

Treatment of Bipolar Disorder

An UPDATE

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Summary of DSM-IV-TR

Classification of Bipolar Disorders

Bipolar I	Bipolar II	Cyclothymic	Bipolar Disorder Not Otherwise Specified
<p>One or more manic or mixed episodes, usually accompanied by major depressive episodes</p> <p>MALE=FEMALE</p>	<p>One or more major depressive episodes accompanied by at least one hypomanic episode</p> <p>FEMALE>MALE</p>	<p>At least 2 years of numerous periods of hypomanic and depressive symptoms*</p>	<p>Bipolar features that do not meet criteria for any specific bipolar disorders</p>

* Symptoms do not meet criteria for manic and depressive episodes.

Bipolar Disorder

- Common illness affecting 2% of the world population (5% if one includes spectrum disorders)
- 6th leading cause of medical disability in the developed nations
- Prominent cognitive abnormalities

¹Cookson J. *Br J Psychiatry*. 2001;178(suppl. 41): s148–s156.

²Strakowski SM, et al. *Expert Opin. Pharmacother*. 2003;4:751-760.

Economic Impact and Disability from Bipolar Disorder

- Consistently among 10 leading causes of medical disability in the world
- Total Annual Cost (in the USA): \$ 80 Billion
 - Lost Productivity: \$ 50 Billion
 - Direct treatment costs: \$ 10 Billion

Bipolar Disorder

- Particularly recalcitrant mental health problem
- Symptomatic at least half the time
- Can have impaired social function even when symptom-free

¹Cookson J. *Br J Psychiatry*. 2001;178(suppl. 41): s148–s156.

²Strakowski SM, et al. *Expert Opin. Pharmacother*. 2003;4:751-760.

Bipolar Disorder- Neurobiology

- Highly heritable (80% genetic contribution)
 - Multiple genes
 - 16 different chromosomal regions
- Structural and Functional Brain Abnormalities
 - amygdala, anterior cingulate and prefrontal cortex, putamen, thalamus/hypothalamus

¹Riedel W J. *Psychol Med.* 2004; 34: 3-8.

²Strakowski SM, et al. *Expert Opin. Pharmacother.* 2003;4:751-760.

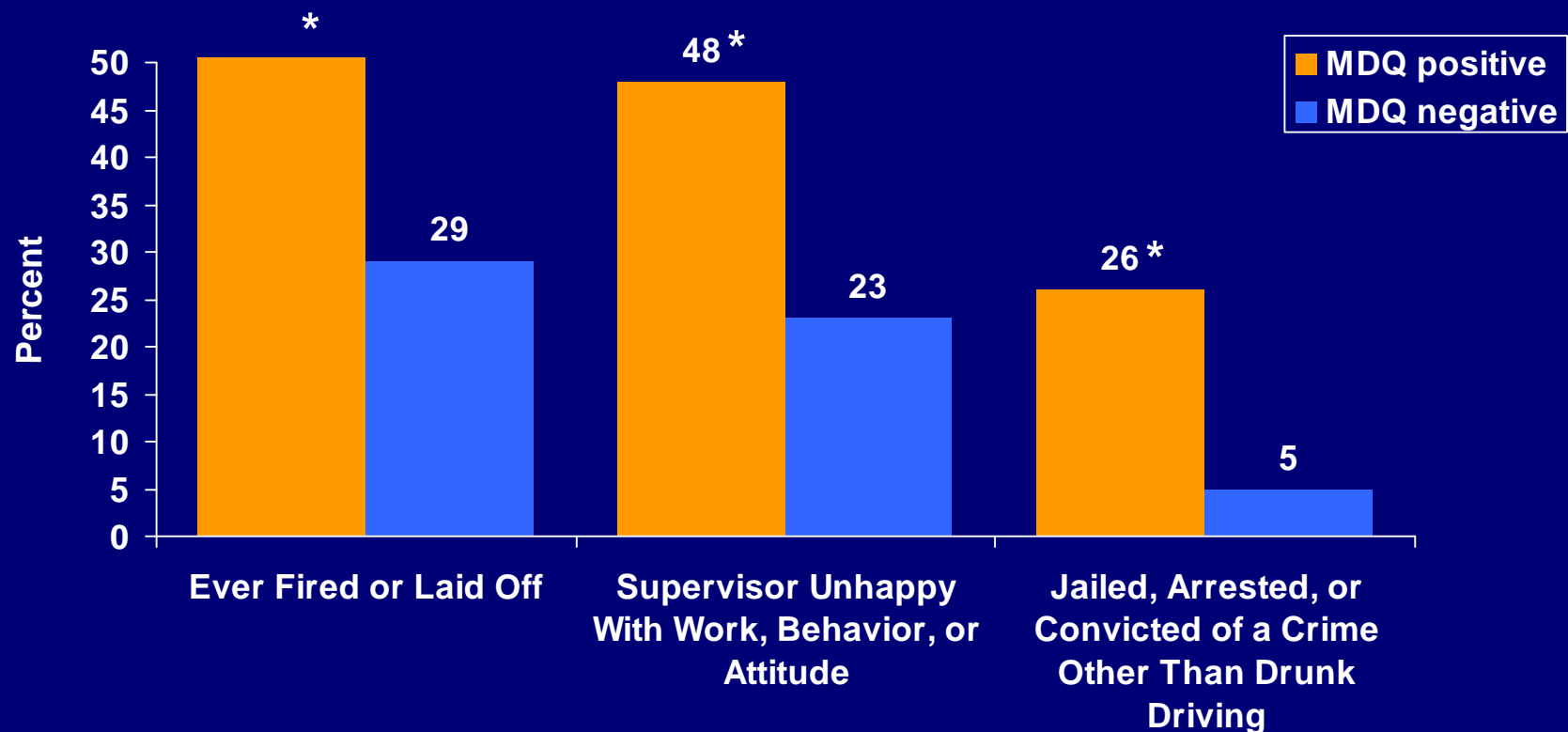
Bipolar Depression

- 50% of first bipolar episodes are depressive episodes
- Depressive episodes in bipolar disorder are associated with considerable morbidity and mortality
- Bipolar depressive episodes have a chronic course

Bipolar Depression

- 80% of patients exhibit significant suicidality
- 60% of patients with dysphoric mania exhibit suicidality
- Depressive episodes dominate course of bipolar disorder (twice the amount of time as in mania)
- 25-30% of patients initially diagnosed with unipolar depression subsequently have a manic or hypomanic episode

Impact of Bipolar Disorder Vs. Unipolar Disorder — Heavy Impact on Daily Life



* $P < 0.0001$

Bipolar Disorder

- > 50% alcohol and/or other substance abuse
- About 50% attempt suicide
 - About 15% succeed

¹Cookson J. *Br J Psychiatry*. 2001;178(suppl. 41): s148–s156.

²Strakowski SM, et al. *Expert Opin. Pharmacother*. 2003;4:751-760.

