The Bipolar Continuum:
Mania, Depression and Mixed States

Michael H. Allen, M. D.

Professor of Psychiatry

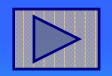
University of Colorado School of Medicine

Director of Research

University of Colorado Depression Center

Senior Investigator

Veterans and Military Suicide Research Consortium



Syndromes and Variations

DSM IV Manic Episode

A. Mood abnormally elevated, expansive or irritable for 1 week

B. At least 3 of the following for euphoric, 5 for irritable

1. Grandiosity
2. Decreased need for sleep
3. Pressured speech
4. Flight of ideas
5. Distractibility
6. Increase in goal directed activity
7. Excessive pleasurable activity with painful consequences

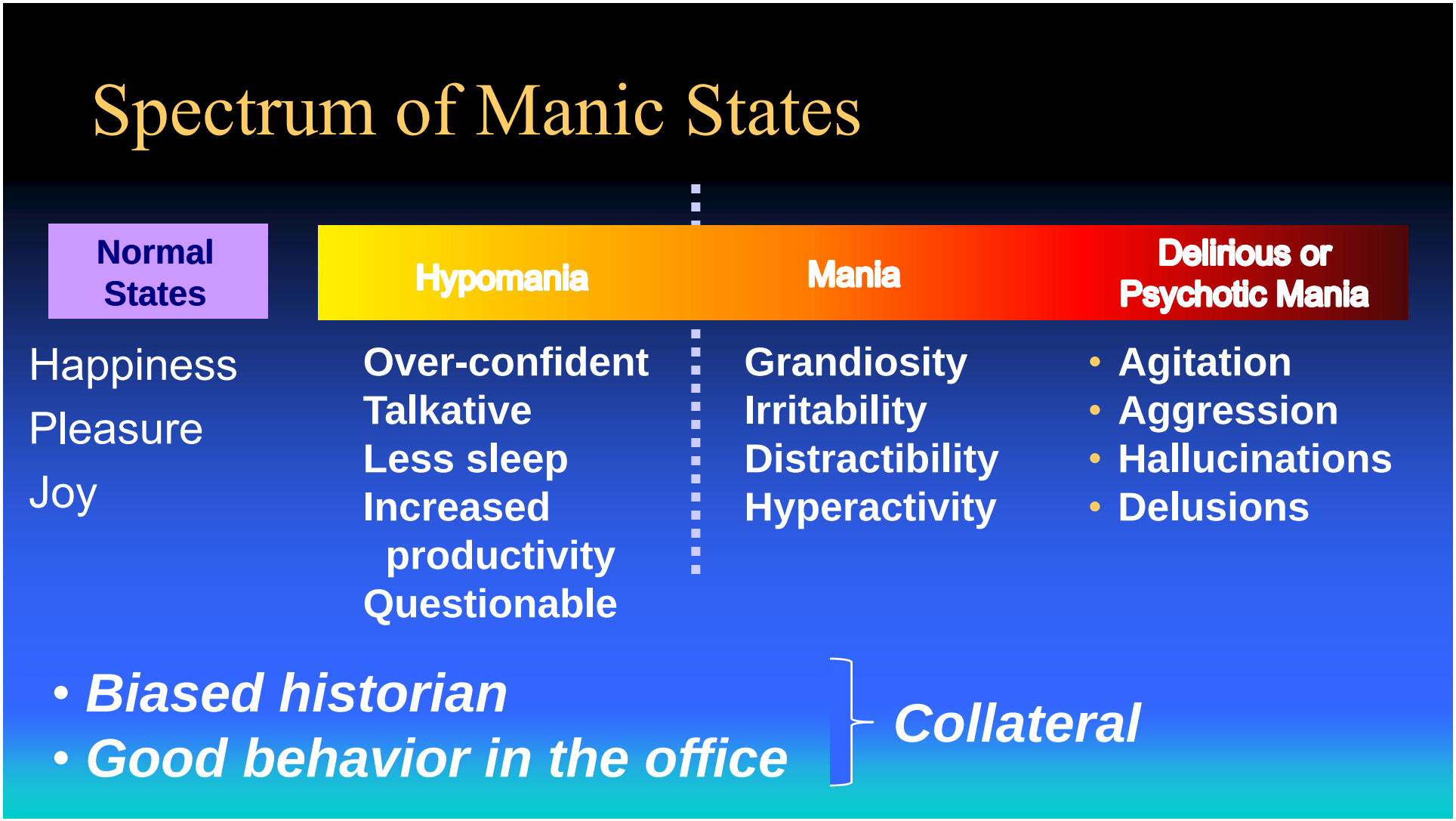
Confident

C. Marked impairment in functioning

D. No delusions or hallucinations for as long as 2 weeks in the absence of prominent mood symptoms

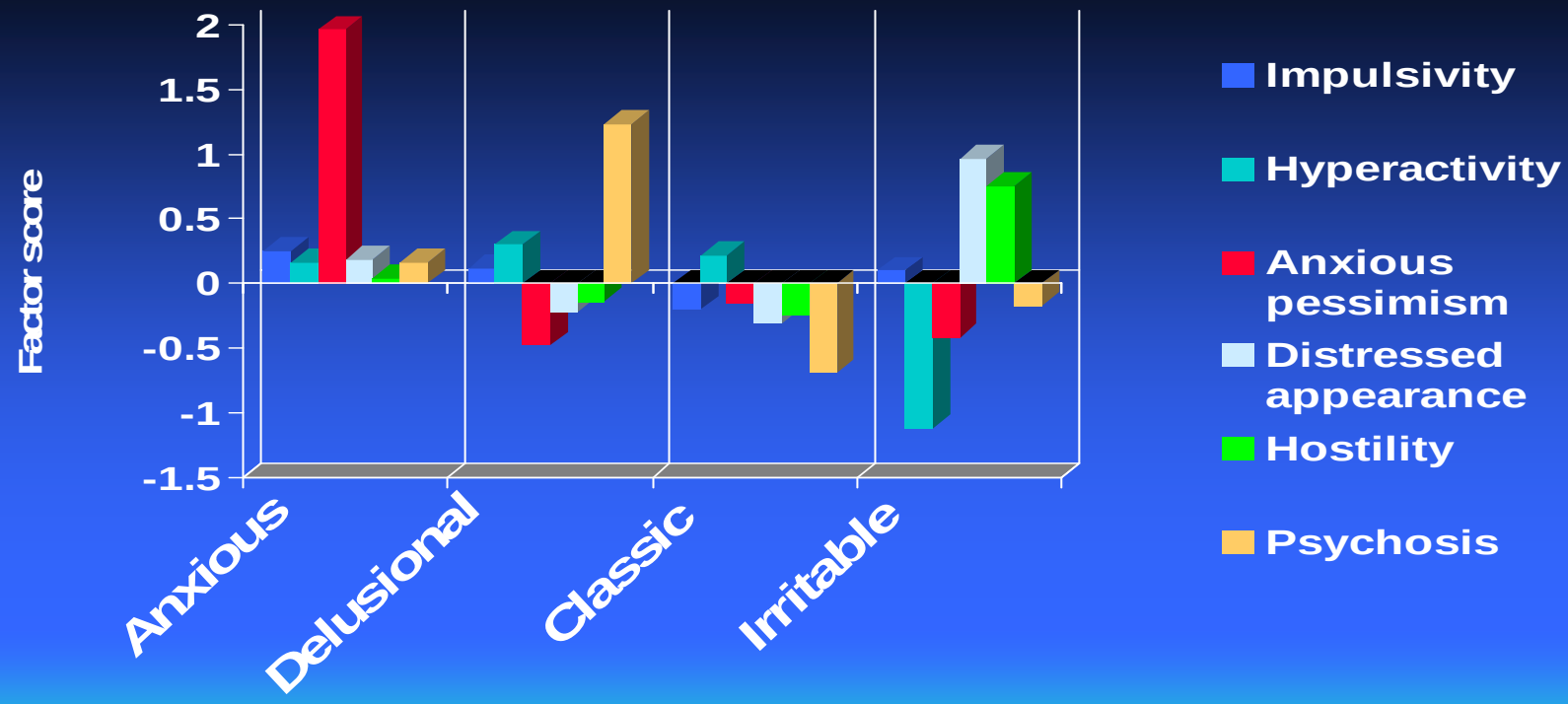
American Psychiatric Association, 1994

Spectrum of Manic States



Cluster Analysis of Mania

Subtypes based on SADS



Swann AC, et al. Am J Psychiatry. 2003 ;160:1252-62

Symptoms Evolve Rapidly

- Subsyndromal symptomatology
  - After recovery (8 consecutive weeks in remission)
- Prognosis of “roughening” at 4 weeks
  - 25% of dysphoric patients will have a major depressive episode (MDE) within 4 weeks
  - ***67% of patients with hypomanic symptoms will be manic within 4 weeks.***

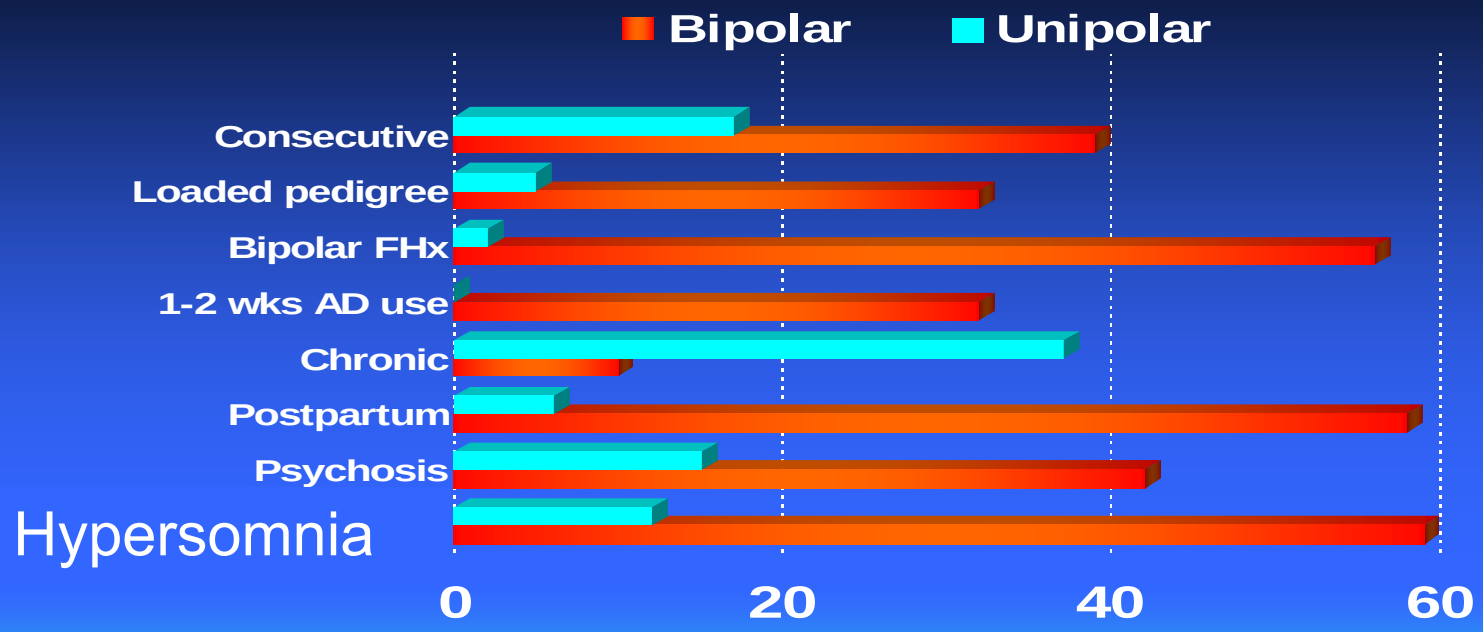
Keller MB. *J Clin Psychiatry*. 1988;49 Suppl:4-7.
Fava GA et al. *Am J Psychiatry.* 1991;148:823-30.

Depression

- Unipolar and Bipolar Depression same criteria
  - DSM-IV Bipolar, Depressed
    "Currently in Major Depressive Episode (see p 327)"
    - Insomnia or ***hypersomnia***
    - Decreased or ***increased appetite***, weight loss or ***gain***
  - Nominally only difference is *history of mania*

Bipolar vs. Unipolar Depression

Reversed vegatative features 5X's more common

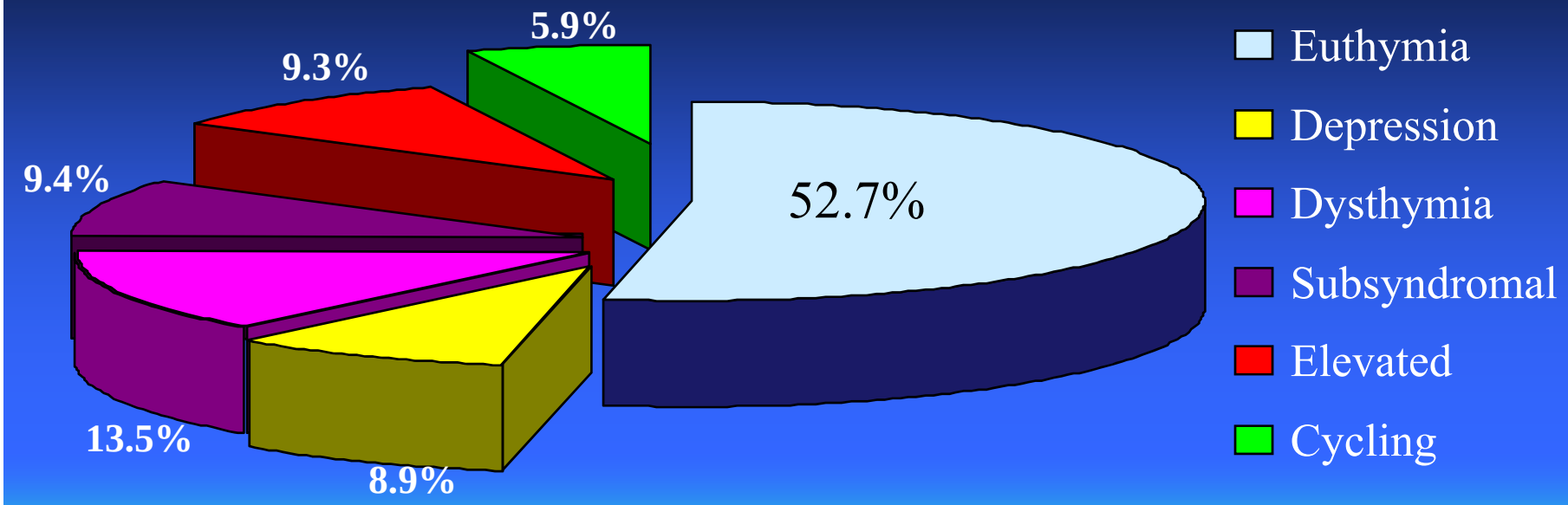


Akiskal HS, et al. JAD 5:115-128, 1983

Depressed 32% of the Time

NIMH Collaborative Depression Study

146 patients followed every 6 months over 12–20 years



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

Time Spent Depressed, BP 1 vs. BP2

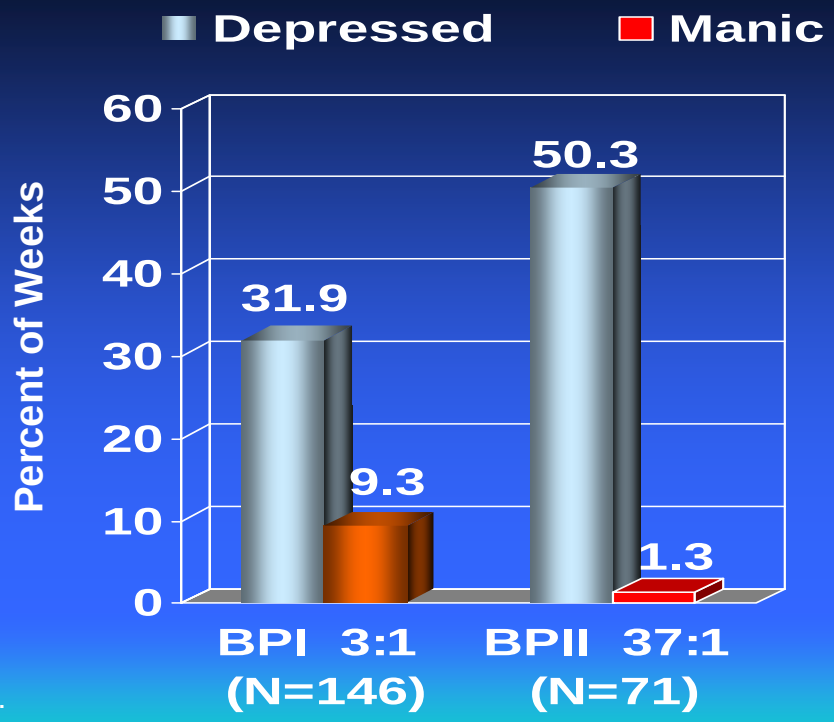
NIMH Collaborative Study, 13 years

BPI

- Depressions:mania 3:1

BP II

- Depression : mania 37:1
- Higher morbidity, chronicity



1. Judd, Lewis L et al. *Arch Gen Psychiatry*. 2002; 59:530-537.
2. Judd, Lewis L et al. *Arch Gen Psychiatry*. 2003; 60:261-269.

Prepubertal Major Depression to Bipolar

	Prepubertal MDD (n = 72)	Normal Controls (n = 28)	*P* Value
Bipolar I or II	48.6%	7.1%	.0001
Bipolar I	33.3%	0	.001
Bipolar II	15.3%	7.1%	.34

- Comorbid ADHD or psychotic depression = study exclusion
  - Both exclusions lowered rates of bipolar outcome
- Mania in parent or grandparent predicted BPI outcome (*P*=0.02)

Geller et al. *Am J Psychiatry*. 2001;158:125-7.

Conversion from Unipolar Depression to Bipolar

Conversion rate depends on onset, severity

- Prepubertal depressives, avg age 10.3[2] 49%
- Adolescents[1]
  19-37%
- Adults, age 30's [1] 5-10%

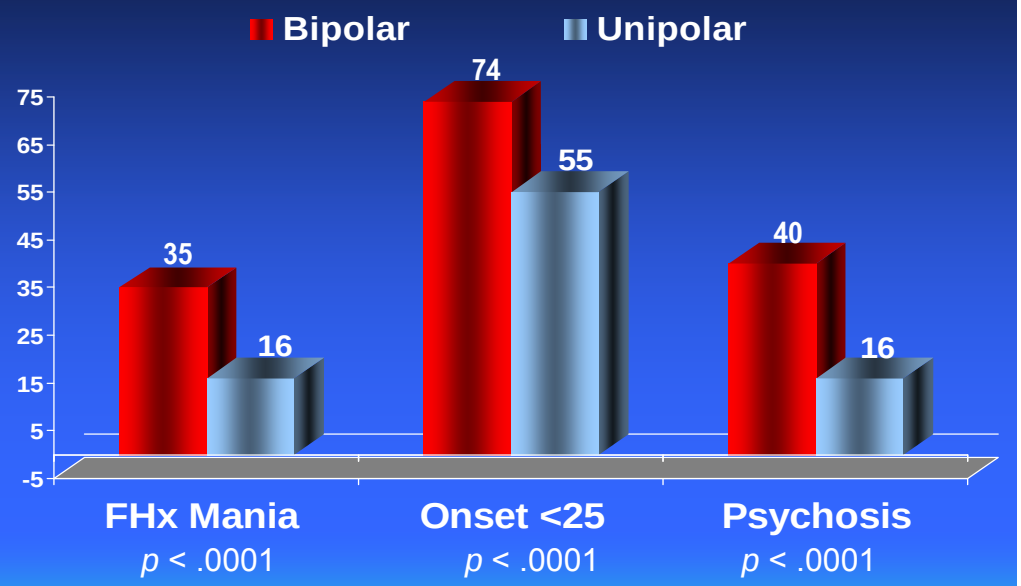
- Hospitalized depressives, age 23[3] 46%
- Hospitalized depressives[4]
  - Retro/pro, age 33.5 50%
  - Prospective only, age 47.9 39%

1. Coryell, William et al. *Am J Psychiatry*. 1995; 152:385-390.
2. Geller et al. *Am J Psychiatry*. 2001; 158:125-127.
3. Goldberg et al. *Am J Psychiatry*. 2001; 158:1265-1270.
4. Angst J, et al. Journal of Affective Disorders 2005; 84:149–157

Risk of Bipolarity in Depressed Outpatients

Depressed outpts, n=744, mania Hx total sample 27%

- 0 indicators 15%
- 1 indicator 19-22%
- 2 indicators 45-55%
- 3 indicators 67%



Othmer E, et al. J Clin Psychiatry 68:47-51, 2007

Bipolarity Index Predicts Response

1. Episode characteristics
2. Family history
3. Age at onset
4. Course
5. Response to treatment

Sachs, GS, Acta Psychiatr Scand Suppl 2004 : (422);7-17

Population At Risk for Bipolar

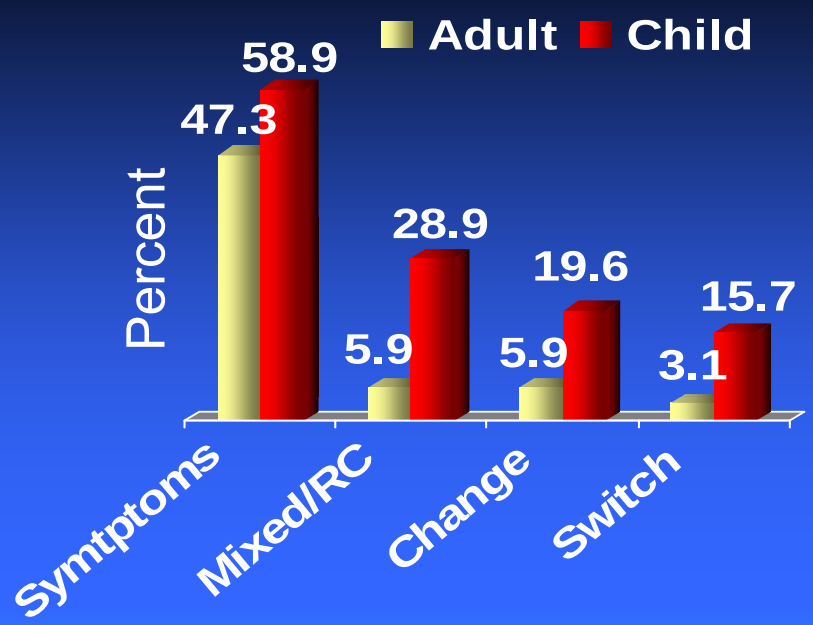
- Depressed but never hypomanic
- Early age at onset
- Reverse vegetative symptoms
- Third generation affective disorder
- Relative with mania

So what?

