ANTIDEPRESSANTS: BASICS

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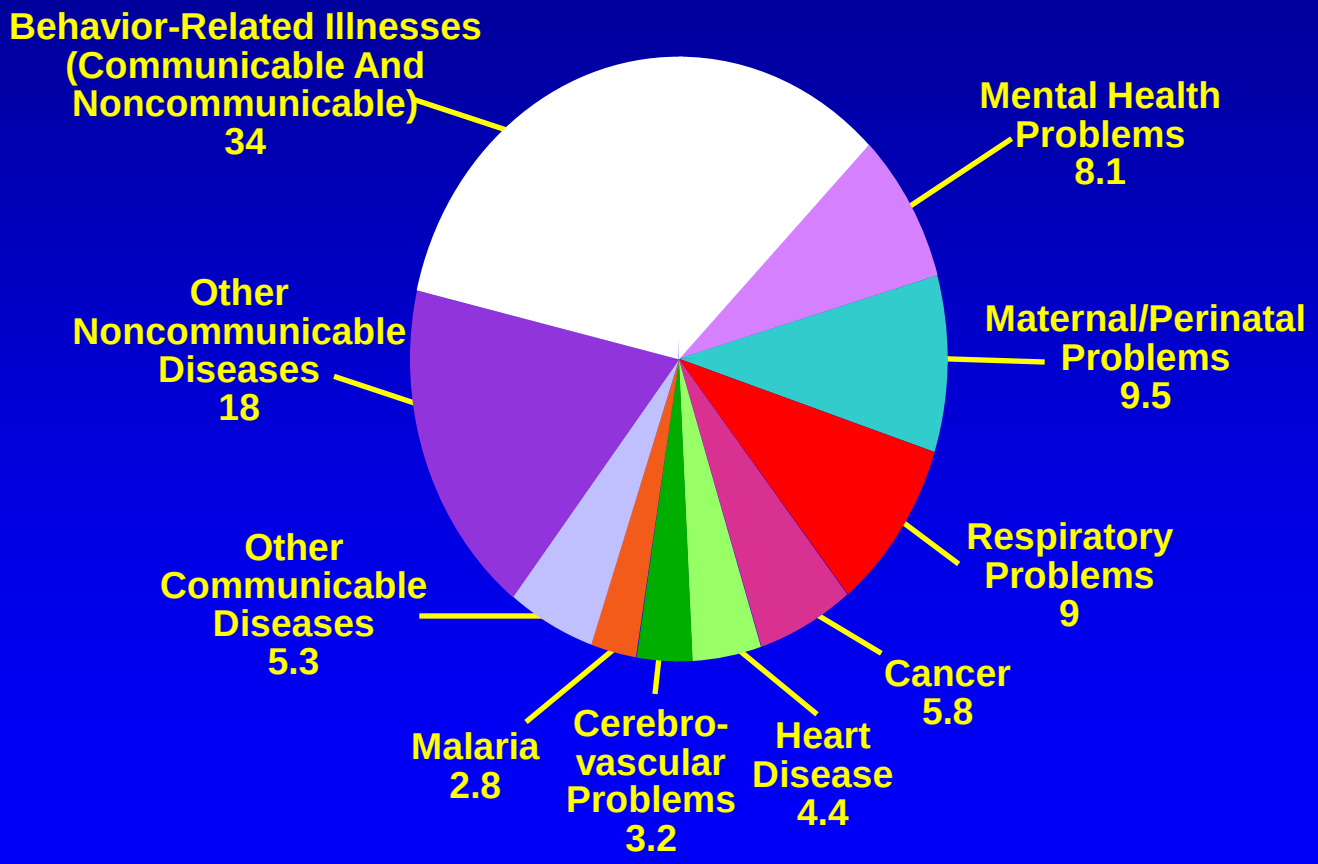
AD Basics: Part 1

Major Depression: Diagnosis , Risk Factors, Comorbidity, and Naturalistic Long-Term Outcome

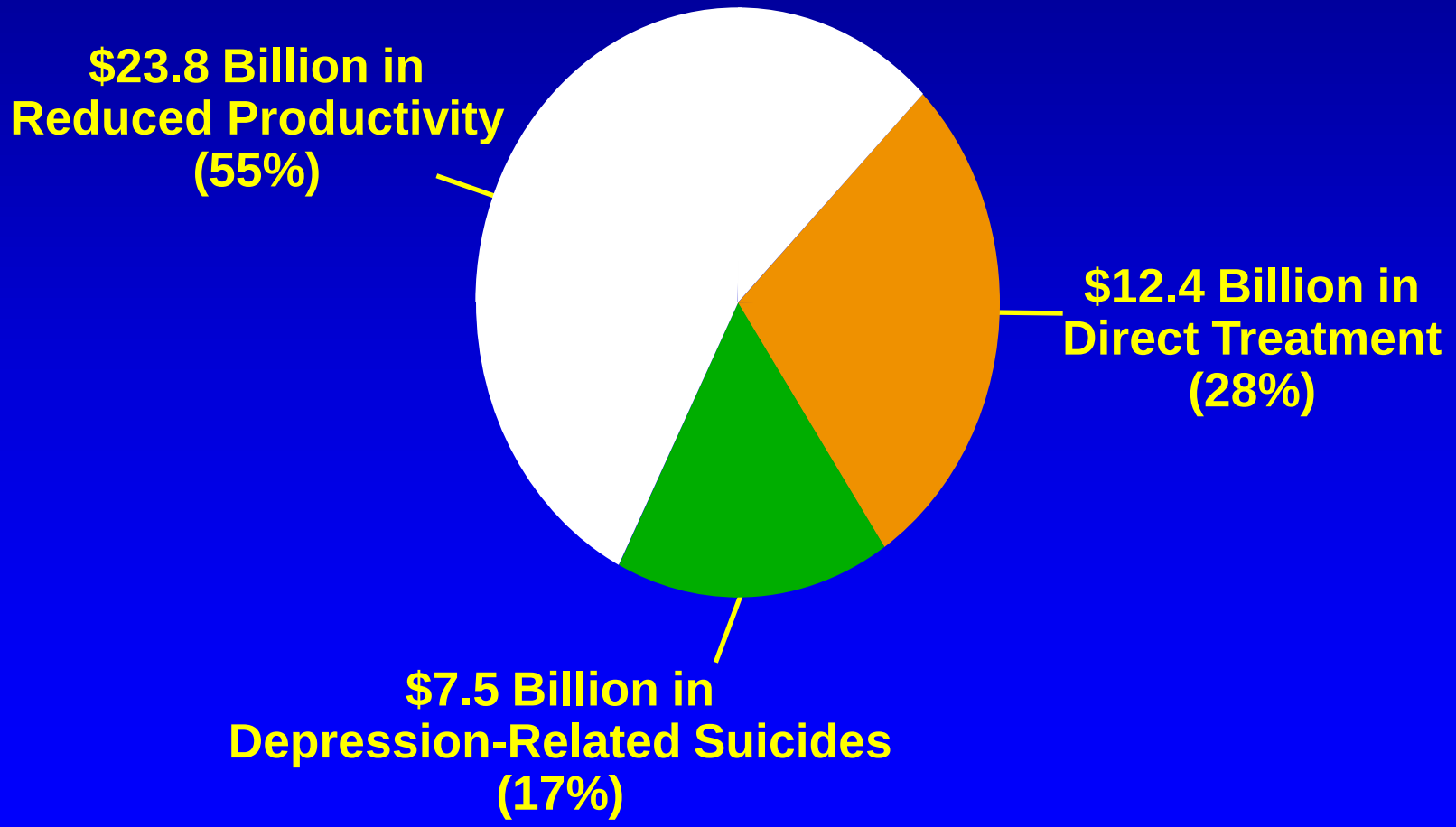
Global Distribution of Health Burdens (1990)*



* Numbers represent percentage of disability-adjusted life years lost

Adapted from The World Bank, 1993, with permission from Oxford University Press, Inc./WPA/PTD Educational Program on Depressive Disorders

Annual Cost of Depression in the US: $43.7 Billion



Greenberg et al, 1993
WPA/PTD Educational Program on Depressive Disorders

“Iceberg” Phenomenon

Watts, 1966
WPA/PTD Educational Program on Depressive Disorders

MAJOR DEPRESSIVE EPISODE

- Depressed mood or anhedonia — at least 2 wks
- At least 5 of the following
  - Depressed mood
  - Decreased interest or pleasure most of the time
  - Insomnia or hypersomnia
  - Anorexia or hyperphagia or 5% weight gain/loss in month
  - Psychomotor agitation or retardation
  - Fatigue
  - Decreased concentration or thinking, indecisiveness
  - Negative thinking — worthlessness, inappropriate guilt
  - Recurring thoughts of death or suicide
- Not organically caused
- Not uncomplicated bereavement

MAJOR DEPRESSIVE DISORDER

- Presence of major depressive episode
- Absence of psychotic disorder*
- Absence of bipolar disorder*

*Unless medically or substance-induced

RISK FACTORS FOR MAJOR DEPRESSION

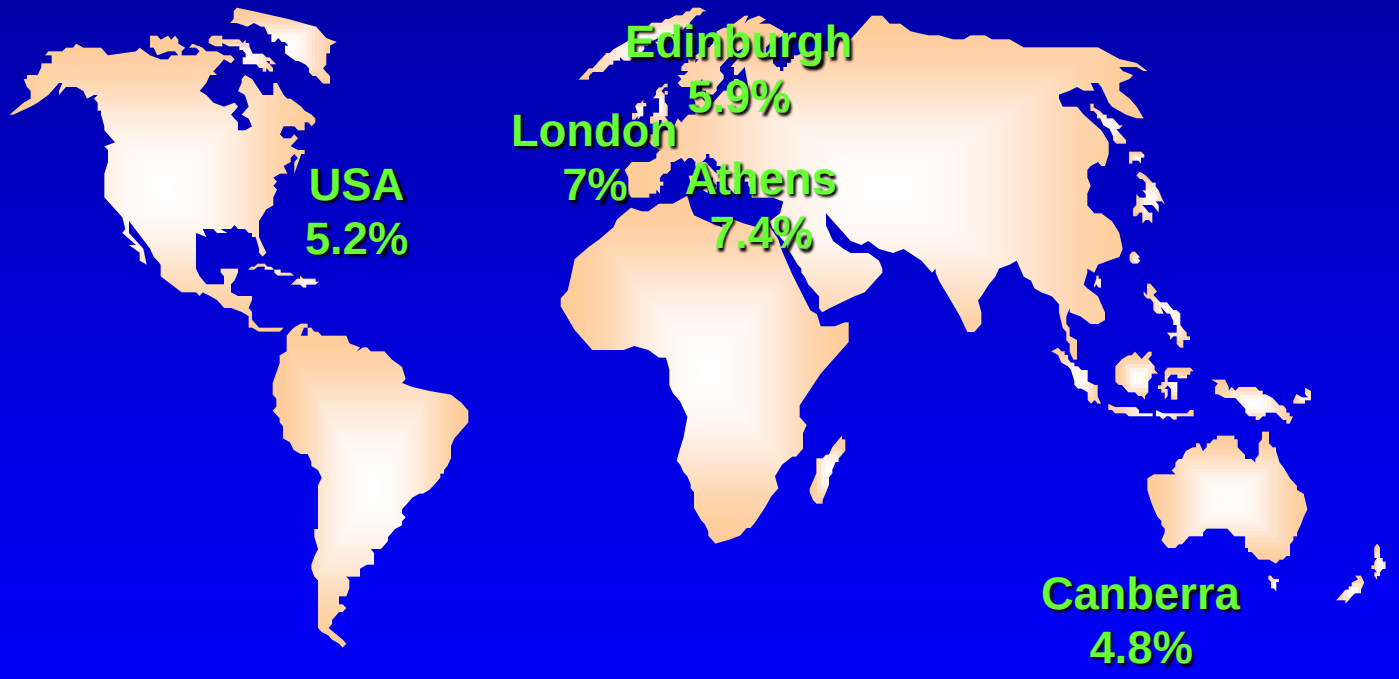
Risk Factor	Association
Gender	Twice as likely in women
Age	Peak age of onset = 20–40 years
Family history	1.5–3.0X higher risk
Marital status	Higher rates in separated, widowed, and divorced persons Married males < never married Married females > never married*

*Highest risk: young mothers stuck at home with children

OCCURRENCE OF DEPRESSION

- Point prevalence 4–5%
  - Women 5–6%
  - Men 3%
- 1 year prevalence (major depression) 11.3%
- Lifetime relapse rate 65–80%
- Lifetime incidence
  - Women ♠20%
  - Men ♠10%

One-Month Prevalence Rates for Affective Disorders



Ustun & Sartorius, 1993

WPA/PTD Educational Program on Depressive Disorders

DYSTHYMIC DISORDER

- Depressed mood most of days, more days than not, for at least 2 years
- Two or more:
  - Poor appetite or overeating
  - Insomnia or hypersomnia
  - Low energy or fatigue
  - Poor concentration, indecisiveness
  - Low self-esteem
  - Hopelessness
- Not symptom-free for 2 or more months

DYSTHYMIC DISORDER

- 2.5% annual prevalence rate

  Equals or Exceeds Major Depression in:

  - Suicide rate
  - Loss of marriage or job secondary to depression
  - Overall impairment

Kessler, 1994

MOOD DISORDER WITH ATYPICAL FEATURES

- Mood reactivity
  - Mood crashes or brightens in response to events
- Two of the following:
  - Increased weight or appetite
  - Hypersomnia
  - Leaden paralysis (heavy, leaden feelings in arms or legs)
  - Chronic rejection sensitivity
- Often associated with anxiety

MOOD DISORDER WITH ATYPICAL FEATURES

- 15–20% of depressive episodes have atypical features
- Do not respond as well to TCAs (<50%) as to MAOIs or SSRIs (♠70%)
  - ε80% are women

MOOD DISORDER WITH ATYPICAL FEATURES

- Atypical features often seen in seasonal affective disorder
  - ε80% of SAD are women
- Seen frequently in PMD (premenstrual dysphoric disorder)
- Seen frequently in bipolar depression
  - Particularly rapid cycling (85% women)

