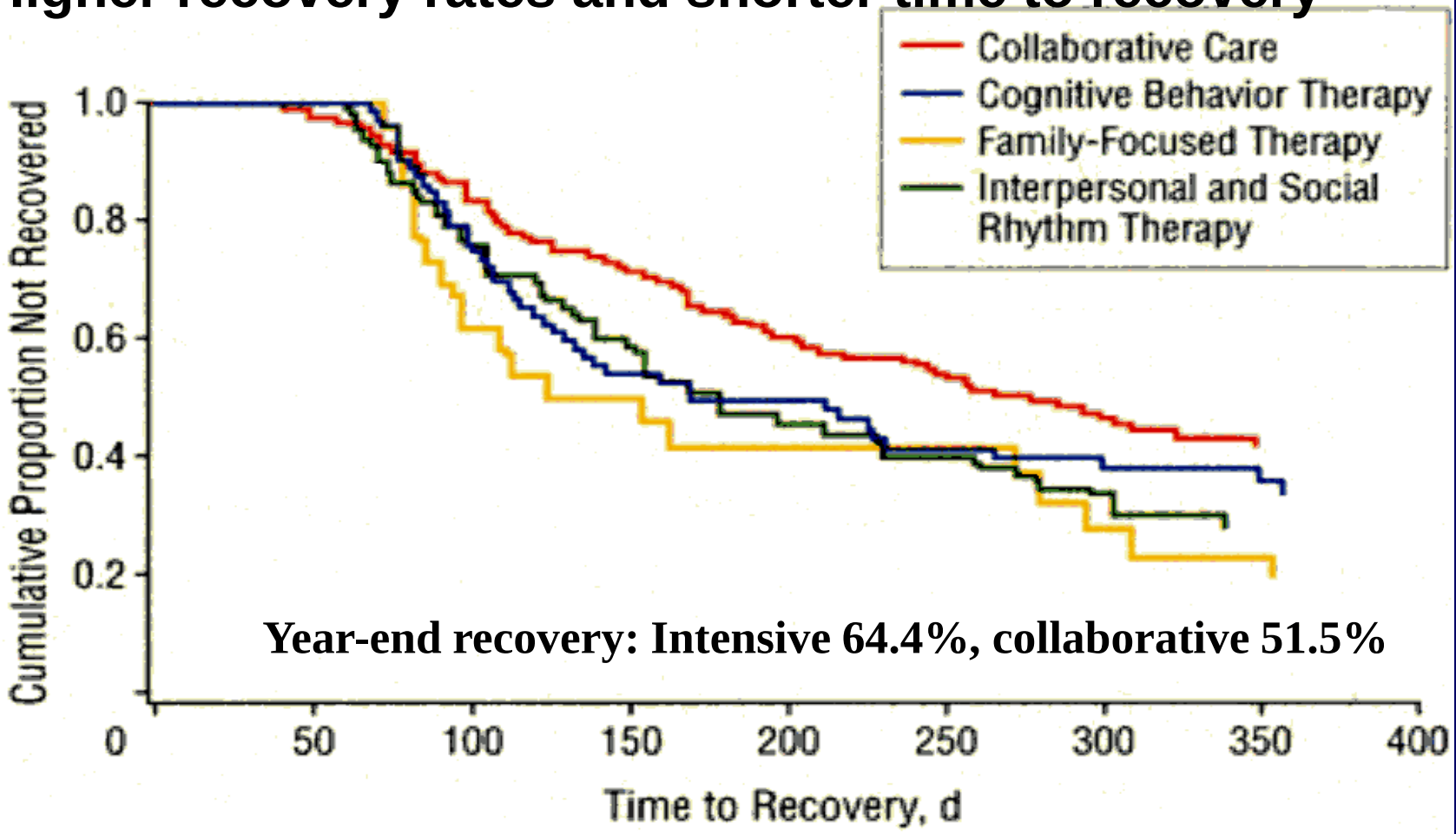
Acute Bipolar I Depression

For a good, timely, data-oriented systematic review, check out:

- **Cerullo MA, Strakowski SM. CNS Spectrums 2013;18:199-208**

STEP-BD: Adjunctive Psychosocial Treatments for Bipolar Depression

Higher recovery rates and shorter time to recovery



Year-end recovery: Intensive 64.4%, collaborative 51.5%

Miklowitz et al. Arch Gen Psychiatry 2007;64:419-427

Rapid Cycling (4 or more episodes/year)

