When and How to Use Clozapine in 2011

ASCP Model Curriculum for Psychopharmacology

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Pre-Lecture Exam Question 1

All of the following suggest that a schizophrenia patient refusing clozapine is not competent to give informed consent, except

A. Patient believes that the clozapine is part of a Bosnian conspiracy to murder patients

B. Patient believes that if blood is drawn from the arm, the arm will fall off.

C. Patient is non-functional, spends most of day in bed, has no interest in any activity, but does not believe he has a mental illness.

D. Patient with severe metabolic syndrome and recent heart attack worries about clozapine risks.

Question 2

Rechallenge with clozapine might be possible after any of the following, except

A. Myocarditis

B. Agranulocytosis

C. Grand mal seizure

D. Severe constipation

Question 3

The P450 enzyme most responsible for clozapine metabolism is

A. 1A2

B. 2C19

C. 2D6

D. 3A4

Question 4

If you need to add an anticonvulsant to clozapine, the best choice would be

A. Valproic acid

B. Clonazepam

C. Carbamazepine

D. Phenytoin

Question 5

All of the following may be useful for hypersalivation from clozapine, except

A. Sublingual atropine drops

B. Glycopyrrolate 2 mg bid

C. Chewing gum

D. Sleeping on your back

Outline of Lecture

- Indications for clozapine
- Pre-treatment workup and consent process
- Initiating and optimizing dosage
- Side effect management
  - Agranulocytosis and neutropenia
  - Seizures
  - Myocarditis and cardiomyopathy
  - Weight gain
  - Others

Major Teaching Points

- Clozapine is underutilized
- Patients incompetent to consent to clozapine should have guardians appointed
- Plasma levels should be used more routinely to guide dosing and assess toxicity
- Morning pseudoneutropenia and benign ethnic neutropenia can be recognized and managed.
- Balance risks of metabolic syndrome vs. the benefits for psychosis
- Constipation, hypersalivation, tachycardia, and sedation can often be managed successfully

Why is Clozapine Underused?

- Realistic concerns about clozapine's adverse effects
- Some clinicians lack experience using clozapine
- Some are too busy with other work to prioritize the time and effort required to titrate doses and deal with the side effects

Indications for Clozapine

- Treatment-resistant schizophrenia
- Suicidal behavior
- Assaultive behavior
- Substance abuse
- Polydipsia/hyponatremia
- Nonadherence

Treatment-Resistant Schizophrenia

Most algorithms and guidelines recommend clozapine after two adequate antipsychotic monotherapy trials.
We will summarize three algorithms.

Int'l Psychopharmacology Algorithm Project Schizophrenia Algorithm (2005)

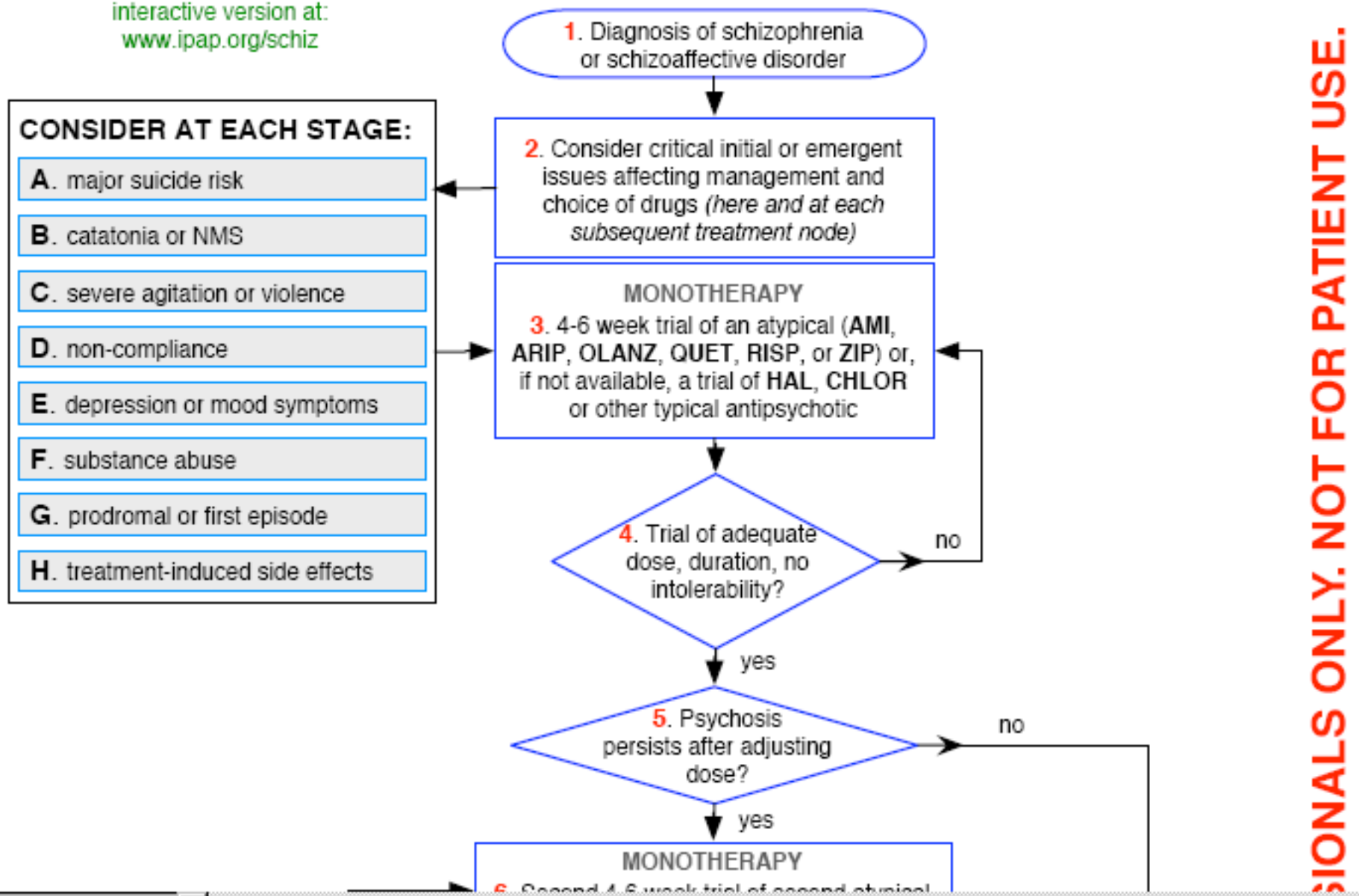
- Developed in association with the Collegium Internationale Neuropsychopharmacologicum (CINP)
- Chair: Herbert Meltzer, M.D. Co-chairs Don Goff, M.D., David N. Osser, M.D.
- 18 content experts from 8 countries
- www.ipap.org

