Antipsychotics

Something Old, Something New, Something Used to Treat the Blues

Objectives

- To provide an overview of the key differences between first and second generation agents
- To an overview the newer second generation antipsychotics
  - Indications
  - Dosage regimens and dosage form
  - Adverse effect profiles
  - Drug Interactions

First Generation Antipsychotics

- Haloperidol, chlorpromazine, fluphenazine, thioridazine, thiothixene, and pimozide
- High affinity dopamine D_2 receptor antagonism
- Effective in treating positive symptoms of psychosis
- Negative symptoms, mood symptoms, and cognitive deficits minimally responsive
- Unfavorable adverse effect profile
  - High rates of EPS, tardive dyskinesia
  - Adverse effects due to action at other receptor sites
    - Sedation, dry mouth
    - Weight gain

Second Generation Antipsychotics

- Key distinction from FGA is decreased risk of extrapyramidal side effects.
- This is possibly due to their lower affinity for the dopamine 2, or D2 receptor.
- Work mainly on
  - Dopamine and serotonin receptors in the central nervous system
  - Cholinergic, adrenergic, and histaminergic receptors.
- The degree and selectivity of receptor inhibition varies which results in the differing side effect profiles that are observed.
- SGAs differ from the FGA, as the serotonin 5-HT2 receptor binding can exceed their affinity for dopamine D2 receptors.

Second Generation Antipsychotics

- “Older” SGAs
  - Clozapine
  - Olanzapine
  - Quetiapine
  - Risperidone
- “Newer” SGAs
  - Asenapine (Saphris)
  - Aripiprazole (Abilify)
  - Lurasidone (Latuda)
  - Paliperidone (Invega)
  - Ziprasidone (Zeldox)

Second Generation Antipsychotics

- Clozapine, olanzapine, quetiapine, risperidone
  - Improved efficacy for mood symptoms or stabilization
  - Minimal EPS, but metabolic effects
- Asenapine, Aripiprazole, Lurasidone, Paliperidone, Ziprasidone
  - Partial agonists at D2 or 5-HT receptors
    - Bind to receptor, initiating a partial response without full inhibition
    - Potential for similar efficacy as older second generation antipsychotics with less pronounced metabolic effects and sedation

FGAs versus SGAs

- All FGAs and SGAs have similar efficacy in treating the positive (psychotic) symptoms of schizophrenia and related disorders.
  - Clozapine may be more efficacious
  - Clozapine is has proven efficacy in treatment resistance schizophrenia
- For first-episode psychosis, SGAs may be more effective
  - Negative symptoms, mood, cognition
  - Studies have had mixed results, inconsistent
- Major differences between the FGAs and SGAs (and among individual SGAs)
  - Side effect profiles, safety and tolerability

Approved Indications

	Schizophrenia	Bipolar Disorder	Major Depressive Disorder
Aripiprazole	X	X	X (Adjunctive)
Asenapine	X	X	
Lurasidone	X	X	
Paliperidone	X		
Ziprasidone	X	X	

Aripiprazole (Abilify)

- Dosage and Indications (adults)
  - Schizophrenia
    - 10 mg to 30 mg daily
  - Bipolar disorder
    - Monotherapy: 15 mg to 30 mg daily
    - Co-therapy: 10 mg to 30 mg daily
  - Adjunctive therapy in MDD
    - 2 mg to 5 mg daily
- Dosage forms: 2, 5, 10, 15, 20 and 30 mg tablets
- Usually given in the morning because it can be activating and cause insomnia
- Changes in dosage should be made no more frequently than every 14 days
  - Uniquely long half-life

Aripiprazole Injection (Abilify - Maintena)

- Once monthly IM injection
- Recommended starting and maintenance dose of 400 mg.
- Dose titration not required.
- Tolerability of aripiprazole should be assessed with oral formulation prior to use.
- After first injection, treatment should be continued with 10 mg to 20 mg oral for 14 consecutive days
- Switching from oral antipsychotics
  - Continue current oral antipsychotic for 14 days following the first dose
- 300mg and 400mg vials that must be reconstituted prior to administration

Aripiprazole – Drug Interactions

- Metabolized via CYP2D6 and CYP3A4 transformations
- Has active metabolite
- 50% dose reduction recommended if concurrently taking potent inhibitor of
  - CYP2D6 (eg, fluoxetine, paroxetine, bupropion)
  - CYP3A4 (eg, clarithromycin)
- Dose increase recommended if concurrently taking potent inducer of CYP (eg, carbamazepine).
- Half-life prolonged in CYP2D6 slow metabolizers.
- Unpredictable effect in combination with other antipsychotics.

