ANTIPSYCHOTICS

Crash Course Lecture

October 2014 Version

ASCP Model Curriculum for Psychopharmacology

David N. Osser, M.D.

Associate Professor of Psychiatry

Harvard Medical School

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 twice daily, with 500 kcal of food for it to be bioavailable?

   A. Ziprasidone

   B. Lurasidone

   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, except

   A. Smoking increases clearance by 40%

   B. Works most quickly when started at 15-20 mg/d

   C. Elevated Hemoglobin A1C the most in CATIE

   D. Increased triglycerides the most in CATIE

   E. Produces clinically significantly better results at doses over 20 mg daily.

Outline of Lecture

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

*Major Teaching Points

- Psychopharmacology algorithms help structure the knowledge base that pertains to decision-making
- Dosing strategies should be informed by the pertinent evidence-base
- Antipsychotic choice should be influenced by the patient's likely susceptibility to the common side effects
- Occasionally, cost considerations may be relevant

Recommended Book

- Taylor D et al. **The Maudsley Prescribing Guidelines in Psychiatry.** 12th edition. Wiley-Blackwell. $80. Due in January 2015:

Chapters 1 and 2 on Schizophrenia and use of blood levels.

Has exceptional commitment to citing evidence to support almost all statements and recommendations. Has useful short algorithms. Some meds are not available in US and vice-versa.

*Antipsychotics: The Menu I. First-Generation (FGAs) – generic and (old) brand names and approx. daily dose equivalence

- Chlorpromazine 300 mg
- Fluphenazine HCl 6 mg
- Haloperidol 6 mg
- Loxapine 30 mg
- Mesoridazine 150 mg
- (Molindone 30 mg)
- Perphenazine 24 mg
- Thioridazine 300 mg
- Thiothixene 15 mg
- Trifluoperazine 15 mg

- Thorazine
- Prolixin
- Haldol
- Loxitane
- Serentil
- (Moban – no longer made)
- Trilafon
- Mellaril
- Navane
- Stelazine

*Antipsychotics: The Menu II. Second-Generation (SGAs) – generic and brand names and dose equivalence to CPZ 300 mg

- Asenapine 5 mg bid SL
- Aripiprazole 15 mg
- Clozapine 400 mg
- Iloperidone 12-24 mg
- Lurasidone 40-80mg
- Olanzapine 15 mg
- Paliperidone 6-12 mg
- Quetiapine 400-600 mg
- Risperidone 4 mg
- Ziprasidone 80 mg bid

- Saphris
- Abilify
- Clozaril
- Fanapt
- Latuda
- Zyprexa
- Invega
- Seroquel
- Risperidal
- Geodon

*Importance of Detecting, Treating Schizophrenia

- Headline. August, 2011. US Army private shoots Afghan detainee in his cell. Diagnosis of soldier: Schizophrenia.
- Average age of onset: 18 for men, up to 25 for women. 2-3 years younger in marijuana users (Large et al, 2011)
- Suicide attempts in 20-50% (Ilgen, 2010)
- Watch for odd, suspicious behavior. Patients often deny their symptoms.

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

*Prevention of Schizophrenia

(Amminger et al. Arch Gen Psych 2010;67(2):146-54)

- 80 very high risk young adults age 13-25 randomized to 2 grams of fish oil twice daily or placebo for 12 weeks. Followed 9 months
- Conversion to schizophrenia:
  - o3FA – 5%
  - placebo – 28% $p < 0.007$, NNT 4
- No side effects
- If replicated – may have great importance

PSYCHOPHARMACOLOGY TREATMENT ALGORITHM

*PSYCHOPHARMACOLOGY ALGORITHM PROJECT AT THE HARVARD SOUTH SHORE PROGRAM at **www.psychopharm.mobi**

David N. Osser, M.D.

General Editor

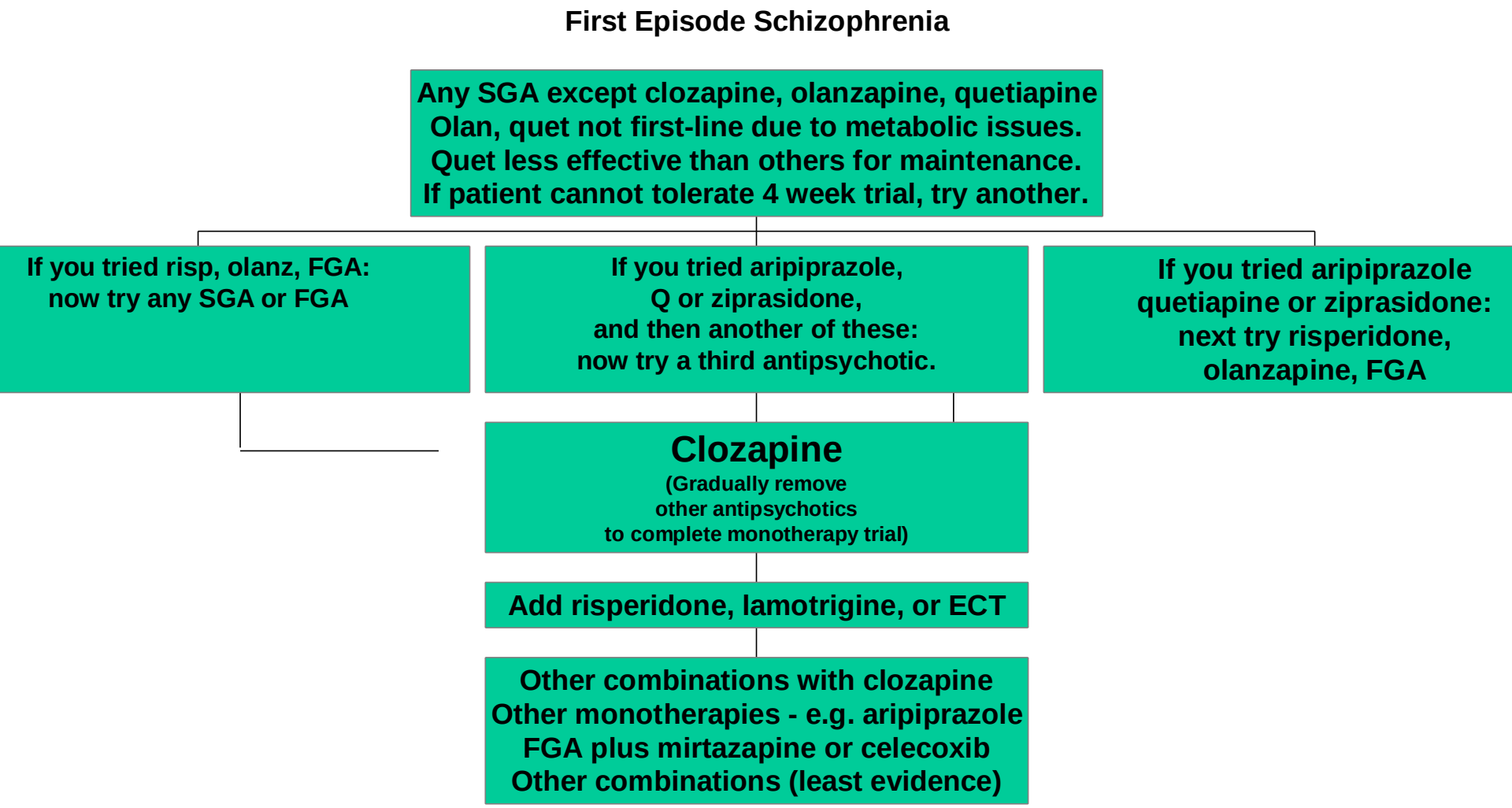
Robert D. Patterson, M.D.

Director of Technology

*Features of the PAPHSS Algorithm for Schizophrenia

- Primarily addresses positive sx of schizophrenia
- Negative sx typically improve with positive sx.
- “Secondary negative symptoms” improve when EPS and sedation are managed successfully.
- Residual primary negative and cognitive sx are very treatment-resistant with few proven remedies
- Unlike other algorithms, assumes there are some differences in effectiveness among the non-clozapine options. (McCue 2006, Suzuki 2007, Komosa 2009; full refs on this slide’s Notes Page)

2014 Schizophrenia Algorithm of the Harvard South Shore Algorithm Project*



*Osser DN, Jalali M, Manschreck T. Harvard Rev Psychiatry 2013; 21(1):18-40

*Antipsychotic Efficacy Differences?

McCue RE et al. Br J Psychiatry 2006;189:433-440

- 327 acute inpatients randomized open label to haloperidol (mean maximum dose 16 mg), aripiprazole 22 mg, olanzapine 19 mg, quetiapine 650 mg, risperidone 5.2 mg, ziprasidone 150 mg.
- Response was defined as being able to be discharged in 3 weeks – a “real world” outcome measure.
- No pharmaceutical firm support
- Olanzapine 92%, haloperidol 89%, risperidone 88%, *aripiprazole 64%, quetiapine 63%, ziprasidone 64%*

SGAs Not Equal? – 2

Suzuki T et al. Psychopharmacology 2007;195:285-95

- 78 patients who never had an adequate trial of a SGA were randomized to olanzapine, risperidone, or quetiapine for up to 8 weeks.
- If no response (30% drop in PANSS) to doses (in mg) O=18, R=5.5, Q=560, they were randomized to one of the other two for up to 8 more weeks. If still no response, they were given the third. **The Results:**

Trial 1 *– O=62%, R=54%, Q=35%. Q did less well.*

Trial 2 *– 60% responded to quetiapine* at the 2nd trial.

Trial 3 **-** Only 2 patients responded to the third SGA.

*SGAs Not Equal? – 3

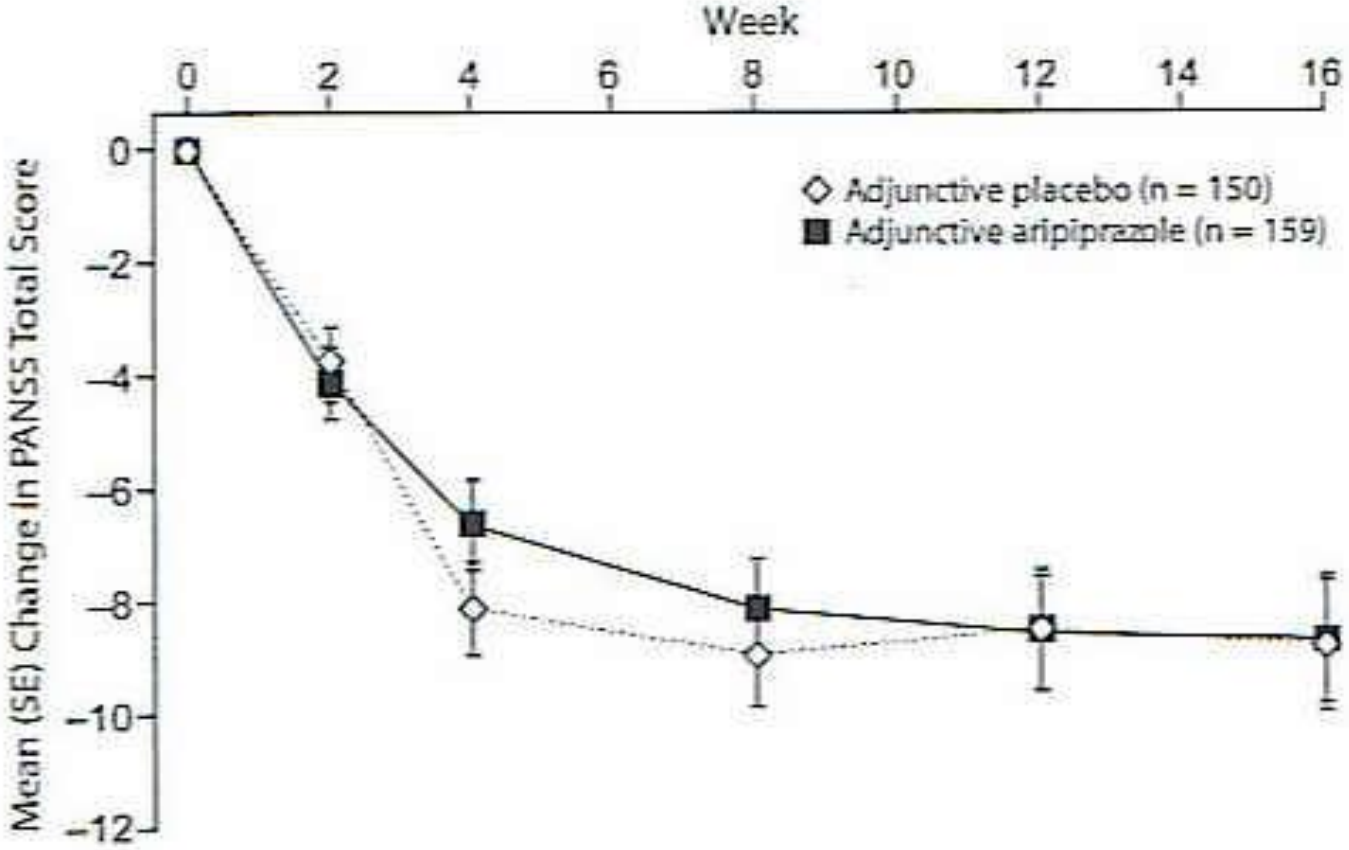
- Cochrane Review (2009) of 9 randomized trials concluded that ***ziprasidone*** appears less effective than olanzapine, risperidone, and amisulpride (not available in US).
  (Komosa K et al. Cochrane Reviews 2009(4) Art. No. CD006627)
- This may be due to issues related to dosage and food intake (to be discussed later)

*Combinations: Role in Algorithm

Kane et al. J Clin Psychiatry 2009;70(10):1348-57

- 323 patients with unsatisfactory response to risperidone (4-8 mg) or quetiapine (400-800 mg) were randomized to aripiprazole 2-15 mg daily (mean: 10) or placebo for 16 weeks.
- About 70% completed the study
- 78% diagnosis schizophrenia
- This data (next slide) strongly suggests that combinations should not have an early role in the algorithm

Figure 2. Mean Change From Baseline to Week 16 in PANSS Total Scores (LOCF)—Efficacy Sample[a]



[a]Baseline mean (SE) PANSS total scores: adjunctive placebo, 75.9 (1.0); adjunctive aripiprazole, 74.3 (1.0).

Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

*Role of Plasma Levels of Antipsychotics

- Confirm bioavailability
- Confirm compliance
- Aripiprazole has well-delineated optimal range of 150 to 210 ng/ml (Sparshatt, 2010)
- Olanzapine 20-40 ng/ml with added toxicity over 80 ng/ml (Bishara, 2013)
- Other possible ranges: risperidone: 20-60 (for risp + pali), haloperidol 5-15. (see Maudsley)

*New Atypical Antipsychotics

- No specific place for them in algorithm
- Iloperidone (™Fanapt) was rejected by FDA in July 2008 due to lack of efficacy. Decision reversed in May 2009. It was equivalent to ziprasidone in one study. Wgt gain ~ 5 lb short term. Some QTc increase
- Asenapine (™Saphris) approved in Aug. 2009. Sublingual administration: hard to evaluate its practicality. One negative and two positive studies. Did not do well in unpublished studies.
- Lurasidone (Latuda) approved in 2010. Two positive studies. Not as effective as olanzapine in 1 study.
- Paliperidone (™Invega), active metabolite of risperidone – will be discussed later

What about High Dose Olanzapine? Why isn't that in the algorithm?*

*See Bishara D et al. J Clin Psychopharmacology 2013;33:329-335

Olanzapine Raised from 20 to 30

- The Volavka study* is often cited as a reason to use above PDR-approved doses of olanzapine.
- 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
- The **mean improvement in positive symptoms** was from 23 to 22 on the PANSS. Only one point.
- Is this clinically significant? Seems unlikely.

*Volavka J et al. Am J Psychiatry 2002

*Olanzapine 10, 20, and 40 mg

Kinon BJ et al. J Clin Psychopharmacol 2008;28(4):392-400

- Kinon's study was more important.
- 599 mostly outpatients (mean PANSS 93) with schizophrenia and suboptimal response to previous antipsychotics were randomized double-blind to one of 3 doses of olanzapine for 8 weeks.
- Over the first 2 weeks, previous medications were tapered

*Olanzapine 10, 20, 40 mg: **Results**

- No difference in efficacy by multiple measures at any weekly treatment point or at end point.
- Weight gain was greater on the 40 mg dose
- However, patients in the top 10% of severity (PANSS > 110) did somewhat better on 40 mg. **But: this group was on higher doses of antipsychotic at study entry.**
- So, the better results at 40 mg relative to 10 and 20 mg were probably due to the fact that 2/3 of these patients were assigned to a lower equivalent dose of olanzapine.

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 of Conley et al.

- 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: Again, no support for high dose olanzapine.

*Is Sudden Cardiac Death another reason to avoid hi dose antipsychotics?

- **Dose-related increase in sudden cardiac death** found in Tennessee Medicaid patients, ? due to QTc. **(Ray et al. NEJM 2009;360:225-35, 294; Taylor D. Evidence-based Mental Health 2009:12;92)**
- On average, the risk was doubled. Individual drugs: clozapine: 3.7x; thioridazine 3.2x; risperidone 2.9x; olanzapine 2.0x, quetiapine 1.9x, haloperidol 1.6x.
- Others **(Tiihonon et al, 2010; Manu et al, 2011)** did not find this in other populations.
- Recommendation in NEJM editorial was to get EKG at baseline and follow-up with all antipsychotics.

*Speed of Response

- Speed is critical in the acute inpatient, managed-care-driven environment.
- If the patient does not achieve a 25% reduction in symptoms in the first 2 weeks, outcome is likely to be poor at 4 weeks. (Leucht S: J Clin Psychiatry 2007)
- More improvement occurs in the first two weeks than the second two weeks. (Leucht S: Biol Ps 2005)
- So, probably switch if no response in 2 weeks
- Risperidone, olanzapine, and conventional antipsychotics may work a bit faster than others*

  (*Osser & Sigadel: J Clin Psychopharmacol 2001, McCue et al: Br J Psychiatry 2006.)

IM Treatment of Agitation in ER

Mantovani C et al. JCPsychopharmacol 2013;33:306-12

- This is the largest and best controlled study but it confirms earlier smaller studies
- 100 patients with schizophrenia mostly, 36 with mania, randomly assigned to haloperidol 2.5 plus midazolam 7.5; haloperidol 2.5 plus promethazine 25; olanzapine 10; or ziprasidone 10.
- In 60 minutes, efficacy was best was H + M or O, but OR for side effects was 1.6 greater with O and 3.64 greater with H + P.

Giving Adequate Trials of Individual Antipsychotics

Dosing, Administration, and
Side Effect Management

*Ziprasidone – caveats from package insert

- Avoid ziprasidone if EKG shows QTc is >500 milliseconds
- Is patient on medications that might prolong the QTc since EKG was done? (haloperidol, tricyclics, quetiapine, 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

- *Only 80 mg bid was better than placebo in All Cause Discontinuation* in meta-analysis of 4 studies.* (In CATIE they used only 110 mg/day, and ziprasidone underperformed)

*Citrome L et al. Schizophrenia Research 2009;111:39-45

*Dosing of Ziprasidone - 2

- Absorption is reduced by at least 50% if not taken with food, more at higher doses. 500 kcal needed – not even 250 is enough. Fat content not important. (Gandelman et al. J Clin Psychiatry. 2009 Jan;70(1):58-62)
- Citrome et al also found NO differences in discontinuation rates due to side effects at 160 mg vs 40 mg.

*Ziprasidone Side Effects

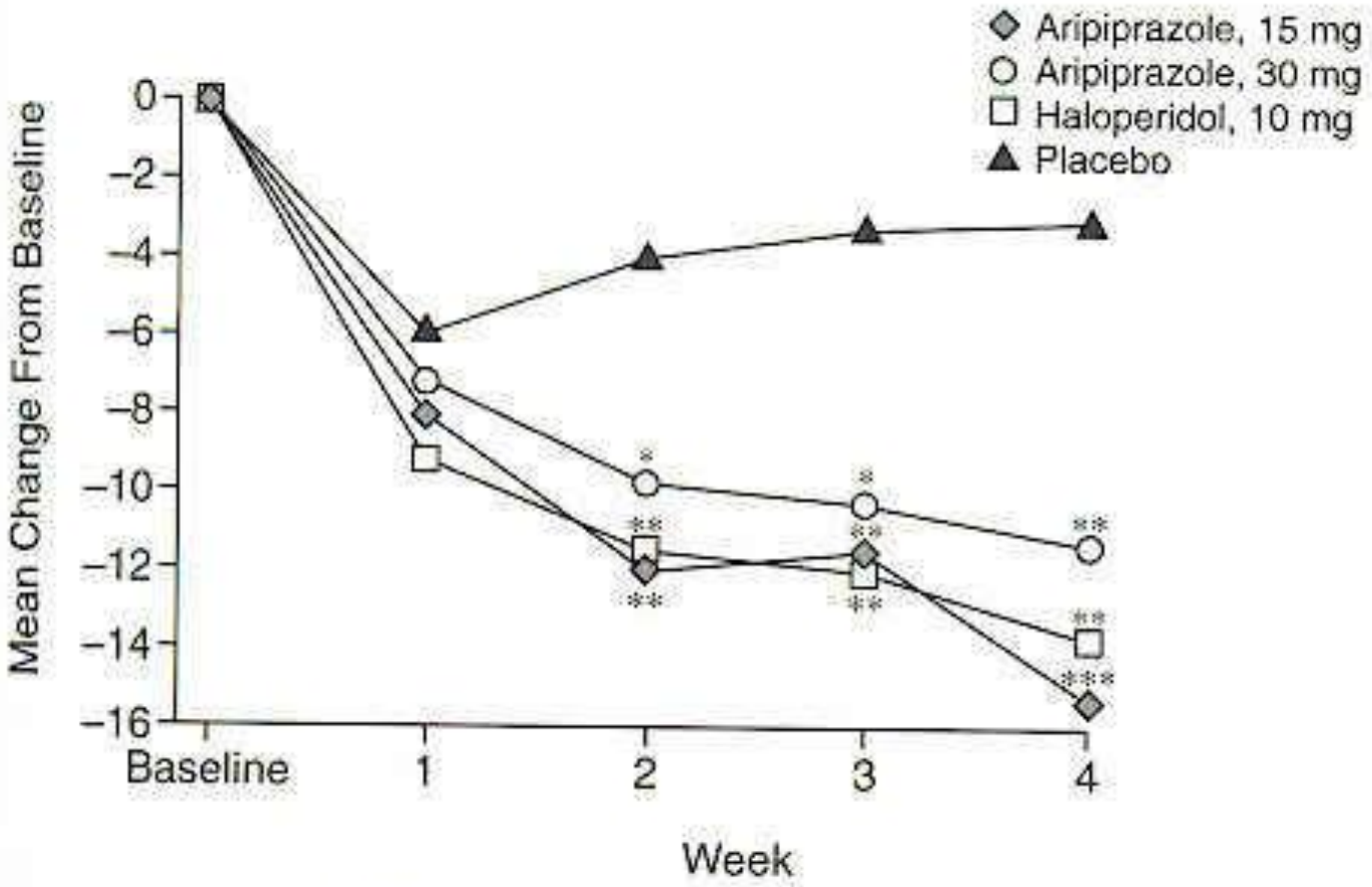
- Activation, especially at low doses
- Sedation
- Nausea, dry mouth
- EPS occasionally
- No QTc problems were seen in CATIE compared to the others. Previous data found ~10 msec greater increase compared to most others
- HOWEVER, since 2007 FDA warning about QTc prolongation and Torsades with haloperidol, “particular caution” is advised when combining with ziprasidone. Prod. Info says “contraindicated”

Aripiprazole – Dosage Issues

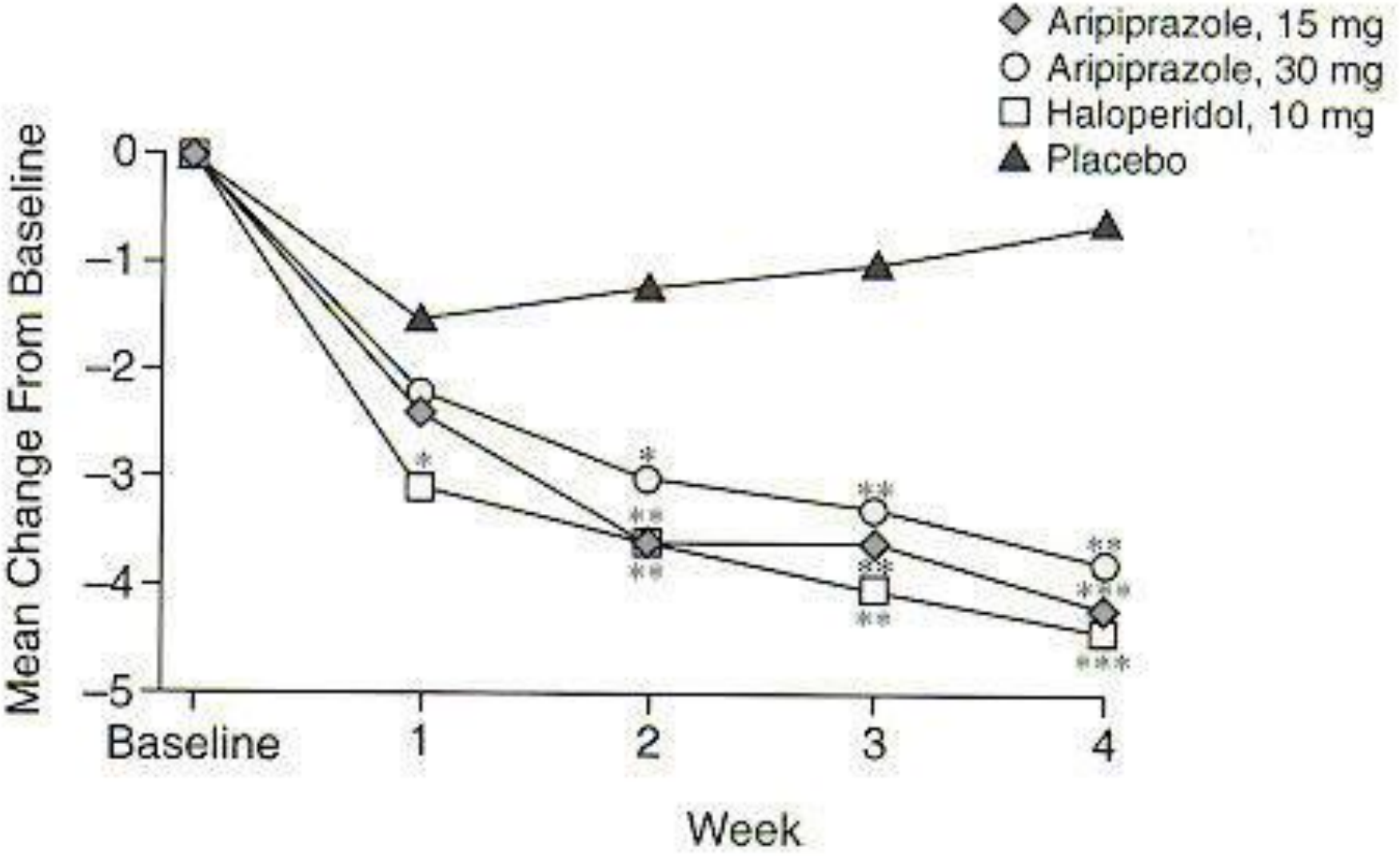
- 4 week multicenter DBPC compared 15 or 30 mg aripiprazole with 10 mg haloperidol
- 414 acutely ill inpatients entered the study.*
- Fixed doses
- Lorazepam and benztropine were allowed
- Dropouts: 45% on placebo; 42% on Haldol and aripiprazole 30; 33% on aripiprazole 15.

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

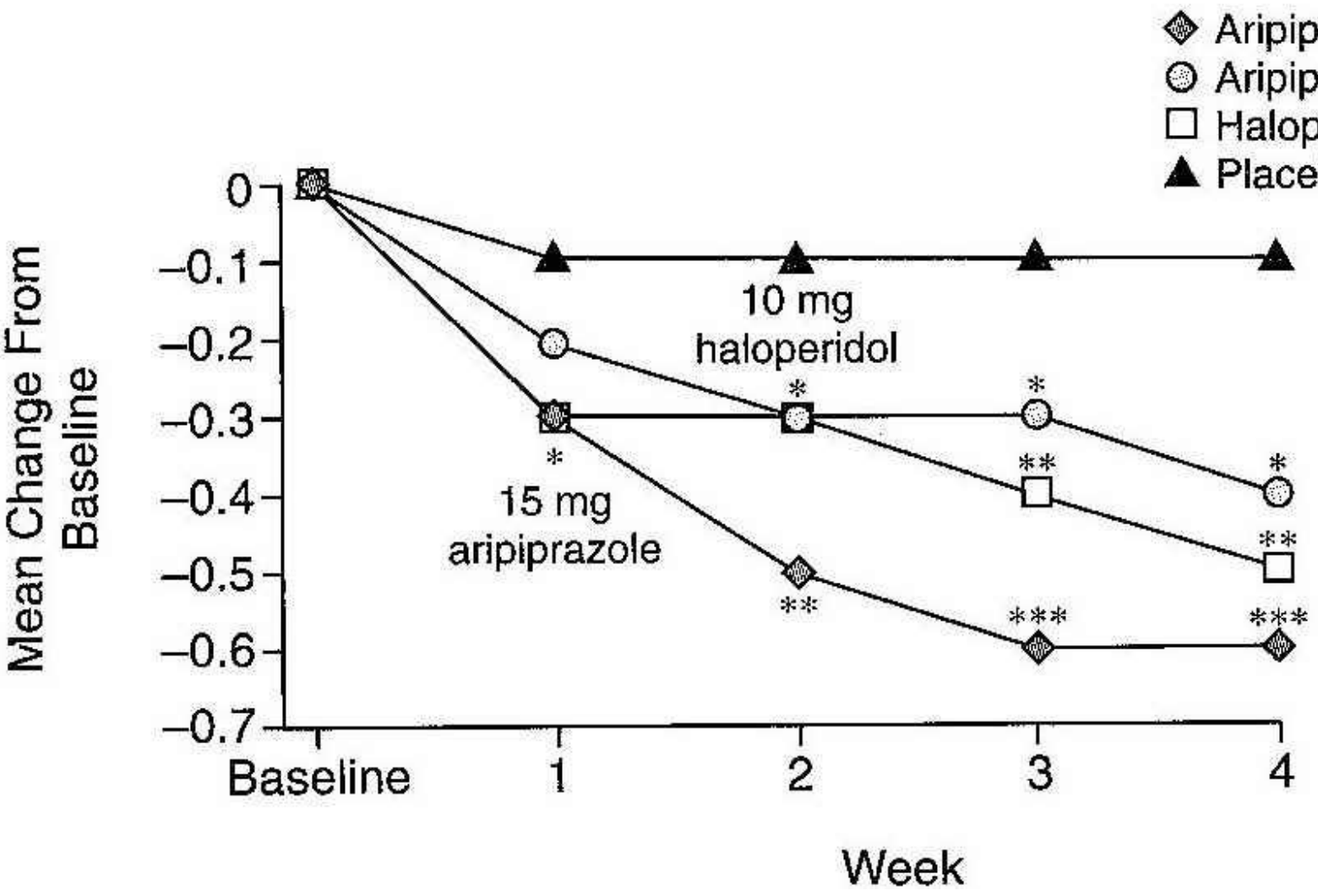
Figure 1. Mean Change in PANSS Total Score From Baseline Over 4 Weeks of Treatment With Aripiprazole (15 mg or 30 mg), Haloperidol 10 mg, or Placebo (LOCF)[a,b]



[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 on Dose of Aripiprazole

- 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

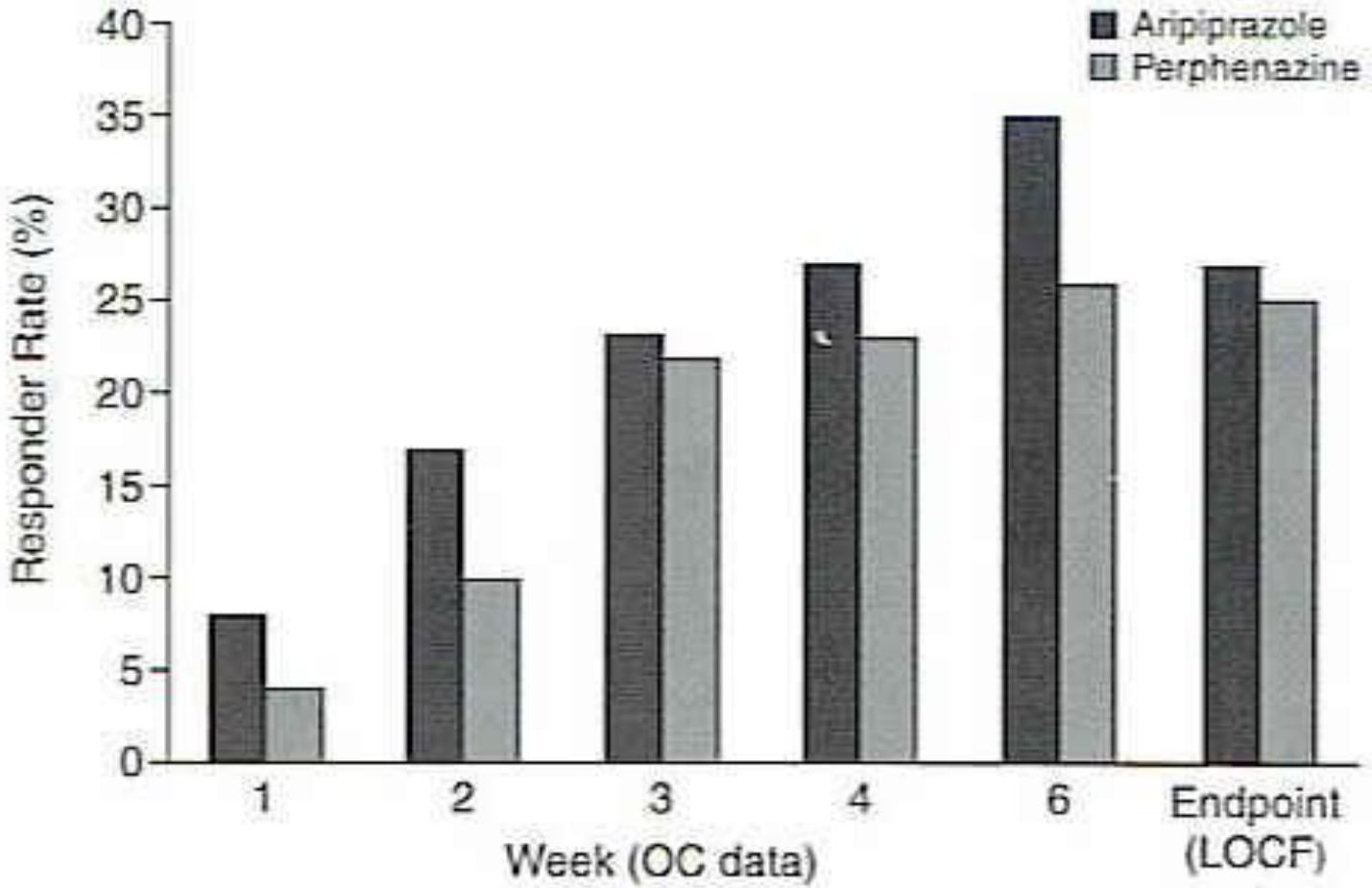
- 75 hour half life
- Substrate for Cytochrome P450 3A4 and 2D6. Paroxetine and fluoxetine will raise levels (use 50% dose), carbamazepine will lower them 50%.
- 8% of population are poor metabolizers of 2D6 and will get 60% higher levels. So, some patients need only 5 mg
- Advantage: aripiprazole, for patients at cardiac risk. It had the least QTc elev. of any antipsychotic (Chung et al, 2011)
- 30 mg? Possible use in tx-resistant schizophrenia* (next slide)

Aripiprazole in TR Schizophrenia*

- 426 TR patients were identified.
- Patients had failed at least 2 AP trials of 6 weeks (one had to be 3 months), then had open trial of 3 weeks of olanzapine or risperidone. If they improved 20% on PANSS they were not eligible.
- Only 2% improved 20%. 300 patients randomized to aripiprazole (93% at 30 mg) or perphenazine: mean dose 39 mg (about double the CATIE dose)
- Response defined as *30% improvement* in PANSS

***Kane JM et al. J Clin Psychiatry 2007;68:213-223**

Figure 3. Percentage of Treatment Responders Through the Study (OC) and at Endpoint (LOCF)



Abbreviations: LOCF = last observation carried forward, OC = observed cases.

Aripiprazole Side Effects-1

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

*Aripiprazole Side Effects-2

- Some patients develop irritability, insomnia, excitement, and nervousness.
- Is this a dopamine agonist effect?
- These side effects may occur more often if the patient was recently on a strong dopamine blocker like a FGA or risperidone.* Also, avoid adding DA stimulants such as bupropion.

***Raja M. Int J Neuropsychopharmacol 2007;10:107-110.**
Jong-Yih L. J Clin Psychopharmacol 2009;29(1):93-5

*Risperidone: Dosing

- 4- <6 mg per day for 3-6 weeks produces optimal benefits and least side effects*
- A dose that produces parkinsonian side effects is probably too high a dose
- Acute exacerbation: 1 mg bid, then 2 mg bid
- First episode: 0.5 mg bid, then 1 mg bid (2- <4mg/d)
- Elderly: Similar to first episode, or less
- P450 Drug Interactions: 2D6 substrate

*Li C et al. Cochrane Reviews 2009(4):art.No. CD007474

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 phase 1 dose was 3.9 mg/day – *slightly* low for non-neuroleptic naïve patients.