Evolution of Early Onset Bipolar

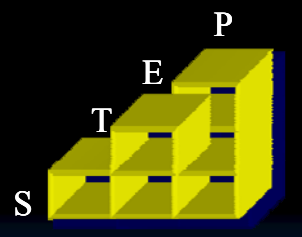
Prospective LIFE, N=263, mean age 13, mean 2 years

- 25% BP NOS → BP 1 or 2
- 20% BP 2 → BP 1
- Youths
  - More time symptomatic
  - More mixed, cycling
  - More changes
  - More switches



Birmaher B, et al. Arch Gen Psych 2006;63:175-183

Age at Onset and Morbidity



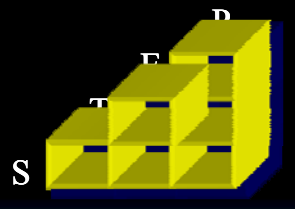
STEP-BD, N=983, early onset predicts

- More lifetime manias and depressions
  - More episodes past year
  - More likely to present depressed or mixed
  - Similar frequency of psychosis
- More comorbid conditions
- More suicide attempts (Onset <13, OR 2.85)
- Lower QOL but not functioning

After controlling entry age and illness duration

Perlis RH, et al. Bio Psych 2004; 55:875

Age at Onset and Relapse



Adult BP I or II, N=3,658, prospective up to 2 yrs

Onset (Years)	Time to Relapse (Median days)	Depressed Relapse	Days Well
< 13	308[a]	74.4 %	42.0 %
13-18	418[b]	74.1 %	47.1 %
>18	542	72.1 %	54.0 %

a. vs. adult, p = .0001
b. vs. adult, p = .01

Perlis, R, et al. Bipolar Disorders 2009; 11: 391-400

DSM IV Mixed Episode

A. Meets criteria for both
   Manic and Major Depressive Episode
   nearly every day for 1 week
   - Depression is all or most of the day
   - Mania can be brief, often episodic or circadian

B. Marked impairment in functioning

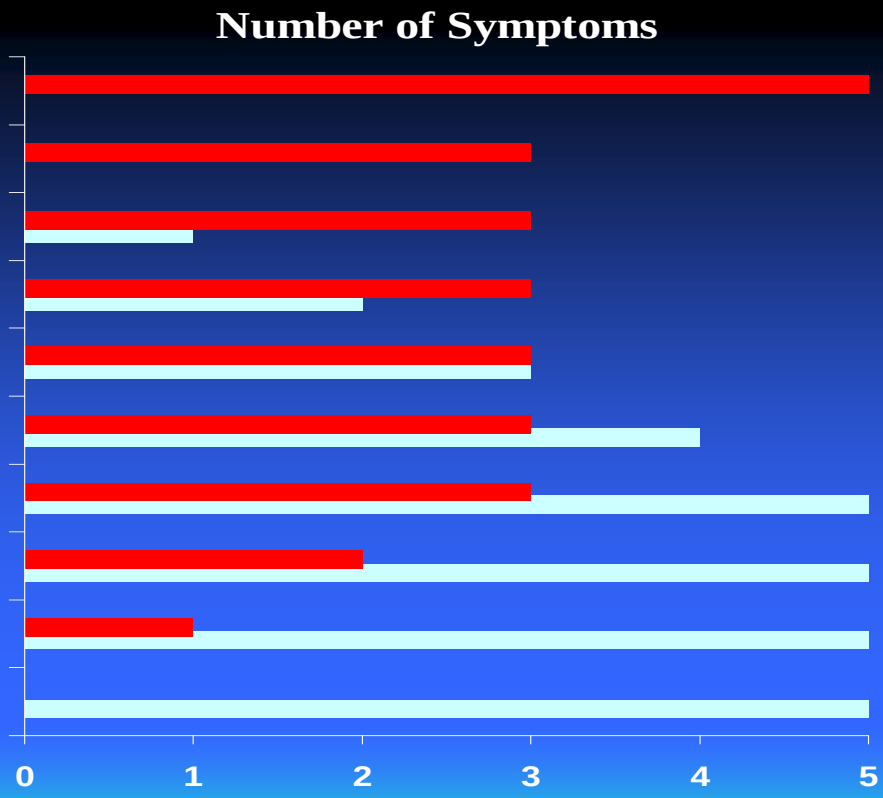
C. Not due to a substance or medical condition

Rates of Mixed States

Study	N	%
Winokur et al., 1969	61	16
Kotin & Goodwin, 1972	20	65
Himmelhoch et al., 1976	84	31
Akiskal & Puzantian, 1979	60	25
Nunn, 1979	112	36
Secunda et al., 1985	18	44
Prien et al., 1988	103	67
Post et al., 1989	48	46
Total	506	40.1

From Goodwin & Jamison, 1990

Depressive vs. Manic Mixed States



Irritable Mania

Euphoric Mania

McElroy (1995) Hypomania + 2 D

McElroy (1995) Mania + 3 D

Benazzi (2001) D + 3 Hypomania

Kukopoulos (1999), Akiskal (1998)

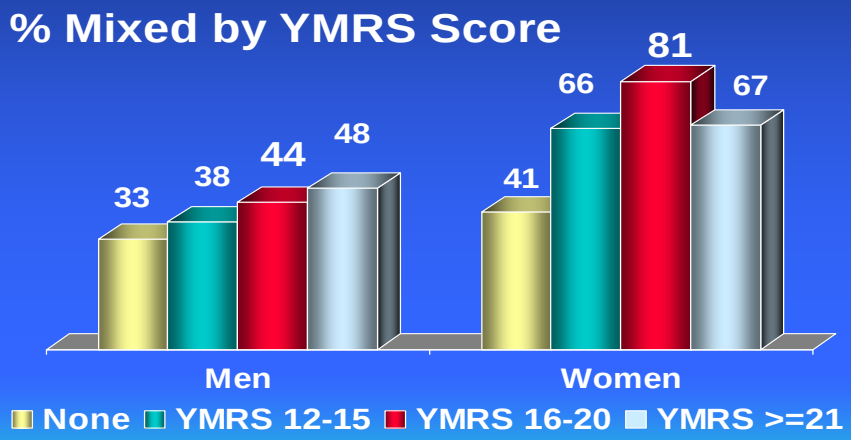
Pure Depression

Berk M, et al. Aus NZ J Psych 2005;39:215

Mixed Hypomania

BD 1 and 2, N=908

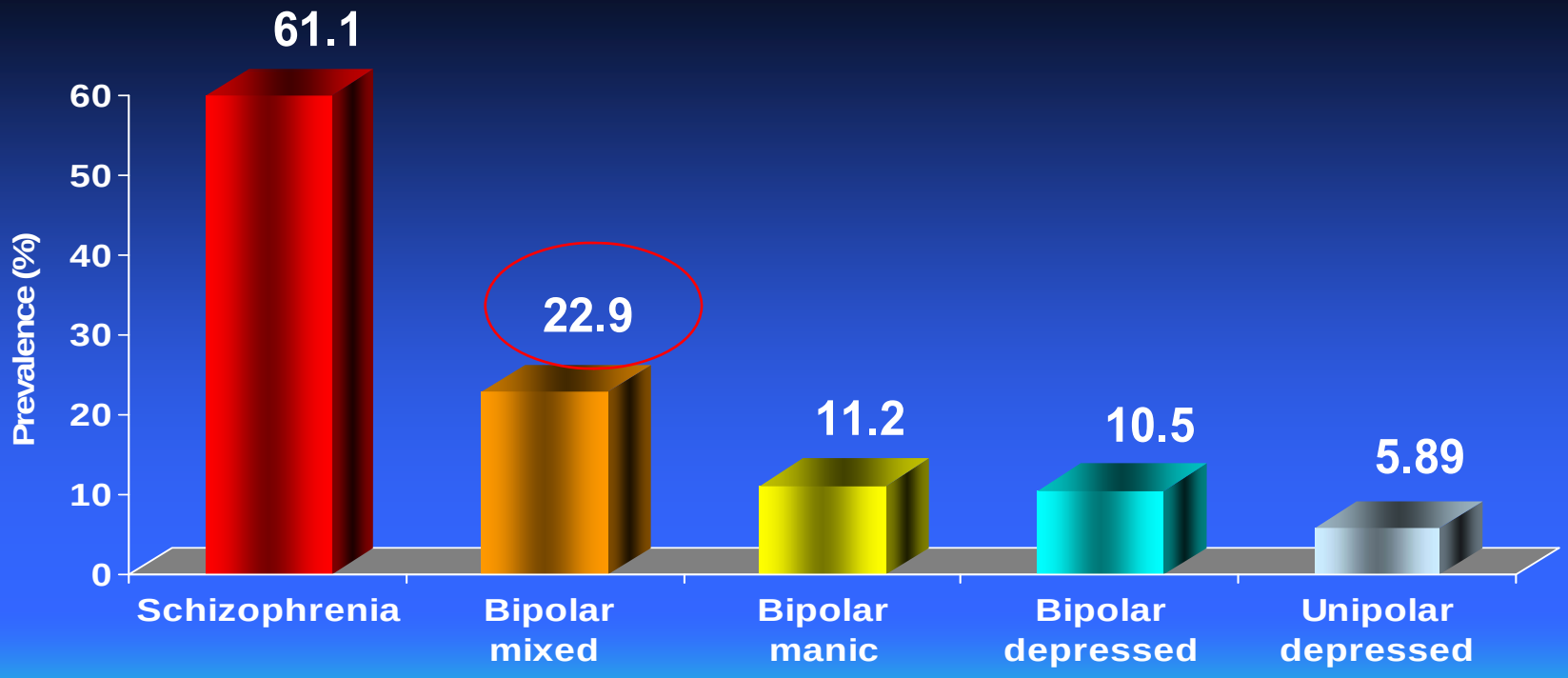
- 392 patients (43%), 1044 hypomanic visits
- 277 (71%) had at least one mixed visit
- BD 1 a/w more hypomanic visits
- Women broadly affected
- Men irritability, agitation



Suppes T, et al. Arch Gen Psychiatry. 2005 Oct;62(10):1089-96

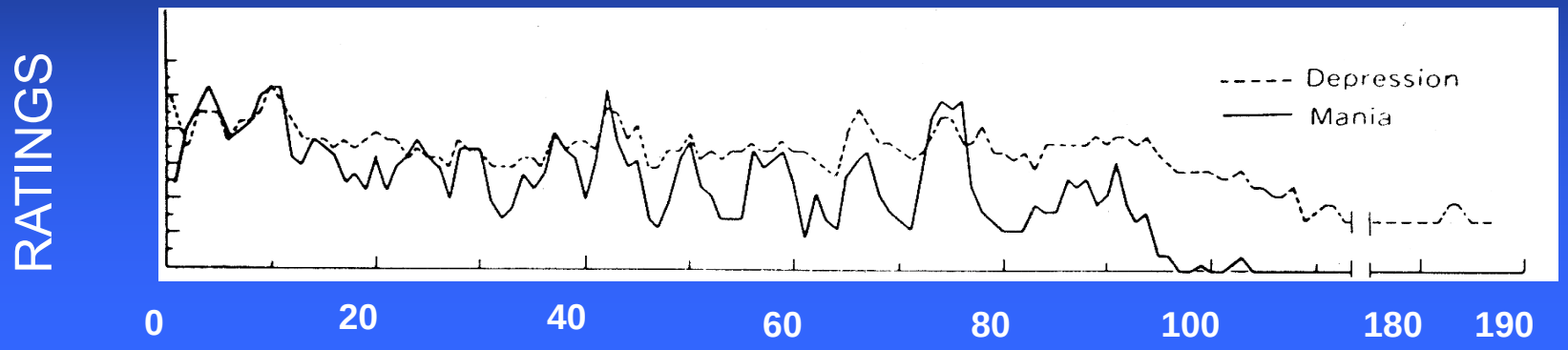
Hallucinations

Schizophrenia >> **Mixed** > Manic = Bipolar D > Unipolar D



Symptom Severity

- Mania more variable
- Depression more persistent
- Peak together rather than alternating



Kotin and Goodwin, 1972

Mixed Symptoms and Suicide Attempt

- **Mania score of only 6 in depressed patients a/w suicide attempts and alcohol abuse**

Sx	Manic				Depressed		
1					Anxiety		
2	Anxiety						
3	Early onset		Suicide attempt		Early onset		Suicide attempt

Swann A. Bipolar Disord. 2007 May;9(3):206-12.

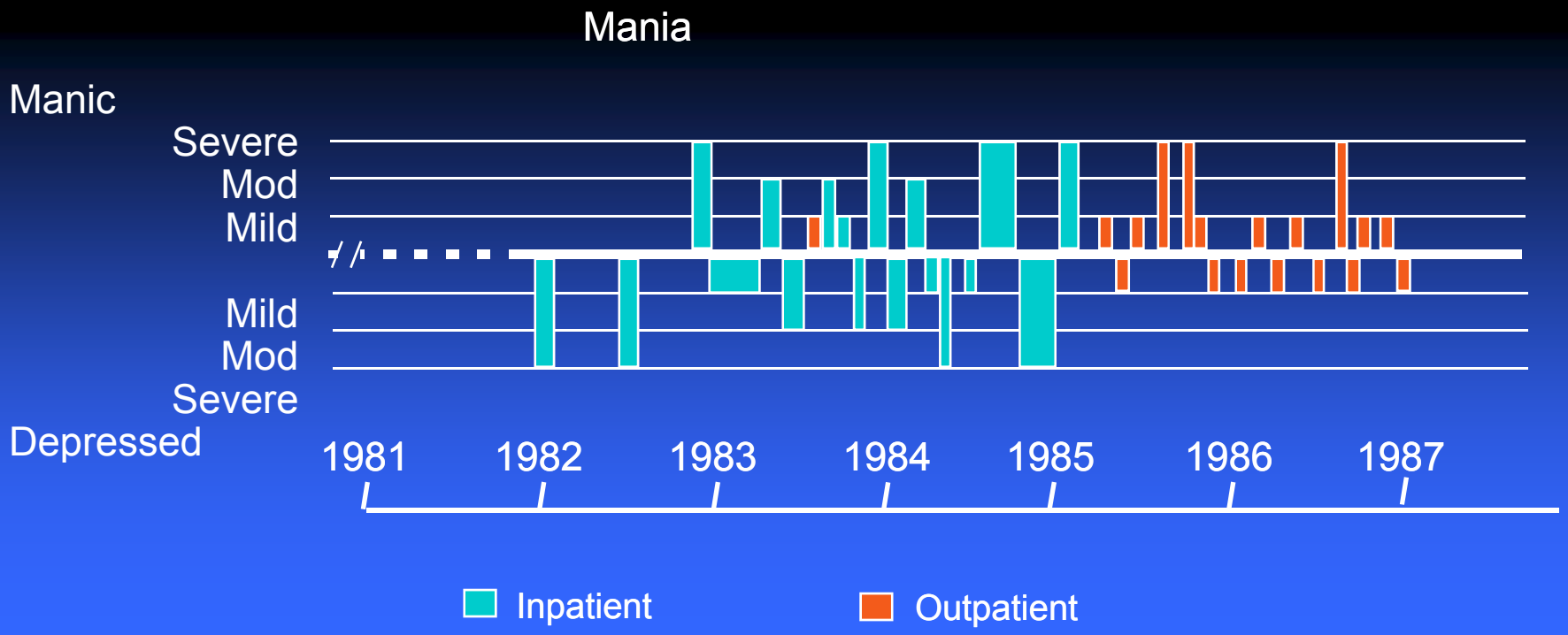
Typcial Mixed Picture

- Depressed and sluggish on awakening
- Struggles with morning routine
- Energy begins to pick up late morning
- Runs of racing thoughts
- Periodically restless, cleaning, errands
- Evening irritable, tired but anxious, distractible
- Bed but racing thoughts, can’t sleep
- Often do not meet criteria for mania
- Frequently associated with antidepressants

DSM IV Rapid Cycling

A. At least 4 episodes in 12 months that meet criteria for Major Depressive, Manic, Mixed or Hypomanic Episode
B. Episodes demarcated by full or partial remission for 2 months or switch to opposite pole

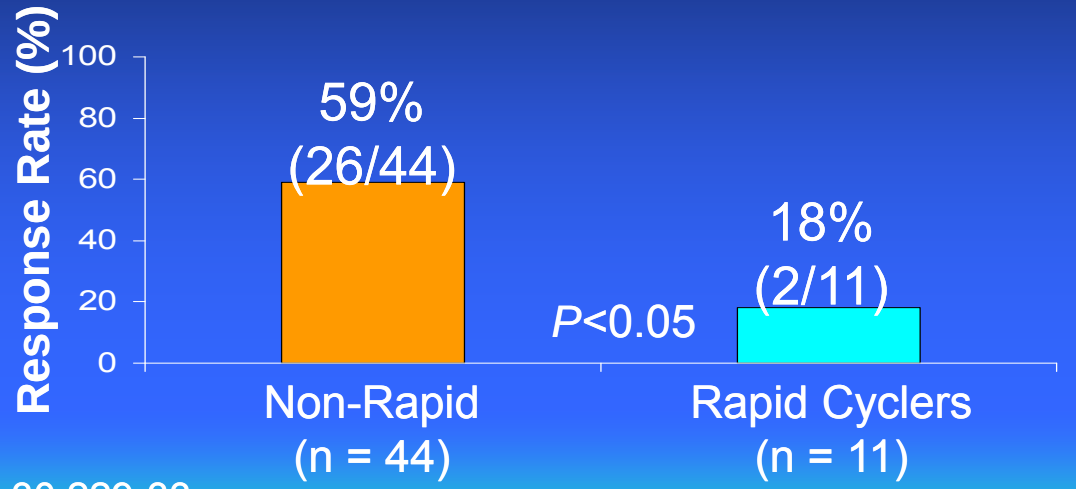
Rapid Cycling Life Chart



Mc Elroy, S.L., et. al., J. Clin. Psychopharmacol., 1988.

Lithium Prophylaxis in Rapid and Non-Rapid Cyclers

- Criteria for lithium nonresponse
  - Hospitalized or treated for depression or mania
  - Symptoms sufficient to warrant Dx of mild depression or hypomania for 2 weeks



Dunner & Fieve. *Arch Gen Psychiatry*. 1974;30:229-33.

Rapid Cycling as a Course Modifier: DSM-IV Work Group

- **D**emonstrate validity as a distinct modifier
  - Rapid cycling defined as ≥4 episodes in preceding year
- **Methods and Subjects**
  - 4-site pooled data reanalysis
  - Retrospective and prospective (>12 months)
  - Rapid cyclers (lifetime) n = 120
  - Non-rapid cyclers n = 119
- **Findings**
  - Rapid cycling is a distinct course modifier with differences in sex and outcome

Bauer et al. *Am J Psychiatry*. 1994;151:506-15.

Prevalence of Rapid Cycling

Tondo et al. *Am J Psychiatry* 1998	
10 studies, N = 2057	24.2 %
Maj et al. *Am J Psychiatry* 1994)	13.6
Coryell et al. *Arch Gen Psychiatry* 1992	18.5
Kukopulos et al. *Pharmakopsychiatr* 1980	19
Dunner & Fieve. *Arch Gen Psychiatry* 1974	20

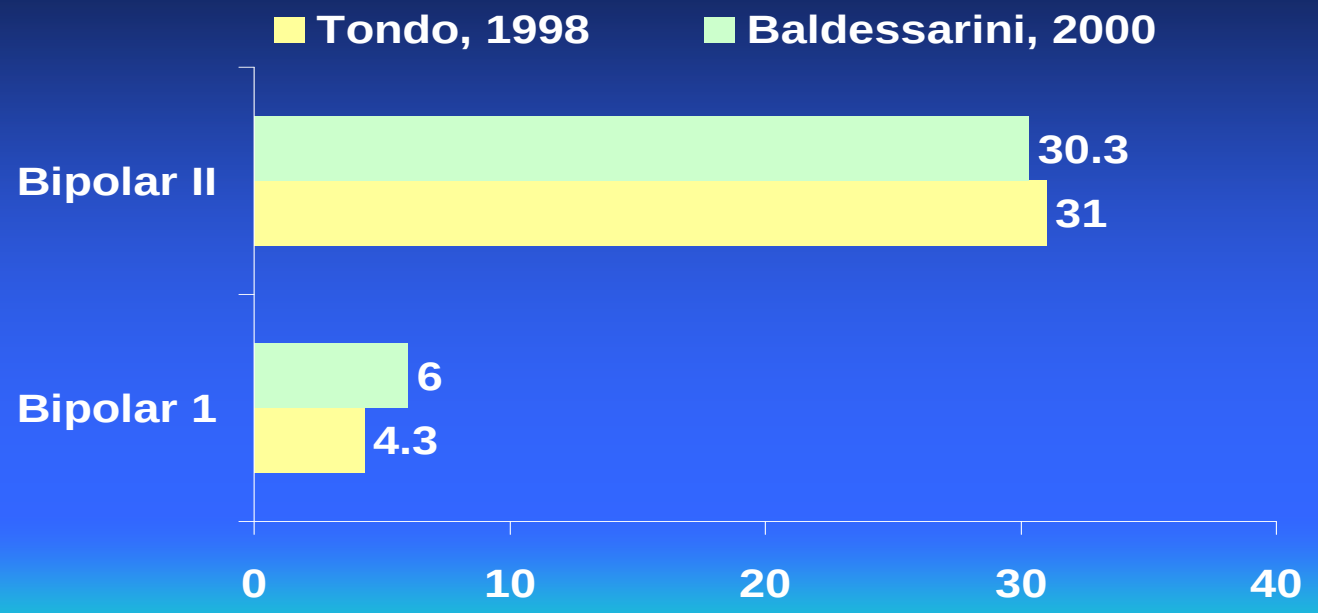
Rapid Cycling: 7 Definitions

1. DSM-IV definition
2. 4 or more episodes/yr, *episodes > 2 wks*
3. 4 or more episodes/yr, mood episode >1 wk,*1 week of euthymia*,
4. Like 1, but duration criteria waived for affective episode, requires *circular course*
5. 4 or more episodes/yr, each at least 24 hours, separated by 24 hours of euthymia or mood in opposite polarity
6. 4 or more episodes/yr of RDC defined mood separated by 2 wks of euthymia or switch
7. 4 or more episodes in any previous year , separated by switch or euthymia as long as proximate episode

Schneck C.

