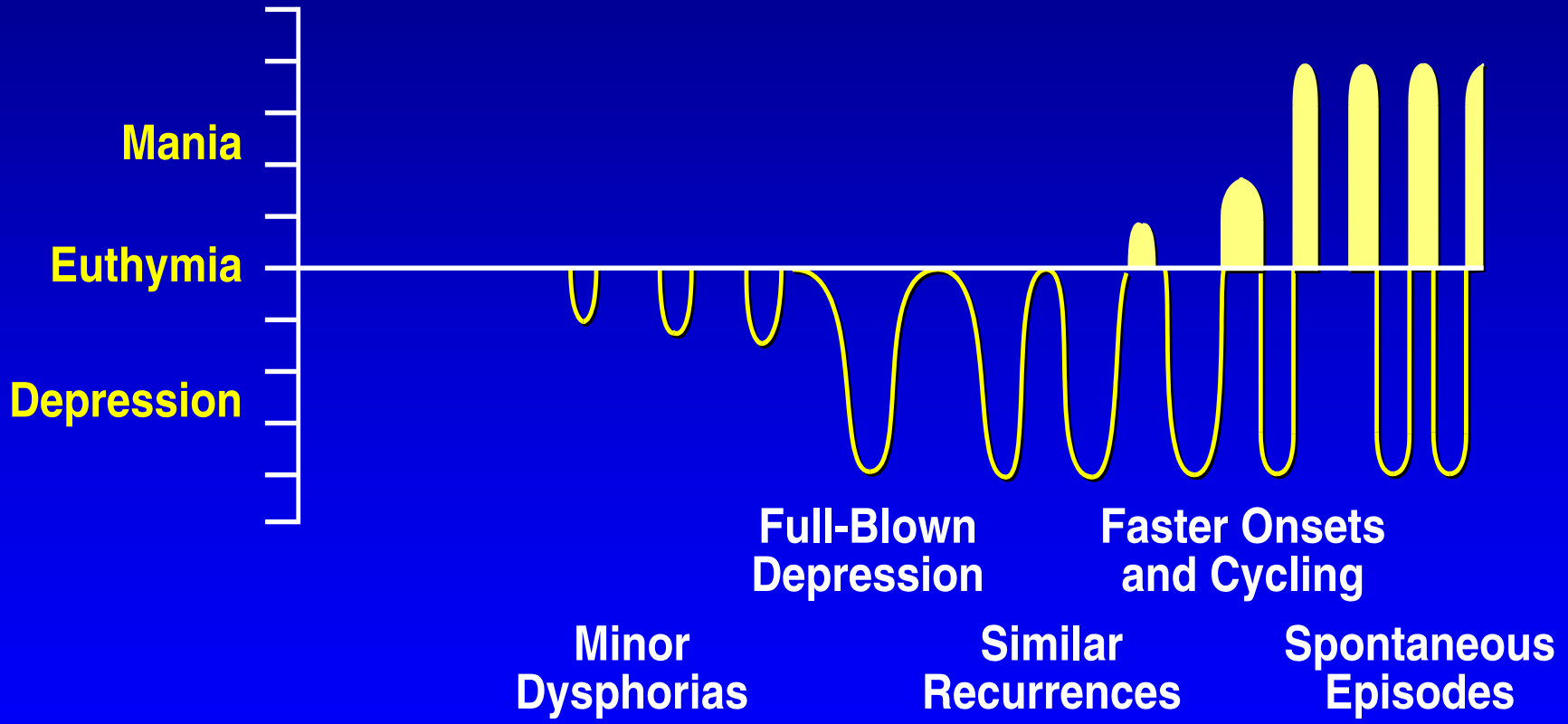
Treatment of Bipolar Depression

R.Bruce Lydiard, PhD, MD
Medical University of South Carolina

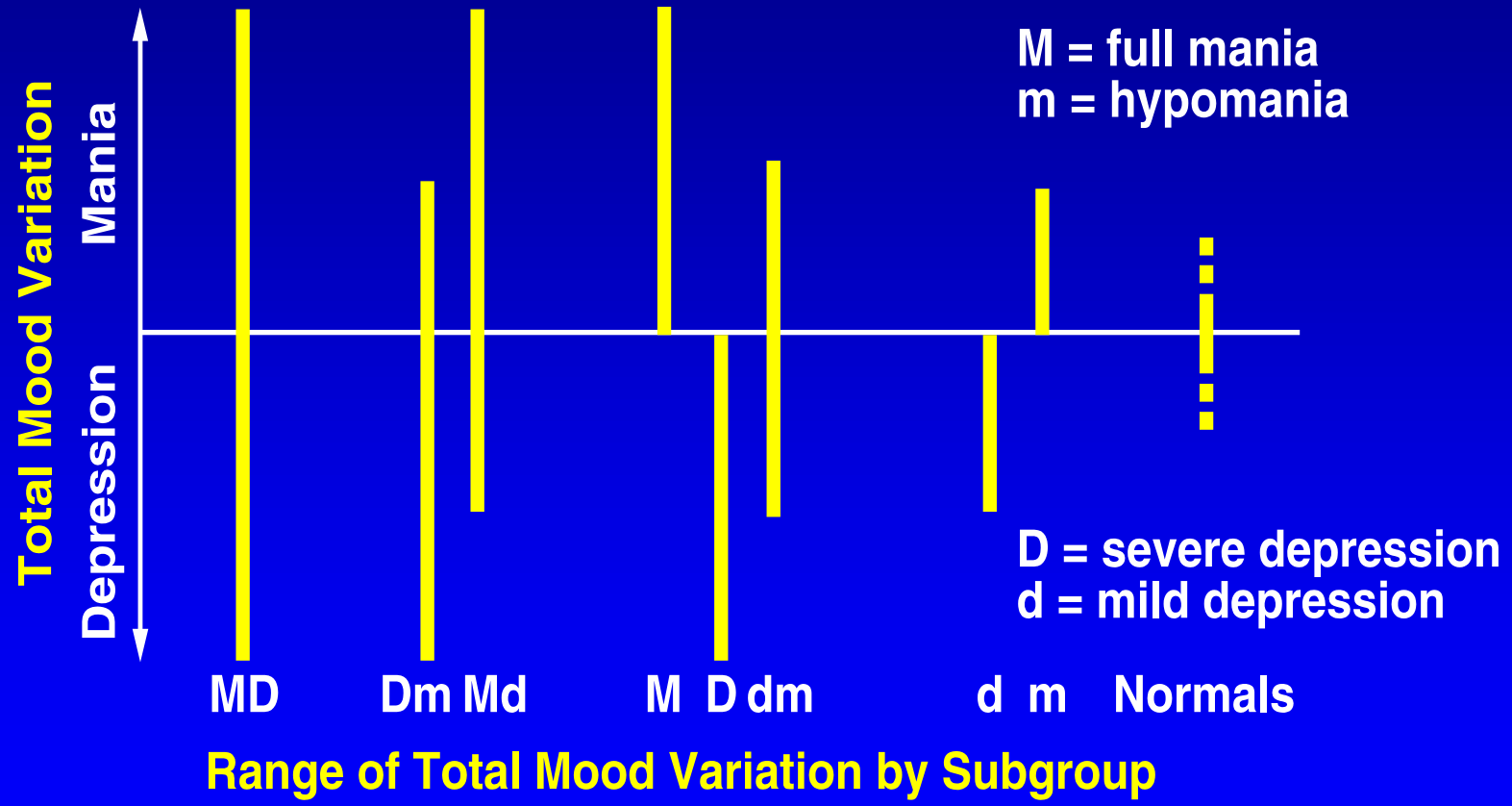
Alan C. Swann, MD
University of Texas - Houston

Model of Evolution of Bipolar Course



Modified from: Post RM, Rubinow DR, Ballenger JC. Conditioning and sensitization in the longitudinal course of affective illness. *Br J Psychiatry* 1986;149:191-201

The Manic-Depressive Spectrum



Goodwin FK, Jamison KR. Manic-Depressive Illness. New York: Oxford University Press; 1990, p. 81

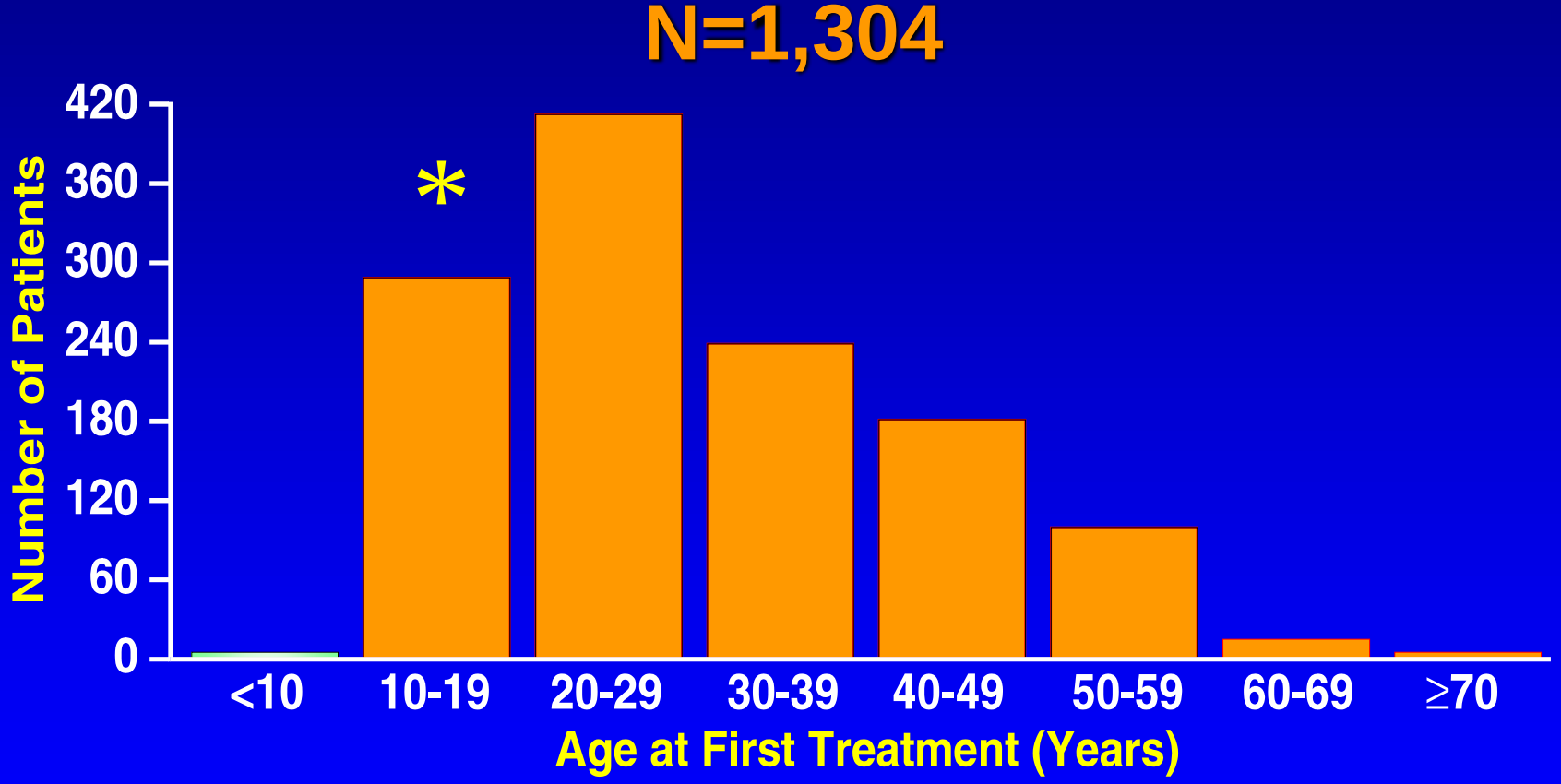
Bipolar Depression

- Differential Diagnosis
- Treatment
- Augmentation Strategies
- “Switch” Risk
- Induction of Rapid Cycling
- Comorbid Substance/Alcohol Abuse
- Comorbid Psychiatric Disorders

