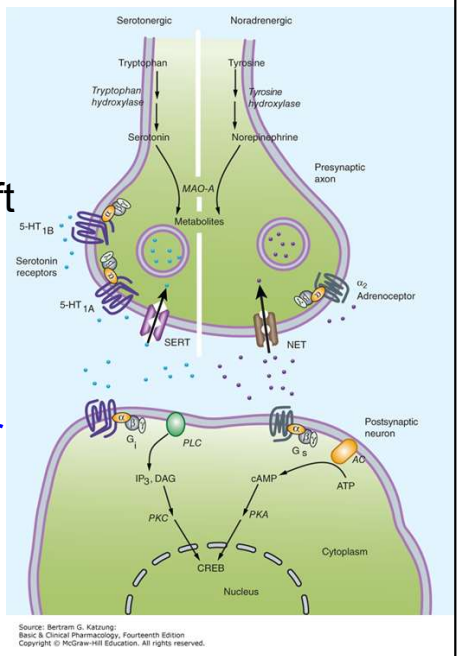
G.J. Klapstein

Katzung:
Depression:Ch 30

Proposed Depression Hypotheses

- The Monoamine Hypothesis
  - decreased levels of monoamines in synaptic cleft
    - serotonin (5-HT)
    - norepinephrine
- Neurotransmitter Receptor Hypothesis
  - Receptors are upregulated as compensatory response to decreased monoamines



Katzung, 14e

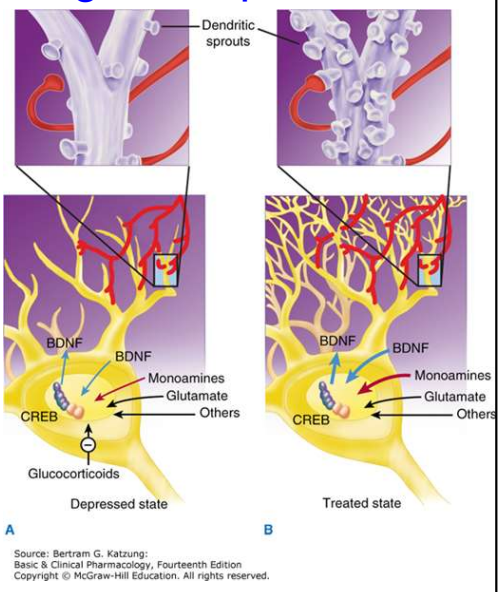
FIGURE 30–2

The amine hypothesis of major depression. Depression appears to be associated with changes in serotonin or norepinephrine signaling in the brain (or both) with significant downstream effects. Most antidepressants cause changes in amine signaling. AC, adenylyl cyclase; CREB, cAMP response element-binding (protein); DAG, diacyl glycerol; 5-HT, serotonin; IP_3, inositol trisphosphate; MAO, monoamine oxidase; NET, norepinephrine transporter; PKC, protein kinase C; PLC, phospholipase C; SERT, serotonin transporter. (Adapted from Belmaker R, Agam G: Major depressive disorder. N Engl J Med 2008;358:59.)

Proposed Depression Hypotheses

•Neurotrophic hypothesis of gene expression

- Decreased signal transduction mechanism at sites distal to receptors leads to decreased gene expression (CREB, BDNF)
  - although the pharmacologic actions of both tricyclic and MAO inhibitors are prompt, the clinical effects require weeks or even months to become manifest.
  - BDNF effects include regulation of neural plasticity, resilience, and neurogenesis

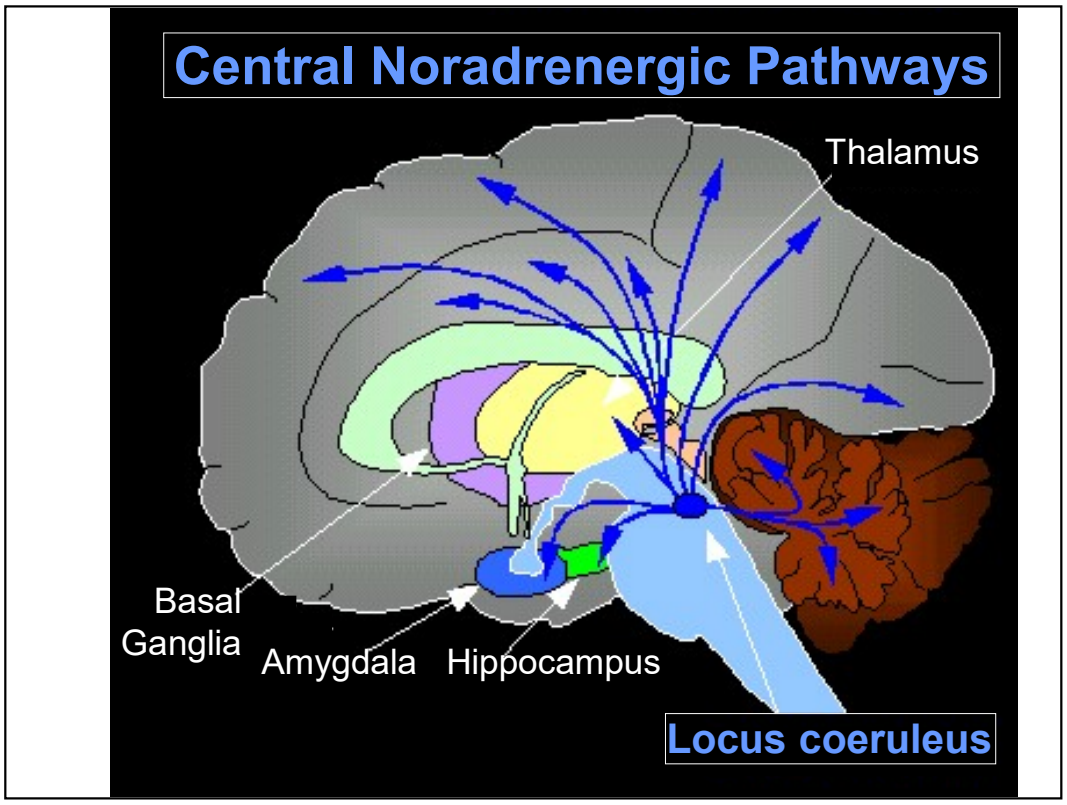


  - Antidepressant-neurogenesis.pdf posted to BB (NIMH report)

