# Antidepressants

David N. Osser, M.D.
Associate Professor of Psychiatry
Harvard Medical School

Model Curriculum for
Psychopharmacology Crash Course
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# DISCLOSURES

- Lecturer has no financial relationships with the manufacturers of any pharmaceutical products.

# Lecture Outline

- Introduction
- Drug costs
- General drug usage
- Dosing
- Augmentations
- Conclusions

# Pre- and Post-Lecture Competency Exam

## Question 1

Which of the following is correct for the typical dosing of citalopram?

A. Begin with 20 mg per day. If no response in 2-4 weeks, increase to 40 mg per day.
B. Begin with 20 mg per day and increase after one week if tolerated, to 40 mg per day. Continue 40 mg per day for 2-4 weeks.
C. Begin with 40 mg per day. If no response in 2-4 weeks, increase to 60 mg per day.

## Question 2

Tricyclic antidepressants should be avoided with all of the following except

A. Recent myocardial infarction
B. Bundle branch block
C. Urinary retention
D. Untreated glaucoma
E. Patients hospitalized for severe melancholic depression

# Question 3

All of the following are reasonable strategies for addressing unsatisfactory response to an antidepressant, except:

A. Augmenting a partial response that is a placebo effect, by adding another medication

B. Trying a sequence of up to three monotherapy trials with different antidepressants

C. Treating insomnia/nightmares with appropriate hypnotics

D. Switching to bupropion or mirtazapine if the patient is having sexual side effects

## Question 4

All of the following augmentation strategies after unsatisfactory response to an SSRI are effective but one is very much more costly than the others:

A. Lithium

B. Tri-iodothyronine (T3)

C. Aripiprazole

D. Buspirone

E. Bupropion

## Question 5

All of the following are findings from the STAR*D study except

A. Depressed patients with high levels of anxiety respond much less well than patients with fewer anxiety symptoms
B. There was a trend toward better results with thyroid (T3) augmentation compared with lithium augmentation
C. There was a trend toward better results with venlafaxine combined with mirtazapine, compared with the MAOI tranylcypromine
D. The remission rate with citalopram was 28%

# Major Teaching Points of this Lecture

- Use antidepressants when indicated: for major depressive syndromes, not necessarily for depressed mood in multiple other contexts.
- Know what the drugs cost.  This will enable you to select cost-effective choices for your patients.
- Do one treatment at a time and use efficient dosing strategies
- Manage side effects by using as little polytherapy as possible
- Be mindful of placebo and non-specific effects of treatment.

# How Are We Doing in Treating Depression?*

- Lifetime prevalence: 16.2%
- 12 month prevalence: 6.6%
- 59% had severe or very severe role impairment
- 51.6% of depressed patients received some treatment
- Of these, 41.9% were rated as adequately treated.

***Kessler et al. JAMA 2003 June 18:3095-3105**

# Antidepressants: The Menu I. Generic and (old) brand names and daily dose equivalence.

SSRIs
- Fluoxetine 20 mg
- Sertraline 50 mg
- Paroxetine 20 mg
- Citalopram 40 mg
- Escitalopram 10 mg
- Fluvoxamine 100 mg

SNRIs
- Venlafaxine 150 mg
- Desvenlafaxine 50 mg
- Duloxetine 60 mg
- Levomilnacipran 40 mg

Other second generation
- Mirtazapine 30 mg
- Bupropion 300 mg
- Nefazodone 400 mg
- Fluoxetine + Olanzapine

SSRIs
- Prozac
- Zoloft
- Paxil
- Celexa
- Lexapro
- Luvox

SNRIs
- Effexor
- Pristiq
- Cymbalta
- Fetzima

Other second generation
- Remeron
- Wellbutrin, Zyban
- Serzone
- Symbyax

# Other Antidepressants: The Menu II. Generic and (old) brand names and daily dose equivalence.

Tricyclics
- Imipramine 150 mg
- Desipramine 150 mg
- Nortriptyline 100 mg
- Amitriptyline 150 mg
- Doxepin 200 mg

MAOIs
- Phenelzine 60 mg
- Tranylcypromine 30 mg
- Isocarboxazid 40 mg
- Selegiline transdermal 6 mg

Others
- Trazodone 400 mg
- Vilazodone 40 mg
- Vortioxetine 20 mg

Tricyclics
- Tofranil
- Norpramin
- Pamelor
- Elavil
- Sinequan

MAOIs
- Nardil
- Parnate
- Marplan
- Emsam

Others
- Desyrel, Oleptro
- Viibryd
- Brintellix

# An Algorithm for Selecting Medications for Depression: STAR*D *Remission* Results*

- **Level 1:** Citalopram: 28% (N=2,876) (“response”=47%)
- **Level 2:** Switch to sertraline 18% (N=238), bupropion SA 21% (N=239), venlafaxine XR 25% (N=250)
- Augment with buspirone 30% (N=286), bupropion SR 30% (N=279)
- Augmenting or switching: retrospective matched comparison showed no difference (OR 1.14 for remission with augmenting)
- **Level 3:** Switch to mirtazapine 12% (N=114), or nortriptyline 20% (N=121)
- Augment with (N=142) lithium 15%, or thyroid (T3) 25%
- **Level 4:** Switch to (N=109) tranylcypromine 7%, or mirtazapine + venlafaxine 14%

