Mood Disorders

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Disclosures

- No conflicts

Pre-Post Lecture Exam

In patients with psychiatric illness, what percent of health care service use is for psychiatric treatment?

a. 20%
b. 40%
c. 60%
d. 80%

Pre-Post Lecture Exam

What percentage of patients with psychiatric difficulties receive no treatment for their psychiatric condition?

a. 10%
b. 25%
c. 50%
d. 70%

Pre-Post Lecture Exam

The most common misdiagnosis of bipolar depression is:

a) anxiety disorder
b) substance abuse
c) borderline personality disorder
d) unipolar depression
e) schizophrenia

Pre-Post Lecture Exam

Treatment of bipolar depression with antidepressants may lead to:

a) anxiety

b) greater mood instability

c) mania induction

d) psychosis

e) b and c

f) all of the above

Pre-Post Lecture Exam

Which of the following are core symptoms of major depressive disorder?

a) depressed mood

b) loss of interest or pleasure

c) insomnia or hypersomnia

d) feelings of worthlessness or guilt

e) suicidal ideation

Pre-Post Lecture Exam

Which of the following antidepressants is least likely to lead to sexual side effects?

a) fluoxetine

b) duloxetine

c) sertraline

d) bupropion

e) venlafaxine

Prevalence and Burden

Neuropsychiatric disorders associated with substantial world-wide disability

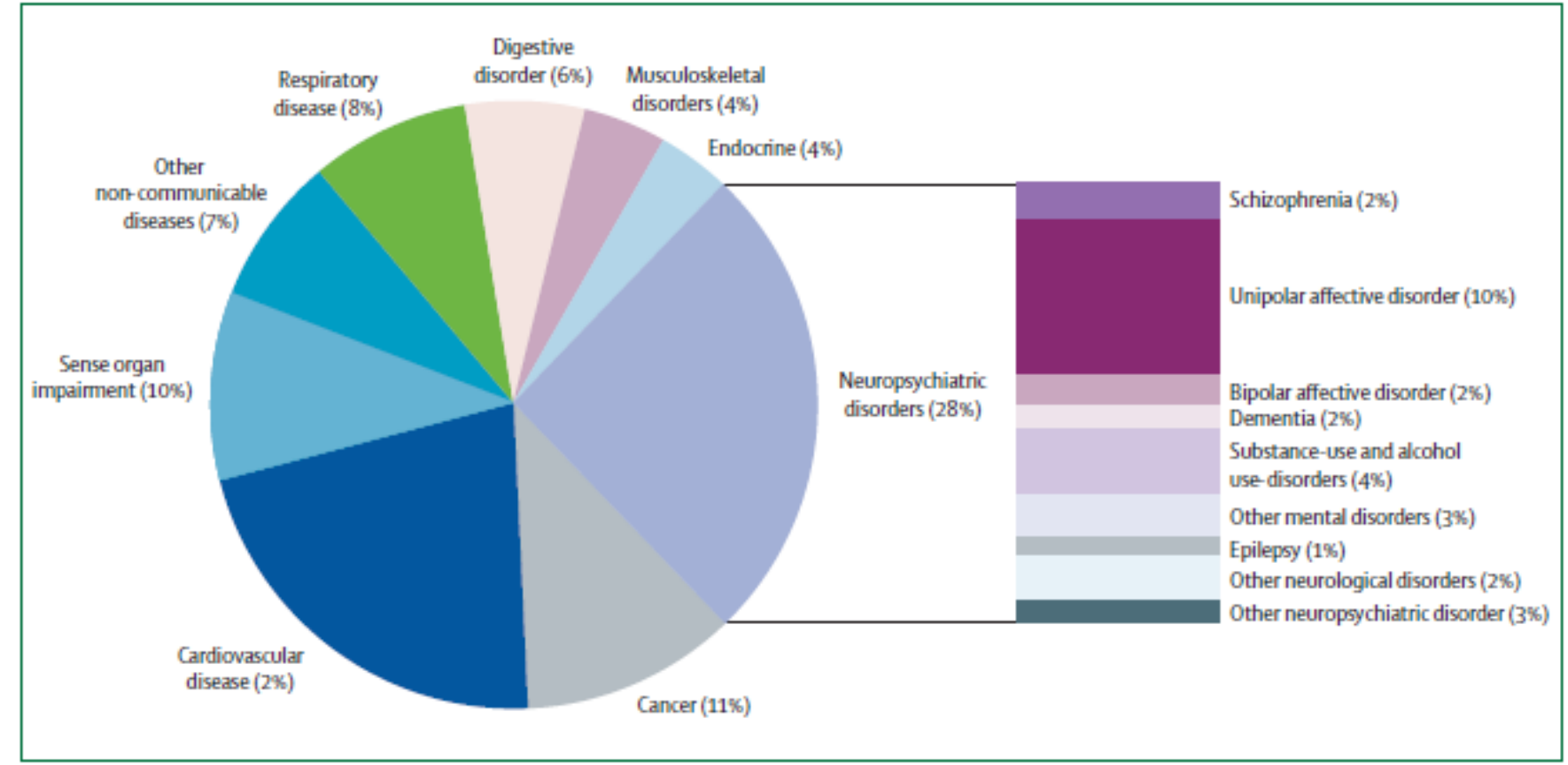
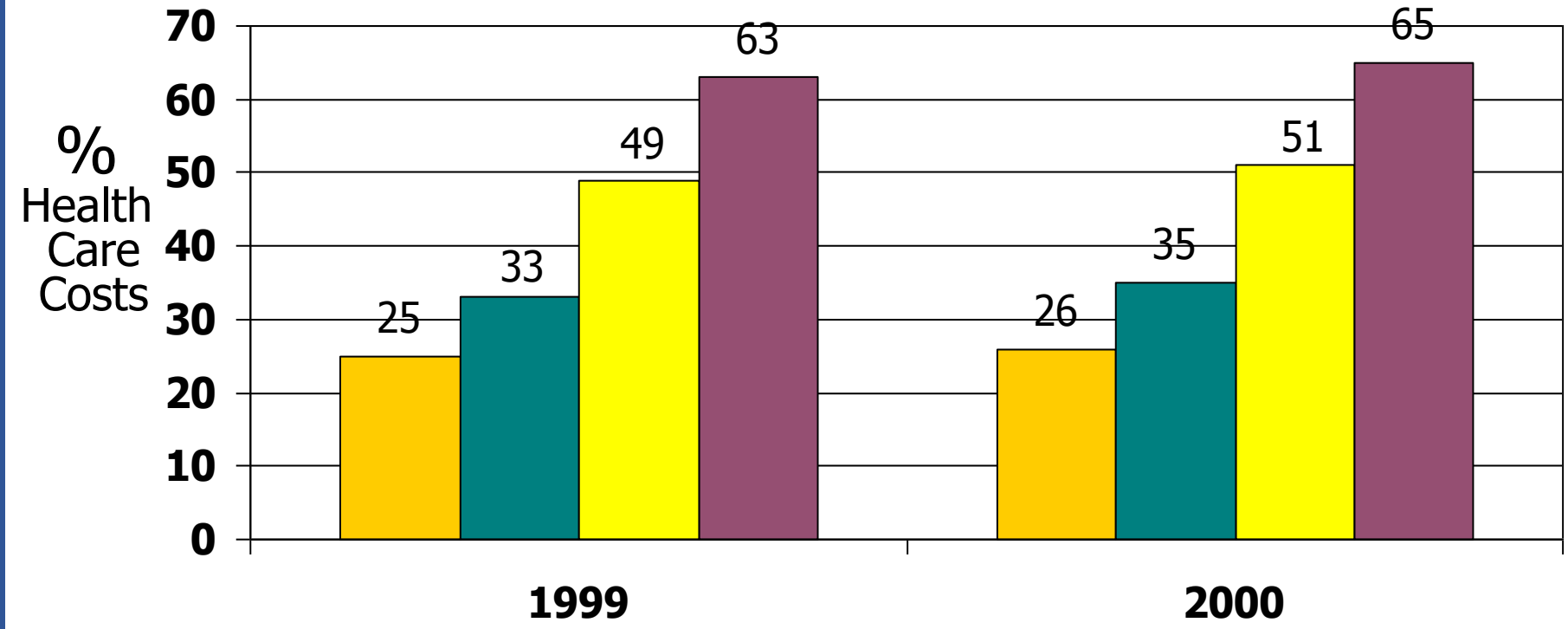


