Boca Raton Regional Hospital
Grand Rounds – April 23, 2019

Evaluation and Primary Treatment Modalities: Major Depressive Disorder

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No Conflicts of Interest

I would like to thank

Daniel G. Orr, MD

Eric Peselow, MD

ASCP Model Curriculum

American Society of
Clinical Psychopharmacology

At the Conclusion of This Morning's Presentation
You Will be To Be Able To:

Identify 3 Subtypes of Major Depressive Disorder (MDD)
Recite 5 Cardinal Characteristics of MDD
Identify 3 Major Classes of Antidepressant Medication
Describe the Neurotransmitter Receptor Hypothesis of MDD

.

Epidemiology of major depression

- Point prevalence (DSM-IV-TR, 2000)
  - Women 5–9%
  - Men 2-3%
- Incidence rate (Kornstein, 1997)
  - Equal in pre-pubertal boys and girls
  - Women 2-3 times more likely to have MDD after puberty
- Lifetime risk (DSM-IV-TR, 2000)
  - Women 10–25%
  - Men 5-12%
- Lifetime prevalence=17.1% (Kessler, 1994)

Genetic risk factors for mood disorders

- Risk in first degree relatives
  - Major depressive probands: Increased by about 2 fold
  - Bipolar probands: Increased by about 7 fold (range 3.7-17.7)
- Twin studies: Concordance rates in MZ twins
  - Major depression: about 50%
  - Bipolar: about 70%

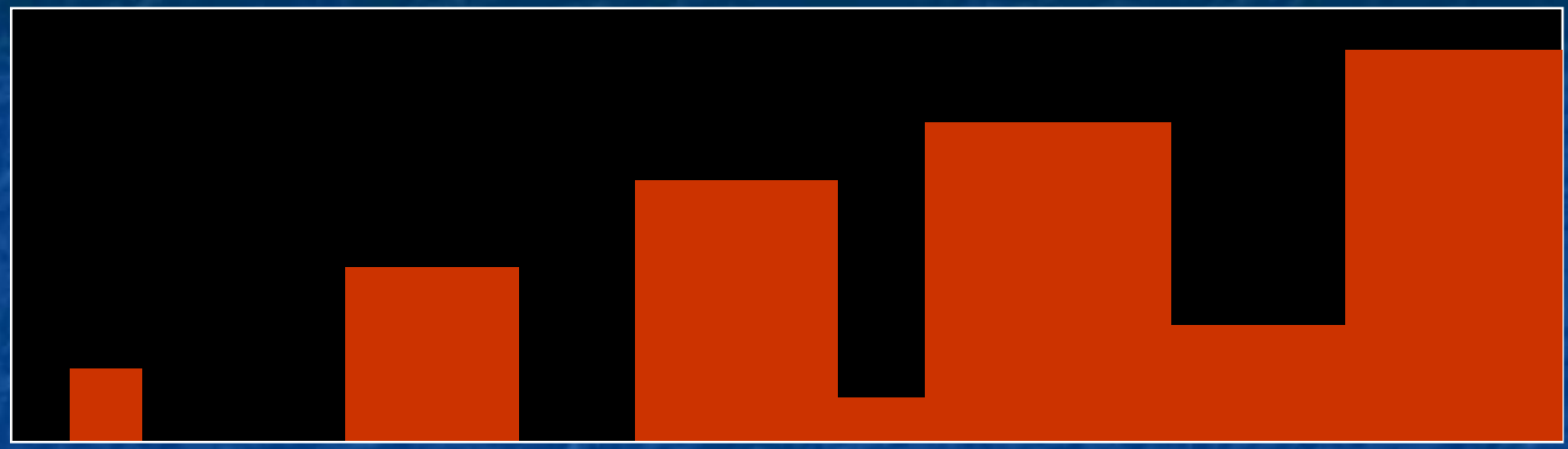
Non Genetic Risk factors for MDD
(Boyd, 1982; Weissman, 1991)

