

# Atypical Antipsychotics

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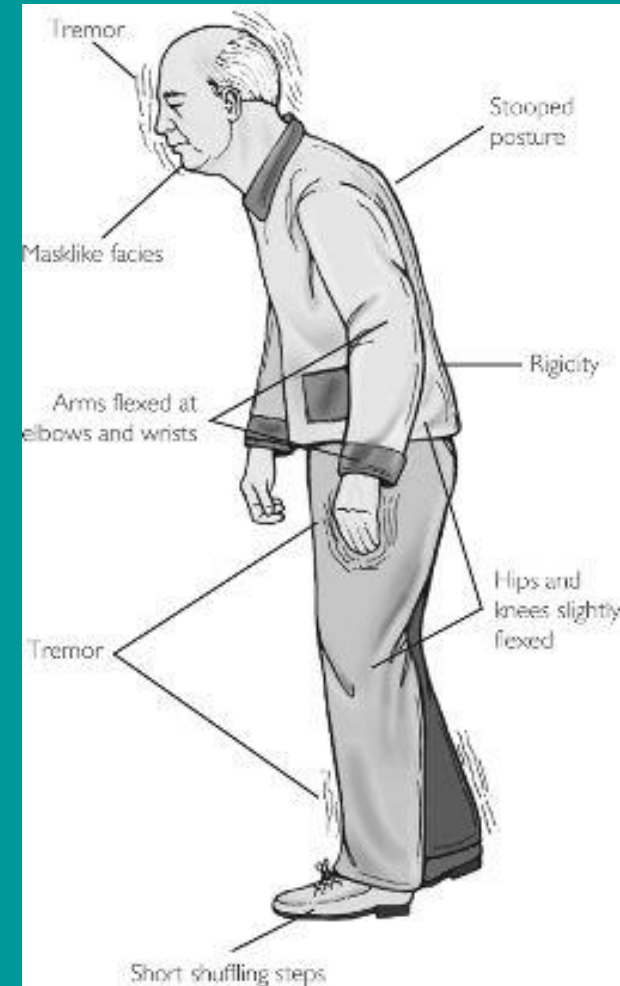


# Overview

- Common Uses
- Adverse Effects
- Cost
- Mechanism of Action
- Tailoring to the clinical scenario
- Drug-Specific Pearls

# Antipsychotics: Typical vs. Atypical

- Typical
  - Typically produce Extrapyraxidal symptoms (EPS)
    - Akathisia
    - Acute dystonic reactions
    - Parkinsonism
    - Tardive dyskinesia
- Atypical
  - Do not typically produce EPS



# What are they?

- Clozapine (Clozaril) – *the very first atypical*
  - Olanzapine (Zyprexa)
  - Quetiapine (Seroquel)
  - Risperidone (Risperdal)
  - Aripiprazole (Abilify)
  - Ziprasidone (Geodon)
  - Paliperidone (Invega)
  - Asenapine (Saphris)
  - Lurasidone (Latuda)
- 
- the most commonly used*
- new atypicals*

# Common Uses

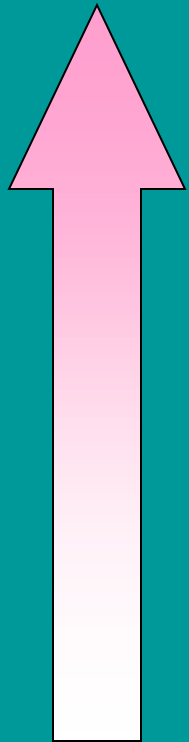
- Primary Psychotic Disorders
- Mood Disorders
- Dementia
- Delirium
- Migraines?
- Insomnia?
- Anxiety

# Most Common Adverse Effect: Metabolic Syndrome

- Central obesity, weight gain
- Hyperlipidemia (High TG, Low HDL)
- Insulin Resistance → Diabetes
- HTN



# Risk of Metabolic Syndrome



Clozapine (Clozaril)

Olanzapine (Zyprexa)

Quetiapine (Seroquel)

Risperidone (Risperdal)

Aripiprazole (Abilify)

Ziprasidone (Geodon)

# Monitoring for Metabolic Syndrome

	Baseline	4 wks	8 wks	12 wks	Quarterly	Annually	Q 5yrs
Personal/Family History	X					X	
Weight (BMI)	X	X	X	X	X		
Waist Circumference	X					X	
BP	X					X	
Fasting glucose	X					X	
Fasting Lipids	X						X



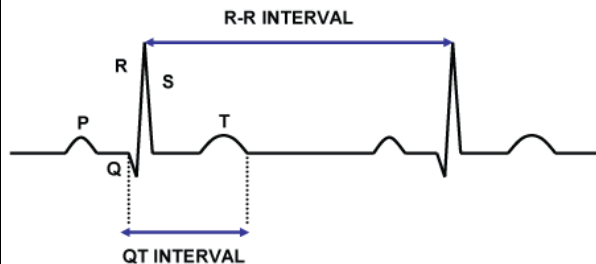
# If Evidence for Metabolic Syndrome

- Coordinate care with pt's PCP
- Diet modification, exercise
- Consider agents for HTN, statins, metformin
- Consider use of lower risk atypical antipsychotic

# Atypical Antipsychotics and QTc Prolongation

- *Must consider* QTc Prolongation
  - >440 msec in men, >460 msec in women
  - Increased risk of Torsades de Pointes >500msec

Normal EKG



Prolonged QT EKG

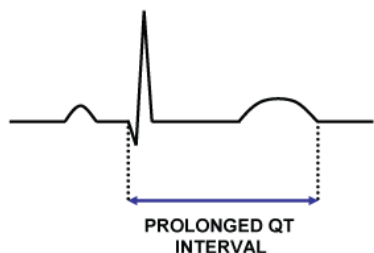
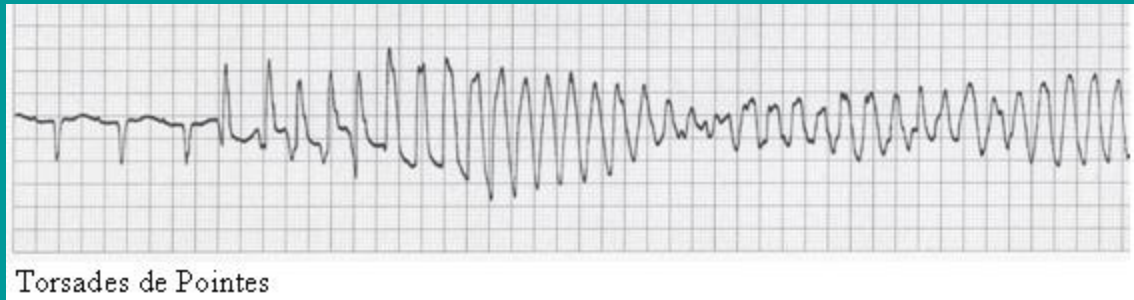


Figure 1



$$QTc = \frac{QT}{\sqrt{R-R}}$$

# How do Atypical Antipsychotics Prolong the QT?

- Physically block flux of  $K^+$  through inward rectifier potassium channel in cardiac myocytes
- Result = prolonged repolarization

# Why worry about this?

- Atypicals are often used for delirium management in complex medically ill patients
- May already have significant cardiac risk
- May be on other QT prolonging medications

# Black Box Warning

- Treatment of behavioral disturbance in elderly pts w/dementia w/atypical antipsychotics is associated with:
  - Increased mortality
    - 1.6-1.7 fold increased risk
    - Heart related (sudden cardiac death, heart failure)
    - Infection related (pneumonia)
  - Cerebrovascular adverse events, including stroke
    - Approximately 3 fold increased risk (olanzapine, risperidone, abilify)

# Cost

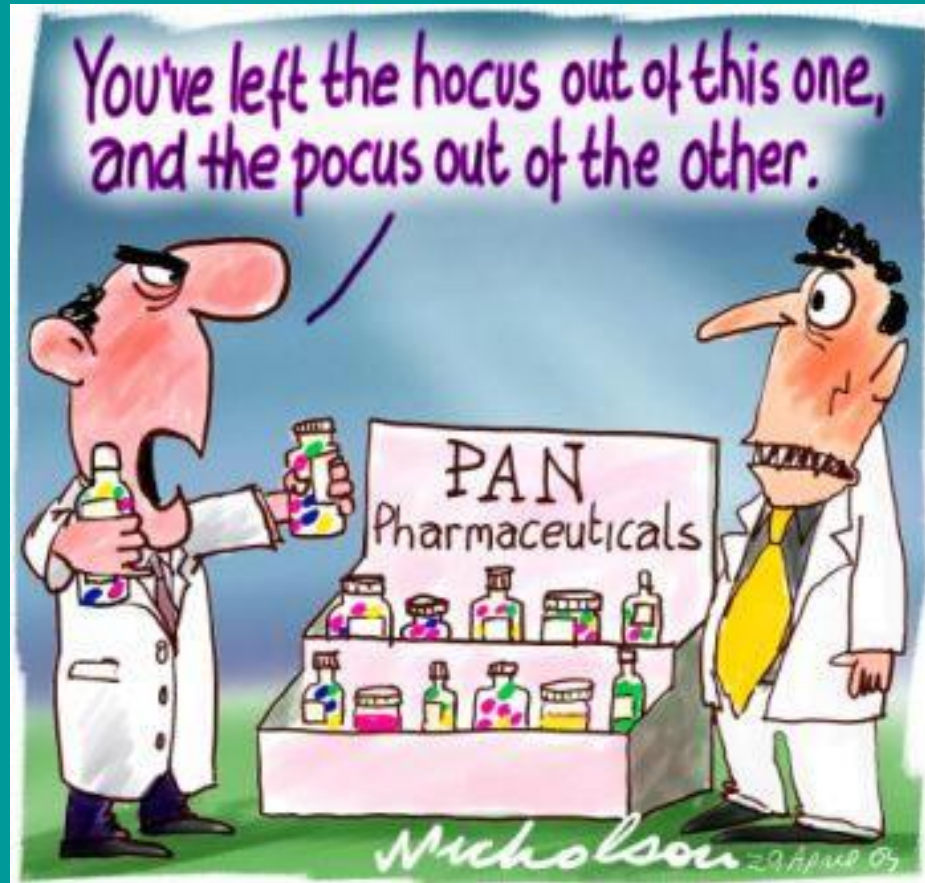
- Brand name atypicals are very expensive
- Even with insurance, range can be \$100-\$1000 for one month supply
- Many atypicals are now “off-patent” and approved by the FDA as generics
- BUT, not necessarily reflective in the price!



# Cost

- Non-FDA Approved generics are available outside the USA – Be Careful!! Not Regulated!
- FDA Approved Generics
  - Clozapine
  - Risperidone
  - Olanzapine
  - Ziprasidone
  - Quetiapine
- Brand Name Only
  - Aripiprazole (Abilify) – comes off patent early 2015
  - Paliperidone (Invega)
  - Asenapine (Saphris)
  - Lurasidone (Latuda)

