DISCLOSURES

None of the faculty, planners, speakers, providers nor CME committee has any relevant financial relationships with commercial interest

There is no commercial support for this CME activity

Antidepressant use in Primary Care

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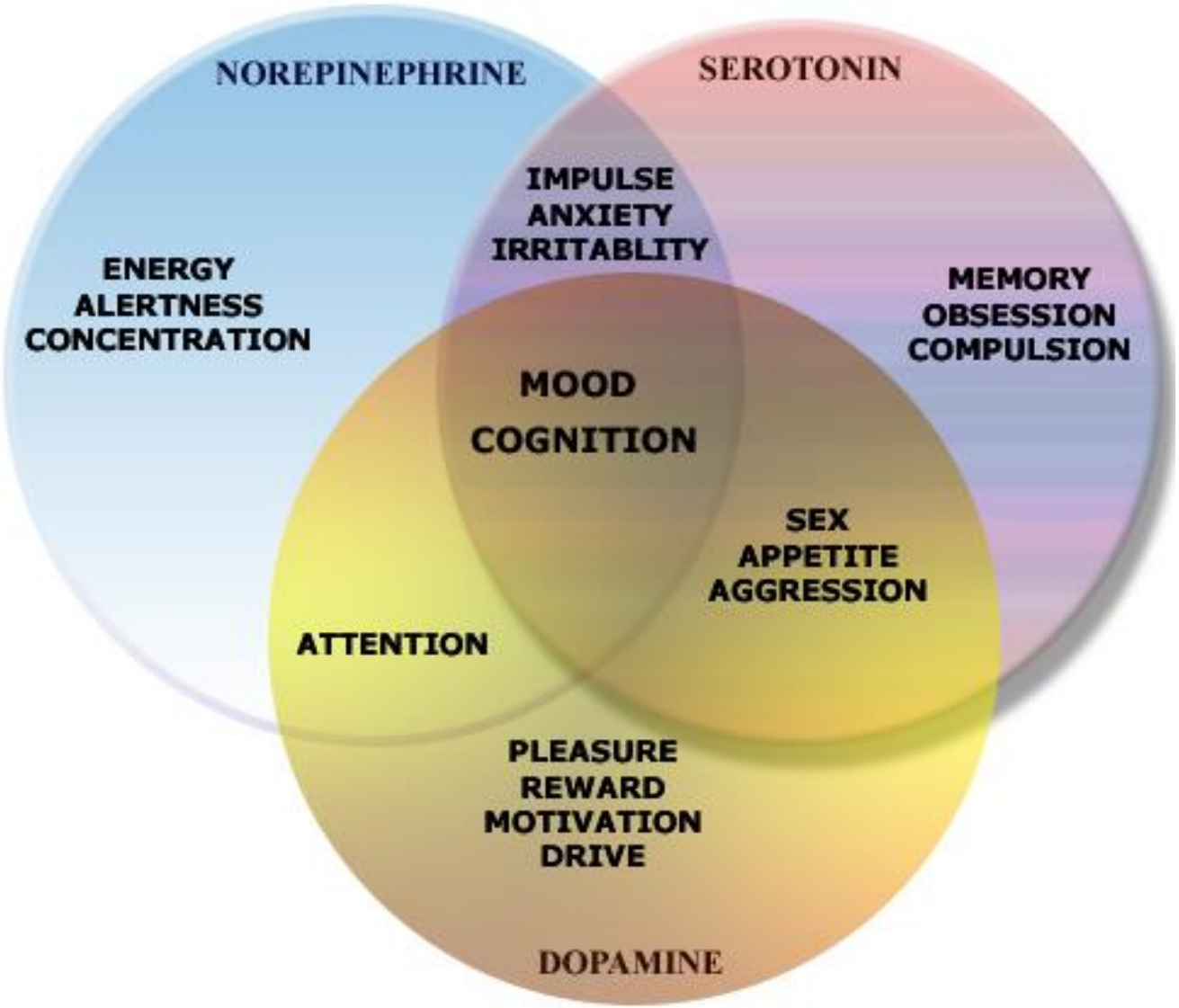
Outline