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

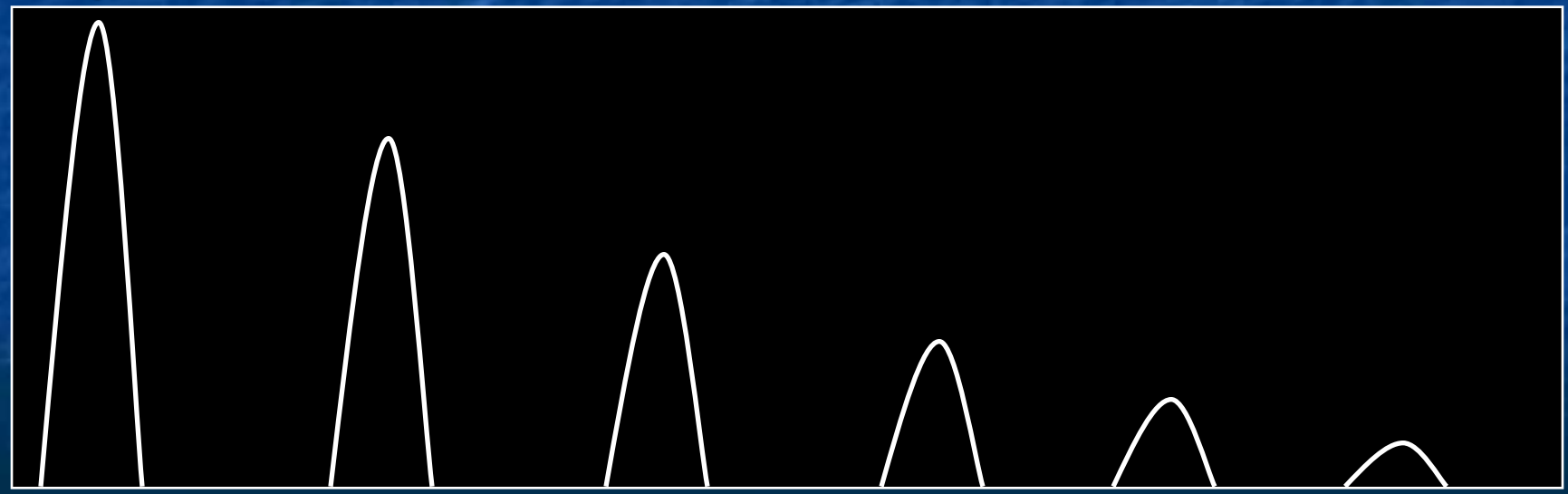
Stress response circuits and depression

- The hypothalamic-pituitary-adrenal (HPA) axis forms a feedback loop via brain regions including the hippocampus and amygdala
- Hypercortisolemia increases excitotoxicity of hippocampal CA3 pyramidal neurons, resulting in atrophy, apoptosis and perhaps reduced neurogenesis
- Loss of function by these neurons by chronic stress can reduce their inhibitory tone on the HPA axis resulting in hyperactivity of the HPA axis
- Treatment with antidepressants appears to contribute to recovery of the hippocampal neurons by increasing neurogenesis

Stressors and depression



Depression

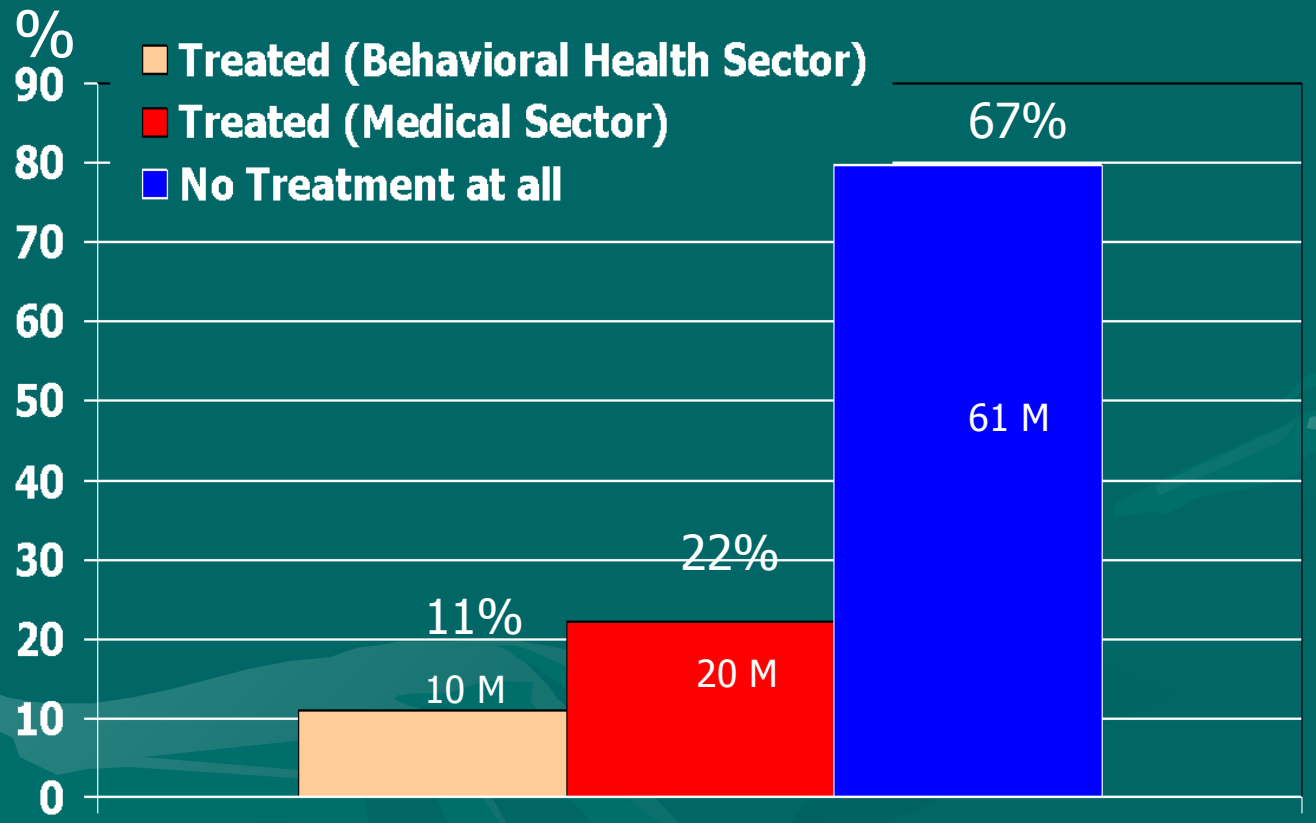


Stressors

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

A. 10%
B. 25%
C. 50%
D. 70%

Lack of Treatment of Mental Illness



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

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

Conditions Associated with Mood Symptoms

- **Substance abuse (cocaine, etc.)**
- **Concurrent medications (eg steroids)**
- **General medical disorders (thyroid)**
- **Anxiety Disorders (OCD, panic etc.)**
- **ADD/ADHD**
- **Other causal non-mood psychiatric disorders (e.g. personality disorders)**
- **Grief reactions**

Depression Screening: PHQ-9

A SCREENING INSTRUMENT BUILT PRIMARILY ON THE FREQUENCY OF SYMPTOMS AND THEIR ASSOCIATION TO FUNCTIONAL CONSEQUENCES.

Over the last 2 weeks, how often have you been bothered by any of the following problems?

0 = Not At All

1 = Several Days

2 = More Than Half the Days

3 = Nearly Every Day

Total Score ____

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

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not Difficult
Somewhat Difficult
Very Difficult
Extremely Difficult

CHARACTERISTIC SYMPTOMS TO SCREEN FOR

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless.
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy.
5. Poor appetite or overeating.
6. Feeling bad about yourself;
   that you are a failure or
   have let yourself or your family down.

7. Trouble concentrating on things, such as reading the newspaper or watching television.

8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual.

