

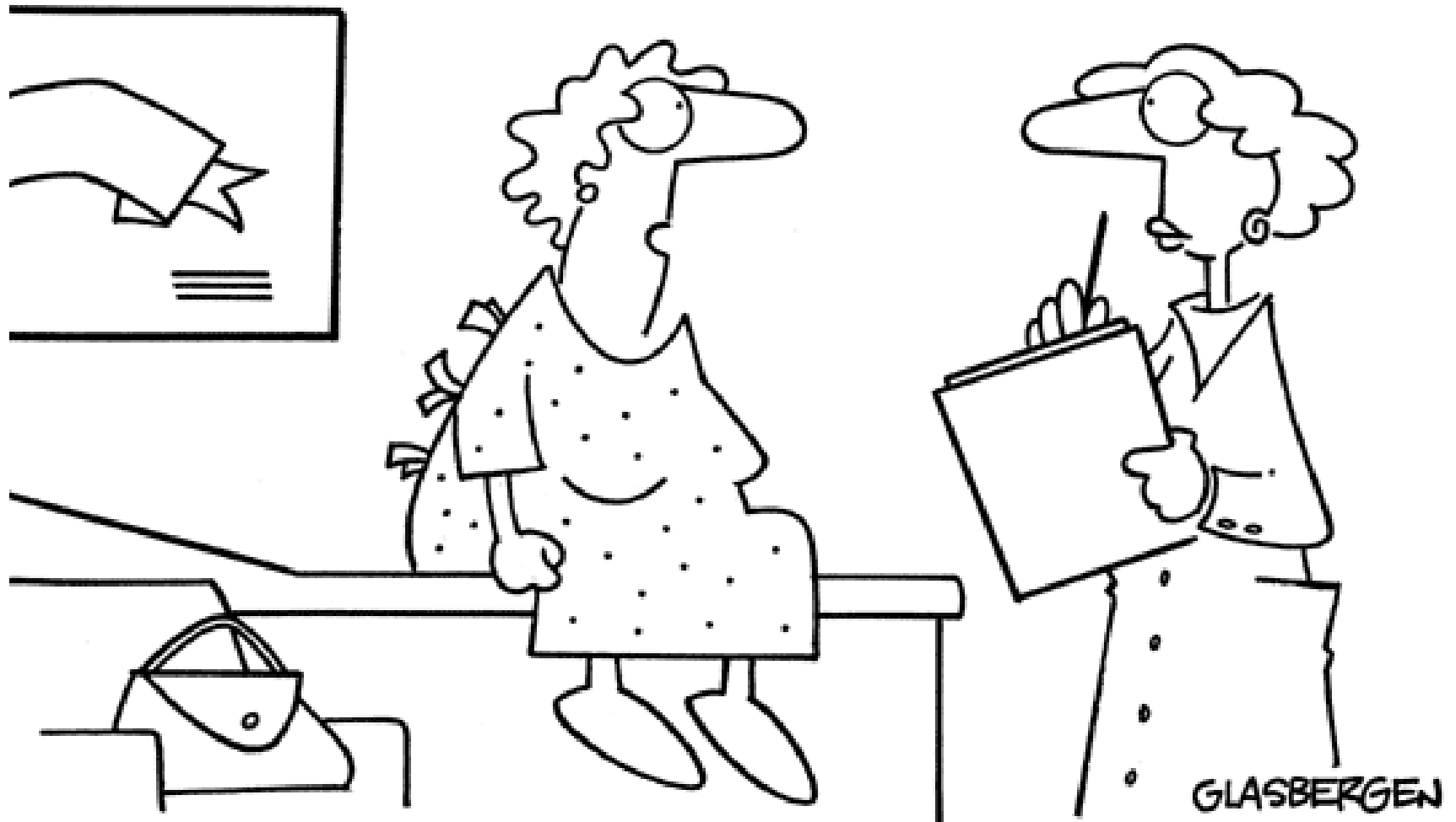
Atypical Antipsychotics



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TM



**“That pill they advertise all the time on TV.
I’m not sure what it is, but I want it!”**

Objectives



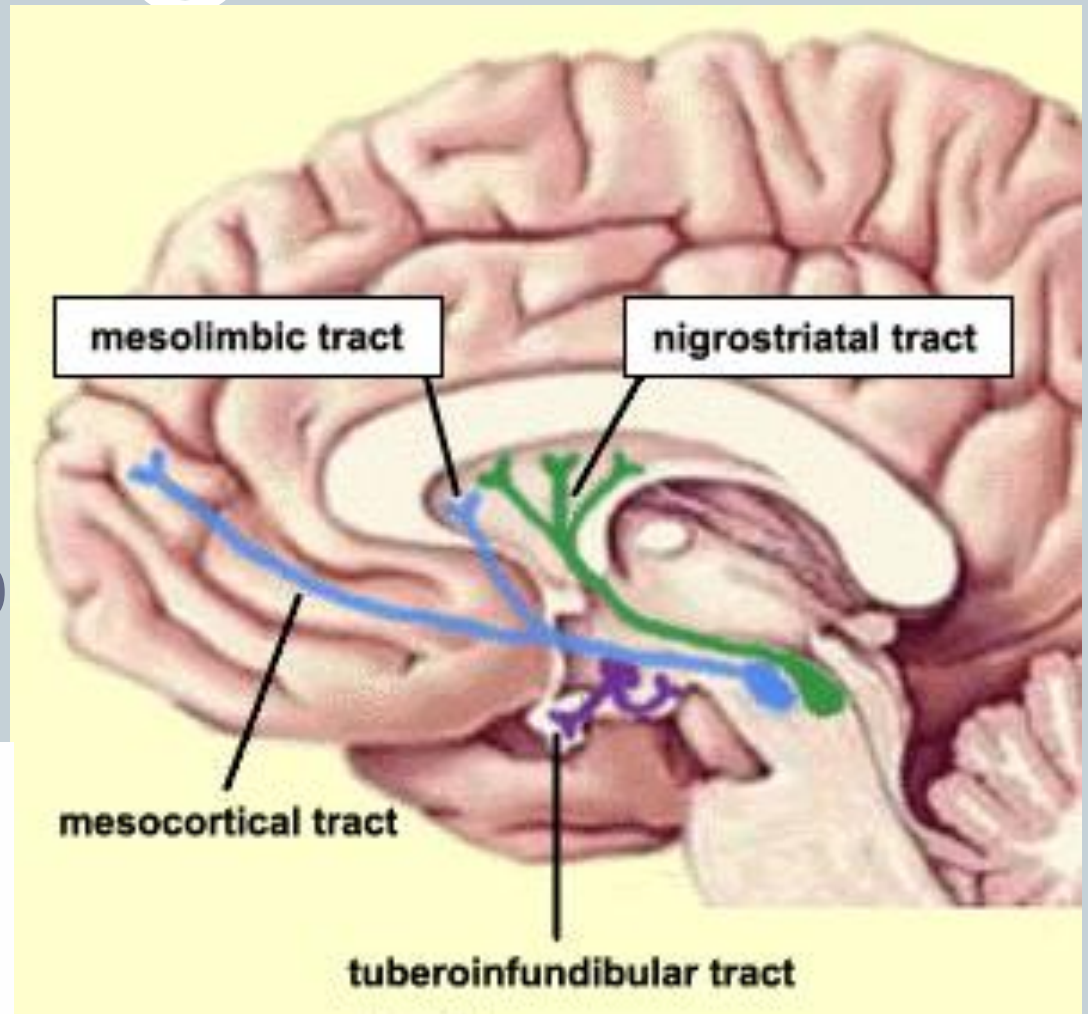
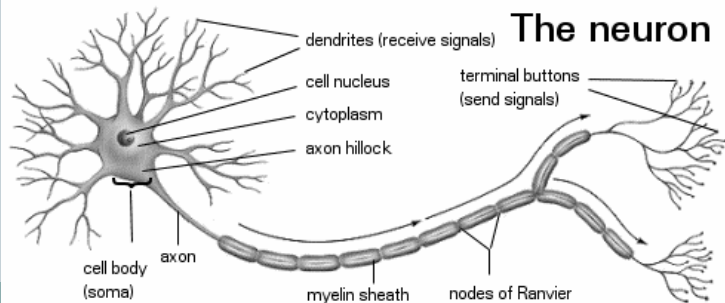
- Review neurochemistry of dopamine
- Compare typical & atypical antipsychotics
- Review atypical antipsychotics
- Describe place in therapy for adults
- Examine place in therapy for children
- Review concerning side effects
- Consider controversies



Dopamine Receptors

• Dopamine pathways

- Mesolimbic (D2)
 - ✦ Positive symptoms
- Mesocortical (D3 & D4)
 - ✦ Negative symptoms
- Niagrostriatal (D2)
 - ✦ Motor control
- Tuberoinfundibular (D2)
 - ✦ Endocrine function



Typical Antipsychotics



- Pharmacology
 - Proposed therapeutic mechanism of action
 - ✦ D2-like receptor subtype antagonism
 - Side effect mechanism of action
 - ✦ D2-like antagonism:
 - Extrapyramidal symptoms (EPS): Parkinson-like symptoms (initially), tardive dyskinesia (TD) with prolonged treatment, dystonia, akathisia
 - Gynecomastia (increased prolactin)
 - ✦ Alpha-1 antagonist: dizziness, orthostatic hypotension & reflex tachycardia
 - ✦ Antimuscarinic: blurry vision, dry mouth, constipation, urinary retention, relieves initial Parkinson-like symptoms & worsens TD
 - ✦ H1 blockade: sedation & weight gain