Endorsement of this algorithm by the World Health Organization

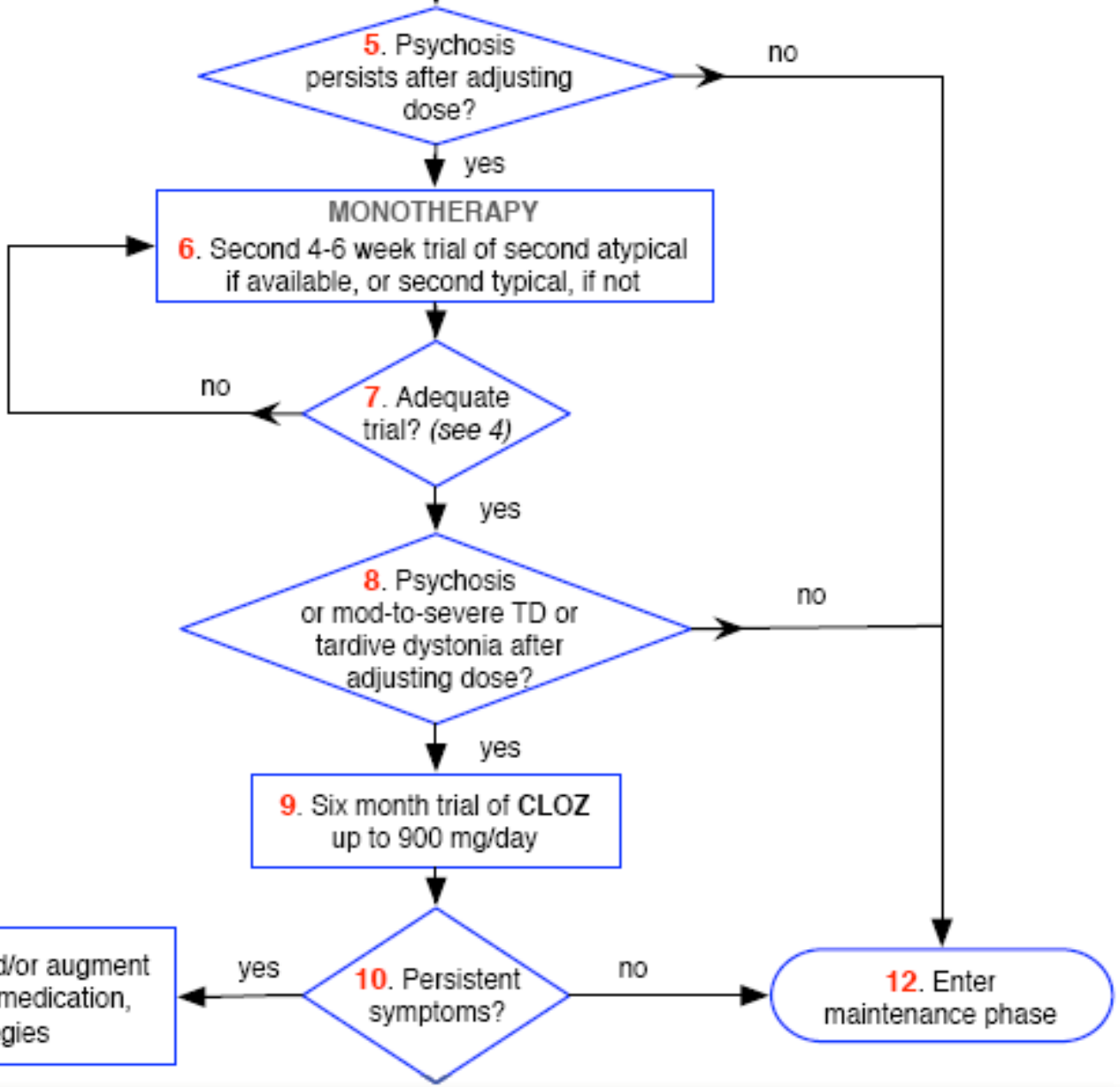
- After reviewing the algorithm and website, the WHO included the following on its website:
- “The WHO Department of Mental Health and Substance Abuse is grateful to the CINP for having made available their algorithms for treatment of schizophrenia which we recommend.” [followed by a link to the site]