9. Thoughts that you would be better off dead or of hurting yourself in some way.

Patient Education

- Anxiety and Depression are medical illnesses
- Recovery is the goal
- Treatments are effective
- Aim of treatment is complete symptom remission
- Recurrence may occur
- Seek treatment early if depression returns

Antidepressants Suicidality

- Risk of Suicidality about 2% above Placebo in youth
- Risk of Suicidality in young adults about 1% above placebo.

NOTWITHSTANDING THE BLACK BOX WARNINGS….

- ******* No Evidence of increased risk of Suicide*******

Reduced Antidepressant use
increases risk of Suicide in Youth !

- ***IN DSM -5 we now use subtype "specifiers."***
- With anxious distress
- With mixed features (Manic)
- With melancholic features
  - Loss of pleasure, lack of reactivity, early morning awakening, morning depression worse
- With atypical features
  - Mood reactivity, weight gain, hypersomnia, leaden paralysis, rejection sensitivity
- With mood congruent or incongruent psychotic features (Delusions or hallucinations)
- With catatonia
  - Immobility, excessive motor activity, negativism, peculiar movements, echolalia or echopraxia
- With peripartum onset (Starts within 4 weeks postpartum)
- With seasonal pattern (Temporal relationship with a time of year)

Pathophysiology of depression: review of the key neurotransmitters

- Norepinephrine
- Serotonin
- Dopamine
- Other neurotransmitters (or their precursors) with reported abnormalities include:
  - GABA ↓
  - Glutamate ↑

Neurotransmitter receptor hypothesis

- Depletion of neurotransmitters causes compensatory upregulation of postsynaptic neurotransmitter receptors

EVIDENCE

- Postmortem studies show increased 5HT2 receptors in frontal cortex of patients who commit suicide
- Neuroimaging studies have suggested abnormalities in 5HT receptors in depressed patients
- ECT may down regulate post synaptic neurotransmitter receptors.

Monoamine deficiency hypothesis of depression

1. When there is a "normal" amount of monoamine neurotransmitter activity, there is no depression present.

2. If the "normal" amount of monoamine neurotransmitter activity is reduced, depleted or dysfunctional, depression may ensue
   (Stahl's Essential Psychopharm)

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EVIDENCE

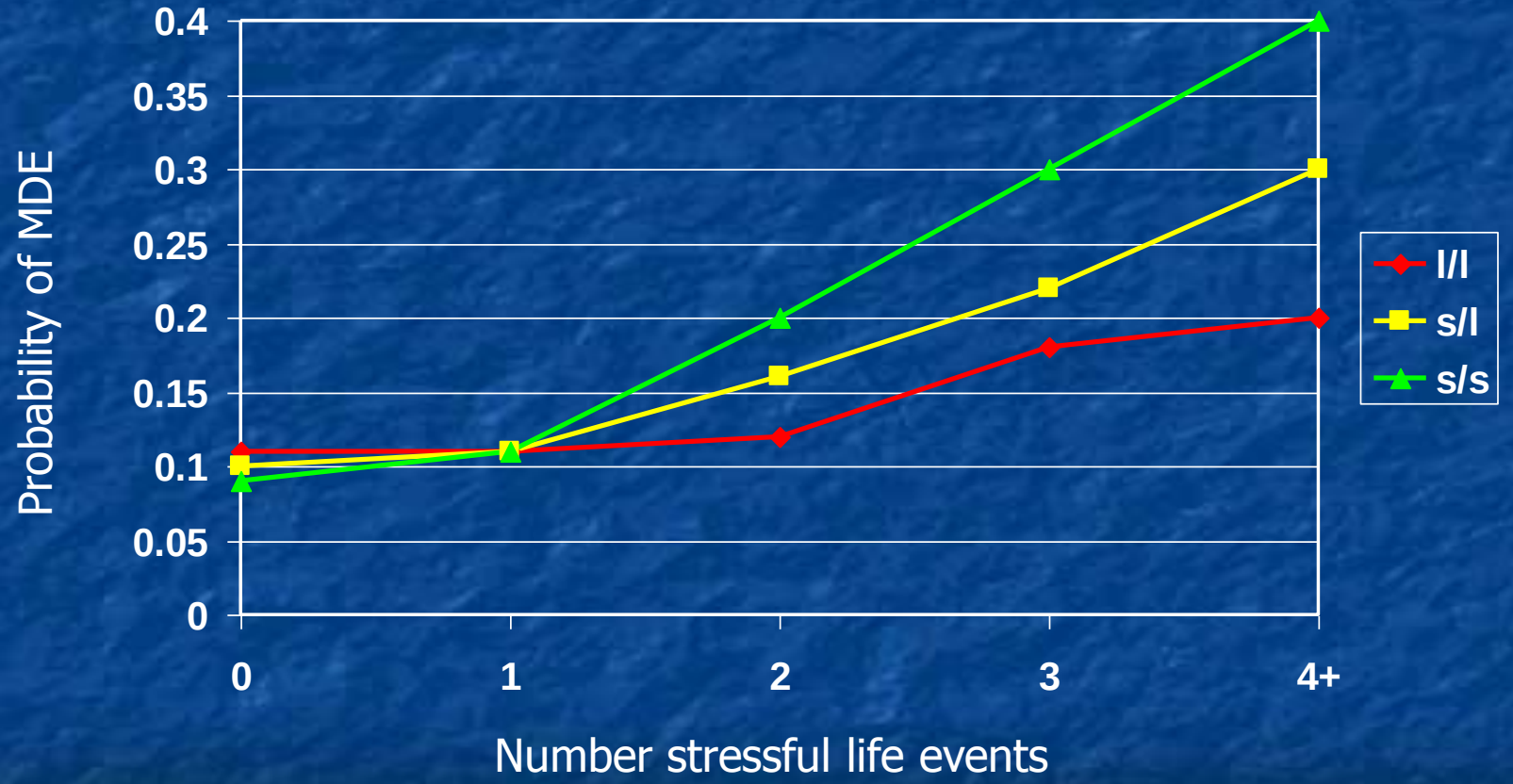
- Deficiency of norepinephrine and serotonin are causally related to symptoms (Schildkraut, ‘65; van Praag & Korf, ‘71)

- Depletion of brain amines by reserpine can precipitate depression

- A serotonin metabolite (5HIAA) may be reduced in the CSF of depressed patients; though not true for all depressed patients

  the correlation is more closely linked with impulse-control problems rather than depression (Stahl)

Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene



Among the small group who experienced severe childhood abuse, s/s allele subjects ran a 63% risk of MDE in young adulthood.