Bipolar Epidemiology

- Lifetime prevalence (adults)
  - Bipolar I — 0.8%
  - Bipolar II — 0.5%
  - (May be underestimates)
- Age of onset
  - Mean age — 21 years
  - Peak age — 15-19 years
- Gender
  - Bipolar I — male = female
  - Bipolar II — female > male

Age at First Treatment (Pooled Data)



Modified from: Goodwin FK, Jamison KR. Manic-Depressive Illness, New York: Oxford University Press; 1990, p. 132

*Peak incidence

NDMDA Survey

- 73% (363/500) of respondents received alternative explanation for Sxs
- 34% of these respondents (124/363) received an initial Dx of unipolar depression

Lish JD et al, *J Affect Disord* 1994

Age of Symptom Onset vs. Recognition of BPAD

- Most frequent age of onset : 15-19 yrs
- DMDA survey: Retrospective recall by 31% suggested Sx present prior to age 14
- 33% had depressive sxs first
- 18% -initial Sx mixed manic & depressive
- 24% had nonaffective Sx (i.e., school probs, etc.)

Lish et al, *JAD* 1994;31:281

Bipolar* vs. Unipolar Depression

- Bipolar- more :
  - Psychomotor retardation
  - Total Sleep /24 hrs
  - Incapacitating depression
  - Fragmented REM sleep
- UNDERTREATMENT
- SUICIDE

'Hibernation' Pattern*

- Nonbipolar-more:
- Anxiety
- Anger/hostility
- Physical Complaints
- Measured daily physical

From Goodwin and Jamieson, 1990

Bipolar "Soft Signs"

- Family History Bipolar (+), good Li response
- Temperament
  - Hyperthymic, cyclothymic, dysthymic, irritable
- Mood seasonality
- Pharmacologic-Type III Reaction
- Depression
  - Abrupt onset/termination
  - Psychosis before age 30

Akiskal HS, Mallya G, *Psychopharmacol Bull* 1987

Mixed Mania vs. Agitated Depression

	Mixed Mania	Agitated MDE
Grandiosity	+	–
Inner Tension	+	+
Hyperactivity (goal-directed)	+	–
Hostility	+	+
Suicidality	+	+
Depressive ruminations	+	+
Racing thoughts	+	–

Completed Suicide in BPAD

Goodwin and Jamieson, 1990

- Rarely occurs during mania
- Most occur during depressive episodes
- Highest risk in mixed states

Lithium Reduces Suicide Risk

- Mortality of long-term lithium patients same as general population
- Reduced suicide and suicide attempts vs. off-lithium periods
- Open, randomized 2 1/2-year study
  - Lithium: no suicides, no attempts
  - Carbamazepine: 4 suicides, 5 attempts

Thies-Flechtner et al, *Pharmacopsychiat* 1996;29:103-107

FDA Approval Status for Agents Used in Bipolar Disorder

Drug	FDA Approval	Off Label Use*
Carbamazepine		
Clozapine		✓
Gabapentin		✓
Lamotrigine		✓
Lithium		
Olanzapine	✓	
Quetiapine	✓	✓
Risperidone		✓
Topiramate		✓
Valproate	✓	

*These drugs are used in patient care and are also the subject of ongoing clinical investigations.

Treatment Options for Bipolar Depression

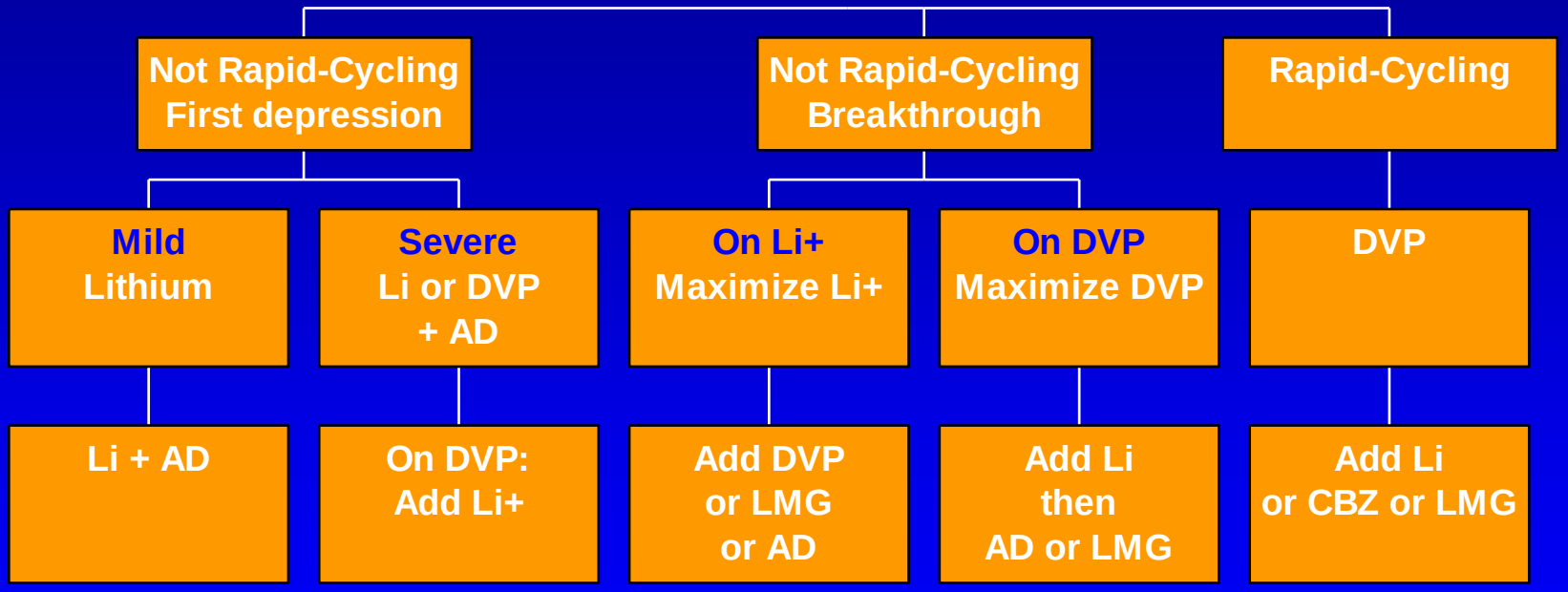
- Lithium
- TCAs
- SSRIs
- MAOIs
- Atypical ADs
- Psychostimulants
- ECT
- Carbamazepine
- Divalproex Sodium
- Lamotrigine
- Gabapentin

EXPERT CONCENSUS GUIDELINES FOR BIPOLAR DEPRESSION

(Frances et al, 1998; JCP 59 (suppl): 73)

Algorithm for Bipolar Depression

Expert Consensus Guidelines: Bipolar Depression



DVP = Divalproex; CBZ = Carbamazepine;
AD = Antidepressant; LMG = Lamotrigine

Bipolar Depression: Common Problems

- Breakthrough: Antidepressant or 2nd mood stabilizer?
  - Differential efficacy with antidepressants?
  - Destabilization?
- Augmentation strategies
- How long to continue added Rx?

Bipolar Depression Controlled Studies

- Lithium
  - (9 studies)
- TCAs
  - (3 studies)
- CBZ (3 studies)
- Lamotrigine

- Li >Pbo in 8/9
- Li = TCAs in 3/3
- CBZ > Pbo in 3/3
- Best evidence

Zorberg and Pope, *J Clin Psychopharm* 1993;13:397-408

Lithium in BP Depression

- First-line Rx by 1998 Consensus Panel
- 9 Pbo-Controlled Studies
- 145 pts with Bipolar Depression
- Li> Pbo in 8/9 studies
- 79% responders
- 36% “uniquivocal” response

Zorberg and Pope, *J Clin Psychopharm* 1993;13:397-408

Lithium Suggestions for Treating BP Depression

- Serum levels [0.5-1.2] meq/L
- 6-8 wks may be necessary for full response
- May have specific anti-suicide advantage