Figure 1: **Contribution by different non-communicable diseases to disability-adjusted life-years worldwide in 2005**
Data adapted from WHO, with permission.[3]

Prince, M., V. Patel, et al. (2007). "No health without mental health." Lancet

High proportion of Health Care Costs are used by Complex Patients



--Deloitte & Touche, 2002

High Utilizers of General Medical Care

- 58% of High Utilizers have panic disorder, generalized anxiety disorder, or depression
- Top 10% Utilizers Account for:
  - 29% of all PC visits
  - 52% of all specialty visits
  - 40% of in-hospital days
  - 26% of all prescriptions

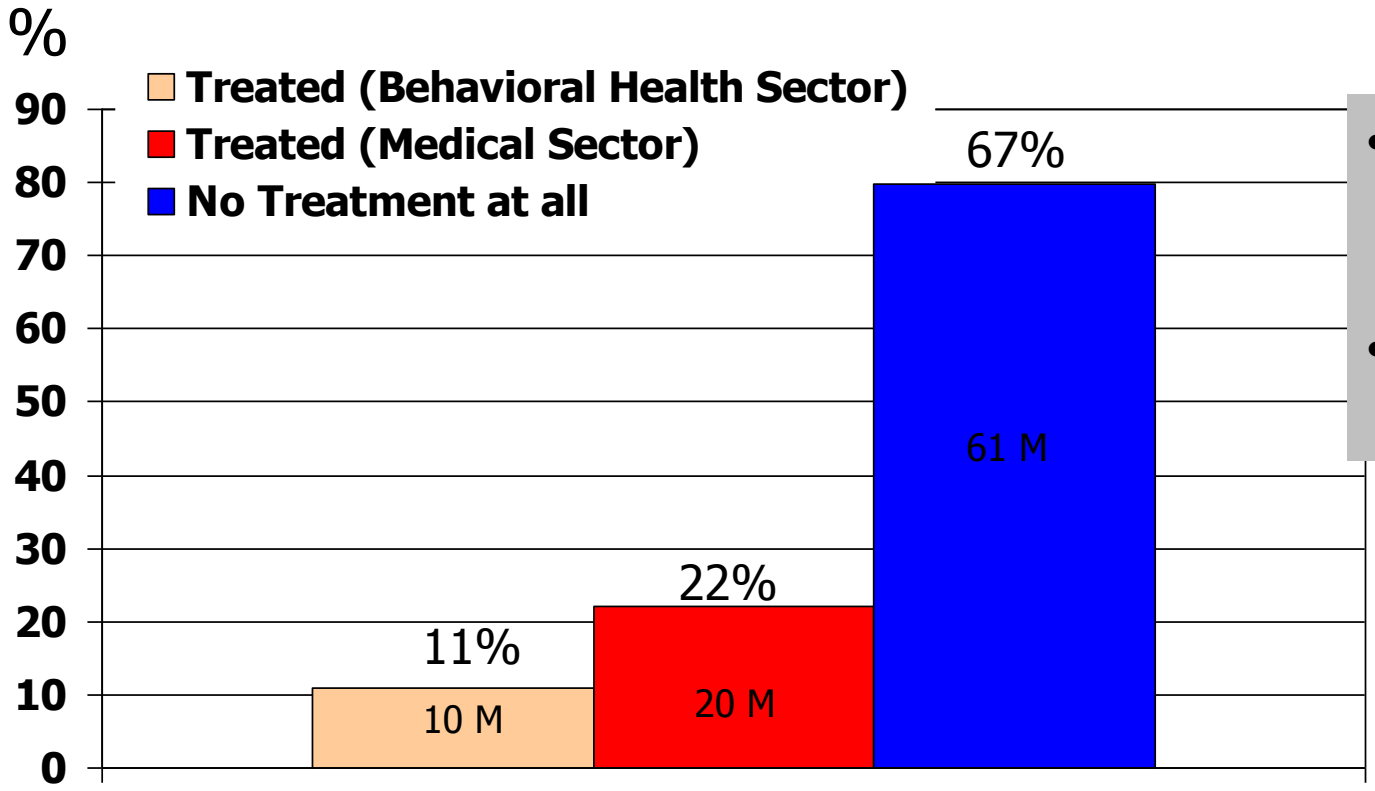
Katon et al, Gen Hosp Psych 12:355-362, 1990

PSYCHIATRY in PRIMARY CARE

- Less than half of primary care patients with mental illness receive ***any*** treatment
- 50-70% MDD is not accurately diagnosed or treated in the primary setting
- Roughly 80% of all antidepressants are prescribed by non-psychiatrists
- More than half of primary care patients on antidepressants do not meet criteria for MDD
- Only 1/3 of internal medicine residents are comfortable treating MDD

Tiemens, Gen Hosp Psychiatry 1999; Chin, Psychosomatics 41:5 October 2000; Unutzer, Psych Services Jan 2006

Poor Treatment of Mental Illness



- 33% of those treated receive "minimally adequate care"
- Only 40% of seriously mentally ill are treated

- annually 30.5% of the population (90.3 million Americans) have mental illness
- in 58.6 million, it is *moderate to severe*

Demyttenaere et al, JAMA 291: 2581-90, 2004; Kessler et al, NEJM 352:2515-2523, 2005; Kessler et al, AGP 62:617-627, 2005

Depressed Patients have Higher Healthcare Utilization

	Depressed	Non-Depressed	*p*
	(N = 714)	(N = 14,472)	
• Primary Care Visits	5.3	2.9	<.001
• Specialist Referrals	1.1	0.5	<.002
• Tests	10.1	6.6	<.001
• Outpatient Charges	$1,324	$701	<.001
• Total Healthcare	$2,808	$1,891	<.001
• Length of Stay (over DRG)	14.1 (7)	9.5 (3)	<.002

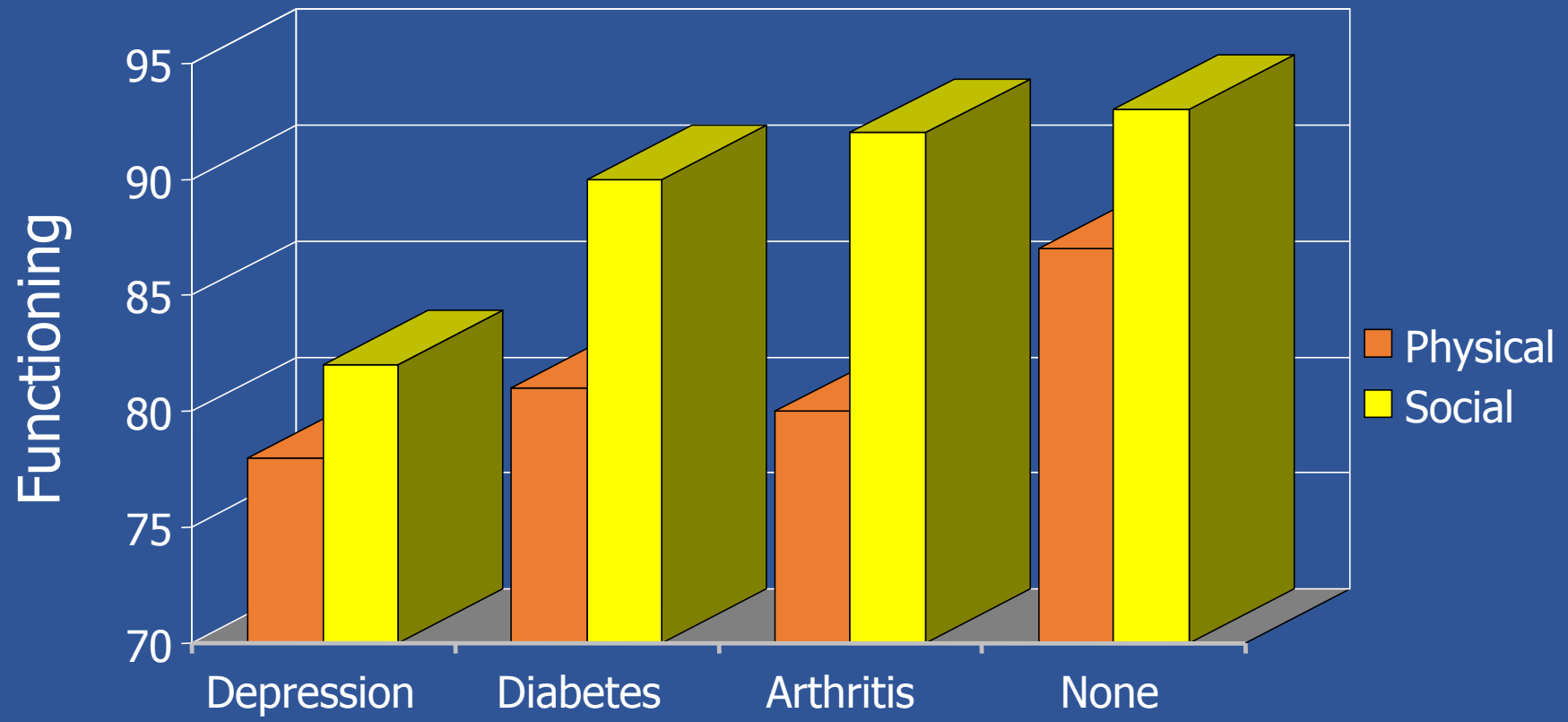
--Luber et al, Int J Psychiatry Med 30:1-13, 2000

Untreated Mental Illness Lowers Productivity

Estimated cost to employers (days lost per year for members with poorly managed depression)	
Absenteeism	*3.4 - 7.5 days*
Productivity Loss	*10.1 - 45 days*

