

Effective Essentials or Deadly Drugs? Using Antipsychotic Medications in Elderly Patients

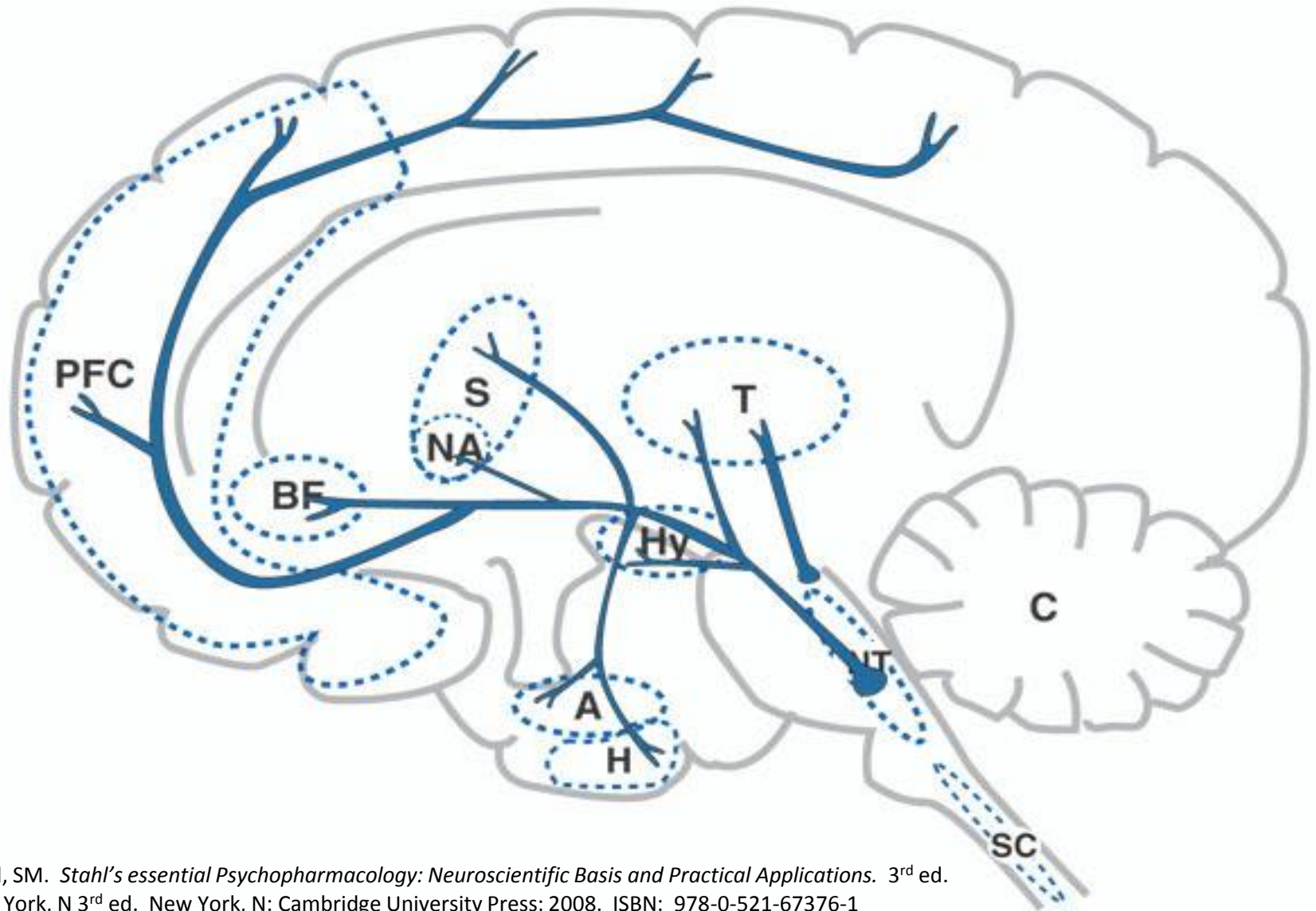
Devon A. Sherwood, PharmD, BCPP
Assistant Professor of Pharmacy Practice



Learning Objectives

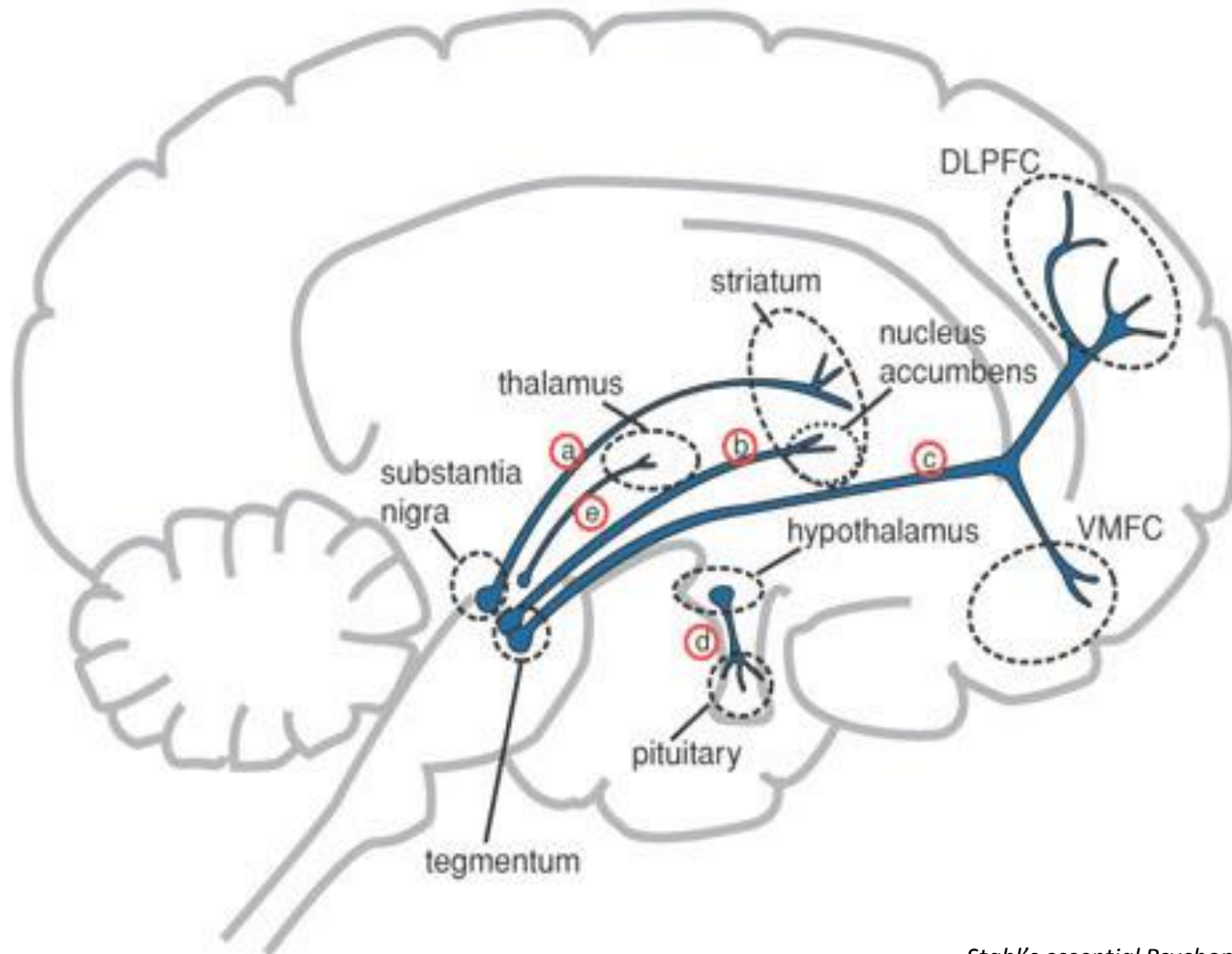
- Differentiate dopamine neurotransmitter pathways associated with antipsychotic medications
- Identify therapy challenges associated with approved antipsychotic therapies by comparison of pharmacokinetic variations and side effect profiles
- Discuss considerations in choosing an antipsychotic for use in an elderly patient through case-based approaches
- Evaluate current evidence to use antipsychotics in elderly patients and subsequently contrast their usage due to safety concerns
- Formulate recommendations regarding antipsychotic treatment options in an agitated geriatric patient with dementia