Atypical Antipsychotics



- Pharmacology

- Proposed mechanism of action

- ✦ More selectively blocks D2 in mesolimbic, D3 & D4 in mesocortical
- ✦ Less blocking of nigrostriatal
- ✦ Requires less receptor blocking to give therapeutic effect
- ✦ Some blocking of muscarinic (less), alpha1, H1 & serotonin (decreases dopamine in mesolimbic)

- Summary

- **Causes less movement side effects than typical antipsychotics**

Risperdal (risperidone)



- FDA approved uses
 - Schizophrenia (elderly, adults & adolescents)
 - Irritability in autism (adolescents & children)
 - Bipolar (elderly, adults, adolescents & children)
 - ✦ Monotherapy (all) or combination therapy (adults)



Risperdal (risperidone)



- **Non-FDA approved uses**
 - Acute psychosis (adults)
 - Behavioral disturbances due to dementias (elderly)
 - Disruptive behavior (children)
 - Psychotic depression (elderly & adults)
 - Tics (adults, adolescents & children)
 - ✦ Tourette's syndrome or ADHD

Risperdal (risperidone)



- Common side effects: mild sedation, hypotension, akathisia, prolactin elevation & weight gain (moderate)
- Other risks: cholestatic hepatitis & pituitary adenomas
- Advantages:
 - Low incidence of EPS $\leq 6\text{mg}$
 - ✦ Increased risk than other atypicals with higher dose
 - Less risk for lipid changes
- Cost ~ \$125-\$400



Risperdal (risperidone)



- Monitoring: EPS, neurologic function, blood glucose, ECG, LFTs, lipids & weight
- Dosage forms
 - Tablets
 - Liquid
 - Rapid-disintegrating tablets
 - Depot injections

Risperdal M-TAB
risperidone Orally Disintegrating Tablets

The convenient, rapidly disintegrating formulation^a

0.5 mg 1 mg 2 mg 3 mg 4 mg

- Disintegrates in the mouth within seconds
- Easy to swallow
- Mint flavored
- No cheeking of medication
- No mixing, no measuring, no beverage required

Phenylketonurics: RISPERDAL M-TAB contains phenylalanine. Pills not shown to size.
^aRISPERDAL M-TAB is bioequivalent to RISPERDAL Tablets.

Zyprexa (olanzapine)

- FDA approved uses
 - Schizophrenia (elderly, adults, adolescents & children)
 - Bipolar
 - ✦ Monotherapy (adults & adolescents) or combination (adults)
 - Acute agitation associated with bipolar or schizophrenia



Zyprexa (olanzapine)



- **Non-FDA approved uses**

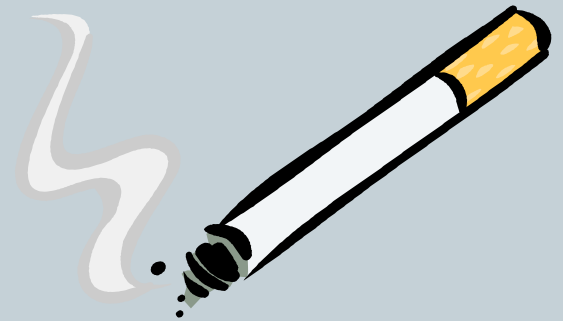
- Behavioral disturbances due to dementias (elderly)
- Acute psychosis (adults)
- Chronic pain
- Prevention of chemotherapy- associated nausea or vomiting



Zyprexa (olanzapine)



- Common side effects: weight gain (higher risk), sedation, akathisia, hypotension, dry mouth & constipation
- Disadvantages: risk of weight gain (associated risk of diabetes) & high cost
- Cigarette smoking decreases concentration
- Cost ~ \$245-\$841



Zyprexa (olanzapine)



- Monitoring: neurologic function, blood glucose, LFTs, lipids & weight
- Dosage Forms
 - Coated tablets
 - Rapid-disintegrating tablets
 - Solution for injection



Seroquel (quetiapine)