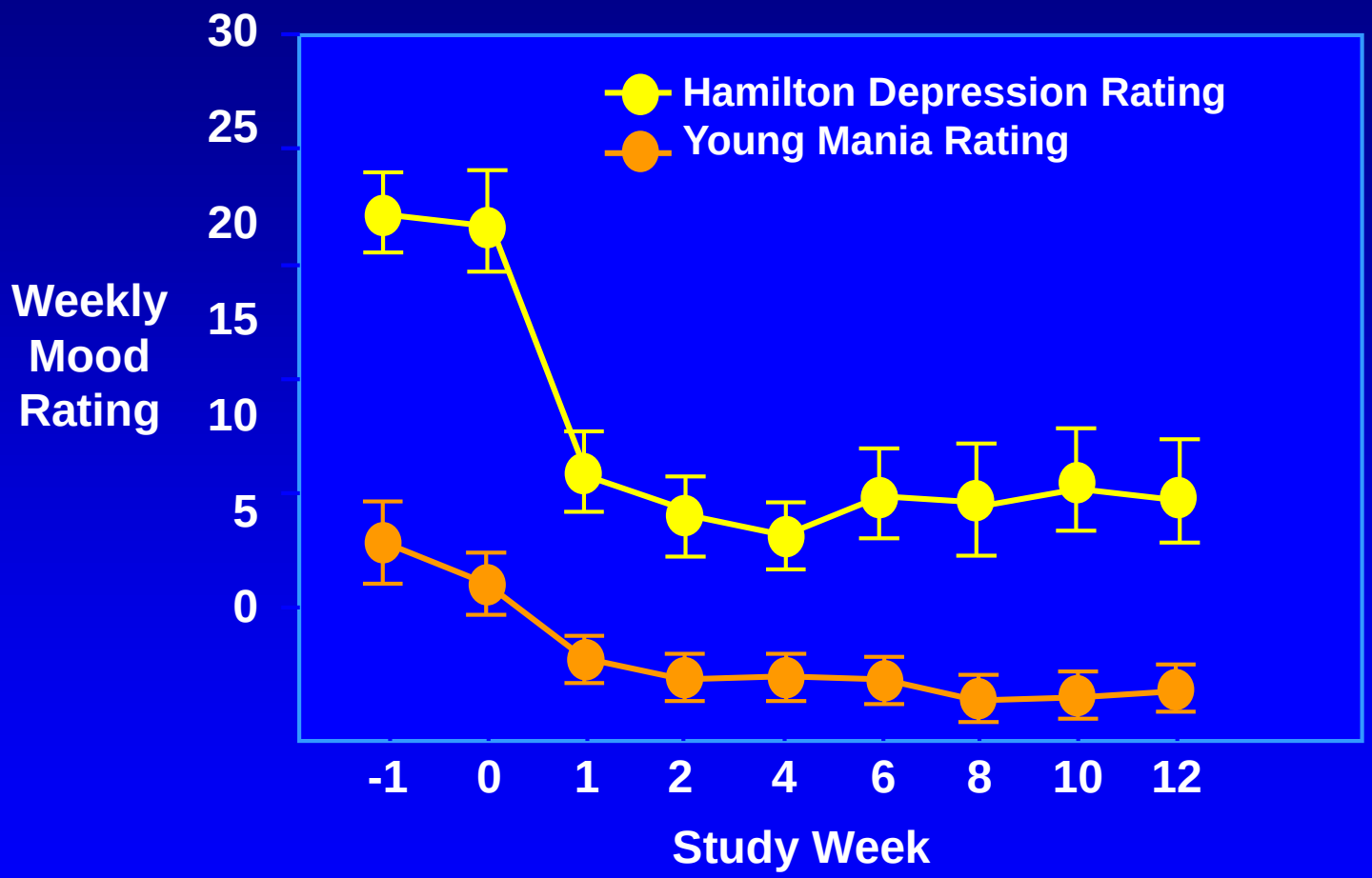
Depression Associated with Mania

Acute Treatment Response to Divalproex vs. Lithium

- Acute double-blind DVPX vs. Li vs. placebo (N=179)
- Even modest depressive sxs in mania associated with:
  - DVPX > Li antimanic response
  - Poorer Li response (unrelated to age, gender, substance abuse, or illness)

Bowden et al, *JAMA* 1994;271:918

DVPX Decreases Both Depression and Mania Scores in Bipolar II Depression



Winsberg ME et al, APA 1997

Divalproex and Maintenance in BPAD

- ≤ 3 mo index manic episode (n= 372)
- Maintenance treatment
- Divalproex, Li or Placebo
- Time to any mood episode not different

Bowden et al, *Arch Gen Psychiatry* 2000;57:481-489

Divalproex and Maintenance in BPAD

- Divalproex > placebo
  - D/C for Recurrence of MDE or Sx
  - Less deterioration in depressive sxs
- Divalproex >Li
  - Duration of successful prophylaxis
  - Less depressive Sx
  - Global Assessment Scale scores

Bowden et al, *Arch Gen Psychiatry* 2000;57:481-489

Treatment of Depressive Symptoms in Bipolar Disorder

Divalproex vs. Lithium

- In review of controlled trials, DVPX equally effective in:
- Elated (pure) mania
- Depressive (mixed) mania
- Li ≈ placebo in pts w/ depressive mania

  Li > placebo in classic mania
- DVPX superior to Li for depressive Sxs
  - Functional status
  - Tolerability

Bowden CL, *J Clin Psychiatry* 1998;59(Suppl 6):13-19;
Swann AC et al, *Arch Gen Psychiatry* 1997;54(1):37-42

CBZ in Bipolar Depression

- Pbo-controlled, CBZ vs. Pbo, BP Dep
- 5/13 receiving CBZ responded
- 3 of 5 had partial relapse after Pbo substitution
- 8-12 μg/L used for study; response correlated with epoxy-CBZ in CSF

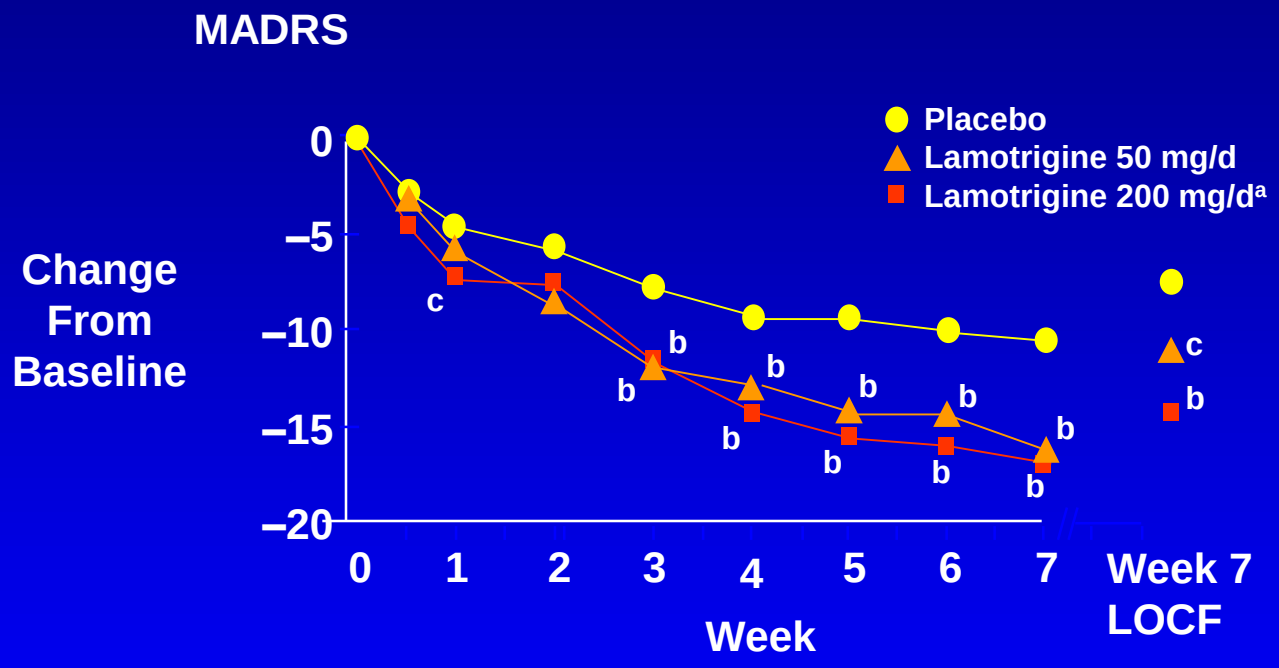
Ballenger and Post, *AJP* 1980;137:782-90

Carbamazepine in Resistant Bipolar Depression

- N=47, resistant BPAD
- 32% responded at 6 wks
- Antidepressant effects less robust than antimanic effects
- Antidepressant effects augmented by Li

Post et al, 1986

Lamotrigine in Bipolar Depression

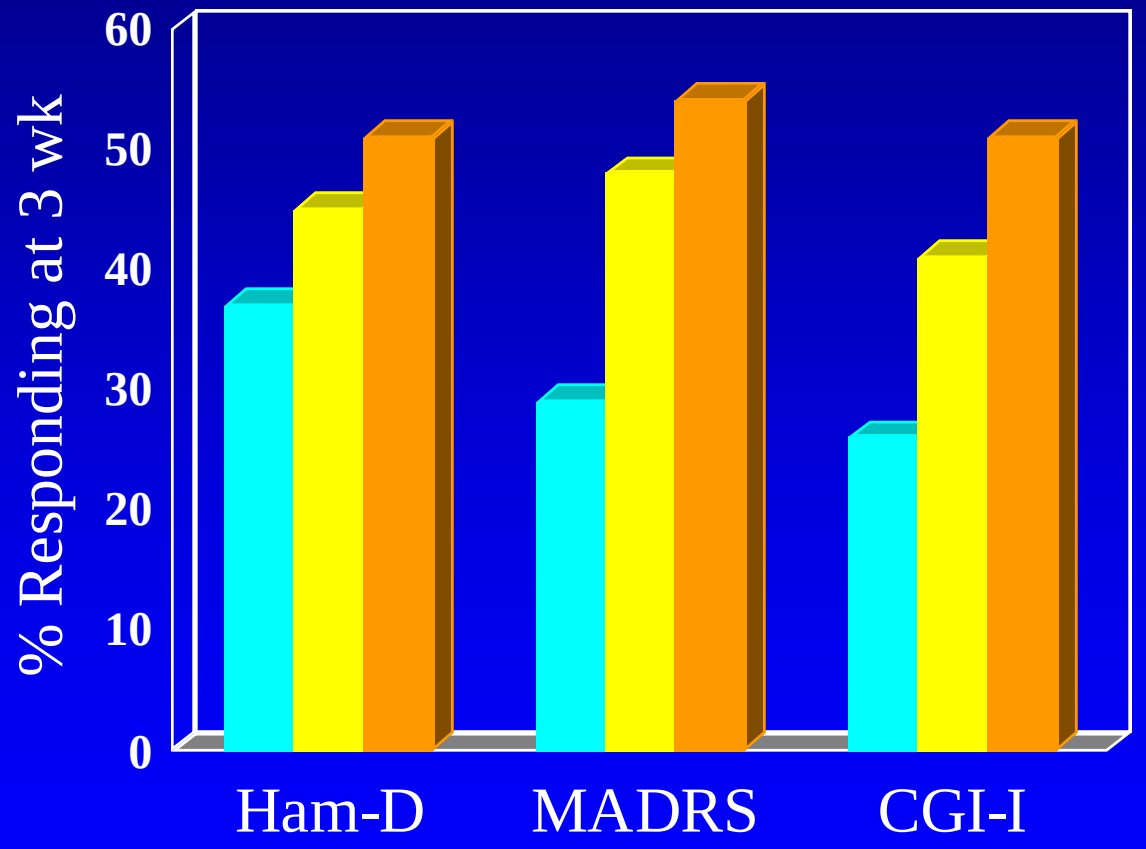


[a] Dose > 50 mg/day in lamotrigine 200-mg/day group only after week 3
[b] P <.05 vs. placebo
[c] P <.1 vs. placebo