MAJOR DEPRESSIVE DISORDER
Neurotransmitters

- State but not trait markers
- Norepinephrine and serotonin abnormalities normalize with Rx
- Norepinephrine
  - First believed to be too low
  - Dysregulation frequently seen
    - Basal rate of firing of noradrenergic neurons high
  - Decreased response of noradrenergic neurons to stimulation

MAJOR DEPRESSIVE DISORDER
Neurotransmitters

- Serotonin
  - First believed to be too low
  - May be low, but $5HT_2$ and/or $5HT_{1a}$ appear to be main receptors involved
- Other neurotransmitters (or their precursors) with reported abnormalities include:
  - GABA ↓
  - Phenylalanine ↓
  - Dopamine ↑ ↓

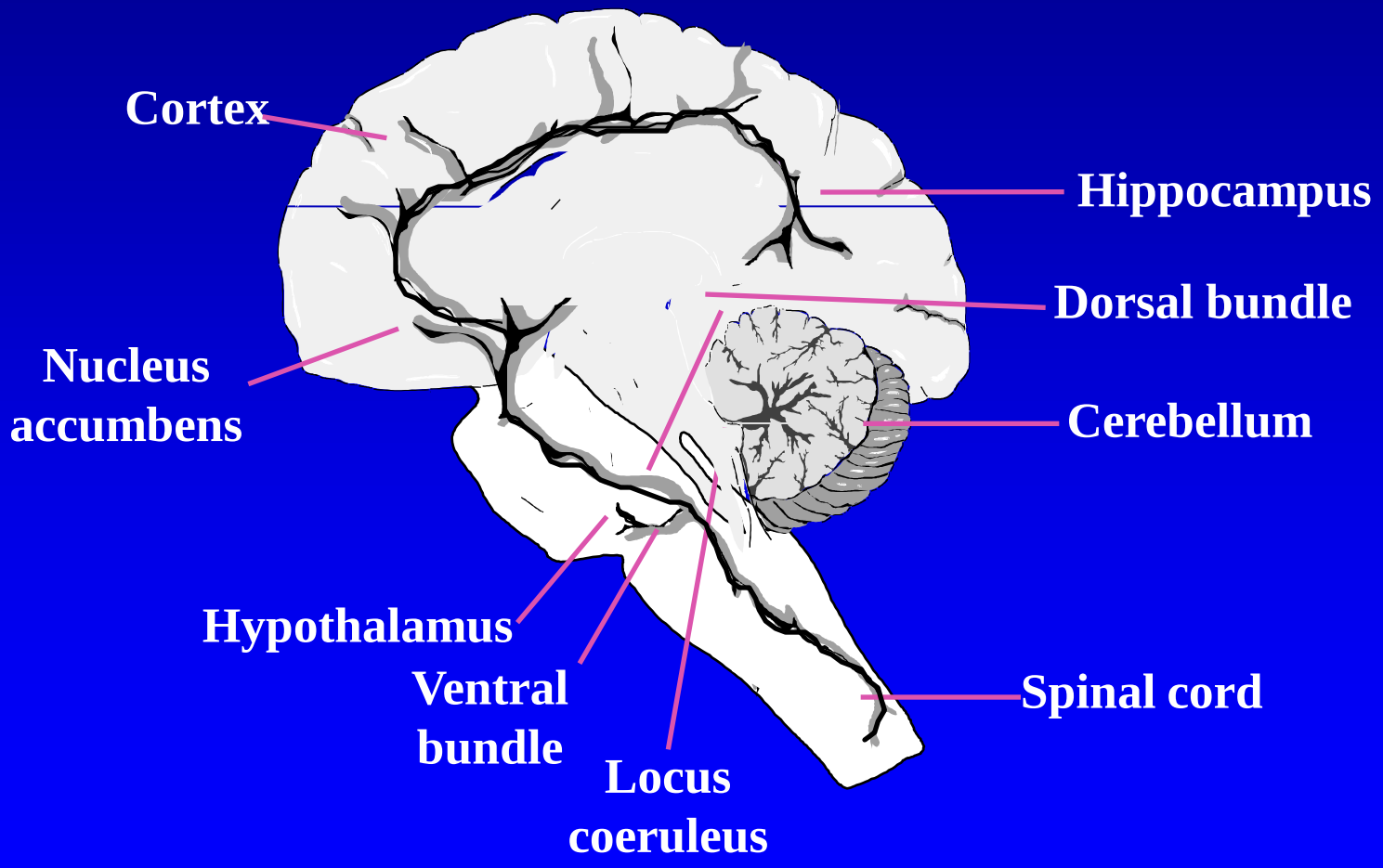
Etiology and Pathogenesis of Depressive Disorders

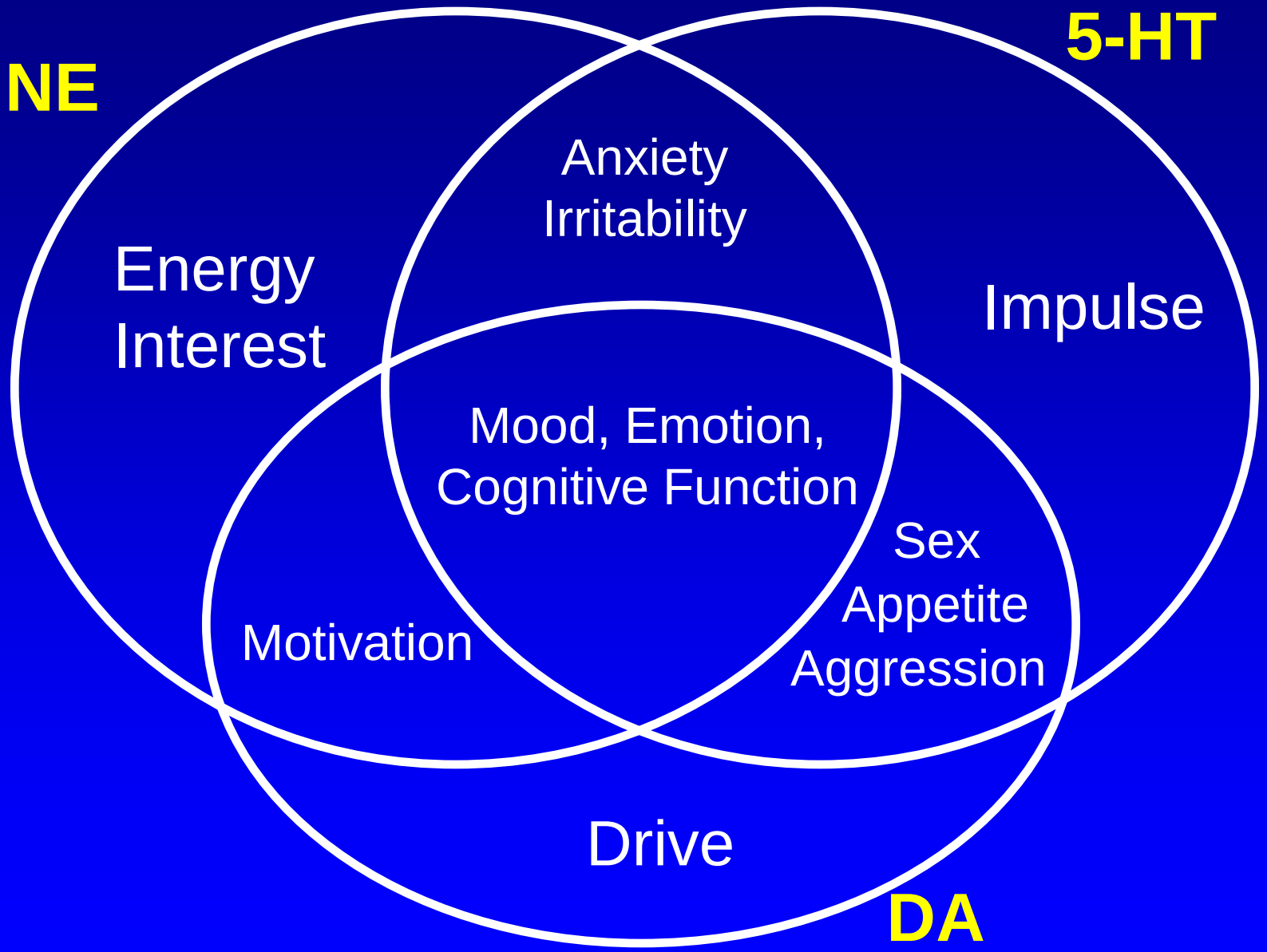
- Neurobiologic factors
- Psychosocial factors
- Developmental factors

Monoamine Deficiency Hypothesis of Depression

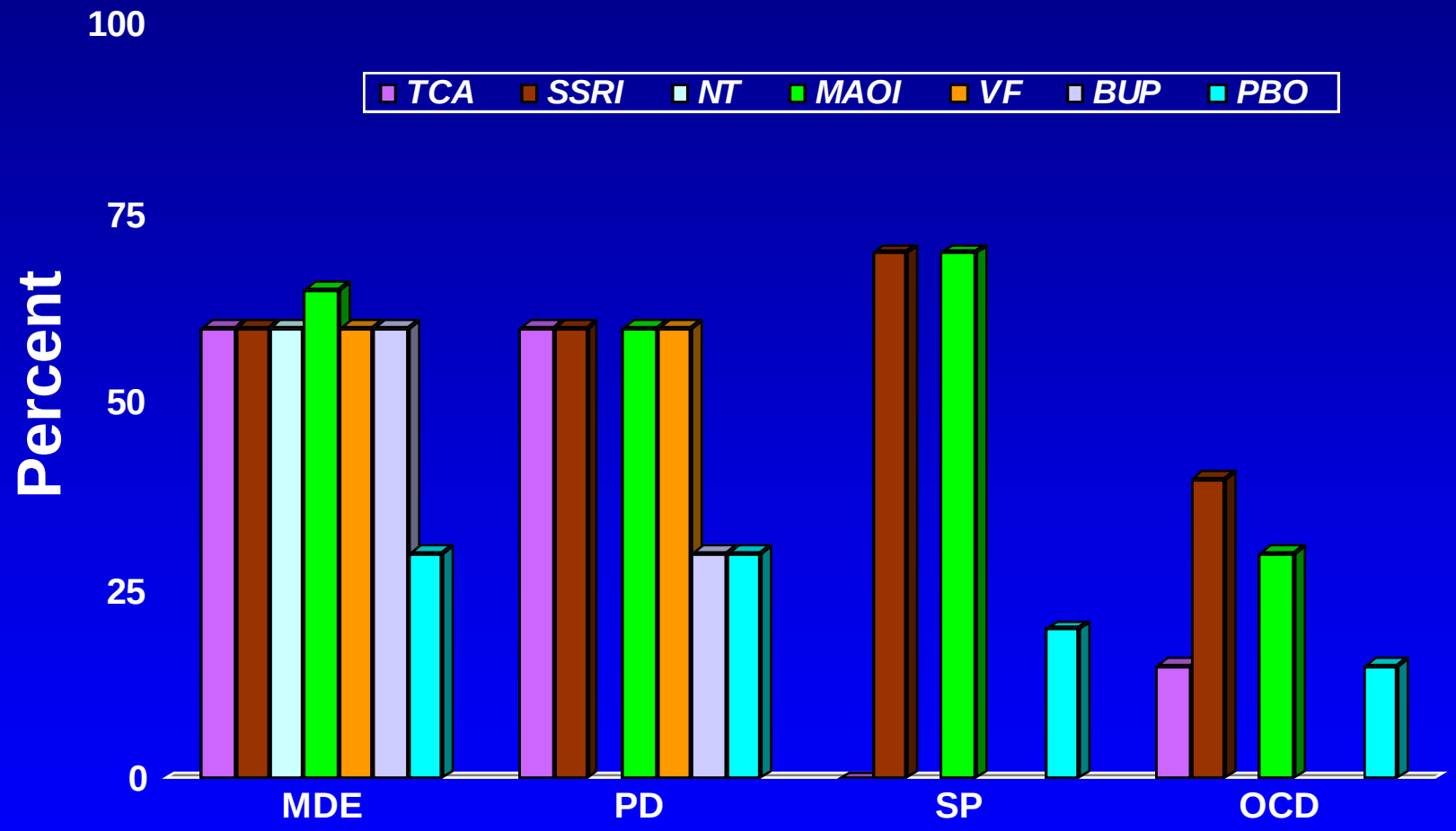
- Deficiency of norepinephrine causally related to symptoms (Schildkraut, 1965)
- Deficiency of norepinephrine and serotonin related to symptoms (van Praag & Korf, 1971)
- Depletion of brain amines by reserpine can precipitate depression
- Reduction in brain norepinephrine in depressed patients can precipitate depression

Distribution of Norepinephrine in the Brain




NE
5-HT
DA
Energy
Interest
Anxiety
Irritability
Impulse
Mood, Emotion,
Cognitive Function
Sex
Appetite
Aggression
Motivation
Drive

RANGE OF EFFICACIES OF AD AGENTS*



*Atypical > TCA

*For purposes of showing differences in range of efficacy-May change with new evidence

Chronic Stress, Anxiety, and Depression

- During chronic stress, synthesis of norepinephrine in the brain is increased
- This leads to overactivity of the noradrenergic system, hyperarousal, and anxiety
- The chronic hypersecretion of cortisol results in secondary changes in neuronal structure and function in the brain (eg, Cushing's disease). This could provide a neurotransmitter basis for depression

MAJOR DEPRESSIVE DISORDER
Acetylcholine
Probable Trait Marker

- Increased cholinergic sensitivity occurs in 40–50%
- Many of patients' relatives have this abnormality
- Abnormality does not improve with treatment

MAJOR DEPRESSIVE DISORDER
Genetics
35–70% Variance Accounted For

- Severe endogenous depression higher — ε50%
- Milder depressions (often atypical) in females lower — 23–30%
  - May have more male relatives with alcoholism

MAJOR DEPRESSIVE DISORDER
40–60% Abnormal Endocrine Challenge Tests
Abnormalities Are More Common in Melancholic Depression