updated 2004-12-23
interactive version at:
www.ipap.org/schiz

IPAP Schizophrenia Algorithm



FOR PROFESSIONALS ONLY. NOT FOR PATIENT USE.



The Texas Medication Algorithm Project (TMAP) Schizophrenia Algorithm

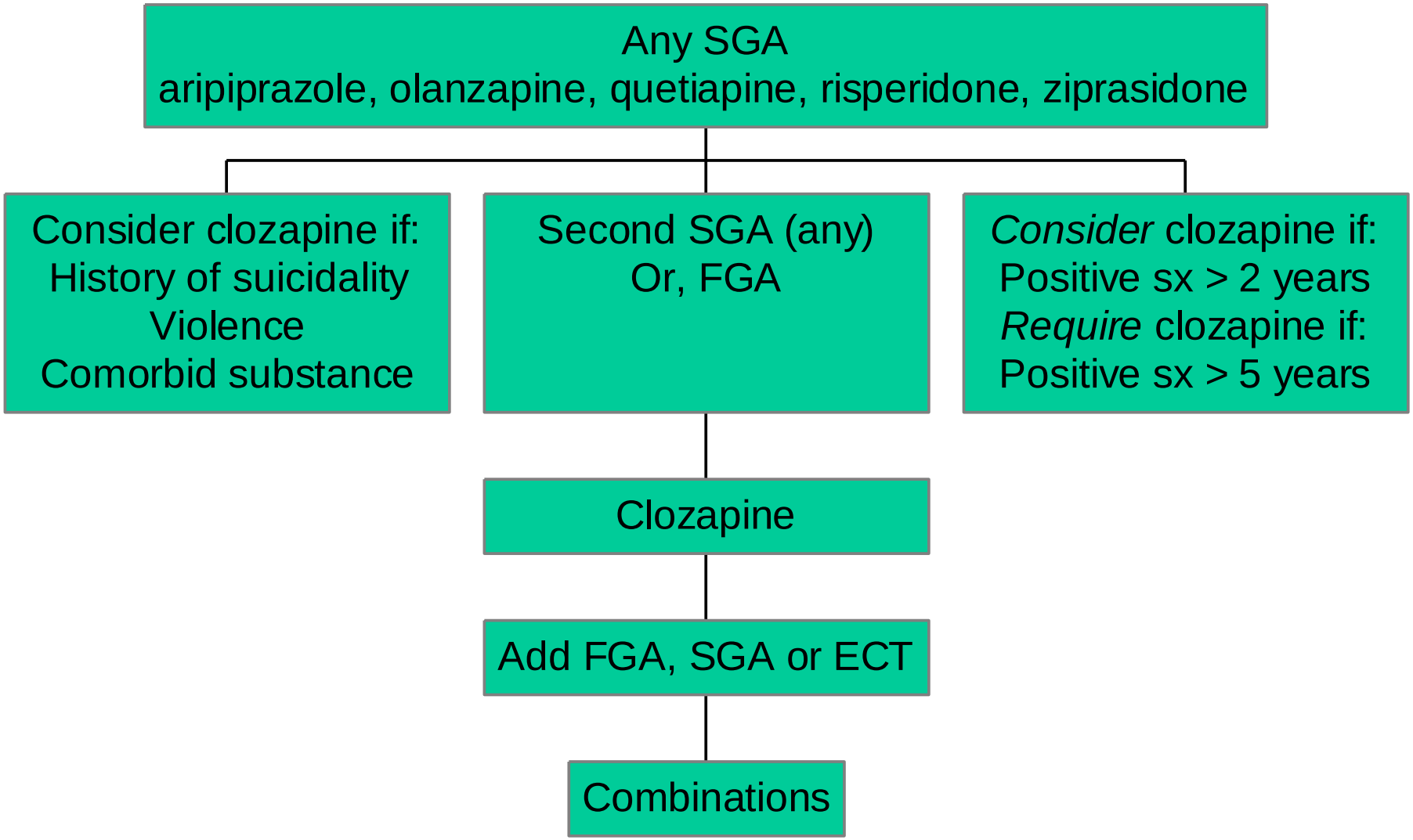
First Published 1996

Latest published version: Moore TA et al.

