ANTIDEPRESSANTS: 2006 BASICS

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Pre and Post Lecture Exam: Question 1

Question: All of the following are symptoms of the DSM-IV Depression with Atypical Features Specifier except

A. Leaden Paralysis
B. Rejection Sensitivity
C. Hypersomnia
D. Phobic Anxiety
E. Appetite Increase/Weight Gain

Question 2

Question: None of the following have long-acting, active metabolites, except

A. sertraline
B. citalopram
C. paroxetine
D. escitalopram
E. fluvoxamine

Question 3

Question: By far, the least costly non-tricyclic antidepressant is

A. citalopram
B. mirtazapine
C. paroxetine
D. bupropion
E. fluoxetine

Question 4

Question: All of the following should usually be avoided in patients with liver disease except

A. venlafaxine
B. duloxetine
C. nefazodone
D. phenelzine

Question 5

Question: The following antidepressants are relatively free of sexual side effects except

A. mirtazapine
B. tranylcypromine
C. nefazodone
D. bupropion
E. venlafaxine

* Outline of Contents

Part One: Diagnosis of Depressive Disorders

Risk Factors

Etiology

Course

Part Two: Role of Psychotherapy

Phases of Response

General Considerations in Drug Selection

SSRI and SNRI Antidepressants

Bupropion, Nefazodone, Mirtazapine

Tricyclic and MAOI Antidepressants

Augmentation Strategies

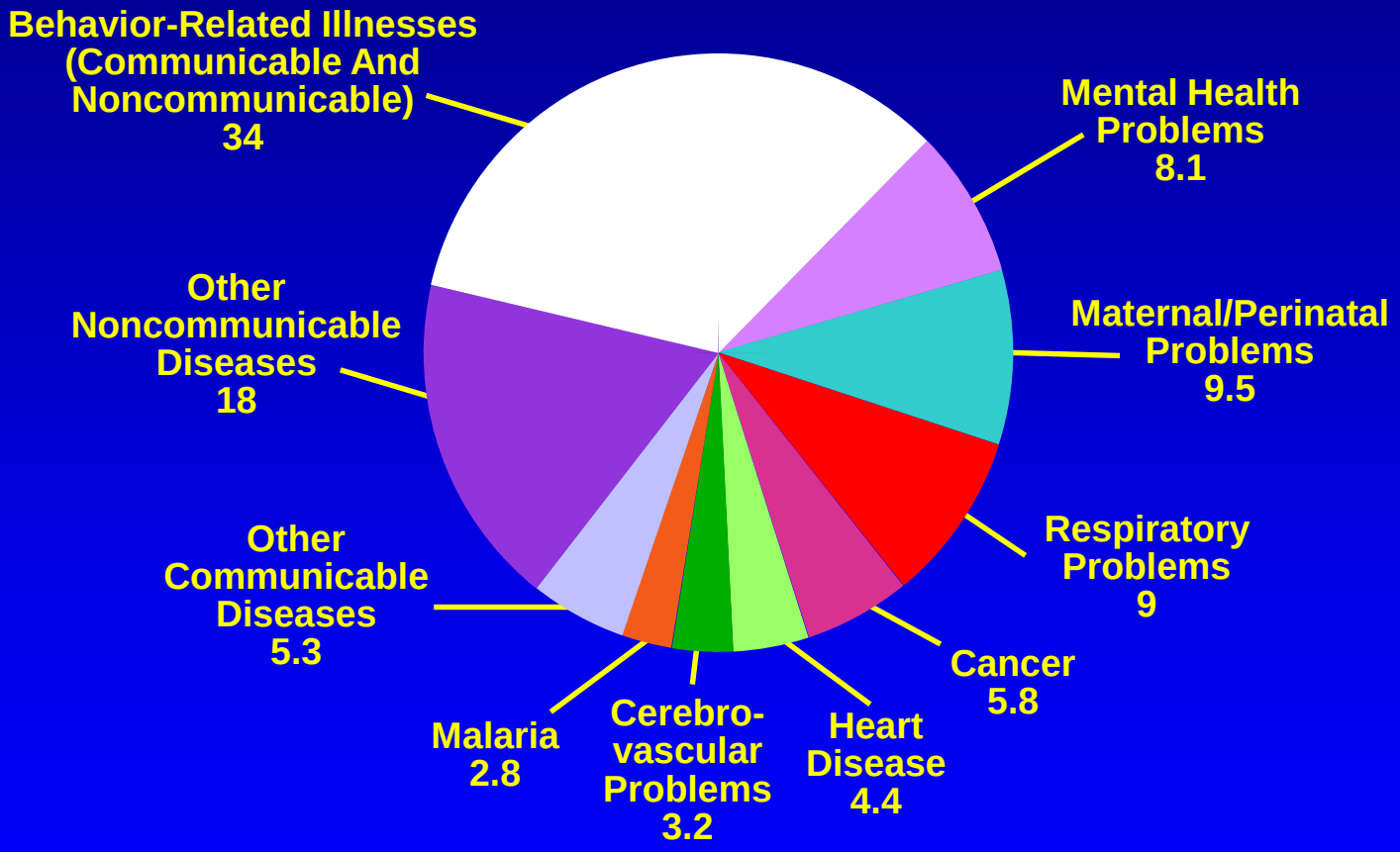
ECT

Recurrence

* Major Teaching Points of this Lecture

- Diagnose depressive disorders accurately according to the DSM-IV criteria so that the psychopharmacology evidence-base can be most applicable.
- Give antidepressants adequate time to work. Avoid unnecessary multiple drug regimens.
- After considering efficacy and side effect risks, prescribe cost-effectively.
- Stay up-to-date. The field is constantly changing.

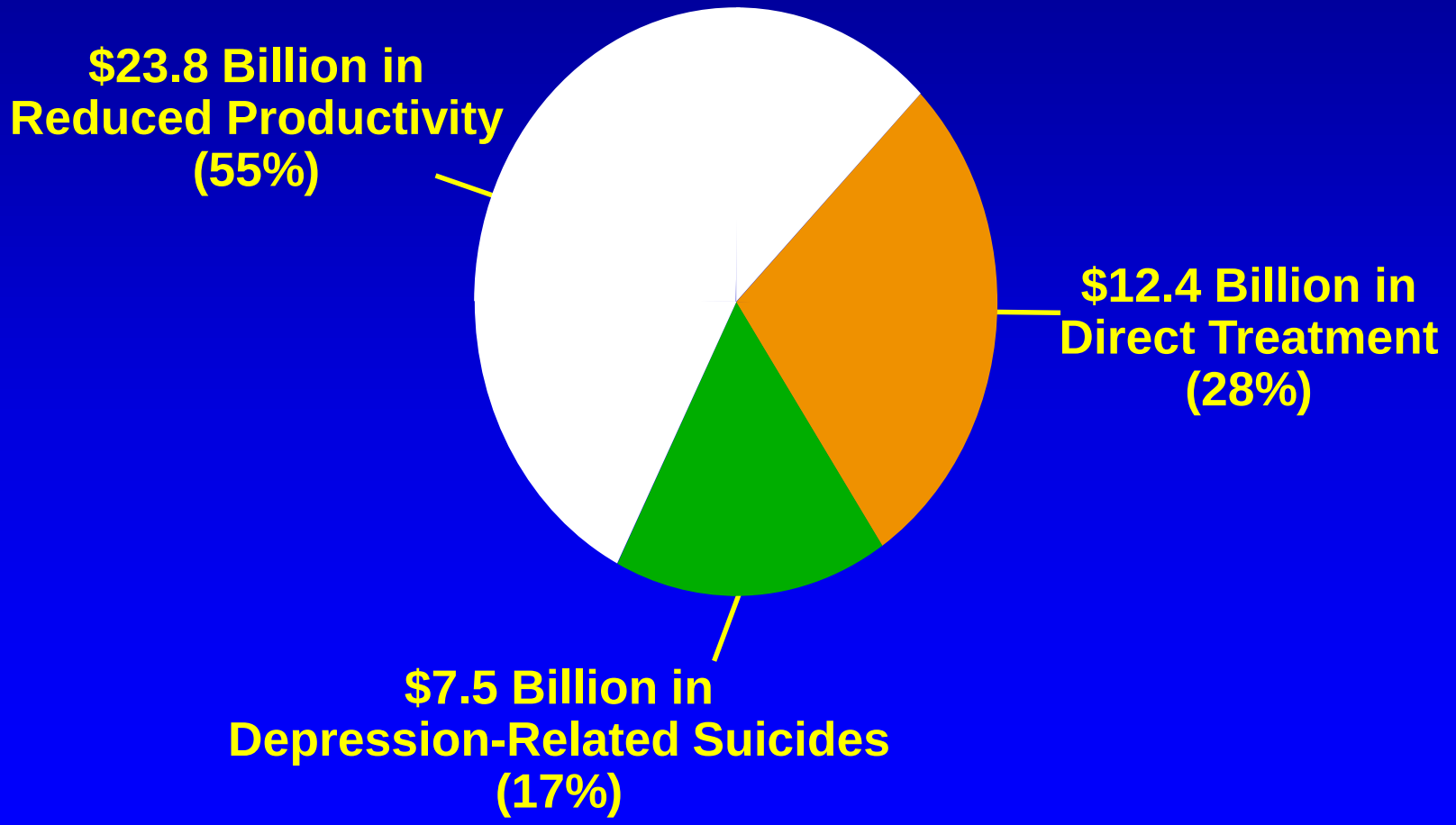
Global Distribution of Health Burdens (1990)*



