

Antidepressants Cost-Effective Usage

David N. Osser, M.D.
Harvard Medical School

ASCP Model Curriculum

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 response, 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 have a similar evidence base but one is very much more costly than the others:

- A. Lithium
- B. Tri-iodothyronine (T3)
- C. Aripiprazole, quetiapine, or ziprasidone
- D. Buspirone
- E. Tricyclics

Question 5

Cost of medications for depression can be reduced by all of the following except:

- A. Avoiding expensive, brand hypnotics
- B. Refraining from use of “free” starter samples
- C. Avoiding frequent dose increases before the response at each dose has plateaued
- D. Preferring early use of “dual action” antidepressants

DISCLOSURES

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

Lecture Outline

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

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. Augmenting a placebo effect with another medication is not an optimal approach.

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 HCl 150 mg
- ◆ Duloxetine 60 mg

Other second generation

- ◆ Mirtazapine 30 mg
- ◆ Bupropion 300 mg
- ◆ Nefazodone 400 mg
- ◆ Fluoxetine + Olanzapine

SSRIs

- ◆ Prozac
- ◆ Zoloft
- ◆ Paxil
- ◆ Celexa
- ◆ Lexapro
- ◆ Luvox

SNRIs

- ◆ Effexor
- ◆ Cymbalta

Other second generation

- ◆ Remeron
- ◆ Wellbutrin, Zyban
- ◆ Serzone
- ◆ Symbvax

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

- ◆ Phenzelzine 60 mg
- ◆ Tranylcypromine 30 mg
- ◆ Isocarboxazid 40 mg
- ◆ Selegeline transdermal 6 mg

Others

- ◆ Trazodone 400 mg
- ◆ Quetiapine 300 mg

Tricyclics

- ◆ Tofranil
- ◆ Norpramin
- ◆ Pamelor
- ◆ Elavil
- ◆ Sinequan

MAOIs

- ◆ Nardil
- ◆ Parnate
- ◆ Marplan
- ◆ Emsam

Others

- ◆ Desyrel
- ◆ Seroquel

What's Reasonable to Expect in the Pharmacotherapy of Depression? The STAR-D *Remission* Results*

- ◆ Level 1: Citalopram: 28% (N=2,876) (“response”=47%)
- ◆ Level 2: Switch to sertraline 18% (N=238), bupropion 21% (N=239), venlafaxine XR 25% (N=250)
- ◆ Augment with buspirone 30% (N=286), bupropion SR 30% (N=279)
- ◆ Level 3: Switch to mirtazapine 12% (N=114), nortriptyline 20% (N=121)
- ◆ Augment with lithium 15% (N=69), thyroid 25% (N=73)
- ◆ Level 4: (N=109) tranylcypromine 7%, mirtazapine plus venlafaxine 14%

* Am J Psychiatry 1/06, 7/06, 9/06; NEJM 3/23/06

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?

General Issues on Prices of Drugs

- ◆ Depends partly on where the patient gets the medication
- ◆ Price differences vary, but usually the ranking by price is similar
- ◆ Generics are usually but not always cheaper (e.g. venlafaxine)
- ◆ Dosage regimen affects cost
- ◆ Pill strength can be important

Antidepressant Monthly Procurement Costs in the VA System – September 2009

◆ fluoxetine 20 mg	\$ 0.72
◆ citalopram 40 mg	1.74
◆ nortriptyline 100 mg	1.86
◆ mirtazapine 30 mg	2.55
◆ sertraline 100 mg	2.70
◆ paroxetine 20 mg	4.38
◆ bupropion SA 150 bid	14.00

Antidepressant Monthly Procurement Costs in the VA System – September 2009

◆ venlafaxine HCl 150 mg	12.00
◆ nefazodone 400 mg	27.00
◆ escitalopram 10 mg	27.00
◆ duloxetine 60 mg	72.00
◆ venlafaxine SA 150 mg	77.00
◆ bupropion XR 300 mg	130.00

Since many depressed patients may need a hypnotic along with their antidepressant, here is a table of options to consider.