Rapid Cycling and Bipolar II

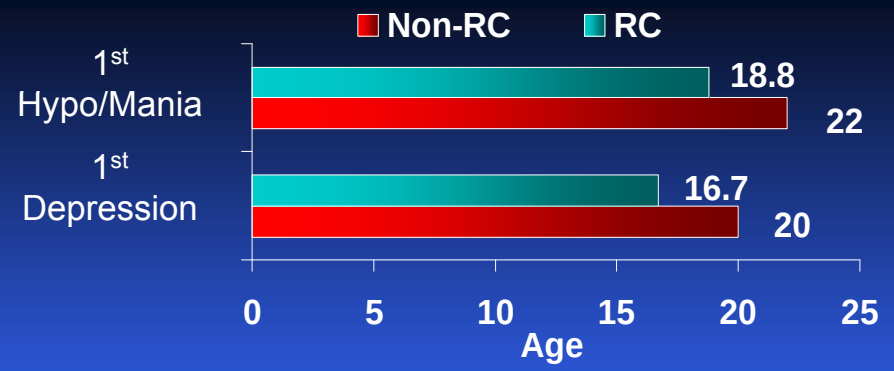
Rapid Cycling 6 times more common in Bipolar II



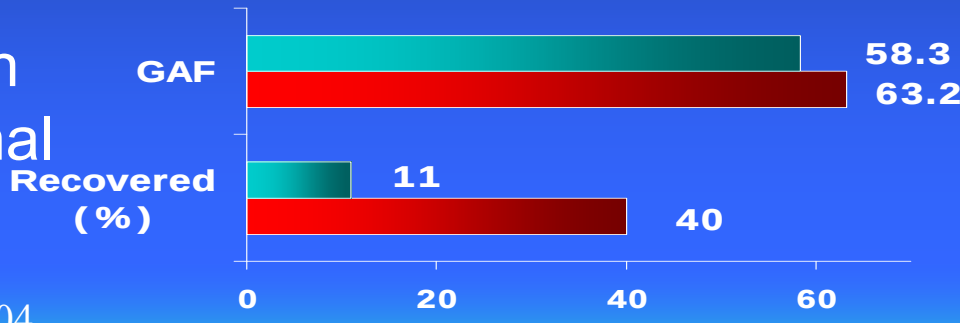
STEP-BD Rapid Cycling

Prevalence 20%

- Younger age of onset



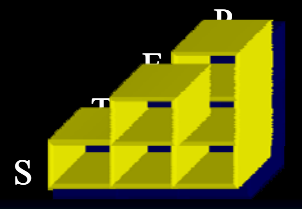
- Greater severity of illness on multiple clinical and functional measures

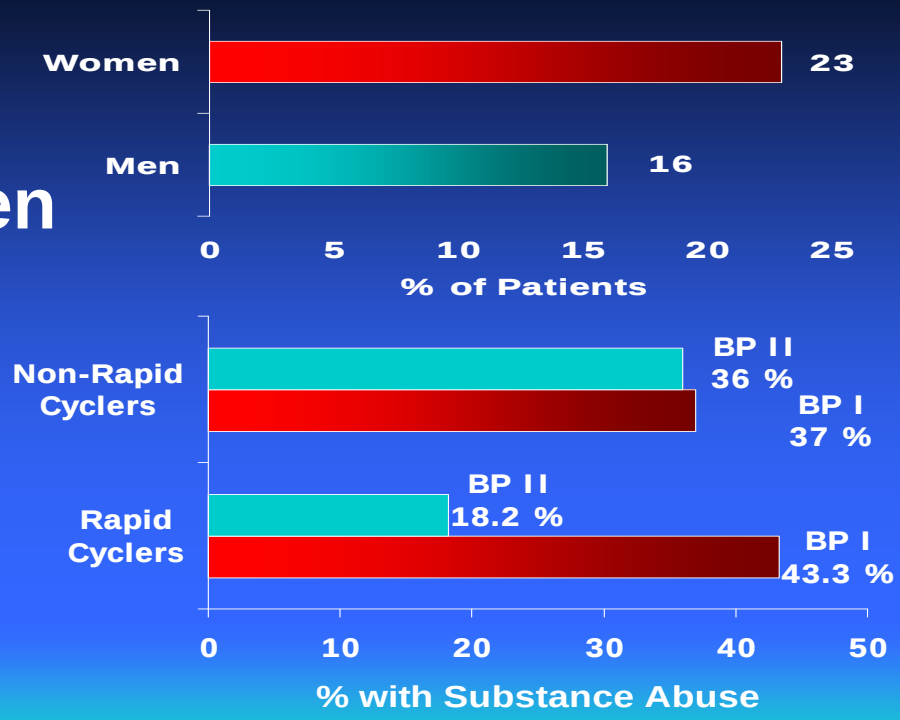


Schneck CD et al. Am J Psych 161:10, Oct 2004

STEP-BD Rapid Cycling

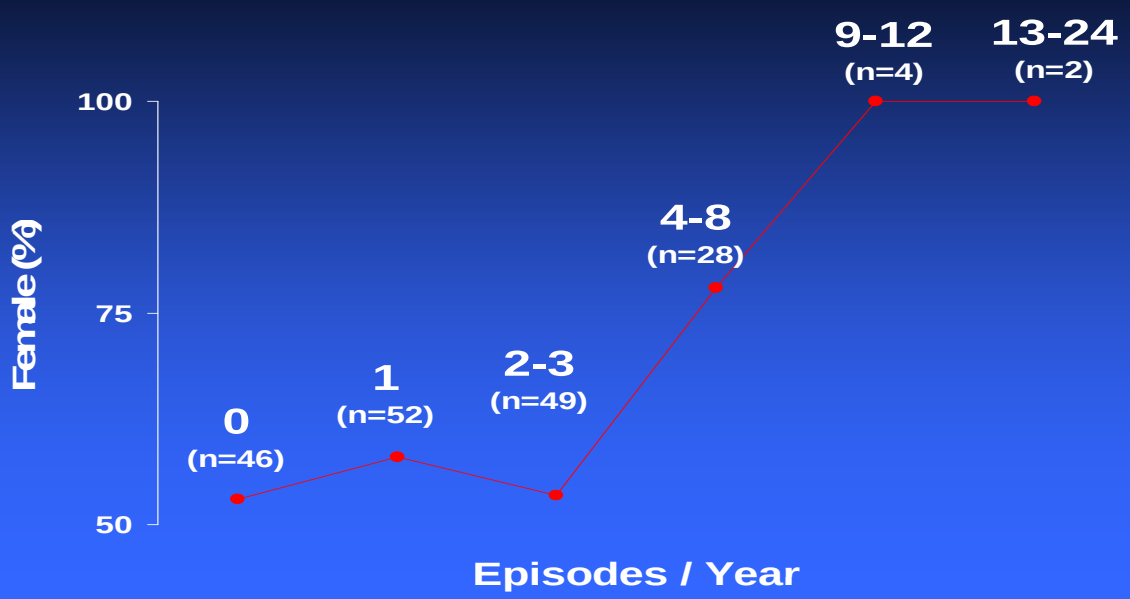
- Women > men
- **No association between RC and BPII**
- More SUD in RC BPI
  43 vs. 18%





Schneck CD et al. Am J Psych 161:10, Oct 2004

Female Predominance in Rapid Cycling



Women

100 % of S's with ≥ 9 episodes

~80 % of S's with 4-8 episodes

Bauer MS, et al. Am J Psych 1994; 151:506.

Factors Related to Rapid Cycling

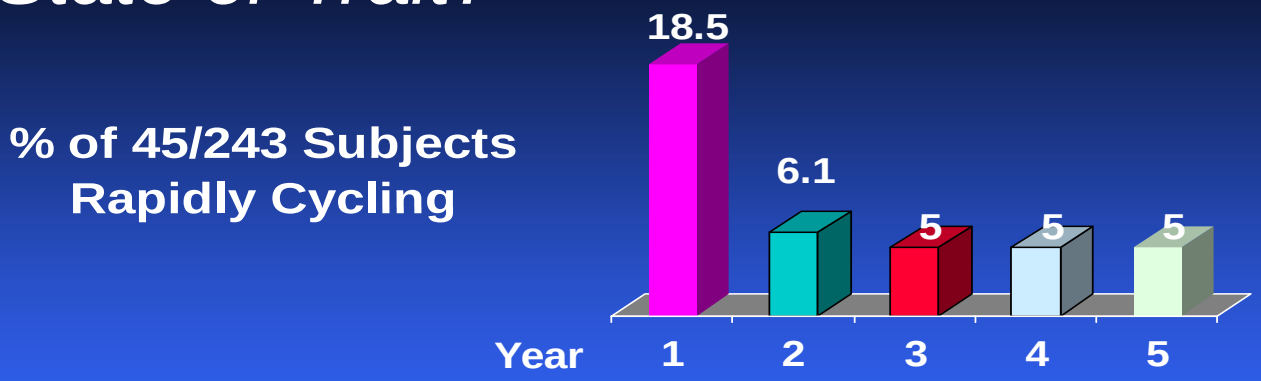
Associated	Not Associated
Female (71%)	Antidepressants
Major depression (84 vs 56%)	Family history
Hypomania (20 vs 9%)	Thyroid disease
Hypomanic cycling (20 vs 7%)	

Only 7% with mania at entry developed rapid cycling

Coryell et al, AM.J. Psychiatry 1992

Course of Rapid Cycling

State or Trait?



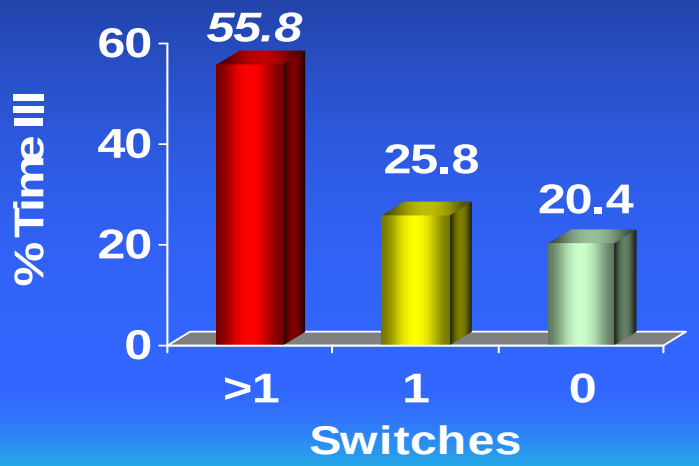
- 64% no rapid cycling after first year
- 18% rapid in year two but not subsequently
- *Only one cycled all five years*

Coryell et al, Arch Gen Psychiatry, 1992

Rapid Cycling or Circularity?

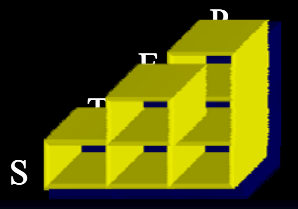
10 year prospective observation, N=194

- BP2 more common among polyphasics
  - 46.4 vs 25.8%
- Pattern frequently retained
  - 65% of depressives
  - 42% manics
- Mult switches predicted
  - Slower recovery
  - More time ill

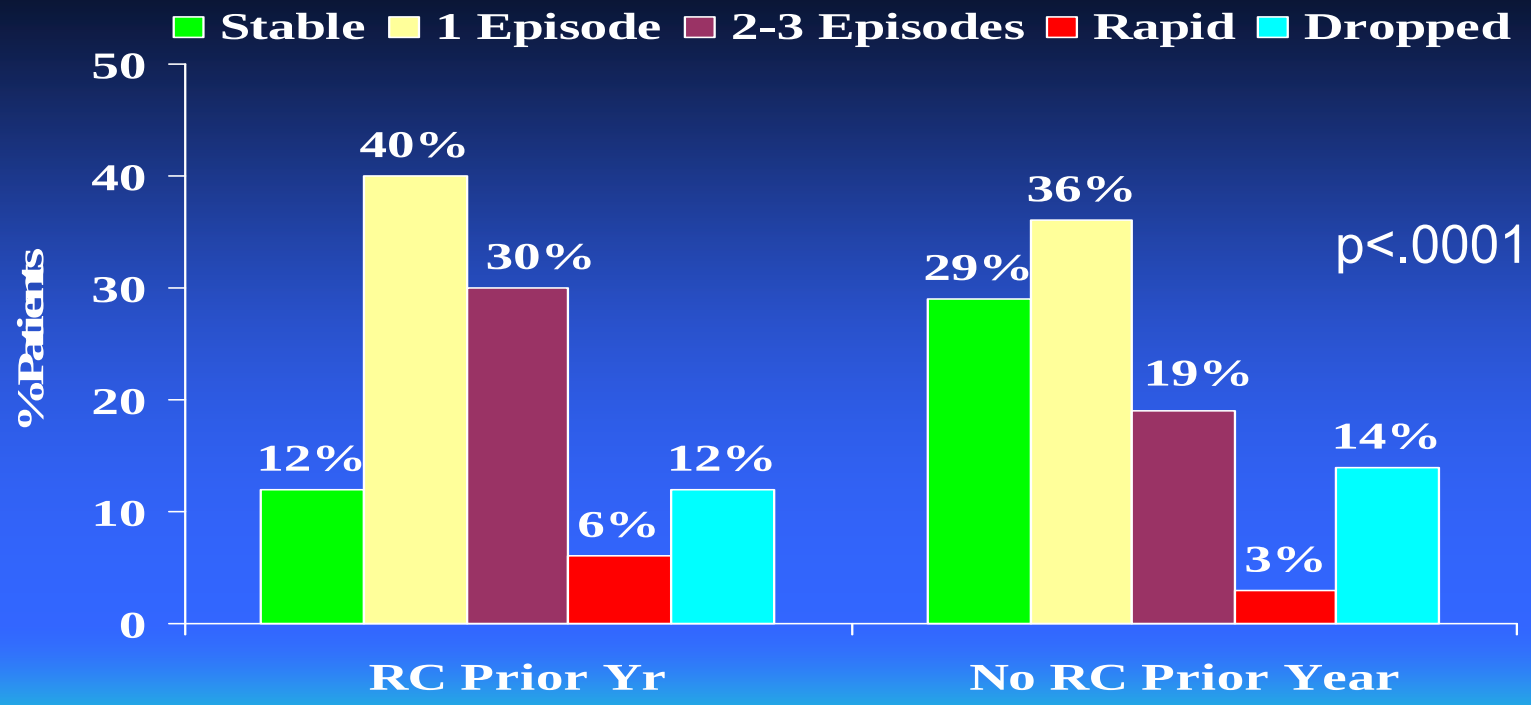


Maj J, et al. Am J Psych 2002; 159:1711-1717

RC in the Prior Year Predicts Cycle Frequency

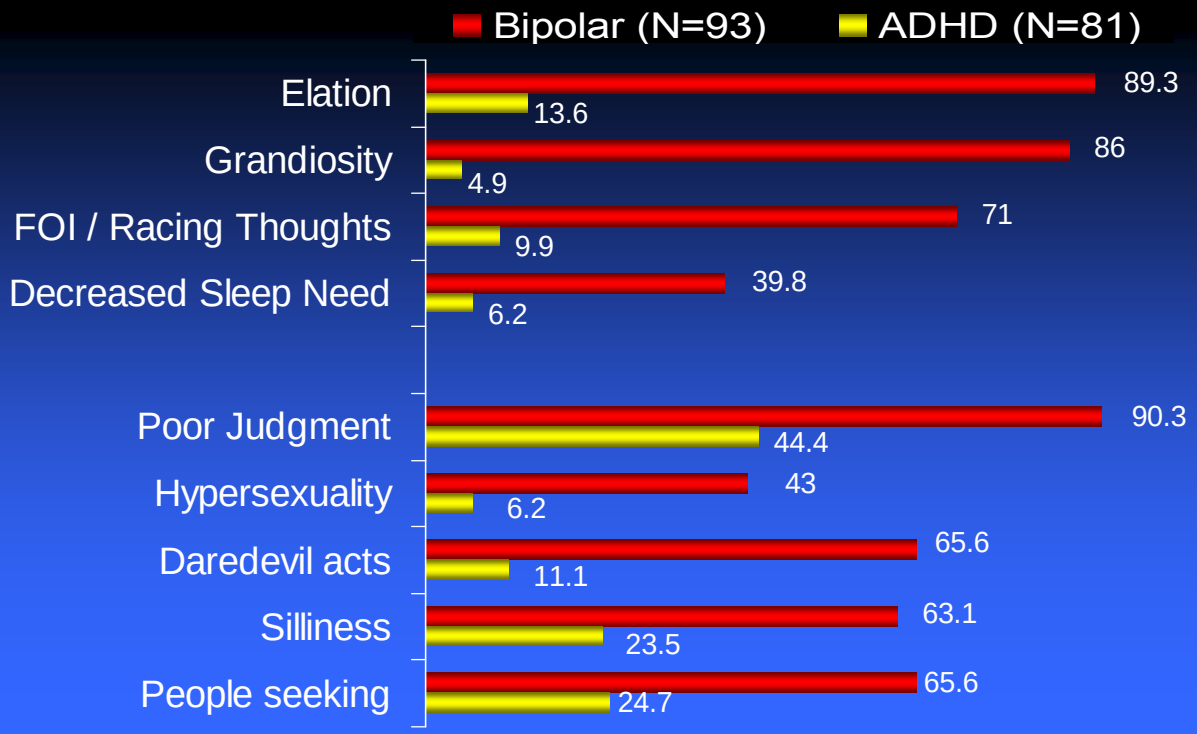


STEP-BD 2000



Schneck et al. American Psychiatric Association. Atlanta, GA 2005

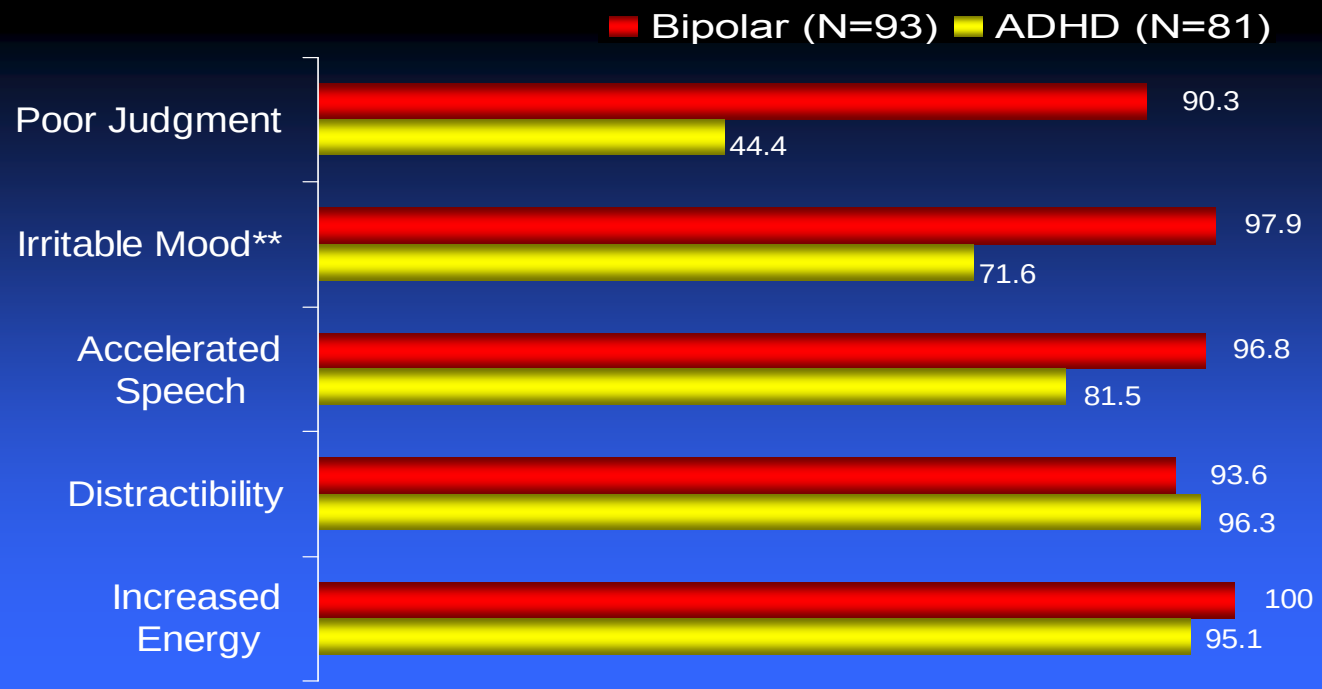
Prepubertal, Early Adolescent Mania vs ADHD



All comparisons *p<.0001*

Craney JL and Geller B. Bip Disord 2003; 5:243-256.

Prepubertal, Early Adolescent Mania vs ADHD



[a] Adapted with permission from Craney & Geller. [11]

*p = .002 for symptoms occurring more frequently in the PEA-BP vs. the ADHD group.

**p < .001 for symptoms occurring more frequently in the PEA-BP vs. the ADHD group.

Abbreviation: ADHD – attention-deficit/hyperactivity disorder.

Summary

Tremendous variation

- Many depressives have a Bipolar diathesis
  - Early onset marker for diagnosis and course
- Bipolar depression persistent, recurrent
- Cycling begets cycling
- Mixity is very problematic
- Subsyndromal states are important
  - Treat mania early and aggressively

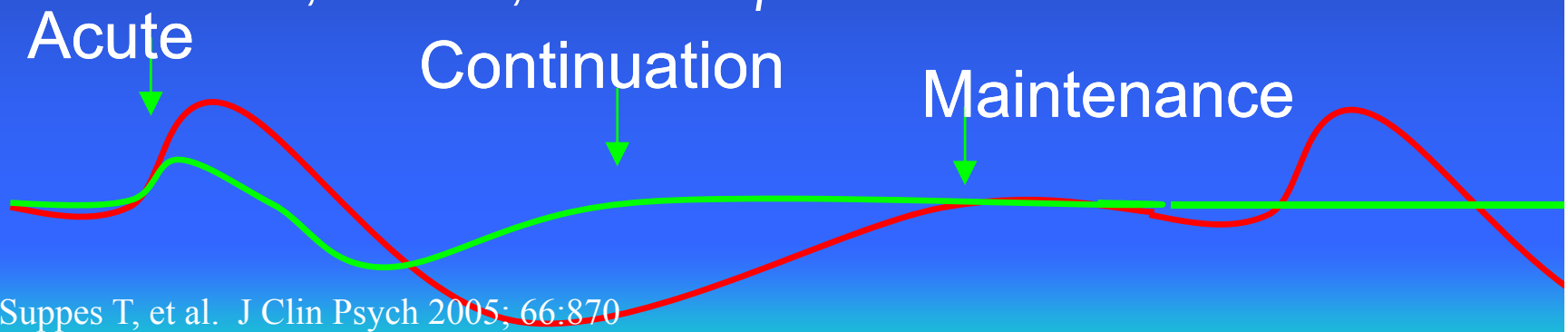
Treating Bipolar Disorder

General Principles

Multiphase Treatment Goals

1. Symptomatic remission
2. Functional recovery
3. Prevention

Fewest, briefest, mildest episodes



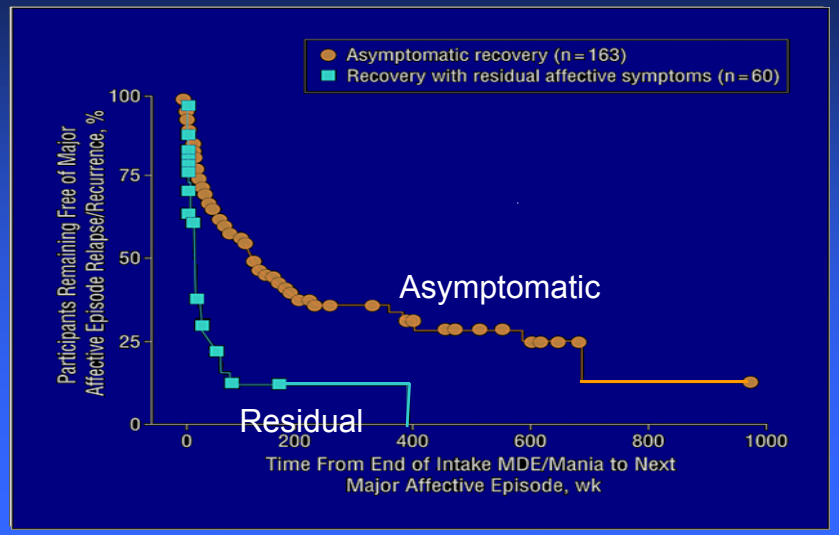
Suppes T, et al. J Clin Psych 2005; 66:870

B1

Residual Symptoms and Relapse

Collaborative Depression Study, BP I/II, median 17yrs

- Median time to relapse
  - 24 weeks for residual
  - 123 weeks for asymptomatic
- Treat to recovery
  - Not random assignment
  - Resistance, relapse traits



Judd, L. Arch Gen Psychiatry. 2008; 65(4):386-394.