* Numbers represent percentage of disability-adjusted life years lost

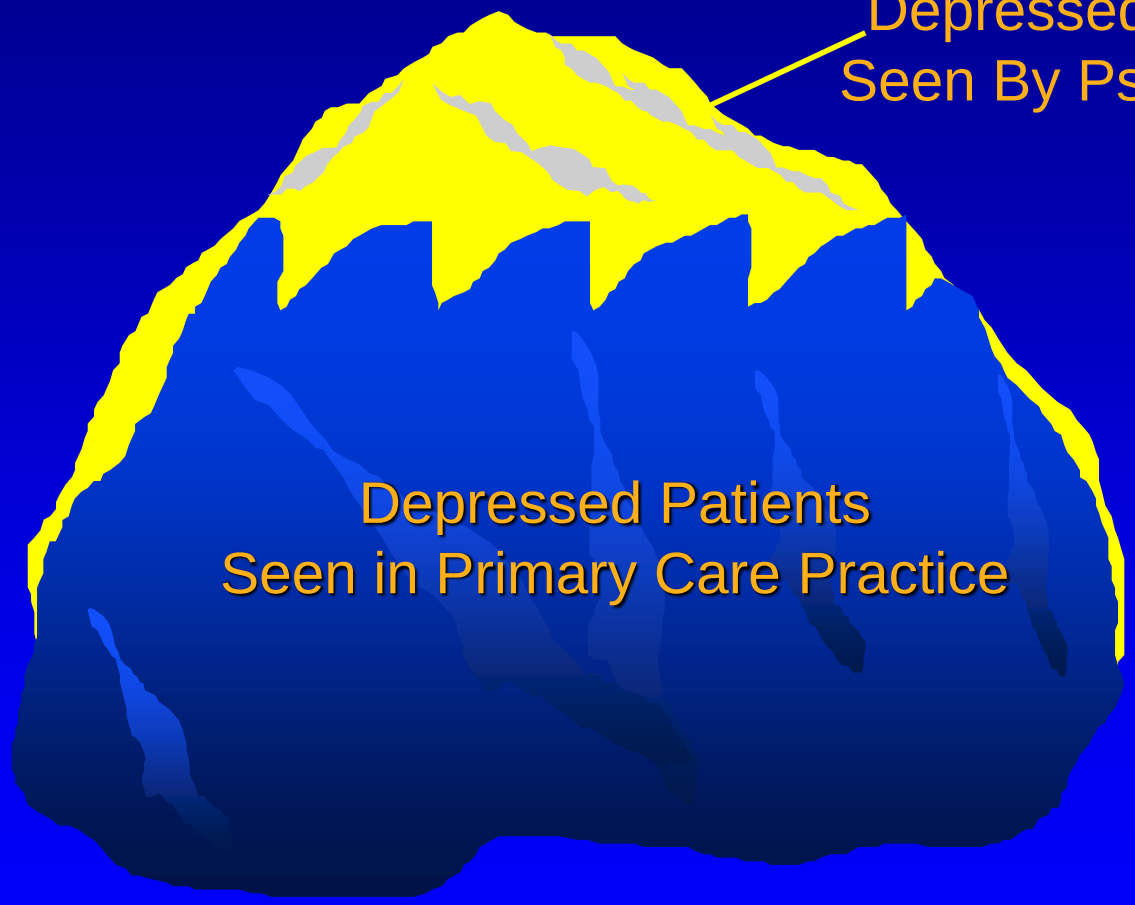
Adapted from The World Bank, 1993, with permission from Oxford University Press, Inc./WPA/PTD Educational Program on Depressive Disorders

Annual Cost of Depression in the US in 1990: $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 — either 1. or 2. below
- At least 5 of the following
  1. Depressed mood most of the day nearly every day
  2. Decreased interest or pleasure most of the day/every day
  3. Insomnia or hypersomnia
  4. Anorexia or hyperphagia or 5% weight gain/loss in month
  5. Psychomotor agitation or retardation
  6. Fatigue
  7. Decreased concentration or thinking, indecisiveness
  8. Negative thinking — worthlessness, inappropriate guilt
  9. Recurring thoughts of death or suicide
- Not organically caused
- Not uncomplicated bereavement

Adapted from DSM IV TR

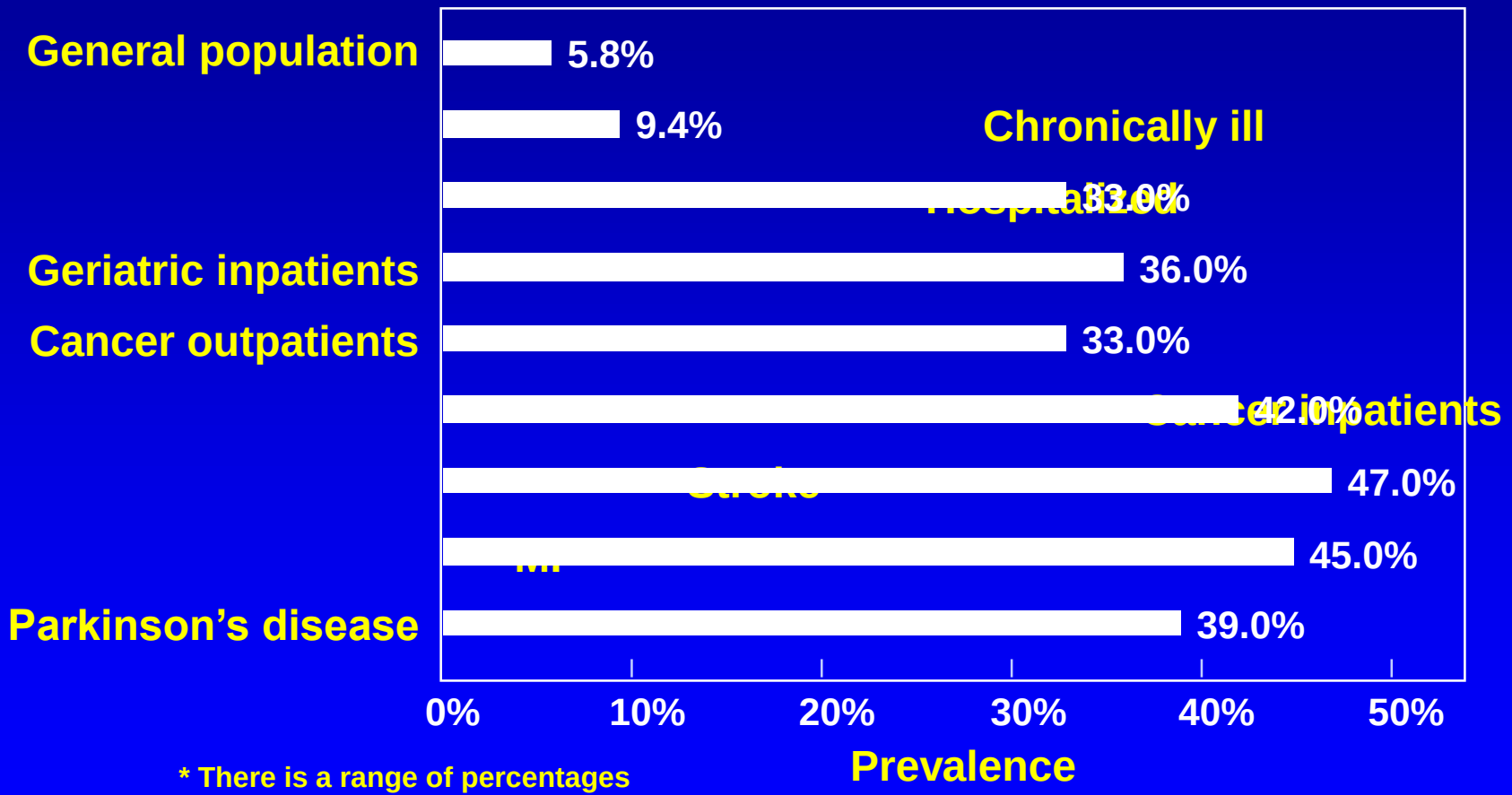
MAJOR DEPRESSIVE DISORDER

- Presence of major depressive episode
- Not attributable to separate psychotic disorder or medical or substance abuse disorder or bipolar disorder

RATES OF MAJOR DEPRESSION

- Point prevalence 4–5%
  - Women 5–6%
  - Men 3%
- 1 year prevalence 11.3%
- Lifetime incidence
  - Women 20%
  - Men 10%

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

RISK FACTORS FOR MAJOR DEPRESSION

Risk Factor	Association
Prior episode	Risk for recurrence increased
Gender	Twice as prevalent 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

* DYSTHYMIC DISORDER

- Depressed mood most of the day, on the majority of days, 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

Adapted from DSM IV TR

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 brightens in response to events
- Two or more of the following:
  - Increased weight or appetite
  - Hypersomnia
  - Leaden paralysis (heavy, leaden feelings in arms or legs)
  - Chronic rejection sensitivity leading to social/occupational impairment

Adapted from DSM IV TR

MOOD DISORDER WITH ATYPICAL FEATURES

- 15–20% of depressive episodes have atypical features
- About 80% of “atypical depressives” are women
- Some studies suggest better response to MAOI than to TCA.[1] Superiority of SSRIs to TCAs is unproven[2].

1. Quitkin et al. Arch Gen Psych 1991;48:319-23;
2. McGrath et al. Am J Psychiatry 2000;157:344-50.

* 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

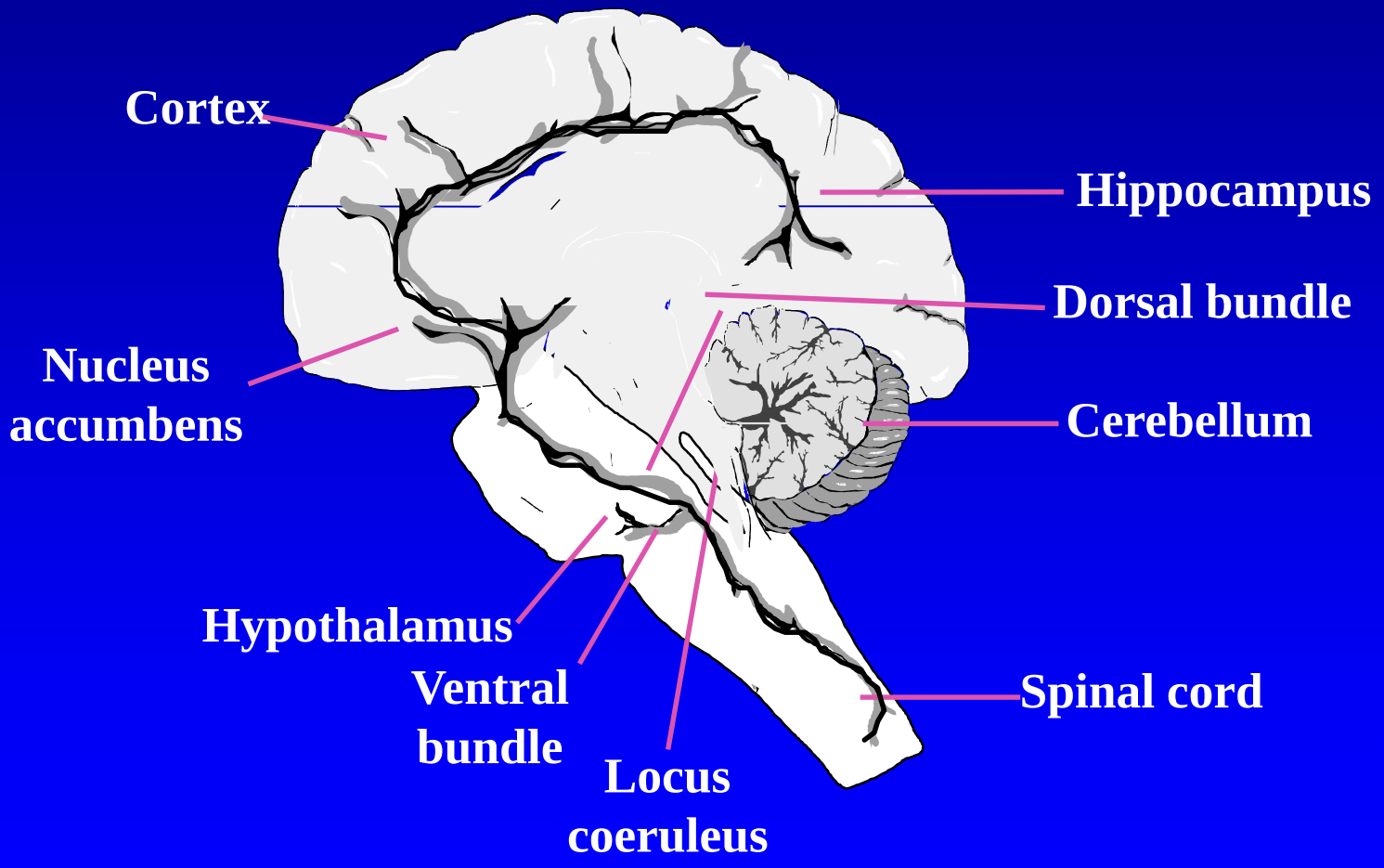
Etiology and Pathogenesis of Depressive Disorders

