An Antipsychotic Roundup: New Agents and Safety Updates

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Home Study Webcast Activity Handout

4 slides per page

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An Antipsychotic Roundup: New Agents and Safety Updates

ACTIVITY DESCRIPTION

New antipsychotic agents were released in 2016 and 2017 (including one agent used specifically for patients with Parkinson's Disease) and also updated availability (long acting agents) since the last APS update in 2015.

TARGET AUDIENCE

The target audience for this activity is **pharmacists, pharmacy technicians,** and **nurses** in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES

After completing this activity, the **pharmacist** will be able to:

- Recognize new antipsychotic agents and administration forms available for use
- Identify important side effects and emerging safety associated with the different antipsychotic agents
- ecommend appropriate education and intervention to address the challenges associated with the use of these antipsychotic agents in patients with serious mental illness

After completing this activity, the **pharmacy technician** will be able to:

- Recognize new antipsychotic agents and administration forms available for use
- Identify important side effects and emerging safety associated with the different antipsychotic agents

ACCREDITATION

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Universal Activity No.: 0798-0000-17-196-H01-P
Credits: 1.0 contact hour (0.1 CEU)

Release Date: 4/18/2018
freeCE Expiration Date: 4/18/2020
ACPE Expiration Date: 10/18/2020

ACTIVITY TYPE

Knowledge-Based Home Study Webcast

FINANCIAL SUPPORT BY

Pharmaceutical Education Consultants, Inc.

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ABOUT THE AUTHOR

Dr. Tammie Lee Demler received her Doctor of Pharmacy, Master of Business Administration, and Bachelor of Science degrees at the State University of New York (SUNY) at Buffalo. Dr. Demler is a Board-Certified Psychiatric Pharmacist and is currently the Director of Pharmacy Services and Pharmacy residency training at the New York State Office of Mental Health (OMH) at the Buffalo Psychiatric Center. She holds numerous adjunct academic appointments, including Clinical Associate Professor for SUNY Buffalo School of Pharmacy and Pharmaceutical Sciences, Clinical Assistant Professor at SUNY School of Medicine Department of Psychiatry, D'Youville College School of Pharmacy, University of Florida School of Pharmacy, and Clinical Instructor for the Erie County >Community College's Pharmacy Technician Certification Program (PTCB). Dr. Demler collaborates with both the National Association of the Boards of Pharmacy (NABP) and the Board of Pharmaceutical Specialties (BPS) to develop board examinations that establish the minimum competencies expected for new practitioners to practice in an ever changing clinical environment. Prior to embarking on her academic and institutional career, Dr. Demler's clinical practice focused on ambulatory care in community pharmacy.
Dr. Demler has authored and co-authored numerous original research articles and expert reviews for printmedia. She is a regular contributor to U.S. Pharmacist Pharmacist's Letter. Dr. Demler is an author for the American College of Clinical Pharmacy's Ambulatory Care Self-Assessment and has also has provided expert pharmacotherapeutic consultation for other books such as the Side Effects of Drugs: Annual Volume 36 and Clinical Consult to Psychiatric Nursing for Advanced Practice. In March 2017, she is publishing her own book Pharmacotherapeutics for Advanced Nursing Practice, and is planning a companion text for Physician Assistants hopefully in 2018.

She has presented medication continuing education programs internationally and nationally, and is an Academic Educator for the New York State Medicaid Prescriber Education program sponsored by the New York Department of Health. Dr. Demler served as President of both the Pharmacists Society of the State of New York and the Pharmacists Association of Western New York.

Dr. Demler is also a local media personality, hosting her own weekly TV talk show as well as a weekly community affairs radio segment. She has won a number of prestigious national, state, and local awards acknowledging both her professional and community-based contributions.

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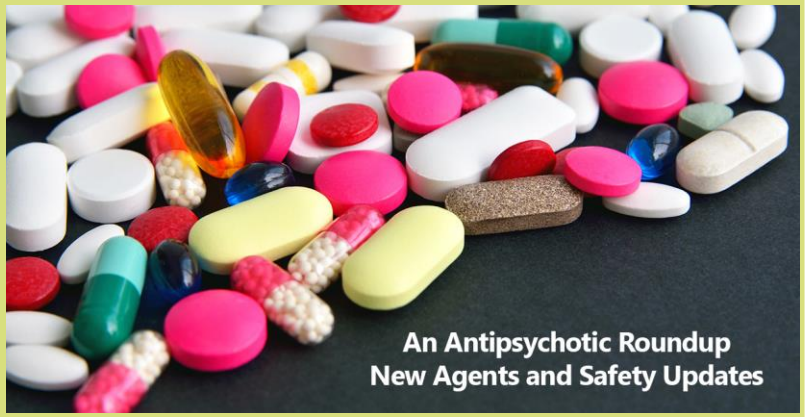

Faculty: Tammie Lee Demler, PharmD, MBA, BCPP

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Objectives for Pharmacy Technicians

- **Recognize** new antipsychotic agents and administration forms available for use
- Identify important side effects and emerging safety associated with the different antipsychotic agents

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Objectives for Pharmacists

- **Recognize** new antipsychotic agents and administration forms available for use
- Identify important side effects and emerging safety associated with the different antipsychotic agents
- Recommend appropriate education and intervention to address the challenges associated with the use of these antipsychotic agents in patients with serious mental illness

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Objective #1

- **Recognize new antipsychotic agents and administration forms available for use**

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Nomenclature and classification

Antipsychotics, psychotropics, neuroleptics:

- First generation antipsychotics (FGA) =AKA Typical/Traditional/Conventional:
  - High D_2, Low 5-HT_{2A}
- Second generation antipsychotics (SGA)= AKA Atypical:
  - Moderate-high D2, High 5-HT2A

General MOA: block D_2 receptors, also antagonize D_1 & 5-$HT2_A$

FDA approved indications for use to guide prescribing; off label use for non serious mental illness (SMI) is often problematic (however, often used for behavioral symptoms for conditions that have no truly defined FDA approved core drug approvals)

Stahl, S. M. (2013). *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. Cambridge university press.