B1 BrugionA, 6/15/2009

General Principles

Initiation

Severity, medical and psychiatric comorbidity, suicidality

Evidence of efficacy and tolerability

Literature and individual patient history

Patient preference

Involvement of significant others

Mood charting or other self monitoring

Visits at least every 2 weeks

Formal psychoeducation and cognitive therapy

Suppes T, et al. J Clin Psych 2005; 66:870

Consider Prophylaxis for Future Episodes

Selection depends on next phase

- Classic euphoric mania
- Depressed or mixed
- Cycling

"Like Breeds Like"

Risk of Relapse to Same Polarity ~ 2:1 or 3:1

	Index Episode	Relative Risk of Relapse to Index Polarity
Baastrup (1970)		1.6
Cundall (1972)		4.2
Stallone (1973)		1.4
Prien (1973a)	Mania	6.1
Prien (1973b, 1974)	Depression	2.6
Fieve (1976)	Mania	21.3
Dunner (1976)	Mania	.47
Bowden (2003)	Mania	1.5
Bowden (2003)	Mania	1.3
Calabrese (2003)	Depression	3.4

Calabrese JR, et al. Biol Psychiatry 2004; 56:957

General Principles

Continuation (4-6 months)

Maintain acute treatments at least 2 weeks beyond first "response" to ensure stability

Continue effective treatments adjusting for tolerability

Discontinue least tolerable medications first

Gradual taper, 2-4 weeks minimum

Add medications for subsyndromal or comorbid symptoms

Overlap and taper

Visits at least monthly for 3 months, then q 2-3 months

Suppes T, et al. J Clin Psych 2005; 66:870

General Principles

Maintenance

Continue effective acute phase treatment or

Switch to one with evidence of maintenance efficacy

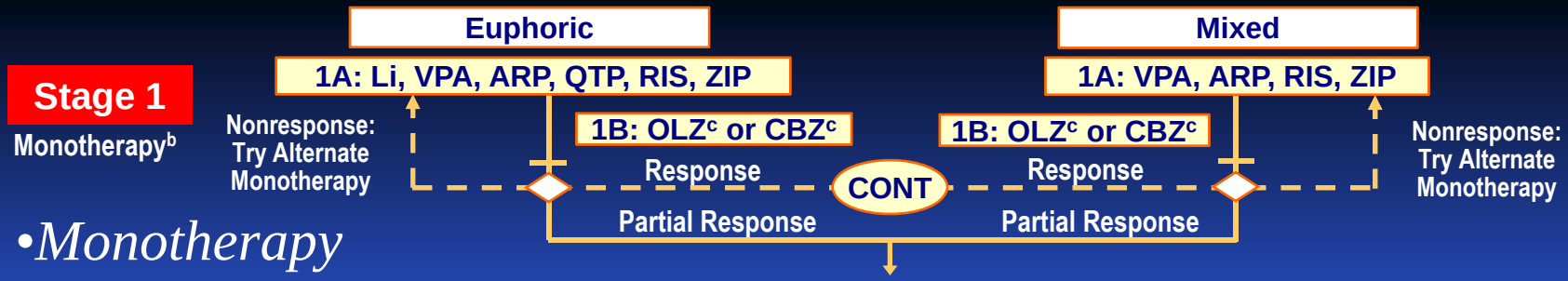
Simplify medication regimen

- Improve tolerability and adherence
- Little data on combinations in maintenance

Suppes T, et al. J Clin Psych 2005; 66:870

Treating Acute Mania

TIMA Bipolar 2005
Acute Mania



- *Monotherapy*
- 6 first line "antimanics" rather than 3 "mood stabilizers"
- Valproate mentioned but divalproex better tolerated
- 4 AAP's for euphoric mania (QTP and ZIP previously Stage 4)
  - 3 for mixed (no evidence on QTP in mixed mania)
- Olanzapine, carbamazepine separate stage due to safety, "complexity"
- No psychotic mania
- Use targeted adjuncts before moving on

ARP = aripiprazole; CBZ = carbamazepine; CONT = continuation; Li = lithium; OLZ = olanzapine; OXC = oxcarbazepine; QTP = quetiapine; RIS = risperdone; VPA = valproate; ZIP = ziprasidone;

Suppes T et al. (2005) J Clin Psychiatry; 66: 870-886

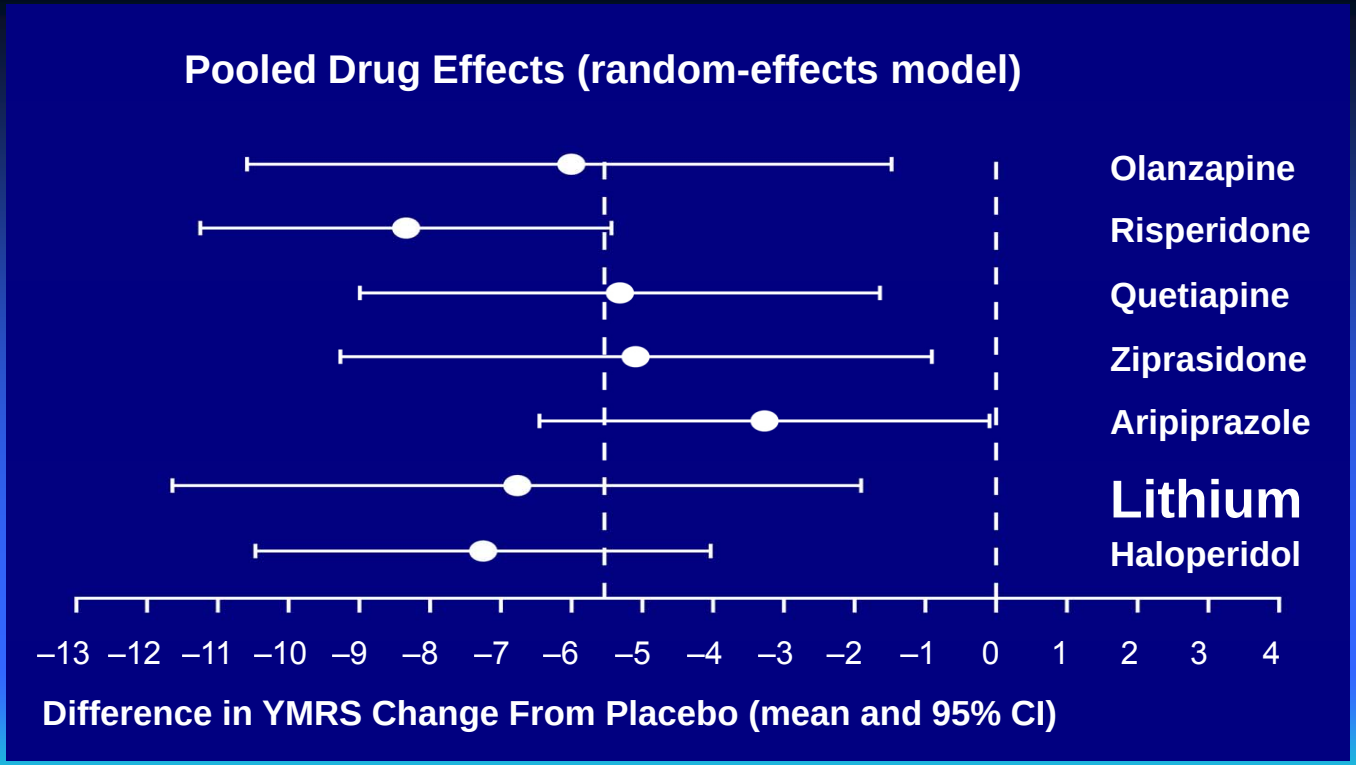
Mania, "More Severe"

American Psychiatric Association, 2002

More Severe	VPA + (OLZ or RIS) *or* Li + (OLZ or RIS) BZD adjunct

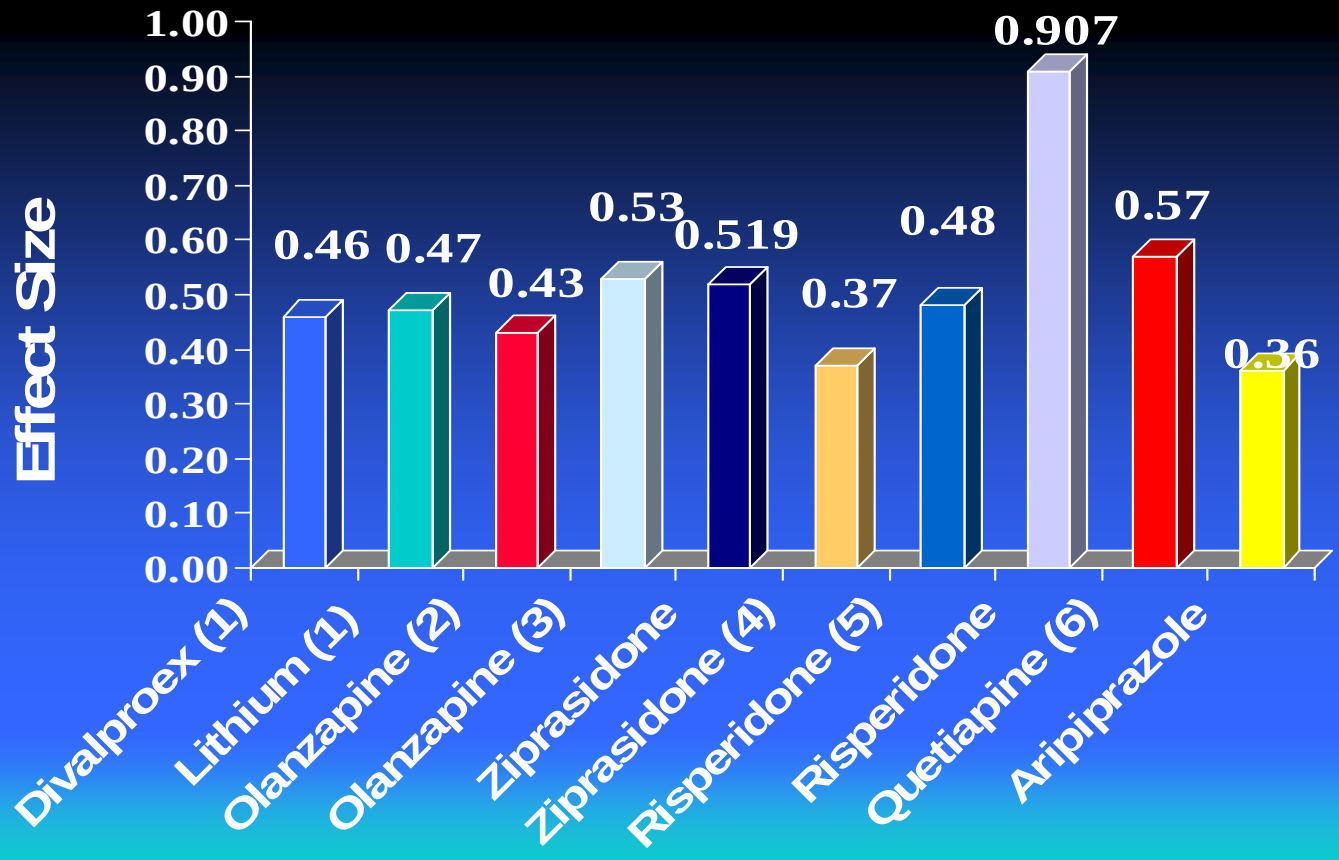
- Combinations indicated initially for severe mania
- Equivalent to Stage 2 in TMAP 2005

Antimanics Similar Effects



Perlis et al 2006. Dotted line on the left indicates pooled difference vs. placebo.

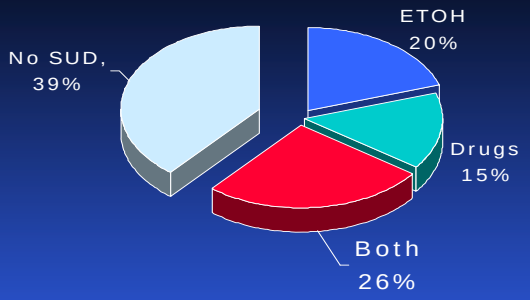
Placebo Corrected Effect Size

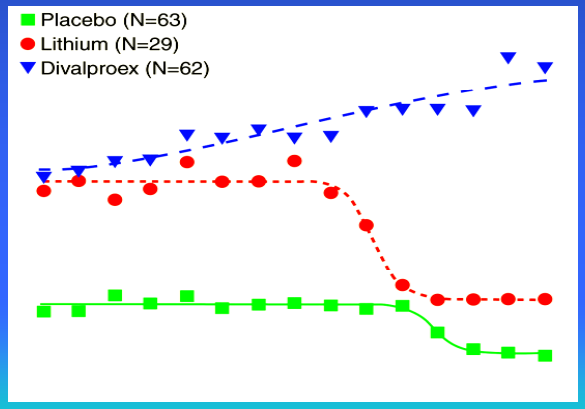


Predictability

Factors influencing response

- Substance use
- Mixed states
- Number of prior episodes
- Prior response





Speed

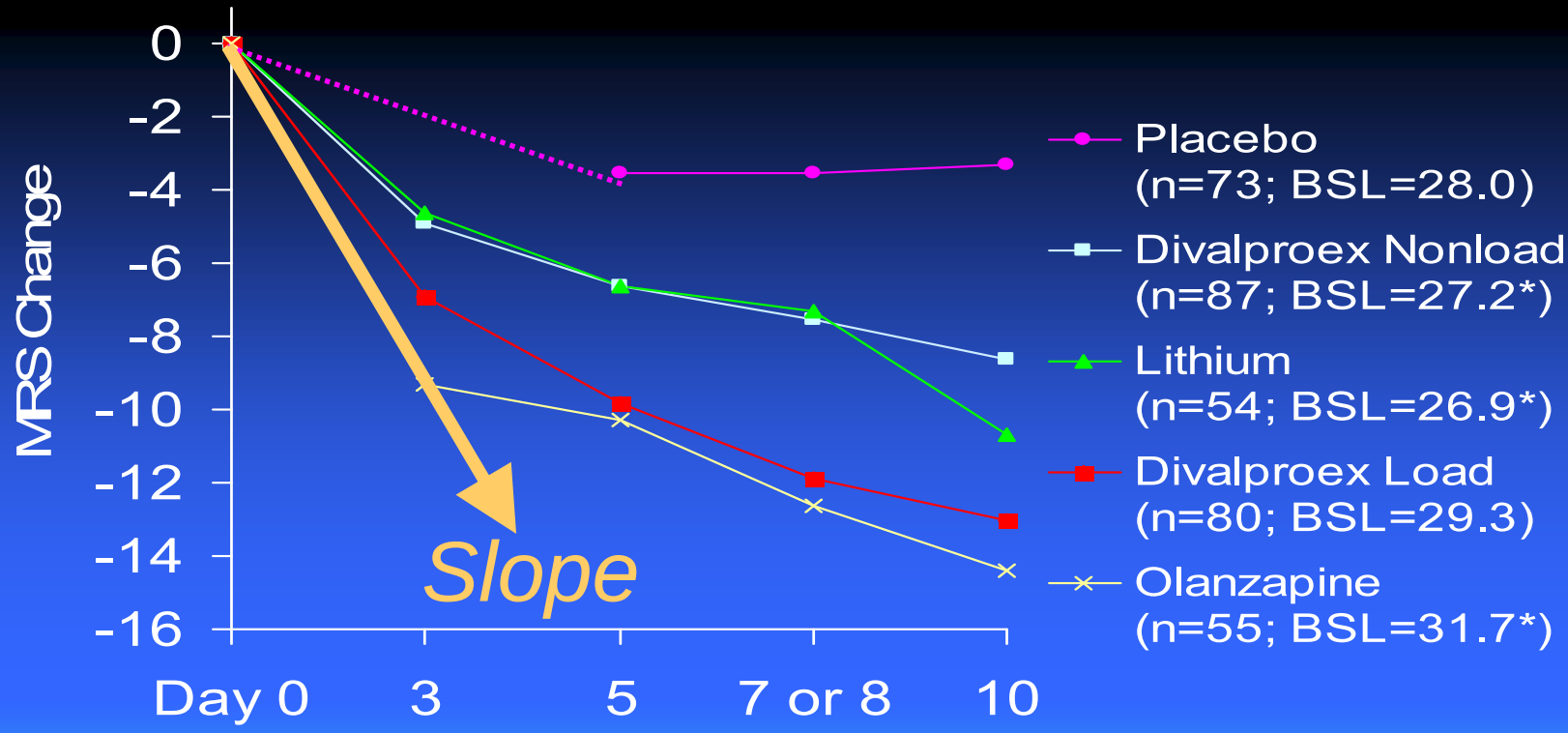
Rapid titration, combinations

- Depakote
- Risperidone, olanzapine, haloperidol

Slower

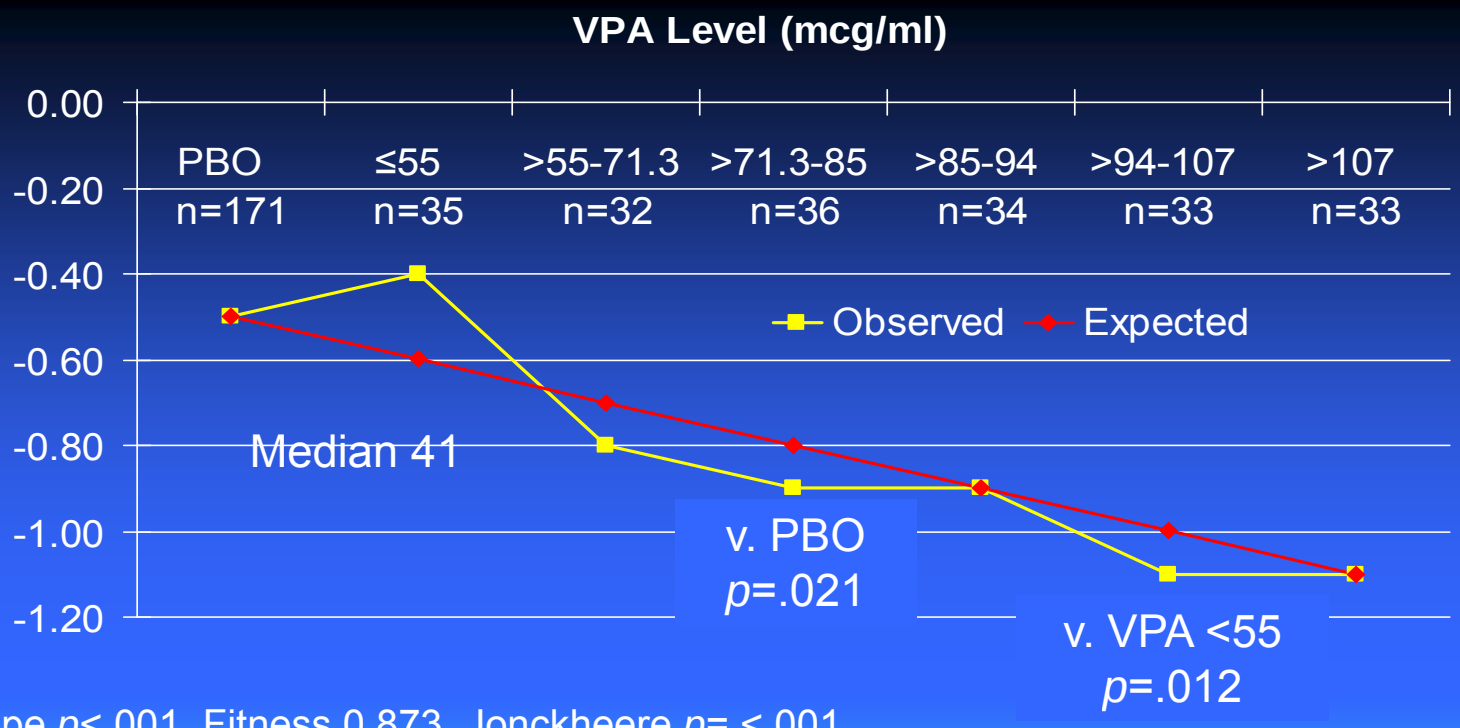
- Lithium slow, combinations more side effects
- Quetiapine titrated

Loading versus Titration



Hirschfeld RMA, et al. J Clin Psych 2003;64:841.

Linear Dose Response of VPA in Mania



Model Slope $p<.001$, Fitness 0.873, Jonckheere $p=.<.001$

Allen MH, et al. Am J Psychiatry 2006; 163(2):272-275.

Optimization

Recommended levels/doses for mania [1]

Lithium level	.7 – 1.2 mEq/l
Valproic acid	>90 µg/ml
Carbamazepine	7 – 12 µg/ml
Oxcarbazepine	900 – 2100 mg
Aripiprazole	15 – 30
Clozapine	200 – 600
Olanzapine	10 – 30
Quetiapine	300 – 800
Risperidone	2.5 – 6
Ziprasidone	80 – 180

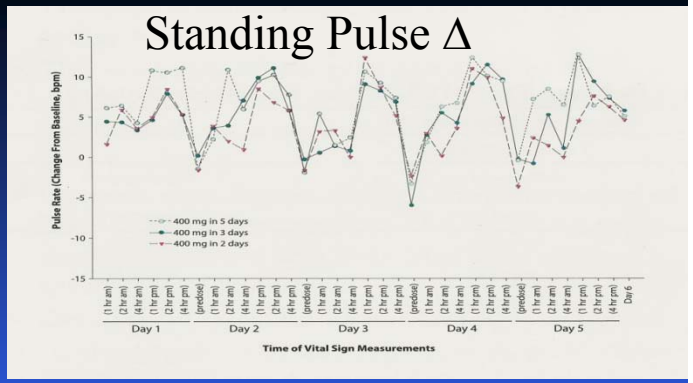
[1] Keck PE, et al. Postgraduate Medicine Spec Report 2004

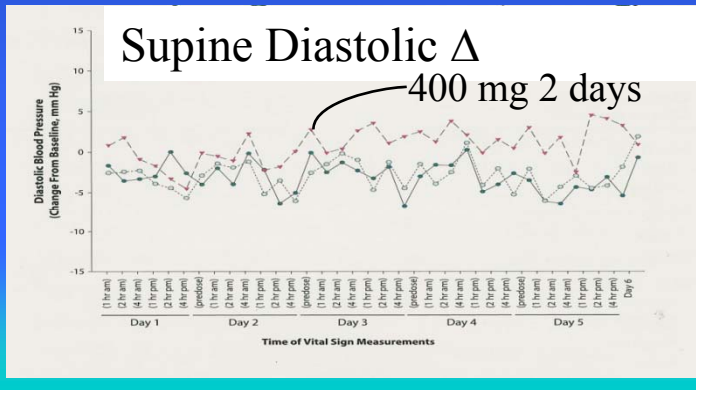
[2] Allen MH, et al. Am J Psych.

