Antidepressants 2006 Cost-Effective Usage

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ASCP Model Curriculum

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Pre- and Post-Lecture Competency Exam

Question 1

Problems with using clinical experience as a guide to future treatment include all of the following except:

A. Investigator Bias: we see what we want to see

B. Failure to recall negative experiences

C. The patient to be treated now is not really similar to the patient(s) treated before

D. Many important treatments have been discovered through clinical experience

Question 2

True or False

Sertraline cost 43 times as much as fluoxetine in the VA Healthcare system in 2005. (procurement cost)

Question 3

Fluoxetine and citalopram are the most cost-effective options for treating depression in all of the following except:

A. Breast feeding mothers
B. Geriatric patients
C. Children and Adolescent patients
D. Adult patients

Question 4

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 5

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 6

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 7

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 8

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.
- Speaker is employed full time by public mental health agencies.
- Off-label indications will be noted and discussed

Lecture Outline

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

Why is it so hard to practice cost-effective psychopharmacology?

- Drug companies are shaping our decision making
  1. Clinical trials bias
  2. Industry-sponsored education
  3. Influence of gifts
  4. Relationships between authors of practice guidelines and the pharmaceutical industry

Common Alternative to EBM: CLINICAL EXPERIENCE

- Definition: Making the same mistakes over and over with increasing confidence over an impressive number of years.
- Investigator bias
- Memories of the experiences are unreliable

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 – March 2006

fluoxetine 20 mg	$ 0.83
nortriptyline 100 mg	2.00
citalopram 40 mg	5.00
mirtazapine 30 mg	8.00
nefazodone 400 mg	8.00
paroxetine 20 mg	18.00

Antidepressant Monthly Procurement Costs in the VA System – March 2006

Lexapro 20 mg	30.00
Zoloft 100 mg	36.00
bupropion SA 300 mg	42.00
venlafaxine 150 mg	60.00
Effexor SA 150 mg	54.00
Cymbalta 60 mg	60.00

Antidepressant Monthly Procurement Costs in a large local HMO

February 2005

fluoxetine 20 mg	$ 1.00
citalopram 40 mg	7.00
paroxetine 20 mg	18.00
Lexapro 20 mg	50.00
Zoloft 100 mg	72.00
bupropion XL 300 mg	73.00
Cymbalta 60 mg	77.00
Effexor XR 150 mg	81.00
Symbyax 12/25 mg	289.00

Antidepressant Monthly Costs to Consumer at a Local Retail Pharmacy – no insurance

November 2005

Drug	Monthly cost
fluoxetine 20 mg	$ 25.00
citalopram 40 mg	50.00
paroxetine 20 mg	50.00
mirtazapine 15 mg	60.00
Lexapro 20 mg	90.00
Zoloft 100 mg	100.00
Paxil CR 25 mg	110.00
Cymbalta 60 mg	124.00
Effexor XR 150 mg	126.00
Wellbutrin SR 300 mg	145.00

Drugs Used as Hypnotics in the VA System
(Monthly Procurement Cost, March 2006)

Drug	Cost
amitriptyline 10 mg	$ 0.40
doxepin 25 mg	0.50
trazodone 50 mg	0.60
lorazepam 2 mg	2.00
prazosin 5 mg	2.00
mirtazapine 30 mg	8.00

Drugs Used as Hypnotics in the VA System
(Monthly Procurement Cost, March 2006)

quetiapine 25 mg	15.00
gabapentin 600 mg	21.00
zolpidem (Ambien) 10 mg	41.00
zaleplon (Sonata) 10 mg	43.00
eszopiclone (Lunesta) 1, 2, or 3 mg	44.00
ramelteon (Rozerem) 8 mg	46.00

Expensive Drug Treatment Strategies for Depression

- Use of “free” starter samples
- 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.

Prescribing Cost-Effectively for Depression - 1

- 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 SSRI for cost-effective prescribing is fluoxetine for adults, children and adolescents. Second choice citalopram

* 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.
- Some experts (ECGS – Physicians' Postgraduate Press) have endorsed citalopram and sertraline as first line, but note editors' conflicts of interest.
- Citalopram is now inexpensive.

