ANTIPSYCHOTICS 2006
COST-CONSCIOUS USAGE

ASCP Model Curriculum

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Pre-Lecture Exam Question 1

1. Which of the following is an antipsychotic dose that is in excess of the optimal?

   A. Aripiprazole 15 mg/day

   B. Ziprasidone 80 mg bid

   C. Haloperidol 20 mg qd

   D. Risperidone 4 mg/day

   E. Quetiapine 300 mg bid

Question 2

2. Which of the following antipsychotics must be taken with food in order to prevent significant loss of absorption?

   A. Ziprasidone

   B. Olanzapine

   C. Clozapine

   D. Aripiprazole

   E. Risperidone

Question 3

3. Which of the following is the recommended starting dose for clozapine?

   A. 25 mg twice a day

   B. 12.5 mg

   C. 25 mg

   D. 50 mg

Question 4

4. All of the following are true of a patient on risperidone who gets parkinsonian side effects, except:

   A. D2 receptor occupancy is 75% or more

   B. The patient is above the “neuroleptic threshold”

   C. Patient is at risk for secondary negative symptoms

   D. Raising the dose is likely to be helpful

Question 5

5. All of the following are true of olanzapine, in Phase 1 of the CATIE study, except

   A. Had superior effectiveness to the others

   B. Produced the most weight gain

   C. Elevated Hemoglobin A1C the most

   D. Increased triglycerides the most

   E. Average dose was above the PDR max.

Outline of Lecture

- Introduction
- Algorithm for selecting antipsychotics
- How to give trials of antipsychotics
- Prescribing antipsychotics in dementia
- Cost-conscious use of antipsychotics and medications added to antipsychotics
- Post-lecture questions and answers

Recommended Handbook

- Taylor RO et al. **2005-2006 Maudsley Hospital Psychopharmacology Practice Guidelines.** 8th edition. Taylor & Francis Press. 1-800-634-7064. $36. Paperback.
- Chapter 2, pp 7-106 on Schizophrenia

Goals of Treatment

- Recovery and normalized activity are the goals of adequate antipsychotic trials.
- Response short of this should be considered unsatisfactory.
- If response is unsatisfactory, review diagnosis, psychosocial factors, and investigate behavioral toxicity

Basic Algorithm For Selection of Antipsychotics in Schizophrenia*

- Begin with aripiprazole, risperidone, or ziprasidone
- If patient had 4-6 week trial with full dose, but response unsatisfactory, try olanzapine next due to its better efficacy.
- If patient intolerant/unable to complete trial of initial agent, try another and then another until you get an adequate trial.
- After 2 or 3 adequate **monotherapy** trials (1 of which should be olanzapine), try clozapine

*Osser DN. Editor Comment on CATIE Study Phase One Results. Cogent Medicine, Oct. 1, 2005. Go to cogentmedicine.com: full URL on notes pg.

Evidence-Based Algorithms On Line

- International Psychopharmacology Algorithm Project (www.ipap.org)
- Algorithm Project at the Harvard South Shore Department of Psychiatry (www.mhc.com/Algorithms)
- Texas Medication Algorithm Project (www.dshs.state.tx.us/mhprograms/TIMA.shtm)

Ziprasidone – caveats from package insert

- Avoid ziprasidone if EKG shows QTc is >500 milliseconds
- On medications that might prolong the QTc since this EKG was done? (tricyclics, quetiapine, thioridazine, floxacins.) If so, repeat EKG
- Check pulse. Low pulse risks Torsades. Is the patient on a drug that lowers pulse? (Beta-blocker – often; SSRI – infrequently)
- Risk for electrolyte problems? (alc. Dependent, purging bulimic) If so, get K+, Mg++ and follow
- History of arrhythmias? Get medical clearance.

Dosing of Ziprasidone - 1

- Package insert recommends starting at 20 mg twice daily, but 3/4 acute treatment studies in patients with schizophrenia failed to show superiority of 20 mg bid to placebo.
- Stable outpatient being switched: could start with 40 mg bid.
- Absorption is reduced by 40% if not taken with food

Dosing of Ziprasidone - 2

- At 40 mg bid and especially at 80 mg bid, robust superiority to placebo is seen. In CATIE it was 110 mg/day, and ziprasidone underperformed a bit
- So, raise the dose, as tolerated, every 1-2 days to 80 bid for the routine case of an acutely ill hospitalized patient with schizophrenia
- If this is a first episode patient, try perhaps half the routine dose.