***AJP 1/06, 7/06, 9/06; NEJM 3/23/06; J Clin Psychopharm 2/12**

# Depressed Patients with High Levels of Anxiety Responded Poorly in STAR*D

Fava et al. **AJP 2008;165:342-51**

- About 50% of STAR*D patients had significant levels of anxiety
- Defined as a score of 7 or more on the Ham D: anxiety/somatization items
- In **Level** 1 remission rate with low anxiety = 33%
- Remission rate with significant anxiety = 22%
- In **Level 2** switch or augmentation studies, remission rates with

| Study | | low anxiety (%) | significant anxiety (%) |
|---|---|---|---|
| Switch | Sertraline | 29 | 8 |
| " | Bupropion | 34 | 10 |
| " | Venlafaxine | 36 | 12 |
| Add | Bupropion | 37 | 18 |
| " | Buspirone | 39 | 9 |

# Generalizability of STAR*D results

- Good, because the patients were more like patients in typical practice than the patients in Phase 3 drug-company-sponsored efficacy trials that comprise most of the studies in meta-analyses*
- Lack of placebo controls limits ability to interpret the outcome data, however.

*Wisniewski SR et al.  AJP May 2009

# And from other evidence: **If the first antidepressant fails, does it matter if you switch in class, out of class, or just continue the first antidepressant?**

No.


Souery D et al. J Clin Psychopharmacol 2011;31(4):512-16

Bschor T. Acta Psychiatr Scand 2010;121:174-9

# Cost-Conscious Treatment

- Physicians have a responsibility know what the medications cost
- After appropriate clinical evaluation and determination of the most evidence-supported treatment, costs should be taken into consideration.

Culture change required?

# Antidepressant Monthly Procurement Costs in the U.S. Dept. of Veterans Affairs– Aug. 6, 2014

- fluoxetine 20 mg $ 0.45
- citalopram 40 mg 1
- nortriptyline 100 mg 2
- mirtazapine 30 mg 2
- paroxetine 20 mg 2
- escitalopram 10 mg 3
- sertraline 100 mg 4
- bupropion SA 150 bid 6

# Antidepressant Monthly Procurement Costs in the VA – Continued

- bupropion XR 300 mg $ 8*
- venlafaxine IR 150 mg 6
- venlafaxine SA 150 mg 44
- nefazodone 400 mg 45
- duloxetine 60 mg 106

*some generics have had problems

Since many antidepressants are activating and there may be a need for a hypnotic, here is a table of options, along with their costs

# Drugs Used as Hypnotics
## (Monthly VA Procurement Costs, Sept. 11, 2014)

| | |
|---|---|
| amitriptyline 10 mg | $ 0.41 |
| trazodone 50 mg | 1 |
| zolpidem 10 mg | 1 |
| hydroxyzine 25 mg | 1 |
| lorazepam 2 mg | 2 |
| prazosin 5 mg | 2 |
| doxepin 10 mg | 3 |
| quetiapine 50 mg | 3 |

# Drugs Used as Hypnotics in the VA System (Monthly Procurement Cost, Continued)

- **zaleplon (Sonata) 10 mg $ 74**
- **eszopiclone (Lunesta) 1, 2, or 3 mg 106**
- **ramelteon (Rozerem) 2 mg 107**
- **Suvorexant (Belsomra) 10 or 20 mg ??**

# Expensive Drug Treatment Strategies for Depression

- Use of “free” starter samples. (Also causes many medication errors.*)
- Treating individual symptoms of the depressed patient (e.g. anxiety, insomnia) with multiple medications targeting these symptoms rather than treating the diagnosis (syndrome) with an evidence-supported monotherapy approach.
- IOM Report, July 2006, at www.nap.edu

# Prescribing Cost-Effectively for Depression: Initial Treatment

- Conclusion of meta-analysis of 46 randomized, controlled comparisons: **“Selection of initial treatment might be based on cost” unless there are individual patient preferences based on ‘expected’ side effects.”***
- First choices for SSRIs are sertraline or escitalopram for adults, children and adolescents.(Cipriani, 2011)
- Bupropion first-choice non-SSRI.

* Hanson RA et al. Ann Int Med 2005;143:415-426

# Dosing Strategies: General

- Avoid frequent dose increases but make contact with patient every 1-2 weeks, as recommended in the 2010 APA Practice Guidelines for Treatment of Depression
- Wait 1-4 weeks* with total non-response (or partial response that has plateaued) before increasing. Wait 8-12 weeks if gradual response that has not plateaued
- When clinically necessary, may have to make above changes earlier than 2-4 weeks.