Drugs Used as Hypnotics in the VA System

(Monthly Procurement Cost, September 2009)

◆ amitriptyline 10 mg	\$ 0.42
◆ trazodone 50 mg	0.53
◆ lorazepam 2 mg	0.78
◆ doxepin 25 mg	1.87
◆ zolpidem 10 mg	2.13
◆ mirtazapine 30 mg	2.55

Drugs Used as Hypnotics in the VA System

(Monthly Procurement Cost, September 2009)

◆ zaleplon (Sonata) 10 mg	13.00
◆ quetiapine 50 mg	14.00
◆ eszopiclone (Lunesta) 1, 2, or 3 mg	50.00
◆ ramelteon (Rozerem) 2 mg	60.00

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

- ◆ Conclusion of meta-analysis of 46 randomized, controlled trials of antidepressants: “Selection of initial treatment might be based on cost” unless there are individual patient preferences based on “expected” side effects.*
- ◆ First choice SSRIs for cost-effective prescribing are citalopram, fluoxetine or sertraline for adults, children and adolescents.
- ◆ * Hanson RA et al. Ann Int Med 2005;143:415-426

Prescribing Cost-Effectively for Depression - 2

- ◆ For the **elderly**: fluoxetine is the only SSRI with an FDA indication.
- ◆ ECGS – (Physicians' Postgraduate Press) endorsed sertraline and citalopram as first line due to fewer drug interactions.

Dosing Strategies: General

- ◆ Avoid frequent dose increases but make contact with patient every 1-2 weeks, as recommended in the 2000 APA Practice Guidelines for Tx of Depression
- ◆ Wait 2-4 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.

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 2-4 weeks if tolerated. If no/partial plateaued response, increase to 60 mg. Change if no response to 60 in 2-4 weeks.
- ◆ 20 mg daily appears to be not different from placebo*

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

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 2-4 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 Sertraline

- ◆ Start with 50 mg in AM (25 mg for elderly, and those with panic disorder, etc.)
- ◆ Maintain 50 mg/day for 2-4 weeks before increasing. If no/partial plateaued response increase in 50 mg increments every 2-4 weeks. Change if no response at 200 mg for 2-4 weeks
- ◆ 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 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 2-4 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 Bupropion SR

- ◆ Contraindicated in patients with history of seizures, 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** (expensive once-daily preparation), PDR max. is 450 mg

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 2-4 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 Nefazodone

- ◆ Begin with 50 mg bid
- ◆ Increase to 100 mg bid after 2-4 days, and to 100 mg tid after 2-4 days; Maintain 100 mg tid for 2 weeks before further increase; if no/partial plateaued response, increase in 100 mg increments to maximum tolerated dose up to 300 bid.
- ◆ Change if no response to 500-600 mg/d for 2-4 weeks.

Nefazodone – Liver Issues

- ◆ 23 reports of liver failure (16 resulted in death or transplantation, out of 8 million patients treated).
- ◆ With risk of $< 1:350,000$ it still has a role. Sedation, low sexual side effects are benefits in some patients
- ◆ Serzone manufacturer stopped production but generic available

Dosing Venlafaxine XR

- ◆ 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)
- ◆ Side effects may be diminished by taking with food according to unpublished data (Schatzberg et al 2007)
- ◆ Like the other “SNRI” venlafaxine, it raises blood pressure but probably not as much

Dosing Tricyclics – e.g. nortriptyline (best)

- ◆ 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.