Katzung, 14e

FIGURE 30–1

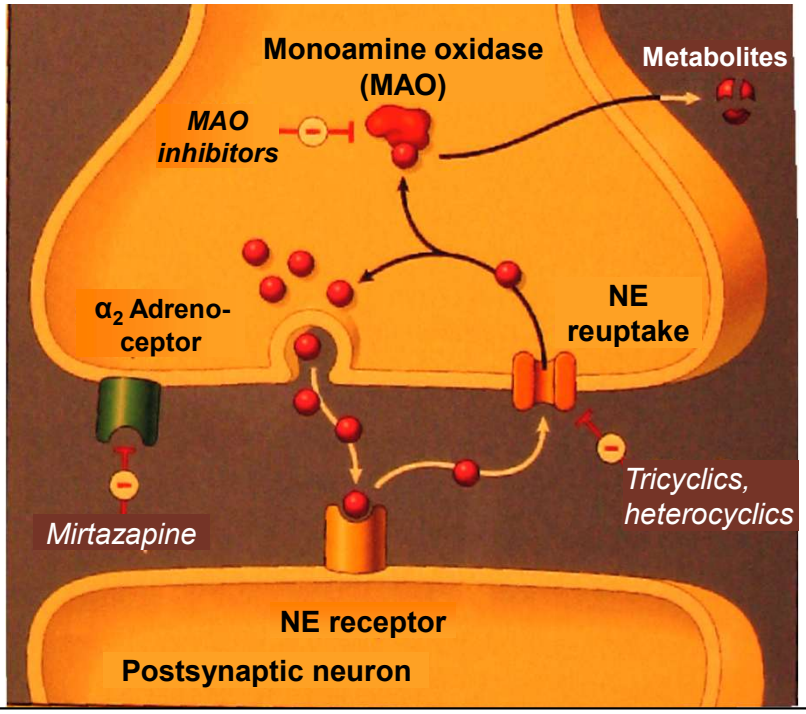
The neurotrophic hypothesis of major depression. Changes in trophic factors (especially brain-derived neurotrophic factor, BDNF) and hormones appear to play a major role in the development of major depression (**A**). Successful treatment results in changes in these factors (**B**). CREB, cAMP response element-binding (protein). BDNF, brain-derived neurotrophic factor. (Reproduced, with permission, from Nestler EJ: Neurobiology of depression. Neuron 2002;34[1]:13–25. Copyright Elsevier.)