Predictors of Suicide in Bipolar Disorder

- High Impulsivity
- Alcohol and Substance Abuse
- DEPRESSION and MIXED Episodes
- History of Abuse in Childhood
- Exacerbated by incorrect treatment

Antidepressants, Adolescents, and Suicide

The Bipolar Confound

- Antidepressants can induce mixed states, rapid cycling, and mania in bipolar disorder
- Mania thus induced more likely to be dysphoric rather than euphoric
- Characterized by high impulsivity & irritability
- DOES THAT EXPLAIN THE INITIAL INCREASED RISK OF SUICIDALITY

Treatment Challenges in Bipolar Disorder

- Often unrecognized
- Often untreated
- Often misdiagnosed
- Often inadequately treated
- Exacerbated by incorrect treatment

The Evolution of Therapies for Bipolar Disorder

1940	1950	1960	1970	1980	1990	2000	2002
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ECT

Lithium*

**First-generation antipsychotics
and antidepressants**

Chlorpromazine*
Trifluoperazine
Fluphenazine
Thioridazine
Haloperidol
Mesoridazine

**Second-generation antipsychotics
and antidepressants**

Clozapine
Risperidone+
Olanzapine*
Quetiapine+
Ziprasidone+
Aripiprazole+

Anticonvulsants

Carbamazepine
Valproate*

Anticonvulsants

Gabapentin
Lamotrigine
Topiramate
Oxcarbazepine

* Approved for use for acute mania
ECT = electroconvulsive therapy

Bipolar Disorder: Summary of Efficacy Evidence from RCTs

Drug	Acute Mania		Acute Depression Maintenance	
	Mono	Combo	Depression	Maintenance
Lithium	++	++	±	++
Divalproex	++	++	±	+
Carbamazepine	++	ND	ND	+
Lamotrigine	-	ND	+	++
Olanzapine	++	+	+	++
Risperidone	++	+	+/-	ND
Quetiapine	++	++	+	ND
Ziprasidone	++	ND	+/-	ND
Aripiprazole	++	ND	ND	+

Lithium

- Uses
 - acute and prophylactic treatment of mania / hypomania
 - acute and prophylactic treatment of bipolar depression
- Adverse events
 - cognitive
 - tremor
 - gastrointestinal
 - weight gain
- Fetal abnormalities

Valproate / Divalproex

- Uses
 - acute mania and maintenance treatment of bipolar disorder
 - ? bipolar depression
- Advantages
 - better tolerability than lithium
 - can be loaded rapidly
 - once-a-day formulation available
- Disadvantages
 - drug-drug interactions
 - fetal abnormalities

Carbamazepine

- Uses
 - acute and prophylactic treatment of mania
- Disadvantage
 - drug-drug interactions
 - lab monitoring
 - adverse events

Oxcarbazepine

- Uses
 - acute treatment of mania
- Probable equivalent efficacy to carbamazepine
- Dosing
 - 1 mg carbamazepine = 1.5 mg oxcarbazepine
 - Less Data
 - Not FDA-approved for mania

Other ANTICONVULSANTS

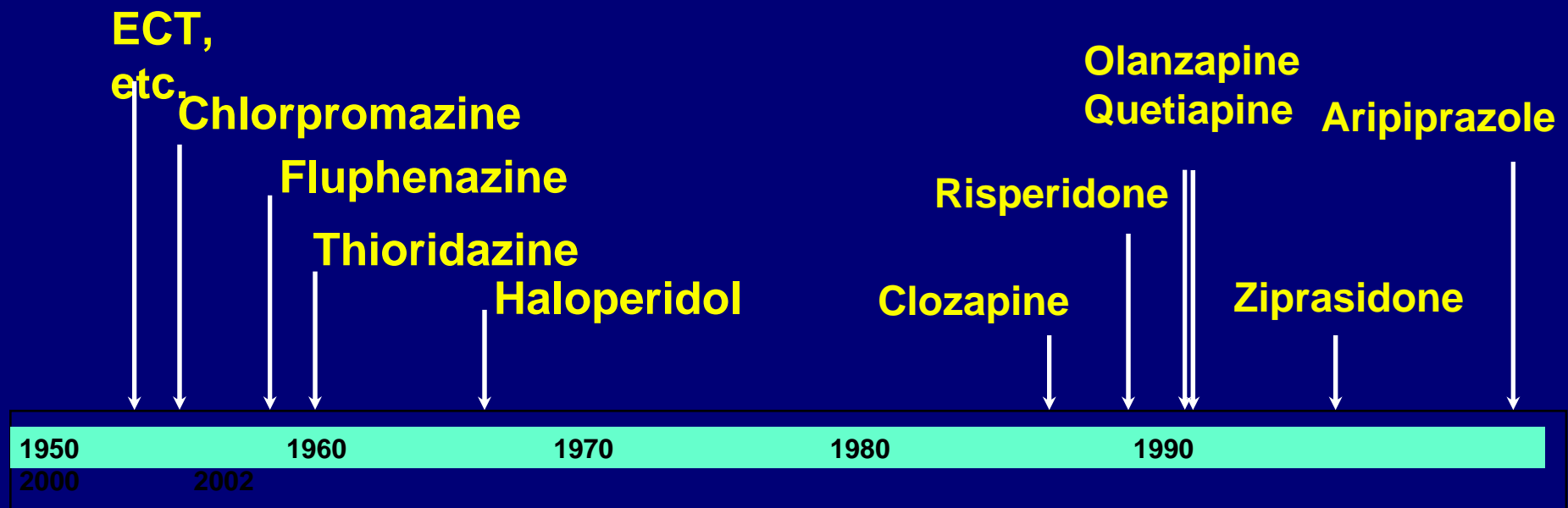
- Gabapentin
- Pregabalin
- Levetiracetam
- Tiagabine
- Topiramate