- General rule #1
  - If an agent normally suppresses a hormone, nonsuppression often occurs in depression
    - e.g., dexamethasone 1 mg given at 11 p.m. normally will suppress cortisol for at least 24 hrs, but in depression, nonsuppression often occurs after 16 hrs

MAJOR DEPRESSIVE DISORDER
40–60% Abnormal Endocrine Challenge Tests
Abnormalities Are More Common in Melancholic Depression

- General rule #2
  - If an agent normally stimulates a hormone, blunting of this response often occurs in depression
    - e.g., thyroid releasing hormone (TRH) increases TSH secretion, but in depression there is blunting of this response

GRIEF *vs* DEPRESSION

Grief	Depression
Functional impairment <2 mo	Impairment >2 mo
Fluctuating anhedonia	Relatively fixed anhedonia
Self-esteem preserved	Self-esteem decreased
Functioning: "muddles through"	Functioning severely impaired
Guilt not generalized: focuses on better care of deceased	Generalized guilt
Passively suicidal or not at all	Often actively suicidal

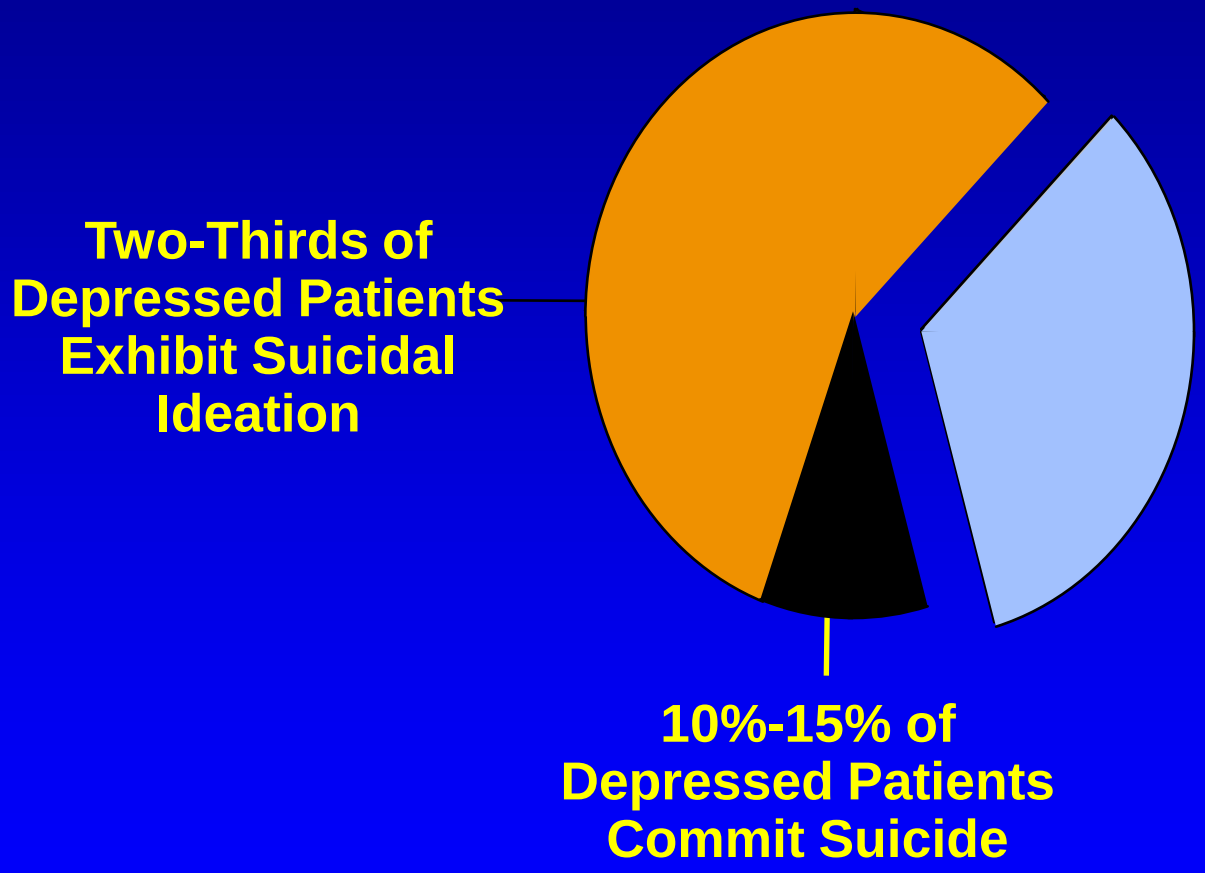
MAJOR DEPRESSIVE DISORDER
Common Presenting Complaint in Medical Settings

- Anxiety: >50% will have depression
- Insomnia
- Fatigue
- Sexual dysfunction
- Chronic pain
  - e.g., tension headaches, back pain, etc.
- Somatization
  - e.g., increase in all “medical” complaints
- Cognitive impairment
  - in elderly (pseudodementia)

SUICIDE RISK IN DEPRESSION
Lifetime Rates

- 10–15% risk in untreated:
  - Major depressive disorder
  - Dysthymic disorder

Suicide Rates Due to Depressive Disorders



Kaplan & Sadock, 1991
WPA/PTD Educational Program on Depressive Disorders

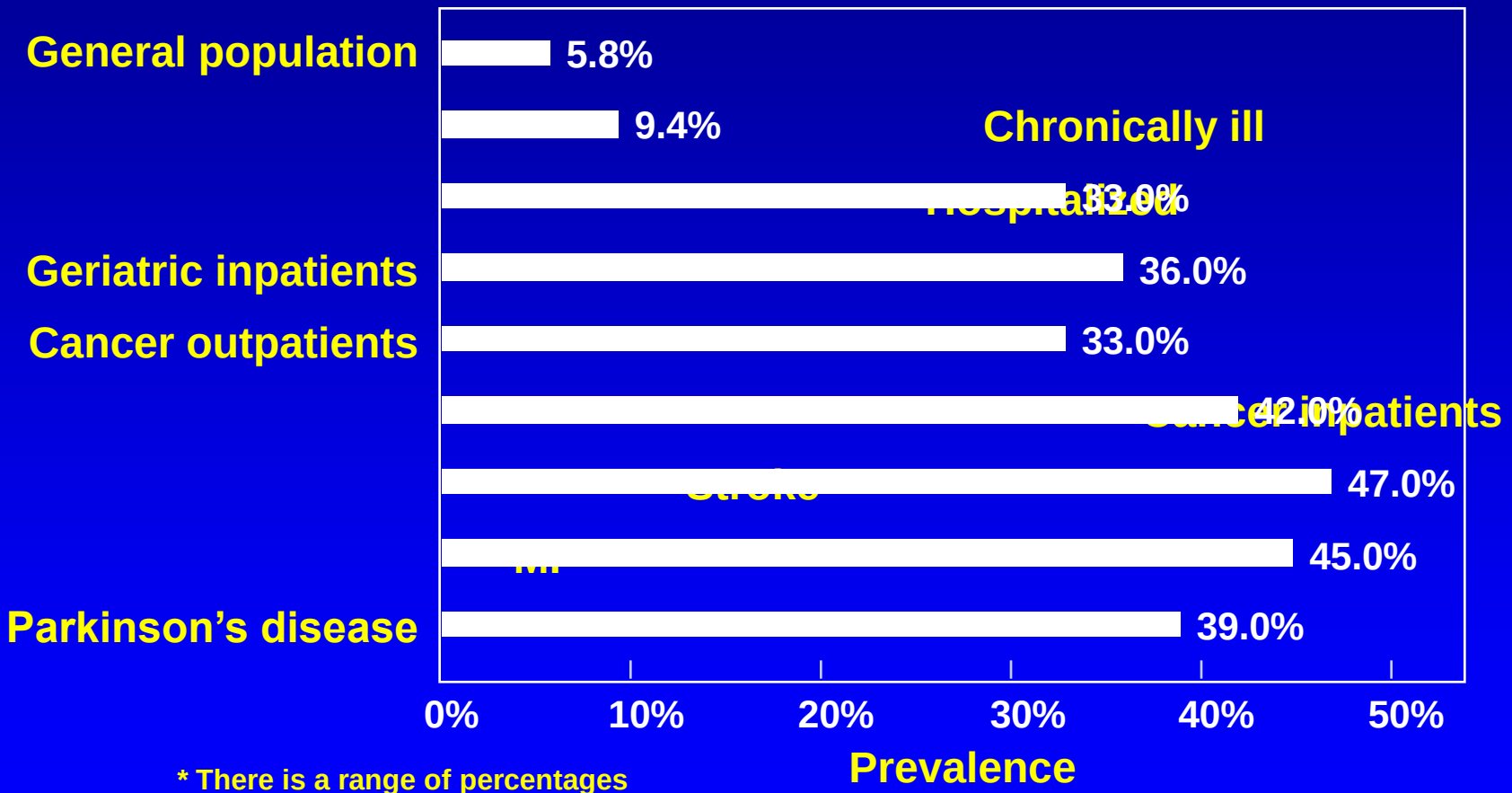
Differential Diagnosis of Depression

Mimicking Condition	Symptoms	Differentiators
Substance abuse – Alcohol – Cocaine – CNS stimulants – Marijuana	Depression Mood changes Apathy Loss of energy	Medical history Family history Blood screen Urine screen
Schizophrenia	Withdrawal Depression Apathy Loss of energy	Difficult to differentiate depression from early schizophrenia
Anemia	Fatigue Apathy Depression	Hemoglobin Hematocrit
Hyperthyroidism/ Hypothyroidism	Apathy Depression	Thyroid function tests
Neoplasia	Depression Mood changes Loss of appetite Apathy	Medical history CT scan MRI Ultrasound

Differential Diagnosis of Depression

Mimicking Condition	Symptoms	Differentiators
Medications – Reserpine – Corticosteroids – Beta- blockers – Estrogen – Progesterone – Benzodiazepines	Depression Fatigue Mania	Medical history
Chronic illnesses – TB – Neoplasia – AIDS – Arthritis	Depression Fatigue Loss of appetite Apathy Anxiety	Medical history Laboratory findings Various imaging techniques
Trauma – Brain injury – Left hemisphere – Injuries	Major depression Loss of appetite Apathy	Medical history CT scan MRI PET scan
CNS disease – Parkinson's – Alzheimer's	Major depression Apathy	Medical history Neurologic exam CT scan MRI,EMG

Prevalence of Depressive Disorders in Various Patient Populations*



* There is a range of percentages depending on the study.

Adapted from WPA/PTD Educational Program on Depressive Disorders

MEDICATION INDUCED DEPRESSION

Very Few Medications Have Been Proven to Cause Depression

- Many cases reported of a med “associated” depression, but causality harder to prove
- Rate of depression must be higher than the baseline of the population studied
  - Interferon for melanoma-80% incidence in 12 weeks documented (Nemeroff et al, 1999 APA)

MEDICATION INDUCED DEPRESSION

Very Few Medications Have Been Proven to Cause Depression

- Often a proper assessment for depression is not made before the drug is started
  - many cases may have already had depression
- Drug might idiosyncratically induce depression in an individual but not in a general population

ESTROGEN-INDUCED DEPRESSION
Oral Contraceptives

Often Characterized by Low Energy, Hypersomnia

- 50 µg qd dose
  - 12% rate of depression
- Not on estrogen
  - 6% rate of depression
- 50% of women depressed on estrogen had low B_6 activity
- Possible mechanism
  - estrogen interferes with B_6 metabolism, competes for B_6 receptor
  - B_6 is important in neurotransmitter metabolism

ESTROGEN-INDUCED DEPRESSION

- Treatment is
  - pyridoxine (B_6) 25–50 mg bid
  - >90% response in low B_6 level group
  - >30% (placebo rate) response in normal B_6 level group
- Unknown if present doses of estrogen (30–35 µg) are depressogenic, and now many women routinely take B_6

CLUES TO MEDICAL CAUSE OF DEPRESSION

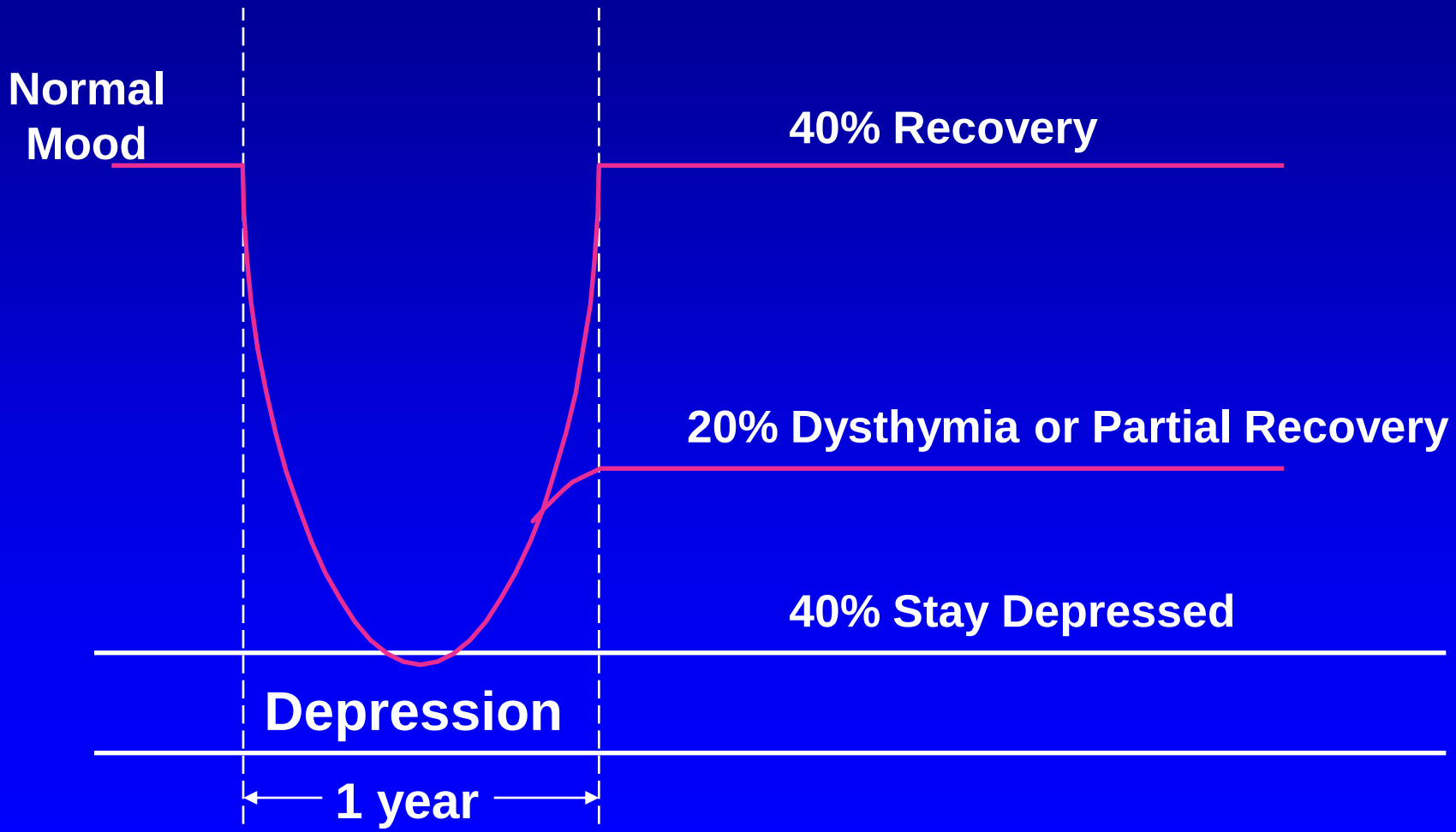
- If there is no pain or discomfort, most medical conditions, unlike depression, have:
  - hypersomnia
  - energy better in a.m.
- Almost no medical condition, unlike depression, has
  - energy better in p.m.
  - hyperphagia