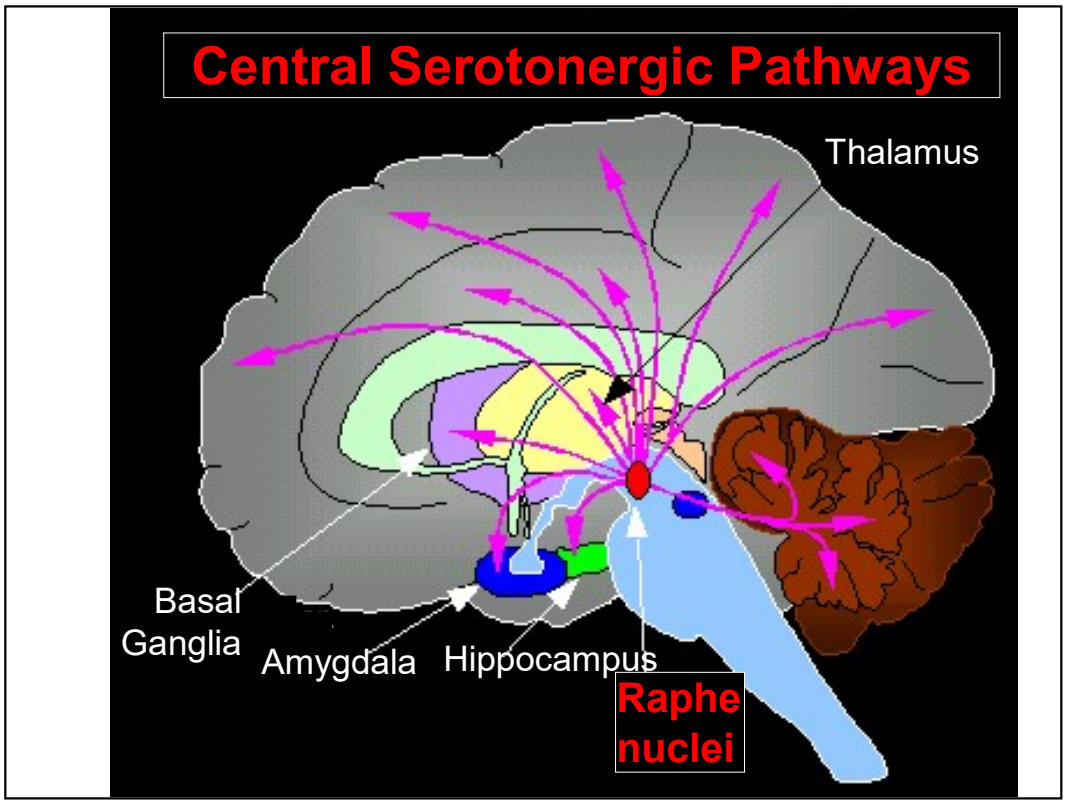
adapted from

http://brain.exp.univie.ac.at/22ssvorlesung/bilder.htm

Noradrenergic neuron



negative feedback loop
transporter can be repackaged or chewed up by enzyme

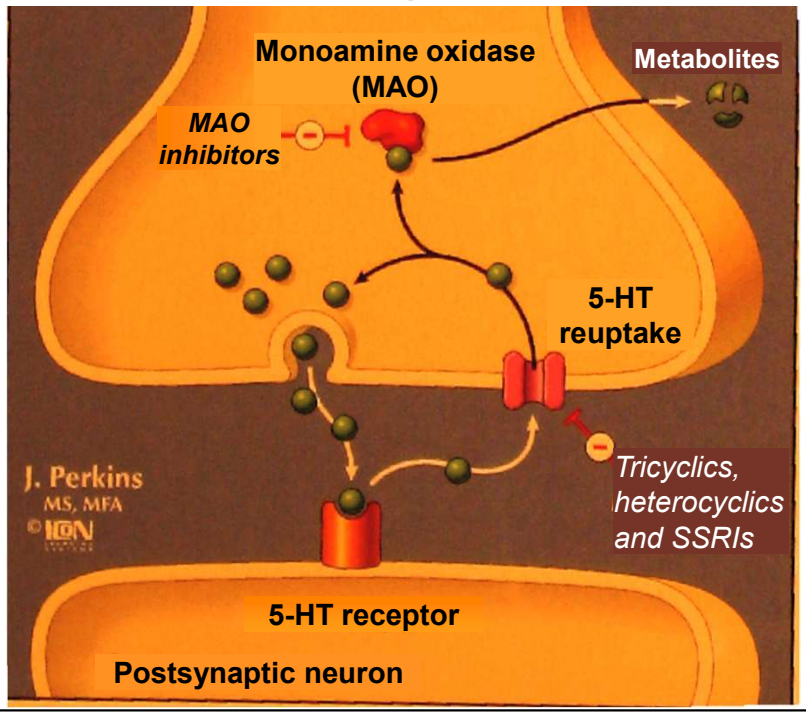


adapted from

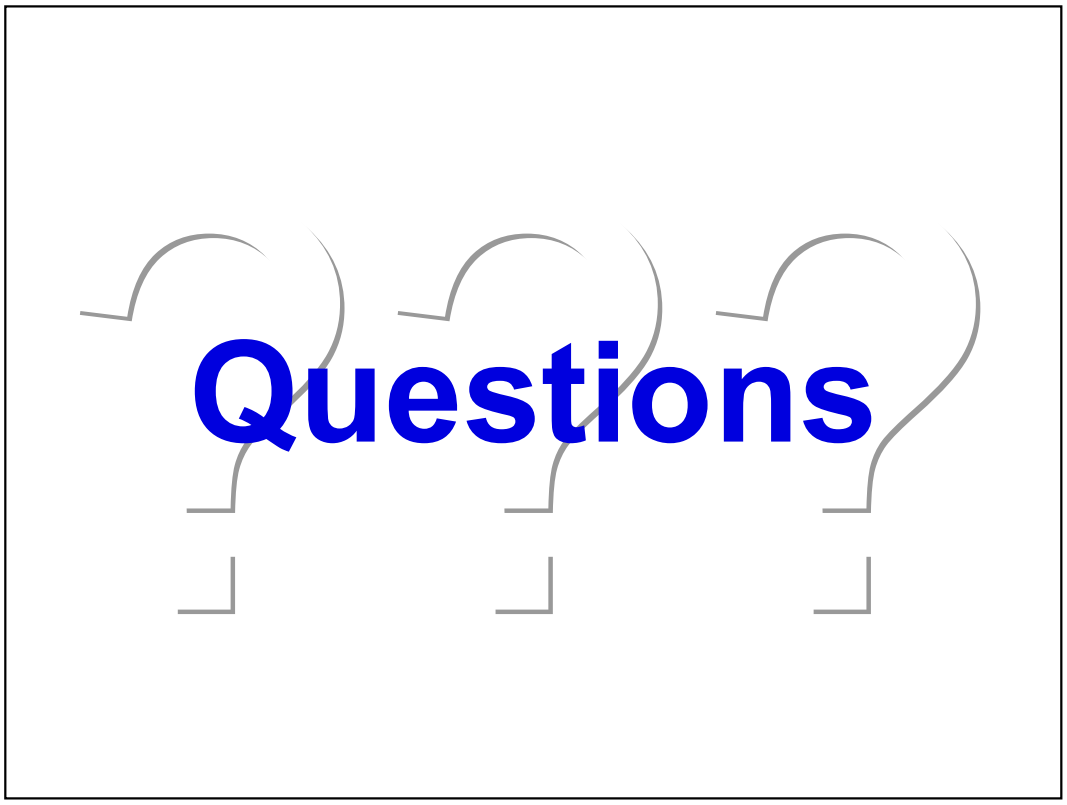
http://brain.exp.univie.ac.at/22ssvorlesung/bilder.htm

raphe nuclei produce serotonin

Serotonergic neuron

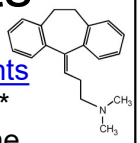


no pre-synaptic receptor but has transporters and enzymes


Questions

highly board relevant

Main Classes of Antidepressants



Selective serotonin reuptake inhibitors (SSRI)
- Citalopram
- Escitalopram
- Fluoxetine*
- Fluvoxamine
- Paroxetine
- Sertraline
- Vilazodone
- Vortioxetine#

5-HT$_2$ antagonists
- Trazodone

Selective serotonin-norepinephrine reuptake inhibitors (SNRI)
- Duloxetine
- Desvenlafaxine
- Levomilnacipran
- Venlafaxine

Tetracyclic/Unicyclic antidepressants
- Amoxapine
- Maprotiline
- Mirtazapine
- Bupropion

NMDA antagonists
- Ketamine
- Esketamine

Tricyclic antidepressants
- Amitriptyline*
- Clomipramine
- Desipramine
- Doxepin
- Imipramine*
- Nortriptyline
- Protriptyline
- Trimipramine

MAOI
- Phenelzine
- Isocarboxazid
- Tranylcypromine
- Selegiline

GABA$_A$ Modulators
- Brexanolone

* denotes drug is a prototype for its' class

^ recently discontinued or withdrawn

atypical serotonin modulator and stimulator

Newer drugs:

Vilazodone approved 2011, SSRI and 5HT1A partial agonist

Levomilnacipran approved 2013, extended release SNRI

- note: Milnacipran approved for MDD in europe (in 1996), but in US only approved for fibromyalgia (in 2009)

Vortioxetine approved 2013, mech. of action not understood – probably serotonin reuptake inhibitor, and 5HT3 antagonist and 5HT1A agonist

Brexpiprazole – atypical antipsychotic - approved 2015 to treat adults with schizophrenia and as an add-on treatment to an antidepressant

medication to treat adults with major depressive disorder (MDD).

Ketamine/Esketamine – approved 2019 – for treatment resistant depression https://go.drugbank.com/drugs/DB11823 https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified

Brexanolone – approved 2019 – approved only for postpartum depression https://go.drugbank.com/drugs/DB11859

Drugs no longer used:

Nefazodone – Serzone, marketing for all dosages discontinued. ****Federal**

Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020152

flame icons are high yield for exams!!

SSRI

- Oral – well absorbed
- peak plasma in 4-8 hours
- ½ life 7-9 days (low risk of withdrawal symptoms)
- Fluoxetine → norfluoxetine (active, longest ½ life =180 h.)
- inhibits various drug metabolizing enzymes

−Citalopram
−Escitalopram
−Fluoxetine*
−Fluvoxamine
−Paroxetine
−Sertraline
−Vilazodone
− Vortioxetine#

SSRI

- Dangerous interaction with MAOI or triptans !!!
  - **leads to Serotonin syndrome (can be fatal)**
    - hyperthermia
    - muscle rigidity
    - myoclonus
    - rapid changes in mental status and vital signs.
- SSRIs often 1st line drug of choice
- SSRIs not more effective than older drugs
  - lack many side effects
  - higher patient acceptance / compliance
  - side effects: nausea, decreased libido/sexual function, GI symptoms

http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/drugsafetyinformationforheathcareprofessionals/ucm085845.htm

FDA ALERT [7/2006]: Potentially Life-Threatening Serotonin Syndrome with Combined Use of SSRIs or SNRIs and Triptan Medications

There is the potential for life-threatening serotonin syndrome (a syndrome of changes in mental status, autonomic instability, neuromuscular abnormalities, and gastrointestinal symptoms) in patients taking 5-hydroxytryptamine receptor agonists (triptans) and selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs) concomitantly (see drug names at the bottom of this sheet). This information is based on reports of serotonin syndrome occurring in patients treated with triptans and SSRIs/SNRIs, and the biological plausibility of such a reaction in persons receiving two serotonergic medications. The FDA recommends that patients treated concomitantly with a triptan and an SSRI/SNRI be informed of the possibility of serotonin syndrome (which may be more likely to occur when starting or increasing the dose of an SSRI, SNRI, or triptan) and be carefully followed.

SNRI

−Duloxetine
−Desvenlafaxine
−Levomilnacipran
−Venlafaxine

- Venlafaxine (Effexor)
  - potent 5-HT reuptake blockade, acts like SSRI at low doses, NE and DA as well at higher doses,
  - withdrawal symptoms (↓[R]), so withdraw slowly
- Milnacipran

  racemic mixture of levomilnacipran and dextromilnacipran
  - approved only for fibromyalgia, not MDD

SNRI

- drugs chemically unrelated
- Venlafaxine, Duloxetine have extensive hepatic metabolism
- active metabolites
  - Venlafaxine →desvenlafaxine
  - both have lowest protein binding (only ~30%)
- Desvenlafaxine conjugated → no oxidative metabolism
  - 45% excreted unchanged in urine

old and cheap
good for pts without insurance
dirty drugs - hit multiple NT receptors

Tricyclics

- Amitriptyline*
- Clomipramine
- Desipramine
- Doxepin
- Imipramine*
- Nortriptyline
- Protriptyline
- Trimipramine

– well absorbed
– long ½ lives
– significant first pass metabolism
– active metabolites
  – Imipramine → desipramine
  – Amitriptyline → nortriptyline
– high lipid solubility and protein binding.