MADRS = Montgomery-Asberg Depression Rating Scale

Calabrese JR et al, *J Clin Psychiatry* 1999

Lamotrigine in Bipolar Depression



N=195
Randomized, double-blind;
50% rating scale improvement or definitely improved CGI at 3 wks

Calabrese et al, *JCP* 1999;60:79-88

Gabapentin in Bipolar Depression

- 53 references from 1995-present
- No double-blind study
- Open label studies suggest improvement in 50-70%
- Controlled studies needed

Antidepressants for Bipolar Depression

- General: less data than unipolar; little/no information on relative effectiveness
- Tricyclics
- SSRIs
- Bupropion
- MAOIs
- Venlafaxine

Tricyclics in Bipolar Depression

- NIMH Collaborative: Hospitalized bipolars=unipolars in TCA response rates
- Generally less efficacious than MAOIs or SSRIs (atypical pattern)
- More likely to precipitate mood switches
- Narrow therapeutic margin
- Advantages : low cost, effectiveness in severe unipolar depressions

SSRI's in Bipolar Depression

- Advantages
  - Data for efficacy > TCAs but small studies
  - Relative lack of wt. gain, sedation, autonomic effects
- Disadvantages
  - Sexual dysfunction, sleep problems

SSRIs in Bipolar Depression

- Cohn et al, 1989
- IMI, FLUOX
  - n=22 each
- Double-blind
- Pbo 10%
- SSRI 86%
- TCA 57%

- Simpson & DePaulo, 1991
- Open Rx BPI
- Prior TCA failures
- 81%

Bupropion in Bipolar Depression

- Advantages
  - Supporting data including report in mixed states
  - Lack of wt. gain, sedation, or sexual dysfunction
- Disadvantages
  - Contrary to beliefs, can precipitate mania
  - Lowers seizure threshold more than others (except SR form)
  - Supporting studies had small numbers

MAOI's in Bipolar Depression

- Advantages
  - Supporting data
  - Lack of sedation or anticholinergic effects
- Disadvantages
  - Interactions/diet
  - Sexual dysfunction, postural hypotension, wt. gain

Venlafaxine in Bipolar Depression

- A combined NE-5HT reuptake blocker, like imipramine
- Advantages
  - Some reports of efficacy **(Amsterdam et al, 1998)**
  - Lack of anticholinergic effects
- Disadvantages
  - Autonomic effects, can ↑ blood pressure at doses >300mg daily

Venlafaxine

- 15 women with BPII depression
- Venlafaxine up to 225 mg for 6 wks
- Retrospective analysis of HAM-D(21), MADRS and CGI scale
- Drug-induced manic switch episodes assessed at each visit
- No episodes of drug-induced hypomania, rapid cycling
- Similar efficacy observed in BP and UP depressed women (p=ns)

Amsterdam et al, *JAD* 59:225-9, 2000

Mood Switch with Antidepressants

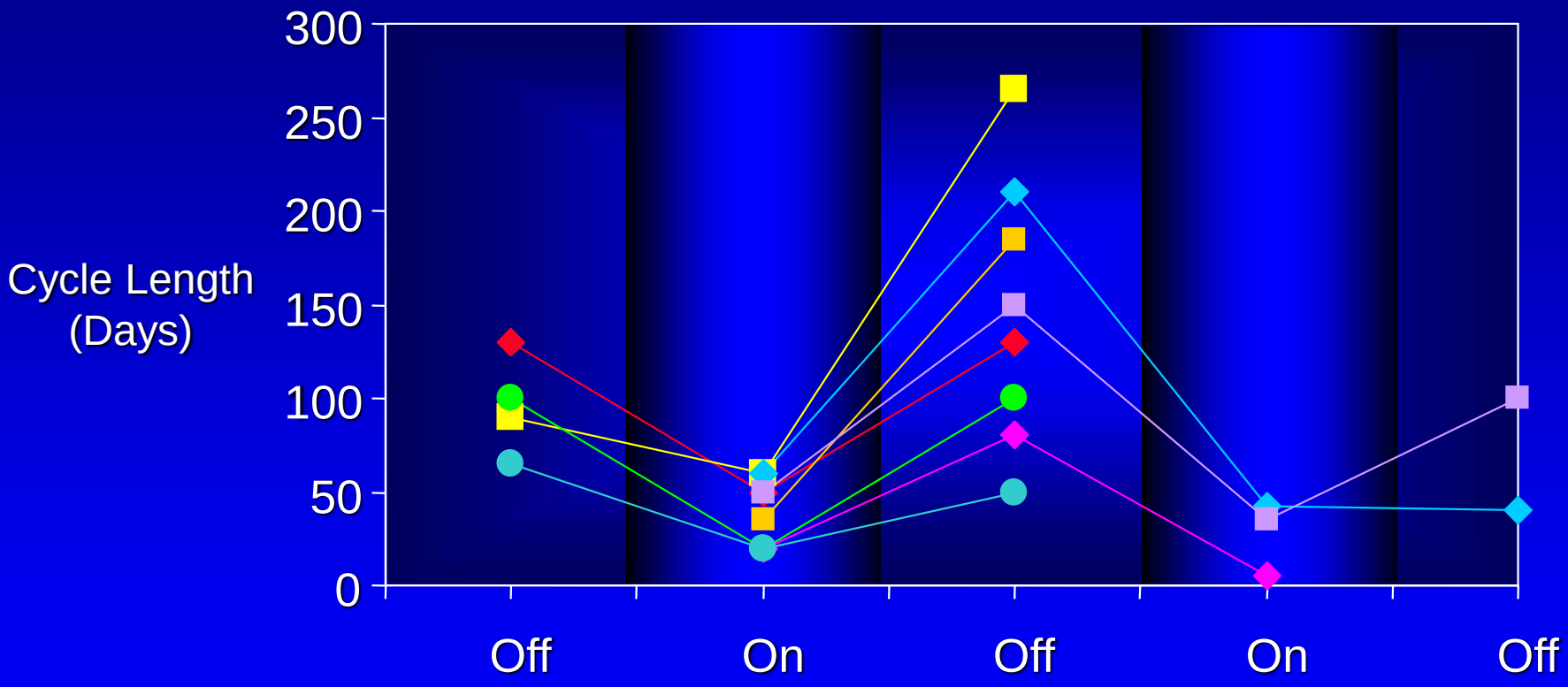
- All antidepressants, phototherapy, sleep deprivation
- Antidepressant-induced episodes
  - Usually mild, self-limited
  - Rapid-cycling may clear
- Mood stabilizer may be protective
  - Long-term destabilization ?
- What is true incidence?

Multi-Center Studies of Unipolar Switch incidence

- Review of all clinical trials to 1994
- Patients with Bipolar Depression
- Switch to mania
  - TCAs (11.2%)
  - SSRIs (3.7%)
  - Placebo (4.2%)

Peet M, Br J Psychiatry 1994;164:549-50

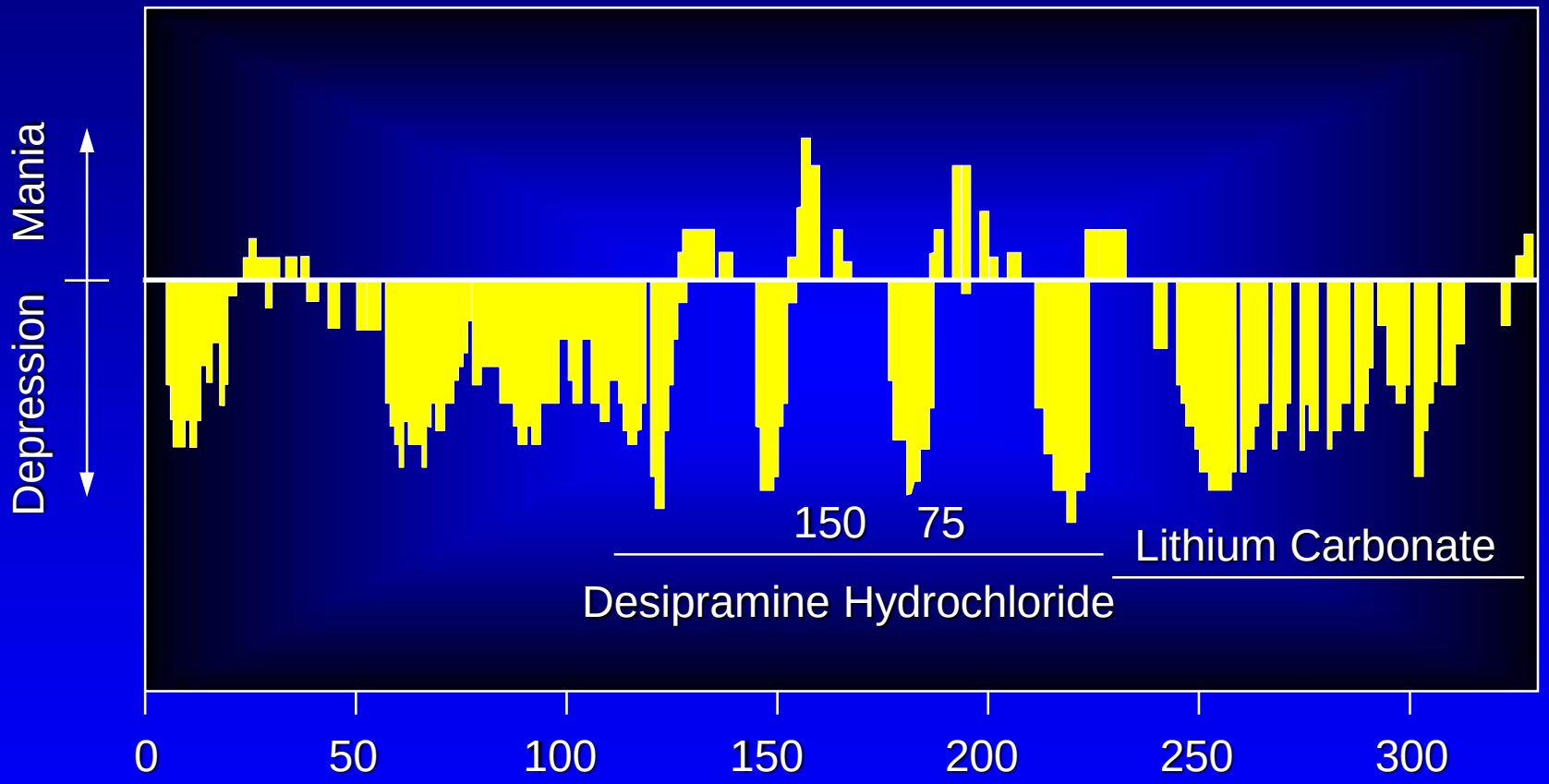
Bipolar Cycle Shortening By TCAs*



*N=10 rapidly cycling bipolar patients

Wehr et al, *Am J Psychiatry* 1987;144:1403

TCAs Increase Frequency Of Bipolar Cycles



Wehr et al, *Arch Gen Psychiatry* 1979;36:555

Evidence for Switch Risk

- Lower switch rates observed with
  - Lamotrigine
  - Paroxetine
  - Moclobemide
- TCAs cause highest risk of switching
- Lack of standard definition for “switch” to mania is problematic

