Good Evening. My name is Dr. Elizabeth Montagnese. I am very pleased to be talking with you about Bipolar Disorder. I believe Bipolar Illness to be a spectrum disorder that has monumental impacts on those afflicted, their families and communities. We’ll first look at symptoms of the disorder and how we diagnose it. Then we’ll focus on treatment options, compare older and newer medications and discuss new treatment algorithms and patient outcomes.
Schizophrenia - The Pharmacist’s Role

Accreditation:
Pharmacists 798-000-08-096-L01-P
Pharmacy Technicians 798-000-08-096-L01-T

Target Audience: Pharmacists & Technicians

Program Overview: This program will give pharmacists understanding of the underlying conditions, potential of currently available treatment options (along with their probable results and possible side effects) and the need to educate patients and family members on drug treatment strategies and the long-term medication and adherence problems commonly encountered with schizophrenia.

Objectives:
- Describe the types of schizophrenia to include the signs and symptoms.
- Provide an update on the pharmacological treatment options for anti-psychotics and their mechanisms of action.
- Compare the efficacy, dosing, safety, and tolerability profiles of available atypical anti-psychotics for the treatment of schizophrenia.
- Review the problems associated with medication noncompliance among patients with schizophrenia and means to enhance adherence.

This program has been supported by PharmCon

PharmCon is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Schizophrenia - The Pharmacist’s Role
(Diagnosis, Treatment Options, and Outcomes)

**Speaker:** Dr. Montagnese is board certified in adult, child, and adolescent psychiatry by the American Board of Psychiatry and Neurology. Dr. Montagnese provides comprehensive psychiatric evaluation and treatment for individuals, couples and families. Her primary area of focus is working with children and adolescents but she also treats adults. Dr. Montagnese received her medical degree at Wayne State University in Detroit, Michigan. She completed her general psychiatry and child psychiatry training at the Penn State University Milton S. Hershey Medical Center. Dr. Montagnese is the medical director at Family and Children Services of Central Pennsylvania. This is a United Way funded nonprofit agency that serves the greater Harrisburg, York and Lancaster areas.

**Speaker Disclosure:** Dr. Montagnese has no actual or potential conflicts of interest in relation to this program.

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What is schizophrenia?

- Theresa - 32 year old woman hospitalized at a State Mental Institution in PA
- Numerous acute hospitalizations in 2 previous years
- Her psychotic presentation
Historical Perspectives

- Emil Kraeplin- German psychiatrist in late 1800’s
- Categorized “dementia praecox” as a disease state
- Also described manic depression
- First descriptive classification system in psychiatry
Emil Kraeplin (contd.)

- Viewed mental illness as brain dysfunction
- Focused on commonality of symptoms from patient to patient
- Disturbance of attention, comprehension
- Hallucinations
- Disturbances in flow of thought
Eugen Bleuler

- Swiss psychiatrist
- Elaborated on idea of somatic cause
- Bleuler’s 4A’s: affect, ambivalence, autism, association (loosening of)
- Proposed specific criteria to diagnose
- Primary and secondary symptoms
Kurt Schneider

- Maximize diagnostic specificity
- First rank symptoms: audible thoughts, voices arguing or commenting, influenced thoughts, delusional perceptions
- Second rank symptoms: perplexity, depression, euphoria, emotional impoverishment
Development of DSM

- 1st DSM: 1952, clinical consensus, universality of diagnostic criteria
- DSM II: 1968
- DSM III: 1972
- DSM IIIR: 1987, not just clinical consensus but scientific evidence
- DSM IV: 1994
- DSM IVTR: 2000
What is psychosis?

- What is real vs. fantasy
- Think of “A Beautiful Mind”
Hallucinations

- Think of 5 senses: visual, auditory, olfactory, gustatory, tactile
- Usually frightening, morbid, macabre
- Can be friendly, company
Delusions

- A fixed false belief
- Bizarre-illogical
- