Antidepressant Pharmacotherapy

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Outline

Phenomenology of MDD
- Risk Factors
- Co morbid conditions
- Economics

Pathophysiology
- Monoamines
- Stress/Neurotrophic factors
-

Classes of Agents
- SSRIs
- TCAs
- SNRIs
- MAOIs
- Other Agents

Future Classes of Drugs

Teaching Points

- Our knowledge of the pathophysiology of depression is incomplete
- Limitation of current treatment include slow onset, tolerability, and lack of adequate efficacy for many patients
- Each class of antidepressants has unique risks and benefits

Pre-Lecture Exam Question 1

The most common side effects early in the course of SSRI treatment leading to discontinuation is

1. GI upset
2. Loss of libido
3. Headache
4. Weight gain

Question 2

The most common cause of death in TCA overdose is

1. Arrhythmia
2. Seizure
3. Congestive heart failure
4. Stroke

Question 3

Noradrenergic side effects of antidepressants may include

1. Sedation
2. Weight gain
3. Tachycardia
4. All of the above

Question 4

The neurotrophic hypothesis of depression suggests

1. Depression is related to loss of neurotrophic support
2. Antidepressants increase neurotrophic factors such as BDNF
3. Depression is associated with a progressive loss of volume in areas such as the hippocampus
4. All of the above

Question 5

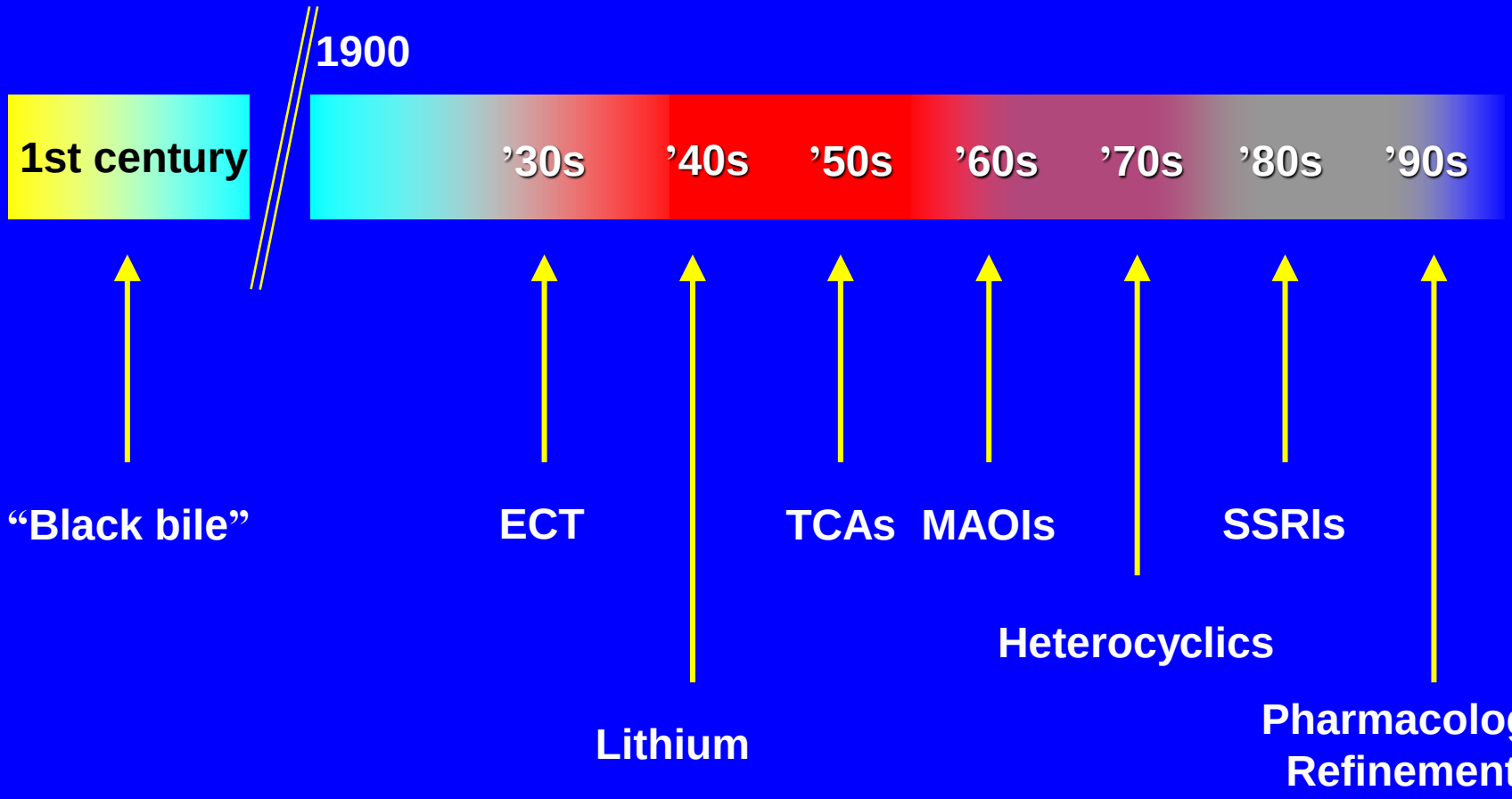
Foods that are likely be problematic for patients on MAOIs include

1. Soy sauce
2. American Cheese
3. Pasteurized Beer
4. All of the above

MAJOR DEPRESSION: DSM-IV DIAGNOSTIC CRITERIA

- Depressed mood most of the day, nearly every day
- Diminished interest or pleasure in activities
- Major change in appetite or weight
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Diminished ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death, dying, or suicide

Developments in Medical Treatment of Depression



Kaplan HI, Sadock BJ. In: *Pocket Handbook of Psychiatric Drug Treatment*. 1996.

Epidemiology of Depression

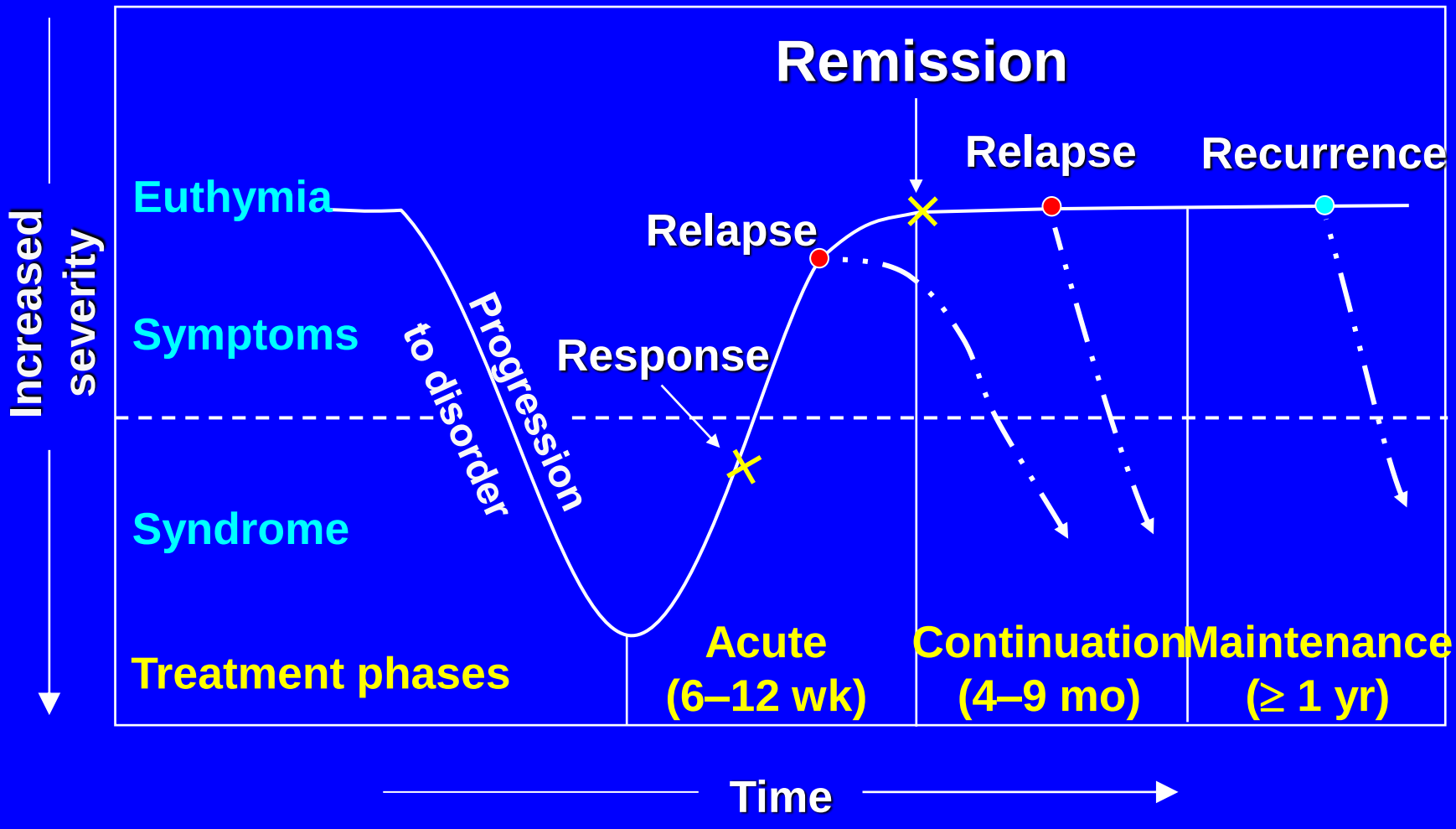
- 17% lifetime prevalence of a major depressive episode
- Up to 15% of patients with major depressive disorder requiring hospitalization commit suicide
- Total annual cost to society – $44 billion, 55% of which is due to lost productivity

Kessler RC et al. *Arch Gen Psychiatry*. 1994;51:8-19.
Depression Guideline Panel. AHCPR publication 93-0550. 1993.
Greenberg PE et al. *J Clin Psychiatry*. 1993;54:405-418.

RISK FACTORS FOR MAJOR DEPRESSION

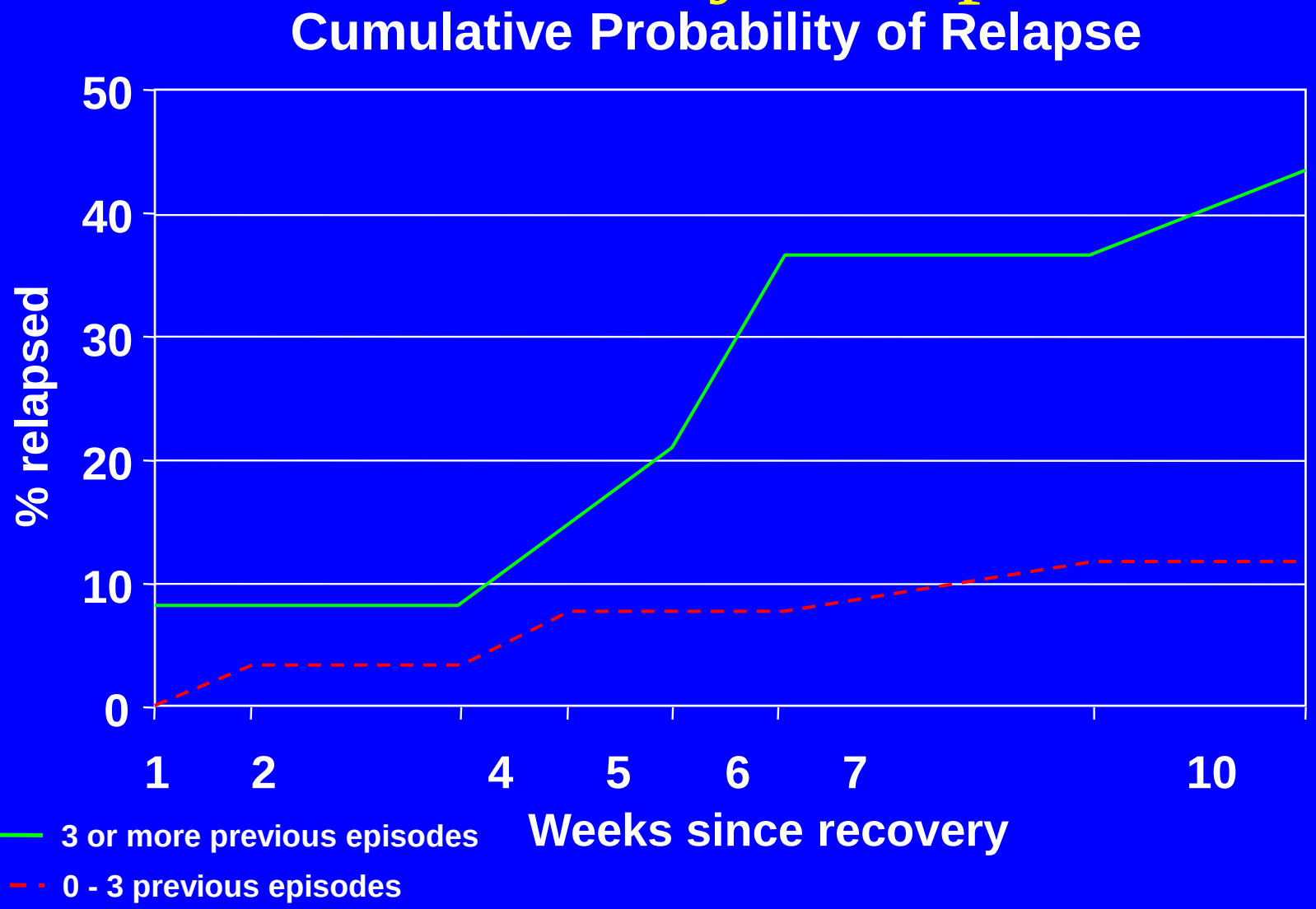
•Risk factor	Association
•**Gender**	**Twice as likely in women**
•**Age** **years**	**Peak age of onset is 20–40**
•**Family history**	**1.5 to 3.0 times higher risk**
•**Marital status**	**Higher rates in separated, widowed, and divorced persons**
•	**Married males lower than never married**
•	**Married females higher than never married**

Phases of Treatment for Depression



Kupfer DJ. *J Clin Psychiatry*. 1991;52(suppl 5):28.

Patients with Major Depression



Keller MB, Boland RJ. *Biol Psychiatry*. 1998;44:348-360.

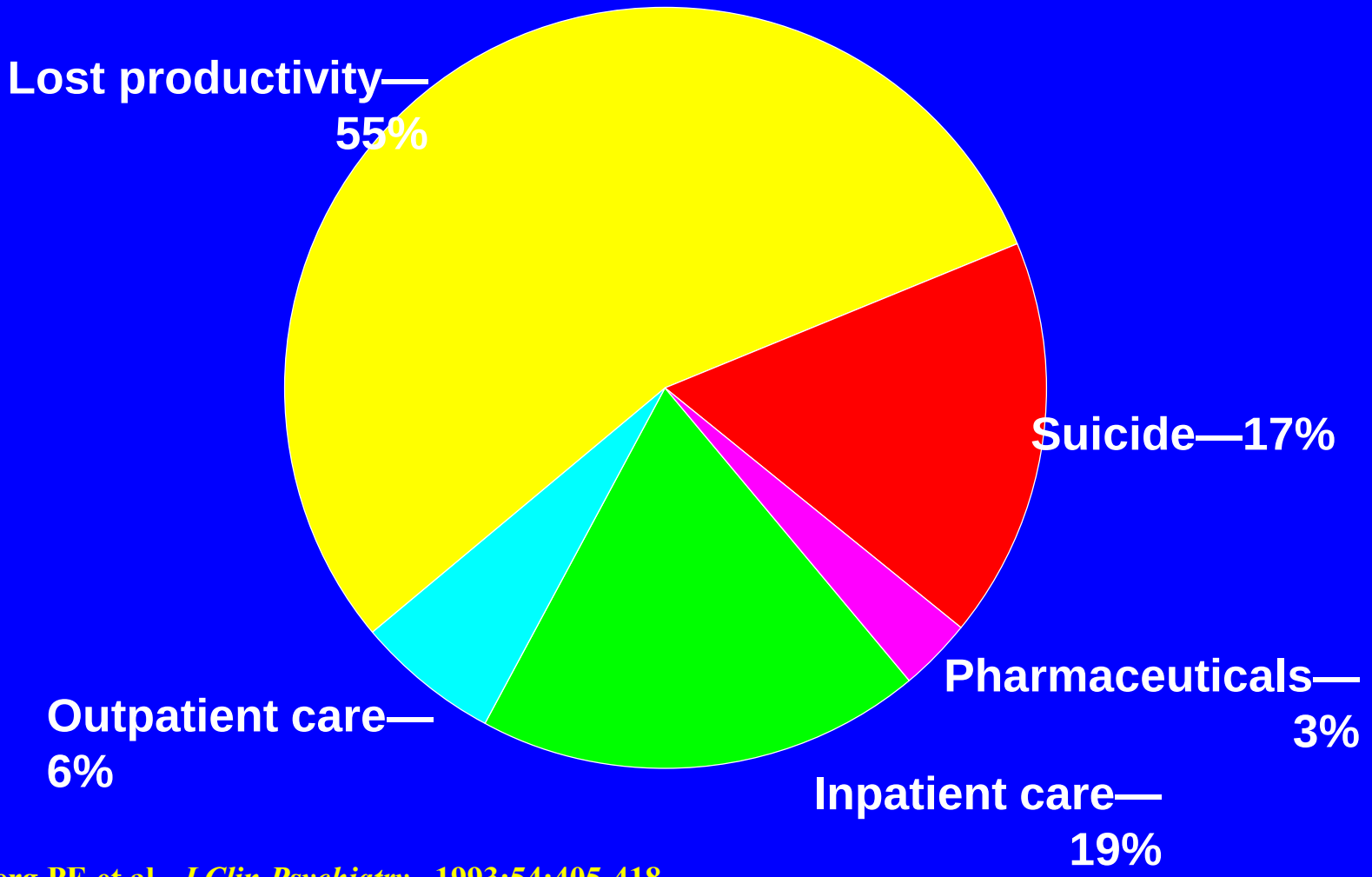
Depression
Impact vs. Other Chronic Medical Conditions

Medical Condition	Physical Function	Social Function	Role Function	Bed Days	Current Health Perception	Bodily Pain
Hypertension	+	+	+	+	+	+
Diabetes	+	+	+	+	+	+
Advanced CAD		+			+	+
Arthritis	+	+	+	+	+	+

+ = Worse Functioning in Depression

Wells, *JAMA*, 1989

Economics of Depression—Total Annual Cost ~$44 Billion



Greenberg PE et al. *J Clin Psychiatry*. 1993;54:405-418.

Monoamines, and Receptors: Proposed Mechanisms of Action of Antidepressants

- Blockade of neuronal re-uptake of monoamines
- Adaptive down-regulation of receptors
- Blockade of serotonin-2 receptors
- Inhibition of MAO
- Post-synaptic cascades giving rise to neuroadaptive changes
- Hormonal effects of antidepressants

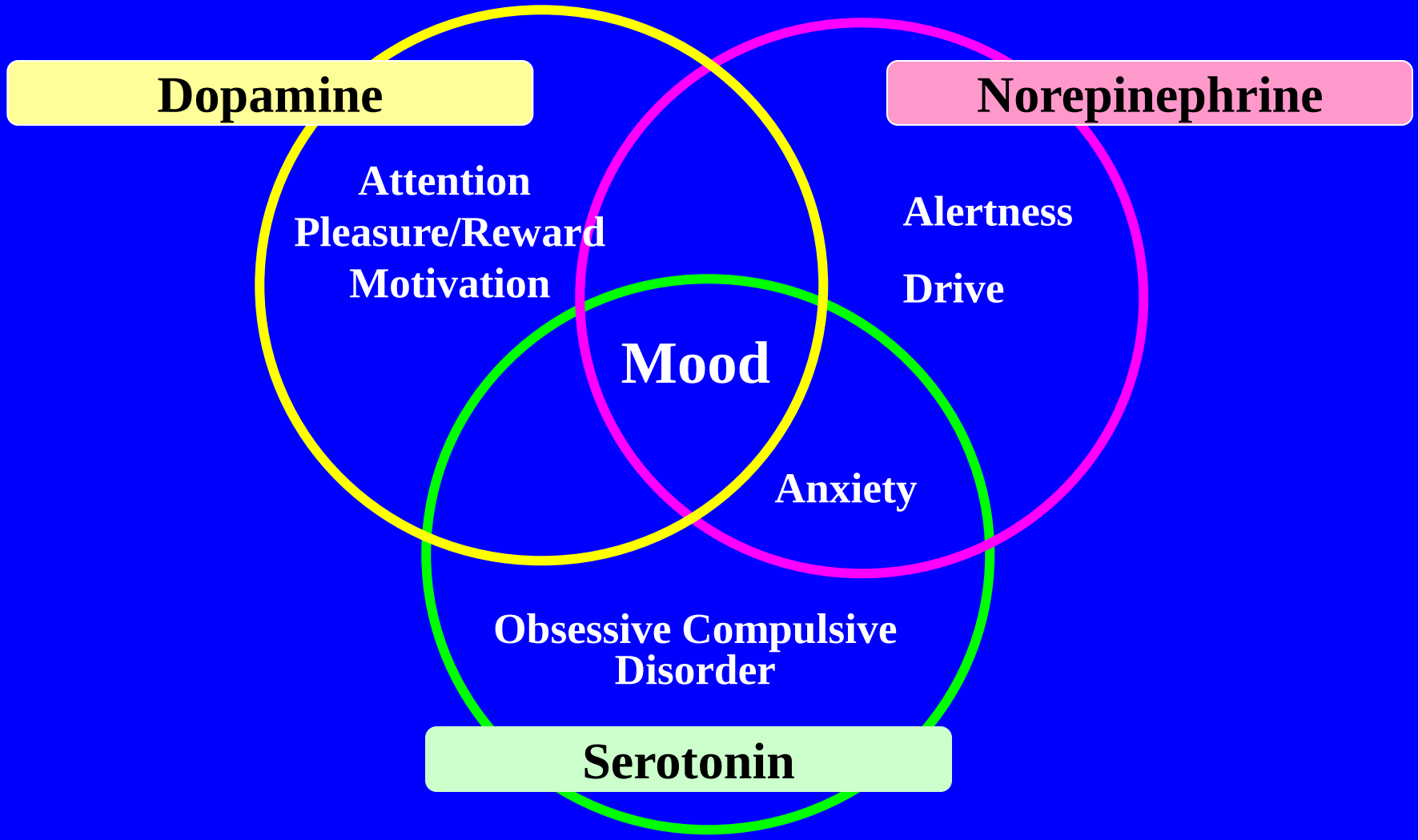
MONOAMINE HYPOTHESIS

Depression is caused by a deficiency of

SEROTONIN,
NOREPINEPHRINE,
or BOTH

Every approved antidepressant can increase
serotonin neurotransmission,
norepinephrine neurotransmission,
or both

Neurotransmitter Regulation of Mood, Cognition, and Behavior



Stahl SM. Essential Psychopharmacology

Foote Sl, Pharmacology and physiology of central noradrenergic systems, Psychopharmacology, 1995

Affinities (K_i) of Antidepressants for Monoamine Transporters and Receptors

	Serotonin	Norepinephrine
Desipramine	163	3.5
Fluoxetine	20	2186
Imipramine	20	142
Nefazodone	549	713
Paroxetine	.83	328
Sertraline	3.3	1716
Venlafaxine	102	1644

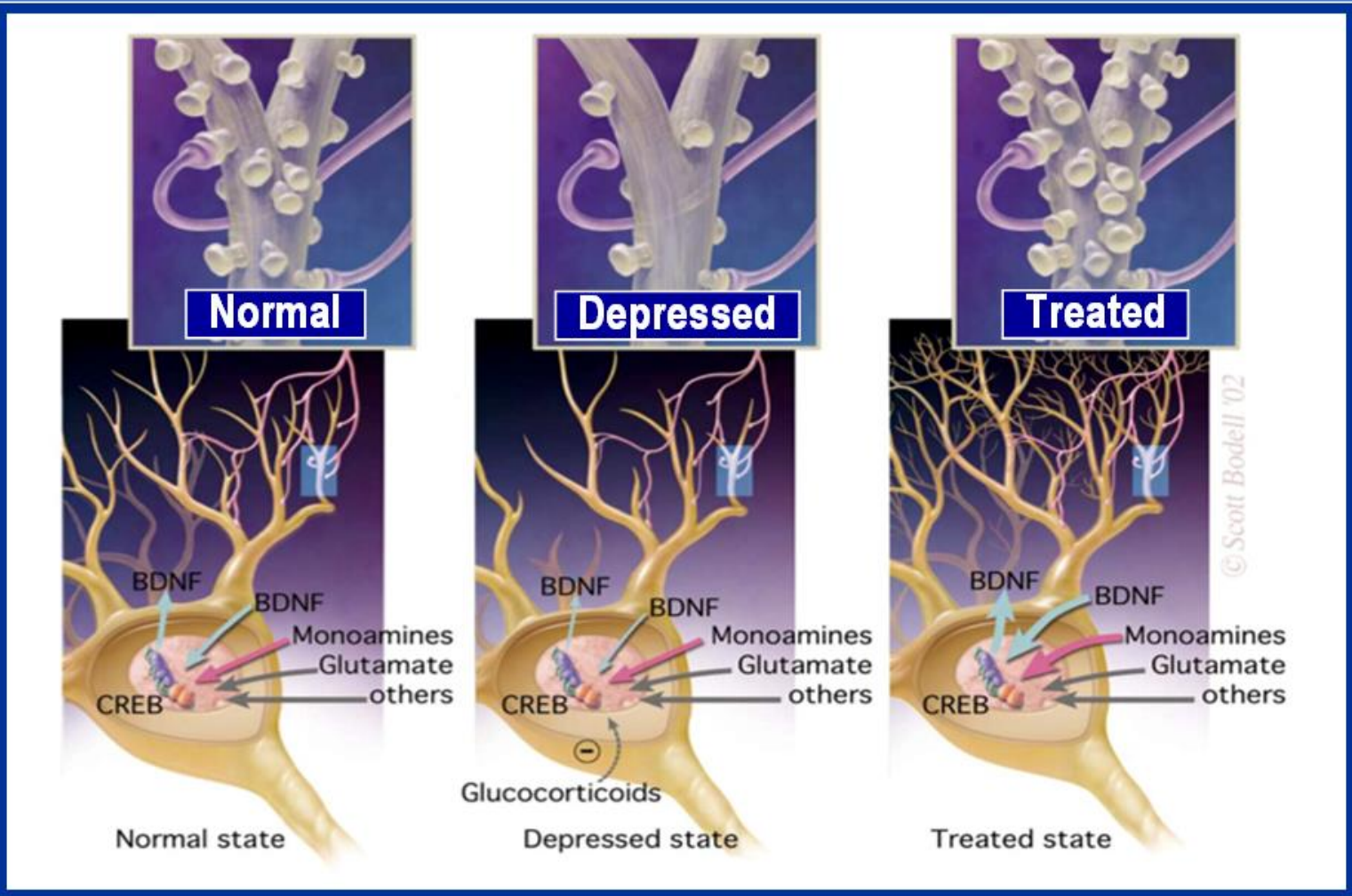
K_i = inhibition constant, nmol/L

Owens MJ et al. *J Pharmacol Exp Ther.* 1997;283:1305-1322.

Neurotrophic Hypothesis of Depression

- Depression is associated with loss of neurotrophic support in key brain regions such as the hippocampus
- All effective antidepressant therapies increase neurotrophic support in specific brain regions through secondary cascade systems

Antidepressants and neurotrophic factors may help restore communication in depression



Nestler EJ, et al. *Neuron*. 2002;34(1):13-25.

Limitations of Current Antidepressants

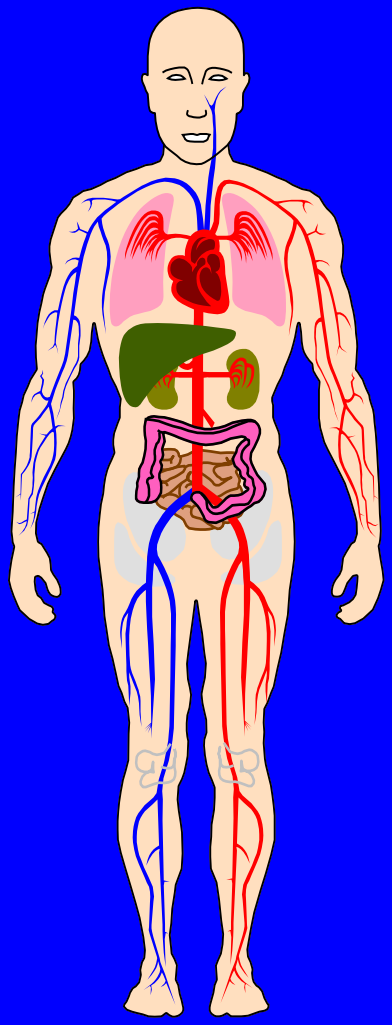
- Slow Onset
- Incompletely effective
- Multiple Side effects
- Non-generics are costly
- Potential for drug interactions

Antidepressant Adverse Effects

Metabolic
Weight changes

Cardiac
Orthostasis, hypertension, heart block

Urogenital
Erectile dysfunction, ejaculation disorder, anorgasmia, priapism



CNS
Dizziness, memory impairment, sedation, light-headedness, somnolence, nervousness, insomnia, headache, tremor

GI
Nausea, constipation, vomiting, dyspepsia, diarrhea

Autonomic NS
Dry mouth, urinary retention, constipation, blurred vision, sweating

Current Depression Treatment Options

- Pharmacologic
  - Antidepressant medications
- Nonpharmacologic
  - Psychotherapy
    - Cognitive behavioral therapy
    - Interpersonal therapy
    - Psychodynamic therapy
  - Electroconvulsive therapy
  - Phototherapy
  - Rapid transcranial magnetic stimulation (RTMS)
  - Vagus nerve stimulation

Depression Guideline Panel. Depression in Primary Care: Vol 1. Detection and Diagnosis. Clinical Practice Guideline No. 5, 1993

New Generation Antidepressants

- Fluoxetine (Prozac) 1988
- Bupropion (Wellbutrin IR) 1989
- Sertraline (Zoloft) 1992
- Paroxetine (Paxil) 1993
- Venlafaxine (Effexor) 1994
- Fluvoxamine (Luvox) 1994
- Nefazodone (Serzone) 1995
- Mirtazapine (Remeron) 1996
- Citalopram (Celexa) 1998
- Escitalopram (Lexapro) 2003
- Duloxetine (Cymbalta) 2004
- Selegiline transdermal (Emsam) 2006
- Desvenlafaxine (Pristiq) 2008

The Utility of Antidepressant Therapy

- 50-60% of depressed patients respond to any given antidepressant, and 80% to 95% respond to one or a combination of therapeutic interventions if multiple therapies are tried (Thase and Rush, *Psychopharmacology: Fourth Generation of Progress*, 1995).
- Half of depressed patients will experience a remission within 6 months of an index case of depression, and perhaps more than 75% will remit by 2 years (Keller et al, *Arch Gen Psychiatry*, 1992).
- Antidepressants appear effective in reducing relapse rates

Limitations of Antidepressant Therapy

- The percentage of patients who remain well during the18-month period following successful treatment for depression is disappointingly low: 19% to 30% in one study (Shea, et al. *Arch Gen Psychiatry*, 1992).
- At least 20% of treatment naïve patients fail to achieve remission even 4 sequential treatment trials with monotherapy and combinations (Rush et al, NEJM, 2006)
- More than half of patients fail to ever attain remission in acute trials, and those that do commonly may not sustain remission

Clinical Correlates of Enhanced Neurotransmission

Serotonergic side effects

- GI upset
- Sexual dysfunction
- Sleep disturbance

With long-term use

- Weight gain
- Suppression of dopamine neurotransmission may lead to:
  - Decrease in ability to experience pleasure
  - Apathy and decreased motivation
  - Decreased attention and cognitive slowing

Noradrenergic side effects

- Tremor
- Tachycardia

Dopaminergic side effects

- Psychomotor activation
- Aggravation of psychosis

Stahl SM. Essential Psychopharmacology
Richelson E., Pharmacology of antidepressants, Mayo Clin Proc, 1994
Kapur, Serotonin-dopamine interaction and its relevance to schizophrenia, Am J Psychiatry, 1996

Deficiencies in Current Antidepressant Therapy

- Slow onset of action
- Inadequate response for many patients
- Expense
- Toxicity
- Stigma

Common Features of Antidepressants

- All work on Monoamines
- All take 3-8 weeks to be maximally effective
- All have equivalent response rates (50-70% and remission rates (35-50 %)
- All have serotonin or NE side effects
- Placebo drug differences are greatest in more severe depression

The Selective Serotonin Reuptake Inhibitors

- Represent over 60-70 % of new prescriptions in MDD
- Easy to use and dose
- High Therapeutic Index
- Broad spectrum of activity

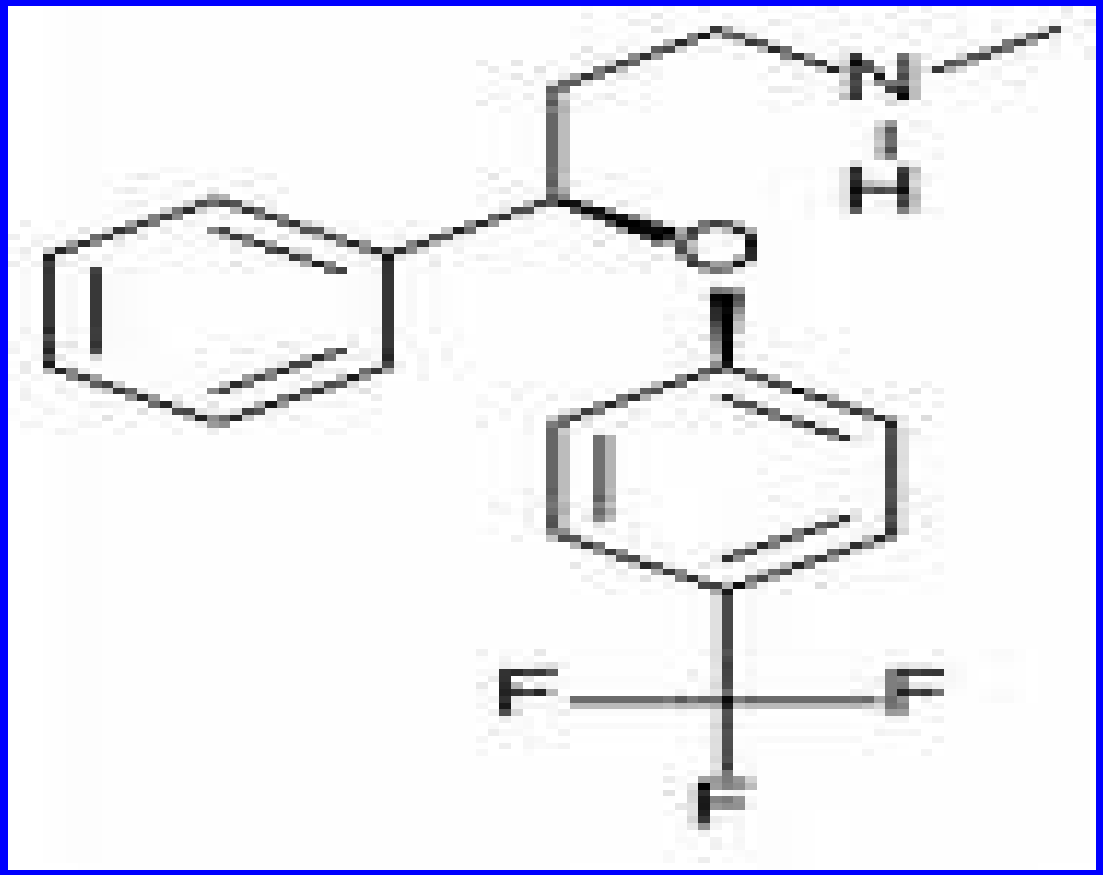
Current SSRIs

- Fluoxetine (Prozac)
- Sertraline (Zoloft)
- Paroxetine (Paxil)
- Fluvoxamine (Luvox)
- Citalopram (Celexa)
- Escitalopram (Lexapro)

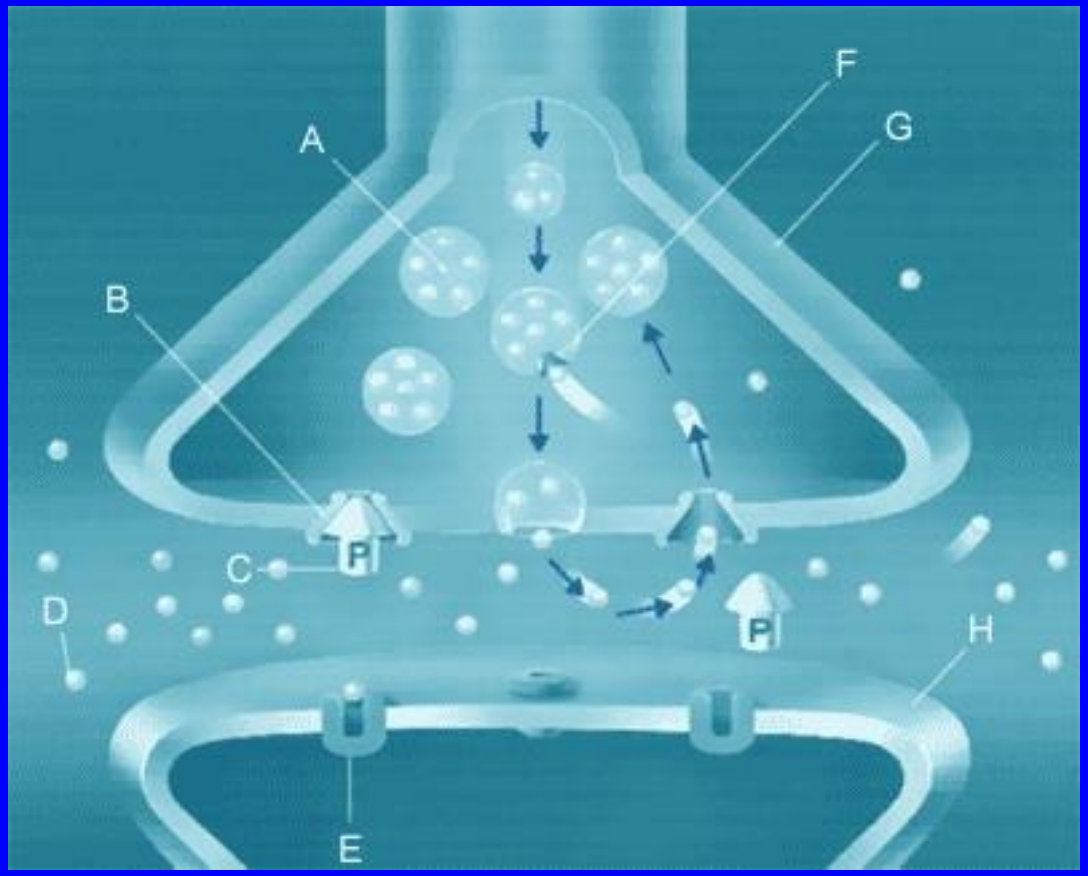
Indications (FDA)

- MDD
- OCD
- Panic
- Social Anxiety
- PTSD
- PMDD

Fluoxetine



Actions of SSRIs



Selective Serotonin Reuptake Inhibitors: Fluoxetine

Pros

- Safe
- Easy dosing
- Few side effects
- Broad Spectrum of activity

Cons

- GI/Sexual AEs
- Slow
- Moderate efficacy
- Cost

In Vitro P450 Inhibition by SSRIs

Drug	1A2	2C9	2C19	2D6	3A
Citalopram	0/+	0	0	+	0
Fluoxetine	+	++	+/++	+++	+/+
+					
Fluvoxamine	+++	++	+++	+	++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+/++	+	+

Cytochrome P450 (CYP450): Enzymes and Selected Substrates

1A2	2C	2D6	3A4
Theophylline	Phenytoin	Codeine	Antihistamines
Warfarin	Warfarin	Venlafaxine	Calcium channel blockers
Antipsychotics	Amitriptyline	Trazodone	Carbamazepine
Benzodiazepines	Clomipramine	Risperidone	Cisapride
Fluvoxamine	Omeprazole	Haloperidol	Corticosteroids
		Codeine	Cyclosporine
		β-blockers	Fentanyl
			Protease inhibitors
			Statins
			Triazolobenzodiazepine

Common SSRI Side Effects

- Central nervous system (CNS)

Activating	Sedating
Insomnia	Somnolence
Anxiety	Fatigue
Agitation	
Nervousness	
Tremors	
Dizziness	

- Gastrointestinal (GI) side effects
  - Nausea, vomiting, abdominal pain, diarrhea, constipation
- Sexual dysfunction
- Weight changes

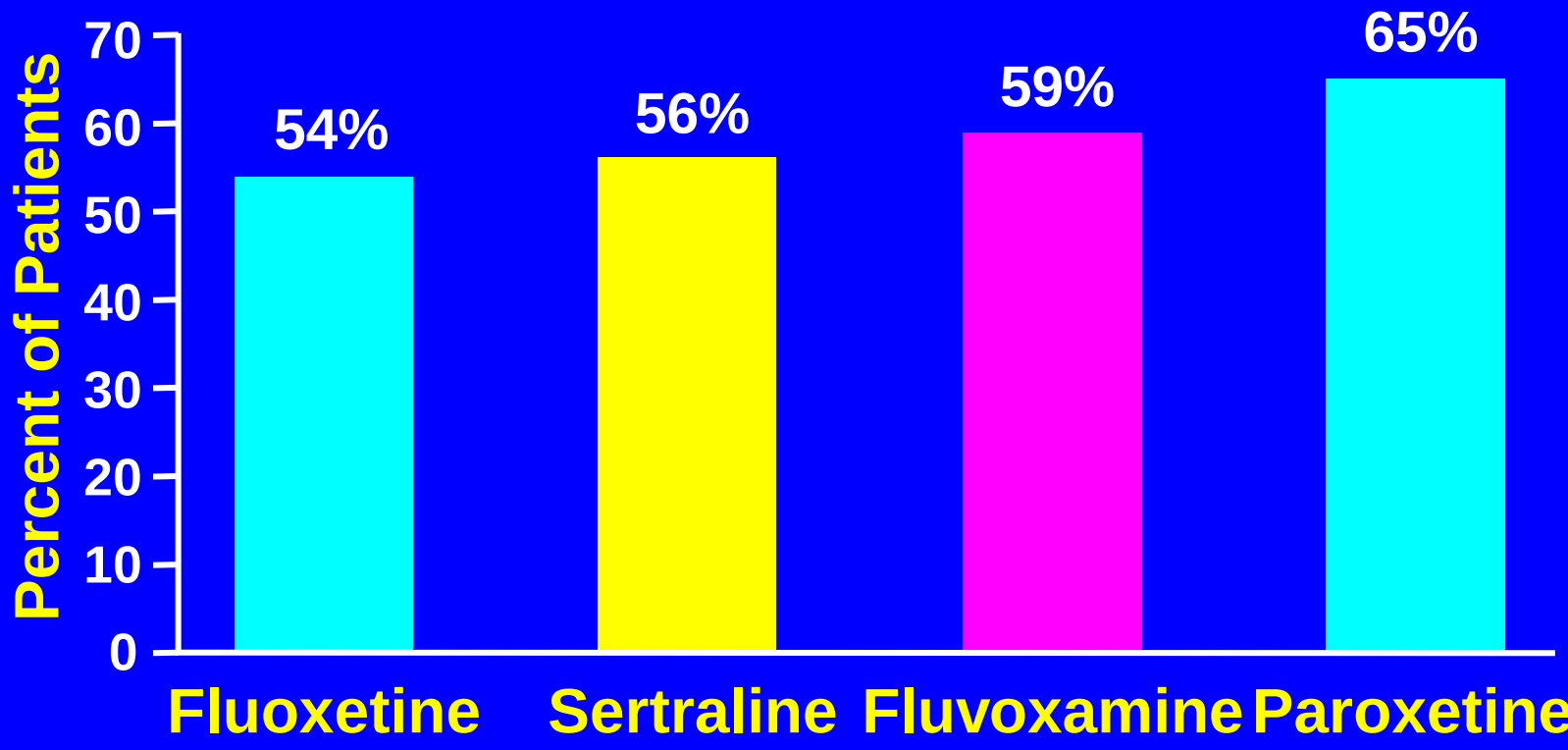
Gastrointestinal Side Effects with SSRIs