*Taylor et al. Arch Gen Psychiatry 2006;63:1217-23

# Dosing Sertraline

- Start with 50 mg in AM (25 mg for elderly, and those with panic disorder)
- Maintain 50 mg/day for 2-4 weeks before increasing. If no response or partial response that plateaus, increase in 50 mg increments every 2-4 weeks. Change if no response at 200 mg for 2-4 weeks
- However: one study showed better outcome with staying with 100 mg for weeks 6-11 vs. going to 200 mg, after response was unsatisfactory for 6 weeks. (Licht and Ovitzau 2002)

# Dosing Escitalopram
## (the s-enantiomer of racemic citalopram)

- Begin 10 mg in AM or PM, including most elderly and hepatic impaired patients.
- If tolerated and no/partial plateaued response in 1-4 weeks, you can increase to 20 mg for 2-4 weeks. However, no difference was found between 10 and 20 mg in fixed dose comparisons. (Pkg insert)
- Note that 10 mg is equivalent to 40 mg of citalopram in clinical potency,* and may produce fewer side effects

*Stahl SM. Essential Psychopharmacology 2005, p. 159.

# Dosing Bupropion SR*

- Contraindicated in patients with history of seizures (any cause), anorexia nervosa and bulimia.
- Begin with 100-150 mg qAM
- Increase to 100-150 mg bid after 4-7 days;
- Maintain 150 bid for 2-4 weeks before increasing. If no/partial plateaued response, increase to 200 bid (PDR max. dose for SR).
- Change if no response to 400/d for 2-4 weeks
- If using **bupropion XR**, PDR max. is 450 mg. Caution: generics have had low bioavailability

*Avoid using bupropion HCl. Seizure rate is 4x higher

# Dosing Citalopram

- Begin 20 mg in AM or PM, 10 mg for elderly, unprecipitated panic attacks.
- Increase to 40 mg after 1 week. Continue 40 mg for 1-4 weeks if tolerated. If no/partial plateaued response, consider switch.
- 20 mg daily may = placebo*
- Study suggests best results if serum level > 50 ng/ml**

*Feighner and Overo. J Clin Psychiatry 1999;60:828 (fig. 4)

**Haji et al. J Clin Psychopharmacol 2011;31(3):281-286

# Citalopram Cardiac Safety Information September 1, 2011

**FDA recommendations re: risk of Torsades**

- Do not use in patients with congenital long QT
- Correct low K and Mg before using and monitor lytes
- Frequent EKGs in patients with CHF, bradyarrhythmias, or **on other meds that prolong QTc e.g., quetiapine (new warning in 2011 also)**
- Hepatic impairment, age >60, 2C19 poor metabolizers, on cimetidine: **use 20 mg**
- Evaluate if any subjective HR or rhythm change
- **Good News:** large cohort study found no adverse outcomes with doses > 40 mg (Zivin, AJP, June 2013)

# Relative QTc Safety of Citalopram vs. Escitalopram (www.fda.gov/Drugs/DrugSafety/ucm297391)

| Citalopram | Mean QTc change (ms) |
|---|---|
| 20 mg | 8.5 |
| 40 mg | 12.6 |
| 60 mg | 18.5 |
| *moxifloxacin 400 mg | 13.4 |
| **Escitalopram** | |
| 10 mg | 4.5 |
| 20 mg | 6.6 |
| 30 mg | 10.7 |
| *moxifloxacin 400 mg | 9.0 |

*used as control in these studies: known to increase QTc

# "Escitalopram (ESC): Superior to Citalopram or a Chiral Chimera?"*

- Chimera = a vain or idle fancy
- Pooled analysis (*Svensson 2004) of 1321 patients in 4 studies using Cochrane methods found no difference in effectiveness in primary outcome measures: secondary measures in post-hoc analysis slightly favored ESC.
- Meta-analysis (Int J Psychopharm 2010) by employees of Lundbeck involving 9 studies and 2000 patients found 72% response rate with ESC and 64% with citalopram. NNT 12.

# Escitalopram: Superior? The CO-MED Study*

- This was an effort to see if it is better to start two antidepressants at once vs. only one.
- 665 outpatients with **chronic or recurring depression** in primary/psychiatric care randomized
  - escitalopram up to 20 mg plus placebo
  - escitalopram plus bupropion (up to 400 mg)
  - venlafaxine plus mirtazapine (up to 300/45 mg)
- Remission rates (%) were
  - escitalopram plus placebo 39
  - escitalopram plus bupropion 39
  - venlafaxine plus mirtazapine 38

*Rush AJ et al. Am J Psychiatry 2011

# Escitalopram: Superior? The CO-MED Study* Conclusions

Escitalopram monotherapy was as good as these two highly regarded combination strategies.