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Second Generation Antipsychotic (SGA)	FDA approved indications
Aripiprazole (Abilify)	Schizophrenia, Bipolar Disorder, MDD, symptoms associated with Autism, Tourette's
Asenapine (Saphris)	Schizophrenia, Bipolar Disorder
Brexpiprazole (Rexulti)	Schizophrenia, MDD
Cariprazine (Vraylar)	Schizophrenia, Bipolar Disorder
Clozapine (Clozaril)	Schizophrenia, Schizoaffective Disorder
Iloperidone (Fanapt)	Schizophrenia
Lurasidone (Latuda)	Schizophrenia, Bipolar Disorder
Olanzapine (Zyprexa)	Schizophrenia, Bipolar Disorder, MDD
Paliperidone (Invega)	Schizophrenia, Schizoaffective Disorder
Quetiapine (Seroquel)	Schizophrenia, Bipolar Disorder, MDD
Risperidone (Risperdal)	Schizophrenia, Bipolar Disorder, Autism (behavioral)
Ziprasidone (Geodon)	Schizophrenia, Bipolar Disorder

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Updates

New formulations of older agents
- Aripiprazole (Abilify Aristada)

Recently approved
- Brexpiprazole (Rexulti)
- Cariprazine (Vraylar)

New agent-different therapeutic class
- Pimavanserin (Nuplazid)

New agent-managing side effects
- Valbenazine (Ingrezza)

Review of currently available SGAs as a comparison

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Aripiprazole (Abilify)	
Unique MOA: partial D_2 and 5-HT_{1A} agonist	
Metabolism: CYP2D6, 3A4	
Clinical pearls	• Little weight gain • May be "activating" and less sedating than others • May cause insomnia, akathisia, restlessness • Associated with impulsivity • Patients and caregivers should be alert for uncontrollable and excessive urges and behaviors while taking aripiprazole
Availability	PO tablet (ODT discontinued), oral solution LAI (monohydrate powder for suspension): Maintena LAI (lauroxil): Aristada Gluteal and deltoid injection options are available Injection needle based on injection site and dosage
Oral dose	Schizophrenia initial: 5 to 15mg daily (Usual 15 to 30mg/day)

Receptor action
D_2 antagonism
✓ D_2 partial agonism
✓ $D_{3\ \&\ 4}$ antagonism
✓ 5-HT_{1A} partial agonism
✓ 5-HT_{2A} antagonism
✓ 5-HT_{2c} antagonism
✓ 5-HT_7 antagonism
✓ α_1 antagonism
✓ H_1 antagonism
M_1 antagonism
M_3 antagonism

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Long acting injection (LAI)

Aripiprazole (Abilify)	
LAI dose	Maintena (oral overlap: 14 days) Aristada (oral overlap: 21 days)
Oral dose	Injection dose
10 to 20mg daily	Maintena: 400mg monthly, may reduce to 300mg based on tolerability Aristada: • 441mg, 662mg or 882mg once monthly, or 882mg once every 6 weeks or 1064mg once every 2 months (8 weeks)

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Update on the "newer agents"

Brexpiprazole (Rexulti)	
Unique MOA: partial 5-HT_{1A} and D_2 (& D_3)receptor agonist and 5-HT_{2A} receptor antagonist	
Metabolism: CYP3A4 & CYP2D6	
Clinical pearls	• Akathisia (dose related), long half-life (91 hours) • Fewer metabolic challenges than others
Availability	Oral tablet only
Oral dose	2-4 mg/day (1-3 mg/day major depression) • MDD 3 mg (2 mg depression) with mod/severe hepatic impairment or CrCl <60 mL/min • ½ - ¼ dose if taken with strong CYP3A4/2D6 inhibitors • 2x dose if taken with strong CYP3A4 inducer

Receptor action
D_2 antagonism
✓ D_2 partial agonism
✓ D_3 partial AGONIST
✓ 5-HT_{1A} partial agonist
✓ 5-HT_{2A} antagonism
✓ 5-HT_{2B} antagonism
✓ 5-HT_7 antagonism
✓ $A_{1A, 1B, 1D, 2C}$ antagonism
✓ H_1 antagonism
✓ M_1 antagonism
M_3 antagonism

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Update on the "newer agents"

Cariprazine (Vraylar)	
Unique MOA: partial 5-HT_{1A} and D_2 (& D_3)receptor agonist and 5-HT_{2A} receptor antagonist (H_1, but no M_1)	
Metabolism: CYP3A4 & CYP2D6	
Clinical pearls	• Akathisia (dose related), long half-life (2-4 days) • Long half life (metabolites present >1 wk)
Availability	Oral capsule only
Oral dose	1.5 to 6mg per day

Receptor action
D_2 antagonism
✓ D_2 partial agonism
✓ D_3 partial agonism
✓ 5-HT_{1A} partial agonism
✓ 5-HT_{2A+2B} antagonism
✓ 5-HT_{2C} antagonism
5-HT_7 antagonism
✓ α_1 antagonism
✓ H_1 antagonism
M_1 antagonism
M_3 antagonism