Dopamine



Pathophysiology

Dopamine Pathways and Key Brain Regions

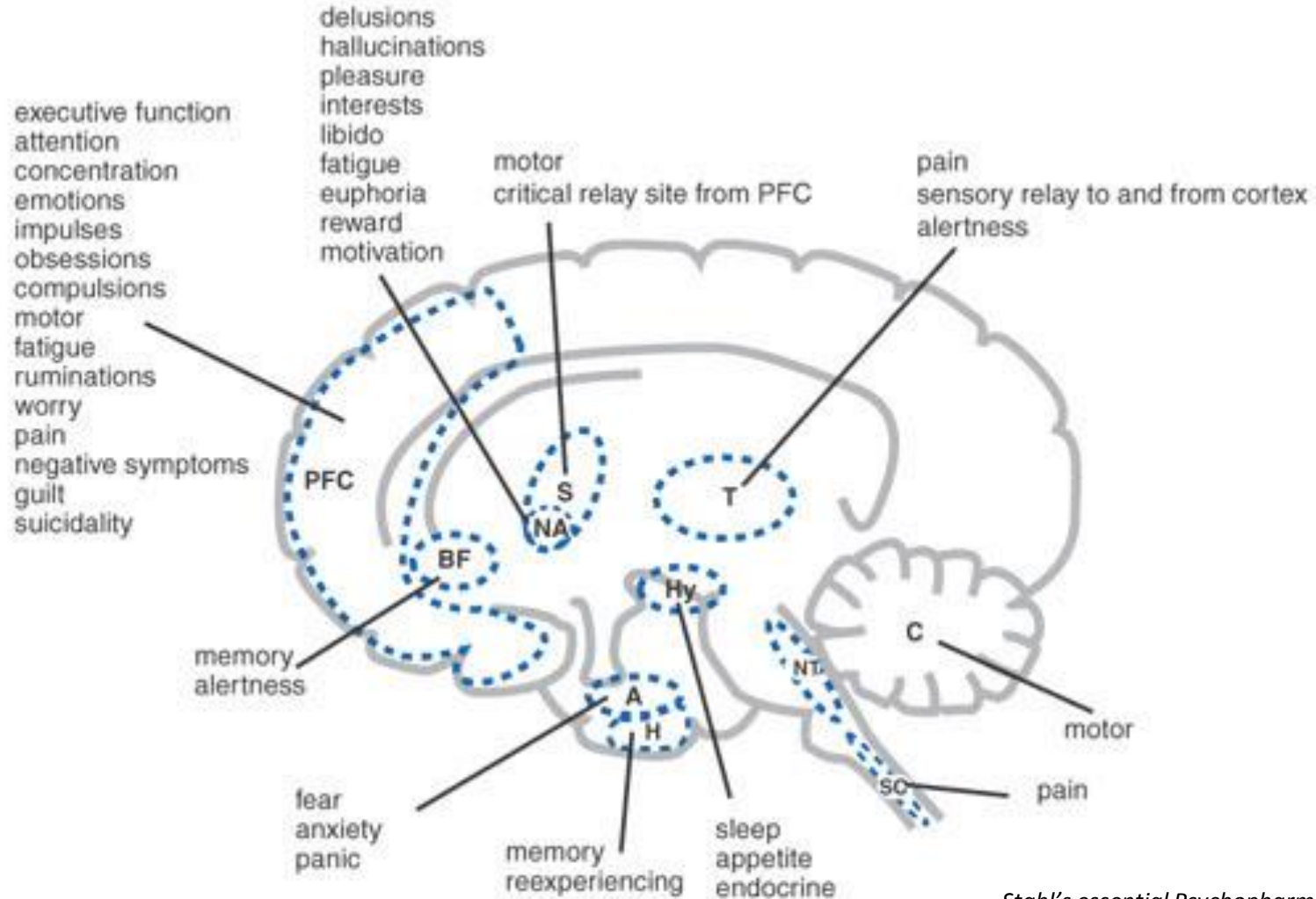


Neurochemical Imbalance



Physical & Behavioral Changes

Some Key Behaviors Hypothetically Linked to Specific Brain Regions



Major Dopamine Pathways

- Nigrostriatal –
- Mesolimbic –
- Mesocortical –
- Tuberoinfundibular –
- Thalamic

Which of the following symptoms of schizophrenia would be least improved by antipsychotic treatment?

- A. Auditory hallucinations
- B. Delusions
- C. Avolition
- D. Disorganized speech
- E. Impaired executive function

Diagnostic Symptoms of Schizophrenia

- Positive Symptoms (see SAPS)
 - Hallucinations
 - Delusions
 - Disorganized speech (association disturbance)
 - Bizarre behavior (behavior disturbance can be disorganized or catatonic)
 - Illusions
 - Positive formal thought disorder

Diagnostic Symptoms of Schizophrenia

- Negative Symptoms (see SANS)
 - Affective flattening (blunting)
 - Alogia
 - Avolition or apathy
 - Anhedonia or asociality
- Cognitive Symptoms
 - Attention
 - Impaired working memory
 - Impaired executive function

Relative Responsiveness to Medication in Schizophrenia

- 1-2 days
 - Hyperactivity, combativeness, hostility, agitation, aggression, anxiety
- 1-2 weeks
 - Hallucinations, sleep, appetite, hygiene, delusions, social skills
- 1-2 months
 - Judgment, insight, abstract thinking
- **20% relapse rate per year**
 - 10-20% relapse rate with atypicals
 - 60-80% relapse with placebo

Typical Antipsychotics

- PROPOSED MECHANISM OF ACTION
 - Block **D₁** and **D₂** receptors mostly
 - May also block other receptors
 - *Alpha*₁ adrenergic
 - Histaminic
 - Cholinergic

Typical Antipsychotic Medications

- Indications: psychosis
- Efficacy: All typicals are equal!
- Similarities: half lives, kinetics, MOA, poorly absorbed
- Differences: potency, SE profile
 - **Hi potency = Hi EPS**
 - **Low potency = Hi Anticholinergic effects**
- Dosing: single vs. multiple, compliance, SE's

Pharmacotherapy: Typical Antipsychotics

Drug Name:

Equivolent Dosage:

Chlorpromazine (Thorazine[®]) 100mg

Thioridazine (Mellaril[®]) 100mg

Loxapine (Loxitane[®]) 10mg

Molindone (Moban[®]) 10mg

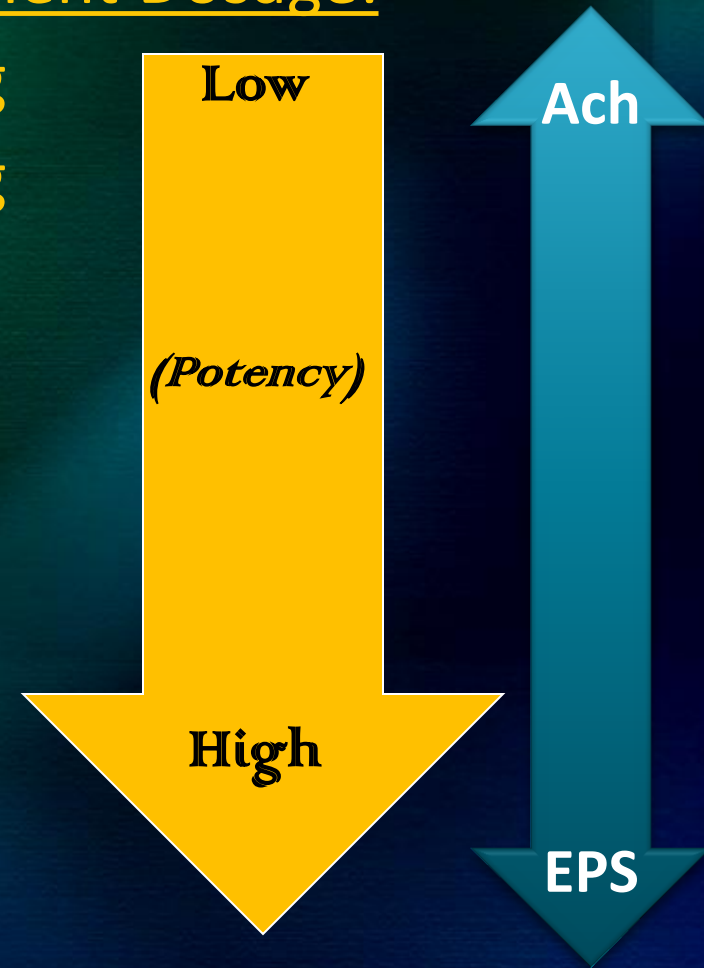
Perphenazine (Trilafon[®]) 10mg

Trifluoperazine (Stelazine[®]) 5mg

Thiothixine (Navane[®]) 4mg

Fluphenazine (Prolixin[®]) 2mg

Haloperidol (Haldol[®]) 2mg



Extrapyramidal Side Effects (EPS)

EPS = Abnormal Motor Movements

- ~1/3 patients on typical antipsychotics will develop over time!
- Elderly more prone to develop



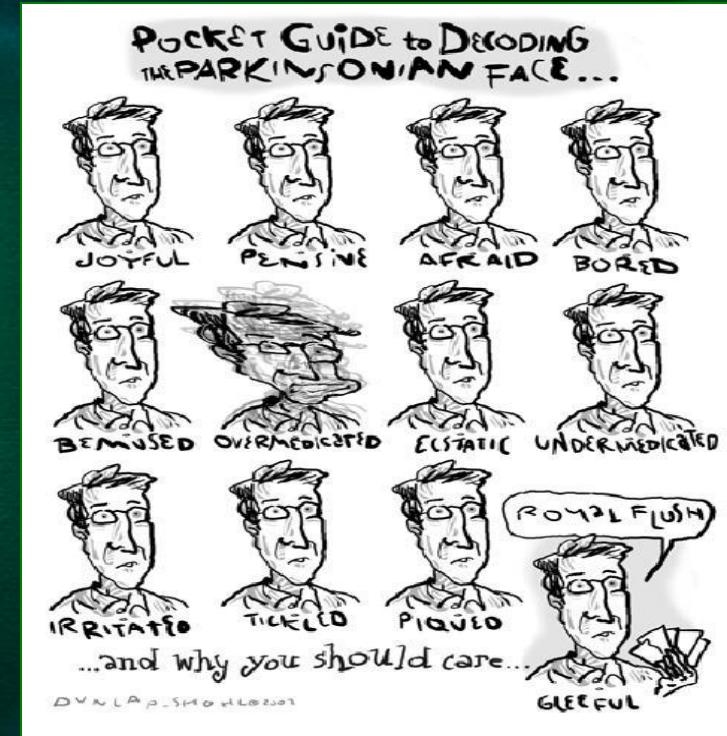
● Acute Dystonias

- Painful contraction of muscles
- Up to 64% of patients without prophylaxis
- Pharyngeal or laryngeal spasm can asphyxiate
- Other terms
 - Trismus, glossospasm, blepharospasm, torticollis, retrocollis

Extrapyramidal Side Effects (EPS)

● Pseudoparkinsonism

- Muscle rigidity, tremors, unsteady/poor balance, shuffled gait, masked face, bradykinesia, etc.
- 15 - 60% of patients
- Do not treat with DA agonists
- Treat with anticholinergic agents

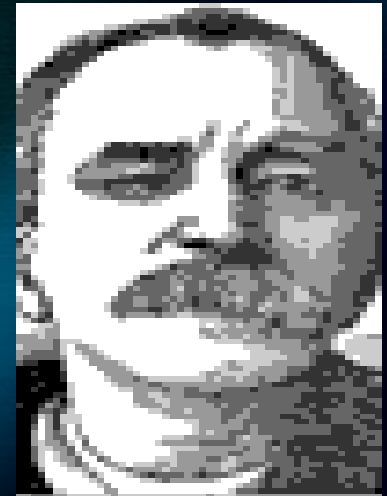


● Akathisias

- “Ants in your pants”: Feeling of internal (and sometimes external) restlessness
- 20 - 40% with high potency medication

Extrapyramidal Side Effects (EPS)

- **Tardive Dyskinesia**
 - From DA upregulation
 - 4% per year for the first 4 years
 - Atypicals are 1/10 risk of typicals
 - Average 20 - 30% of patients
 - **Generally IRREVERSIBLE – Prevention is key!**
 - T.D. Clinic referral and monitoring



Treatment of EPS

Note: Prophylaxis for EPS (excluding akathesia) when giving PO/IM/IV typical antipsychotic often done as a precaution - especially in children!

(ie. "B-52" = Benadryl 50mg/Haldol 5mg/Ativan 2mg)

- Diphenhydramine (Benadryl[®])
 - 25-100mg (Usual dosage 25-50mg q4-6h prn)
 - Max = 400mg/d
 - PO, IM or IV
- Benztropine (Cogentin[®])
 - 0.5 – 4mg (Usual dosage 2mg BID)
 - Max = 8mg/d
 - PO, IM or IV

Treatment of EPS

- Trihexyphenidyl (Artane[®])
 - 1-15mg (Usual dosage 5mg TID)
 - Max 15mg/d
 - PO only

- Propranolol (Inderal[®])
 - 60-320mg (Usual dosage 40mg BID)
 - Give PO
 - Used for treating akathisia only*