- 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



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
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 ↑ ↓

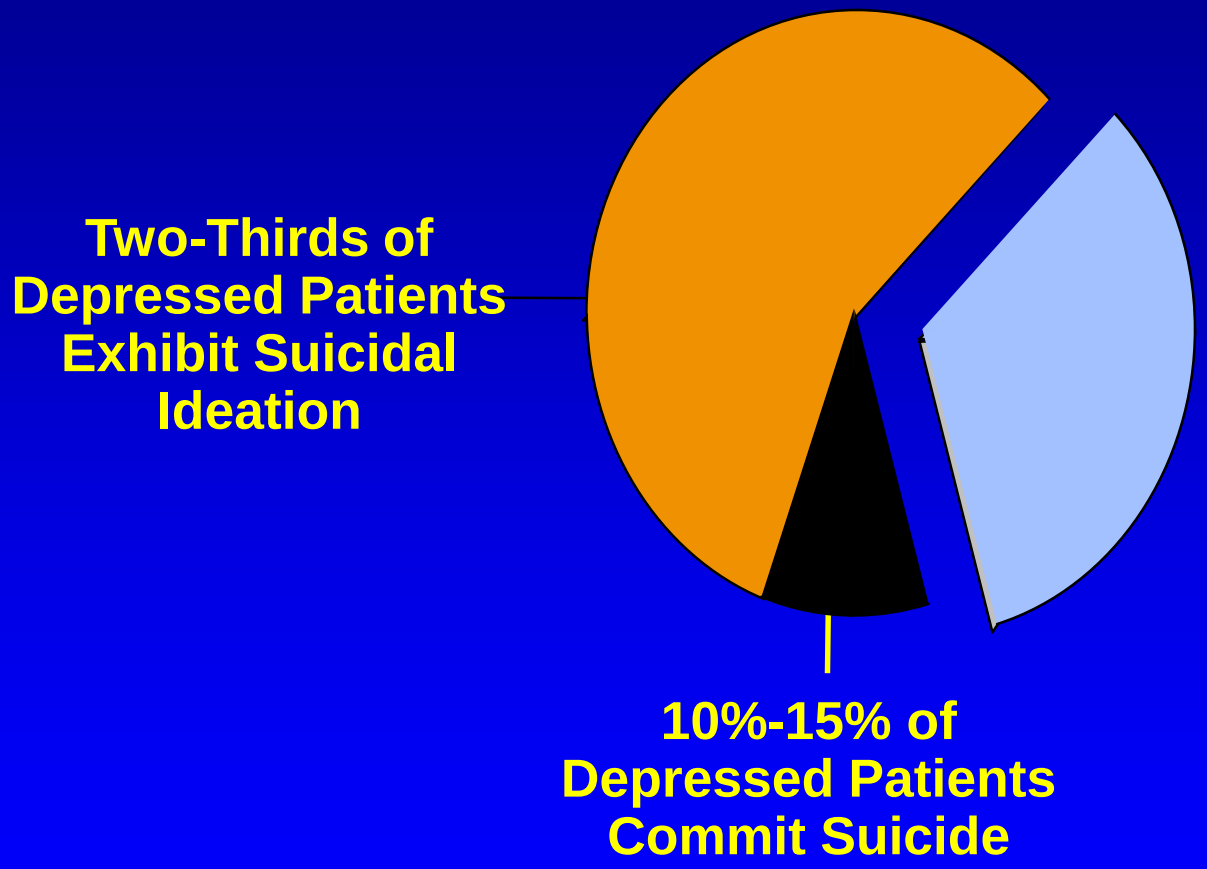
MAJOR DEPRESSIVE DISORDER
Genetics
35–70% Variance Accounted For

- Severe “endogenous” type depression higher — ≥50%
- Milder depressions (often atypical) in females lower — 23–30%
  - May have more male relatives with alcoholism

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 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

DSM-IV

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

DSM-IV

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

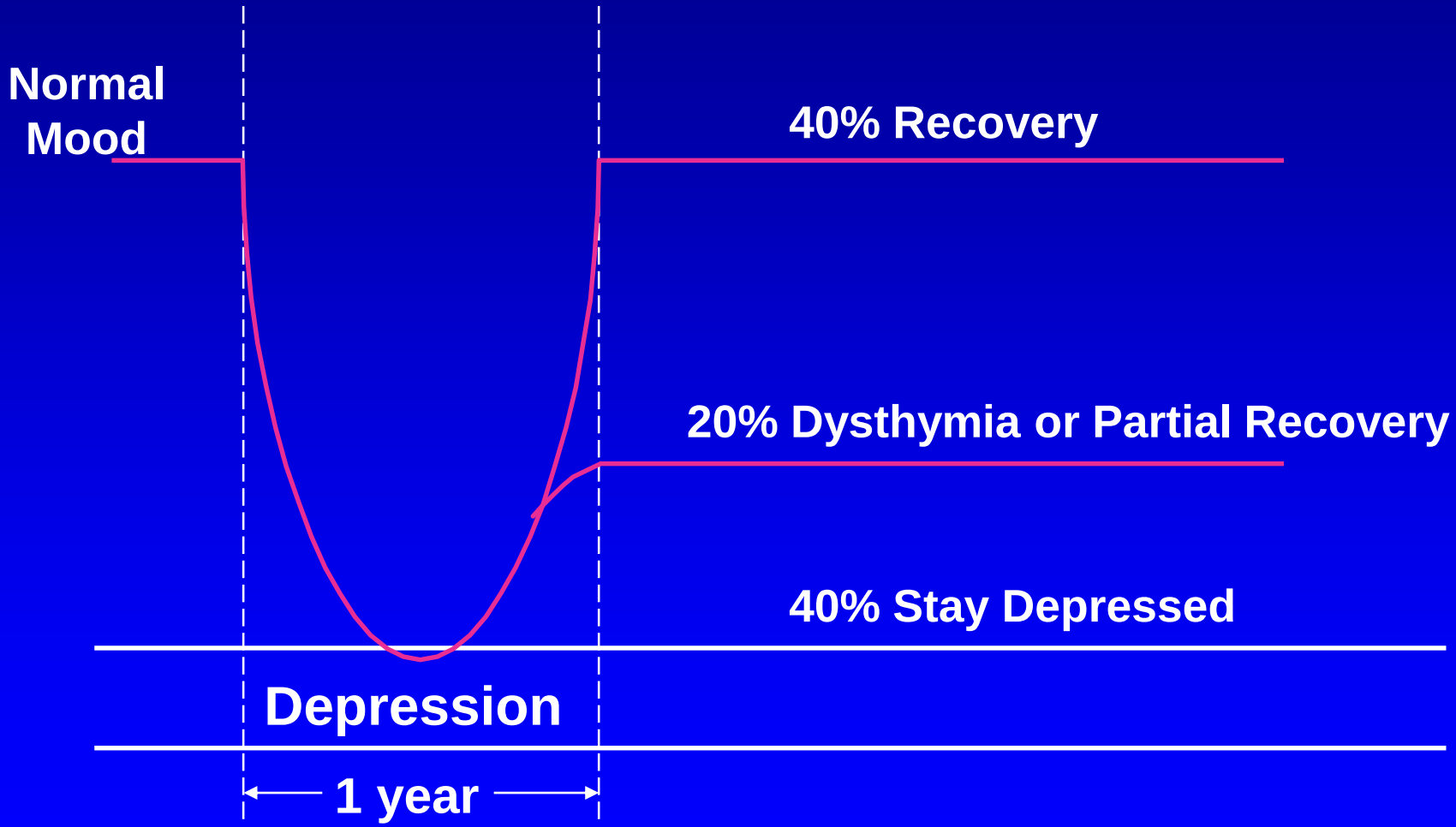
Very Few Medications Have Been Proven to Cause Depression

- 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

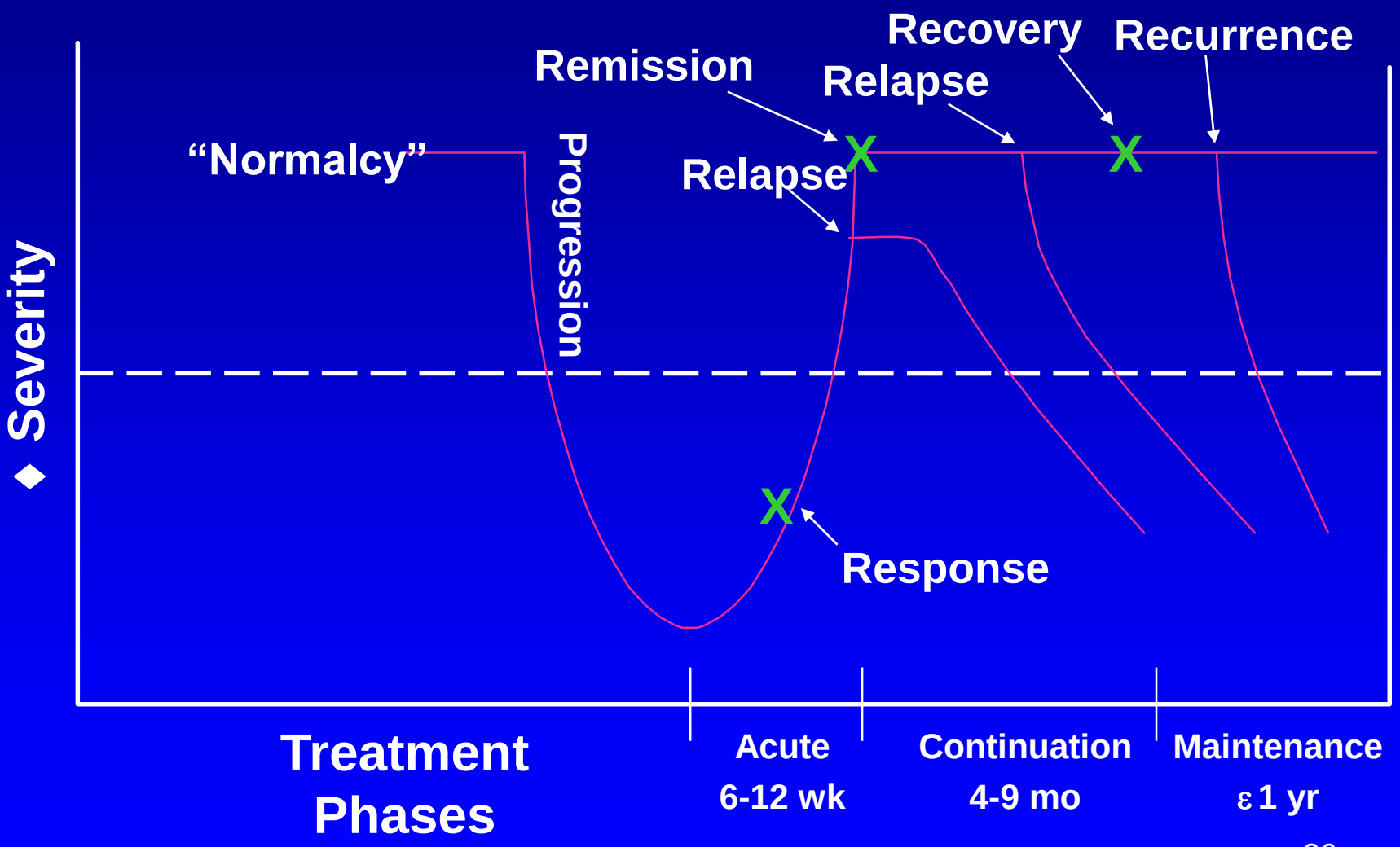
CLUES TO MEDICAL CAUSE OF DEPRESSION

- Most depression-mimicking medical conditions are associated with:
  - hypersomnia
  - energy better in a.m.
- Unlike Major Depression, almost no medical condition is associated with:
  - energy better in p.m.
  - hyperphagia