Kessler et al JAMA 289:3095-3105, 2003

Depression Associated with Decreased Functional Status

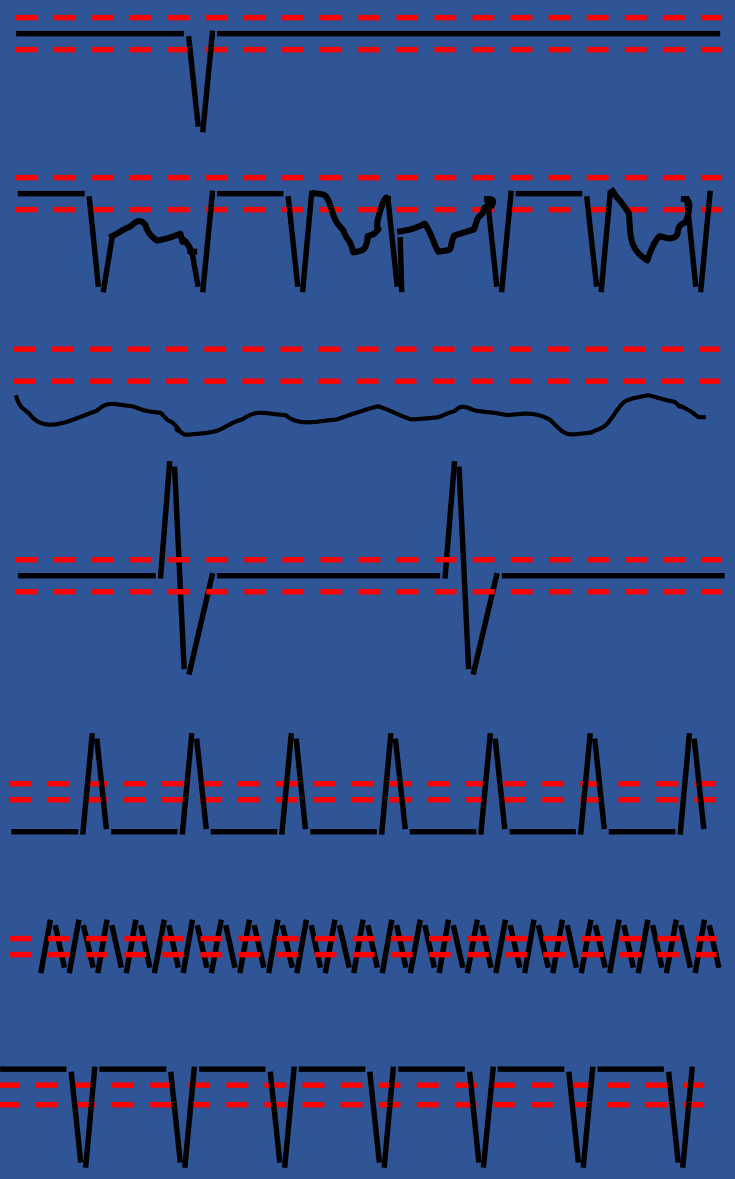


Wells et.al., JAMA 262:914-919,1989

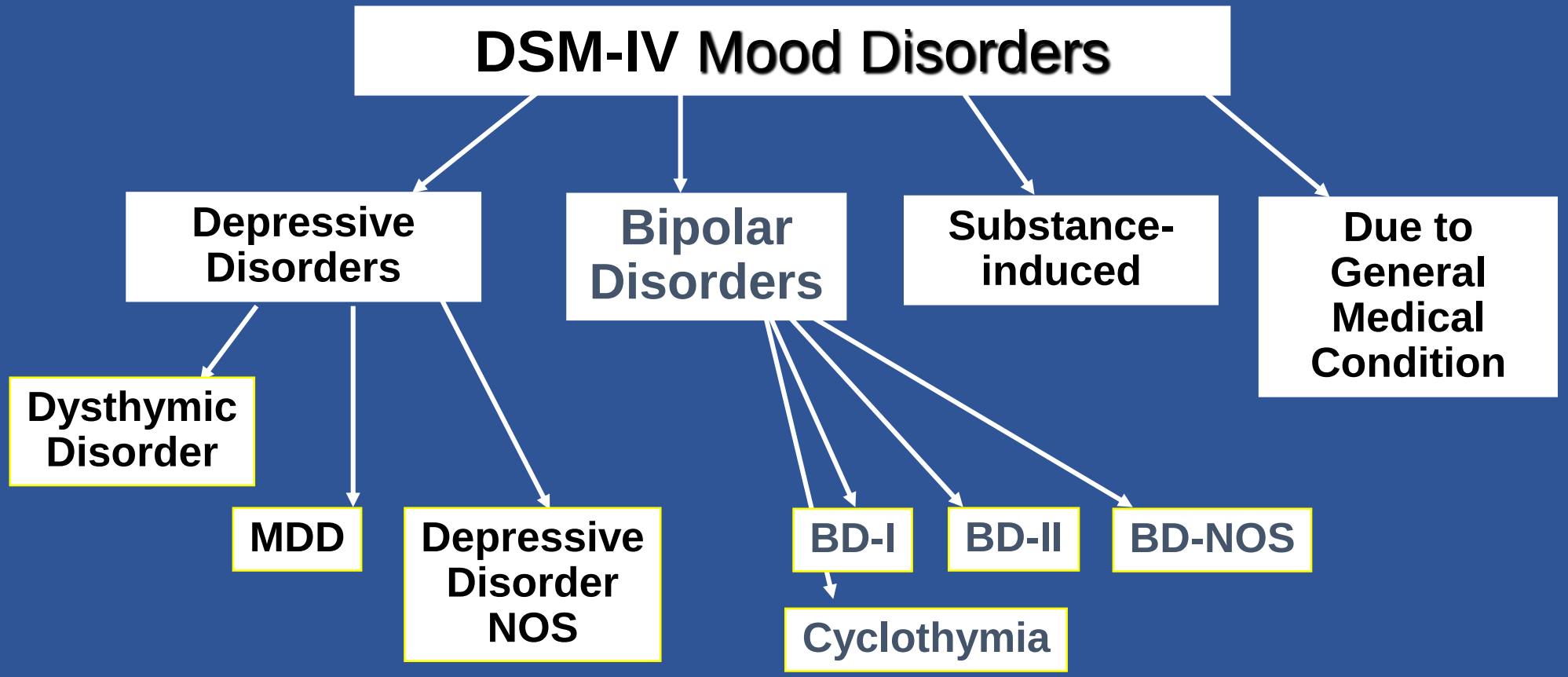
Classification and Diagnosis

Classification of Mood Disorders

- Unipolar
  - Unipolar single episode
  - Unipolar recurrent
  - Dysthymia
- Bipolar
  - Bipolar I
  - Bipolar II
  - Cyclothymia
  - Unipolar-Hyperthymic



Mood Disorders: DSM-IV Classification



APA (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, D.C.: APA

DSM-5 Classification

- **Depressive Disorders**
  - Major Depressive Disorder
  - Disruptive Mood Dysregulation Disorder
  - Persistent Depressive Disorder (Dysthymia)
  - Premenstrual Dysphoric Disorder
  - Substance/Medication-Induced Depressive Disorder
  - Depressive Disorder due to Another Medical Condition
  - Other Specified Depressive Disorder
  - Unspecified Depressive Disorder

DSM-5 Classification

- **Bipolar Disorders**
  - Bipolar I Disorder
  - Bipolar II Disorder
  - Cyclothymic Disorder
  - Substance/Medication-Induced Bipolar and Related Disorder
  - Bipolar and Related Disorder due to Another Medical Condition
  - Other Specified Bipolar and Related Disorder

Bipolar Disorders

Bipolar Disorder Challenges

- Prevalence: 1-4% or higher (narrow vs spectrum)
- Onset in young adulthood (for cases >60 years: medical disorders should be first thought)
- Chronic episodic course
- Morbidity (disability, hospitalization, maladjustment, substance problems, psychiatric disorder, medical problems)
- Mortality (suicide, accidents, and medical co-morbidities)

Bipolar Disorder Challenges

- Onset to proper diagnosis: 3-10 year lag (35% wait >10 years for correct diagnosis)
- Misdiagnoses: unipolar depression (60%); anxiety disorders (26%); schizophrenia (18%); personality disorder (17%); alcohol/substance abuse (14%).
- Significant co-morbidities (e.g., 60% lifetime prevalence of alcohol and drug use disorders)
- Significant complications: cognitive, personal and occupational functioning

Regier et al, 1990; Hirschfeld et al, 2003; Klassen et al, 2009; Wingo & Ghaemi, 2007

Epidemiology

- Equal prevalence among men and women.
- Manic episodes – more common in males.
- Depressive episodes -- more common in females.
- Rapid cycling – more common in females.
  - rapid cycling >4 episodes manic in 1 yr
- Age of onset—5 to 50 yrs .
- Marital status -- more common in single/divorced.
- Comorbidity—substance use, panic disorder, OCD

Clinical Features Predictive of Bipolar.

- Bipolar family history.
- High-density, 3 generation pedigrees.
- Trait mood lability (cyclothymia).
- Hyperthymic temperament.
- Hypomania associated with antidepressants.
- Repeated (at least 3 times) loss of efficacy of antidepresssants after initial response.
- Depressive mixed state (with psychomotor excitement, irritable hostility, racing thoughts, and sexual arousal during major depression).

Course of Bipolar I

- Bipolar I often starts with depression --- 75% in females, 67% in males.
- 10-20%-- only manic episodes.
- Untreated manic episodes lasts about 3 months. Hence should not stop drugs before that time.
- Single manic—90% will have another episode.
- After 5 episodes, inter episode interval stabilizes to 6-9 months.
- 5-15% are rapid cyclers.