- Similarities > differences
- Adaptation: 1-2 weeks
- May be managed by dose reduction

Antidepressant-Induced Sexual Dysfunction

- Most patients will not complain of antidepressant-induced sexual dysfunction early in treatment because of low libido caused by the depression itself
- The incidence of antidepressant-induced sexual dysfunction was originally thought to be negligible because physicians relied on **spontaneous reporting** of sexual problems
- We now know that the incidence of antidepressant-induced sexual dysfunction is over 50% for most of the SSRIs and newer agents

The Incidence of Sexual Dysfunction Among SSRIs



Montejo-Gonzalez AL et al. J Sex Marital Ther. 1997;23(3):176-194

Weight Gain Associated with Long-Term (6-24 Months) Use of Antidepressants in Double-Blind Studies

Gain	Mean Weight Gain (lbs)	≥7% Weight (%)
Sertraline[1]	1.7	4
Fluoxetine[1]	-2.2	7
Paroxetine[1, 2]	6.0	26
Mirtazapine[2]	4.0	13
Nefazodone[3, 4]	1.2	8
Citalopram[5, 6]	3.0	5
Bupropion[7]	-2.6	N/A

[1]Fava et al, 2000; [2]Data on file: Organon Inc.; [3]Feiger, 1999; [4]Data on file: Bristol-Myers Squibb Company; [5]Mackle & Kocsis. ACNP, 1998; [6]Data on file: Forest Pharmaceuticals, Inc.; [7]Weihs et al. APA, 2000 (Poster presentation)

Weight Change Associated with Antidepressants

- Some associated with weight changes, particularly with long-term treatment
- Weight decreases in short-term treatment may be followed by weight increases in long-term treatment
- Weight increase may be associated with improved appetite (treatment success)

SSRI Discontinuation Syndrome

- Dizziness, vertigo, ataxia
- Nausea
- Sleep disturbances
- Flu-like symptoms
- Paresthesia
- Anxiety/agitation/irritability
- Crying spells/irritability

Schatzberg AF et al. J Clin Psychiatry. 1997;58(suppl 7):5-10

The Tricyclic Antidepressants

- Dominated MDD treatment from 1958 to1988
- Might be more effective than SSRIs in melancholic depression
- Need for titration to reach a therapeutic dose
- Numerous side effects
- Highly lethal in overdose

TCA Agents

Tertiary Amines TCAs

- Imipramine (Tofranil)
- Amitriptyline (Elavil)

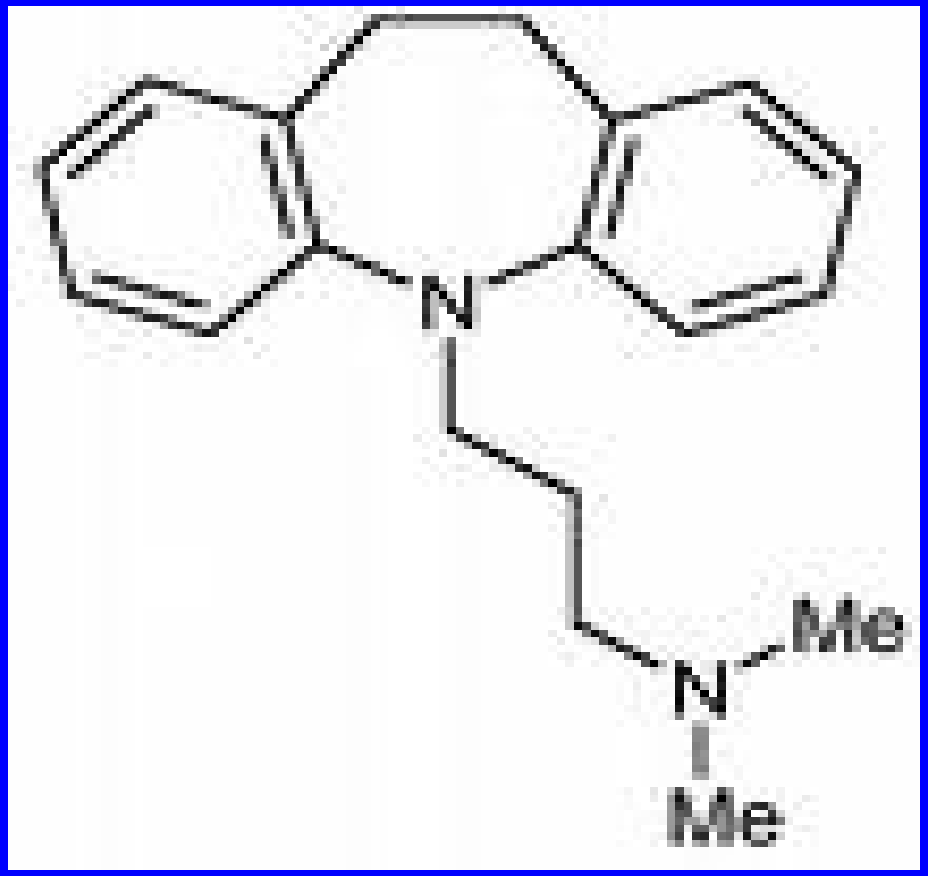
Secondary Amine TCAs

- Desipramine (Norpramin)
- Nortriptyline (Pamelor)

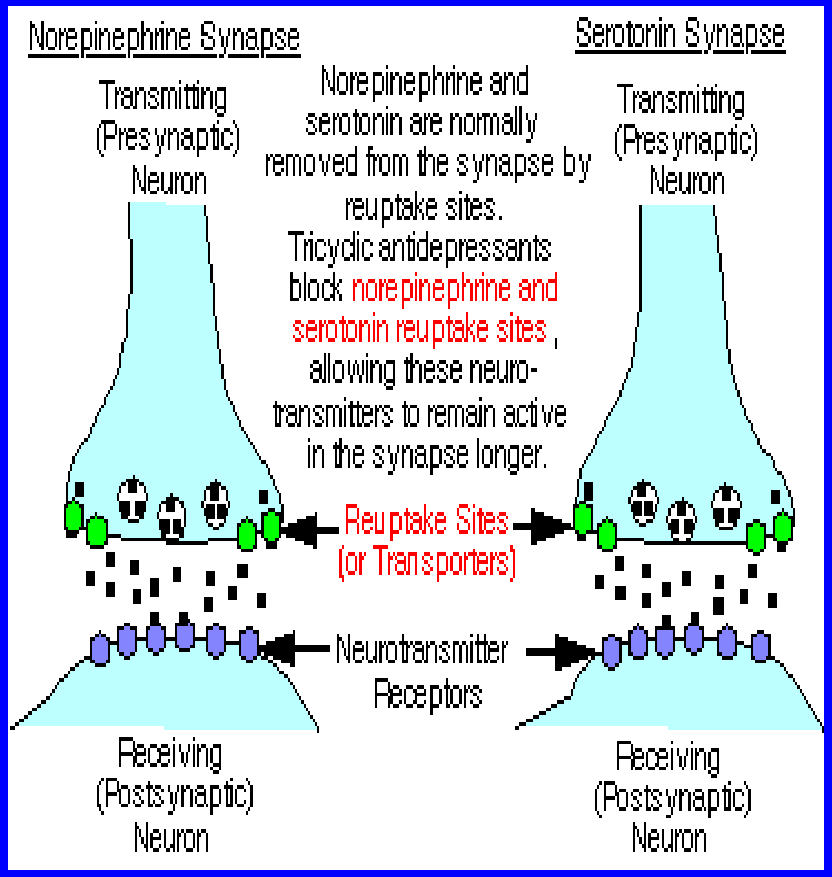
TCA indications

- MDD
- Panic
- Enuresis
- OCD (Clomipramine)
- Also used in PCP setting for pain, migraine prevention, sleep)

Imipramine

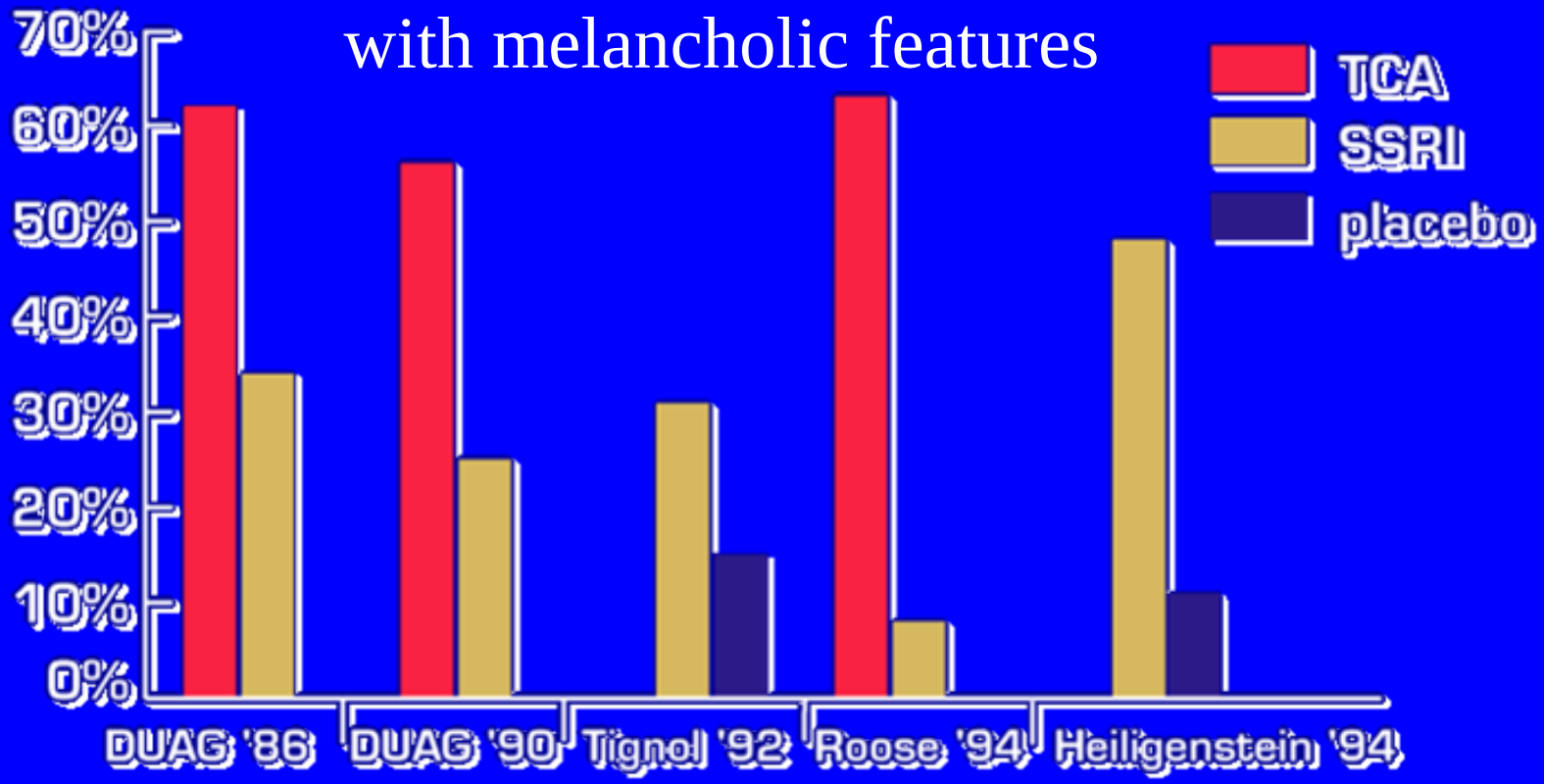


TCA Actions


Norepinephrine Synapse
Serotonin Synapse
Transmitting (Presynaptic) Neuron
Norepinephrine and serotonin are normally removed from the synapse by reuptake sites. Tricyclic antidepressants block norepinephrine and serotonin reuptake sites, allowing these neuro-transmitters to remain active in the synapse longer.
Transmitting (Presynaptic) Neuron
Reuptake Sites (or Transporters)
Neurotransmitter Receptors
Receiving (Postsynaptic) Neuron
Receiving (Postsynaptic) Neuron