Tricyclics

- "dirty drugs" with varying selectivity
  - Dirty drugs produce more side effects!!
  - NMDA antagonist
  - alpha 2 agonist, alpha 1 antagonist
  - adenosine reuptake blocker, alter opioid binding
  - inhibit sodium, potassium, and calcium channels
- overdose extremely dangerous (Note suicide risk!)
  - prescribe few pills, no refills
- Amytriptyline, Clomipramine, Doxepin, Imipramine
  - high sedation additive with other sedative drugs (alcohol!)
  - antimuscarinic: blurred vision, constipation, confusion.

Antidepressant-Suicide movie

especially if just diagnosed depression start with a few pills and tell them to come back - bc more likely to overdose so have them come base and give them a small rx and keep an eye on them

5-HT_2 Antagonists

–Trazodone

- Trazodone
  - rapidly absorbed
  - extensive hepatic metabolism
  - high protein binding
  - short ½ life (2-6 hrs)
  - useful as a hypnotic (for sleep)
  - unpredictable efficacy for depression
  - active metabolites
    - also exhibit 5-HT_2 antagonism

bc highly sedative and only lasts for ~3 hrs no carryover

–Nefazodone no longer marketed in USA

–potent inhibitor of CYP3A4 (drug interactions)

–NOT discontinued or withdrawn by FDA

Tetracyclics

−Amoxapine
−Maprotiline
−Mirtazapine

– Amoxapine
  - variable bioavailability, half-life
  - active metabolite (7-hydroxyamoxapine) potent D_2 blocker (antipsychotic)
  - some DA receptor antagonism
    - good for depression in psychotic patients
    - side effects: akathisia, parkinsonism, amenorrhea, tardive dyskinesia, etc…

Tetracyclics

– Maprotiline

- dose-dependent seizures

– Mirtazapine

- Also blocks α_2 adrenoceptor on presynaptic terminal, so NE cannot inhibit further NE release through autoinhibition
- antihistaminic → sedation
- weight gain
- few adverse sexual effects

Unicyclics

−Bupropion

– Bupropion also approved for use in smoking cessation

- 3 active metabolites
- biphasic elimination (1 hour / 14 hours)

MAOI

−Phenelzine
−Isocarboxazid
−Tranylcypromine
−Selegiline

- well absorbed
- extensive first-pass metabolism
  - Selegiline available transdermal, sublingual
- MAO inhibition persists even after plasma levels become undetectable
- drug effect persists after discontinuation of drug
  - tranylcypromine -- 7 days
  - phenelzine -- 2 or 3 weeks

- Reversible MAOIs (not available in U.S. (yet) ???)
  - Moclobemide approved for investigational use
  - Others: Brofaromine, Caroxazone, Metralindole, Minaprine, Pirlindole, Toloxatone
  - limited efficacy, still have serious interactions.

2 isozymes A and B

MAOI

- MAO-A oxidation of NE, 5-HT, tyramine
- allows accumulation of tyramine (aged cheese, red wine, liver, ferments) or sympathomimetic drugs
  - can result in hypertensive crisis! (can be fatal)
- interaction with SSRIs (serotonin syndrome)
- MAO-B oxidation of dopamine
  - Selegiline for Parkinson's (dose dependent!)
- MAOIs can potentiate the action of a number of other drugs, such as opiates, ephedrine, adrenaline, etc..

exam question:
party eat a bunch of hor-deourves/wine and cheese/kbbq = MAO-A involved!!

if dietary think MAOI as a differential

NMDA antagonists

−Ketamine
−Esketamine

- Esketamine (S-enantiomer of ketamine)
  - potent, high-affinity, noncompetitive NMDA block
  - Approved for treatment-resistant MDD (in 2019)
  - Rapid onset (24 hours), short duration (5-7 days)
  - Intranasal administration
  - Under review for treating acute suicidal ideation
- Ketamine old drug
  - Dissociative anesthetic (burn pts, veterinary use)
  - Short acting analog of phencyclidine (PCP, angel dust)
  - IV administration only
  - Abuse potential, common “club” drug

still pain but don't care

more immediate effect

$GABA_A$ modulator

–Brexanolone

- Brexanolone (allopregnanolone)
  - Neuroactive steroid, derivative of progesterone
  - $GABA_A$ receptor positive allosteric modulator (increases chloride current)
  - Approved for post-partum depression
  - Administered via 60-hour IV infusion
  - Rapid onset (within 60 hours)
  - Effect lasts >30 days


???
Questions

Table 30–1 Pharmacodynamic Characteristics of Selected Antidepressants

Drug	Sedation	Muscarinic Receptor Block	NE ReuptakeBlock	5-HT ReuptakeBlock
Tricyclics				
Amitriptyline[a]	+++	+++	+	++
Desipramine	+	+	+++	+
Doxepin[a]	+	++	+++	+
Imipramine	++	++	+	++
Nortriptyline	++	+	++	+
SSRIs				
Citalopram, etc	0	0	0	+++
Heterocyclics -SNRIs				
Duloxetine	0	0	++	+++
Venlafaxine	0	0	+	+++
Heterocyclics -5-HT$_2$ antagonists				
Nefazodone	++	+	0/+	+
Trazodone	++	0	0	+
Heterocyclics -other				
Amoxapine	++	++	++	+
Bupropion	0	0	0	0
Maprotiline	+	+	++	0
Mirtazapine[b]	++	++	+	0

[a]Significant α_1 antagonism. [b]Significant H_1 and α_2 antagonism.

Table 30–1 Pharmacodynamic Characteristics of Selected Antidepressants

SNRI, serotonin-norepinephrine reuptake inhibitor.

[a]Significant α_1 antagonism.

[b]Significant H_1 and α_2 antagonism.

0/+, minimal activity; +, mild activity; ++, moderate activity; +++, high activity.

textbook there for you
some students just read the textbook and did fine

Table 30–2 Drug Interactions Involving Antidepressants.

Antidepressant	Taken With	Consequence
Fluoxetine	Lithium, TCAs, warfarin	Increased blood levels of second drug
Fluvoxamine	Alprazolam, theophylline, TCAs, warfarin	Increased blood levels of second drug
MAO inhibitors	SSRIs, sympathomimetics, tyramine-containing foods	Hypertensive crisis, serotonin syndrome
Nefazodone	Alprazolam, triazolam	Increased blood levels of second drug
Paroxetine	Theophylline, TCAs, warfarin	Increased blood levels of second drug
Sertraline	TCAs, warfarin	Increased effects of second drug
TCAs	Ethanol, sedative hypnotics	Increased CNS depression

Table 30–2 Drug Interactions Involving Antidepressants.