***Nyberg S et al, 1999**

*Risperidone dosing - III

- 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 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

Paliperidone (™Invega)

- Also approved for schizoaffective disorder, July 2009
- Paliperidone is the major active metabolite of risperidone, the result of hydroxylation mediated primarily by CYP P450 2D6.
- 80% renally excreted.
- Slow release formulation – 1 day half-life – tablet should not be crushed or chewed.
- Recommended dose is 6 mg in AM. Maximum is 12. Efficacy more robust at 9-12.

*See Carlat Report: 3/07, Psychopharm Review: 7/07, Current Psychiatry 9/07

*Paliperidone: When to Use?

Probably not too often:

- Efficacy appears the same as risperidone.
- Patients who are slow metabolizers of risperidone at 2D6, or are taking drugs that inhibit 2D6 metabolism like paroxetine, may develop high risperidone blood levels and more side effects. Use of paliperidone will avoid this problem.
- However, paliperidone itself causes a lot of EPS and other side effects, especially at 12 mg where it may give more EPS than comparable doses of risperidone.

Paliperidone: When to Use - 2

- No difference from risperidone in hyperprolactinemia, weight gain, sexual side effects, or metabolic side effects
- Avoid if patient has impaired renal clearance.
- Avoid for inpatients where rapid effect is important and who may need crushed medication to deal with non-compliance.

Asenapine (™Saphris)

*See Janicak PG, Rado JT. Asenapine: a review of the data. Psychopharm Review 2009;44(12):89-94

- Sublingual medication. If swallowed, only 5% bioavailable due to first-pass liver metabolism to inactive metabolites.
- Patient must not chew or swallow tablet. May not eat or drink for 10 minutes.
- Starting and usual final dose for schizophrenia is 5 mg bid
- CYP 1A2 substrate, like clozapine and olanzapine
- Side effects: 2-5 msec QTc prolongation. Oral hypoesthesia. Somnolence. Low weight gain & EPS.

*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)

**McEvoy JP, Stiller RL, Farr R. J Clin Psychopharmacol 1986; 6:133-138.*

*Perphenazine - Dosing

- Comes in 2, 4, 8, and 16 mg tablets
- Begin with 4 mg twice daily and increase by 4 mg twice daily every other day until cogwheel rigidity is noted.
- Average dose in CATIE was 20 mg daily (equivalent to 6 mg haloperidol*).
- Maximum dose is 64 mg daily.

*Kane et al 2003: Expert Consensus Guideline, J Clin Psychiatry

*Quetiapine…Dosing

- Standard recommendation is 25 mg bid, 50 mg bid on day 2, 100 bid on day 3, 150 bid on day 4, and 200 bid on day 5. PDR max is 800.
- Pilot randomized study showed equivalent safety and faster results with 100 bid on day 1, 200 bid on day 2, 300 bid on day 3 and 400 bid on day 4. (Pae C-U et al: J Clin Psychiatry 2007)
- CATIE patients received 543 mg/d
- A study comparing 600 & 1200 mg found no difference in efficacy (Lindenmeyer et al, 2011)

*Quetiapine side effects

- Agitation, Insomnia, Sedation, Headache, Dyspepsia
- Weight gain (not dose-related) and related metabolic side effects; insulin resistance (Ngai et al, 2014)
- Seizures occurred 0.8% in premarketing studies, which is similar to olanzapine 0.9% and higher than risperidone's 0.4%.
- QTc prolongation. Avoid combining with 13 drugs.
- 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. Not a problem in CATIE.

Quetiapine Sustained Release

Kahn et al. Schizophrenia Bull 2007;33:435

- Once daily preparation
- Starting dose 300 at bedtime. Increase to 600 at bedtime on second day.
- Same effectiveness as standard-release preparation compared with placebo

*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? Generally, no. (Bishara et al, 2013)

* Osser DN, Sigadel R (2001)

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

*Metabolic Issues w. Olanzapine

- 30% of olanzapine patients gained > 7% body wgt in CATIE. Positive relationship with serum conc.*
- Elevated triglycerides – highest with olanzapine
- HgbA1C – increased the most with olanzapine
- Triglycerides v. strongly correlated with insulin resistance (IR)
- **IR develops even after one dose!!** (Hahn et al 2013)
- 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.

*Simon et al. J Clin Psychiatry 2009;70(7):1041-50

Olanzapine Metabolic Issues - 2

- Consensus panels and the FDA have concluded that olanzapine has higher risk of weight gain, elevated lipids and diabetes.
- Several studies (non-industry sponsored) show increased insulin secretion and increased triglycerides within 1 to 2 weeks of starting olanzapine, before any weight change. This is not seen with risperidone.

J Clin Psychiatry 2004;65:267-72. Olanzapine Package Insert, PDR, 2008. J Clin Psychopharmacology 2006;26:504-7

*Other Olanzapine Side Effects

- Liver enzyme elevation (use with caution in hepatitis patients, and if patient on other medications that irritate liver e.g. statins, valproate, carbamazepine, naltrexone)
- Sedation
- EPS, prolactin elevation, & neuroleptic dysphoria can occur at doses over 20 mg
- Pregnancy: olanzapine had the highest placental passage of 4 antipsychotics: more low birth weights and neonatal ICU admissions (both 31%!). Lowest rates were with quetiapine.

(Newport DJ et al Am J Psychiatry 2007;164:1214-20)

*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 (**Schuster J-P, 2012 found good switch results**), or treat medically

- If FBS elevated, get glucose tolerance test. If abnormal, this predicted 96% of patients who developed diabetes (van Winkel et al JCP 2006;67:1493-1500)

Medication Treatments for Weight Gain from Olanzapine

- Nothing is FDA-approved
- Metformin has best evidence to treat, or perhaps better, to prevent weight gain with least side effects long term. However, wgt loss is modest compared to what was gained.
  - Often, better option is switching to another AP
  - Psychoeducation/diet counseling (See Correll 2013)
- Second choice: topiramate. Can also *prevent* weight gain if used initially.

Rado et al. Psychopharm Review 2013;48:7. Mahmood S, JCPsychopharmacol 2013. Narula PK, Sch Research 2010.

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	**+ 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

*QTc prolongation with antipsychotics

- Least: Aripiprazole
- Moderate: Haloperidol, risperidone
- Most: Ziprasidone, quetiapine

(Chung et al, J Psychopharmacology. 2011 plus package insert information)

*Depot Antipsychotics (AKA Long Acting Injectables – LAIs)

- Fluphenazine Decanoate: 12.5 mg (0.5 cc test dose) to 50 mg (2 cc) every 2-3 weeks.
- Haloperidol Decanoate 25 mg (0.5 cc test dose) to 200 mg every 4 weeks.
- Risperidone Consta. 25-50 mg IM every 2 weeks
- Paliperidone Palmitate. 50-100 mg eq every 4 w
- Olanzapine Long Acting Injectable (Relprevv). Use dose equal to 20 mg po/day. ? Stopped advertising
- Aripiprazole ER (Abilify Maintena). 400 mg q 4 w