- Antidepressants – classes
- Indications, off-label use
- Safety, potential ASE
- DDIX


NOREPINEPHRINE
SEROTONIN
IMPULSE
ANXIETY
IRRITABLITY
ENERGY
ALERTNESS
CONCENTRATION
MEMORY
OBSESSION
COMPULSION
MOOD
COGNITION
SEX
APPETITE
AGGRESSION
ATTENTION
PLEASURE
REWARD
MOTIVATION
DRIVE
DOPAMINE

Selective Serotonin Reuptake Inhibitors (SSRI)

Prozac	Fluoxetine
Paxil	Paroxetine
Zoloft	Sertraline
Celexa	Citalopram
Lexapro	Ecitalopram
Luvox	Fluvoxamine
Brintellix	Vortioxetine
Viibryd	Vilazodone

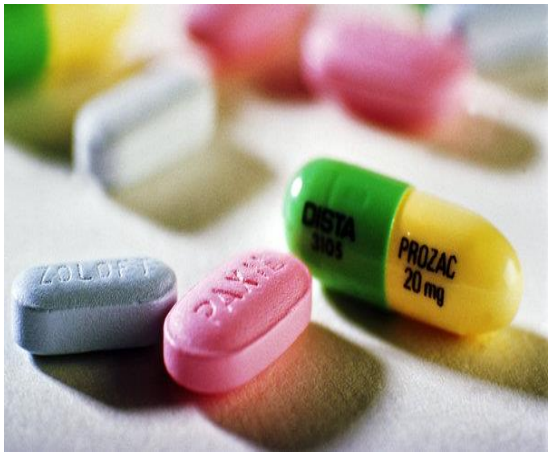


Table 1. FDA-Approved SSRIs

Generic	Trade Name	Approved Uses
Citalopram	Celexa	Depression
Escitalopram	Lexapro	Depression, generalized anxiety
Fluoxetine	Prozac	Depression, OCD, bulimia, panic disorder
	Sarafem	PMDD
Fluvoxamine	Luvox	OCD
Paroxetine	Paxil	Depression, OCD, generalized anxiety, panic disorder, social anxiety, PTSD
Sertraline	Zoloft	Depression, OCD, panic disorder, social anxiety, PTSD, PMDD
Vilazodone	Viibryd	Depression

OCD: obsessive-compulsive disorder; PMDD: premenstrual dysphoric disorder; PTSD: posttraumatic stress disorder; SSRI: selective serotonin reuptake inhibitor.

SSRIs

- High Serotonin receptor affinity, though also bind other receptors
- FDA approved for a range of disorders: MDD, OCD, GAD, Social Anxiety, PTSD, Panic, Bulimia, PMDD
- Well absorbed orally, with or without food
- Peak plasma levels 3-8h
- Half life 20-35h, except Prozac 4-7d
  - Prozac has 4-6wk wash-out period, i.e., "self tapers"
- Once a day dosing – except Prozac Weekly 90mg qwk

SSRIs

- Take 4-6wk to take effect
- Initial dose may be effective
- Protein-bound: Prozac, Paxil, Zoloft most, Lexapro least
- All metabolized in the liver by CYP 450
- Wide therapeutic index –> not lethal in overdose, but can cause "Serotonin Syndrome"
- Most metabolized by CYP 2D6, Lexapro/Celexa 3A4
- Pregnancy risk category C, except Paxil is category D

SSRI - ASE

- Early ASE:
- GI (nausea, diarrhea), HA
- Anxiety, activation, insomnia – Prozac, Zoloft
- Sedation – Paxil
- Switch to hypomania or mixed states

- Later ASE:
- Weight gain, Anti-Cholinergic – Paxil
- QT prolongation – Celexa >40mg
  - max dose 20mg/d in >60y/o or liver impairment, decreased K or Mg, taking Omeprazole or Cimetidine