Phases of Bipolar Disorder

- Acute mania
- Bipolar depression
- Maintenance

Treatment: Challenges of Bipolar Disorder

- Complexity of the clinical presentation (heterogeneous symptom picture, co-morbid psychiatric disorders, and medical disorders)
- Recognition of bipolar depression
- Lack of adherence to treatment & education about the illness
- Necessity of phase relevant treatments & life long strategies.

Foster et al, Cur Psychiatry, 2011; 10: 45-53

Treatment Goals

- Acute mania

  Rapid onset of action, relief of symptoms, no depression induction
- Bipolar depression

  Relief of symptoms, no mania induction
- Maintenance

  Prevention of relapse into depression or mania; reduction of co-morbid anxiety

Selecting Medication(s)

- Phase specific considerations
- Prior response and tolerability
- Medical and psychiatric co-morbidities
- Side effects
- Drug interactions
- Patient preferences

Acute Mania: FDA Approved

- 1970 Lithium
- 1973 Chlorpromazine
- 1995 Divalproex
- 2004 Carbamazepine ER
- 2005 Divalproex ER

FDA Approved Atypical Antipsychotics for Mania

- Olanzapine (Zyprexa) 2000*
- Risperidone (Risperdal) 2003**
- Aripiprazole (Abilify) 2004**
- Quetiapine (Seroquel) 2004**
- Ziprasidone (Geodon) 2004
- Asenapine (Saphris) 2009

*Adolescent mania (13-17) 2009/**Pediatric mania (10-17): RIS 2007/ARI 2008/QTP 2009

Acute Mania: First-Line

- Severe
  - lithium or divalproex + antipsychotic
- Less severe
  - lithium or divalproex or antipsychotic or carbamazepine ER

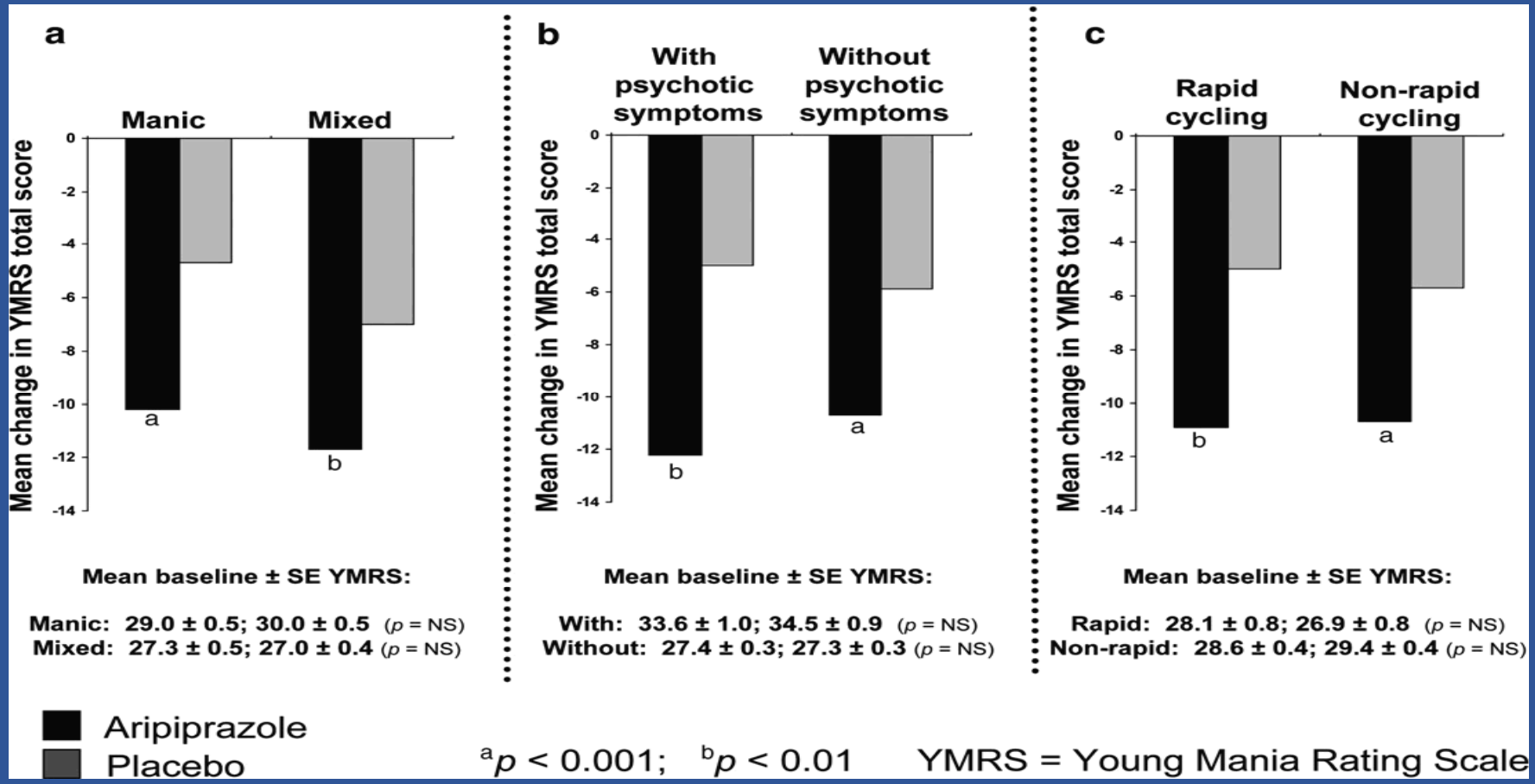
APA Bipolar Guidelines, Revised 2002
APA Bipolar Guidelines Watch 2005
CANMAT & ISBN Guidelines 2009
Weisler et al, J Clin Psych, 2005

Second Generation Antipsychotics in Mania

- All apparently effective
- Generally no worsening of depression (unlike conventional antipsychotics)
- Antidepressant effects (e.g., as seen with quetiapine) & some adjunctive mood stabilization effects
- Less EPS but be wary of metabolic risks, especially weight gain (except possibly for aripiprazole & ziprasidone) and abnormalities in glucose, lipids, or prolactin