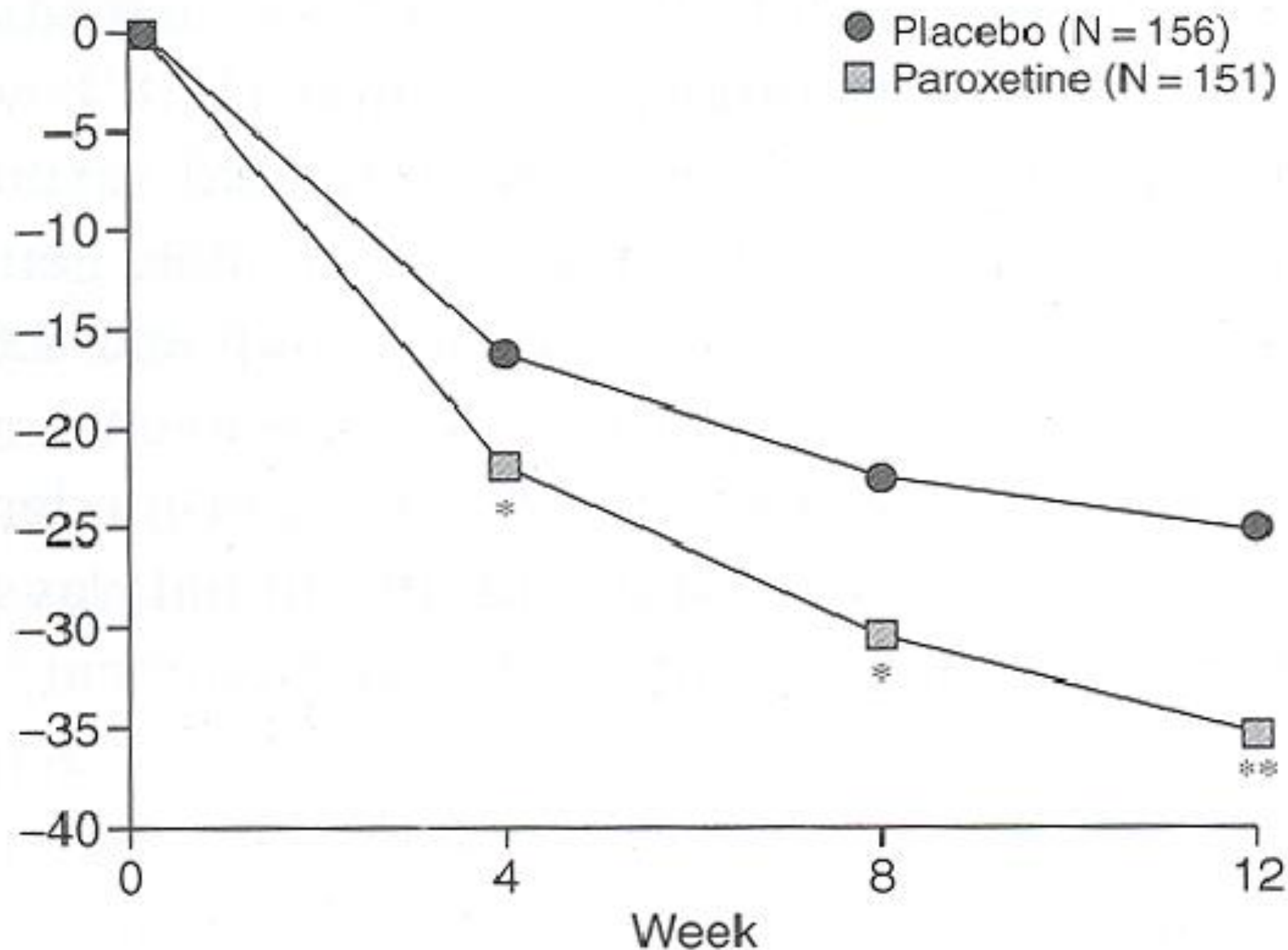
Dosing the MAOI tranylcypromine

- ◆ 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.

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 cost-effective.

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



“Poop-out.” How much is 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.
- ◆ This was a meta-analysis of acute followed by continuation studies of SSRIs vs placebo.
- ◆ Using a formula by Quitkin et al (1993), he found that most relapses during continuation treatment seem to occur in patients who were not true drug responders

Switching Antidepressants

- ◆ Fluoxetine can be abruptly stopped.
- ◆ Paroxetine (regular release) and venlafaxine have the most withdrawal symptoms: tremor, nightmares, dizziness, nausea, disorientation
- ◆ If the next medication is a substrate for 2D6 e.g. bupropion, and the medication stopped is fluoxetine, start at lower dose. There may be seizure risk with bupropion.

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, nefazodone (liver risk).
- ◆ **Add-ons:** Cochrane Review (2004,5) found sildenafil was clearly better than placebo (in men only). There also was support for tadalafil. More recently 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 agent.”²
- ◆ Benzodiazepine, for patient with no substance abuse history.
- ◆ Consider doxepin 10-25 mg.
- ◆ Antihistamines: problem of tolerance
- ◆ Quetiapine: problem of the “munchies”

¹Sleep Med 2004 Jan;5(1):7-8

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

Sweating

- ◆ 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.
 - Risk increase is up to 2 fold
 - 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 pre-warning levels.
- ◆ **Adults >24:** No FDA warning. Some studies show small suicide effect (Arch GS Dec. 2006:1358-67) and some do not (Am J Psych Jan. 2006:41-47)

Suicidal Ideation from Antidepressants: How to recognize.

