Currently Available Antipsychotic Medications

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First-Generation Antipsychotic Medications (FGAs)

- Sole antipsychotic action is dopamine D2 (DAD2) receptor blockade
- Other pharmacological actions determine each individual SGA's side effect profile
- Efficacy is largely confined to positive psychopathology
- Can worsen affective, cognitive, and negative psychopathology with increasing dose

FGAs

- DAD2 blockade in movement-related structures produce a variety of extrapyramidal side effects (EPSE), including dystonia, bradykinesia-rigidity, akathisia, and tremor
- Maximum available therapeutic benefit is achieved at doses below those producing coarse EPSE in most patients (the neuroleptic threshold)

Anitcholinergic Activity

- Can reduce acute EPSE while the dose of the FGAs are being reduced
- Intrinsic in some FGAs, e.g. thioridazine
- Associated with dose-related dry mouth, blurred vision, constipation, and cognitive impairment (new memory acquisition, delirium)

Tardive Dyskinesia

- Arises after months or years of treatment with FGAs
- Associated with excessive doses that produced coarse EPSE
- Choreiform
- May not resolve if FGAs discontinued

Loxapine

- Serotonin 5HT2 receptor blockade is as strong as DAD2 receptor blockade
- The crossover to the SGAs
- Well-tolerated by many patients at doses of 5-25 mg daily

Second Generation Antipsychotic Medications (SGAs)

- Serotonin 5HT2 receptor blockade is stronger than DAD2 receptor blockade
- Greatly reduce propensity to induce EPSE
- Ameliorates tardive dyskinesia
- Less likely to worsen affective, cognitive, and negative psychopathology. May have beneficial effects on affective psychopathology

Weight Gain and Metabolic Side Effects

- Risperidone, olanzapine, and quetiapine (and paliperidone) are associated with substantial weight gain, insulin resistance, dyslipidemias, and inflammation
- These side effects contribute to cardiovascular risk and accelerated morbidity and mortality

Olanzapine

- Appears to have more therapeutic efficacy than all the other non-clozapine antipsychotic medication
- The pharmacological mechanism for this is unknown
- However, because of its effects on weight and cardiovascular risk, it is a second-line agent

Aripiprazole

- Strong antagonism at serotonin 5HT2 receptors
- Partial agonist at DAD2 receptors
- Can ameliorate EPSE and tardive dyskinesia
- Can lower prolactin levels

Refinements of the SGA Concept

- Asenapine and lurasidone have the positive aspects of earlier SGAs with much less associated weight gain and metabolic side effects. They also do not elevate prolactin levels.

Clozapine

- Weak DAD2 receptor blockade with strong 2HT2 receptor blockade
- Substantial therapeutic efficacy in patients who show little benefit from other antipsychotic medications
- Reduces otherwise treatment-resistant aggressive behaviors, self-injurious behaviors, water intoxication, and substance use

Clozapine

- Despite it's impressive efficacy for otherwise treatment-resistant positive and affective psychopathology, clozapine offers little, if any, benefit for cognitive and negative psychopathology
- The pharmacological mechanisms underlying clozapine's superior efficacy for positive psychopathology are unknown

Clozapine Side Effects

- Agranulocytosis
- Myocarditis
- Weight gain and metabolic side effects
- Constipation
- Venous thrombo-embolism
- Enuresis and urinary incontinence
- Hyper-salivation

Clozapine

- Third line agent
- Advances to second line in the presence of severe aggressive or self-injurious behaviors
- Should be used by experienced clinicians who have procedures in place for monitoring patients and are comfortable with methods to mitigate and respond to clozapine's side effects

The CATIE Schizophrenia Trials

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CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness.

The Time and Place

- Second Generation Antipsychotic (SGA) medications began appearing in the early 1990s and became widely used
- The National Institute of Mental Health released an RFA to compare the effectiveness and tolerability of the SGAs, each against the others, and relative to an exemplar of the First Generation Antipsychotic (FGA) medications

The Time and Place

- Risperidone, olanzapine, and quetiapine were approved, and the New Drug Application for ziprasidone was under review

The Five Questions
Study 1 and 1A

- Are any or all of the SGAs more effective and tolerable than an exemplar of the FGAs (ie, perphenazine)?
- Are any of the SGAs more effective and tolerable than others of the SGAs?

The Five Questions
Study 1B

- Among individuals who discontinued perphenazine in Study 1, is olanzapine, quetiapine, or risperidone more effective and tolerable than any of the others?