MAO, monoamine oxidase; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

if a patient on warfarin be careful about prescribing anything else

Drug choice

- Controlled comparison studies of available antidepressants indicate that they are roughly equal
- Drug choice does vary with patient – empirical choice
- Differences occur with respect to :
  - onset of action
  - adverse sedative and autonomic effects
    - drugs with more sedative effects may be preferable on markedly anxious or agitated depressives
    - Drugs with fewer sedative effects may be preferable for patients with psychomotor withdrawal
  - toxicity when overdoses are taken
- Many antidepressants are also useful in general anxiety disorder, social anxiety disorder, panic disorder.

Controversy:

Newsweek article sites 2010 study suggesting antidepressants are no more effective than placebo:

http://www.newsweek.com/why-antidepressants-are-no-better-placebos-71111

Flaws in 2010 study:

http://www.psychiatrictimes.com/articles/newsweek%E2%80%99s-topsy-turvy-take-antidepressants

trial and error to see what best for each patient

first thing a patient will see is a side effect bc antidepressant action will take 6-8 weeks
want to choose a drug that the patient can tolerate as the first choice

Drug choice

- MAO inhibitors are helpful in patients with atypical depression
  - attendant anxiety
  - phobic features
  - hypochondriasis
- TCAs have better efficacy but less compliance
- SSRIs are popular despite higher cost
  - usual first-choice
- Venlafaxine at high doses may be more efficacious than SSRIs.

Unresponsive Patients

- Five D's
  - Diagnosis (reassess in patients with little response, 2-3 weeks)
  - Drug: change drug or use combinations
    - SSRI + desipramine or bupropion or maybe mirtazapine
    - Venlafaxine + SSRI
  - Dose: most failures result from inadequate drug dose
  - Duration: may take months to achieve an effect
  - Different treatment
    - electroconvulsive therapy
    - vagal stimulation.

Drug response movie

may want to refer to a psychiatrist that is more experienced with using different combos of drugs

CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 75 • NUMBER 1 JANUARY 2008

BRADLEY N. GAYNES, MD, MPH*
Associate Professor of Psychiatry, University of North Carolina School of Medicine; Investigator, Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study

A. JOHN RUSH, MD*
University of Texas Southwestern Medical Center at Dallas; Professor of Clinical Sciences and Psychiatry; Principal Investigator, STAR*D study

MADHUKAR H. TRIVEDI, MD*
University of Texas Southwestern Medical Center at Dallas; Professor of Psychiatry; National Coordinating Center, STAR*D study

STEPHEN R. WISNIEWSKI, PhD*
University of Pittsburgh School of Medicine; Associate Professor of Epidemiology; Data Coordinating Center, STAR*D study

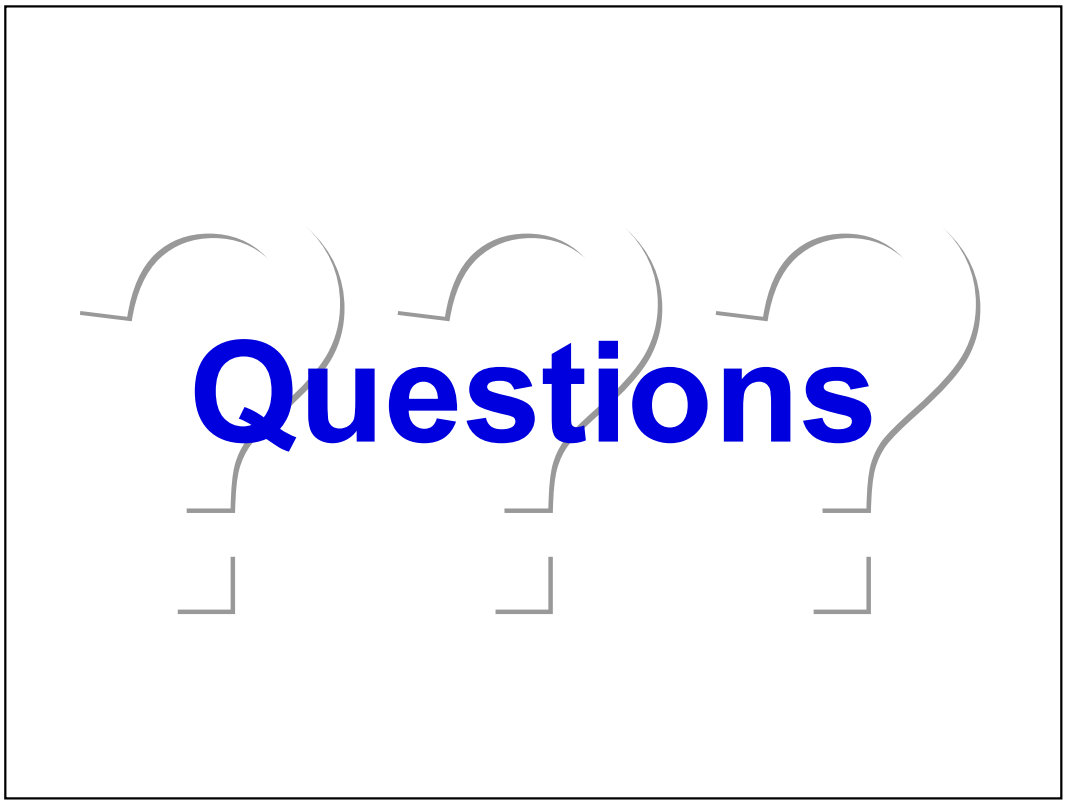
DONALD SPENCER, MD, MBA*
University of North Carolina School of Medicine; Professor of Family Medicine; Investigator, STAR*D study

MAURIZIO FAVA, MD*
Massachusetts General Hospital, Boston; Professor of Psychiatry; Investigator, STAR*D study

The STAR*D study: Treating depression in the real world

- article posted on Canvas
- Major findings:

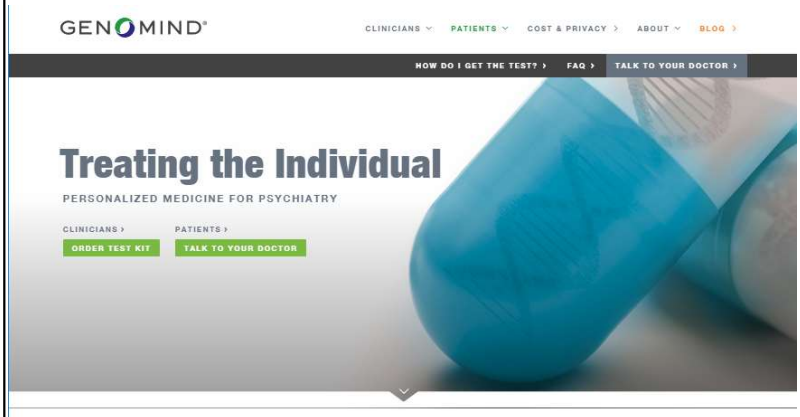
- Remission (ie, complete relief from a depressive episode) rather than response (merely substantial improvement) should be the goal of treatment, as it is associated with a better prognosis and better function.
- Should the first treatment fail, either switching treatment or augmenting the current treatment is reasonable.
- For most patients, remission will require repeated trials of sufficiently sustained, vigorously dosed antidepressant medication. Physicians should give maximal but tolerable doses for at least 8 weeks before deciding that an intervention has failed.
- After two well-delivered medication trials, the likelihood of remission substantially decreases. Such patients likely require more complicated regimens. Given the thin existing database, these patients are best referred to a psychiatrist for more complex treatments.
- With persistent and vigorous treatment, most patients will enter remission: about 33% after one step, 50% after two steps, 60% after three steps, and 70% after four steps (assuming patients stay in treatment).