# Dosing Fluoxetine

- Begin 10-20 mg/morning, 5-10 mg for age > 60 or if hx of unprecipitated panic attacks, or to avoid side effects.
- Increase to 20 mg after 1 week. Continue with 20 for 1-4 weeks. If no/partial plateaued response, increase in 20 mg increments every 2-4 weeks as tolerated (Fava M et al. J Clin Psychopharmacol 2002; 22:379-387)
- Change if no improvement after 2-4 weeks at 60 mg/d

# Dosing Mirtazapine

- Avoid if weight gain risk a major concern
- Begin with 15 mg qPM
- Increase to 30 mg in one week if tolerated (STAR*D dosing protocol). Continue for 1-4 weeks before increase. If no/partial plateaued response increase to 45 mg (PDR maximum).
- Change if no response to 45 mg after 2-4 wk
- Somnolence may be less at higher doses (Fawcett and Barkin, J Affect Disord 1998;51:267-285)

# Dosing Venlafaxine SR

- Dosing protocol (STAR*D): Start with 37.5 mg in AM for one week
- Increase to 75 mg/day in second week;
- Increase to 150 mg/d. Hold 3 weeks before next increase
- If no/partial plateaued response, increase in 75 mg increments every 2-4 weeks, if tolerated.
- Change if no response after 2-4 weeks at 300 mg/day (but 225 is the PDR max for XR)
- Hypertension risk – 1-2% low doses, up to 10% at doses 300 mg daily and higher. Check pre-treatment blood pressure.

# Duloxetine Dosing

- Begin with 40 mg daily in single or divided dose (may help with nausea)
- After 3-7 days, increase to 60 mg
- If no response/partial plateaued response after 2-4 weeks at 60 mg, you could consider going to 120 mg daily but an RCT found this no more effective, but more toxic, than placebo. (Kornstein et al 2008)
- GI side effects may be reduced by taking with food (unpublished data cited in Schatzberg text, 2007)
- Olanzapine 1.25-2.5 mg can also help (Zhong 2014)
- Like the other “SNRI” venlafaxine, it raises blood pressure but probably not as much

# "Duloxetine does not relieve painful physical symptoms in depression: a meta-analysis."*

*Spielmans GI. Psychother Psychosom 2008;77:12-16

- Analyzed 5 studies with 1,448 patients involving 714 on duloxetine, 562 on placebo and 172 on paroxetine.
- Effect size on the analgesic effect was tiny: 0.115 by Cohen's d.
- **Conclusion: the claims being made in advertising are not supported by solid evidence.**
- **Costs of alternative: amitriptyline 50 mg - $0.02**
  **vs. duloxetine 40 mg - 4.25**

# Dosing Tricyclics – e.g., nortriptyline

- Caution: Overdose risk.  10 day supply can be fatal
- Contraindicated if recent MI, ischemic heart disease, cardiac conduction defects, urinary retention, narrow angle-closure glaucoma, renal failure, orthostasis (nortriptyline has least)
- Obtain baseline EKG.  If bundle branch block, risk of serious arrhythmia is higher.
- Begin with 10 mg bid or 25 mg hs.  (5 bid in elderly). Increase by 10 mg every two days until you get to 50 mg and then increase by 25 mg every two days until you get to 100 – 150 mg given in one dose.  If response unsatisfactory after 4 weeks and results have plateaued get a blood level. Therapeutic range is 50-150 ng/ml. Do not exceed 150.
- Check at least one blood level to rule out slow metabolism and potentially toxic level.

# Dosing the MAOI tranylcypromine

- Initiate with 10 mg bid
- Increase to 10 tid after a week.  If no response or partial response that plateaus at an unsatisfactory level, raise by 10 mg every 1-3 weeks until maximum dose of 60 mg daily.
- MAOI diet required to avoid tyramine-induced hypertension Watch for orthostatic hypotension, insomnia, agitation
- Seizures, hepatotoxicity
- Trazodone may be used (cautiously) for sleep. Also benzodiazepines.
- Low frequency of sexual side effects and weight gain compared with phenelzine and isocarboxazid.