The Five Questions
Studies 2(Cloz) and 2(Zip)

- Among individuals who had discontinued one of the SGAs in Studies 1, 1A, or 1B, is clozapine more effective and tolerable than switching to another of the SGAs?
- Among individuals who had discontinued one of the SGAs in Studies 1, 1A, or 1B, is ziprasidone more effective and tolerable than switching to another of the SGAs?

Who Participated?

- Individuals with schizophrenia (schizoaffective disorder)
- Individuals 18 to 65 years of age
- Those with comorbid medical disorders were welcome
- Those with comorbid substance abuse disorder were welcome

Who Was Excluded?

- First-episode psychosis
- Individuals taking a long-acting injected antipsychotic medication
- Individuals treated with clozapine

The Primary Outcome Measure

- All-cause treatment discontinuation (ACTD)
- Survival analyses addressed time to ACTD

Secondary Outcome Measures

- Reasons for treatment discontinuation, including administrative, clinician's decision (inadequate therapeutic effect or intolerable side effect), and patient decision
- Positive and Negative Syndrome Scale (PANSS), Calgary Depression Rating Scale (CDRS), QOL
- Assessments for extrapyramidal side effects (EPSE), weight and metabolic measures, and an AE/SE scale

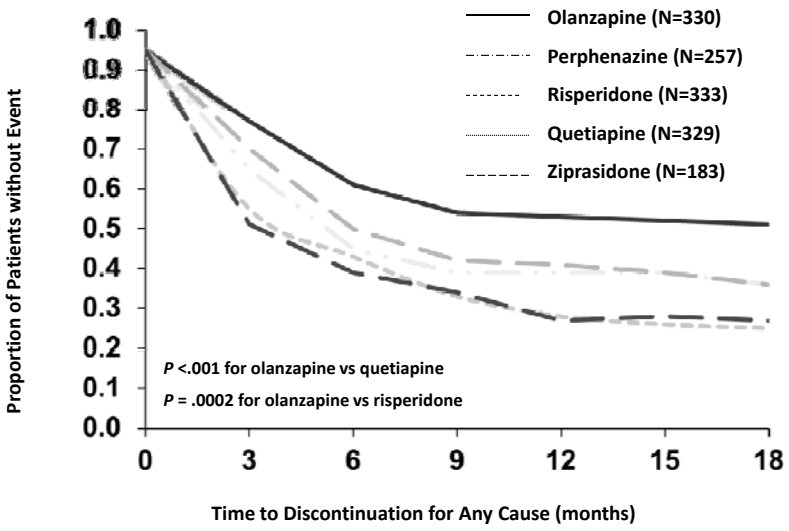
Why Perphenazine?

- Experienced clinicians believed that the distance between the dose-therapeutic response and the dose-EPSE curves was larger for perphenazine than haloperidol
- Restricted-dose perphenazine
- The “stigma” of haloperidol

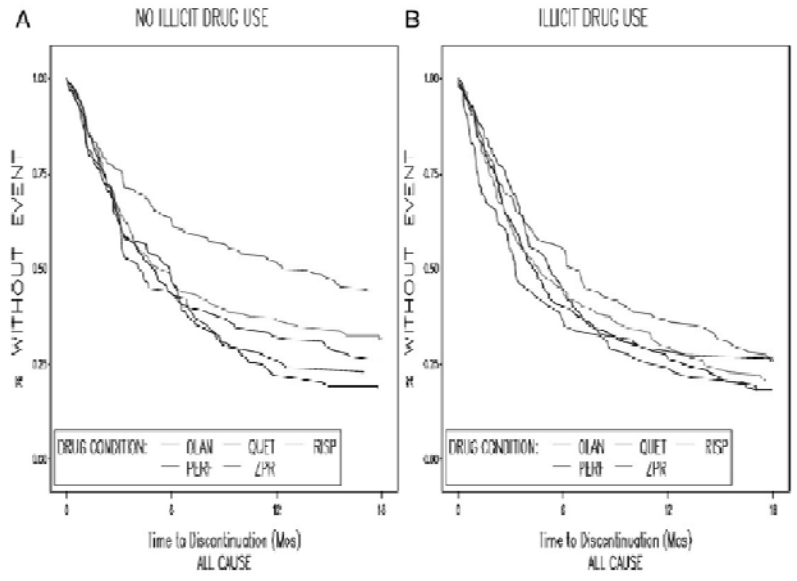
Question 1

- Are any or all of the SGAs more effective and tolerable than an exemplar of the FGAs (ie, perphenazine)?
- Yes, individuals treated with olanzapine had significantly longer times to ACTD than individuals treated with perphenazine

CATIE Trial: Effectiveness of Antipsychotic Drugs in Chronic Schizophrenia



Lieberman JA, Stroup TS, McEvoy JP, et al. *N Engl J Med*. 2005;353:1209-1223.