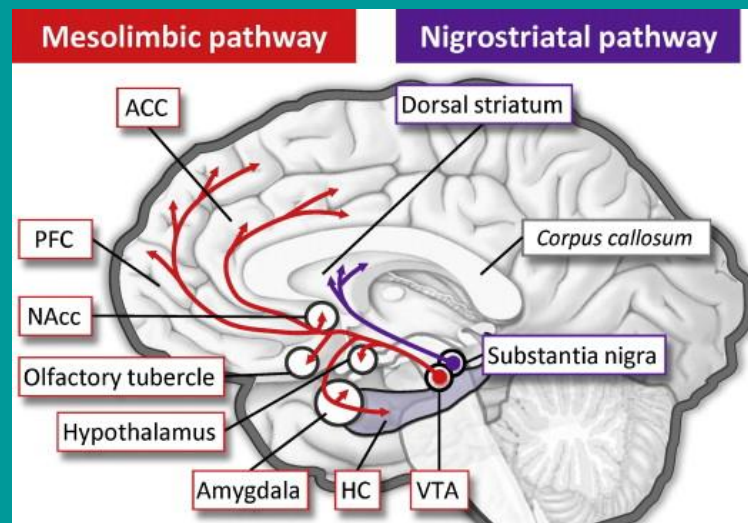
# Mechanism of Action





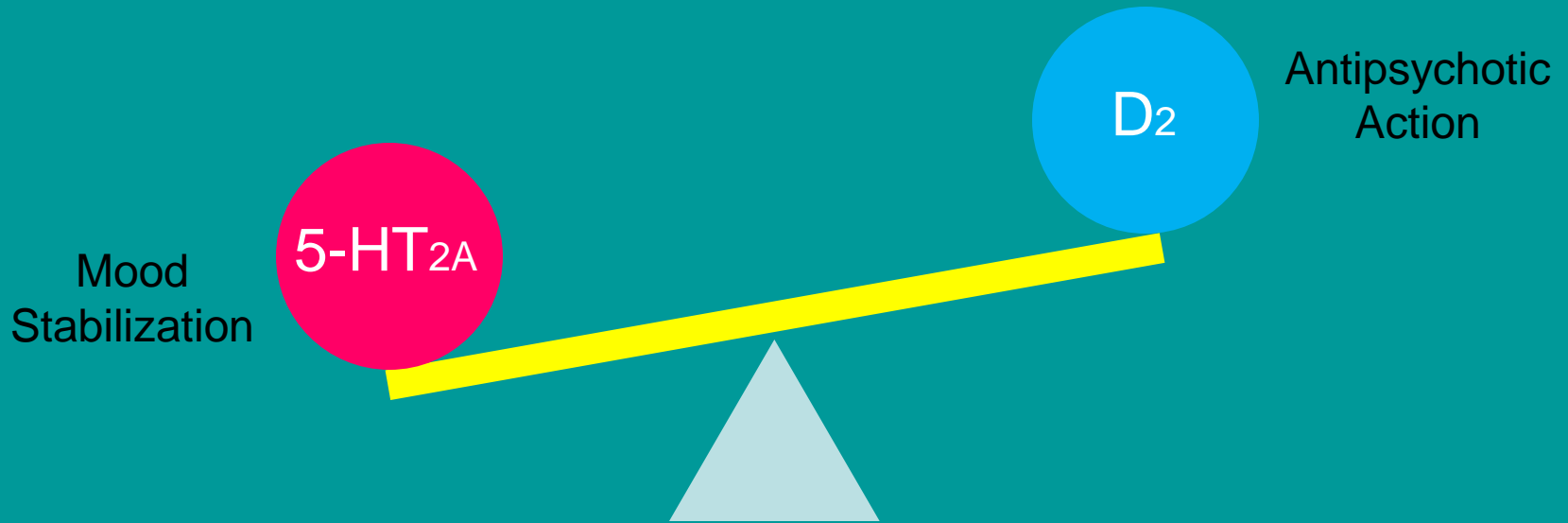
# “Typical” Antipsychotics

- Blockade of D2 receptors in **mesolimbic** system → antipsychotic action
- Blockade of D2 receptors in **dorsal striatum** → EPS



- Blockade of D2 receptors in **mesolimbic** system → antipsychotic action
- Blockade of serotonin 5-HT<sub>2A</sub> receptors → dopamine release in **dorsal striatum** → no EPS

# Mechanism of Action



- Each Atypical Antipsychotic has different “balance” of Serotonin 5-HT<sub>2A</sub> vs. Dopamine D<sub>2</sub> Antagonism

# Mechanism of Action

- Blockade of many other receptor types
  - Antipsychotic action and Mood Stabilization
    - Dopaminergic
    - Serotonergic
  - Side Effects
    - Noradrenergic
    - Histaminergic
    - Cholinergic
- Each atypical has slightly different activity at these receptors
- Can use this to tailor to individual patients!

# “Tailoring” for Side Effects

- **Anti-cholinergic (M1 muscarinic blockade)**

- Dry mouth
- Constipation
- Urinary Retention
- Confusion
- Mydriasis

- **Consider co-morbid conditions**

- Dental, periodontal disease
- Ileus, small bowel obstruction
- Urinary obstruction
- Glaucoma

- **Atypicals**

- Clozapine, Olanzapine, Quetiapine

# “Tailoring” for Side Effects

- **Nor-adrenergic Blockade ( $\alpha_1$ )**
  - Sedation
  - Orthostatic Hypotension
  - quetiapine > risperidone > olanzapine > ziprasidone > aripiprazole
- **Caution with**
  - Known low blood pressure
  - Fall risk, Gait instability
  - Concurrent use of anti-hypertensives, erectile-dysfunction medications