Calabrese Eur Neuropsychopharmacol 1999; August 9 (Suppl 4):S109-12

Antidepressants and Mania

Investigator	Dx	n	%	M /Hypo	Note
Akiskal 1977	BPI	40	35	Hypo	
	Cyclo	25	44	Hypo	
Akiskal 1979	BPI &II	50	50	Hypo	
Wehr & Goodwin 1979	BPI &II	70	35	M	M-21d
			35	Hypo	H-35d
Quitkin 1981	BPI	24	24	either	IMI + Li
Prien 1984	BPI	36	53 (IMI only)		M/H
	BPII	36	28 (IMI + Li)		M/H
Kupfer 1988	BPII	33	3	Hypo	Very strict criteria

Goodwin and Jamison, 1990

Antidepressant-Induced "Switch"

- 79 episodes MDE (n=29 BPAD)
  - 31 episodes -Mood Stab only
  - 29 episodes- Mood Stab + AD
- More switches~more prior manic episodes
- NO difference in rate between Rx groups (i.e., antidepressant or not)
- TCAs,MAOIs >> SSRIs in those taking both AD and mood stabilizer

Boerlin et al, *JCP* 1998;59:374

TCA vs. MAOI for Bipolar Depression

Drug	N	Response Rate (%)	Switch Rate (%)
Imipramine	24	46	25
Tranylcypromine	25	84	20

Thase, 1988

Imipramine "Switch" in BPAD:Prospective Studies

Kupfer, Carpenter & Frank, AJP, 1998

- Unipolar (n= 197) 2.5%
- Bipolar (n= 33) 3.0%
- Four of six observed occurred at discontinuation of medication
- Very strict criteria used

Bupropion and "Switch" to Mania-Open Label Studies

- Haykal & Akiskal,1990
  - Added bupropion for 6 rapid-cycling BPII taking lithium and/or T4
  - 2 yr follow-up $\Rightarrow$ 0/6 switched
- Fogelson et al, 1992
  - 11 BPAD (3 rapid)
  - Bupropion added to existing tx
  - 7/11 some improvement;
    5 cycled more rapidly

Bupropion vs. Desipramine in BPAD "Switch"

- Sachs et al, 1993
- 19 pts with BPAD
- Bupropion added to Li+ or anticonvulsant
- 1/9 bupropion vs. 5/10 DMI showed cycled into mania/hypomania

Atypical Neuroleptics in Bipolar Depression

Frye et al JAD 1998; 48: 91

- Clozapine
  - Better antimanic than antidepressant effects
  - Effective as mood stabilizer
- Risperidone better antidepressant than antimanic; risk for inducing switch
- Olanzapine- sertindole $\Rightarrow$ need more info

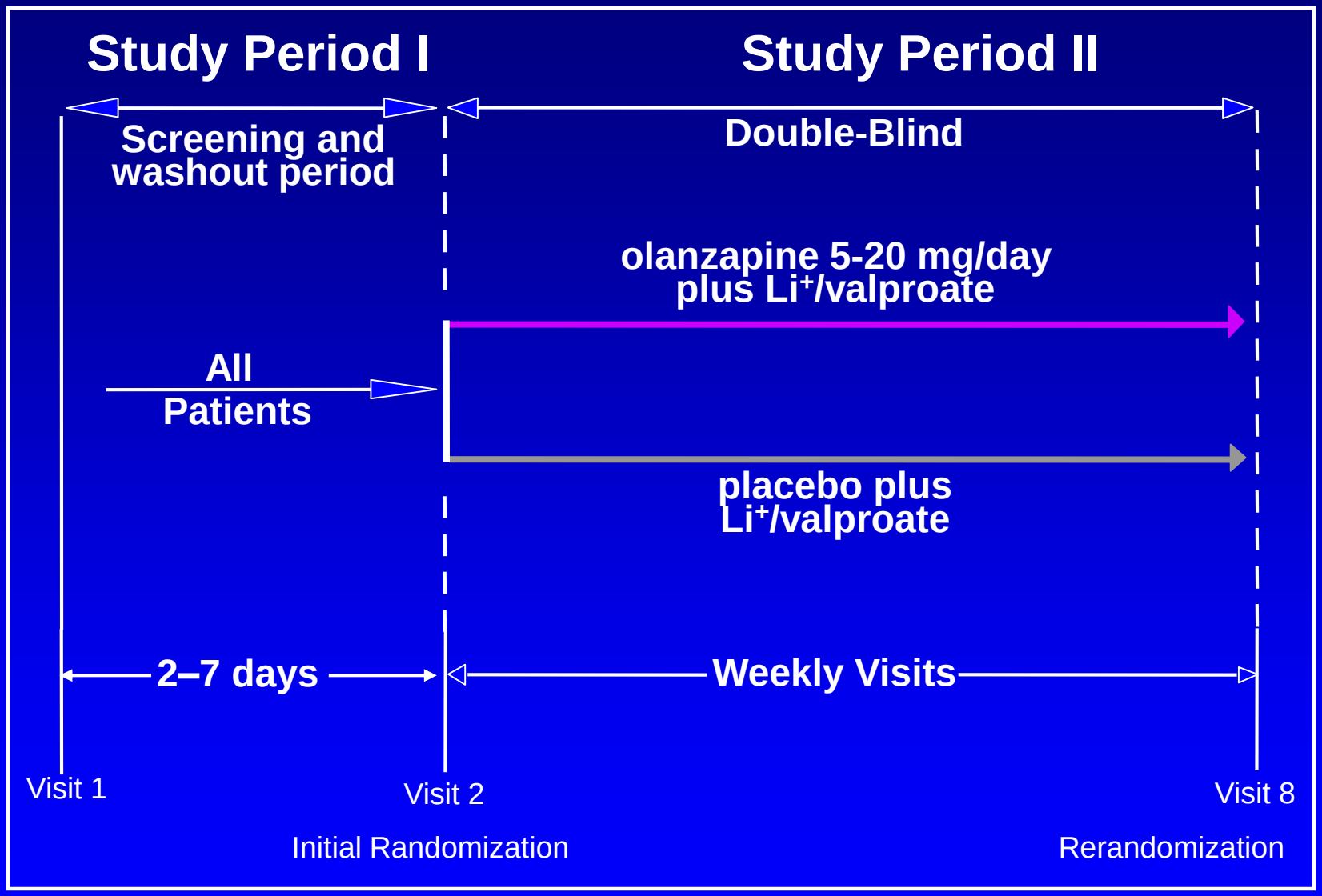
Atypical Neuroleptics in Bipolar Depression

Frye et al JAD 1998; 48: 91

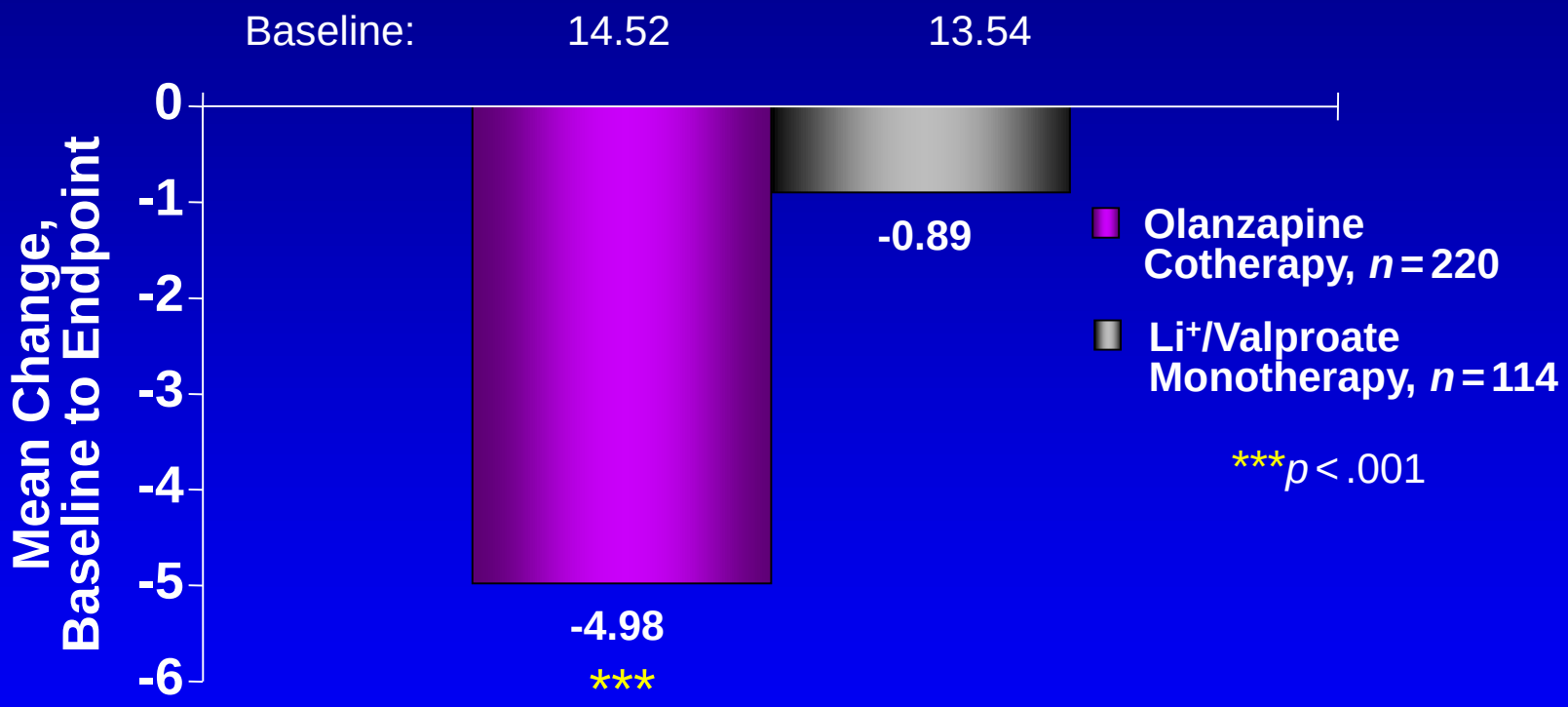
- Clozapine
  - Antimanic > Antidepressant effects
  - Effective mood stabilizer

- Risperidone better antidepressant than antimanic; risk for inducing switch
- Sertindole $\Rightarrow$ need more info