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Pimavanserin (Nuplazid) approved by the FDA in April 2016	
Unique MOA: primarily sertononin (5HT) with sigma-1 σ	
Metabolism: CYP3A4 and CYP3A5	
Clinical pearls	• Indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis • Inverse agonist and antagonist activity at 5-HT_{2A} • Carries same BBW as all others for dementia related psychosis • Not recommended with any degree of hepatic impairment • Not recommended for renal compromise < 30ml/min • Avoidance of certain drug combinations (or reduced dosage) recommended • QTc warnings
Availability	Oral tablet only
Oral dose	34 mg (taken as two 17-mg tablets) PO once daily, without titration Administer without regard to food

Receptor action
D_2 antagonism
D_2 partial agonism
D_3 partial agonism
5-HT_{1A} partial agonism
✓ 5-HT_{2A} inverse agonism and antagonism
✓ 5-HT_{2C} antagonism
5-HT_7 antagonism
α_1 antagonism
H_1 antagonism
M_1 antagonism
M_3 antagonism
✓ σ antagonism/ inverse agonism

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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New Agent
Aanaging serious adverse events (TD)

Valbenazine (Ingrezza)

- Indicated for the treatment of tardive dyskinesia
- MOA: reversible inhibition of vesicular monoamine transporter 2 (VMAT2)
- Inhibition of dopamine release via this mechanism
- Active metabolite of valbenazine, also binds with relatively high affinity to human VMAT2.
- 40 mg PO once daily x 1 week then increase the dose to the recommended dose of 80 mg once daily
- Continuation of 40 mg once daily may be considered for some patients.
- May cause an increase in the QTc interval in patients who are CYP2D6 poor metabolizers

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Review: available FGA antipsychotics

First Generation Antipsychotic (FGA)	Class related side effects
Chlorpromazine (Thorazine) Fluphenazine (Prolixin) Haloperidol (Haldol) Loxapine (Loxitane) Perphenazine (Trilafon) Thiothixine (Navane) Trifluoperazine (Stelazine) Thioridazine (Mellaril)	• Extrapyramidal side effects (EPS) • QTc prolongation • Prolactin elevation • Dermatologic • Photosensitivity • Blue-gray skin • Orthostatic Hypotension • Altered thermoregulation • Black box: dementia related psychosis

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Review: Available SGA antipsychotics

Second Generation Antipsychotic (SGA)	Class related side effects

Aripiprazole (Abilify)
Asenapine (Saphris)
Brexpiprazole (Rexulti)
Cariprazine (Vraylar)
Clozapine (Clozaril, others)
Iloperidone (Fanapt)
Lurasidone (Latuda)
Olanzapine (Zyprexa)
Paliperidone (Invega)
Quetiapine (Seroquel)
Risperidone (Risperdal)
Ziprasidone (Geodon)
	• Metabolic syndrome
	  • Hypertriglyceridemia
	  • Hyperglycemia
	  • Weight Gain (waist circumference)
	• QTc prolongation
	• Blood dyscrasia/neutropenia
	• Seizure threshold
	• Anticholinergic effects
	• Sedation
	• Prolactin elevation
	
	• Black box: Dementia related psychosis

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Review: available SGA antipsychotics focusing on my "boxed highlights"

Asenapine (Saphris)	
MOA: High affinity D_2 and $5HT_{2A}$	
Metabolism: CYP1A2 and UGT1A4	
Clinical pearls	• Little weight gain • Among the least sedating & anticholinergic agents • Do not drink anything for minimum 10 minutes after dose • Not recommended for severe hepatic impairment • High risk for QTc prolongation (rare, but serious side effect)
Availability	Sublingual tablet only
Oral dose	Initial: 5 mg SL BID (Usual: 10-20 mg/day)

Receptor action
✓ D_2 antagonism
D_2 partial agonism
✓ D_3 antagonism
✓ $5\text{-}HT_{1A \text{ and } 1B}$ antagonism
✓ $5\text{-}HT_{2A \text{ and } 2B}$ antagonism
✓ $5\text{-}HT_{2c}$ antagonism
✓ $5\text{-}HT_{5\text{-}7}$ antagonism
✓ α_1 antagonism
✓ H_1 antagonism
M_1 antagonism
M_3 antagonism

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Review: available SGA antipsychotics focusing on my "boxed highlights"

Clozapine (Clozaril, Fazaclo)

MOA:
antagonist D_1 & D_4(D_2 less), 5-HT_2, and others (see right)
& agonist M_4

Metabolism: CYP1A2, CYP2D6, CYP3A4

Clinical pearls
- Gold standard treatment refractory illness (suicidality)
- QTc prolongation, seizure, myocarditis,
- Constipation, hypersialorrhea
- 350 ng/mL or greater is the goal; however greater than 600 mg/day (increased seizure risk)
- Metabolic conditions (worst offender)

Receptor action
✓ $D_{1,2}$ & $_4$ antagonism
D_2 partial agonism
D_3 antagonism
✓ 5-HT_{1A} partial agonism
✓ 5-$HT_{2A + 2B}$ antagonism
✓ 5-HT_{2c} antagonism
✓ 5-HT_7 antagonism
✓ α_1 antagonism
✓ H_1 antagonism
✓ M_1 antagonism
✓ M_3 antagonism
✓ M_4 AGONIST

Review: available SGA antipsychotics focusing on my "boxed highlights"

