Antidepressants 2007 Cost-Effective Usage

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

ASCP Model Curriculum

1/13/2020

January 2008 Version

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. Risperidone, 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

- Speaker 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**

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 – July 2007

citalopram 40 mg	$ 0.60
fluoxetine 20 mg	0.90
sertraline 100 mg	1.80
nortriptyline 100 mg	2.00
mirtazapine 30 mg	3.30
bupropion SA	4.20
paroxetine 20 mg	9.00

Antidepressant Monthly Procurement Costs in the VA System – July 2007

- **nefazodone 400 mg 29.00**
- **Lexapro 20 mg 41.00**
- **Cymbalta 60 mg 64.00**
- **Effexor SA 150 mg 67.00**
- **venlafaxine 150 mg 88.00**
- **bupropion XR 300 mg 104.00**

Drugs Used as Hypnotics in the VA System
(Monthly Procurement Cost, July 2007)

amitriptyline 10 mg	**$ 0.40**
doxepin 25 mg	**0.50**
trazodone 50 mg	**0.60**
zolpidem 10 mg	**0.83**
lorazepam 2 mg	**2.00**
mirtazapine 30 mg	**3.30**

Drugs Used as Hypnotics in the VA System
(Monthly Procurement Cost, July 2007)

- **quetiapine 50 mg** **13.00**
- **eszopiclone (Lunesta) 1, 2, or 3 mg** **44.00**
- **zaleplon (Sonata) 10 mg** **56.00**
- **ramelteon (Rozerem) 2 mg** **42.00**

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

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

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

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 response increase in 50 mg increments every 4 weeks. Change if no response at 200 mg for 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 4 weeks. If no response, increase in 20 mg increments every 4 weeks as tolerated (Fava M et al. J Clin Psychopharmacol 2002; 22:379-387)
- Give up if no improvement after 4 weeks at 60 mg/d
- Partial response: difficult to interpret. Try to determine if it was due to non-specific (placebo) effects.

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 response, increase to 200 bid (PDR maximum 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 response increase to 45 mg (PDR maximum).
- Change if no response to 45 mg after 2-4 weeks
- 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 response that has plateaued, 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 generics still 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 for 3 weeks before increase
- If no/partial response that has plateaued, increase in 75 mg increments every 2 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.

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, untreated glaucoma, renal failure, orthostasis
- Obtain baseline EKG. If bundle branch block, risk of serious arrhythmia is higher.
- Begin with 10 mg tid or 25 mg hs. (5 tid 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.

Duloxetine Dosing

- Begin with 40 mg daily in single or divided dose (may help with nausea)
- After 3-7 days, increase to 60 mg in single or divided dose
- If no response/partial response that plateaus after 4 weeks at 60 mg, you could consider going to 120 mg daily but no evidence confirms that this is an effective strategy.
- Side effects may be diminished by taking with food according to unpublished data cited by Schatzberg et al 2007
- Like the other “SNRI” venlafaxine, it raises blood pressure but probably not as much

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.

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 studies* show only very small risks of birth defects and no association with fetal heart defects, even though paroxetine got a D rating in 2005 because of earlier data suggesting the latter.

(*NEJM June 28, 2007;2675-92)

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
- Summary: Antidepressants in Pregnancy: “Scylla vs Charybdis” (Rubinow DR. Am J Psychiatry 2006;163:954-6)

Side Effect Management

- **Sexual side effects**, a significant problem in primary care patients:[1] switch, to bupropion, mirtazapine, nefazodone (liver risk). Cochrane Review (2004) found only sildenafil clearly better than placebo (in men only) as add-on.
- **Insomnia/nightmares**: trazodone 25-100 mg is cost-effective,[2] or benzodiazepine for patient with no substance abuse history. Consider amitriptyline 10 mg or doxepin 12.5-25 mg. Avoid antihistamines.
- **Sweating**: Benztropine 0.5 mg bid, clonidine 0.1 mg bid, ?terazosin 1-5 mg/d

[1]JAMA 2003 July 2:57-65.

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

SUICIDAL IDEATION AS A SIDE EFFECT: THE CONTROVERSY

- **Children and adolescents:** FDA warning, which was recently extended to young adults up to 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:** No FDA warning now. Some studies show small suicide effect (Arch GS Dec. 2006:1358-67) and some do not (Am J Psych Jan. 2006:41-47)

The Risk of Suicide with SSRIs in the Elderly
(Juurlink DN et al. Am J Psychiatry 2006;163:813-821)

- An FDA analysis (2006) suggested that, in clinical trials, the risk of suicidal ideation is lowest in those over 65.
- However: consider this population study of 1 million Ontario, Canada residents over age 65
- Found 1,329 suicides. Of these, 32% received an antidepressant in the 6 months prior to their death. Matched them to comparison subjects on 50 suicide propensity factors
- During the first month of treatment with SSRIs, there was a 5-fold higher suicide rate compared with non-SSRIs. (NS in women)

Risk of Suicide on SSRIs in the Elderly - II

- In the subsequent months, there was no difference in the suicide rate.
- SSRIs were more strongly associated with suicides of a violent nature.
- *Absolute* risk of suicide on SSRI was low: 1 in 3,353 SSRI-treatment patients. Risk was transient.
- Assuming that the many of the untreated patients might not have committed suicide if given an SSRI, the benefits of treating are probably much greater than the risk of death from the SSRI
- Possible mechanisms: akathisia-like symptoms or dysphoria from SSRI, genetic influence on tolerability/response

INCRASED FRACTURE RISK WITH SSRIs

(Richards JB et al. Arch Intern Med 2007;167:188-194)

- 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.