NO PROVEN EFFICACY

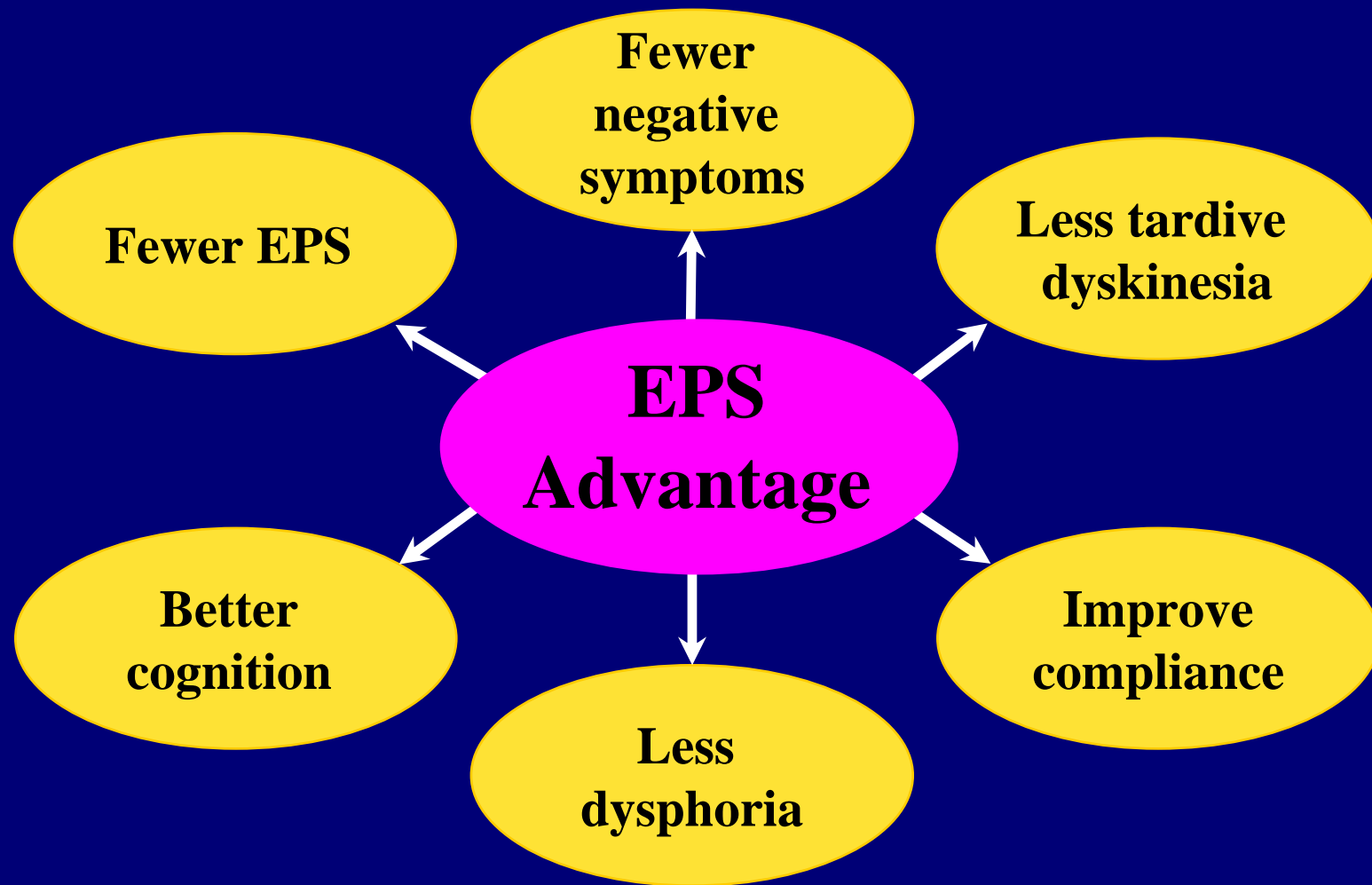
Antipsychotics

Current Antipsychotic Therapies

14 First-Generation Typicals vs. 6 Second-Generation Atypicals



Essence of Atypicality



Summary

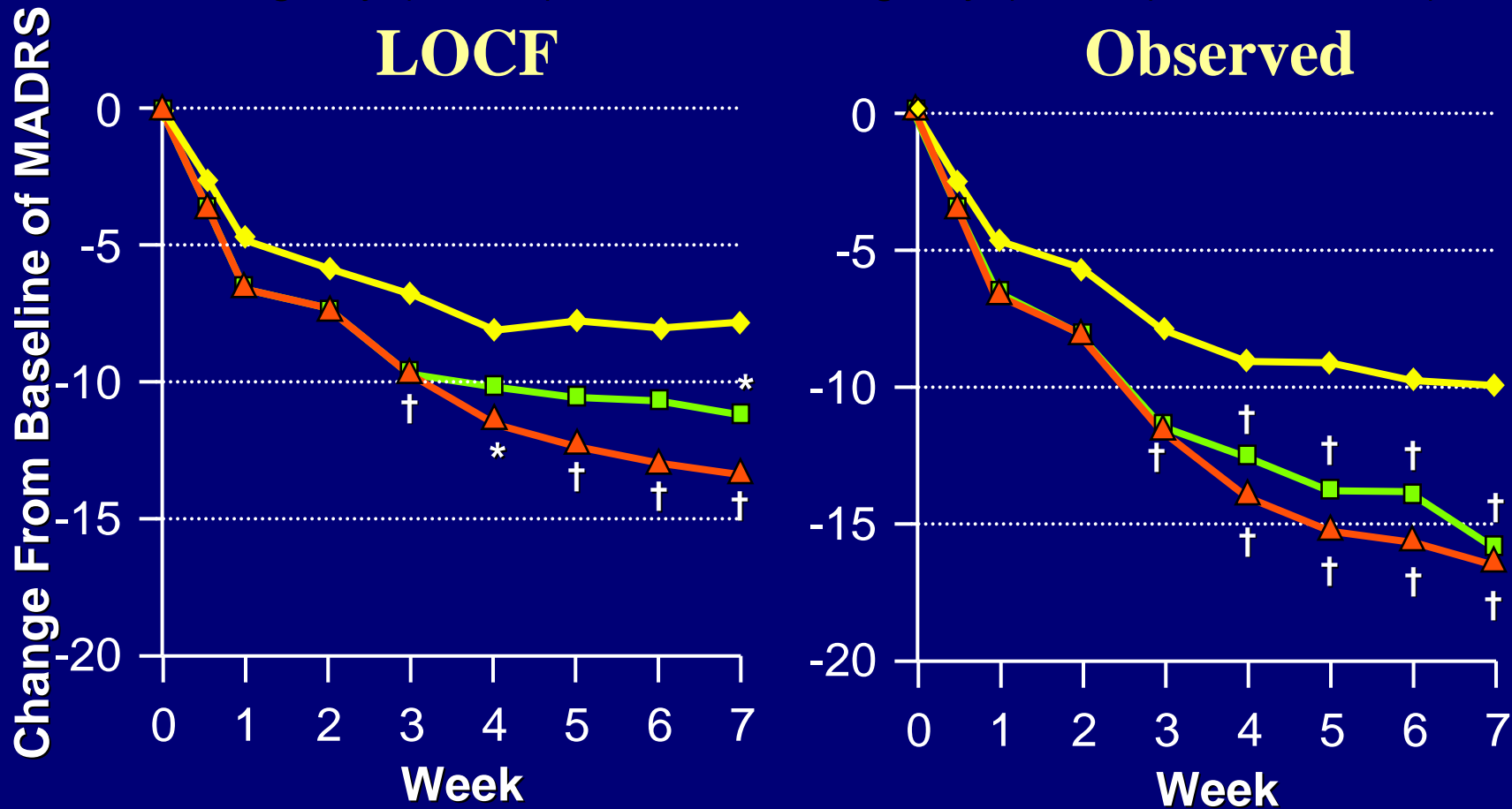
Atypical Antipsychotics

- Convincing evidence for efficacy in acute treatment of mania, especially for olanzapine, risperidone, aripiprazole, ziprasidone, and quetiapine. Onset of action within 2-4 days
- Strong evidence for maintenance efficacy (both mania and depression) for olanzapine

Bipolar Depression

Lamotrigine in Acute Treatment of Bipolar Depression

■ LTG 50 mg/day (n = 64) ▲ LTG 200 mg/day (n = 63) ◆ Placebo (n = 65)



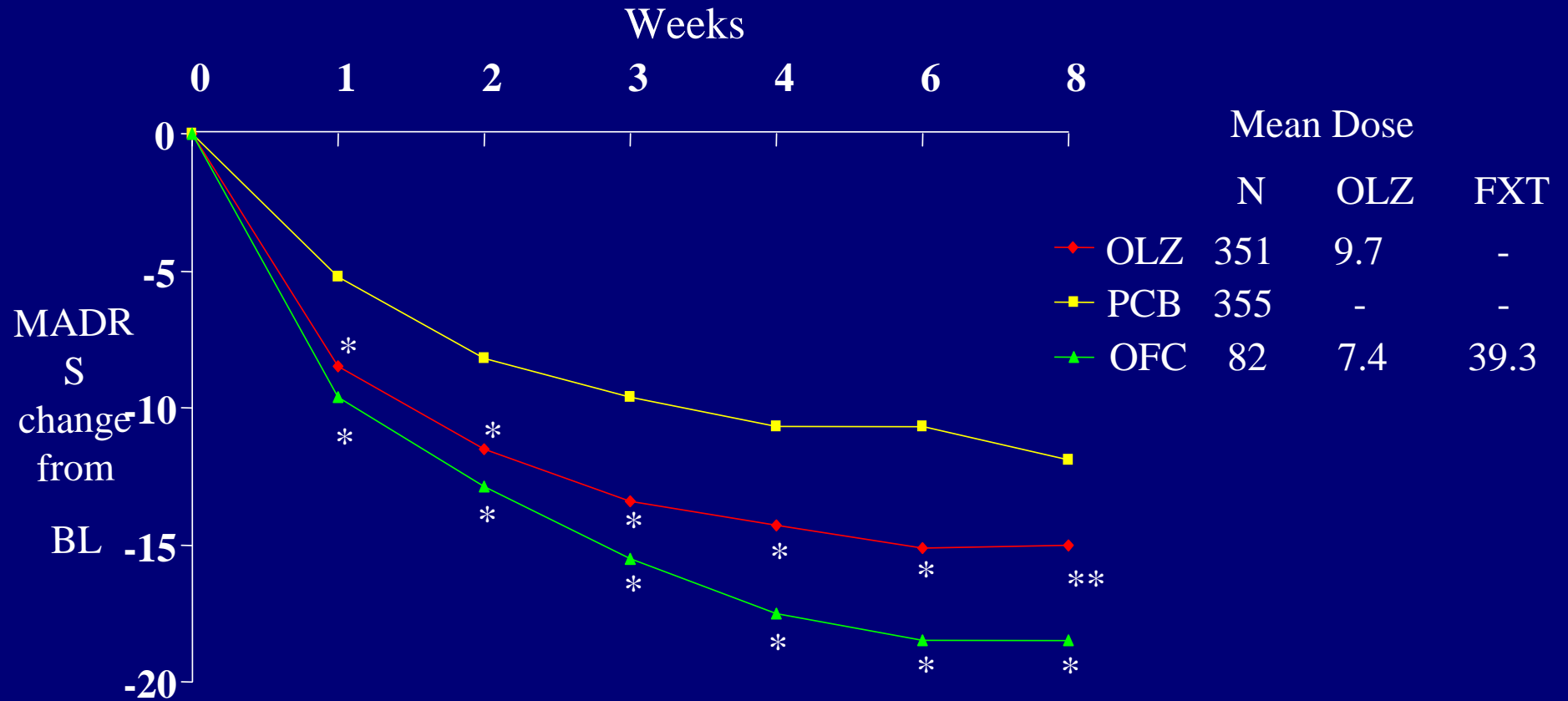
* $P < 0.1$; † $P < 0.05$. LOCF = last-observation-carried-forward.

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

Olanzapine for Bipolar I Depression

- Double blind, random assignment, 8 week inpatient study
- 6 months open extension
- Treatment groups
 - Olanzapine monotherapy (N = 351)
 - Olanzapine + Fluoxetine (N = 82)
 - Placebo (N = 355)

Improvement over 8 weeks



* P < 0.001; ** P < 0.01

Paroxetine for Bipolar Depression

- Most well studied: three double blind studies
- All add-on
- All double blind against placebo, imipramine, venlafaxine, and combined lithium and divalproex

Young et al., *Am J Psychiatry* 2002; Nemeroff et al., *Am J Psychiatry* 2001; Vieta et al., *J Clin Psychiatry* 2002

Paroxetine for Bipolar Depression

Conclusions

- Lithium alone as good as lithium combined with antidepressant either (PXT or IMI), except
 - At low lithium levels (< 0.8), antidepressants better than lithium alone
- Combination mood stabilizers equal to combined mood stabilizer and paroxetine (but mood stabilizer combination has more side effects)
- Venlafaxine and paroxetine equally effective
- Paroxetine has very low switch rates

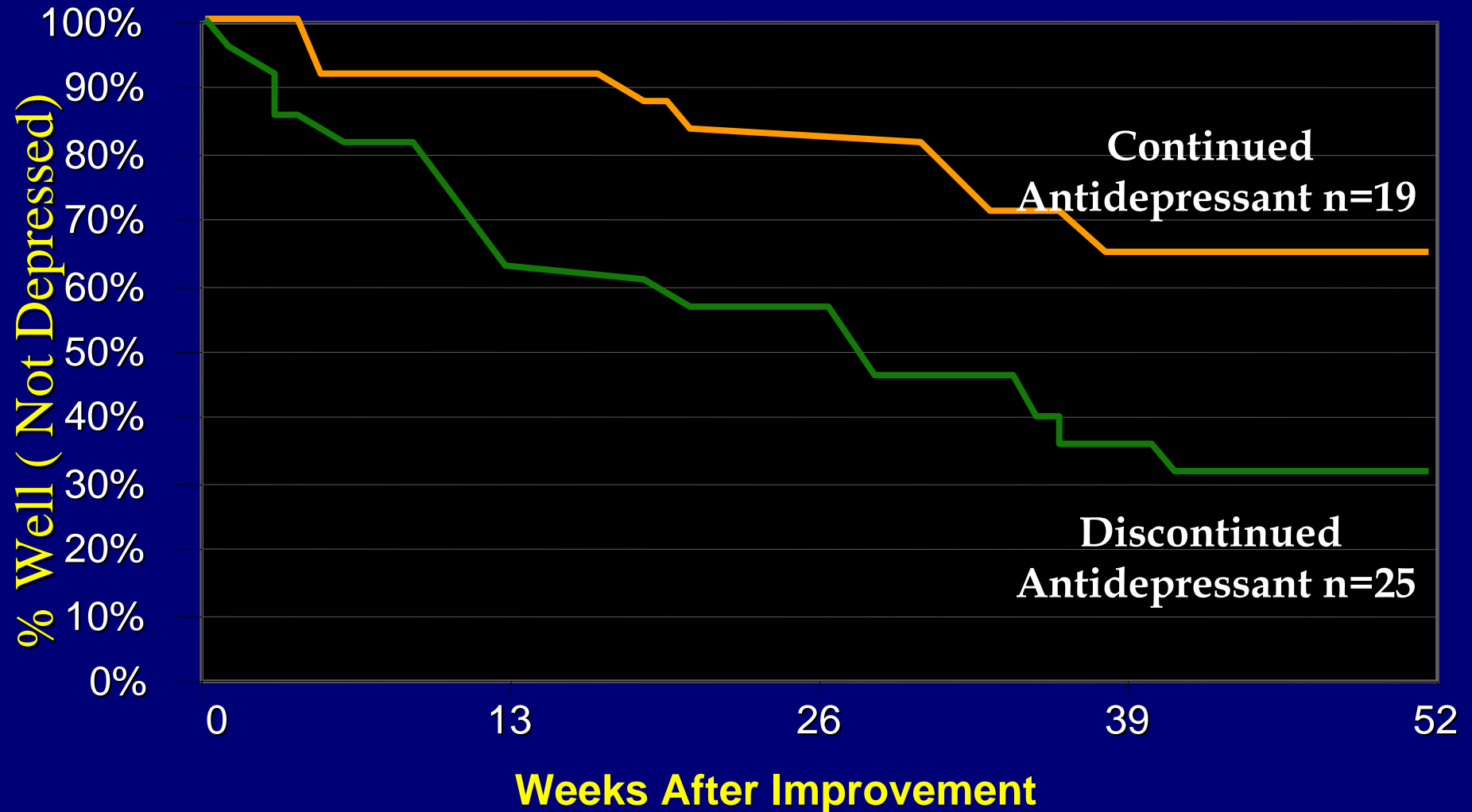
Young et al., *Am J Psychiatry* 2002; Nemeroff et al., *Am J Psychiatry* 2001; Vieta et al., *J Clin Psychiatry* 2002

Switch Rates on Antidepressants

- All while on mood stabilizers
- High rates of switch (over 10% short term)
 - TCA's, venlafaxine, MAOI's
- Low rates of switch (under 10% short term)
 - Bupropion, SSRIs
- Much higher if not on a mood stabilizer

ON THE OTHER HAND

Depression Following Antidepressant Discontinuation in Bipolar Patients (Chart Review)