QTP Titration Schedules

- SZP, PANSS ≥60, *n*=69
  - –No significant baseline differences
- RDB, BID dosing
  - –QTP 400 mg in 2 days
  - –QTP 400 mg in 3 days
  - –QTP 400 mg in 5 days
- 80-91% AE rate, mild-mod
- Withdrawals d/t agitation
  - –1 in 5 day, 2 in the 2 day group

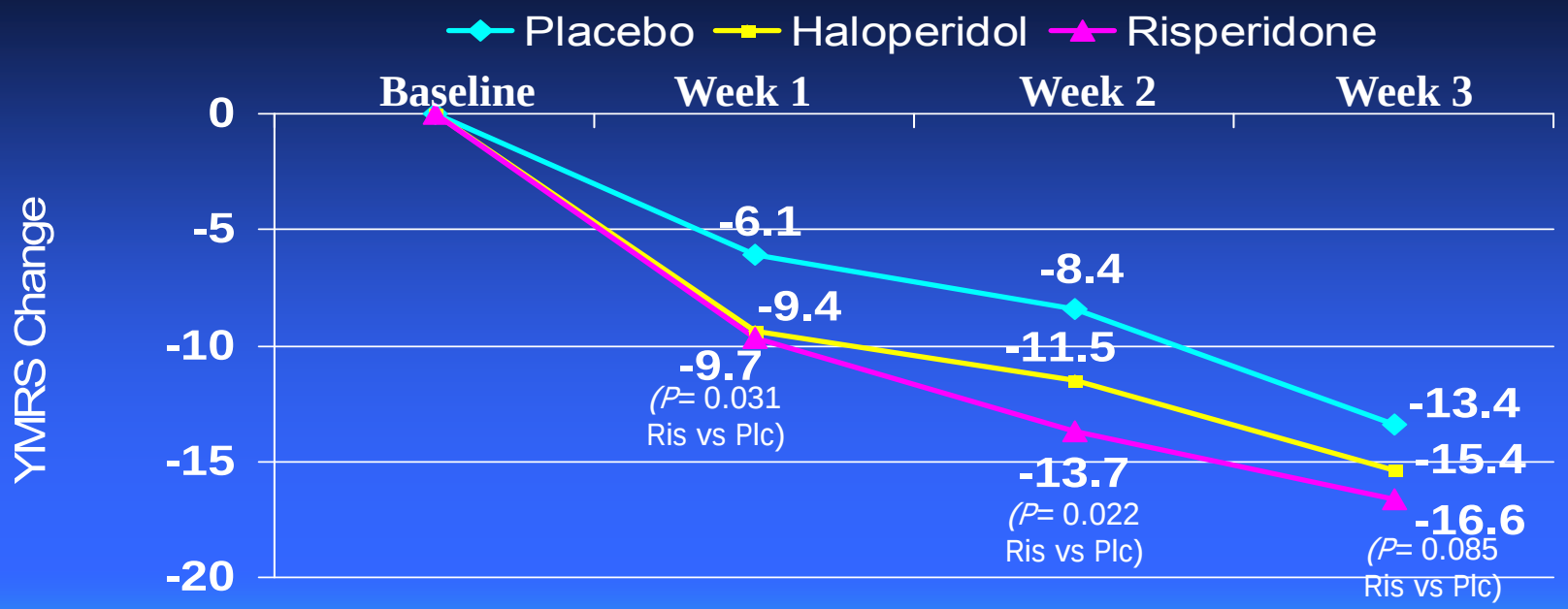
Smith MA, …, Brecher M, et al, AstraZeneca





Risperidone plus MS for Acute Mania

N=156, 70% Divalproex

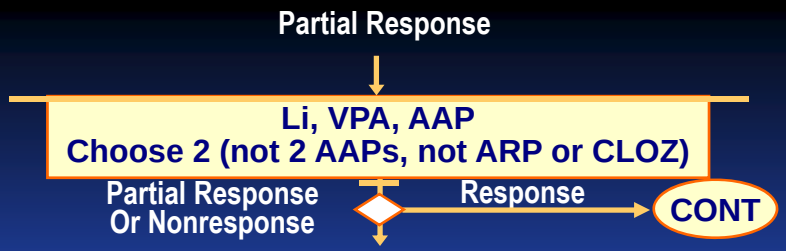


Sachs G, et al. Am J Psychiatry 2002; 159:1146–1154

TIMA Bipolar 2005
Acute Mania

Stage 2

Two-Drug Combination[b]



- *Combinations (initial strategy for more severe mania)*
- Try more than one combination before moving on
- 2 anticonvulsants dropped
- 2 AAP's not recommended
- No combination data with aripiprazole
- Clozapine appears later
- Oxcarbazepine was Stage 2, now Stage 3

AAP = atypical antipsychotic; ARP = aripiprazole; CLOZ = clozapine; CONT = continuation; Li = lithium

Suppes T et al. (2005) J Clin Psychiatry; 66: 870-886

Summary

Considerations

- Speed of acute behavioral onset
  - Rapid titration
  - Combinations
- Future prophylaxis
- Chronic tolerability

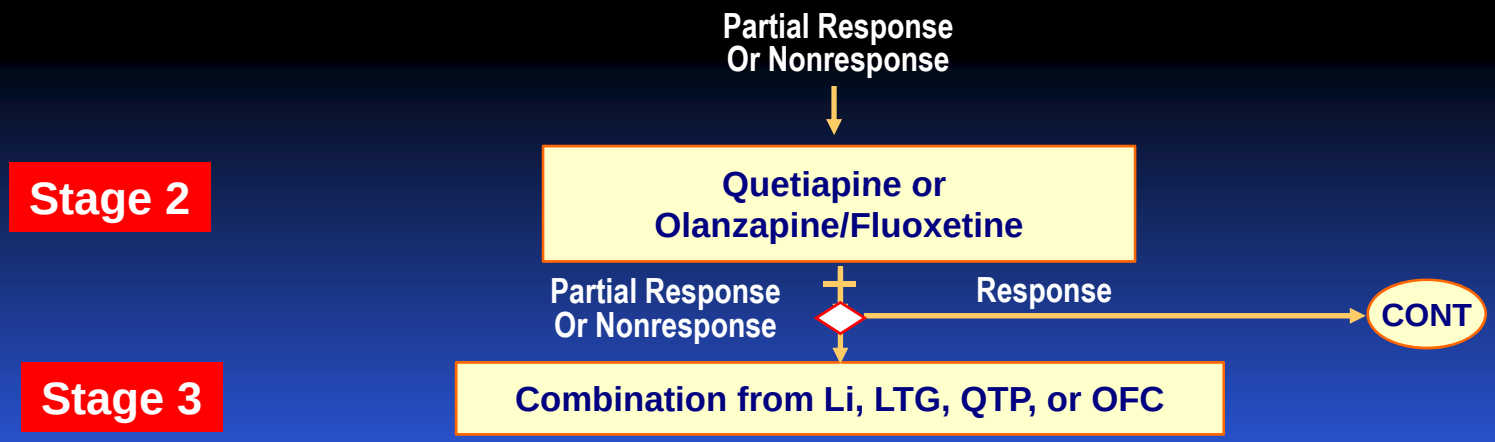
Treating Acute Bipolar Depression

TIMA Bipolar 2005
Acute Depression

- Lamotrigine not antimanic
- If history of recent or severe mania, add or optimize antimanic
- Otherwise, lamotrigine monotherapy may be appropriate

Suppes T et al. (2005) J Clin Psychiatry; 66: 870-886

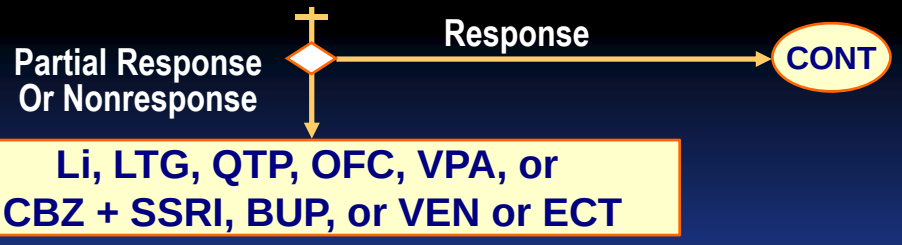
TIMA Bipolar 2005



- Designed to minimize cycle risk
- Note no anticonvulsant except LTG until Stage 4
- Overlap and taper
- Follow ADA guidelines regarding metabolic monitoring

Suppes T et al. (2005) J Clin Psychiatry; 66: 870-886

TIMA Bipolar 2005 Acute Depression



Stage 4

Combinations (OFC combinations = 3 drugs)

- Lamotrigine should not be combined with AD without antimanic
  - Incudes VPA and CBZ at this point
- SSRI's include CTP, FLX, PRX, SRT and FLV
- Some advocate the use of AD earlier but evidence is lacking
- Venlafaxine associated with more mania induction

BUP = bupropion; CBZ = carbamazepine; ECT = electroconvulsive therapy; Li = lithium; LTG = lamotrigine; OFC = olanzapine-fluoxetine combination; QTP = quetiapine; SSRI = selective serotonin reuptake inhibitor; VEN = venlafaxine; VPA = valproate

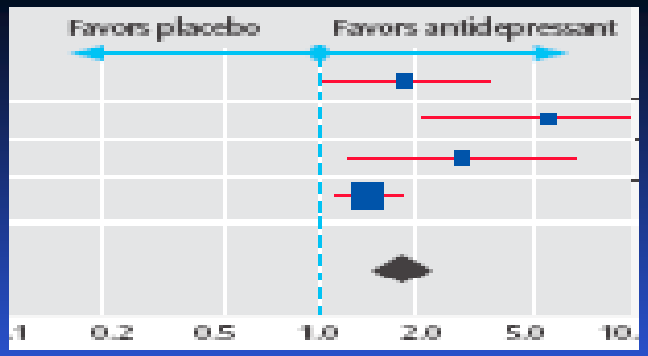
Suppes T et al. (2005) J Clin Psychiatry; 66: 870-886

Meta-Analysis of Antidepressant Trials

Response, N=662

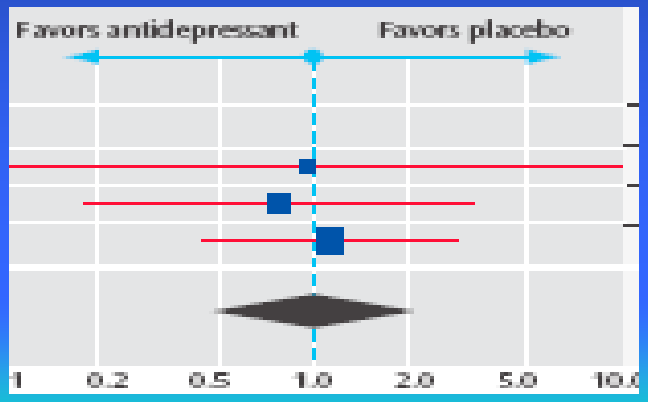
Mendelowicz (1980) only 34/58 BP
Himmelhoch (1982) only 29/59 BP
Cohn (1989) FLX v. IMI v.PCB; 25% lithium
Tohen (2004) 456/662=72%, 100% OLZ

RR 1.86



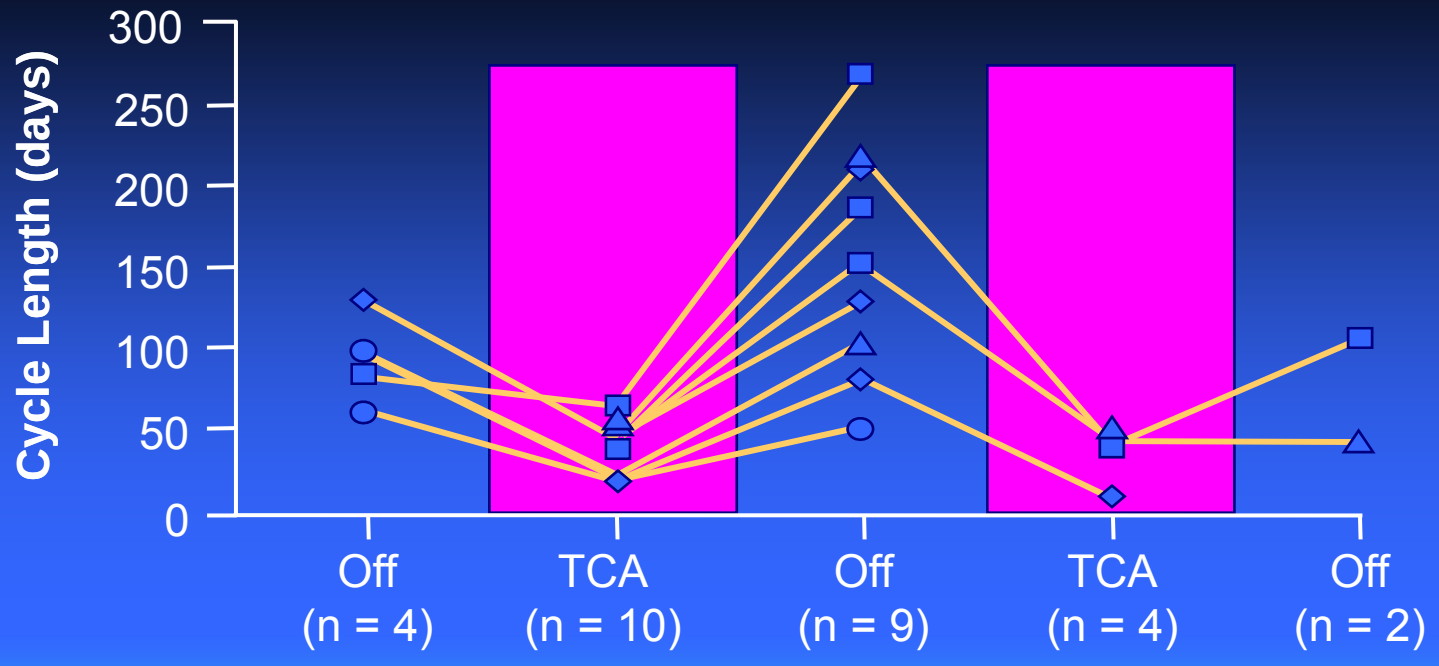
Manic switching

RR 1.00 (CI .47-2.13)



Gijsman HJ, Geddes JR, et al. Am J Psych 2004; 161:1537.

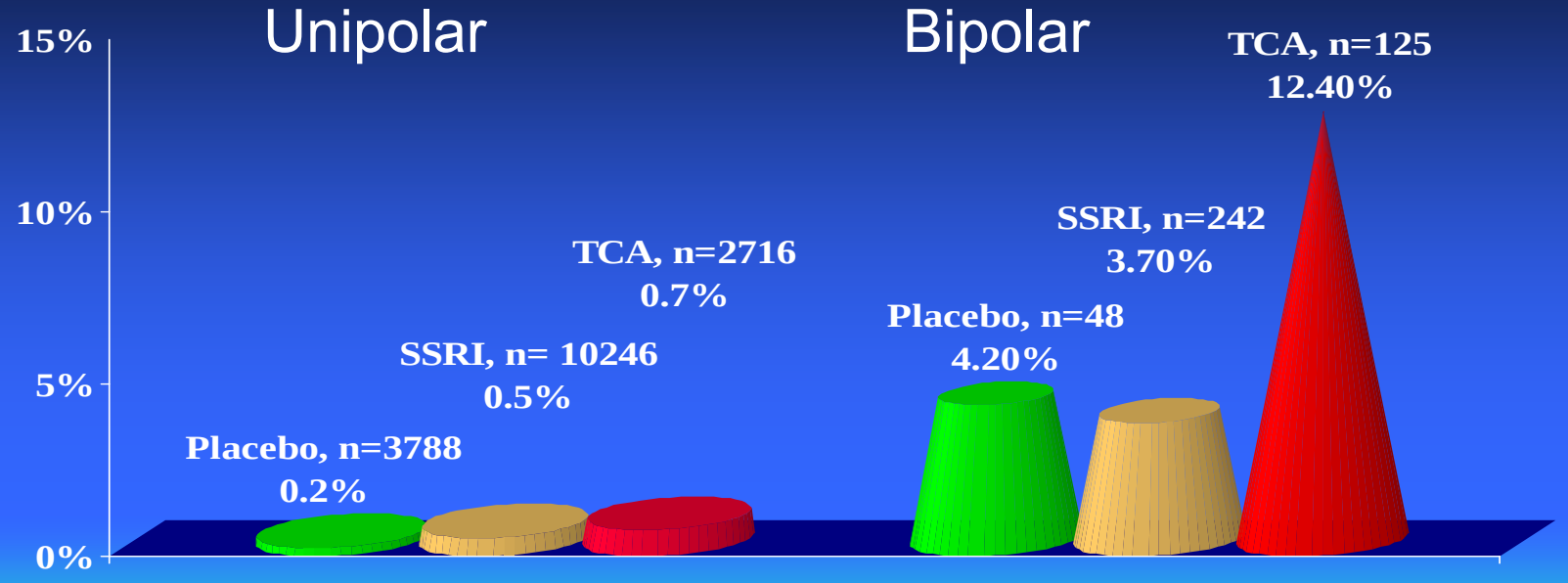
Tricyclic-Induced Shortening of Bipolar Cycle Length (N = 10)



Wehr et al. *Am J Psychiatry*. 1988;145:179-84.

Meta-Analysis of Antidepressant Switch

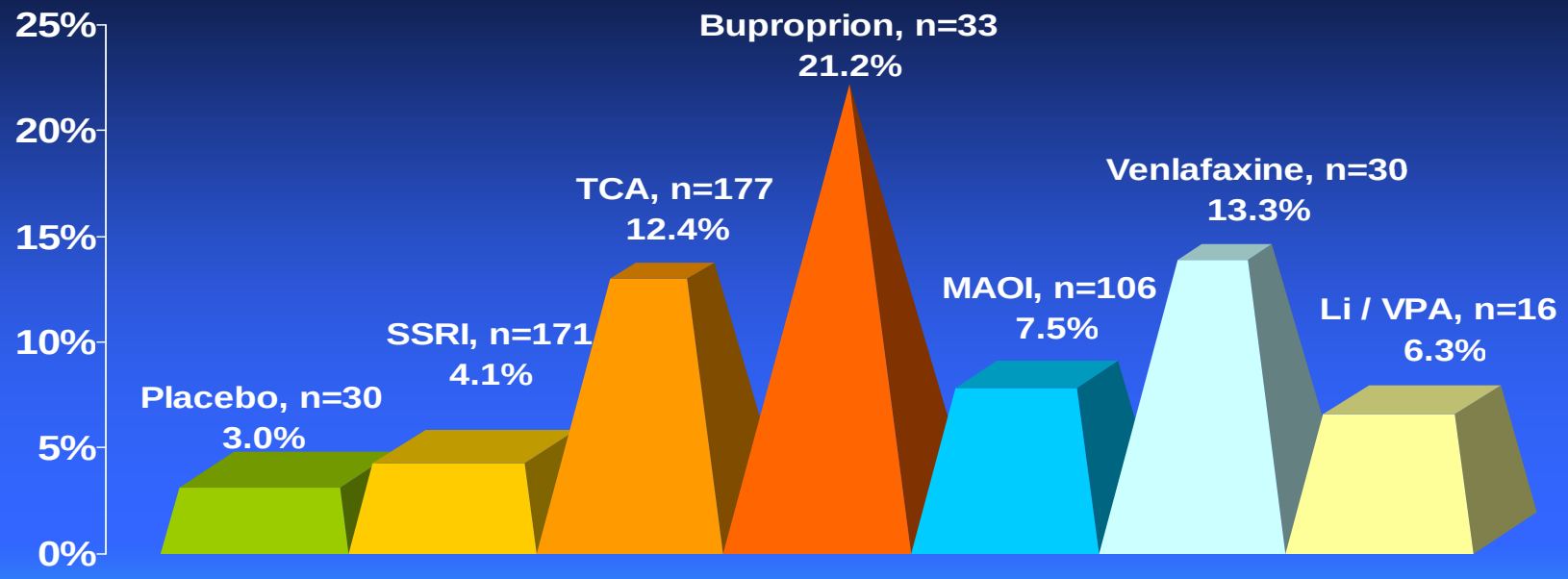
SSRI = placebo, TCA significantly higher



Peet M. Br J Psychiatry 164:549, 1994

Antidepressant Switch Rates

12 studies, many including mood stabilizers

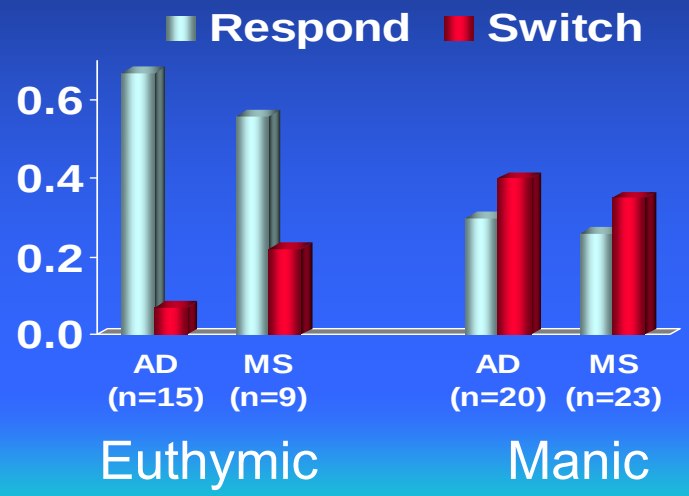


Goldberg JF and Truman CJ. Bipolar Disorders 5:407, 2003

Depression After Euthymia or Mania

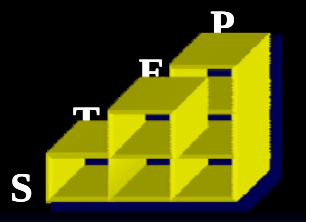
Prospective depressions, N=67, LCM avg 36.8 months