Remission Rates for TCAs, SSRIs, and Placebo

In endogenous depression or major depression with melancholic features



TCA Side Effects

- Dry mouth, constipation, blurred vision, urinary retention,
- Hypotension
- Sedation, Wt gain
- Sexual A Es
- Cardiac conduction AEs

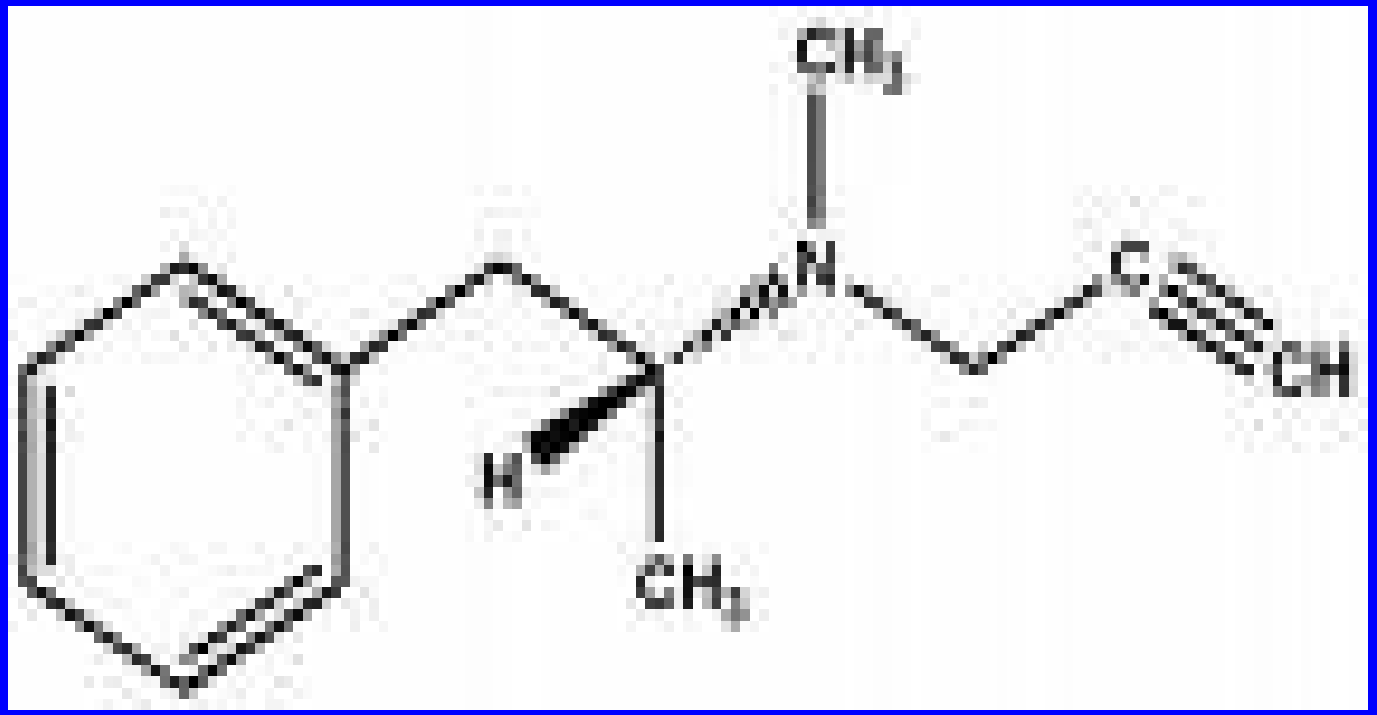
The Monoamine Oxidase Inhibitors (MAOIs)

- Oldest class of antidepressants
- More rarely used currently: treatment resistant depression
- Potential for serious drug interactions (Serotonin Syndrome)
- Tyramine Pressor effects (Hypertensive crisis)

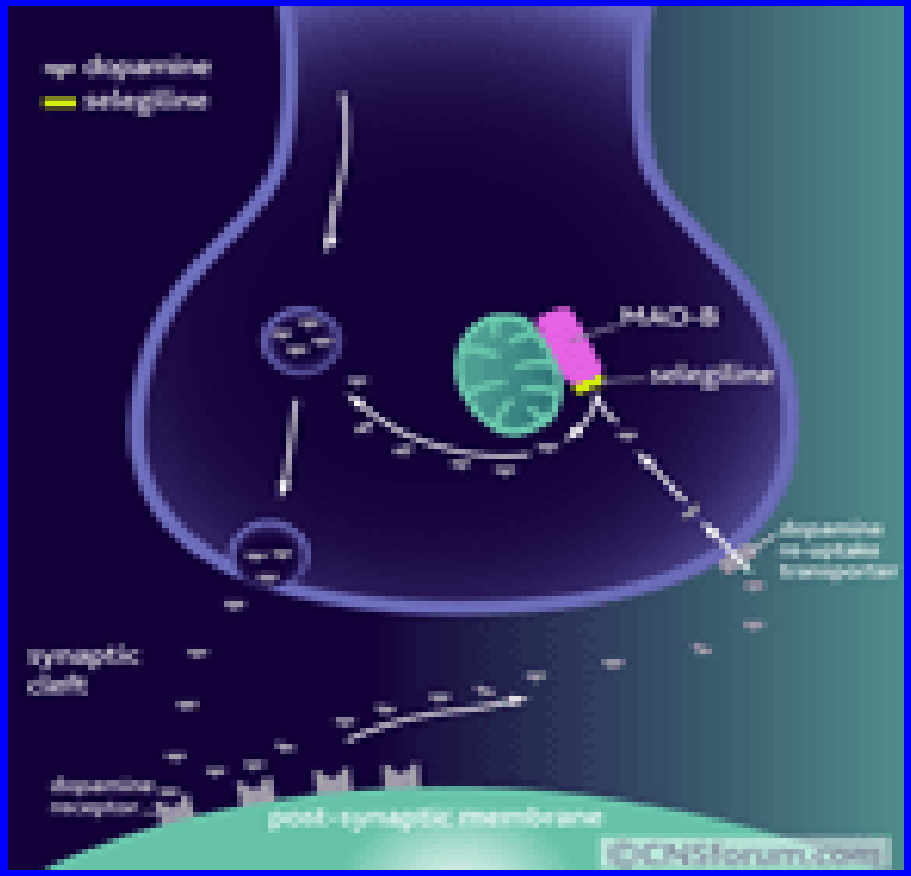
MAOIs

- Trandermal Selegeline (Emsam)
- Phenelzine (Nardil)
- Tranylcypramine (Parnate)

Selegiline



Selegiline Mechanism



MAOI Side Effects

- Hypotension
- Sexual AE s
- Weight gain
- Sedation/activation

MAOI Drug interactions

- Serotonergic drugs (SSRIs, clomipramine, meperidine, tramadol); Serotonin syndrome

- Sympathomimetics and Tyramine Foods: Hypertensive crisis

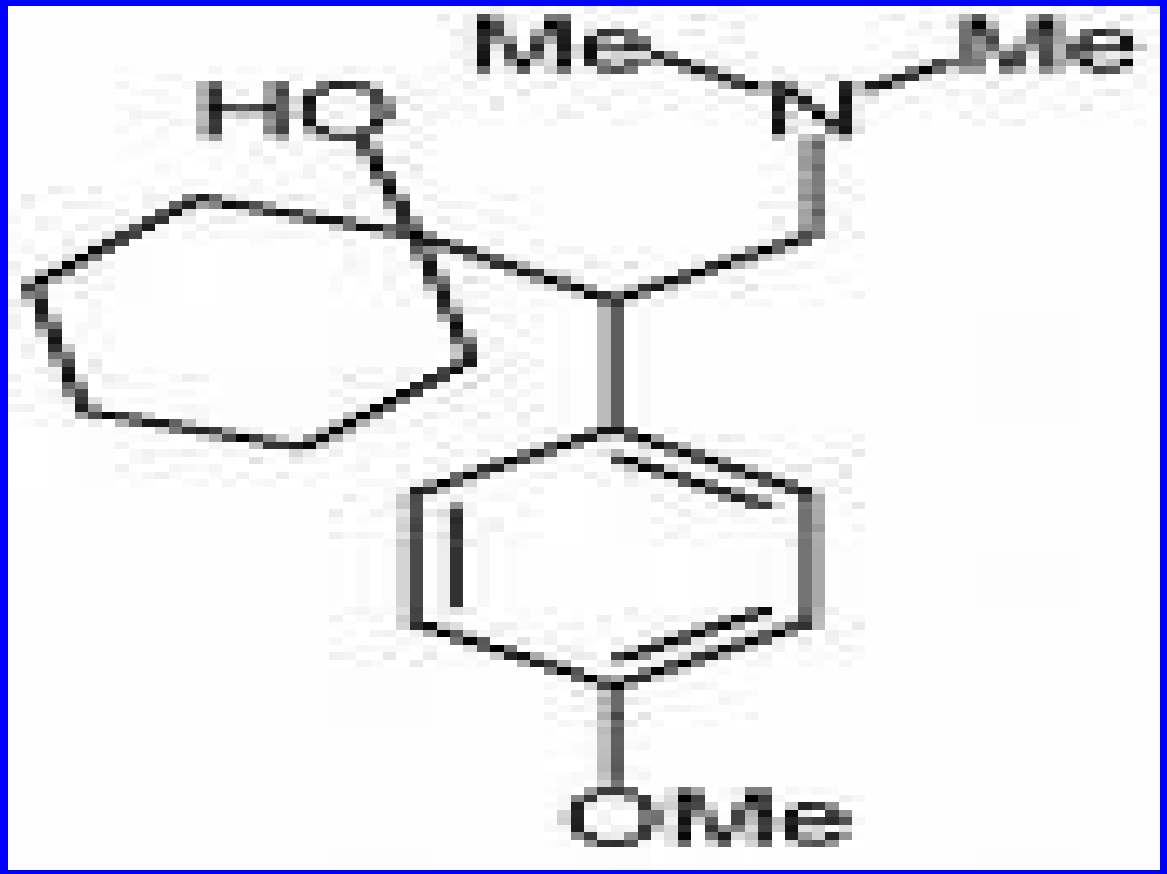
High Tyramine Food Examples

- Aged cheeses (stilton, blue)
- Dried sausage/salami
- Pickled herring
- Soy sauce, tofu
- Fava bean pods
- Marmite, brewers yeast
- Tap beer, chianti