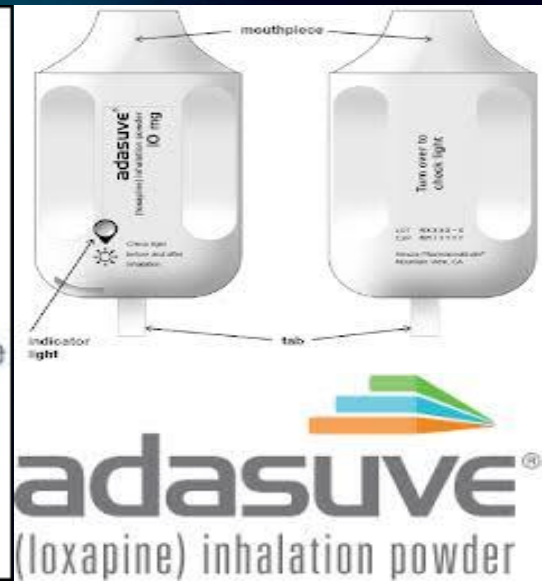
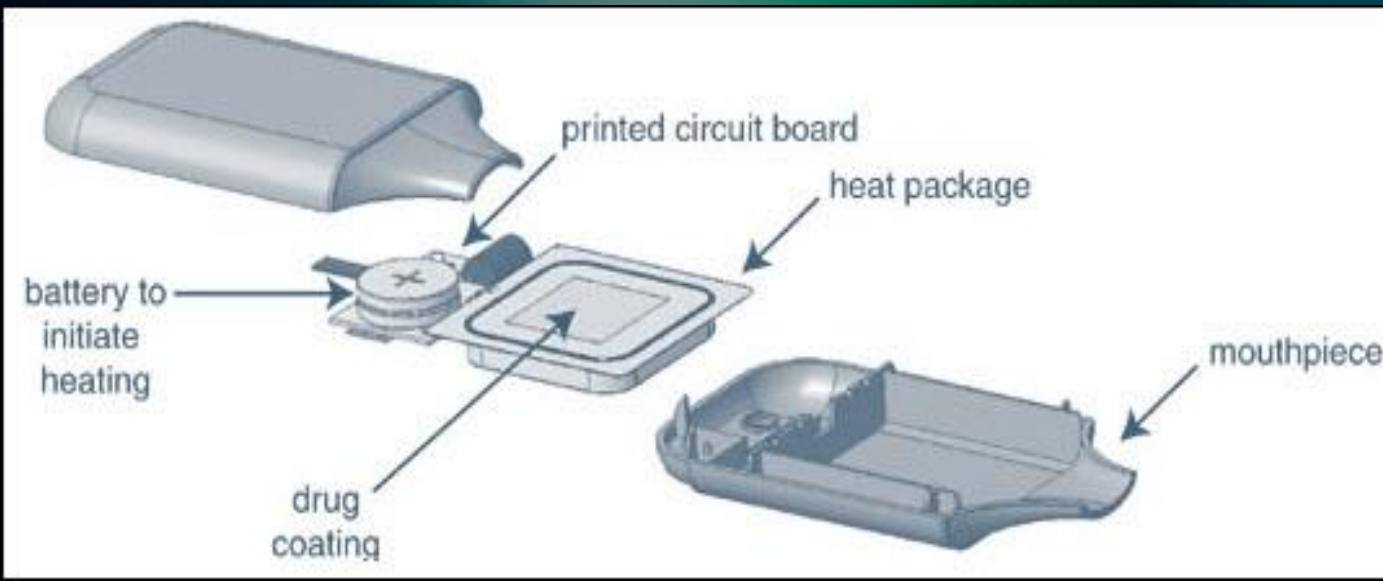
Other Typical AP Adverse Effects

- **Cardiovascular**
 - Arrhythmias
 - Tachycardia
 - Vagal inhibition
 - Reflex tachycardia
 - Quinidine-like effects
- **Pigmentary Retinopathy**
 - Thioridazine max. dose
- **Photophobia**
 - Photosensitivity
- **Dermatological**
 - Blue-gray skin
- **Hepatologic**
 - Up to 50% have transiently ↑ LFTs
- **Hematologic**
- **Hormonal**
 - ↑ prolactin
 - Sexual Dysfunction
 - 25-60% of patients
- **Thermoregulation**
- **Seizures**
- **Sudden Death**
- **Neuroleptic Malignant Syndrome**

Loxapine Inhalation Powder (Adasuve®)

Available March 3, 2014

- FDA Approved to treat **psychomotor agitation** in Bipolar I Disorder and Schizophrenia
- **Contraindications: asthma, COPD, respiratory dz.**
- **PK:**
 - $T_{max} = 1.13$ minutes
 - $F =$ linear, dose dependent
 - Active metabolite: N-desmethyl loxapine (amoxapine), 8-hydroxyloxapine
- **ADR: Taste sense altered (14%), Sedated (12%)**



ATYPICAL ANTIPSYCHOTICS



In the 1990's



- A new awakening about the treatment of schizophrenia
- Typical antipsychotics only treated half of the disease
- Atypical antipsychotics (aka second-generation antipsychotics) emerged as the standard of care

Early 2000's: Where Typical AP's caused EPS,
Atypical AP's cause ~**METABOLIC SYNDROME**~

All antipsychotics block D₂ receptors in the brain. Atypical antipsychotics differ from conventional (a.k.a. typical) antipsychotics in that they also block _____ receptors, which likely reduces the risk of extrapyramidal symptoms (EPS) and improves negative symptoms of schizophrenia.

- A. Serotonin
- B. Norepinephrine
- C. Anticholinergic
- D. Glutamate
- E. Muscarinic

What makes an antipsychotic atypical?

- Low risk of EPS (Extrapyramidal Side effects), TD (Tardive Dyskinesia) and Prolactin elevations
- Atypicals improve **positive and negative** symptoms & potentially **cognitive deficits** in schizophrenia (5-HT_{2A} effects)
- Block specific dopamine receptors
 - **Mesocortical** and **Mesolimbic specific**
 - Blocking other receptors may not cause antipsychotic effect

Patterns and Trends in Antipsychotic Prescribing for Parkinson Disease Psychosis

- Weintraub et al (2011):
 - Veterans Affairs outpatient facilities data, rates & predictors of AP prescribing were determined for PD patients with psychosis stratified by dementia status
 - PD and psychosis (N=2597) compared to no PD with dementia and psychosis (N=6907).
 - Fiscal year 2008 and FY2002 data were compared to examine changes in AP prescribing over time.
 - Main Outcome Measure: Antipsychotic prescribing, including overall, class, and specific medications.

Patterns and Trends in Antipsychotic Prescribing for Parkinson Disease Psychosis

- Results: 50% of patients with PD having a diagnosis of psychosis were prescribed an AP.
 - Among treated patients, quetiapine was most frequently prescribed (66%)
 - 30% received high-potency APs
 - Clozapine was rarely prescribed (<2%)
 - In multivariate models, diagnoses of PD and dementia were associated with AP use.

Patient Case 2: LD

- LD is a 74yo WM patient with advancing Parkinson's disease who develops hallucinations. All possible medications were discontinued, except carbidopa/L-dopa therapy which was reduced. This did not resolve LD's psychosis and an antipsychotic is needed. Which of the following is/are considered the treatment of choice for LD: (SELECT ALL THAT APPLY)

- Asenapine
- Aripiprazole
- Clozapine
- Iloperidone
- Lurasidone

- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone

Dopamine Blockade

- Need 65% occupancy at D₂ receptors for antipsychotic effect
 - If > 78-80%, then EPS occurs
 - Clozapine and Quetiapine never exceed this
 - Olanzapine, Ziprasidone and Risperidone may exceed this in a dose-dependent fashion

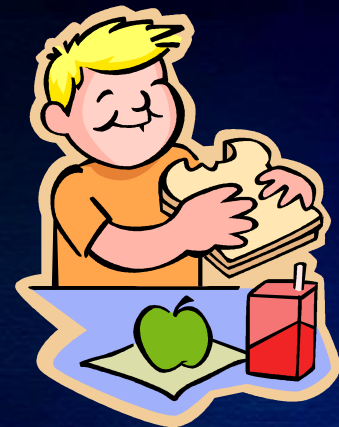
Transient Blockade

- **Relatively loose** binding allows for natural dopamine to attach to receptors when needed
 - Reduces or eliminates:
 - EPS / ↑Prolactin / Secondary negative symptoms
- Related to molecular structure / drug potency
 - ie. **Clozapine has 100 times** less receptor affinity than **haloperidol**
 - **Quetiapine** and **Clozapine** have similar binding
 - **Risperidone** and **Ziprasidone** less transient

“A New Generation of Side Effects”

● Metabolic Syndrome or Syndrome X

- High cholesterol
 - HDL \leq 40 Males, \leq 50 Females
 - TG \geq 150mg/dL (or \uparrow lipids)
- High blood pressure
 - BP $>$ 130/85mmHg (or HTN)
- High blood sugar
 - Fasting BS \geq 100 (or DM)
- Overweight: Waist Circumference
 - Male $>$ 40, Female $>$ 35 (or BMI above 30kg/m²)



Which of the following has the least chance of causing metabolic syndrome?

- A. Aripiprazole
- B. Iloperidone
- C. Quetiapine
- D. Olanzapine
- E. Paliperidone

FDA Black Box Warning, April 2005

● Black Box Warning:

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death

● 17 randomized clinical trials involving risperidone, olanzapine, quetiapine and aripiprazole = health advisory to warn about a 1.6-1.7x higher risk of all-cause mortality relative to placebo.

- Small RCT's, generally short in duration, very low event rate, and ***reliable estimates of mortality risk could be generated only when data were combined in a meta-analysis.***

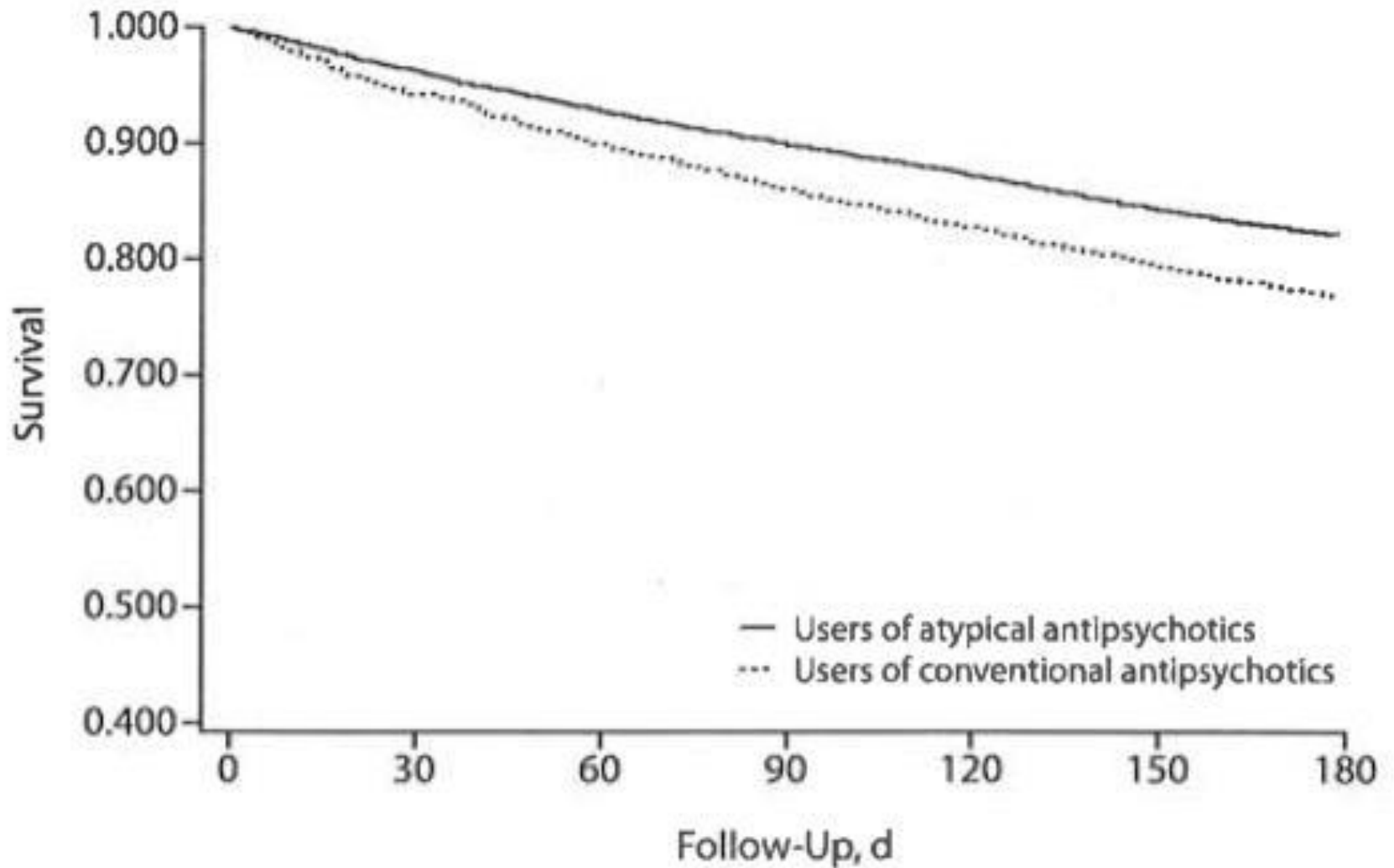
Updated FDA Black Box Warning: All Antipsychotic Medications

- Observational studies suggested conventional APs may pose an even greater risk of death compared to atypical agents
 - NO conclusive evidence about risk of death associated with APs to date among dementia patients in LTCs
 - Studies done in outpatient users of APs based on Rx databases regardless of indications
 - Only 1 study included dementia patients:
 - Showed atypical and conventional agents demonstrated similar mortality risks.

All-Cause Mortality Associated with Atypical and Conventional Antipsychotics Among Nursing Home Residents with Dementia: A Retrospective Cohort Study

- Liperoti et al. (2009):
 - Monitored 1,581 Medicare or Medicaid-certified nursing homes in 5 US states (Kansas, Maine, Mississippi, Ohio, South Dakota) from 1998-2000
 - 6,524 new users of atypical antipsychotics
 - 3,205 new users of typical antipsychotics
 - Outcome of all-cause mortality determined at 6 months of follow-up.

Figure 1: Survival Curves



Atypical users at risk, n (no. of events)	6,524 (0)	6,055 (469)	5,690 (365)	5,362 (328)
Conventional users at risk, n (no. of events)	3,205 (0)	2,881 (324)	2,652 (229)	2,461 (191)

Table 2:

Effect of Antipsychotics on the Risk of Death (atypical antipsychotics as reference category)

Antipsychotic	No. of Events	Total Follow-Up (person-years)	Crude IR per 100 Person-Years	Crude HR	Adjusted HR ^a	95% CI
Atypical	1,162	2,904	40.0	
Conventional	745	1,372	54.3	1.41	1.26	1.13–1.42

^aAdjusted for age, race/ethnicity, gender, body mass index, Activities of Daily Living score, Cognitive Performance Scale score, severity of behavioral symptoms, cardiovascular and cerebrovascular comorbidities, and use of concomitant medications, including cardiovascular drugs, aspirin/antiplatelets/anticoagulants, benzodiazepines, and antidepressants.

Abbreviations: HR = hazard ratio, IR= incidence rate.