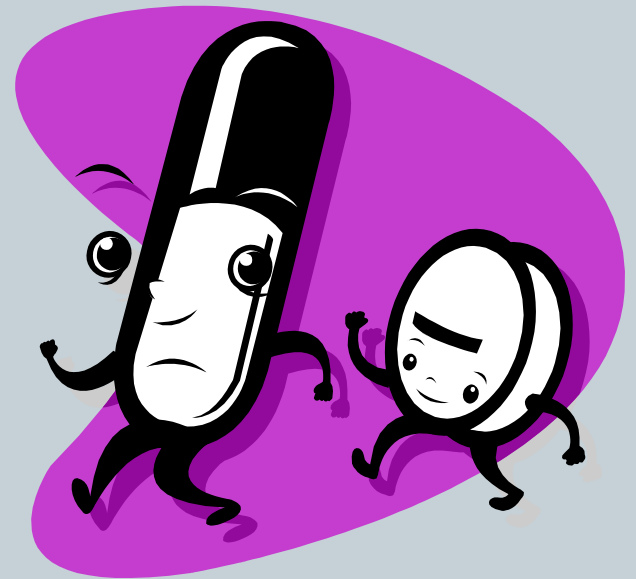


- FDA approved uses
 - Treatment resistant Major Depressive Disorder (elderly & adults)
 - Bipolar (elderly, adults, adolescents & children)
 - Schizophrenia (elderly, adults & adolescents)

Seroquel (quetiapine)



- Non-FDA approved uses
 - Behavioral disturbances due to dementias (elderly)
 - Acute psychosis (adults)
 - Obsessive-compulsive disorder (adults)
 - ✦ Combination therapy with SSRI



Seroquel (quetiapine)



- Common side effects: sedation (transient), orthostatic hypotension, akathisia, dry mouth & weight gain (moderate)
- Advantages: low risk of EPS (all doses)
- Disadvantages: sedation & hypotension
- Monitoring: neurologic function, blood glucose, LFTs, lipids, weight & **eye exam (cataracts)**
- Dosage forms
 - Immediate or sustained release
- Cost ~ \$160-\$700



Geodon (ziprasidone)



- **FDA approved uses**
 - Schizophrenia (elderly & adults)
 - Bipolar (elderly & adults)
- **Non-FDA approved uses**
 - Tourette's syndrome (children)
 - Behavioral disturbances due to dementias (elderly)



Geodon (ziprasidone)



- Common side effects: mild sedation (transient), nausea, weakness, nasal congestion & mild QT prolongation
- Advantages: less weight gain & risk of lipid changes
- Disadvantages: BID dosing & cardiac problems

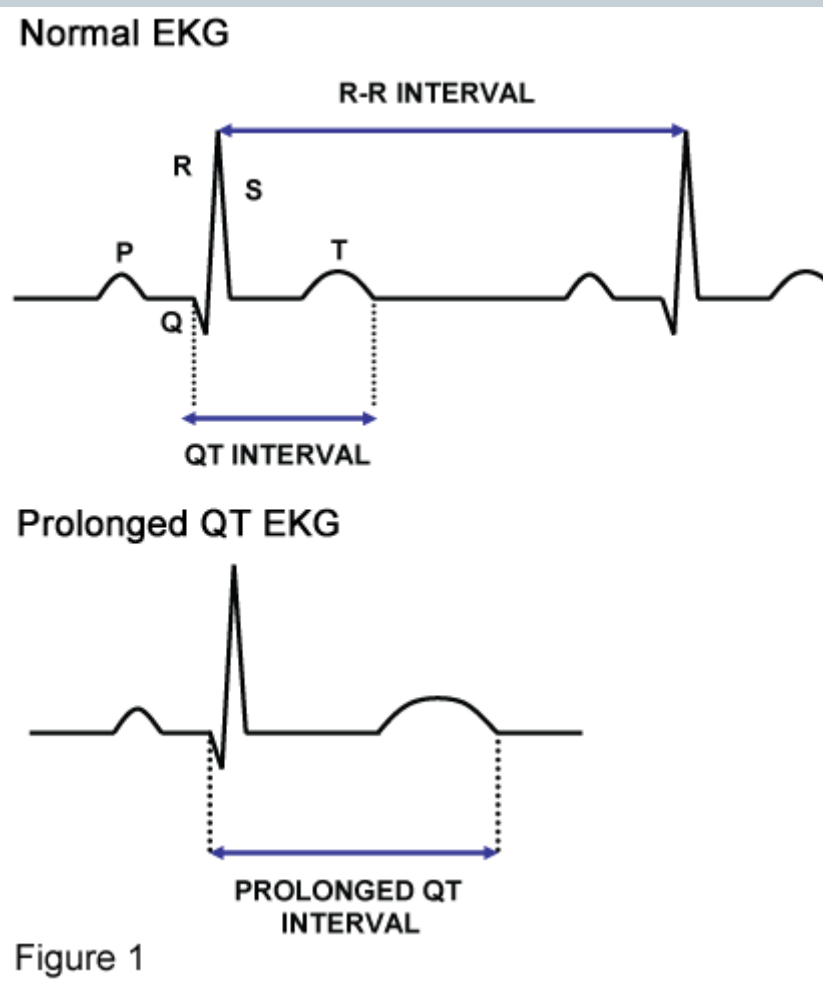


Figure 1

Geodon (ziprasidone)