DEPRESSION AND DEATH

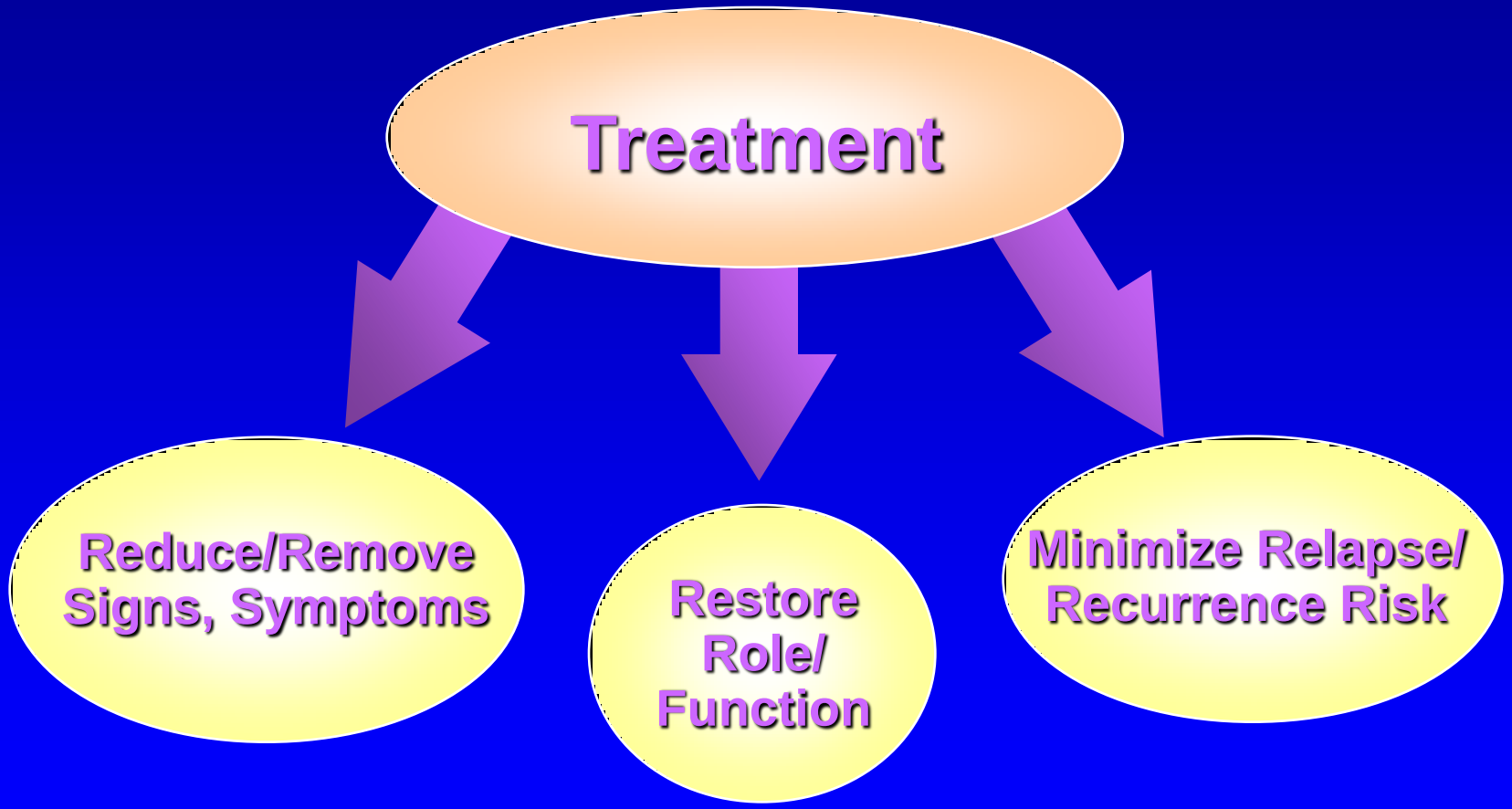
- Population studied: 3,007 adults in New Haven
- Follow-up period: 15 months
- Main findings:
  - 4.3 times more deaths in depressed
    - None from suicide
    - Increased risk same for physically healthy and not healthy
  - None were treated for depression
  - Cause of death
    - 63% cardiovascular
    - 22% cancer
    - 15% other (most pulmonary)

Bruce NL, Leaf PJ. AJPH 1989;79(6)

NATURAL COURSE OF UNTREATED DEPRESSION



Depressive Disorders: Treatment Goals

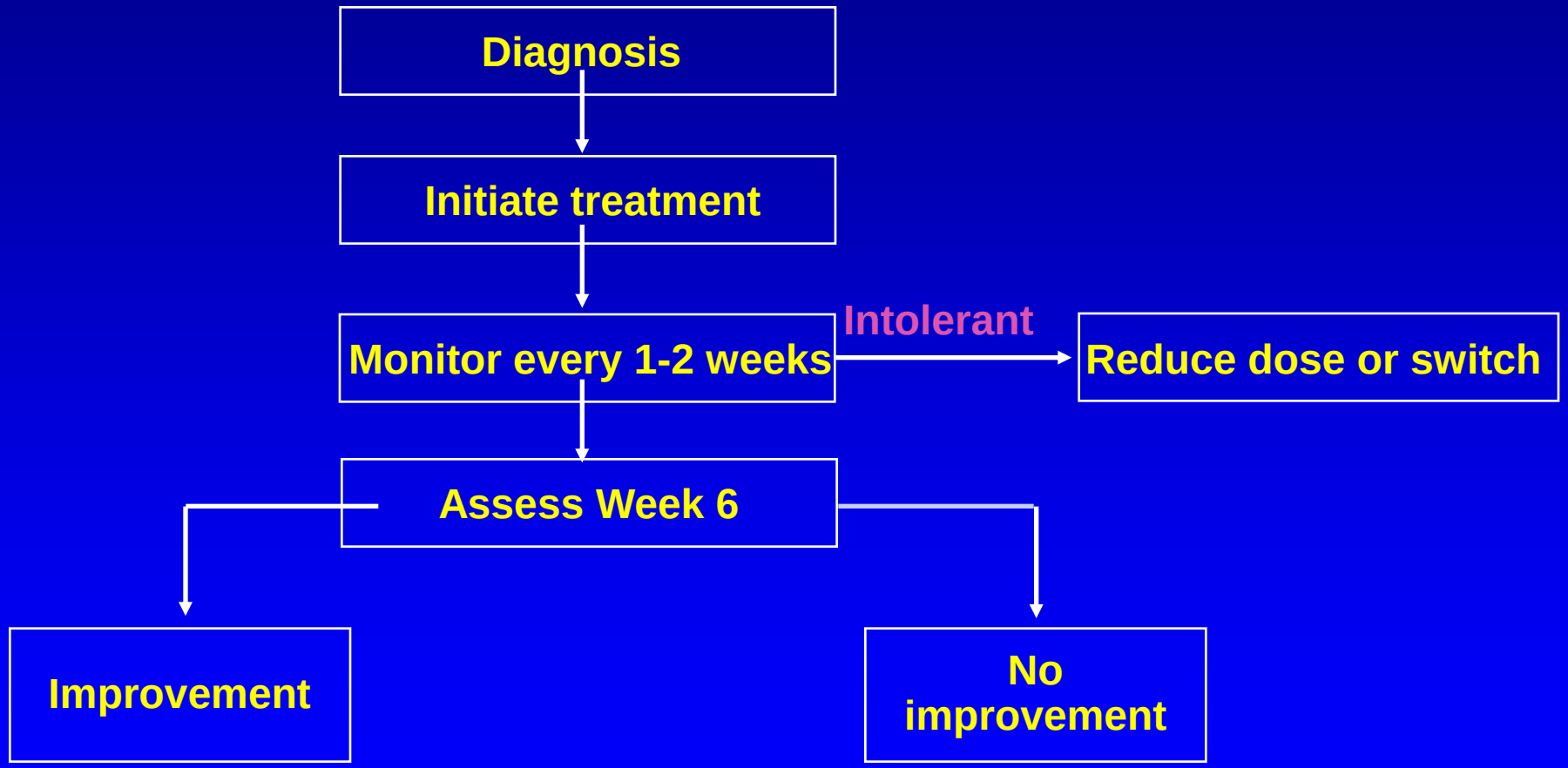


Adapted from WPA/PTD Educational Program on Depressive Disorders

THREE TREATMENT PHASES

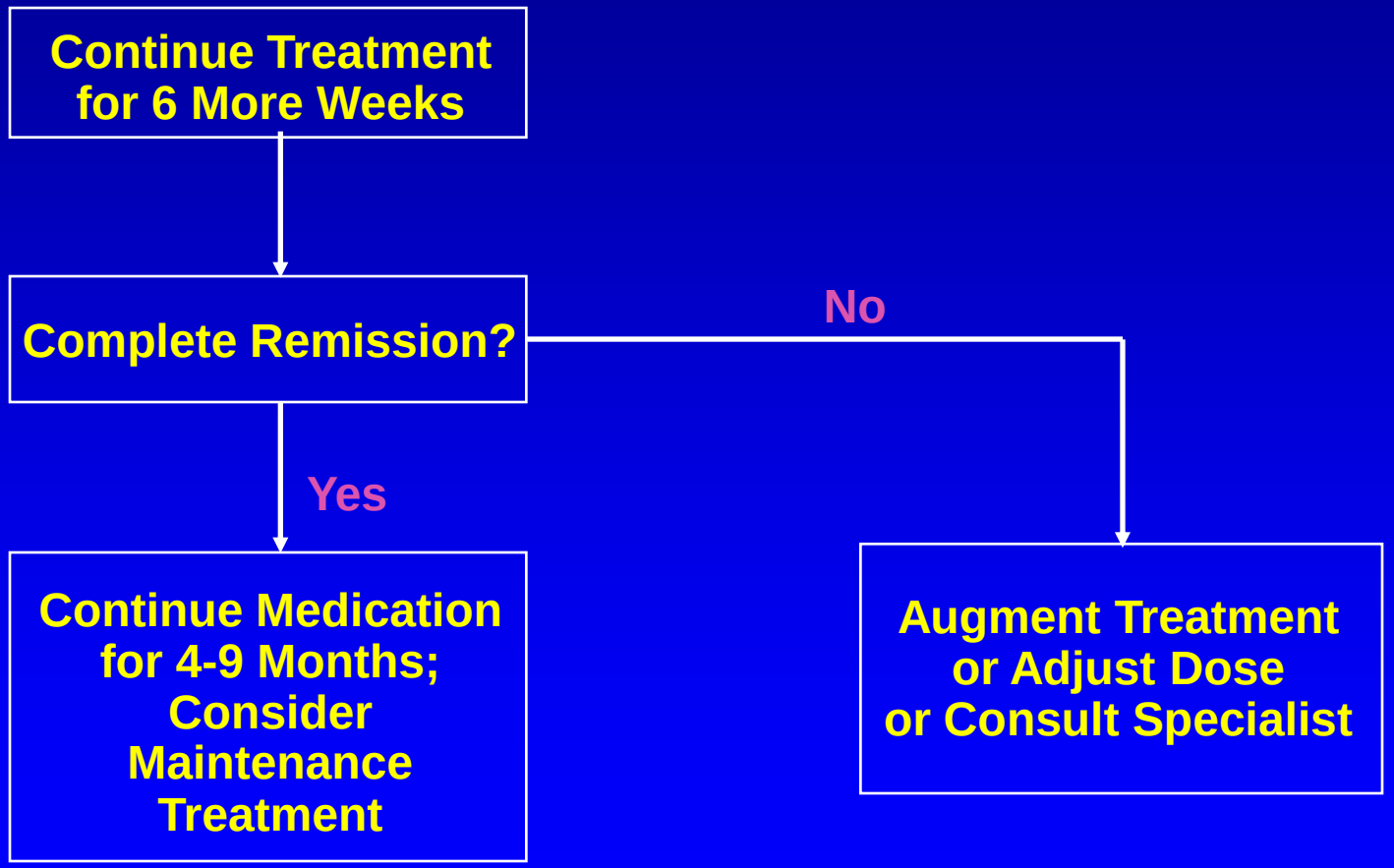
- Acute 6–12 weeks
- Continuation 4–9 months
- Maintenance 1 or more years