- After adjusting for all potential confounders, relative to users of atypical antipsychotics, the rate of death was increased for users of conventional agents (adjusted HR, 1.26; 95% CI, 1.13–1.42)

Association of Antipsychotic Use With Hospital Events and Mortality Among Medicare Beneficiaries Residing in Long-Term Care Facilities

- Simoni-Wastila et al. (2009):
 - Medicare Current Beneficiary Survey linked to Institutional Drug Administration and Minimum Data Set files from 1999-2002
 - 2,363 total LTC Medicare beneficiaries
 - Outcomes:
 - AP use not related to hospital events (HR=0.98, 95% CI = 0.82-1.63, p=0.791)
 - AP use associated with reduced mortality in adjusted and intermediate models, but loss of significance in the final model (HR=0.83, 95% CI = 0.69-1.00, p=0.0537)

Pharmacotherapy

- Atypical Antipsychotics
 - Aripiprazole (Abilify[®])
 - Ziprasidone (Geodon[®])
 - Paliperidone (Invega[®])
 - Risperidone (Risperdal[®])
 - Quetiapine (Seroquel[®])
 - Olanzapine (Zyprexa[®])
 - Clozapine (Clozaril[®])
- Newer FDA approved:
 - Iloperidone (Fanapt[®])
 - Asenapine (Saphris[®])
 - Lurasidone (Latuda[®])

Drug Name	Usual Oral Dosage (mg/day)	Max Dosage (mg/day) -per manufacturer-
Aripiprazole (Abilify®)	10 -30	30
Asenapine (Saphris®)	10	20
Clozapine (Clozaril®)	300-600	900
Iloperidone (Fanapt®)	12-24	24
Lurasidone (Latuda®)	40	80
Olanzapine (Zyprexa®)	10-20	20
Paliperidone (Invega®)	6	12
Quetiapine (Seroquel®)	300-800	800
Risperidone (Risperdal®)	4-8	16
Ziprasidone (Geodon®)	40-160	160

Which medication has variable drug absorption based on food intake, thus limiting its usage in some patients?

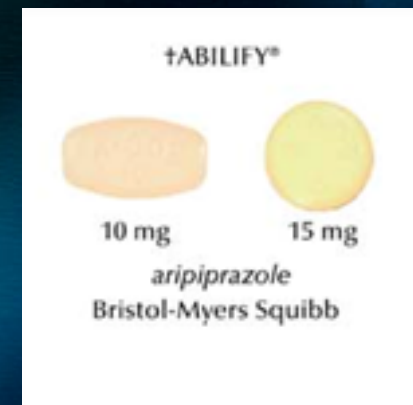
- A. Asenapine
- B. Iloperidone
- C. Paliperidone
- D. Lurasidone
- E. Aripiprazole

Aripiprazole (Abilify®)

- Indications:
 - Schizophrenia (agitation and maintenance) in adults and adolescents (13-17yo)
 - Bipolar disorder (acute or maintenance treatment for manic or mixed episodes) in adults and adolescents (13-17yo)
 - Treats as monotherapy or adjunctive therapy to lithium or valproate
 - Adjunctive treatment for MDD in adults
 - Irritability/agitation associated with Autistic Disorder
 - Approved for children/adolescents (6-17yo)

Aripiprazole (Abilify®)

- Metabolized by **CYP 2D6** and **3A4**
 - Drug interactions with known inhibitors/inducers
- Mechanism of action = 3rd generation
 - Partial dopamine-2 and 5HT_{1A} agonist
 - 5HT_{2A} antagonist
 - Also blocks α_1 and H₁ receptors
- Not very sedating, and sometimes activating
 - Minimal or rare side effects:
 - Headache and early onset nausea, usually resolves
 - Sedation or drowsiness at HIGHER doses
 - Minimal weight gain reported (lowest metabolic sx risk)



Aripiprazole

(Abilify[®], Abilify Maintena[®])

● Dosing

- Target dose = 10 to 15mg daily (Max=30mg/day)
 - Do not adjust doses < 2 weeks
 - Available in 2, 5, 10, 15, 20, & 30mg tablets, oral solution (tablet dosage equal mg/kg, except pts on 30mg tablet use 25mg oral)

● Available IM for acute treatment:

- 5.25 to 9.75mg IM

● Adverse effects

- | | |
|------------------|-------------------------|
| ● Headache (32%) | ● Akathisia (10%) |
| ● Anxiety (25%) | ● Constipation (10%) |
| ● Insomnia (24%) | ● Lightheadedness (11%) |
| ● Nausea (14%) | ● Somnolence (11%) |
| ● Vomiting (12%) | |



Abilify Maintena[®]

- Once monthly IM injection for maintenance use
- Aripiprazole monohydrate lyophilized powder for reconstitution
 - Aqueous suspension of poorly soluble salt form
 - No loading dose used = 2 weeks of po overlap required
 - Dosed q4weeks (by gluteal IM injection)



Patient Case 1: AC

- AC is a 65yo WF who comes into your clinic for advice on an antipsychotic medication she received a few days ago in Florida. She is complaining that she can't remember the name, but knows what it looks like and takes it daily In the morning. Her doctor told its a newer class that shouldn't make her shake or muscles contract as some of her treatments have in the past. She is complaining today of feeling restless, unable to sit still, and thinks it is due to the medication as she just increased the dosage.
 - What is the adverse effect that AC is likely experiencing?
 - Which antipsychotic is most likely the cause of this side effect?
- You decide to contact her MD in Florida to notify him of AC's current side effect. The MD suggests to start her on Cogentin, but asks what dosage you recommend?
 - What recommendations do you have for the MD?

Asenapine (Saphris®)



- Newer atypical antipsychotic FDA approved for:
 - Acute and maintenance treatment of schizophrenia
 - Monotherapy or adjunctive therapy with lithium or valproate in acute treatment of bipolar mixed or manic episode
- Mechanism of action
 - Primarily works by antagonistic activity at D_2 and $5-HT_{2A}$ receptors
 - High affinity serotonin, dopamine, alpha, and histamine receptors = sedating;
 - Good for oral Emergency Treatment Option (ETO)

Asenapine (Saphris®)

- Metabolism: Glucuronidation & **CYP 1A2**
- $T_{1/2} = 24\text{hrs}$
- Only formulation = sublingual tablets:
 - 5 and 10mg
 - Do not swallow, Do not eat or drink for 10 minutes after administration
- Starting and target dose = **5mg BID**
 - No improved benefit demonstrated at higher doses
 - Max dosage = **10mg BID**
- Common adverse effects:
 - Weight gain: 3-5%
 - Oral hypoesthesia: 5%
 - Akathisia: 4-6%
 - ◆ **Dizziness: 5-11%**
 - ◆ **EPS: 7-10%**
 - ◆ **Somnolence: 13-24%**



Clozapine (Clozaril®)

- First-of-its-kind atypical
 - Discovered in 1958
 - Structural analogue of **Loxapine**

- Indicated for **Treatment Resistant Schizophrenia** and **Resistant Bipolar**
 - Effective in **30-60%** of refractory patients



Clozapine (Clozaril®)

- Dosing
 - Start at 12.5mg BID
 - Increase by 25-50mg/d up to 300 over 14 days
 - Plasma levels > 350 ng/ml may ↑ efficacy
 - Max dosage = 900mg/d (recommended blood level above 600mg/d)
 - Available in 25mg and 100mg tablets
- Clozaril® National Registry (CNR):
 - \$ cost / labs / time consuming paperwork
 - Now brand Clozaril® + 6 Generic registries!
 - No more than a 1, 2 or 4 week supply can be dispensed at any one time
 - Two week supply only after 6 months of continuous therapy has been documented, 4 weeks after 1 year

Which of the following is NOT an adverse effect associated with clozapine?