Clozapine (Clozaril, Fazaclo)

Clinical pearls cont'd
- Blood dyscrasias ANC as per REMS monitoring
- Central registry required, can now switch brands
- Baseline blood values, no longer substantial drops (BEN)
- Clozapine REMS monitoring program:
  - First 6 months: max. 1 wk. supply & weekly draws
  - Next 6 months: max. 2 wk. supply & biweekly draws
  - After 1 year: max. 1 mo. Supply & draws
- Patient's schedule can be change if no lab abnormalities

Availability: PO tablet, ODT, oral suspension

Oral dose
- Initial: 12.5 mg BID, MDD: 900 mg
- Increase by 25 – 50 mg every 3 days
- Continue until 450 mg/day or side effect tolerability
- If interruption >48 hours, restart at lowest dose

Review: available SGA antipsychotics focusing on my "boxed highlights"

Iloperidone (Fanapt)

MOA: high affinity D_2, D_3 and $5HT_{2A}$,
moderate D_4, $5HT_6$, $5HT_7$, alpha$_1$

Metabolism: CYP2D6, 3A4

Clinical pearls
- Among the most likely to cause orthostatic hypotension
- No notable prolactin elevation reported
- QTc warnings (rare, but serious side effect)
- Less sedating when compared to other SGAs
- Requires 50% dose reduction if given with conflicting CYP inhibitors
- Not recommended in severe hepatic impairment

Availability: PO tablet

Oral dose: Dose: Initial: 1 mg BID (Usual: 6-12 mg BID)
slow titration needed!

Receptor action
✓ D_2 antagonism
D_2 partial agonism
✓ D_3 & $_4$ antagonism
✓ 5-HT_{1A} antagonism
✓ 5-HT_{2A} antagonism
5-HT_{2c} antagonism
✓ 5-$HT_{6\ \&7}$ antagonism
✓ Alpha $\alpha_{1a,\ 1b,\ 1d,\ 2C}$ antagonism
H_1 antagonism
M_1 antagonism
M_3 antagonism

Review: available SGA antipsychotics focusing on my "boxed highlights"

Lurasidone (Latuda)

MOA: antagonist D_2 and 5-HT_{2A} , Partial agonist 5-HT_{1A}; No H, or M

Metabolism: CYP3A4

Clinical pearls
- No notable prolactin elevation or weight gain
- Less sedation and orthostasis compared to other SGAs
- Renal and hepatic dose adjustments needed
- Approved for adolescent use (schizophrenia) MDD 80mg
- Depression associated with bipolar I disorder as monotherapy or as an adjunct to lithium or valproate (lower dose 20mg daily with MDD=120mg)

Availability: Oral tablet

Oral dose: Schizophrenia: 40mg daily with food (350 calories recommended)
Effective range 40mg-160mg (MDD 160mg)

Receptor action
✓ D_2 antagonism
D_2 partial agonism
D_3 antagonism
✓ 5-HT_{1A} partial agonism
✓ 5-HT_{2A} antagonism
5-HT_{2c} antagonism
5-HT_7 antagonism
✓ Alpha $\alpha_{2a,\ 2c}$ antagonism
H_1 antagonism
M_1 antagonism
M_3 antagonism

Olanzapine (Zyprexa)

MOA: antagonist: D2 (1-4), 5HT2A, H1, M(1-5)

Metabolism: CYP1A2

Clinical pearls
- Post-injection delirium/sedation syndrome (PDSS)-REMS program for LAI
- DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)
- Sedation, metabolic issues, QTc, ANC
- PO: Schizophrenia and acute BPD mono (+12)
- Timings and warnings of co-administration with lorazepam injection

Availability: PO tablet, ODT, short acting IM, LAI (Relprevv)

Oral dose
- Initial: 5-10 mg/day
- Usual: 10-20 mg/day (MDD: 20mg, 30mg short acting injection)

LAI dose

Oral dose	Injection dose
10mg daily	210mg every 2 weeks x 8 weeks then 150mg every 2 weeks 405mg every 4 weeks X 8 weeks then 300mg every 4 weeks
15mg daily	300mg every 2 weeks x 8 weeks then 210mg every 2 weeks or 405mg every 4 weeks
20mg daily	300mg every 2 weeks

Receptor action	
✓	D_2 antagonism
	D_2 partial agonism
✓	$D_{1,3-4}$ antagonism
	$5\text{-}HT_{1A}$ antagonism
✓	$5\text{-}HT_{2A}$ antagonism
✓	$5\text{-}HT_3$ antagonism
✓	$5\text{-}HT_6$ antagonism
✓	α_1 antagonism
✓	H_1 antagonism
✓	$M_{1\text{-}5}$ antagonism

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Paliperidone (Invega)

MOA: antagonist D_2 and $5\text{-}HT_{2A}$

Metabolism: CYP3A4

Clinical pearls
- Metabolite of risperidone, similar ADR
- Deltoid or gluteal injection
- No PO overlap required
- Food increases bioavailability
- Must be maintained on Sustenna for at least 4 months before Trinza

Availability: Oral: OROS Tablet ("ghost" may be seen in stool)
LAI: Invega Sustenna & Invega Trinza

Oral dose: Initial: 1.5-6 mg/day with usual range 3-12 mg/day

Sustenna usual initial dose: 234mg with 156mg week 2 (deltoid), then 117mg monthly*

Oral dose	Sustenna dose (monthly)	Trinza dose (every 3 months)
3mg	39 to 78mg	273mg
6mg	117mg	410mg
12mg	234mg	819mg