Questions

Personalized Medicine

(psychopharmacogenomics)

https://genomind.com/ Co-founded by Jay Lombard, DO



GENECEPT ASSAY

Genetic testing can help unlock what your body needs to feel better, faster.

•patient-specific genetic markers that indicate which treatments are likely to work as intended, have no effect, or cause adverse effects

•See notes section of slide for refs.

The Genecept Assay® is a genetic test designed to help clinicians optimize treatment decisions for their patients with mental illness. It identifies patient-specific genetic markers that indicate which treatments are likely to work as intended, have no effect, or cause adverse effects. It is an easily administered cheek swab test that analyzes key genes, selected based on hundreds of studies showing that variations in these genes can inform treatment decisions.

The Assay is used to guide treatment for a range of psychiatric conditions, including:

depression

anxiety

obsessive-compulsive disorder (OCD)

attention deficit hyperactivity disorder (ADHD)

bipolar disorder

post traumatic stress disorder (PTSD)

autism

schizophrenia

chronic pain

substance abuse

The Assay has been shown in peer reviewed published studies to improve patient outcomes and reduce overall medical costs. Each Assay provides clinicians with an easy to read patient report and a complimentary psychopharmacogenomic consultation.

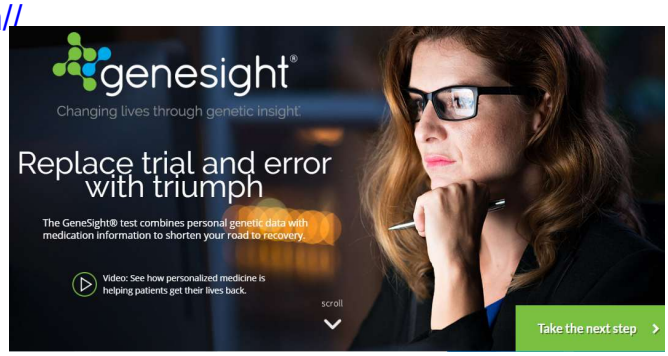
Brennan FX *et al*. A Naturalistic Study of the Effectiveness of Pharmacogenetic Testing to Guide Treatment in Psychiatric Patients with Mood and Anxiety Disorders. Primary Care Companion CNS Disorders. 2015;17(2).

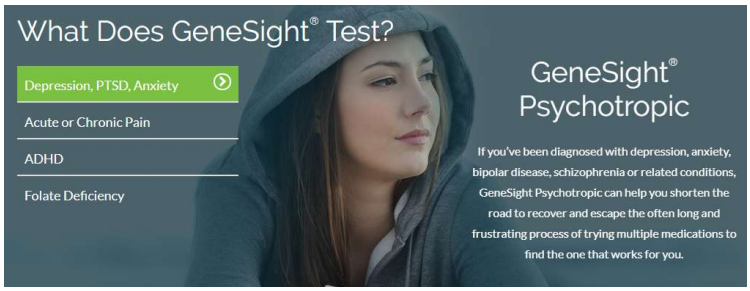
Fagerness J *et al*. Pharmacogenetic-Guided Psychiatric Intervention Associated With Increased Adherence and Cost Savings. American Journal of Managed Care. 2014;20(5):e146-e156.

Personalized Medicine

(psychopharmacogenomics)

https://genesight.com//





Special considerations

- Bipolar depression
- Children
- Drug interactions.

Danger in undiagnosed bipolar depression

- May produce sudden switch from depression to hypomanic or manic excitement or mixed, dysphoric-agitated, manic depressive states
- Use with extreme caution in patients with bipolar disorders. When correctly used by a psychiatrist, antidepressants can be used to treat a depressive episode in a patient with bipolar depression

Know when to refer your patient!

pt not an accurate reporter of their own symptoms

Danger in children/adolescents
- FDA Black Box Warning -

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert established name] is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use) [This sentence would be revised to reflect if a drug were approved for a pediatric indication(s). Such as, [Insert established name] is not approved for use in pediatric patients except for patients with [Insert approved pediatric indication(s)]. (See Warnings and Precautions: Pediatric Use)]

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Overdoses

- Tricyclics: extremely dangerous
- – coma, shock, respiratory depression, agitation/delerium, muscle seizures, cardiac arrhythmias, hyperpyrexia
  - Mnemonic: 3 C's, + hot and breathless
    - Coma
    - Convulsions
    - Cardiotoxicity

any charged particle will adhere to charcoal and will come out when sucking out the charcoal
anything in stomach that's not in intestine won't have a chance to move on

- – Overdose management
  - activated charcoal lavage
  - lidocaine, propranolol and phenytoin
  - sodium bicarbonate i.v. can relieve conduction block
  - physostigmine may be used in small boluses to awaken patients
    - but may worsen cardiac toxicity and cause seizures

Overdoses

- Tetracyclics:
  - amoxapine: severe neurotoxicity and seizures
  - maprotiline: seizures and cardiotoxicity
- MAO inhibitors
  - agitation, delirium, seizures, shock and hyperthermia
- SSRIs
  - low likelihood of fatalaties from overdose.

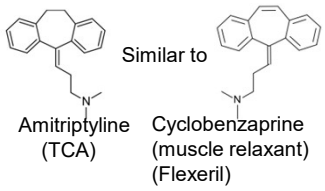
reason why often the first choice bc one of the safest antidepressant classes

Other Uses for Antidepressants

- Anxiety disorders: Panic, Generalized Anxiety, Social Phobia
  - SSRIs, venlafaxine, duloxetine effective, but require 6-8 weeks of treatment, so benzodiazapines are still preferred
  - May be useful when there is comorbidity with depression
- Obsessive-Compulsive disorders
  - Fluvoxamine and Clomipramine very effective
- Enuresis
  - Tricyclics useful, but drug therapy not preferred due to CV and overdose risks

Other Uses for Antidepressants

- Chronic pain
  - Some antidepressants may work directly on pain pathways
    - TCAs, venlafaxine, duloxetine
  - SSRIs not effective