Treatment with Antidepressant: Acute Phase



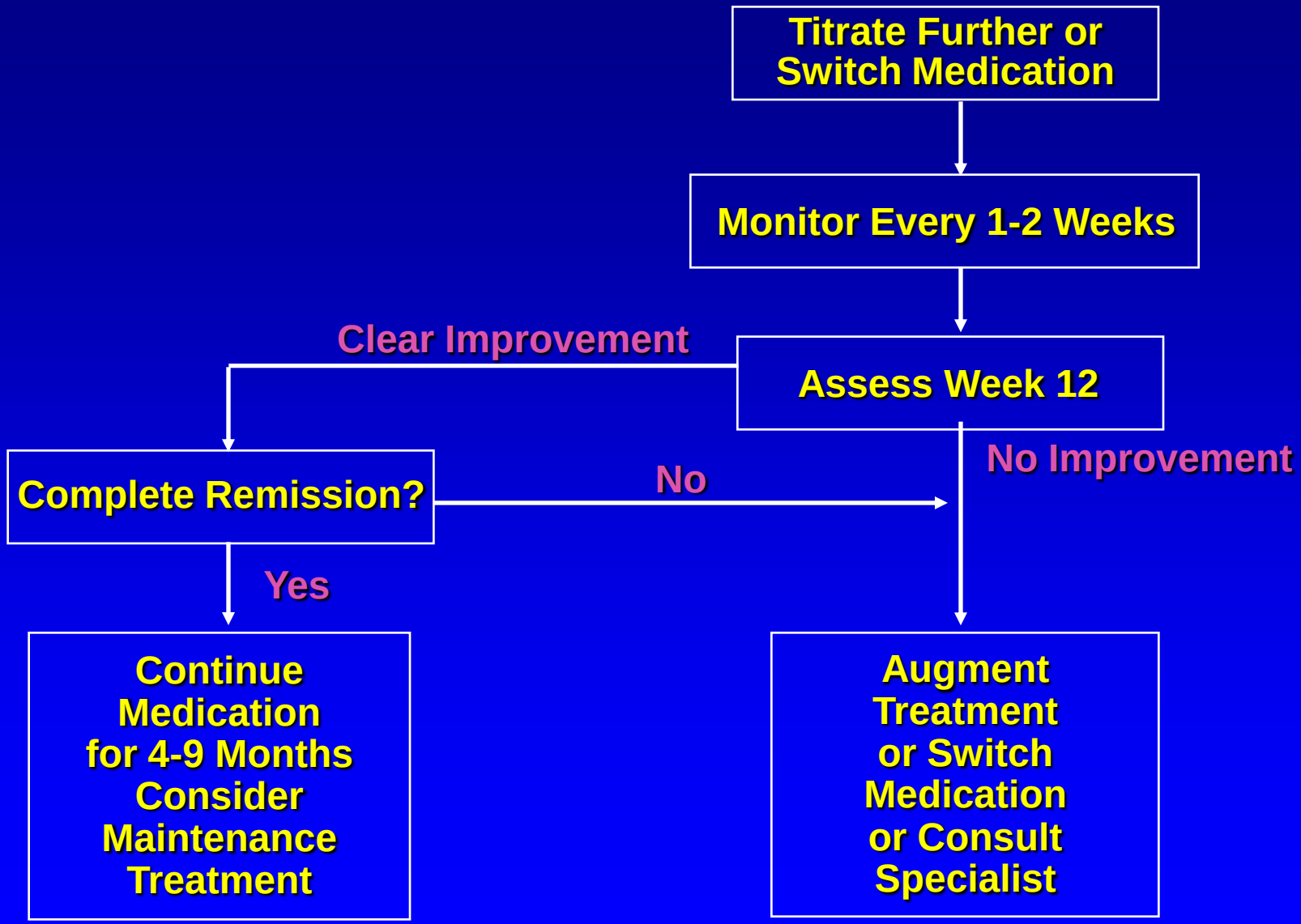
Adapted from WPA/PTD Educational Program on Depressive Disorders

6-Week Assessment: Clear Improvement



Adapted from WPA/PTD Educational Program on Depressive Disorders

6-Week Assessment: No Improvement



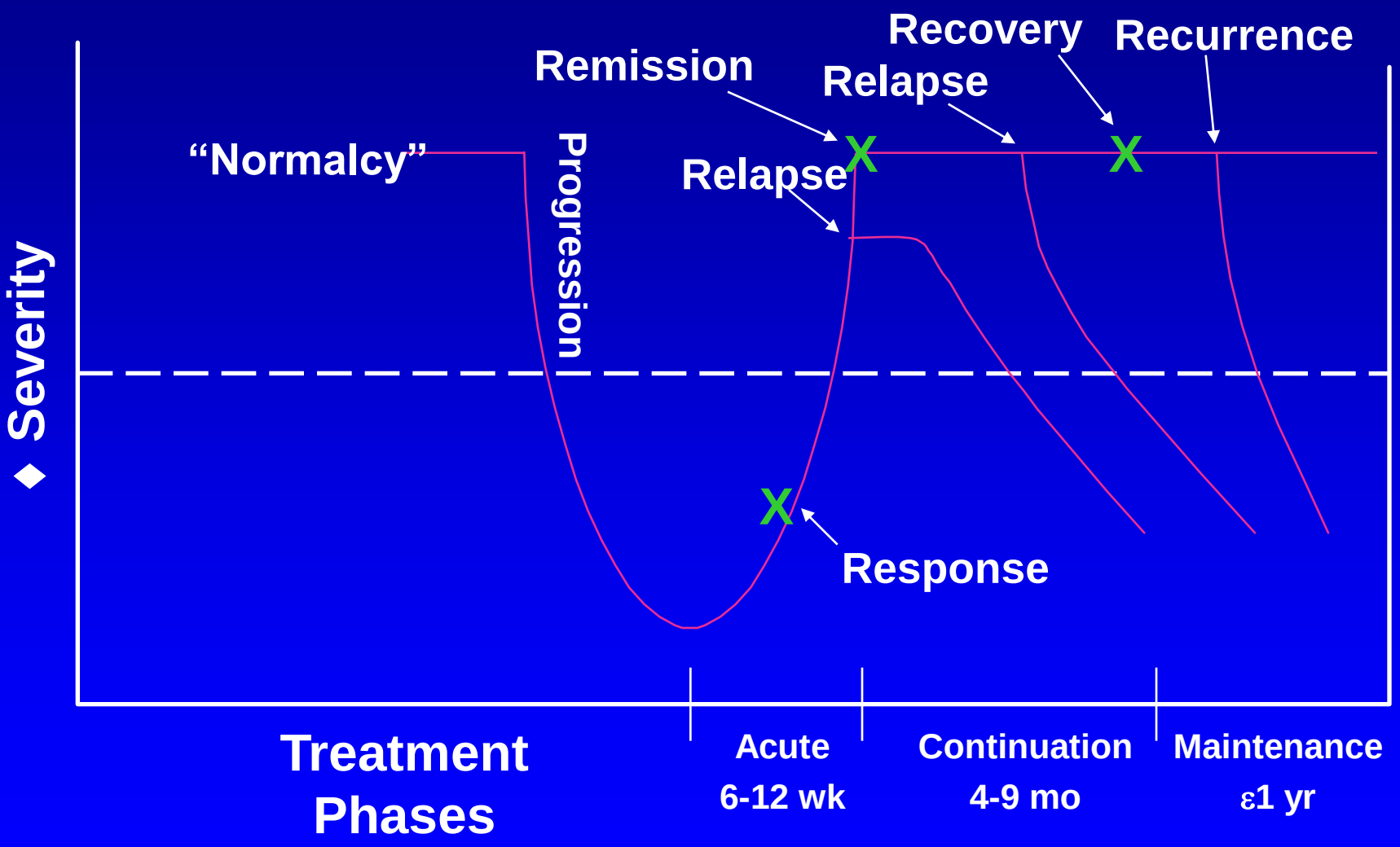
Adapted from WPA/PTD Educational Program on Depressive Disorders

Indications for Formal Psychotherapy as Monotherapy

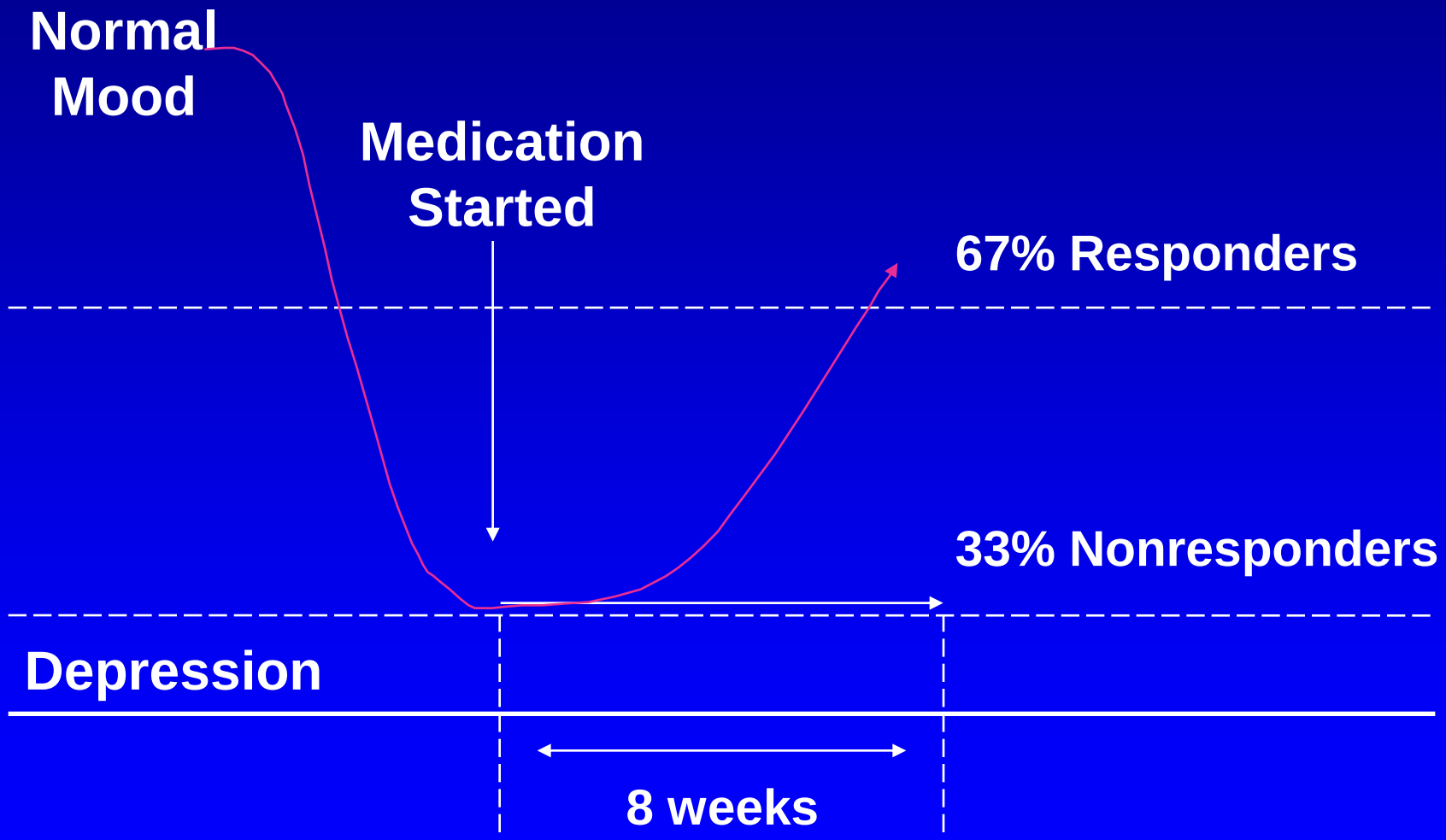
Psychotherapy only if

- Mild disorder
- Psychotic or melancholic features are absent
- History of chronic psychosocial problems

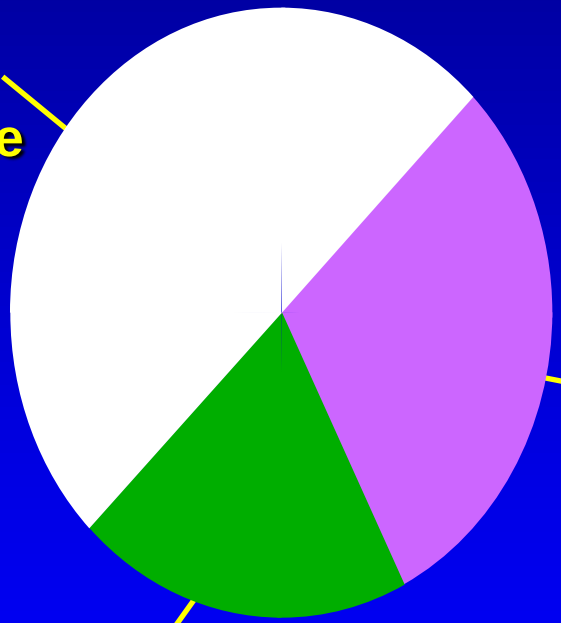
Clinical Status And Treatment Phases Of Depression