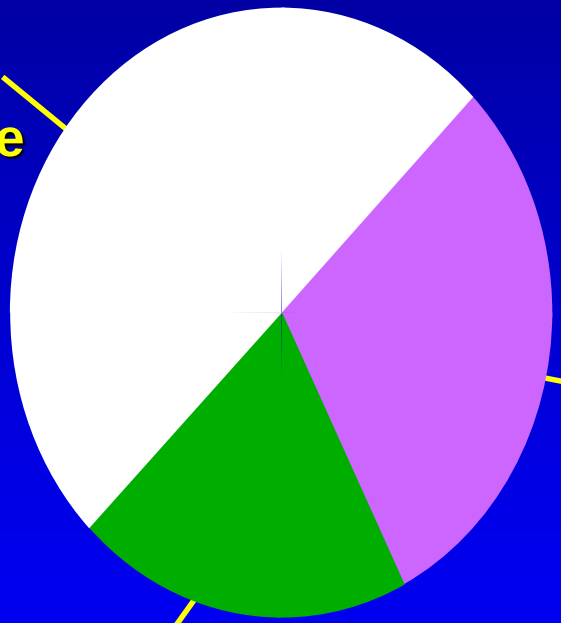
NATURAL COURSE OF UNTREATED DEPRESSION



* Clinical Status And Treatment Phases 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

ANTIDEPRESSANTS: 2006 BASICS

Part 2

Treatment Considerations

Role of Psychotherapy

Phases of Response

General Considerations in Drug Selection

SSRI and SNRI Antidepressants

Bupropion, Nefazodone, Mirtazapine

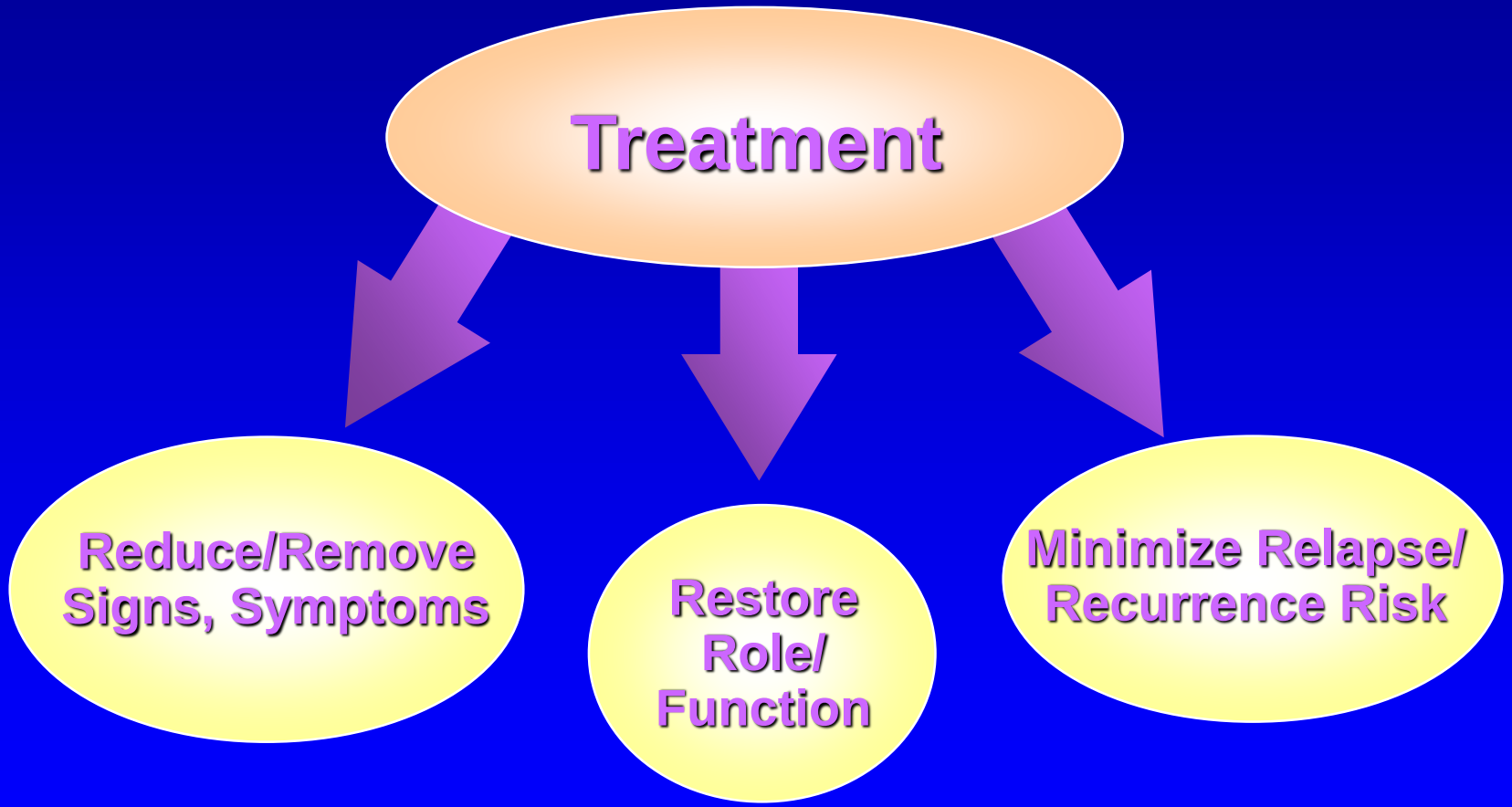
Tricyclic and MAOI Antidepressants

Augmentation Strategies

ECT

Recurrence

Depressive Disorders: Treatment Goals



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

PSYCHOTHERAPY OF DEPRESSION

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

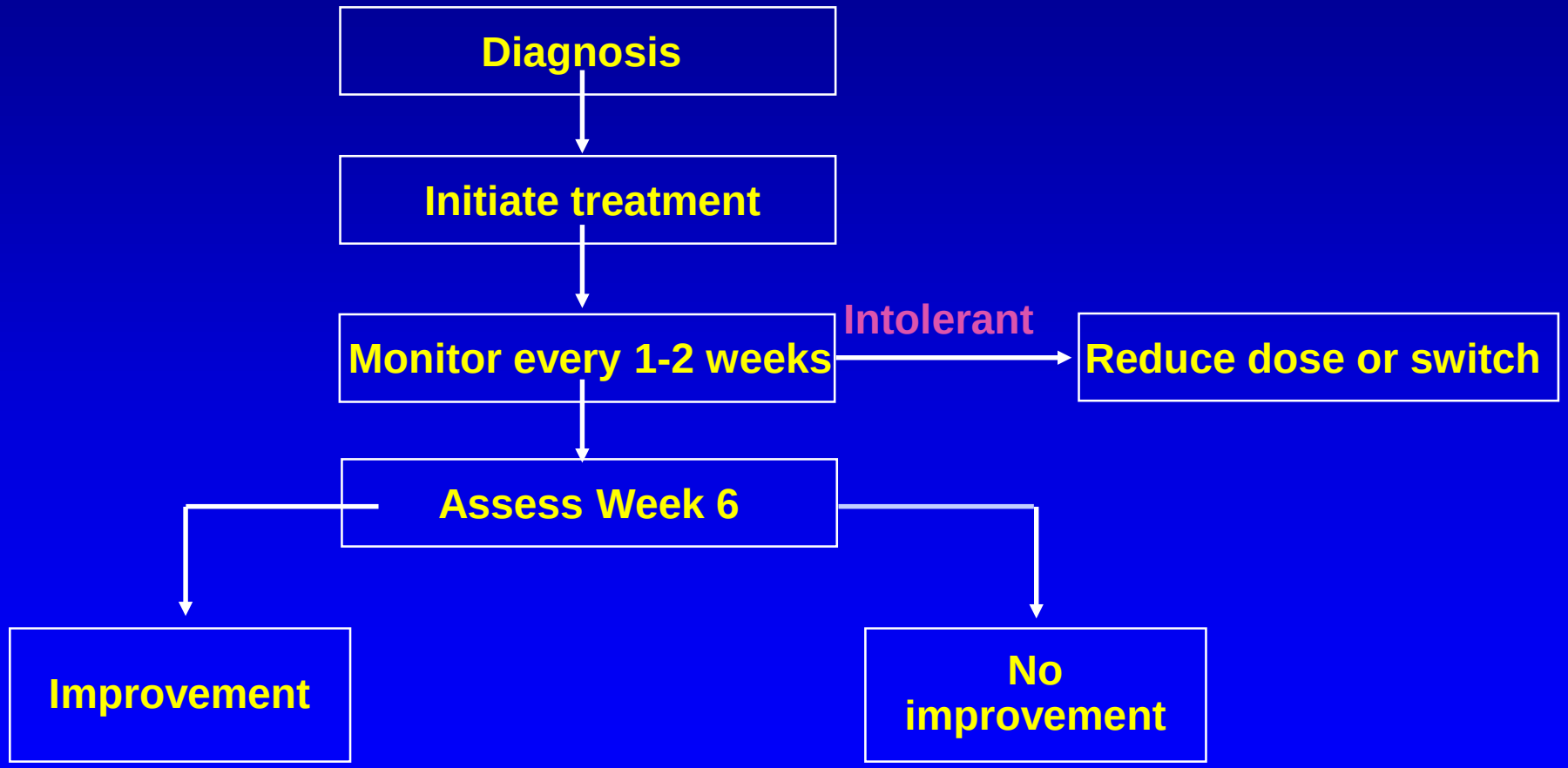
Consider for Medication Referral:

- Patient preference
- Previous positive response to medications
- Moderate to severe vegetative symptoms
- Psychotic or bipolar features
- Significant residual symptoms after 6 weeks of psychotherapy
- 2 or more episodes