See also: Cipriani et al, Lancet 2011; 378: 1306-15

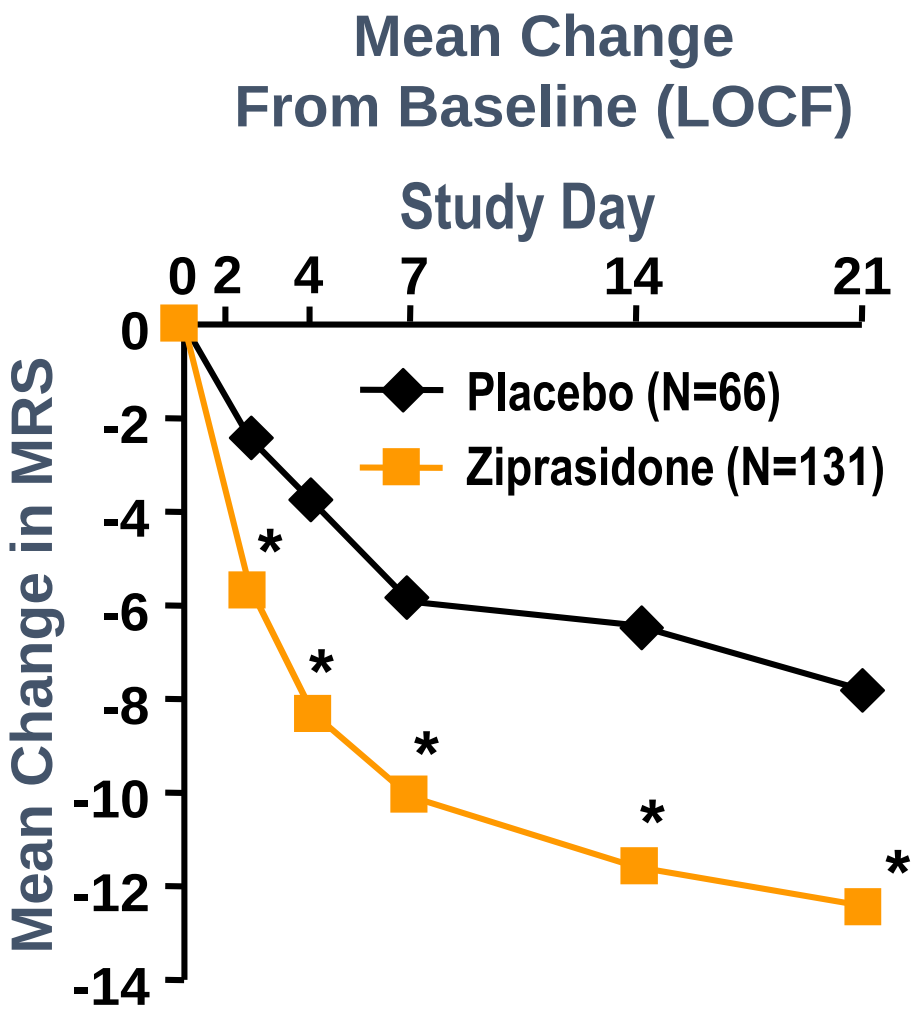
Aripiprazole in Acute Mania: Mean Change From Baseline in YMRS



Mean change in YMRS total scores from baseline to trial end point(21 days)

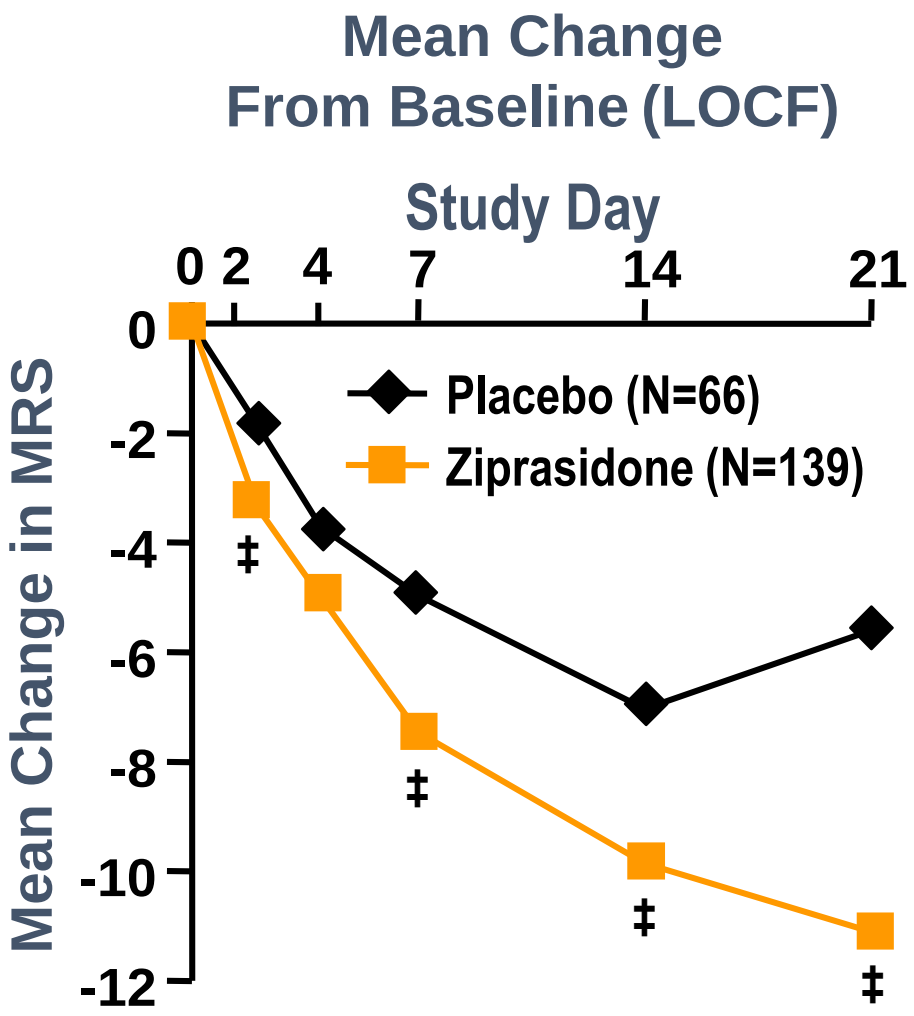
Jody et al. *Int J Neuropsychopharmacol*. 2002;5(suppl 1):S57

Ziprasidone: Efficacy in Acute Mania



*p<0.01;

Keck et al., Am J Psychiatry 2003;160:741-748



‡p<0.05;

Potkin et al.,J Clin Psychopharmacol 2005;25:301-310

Antipsychotics

- Caution with over-use and off-label use
  - Should not be first-line for anxiety or insomnia
- Be aware of side effects
  - Extrapyramidal symptoms
  - Tardive dyskinesia
  - Weight gain
  - Metabolic syndrome
- Be aware of black-box warning
  - Increased risk of death among patients with dementia with atypical antipsychotics

ADA/APA Consensus Conference on Antipsychotic Drugs

Drug	Weight Gain	Risk for Diabetes	Worsens Lipid Profile
Clozapine (Clozaril)	+++	++	++
Olanzapine (Zyprexa)	+++	++	++
Risperidone (Risperdal) Paliperidone (Invega)	++	+/-	+/-
Quetiapine (Seroquel)	++	+	+
Aripiprazole (Abilify)	+/-	-	-
Ziprasidone (Geodon)	-	-	-