Prescribing Cost-Effectively for Depression - 3

- Only one randomized, prospective comparison of sertraline and fluoxetine in the elderly*: 236 patients, 12 weeks.
- Equal response rates (> 70%).
- No safety differences.
- Several measures showed better cognition with sertraline (not a primary outcome measure, and clinical significance questionable). Dose of fluoxetine 20-40 was somewhat high for the elderly. Sertraline was 50 to 100.

*Newhouse et al. J Clin Psychiatry 2000;61:559-68

Prescribing Cost-Effectively for Depression - 4

- There are P450 2D6 blockade issues with fluoxetine, but for most patients this is not a problem. One study – 15% (Gregor KJ et al. J Affect Disord 1997;46:59-67)
- Some drugs that are 2D6 substrates: codeine, risperidone, beta-blockers
- Adjust dose or use other alternatives. See www.genelex.com for online drug interaction information.

Dosing Strategies

- Avoid frequent dose increases but make contact with patient every 1-2 weeks, as recommended in the APA Practice Guidelines for Tx of Depression
- Wait 4 weeks with total non-response (or partial response that has plateaued) before increasing. Change if no response after 4 weeks at 60 mg fluoxetine per day (for adults).
- Wait 8-12 weeks if gradual response that has not plateaued
- When clinically necessary, may have to make above changes earlier than 4 weeks.

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. If so, switch. If not, augment

Dosing Citalopram

- Begin 20 mg in AM, 10 mg for elderly, unprecipitated panic attacks, etc.
- 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.

Dosing Bupropion SR

- Begin with 100-150 mg qAM
- Increase to 100-150 mg bid after 4-7 days;
- Maintain 150 bid for 4 weeks before increasing. If no/partial response, increase to max. of 200 bid. Change if no response to 400/d for 4 weeks

Dosing Mirtazapine

- Begin with 15 mg qPM
- Continue for 4 weeks before increase. If no/partial response increase in 15 mg increments every 4 weeks. Change if no response to 45 mg after 4 weeks

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 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

- Start with 37.5 mg – 75 mg in AM
- Increase to 75 –150 mg/day after two weeks; maintain 75-150 mg/d for 4 weeks before increase
- If no/partial response that has plateaued, increase in 37.5 to 75 mg increments every 2-4 weeks.
- Change if no response after 4 weeks at 225 mg/day

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 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. Check at least one blood level to rule out slow metabolism and risk of fatal cardiac toxicity.
- Begin nortriptyline10 mg bid or tid. (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.

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)
- Most (but not all) studies show no increased fetal abnormalities or pregnancy loss with fluoxetine. Other SSRIs: fewer data, but similar safety. Exception: paroxetine - associated with fetal heart defects.

Antidepressants in Pregnancy/Lactation - 2

- Most recent concern: 6 fold increased risk of pulmonary hypertension in newborn (Chambers CD et al NEJM 2/9/06)
- All SSRIs are FDA category C except paroxetine which was reclassified D in Dec. '05. Bupropion - B. Nortriptyline - D.
- Breast feeding: lowest infant serum levels appear to be with sertraline and paroxetine (though latter has the "D")

Unsatisfactory Response - 1

- If unsatisfactory response, switching is 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] Switch to same or different chemical class

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

Unsatisfactory Response - 2

- **Sexual side effects**, a significant problem in primary care patients:[2] switch, to bupropion or mirtazapine (nefazodone if appropriate).
- **Insomnia/nightmares**: trazodone 25-100 mg is cost-effective,[3] or benzodiazepine for patient with no substance abuse history. Consider amitriptyline 10 mg or doxepin 25 mg. Avoid antihistamines.