Response Rate After Pharmacologic Treatment Of Depression



Recurrence of Depressive Disorders



50% of Patients With a Major Depressive Disorder Experience One Episode

30% of Patients Become Chronically Depressed

20% of Patients Exhibit a Recurrent Course

Merikangas et al, 1994
WPA/PTD Educational Program on Depressive Disorders

INCIDENCE OF RECURRENT MAJOR DEPRESSION

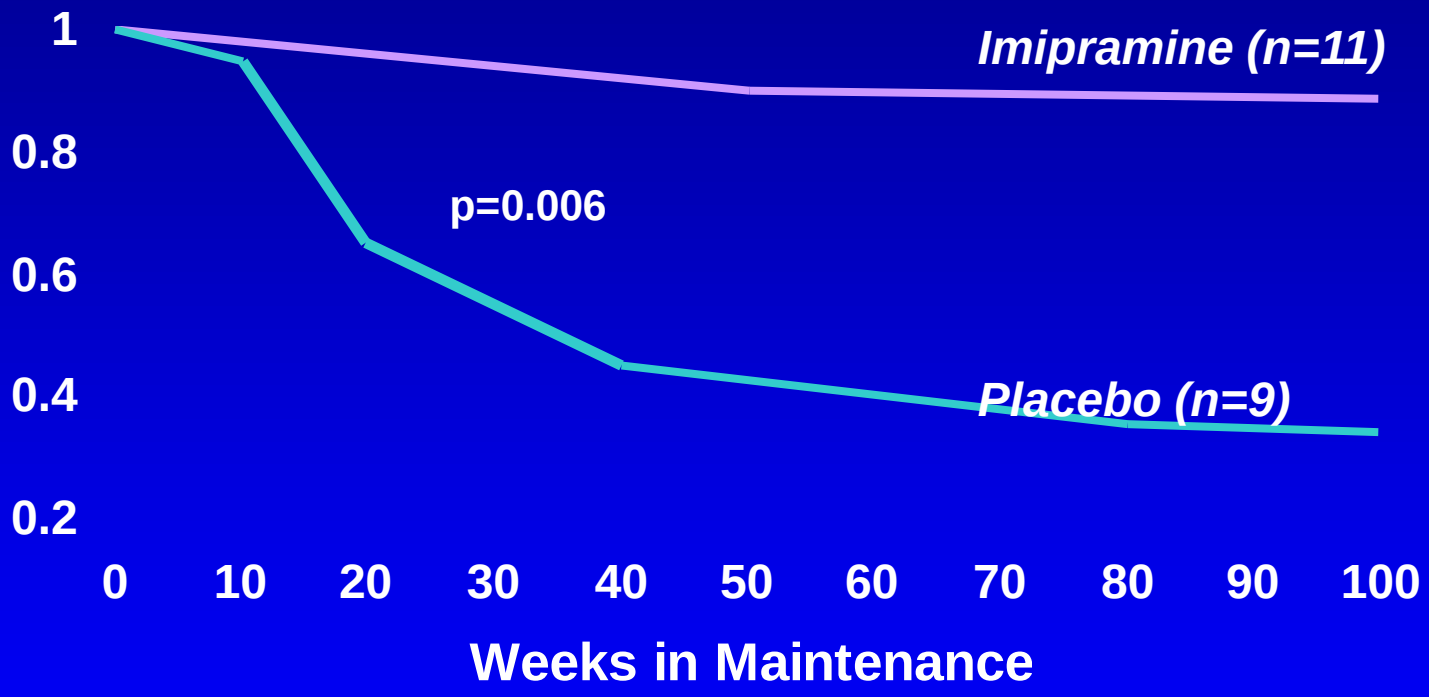
- 50% or more of depressed patients will have at least one subsequent episode of depression during their lifetime
- Even when treated, the risk of recurrence of major depression is significant
  - 50% after 1 episode
  - 70% after 2 episodes
  - 90% after 3 episodes

Kupfer, 1991

CONSIDERATIONS FOR MAINTENANCE TREATMENT

- Very strongly recommended
  - ε3 episodes of major depression
- Strongly recommended
  - 2 episodes of major depression and
    - Positive family history of bipolar disorder
    - History of recurrence within 1 year after previously effective Rx discontinued
    - Early onset of first depressive episode (before age 20 years)
    - Both episodes severe, sudden, or life-threatening in the past 3 years

FIVE-YEAR OUTCOME FOR FULL-DOSE MAINTENANCE THERAPY OF RECURRENT DEPRESSION*

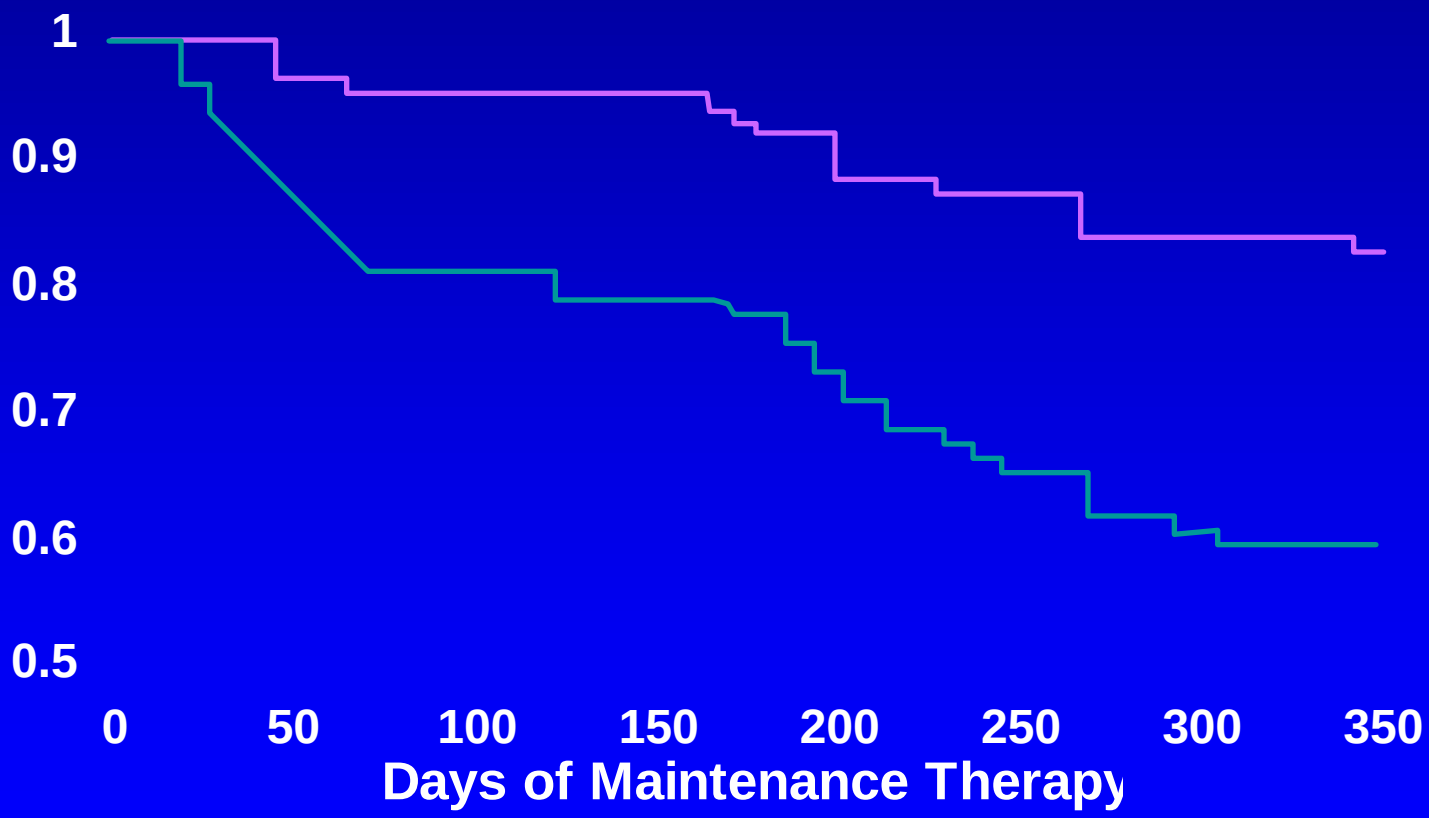


*Patients with no recurrence during a 3-year, full-dose maintenance trial were randomized to 2 years of imipramine or placebo.

Kupfer et al. Arch Gen Psychiatry 1992;49:769

REAPPEARANCE OF DEPRESSION DURING 1-YEAR MAINTENANCE STUDY OF PAROXETINE

Time to Reappearance



Montgomery et al. Presented at ACNP, 1991

PSYCHOTHERAPY OF DEPRESSION

	Response Rate
Mild depression	Placebo = medication
Moderate depression	
– Cognitive-behavioral	70%
– Interpersonal	70%
– Antidepressants	70%
Moderate-severe depression	Antidepressant > psychotherapy

AD Basics : Part 2

Treatment Considerations

PREDICTORS OF TRICYCLIC RESPONSE

- Increased response
  - insomnia
  - anorexia
  - psychomotor retardation
  - anhedonia
  - insidious onset
  - guilt
- Decreased response (response to TCA ≤50% when one of the following symptoms is present
  - hypersomnia*
  - hyperphagia*
  - mood worse in p.m.*
  - panic/severe anxiety (TCAs initially worsen this)

***Atypical symptoms**

BLOOD LEVELS AND CLINICAL RESPONSE

Drug	Curvilinearity*	Optimal Plasma Levels (ng/ml)
Nortriptyline	+	50–150
Amitriptyline	±	70–180 total
Imipramine	–	ε 225 total
Protriptyline	±	70–150
Doxepin	+ (?)	100–200
Desipramine	+ (?)	100–200

For imipramine, doxepin, desipramine, & amitriptyline: typical dose to give effective plasma dose is 3 mg/kg

* + curvilinearity = “therapeutic” with too low or high dose less effective

Adverse Effects Associated With Specific Neuroreceptors

NE	Tremors, tachycardia, augmentation of pressor effects of sympathomimetic amines, sexual dysfunction
5HT	GI disturbances, increase or decrease inanxiety, sexual dysfunction
D_1	Psychomotor activation, antiparkinsonian effects, aggravation of psychosis
D_2	Extrapyramidal movement disorders, endocrine changes, sexual dysfunction (males)

Richelson E. *Mayo Clin Proc.* 1994.

Adverse Effects Associated With Specific Neuroreceptors (cont.)

H_1	Potentiation of central depressant drugs, drowsiness, sedation, weight gain, hypotension
Musc	Blurred vision, dry mouth, sinus tachycardia, constipation, urinary retention, memory dysfunction
$\alpha_{1\&2}$	Postural hypotension, dizziness, reflex tachycardia

AGE AND CONFUSIONAL RISK WITH TCAs

Age	Risk Rate
10–29	0%
30–39	4%
40–49	25%
50–59	33%
60–69	43%
70–79	50%

INITIATING TCA TREATMENT
Imipramine

- Example
  - 70 kg man
- Target dose
  - 200–250 mg/day
- First dose
  - 25–50 mg qhs X2–5 days until tolerance to side effects develops
- Later dose increases
  - varies depending on side effects
  - 25–75 mg increases
- Maintenance dose = acute effective dose

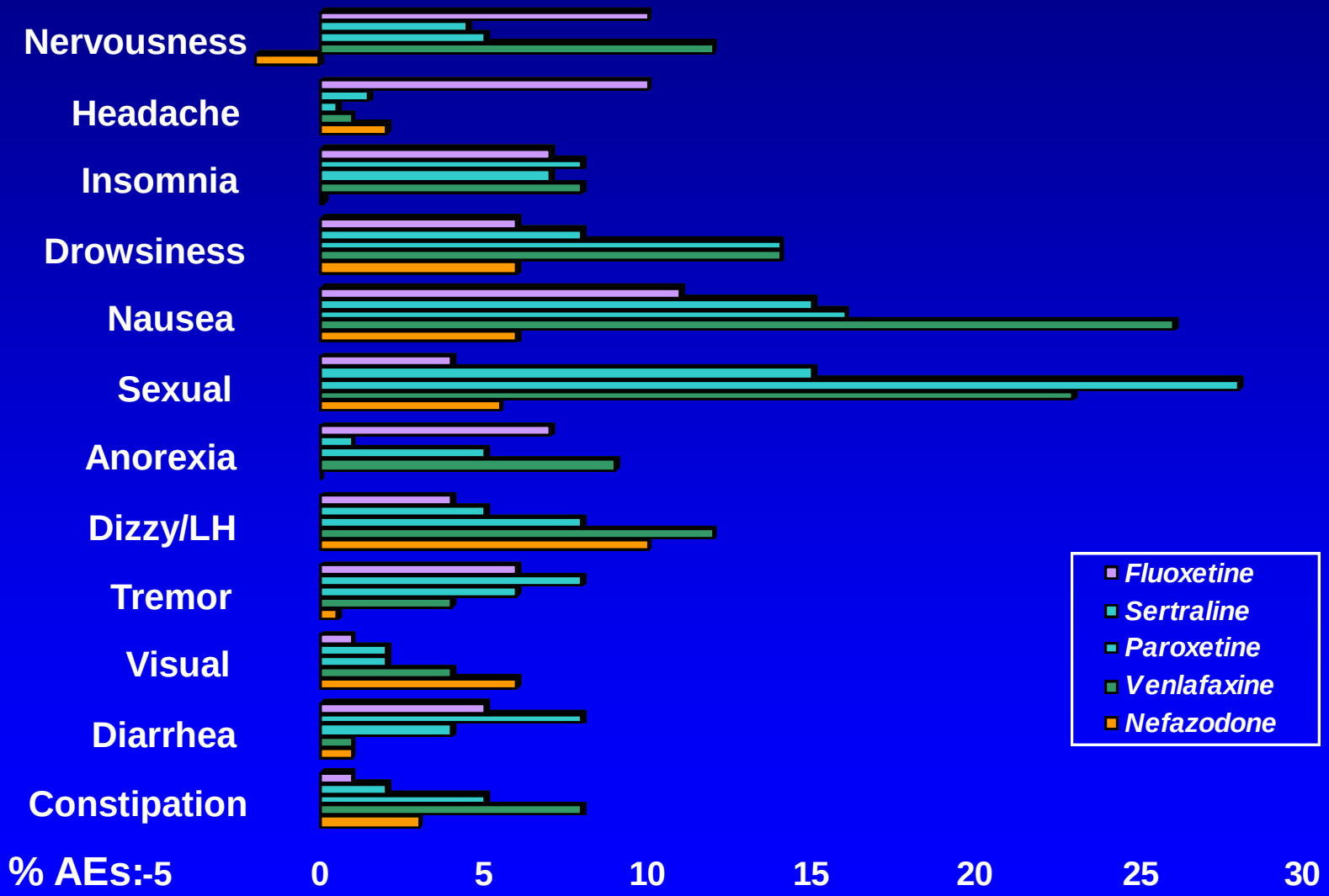
DYSTHYMIC DISORDER
Most with "Typical" Symptoms

- 4 weeks Rx
  - Imipramine = placebo = 50% decrease
- 6 weeks Rx
  - Imipramine (74%) > placebo (50%)
- Conclusion
  - High placebo response
  - Need longer trials

ADVANTAGES TO POST-TCA ANTIDEPRESSANTS

- Lower side effects
- Lower dropout rate
- Very low toxicity in overdose

PDR: ADVERSE EFFECT INCIDENCE



DROPOUTS SECONDARY TO SIDE EFFECTS

Paroxetine	21%
Venlafaxine	19%
mirtazapine	16%
Nefazodone	16%
Sertraline	15%
Fluoxetine	15%
Bupropion SR	9%
TCAs	30%
Tertiary	>32%
Secondary	26%

LOW TOXICITY IN OVERDOSE

- Fluoxetine
- Sertraline
- Paroxetine
- Trazodone
- Venlafaxine
- Nefazodone
- Citalopram
- Mirtazapine
- Reboxetine

SEROTONIN REUPTAKE INHIBITORS *vs* TCA

- Typical depression: same
  - TCA possibly superior in geriatric/severe melancholic depression (still controversial)
- SSRI superior in depression with
  - panic disorder
  - hypersomnia
  - hyperphagia
  - mood reactivity
  - mood worse in p.m.
  - profound anergy
  - delusions (?)