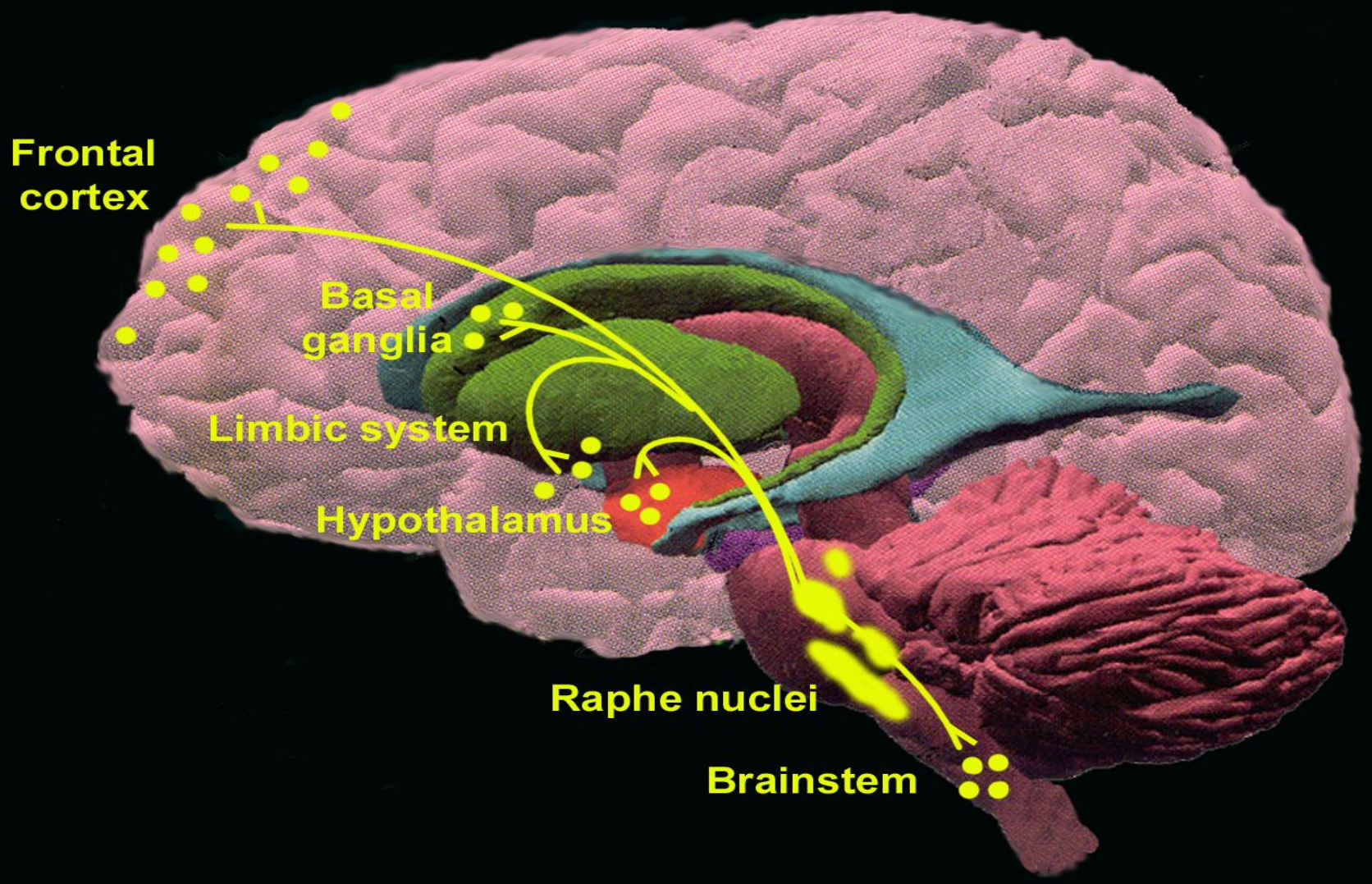
Patients with s/s allele may not respond to citalopram as well as other patients

Caspi, A et al SCIENCE 301; 386 ff, JULY 18, 2003

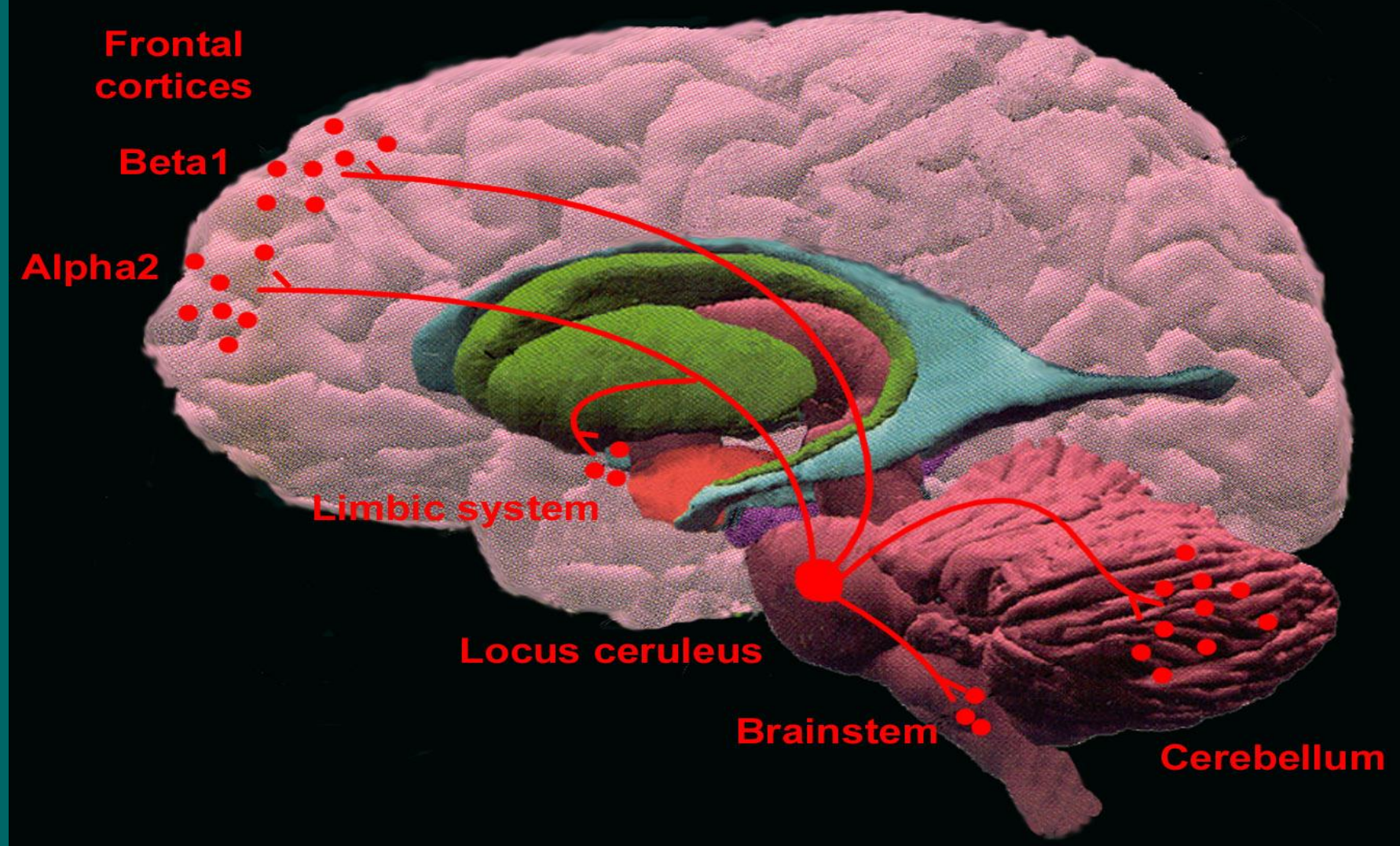
Inter-regulatory pathways

- In reality, the monoamine hypothesis and neurotransmitter receptor hypotheses are likely too simplified, as there is complex inter-regulation between NE, 5HT and DA
- For example, serotonin can increase or decrease DA release, NE can accelerate or inhibit 5HT release, etc.

Serotonin


Frontal cortex
Basal ganglia
Limbic system
Hypothalamus
Raphe nuclei
Brainstem

Norepinephrine



Cardinal Characteristics of Depression

- Depressed mood
- Apathy/anhedonia
- Sleep disturbance
- Fatigue/loss of energy
- Concentration/executive functioning
- Psychomotor agitation/retardation
- Appetite and weight changes
- Suicidal ideation, guilt, worthlessness

From: Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Third Edition.

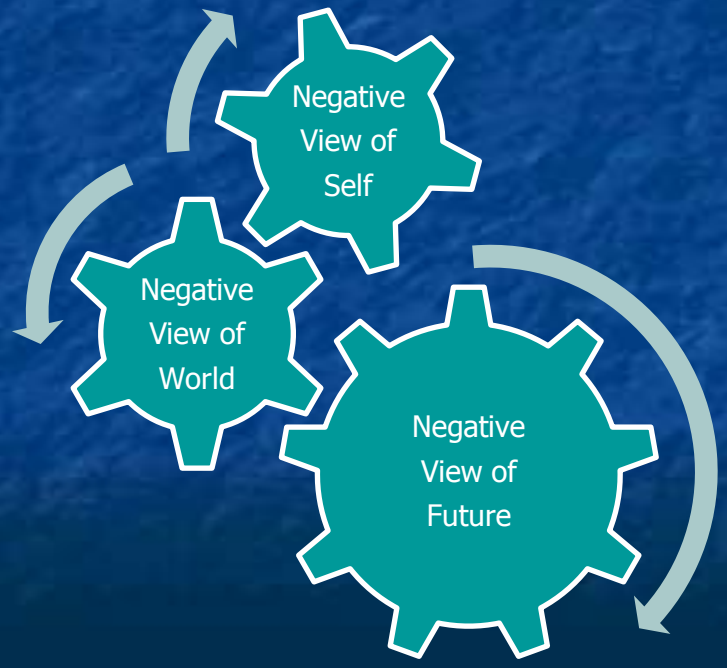
Psychological factors

Loss of a parent at an early age or childhood abuse
- Probably more important in MDD than Bipolar disorder

Psychoanalytic interpretations of depression
- Real or imagined loss of an ambivalently held love object, with resultant anger turned against self and loss of self-esteem

Interpersonal theory of depression
- Problem areas: grief, interpersonal role disputes, role transitions, interpersonal deficits

Cognitive theories of depression
- Learned Helplessness
- Negative cognitive distortions
  - e.g., "all or nothing"
  - overgeneralization
- Cognitive triad (self, world, future)
- Negative attribution style



Treatment options

- Pharmacologic
  - Antidepressant medications
- Non-pharmacologic
  - Psychotherapy
    - Cognitive behavioral therapy
    - Interpersonal therapy
    - Psychodynamic therapy
  - Electroconvulsive therapy
  - Phototherapy
  - Rapid transcranial magnetic stimulation (rTMS)
  - Vagus nerve stimulation (VNS)