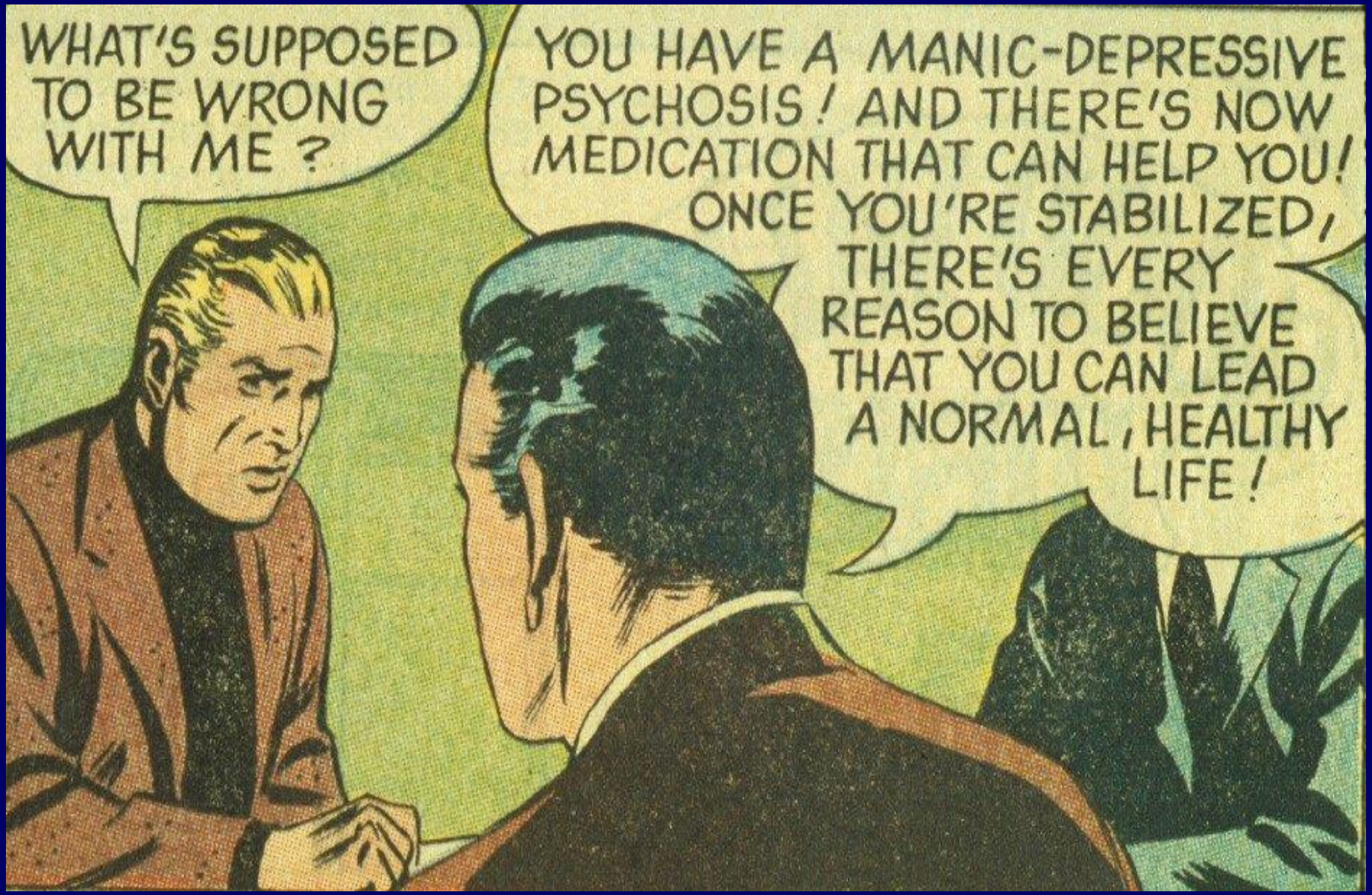
- Stop antidepressants
- Use lithium or valproate
- Alternative – lamotrigine
- Combinations
  - add antipsychotic
  - add mood stabilizer

APA Bipolar Guidelines, Revised 2002

Lamotrigine Add-On to Li and DVPX for Rapid-Cycling

- Open label Li + DVPX up to 16 weeks (n=133)
- If not stabilized, double-blind LTG or PBO (n=49) for 12 weeks
- LTG = PBO for decreasing depression severity
- Small sample size, so don't give up hope

Kemp DE., Bipolar Disorders 2012;14:780-789


WHAT'S SUPPOSED TO BE WRONG WITH ME ?
YOU HAVE A MANIC-DEPRESSIVE PSYCHOSIS ! AND THERE'S NOW MEDICATION THAT CAN HELP YOU ! ONCE YOU'RE STABILIZED, THERE'S EVERY REASON TO BELIEVE THAT YOU CAN LEAD A NORMAL, HEALTHY LIFE !