SSRI - ASE

- Later ASE:
- Sexual dysfunction
- decreased libido, anorgasmia, delayed ejaculation, ED, inadequate lubrication in women
- Paxil >> Luvox, Zoloft, Prozac = Lexapro = Celexa
- Dose dependent
- Incidence: 15-80%, most studies suggest 30-50%
- 58% report when MDs ask vs 14% spontaneous
- F > M – higher depression incidence -> tx'd more -> more freq ASE

SSRI - ASE

- Tx:
- If good response to SSRI: wait 2-8 weeks for spontaneous remission of ASE - used most commonly but not effective
- If sxs persist, reduce dose - effective
- Switch: bupropion, mirtazapine, Cymbalta, Effexor
- Add Serotonergic agent – cyproheptadine, Amantadine (but supportive evidence re efficacy is weak)
- Add Phosphodiesterase 5 (PDE5) inhibitors, such as sildenafil and tadalafil
  - Can tx SSRI-related inorgasmia in women, BUT not decreased libido
  - No clear evidence of efficacy in treating sexual dysfunction in women

SSRI Withdrawal

- 1-3d: anxiety, mood swings, insomnia
- 7-14d: anxiety, irritability
- 3-4wks: symptoms vary in severity, start to subside
- May resolve slowly over 2-3 months

SSRI – Serotonin Syndrome

- "Fever MAD"
- Fever (up to 106 F)
- M – Mental Status Changes (AMS), agitation
- A –Autonomic/GI sxs (tachycardia, inc BP, dilated pupils, sweating, diarrhea)
- N – Neuromotor sxs – brisk reflexes, myoclous, tremor
- Rapid onset, hypertonia, persistent clonus LE>UE
- Severe cases: metabolic acidosis, rhabdomyolysis, seizures, renal failure, and disseminated intravascular coagulation

Serotonin Syndrome

- Brought on by 2 or more 5HT agonists, ex:
- SSRI + MAOI or SSRI + TCA
- Li + SSRI
- Illicit drugs: cocaine, methamphetamines, ecstasy (MDMA)
- Rx meds: Triptans, Tramadol, metoclopramide, ondansetron, dextromethorphan, meperidine
- OTC: St. John's Wart

SSRIs - Cautions

- Anticoagulation effect
  - several different mechanisms, such as impairment of platelet aggregation, depletion of platelet serotonin levels, and reduction in platelet count
  - Serotonin promotes platelet aggregation and SSRIs reduced uptake of serotonin into platelets
  - Not dose dependent

SSRIs - Cautions

- Hyponatremia
  - risk of hyponatremia seems to be increased during concomitant treatment with diuretics

SSRIs - Cautions

- Extrapyramidal Symptoms or Akathesia

- may be a consequence of serotonergically-mediated inhibition of the dopaminergic system
- Incidence rare
- Relative Risk yet to be established
- Can develop with short or long term use
- Who's at risk:
  - Elderly
  - High levels of serotonin – either due to high dose or DDIx
  - history of drug-induced akathisia and/or EPS
  - concurrent antidopaminergic and/or serotonergic therapy
  - recent monoamine oxidase inhibitor discontinuation
  - Preexisting neurologic disease, ex head trauma or PD
  - possibly deficient CYP P450 isoenzyme status – A1 allele implicated

SRIs – EPS risk

- there may be a distinct form of melancholic or endogenous depression with neurobiological underpinnings similar to other basal ganglia disorders such as Parkinson's disease

- Treatment:
- avoid rapid and unnecessary dose titration
- Dose reduction or med discontinuation
- Switch to an alternate AD
- Reduce co-administered med that may have led to inc SSRI drug level

SSRIs – EPS risk

- Study: conducted an analysis of cases from the FDA Adverse Event Reporting System (AERS) and literature review was conducted using PubMed, Ovid, MEDLINE, PsycINFO, and the Cochrane Database
- Review included all antidepressant classes
- cases reported between July 2005 and March 2008
- Reports of patients who were on concurrent psychotropics were excluded
- Results:
- Literature Review: 1 report each of EPS for duloxetine, nefazodone, and bupropion, 3 for escitalopram, and 4 for citalopram
- FDA AERS analysis: 89 cases met criteria. Of those, duloxetine implicated in 66% of cases, sertraline in 10%, escitalopram in 7%, and bupropion in 6%