- Response rate increases at >80 mg daily
- Monitoring: neurologic function, blood glucose, LFTs, lipids, weight & ECG
- Cost ~ \$430-\$520
- Dosage forms
 - Capsules
 - Intramuscular injection



Abilify (aripirazole)

- FDA approved uses
 - Schizophrenia (elderly, adults & adolescents)
 - Bipolar (adults, adolescents & children)
 - Adjunct therapy for Major Depressive Disorder (adults)
 - Irritability associated with autism (adolescents & children)



Abilify (aripirazole)



- **Non-FDA approved uses**
 - Acute psychosis (adults)
 - Aggression, conduct disorder or Tourette's syndrome (children)
 - Behavioral disturbances due to dementias (elderly)

Abilify (aripirazole)

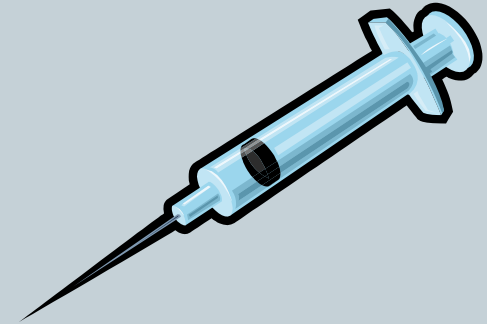


- Common side effects: headache, nausea, vomiting, akathisia, tremor & constipation
- Advantages: low risk of weight gain, no cardiac effects, lower risk of EPS, long elimination half-life
- Disadvantages: unpredictable effect on other antipsychotics (agonist and antagonist activity) & alternate dosing strengths with concomitant use of inducers or inhibitors (CYP 3A4 or 2D6)
- Cost ~ \$450-\$635

Abilify (aripirazole)



- Monitoring: blood glucose, LFTs, weight, lipids & neurologic function
- Dosage forms
 - Tablets
 - Oral-disintegrating tablets
 - Intramuscular injection



AVAILABLE TABLET STRENGTHS

5 mg



10 mg



15 mg



20 mg



30 mg



Invega (paliperidone)



- **FDA approved uses**
 - Schizophrenia (elderly & adults)
 - Schizoaffective disorder (elderly & adults)
- **Non-FDA approved uses**
 - Behavioral disturbances due to dementias (elderly)



Invega (paliperidone)



- Common side effects (dose dependant): EPS, including parkinsonism, dystonia, dyskinesia & akathisia, weight gain (mild-moderate), prolactin elevation, tachycardia & QT prolongation
- Primary metabolite of Risperdal
- Bioavailability increased ~50% with high calorie meal
- Cost ~ \$350-\$525



Invega (paliperidone)



- Do not chew or crush (extended release)
- Monitoring: none required at this time
- Dosage forms
 - Extended release
 - Intramuscular injection



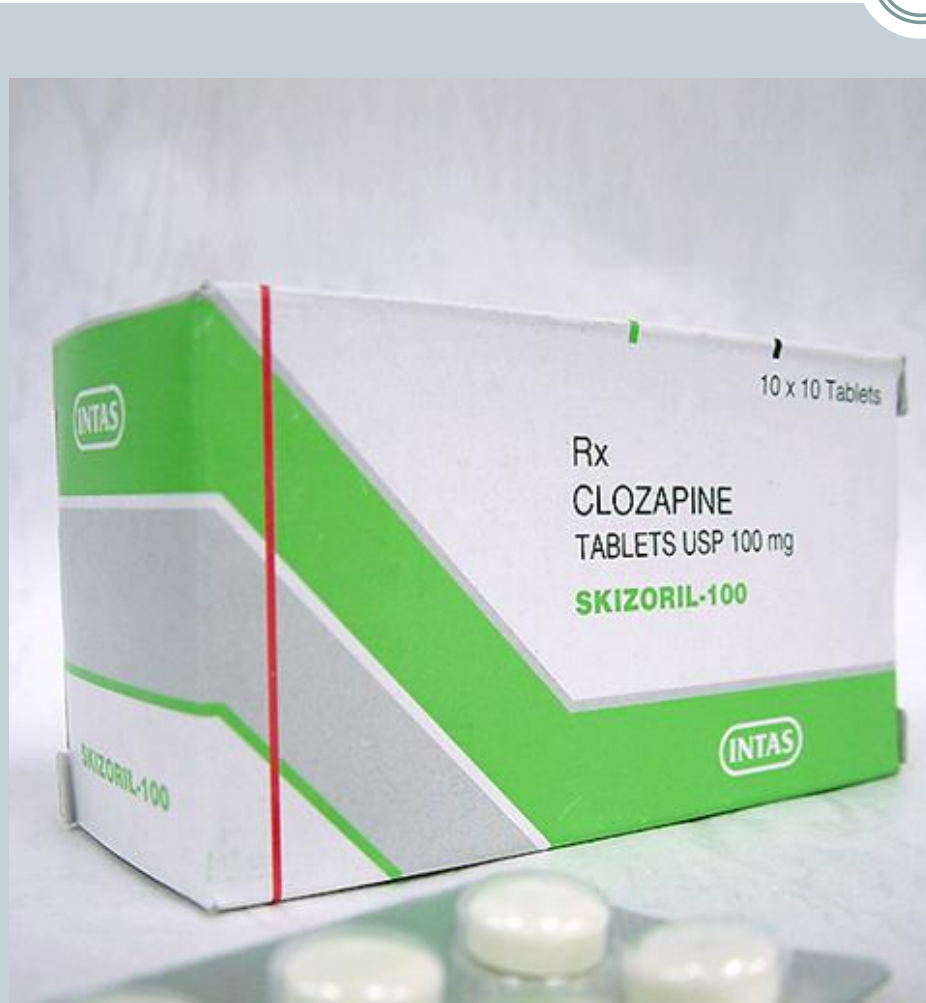
Fanapt (iloperidone)