+ = increase effect; - = no effect

Acute Bipolar Depression

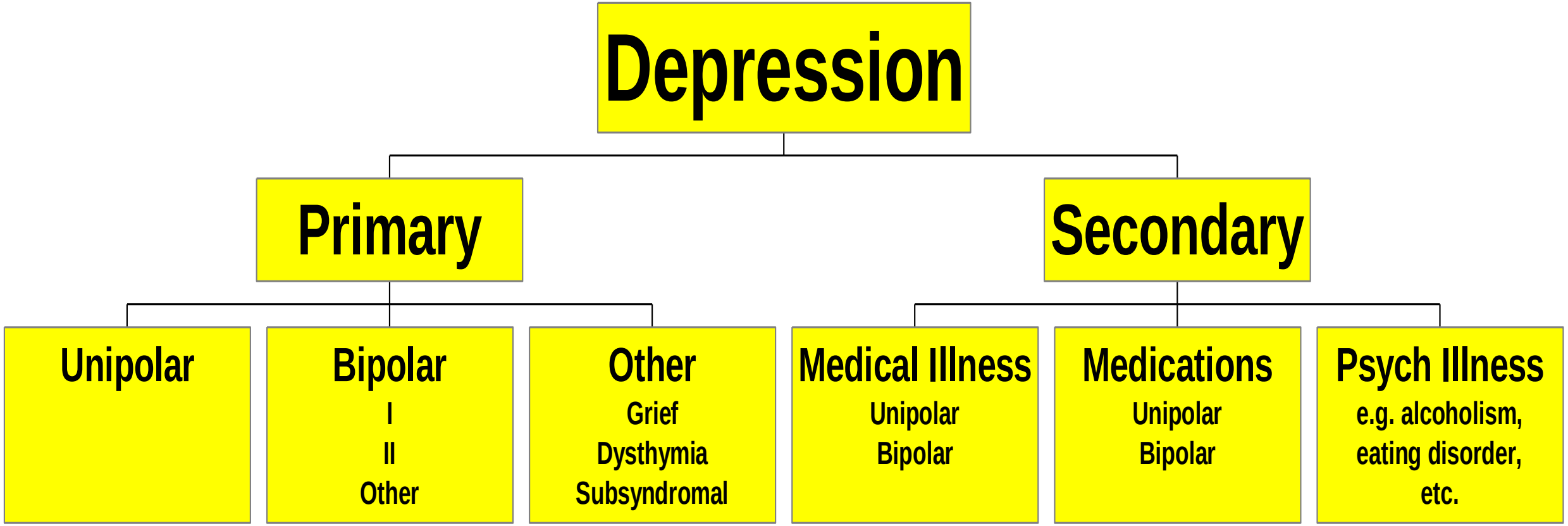
- Symbyax –olanzapine + fluoxetine
- Lamotrigine
- Lurasidone
- Quetiapine
- Cariprazine?
- Treatment resistant – ECT, TMS?, ketamine?

Maintenance Treatment

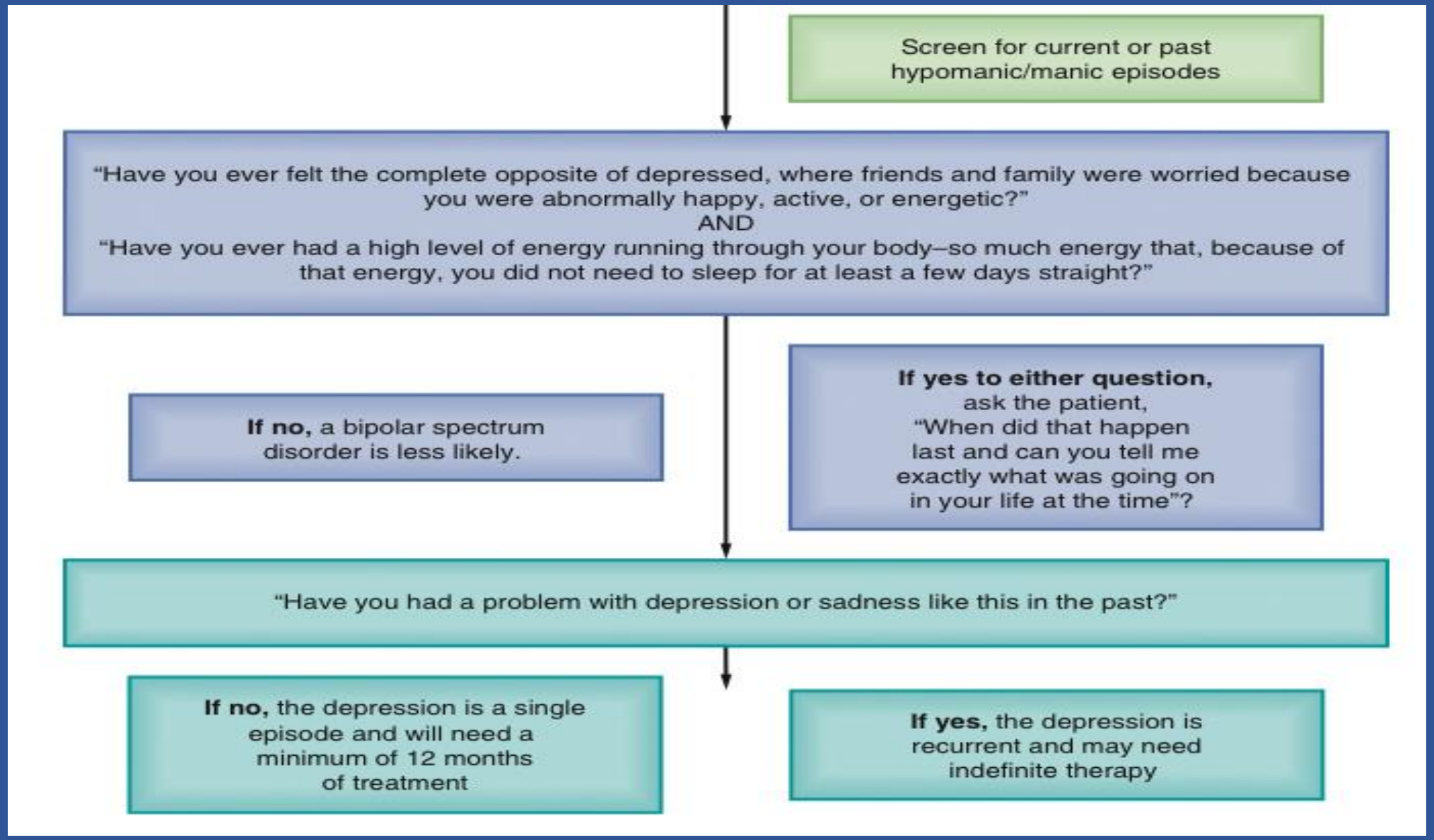
- Lithium
  - Thyroid supplementation is frequently necessary.
  - With lithium, develop hypothyroidism
  - Idiopathic thyroid dysfunction
  - Augmentation with T3 or T4
- Valproic acid, quetiapine, or lamotrigine
  - Lamotrigine (200 mg per day) — slow uptitration , due to Stevens Johnson syndrome
- Aripiprazole, olanzapine, or risperidone
- Combination: lithium or valproate + SGA

Depressive Disorders

Depression Differential



Checking For Mania…



Lippincott's Primary Care Psychiatry – McCarron, Xiong, Bourgeois 2009

Primary MDD Patient Characteristics

- Age of onset—teens to mid 40s
- Sex—Female 2:Male 1
- Family History—increase in depression
- Treatment Response—50% intent to treat; 70% completer
- Course—intermittent with average duration 6 to 12 months
- Recurrence—50% will have a recurrent episode

AHCPR Depression Guidelines, 1993

Conditions Associated with Mood Symptoms

- Substance abuse
- Concurrent medications
- General medical disorders
- Other causal non-mood psychiatric disorders
- Grief reactions

Baseline and Follow-up Depression Symptoms: PHQ-9

Over the last 2 weeks, how often have you been bothered by any of the following problems? Read each item carefully, and insert the number of your response.