PHARMACOTHERAPY: THREE TREATMENT PHASES

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

Treatment with Antidepressant: Acute Phase



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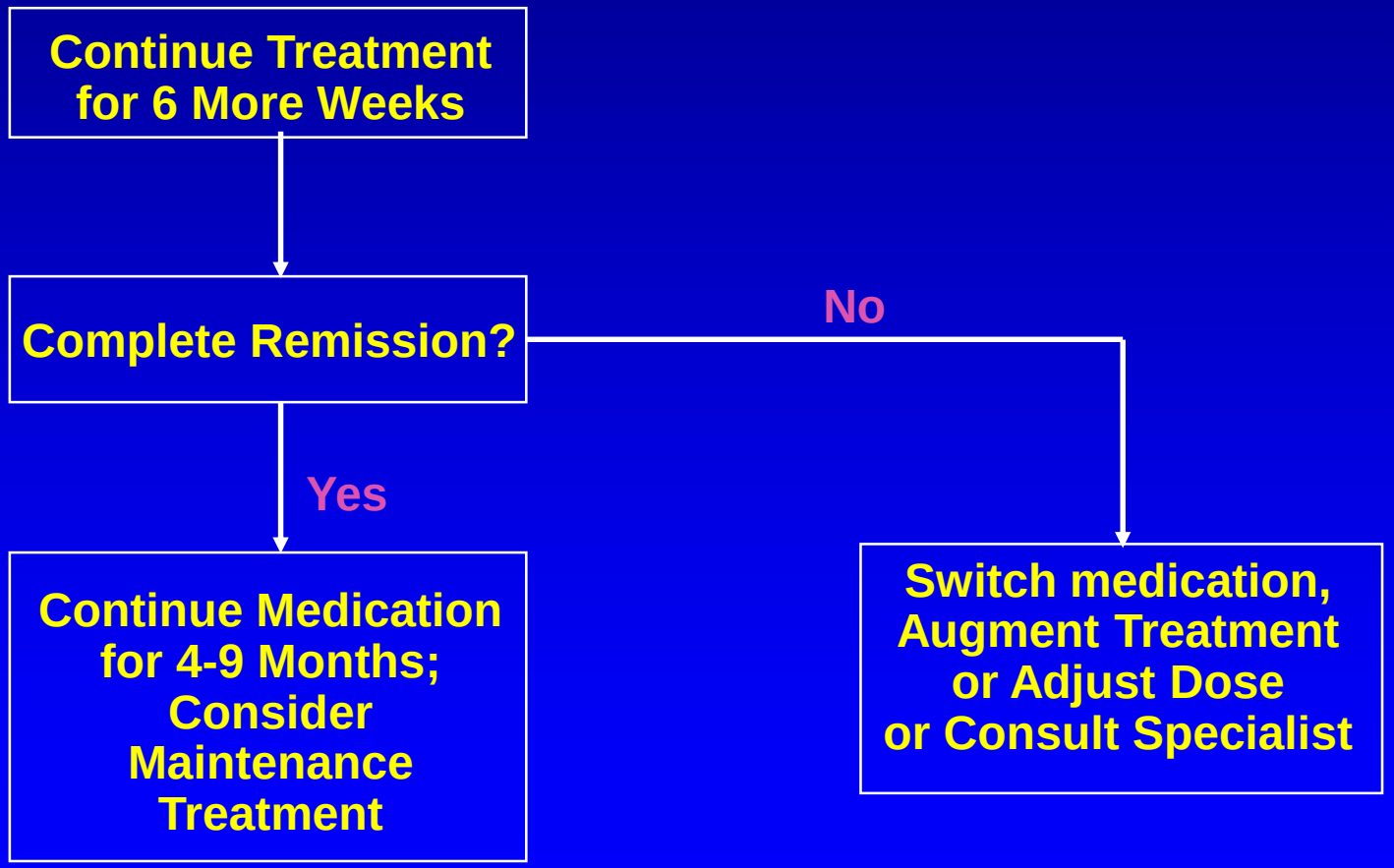
6-Week Assessment: Clear Improvement



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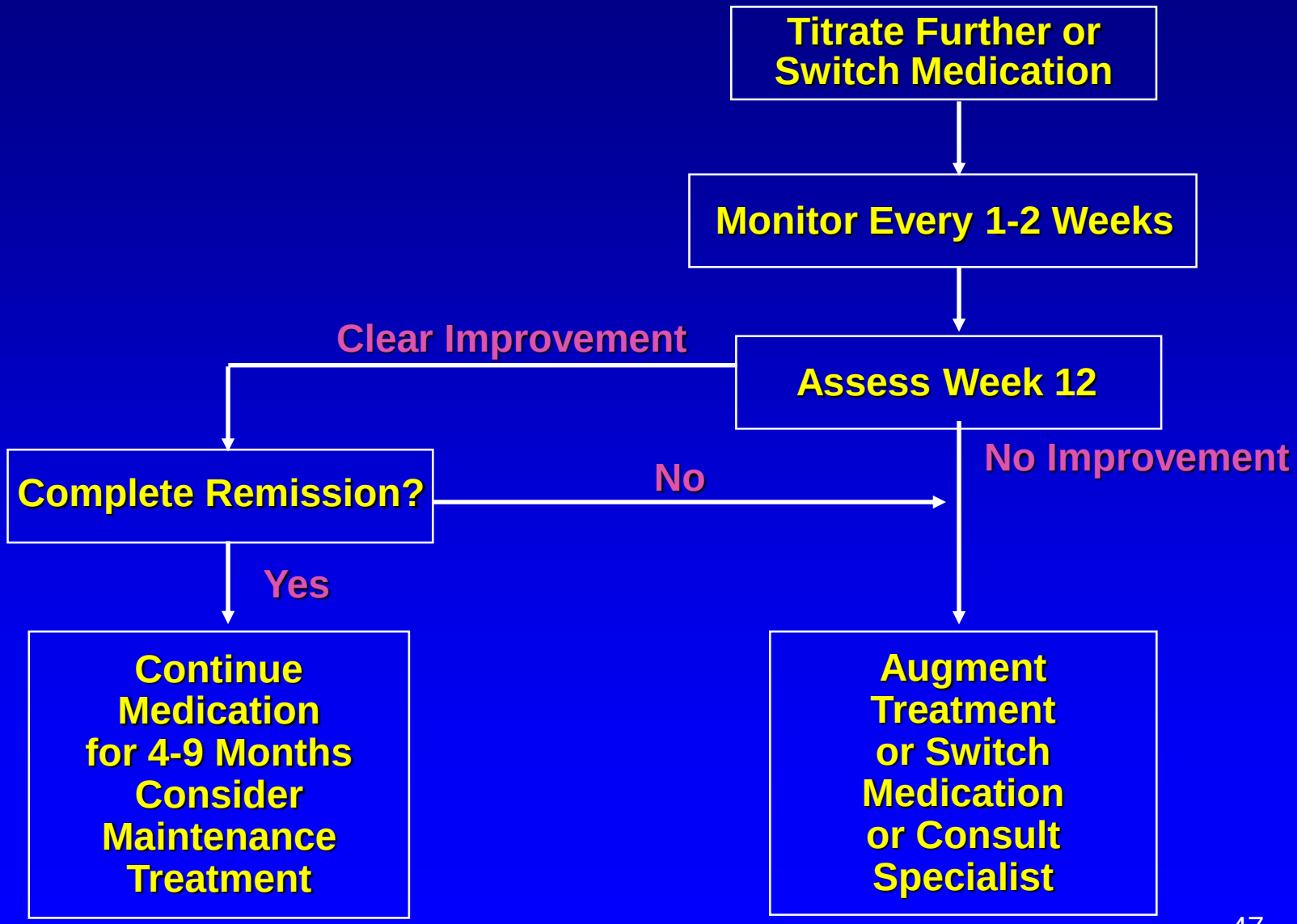
6-Week Assessment: No Improvement



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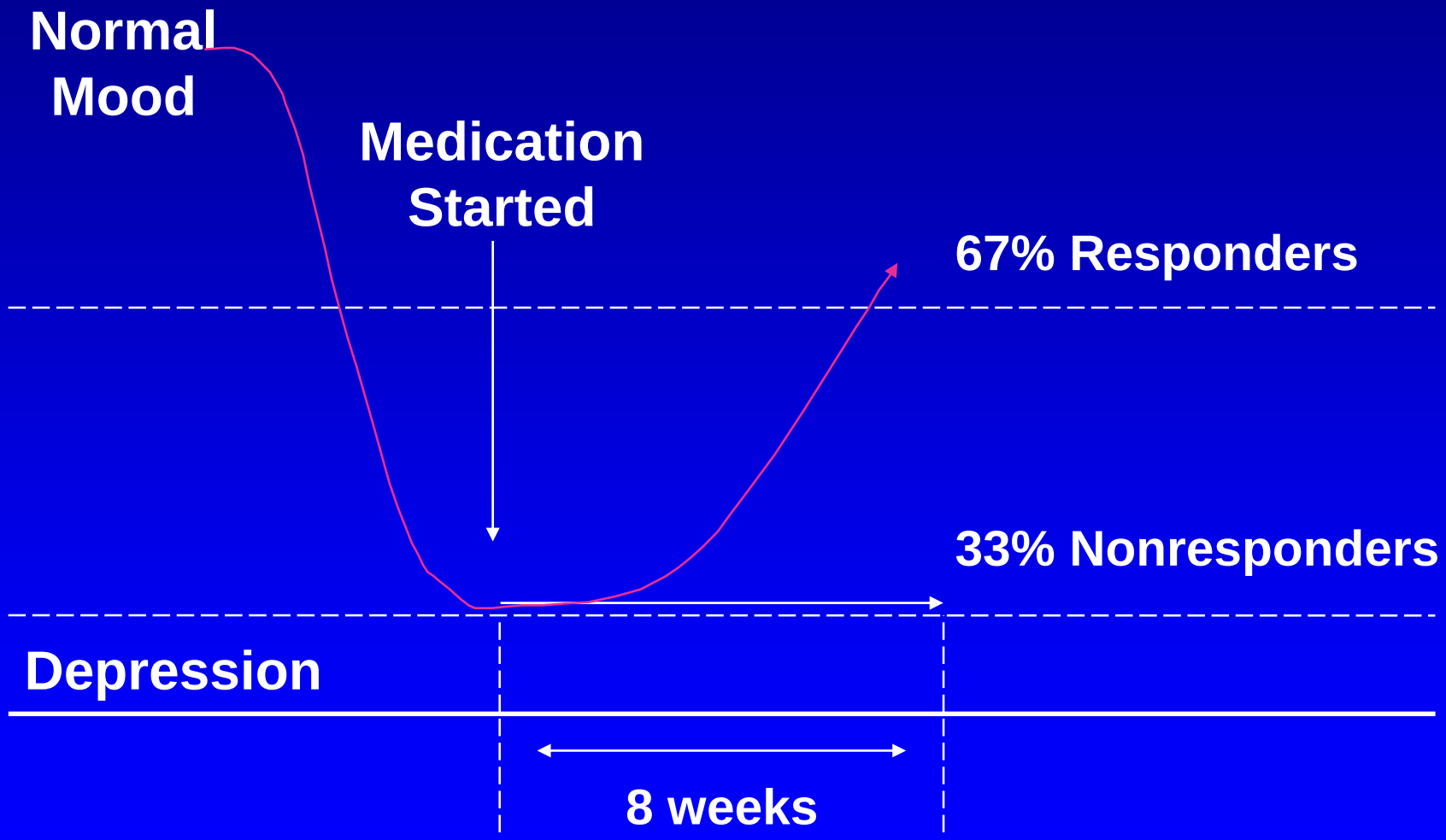
Response Rate After Pharmacologic Treatment Of Depression