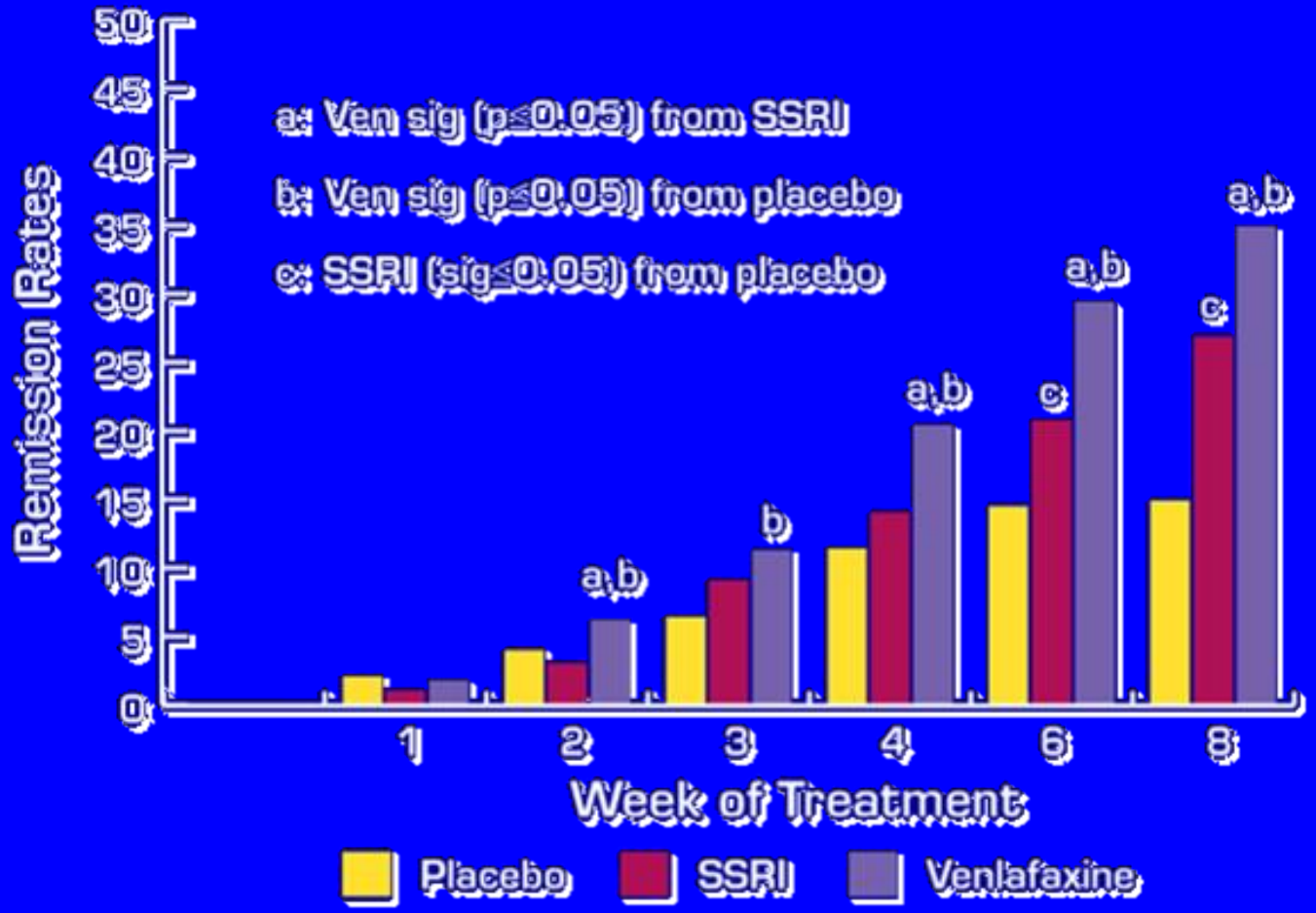
SNRIs; Venlafaxine, Desvenlafaxine, Duloxetine

- Similar to TCAs in mechanism but without the anti ACH, anti-H, and anti-alpha
- Useful in some pain syndromes
- May be useful in stress incontinence
- Appear useful in vasomotor symptoms in menopause
- May be more effective than SSRIs in serious depression

Venlafaxine



Remission Rates (HAM-D<8):
venlafaxine-SSRI Pooled Studies



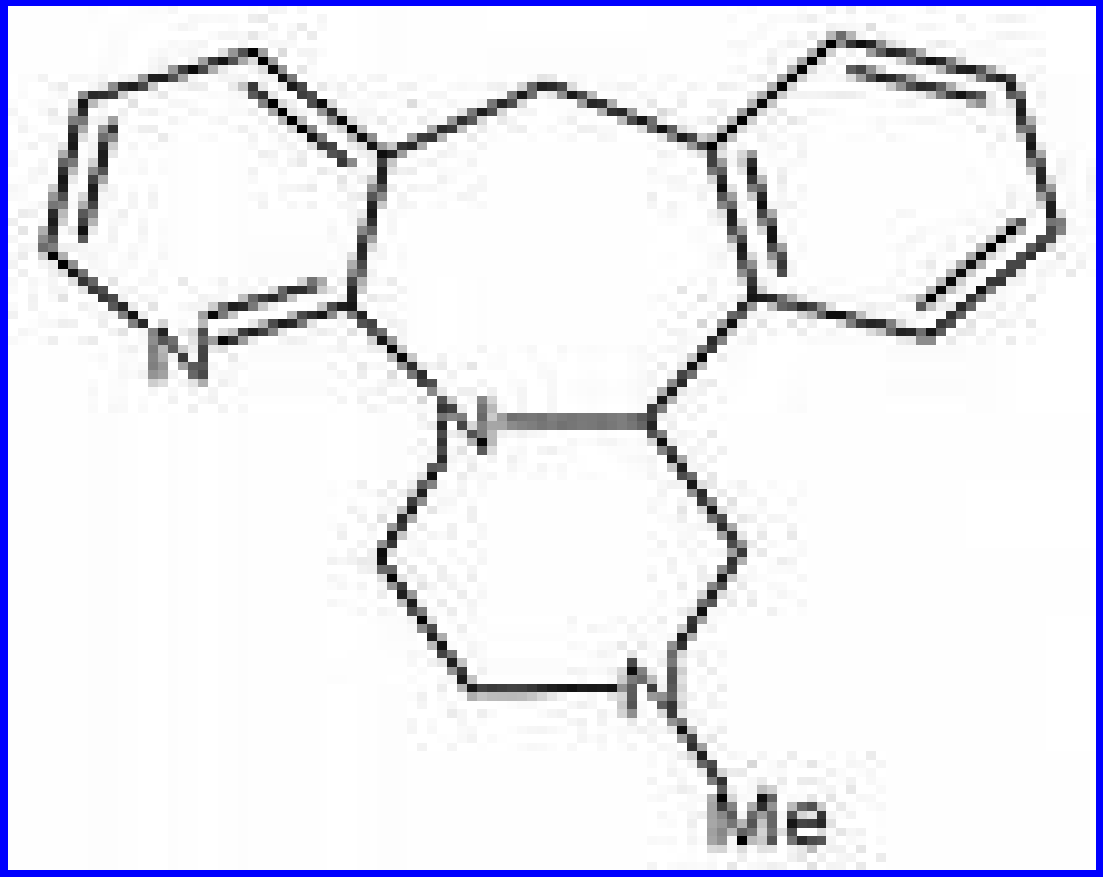
SNRI side effects

- GI
- Sexual
- Activation/somnolence
- Hypertension/tachycardia
- Urinary retention
- Dry mouth, constipation

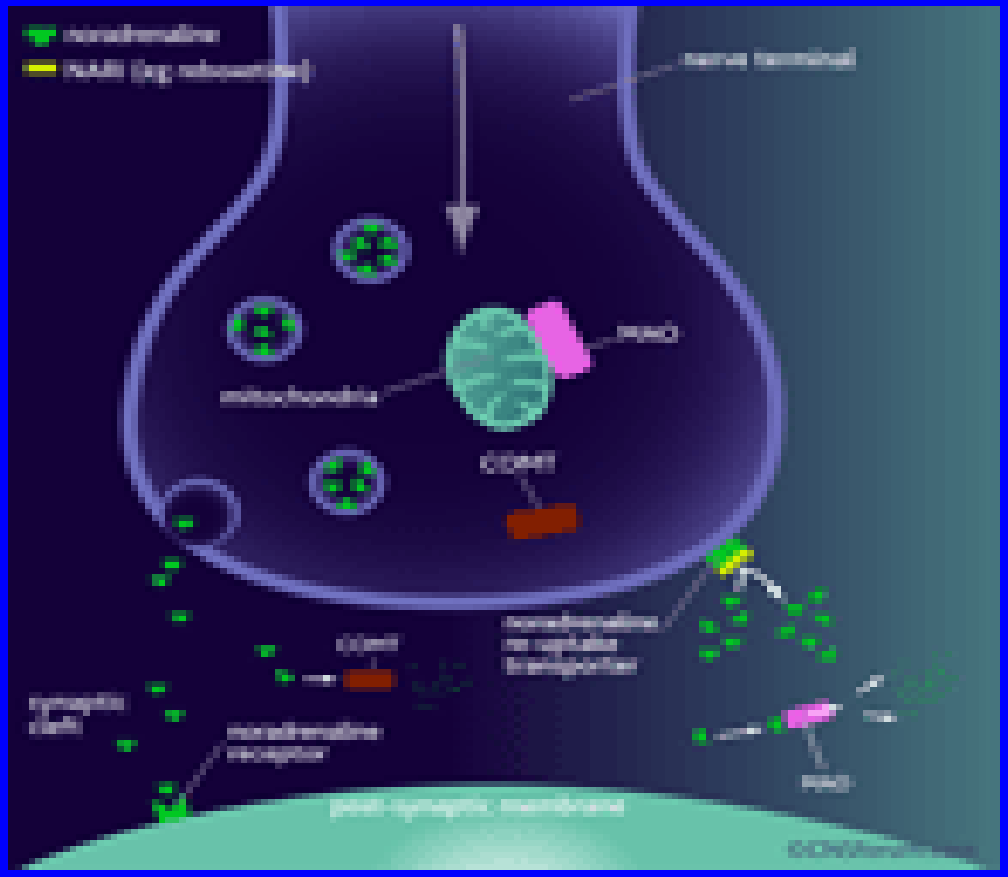
Mirtazapine (Remeron)