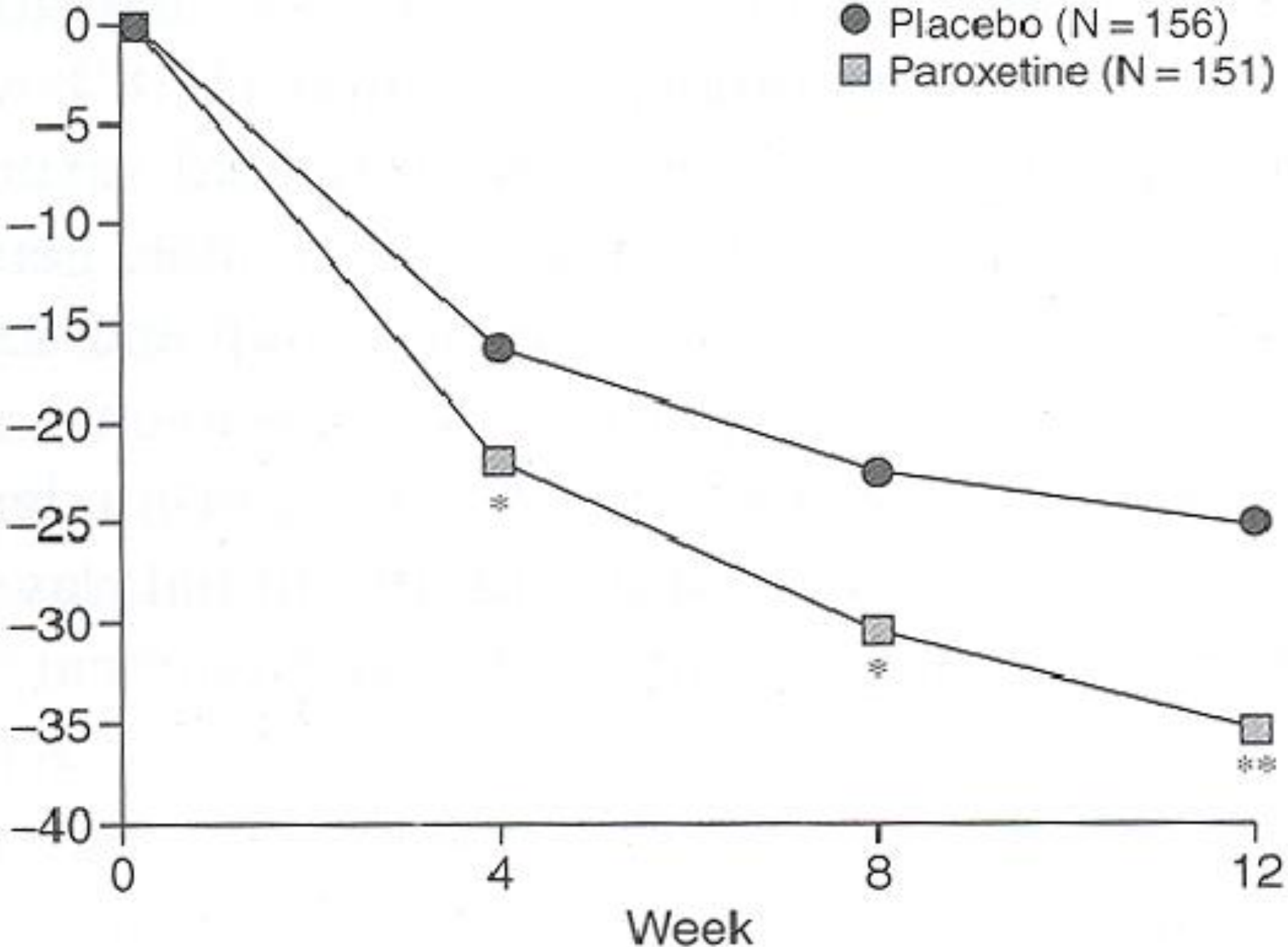
# Something New? Vilazodone

- SSRI plus a 5-HT1a inhibitor (like buspirone).
- Two 8-week placebo-controlled studies, (J Clin Psychiatry 2009;70:326-33; 2011;72:441-7) but hasn't been compared to other antidepressants
- Dosing: 10 mg for one week, 20 mg for second week, 40 mg for third week and maintain on 40. Must take with food.
- Sedating. Nausea, vomiting, diarrhea. No weight gain. Has sexual side effects but unclear if they are less common than with SSRIs. (Laughren TP et al, 2011)

# Remission vs. Partial Response

- The goal of therapy is remission.* Rates are about 35-45%. "Response" is 60-70%. Prognosis is worse for partial responders.
- Partial response is often placebo response. Evaluate carefully. Rapid early response that does not improve further or loses steam is often placebo response.
- "Augmenting" a placebo response with another drug is not best practice.

***Keller MB. JAMA 2003 June 18:3152-3160**


Placebo (N = 156)
Paroxetine (N = 151)
0
−5
−10
−15
−20
−25
−30
−35
−40
0
4
8
12
Week
*
*
**

# "Poop-out." How often is it due to loss of placebo response?

from Zimmerman and Thongy, J Clin Psychiatry 2007;68:1271-1276

- Patients who initially improve include drug responders and placebo responders.
- When patients "relapse," some of these relapses are in patients who never experienced a true drug response in the first place.
- Zimmerman's meta-analysis involved studies of acute and continuation treatment with SSRIs or placebo.
- Using a formula by Quitkin et al (1993), he concluded that **most relapses during continuation treatment occurred in patients who were initial placebo responders**.