Swartz MS, Wagner HR, Swanson JW, et al. *Schizophrenia Research*. 2008;100:39-52.

Comorbid Substance Use Disorder

- Adds “noise” or “chaff”
- Cannot compare the effectiveness and tolerability of oral medications in individuals who often do not take them

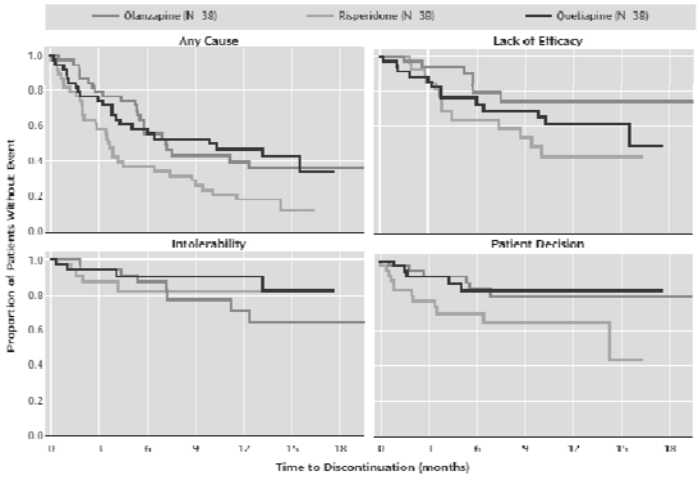
Question 2

- Are any of the SGAs more effective and tolerable than other of the SGAs?
- Yes, individuals treated with olanzapine had significantly longer time to ACTD than patients treated with quetiapine or risperidone
- Small sample size with ziprasidone limited power to detect differences

Question 3

- Among individuals who discontinued perphenazine in Study 1, is olanzapine, quetiapine, or risperidone more effective and tolerable than any of the others?
- Yes, individuals treated with olanzapine or quetiapine had significantly longer times to ACTD than patients treated with risperidone

Time Until Discontinuation for Patients Randomly Assigned to Olanzapine, Quetiapine, or Risperidone in CATIE Phase 1B After Discontinuation of Perphenazine in Phase 1

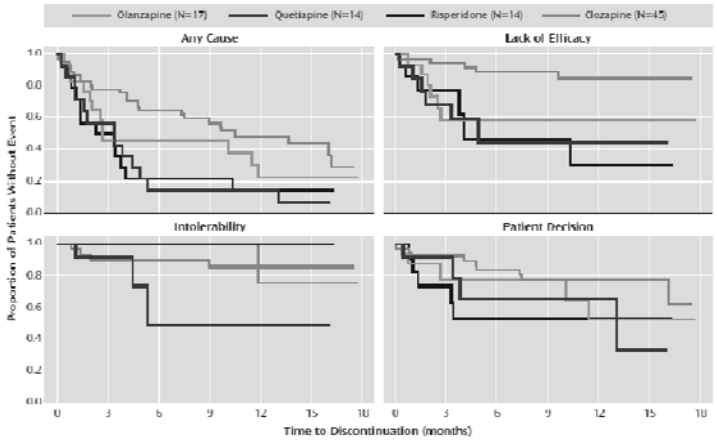


Stroup TS, Lieberman JA, McEvoy JP, et al. *Am J Psychiatry*. 2007;164:415-427.

Question 4

- Among individuals who had discontinued one of the SGAs in Studies 1, 1A, or 1B, is clozapine more effective and tolerable than switching to another of the SGAs?
- Yes, individuals treated with clozapine had significantly longer times to ACTD than patients treated with quetiapine or risperidone

Discontinuation Survival Curves of Patients Randomly Assigned to Clozapine or Another Atypical Antipsychotic