J Clin Psychiatry 2007;68(11):1751-62

2006 TMAP Algorithm

First Episode Schizophrenia



PSYCHOPHARMACOLOGY ALGORITHM PROJECT AT THE HARVARD SOUTH SHORE PROGRAM

www.mhc.com/Algorithms

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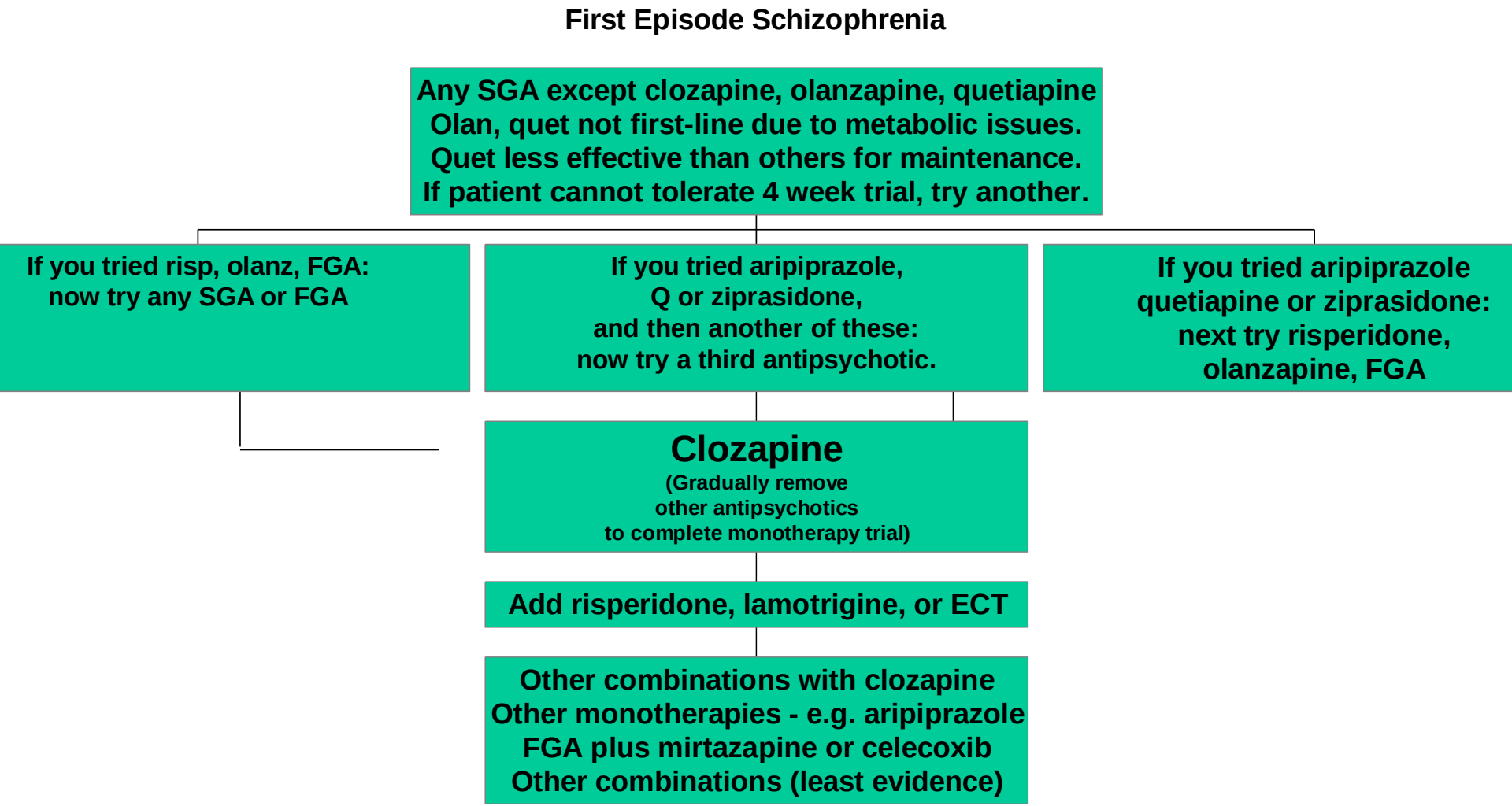
Director of Technology

Features of the PAPHSS Algorithm

- 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-see Notes Page for full refs)