*Risperidone “Consta®” - Efficacy

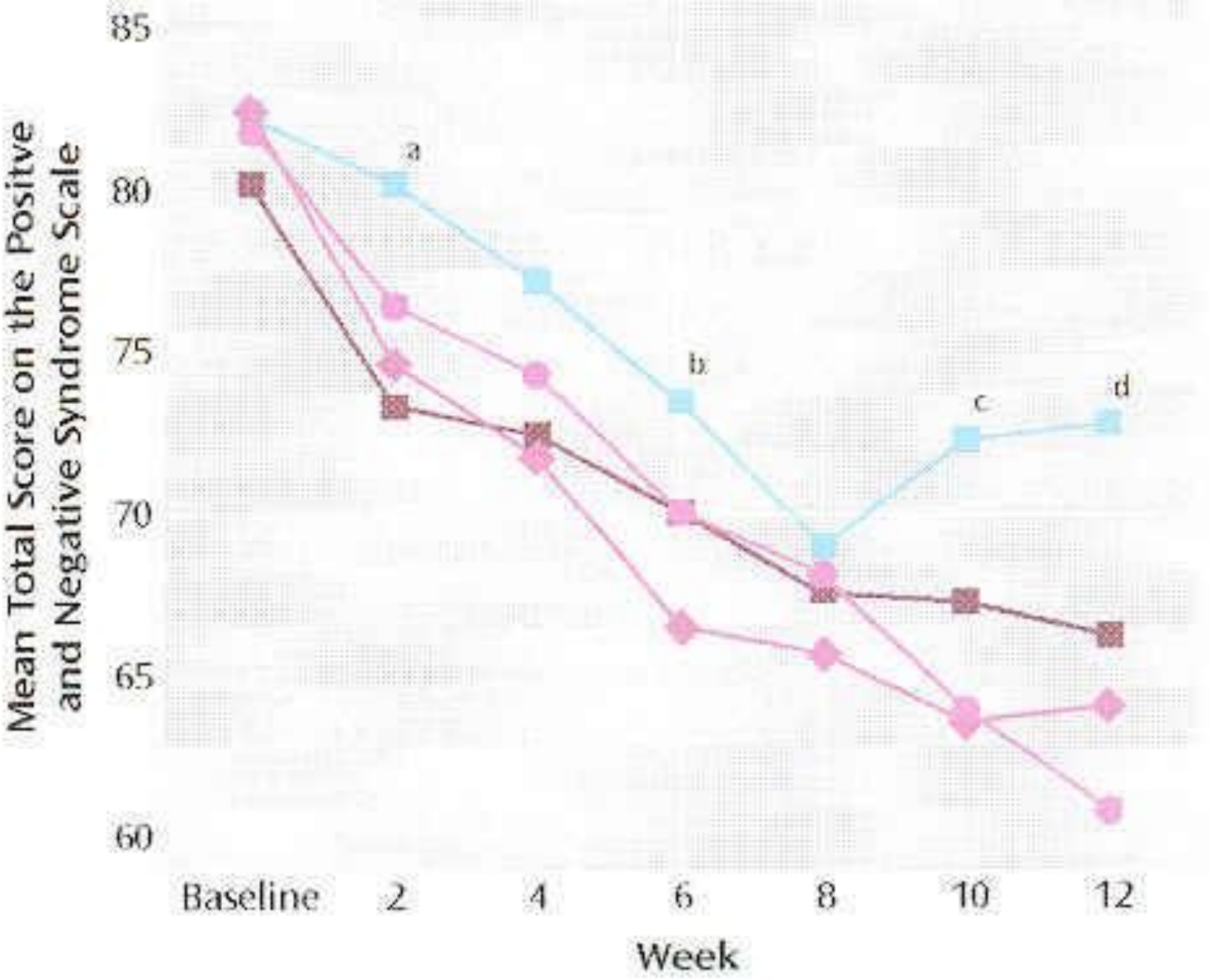
- 12-week randomized trial of IM risperidone 25, 50, 75 mg, or placebo. (Kane et al ’03)
- 461 patients entered the study.
- Patients’ CGI at start averaged 3, “mildly ill”
- Switched to oral risperidone for 1 week before the IM: 2 mg per day, then 4 mg per day after three days. Oral continued for 3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

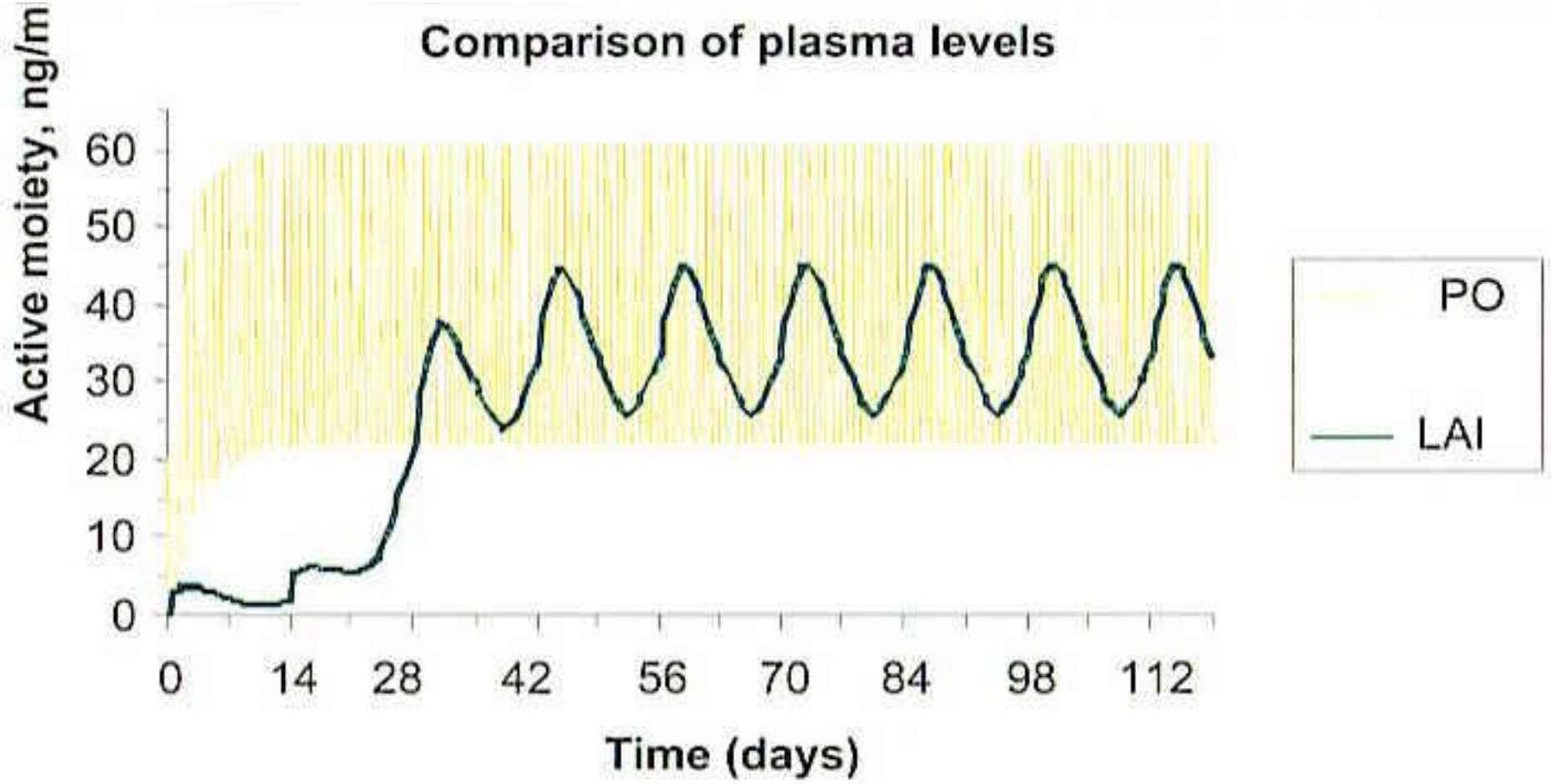
TABLE 2. Reasons for Study Discontinuation Among Patients With Schizophrenia Randomly Assigned to 12 Weeks of Double-Blind Treatment With Long-Acting Injectable Risperidone (25, 50, or 75 mg) or Placebo

	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 efficacy 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

Real World Comparison of Depot Neuroleptics and R. Consta®

- Observational study of California Medicaid patients with schizophrenia initiated on one of the three depots in 2003-4. N=2,695 patients
- Most were taking < 80% of their oral medication in the 6 months prior to depot. (mean: 60%)
- 2/3 were on more than one oral antipsychotic and about half were on concomitant mood stabilizers, antidepressants, and anxiolytics.