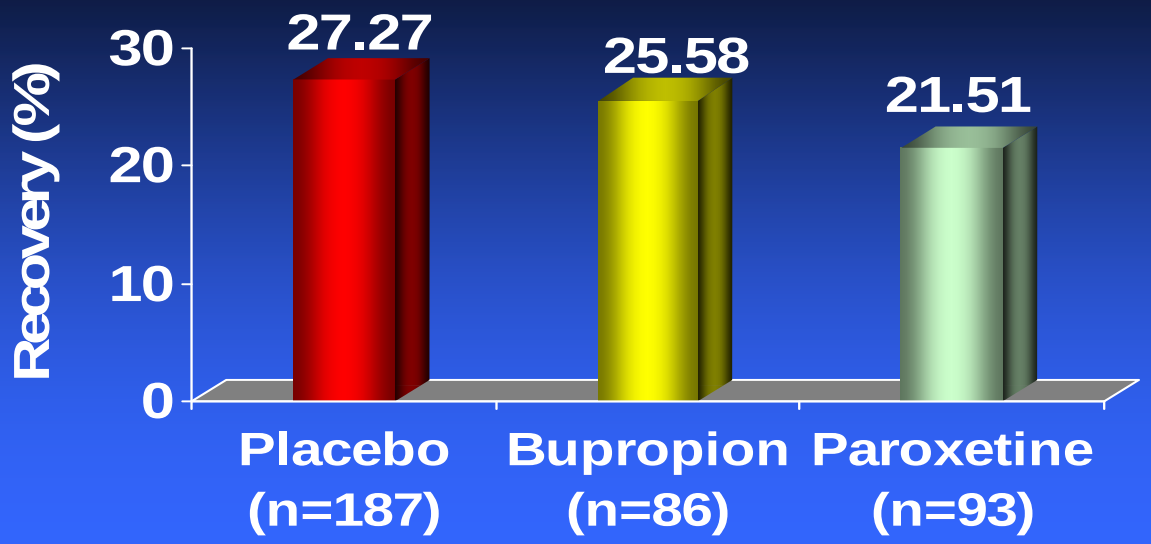
- Response to AD better after euthymia
  - 62.5% vs. 27.9%, (p<.05)
- AD response : switch ratio better
  - 10:1 vs .75-1



MacQueen GM, et al. Acta Psych Scand 2002; 105:414

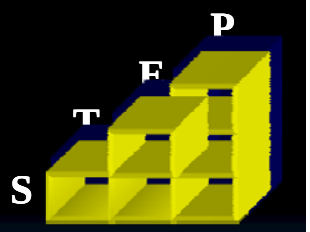
Durable Recovery by Treatment

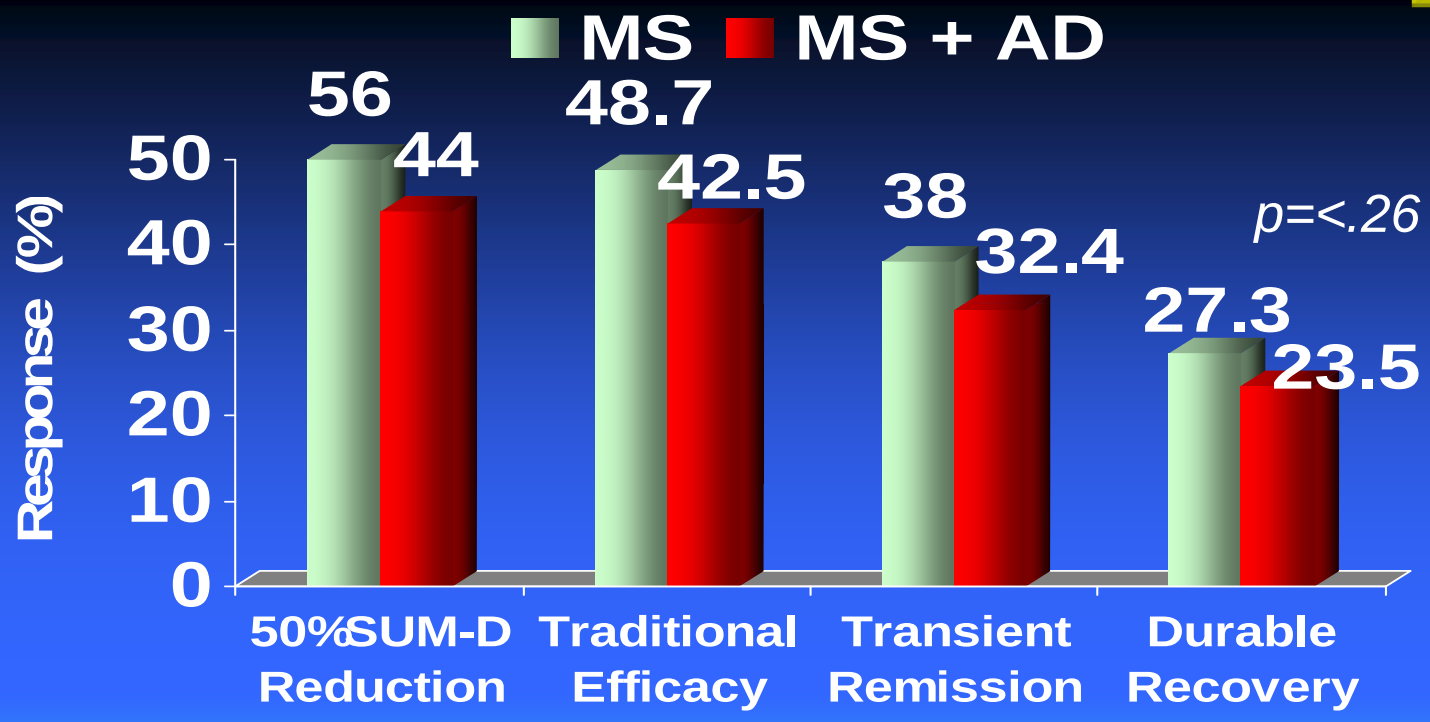




Sachs G, et al. NEJM 2007;356.

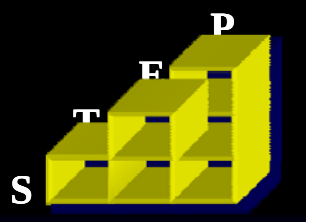
Randomized Acute Depression

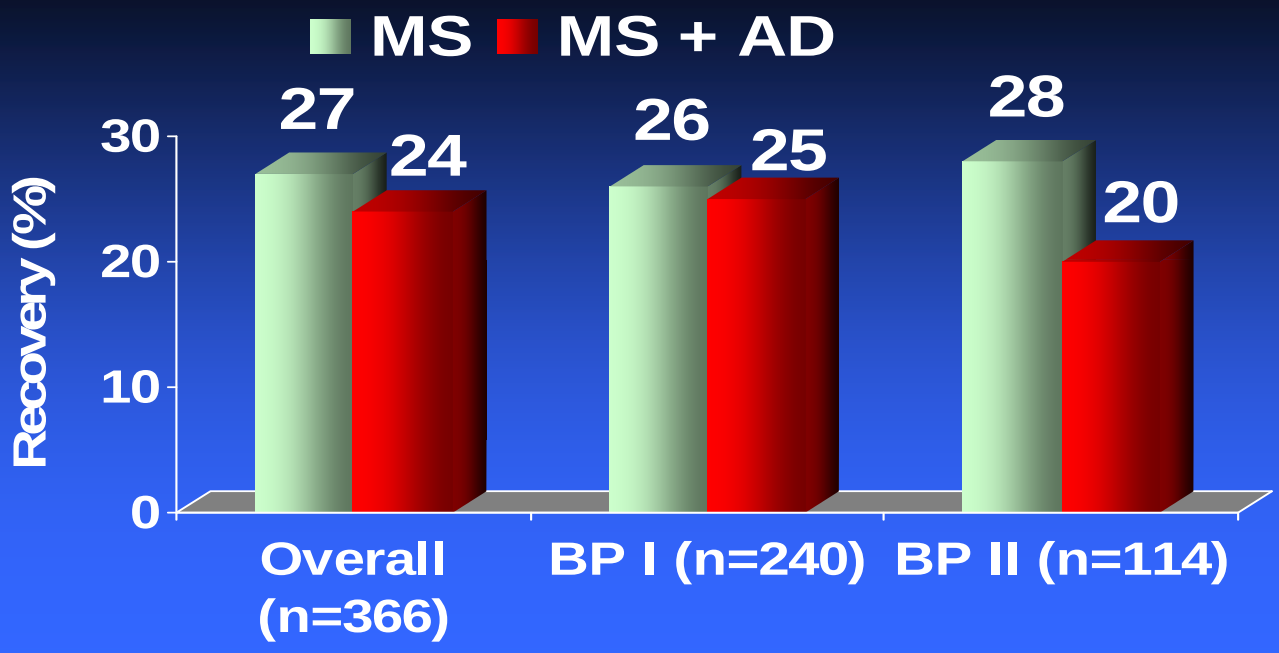




Sachs G, et al. NEJM 2007;356.

Remission by Bipolar Type

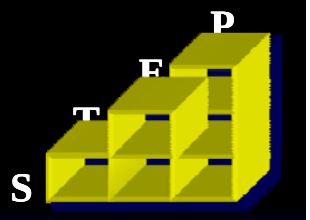


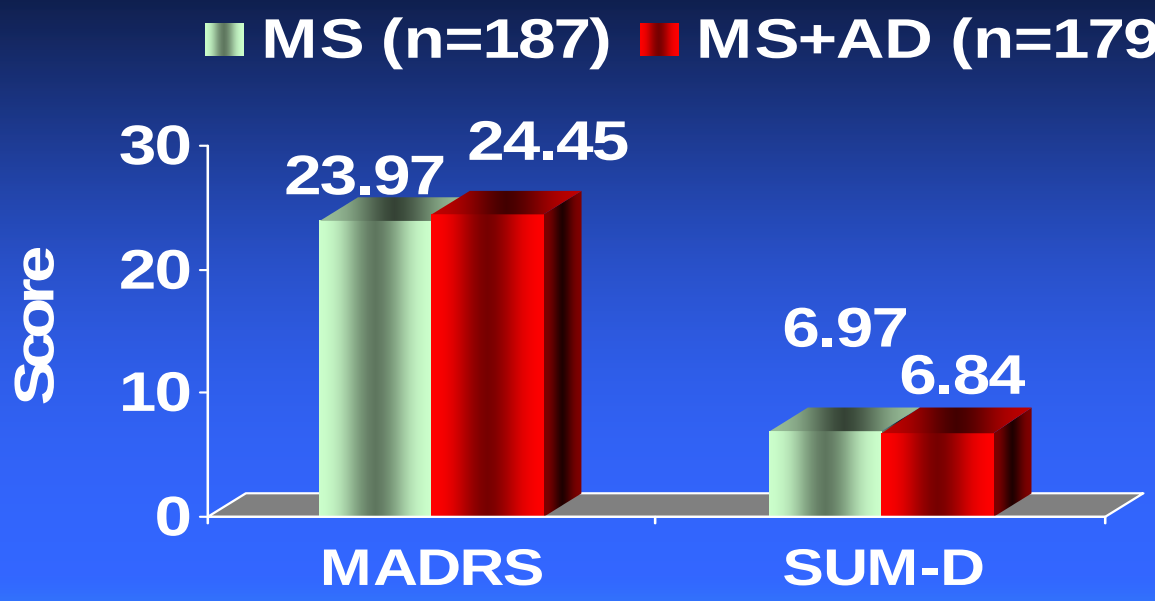


p=<.26

Sachs G, et al. NEJM 2007;356.

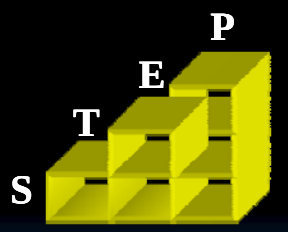
Depression Scores by Treatment





Sachs G, et al. NEJM 2007;356.

Open, Selective Treatment

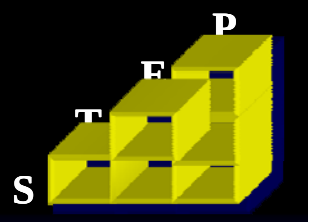


MS + AD numerical superiority with anxiety

Standard Care, *n* = 960

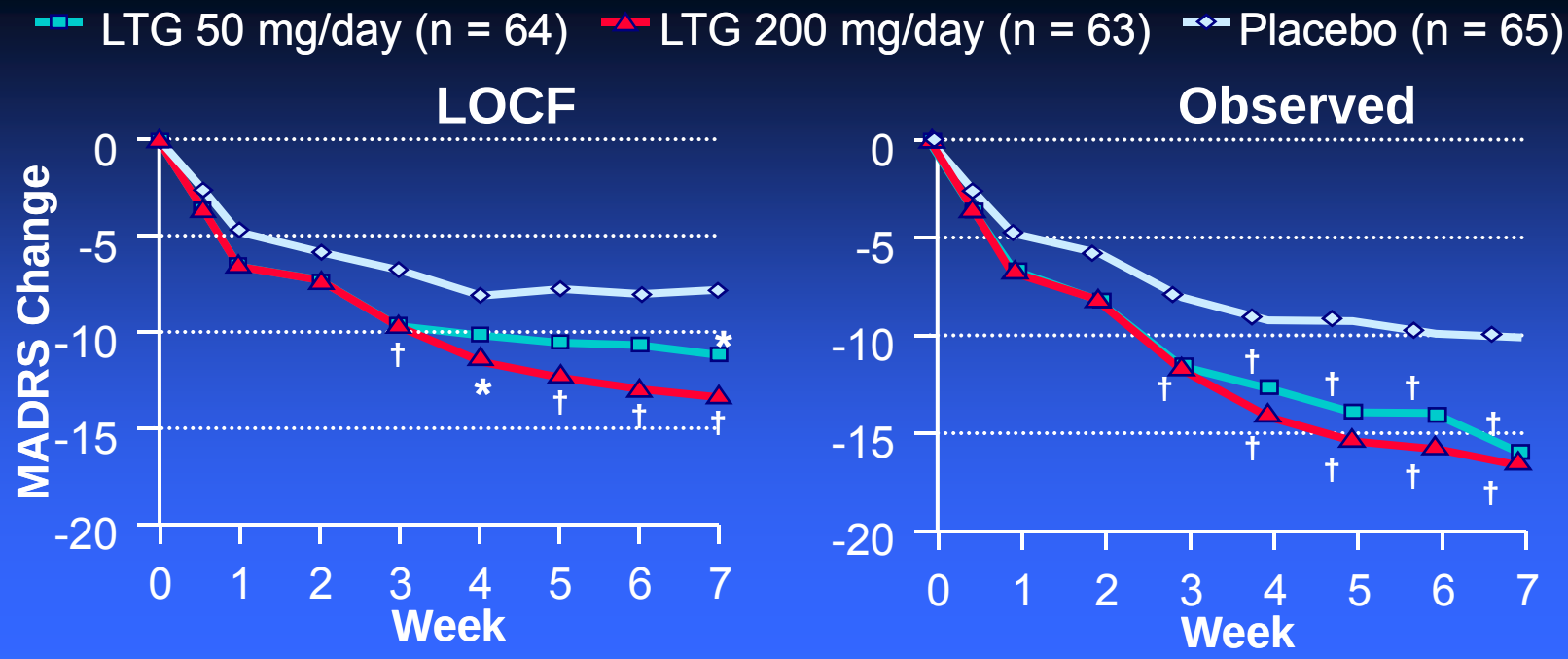
Outcome	No MS, No AD N=91	AD Alone N=51	*p*	MS Alone N=211	MS + AD N=509	*p*
Transient Remission	34.1%	33.3%	.9294	36.3%	38.4%	.5959
Durable Recovery	23.1%	33.3%	.1854	33.9%	36.0%	.5909
Any Response	57.1%	66.7%	.2652	70.2%	74.4%	.2574
50% Improvement	25.3%	33.3%	.3057	39.1%	36.5%	.5203
Affective Switch	6.6%	9.8%	.4923	13.0%	15.6%	.3533

Open Selective Antidepressant Treatment



- Much larger sample
- Mood stabilizer, MS + AD, AD only
- Numerical differences favor AD
- Anxiety predicted response

Lamotrigine



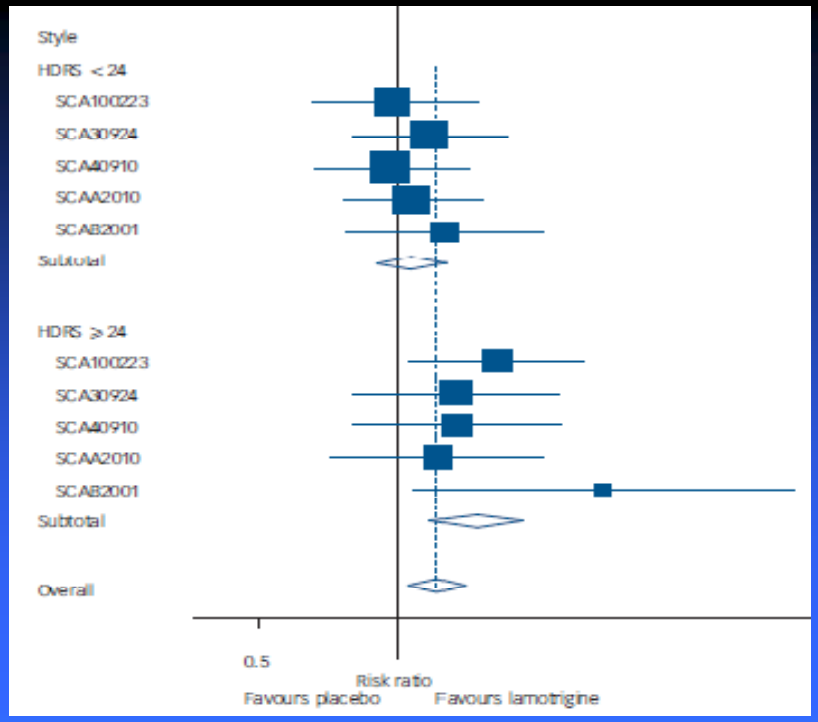
* $P<0.1$; † $P<0.05$. LOCF = last-observation-carried-forward.

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

Lamotrigine, Hamilton ≥ 24

"Modest benefit"

- Overall NNT = 11
- Ham ≥ 24, NNT = 7



Geddes J R et al. BJP 2009;194:4-9

THE BRITISH JOURNAL OF PSYCHIATRY

MADRS Difference from Baseline

Aripiprazole, p=.236

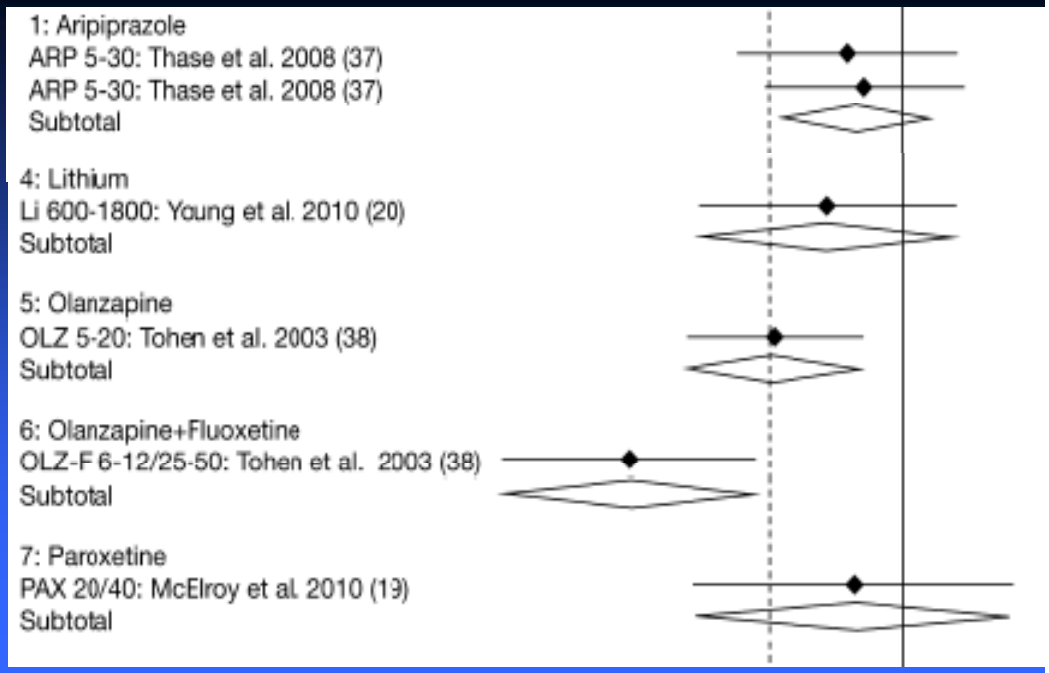
Lithium, p=.245

Olanzapine, p=.004

OFC, p=.000

MADRS -6.6 vs placebo

Paroxetine, p=.554

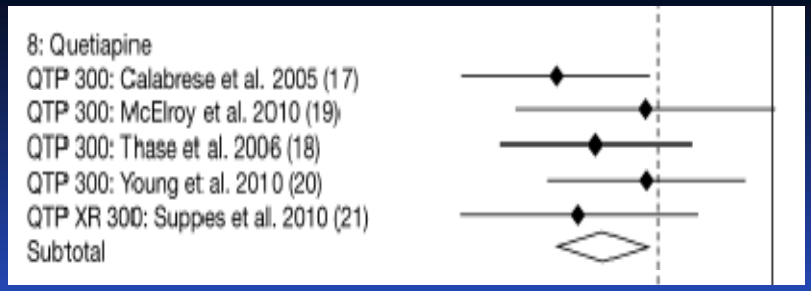


Vieta E, et al. J Clin Psychopharm 2010; 30(5): 579-90

MADRS Difference from Baseline

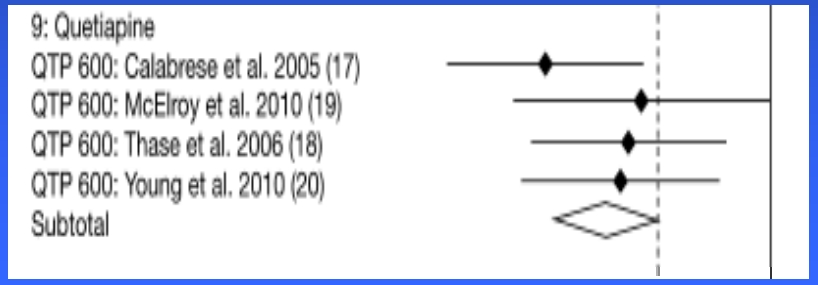
Quetiapine 300 mg, p=.000

MADRS -4.84 vs placebo



Quetiapine 600 mg, p=.000

MADRS -4.75 vs placebo

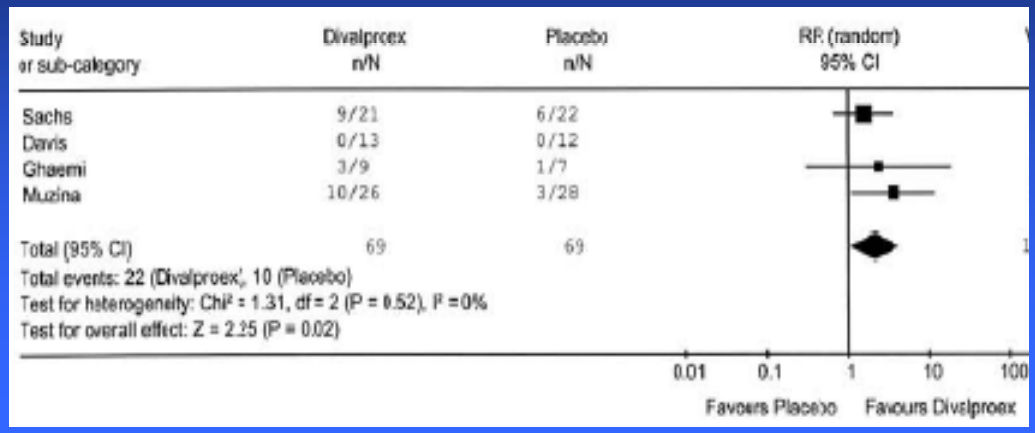


Vieta E, et al. J Clin Psychopharm 2010; 30(5): 579-90

Divalproex Response vs Placebo

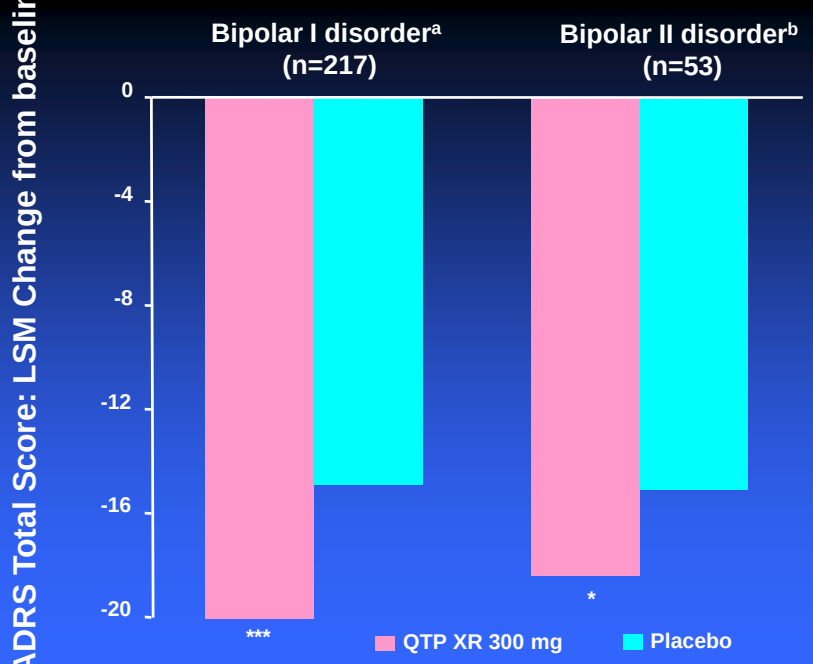
Divalproex Monotherapy in Bipolar Depression