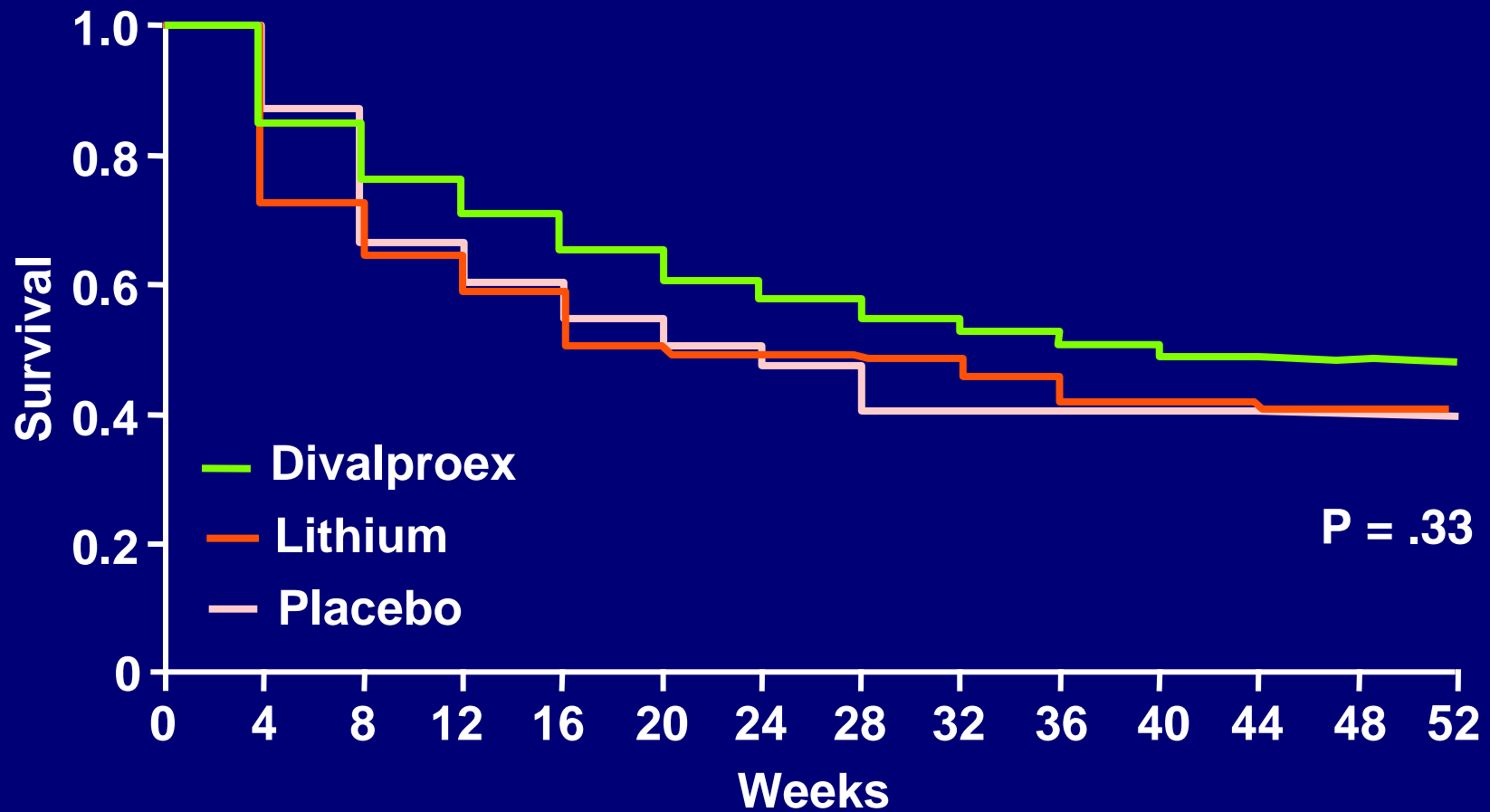
Altshuler et al., J Clin Psychiatry, 2001; 62:612-616.