Unsatisfactory Response

- If unsatisfactory response, switching is sometimes more cost-effective than augmentation and equally efficacious.
- Two-thirds of depressed patients experience *remission* (HamD of 7 or <) with three monotherapies in sequence.[1,2] Switch to same or different chemical class

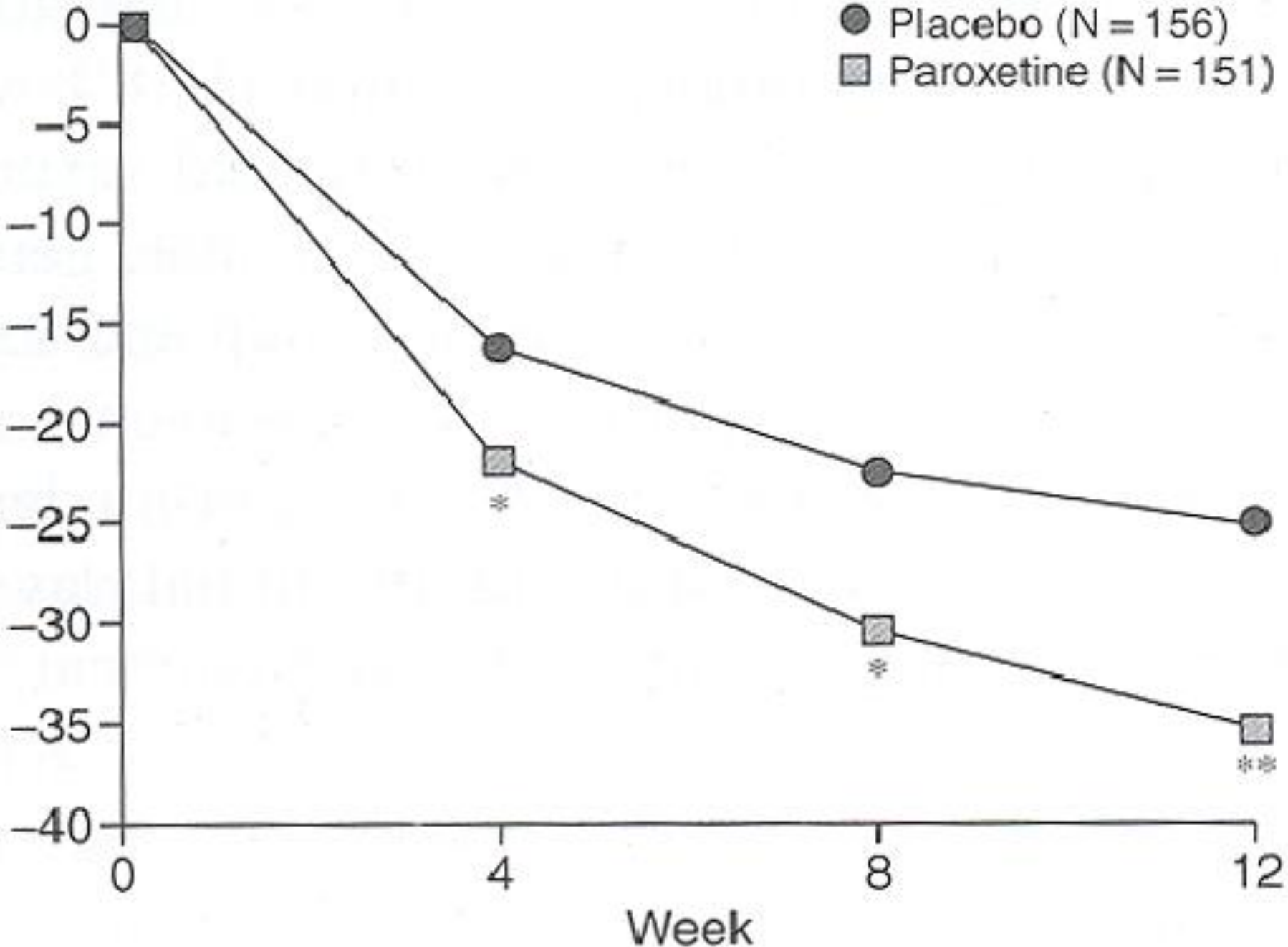
[1]**Quitkin JW et al. J Clin Psychiatry 2005;66:670-6**

[2]**Star*D: Am J Psychiatry 1/06, 7/06, 9/06; NEJM 3/23/06**

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**


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

“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

More on non-specific/placebo effects: Antidepressants for Depression in Patients with Acute Coronary Syndrome (ACS)

(Glassman AH et al. Arch Gen Psychiatry 2006;63:283-288)

- 369 patient admitted to medicine with ACS & depression.
- Randomized, placebo-controlled trial of sertraline.
- Predictors of sertraline efficacy:

  - The major depression started *before* the episode of ACS (found in 53% of patients – so the depression may have contributed to the ACS in these cases);

  - those with very severe depression;

  - those with *past history* of depression.

- No efficacy for sertraline compared with placebo *when first onset of depression was during the ACS*.

  - high placebo response: adjustment disorder

Augmentations: Evidence-Base and VA Costs

Augmentation	Evidence Rating*	Added $ Monthly Cost
lithium 900 mg (to TCA)	A	2
T3 25 ug (TCA or SSRI)	A	3
Abilify 10 mg (to SSRI)	A	175
mirtazapine 15 mg	A/B	3
buspirone 40 mg	B	4
bupropion SA 300 mg	B	4
lithium 900 mg (to SSRI)	B	2
Zyprexa 10 mg	B	189
Provigil 200 mg	B/C	110
nortriptyline 100 mg	C	2
pindolol 10 mg	C	2
Effexor SA 150 mg	C	67
other atypicals	A-C	70-158

*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
D= Anecdotal reports but experts have not endorsed

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)

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. Risperidone, 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