- A. Agranulocytosis
- B. Diarrhea
- C. Hypersialorrhea
- D. Seizure
- E. Sudden cardiac death

Clozapine Adverse Effects

MOST COMMON

- Drowsiness
- Dizziness
- Tachycardia (reflex)
- Orthostatic hypotension
- GI upset / complications
- Visual disturbances
- Constipation/GI complications
- Weight gain
- Hyperglycemia / DM II
- Hypersialorrhea
- Sudden Cardiac Death

AGRANULOCYTOSIS

- Rare
 - 1-2%
 - Peaks in 3rd month

SEIZURES

- <300mg = 1-2%
 - 300-600mg = 3-4%
 - 600-900mg = 5-14%
- May worsen OCD

Iloperidone (Fanapt[®])

- Only approved for maintenance of schizophrenia in adults
- Metabolized by CYP 2D6 and 3A4
- Dosing:
 - Initial: 1mg BID day 1, then titrate 2mg, 4mg, 6mg, 8mg, 10mg and 12mg BID on days 2-7
 - Target maintenance dose 6mg BID
 - Max = 12mg BID
 - Available doses = 1, 2, 4, 6, 8, 10, and 12mg tablets

Iloperidone (Fanapt®)

- Common adverse effects:

- Orthostatic hypotension (3-5%)*
- Tachycardia (3-12%)
- ↑Prolactin (26%)
- Weight Gain (1-18%)
- Xerostomia (8-10%)

- Dizziness (10-20%)*
- Somnolence (9-15%)
- Nasal congestion (5-8%)
- Fatigue (4-8%)
- GI upset (diarrhea 5-7%, nausea 7-10%)
- QT prolongation (~9msec, similar to Geodon)*

*Orthostatic hypotension, dizziness and QT prolongation limit use in the elderly

Lurasidone (Latuda[®])

- Available February 2011 for schizophrenia
 - Recently approved for bipolar depression June 2013
- Mechanism of action: **D₂** and **5HT_{2A}** antagonist
- Starting dose: 40mg once daily
 - Titration not required
- Average dose in studies: 40 – 120mg/day
 - Dose related increase in ADR's noted (**EPS**)
 - Max recommended dosage is 80mg/day
 - EPS associated with increasing dosage
 - Recommended **to take with food (350 calories req)**
 - **Bioavailability decreased ~ 50%**
 - Metabolized by **CYP3A4**
 - **99.8% protein bound**



Olanzapine (Zyprexa®)

- Indications:
 - Schizophrenia (agitation and maintenance) in adults and adolescents (13-17yo)
 - Bipolar disorder (acute or maintenance treatment for manic or mixed episodes) in adults and adolescents (13-17yo)
 - Treats as monotherapy or adjunctive therapy to lithium or valproate
 - Adjunctive treatment for MDD in adults
- Caution: Not 1st line tx in children/adolescents due to increased potential for weight gain and hyperlipidemia
 - Elderly may have weight gain, but suggested less risk than pediatrics or adults.

Olanzapine (Zyprexa[®], Zyprexa Relprevv[®])

- Metabolism: CYP 1A2 –
 - Cigarette smoking can decrease concentrations 50%!!
- Dosing
 - Initially 5mg, increasing up to target dose of 10mg
 - Average = 10-20mg/d (FDA Max = 20mg)
 - 5 - 30mg QD at bedtime commonly used
 - Zyprexa Intramuscular injection (for acute agitation):
 - 5 – 10mg IM for acute agitation
 - Zyprexa Relprevv = Long-Acting Injection



Olanzapine (Zyprexa[®], Zyprexa Relprevv[®])

- Available in 2.5, 5, 7.5, 10, 15 and 20mg tablets
 - Zyprexa Zydis[®]: 5, 10, 15 and 20mg tablets
 - *Dissolvable oral tablet*
 - Zyprexa Intramuscular injection:
10mg vial
 - Zyprexa Relprevv:
 - 210mg, 300mg, 405mg vials



Target Oral Olanzapine Daily Dose	First 8 weeks of therapy	After 8 weeks of therapy
10mg	210mg/2weeks or 405mg/4weeks	150mg/2weeks or 300mg/4weeks
15mg	300mg/2weeks	210mg/2weeks or 405mg/4weeks
20mg	300mg/2weeks	300mg/2weeks

Risperidone

(Risperdal[®], Risperdal Consta[®])

- **Indications:**

- Schizophrenia – acute & maintenance adults/adolescents (13-17yo)
- Bipolar Mania – acute manic or mixed episodes for short-term treatment in adults, children & adolescents (10-17yo)
 - Approved for monotherapy or combination therapy with lithium or valproate
- Irritability associated with Autistic Disorder – approved for children/adolescents (5-16yo)

Risperidone (Risperdal[®], Risperdal Consta[®])

- Mechanism of action

- D_2 and $5HT_{2A}$ antagonist: First to recognize atypicality profile!

- Metabolism: CYP 2D6 – Drug interactions with inducers/inhibitors

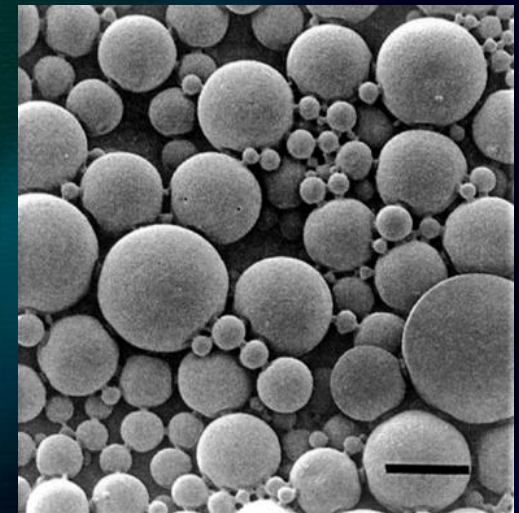
- Active metabolite: 9-hydroxyrisperidone

- Half life:

- Risperidone = 3-20hrs
- 9-Hydroxyrisperidone = 21-30hrs
- Combined overall mean $T_{1/2} = 20$ hrs

- **Risperdal Consta**

- **Elimination $T_{1/2} = 3-6$ days** for erosion of microspheres and subsequent absorption
- Elimination phase complete approx **7-8 weeks** after last inj.



Risperidone (Risperdal[®], Risperdal Consta[®])



● Dosage

- Start at 2mg/d (2mg QHS or 1mg BID) in adults
- Increase by 1-2mg/d to target of 4-8mg/d
- Max dose = 16mg, but generally do not exceed 12mg/d
- **Risperdal Consta: 25mg IM q2weeks**
 - Max dose = 50mg IM q2weeks

● Availability

- 0.25mg, 0.5mg, 1mg, 2mg, 3mg, and 4mg tabs
- **Liquid formulation** 1mg/ml
- **M-Tabs** 0.5mg, 1mg and 2mg
- **Risperdal Consta[®] IM injection** 12.5/25/37.5/50mg
 - 2 week long acting formulation (NOT a depot injection)



Risperidone (Risperdal[®], Risperdal Consta[®])

• Common Side Effects ($\geq 10\%$)

- Somnolence / Fatigue
- Rhinitis / URI / coughing
- GI upset (N/V/D, abdominal pain, constipation, dyspepsia)
- EPS (Parkinsonianism, dystonia, akathisia, tremor)
 - Usually dose dependant
- Hyperprolactinemia (children/adolescents high risk)
- Orthostatic hypotension /dizziness
- Xerostomia or hypersiallorhea
- Urinary incontinence
- Appetite increase (weight gain mostly in adolescents)

Patient Case 2: VJ

VJ is a 71yo HM currently taking Risperidone 3mg po BID and Fluoxetine 40mg po QHS, as prescribed by his psychiatrist for Bipolar Type . He comes to your clinic complaining he hates his medication and what else you could change him to. Upon questioning why he hates his medication, he mentions it's hard for him to remember every dose. He also feels the medication is diminishing his sexual drive, and at times he feels like his movements are slowed.