double bond vs single bond

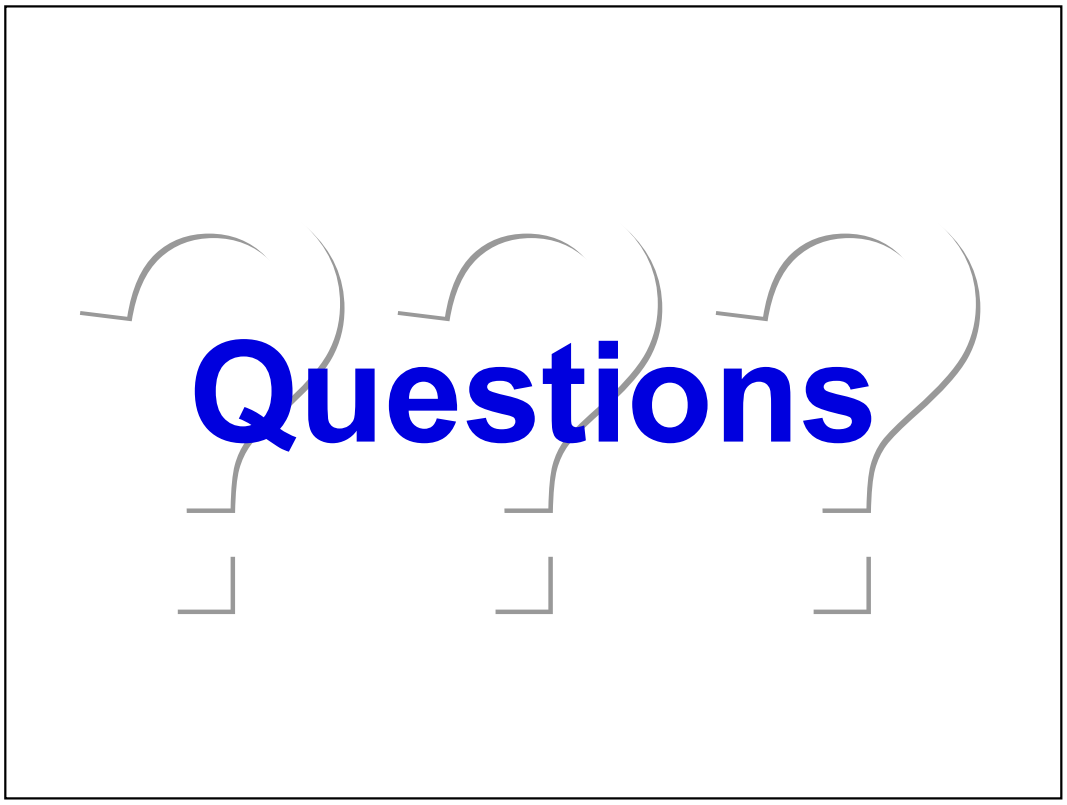
- Other disorders
  - Bupropion for smoking cessation
  - Fluoxetine for bulimia and premenstrual dysphoric disorder
  - Imipramine, Desipramine, Atomoxetine for attention deficit hyperkinetic disorder (amphetamine, methylphenidate still more common)

Amitriptyline is commonly prescribed for chronic pain. Cyclobenzaprine (muscle relaxant) is also a tricyclic compound with a similar structure to Amitriptyline

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics & Drug Interactions	Toxicities
Tricyclic antidepressants				
Amitriptyline,clomipramine, imipramine, etc	Block norepinephrine (NE) and 5-HT transporters	Major depression (backup), chronic pain, obsessive-compulsive disorder (OCD)—clomipramine	CYP substrates: interactions with inducers and inhibitors Long half-lives	α block, M block, sedation, weight gain • overdose: arrhythmias, seizures
Selective serotonin reuptake inhibitors (SSRIs)				
Citalopram,fluoxetine, paroxetine,sertraline, etc	Block 5-HT transporters	Major depression, anxiety disorders, OCD, PMDD, PTSD,bulimia, etc	CYP 2D6 and 3A4 inhibition (fluoxetine,paroxetine) • 1A2 (fluvoxamine) Half-lives: 15+ h	Sexual dysfunction
Serotonin-norepinephrine reuptake inhibitors (SNRIs)				
Venlafaxine Desvenlafaxine Duloxetine	Block NE and 5-HT transporters	Major depression, chronic pain,fibromyalgia, menopausal symptoms	Half-lives: 10+h	Anticholinergic, sedation,hypertension (venlafaxine)
5-HT$_2$ antagonists				
Trazodone	Block 5-HT$_2$receptors	Major depression, hypnosis (trazodone)	Usually require bid dosing • CYP3A4 inhibition (nefazodone) Short half-lives	Sedation • modest α and H$_1$ blockade (trazodone)
Other heterocyclics				
Amoxapine Bupropion Maprotiline Mirtazepine	Mirtazepine blocks presynaptic α$_2$receptors • mechanism of action of others uncertain	Major depression, smoking cessation (bupropion), sedation (mirtazepine)	Extensive hepatic metabolism • CYP2D6 inhibition (bupropion)	Lowers seizure threshold (amoxapine,bupropion) • sedation and weight gain (mirtazepine)
Monoamine oxidase inhibitors (MAOIs)				
Isocarboxazid Phenelzine Selegiline	Inhibit MAO-A and MAO-B • selegiline more active vs MAO-B	Major depression unresponsive to other drugs	Hypertension with tyramine and sympathomimetics Serotonin syndrome with SSRIs Very long half-lives	Hypotension, insomnia

Note: St. John's wort induces cytochrome P450 enzymes, and can cause loss of therapeutic effect of some antidepressants.

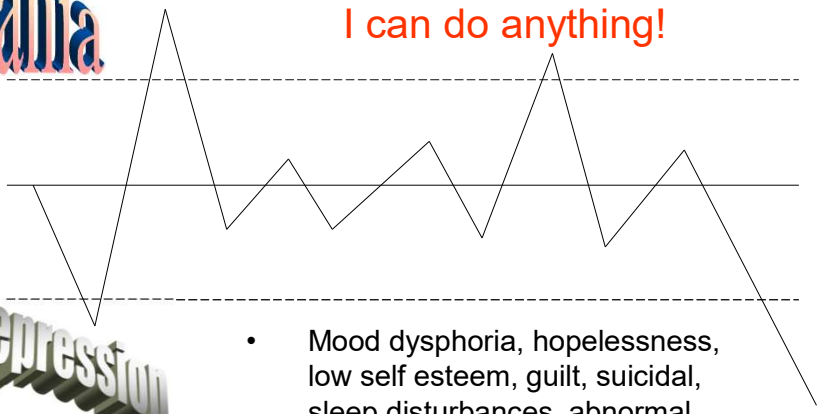
Note: St. John's wort also increases serotonin levels and can increase likelihood of serotonin syndrome


Questions

Bipolar Disorder

- Grandiosity, bellicosity, paranoid thoughts and overactivity

I can do anything!



- Mood dysphoria, hopelessness, low self esteem, guilt, suicidal, sleep disturbances, abnormal appetite, decreased libido, etc.

I just want to go back to bed.