- FDA approved uses
 - Schizophrenia (elderly & adults)
- Common side effects: dizziness, orthostatic hypotension, tachycardia, weight gain (moderate), dry mouth & sedation
- Less EPS than risperidone but more QT prolongation
- Monitoring: currently none required
- Cost ~ \$630
- Dosage forms
 - Tablet



Clozaril (clozapine)

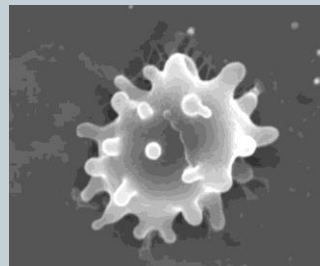


- **FDA approved uses**
 - Treatment-resistant schizophrenia (elderly, adults, adolescents & children)
- **Non-FDA approved uses**
 - Bipolar (adults)
 - Tremor/dyskinesias in Parkinson's (adults)
 - Behavioral disturbances due to dementias (elderly)

Clozaril (clozapine)



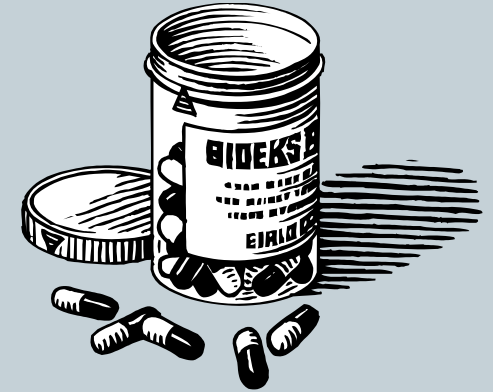
- Common side effects (prominent & persistent): orthostatic hypotension, tachycardia, weight gain, metabolic syndrome, sialorrhea, sedation & constipation
- Disadvantages: increased seizure risk, potentially fatal myocarditis (rare), risk of agranulocytosis (close monitoring)
- Monitoring: blood glucose, lipids, LFTs, weight, **WBC** & neurologic function
- Cost ~ \$38-\$865
- Dosage forms
 - Tablet



Place in therapy (adults)



- Schizophrenia
- Bipolar disorders
- Treatment-resistant MDD
- Acute psychosis
- Behavioral disturbances in dementias
 - Agitation, aggression & psychosis
 - ✦ Parkinson's, Alzheimer's, organic brain syndromes



Drug	Schizophrenia	Bipolar	Acute psychosis	Dementia behavior	MDD	Other
Risperdal	X	X	X	X		Psychotic depression & Tics
Zyprexa	X	X	X	X		Chronic pain N/V (chemo)
Seroquel	X	X	X	X	X	OCD
Geodon	X	X		X		
Abiligy	X	X	X	X	X	
Invega	X			X		
Fanapt	X					
Clozapine (tx-resistant)	X	X		X		

Place in therapy (children)



- Autism, bipolar, schizophrenia, severe disruptive & aggressive behavior disorders
- Side effects are the same as adults
 - Including hyperglycemia & dyslipidemia
 - Prone to rapid & significant weight gain
- Risperidone (good 1st choice)
 - More evidence, generic
- Abilify
 - Less weight gain & dyslipidemia
 - More activating than sedating (start low & go slow)
- Monitoring: weight, BP, lipids & glucose (every 6 mo)



Drug	Schizophrenia	Bipolar	Tics	Autism	Disruptive behavior
Risperdal		X	X	X	X
Zyprexa	X	X			
Seroquel		X			
Geodon				X	
Abilify		X	X	X	X
Clozapine	X (tx-resistant)				