- What drug interaction might VJ be experiencing?
- What alternative(s) could help this patient's compliance issue? Please include all dosing parameters in your recommendation.

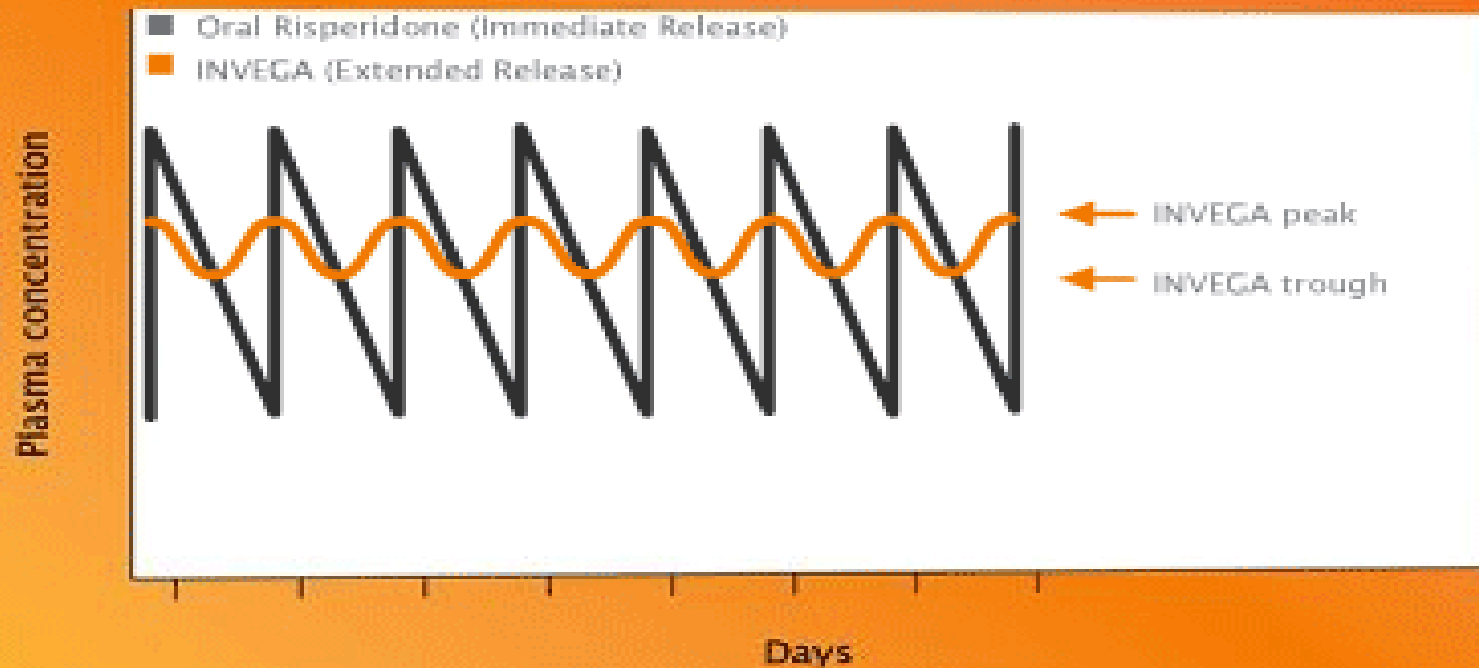
Paliperidone (Invega[®], Invega Sustenna[®])

- Indication: schizophrenia (acute & maintenance) in adults
- Active metabolite of risperidone
- Same side effect profile, but improved due to long acting once daily formulation; **renal elimination**
- 6mg = close to placebo regarding weight gain, but higher doses = similar to risperidone



Paliperidone (Invega[®], Invega Sustenna[®])

* PLASMA LEVEL VARIATION AT STEADY STATE



Pharmacokinetic simulation.

Paliperidone (Invega[®], Invega Sustenna[®])



- Available in 3, 6 and 9mg tablets
(Max=12mg/d)
 - OROS formulation: **Watch for ghost capsule!**
 - Best taken in AM to allow for full absorption
- Paliperidone palmitate (Invega Sustenna[®]) is newly approved LA injectable given **q4weeks**:
 - Initial dosage = 234mg IM & 156mg IM one week later
 - Maintenance = 117mg (range 39-234mg) IM monthly
 - **NOT a depot injection**

Quetiapine (Seroquel[®], Seroquel XR[®])

- Indicated for **acute** and **maintenance** of both **schizophrenia** and **bipolar (depressed phase or mania)**, adjunct therapy for Major Depressive Disorder
- Mechanism of action:
 - **5HT_{1a-2}**, **D₁₋₂**, **Ach**, **alpha₁₋₂** and **H₁** antagonist
- Half-life:
 - Immediate release: $T_{1/2} = 6$ hours
 - Extended release: $T_{1/2} = 7$ hours
 - N-desalkyl quetiapine (extended release): $T_{1/2} = 9-12$ hrs

Quetiapine (Seroquel[®], Seroquel XR[®])

- Immediate Release (Seroquel[®]):

- Start at 25 to 50mg BID
 - Titrate up to 400mg by day 4 or 5
- Target dose is **400 - 800mg/d** divided
 - Maximum dose is 800mg/d total, but higher doses are well tolerated
- Available as: 25, 100, 200 and 300mg tablets



- Extended Release (Seroquel XR[®])

- Start at 300mg daily
- Dosage increases of 300mg may occur at 300mg/d
- Target dose is **400 – 800mg/d**
- Available as: 200mg, 300mg, 400mg tablets



Quetiapine (Seroquel[®], Seroquel XR[®])

- Drug Interaction

- Phenytoin increases clearance up to 500%
- Need to ↑ dose of quetiapine

- Common Side Effects

- Postural hypotension / Dizziness
- Somnolence
- Rare to non-existent EPS or prolactin ↑ at any dose
- Little weight gain / hyperglycemia

Ziprasidone (Geodon[®])

● Indication

- Schizophrenia – acute & maintenance in adults
- Bipolar Mania – acute manic or mixed episodes in adults, or combination therapy with lithium or valproate

● Mechanism of action:

- 5HT_{1d,2a,2c}, D₂₋₃, *alpha*₁ and H₁ antagonist
- Also inhibits the reuptake of 5HT and NE



● Dosing

- Begin with 20mg BID (**with food**)
- Adjust dose up to 80mg BID (Max = 160mg daily)

Ziprasidone (Geodon[®])

- Pharmacokinetics
 - Metabolized by CYP3A4
 - >99% protein bound
 - $T_{1/2} = 7$ hours
- Common Side Effects
 - Somnolence
 - Dose-related EPS
 - At higher than recommended doses
 - Respiratory symptoms
 - Rare QT prolongation (~9msec)
 - EKG not required but recommended for those at risk (generally recommended before treatment initiation)

Ziprasidone (Geodon®)

- Availability

- Capsules – 20mg, 40mg, 60mg and 80mg
- Immediate acting IM injection – 20mg/vial

- Drugs that prolong the QT interval generally contraindicated

- ie. Citalopram, Quinidine, Pimozide, Sotalol, Thioridazine



AP's in the Elderly – Key Points:

- AP's are effective tools treating psychosis, agitation and may help some behavioral disturbances in geriatrics.
- There are some linkages to increased morbidity, mortality, and side effects in elderly patients.
- Medications must be selected with caution and managed closely, especially considering the their link to increased risks of adverse effects
 - Mortality
 - Cerebrovascular events
 - Metabolic effects
 - EPS
 - Falls
 - Cognitive worsening
 - Cardiovascular effects
 - Pneumonia
 - Neuropsychiatric symptoms

Questions?