- Depakote, 22/69 vs Placebo, 10/69, p=.02
- RR of response = 2.1



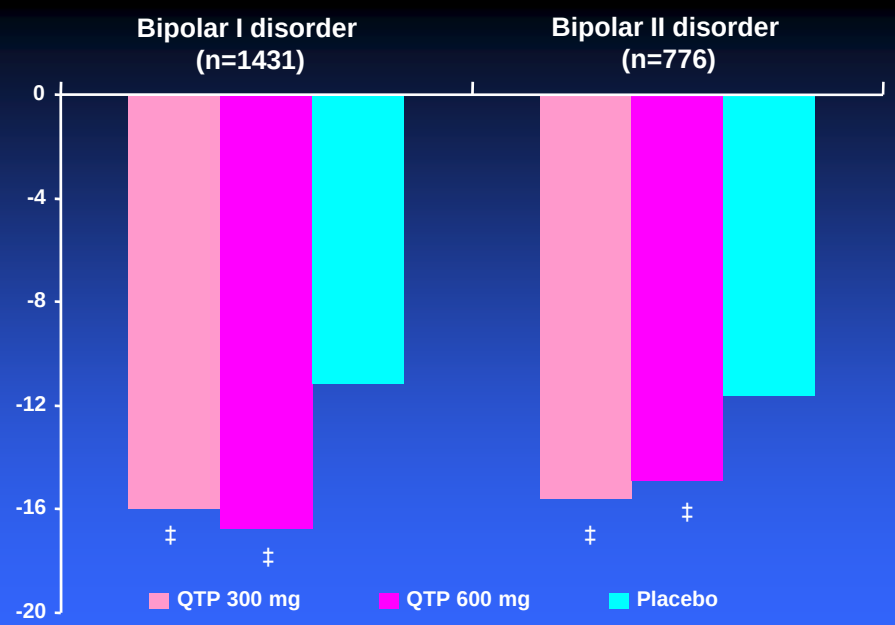
Bond DJ, et al. J Affective Disorders 124 (2010) 228–234

Quetiapine in Bipolar I and Bipolar II



Trial 002
Baseline values: [a]quetiapine XR, 30.2; placebo, 30.1; [b]quetiapine XR, 28.1; placebo, 30.3
MITT, MMRM, OC

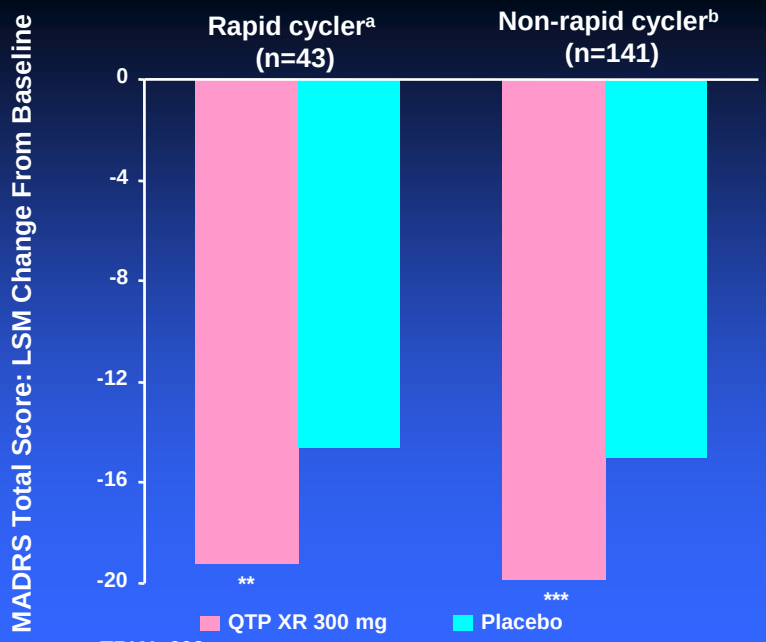
Suppes et al 2010. *p<0.05; ***p<0.001 vs placebo



EMBOLDEN I and II; BOLDER I and II
ITT, LOCF

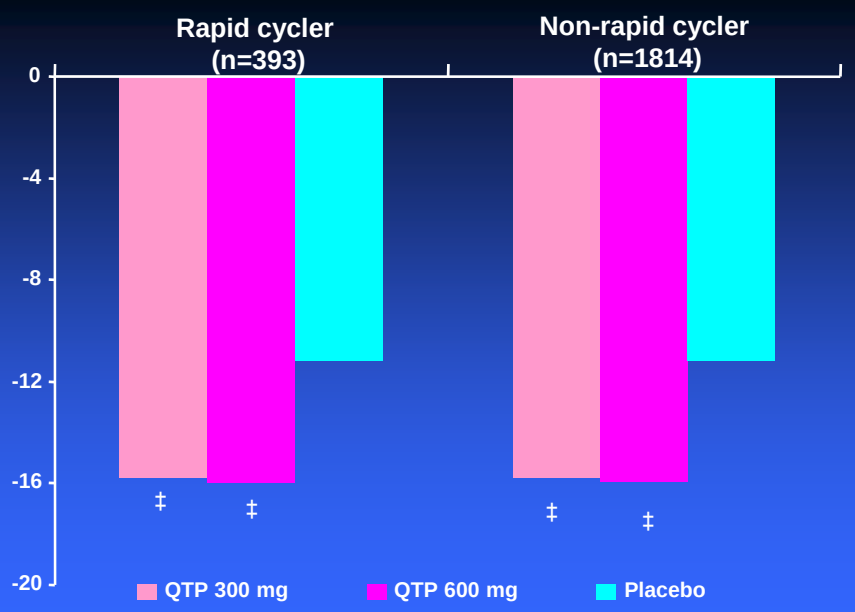
AstraZeneca Data on File. ‡p<0.001 vs. placebo.

Quetiapine and Rapid Cycling



TRIAL 002
Baseline values: [a]quetiapine XR, 29.5; placebo, 30.6; [b]quetiapine XR, 29.9; placebo, 30.0
MITT, MMRM, OC

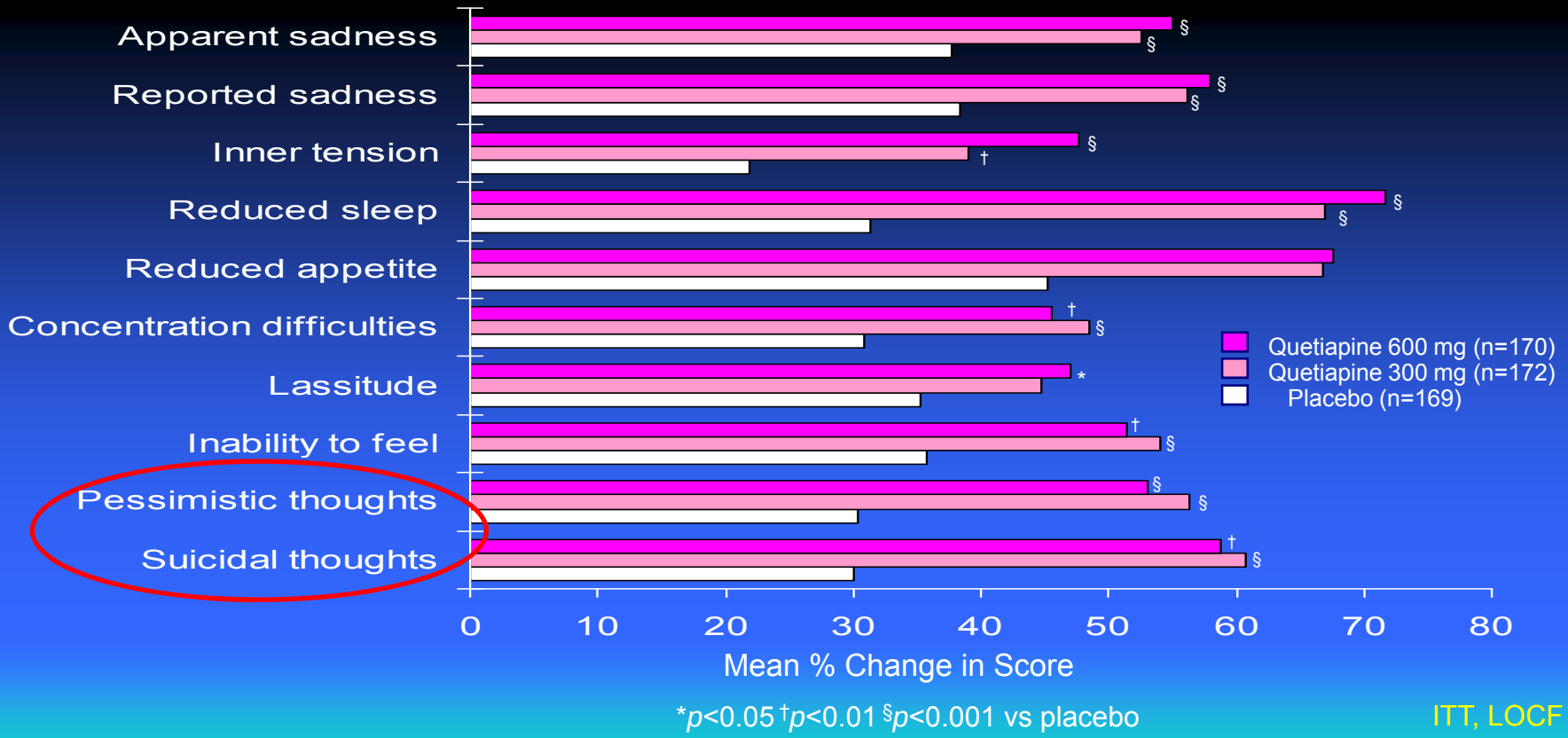
Suppes et al 2010. **p<0.01; ***p<0.001 vs placebo



EMBOLDEN I and II; BOLDER I and II
Rapid cycling, ≥4 episodes in past year.
ITT, LOCF

AstraZeneca Data on File. ‡*P*<0.001 vs. placebo.

Quetiapine Item Analysis



*$p<0.05$ †$p<0.01$ §$p<0.001$ vs placebo

ITT, LOCF

Summary Bipolar Depression

- Antidepressants
  - Little evidence favoring, some adverse
- Olanzapine, olanzapine/fluoxetine
  - 1 study, large effects
- Lamotrigine
  - 5 studies, “modest benefit”
- Depakote
  - Small numbers, doubled response rate
- Lithium
  - Mostly antimanic
- Quetiapine
  - 4 studies, array of symptoms, BP 1 and 2, RC

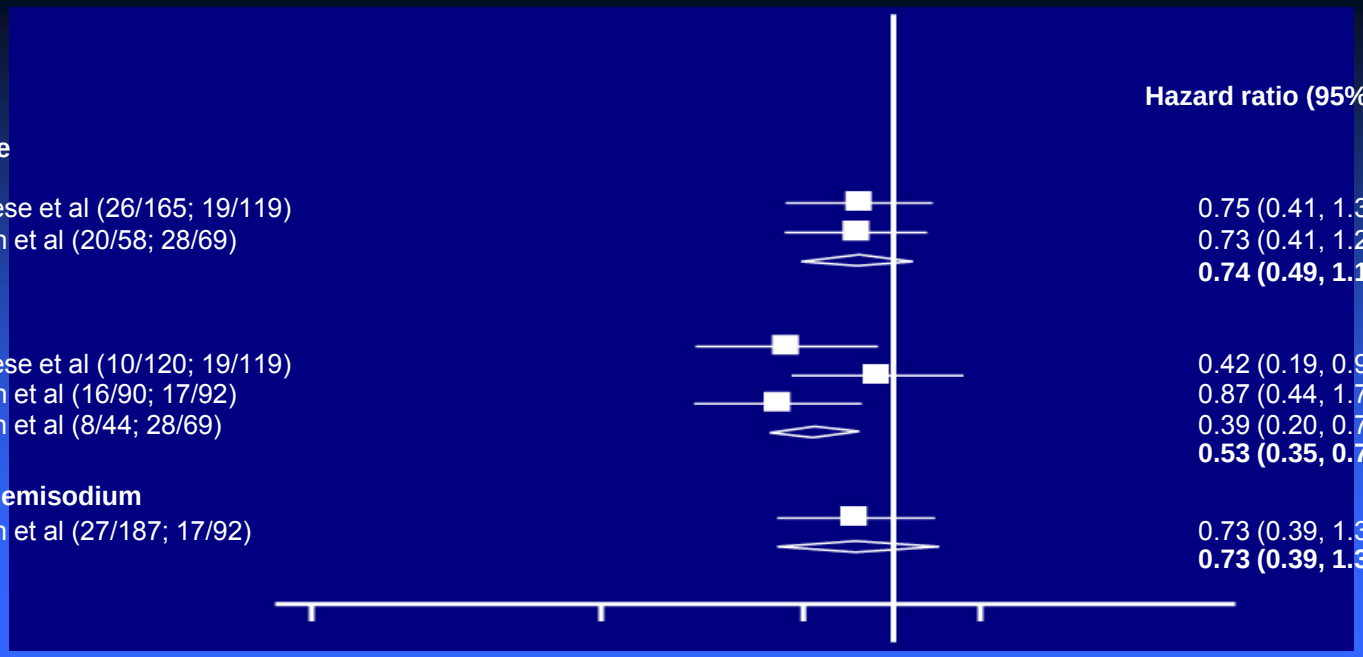
Maintenance Treatment

General Principles

Maintenance Phase

- Anticipated maintenance treatment influences acute treatment
  - Tendency to relapse to the same or opposite polarity?
  - Agents vary in prevention of different polarity
- Continue effective acute phase treatment(s)
- Switch to one with evidence of maintenance efficacy ??
  - "Maintenance" = enrichment, discontinuation
  - Discontinuation, even AD, is associated with relapse
- Improve tolerability and adherence
  - Little data on combinations in maintenance

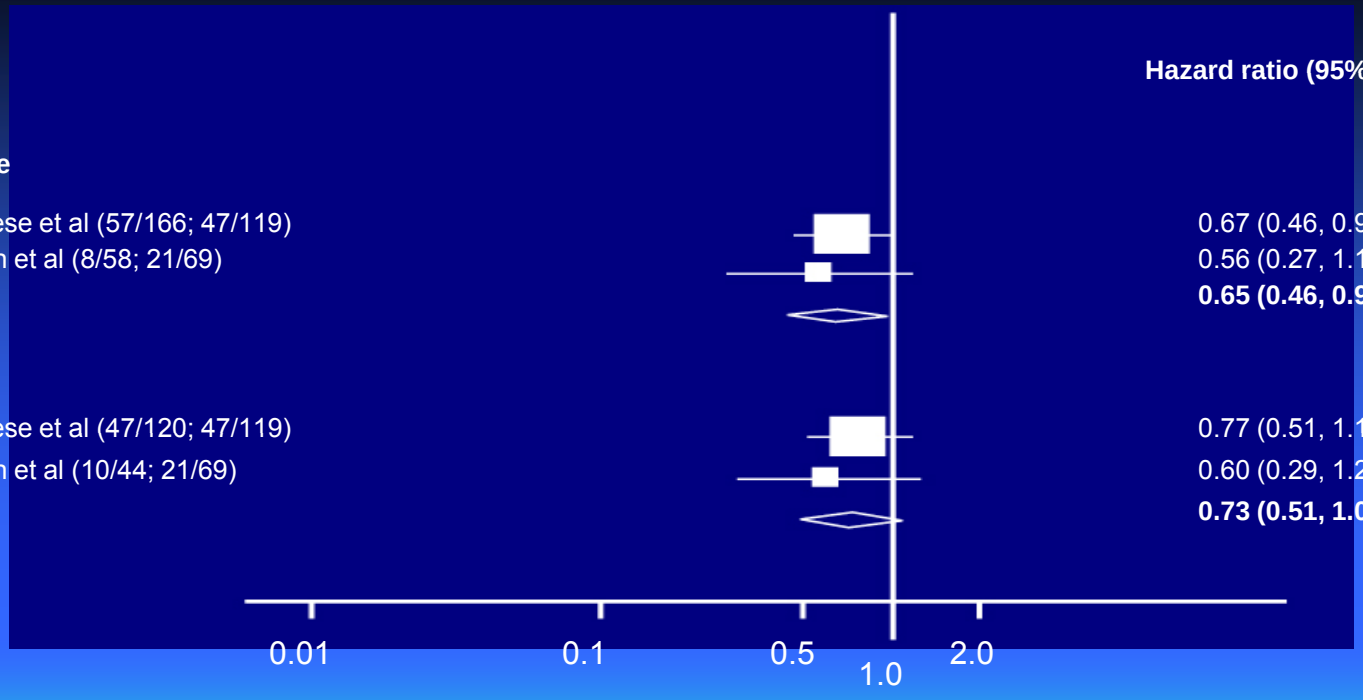
Relapse to Mania Relative to Placebo



Study	Hazard ratio (95% CI)	% Weight
Lamotrigine		
Calabrese et al (26/165; 19/119)	0.75 (0.41, 1.35)	47.9
Bowden et al (20/58; 28/69)	0.73 (0.41, 1.29)	52.1
Subtotal	**0.74 (0.49, 1.11)**	**100.0**
Lithium		
Calabrese et al (10/120; 19/119)	0.42 (0.19, 0.90)	28.1
Bowden et al (16/90; 17/92)	0.87 (0.44, 1.72)	35.3
Bowden et al (8/44; 28/69)	0.39 (0.20, 0.76)	36.7
Subtotal	**0.53 (0.35, 0.79)**	**100.0**
Valproate semisodium		
Bowden et al (27/187; 17/92)	0.73 (0.39, 1.36)	100.0
Subtotal	**0.73 (0.39, 1.36)**	**100.0**

Smith et al 2007.

Relapse to Depression Relative to Placebo



Smith et al 2007.