- ◆ Instruct patient to pay close attention to any changes, especially sudden, in mood, behavior, thoughts or feelings
- ◆ Call prescriber right away if any thoughts of suicide or dying, or suicide attempts
- ◆ Call if worsened anxiety, depression, sleep, agitation, irritability, anger, or extreme increase in activity
- ◆ Meet with or at least speak to patient weekly for the first month, biweekly for the second month.

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.)

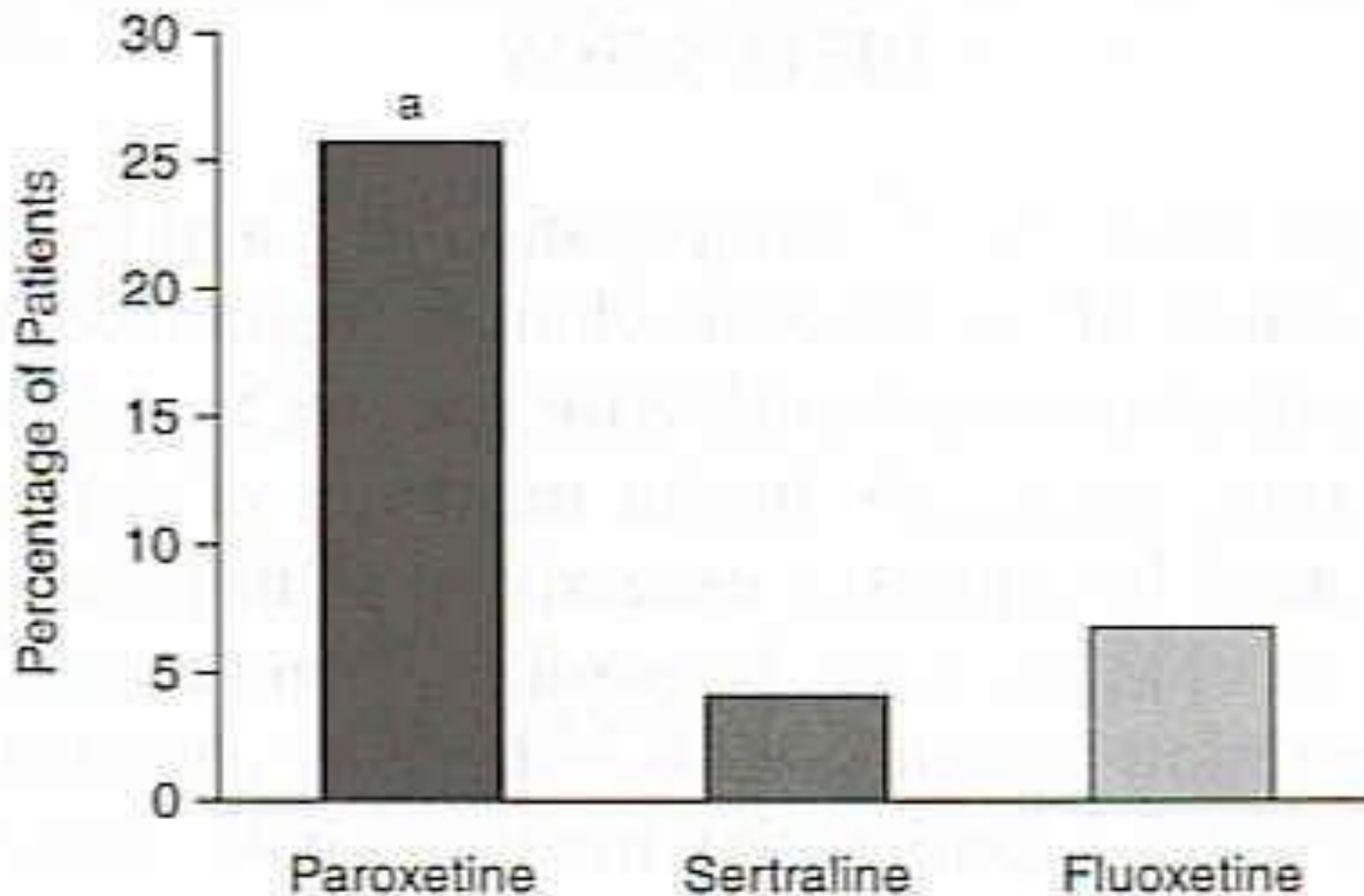
- ◆ Observational study of 5000 adults over age 50, of whom 137 were on SSRIs:
- ◆ Risk of Fragility Fracture increased 2.1 fold in the SSRI group, after adjustment for covariates.
- ◆ Effects were dose dependent
- ◆ SSRI patients also had increased falls, decreased bone mineral density.
- ◆ Recommendation: adequate Ca^{++} intake, weight-bearing exercise, smoking cessation, and BMD 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 ratio)