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

Initial selection

Chose psychotherapy only

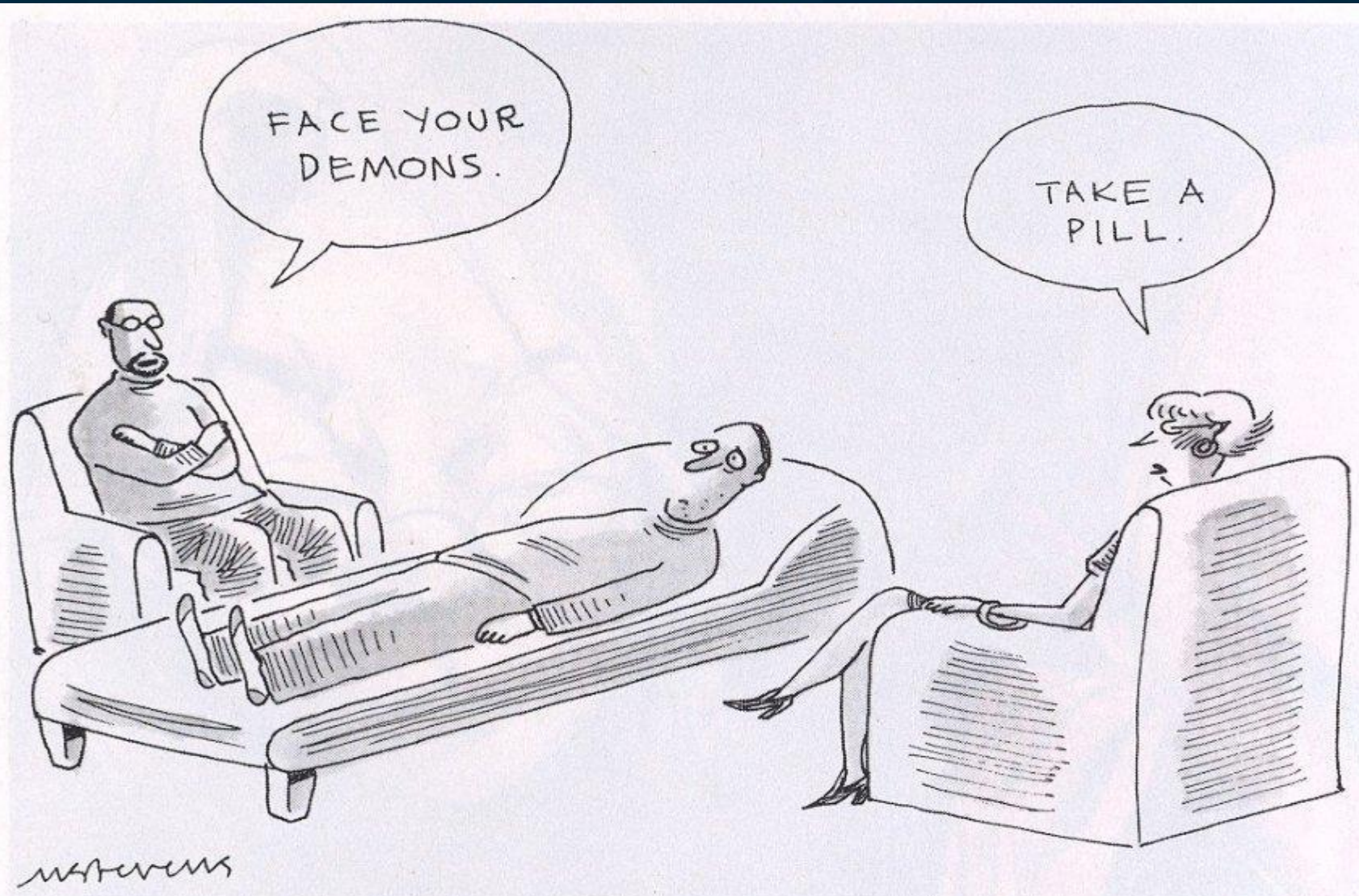
- Mild – if preferred and available
- Moderate/severe
  - pregnancy, lactation or wish to become pregnant
  - Previous good response
  - Medications ineffective

Chose medication only

- Mild – if preferred
- Moderate/severe –treatment of choice

Chose psychotherapy plus medication

- Clinically significant psychosocial issues, interpersonal problems, history physical or sexual trauma, or a comorbid personality disorder
- History of only partial response to single treatment modality
- Poor adherence to past medication trials
- Chronic major depressions (e.g. chronic major depression, double depression)


FACE YOUR DEMONS.
TAKE A PILL.
?
GOOD SHRINK, BAD SHRINK

Selecting the right antidepressant

- Initial Selection
  - Past History
  - Patient Preferences
  - Side Effects
  - Co-morbidities
  - Other Clinical Features
  - Pharmacologic Differences
- Next Steps When Necessary

"I medicate first and ask questions later."

Which medication for which patient?

- Review of 46 head-to-head randomized, controlled trials from multiple sources to evaluate comparative data on efficacy, effectiveness and tolerability of commonly prescribed second-generation antidepressants in treatment of MDD.
- Conclusion: Overall, second-generation antidepressants probably do not differ substantially for treatment of major depressive disorder.
- Choosing the agent that is most appropriate for a given patient is difficult.

Hansen, R. A., et. al., Ann Intern Med. 2005;143:415-426.

Matching patient to treatment: clinical subtype

Example of Subtype	Treatment Considerations
Comorbid anxiety disorder	SSRI, SNRI, Trazodone,Mirtazapine, benzodiazepine
Bipolar depression	Lamotrigine, atypical antipsychotics, antidepressant (+ mood stabilizer
Neuropathic pain	SNRI (e.g. duloxetine)
Psychotic features	Antipsychotic plus antidepressant, ECT
Seasonal	Bright light, Bupropion XL
Atypical features	MAOIs, SSRI
Severe, highly refractory	ECT, VNS, TMS, DBS?