* Selecting a Safe and Effective Antidepressant Medication

- 1) Efficacy
- 2) Side effect profile relative to your patient's needs
- 3) Drug interaction potential
  - Cytochrome P450 binding
- 4) Cost-effectivenes

All Antidepressants Are Efficacious

- 70 - 80% efficacy with any marketed antidepressant
- SRI's or Bupropion are excellent first line choices
- TCA's may be superior for some "severe" depressions
- MAO-I's may be preferred for some atypical depressions

Antidepressant Cost-Effectiveness

- Unit Cost is often considered primary
- Cost Offset must also be considered
  - Medical Visits and Laboratory studies more frequent with TCAs
  - Quality of life is affected by side effect profile

Comparison of Medications by Mechanism/Receptor Binding

- TCA → NE/5HT reuptake inhibitors
- MAOI → MAO inhibition
- SRI
  - SSRIs → 5HT reuptake inhibition
  - SNRIs → 5HT and NE reuptake inhibition
  - Nefazodone → SARI
- Mirtazapine → SANPA
- Bupropion → NDRI

Antidepressant Receptor Binding Profiles: An Important Determinant of Side Effect Profiles

	NE RI	5HT RI	α_2 NE	α_1 NE	ACh	H1	$5HT2_a$	$5HT_3$
Amitriptyline	+/-	+	+/-	+	+	+	+	-
Nortriptyline	+	+/-	-	+	+	+	-	-
Imipramine	+	+	-	+	+	+	-	-
Desipramine	+	-	-	+	+	-	-	-
Paroxetine	-	+	-	-	+	-	-	-
Other SSRIs	-	+	-	-	-	-	-	-
Bupropion	+	-	-	-	-	-	-	-
Duloxetine	+	+	-	-	-	-	-	-
Venlafaxine	+	+	-	-	-	-	-	-
Nefazodone	-	+	-	+	-	-	+	-
Mirtazapine	-	-	+	-	-	+	+	+

* CYP P450 Microsomal Enzyme Inhibition

- A potential cause of toxic “drug-drug” pharmacokinetic interactions
- Available antidepressants differ in their effects on the P450 enzymes
- Concurrently administered drugs may affect plasma levels of some antidepressants
- Much inter-individual variability
- Some pharmacogenetic variability

SSRIs (Selective SRIs)

- Fluoxetine
- Citalopram
- Fluvoxamine
- Paroxetine
- Sertraline
- Escitalopram

* Serotonin Reuptake Inhibitors: A First Line Choice for Treatment of Depression and Various Anxiety Disorders

- Similar efficacy to earlier agents
- More acceptable side effect profile
- Relative medical safety/ease of use
- Reduced lethality with overdose

* PHARMACOLOGY OF SSRI ANTIDEPRESSANTS

	Half-Life	Protein Binding	Enzyme Inhibition Effects*
Fluoxetine	48–72 hr	94%	>80% IID6
Norfluoxetine	7–9 day		
Sertraline	26 hr	98%	30% IID6 <20% IIIA3/4 IID6
Desmethylsertraline	72 hr		
Paroxetine	26 hr	94%	>80% IID6
Fluvoxamine	15.6 hr	80%	Inhibits IIIA3/4
Citalopram	35 hr	80%	
Escitalopram	27-32 hr	56%	

* “Common” SRI Adverse Effects

- GI disturbances
- Headache changes
- Sleep disturbances
- Appetite changes
- Sexual function changes
- Anxiety level changes
- Allergic reactions

* Unusual SRI Adverse Effects

- Withdrawal reactions
- Electrolyte disturbances
- Bruxism/myoclonus
- Hypotension/bradycardia
- Word-finding difficulties
- Photosensitivity
- Blunted emotional reactivity
- Paradoxical/unusual sexual effects
- Suicidal risk (a subject of controversy)

* LOW TOXICITY IN OVERDOSE

- Fluoxetine
- Sertraline
- Paroxetine
- Trazodone
- Venlafaxine
- Nefazodone
- Citalopram
- Escitalopram
- Mirtazapine
- Duloxetine
- Bupropion

Toxicity of newer antidepressants in overdose can be significant. Venlafaxine and citalopram have proconvulsant effects and citalopram has been observed to cause QT prolongation. Nefazodone and mirtazapine were considered safer in overdose in one review.[1] Bupropion has both adverse proconvulsant and cardiac effects in overdose.

1. Kelly et al. J Toxicol Clin Toxicol 2004;42:67-71

* Prescribing Cost-Effectively for Depression

- Meta-analysis of 46 randomized, controlled trials of antidepressants: "Selection of initial treatment might be based on cost" unless there are individual patient preferences based on "expected" side effects.[1]
- First choice SSRI for cost-effective prescribing is fluoxetine for adults, children and adolescents.[2] 2nd = citalopram

[1]Hanson RA et al. Ann Int Med 2005;143:415-426

[2]Cipriani A et al Fluoxetine vs other types of pharmacotherpay for depression. The Cochrane Library 2006, Issue 1

* General Dosing Strategy

- Avoid frequent dose increases but make contact with patient every 1-2 weeks, as recommended in the APA Practice Guidelines for Tx of Depression
- Wait 2-4 weeks with total non-response (or partial response that has plateaued) before increasing. Change if no response after 4 weeks at 60 mg fluoxetine per day (for adults).
- Wait 8-12 weeks if gradual response that has not plateaued
- When clinically necessary, may have to make above changes earlier than 4 weeks.

* Fluoxetine

- Typical acquisition cost in large health plans is $1 for 30 days at 20mg.
- Usually NOT more activating than other SSRIs (Fava M et al, J Clin Psychopharmacol 2002;137-147)
- Fluoxetine has CYP 2D6 blocking effects, but only 15% of patients will be on other drugs that interact, according to one study. (Gregor KJ et al J Affect Disord 1997;46;59-67)

* Fluoxetine Dosing

- Begin 10-20 mg/morning, 5-10 mg for age > 60 or if hx of unprecipitated panic attacks, or to avoid side effects.
- Increase to 20 mg after 1 week. Continue with 20 for 4 weeks. If no response, increase in 20 mg increments every 4 weeks as tolerated (Fava M et al. J Clin Psychopharmacol 2002; 22:379-387)
- Give up if no improvement after 4 weeks at 60 mg/d
- Partial response: difficult to interpret. Try to determine if it was due to non-specific (placebo) effects. If so, switch. If not, augment

* Citalopram

- Generic and low acquisition costs ~$7 for 30 days at 40 mg/day (for large provider organizations)
- Response rate 47%, remission rate 28% in a highly generalizable sample of 2,876 patients with considerable axis I and III comorbidity. (Trivedi MH et al. Am J Psychiatry 2006;163:28-40)
- Minimal P450 inhibition
- Recommended by Expert Consensus Guideline Series for the elderly.

* Citalopram Dosing

- Begin 20 mg in AM, 10 mg for elderly, unprecipitated panic attacks, etc.
- Increase to 40 mg after 1 week. Continue 40 mg for 4 weeks if tolerated.
- If no/partial response after 4 weeks, increase to 60 mg.
- Change if no response to 60 mg in 4 weeks.

* Sertraline

- The most expensive SSRI right now but it will soon be generic and price may come down.
- FDA approved for depression, panic disorder, PTSD, social anxiety disorder, OCD, and premenstrual dysphoric disorder.
- In addition to SRI effect, it is a mild dopamine reuptake blocker (i.e. – enhances dopamine)
- Relatively long half-life metabolite (3 days) means milder withdrawal symptoms.

* Sertraline Dosing

- Start with 50 mg in AM (25 mg for elderly, and those with panic disorder)
- Maintain 50 mg/day for 2-4 weeks before increasing. If no/partial response increase in 50 mg increments every 4 weeks. Change if no response at 200 mg for 4 weeks…but…
- One study showed better outcome with staying with 100 mg for weeks 6-11 vs going to 200 mg, after response was unsatisfactory for 6 weeks. (Licht and Ovitzau 2002) So it may NOT be worthwhile to move to 200 mg very quickly.

SNRIs (5HT/NE RIs)

- Venlafaxine
- Duloxetine

* Venlafaxine (Effexor)

- At lower doses, 5HT reuptake inhibitor
- At higher doses, NE/DA reuptake inhibitor
- $T_{1/2}$ = 19-22 hours
- No lower in sexual side effects than SSRI
- May have role in treatment of ADHD
- May have less safety in the frail elderly (Oslin DW et al. J Clin Psychiatry 2003;64:875-882)
- Costly, even in generic form (e.g. $60 for 30 d.)

* Venlafaxine: Adverse Effects

- More frequent
  - Dizziness
  - Dry mouth
  - Nausea
  - Drowsiness, fatigue
  - Confusion
  - Constipation
- SBP increase:
  - 3% (75 mg) – 13% (375 mg) increase (10–15 mm Hg) in systolic blood pressure
- Infrequent
  - Headache
  - Tremors
  - Insomnia
  - Diarrhea
  - Urinary retention
  - Sexual Dysfunction

Preskorn S: J Clin Psychiatry 1995;56(Suppl 6):71-80

* VENLAFAXINE: DUAL-ACTION WITHOUT ANTICHOLINERGIC OR ANTIHISTAMINIC SIDE EFFECTS

- 5HT reuptake inhibitor at low dose
- Dual-action (5HT/NE) at higher dose
- 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
- Modest success with highly resistant patients
- Side effects
  - Nausea (often time-limited)
  - Insomnia/sedation
  - Increased blood pressure (dose-related risk)
  - Sexual dysfunction similar to SSRIs

* 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

* Duloxetine (Cymbalta)

- Dual action 5HT/NE reuptake inhibitor across dose range
- Approved also for neuropathic pain syndrome
- Side effect profile similar to venlafaxine except new alert regarding 1% risk of significant LFT increase: avoid in patients with liver disease.
- Cost similar to venlafaxine
- Discontinuation syndrome risk less than venlafaxine due to longer elimination half-life

NDRI

- Bupropion

* Bupropion (Wellbutrin)

- NDRI with comparable antidepressant efficacy
- Seizure risk up to 0.44/1,000 at higher doses
- Equally effective as SSRIs for the non-specific anxiety symptoms that typically are present in depressed patients. (Rush AJ et al. Neuropsychopharmacol 2001;25:131-138) But, probably not effective for panic disorder.
- Contraindicated in patients with history of bulimia or anorexia nervosa because of increased seizure risk