Side Effect Summary



- **QT prolongation**
 - Invega, Fanapt & Geodon
- **Weight gain**
 - Least: Geodon & Abilify
 - Most: Zyprexa & clozapine
- **Sedation**
 - Worst: clozapine, Zyprexa, Seroquel
- **Seizures**
 - Highest risk: clozapine & Zyprexa
 - Lowest risk: Geodon



Controversial Issue

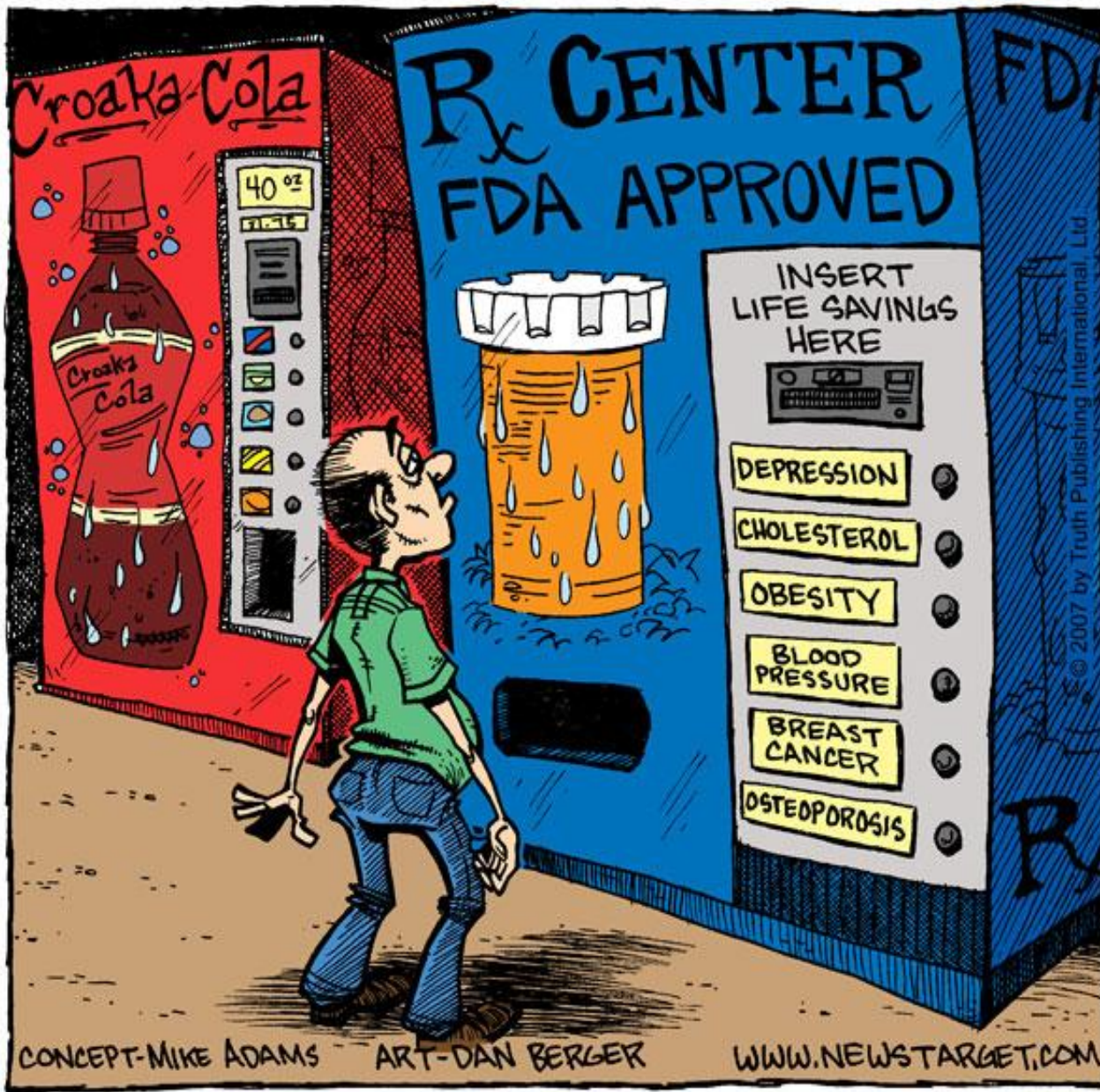


- Drug companies pressuring primary care providers to prescribe antipsychotics
 - Within the scope of practice?
 - ✦ Schizophrenia, bipolar, mania
 - ✦ Agitation with dementias & ADHD, Tics
 - Require close monitoring of therapeutic effects & side effects
 - Patients may need polytherapy