# Management of Selected Side Effects

# Sexual Dysfunction (SD)

- A big problem in primary care:(**JAMA 2003 July 2:57-65)**
- Meta-analysis (Serretti and Chiesa 2009) found treatment-emergent SD in 40-80% for most SSRIs, SNRIs. Placebo: 14%.
- First Choice: switch, to bupropion, mirtazapine (weight gain), nefazodone (liver risk). Trazodone?
- **Add-ons**: Cochrane Review (2004,5) found sildenafil was clearly better than placebo (in men only). There also was support for tadalafil. Later Nurnberg (2008) found benefit for women in an RCT (N=98). No other options are supported by adequate evidence. Bupropion helped sexual desire (only) in one RCT, but had no benefit in another, when used at a lower dose.

# Insomnia/Nightmares

- Trazodone 25-100 mg has efficacy,[1] is cost-effective, no dependence, short half life: “in many ways an ideal hypnotic.”[2]
- Benzodiazepine, for patient with no substance abuse history. ? In PTSD.
- Antihistamines: problem of tolerance
- Nightmares/disturbed awakenings due to PTSD: prazosin 1-20 mg hs)
- Quetiapine: problem of the “munchies” and metabolic consequences

[1]Sleep Med 2004 Jan:5(1):7-8

[2]Stahl SM. CNS Spectr 2009:14(10):536-46.)

# Sweating

- Research needed.  The following could help:
- Benztropine 0.5 mg bid
- Clonidine 0.1 mg bid
- Alpha –1 adrenergic blocker, e.g. terazosin 1-5 mg/d

# SUICIDAL IDEATION AS A SIDE EFFECT

- **Children and adolescents:** FDA warning, which was extended to young adults through age 24.
  - Ideation increase is up 2 fold. Actual suicide: no incr.
  - Antidepressants are not very effective for depression in children and adolescents. They are better for non-OCD anxiety disorders. (JAMA April 18, 2007; 1683-96)
  - After the warning, antidepressant prescription rates initially went down and suicide rates went up. Recently, though, usage seems to have returned to reduced suicide rates (Scandinavia)
- **Adults >24:** No FDA warning. Some studies show small suicide ideation effect (Arch GS Dec. 2006:1358-67) and some do not (Am J Psych Jan. 2006:41-47)

# DECREASED BONE MINERAL DENSITY & INCREASED FRACTURE RISK w. SSRIs

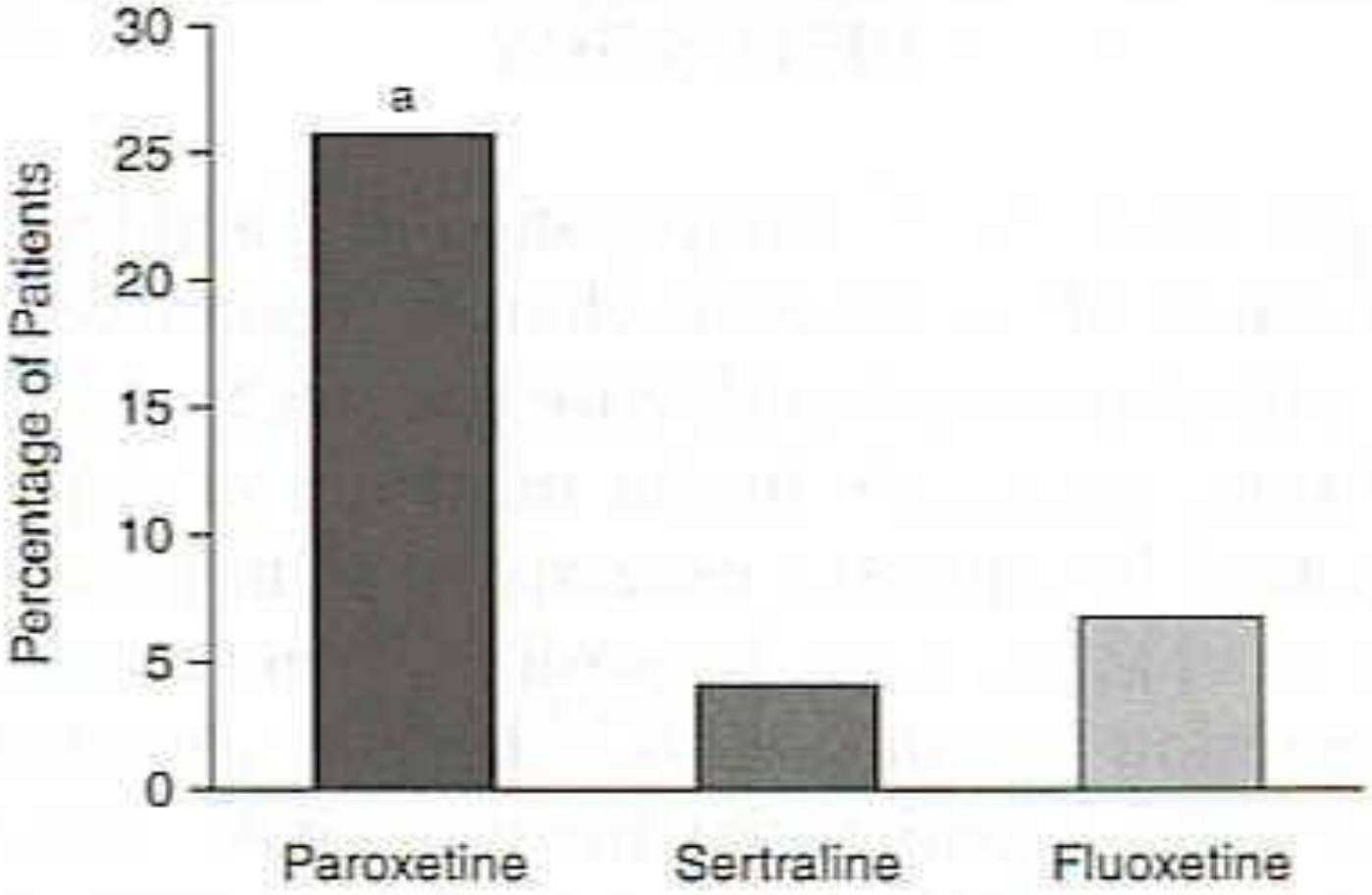
(Richards JB et al. Arch Intern Med 2007;167:188-194
Rivelli SK, Muzyk AJ. Psychopharm Review 2009;44(8):1-8.)