Figure 2. Percentage of Patients With $\geq 7\%$ Weight Gain at Endpoint After 26 to 32 Weeks of Therapy



^aSignificant 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 could be as low as 100
- ◆ Risk increased by concomitant NSAIDs and antiplatelet agents like clopidogrel (Plavix), alcohol excess, and previous history of bleeding
- ◆ Venlafaxine may have higher risk than SSRIs
- ◆ 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 - 1

(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)
- ◆ Latest large observational study* showed 0.9% cardiac septal defects vs 0.5% in controls. Odds ration 2.0 for all SSRIs. Paroxetine got a D safety rating in 2005 for cardiac effects but all seem to do it.

*Pederson LH et al. BMJ 2009 Sep 23;339:b3525

Antidepressants in Pregnancy/Lactation - 2

- ◆ Another concern: 6 fold increased risk of pulmonary hypertension in newborn. (Chambers CD et al NEJM 2/9/06)
- ◆ 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
- ◆ Use psychotherapy for mild-moderate depression*
- ◆ 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	2
T3 25 ug (TCA or SSRI)	A	17
Abilify 10 mg (to SSRI)	A	96
Risperdal 2 mg (to any)	A	105
mirtazapine 15 mg	A/B	2
bupirone 40 mg (SSRI)	B	4
bupropion SA 300 mg	B	14
lithium 900 mg (to SSRI)	B	2
Seroquel 300 mg	B	105
Zyprexa 10 mg	B	204
Provigil 200 mg	B/C	138
nortriptyline 100 mg	C	2
pindolol 10 mg	C	2
Effexor SA 150 mg	C	77

*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
September 2009

Role of Psychotherapy

(Parker G, 2005: Modelling and Managing Depressive Disorders)

- ◆ The non-specific aspects of care: very effective
- ◆ Psychotherapy (cognitive, psychodynamic): very effective
- ◆ In Non-melancholic depression (psychomotor retardation absent; mood very reactive) – acute and chronic stress and personality type affect vulnerability. Psychological interventions can be particularly important:
 - Perfectionist personality type
 - Anxious-Worrying type
 - Irritable type
 - Socially avoidant type
 - Rejection sensitive type
- ◆ Depressive reactions to losses – should not be diagnosed major depression and automatically given medication.

(Wakefield JC et al. Arch Gen Psychiatry 2007;433-440)

Some Recent Reviews Question if Antidepressants Are Very Effective.

*Kirsch I et al. PloS Med 2008;5:e45; Turner et al. NEJM 2008;358:252-60
Fournier JC et al. JAMA 2010;303(1):47-53

- ◆ 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 antidepressants work?

Answer #1

Mathew SJ and Charney DS. Am J Psychiatry 2009;166:140-5

- ◆ Inclusion of these unpublished negative studies changes things: with them, antidepressants in fact do not seem to work very well.
- ◆ However, mean change score differences do not capture patient differences very well. Measuring “Percent Responders” is better. Data are incomplete, but there is some suggestion that results are slightly more favorable.
- ◆ We need better antidepressants and study methods

Do they work?

Answer #2

Parker G. British Journal 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.

Conclusions and Recommendations

- ◆ Prescribe antidepressants – when indicated.
- ◆ 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 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 response, 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 have a similar evidence base but one is very much more costly than the others:

- A. Lithium
- B. Tri-iodothyronine (T3)
- C. Aripiprazole, quetiapine, or ziprasidone
- D. Buspirone
- E. Tricyclics

Question 5

Cost of medications for depression can be reduced by all of the following except:

- A. Avoiding expensive, brand hypnotics
- B. Refraining from use of “free” starter samples
- C. Avoiding frequent dose increases before the response at each dose has plateaued
- D. Preferring early use of “dual action” antidepressants

Answers to Competency Examination

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