Maintenance

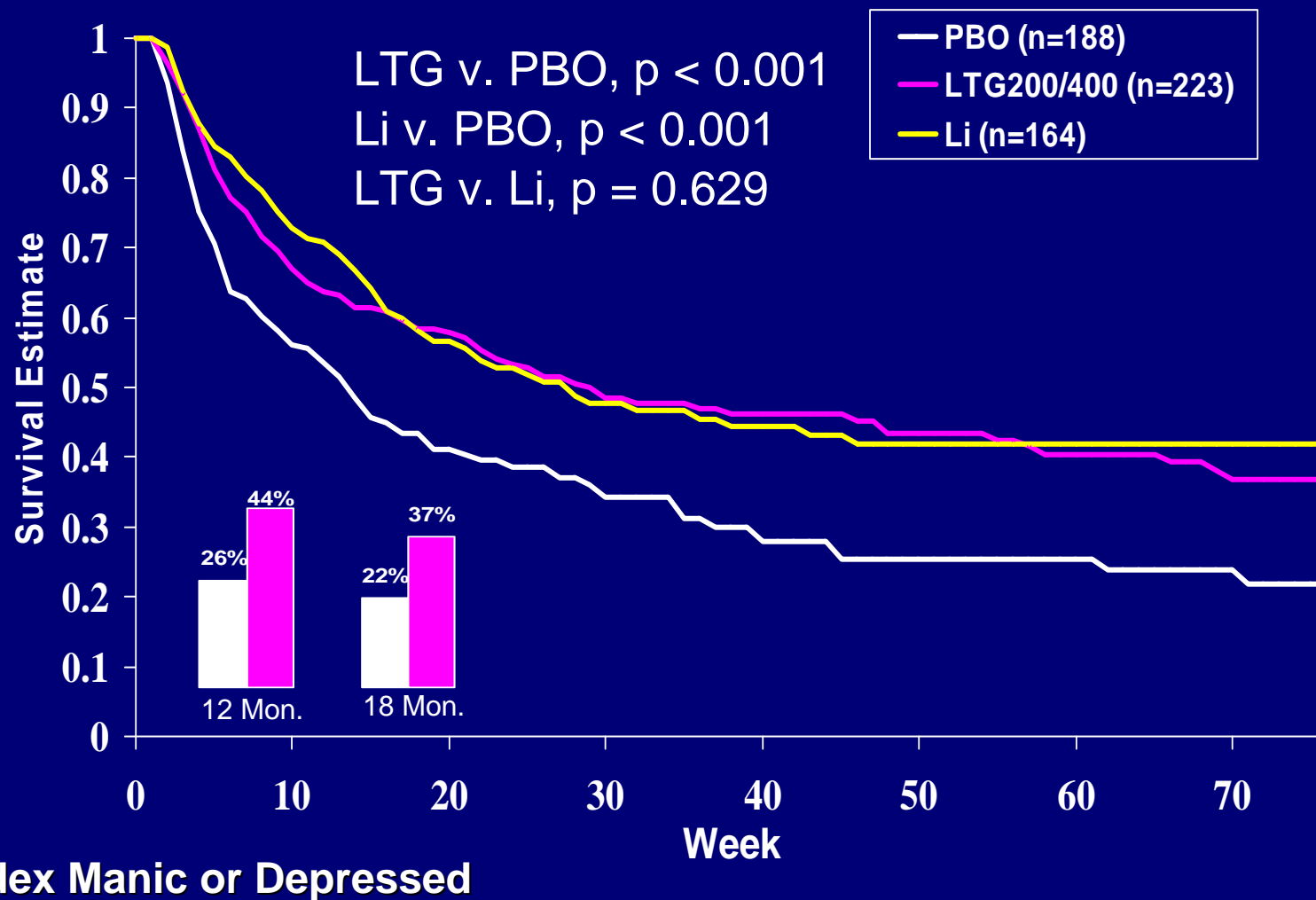


Maintenance Treatment with Divalproex

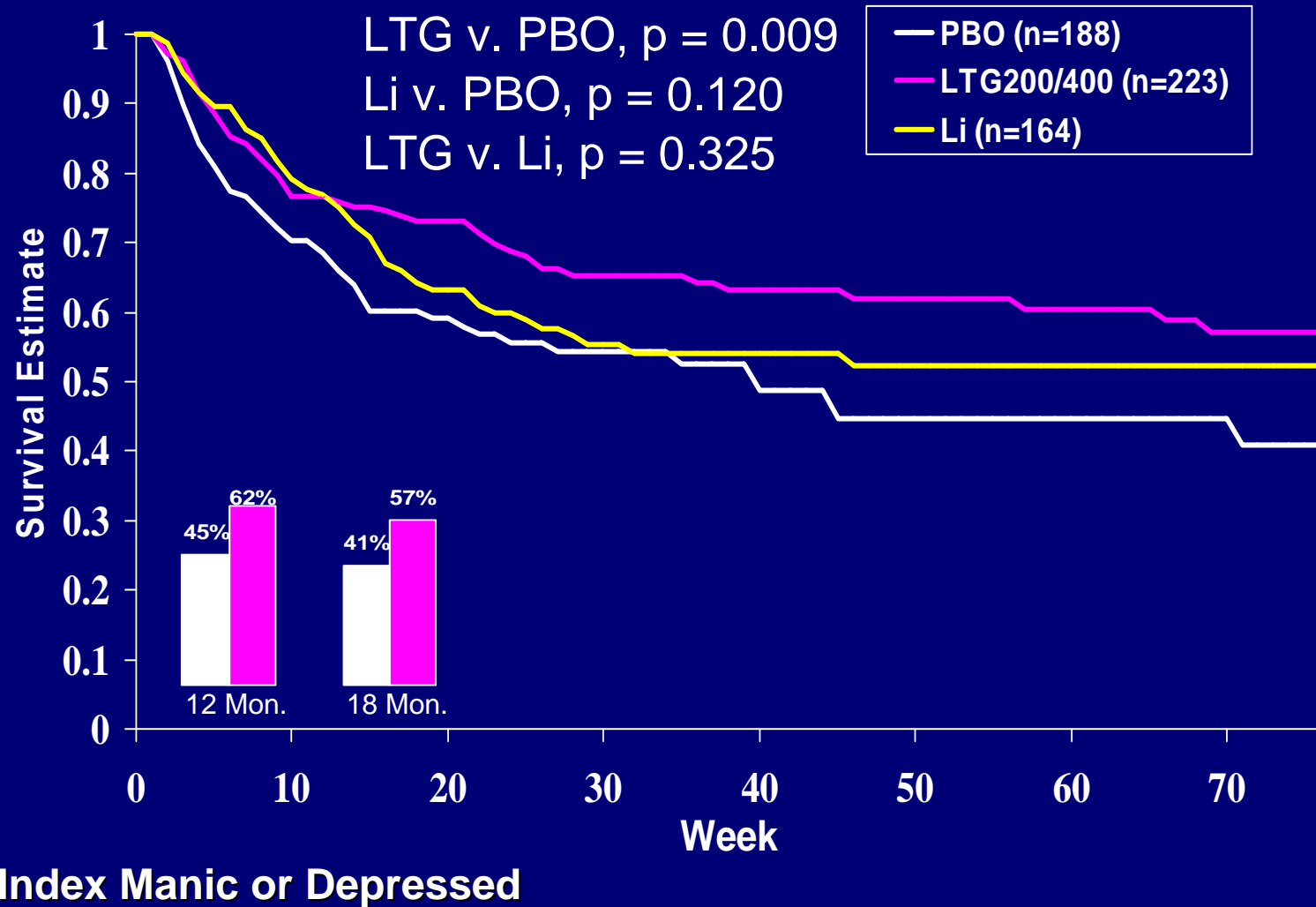
Time to Any Affective Episode



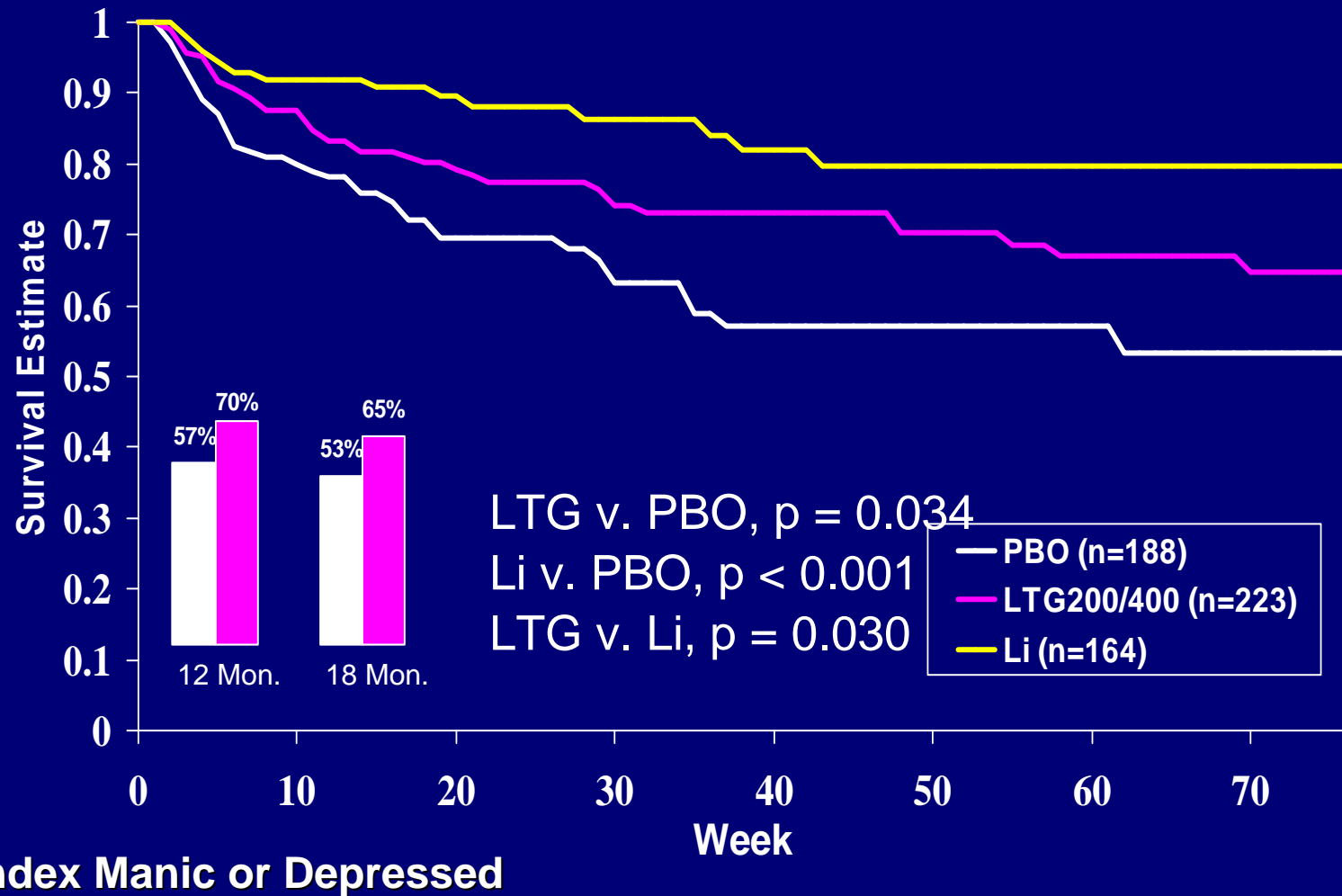
Time to Intervention for a Mood Episode Lamotrigine vs Lithium vs Placebo