2011 Schizophrenia Algorithm of the Harvard South Shore Algorithm Project*



*Jalali M, Manschreck T, Osser DN

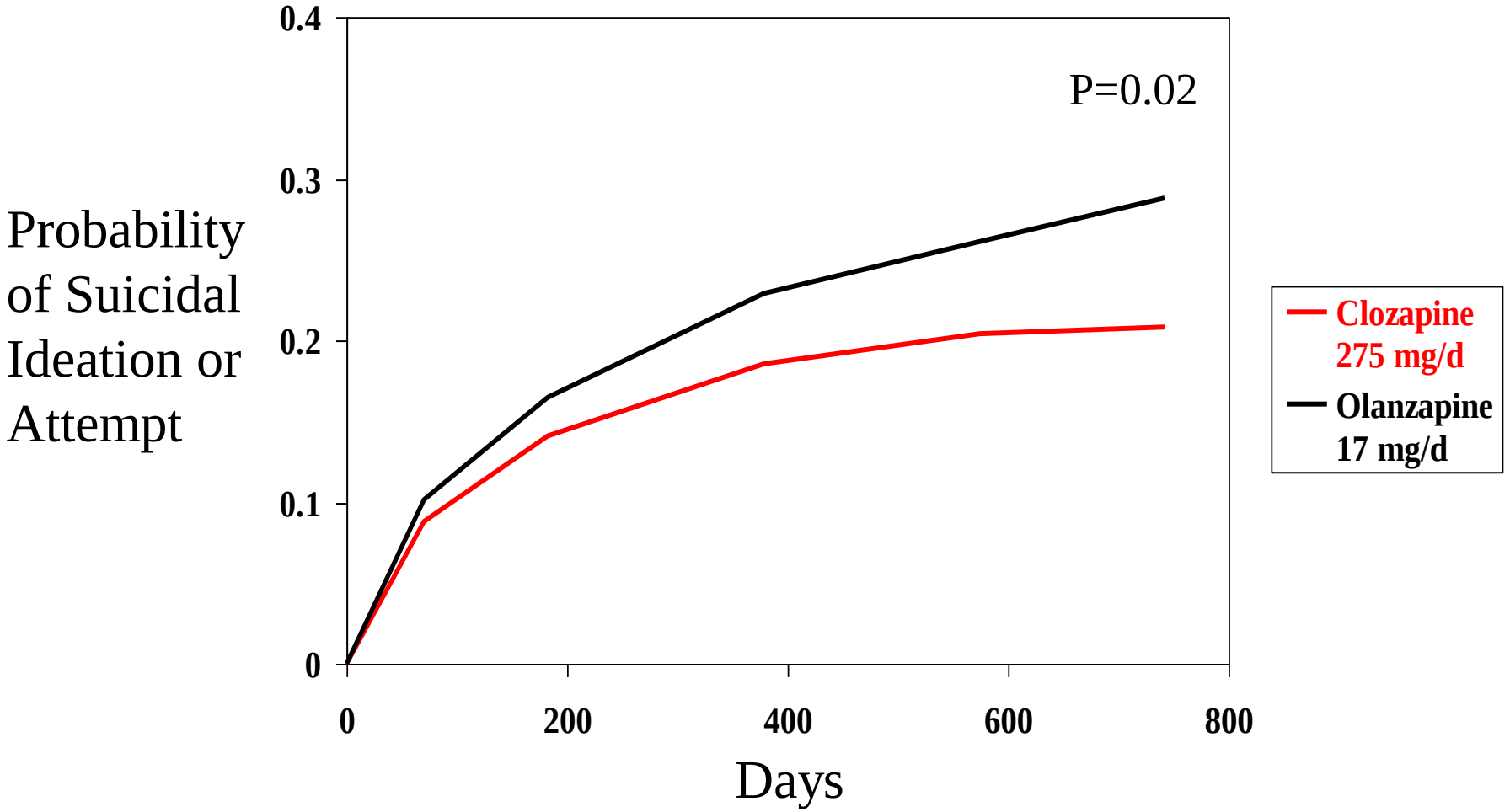
Clozapine Indication: Suicidal Behavior

- In the InterSePT trial*, 980 patients were randomized to olanzapine or clozapine
- All had history of suicide attempt or hospitalization to prevent an attempt within the last 3 years.
- All had suicidal ideation with command hallucinations to do self-harm within a week of baseline
- Only 27% were treatment-resistant
- Followed for 2 years

*Meltzer HY, et al., Arch Gen Psychiatry 2003;60:82

*

Prevention of Suicide: InterSePT*



*Meltzer HY, et al., Arch Gen Psychiatry 2003;60:82

Adverse Events in InterSePT

(note that weight gain > with olanzapine)

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

Indication: Assaultive Behavior

- Krakowski et al (2006) found clozapine better than olanzapine or haloperidol for persistent aggressive behavior in a group of non-treatment-resistant inpatients.
- This replicated previous reports that clozapine reduced violence and seclusion/restraint utilization. (Volavka et al 2004, Chiles et al, 1994)

Indication: Substance Abuse

- Brunette et al (2006) found clozapine was effective for patients with schizophrenia and comorbid substance use disorders
- Other data (Green AI, 2006) suggests clozapine prevents relapse of substance use disorders

Polydipsia and Hyponatremia

- Spears et al (1996) reported that clozapine produces significant improvement in patients with schizophrenia who drink water excessively and develop hyponatremia.

Indication: Poor Adherence

- Although adherence is often poor in patients with treatment-resistant schizophrenia, adherence rates with clozapine seem better. (Meltzer HI, 1992).
- The assumption that a previously nonadherent patient would be unlikely to comply with clozapine and its required blood draws, may be incorrect.
- Once stabilized on clozapine, patients are more adherent when blood draws are more frequent. (Patel et al, 2005)

Clozapine Pretreatment Workup and Informed Consent Process

Pretreatment Workup

- Vital signs, liver function tests, EKG, urinalysis, physical examination within 3 months.
- If history of seizures, use with caution.
- Weight, body mass index, waist circumference recommended by recent guidelines
- Baseline CBC must be > 3,500 cells/mL. Absolute neutrophil count (ANC) must be greater than 2,000.
- Avoid combining with other drugs that can cause granulocytopenia like carbamazepine.
- Avoid combining with benzodiazepines if possible (Faisal et al, 1997)

Informed Consent: Competent Pt.