Ziprasidone Side Effects

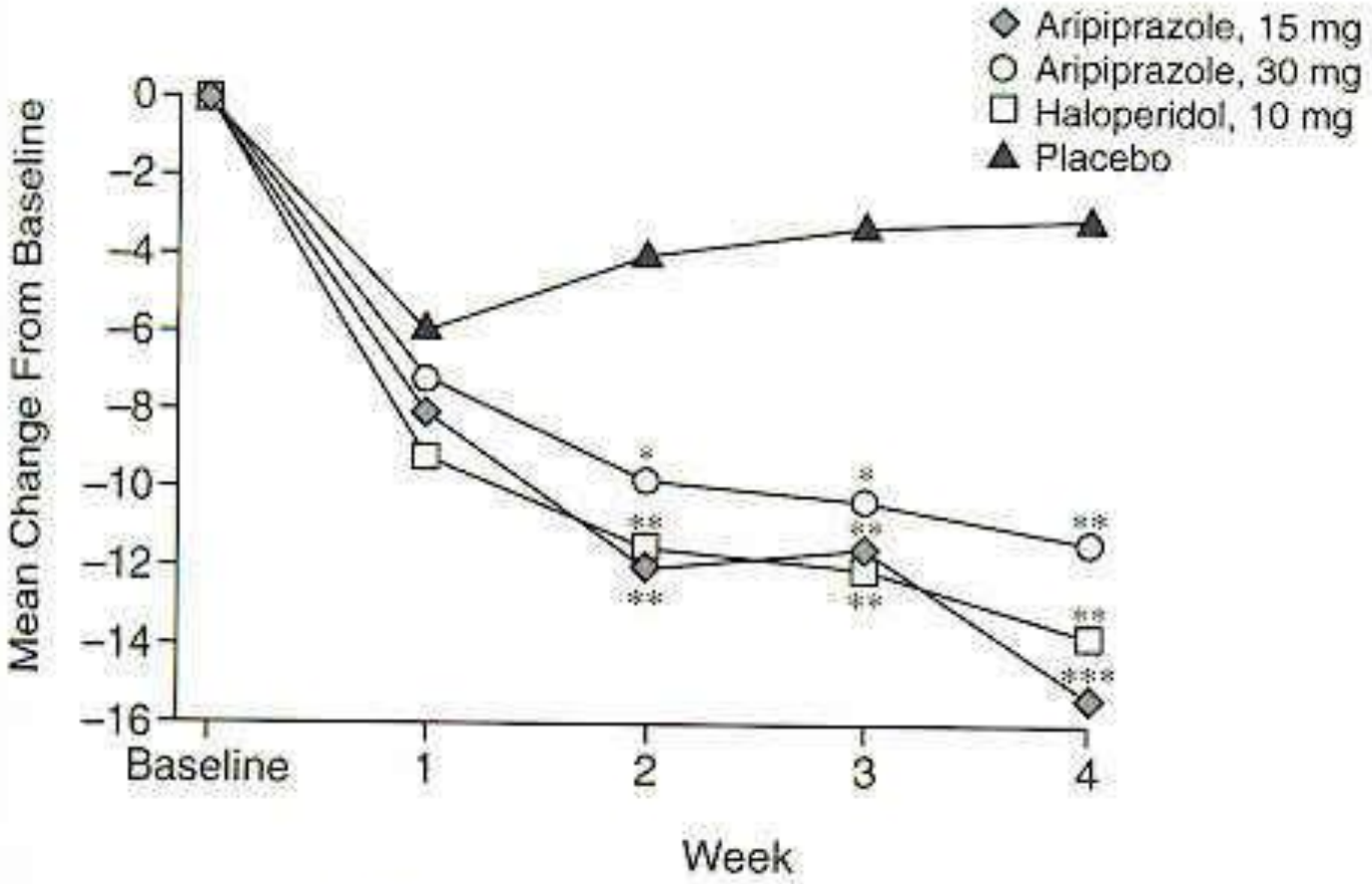
- Activation, especially at low doses
- Sedation
- Nausea, dry mouth
- EPS occasionally
- No QTc problems were seen in CATIE compared to the others

Aripiprazole – Dosage Issues

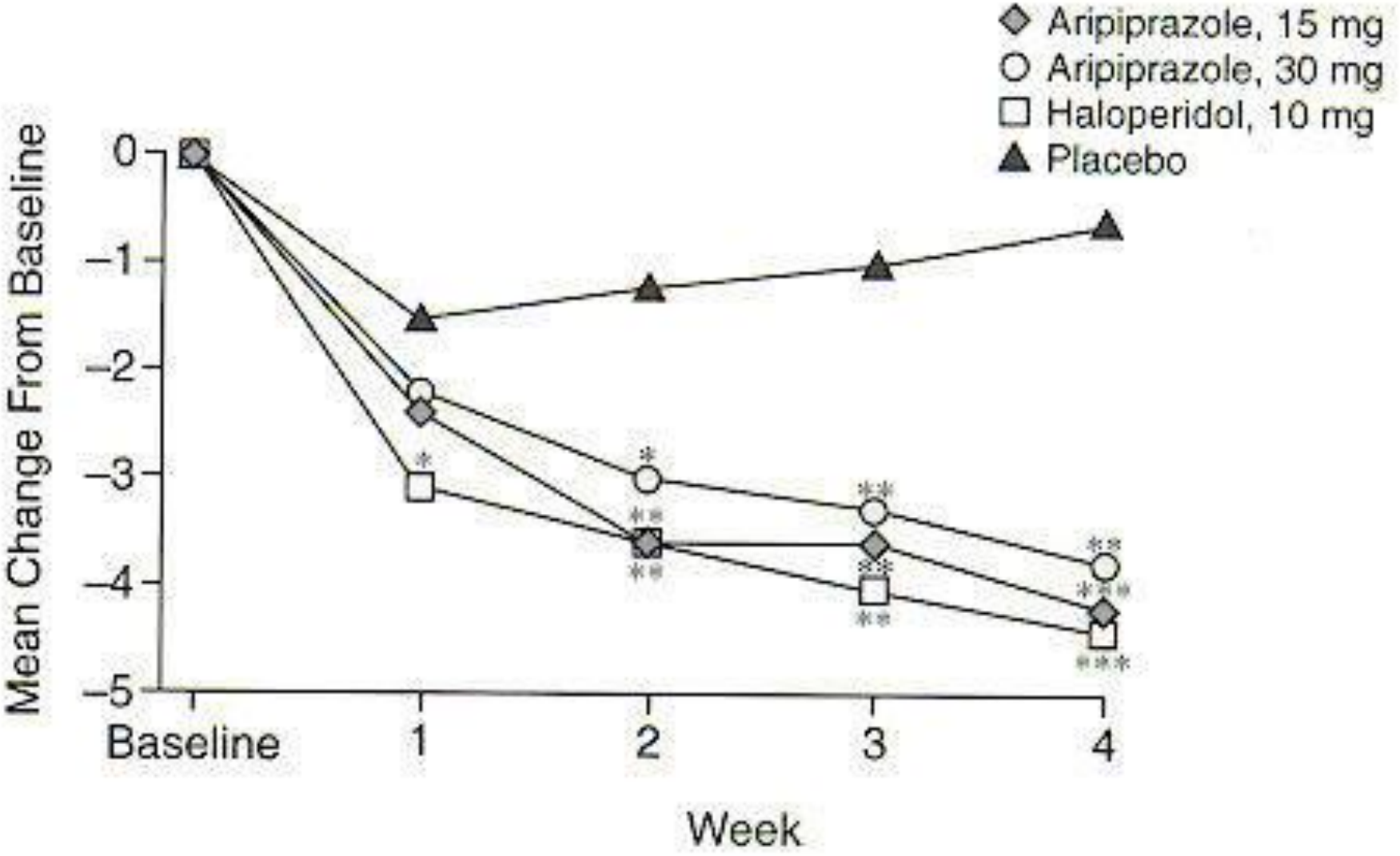
- 4 week multicenter DBPC compared 15 or 30 mg aripiprazole with 10 mg haloperidol
- 414 acutely ill inpatients entered the study.*
- Fixed doses
- Lorazepam and benztropine were allowed
- Dropouts: 45% on placebo; 42% on Haldol and aripiprazole 30; 33% on aripiprazole 15.

***Kane et al. J Clin Psychiatry 2002;63:763-771**

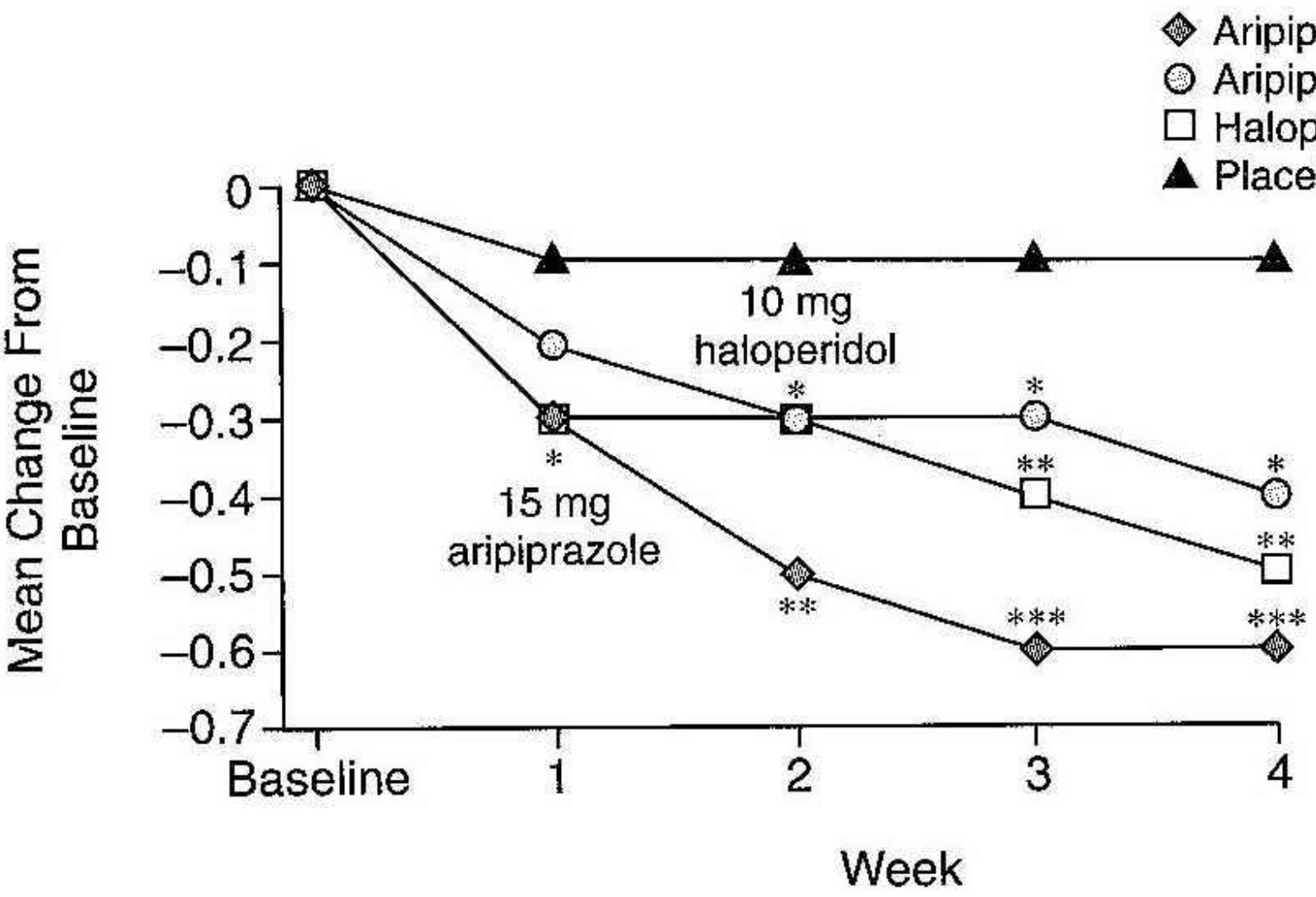
Figure 1. Mean Change in PANSS Total Score From Baseline Over 4 Weeks of Treatment With Aripiprazole (15 mg or 30 mg), Haloperidol 10 mg, or Placebo (LOCF)[a,b]



[a]Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.
[b]Pairwise comparison p values (vs. placebo): *p < .05; **p < .01; ***p < .001.



Mean Change in PANSS Positive Symptoms


Aripiprazole, 15 mg
Aripiprazole, 30 mg
Haloperidol, 10 mg
Placebo
Mean Change From Baseline
0
–0.1
–0.2
–0.3
–0.4
–0.5
–0.6
–0.7
10 mg haloperidol
15 mg aripiprazole
*
**
***
Baseline
1
2
3
4
Week

CGI Outcome

Conclusions

- 15 mg is superior to 30 mg, at all data points and even after 1 week
- There is no advantage to a “loading dose”
- Results develop slowly compared to haloperidol 10 mg, but patience is rewarded. There is no advantage to raising dose.
- Six-month relapse rates are somewhat higher than other antipsychotics (27%, compared to 15-19%)*

*Pigott TA J Clin Psychiatry 2003;64:1048-1056

Aripiprazole Issues

- 75 hour half life
- Substrate for Cytochrome P450 3A4 and 2D6. Paroxetine and fluoxetine will raise levels (use 50% dose), carbamazepine will lower them.
- 8% of population are poor metabolizers of 2D6 and will get 60% higher levels. So, some patients need only 5 mg
- 30 mg? Used in mania, resistant schizophrenia

Aripiprazole Side Effects

- Dizziness
- Insomnia
- Akathisia, agitation
- Headache
- Sedation
- Metabolic syndrome – minimal risk

Risperidone Dosing

- 3-6 mg per day for 3-6 weeks
- A dose that produces parkinsonian side effects is probably too high a dose
- First exposure: 0.5 mg bid, then 1 mg bid
- Acute exacerbation: 1 mg bid, then 2 mg bid
- Elderly: 50% of above, or less
- P450 Drug Interactions: 2D6 substrate

Risperidone dosing - II

- Chinese and other East Asian ethnic individuals (and many Africans) usually need somewhat lower doses of antipsychotics metabolized by 2D6, probably because 35-50% have a less active form of the 2D6 enzyme, rendering them "Slow Metabolizers" (SM's).
- Poor metabolizers (PM's) are comparatively rare among Asians, being found in 1-6% compared to 5-10% in Caucasians. They are very prone to EPS

Risperidone dosing and D2 receptor occupancy

- In first-episode and drug free patients, risperidone at 6 mg per day produced EPS in almost everyone and dopamine D2 receptor occupancy averaging 82%*
- At risperidone 3 mg, EPS were usually not present and the average D2 occupancy was 72%.*
- Previous studies have shown that the optimal D2 occupancy level for maximizing benefits and minimizing EPS is 70-80%.
- CATIE dose was 3.9 mg/day

***Nyberg S et al, 1999**

Risperidone Side Effects

- Prolactin elevation, probably greater than that seen with the typical neuroleptics.
- Agitation. This can look like akathisia, or it may present as hypomania or mania. It is unclear whether these reports represent true side effects of the atypicals or coincidental exacerbations of the patient's underlying condition.
- Anxiety, insomnia, headache and nausea.
- Weight Gain and the Metabolic Syndrome – low to medium risk

Haloperidol Dosing

- With acute treatment, check for cogwheel rigidity daily as haloperidol, started at 2 mg per day, is increased by 2 mg every other day.
- McEvoy* found this “neuroleptic threshold” in 44 of 47 patients (94%) at a median dose of 4 mg per day. (2 mg in neuroleptic naïve patients)
- If poor response *and* no parkinsonian effects, despite dose of 10-20 mg, check plasma level to assure absorption/compliance. (5-15 ng/ml)