Tohen et al Study Design



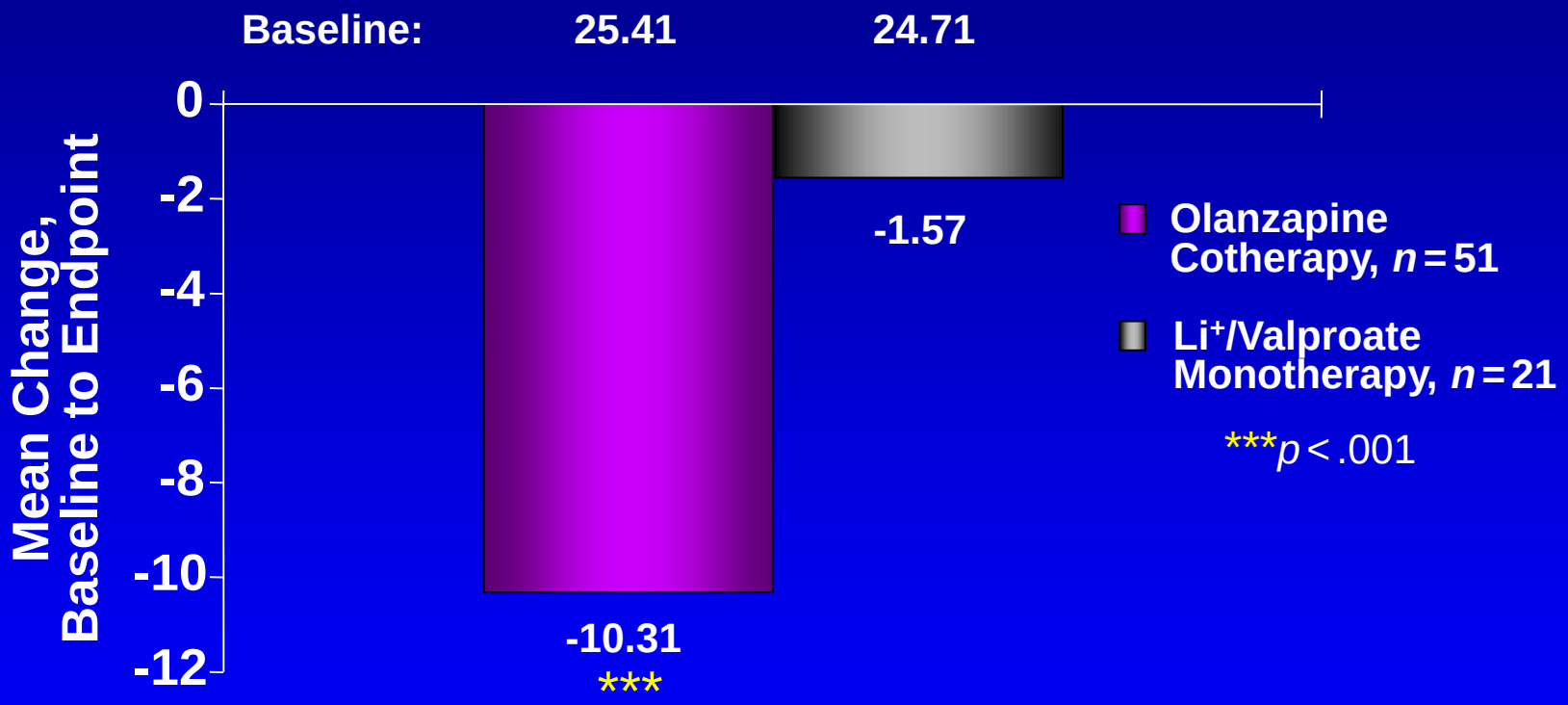
Depressive Symptoms and Olanzapine: HAMD-21



- Patients receiving olanzapine cotherapy improved significantly more on their HAMD-21 total scores than did monotherapy-treated patients.

Patients with Moderate-to-Severe Depressive Symptoms[a]

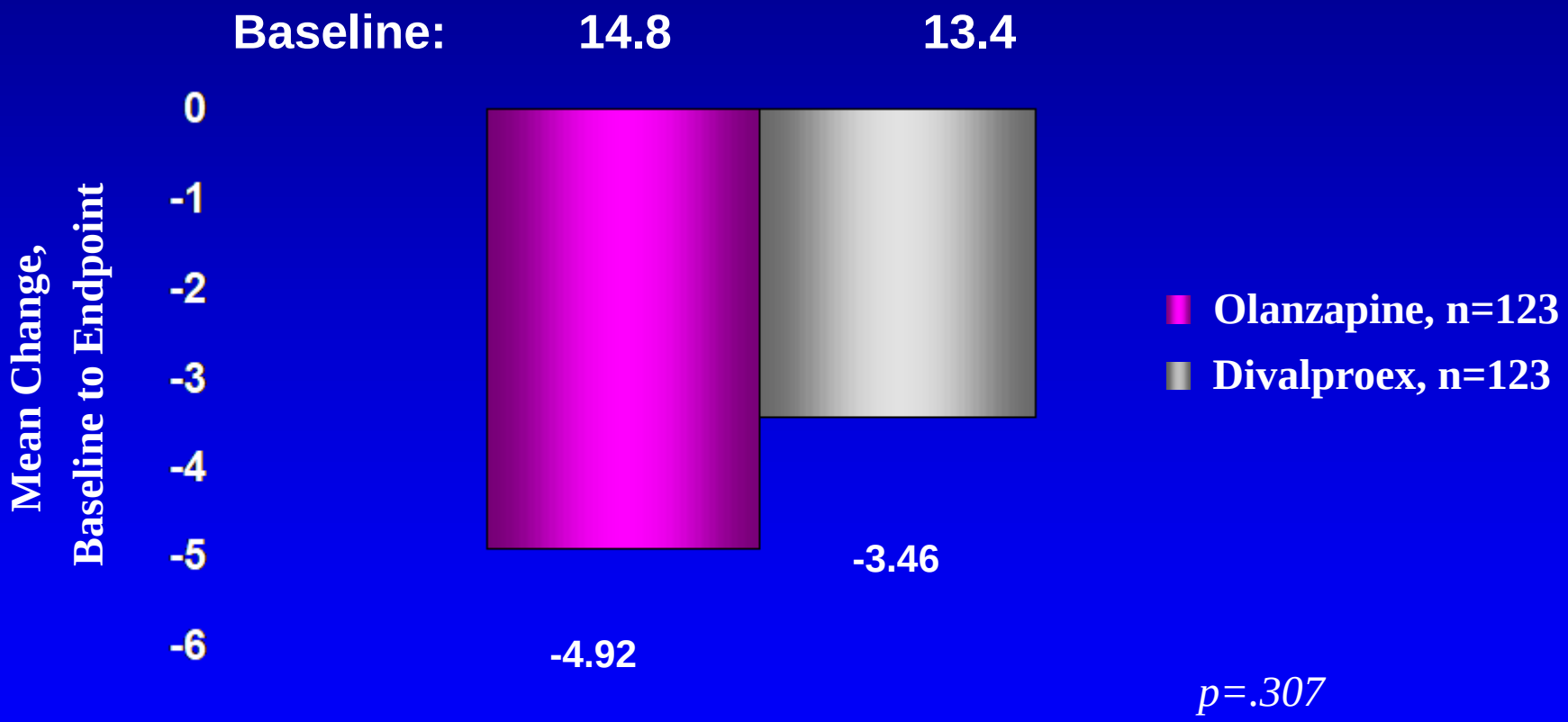
(Tohen et al)



[a] *A priori* definition of *DSM-IV* mixed episode diagnosis and HAMD-21 total score ≥20 at baseline.

Olanzapine cotherapy --> significantly greater mean improvement in HAMD-21 vs. monotherapy.

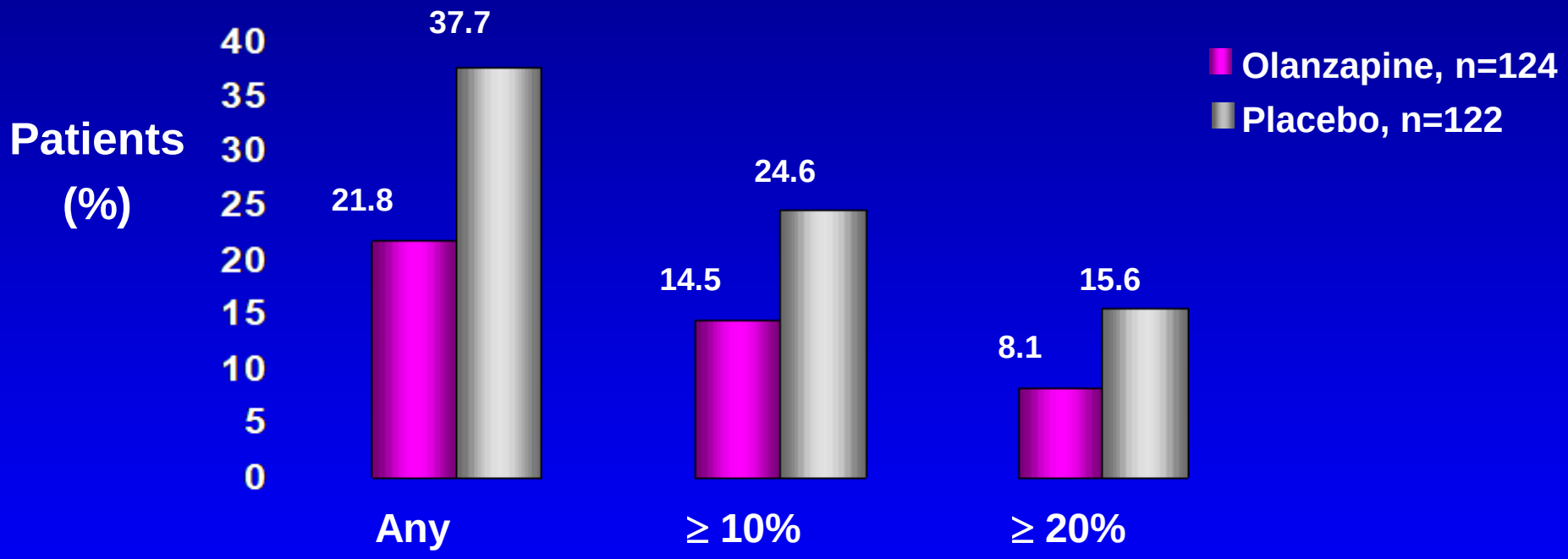
Hamilton Depression Rating Scale (HAM-D)