(Key: Not at all = 0; Several days = 1; More than half the days = 2; Nearly every day = 3)

1. Little interest or pleasure in doing things ___
2. Feeling down, depressed, or hopeless ___
3. Trouble falling asleep, staying asleep, or sleeping too much ___
4. Feeling tired or having little energy ___
5. Poor appetite or overeating ___
6. Feeling bad about yourself, feeling that you are a failure, or feeling that you have let yourself or your family down ___
7. Trouble concentrating on things such as reading the newspaper or watching television ___
8. Moving or speaking so slowly that other people could have noticed. Or being so fidgety or restless that you have been moving around a lot more than usual ___
9. Thinking that you would be better off dead or that you want to hurt yourself in some way___

Total Score for 1 to 9: ____

(Scoring Key: Minimal <5; Mild 5 to 9; Moderate 10 to 14; moderately severe 15 to 19; Severe >19)

Impairment: If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not Difficult at All = 0; Somewhat Difficult = 1; Very Difficult = 2; Extremely Difficult = 3

Assessing risk for suicide

- Over 50% of those who kill themselves have seen their primary care doctor within one month of doing so.
- Over 50% of suicides will end up in litigation
- Risk Factors
  - Suicidal or homicidal ideation, intent or plan
  - Access to means of suicide
    - Firearms – ask about access
  - Command hallucinations or other psychosis
  - Anxiety
  - History of previous attempt
  - Family history or recent exposure to suicide
  - Substance abuse

Acute Treatment of Depression

- Patient education/reassurance
- Response times
  - Psychotherapy: 4-8 weeks
  - Medication: 3-6 weeks
  - ECT: 1-3 weeks
- Light: Seasonal Affective Disorder
- Other: Transcranial Magnetic Stimulation

Patient Education

- Anxiety and Depression are medical illnesses
- Recovery is the rule
- Treatments are effective
- Aim of treatment is complete symptom remission
- Risk of recurrence is significant
- Seek treatment early if anxiety or depression returns

Major Depression

- Can last for a year without treatment
- High relapse and recurrence rates, particularly without treatment →shorter well periods, increased frequency and severity of illness
- Most common cause of disability in the world
- Lifetime risk 10-25% females, 5-12% men
- Risk factors: stressors, poor social support, early parental loss, family history, negative cognitive style

Treatment Options

- Psychotherapy
- Pharmacological treatment
  - SSRIs (sertraline, fluoxetine, citalopram, escitalopram, paroxetine)
  - SNRIs (venlafaxine, duloxetine, desvenlafaxine, levomilnacipran)
  - Tricyclics/Tetracyclic (amitriptyline, nortriptyline)
  - Bupropion, mirtazapine
  - MAOIs (phenelzine, tranylcypromine, EMSAM)
- Hormonal Treatment
  - Perimenopausal women
  - Post-partum depression
- Best Treatment-therapy and meds together

General Treatment Rules

- Often takes 4-6 weeks for response
- Monitor for response versus remission
- Vegetative symptoms tend to improve first, cognitive symptoms take longer
- SSRIs are the first line of treatment for most patients with MDD
- Address biopsychosocial needs and maintain meds for 6-12 months

Antidepressants are effective in Primary Care Depression

- Both SSRIs and TCAs are effective in primary care
  - Significant benefit seen over placebo after 4 weeks of tx in 14 RCTs
- More adverse effects with TCAs
  - Drop-out rate 10.2% (vs 5.2% for SSRIs)
- Number needed to treat:
  - SSRIs: 7 to 8
  - TCAs: 6 to 16

Arroll et al, Cochrane Database of Systematic Reviews 2009 Issue 3.

Selective Serotonin Reuptake Inhibitors

- Fluoxetine, Paroxetine, Sertraline, Citalopram, Escitalopram, Fluvoxamine
- Produce response rates close to 70%
- Safer and better tolerated than TCA's
- Given once daily
- Starting and therapeutic doses often similar
- Most common side effects include GI symptoms, HA, insomnia, anxiety, and sexual dysfunction

Novel or Atypical Antidepressants

- Bupropion (NE and DA reuptake inhibition)
- Trazodone (5-HT2 receptors and alpha-1 adrenergic receptors)
- Venlafaxine, Duloxetine, Milnacipran, Levomilnacipran (NE and 5-HT reuptake blockers – SNRI's)
- Mirtazapine (presynaptic alpha-2 adrenergic antagonist, and 5-HT2 and 5-HT3 receptor antagonist)
- Vilazodone (blocks 5-HT reuptake, agonizes 5-HT1A receptors)
- Votrioxetine (blocks 5-HT reuptake, antagonizes 5-HT3 receptors, agonizes 5-HT1A receptors)
- EMSAM – daily patch

Depression and cardiovascular disease

- Depression is an independent risk factor for development of cardiovascular disease.

  (Ford 1998, Pennix 2001, Janszky 2007, Van der Kooy 2007)

- Among patients with established CVD, depression is a predictor of future cardiac events and mortality.

  (Carney 1988, Ladwig 1991, Frasure-Smith 1995, Barefoot 1996)

- Issues in treatment of depression in patients with CVD:
  - Safety, tolerability
  - Does treatment impact cardiac events? Mortality?

RCTs of antidepressants to treat depression in pts with CAD

STUDY Antidepressant	SADHART sertraline	MIND-IT mirtazapine	CREATE citalopram
Patients	MI, Acute coronary syndrome	> 3 months post-MI	Stable outpatients
Efficacy	Yes	Maybe	Yes (Interpersonal Psychother. - No)
Safe	Yes	Yes	Yes
Prevent adverse cardiac outcomes	Maybe, if depression is adequately treated	Maybe, if depression is adequately treated	unknown

Side-Effects of Antidepressants

	SEXUAL DYSFUNCTION/DECREASED LIBIDO	WEIGHT GAIN	SEDATION	CARDIAC
SSRIs	+++	+[a]	+/−[a]	0
Venlafaxine	+++	+/−	+/−	+ (↑ BP)
Mirtazapine	+	+++	++	+/−
Bupropion	0	0	0	+/− (↑ BP)
TCAs	++	++	+++	+++ (ECG, BP)

BP, blood pressure; ECG, electrocardiogram abnormalities; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

[a] Paroxetine and fluvoxamine are more likely to cause sedation and weight gain.

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Which of the following antidepressants is least likely to lead to sexual side effects?

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b) duloxetine

c) sertraline

d) bupropion

e) venlafaxine

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