Receptor action	
✓	D_2 antagonism
	D_2 partial agonism
	D_3 antagonism
	$5\text{-}HT_{1A}$ antagonism
✓	$5\text{-}HT_{2A}$ antagonism
	5-HT2c antagonism
	$5\text{-}HT_7$ antagonism
✓	$\alpha_{1\ \&\ 2}$ antagonism
✓	H_1 antagonism
	M_1 antagonism
	M_3 antagonism

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Review: available SGA antipsychotics focusing on my "boxed highlights"

Quetiapine (Seroquel)

MOA: antagonist D_2 and $5\text{-}HT_{2A}$

Metabolism: CYP3A4

Clinical pearls
- Sedation, metabolic issues, QTc
- May be misused
- Often used inappropriately as off label "sleep aid" for non SMI indications

Availability: PO tabs (IR and XR)

Oral dose
- Immediate release (IR): 25-50 mg BID up to 800 mg/day (Usual: 300-800mg daily in divided doses)
- Sustained release (XR): Start 300 mg may increase to 800 mg

Receptor action	
✓	D_2 antagonism
	D_2 partial agonism
✓	D_1 antagonism
✓	$5\text{-}HT_{1A}$ antagonism
✓	$5\text{-}HT_{2A}$ antagonism
	$5\text{-}HT_{2C}$ antagonism
	$5\text{-}HT_7$ antagonism
✓	$\alpha_{1\ \&\ 2}$ antagonism
✓	H_1 antagonism
	M_1 antagonism
	M_3 antagonism

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Risperidone (Risperdal)

MOA: antagonist D_2 and $5\text{-}HT_{2A}$

Metabolism: CYP2D6

Clinical pearls
- Aqueous injection for IM administration (needles are specific) for deltoid & gluteal
- Administration delay: may save reconstituted product—see PI for beyond use date
- Refrigeration required; limited room temp storage allowed
- Notable prolactin elevation (gynecomastia, abnormal menses, etc.)

Availability: PO, ODT: "M-tabs," oral solution, LAI (Consta)

Oral dose: Initial : 1-2 mg/day (usual: 2-8mg/day)

LAI dose: Consta (25-50mg IM Q2Wks) Oral overlap for 3 weeks

Oral dose (approximate)	Injection dose
2mg	25mg
4mg	37.5mg
>6mg	50mg

Receptor action	
✓	D_2 antagonism
	D_2 partial agonism
✓	D_1 antagonism
✓	$5\text{-}HT_{1A}$ antagonism
✓	$5\text{-}HT_{2A}$ antagonism
✓	$5\text{-}HT_{1C}$ & $_{1D}$ antagonism
	$5\text{-}HT_7$ antagonism
✓	$A_{1\ \&\ 2}$ antagonism
✓	H_1 antagonism
	M_1 antagonism
	M_3 antagonism

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Ziprasidone (Geodon)	
MOA: antagonist D_2 and 5-HT_{2A}	
Metabolism: CYP3A4	

Clinical pearls	• Give with food to improve absorption
	• DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) May result in death
	• Initially presents as rash other symptoms develop:
	  • Fever
	  • Swollen lymph nodes
	  • Inflammation of organs
	  • High level of eosinophils

Availability	PO capsules IM short acting injection (reconstitution required)
Oral dose	Initial: 20-40 mg PO BID Usual: 80-160 mg/day in divided doses

Receptor action
✓ D_2 antagonism
D_2 partial agonism
✓ D_3 antagonism
✓ 5-HT_{1A} agonism
✓ 5-HT_{1D} & $_{2A}$ antagonism
✓ 5-HT2c antagonism
5-HT_7 antagonism
✓ α_1 antagonism
✓ H_1 antagonism
M_1 antagonism
M_3 antagonism

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Objective #2

- **Identify important side effects and emerging safety associated with the different antipsychotic agents**

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Treatment Considerations

New alerts and warnings

DRESS: olanzapine (Zyprexa) now in addition to ziprasidone (Geodon)

- Per FDA: Health care professionals should immediately stop treatment with olanzapine if DRESS is suspected. When prescribing the medicine, explain the signs and symptoms of severe skin reactions to your patients and tell them when to seek immediate medical care.

FDA update Feb 2017

- The labeling now states that antipsychotic drugs can cause somnolence, postural hypotension, and motor and sensory instability that could lead to falls and subsequently fractures or other injuries.
- For patients with conditions, or medications that could exacerbate these effects, fall risk assessments should be done when initiating treatment with an APS and repeated in patients on long-term therapy

FDA Drug Safety Communication: FDA warns about rare but serious skin reactions with mental health drug
https://www.fda.gov/Drugs/DrugSafety/ucm499441.htm

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Treatment Considerations

New alerts and warnings

Hazardous psychiatric medications and NIOSH 2016

- Antipsychotics and other mental health agents included on this list
- Now includes recommendations for safe handling to **limit occupational exposures**
- Provides general guidance, facility specific **"risk assessments"** will be required
- **Paliperidone, risperidone, ziprasidone are among the drugs listed**
- **Outlines specific activities**: handling intact tablet/capsule, cutting/crushing tabs, administering oral liquids, preparing (drawing up) and administering IM injections
- Provides guidance when and **what type of PPE to use** to limit exposure:

  Gloves, gown, eye/face protection, respiratory protection, engineering controls, etc.

NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016
https://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf

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Objective #3

- Recommend appropriate education and intervention to address the challenges associated with the use of these antipsychotic agents in patients with serious mental illness

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Antipsychotic update

Challenges to caring for our patients:

- Adherence to medication (complicated, pill burden)
- Medication "unknowns" (drug interactions, etc.)
- Delayed follow up post inpatient hospitalization
- Lack or insufficient support (includes family) post discharge
- Insurance barriers
  - Prediction for Medicare Part D and Medicaid
  - Formulations not covered
  - Dosing schedules outside of quantity limits
  - Concurrent oral when LAI is also being administered for same agent

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Antipsychotic update

Challenges to caring for our patients:

- Newer agents have not demonstrated increased efficacy over the older traditional agents and are more expensive
- Newer agents may have more potential permanent side effects than the older
- Though the range of potential risk varies among patients, these all carry the same class warning and potential
- Polypharmacy of any combination of agent has not demonstrated improved outcomes or efficacy; strategize to optimize monotherapy whenever possible
- Use for indications other than SMI=risk>benefit
- A limited number of SGAs are approved for augmentation therapy for MDD; must ensure primary agent (antidepressant) dose and duration were optimal and adequate of treatment prior to using any augmentation treatments

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As promised....receptor implications

Receptor action	Potential clinical implications of receptor activity of APS*
D_2 antagonism	Positive symptom efficacy High 5-HT_{2A}/ D_2 affinity ratio=reduced EPS (versus pure D_2 antagonism) (-EPS, endocrine effects)
D_2 partial agonism	Reduced positive symptoms, lowers risk of EPS
D_3 antagonism	Reduced positive and negative symptoms also pro-cognitive and antidepressant effects
5-HT_{1A} antagonism	Reduced EPS and endocrine effects also antidepressant & anxiolytic effects
5-HT_{2A} antagonism	Reduced EPS and endocrine effects (- cardiometabolic effects)

Compiled and presented 2012 NEI Global Psychopharmacology congress Dr. Steven Stahl

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Receptor implications

Receptor action	Potential clinical implications of receptor activity of APS*
5-HT_{2c} antagonism	Antidepressant effects (- cardiometabolic effects)
5-HT_7 antagonism	Reduced circadian rhythm dysfunction, reduced negative symptoms
α_1 antagonism	Reduced nightmares; Postural hypotension, dizziness & sedation
H_1 antagonism	Sedative/hypnotic effects (-cardiometabolic , weight gain and excessive sedation)
M_1 antagonism	Anticholinergic side effects (ie: cognitive impairment)
M_3 antagonism	Reduced EPS (-cardiometabolic, anticholinergic effects)
M_4 agonism	clozapine only, increases hypersalivation

Compiled and presented 2012 NEI Global Psychopharmacology congress Dr. Steven Stahl

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Comparative Receptor implications

Agent	Sedation	EPS	Anticholinergic	Orthostasis	Weight gain	Prolactin
Chlorpromazine	4+	3+	3+	4+	2+	3+
Clozapine	4+	1+	4+	4+	4+	1+
Fluphenazine	1+	4+	1+	1+	1+	4+
Haloperidol	1+	4+	1+	1+	1+	4+
Iloperidone	1+	+/-	2+	3+	2+	1+
Olanzapine	2+	2+	2+	2+	4+	1+
Paliperidone	1+	2+	1+	2+	2+	4+
Perphenazine	2+	4+	2+	1+	1+	4+
Quetiapine	2/(3)+	1+	1+	2+	2+	1+
Risperidone	1+	2+	1+	2+	2+	4+
Thioridazine	4+	3+	4+	4+	1+	3+
Thiothixene	1+	4+	1+	1+	1+	4+

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Managing the challenges of side effects

Side effect	Clinical pearls
Extrapyramidal Side Effects (EPS)	Abnormal motor movements 30% will develop on FGA Confirm diagnosis and monitor to prevent AIMS (abnormal involuntary movement scale)
Acute Dystonias	Painful prolonged muscle contractions Dose initiation or change (24-72 hours) Risk: high potency/dose FGA, younger, males Treatment: anticholinergics or benzodiazepines (IM)
Pseudoparkinsonism	Akinesia, bradykinesia, difficulty initiating movement, slowness, masked facial expression, micrographia, slowed speech, decreased arm swing Tremor, pill rolling, cogwheel rigidity, postural and oral abnormalities 1-2 weeks after initiation/dose change Risk: Increased age, female Treatment: Anticholinergics (i.e. diphenhydramine, others)

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Managing the challenges of side effects

Side effect	Clinical pearls
Tardive Dyskinesia	Abnormal involuntary movements; worsen with stress, disappear during sleep tongue thrusting, chewing movements, lip smack, grimacing, limb twisting, rocking Late onset; often irreversible Risk: old age, females; duration of therapy, dose (daily & cumulative), duration Treat: Prevention and education is key; switching APS (clozapine); use of Ingrezza Caution: Anticholinergics MASK symptoms
Akathisia	Internal and external restlessness; pacing, shifting, shuffling, feet tapping, compulsion to stay in motion Risk: high potency FGAs, risperidone & paliperidone Treatment: decrease dose, B-Blockers
Anticholinergic	Highest risk with low potency FGA, clozapine and olanzapine Dry mouth, constipation, urinary retention, blurred vision, tachycardia, impaired memory Constipation from slowed peristalsis and can develop into paralytic ileus or even bowel perforation (bowel preps)

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Managing the challenges of side effects