Asenapine (Saphris)

- Dosage and Indications
  - Schizophrenia
    - 5mg to 10mg bid
    - No clear benefit of 10mg dose over 5mg
  - Bipolar disorder
    - Monotherapy: 5mg to 10mg bid
    - Co-therapy: 5mg to 10mg bid
- Dosage forms
  - 5 and 10 mg sublingual tablet
- Cannot eat or drink within 10 mins of administration

Asenapine – Drug Interactions

- Hepatically metabolized by CYP1A2 and glucuronidation (UGT1A4)
- Fluvoxamine (CYP1A2 inhibitor) should be coadministered with caution or avoided when possible
- Asenapine weakly inhibits CYP2D6
  - Caution recommended if coadminister with drugs that are both metabolized by CYP2D6 and can inhibit this enzyme
    - E.g. paroxetine, dextromethorphan
- Pharmacodynamic considerations
  - Additive QTc prolongation
  - Alpha-1 antagonism
    - Potentiation of alpha blockers – hypotension, dizziness

Lurasidone (Latuda)

- Dosage and Indications
  - Schizophrenia
    - 40 mg to 80 mg daily
  - Bipolar disorder (depressive episodes)
    - Usual dose of 20 mg-60 mg/day as monotherapy or adjunctive therapy with lithium or valproate
- Dosage forms:
  - 40, 80 and 120 mg tablets
- Should be administered with food
  - At least 350 calories independent of fat content
- Dosage adjustment required for renal impairment

Latuda – Drug Interactions

- Hepatic metabolism includes CYP3A4 transformation and active metabolites
- Coadministration with strong CYP3A4 inhibitors (eg, oral ketoconazole) or inducers (eg, rifampin) is contraindicated
- Maximum recommended dose with moderate CYP3A4 inhibitors (eg, diltiazem) is 80 mg per day.
- Grapefruit interactions

Paliperidone (Invega)

- Schizophrenia
  - Extended-release tablet: 3 to 12 mg once daily
  - Must be swallowed whole and must not be chewed, divided, or crushed.
- Dosage forms
  - 3, 6, and 9mg extended release tablets
  - Food increases absorption; however, clinical trial dosing was carried out without regards to meals
    - Taken in the morning, without regard to food
    - Change in absorption with food not considered clinically meaningful

Paliperidone (Invega Sustena)

- Schizophrenia
  - Prolonged-release injection: 150 mg on day 1, 100 mg on day 8, then 25–150 mg once monthly
    - usual maintenance dose is 75 mg monthly
- Dosage forms
  - 50 mg, 75 mg, 100 mg, and 150 mg prolonged release injection (Invega Sustenna)

Paliperidone – Drug interactions

- Minimal hepatic metabolism
- Paliperidone is excreted primarily unchanged in urine necessitating dose reduction in renal insufficiency.
- Pharmacodynamic considerations
  - Additive QTc prolongation
  - Alpha-1 antagonism
    - Potentiation of alpha blockers

Ziprasidone (Zeldox)

- Schizophrenia
  - 20 mg twice daily to 100 mg
- Bipolar disorder
  - 40 mg twice daily to 80 mg
- Dosage forms
  - 20, 40, 60, and 80 mg capsules
- Should be administered with a meal
  - Absorption increased up to 2-fold

Ziprasidone – Drug Interactions

- Hepatic metabolism includes CYP3A4 and other transformations
  - Dosage adjustments may be required in presence of inducers and inhibitors of CYP3A4, but clinical significance of such drug interactions remains unknown.
- Pharmacodynamic considerations
  - Additive QTc prolongation
  - Alpha-1 antagonism
    - Potentiation of alpha blockers

Comparative Adverse Effects

Receptor Binding and Adverse Effects

NEUROTRANSMITTER AND RECEPTORS	ACTION
Dopamine—D1, D2, D3, D4	Dyskinesia, extrapyramidal symptoms, hyperprolactinemia
Serotonin—5HT1A, 5HT2A, 5HT2C	Sedation, weight gain, sexual dysfunction
Histamine—H1	Somnolence, sedation, weight gain
Alpha—alpha1, alpha2	Orthostatic hypotension
Acetylcholine	Dry mouth, tachycardia, urinary retention

Selected Adverse Effects

	Weight gain/DM	↑ Chol	EPS/ TD	Prolactin elevation	Sedation	Anti-chol SE	Ortho-static hypo-tension	QTc prolongation
Aripiprazole	–	–	+	–	+	–	–	–
Asenapine	+	–	+	++	++	–	+	+
Lurasidone	–	–	+	+	++	–	+	–
Paliperidone	++	+	++	+++	+	–	++	+
Ziprasidone	–	–	+	+	+	–	+	++

Metabolic Monitoring for Patients Taking Antipsychotics

Table 4 ADA–APA consensus guidelines[a]

	Base	At 4 weeks	At 8 weeks	At 12 weeks	Every 3 months	Annual	Every 5 years
Medical history[b]	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting glucose	X			X		X	
Fasting lipids	X			X			X

[a]From ADA–APA (32)

[b]Personal and family history of obesity, diabetes, hypertension, and cardiovascular disease

Summary

- A number of newer atypical antipsychotics have entered the market over the past few years
- Provide alternatives to those patients not adequately managed on second generation atypicals or who are intolerant
- Within the newer agents there are differences in
  - Dosage form
  - Approved indications
  - QTc interval prolongation
  - Use in renal impairment
- Selection amongst agents may be influenced by a number of factors