PHARMACOLOGY OF SSRI ANTIDEPRESSANTS

	Half-Life	Protein Binding	Enzyme Inhibition Effects*
Fluoxetine	48–72 hr	94%	>80% IID6
Norfluoxetine	7–9 dy		
Sertraline	26 hr	98%	30% IID6 <20% IIIA3/4
Desmethylsertraline	72 hr		IID6
Paroxetine	26 hr	94%	>80% IID6
Fluvoxamine			

*At starting dose

SSRI SIDE EFFECTS
Similarities (Drug Minus Placebo)

	Fluoxetine	Sertraline	Paroxetine
Insomnia	7%	8%	7%
Diarrhea	5%	8%	4%
Sweating	5%	6%	9%
Sexual dysfunction	30–35%	30–35%	30–35%

SSRI SIDE EFFECTS
Differences (Drug Minus Placebo)

	Fluoxetine	Sertraline	Paroxetine
Nausea	11%	15%	16%*
Somnolence	—	8%	14%*
Nervousness/ Agitation	6%*	—	—
Anorexia	7%*	1%	5%
Dry mouth	—	7%*	6%
Headache	5%*	1%	0%
Constipation	1%	2%	5%*

*Drug with most

SSRI DOSING AND OUTCOME IN DEPRESSION

- Fluoxetine 20 = 40 ε 60; 10 = 20?
- Sertraline 50 = 100 = 150
- Paroxetine 20 = 40 = 50

CITALOPRAM
Characteristics

- Substrate of P450 2C19
- Minimal P450 inhibition
- 80% protein-bound
- Peak plasma level: 1–6 hours
- Parent elimination half-life: 33 hours
- No active metabolites
- Standard dose range: 10–60 mg/day

European Prescription Data

	Fluoxetine	Paroxetine	Citalopram	Sertraline
Recommended Starting Dose	20 mg/day	20 mg/day	20 mg/day	50 mg/day
Average Daily Dose	21.5 mg/day	22.2 mg/day	21.4 mg/day	63.3 mg/day
Prescriptions > Rec. Starting Dose	6.5 %	12.6 %	9.3 %	23.2 %

IMS Data from France, Germany, Italy, the UK and Spain

SSRIS
Pros

- Low side effects and dropout rates
- Once a day dosing
- Starting dose often sufficient
- Very low toxicity in overdose
- Very low mania induction
  - <3% in bipolars
- Effective in atypical and typical depressions
- Effective in broad spectrum of comorbid disorders
  - e.g., anxiety disorders, anger, impulsive, premenstrual dysphoric disorder

SSRIS
Cons

- Significant sexual side effects
- All with insomnia, diarrhea, sweating, and nausea risk
- Significant drug interactions with other meds
  - Especially with fluoxetine, paroxetine, and fluvoxamine
- Nervousness, agitation, and/or anorexia occasional problem with fluoxetine
- Somnolence a problem with paroxetine and occasional problem with sertraline

PHARMACOLOGY OF ATYPICAL ANTIDEPRESSANTS

	Half-Life	Protein Binding	Enzyme Inhibition Effects*
Venlafaxine	5 hr	30%	None
Nefazodone	3–26 hr	99%	III-A3/4
Bupropion	4–24 hr	80%	IIB6

*At starting dose

COMPARING ATYPICAL NEW DRUGS
Drug Minus Placebo Rates in %

	Nefazodone	Venlafaxine	Bupropion
Dry mouth	12	11	9
Somnolence	11	12	0
Nausea	10	26	3
Dizziness	12	12	6
Constipation	6	8	6
Insomnia	2	8	3
Headache	3	1	3
Sweating	0	9	8
Agitation	0	2	10

SPECIAL SIDE EFFECTS OF ATYPICAL NEW ANTIDEPRESSANTS

- Venlafaxine
  - 3% (75 mg) – 13% (375 mg) increase (10–15 mm Hg) in systolic blood pressure
- Nefazodone
  - 2.6% over placebo postural blood pressure
  - 1.5% over placebo bradycardia risk
- Bupropion SR
  - 0.4% seizure risk at ε400 mg qd
  - 0.1% seizure risk up to 300 mg qd
  - Still not recommended for bulimics and extreme caution advised in seizure disorder, head-injured, or on meds that increase seizure risk

NEFAZODONE (Serzone®) IS CHEMICALLY RELATED TO TRAZODONE

With the Advantage of Less Sedation and Less Sexual Side Effects

- Combined actions
  - 5HT2 antagonism and SARI
- Downregulates post-synaptic $5HT_2$ receptors

NEFAZODONE CHARACTERISTICS

- Protein binding >99%
  - Studies with normal volunteers demonstrate no availability effects on other extensively protein-bound drugs (ε20 drugs studied)
- P450IIIA$_4$ inhibitor
  - Triazolobenzodiazepines increased, use caution (alprazolam, estazolam, triazolam, midazolam increased)
  - Two H_2 blockers are contraindicated
    - terfenadine (Seldane®) increased
    - astemizole (Hismanal®) increased
- Nefazodone inhibits its own metabolism
  - Multiple dosing resulting in higher levels than expected

DOSING OF NEFAZODONE

- Goal
  - 300–600 mg/day in nonelderly
  - 150–500 mg/day in elderly
- Begin
  - 100 mg bid
  - In elderly or debilitated 25–50 mg bid
- Food
  - Delays & decreases in absorption
- Renal disease
  - No effect of clearance
- Liver disease
  - 25% increase in levels
- Elderly
  - multiple dosing
  - 10–20% increase in levels

NEFAZODONE (Serzone®)
Infrequent But Important Events

	Nefazodone	Placebo
Postural hypotension	5.1%	2.5%
Bradycardia	1.5%	0.4%
Mania		
Unipolar	0.3%	0.4%
Bipolar	1.5%	0%
New seizures	0%	0%
– Priapism	0% (but possible)	
– Lethal overdose	0% (7 attempts 1000–11200 mg)	

Nefazodone In Severe Melancholic Inpatient Depression

- HAM-D average: 29.7
- Average dose: 500 mg
- Nefazodone response: 54%
- Placebo response: 18%
- Percent of treatment-resistant patients was not reported

NEFAZODONE
Pros

- Dropouts only 16%
- Low/limited sexual side effects
  - Good substitute for SSRIs
- Weight gain or loss not frequent
- OK in renal and liver disease
- Low mania induction in bipolars
- Low seizure rate
- Effectively treats comorbid anxiety and insomnia
- Effective in severe, melancholic inpatient depressions

NEFAZODONE
Cons

- BID dosing
  - 2 new studies demonstrated qd dosing equally effective
- Priapism theoretical risk
- Mild bradycardia risk
- Very protein bound (>99%)
- Mild postural hypotension risk

BUPROPION SR
Pharmacodynamics

- Weak neuronal uptake of NE, 5HT, and DA
- Unknown mechanism of action, but believed to be NE and/or DA
- Ultimately downregulates adrenergic receptors

BUPROPION SR
Pharmacokinetics

3 main metabolites

Bupropion metabolized by P450 IIB6

Metabolite	T$_{\frac{1}{2}}$ (hr)	Peak Level*	Potency
Bupropion	21±9	1	1
Hydroxybupropion	20±5	17 times	1
Theohydrobupropion	37±13	1.5 times	0.1–0.5
Erythrohydrobupropion	33±10	7 times	0.1–0.5

*Proportion compared to bupropion

DOSING OF BUPROPION SR

- Goal: 300 mg/day
  - May have therapeutic “window,” with 300 mg/day superior to 450 mg/day
- Begin: 100–150 mg qAM X4+ days
- Increase to 100–150 mg BID (at least 8 hours between doses)
- Renal disease
  - Unknown effects on clearance
- Liver disease
  - ≈ 50% increase in $T_{1/2}$ of hydroxybupropion
  - No effect on bupropion and other metabolites
  - Start with 100 mg qAM

BUPROPION FOR FLUOXETINE-INDUCED SEXUAL DYSFUNCTION

Sexual Dysfunction = Orgasm Delay or Failure

- N=39 (22 females, 17 males) with sexual dysfunction on fluoxetine
  - 31 completed
- On bupropion monotherapy
  - 26 patients (84%) — complete remission
  - 3 patients (10%) — partial remission
    - 2 had pre-existing sexual dysfunction

Treatment-Resistant Depression

Bupropion

- TCA nonresponders (n=1,301)
  - 54% had good or better response to bupropion
- Fluoxetine nonresponders
  - 47% responded to bupropion
- Bupropion's unique mechanism of action may be an advantage

BUPROPION SR
Pros

- Low overall side effects make it the lowest in dropouts (10%)
- Unique (but unknown) mechanism of action makes it a high choice in treatment-resistant depression
- Low mania induction
- Low/no sexual side effects
- Minimal drug metabolism interactions through P450 IIB6 metabolism

BUPROPION SR
Pros

- Equally effective in
  - Anxious and nonanxious depressions
  - Typical and atypical depressions
- Low suicide risk
- Dual effectiveness in ADHD with depression
- Can reduce addiction risk (cocaine, nicotine), particularly in those with depression
  - Approved for nicotine dependence (10-week quit rate: 46% on bupropion *vs* 20% on placebo)

BUPROPION
Cons

- Not proven effective for panic or other anxiety disorders

Venlafaxine Has A Profile Similar To Clomipramine
But Without the Anti-Ch and Anti-H Effects

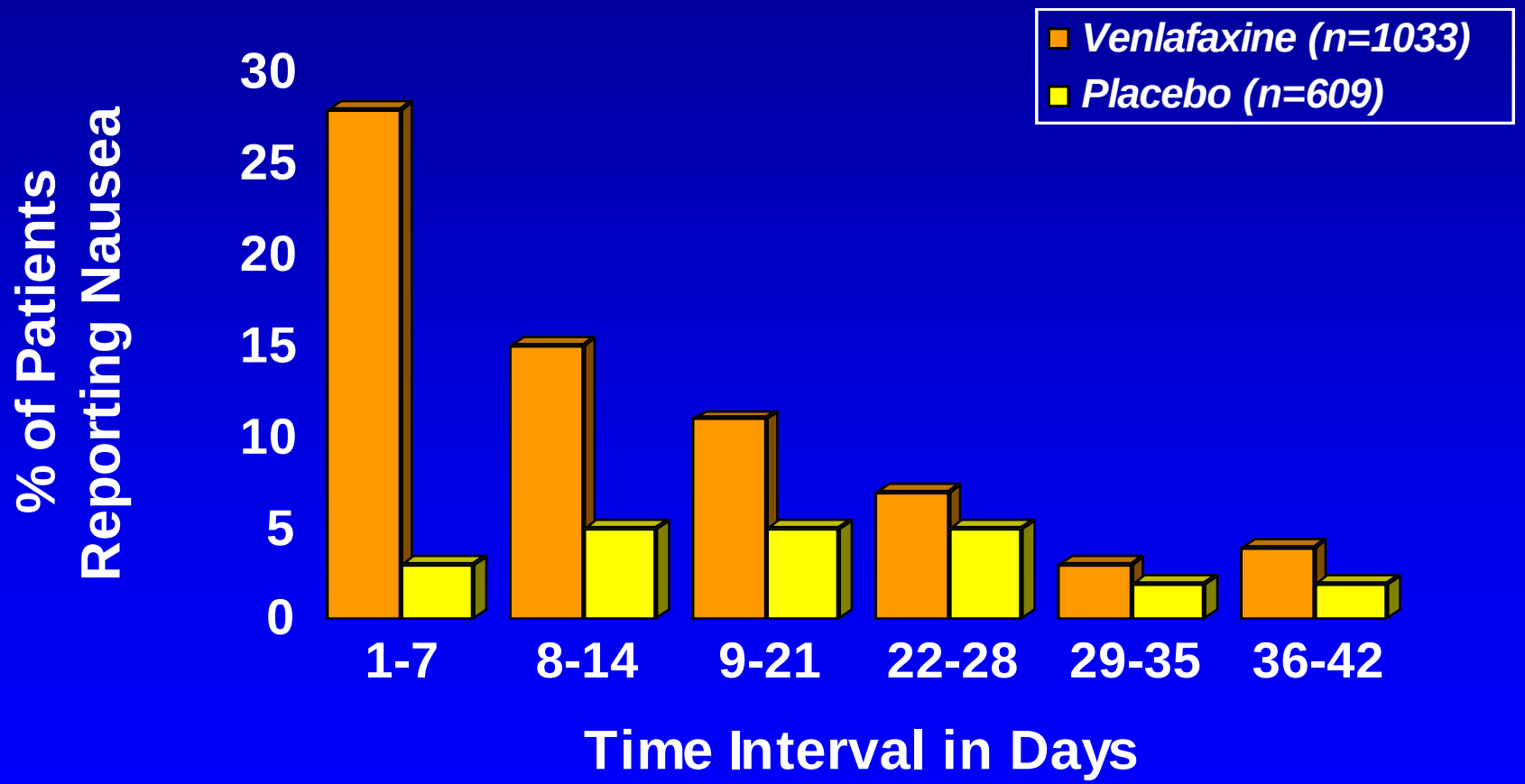
- NE and 5HT reuptake inhibitor
- As effective as other antidepressants
- Modest success with highly resistant pts
- Doses 75 to 375 mg
  - Start at 37.5 or 18.25 mg to avoid nausea
  - Higher doses may be more effective than lower ones
- Side effects
  - Nausea
  - Insomnia (lower doses) and sedation (higher doses)
  - Increased blood pressure (dose-related risk)
  - Sexual dysfunction at >225 mg qd