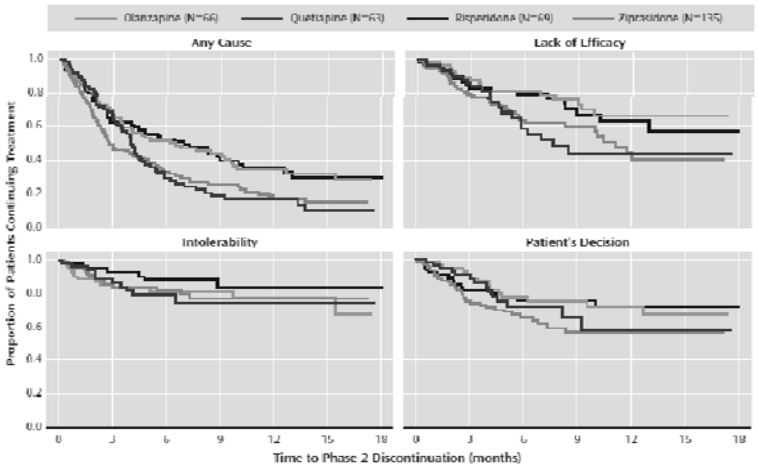


McEvoy JP, Lieberman JA, Stroup TS, et al. *Am J Psychiatry*. 2006;163:600-610.

Question 5

- Among individuals who had discontinued one of the SGAs in Studies 1, 1A, or 1B, is ziprasidone more effective and tolerable than switching to another of the SGAs?
- No, individuals treated with olanzapine or risperidone had significantly longer times to ACTD than did individuals treated with quetiapine or ziprasidone

Time Until Discontinuation Among Schizophrenia Patients Randomly Assigned to Double-Blind Treatment With Olanzapine, Quetiapine, Risperidone, or Ziprasidone



Stroup TS, Lieberman JA, McEvoy JP, et al. *Am J Psychiatry*. 2006;163:611-622.

Psychopathology

- Olanzapine produced the greatest reductions in psychopathology (PANSS)

Side Effects

- Across the trials, olanzapine, followed by quetiapine and risperidone, produced the most weight gain, cholesterol elevations, and insulin resistance
- Risperidone produced the most prolactin elevation
- Perphenazine was associated with more discontinuations due to EPSE

Take-Aways

- Many individuals (not everyone) do very well on low-dose perphenazine with no weight gain, metabolic side effects, or prolactin elevations
- Olanzapine offers greater therapeutic effectiveness, but at the cost of substantial weight gain and metabolic side effects (second line with risk management)

Long-Acting Injected Anti-Psychotic Medications

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What's the Point?

- Real-time accurate intelligence about compliance
- The decision about taking meds only has to be made once every 2-4 weeks, not every day
- Shared decision-making works best when everyone speaks facts and follows through

For Whom?

- Two recent comparisons of Risperidone microspheres versus oral meds showed no difference in relapse rate
- To get into these studies, patients had to demonstrate characteristics of those likely to take oral meds

Rapid Onset

- Prevention of early loss
- Nearly 50% of individuals released from an psychiatric hospitalization never fill the first prescription

Del Guidice

- Patients recruited in hospital for treatment of an acute psychotic episode
- Randomized to:
- LAI fluphenazine and placebo pills
- LAI placebo and fluphenazine pills
- Placebo pills
- Re-hospitalization least likely with LAI-FLU

Fluphenazine - D

- Dose range is 6.25 to 12-5 mg Q2weeks for most patients
- Interval can be widened slightly

Haloperidol-D

- Dose range is 25 to 50 mg Q4weeks for most people
- Is it better to go to Q4weeks with appropriate candidates?

Risperidone Microspheres

- Long delay in initiation of action
- Q 2 weeks
- Weight gain
- Prolactin related side effects
- Really expensive
- No evidence it is better than FLU-D or HPL-D

Paliperidone Palmitate

- Loading dose for faster onset
- Basically risperidone
- Weight gain
- Prolactin related side effects
- Very expensive
- Results soon from comparison with HPL-D

Olanzapine Pamoate

- Only for those who: 1. have a differential response to OLZ, and 2. are expected to have poor compliance to oral OLZ
- PDSS
- OLZ side effects: weight gain, insulin resistance, dyslipidemia
- Very expensive

Aripiprazole LAI

- Delayed onset of action
- Only for those who have a differential tolerability with ARIP, and who are expected to be non-compliant with oral ARIP
- Very expensive

An Update on Starting and Managing Patients on Clozapine

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Indications for Clozapine

- Treatment-resistant psychotic disorders

- Aggression
- Self-injurious behaviors
- Co-morbid substance use disorder
- Water intoxication

Indications for Clozapine

- Early-onset psychotic disorders
- Childhood Schizophrenia

Indications for Clozapine

- Borderline Personality Disorder with severe suicidal or self-injurious behaviors

In Preparation

- Explain to patients and their families that treatment with clozapine will require monitoring for dangerous early side effects (all of which are reversible if detected) and the use of concomitant medications to reduce risk for clozapine's long term side effects
- Clozapine should be prescribed by clinicians who use a lot of clozapine