* Bupropion II

- More costly than SSRIs even in generic SR form (e.g. $42 for 30 day supply at 300 mg/d)
- Minimal sedation
- May enhance sexual functioning
- Weight neutral or slight weight loss on average
- Minimal cardiac or other medical effects
- Slightly better results than sertraline or venlafaxine in bipolar depression (Leverich GS et al, AJPsychiatry 2006;163:232-239). Note: only 16% of trials produced a sustained antidepressant effect

* BUPROPION'S OTHER THERAPEUTIC EFFECTS

- FDA indicated for treating nicotine dependence
- Effective in treating adult ADD patients (Wilens TE et al. Biol Psychiatry 2005;57:793-801)

* DOSING OF BUPROPION

- SR associated with lower seizure risk than regular release (0.1/1,000) in 150 mg bid dose. XL used when single daily dose administration is needed.
- Begin: 100–150 mg qAM X 4+ days
- Increase to 100–150 mg BID (at least 8 hours between doses)
- In patients with liver disease
  - ~ 50% increase in $T_{1/2}$ of hydroxybupropion
  - No effect on bupropion and other metabolites
  - Start with 100 mg qAM

* Bupropion: Adverse Effects

- More frequent
  - Tremors
  - Dry mouth
  - Constipation
  - Sweating
  - Dizziness
  - Insomnia
  - Nausea
- Infrequent
  - Headache
  - Drowsiness, Fatigue
  - Palpitations
  - Nausea
  - Rash
  - Diarrhea
  - Sexual dysfunction

Preskorn S: J Clin Psychiatry 1995;56(Suppl 6) p.18

Bupropion Dosing

- Caution with concurrent medications that lower seizure threshold
- Avoid if history of seizure disorder
- IR dosage: Do not exceed 450 mg/d, 150 mg/dose
- SR dosage: Do not exceed 400 mg/d, 200 mg/dose
- XR dosage: Do not exceed 450 mg/d, single dose
- Avoid rapid dose increase

from PDR 2001-6

* SARI: Nefazodone

- Serzone manufacturer withdrew it but still available as generic.
- 5HT reuptake blocker, Postsynaptic 5HT2 blocker
- $T_{1/2}$ = 2-4 hr, but active metabolite $t_{1/2}$ = 20 hours
- Typical side effects:
  - Dizziness
  - Dry mouth
  - Nausea
  - Drowsiness
  - Less sexual dysfunction than SSRIs

* Nefazodone - II

- Postural hypotension: 2.6% > placebo
- Bradycardia: 1.5% > placebo
- Less sedating than it's cousin trazodone
- Does not adversely affect sleep architecture
- Very strong inhibitor of CYP 3A4. (Statins, alprazolam, macrolide antibiotics, and many others are substrates)
- Should not be a first-line agent due to concerns about hepatotoxicity, which caused death in 1 out of 250,000 patients treated with nefazodone. (Gelenberg AJ, Biological Therapies in Psychiatry 2002;25(1):2)

* Nefazodone Dosing

- Begin with 50 mg bid
- Increase to 100 mg bid after 2-4 days, and to 100 mg tid after 2-4 days
- Maintain 100 mg tid for 2 weeks before further increase; if no/partial response that has plateaued, increase in 100 mg increments to maximum tolerated dose up to 300 bid.
- Change to something else if no response to 500-600 mg/d for 4 weeks.
- Largest effect size was at 500 mg per day. (Preskorn SH et al, 1995.)

* SANPA: Mirtazapine (Remeron)

- Presynaptic alpha 2 NE blocker but not much orthostatic blood pressure effects clinically
- Postsynaptic 5HT2 and 5HT3 blocker
- Antihistaminic, but minimally anticholinergic
- $T_{1/2}$ = 21.5 hours
- Sedation
- Weight gain
- Low sexual side effects
- Role with severely depressed inpatients? (See Guelfi JD et al. J Clin Psychopharmacol 2001;21:425-431)

* MIRTAZAPINE
Dosing

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

  30 mg X≥2 weeks

  45–60 mg if 30 mg ineffective or if too much sedation
- Geriatric: 15 mg X≥3 weeks

* MIRTAZAPINE
Clearance in High-Risk Populations

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

* MIRTAZAPINE WARNING Agranulocytosis

- N=2,796 in registration studies
- 2 with agranulocytosis
  - < 500 neutrophils/mm^3
  - Symptoms: fever, infection
  - Occurred 9 to 61 days after starting Rx
- 1 with neutropenia
  - < 500 neutrophils/mm^3 and asymptomatic
- All recovered
- Post-marketing data suggest the incidence is < 1/100,000 (Stahl S, Sussman N. Mirtazapine: a clinical profile. Primary Psychiatry. 1997;4:83.)

* Mirtazapine – Agranulocytosis II

- Probably should avoid this drug if patient has pre-existing problems with absolute neutrophil count.
- But, in other ways, medically ill patients with nausea and weight loss due to illness like cancer and HIV would seem like ideal candidates for mirtazapine.
- Consult with internist

* Tricyclics/Tetracyclics

Nortriptyline

Amitriptyline

Desipramine

Imipramine

Doxepin

Protriptyline

Trimipramine

Maprotiline

Clomipramine

Amoxapine

Dothiepin

* PREDICTORS OF TRICYCLIC RESPONSE

- Increased response
  - Inpatients with severe melancholic depression*
  - Psychotic depression** (patient should also should be on antipsychotic)
  - Post-psychotic depression in schizophrenia

*Nobler MS, Roose SP. Differential response to antidepressants in melancholic and severe depression. Psychiatric Annals. 1998;28:84-88

**Spikar DG et al. Am J Psychiatry 1985;142:430-436

* INITIATING TCA TREATMENT
nortriptyline (tricyclic of choice)

- Caution: Overdose risk. 10 day supply can be fatal
- Contraindicated if recent MI, ischemic heart disease, cardiac conduction defects, urinary retention, untreated glaucoma, renal failure, orthostasis (but nortriptyline has least)
- Obtain baseline EKG. If bundle branch block, risk of serious arrhythmia is higher. Check at least one blood level to rule out slow metabolism and risk of fatal cardiac toxicity. (Preskorn, 1994)
- Begin nortriptyline10 mg bid or tid. (5 tid in elderly). Increase by 10 mg every two days until you get to 50 mg and then increase by 25 mg every two days until you get to 100 – 150 mg given in one dose. If response unsatisfactory after 4 weeks and results have plateaued get a blood level.

* 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

* META-ANALYSIS OF PLASMA LEVELS vs CLINICAL RESPONSE with TCAs

Tricyclic therapeutic range, ng/ml	Window or Threshold	% Response In range, Out of Range
Nortriptyline (58-148)	Window	66, 26
Amitriptyline (93-143)*	Window	50, 30
Imipramine (175-350)*	Window	67, 39
Desipramine (> 115)	Threshold	51, 15

*Total of patent compound and metabolite: amitriptyline plus nortriptyline; imipramine plus desipramine.
All other tricyclics not listed: therapeutic plasma level not well established.
Source: Perry PJ et al. J Clin Psychopharmacol 1994;14:230-240

* Tricyclic Side Effects Associated with Specific Neuroreceptors

Richelson E, Mayo Clinic Proceedings, 1994

- Norepinephrine: tremors, tachycardia, sexual dysfunction, postural hypotension (least with nortriptyline), reflex tachycardia
- Serotonin: GI disturbance, anxiety, sexual dysfunction
- Dopamine: EPS and prolactin increase (amoxapine)
- Histamine: drowsiness, weight gain (amitriptyline, clomipramine)
- Acetylcholine: Blurred vision, dry mouth, constipation, urinary retention, impaired memory (least with desipramine, most with amitriptyline)

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%

* MAOIs

- Phenelzine (Nardil)
- Tranylcypromine (Parnate)
- Isocarboxazid (Marplan)

Monoamine Oxidase Inhibitors

- Indications: **Atypical Depression** (if SSRIs fail): DSM-IV Criteria: 2 out of 4 of…
  - Hypersomnia
  - Appetite Increase
  - Leaden paralysis (heavy sensation in limbs)
  - Rejection sensitivity
- Indication: Refractory Depression
- Indication: Social Anxiety Disorder and other refractory anxiety disorders

* Comparative Side Effects

(Rabkin et al. J Clin Psychopharmacol 1994;4:276)

Side Effect	% on Phenelzine N=141	% Tranylcypromine N=41
Hypertensive crisis	8	2
Syncope, falls	11	17
Disorientation	5	2
Edema	4	0
Weight gain > 15 lb	8	0
Urinary Retention	5	2
Paresthesias	4	5
Drowsiness	3	0
Anorgasmia, impotence	22	2

* Dosing MAOIs

- Begin MAOI diet several days before starting
- Discontinue fluoxetine x 5 weeks; others 2 wk
- Phenelzine may start at 15 mg bid or tid and increase to 15 qid if tolerated in a week, which is the minimal effective dose usually. Maximum 90 mg/day.
- Tranylcypromine may start at 10 mg bid and increase in a week to 10 mg tid. Maximum 60 mg. Insomnia may be treated with trazodone 50 mg or clonazepam 0.5 mg.

(Rosenbaum et al. Handbook of Psychiatric Drug Therapy, 2005;112)

* MAOIs – Liver Issues

Phenelzine and isocarboxazid are hydrazide-related MAOIs and as such carry a small but significant risk of hepatocellular injury. Avoid in patients with liver disease.

* MAOI Dietary/Medication Interactions

- Foods to Avoid
  - Aged cheeses
  - Yeast extract
  - Red wine, beer, ale
  - Overripe, fermented or pickled foods
  - Fava beans
  - Ginseng
  - Caffeine*
  - Soy sauce*
- Medications to Avoid:
  - Many antidepressants
  - Meperidine
  - Stimulants*
  - Decongestants
  - L-DOPA*
  - Propranolol*
  - Dextromethorphan
  - Some anesthetics*
  - If uncertain, ask!