Lithium Meta-analysis

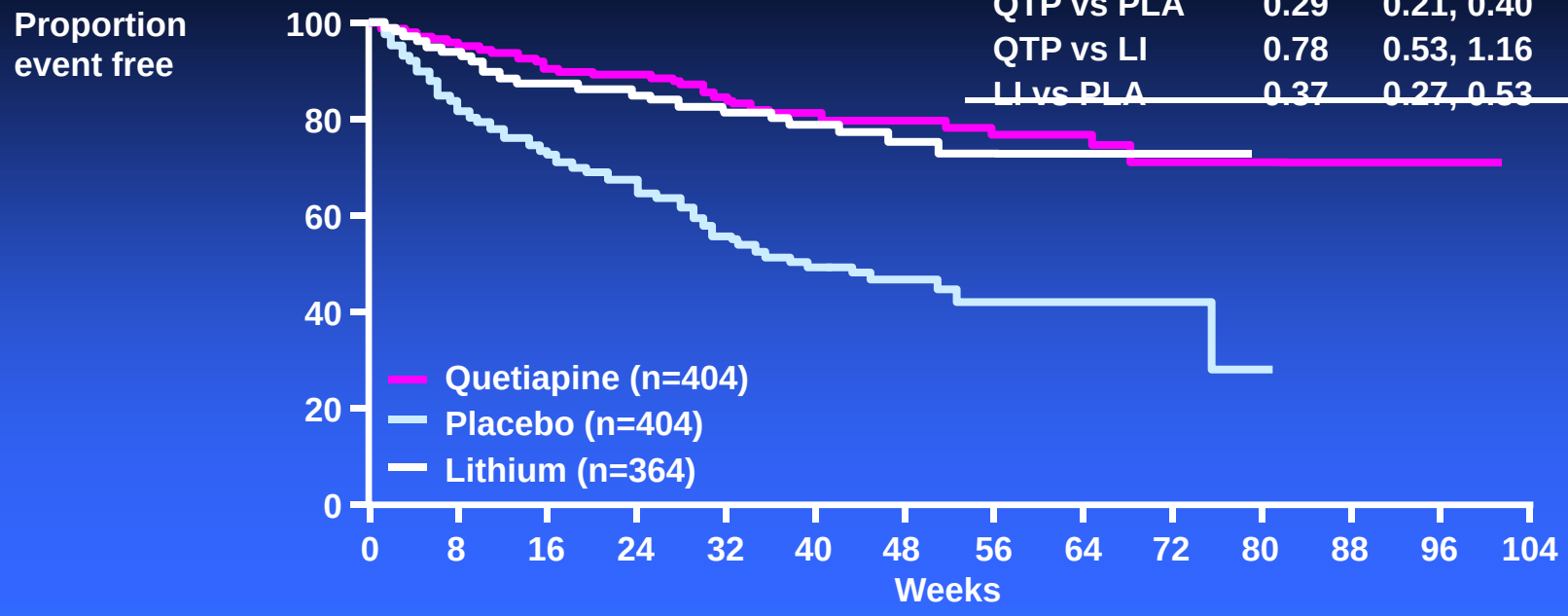
Five RCT's, Li vs. placebo, n=770

- One relapse prevented for every 14 patients treated 1-2 years
  - One mania for every 10 patients
  - One depression for every 14 patients
- Better for manic than depressive relapse

Geddes et al. Am J Psych 161:217, 2004

Recurrence of Mania, Quetiapine vs. Lithium or Placebo

	HR	95% CI	p-value
QTP vs PLA	0.29	0.21, 0.40	<0.001
QTP vs LI	0.78	0.53, 1.16	NS
LI vs PLA	0.37	0.27, 0.53	<0.001

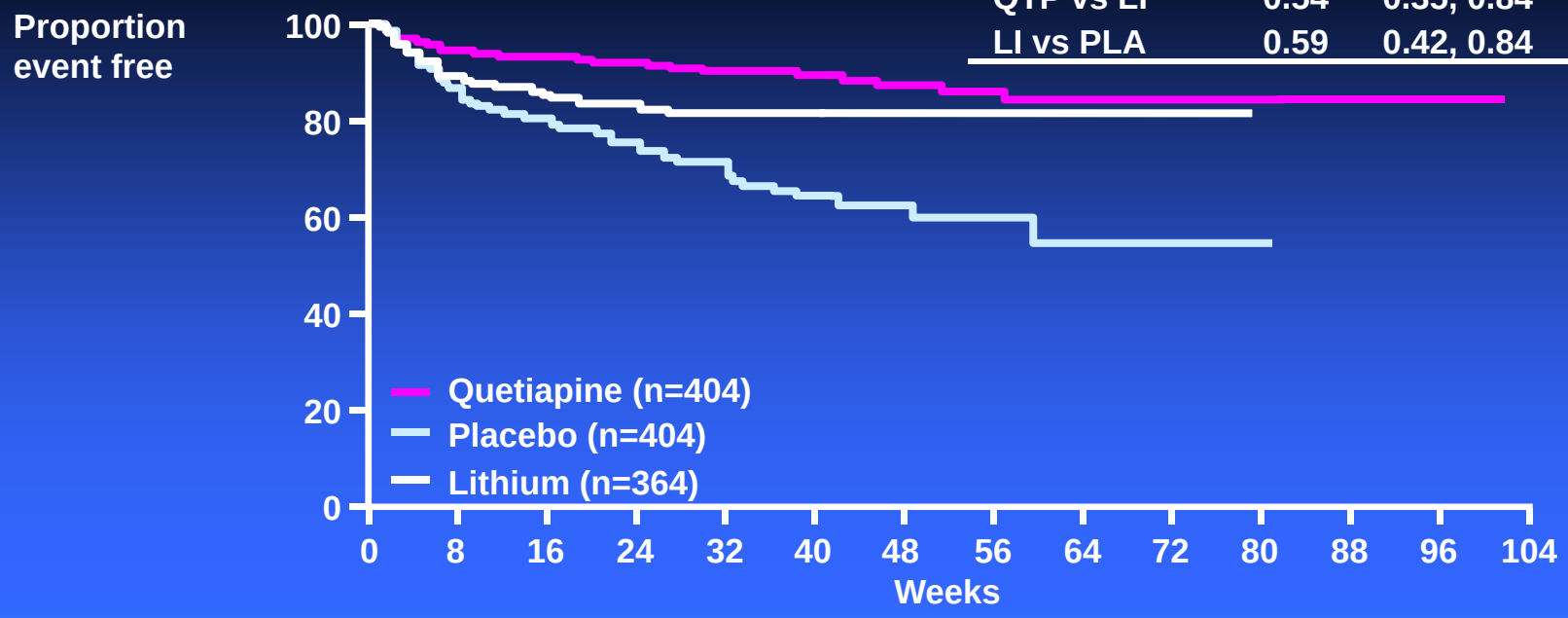


Study 144, ITT population

Nolen et al 2009

Recurrence of Depression
Quetiapine vs. Lithium or Placebo

	HR	95% CI	p-value
QTP vs PLA	0.30	0.20, 0.44	<0.001
QTP vs LI	0.54	0.35, 0.84	<0.01
LI vs PLA	0.59	0.42, 0.84	<0.01



Study 144, ITT population

Nolen et al 2009

Psychotherapy

Psychotherapy Interventions

Therapies may use some or all

- Adjust to Dx and Rx
- Enhance adherence
- Improve self-esteem
- Reduce risky behaviors
- Modify destabilizing biospychosocial factors
- Manage stressors
- Teach coping strategies
- Teach early recognition
- Modify attitudes/beliefs
- Homework

Scott J and Gutierrez MJ. Bipolar Disorders 2004; 6:498

Evidence Based Therapies

Impact relapse and rehospitalization rates

- Group psychoeducation
  - 25 % hospitalized vs 35 % in unstructured group [4]
- Cognitive behavioral therapy (CBT)
  - 1 year relapse 44 % vs 75 % usual care [3]
- Family focused therapy (FFT)
  - 2 year relapse 28 % vs 60 % supportive [2]
  - Perceived criticism may be an indicator [1]
- Interpersonal social rhythm therapy (IPSRT)
  - Trend to earlier recovery, no effect on relapse [4]

[1] Miklowitz DJ, et al. Psych Res 2005.

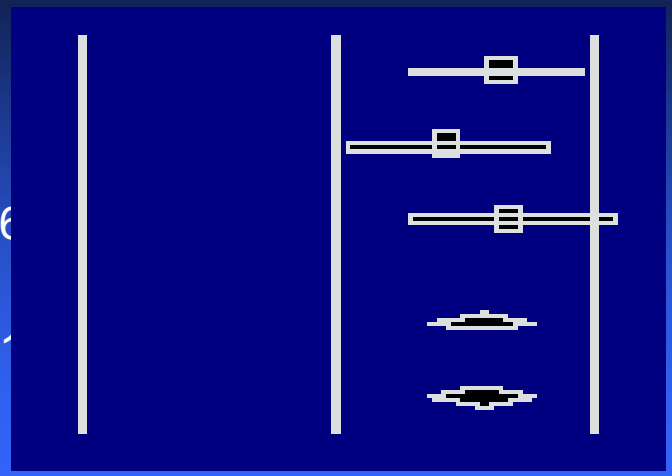
[2] Rea M, et al. J Consult Clin Psychol 2003; 3: 233.

[3] Lam DH, et al. Arch Gen Psych 2003; 60:145.

[4] Colom F, et al. Arch Gen Psych 2003; 60:402.

Psychotherapy Improves Relapse Rate

Effect size in large RCT's = .37



Study	N			
Effect	*p*			
Colom, et al, 2003	120		.41	.02
Lam, et al, 2003	96			.26
.00				
Miklowitz, et al, 2000	101			.46
.08				
Fixed (3)	317			.37
.00				
Random (3)	317			.37
.00				

Scott J and Gutierrez MJ. Bipolar Disorders 2004; 6:498

Interpersonal & Social Rhythm Therapy (IPSRT)

- Stabilize daily routines and sleep/wake cycles
- Gain insight into the bi-directional relationship between moods and interpersonal events
- Ameliorate interpersonal problems related to grief, role transitions, role disputes, interpersonal deficits

Frank E, et al. *Biological Psychiatry*. 2000;48:593-604.

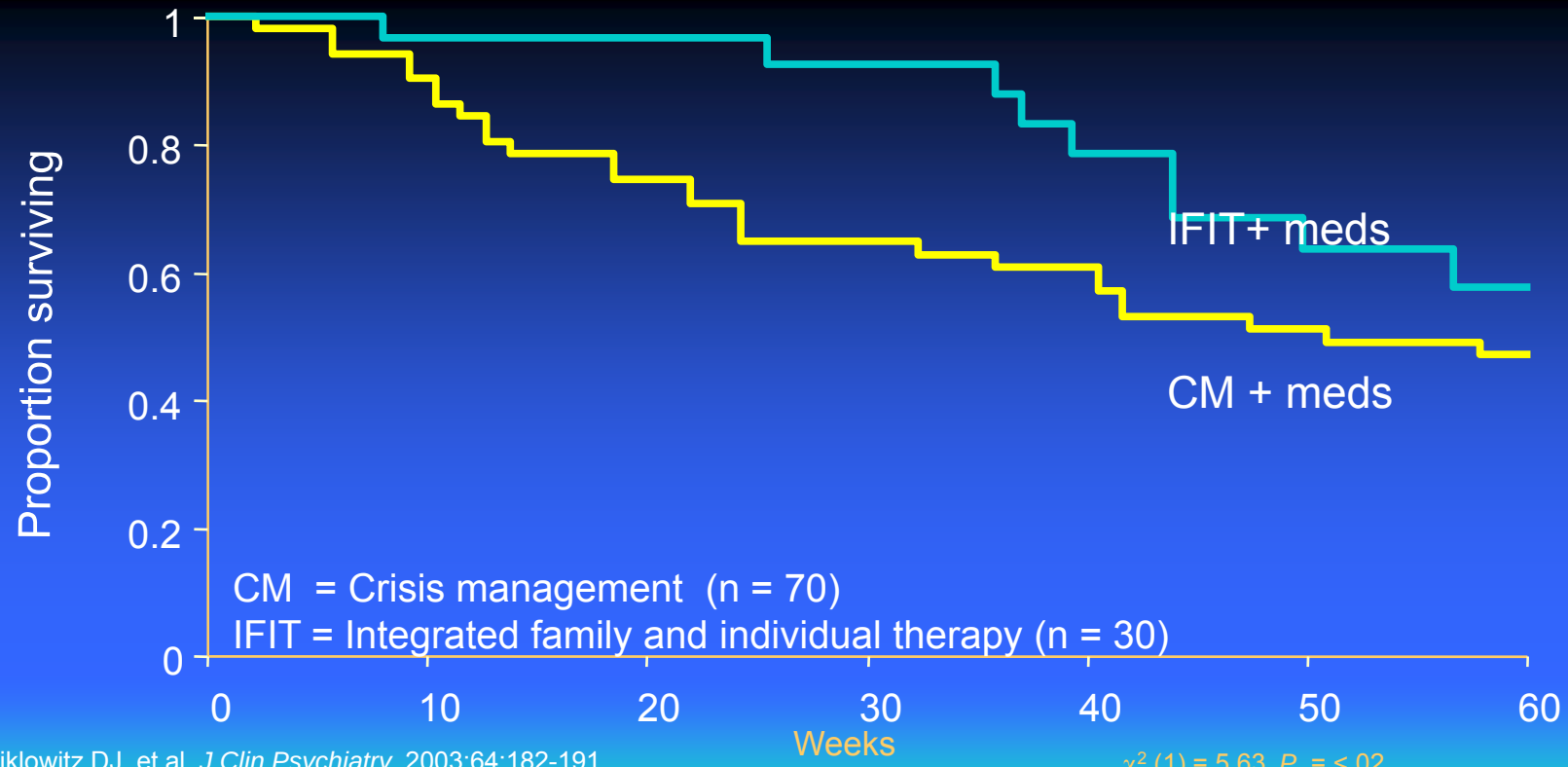
Interpersonal Social Rhythm Therapy

RCT, IPSRT vs ICM, n=175 BP1, 2 years

- Effect size of *.58*
  - after controlling marital status, index polarity, anxiety, medical burden
- Mediated by improved social rhythms
  - Not adherence
  - Better if married
- Best initiated in early maintenance
- ICM better if medically ill and anxious
  - Intensive Clinical Management

Frank E, et al. Arch Gen Psych 2005; 62:996

Integrated Family & Individual Therapy (IFIT) Increases Time in Remission



Miklowitz DJ, et al. *J Clin Psychiatry*. 2003;64:182-191.

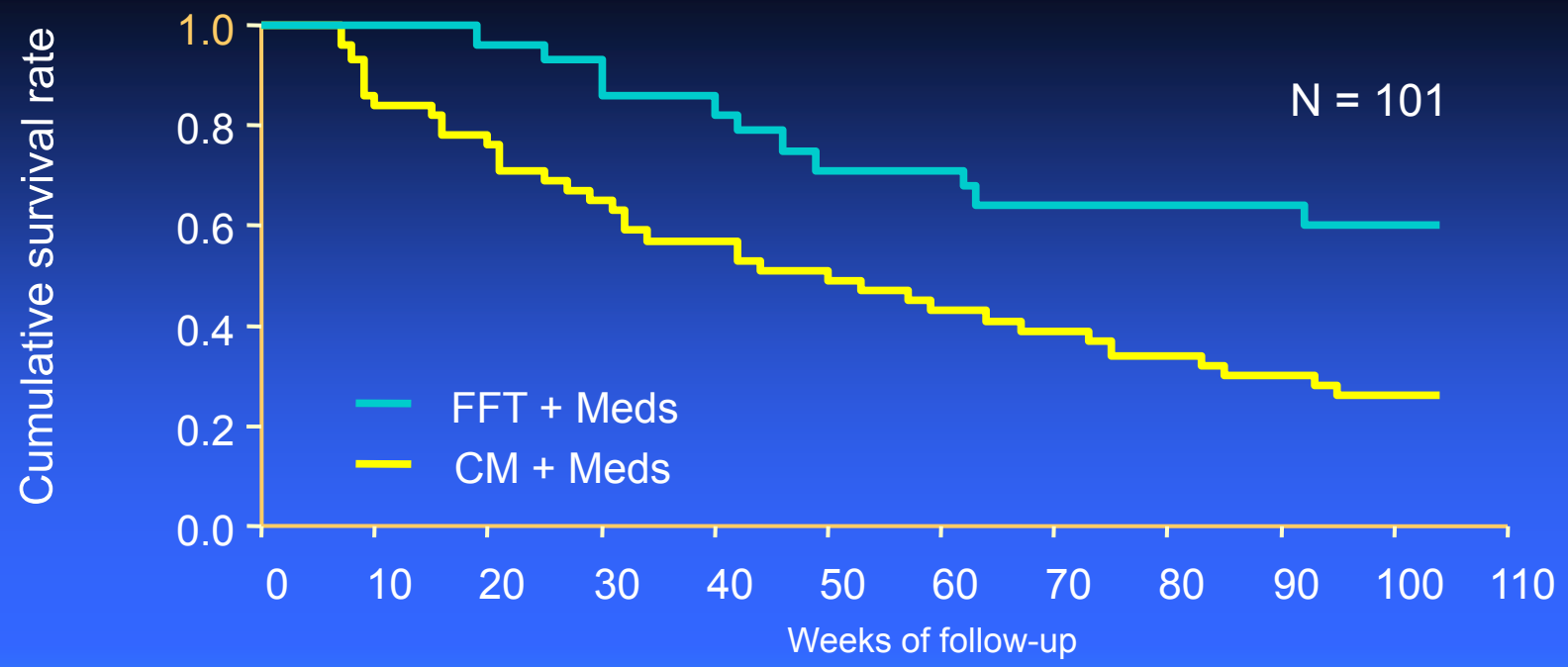
χ^2 (1) = 5.63, *P* = <.02.

Family-Focused Treatment (FFT) of Bipolar Disorder

- 21 outpatient sessions over 9 months
- Assessment of patient and family
- Psychoeducation about bipolar disorder
  - *symptoms, early recognition, etiology, treatment, self-management*
- Communication enhancement training
  - *rehearsal of effective speaking and listening strategies*
- Problem-solving skills training

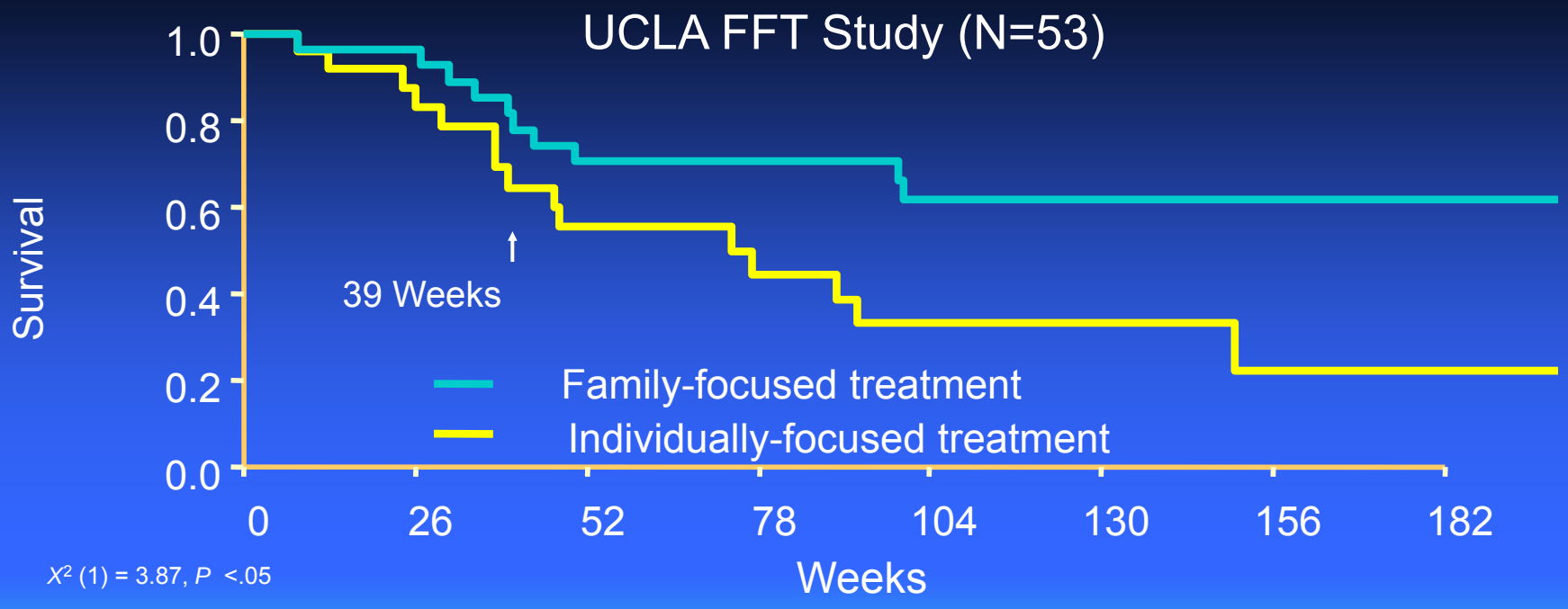
Miklowitz DJ & Goldstein MJ. *Bipolar Disorder: A Family-Focused Treatment Approach*. NY: Guilford Press, 1997.

FFT + Meds Delays Relapse More Than Crisis Management + Meds



CM vs. FFT χ^2 (1) = 8.71, p = .003; FFT, mean survival = 73.5 weeks; CM, 53.2 weeks.
Miklowitz DJ, et al. *Arch Gen Psychiatry*. 2003

FFT Delays Rehospitalization vs Individual



X^2 (1) = 3.87, P <.05

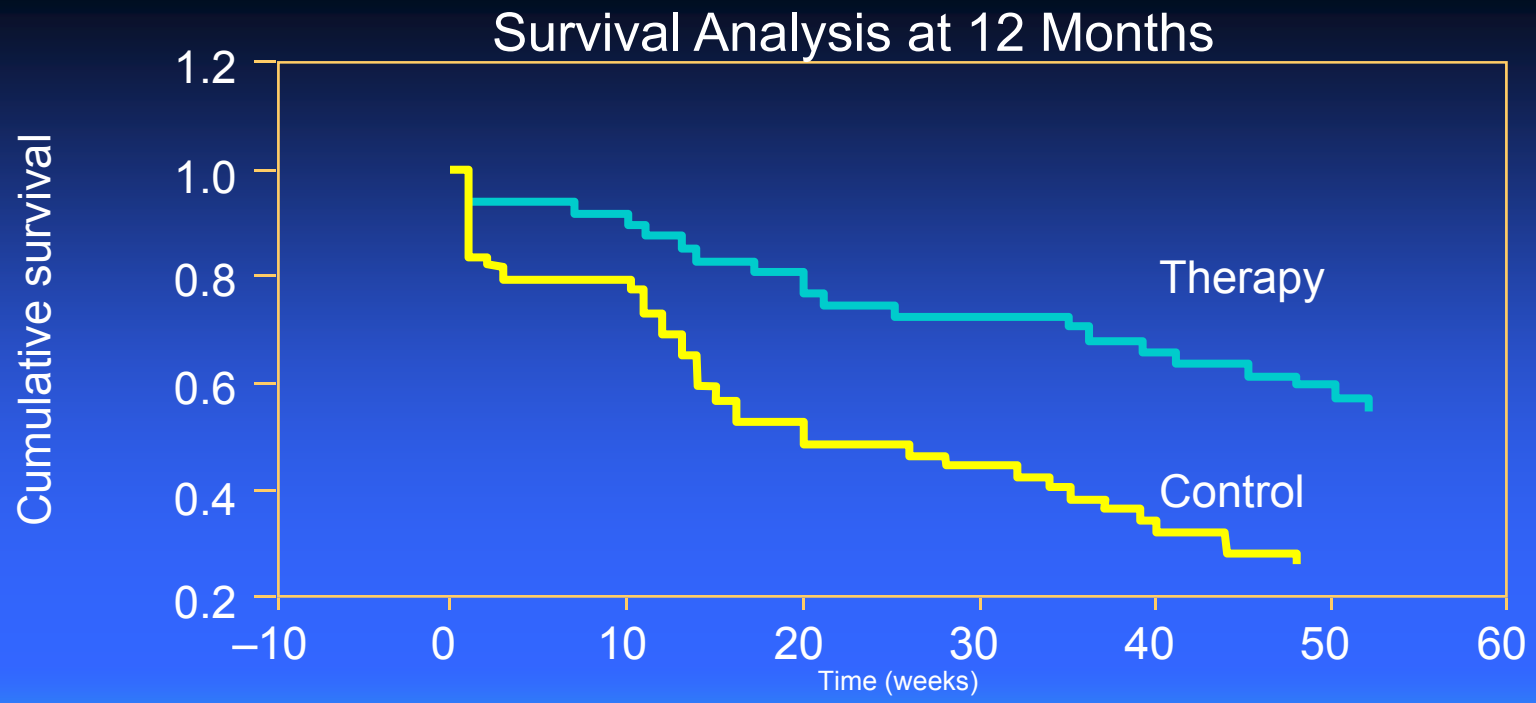
Rea, Tompson, Miklowitz et al. *J Consult Clin Psychol*. 2003.

CBT for Bipolar

- Psychoeducation: a diathesis-stress model
- Cognitive behavioral skills: to monitor mood and prodromes; to modify behavior
- Importance of routine and sleep
- Dealing with long-term vulnerability issues: e.g., dysfunctional high goal-attainment beliefs

Lam DH, et al. *Arch Gen Psychiatry*. 2003;60:145-152.

Cognitive Therapy + Meds vs. Meds Only



Hazard ratio for relapse = 0.40, *P* = .004, controlling for med. compliance.
Lam DH, et al. *Arch Gen Psychiatry*. 2003 ;60:145-152.