Keep in mind past and family history of response and side effects

Antidepressants (SSRI, SNRI, other)

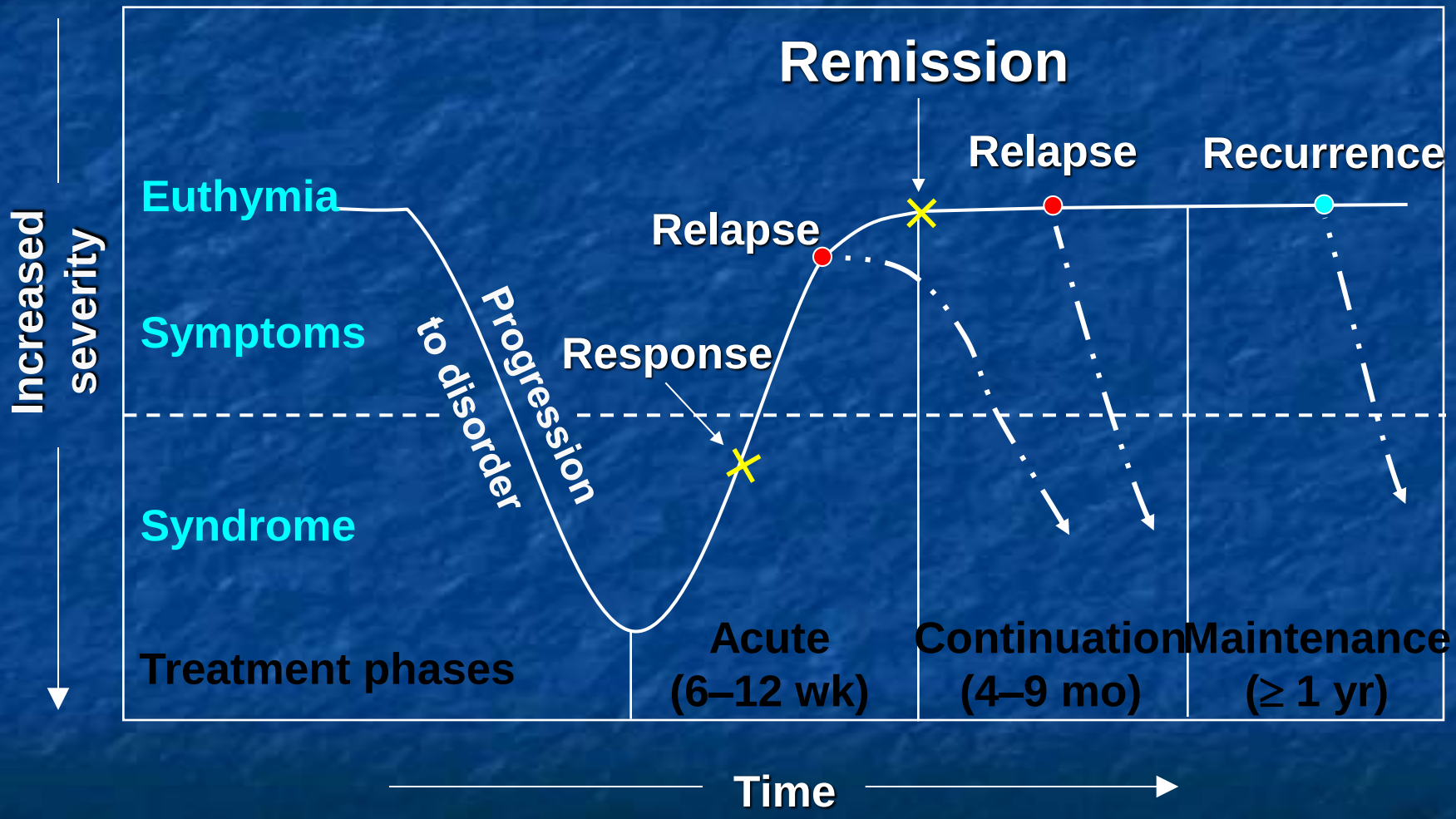
Citalopram	Celexa
Sertraline	Zoloft
Fluoxetine	Prozac, Sarafem
Paroxetine	Paxil, Paxil CR, Pexeva
Fluvoxamine	Luvox, Luvox CR
Escitalopram	Lexapro
Venlafaxine	Effexor, Effexor XR
Desvenlafaxine	Pristiq
Duloxetine	Cymbalta
Trazodone, Trazodone ER	Oleptro
Budeprion SR/XL, Bupropion IR/SR/XL, Bupropion HCl, Bupropion HBr	Wellbutrin, Wellbutrin SR/XL, Aplenzin
Maprotiline	-
Mirtazapine	Remeron, Remeron SolTab
Nefazodone	-

Newer: Vortioxetine and vilazodone Trintellix and Viibryd

Antidepressants (TCA, MAOI)

Amitriptyline	Elavil
Amoxapine	-
Clomipramine	Anafranil
Desipramine	Norpramin
Doxepin	-
Imipramine	Tofranil, Tofranil PM
Nortriptyline	Pamelor
Protriptyline	Vivactil
Trimipramine	Surmontil
Selegiline transdermal	Emsam
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate

Phases of treatment for depression



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

Depression & pharmacotherapy

- More than 16% of Americans will be affected by depression at least once during their lifetime
- Pharmacotherapy:
  - Almost 40% of people will not respond to the first antidepressant they take
  - More than 60% will experience at least one side effect
  - Many people need to try several different antidepressants before finding one that works for them and that they can tolerate.

(AHRQ Pub. No. 07-EHC007-3; August 2007)

"I think the dosage needs adjusting. I'm not nearly as happy as the people in the ads."

Unsatisfactory response

- Suboptimal response after optimizing dose and duration (e.g., non-remission or intolerance) requires "next step" strategies. Switching to a different treatment (medication or psychotherapy) or augmenting with another treatment (to a second antidepressant, Li, T-3, atypical antipsychotic, psychotherapy, etc) are the strategies most highly recommended, but there is a paucity of data to guide which specific strategy is optimal for individual patients.

- Two-thirds of depressed patients experience *remission* (HamD of 7 or <) with three monotherapies in sequence. Switch to same or different chemical class

Gaynes BN, et al. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr Serv. 2009 Nov;60(11):1439-45.