*Olfson M et al. Schizophrenia Bull 2007;33(6):1379-87

*Results of Comparison of Depots

- *Very few* of these treatment-resistant, partly-compliant Medicaid patients stayed on their Depot for six months:
  - Haloperidol Dec: 9.7%
  - Fluphenazine Dec: 5.4%
  - Risperidone Consta: 2.6% ($p<0.0001$)
- Speculate: Depots more helpful in more routine, less treatment-resistant patients – as is more common in Europe. Or, maybe it is the structure that helps: e.g. “Prolixin Clinics”

Paliperidone Palmitate

- Reaches steady state more rapidly than R. Consta: After second weekly injections of 50 or 100 mg, plasma concentrations are robust.
- Then, injections are every 4 weeks.
- 7 days of oral paliperidone 6 or 12 mg were given prior to the first injection.
- Strong separation from placebo in acutely ill patients. Side effects: prolactin, injection pain

*Kramer M et al. Int J Neuropsychopharmacol 2010;13:635-47

RCT comparing Paliperidone Palmitate and Haloperidol Dec.

- 311 patients at 22 sites received ~144 mg PP or ~75 mg HD IM monthly for up to 24 months
- Efficacy failure = hospitalization or “crisis” stabilization, big increase in outpatient visits, or inability to stop oral medication in 8 weeks.
- Results: no difference in efficacy failure-HR 0.98
- Side effects: More weight gain and prolactin increase with PP, more akathisia with HD

*McEvoy JP et al. JAMA 2014;311(19):1978-86. Editorial 1973-4

*Recent Studies of Effectiveness of Depots

- Rosenheck et al (NEJM, 2011) in a non-blinded trial in 369 veterans with unstable schizophrenia found non-significant advantage to depot risperidone vs. oral (HR 0.87 for rehospitalization)
- However, a study from Finland (Tiihonon et et al, 2011) and a meta-analysis (Leucht et al, 2011) found that depots reduce relapse.
- Depots probably underutilized in the US, especially early in the illness. Many patients are not very compliant and may do better with a depot.

*Olanzapine Long-Acting Injection

- The major study compared 4 doses of OLAI with oral olanzapine for 24 weeks. N=1065. (Kane et al. AJP. 2010)
- Pts were initially treated with oral olanzapine 10-20 mg for 4-8 weeks. 60% were already on olanzapine. Despite this, about *2/3 were unstable and not admitted to the study*.
- The 4 IM doses were equivalent to 1.5 mg daily (control), 10, 15, and 20 mg vs. continuing on the initial oral olanzapine.

*OLAI Study Results at 24 Weeks

- Best results were with oral olanzapine (93% survival) or the highest dose (95%)
- The other three doses had 90, 84, and 69%
- One group had injections every 2 weeks, the other every 4 – results were the same.
- Steady state plasma levels attained at 12 wks
- Weight gain comparable to oral olanzapine.

*OLAI Adverse Effects: PTSS

- Two patients (0.27%, but many received low doses) developed the Post-injection Delirium/Sedation Syndrome (PTSS): dizziness and malaise starting 10 to 20 minutes after injection progressing to severe sedation or delirium. Requires hospitalization. Recovery within 72 hours.
- This is probably due to inadvertent intravascular injection.

OLAI PTSS

- Because of PTSS, the FDA has limited distribution of OLAI to facilities that enroll in a Patient Care Program with emergency care immediately available.
- Patients have to wait at least 3 hours after the injection.
- All clinical activity is monitored by the manufacturer's Coordinating Center
- 2 deaths reported in 2013 – being investigated. Had high olanzapine levels.

*OLAI Study: Conclusions

- The population in this study was not representative of usual patients given depots. They were very stable and cooperative. Most were already on oral olanzapine when screened and wanted to continue.
- Switching to OLAI had equivalent outcome (actually, only at the highest dose) to staying on oral, but patients had to risk a new severe side effect.
- One might assume that the benefits of OLAI compared to oral might be greater in “real world” depot candidates, thus making the risks acceptable. But, as we saw in the Olfson et al study, the results in this population are quite disappointing.

*Aripiprazole LAI (Abilify Maintena)

See Kane J et al. J Clin Psychiatry 2012; 73(5):617-24

- Patients first stabilized on oral (10-30 mg daily).
- Patients were given 400 mg IM monthly or switched to IM placebo. Dose could be decreased to 300 mg for tolerability
- Oral is continued for 2 weeks.
- Followup for 1 year
- Efficacy: More relapses on placebo ($P<0.0001$)
- Side Effects: More akathisia on aripiprazole LAI
- Drug interactions: Patients on CYP 2D6 or 3A4 inhibitors (or slow metabolizers) may require lower doses. 3A4 inducers (carbamazepine: higher doses)

*Clozapine – a brief introduction

- Our most powerful treatment. Should not be left as a last resort.
- A full lecture on when and how to use clozapine is available in the Model Curriculum
- Pre-treatment workup similar to olanzapine plus WBC and ANC levels, EKG. Avoid combining with other drugs that can cause granulocytopenia like carbamazepine. (lesser risk: gabapentin, mirtazapine)
- Avoid combining with benzodiazepines if possible (possible respiratory depression risk)

*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 (absolute neutrophil count) 1.5-2.0, get repeat CBC and 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 – in brief

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

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 Acute 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)
- More recent CATIE-AD study had very similar results. (NEJM 2006, Oct 12;355(15):1525-38.)
- 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)
- It's usually not cost-effective to combine two second-generation antipsychotics.
- Risperidone became generic in mid-2008 and costs ~1% of the brand products. Quetiapine and olanzapine will follow soon.

*Antipsychotic Procurement Costs in the VA System – 1

Monthly costs as of July, 2013

- Fluphenazine 5 mg $ 2
- Haloperidol 5 mg 2
- Perphenazine 16 mg bid 49
- Risperidone 2 mg bid 3
- Paliperidone 12 mg NF 283
- Quetiapine 50 mg 3
- Quetiapine 300 mg bid 26

*Antipsychotic Monthly Procurement Costs in the VA System – 2

• Olanzapine	10 mg	$ 36
• Olanzapine	20 mg	70
• Ziprasidone	20 mg bid	192
• Ziprasidone	80 mg bid	233
• Aripiprazole	2.5, 5, or 7.5	157
• Aripiprazole	10 or 15 mg	221
• Aripiprazole	20 or more	443
• Asenapine	5 mg bid	189
• Lurasidone	40 mg	84
• Clozapine	300 mg	40

*LAI Antipsychotics Costs in VA for 4 weeks of treatment (July, 2013)

- Fluphenazine Decanoate 25 mg $ 1.
- Haloperidol Decanoate 100 mg 9.
- Risperidone Consta 50 mg 693.
- Paliperidone Palmitate (PP) 156 mg 685.
  - PP for first 5 weeks 2055.

Post-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, except

   A. Smoking increases clearance by 40%

   B. Works most quickly when started at 15-20 mg/d

   C. Elevated Hemoglobin A1C the most in CATIE

   D. Increased triglycerides the most in CATIE

   E. Produces clinically significantly better results at doses over 20 mg daily.

Answers to Pre & Post Competency Exam

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