- Ann Clin Psychiatry 2010 Aug;22(3):148-56. Madhusoodanan S, Alexeenko L, Sanders R, Brenner R

SSRIs in Pregnancy

- SSRIs are the most commonly rx'd ADs during pregnancy
- cross placenta and fetal blood-brain barrier
- Due to anticoagulant effect, can cause postpartum hemorrhage
- third trimester exposure associated with preterm birth (eg, <37 weeks gestational age)…vs first trimester exposure is not
- Low birth weight – mixed results, insignificant difference (74g less in some studies)
- Persistent pulmonary hypertension of the newborn (PPHN) – small increase in incidence
- Serotonin withdrawal: mild, self-limited, and rarely last longer than two weeks

- *The risks of untreated moderate to severe maternal major depression, to both the mother and fetus, often outweigh the risks associated with antidepressants*

SSRI DDIx

- SSRI + MAOI: Serotonin Syndrome
- SSRI + TCA: Serotonin Syndrome
- SSRI + Warfarin: inc Warfarin level
  - increased INR, inc bleeding risk
- SSRI + NSAIDS: inc bleeding risk
- SSRI + OCP: higher risk of Venous thromboembolism (VTE)

SSRIs - Special populations

- Elderly: Avoid Paxil (highest Anti-Ch and risk of withdrawal)
- Renal impairment: no difference, but Celexa and Zoloft preferred
- Hepatic Impairment: Avoid Prozac (long half life), Celexa and Lexapro DOC due to minimal effect on hepatic enzymes
- Pt on Warfarin: Zoloft, Celexa or Lexapro; avoid Prozac, Luvox and Paxil. Or chose an SNRI.
- Pregnant: Zoloft, Celexa or Lexapro

SSRI off-label use

- Tx for Premature ejaculation in adult males:
  - 5 mg to 20 mg/day PO has been shown to increase ejaculatory latency
  - Up to 40-60mg qd after 1 week was effective

- Tx of hot flashes in women with breast ca experiencing sxs of menopause
  - One study showed 20 mg/day reduced weekly incidence and severity of hot flashes by 50% compared to 36% with placebo


IT'S NOT YOU!
IT'S YOUR
Antidepressant
WITHDRAWAL!

Selective Norepinephrine Reuptake Inhibitors (SNRI)

• Effexor	Venlafaxine
• Pristiq	Desvenlafaxine
• Cymbalta	Duloxetine

Table 4

Serotonin-Norepinephrine Reuptake Inhibitors

Medications	Initial/Max Dose	Comments	Adverse Effects
Desvenlafaxine (Pristiq)	50 mg/100 mg daily (50 mg max effective dose)	Active metabolite of venlafaxine; BP elevation reported to be less common than with venlafaxine	Similar adverse effects to SSRIs, except more incidence of BP elevation with SNRIs
Duloxetine (Cymbalta)	40 mg/ 60 mg daily	$t_{1/2}$ = 12 h; moderate inhibitor of CYP2D6; GI adverse effects (nausea, dry mouth, constipation) are common; unique beneficial treatment for physical pain associated with depression	
Venlafaxine (Effexor)	25 mg tid/ 225 mg daily	5HT > NE at lower doses; NE > 5HT at higher doses; $t_{1/2}$ = 11 h; inhibitor of CYP2D6	

BP: blood pressure; 5HT: serotonin; GI: gastrointestinal; max: maximum; NE: norepinephrine; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; $t_{1/2}$: half-life.

Source: References 4, 10.