Bipolar Maintenance: FDA-Approved

Lithium-1974
Lamotrigine-2003
Olanzapine-2004**
Aripiprazole-2005, 2011**
Quetiapine-2008*
Risperidone L-A injection-2009**
Ziprasidone-2009*

****Approved for monotherapy and adjunctive to lithium and valproate**
***Approved only as adjunct to lithium or valproate**

Lithium + Valproate Combo vs. Monotherapy for Bipolar I Maintenance (BALANCE*)

- 41 sites (UK, France, Italy, USA)
- 4-8 week run-in on Li+VPA, then open-label randomized to Li (n=110), VPA (n=110) or combo (n=110)
- Follow-up: Up to 2 years
- Primary outcome: New intervention for mood episode

Lancet. 2010;375:385-395

*BALANCE= Bipolar Affective disorder: Lithium/ ANtiConvulsant Evaluation

Lithium + Valproate Combo vs. Monotherapy for Bipolar I Maintenance (BALANCE*)

- **Primary outcome (new intervention):**

  Li+VPA 54%, Li 59%, VPA 69%

  Li+VPA > VPA (NNT=7, p=0.0014)

  Li+VPA = Li (NNT=19, p=n.s.)

  Li > VPA (NNT=10, p=0.047)

- **Results: Li and Li+VPA preferred over VPA**

Lancet. 2010;375:385-395

***BALANCE= Bipolar Affective disorder: Lithium/ANtiConvulsant Evaluation**

Lamotrigine vs. Lithium for Bipolar I Maintenance (randomized, open-label, DUAG-6 Trial)

- Li, n=78, 0.5-1.0 mmol/l; LTG, n=77, 400mg max

Licht et al. Bipolar Disorders 2010;12;483-483

Lamotrigine vs. Lithium for Bipolar I Maintenance (randomized, open-label, DUAG-6 Trial)

- Li, n=78, 0.5-1.0 mmol/l; LTG, n=77, 400mg max
- No significant difference in effectiveness (trend favored Li for mania, LTG for depression)

Licht et al. Bipolar Disorders 2010;12;483-483

Lamotrigine vs. Lithium for Bipolar I Maintenance (randomized, open-label, DUAG-6 Trial)

- Li, n=78, 0.5-1.0 mmol/l; LTG, n=77, 400mg max
- No significant difference in effectiveness (trend favored Li for mania, LTG for depression)
- LTG better tolerated, but no effect on outcome

Licht et al. Bipolar Disorders 2010;12;483-483

Lamotrigine vs. Lithium for Bipolar I Maintenance (randomized, open-label, DUAG-6 Trial)

- Li, n=78, 0.5-1.0 mmol/l; LTG, n=77, 400mg max
- No significant difference in effectiveness (trend favored Li for mania, LTG for depression)
- LTG better tolerated, but no effect on outcome
- **Almost no patients maintained successfully on monotherapy with either drug!!!**

Licht et al. Bipolar Disorders 2010;12;483-483

Risperidone Long-Acting Injection

Risperidone Long-Acting Injection for Bipolar I Maintenance: Monotherapy

- 26-week, open-label stabilization, n=501
- 60% who maintained response randomized to double-blind for up to 24 months
- Time to recurrence: RIS > PBO ($p<0.001$)
- Recurrence: RIS 30%, PBO 60%
- NNT for relapse prevention at 9 months: 3.3

Quiroz et al. Biol Psychiatry 2010;68:156-162

Words of Caution

Bipolar Maintenance Studies

- Dropout rates remain disturbingly high
- Active drug keeps patients around longer than placebo, but completion rates rarely exceed 50%
- Probably not news to those of you in the trenches.
- But, the combination of art and science will prevail (I hope)

Post-Test Question #1

1. The most current Bipolar Treatment guideline is which of the following?

A. APA Practice
B. TIMA Algorithms
C. WFSBP
D. CANMAT
E. Br Assoc Psychopharm

Post-Test Question #2

2. The most prominent proponent of blood-letting for mania was which of the following?

A. Benjamin Rush
B. John Rush
C. Rush Limbaugh
D. Rush University Medical School
E. Pass Rush

Post-Test Question #3

3. Which of the following is FDA-approved for the treatment of Bipolar Depression?

A. Aripiprazole
B. Risperidone
C. Lurasidone
D. Escitalopram
E. Modafinil

Post-Test Question #4

4. The BALANCE study of bipolar maintenance found which of the following?

A. Lithium = valproate

B. Lithium > valproate

C. Valproate > lithium

Post-Test Question #5

5. The first antipsychotic FDA-approved for the treatment of mania was which of the following?

A. Aripiprazole
B. Risperidone
C. Olanzapine
D. Chlorpromazine
E. Haloperidol

Post Test Answers

1- Ans: D (CANMAT)
2- Ans: B (Benjamin Rush)
3- Ans: C (lurasidone)
4- Ans: B (lithium > valproate)
5- Ans: D (chlorpromazine in 1972)

The End