Early Dangers

- Agranulocytosis
- Myocarditis
- Thromboembolism

Agranulocytosis

- Prior to starting clozapine discontinue, if possible, valproate, carbamazapine, or other medications that may lower WBCs
- Consider starting lithium. Lithium releases the marginal pool of granulocytes and stimulates granulocyte development

Agranulocytosis

- 1/100
- Risk is highest in the first 6-12 weeks, then decreases markedly but never goes away entirely
- CBC with differential every week for 6 months, then every two weeks for 6 months, then every month forever

Myocarditis

- 1/500 – 1/2500
- Risk is highest around two weeks. The risk seems to go to zero after 4 weeks if no evidence of activity prior to that.
- At autopsy, damaged myocytes infiltrated by eosinophils

Monitoring for Myocarditis

- At baseline and weekly for four weeks:
- Inflammation: sedimentation rate or C-reactive protein
- Eosinophil count: part of the CBC
- Myocardial damage or dysfunction: creatine phospho-kinase (CK, CKMB), troponins, brain natriuretic peptide (BNP)
- Electrocardiogram

Monitoring for Myocarditis

- Temporary blips in one or another marker are common. The pattern of change of all markers is what is key
- If a worrisome pattern develops, stop clozapine
- Re-challenge?

Venous Thrombo-Embolism

- Incidence increased 7-10 fold in patients taking clozapine. May present as sudden death
- Aspirin
- Statins
- Omega-3 fatty acids

Long-Term Risks

- Accelerated atherosclerotic cardiovascular disease (ASCVD), mediated through weight gain, insulin resistance and dyslipidemia
- Constipation, at times proceeding to ileus, sepsis and death
- Seizures

Monitoring for ASCVD Risk

- Lipid profile at baseline and four weeks, then yearly. Fasting is desirable.
- C-reactive protein at baseline and four weeks, then yearly.
- Hemoglobin A1c at baseline and four weeks, then every 6 months

Lipid Profile

- Non-HDL-cholesterol provides information about the lipids that are getting carried to and into atherosclerotic plaques. Treatment is through statins
- HDL-cholesterol provides information about the lipids being removed from plaques. Treatment is through exercise and niacin
- Triglycerides are leading indicators of insulin resistance. Treatment is through exercise, metformin, and omega-3 fatty acids

C-Reactive Protein

- Atherosclerosis is an inflammatory process
- CRP is an independent predictor of heart attack and stroke, over and above lipid measures

Hemoglobin A1c

- Integrated measure of glucose levels over several weeks
- Need not be drawn fasting
- Current primary criterion of ADA for diagnosis of diabetes mellitus

Metformin

- Prevents or reduces weight gain
- Reduces insulin resistance and preserves pancreatic Beta-cell function
- Contra-indicated in renal disease (creatinine > 1.5)

Aspirin

- Value of aspirin in preventing heart attack and stroke is related to individual's risk level for ASCVD.
- Any one taking clozapine should be considered at high risk for ASCVD.

- Enteric coated
- 325 mg vs 81 mg

Fish Oil

- Individuals with psychotic disorders have low levels of omega-3 fatty acids in a variety of structural lipids

- May mitigate insulin resistance, hyper-coagulable states

Constipation

- Fluids
- Fiber
- Exercise

- Stool softeners
- Polyethylene glycol (miralax)

- May present as nausea and vomiting

Seizures

- Know prior seizure history (e.g. febrile convulsions)

- Related to dose and plasma level

- Myoclonic jerks foreshadow seizures

Annoying Side Effects

- Hyper-salivation, drooling
- Bed-wetting
- Sleepiness

Hyper-salivation

- Related more to reduced swallowing than to excessive saliva production
- During the day, consider sugarless gum with the hope that chewing will trigger swallowing
- At night, use a towel, and consider benztropine 1 mg QHS

Enuresis

- Unless you ask, you will only rarely learn when this occurs. It may lead to medication non-compliance or discontinuation
- Relaxation of the urethral sphincter
- Ephedrine 25 mg QHS or pseudoephedrine 30 mg bid tightens the sphincter

Somnolence

- Dose and blood level related
- Slow-release stimulant

Plasma Level Monitoring

- Only clozapine levels matter. Ignore nor-clozapine
- Standards based on 12-hour trough levels during BID dosing: goal for most patients 200-300 ng/ml
- Outliers exist

Augmentation of Clozapine (Exploratory)

- Aripiprazole
- Lamotrigine
- Minocycline