Quetiapine…Dosing

- Standard recommendation is 25 mg bid, 50 mg/day on day 2, 100 bid on day 3, 150 bid on day 4, and 200 mg on day 5. PDR max is 800.
- Pilot randomized study showed equivalent safety with 100 bid on day 1, 200 bid on day 2. (Smith, J Clin Psychopharmacol, Aug. 2005)
- CATIE patients received 543 mg/d
- A study is underway comparing 600 & 1200 mg

Quetiapine side effects

- Agitation, Insomnia, Sedation, Headache, Dyspepsia
- Seizures occurred 0.8% in premarketing studies, which is similar to olanzapine 0.9% and higher than risperidone's 0.4%.
- Postural dizziness from alpha-adrenergic blockade will sometimes prevent rapid dosage
- Liver function tests are elevated about as often as olanzapine and more frequently than risperidone.
- Focal Cataracts in dogs. No problems in CATIE.

Olanzapine Dosing

- Works most quickly when *started* at 10-20 mg/d*
- Smoking increases clearance by 40%** (58-88% of patients with schizophrenia smoke)
- Female gender decreases clearance by 30%**
- Should you exceed the PDR max. dose of 20 mg? (the *average* dose used in CATIE) Not routinely.

* Osser (2001)

**Package Insert, Weiss (2005), Carrillo (2003)

High Dose Olanzapine vs Clozapine

- 16 week DB crossover study comparing 50 mg of olanzapine with 450 mg of clozapine*
- 13 patients met rigorous criteria for treatment-resistant schizophrenia
- Criteria for response was 20% improvement on BPRS, final score <35 or CGI improvement score greater than 1.0

*Conley RR et al J Clin Psychopharmacology 2003;23:668-71

Results and Conclusions

- Clozapine response was good: 30% had BPRS drop of 20%. Similar to other clozapine studies. Effect size 0.5
- No olanzapine patients improved.
- Six of 13 patients dropped out when in the olanzapine phase vs none in the clozapine phase.
- Conclusion: No support for high dose olanz.

Olanzapine Raised from 20 to 30*

- 39 patients were treated with olanzapine for 8 weeks at a mean dose of 20 mg.
- If results were unsatisfactory, dose was increased to a mean of 30 mg for 6 more weeks
- There was an improvement in positive symptom scores from 23 to 22 on the PANSS
- Is this clinically significant?

*Volavka J et al. Am J Psychiatry 2002

Metabolic Issues w. Olanzapine

- 30% of olanzapine patients gained > 7% body wgt
- Elevated triglycerides – highest with olanzapine
- HgbA1C – increased the most with olanzapine
- Triglycerides v. strongly correlated with insulin resistance (IR)
- Mechanisms: Fat, especially abdominal, increases IR. Pancreas responds with increased insulin levels to compensate. If you have bad genes, beta cells eventually can't keep up: Diabetes.

Other Olanzapine Side Effects

- Liver enzyme elevation (use with caution in hepatitis patients, and if patient on other medications that irritate liver such as statins, valproate, carbamazepine, naltrexone)
- Sedation
- EPS, prolactin elevation, & neuroleptic dysphoria can occur at doses over 20 mg

Monitoring Recommendations

If the patient has pre-existing diabetes, hypertension, or obesity, consider another antipsychotic

- Baseline: FBS, HbA1C, lipids, LFTs, weight, abdominal circumference (ac)
- Followup at 1 month: weight, ac, FBS, HbA1C
- Followup at 3 months: same, plus lipids

If metabolic problems develop, consider another antipsychotic, or treat medically

Some Side Effect Comparisons - 1

Side effect	typicals	cloza-pine	risperi-done	olanza-pine	quetia-pine	ziprasi-done	aripipra-zole
Weight gain	+ - +++	12 lbs avg/10 weeks	4 lbs avg/6 weeks	12 lbs avg/12 weeks	6 lbs avg/6 weeks	0	1.5 lbs avg/6 weeks
Sedation	some - +++	+++	+	++	++	0 - ++	0 - +
LFT increase	0 - ++	++	0 - +	++	++	0 - +	0 - +
CYP450 Substrate for…	**various**	**1A2**, 2D6, 3A4	2D6	1A2, 2D6	3A4	3A4	2D6, 3A4

Some Side Effect Comparisons - 2

Side effect	typicals	cloza-pine	risperi-done	olanza-pine	quetia-pine	ziprasi-done	aripipra-zole
EPS	+ - +++	0	**+ less if dose < 4 mg**	**0 - + (if dose < 10 mg)**	0	0 - +	0 - +
Seizure risk (~ %)	0.1 - 0.3	2 – 6	0.3	0.9	0.8	0.4	0.1
Ortho-stasis	some - +++	+++	++	+	++	+ - ++	+ - ++
Prolactin increase	++ - +++	**transient**	+++	+, if > 20 mg	0	0 - +	0

Depot Neuroleptics

- Fluphenazine Decanoate: 12.5 mg (0.5 cc test dose) to 50 mg (2 cc) every two weeks.
- Haloperidol Decanoate 25 mg (0.5 cc test dose) to 200 mg every 4 weeks.
- Underutilized in the US. Many more patients are non-compliant or not as compliant as we think

Risperidone “Consta®”

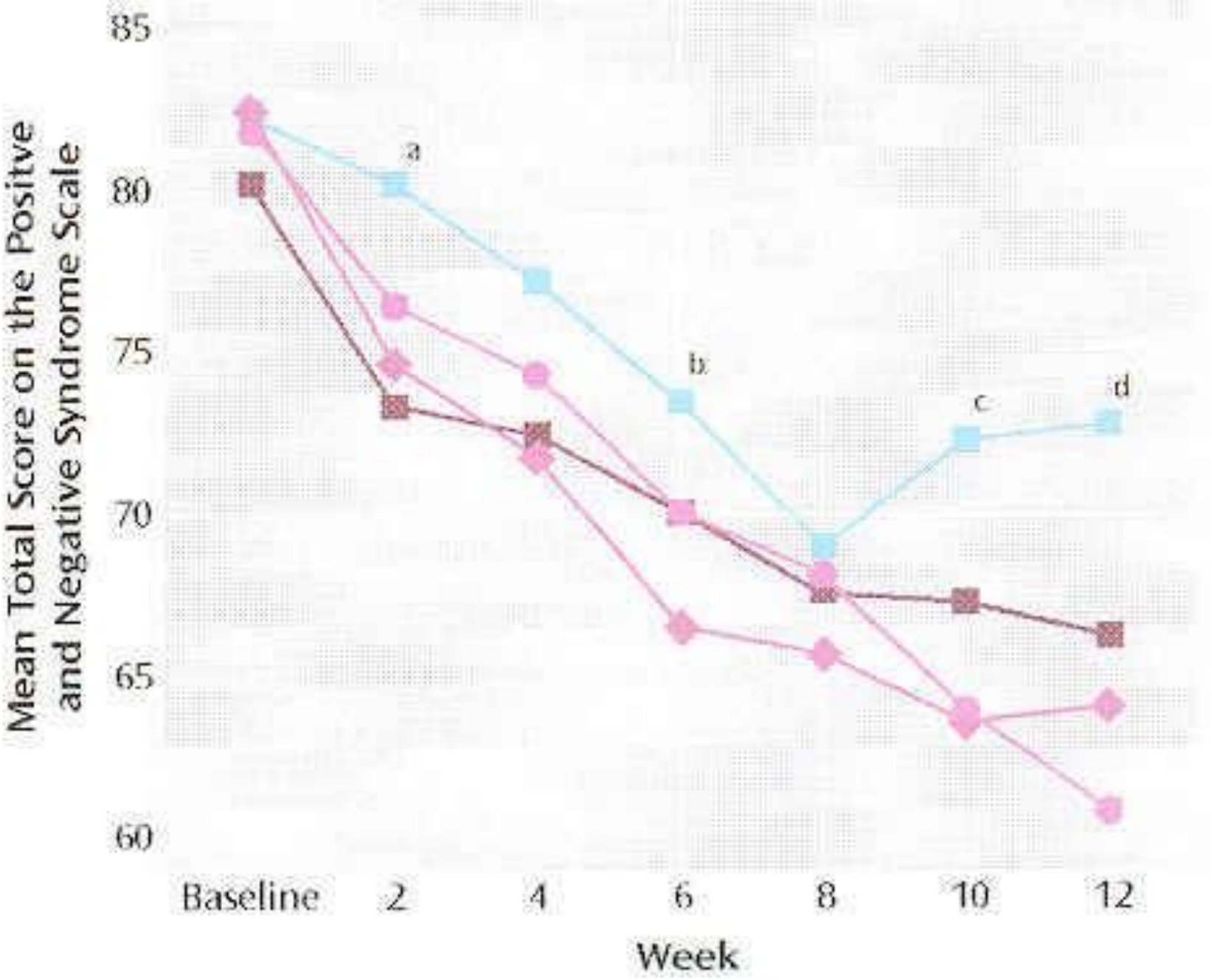
- 12-week, DBPC randomized trial of IM risperidone 25, 50, or 75 mg. (Kane et al ’03)
- 461 patients entered the study.
- Patients’ CGI at start averaged 3, “mildly ill”
- Switched to oral risperidone for 1 week before the IM: 2 mg per day, then 4 mg per day after three days. Oral continued for 3 more weeks after the IM.
- 15% dropped out in the first week