p=.307

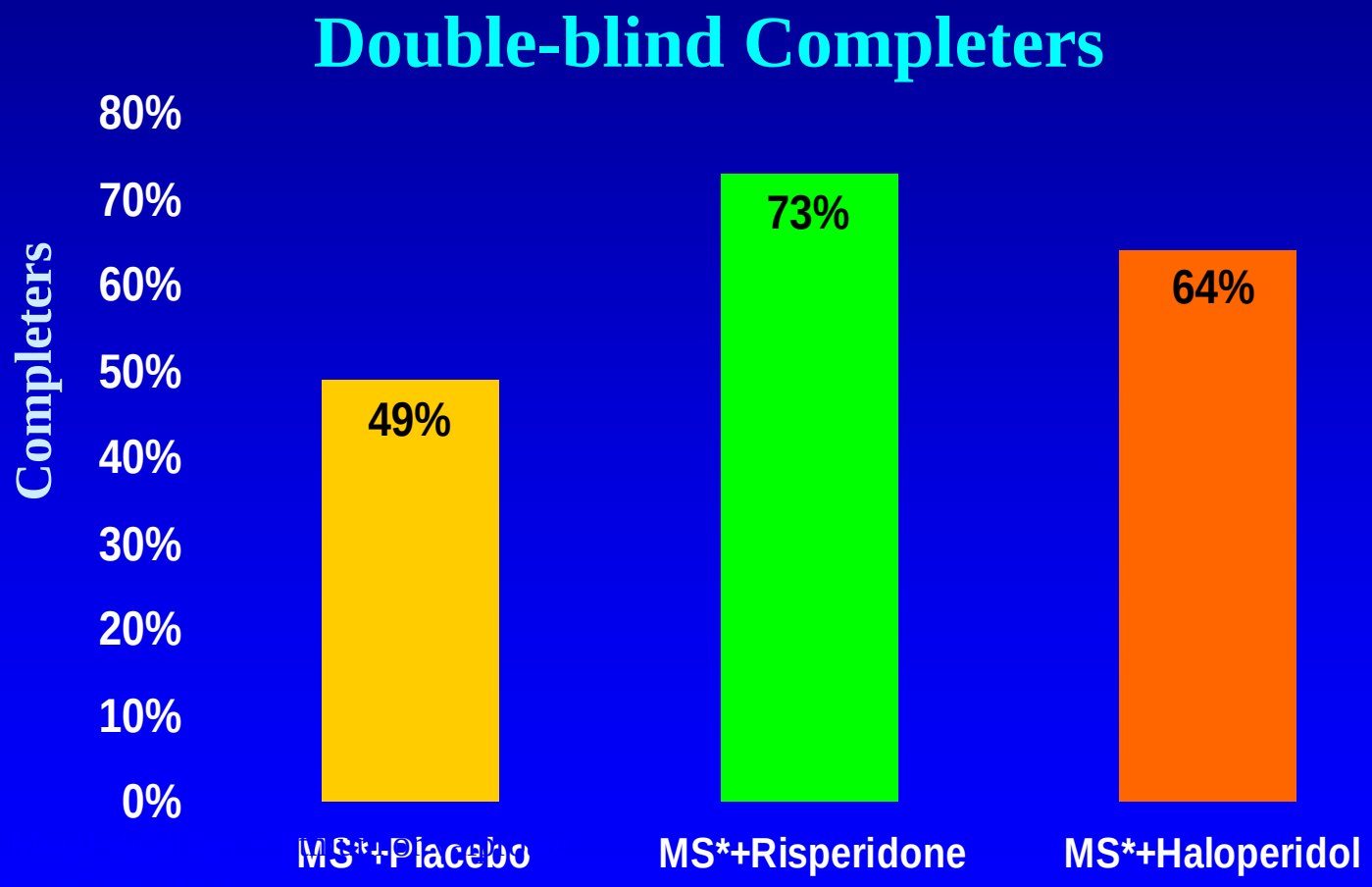
Worsening of Mania

(Milton et al)



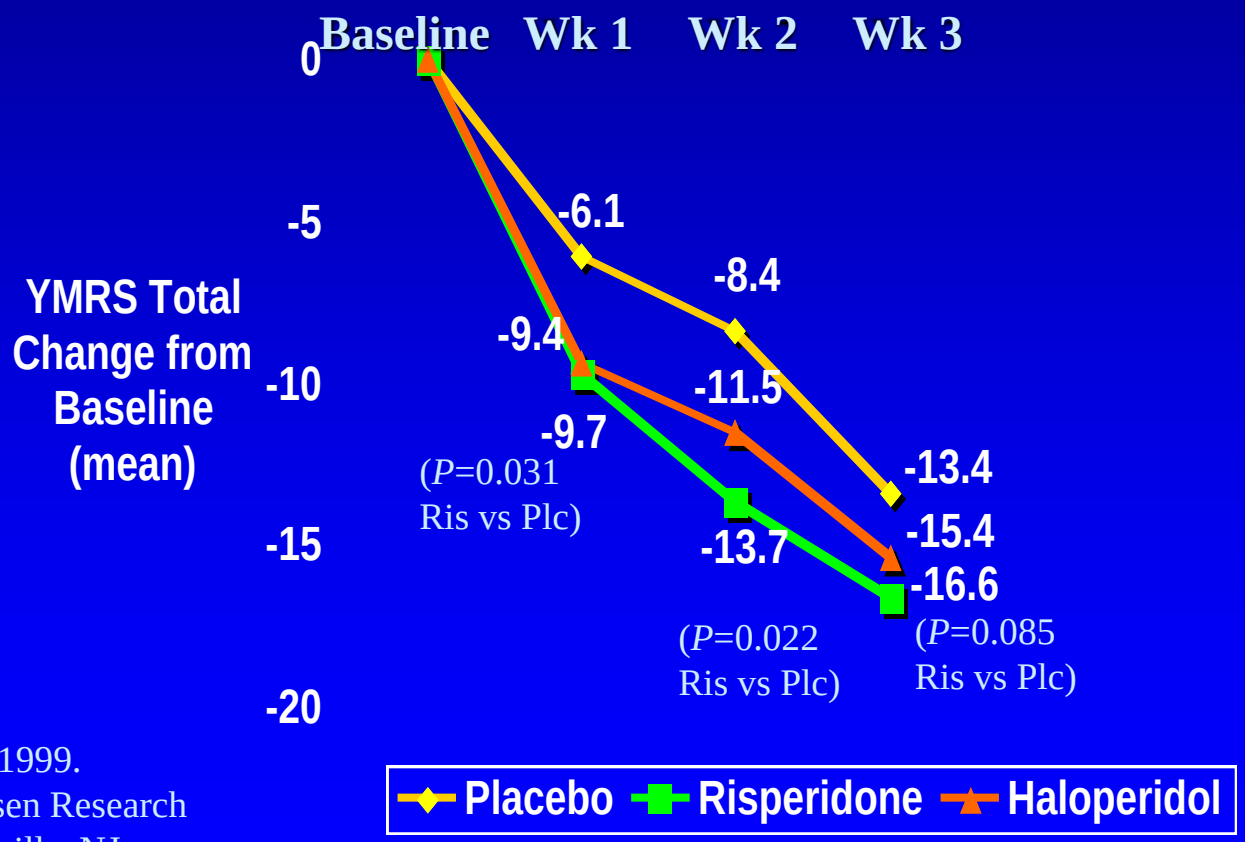
Placebo-treated patients ---->more worsening in endpoint Y-MRS total (LOCF) vs. olanzapine-treated patients; for any (p=.006) and ≥ 10% (p=.046), and near- significance for ≥ 20% (p=.068).

Risperidone Plus Mood Stabilizer (Li or VPA) Double-Blind Comparison Study



Risperidone Plus Mood Stabilizer (Li or VPA) Double-Blind Comparison Study

ITT Population YMRS-Mean Changes



Sachs, G. *ACNP*. 1999.
Data on file, Janssen Research Foundation, Titusville, NJ.

Drug Combinations

- Start with
  - Mood stabilizer?
  - Antidepressant?
  - Antidepressant + mood stabilizer?
- Breakthrough depression on mood stabilizer: add additional mood stabilizer or antidepressant?
- Augmentation strategies

Does Combination with Lithium Improve Treatment Outcome?

- In bipolar depression: Yes
  - N=40, DMI + Li or Pbo
  - Li significantly greater ↓ in HRDS at end of study **(Ebert et al, 1995)**
- In nonbipolar depression (n=31): No?
  - DMI + Li or placebo
  - 10/15 DMI only
  - 9/12 DMI + Li; more AE **(Bloch et al, 1997)**

Lithium Augmentation

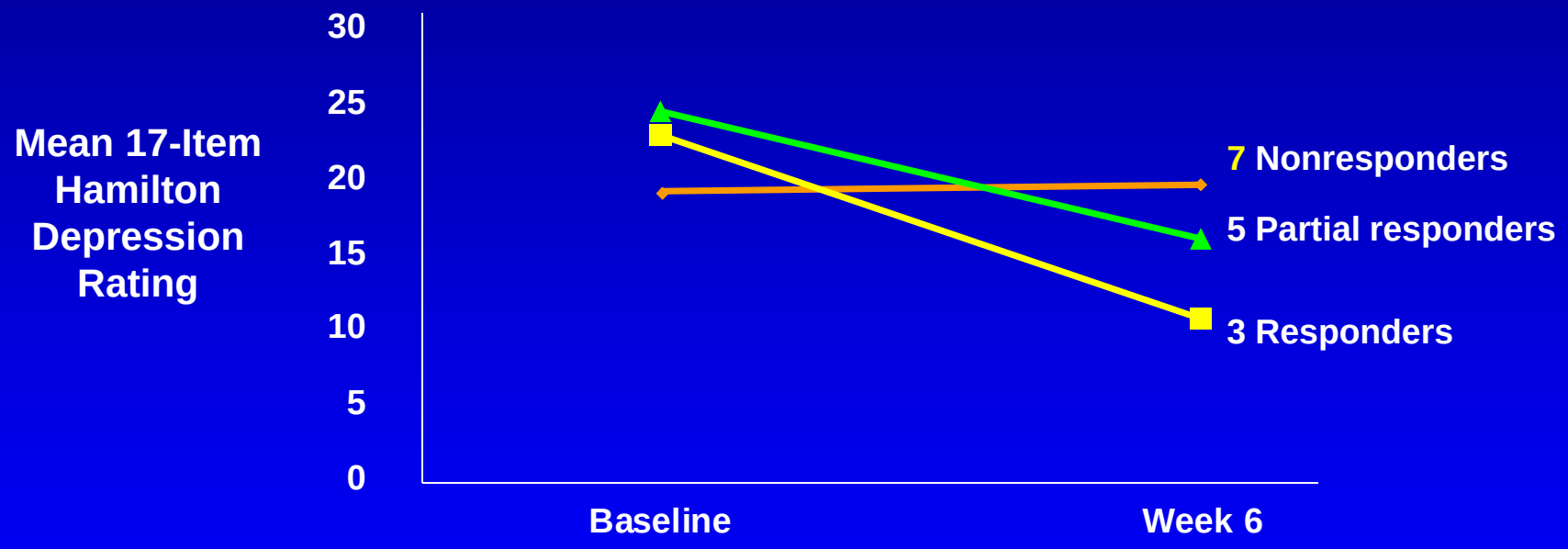
- Bipolar or unipolar depressions
- Onset often in 1st wk though full effect takes longer
- Possibly best w/ ‘serotonergic’ antidepressants though reported w/ all
- Li should be continued if it works