Drug-drug interactions

- Pharmacodynamic: when two drugs act at a receptor site causing a combined effect
- Pharmacokinetic: interactions of two drugs that cause a change in a drug's absorption, distribution, metabolism or excretion
  - Cytochrome P450 system is the family of more than 200 enzymes that perform phase I metabolism (oxidation and/or hydrolysis), but 6 are responsible for almost 90% of all the metabolic activity of P450 enzymes
    - 1A2, 3A4, 2C9, 2C19, 2D6 and 2E1
  - Each of the SSRIs has unique P450 metabolisms and inhibitions

Tolerability

- 15% of people discontinue an antidepressant because of side effects.
- TCA's are no longer considered first line agents due to tolerability and toxicity; however they are efficacious.
- Venlafaxine is more likely than an SSRI to be discontinued due to side effects (11.5% vs 8.5%)

AHRQ Pub. No. 07-EHC007-3; August 2007;
APA: Guideline Watch (2005).http:www.psych.org/psych_pract/treatg/pg/prac_guide.cfm

Side effects: sexual dysfunction

- Overall prevalence rate of sexual dysfunction (e.g. affecting the sexual response cycle: desire, arousal, excitement or orgasm) in patients with MDD on antidepressants is ≥50%
- 32% women and 34% men experience treatment-emergent sexual adverse effects with SSRIs or SNRIs
- All SSRIs have been associated with delayed or absent orgasm/ejaculation and in some instances reduced libido and arousal
- Dysfunction is partially due to 5-HT2 agonist effects, cholinergic receptor blockade and nitric oxide synthase inhibition (e.g. paroxetine)
- There is some evidence that noradrenergic agents may be associated with lower rates of sexual side effects (e.g. SNRIs, mirtazapine, bupropion, and nefazodone)

Side effects: weight change

- Mirtazapine causes higher weight gain than SSRI's , with a mean range of 2-7 lbs at 6-8 weeks treatment.
- Paroxetine is the SSRI with the highest average weight gains (3.6% of body weight; 25% people gain >7% of body weight)
- Bupropion causes moderate weight loss (about 2.5 lbs from baseline)

(AHRQ Pub. No. 07-EHC007-3; August 2007)

Question 15

Question 14

Question 3

Question 11

Question 1

Discontinuation Syndrome is most likely seen when abruptly stopping all of the following except:

A. Duloxetine
B. Paroxetine
C. Fluoxetine
D. Desvenlafaxine

Discontinuation Syndrome

Some Symptoms Include:

- Dizziness
- Nausea
- Headaches
- Irritability
- Insomnia
- Diarrhea
- Anxiety

- Fatigue
- Abn. Dreams
- Hyperhidrosis
- Dysphoric Mood
- Agitation
- Paresthesia

- Confusion
- Lethargy
- Emotional Lability
- Tinnitus
- Hypomania
- Seizures

Reduce Doses in small increments and slowly

Thank You. The End.

Vignette #1

31 year old female elementary school teacher complains of increased agitation, decreased motivation, decreased interest and pleasure at work and home and hypersomnolence over the past 6 months. She and her husband has been seeing a marriage counselor. One marital issue is that her husband wants more children, she does not as they have 2 already. 9 months she started birth control pill, Ortho Novum 1:35. After each pregnancy, she became depressed and was treated with Citalopram for 6 months. She did not breast feed while taking the SSRI. Past history revealed that while in college, after breakup from a long term relationship, she became depressed and dropped one course. With time, the depression cleared and she never sought medical help.

Vignette # 1 (cont'd)

Her family history is significant in that her mother suffered from depression and one of her sisters was diagnosed with bipolar disorder. Other than her birth control pills, she takes no medication. Her PHQ=14. A brief physical exam and some lab tests: CBC, comprehensive metabolic profile and TSH revealed no abnormalities. You decide to initiate Citalopram 20 mg per day and have her return 3-4 weeks and to call if any problems occur. At her next visit, a repeat PHQ=10. She states that her depression is a tad better but she reports that she is apathetic and her libido is gone.

WHAT ARE YOUR NEXT STEPS?

Vignette #2

- You have a new patient in the nursing home. He is a 75 yr. old male who has been diagnosed with Parkinson's Disease, chronic constipation, depression and dementia. His presents medications include: Reglan for 1 yr., Sinemet for 6 months, Amitriptyline 50 mg at bedtime for 3 yrs., Dulcolax, Milk of Magnesia, and Fibercon all for 2 yrs. His physical exam show no new findings and his lab results are basically normal which include a CBC, a comprehensive metabolic screen and a TSH.
- What are your first steps?
- You decide to stop his Reglan and remarkably within 1 month his rigidity and the majority of his Parkinson's symptoms improve. He is less depressed and his memory is somewhat better.
- Next, you decide to switch his Amitriptyline to the SSRI, Citaloprim and over the next 3 wks., his memory is somewhat improved and he has less trouble with constipation. He still remains moderately depressed, however, his Parkinson's disease in 90% improved. You slowly wean him off his Sinemet and his Parkinson's symptoms maintain their improvement. You still want to address his moderate depression and memory problems.
- What do you decide to do next?

Serotonin (5HT)

- Synthesis
  - Tryptophan enters 5HT neurons
  - Tryptophan → 5-hydroxytryptophan → 5HT
  - 5HT is then packaged into vesicles and stored in neuron terminals
- Termination
  - After 5HT release into the synapse, it's action is terminated by reuptake via the serotonin transporter (SERT) located on the presynaptic 5HT neuron
  - Monoamine oxidase (MAO) B: destroys 5HT in the presynaptic cells when 5HT is at high concentrations
  - MAO A/B: destroy 5HT outside of the neuron

Serotonin Receptors

- 5-HT1 - Brain, intestinal nerves - Neuronal inhibition, behavioral effects, cerebral vasoconstriction
- 5-HT2 - Brain, heart, lungs, smooth muscle control, GI system, blood vessels, platelets - Neuronal excitation, vasoconstriction, behavioral effects, depression, anxiety
- 5-HT3 - Limbic system, ANS - Nausea, anxiety
- 5-HT4 - CNS, smooth muscle - Neuronal excitation, GI
- 5-HT5, 6, 7 – Brain – Depression