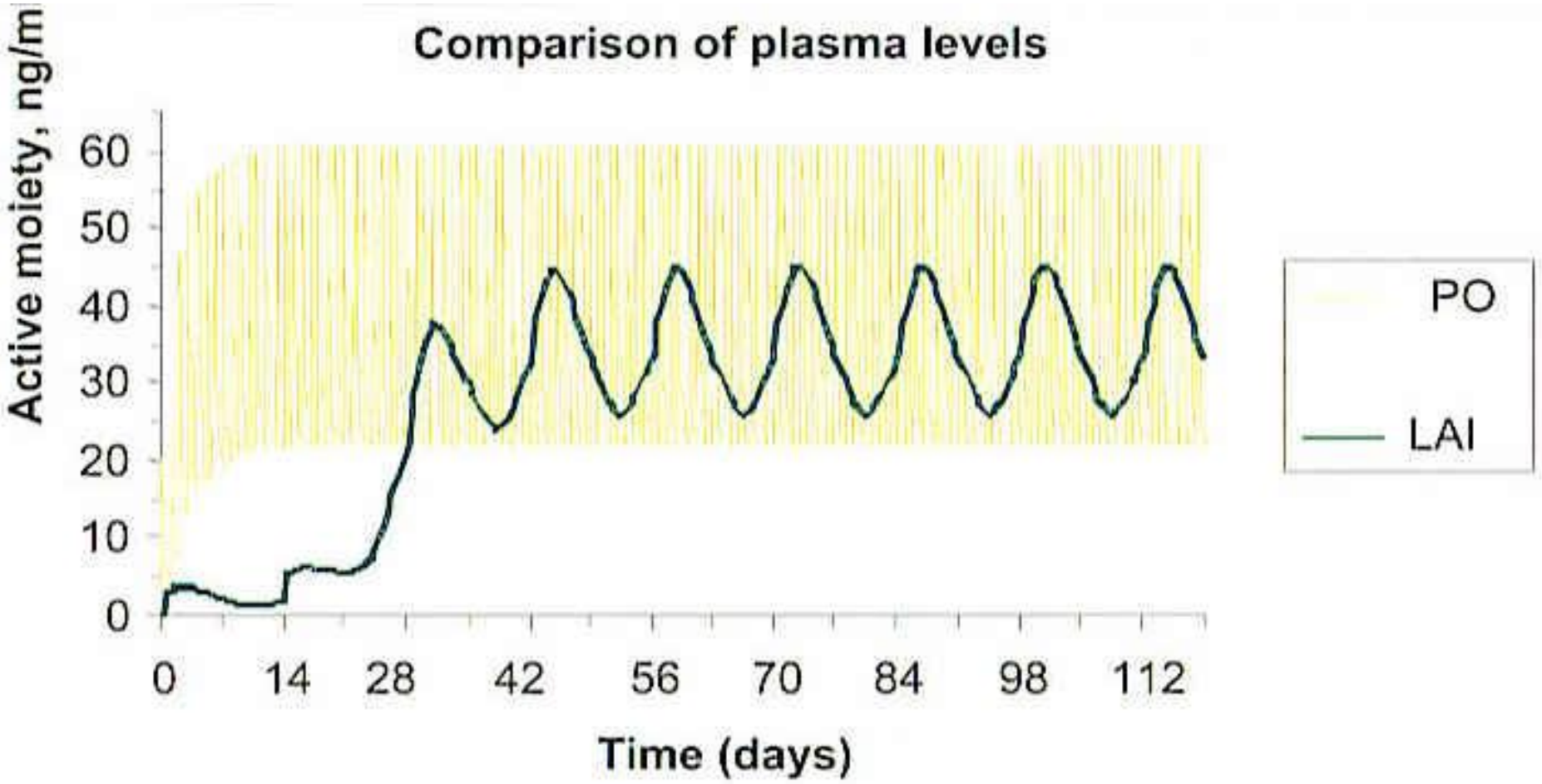
TABLE 2. Reasons for Study Discontinuation Among Patients With Schizophrenia Randomly Assigned to 12 Weeks of Double-Blind Treatment With Long-Acting Injectable Risperidone (25, 50, or 75 mg) or Placebo

	Patients Giving Reason (%)			
		Long-Acting Injectable Risperidone[a]		
Reason	Placebo (N=98)	25 mg (N=99)	50 mg (N=103)	75 mg (N=100)
Any reason	68	52	51	52
Insufficient response	30	22	15	12
Adverse event	12	11	12	14
Withdrew consent	10	7	13	11
Lost to follow-up	6	2	3	6
Noncompliance	4	0	3	3
Ineligibility	0	3	3	2
Death	1	0	0	0
Other	5	6	4	4

[a] Dose administered every 2 weeks.

Kane et al. Am J Psychiatry 2003:160:1125-1132


Mean Total Score on the Positve and Negative Syndrome Scale
85
80
75
70
65
60
a
b
c
d
Baseline
2
4
6
8
10
12
Week



Mannaert E et al. Poster 530. CINP. Paris, June 20-24, 2004

Comments on this study

- These mildly-ill, cooperative patients are not the usual population treated with depot, and yet 2/3 of them did not “survive” the transition to risperidone long-acting injectable.
- For those who did “survive,” the results were fair vs placebo by 12 weeks, with 25 mg.
- 50 mg was no better than 25 mg* **(See Turner, 2004)**
- Probably should continue oral for 6-8 weeks
- For more severely ill people, benefits unknown

Clozapine

- Our most powerful treatment. Should not be left to last resort after repetitive monotherapy trials and non-evidence-supported combinations
- Pre-treatment workup similar to olanzapine plus WBC and ANC levels, EKG. Avoid combining with other drugs that can cause granulocytopenia like carbamazepine.
- Avoid combining with benzodiazepines if possible