**May be safe in limited amounts and/or with appropriate monitoring*

* PSYCHOTIC DEPRESSION:
Response Rates
(Spikar DG. Am J Psychiatry 1985;142:430-436)

- TCA antidepressants alone (amitriptyline) 41%
- Antipsychotics (perphenazine) 19%
- Antipsychotics (olanzapine) 47%
- TCA Antidepressant + antipsychotics 77%
- ECT 78–85%

SSRI alone (e.g. fluvoxamine) trials reported ≥65% efficacy.
Patients were not as severely depressed or delusional as those treated By Spikar et al. (Zanardi R et al. J Clin Psychiatry 2000;61:26-29)

*Augmentations: Evidence-Base & Costs

Augmentation	Evidence Rating*	Added $ Monthly
lithium 900 mg (to TCA)	A	2
T3 25 ug (to TCA)	A	3
mirtazapine 15 mg	A/B	18
buspirone 40 mg	B	4
Wellbutrin SR 300 mg	B	42
Zyprexa 10 mg	B	172
Provigil 200 mg	B/C	110
nortriptyline 100 mg	C	2
pindolol 10 mg	C	2
lithium 900 mg (to SSRI)	C	2
T3 25 ug (to SSRI)	C	3
Effexor XR 150 mg	C	54
other atypicals	C	70-158

*Thase ME. CNS Spectrums 2004;9(11):808-821.(updated)

A= >1 RCTs
B= 1 RCT, plus c
C= Case series, anecdotal report, expert opinion
D= Anecdotal reports but experts have not endorsed

* Electroconvulsive Therapy

- Underused modality, especially suitable with:
  - Antidepressant intolerance or non-response
  - Prior positive response to ECT
  - Delusions
  - Catatonia
  - Bipolar states
  - Emergency
- High response rates documented[1]

1. Seiner and Henry 2003

ECT and Medical Status Concerns

- **Cardiac:** Recent MI, unstable angina, arrhythmias, severe valvular diseases, CHF, hypertension
- **Pulmonary**: COPD, asthma, infections
- **Gastrointestinal**: Aspiration or laryngospasm risk factors
- **Musculoskeletal:** Stress to bones, joints, vertebrae during treatment or in subsequent falls
- **Neurologic**: Intracranial lesions “substantially increase” risk[1]

1. APA Task Force 2001

ECT and Memory Loss

- A major concern of patients and families
- ECT may improve depression-impaired cognition but exacerbate impaired cognition of dementia
- Preparation should include:
  - Psychoeducation of patient/family
  - Pre-screening of memory to establish baseline
  - Monitoring of memory throughout treatment course
  - Decreased treatment frequency when memory disturbance is pronounced
  - Use of unilateral treatment when reasonable

ECT: Other Considerations

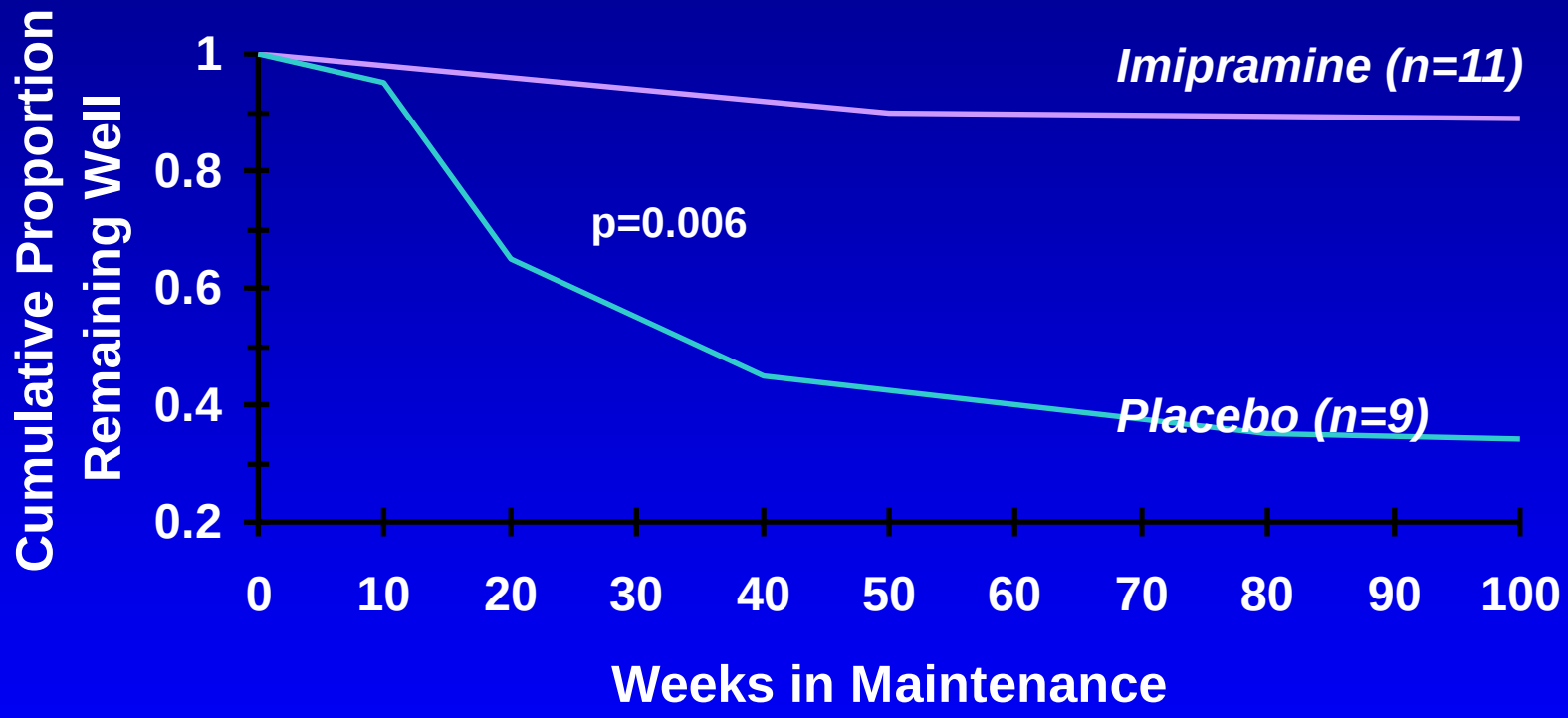
- Psychosocial aspects of ECT:
  - Informed consent and ongoing reassessment
  - Addressing stigma and misinformation
  - Addressing family members' concerns and conflict
  - Recognizing effects of memory loss on grieving process in bereaved patients
- Maintenance Treatment
  - May be combined with pharmacotherapy
  - Can be used alone with medication intolerant
  - Shown to prevent relapse[1,2]

1. Gagne et al. 2000; 2. Petrides et al. 1994

CONSIDERATIONS FOR MAINTENANCE TREATMENT

- Very strongly recommended
  - ≥3 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[a]

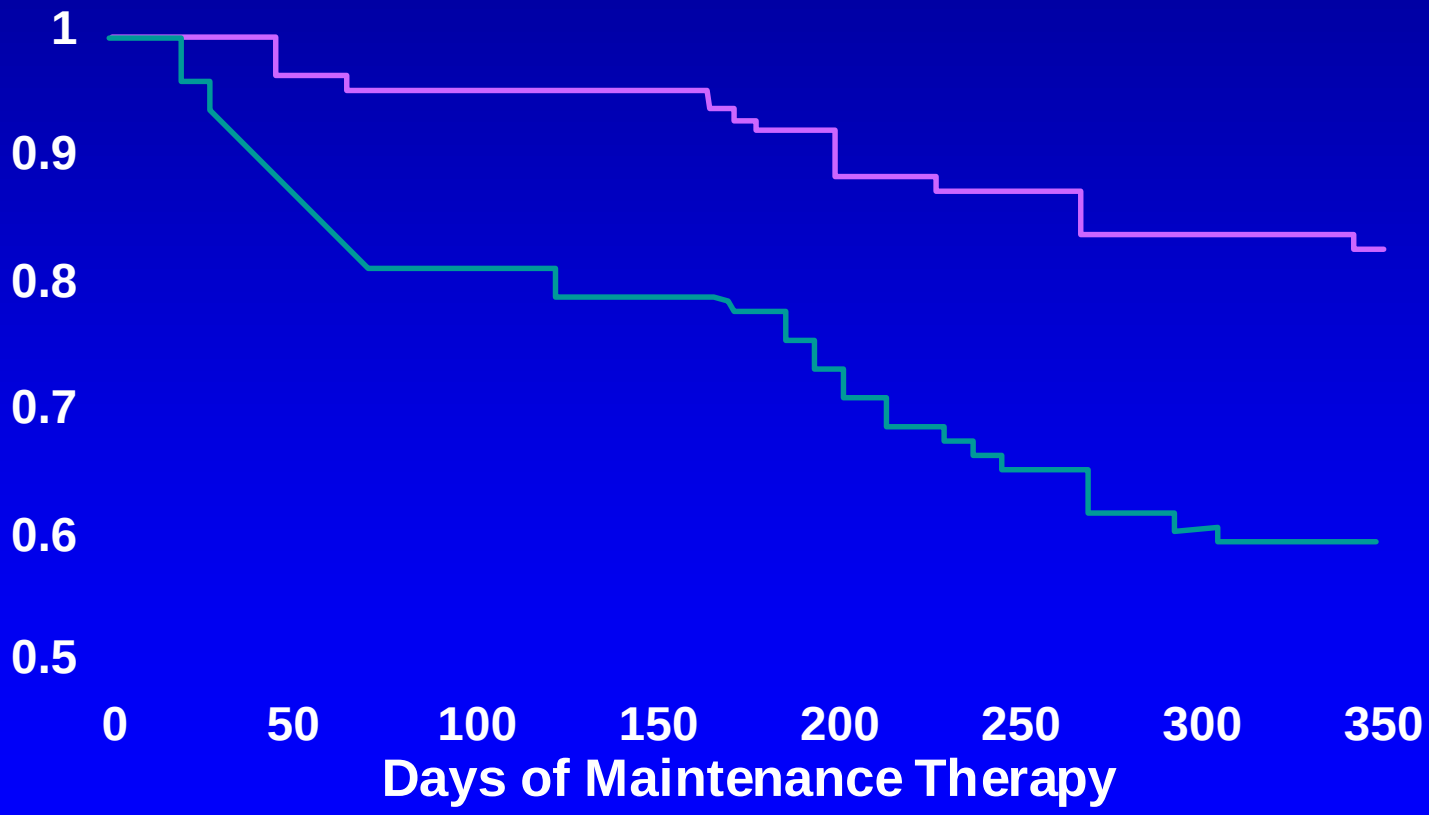


[a]Patients with no recurrence during a 3-year, full-dose maintenance trial were randomized to 2 years of imipramine or placebo.

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

Antidepressant Discontinuation: Cautions

- Avoid abrupt withdrawal (discontinuation sx)
- Prepare patient for physical symptoms
- Discuss psychological impact of discontinuation
- What “tools” are in place to aid this transition?

Pre and Post Lecture Exam: Question 1

Question: All of the following are symptoms of the DSM-IV Depression with Atypical Features Specifier except

A. Leaden Paralysis
B. Rejection Sensitivity
C. Hypersomnia
D. Phobic Anxiety
E. Appetite Increase/Weight Gain

Question 2

Question: None of the following have long-acting, active metabolites, except

A. sertraline
B. citalopram
C. paroxetine
D. escitalopram
E. fluvoxamine

Question 3

Question: By far, the least costly non-tricyclic antidepressant is

A. citalopram
B. mirtazapine
C. paroxetine
D. bupropion
E. fluoxetine

Question 4

Question: All of the following should usually be avoided in patients with liver disease except

A. venlafaxine
B. duloxetine
C. nefazodone
D. phenelzine

Question 5

Question: The following antidepressants are relatively free of sexual side effects except

A. mirtazapine
B. tranylcypromine
C. nefazodone
D. bupropion
E. venlafaxine

Answers

Question 1. d

Question 2. a

Question 3. e

Question 4. a

Question 5. e