SNRI - ASE

- Elevated BP, tachycardia
  - Effexor > Cymbalta
- Activation!
- Appetite suppression
- Insomnia
- Restlessness
- Worsened anxiety
- Venlafaxine: seizures in OD, dose-dependent QT prolongation, QRS prolongation (potent Na channel blocker) - ventricular arrhythmia and cardiac arrest MCC of death on OD
- Duloxetine: QT prolongation in OD, rare

SNRI

- When to choose SNRI over an SSRI as first line
- When neuro-vegetative symptoms dominate – low energy, poor concentration, amotivation, psychomotor slowing
- Accompanying neuropathic pain d/o
- Avoid in anxious depression
- Failed 2-3 trials with SSRIs
- Intolerable ASE, ex sexual dysfunction, with SSRI, or sexual dysfunction already exists
- Use as adjuncts in partial response to SSRI

Norepineohrine-Dopamine Reuptake Inhibitor (NDRI)

- Wellbutrin Bupropion

- MOA not fully understood but it enhances both noradrenergic and dopaminergic neurotransmission
- Also, non-competitive antagonist of nicotinic acetylcholine receptors

- Ix:
- Major Depressive d/o
- Seasonal Affective d/o
- Tobacco Cessation

- Off-label:
- ADD in adults
- Neuropathic pain, including DM PN and post-herpetic neuralgia

Wellbutrin

- 37.5mg to 450mg qd – usual start dose 50 or 75mg qam
- Half life 12-37h
- IR – t ½ 8-10h
- SR – 12h
- XL – >24h

- ASE: restlessness, insomnia, activation, tremors

- *Not associated with sexual dysfunction*

- Seizures – in Bulimia, alcoholics, epileptics, brain injury
  - I: 0.1 to 0.4% at 300-450mg
  - Dose dependent!
  - In OD

Wellbutrin

- Tob cessation:

- Zyban – 150mg qd x3d, then 150mg bid, NTE 300mg qd
- Initiate 1-2wk prior to quit day
- Tx duration 7-12wks
- Can be used in combo with Nicotine TD – same dose as above
  - outcome slightly better at 10wks with combo but abstinence rates no different with TD vs alone at 1y

Serotonin-2 antagonist/reuptake Inhibitor

- Trazodone

- Also blocks alpha-1adrenergic receptors
- moderates cortisol suppression of the hypothalamic-pituitary-adrenal axis, which likely contributes to the efficacy of trazodone for insomnia
- moderate antihistamine H-1and low anticholinergic activity

- Ix: MDD

- Off-label: insomnia
- widely used for replacement of benzodiazepines or benzodiazepine-type sleeping drugs due to its anxiolytic efficacy and sleep normalizing effect in depression

Trazodone - Pros

- 25-300mg po qhs, taken 30min before sleep

- Why choose Trazodone vs Ambien or benzos

- Half-life 3-6h –> no day time drowsiness
- Helps initiate and maintain sleep
- effective in decreasing sleep latency and increasing sleep duration
- significant improvement in quality of sleep

- Innov Clin Neurosci. 2017 Jul-Aug; 14(7-8): 24–34. Trazodone for Insomnia: A Systematic Review; Karim Yahia Jaffer

Trazodone - Pros

- Trazodone vs Ambien or benzos

- Effective in treating primary and secondary insomnia
  - secondary insomnia due to
  - Depression
  - Post-menopause
  - Advanced cancer
  - Dementia
  - Methadone maintenance
  - Alcohol use
  - chronic caffeine intake
  - Post-traumatic stress disorders (PTSD)
  - Somatoform pain disorders, chronic pain, FMS

- Innov Clin Neurosci. 2017 Jul-Aug; 14(7-8): 24–34. Trazodone for Insomnia: A Systematic Review; Karim Yahia Jaffer

Trazodone - Pros

- Why choose Trazodone vs Ambien or benzos

- Tx of insomnia in depression, dementia, and people in otherwise good health
- "Improved sleep quality" - increases slow-wave sleep
- Weight neutral
- Does not decrease sexual function
- No rebound insomnia, no tolerance