# “Tailoring” for Side Effects

- **Histamine Blockade (H1)**

- Sedation
- Weight Gain
- Anti-emetic properties

- May be advantageous

- Nausea, vomiting
- Pts on chemotherapy
- Pruritis

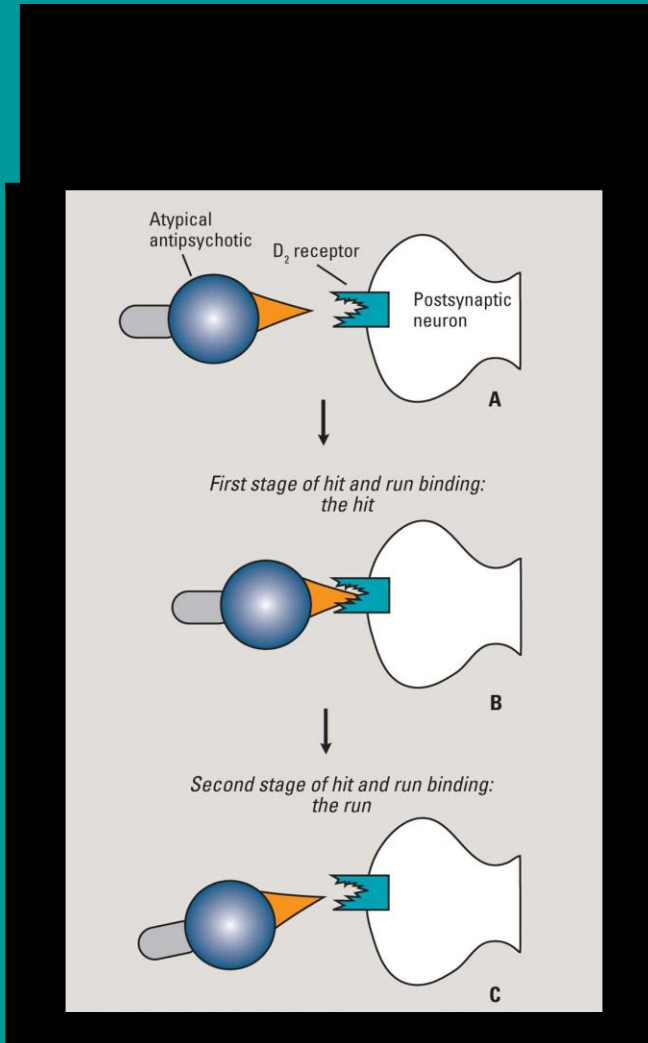
- Atypicals

- quetiapine
- olanzapine
- clozapine



# “Tailoring” for Side Effects

- “Hit and Run” Binding at D2 Receptor
  - Hit → sufficient binding affinity for antipsychotic effect
  - Run → weak enough binding to dissociate off receptor before causing EPS
  - Most Prominent with
    - Clozaril
    - Quetiapine
    - Best atypicals for patients with Parkinson’s



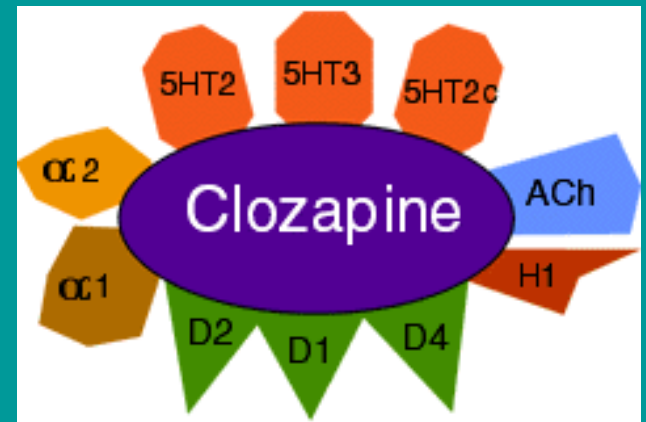
# Drug Specific Pearls





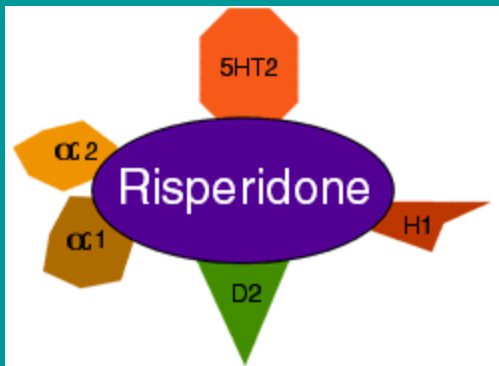
# Clozapine (Clozaril)