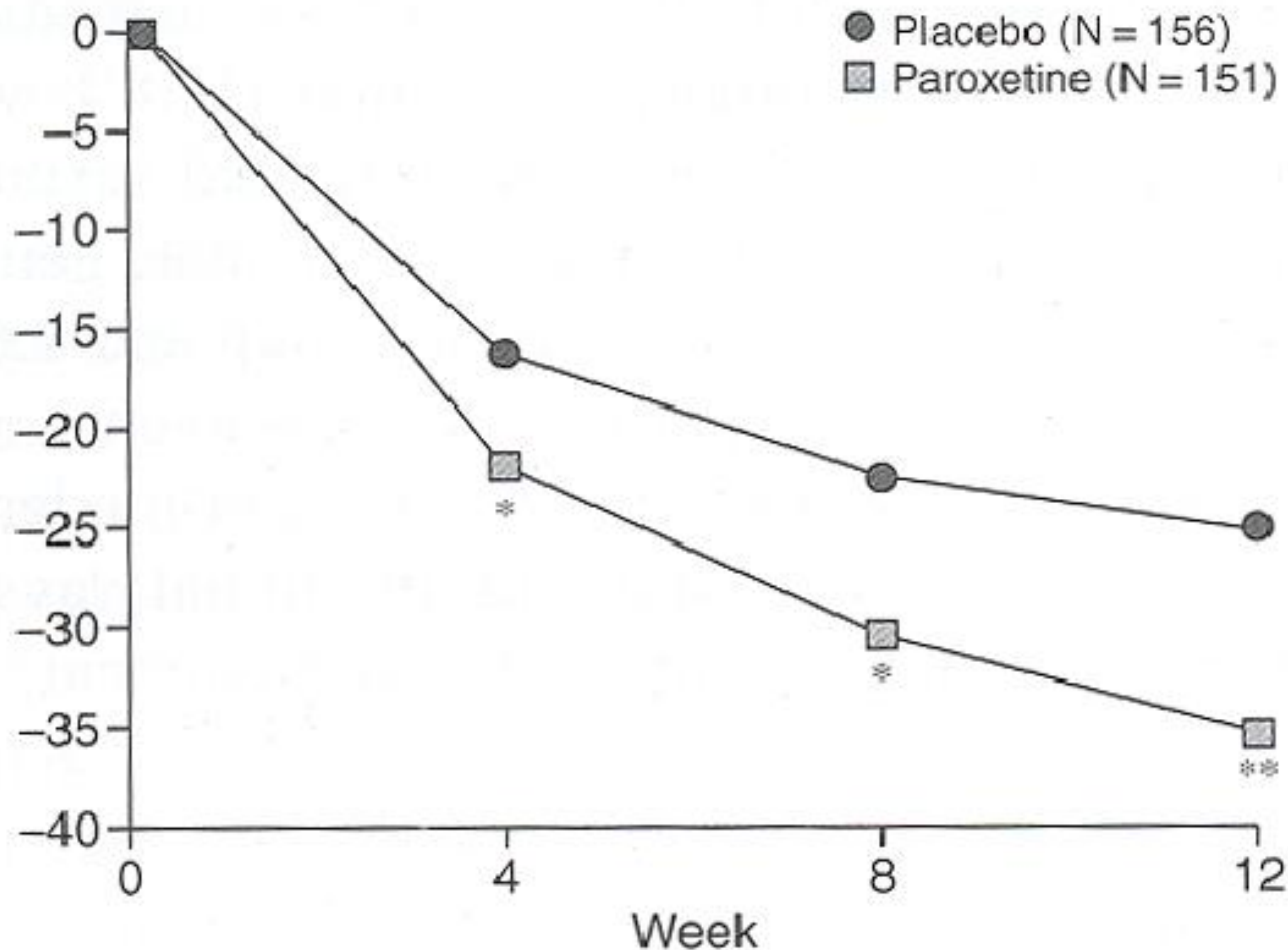
[2] JAMA 2003 July 2:57-65.

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

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**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Augmentations: Evidence-Base and VA Costs

Augmentation	Evidence Rating*	Added $ Monthly Cost
lithium 900 mg (to TCA)	A	2
T3 25 ug (to TCA)	A	3
mirtazapine 15 mg	A/B	18
buspirone 40 mg	B	4
Wellbutrin SR 300 mg	B	42
Zyprexa 10 mg	B	172
Provigil 200 mg	B/C	110
nortriptyline 100 mg	C	2
pindolol 10 mg	C	2
lithium 900 mg (to SSRI)	C	2
T3 25 ug (to SSRI)	C	3
Effexor XR 150 mg	C	54
other atypicals	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

Conclusions and Recommendations

- Knowledge of drug costs and cost-effective hierarchies will increase our flexibility to deal with formulary issues and benefit our patients
- Consider consulting evidence-based practice guidelines and algorithms to assist with clinical decision-making

www.mhc.com/Algorithms

www.genelex.com

Pre- and Post-Lecture Competency Exam

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Answers to Competency Examination

- Question 1 – D
- 2 – True
- 3 – A
- 4 – B
- 5 – E
- 6 – A
- 7 – C
- 8 – D