- Observational study of 5000 adults over age 50, of whom 137 were on SSRIs:
- Risk of Fragility Fracture increased 2.1 fold in the SSRI group, after adjustment for covariates. Effects dose-dependent
- SSRI patients also had increased falls, decreased bone mineral density.
- Note new study did not find bone loss from SSRIs: (Diem SJ. J Cl Endo & Metab 9/3/13)
- Recommendation: adequate $Ca^{++}$ intake, weight-bearing exercise, smoking cessation, and bone mineral density screening.

# Diabetes Risk with Antidepressants
(Andersohn et al. Am J Psychiatry 2009;166:591-8)

- Case-controlled observational study from U.K. General Practice examined 2,243 cases of diabetes.
- Two year use of moderate or greater dose of antidepressants increased risk of diabetes by 1.84 incidence ratio.
- **Paroxetine associated with the most diabetes among the commonly prescribed SSRIs (1.33 risk ratio)**

## Figure 2. Percentage of Patients With ≥ 7% Weight Gain at Endpoint After 26 to 32 Weeks of Therapy




[a]Significant difference for paroxetine vs. sertraline ($\chi^2 = 8.63$, df = 1, p = .003) and paroxetine vs. fluoxetine ($\chi^2 = 5.78$, df = 1, p = .016) at endpoint.

From: Fava M et al. J Clin Psychiatry 2000;61:863-7.

# Upper GI Bleeding and SSRIs

- Risk is increased by an odds ratio of 1.3 x to 6.3 x in different observational studies. NNH ~ 100.
- Risk increased to 10x or more by concomitant NSAIDs and antiplatelet agents like clopidogrel (Plavix), alcohol excess, ginkgo, & previous hx bleeding.
- Risk reduced by taking acid-suppressants like omeprazole
- SNRIs and vilazodone have same or higher risk
- **Recommend: Avoid SSRIs in high risk patients, avoid NSAIDS, instruct patients, maintain awareness**

Opatrny L. Br J Clin Pharm. May, 2008
deAbajo et al. Arch Gen Psych 2008;65(7):795-803
Loke et al. Aliment Pharmacol Ther 2008;27:31-40

# Antidepressants in Pregnancy/Lactation

(see Lattimore KA, J Perinatology 2005;25:595-604)

- Severely depressed pregnant women have higher suicide risk. Also ? low birthweight and preterm delivery of fetus.
- High risk of recurrence when antidepressants are stopped, (Cohen LS et al, JAMA Feb. 1, 2006)
- Largest observational study* showed 2.0% cardiac defects vs 1.3% without exposure with ***fluoxetine***. But, ***paroxetine*** has D safety rating since 2005 for cardiac effects. Recent studies did not confirm this.

*Malm H et al. Obstet Gynecol 2011 Jul: 118:111.