- Innov Clin Neurosci. 2017 Jul-Aug; 14(7-8): 24–34. Trazodone for Insomnia: A Systematic Review; Karim Yahia Jaffer

Trazodone - Pros

- Insomnia in Pregnancy
- sedative effects of trazodone for the treatment of insomnia evaluated in 67 pregnant patients who were randomized to receive one of the following: trazodone (50mg/d), diphenhydramine, or placebo
- a wrist actigraphy used to record total sleep time and assess sleep efficiency
- Conclusion: use of trazodone or diphenhydramine to treat insomnia during the third trimester of pregnancy could help prevent postpartum depression

- *Psychiatry Res. 2013 Dec 30; 210(3):901-5.* Insomnia treatment in the third trimester of pregnancy reduces postpartum depression symptoms: a randomized clinical trial. *Khazaie H*

Trazodone vs Quetiapine

- One study done
- Conclusion: more effective than quetiapine for improvement of total sleep

- Doroudgar S, Chou TI, Yu J, et al. Evaluation of trazodone and quetiapine for insomnia: an observational study in psychiatric inpatients. Prim Care Companion CNS Disord. 2013;15(6)

Trazodone - ASE

- MC: drowsiness, morning grogginess, HA
- Orthostasis – caution in elderly, post-CVA
- dry mouth
- Vivid dreams
- Priapism- incidence1 in 1,000 and 1 in 10,000
- increased libido
- can be used for tx of ED (Trazodone for erectile dysfunction: a systematic review and meta-analysis.*Fink HA, MacDonald R, Rutks IR, Wilt TJ; BJU Int. 2003 Sep; 92(4):441-6)*

- Some case reports of cardiotoxicity in select cardiac patients- one case report of QT prolongation in a woman in Trazodone OD (Complete heart block following a single dose of trazodone.*Rausch JL, Pavlinac DM, Newman PE; Am J Psychiatry. 1984 Nov; 141(11):1472-3.*)

Trazodone - ASE

- Trazodone + MAOI – hypertensive crisis, Serotonin Syndrome
- =>at least 2wk wash-out period

Norepinephrine Alpha-2 antagonist

- Remeron Mirtazapine
- noradrenergic and specific serotonergic antidepressant (NaSSA)
- MOA: antagonization of adrenergic alpha2-autoreceptors and alpha2-heteroreceptors as well as by blocking 5-HT2 and 5-HT3 receptors
- Increases serotonin and norepinephrine, histamine receptor antagonism

Mirtazapine

- Ix: MDD
- Administered as 7.5mg-45mg po qhs
- Half-life 20-40h
- Need 15mg or higher for antidepressant effect
- Lower dose more sedating
- Anti-emetic use – 5HT-3 effect, low dose efficacious
  - Cyclical Vomiting Syndrome
  - Pts undergoing chemo
  - Refractory gastroparesis

Mirtazapine

- Tx of Anorexia/appetite stimulant

- Benefit in cancer-related cachexia/anorexia was suggested in a phase II trial in which 17 non-depressed patients with CACS received an eight-week course of mirtazapine (15 to 30 mg by mouth daily)
- Four of 17 patients gained 1 kg or more, and 24 percent reported improved appetite
- Conclusion: definitive proof of benefit would require a randomized, placebo-controlled trial

- Phase II trial of mirtazapine for cancer-related cachexia and anorexia.AURiechelmann RP, Burman D, Tannock IF, Rodin G, Zimmermann C SOAm J Hosp Palliat Care. 2010;27(2):106. Epub 2009 Sep 23.