Clozapine Dosing

- 12.5 mg for first dose. Thereafter, divided doses
- Increase by 25-50 mg per day as tolerated, to 300-400 mg per day. Maximum is 900 mg/d
- If response unsatisfactory, check plasma level. Best results are with levels of parent compound greater than 400 ng/ml
- For outpatients go at half this pace
- No single dose should exceed 450 mg

New CBC Monitoring with Clozapine

- Weekly CBC for six months. Then biweekly for six months. Then every 4 weeks
- If WBC < 3.5 or ANC 1.5-2.0, get repeat CBC and get biweekly CBC until levels rise.
- If WBC < 3.0 or ANC 1.0-1.5, hold clozapine, get daily CBC until levels rise. Rechallenge possible
- If WBC <2.0 or ANC <1.0, stop clozapine. Monitor daily. Rechallenge not advised, though some have done so with prophylactic Neutrophil Stimulating Factor.

Clozapine Side Effects

- Though the rewards are great, the side effects are many and challenging. Besides wgt gain:
- Seizures (2-10%)
- Respiratory depression (If interrupt therapy by 48 hours, restart at 12.5 mg for first dose)
- Myocarditis (fatal in 1/500,000)
- Neuroleptic Malignant Syndrome
- Pulmonary embolus, anticholinergic toxicity, temperature elevations, eosinophilia

Adverse Events

Event	Clozapine %	Olanzapine %
Weight Gain	31	56
Somnolence	46	25
Dizziness	27	12
Constipation	25	10
Hypersalivation	48	6
Seizures	2.3	0.4
Drug Abuse	1	3
WBC Decrease	6	1

Clozapine Side Effects – A Promising Strategy

- 68 Han Chinese received clozapine or clozapine plus 50 mg fluvoxamine to inhibit metabolism to norclozapine. Study was open label.
- Norclozapine may be more responsible for myelotoxicity, weight gain, and seizures.
- Only needed dose of 130 to get blood level of 500 ng/ml.
- All side effect parameters much improved on the combination
- Strategy needs longer-term study, monitoring

Lu et al. J Clin Psychiatry 2004;65:766-771

Antipsychotics for Psychosis or Agitation in Dementia

- 15 placebo-controlled studies of atypicals were reviewed*
- Most found no benefit, and most were never published.
- Meta-analysis showed modest efficacy, NNT = 10
- Death from stroke and related disorders was greater than placebo. Number Needed to Harm (NNH) = 100.
- Thus, for every 10 patients with good effect, 1 may die
- Typicals are not safer (NEJM Dec. 1, 2005)
- What to do? Milieu management; AP's very briefly

***Schneider LS et al. JAMA Oct. 19, 2005;1934-43**

Cost-Conscious Prescribing

- Be aware of costs of different pill sizes
- Better to diagnose cause of anxiety, depression, insomnia, somnolence, agitation and treat cause. (may result in < rather than > # of medications)
- If you must do add-on, take cost of your selection into consideration (see following slides for costs)

Antipsychotic Monthly Procurement Costs in the VA System - 1

March, 2006

- Risperidone 1.5 mg bid 110
- Risperidone 3 mg qd 148
- Risp. Consta 25 mg IM 155
- Olanzapine 10 mg 172
- Olanzapine 20 mg 343
- Olanzapine Zydis 20 mg 362
- Olanzapine 25 mg 454

Antipsychotic Monthly Procurement Costs in the VA System – 2

• Quetiapine	25 mg	15
• Quetiapine	300 mg bid	139
• Quetiapine	100 mg bid	52
• Quetiapine	75 mg tid	131
• Ziprasidone	80 mg bid	133
• Ziprasidone	20 mg bid	145
• Ziprasidone	100 mg bid	278
• Aripiprazole	5,10,15, or 20 mg	158
• Aripiprazole	30 or 40 mg	316

Antidepressant Monthly Procurement Costs in the VA System – 1 (March 06)

- 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 XR 150 mg 54.00
- Cymbalta 60 mg 60.00

Drugs Used as Hypnotics in the VA System – 1

(Monthly procurement costs, March 2006)

• 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 - 2

- 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

Post-Lecture Exam Question 1

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   B. Ziprasidone 80 mg bid

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2. Which of the following antipsychotics must be taken with food in order to prevent significant loss of absorption?

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   B. Olanzapine

   C. Clozapine

   D. Aripiprazole

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3. Which of the following is the recommended starting dose for clozapine?

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   B. 12.5 mg

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4. All of the following are true of a patient on risperidone who gets parkinsonian side effects, except:

   A. D2 receptor occupancy is 75% or more

   B. The patient is above the “neuroleptic threshold”

   C. Patient is at risk for secondary negative symptoms

   D. Raising the dose is likely to be helpful

Question 5

5. All of the following are true of olanzapine, in Phase 1 of the CATIE study, except

   A. Had superior effectiveness to the others

   B. Produced the most weight gain

   C. Elevated Hemoglobin A1C the most

   D. Increased triglycerides the most

   E. Average dose was above the PDR max.

Answers to Pre & Post Competency Exam

1. C
2. A
3. B
4. D
5. E