VENLAFAXINE
Characteristics

- Metabolized by P450 IID6
- Very weak inhibitor of IID6
- 87% renal secretion
- O-desmethylvenlafaxine only major active metabolite

	Protein Binding	T 1/2
Venlafaxine	27±2%	5 hr
O-desmethylvenlafaxine	30±12%	11 hr

NAUSEA: ADAPTION TO VENLAFAXINE
Summary of Placebo-Controlled Trials



Data on file: Wyeth-Ayerst Labs

VENLAFAXINE
Hypertension

	Placebo	Venlafaxine (mg)			
		75	150	225	375
Treatment-emergent hypertension	1.1%	1.1%	—	2.2%	4.5%
Sustained diastolic BP (avg. sustained = 10–15 mm Hg)	2%	3%	5%	7%	13%
Average change in BP (mm)	–2.2	0	0	0	7.2

VENLAFAXINE
Side Effects That Decrease With Dose Increase

	% Treatment Emergent			
	Placebo	150 mg	225 mg	375 mg
Anxiety	4.3	11.2	4.5	2.3
Nervousness	4.3	21.3	13.5	12.5
Insomnia	9.8	22.5	20.2	13.6

Venlafaxine Was Effective For Severely Refractory Depressed Patients

- 70 unipolar
- Mean HDRS
- Documented failure of at least:
  - 3 adequate antidepressant trials
  - 1 attempt at augmentation
- Rapid titration up to 376 mg
- 32.9% responded acutely

Nierenberg et al., 1994

VENLAFAXINE
Pros

- Broad spectrum antidepressant efficacy (GAD-approved)
  - Looks like a TCA and SSRI combined
- Does not inhibit metabolism of other drugs
- Does not significantly displace other protein-bound drugs
- Effective in very treatment-resistant patients

VENLAFAXINE
Cons

- Nausea most common cause of dropouts
- P450 IID6 inhibitors can significantly increase venlafaxine levels
- BID dosing
- High doses risk hypertension, sedation, and sexual dysfunction

MIRTAZAPINE
Pharmacodynamics

- Probable antidepressant effects
  - Noradrenergic and specific serotonergic antidepressant (NaSSA)
- Potent antagonist
  - Post-synaptic $5HT_2$, post-synaptic $5HT_3$ (antinausea?), presynaptic adrenergic autoreceptors and heteroreceptors
- Minimal antagonism
  - $5HT_{1A}$ or $5HT_{1B}$
- No effect on reuptake

MIRTAZAPINE
Results

- $5HT_1$ specifically enhanced
- NE and 5HT release enhanced by adrenergic presynaptic effect
- No SSRI side effects
  - Sexual, nausea, diarrhea, insomnia
- Net effects look like desipramine + buspirone

MIRTAZAPINE
Pharmacokinetics

- Half-life: 20–40 hours
  - 37 hours in women
  - 26 hours in men
- Peak levels: 2–3 hours
- Metabolism: IID6, IIIA4
- Plasma level by dose: linear increase
- Steady state: ε5 days

Pharmacokinetics of Mirtazapine
Side Effects

- Potent H1 blockade
  - Sedation
  - Appetite increase
  - Weight gain
- Minimal muscarinic affinity = minimal dry mouth, constipation, confusion
- Minimal adrenergic blockade
  - Minimal orthostatic blood pressure

MIRTAZAPINE
Dosing

- Range: 15–60 mg qd
- Usual: 15 mg X4–7 days

  30 mg Xε2 weeks

  45–60 mg if 30 mg ineffective or if too much sedation
- Geriatric: 15 mg Xε3 weeks

MIRTAZAPINE
Clearance in High-Risk Populations

- Liver disease: 30% decrease
- Renal disease: 30–50% decrease
- Geriatric: Men: 40% decrease
  Women: 10% decrease

MIRTAZAPINE
Suicide Risk

- 1 fatal in 9 overdoses
  - The one had multiple other meds and normal therapeutic level
- None on mirtazapine alone
- No lab or EKG abnormality up to 900 mg
- Sedative effect could amplify other sedatives

MIRTAZAPINE
Side Effects and Dropout Rate
Drug Minus Placebo

- Somnolence* 36% (10% discont 2° to this)
- Increased appetite 15%
- Weight gain 10%
- Dry mouth 10%
- Constipation 6%
- Dizziness 4%
- Dropouts
  - mirtazapine 16%
  - Placebo 7%

Higher in 15–30 mg range; lower in 45–60 mg range

MIRTAZAPINE WARNING
Agranulocytosis

- N=2,796
- 2 with agranulocytosis
  - <500 mm3 neutrophiles
  - Symptoms: fever, infection
- 1 with neutropenia
  - <500 mm3 neutrophiles and asymptomatic
- Detection
  - 9 to 61 days of Rx
  - All recovered

MIRTAZAPINE
Pros

- Unique mechanism of action
  - May be useful in treatment resistance
- Dropout rate comparable to SSRIs
- Ideal in medically ill with nausea and/or weight loss (e.g., cancer, AIDS)
- Once-a-day dosing
- Multiple degradation pathways reduce risk of drug metabolism interactions

MIRTAZAPINE
Cons

- 0.1% blood dyscrasias
- Significant sedation at low dose range (≤30 mg)
- Significant weight gain
- Untested in treatment-resistant populations
- Not substantially compared with SSRIs and newer drugs

Reboxetine Dosing

- Starting dose - 4-mg bid
- Maximum dose - 10-mg daily
- Elderly Starting dose- 2-mg bid
- Maximum dose- 6-mg daily

Reboxetine Pros

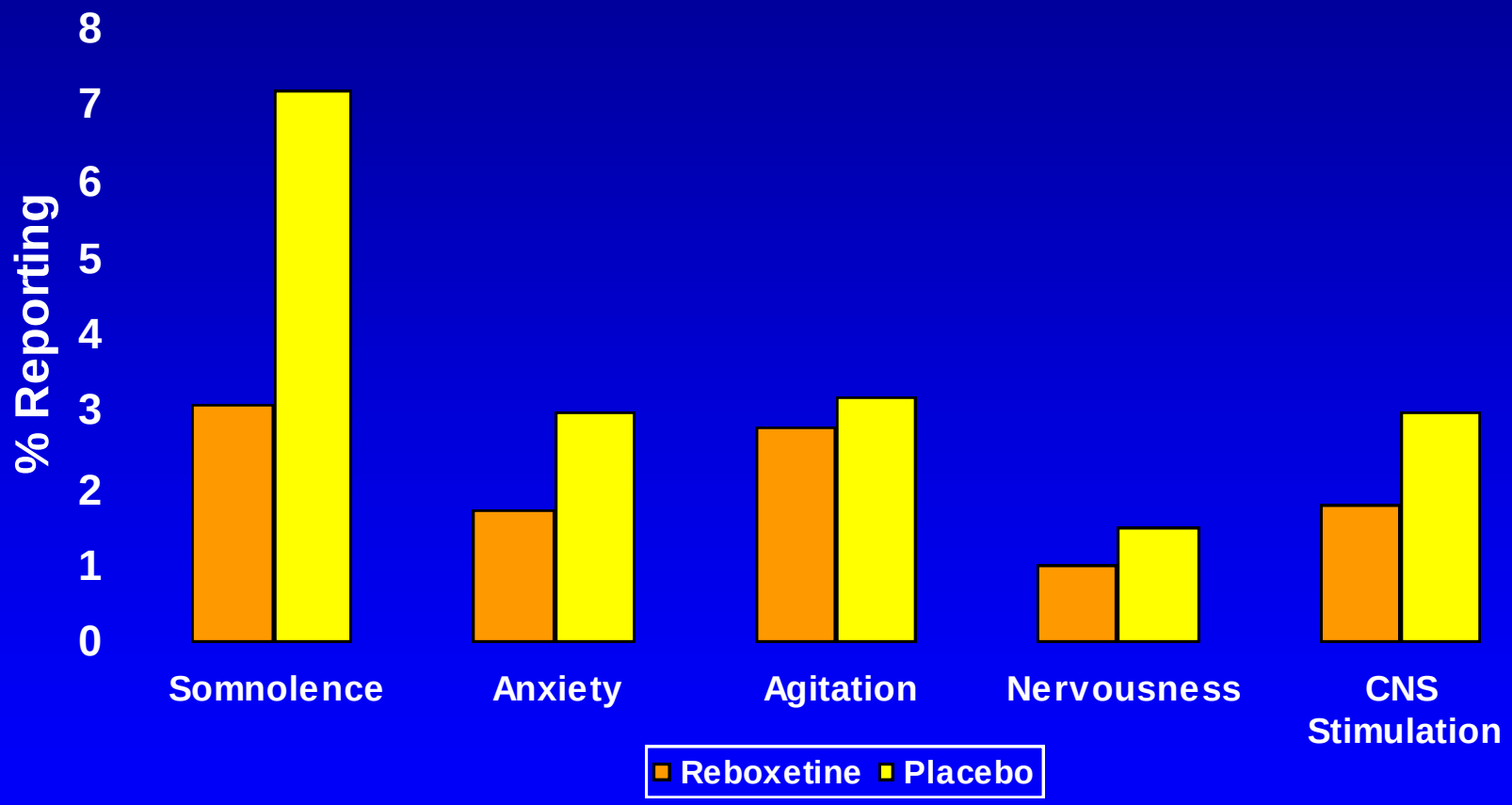
- Efficacy comparable to older, newer ADs
- NE-Selective with better side effects profile
- Safety in overdose
- May be useful in combination with SSRIs

Reboxetine cons

May have more adverse effects than newer agents--still too early to tell

Event	Reboxetine	Placebo
Dry mouth	27 %	15.2%
Constipation	17.8%	9.0%
Headache	14.4%	13.9%
Sweating	12.1%	7.7%
Insomnia	12%	7%
Dizziness	10.2%	5.7%

Reboxetine Treatment Emergent Behavioral Effects -- Daytime Somnolence\Activation Summary



MAOI RESPONDERS

- Typical depression
  - Post (1980) studies suggest efficacy = TCA
- Depression with panic disorder
- Atypical depression
  - hypersomnia
  - hyperphagia
  - mood worse in p.m.
  - (increased reactivity ?)
- Refractory depression
  - regular dose
  - high-dose Parnate (90–170 mg)

MAOI
Administration

- Can be increased to target dose in days
- Low tyramine diet should be started ♠12 hours prior to 1st dose
- Give list of high tyramine foods and dangerous drugs
- Can be given to hypertensive patients
  - Were originally developed as antihypertensives
  - Most common side effect is hypotension

MAOI
Blood Pressure

- Patient should have own blood pressure cuff and learn how to monitor blood pressure
- Nifedipine 10 mg PO bite and swallow is still the best way to bring down acute blood pressure at home
  - No longer recommended in hypertensive medical patients because of risk of overshoot
  - MAOI patients are not chronically hypertensive, and risk of stroke is significant if blood pressure is high enough

PHENELZINE
Long Term Side Effects

- Weight gain (74%)
  - Infrequent with tranylcypromine
- Ankle edema
- Muscle twitching
  - Cyproheptadine?
- Anorgasmia (22%)
  - <2% with tranylcypromine
- Neuropathy
  - Pyridoxine

PSYCHOTIC DEPRESSION
Response Rates

• TCA antidepressants	36%*
• Antipsychotics	47%
• Antidepressants + antipsychotics	77%**
• ECT	78–85%

*2 SSIR alone trials reported ε65% efficacy
**Med trials at least 5 weeks

BUPROPION SR
Cons

- May increase psychosis risk in psychotics and borderlines
- Seizure risks significantly higher in “at-risk” individuals
  - Bulimics, head injury, seizure history
- Seizure risk at 400 mg higher than with most other antidepressants (0.4%)
  - At 300 mg, only 0.1% seizure risk
- Requires BID dosing, although low seizure risk patients may try QD dosing

ADJUNCTIVE NEUROLEPTICS

- First choice for psychotic depression
- Probable choice for
  - "soft" psychotic symptoms
  - negative over-valued ideas
  - disorganized thinking
- Avoid low-potency neuroleptics

ADJUNCTIVE ATYPICAL NEUROLEPTICS

- Risperidone, clozapine, olanzapine, quetiapine
- Direct antidepressant effects
- Best data in severe bipolar depression
- Risk of inducing mania

MINIMAL ANTIDEPRESSANT RESPONSE

- After 3–5 weeks of treatment
- Consider
  - increased dose, if well-tolerated
  - augmentation with another drug

ANTIDEPRESSANT AUGMENTATION

Higher Doses of Li Are Better Than Lower Doses

	Response
• Placebo	4/18 (22%)
• 250 mg Li (0.2)	6/34 (18%)
• 750 mg Li (0.7)	15/34 (44%)
	p<0.001

Stein & Bernadt, 1993

T_3 AUGMENTATION

- Combined studies
  - 50 µg: 55% response
    - may help females > males
  - 25 µg: placebo response
- Always get TSH first to rule out hyperthyroidism

T3 vs T_4 AUGMENTATION

Euthyroid Depressed Patients

		Response
• T_3	37.5 µg	9/17 (53%)
• T_4	150.0 µg	4/21 (19%)*

- Recent NIMH study $T_4 \varepsilon T_3$ as augmentation in highly treatment-resistant population

*Significantly worse than placebo response

Joffe et al., 1991

OTHER AUGMENTATIONS TO CONSIDER

- Add TCA to SSRI or atypical
- Buspirone
- Sleep deprivation
- Stimulants
- Dopaminergic agents

Indications for ECT

- Life-threatening depression
- Inability to take medication
- Contraindications to medication
- Lack of response to medication