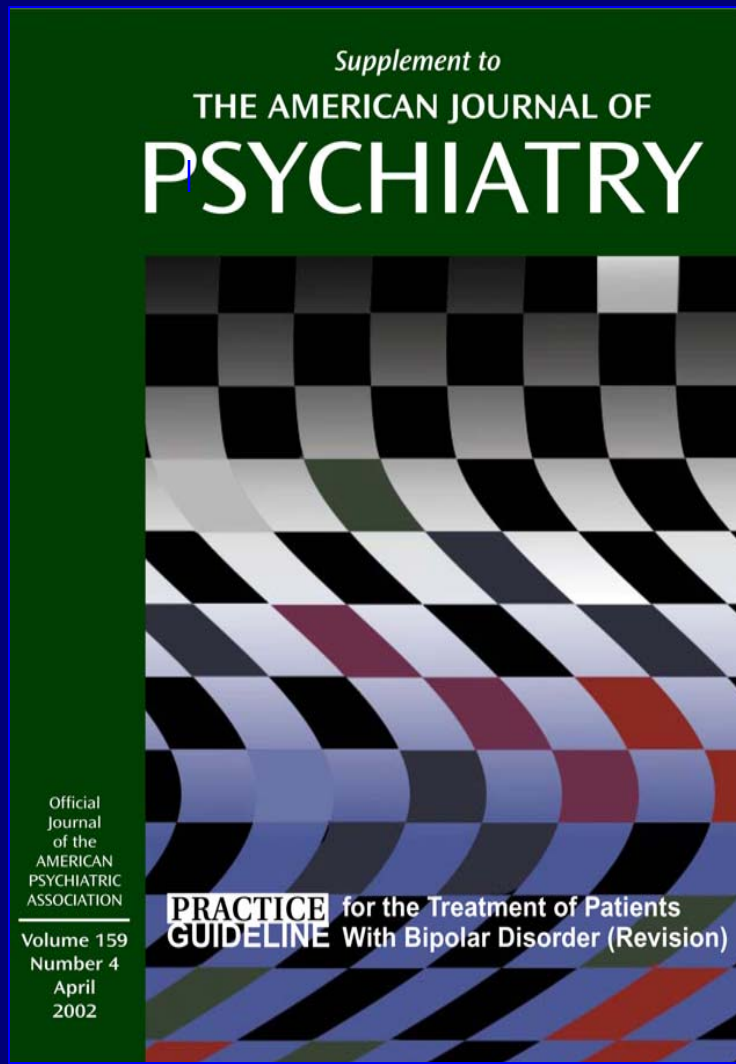
Time to Intervention for Depression



Time to Intervention for Mania



APA Guidelines for Bipolar Disorder



- Revised APA guidelines released April 2002, updated 2004
- Changes in the pharmacotherapy of manic and mixed episodes
- Refocus of the approach to depression
- New approaches to maintenance therapy and to rapid cycling
- New section on children and adolescents

Approach to the Patient With Mania

- Initiate either lithium or divalproex plus a second-generation antipsychotic
- For less ill patients, monotherapy with lithium, divalproex, or antipsychotic may be sufficient
- For mixed episodes, divalproex or antipsychotic is preferred over lithium
- Atypical antipsychotics are preferred over typicals
- Carbamazepine or oxcarbazepine are alternatives to lithium or divalproex

APA Practice Guidelines

Approach to the Patient With Mania

- For breakthrough episodes, first optimize the maintenance medication dose
- Consider adding an antipsychotic
- If this does not work, consider adding lithium, divalproex, carbamazepine, or oxcarbazepine
- Clozapine or ECT should be considered for treatment-refractory patients

APA Practice Guidelines

Approach to the Patient With Bipolar Depression

Is the patient already in treatment with a mood stabilizer?

- Yes
 - Then optimize the dose of the mood stabilizer
 - Then add antidepressant
- No
 - Then ...

APA Practice Guidelines

Approach to the Patient with Bipolar Depression Then...

- For less severely ill patients
 - initiate lithium or lamotrigine
- For more severely ill patients
 - initiate lithium and an antidepressant
- For those with psychosis or at high suicide risk
 - add antipsychotic
 - ECT

APA Practice Guidelines

Emerging Trends

Pharmacotherapy of Acute Mania

- Combination treatment the rule, not the exception
- Continued use of Lithium and Divalproex as cornerstones of treatment
- Increasing use of atypical antipsychotics for acute treatment and ?for maintenance

BIPOLAR DISORDER

The Major Challenge: Misdiagnosis

NDMDA survey of its bipolar members

Rate of misdiagnosis	
1994	73%
2000	69%

- Most frequent misdiagnosis: **Unipolar depression**
- Treatment as unipolar depression can lead to **worsening of symptoms by switching into mania or cycle acceleration**

Steps to Increase Recognition of Bipolar Disorder and to Improve Diagnosis

- Education of physicians about the illness, particularly how it presents itself in clinics
- Ask patients directly about history of symptoms of Bipolar Disorder
- Involve family members in clinical evaluations
- Increase patients' and families' awareness of the illness
- Screen for Bipolar Disorder, especially in depressed patients

Screening for Bipolar Disorder Mood Disorder Questionnaire

THE MOOD DISORDER QUESTIONNAIRE

Instructions: Please answer each question as best you can.

	YES	NO
1 Has there ever been a period of time when you were not your usual self and...		
... you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	<input type="radio"/>	<input type="radio"/>
... you were so irritable that you shouted at people or started fights or arguments?	<input type="radio"/>	<input type="radio"/>
... you felt much more self-confident than usual?	<input type="radio"/>	<input type="radio"/>
... you got much less sleep than usual and found you didn't really miss it?	<input type="radio"/>	<input type="radio"/>
... you were much more talkative or spoke much faster than usual?	<input type="radio"/>	<input type="radio"/>
... thoughts raced through your head or you couldn't slow your mind down?	<input type="radio"/>	<input type="radio"/>
... you were so easily distracted by things around you that you had trouble concentrating or staying on track?	<input type="radio"/>	<input type="radio"/>
... you had much more energy than usual?	<input type="radio"/>	<input type="radio"/>
... you were much more active or did many more things than usual?	<input type="radio"/>	<input type="radio"/>
... you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	<input type="radio"/>	<input type="radio"/>
... you were much more interested in sex than usual?	<input type="radio"/>	<input type="radio"/>
... you did things that were unusual for you or that other people might have thought were excessive, foolish or risky?	<input type="radio"/>	<input type="radio"/>
... spending money got you or your family into trouble?	<input type="radio"/>	<input type="radio"/>
2 If you checked YES to more than one of the above, have several of these ever happened during the same period of time?	<input type="radio"/>	<input type="radio"/>
3 How much of a problem did any of these cause you - like being unable to work; having family, money or legal troubles; getting into arguments or fights? Please circle one response only.		
No problem Minor problem Moderate problem Serious problem		
4 Have any of your blood relatives (i.e. children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?	<input type="radio"/>	<input type="radio"/>
5 Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?	<input type="radio"/>	<input type="radio"/>