- The “art” of medicine includes the ability to present an appropriately positive and convincing description of the clozapine’s potential benefits such as its ability to improve quality of life.
- The limitations of alternative approaches should be stressed (e.g. - see Kane et al. J Clin Psychiatry 2009;70:1348-57)
- If the complexities of administering a trial seem unworkable for outpatient care, consider an elective inpatient or day hospital admission

Informed Consent: Incompetent Pt.

Competence is questionable, and application for guardianship may be appropriate, if:

- Prominent negative symptoms with little interest in any potentially difficult treatment
- Patients who believe incorrectly that they are doing “fine” while it is obvious they are totally disabled by their disease.
- Exaggerated/paranoid fears of side effects

Incompetent Patient, Unwilling, Hospitalized, Guardian Allows Clozapine:

- Try crushed tablets, mixed with food or liquids
- Rapidly orally disintegrating tablet (FazaClo)
- Observe for 15-30 minutes to be sure the patient does not cheek or vomit medication
- Confirm absorption using blood levels, even weekly, during the titration process
- Firmly state to patient that he/she must allow blood tests as required by the Court or guardian

Initiating and Optimizing Dosage of Clozapine

Clozapine Dosing

- 12.5 mg for first dose. May give twice on day 1
- Elderly: 6.25 mg
- Increase by 25-50 mg per day as tolerated, to 300-400 mg per day. Maximum is 900 mg/d. No single dose should exceed 450 mg.
- For outpatients go at half this pace
- If response unsatisfactory, check plasma level. Best results are with levels of **parent compound** greater than 350 - 450 ng/ml (Schulte P, 2003)
- If dose interrupted for 48 hours, resume 12.5 mg

Clozapine Dosing - 2

- At plasma levels > 600 ng/ml, there is increased toxicity including seizures.* If going above this level, get EEG first and if seizure activity is seen, add valproate.
- Many patients do well with lower levels. Use clinical judgment with the blood level data to find the best response while minimizing side effects.

*Freudenreich et al, 1997.

Clozapine Dosing - 3

- Clozapine primarily metabolized to norclozapine by Cytochrome P450 1A2 enzyme
- 1A2 ultra-rapid metabolizers and **cigarette smokers** may have low clozapine levels at high doses
- Fluvoxamine is a strong inhibitor of 1A2 and can increase blood levels 500%.
- Lu et al* found that 100 mg of clozapine combined with 50 mg of fluvoxamine put 2/3 of patients >350 ng/ml. Norclozapine levels were very low.
- Low incidence of weight gain & other side effects

***Lu MI et al, J Clin Psychiatry 2000;61(8):594-99**

www.GeneMedRx.com

To look up drug interactions…

Managing the Adverse Effects of Clozapine

Agranulocytosis and Neutropenia

New U.S. CBC Monitoring Algorithm

- 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 until WBC > 3 and ANC >1.5, then twice weekly until WBC > 3.5 and ANC >2, then weekly x 4 weeks. Consider giving granulocyte colony stimulating factor*

***Ghaznavi S et al, Am J Psychiatry 2008;165:813-818**

Benign Neutropenias

- Morning Pseudoneutropenia
- Ethnic Neutropenia

Diurnal Variation of Neutrophils

- Circadian variation in neutrophils, with lower numbers in the morning, is driven by the cortisol cycle
- Esposito et al* hypothesized that clozapine may amplify this normal variation: **“Morning Pseudoneutropenia”**
- Clozapine CBCs are typically drawn in the morning, when ANCs may be lowest
- Thus, when neutropenia develops, it may be useful to repeat the test in the AM and at 2:00 PM for a few days
- If the ANC is normal in the PM, clozapine could be continued and levels checked routinely in the PM

Esposito et al, 2006; Porter R, Mohamed A., 2006

Ethnic Neutropenia

- Caucasian normal range for WBC: 3.6 – 9.5
- African-Americans (AA): 2.8 to 9.5.
- Thus, the range for AA patients is more likely to overlap with the range of levels that require discontinuation of clozapine.
- 25% of AA patients may be unable to start or continue clozapine because of this

***Kelly DL et al. Schizophr Bull 2007;33:1221-1224**

Lithium for Benign Neutropenias*

- Lithium stimulates WBC formation – has a mild granulocyte colony stimulating factor-like effect.
- Lithium does not protect against true clozapine-induced agranulocytosis
- Consider lithium in patients with low baseline WBC/ANC levels such as AA patients
- Dose is 300-600 mg daily

*Taylor D et al. Maudsley Prescribing Guidelines, 10th ed. Informa Health Care. 2009:68-70

Seizures

Managing seizures

- Seizure disorder is not a contraindication for clozapine but neurology consultation is advised to help weigh the risks versus the benefits.
- Myoclonic jerking during clozapine titration may be a prodrome: check plasma level and if elevated, adjust dose down to 350-500 ng/ml.
- If seizure occurs, reduce dose by 50% and add valproate, before increasing clozapine again.