COUNTERTHINK

WHAT THE DRUG COMPANIES REALLY WANT



CONCEPT-MIKE ADAMS

ART-DAN BERGER

WWW.NEWSTARGET.COM

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Upcoming



- **Serlect (sertindole)**
 - Not available in US
 - Withdrawn due to concerns of sudden cardiac death & arrhythmias (QT prolongation)
 - ✦ April 2009 FDA Psychopharmacologic Drugs Advisory Committee recommended approval
- **Zoleptil (zotepine)**
 - Not available in US
 - Used in Europe since 1998
- **OPC-34712 by Otsuka**
 - Phase I trials for schizophrenia

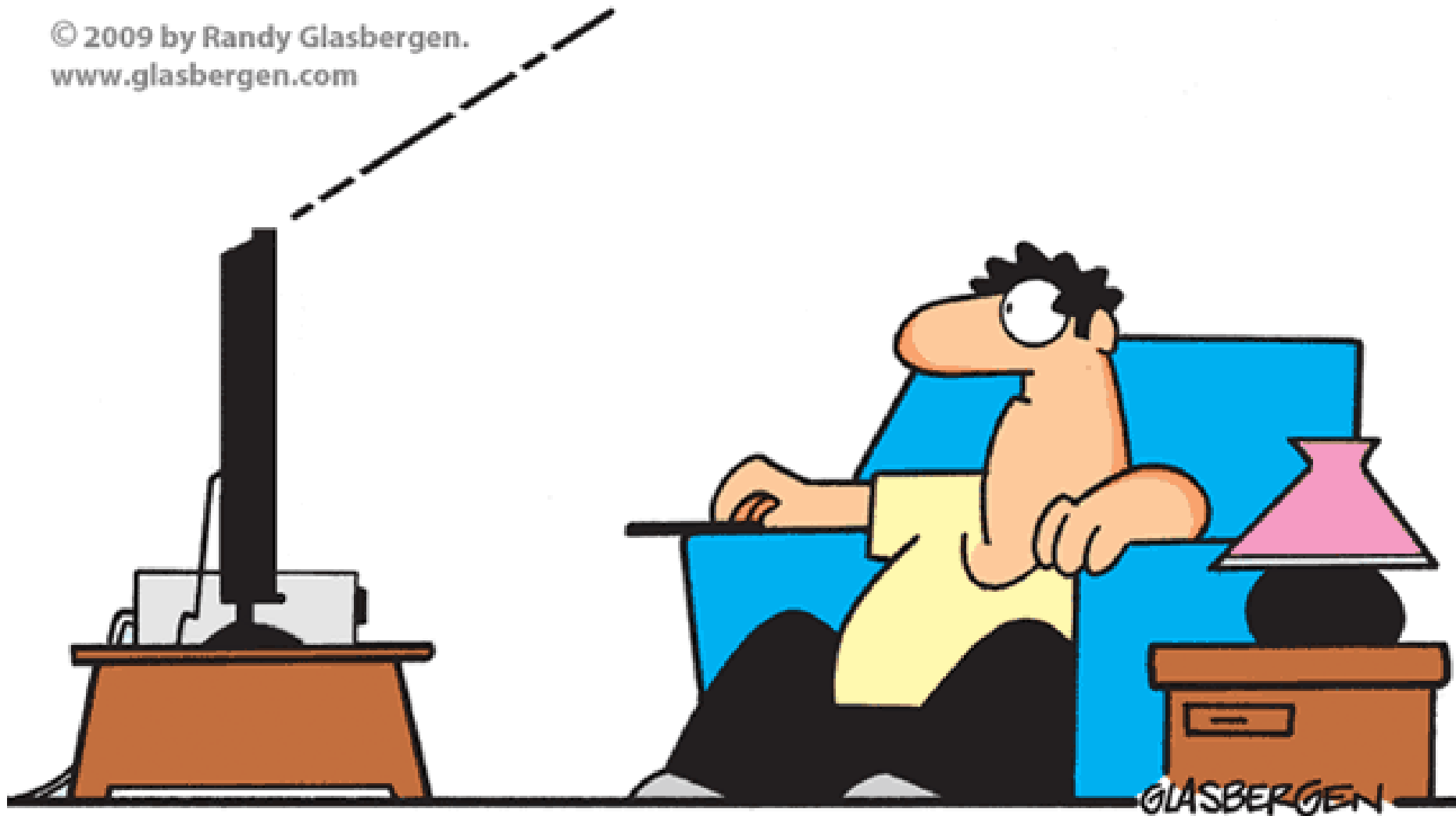


Summary



- Atypical antipsychotics have less movement side effects than typical antipsychotics.
- The side effect profiles often limit their use.
- There is a place in therapy for antipsychotics other than just schizophrenia.
- Pros and cons must be weighed in the decision to use atypical antipsychotics.
- There are times when atypical antipsychotic use is warranted in elderly, adults, adolescents and children.

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**“This program is brought to you by pills! Red pills, blue pills,
green pills, purple pills, pink pills! Pills, pills, and more pills!
Ask your doctor if pills are right for you!”**

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