# Antidepressants in Pregnancy/Lactation - 2

- **Another concern: 6 fold increased risk of pulmonary hypertension in newborn. (Chambers CD et al NEJM 2/9/06)**
- **Mothers: Study of 5700 pregnancies found that SSRI gave gestational hypertension in 19%, pre-eclampsia in 15%, vs. 9% and 5% in pregnant control women. (Toh et al. Am J Psychiatry 2009;166:320-328)**
- **All SSRIs and bupropion are FDA category C except paroxetine - D, Nortriptyline - D.**
- **Breast feeding: lowest infant serum levels appear to be with sertraline and paroxetine**
- **Psychotherapy for mild-moderate Sx. Severe, psychotic, bipolar, suicidal depression: collaborative decision-making. (Yonkers KA et al. Gen Hosp Psychiatry 2009;31:403-)**

# Augmentations: Evidence-Base* and Costs**

| Augmentation | Evidence Rating* | Added $US Monthly Cost |
|---|---|---|
| lithium 900 mg (to TCA) | A | 1 |
| T3 25 ug (TCA or SSRI) | A | 2 |
| aripiprazole 10 mg (to SSRI) | A | 245 |
| quetiapine 300 mg (to SSRI) | A | 12 |
| risperidone 2 mg (to any) | A | 1 |
| l-methylfolate (Deplin) 15 mg | A/B | 120 |
| folate 1 mg | B | 2 |
| mirtazapine 15 mg | A/B | 2 |
| buspirone 40 mg (to SSRI) | B | 3 |
| bupropion SA 300 mg | B | 6 |
| lithium 900 mg (to SSRI) | B | 1 |
| modafinil 200 mg | B/C | 101 |
| venlafaxine SA 150 mg | C | 4 |

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

A= >1 RCTs
B= 1 RCT, plus c
C= Case series, anecdotal report, expert opinion

**US Dept. of Veterans Affairs procurement cost Sept. 11, 2014

# Some Reviews Question if Antidepressants Are Very Effective.

*Kirsch I et al. PloS Med 2008:5e45; Turner et al. NEJM 2008;358:252-60
Fournier JC et al. JAMA 2010;303(1):47-53; Khin NA. J Clin Psy 2011:72;464

- **32 randomized trials (published and unpublished) submitted to the FDA for approval of the antidepressants fluoxetine, nefazodone, paroxetine and venlafaxine produced an effect size of 0.32 and a drug-placebo difference of 1.8 points on the Hamilton Depression Rating Scale. This is of doubtful clinical significance.***
- **About one third of all antidepressant trials were never published. 33 of 36 of these studies produced either negative or questionable results.**
- **In 6 placebo-controlled trials (imipramine – 3, paroxetine – 3), there was minimal to non-existent antidepressant effect in mild to moderately ill subjects**

# Do they work? Answer

Parker G. British Journl of Psychiatry 2009;194, 1-3

- Antidepressants often do not work – but...
- Many of the studies are of extremely poor quality
- But most importantly, there are problems with the diagnostic criteria for major depression used in studies and by clinicians
  1. The more “biological” depressions that respond best to drugs are those with melancholia, especially with psychomotor retardation
  2. Milder, briefer, and personality-based depressions spontaneously remit or respond well to attention.

# Lecture Conclusions and Recommendations

- Prescribe antidepressants – when indicated and likely to be effective.
- Knowledge of drug costs and cost-effective hierarchies will increase flexibility to deal with formulary issues and benefit patients
- Consider consulting evidence-based practice guidelines and algorithms to assist with clinical decision-making

# Pre- and Post-Lecture Competency Exam

## Question 1

Which of the following is correct for the typical dosing of citalopram?

A. Begin with 20 mg per day. If no response in 2-4 weeks, increase to 40 mg per day.
B. Begin with 20 mg per day and increase after one week if tolerated, to 40 mg per day. Continue 40 mg per day for 2-4 weeks.
C. Begin with 40 mg per day. If no response in 2-4 weeks, increase to 60 mg per day.

## Question 2

Tricyclic antidepressants should be avoided with all of the following except

A. Recent myocardial infarction
B. Bundle branch block
C. Urinary retention
D. Untreated glaucoma
E. Patients hospitalized for severe melancholic depression

# Question 3

All of the following are reasonable strategies for addressing unsatisfactory response to an antidepressant, except:

A. Augmenting a partial response that is a placebo effect, by adding another medication

B. Trying a sequence of up to three monotherapy trials with different antidepressants

C. Treating insomnia/nightmares with appropriate hypnotics

D. Switching to bupropion or mirtazapine if the patient is having sexual side effects

## Question 4

All of the following augmentation strategies after unsatisfactory response to an SSRI are effective but one is very much more costly than the others:

A. Lithium

B. Tri-iodothyronine (T3)

C. Aripiprazole

D. Buspirone

E. Bupropion

## Question 5

All of the following are findings from the STAR*D study except

A. Depressed patients with high levels of anxiety respond much less well than patients with fewer anxiety symptoms
B. There was a trend toward better results with thyroid (T3) augmentation compared with lithium augmentation
C. There was a trend toward better results with venlafaxine combined with mirtazapine, compared with the MAOI tranylcypromine
D. The remission rate with citalopram was 28%

# Answers to Competency Examination

- 1 – B
- 2 – E
- 3 – A
- 4 – C
- 5 – B