Myocarditis and Cardiomyopathy

Symptoms and Course

- Myocarditis usually occurs in first 6-8 weeks of treatment; cardiomyopathy (enlarged heart) later, median 9 months.*
- Fatality risk estimated 1:67,000 in U.S., 1:12,500 in Canada, 1:1,300 in Australia**
- Symptoms: Tachycardia, fever, fatigue, dyspnea, chest pain, flu-like symptoms
- Signs: Eosinophilia, EKG shows ST depression, enlarged heart on echo

***Taylor D et al. Maudsley Prescribing Guidelines, 10th ed 2009**

****Ronaldson KJ et al. Schizophrenia Res 2011;128(1-3):161-5**

Management

- Heavy alcohol consumption is a risk factor
- Stop clozapine immediately
- May require medical hospitalization
- For extremely treatment-resistant patients, successful rechallenge has been reported, but recurrence is possible. Monitoring guidelines are available.*

Reinders J et al, Aust NZ J Psychiatry 2004; Roh S et al, Exp Clin Psychopharmacol 2006. *Ronaldson et al. Aust NZ J Psychiatry 2011.

Weight Gain
and Metabolic Syndrome:
Insulin Resistance
Hypertriglyceridemia
Type 2 diabetes

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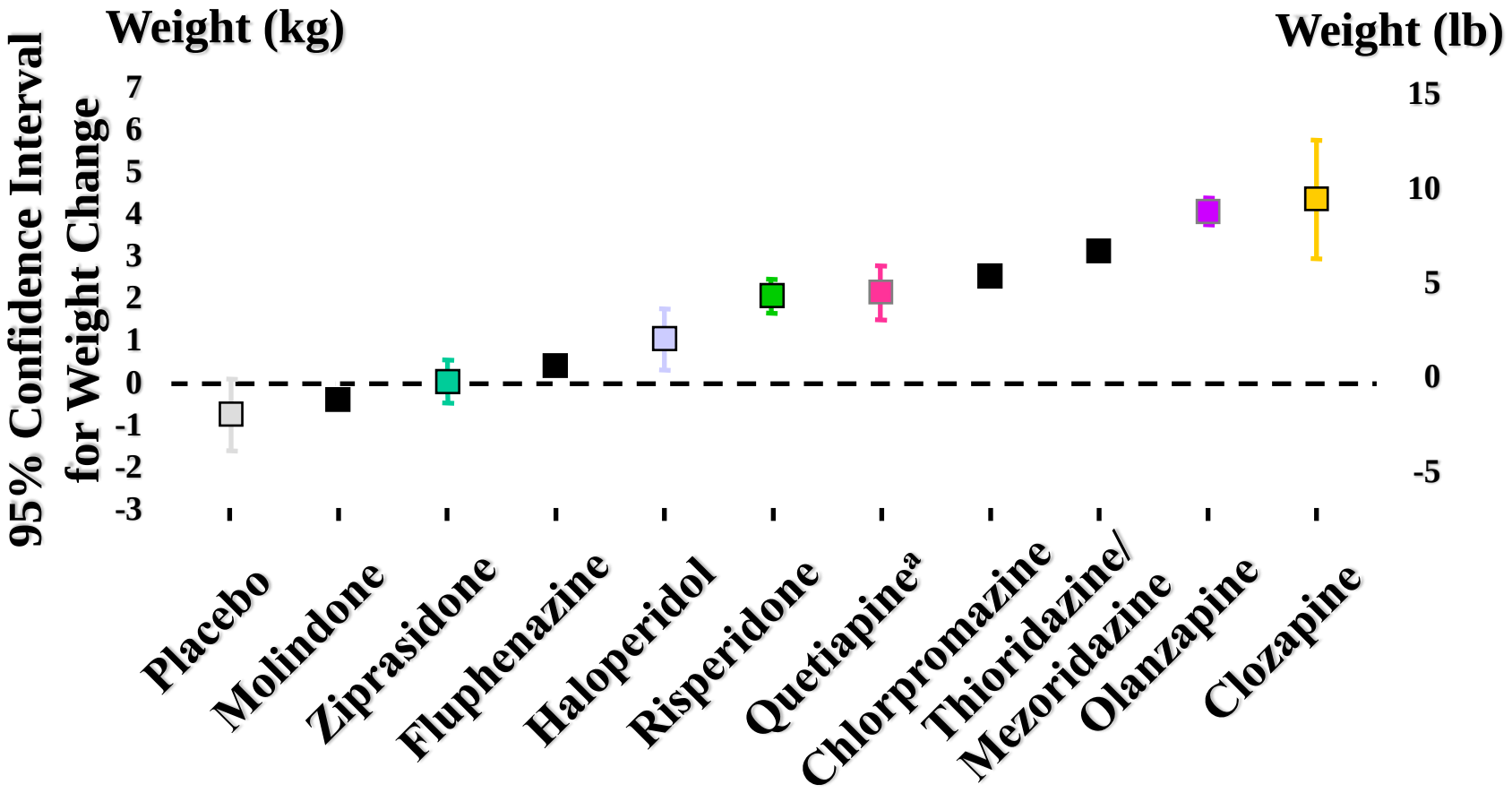
Meta-analysis of Antipsychotic-related Weight Gain

Estimate at 10 Weeks[a]