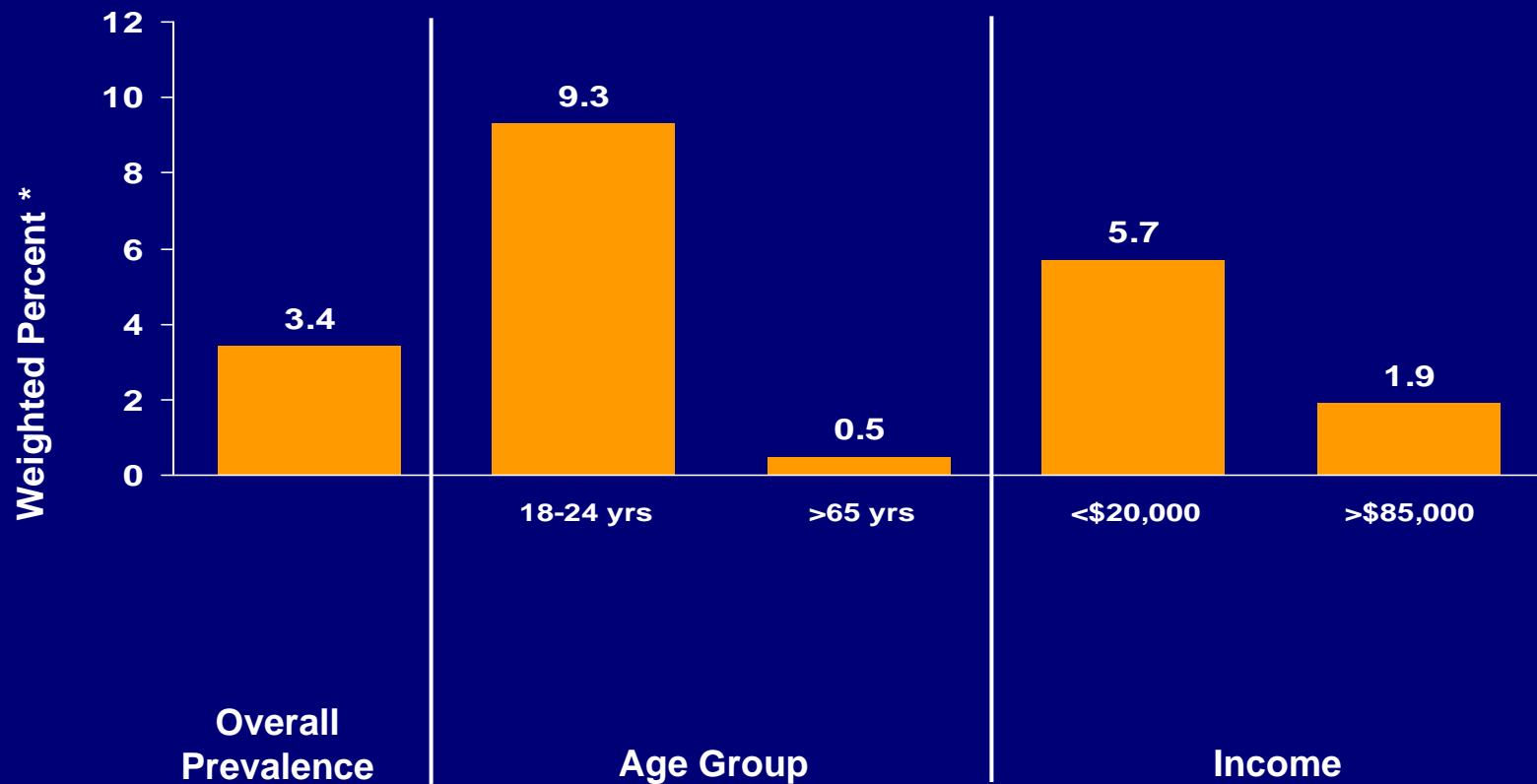
THANK YOU FOR COMPLETING THIS QUESTIONNAIRE. PLEASE RETURN THIS FORM TO YOUR DOCTOR.

© 2000 by The University of Texas Medical Branch. All rights reserved. This instrument is designed for screening purposes only and is not to be used as a diagnostic tool.

- A brief, simple, self-report questionnaire for bipolar disorder--13 yes-no items regarding bipolar disorder
- Well validated in psychiatric clinical and general population samples
- Translated into several languages

Hirschfeld RMA, et al. Am J Psychiatry. 2000; 157:1873-1875

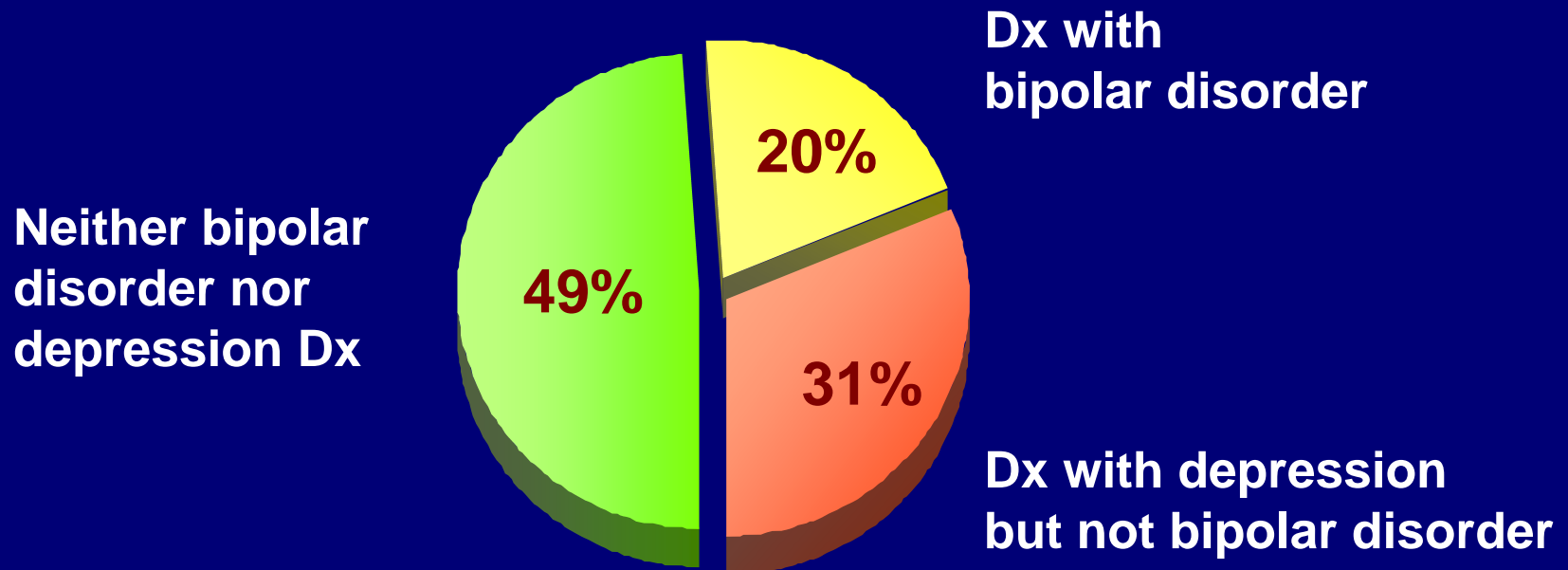
Bipolar Disorder — 3.4% of the US Population Screened Positive by MDQ —



* Weighted to match US census data.

Hirschfeld et al. *J Clin Psychiatry*. 2003; 64:53-59.

Physician Diagnoses Among MDQ Positives in the Community



80% of patients who screened positive for BP were not diagnosed w/ BP