- Indicated in MDD only
- May be effective in augmenting SSRIs, SNRIs
- Highly sedating
- Associated with weight gain
- Safe in overdose
- Few sexual AEs

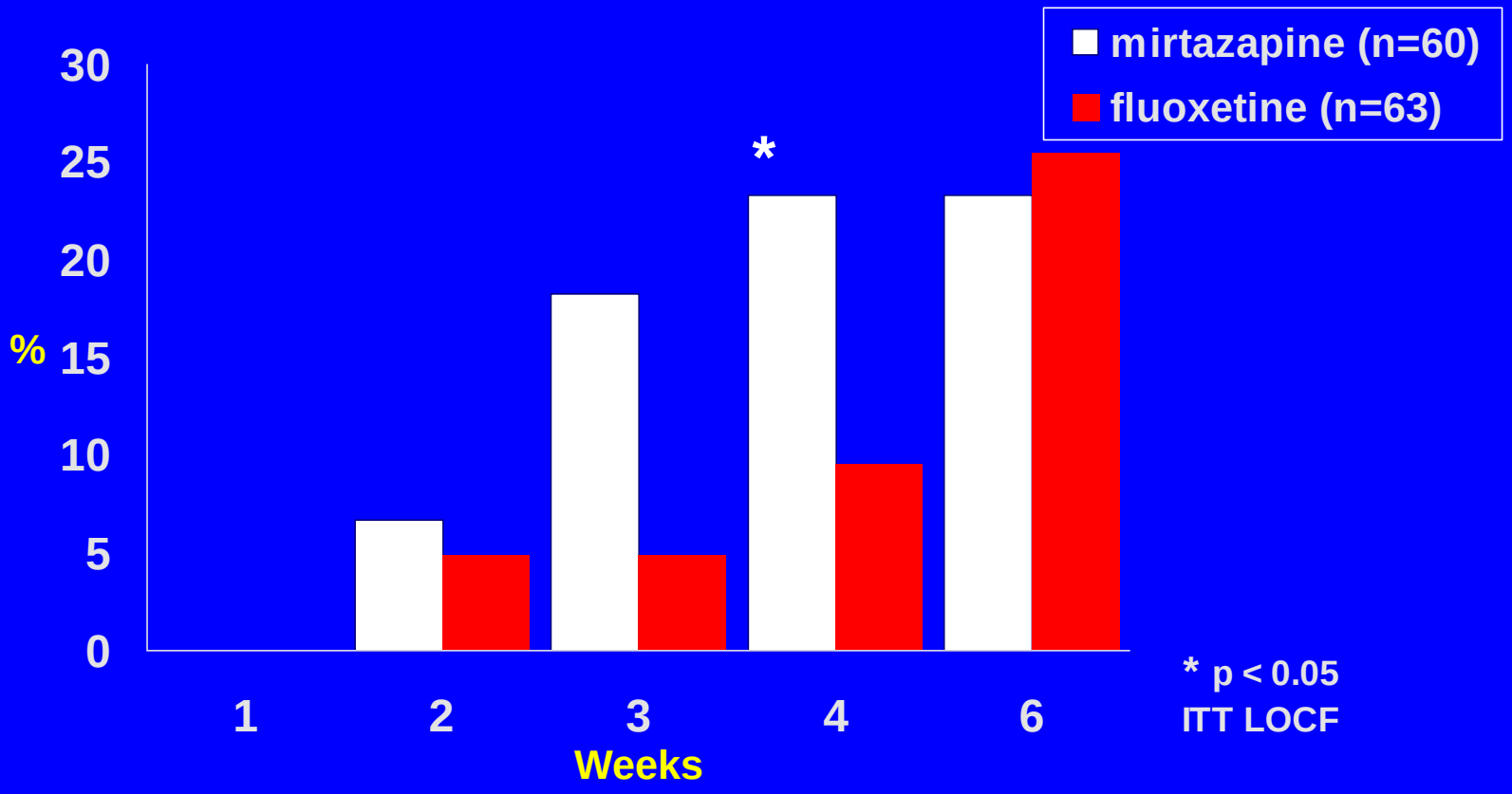
Mirtazapine



Mirtazapine Mechanism



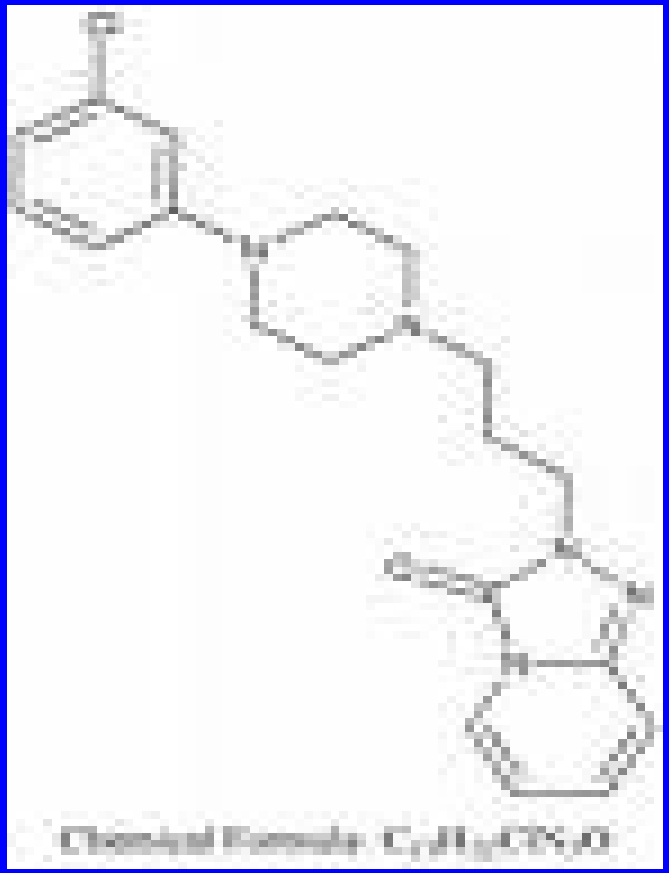
Mirtazapine versus Fluoxetine Remission rates (HAMD<7)



5HT-2 Antagonists (Nefazodone, Trazodone)

- Indicated in MDD
- Nefazodone associated with hepatoxicity
- May be useful in GAD
- Trazodone commonly used as a hypnotic
- Perceived as less robust antidepressants

Trazodone



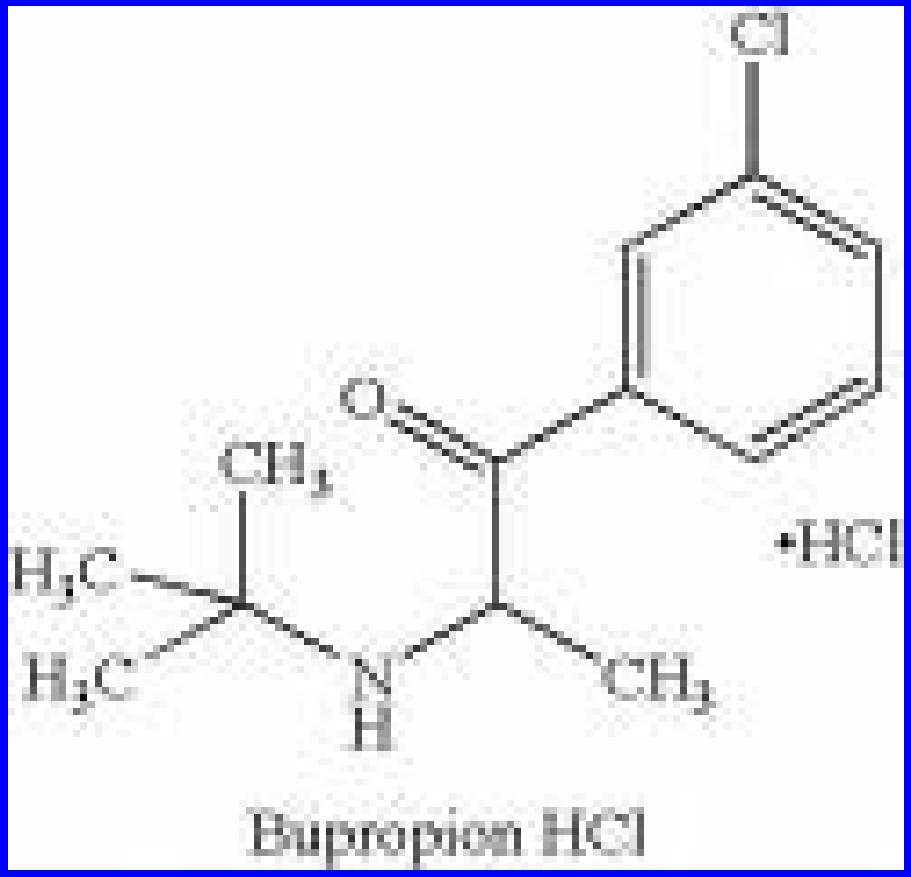
5HT2 Antagonist AEs

- Sedation
- Weight gain
- Orthostatic hypotension
- Priapism (trazodone)

Bupropion

- Indicated in MDD
- Indicated in smoking cessation
- Commonly used to augment SSRI and SNRI antidepressants
- Not effective in the treatment of anxiety disorders
- Few sexual side effects
- Mildly anorexiant

Bupropion



Bupropion Mechanism

- Unknown
- Indirect NE agonist
- Modest DA reuptake in human studies

Bupropion AEs

- CNS activation
- Tremor
- Weight loss
- Few sexual side effects
- Dose related risk of seizure for IR form

Potential Antidepressants

- Glucocorticoid Receptor Antagonists
  - Mifepristone
  - Org 34571
- CRF antagonists
  - - ONO-2333Ms (Ono)
  - - GSK-561679 (GSK)
  - - Pexacerfont
- Triple reuptake inhibitors
  - NS 2359
    DOV 216303
- Melatonin Agonists
  - Agomelatine

Conclusions

- Depression is common
- There are limitations to all current antidepressants but new strategies are evolving.
- There is a need for faster, more effective, better tolerated agents

Post-Lecture Exam Question 1

The most common side effects early in the course of SSRI treatment leading to discontinuation is

1. GI upset
2. Loss of libido
3. Headache
4. Weight gain

Question 2

The most common cause of death in TCA overdose is

1. Arrhythmia
2. Seizure
3. Congestive heart failure
4. Stroke

Question 3

Noradrenergic side effects of antidepressants may include

1. Sedation
2. Weight gain
3. Tachycardia
4. All of the above

Question 4

The neurotrophic hypothesis of depression suggests

1. Depression is related to loss of neurotrophic support
2. Antidepressants increase neurotrophic factors such as BDNF
3. Depression is associated with a progressive loss of volume in areas such as the hippocampus
4. All of the above

Question 5

Foods that are likely be problematic for patients on MAOIs include

1. Soy sauce
2. American Cheese
3. Pasteurized Beer
4. All of the above

Answers to Pre- and Post-Lecture Exams

1. 1
2. 1
3. 3
4. 4
5. 1