- Special Populations
  - Treatment refractory schizophrenia
  - Negative symptoms of schizophrenia
  - Parkinson's Disease with psychosis
- Black Box Warnings
  - **Agranulocytosis (ANC <500)**
  - Decreased seizure threshold
  - Myocarditis
  - Respiratory/Cardiac arrest



# Risperidone (Risperdal)

- Special Formulations
  - Risperdal M-Tab (orally disintegrating, NOT sublingual)
  - Risperdal Consta (IM Depot)
  - Risperdal Oral Solution
  - Generic oral disintegrating, oral solution
- Special Indications
  - Tourette's Syndrome
  - Autism





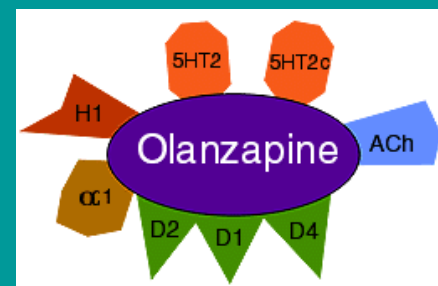
# Olanzapine (Zyprexa)

- Special Formulations

- Zyprexa Zydis and generic orally disintegrating (not SL)
- Zyprexa and generic Intramuscular Injection (IM)
  - Do not use with ativan – high risk respiratory depression, death

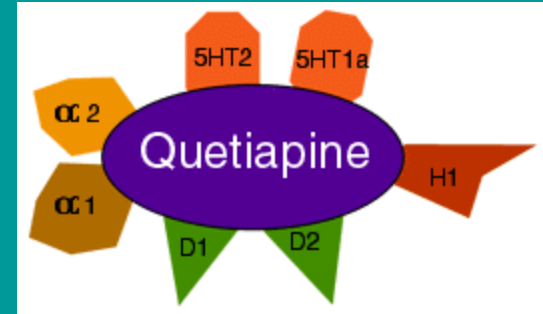
- Special Indications

- Delirium
  - Treatment of hyper-dopaminergic state
  - Sedation → regulation sleep/wake cycle
- Anti-emetic effect
- Anorexia nervosa
- Migraine? (Dusitanond and Young. 2009. CNS Agents in Medicinal Chemistry.)
  - May be 2<sup>nd</sup>, 3<sup>rd</sup> line in treatment refractory cases
  - Via antagonism D2 and 5-HT<sub>2A</sub>



# Quetiapine (Seroquel)

- Special Formulations - none
- Special Indications
  - Parkinson's psychosis
  - Anxiety
    - In the inpatient medical setting when risk of benzos is too high (delirium)
    - Ventilator weaning
  - Insomnia
    - Isolated insomnia in the absence of mood d/o, psychotic d/o or delirium is NOT an indication
    - Must carefully weigh risk of metabolic syndrome
  - Migraines?
    - No evidence in acute or preventive migraine treatment



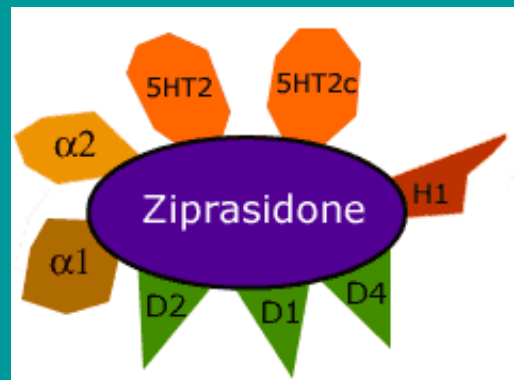
# Aripiprazole (Abilify)

- Special Formulations
  - Abilify Discmelt, orally disintegrating
  - Abilify Intramuscular
  - Abilify oral solution
- Special Indications
  - Delirium management in pts with prolonged QT



# Ziprasidone (Geodon)

- Special Formulations
  - PO formulation is capsule – needs to be taken with food for absorption
  - IM formulation
    - Caution with QT prolongation



# Newer Atypicals

- Paliperidone (Invega)
  - Active Metabolite of Risperidone
  - Special Formulations
    - Invega Sustenna (IM Depot)
- Asenapine (Saphris)
  - Only atypical with Sub-Lingual Formulation
    - May have advantage in patients with poor GI absorption
    - Prolonged NPO status
- Lurasidone (Latuda)
  - Metabolized by CYP3A4 (beware of co-administration with inducers – e.g. rifampin, ketoconazole)

# Thank You