[a] Quetiapine weight gain estimated at 6 weeks

Allison DB, et al., Am J Psychiatry 1999;156:1686

Treatment Approaches

- Proper nutrition and exercise: patients may be more willing and able to cooperate when they have improved
- Pharmacological: Cochrane review concluded no agent is favored over any other for atypical antipsychotic-induced weight gain.* **Topiramate** and **metformin** have had modest success with olanzapine. Others with mixed results include **sibutramine**, **nizatidine**, and **amantadine**. Adjunctive **aripiprazole** was helpful in 2 reports and not helpful in a third.**

***Faulkner G et al. Schizophrenia Bull 2007;33:654-656;**

****Mitsonis CI et al. Prog Neuropsychopharmacol Biol Ps 2007;31:373-7**

Constipation

Constipation: A Major Side Effect

- Affects 14% of patients and often persists
- Palmer et al. reported 102 cases of life-threatening constipation from clozapine with a mortality rate of 27.5%*
- Death was from paralytic ileus, megacolon, and bowel ischemia

Palmer SE et al. J Clin Psychiatry 2008;69:759-68

Constipation: Management

- Avoid excessive doses and blood level
- Avoid concomitant anticholinergics
- High fiber diet, adequate hydration (e.g. during febrile illness), exercise
- Bulk laxatives, fiber supplements, stool softeners – unless obstructive symptoms present (pain, distension, vomiting)

Other Clozapine Side Effects - 1

- **Sedation**: Affects 40%. **Caffeine** helpful, but prescription stimulants including modafinil may induce psychosis
- **Hypersalivation**: Affects 30%. Encourage swallowing, e.g. sugarless gum, sleep on side. Medications include **glycopyrrolate** 1-4 mg bid (has RCT*), **sublingual atropine** drops.

Praharaj SK et al. Psychopharmacology 2006;185:265-73;

***Liang C-S et al. Schizophrenia Res 2010;119(1-3):138-144**

Other Clozapine Side Effects - 2

- **Tachycardia**: Affects 25-50%. Usually does not indicate myocarditis **if** the other signs/symptoms are not present. Can go over 120 beats/minute. Delay dose increases until pulse decreases. Check EKG. Reduce caffeine. May use **propranolol or atenolol**
- **Hypotension/dizziness**: Affects 20%. Reduce rate of dose increase, advise patients to rise slowly from bed or chair, hydrate adequately, consider use of support hose

Other Clozapine Side Effects - 3

- **Sweating:** Biperiden (Akineton), an antiparkinsonian agent with selective M1 muscarinic blocking effect, may be helpful. Clozapine is a partial agonist at this receptor. Dose is titrated to 2 mg tid.

  (Richardson C et al. Am J Psychiatry 2001;158(8):3129-30)

Other Clozapine Side Effects - 4

- **Obsessive-compulsive symptoms**: Affects 10%. May consider an SSRI- **sertraline** (but avoid citalopram or escitalopram – recent package insert warning of metabolism inhibition and elevated clozapine levels). Avoid fluvoxamine and fluoxetine for same reason. Avoid clomipramine because of anticholinergic effects. Aripiprazole useful.**

*De Haan L et al. J Clin Psychiatry 1999;60:364-5

**Glick ID et al. J Clin Psychiatry 2008;69(12):1856-9

Other Clozapine Side Effects - 5

- **Rebound psychosis after stopping clozapine abruptly**: These exacerbations may respond less well than the original psychosis when clozapine restarted.
- Mechanism may be cholinergic hypersensitivity.
- Can have nausea, vomiting, diarrhea, headaches, restlessness, agitation, diaphoresis
- Try immediately starting an anticholinergic (e.g. **benztropine**), then taper slowly as clozapine or the next antipsychotic is given

Miodownik C et al. J Clin Psychiatry 2006;67:1204-8

Conclusion and Case Vignette

This lecture has focused on using clozapine when indicated and considering available strategies for managing adverse effects that might otherwise prevent completion of an adequate trial.

Case Vignette

50 year old man has a 35 year history of schizophrenia and hospitalized most of his adult life because of severe paranoia and assaultiveness toward other patients, family, and staff. Also has temporal lobe seizure disorder with occasional grand mal and multiple focal seizures daily. Obese, 300 lb. Current admission lasting 6 years with frequent changes of ward because of harming others.

After staring clozapine, glucose level suddenly rose to 500 mg/dL. Diagnosis: diabetes. Managed with insulin while continuing clozapine. Psychosis improved over a 6 month period. Paranoia and assaultiveness abated. Patient lost 60 lb and diabetes eventually managed with oral agents. No grand mal seizures, and his focal seizures stopped as well – they probably were pseudoseizures, in retrospect.

After 6 months on clozapine, WBC and ANC levels began to gradually drop. When ANC was found to be 1300 cells/mL, interrupting or stopping clozapine seemed necessary. However, 2:00 PM ANC was found to be 3000 cells/mL. “Morning pseudoneutropenia” was diagnosed and patient continued on clozapine with twice weekly CBC at 2:00 PM. Patient was successfully discharged.

Post-Lecture Exam Question 1

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Answers to Pre & Post Competency Exam

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