Side effect		Clinical pearls
Neuroleptic Malignant Syndrome (NMS)	Rare, potentially lethal High potency drugs (but possible with all APS, including clozapine) Injectable/depot FGAs Patients at risk: • Dehydrated • Organic mental disorder	• Onset: any point: early to months later • Develops rapidly 24-72 hrs • Hyperreflexia and or pyrexia/Labile Blood Pressure • Confusion • Increased Muscle Tone/Rigidity • Increased WBC, CPK, LFTs
Treatment: Discontinue antipsychotic(DA agonists-bromocriptine,etc) Rechallenge: Acceptable in most with observation for at least 2 weeks Different SGA or low potency FGA, slow dose titration		
DRESS: Discontinuation of offending agent and supportive care; confirmation diagnosis (eosinophils, etc)		

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Metabolic monitoring and clinical treatment

Definition of metabolic syndrome (3 or more criteria)	
Central or abdominal obesity	Men - 40 inches or above Women - 35 inches or above
Abnormal lipid Panel: Triglycerides:	Greater than or equal to 150 milligrams per deciliter of blood (mg/dL)
HDL Cholesterol:	Men - Less than 40 mg/dL Women - Less than 50 mg/dL
Blood pressure	Greater than or equal to 130/85 millimeters of mercury (mmHg)
Fasting glucose	Greater than or equal to 100 mg/dL

International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. International Diabetes Federation (IDF). 2006. https://www.idf.org/our-activities/advocacy-awareness/resources-and-tools/60:idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html

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Testing, monitoring and treatment plans

Goals: Prevent primary & secondary ASCVD events

Cardiovascular disease (ASCVD) which is defined as history of 1 or more of the following comorbidities:

- Myocardial infarction / acute coronary syndrome(s)
- Stable or unstable angina
- Coronary or other arterial revascularization
- Stroke
- Transient ischemic attack
- Peripheral artery disease presumed to be of atherosclerotic origin

Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.Circulation. 2014;129(25 Suppl 2):S1-45.

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Testing, monitoring and treatment plans

Abnormal lipid panel

- **Lipids** include cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL)
- **Hyperlipidemia: new goals based on risk groups, statin "intensity" with % reduction**

Statin Benefit Group	Additional Factors	Intensity Type
Clinical ASCVD	≤ 75 years old	High-Intensity
	> 75 years old	Moderate-intensity
LDL ≥ 190 mg/dL		High-Intensity
Diabetic patients	ASCVD ≥ 7.5%	High-Intensity
Age 40 – 75 & LDL 70 – 189 mg/dL	ASCVD < 7.5%	Moderate-intensity
Non-diabetic patients	ASCVD ≥ 7.5%	Moderate to high
Age 40 – 75 LDL 70 – 189 mg/dL	ASCVD < 7.5%	Weigh risk/benefit

Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.Circulation. 2014;129(25 Suppl 2):S1-45.

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Testing, monitoring and treatment plans

Abnormal lipid panel

Preferred pharmacologic therapy:

- Statins (high intensity for specific "risk groups": atorvastatin 40 or 80mg & rosuvastatin 20 or 40mg); moderate or low for other risk groups; limited use of non-statins
- Non-statin fibrates and/or niacin no longer combined with statins

Non-pharmacologic activities:

- Diet, exercise, weight loss, review medications for potential contribution

Managing co-occurring medical and behavioral conditions

- Patients may experience myalgia & not desire rechallenge
- Hypothesized risk of low cholesterol contributing to possible aggression
- Memory impairment associated with statins?

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Testing, monitoring and treatment plans

Hypertension

Goals: BP < 140/90 for most patients (geriatric and frail less strict goals)

Preferred pharmacologic therapy:

- Thiazides, ACE/ARB, CCB

Non-pharmacologic activities:

- Smoking cessation
- Weight loss
- Dietary (DASH) interventions
- Exercise

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Testing, monitoring and treatment plans

Managing co-occurring medical and behavioral conditions

Hypertension:

- Drug interactions with mental health: Li, etc.
- Antipsychotic agents may cause hypotension
- Not all populations respond the same to 1st line agents
- May need 2 different agents from unique classes to control BP
- May already be using BP meds (i.e. BB) for tremor and other behavioral symptom control

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Testing monitoring and treatment plans

Hyperglycemia

Goals: HbA1C goals should be individualized for each patient with type 2 diabetes (T2DM): less than 7% for most patients and less than 8% for specific high-risk subgroups (i.e. older adults)

Preferred pharmacologic therapy:

- Metformin as 1st line for most patients with T2DM
- If after 3 months of maximized metformin patient has not achieved A1C goals; consider adding 2nd agent based on patient specific factors to achieve goal

Non-pharmacologic activities: diet, exercise, weight loss, consider:

- APS induced increases appetite; other MOA unknown
- Risk and extent of weight gain are higher in younger first-episode psychosis patients with no previous APS exposure compared with patients in long-term treatment

Alvarez-Jiménez, M., González-Blanch, C., Crespo-Facorro, B., Hetrick, S., Rodríguez-Sánchez, J. M., Pérez-Iglesias, R., & Vázquez-Barquero, J. L. (2008). Antipsychotic-induced weight gain in chronic and first-episodepsychotic disorders: *A systematic critical reappraisal.CNS Drugs, 22*, 547-562.