Lithium Augmentation Meta-analysis

- Of 234 pts, only 14 w/ bipolar disorder (no difference in antidepressant response)
- Li+ recipients: 3.3 x more likely to respond vs placebo
  - Disproportionate TCA use
  - TCA and SSRI equal efficacy
- Need level >0.5, duration >7 days

Bauer et al, *J Clin Psychopharmacol* 1999

Adjunctive Gabapentin in Bipolar Depression



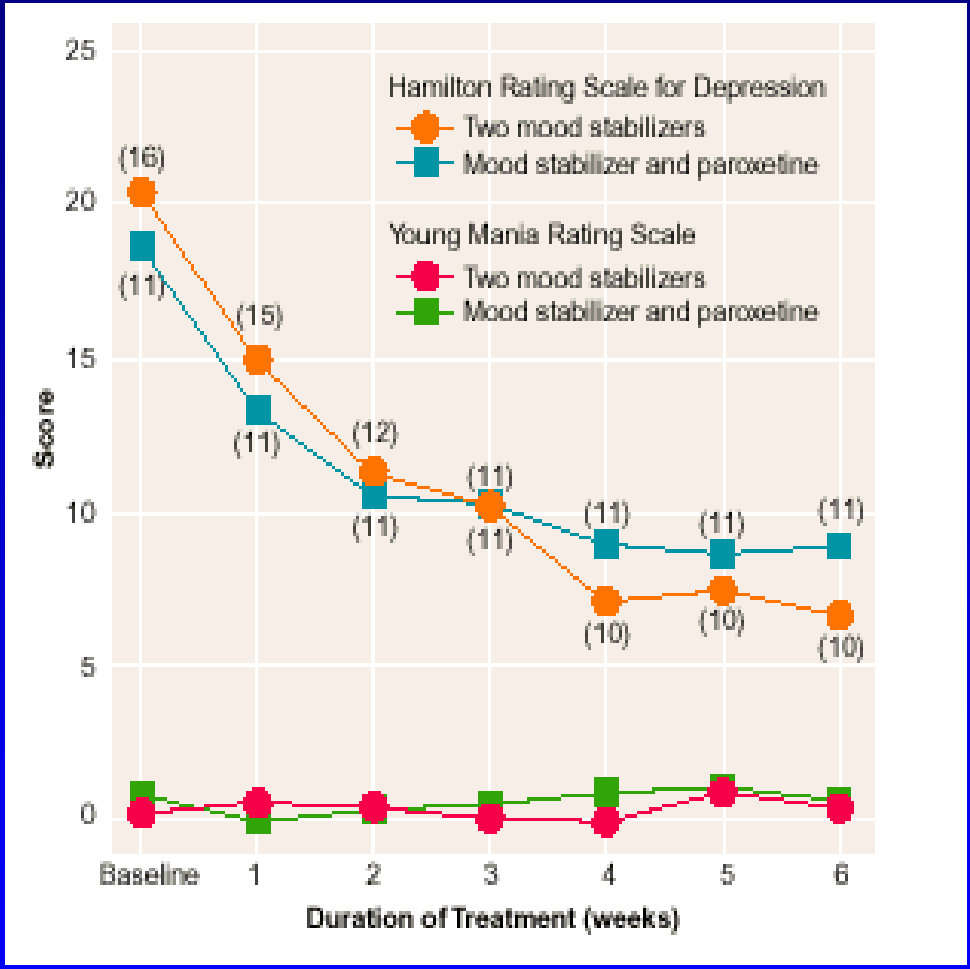
Young LT, et al. Biol Psychiatry 1997

Emergent Bipolar Depression

- 27 resistant BPAD I or II, with MDE
- No substance abuse
- ≥3 mo on maintenance with Li+ or VPA
- Added second mood stabilizer or paroxetine (double-blind) x 6 wks
- Both groups had improvement in depression
- Fewer drops for AEs in AD-added group

Young et al, *AJP* 2000;157:124-6

Adding SSRI vs. Mood Stabilizer

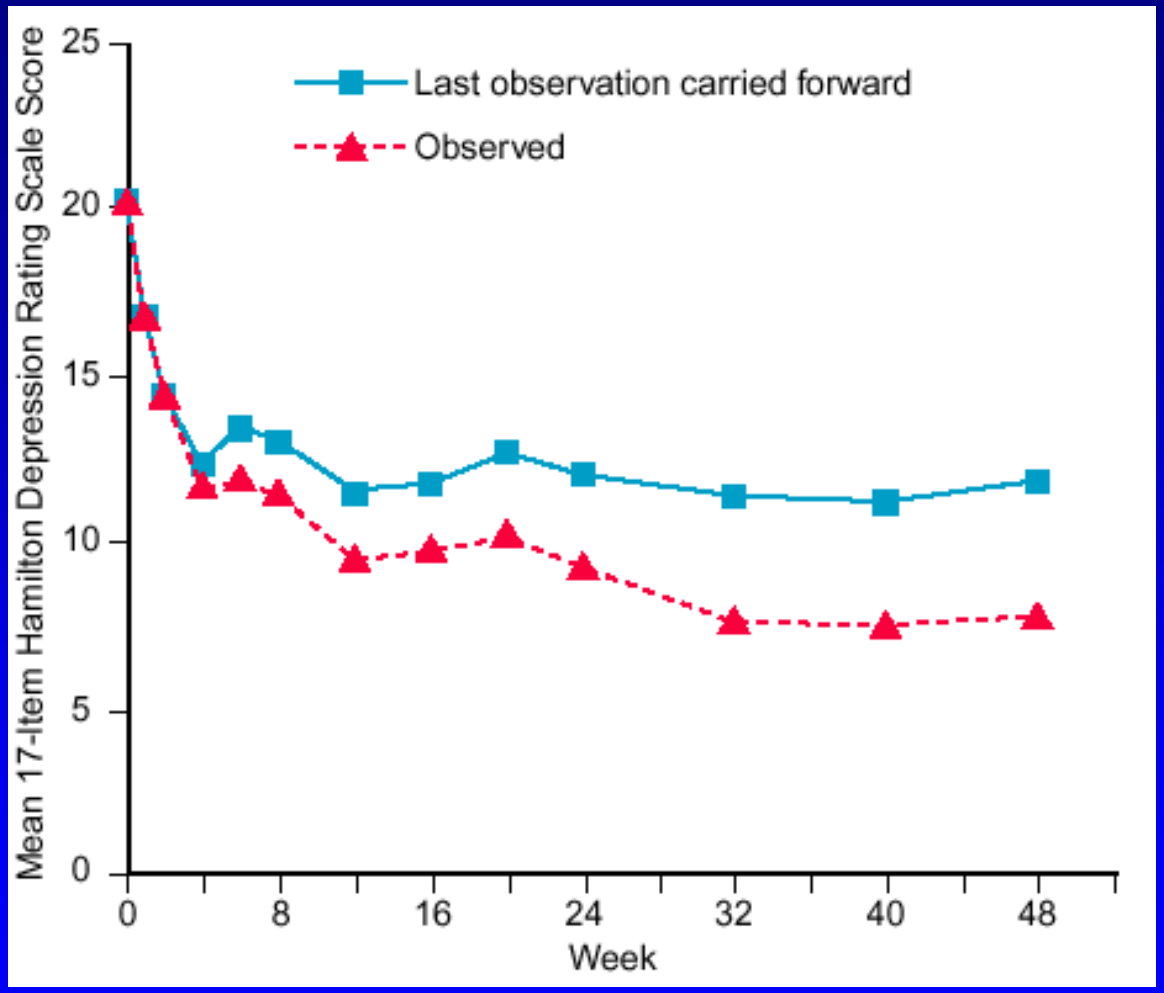


Young et al, *AJP* 2000;157:124-6

Open-label Lamotrigine Adjunctive Rx in Resistant Bipolar I and II Depression

4 - mania
- 2 were rapid cyclers at entry

50% drop For A/E
1 rash



48 wk open Adjunctive LMT up to 500 mg/d

n= 40

48%marked 20% moderate

17-item HAMD

Calabrese et al, *Am J Psychiatry* 1999;156:1019–1023

Adjunctive Thyroid Hormones

- Liothyronine (T3)
  - Antidepressant?
  - Faster onset/more effective than T4
  - Dose 5–50 μg/day
- Levothyroxine (T4)
  - Mood stabilizer?
  - Slower onset/better tolerated than T3
  - Dose 25–200 μg/day
- Knowledge base inadequate

Thyroid Hormones

T3 + T4 — Additional benefit?

Tremor, tachycardia, sweating, GI, anxiety, wt. loss, bone depletion

Positive cognitive & mood effects in thyroid replacement pts vs. T4 only (Prange et al, *NEJM)*

Psychosocial Interventions for the Optimal Management of Bipolar Disorder

- Psychoeducation
- Family contact
- Support groups
- Management of comorbid conditions
- Maximize adherence
- Chronobiological hygiene

Bipolar Depression Strategy

- Investigate psychosocial changes
- ↑ contact
- Assess for substance abuse
- Optimize mood stabilizer; add Li if possible
- Consider Lamotrigine
- Add antidepressant based on previous response, tolerability

Bipolar Depression Strategy

- Optimize mood stabilizer; (incl lithium)
- 1st antidepressant ineffective
  - Add or substitute depending on tolerability
- Optimal mood stabilization + 2 ADs ineffective:
  - ⇒ **ECT**
- Gradual taper of antidepressant about 2-4 months after maximal effect, or less if past mood instability
- Aim for maintenance on mood stabilizers only

Special Problems

- Depression in context of mixed state or rapid-cycling
  - Maximal mood-stabilizer Rx; if severe consider ECT, atypical antipsychotics
- Bipolar depression during pregnancy
  - ECT
  - Antipsychotic plus antidepressant

Summary of Treatments

- Lithium:First Choice
- TCAs:>Pbo
  - Mania/Rapid cycling
- MAOIs:Anergic bipolar depression
  - ? less risk for switch
- SSRIs:Promising
  - Paroxetine better?
- Venlafaxine: Limited but positive data
  - Need more studies
- Bupropion: Promising
  - More studies needed
- ECT: Effective
  - Low switch rate

Remaining Questions

- Which antidepressants or mood-stabilizers are superior?
- What are the short or long-term impact of ‘antidepressants’?
- Algorithm needs testing on a large scale
- How long to continue additional txs?
- When to use ECT?