Mood Stabilizing Agents
Drug List

- lithium carbonate (Li^+)
  - for acute mania and prevention of recurrent manic and depressive episodes
  - probably more effective than other agents

everywhere you have water in body Li can go

Antiseizure drugs

for acute mania and to prevent recurrence of mania

- valproic acid (= sodium valproate [divalproex])
  - Esp if Li+ is ineffective
- carbamazapine

to prevent recurrence of mania

- lamotrigine

Mood Stabilizing Agents

Antipsychotic drugs

for acute mania

- aripiprazole
- chlorpromazine
- Olanzapine
  - olanzapine + samidorphan (opioid antagonist) for manic or mixed or adjunct to Li or valproate
- quetiapine
- risperidone
- ziprasidone

for bipolar depression

- olanzapine + fluoxetine in combination
- quetiapine
- lurasidone

Lybalvi (olanzapine and samidorphan)

Approved June of 2021 for the treatment of schizophrenia

Approved June of 2021 for the treatment of adults with bipolar 1 disorder

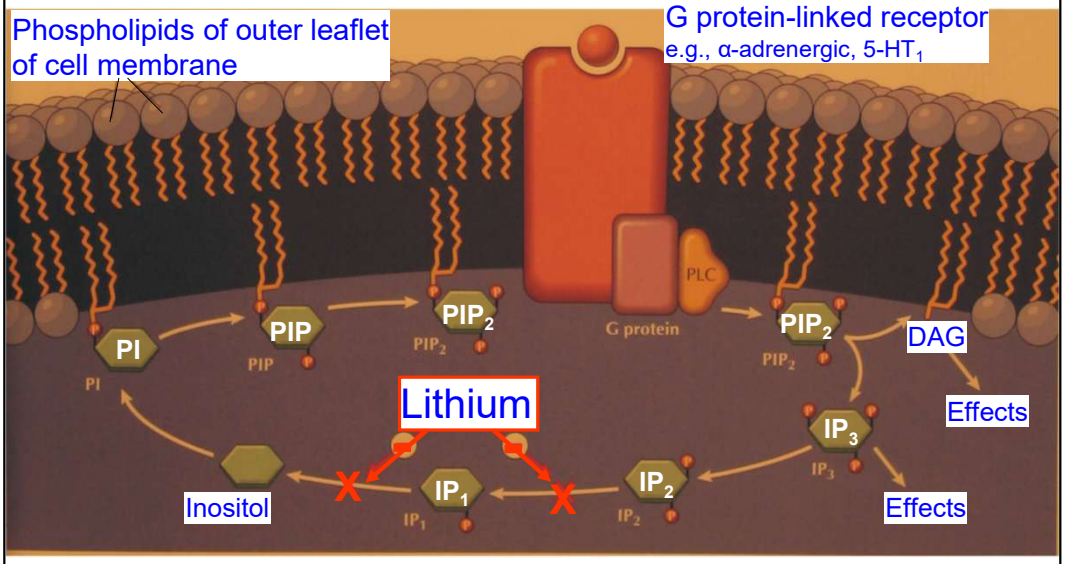
Li^+ Pharmacokinetics

- Monovalent cation that is well absorbed.
  - Complete in 6-8 hours,
  - peak levels in 30min-2 hours
- Distributed in total body water, some sequestration in bone. No protein binding
- not metabolized
- excreted in urine (90%)
- plasma ½ life 20 hours

Li^+ Pharmacodynamics

- Resembles Na^+ ion
  - substitute for sodium in action potential
  - Li^+/Na^+ exchanger
- Effects on neurotransmitters
  - enhances some actions of serotonin
  - ↓ norepinephrine and dopamine turnover
  - may block the development of dopamine receptor sensitivity
  - may augment the synthesis of acetylcholine, perhaps by increasing choline uptake into nerve terminals

Li^+ mechanism of action



Li^+ Adverse effects

- GI
  - vomiting, nausea, diarrhea
- Neurologic
  - motor movement disorders: Tremor
    - propranolol and atenolol reduce this effect
  - mental confusion (toxic doses)
- Thyroid (hypothyroid-like symptoms)
- Renal: polydipsia and polyuria
- Edema
- Cardiac: “sick sinus” bradycardia-tachycardia
- Pregnancy: renal clearance increases during pregnancy and decreases postpartum (watch for toxicity)
  - enters breastmilk at 30-50% of plasma levels → (poor suck reflex, cyanosis, hepatomegaly)
  - dismorphogenesis unclear- may cause cardiac malformations
- Leukocytosis

test more frequently when first dx but once chronic can do less

bipolar woman who is pregnant - need to increase dosage bc peeing more but will need to decrease after birth
lithium gets in the breast milk too can cause cyanosis

having side effects is better than a manic episode

Alternatives to Li^+

Antiseizure drugs

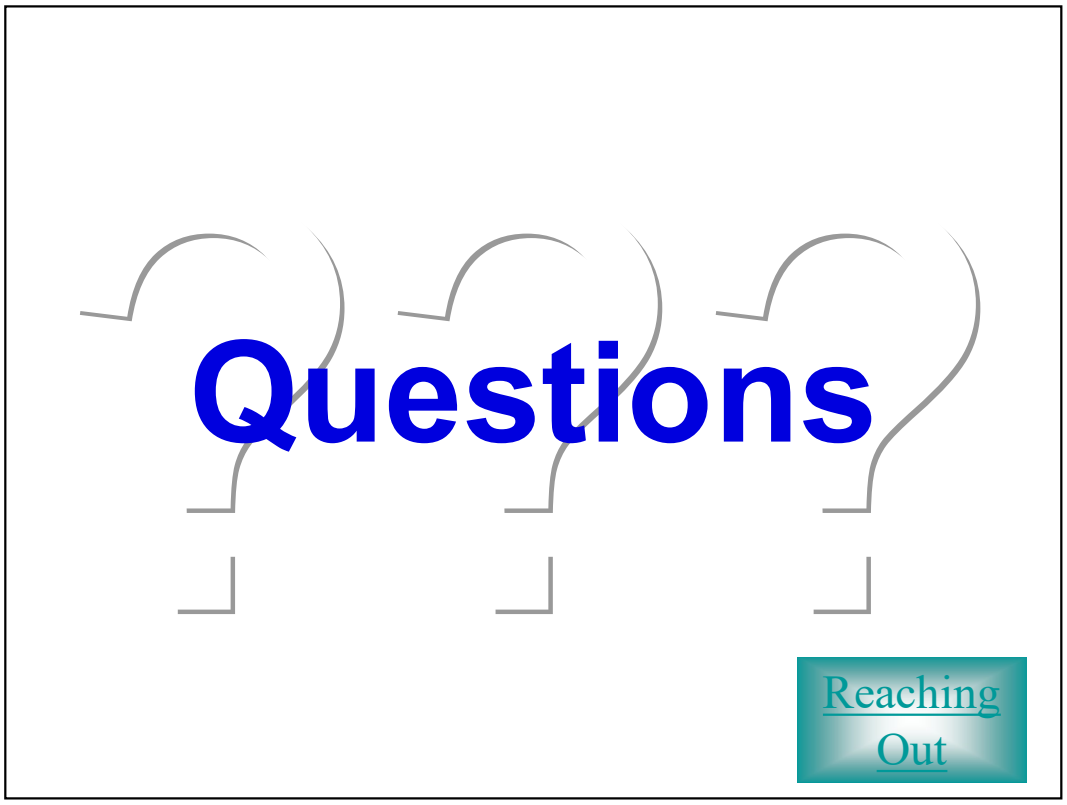
for acute mania and prevention of recurrence

- Valproic Acid (or sodium valproate [divalproex])
  - Efficacy = lithium during early weeks of therapy
  - May be useful in patients who fail to respond to Li^+
  - Can be used in combination with Li^+
  - Teratogenic – do not give during pregnancy
    1-2% risk of spina bifida
- Carbamazapine
  - less efficacious
  - can be used as a monotherapy or in combination for refractory patients

hugely dirty drug

do a pregnancy test don't just ask

if sexually active do not give



no specific anti-psychotic drugs on this exam but is on the next
just know anti-psychotics as a drug class

videos:
use EEG to see if have effect in 1-2 weeks or if need to change