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Testing monitoring and treatment plans

Here caveats to consider when selecting and using different types of diabetic agents

- **Insulin:** Injection, high risk/high alert errors associated; consider cognitive ability, motor skills and visual acuity
- **Glucagon like peptide receptor agonists (GLP-1 RA):** injection: consider cognitive ability, motor skills, visual acuity and cost/coverage limitations
- **SGLT2:** increased risk of UTI (already a common infection in mental illness)
- **Dipeptidyl peptidase 4 inhibitors (DPP-4):** increased risk of pancreatitis, renal adjustments often needed as well as cost/coverage limitations
- **Sulfonylureas:** Beers list, increased risk of hypoglycemia, weight gain,
- **Thiazolidinediones (TZDs):** Beers list, use cautiously (hypoglycemia)

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Patient counseling tips

- **Adequate time** on a given medications at an **optimal therapeutic dose** is the most important variable in predicting medication response
- **Long term maintenance** antipsychotic treatment is necessary for the vast majority of patient with schizophrenia in order to prevent relapse
- Drug therapy decisions must be guided by systematic monitoring of patient symptoms and **ongoing surveillance of potential adverse effects** so encourage patients to report

Clinical Pharmacology (online database). Tampa, FL: Gold Standard, Inc; 2013.

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Questions?

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Exam Questions:

Questions 1-5

CC is a 23-year-old female who has been diagnosed with schizophrenia since the age of 21. She has been using haloperidol long acting injection with success since the time of her diagnosis, however has recently has felt more sensitive to the sedating effects of this first-generation antipsychotic. She is not on any other medications now and has no known allergies.

1. CC would like to try a second-generation antipsychotic with the less sedation and asked about a trial of the "new" aripiprazole (Abilify) long acting injection (LAI) that she saw advertised on television. What would you advise for CC now for her to make the change to Aripiprazole LAI?
    a. She **would need** an oral challenge, **and** an oral overlap of aripiprazole
    b. She **would need** an oral challenge, **but not** an oral overlap of aripiprazole
    c. She would **need neither** an oral challenge, **nor** an oral overlap of aripiprazole
    d. She would **not need** an oral challenge, but **would need** an oral overlap of aripiprazole

2. CC's psychiatrist recommends a trial of paliperidone LAI (Invega Sustenna) and he has instructed her to pick up a prescription for one oral paliperidone tablet before she gets her shot. When picking up this prescription from your pharmacy, she mentions that her brother had to take oral tablets for a few weeks after his first injection of risperidone (Risperdal) Consta and wonders if this 1 tablet is a mistake. How would you reply?
    a. This was probably a mistake
    b. Sustenna does not require an oral challenge
    c. This is an oral challenge only to rule out allergy
    d. The required oral overlap is only 24 hours long

3. CC is worried about developing facial "ticks" like her brother did when he was on risperidone and has heard that there is a new medication that can treat tardive dyskinesia (TD) if she were to develop it. Which of the following is a new medication available to her to treat TD?
    a. Pimavanserin
    b. Perphenazine
    c. Cariprazine
    d. Valbenazine

4. CC would like to know the most significant differences between the FGA and SGA agents so she can make an informed decision for future therapy. What would you advise of the differences generally associated with **most SGAs** when compared to **most FGAs**?
    a. SGAs are more likely to cause movement disorders
    b. SGAs are more likely to cause metabolic disorders
    c. SGAs are more likely to cause tardive dyskinesia
    d. SGAs are more likely to prolactin elevation

5. CC has also heard of a new agent called pimavanserin (Nuplazid) and would like to know more about this drug. How would you describe the role this new drug?
    a. This agent is used to treat EPS
    b. This agent is used to treat DRESS
    c. This agent is used to treat Tardive Dyskinesia
    d. This agent is used to treat Parkinson Disease psychosis

6. The FDA has issued a recent warning about a new adverse drug reaction called DRESS which is associated with the the use of SGAs. Which of the following was included in the warning issued by the FDA describing the manifestation of DRESS?
    a. DRESS: Drug Reaction with Esophageal and Systemic Symptoms
    b. DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms
    c. DRESS: Drug Reaction with Extrapyramidal and Systemic Symptoms
    d. DRESS: Drug Reaction with Erectile Dysfunction and Systemic Symptoms

7. Which of the following medications have been identified as potentially causing DRESS?
    a. Ziprasidone (Geodon) and olanzapine (Zyprexa)
    b. Lurasidone (Latuda) and Risperidone (Risperdal)
    c. Clozapine (Clozaril) and Asenapine (Saphris)
    d. Aripiprazole (Abilify) and Brexpiprazole (Rexulti)

8. NIOSH has identified several psychiatric medications including, but not limited to, paliperidone, risperidone, and ziprasidone on its 2016 list. What does inclusion on this list mean?
    a. Identifies potential risks to patients who are taking these drugs
    b. Identifies potential risks of occupational exposure when handling these drugs
    c. Identifies potential risks to environment when flushing these drugs down the drain
    d. Identifies potential risk of addiction due to diversion and mishandling of these drugs

9. What are some of the challenges that must be considered when using SGA agents when compared to FGA agents in the management of patients with serious mental illness?
    a. SGAs are generally considered less effective than older agents
    b. SGAs may have less risk of DRESS, but may have more risk of EPS
    c. SGAs may have less risk of EPS, but more risk of metabolic complications
    d. SGAs may have less risk of metabolic complications, but more NIOSH risk

10. Which of the following statements is true when using SGA agents?

a. Using SGAs for insomnia is associated with fewer side effects than for psychosis
b. Using SGAs polypharmacy is always more effective than optimized monotherapy
c. SGAs are all associated with similar class effects and the same black boxed warnings
d. SGAs all have the same side effects and no differences when compared to each other