Mirtazapine - ASE

- MC: somnolence, increased appetite, weight gain, dizziness
- Agranulocytosis, neutropenia – similar to APs
- Overlap with MAOI – Serotonin Syndrome
- =>2wk washout period
- Weight gain – incidence 17%, gain about >= 7% of body weight
- Hyperlipidemia:
  - incidence 15%, nonfasting cholesterol increase of >= 20% above upper limit of normal
  - nonfasting triglyceride increases to ≥500 mg/dL in 6% of pts

Mirtazapine - DDIx

- Dilantin and Tegretol increase its clearance by two-fold, therefore, dose may have to be adjusted
- Mirtazapine has no reciprocal effect on them
- Excessive sedation when combined with other sedatives, etoh
- Mirtazapine + MAOI – hypertensive crisis, Serotonin Syndrome
- =>at least 2wk wash-out period

Mirtazapine - Cautions

- Elderly males: renal clearance reduced by 40% vs younger males
- Elderly females less effected – Cr Cl reduced by 10% vs in younger females
- => Lower dose recommended

- Longer half-life in females vs males across all ages (mean half-life of 37 hours for females vs. 26 hours for males)

Tricyclic Antidepressants (TCA)

- Elavil Amitriptyline
- Ix: MDD
- Off-label:
- Social anxiety d/o, Panic d/o, neuropathic pain including DM PN, postherpetic neuralgia, migraine prophylaxis, FMS, insomnia, hiccups
- Dosage: 10-300mg, avg 50-75mg qhs

Elavil

- ASE:

- QT prolongation
- Lethal in overdose
- Orthostasis
- Anti-cholinergic ASE
- Pt on Warfarin: TCAs increase Prothrombin Time in a dose-dependent manner

So…when & how to titrate, add or switch

- Sequenced Treatment Alternatives to Relieve Depression (**STAR*D**) was a collaborative study on the treatment of depression, funded by the National Institute of Mental Health
- 2006 study
- Its main focus: treatment of depression when the first prescribed antidepressant proved inadequate
- N = 4,041, outpatients with nonpsychotic depression at 23 psychiatric and 18 primary care sites
- Three combination options (either an antidepressant or CBT added to citalopram), and four switch options (to either a different antidepressant or CBT)
- Switched if failed to achieve remission or response (50% reduction in symptoms) after a specified number of weeks

STAR*D Study Overview

- N = 4000 outpatients aged 18 to 75 years old
- Primary diagnosis of nonpsychotic major depressive disorder, confirmed by study clinician
- Most Axis I comorbidities, other general medical conditions allowed
- Treatment setting: specialty and primary care
- $HRSD_{17}$ score ≥14 at study entry
- 12–14 weeks per treatment level; 1-year naturalistic follow-up
- Equipoise-stratified, randomized design allowed patients to select treatment strategy and allowed randomization to different treatment options within the selected strategy

Rush AJ, et al. *Control Clin Trials*. 2004;25:119-142.

RESPONSE AND REMISSION

STAR*D "Switch" and "Augment" Algorithms

SWITCH

Initiate Citalopram
(maximum dose)
(20mg)

If intolerant or inadequate response switch to...

- Buproprion SR (400mg)
- Sertraline (200mg)
- Venlafaxine ER (375mg)

AUGMENT

Initiate Citalopram
(maximum dose)
(20mg)

If inadequate response add...

- Best choice: Buproprion SR (400mg)
- Second best choice: Buspiron (60mg)

Table 4 – Four steps of the STAR*D algorithm[2]

	Treatment	Treatment duration	Results	Symptom remission achieved
Step 1	Citalopram	12 to 14 weeks	If symptom remission was not achieved or citalopram not tolerated, patient is invited to move to step 2	36.8%
Step 2	◗ Switch to bupropion SR, sertraline, venlafaxine ER, or cognitive therapy ◗ Augment with bupropion SR, buspirone, or cognitive therapy	12 to 14 weeks	If symptom remission was not achieved or step 2 treatment not tolerated, patient is invited to move to step 3	30.6%
Step 3	◗ Switch to mirtazapine or nortriptyline ◗ Augment with lithium or triiodothyronine	12 to 14 weeks	If symptom remission was not achieved or step 3 treatment not tolerated, patient is invited to move to step 4	13.7%
Step 4	◗ Switch to tranylcypromine or the combination of mirtazapine and venlafaxine ER	12 to 14 weeks	–	13%


HAPPY

Please feel free to contact Socorro with an question you may have

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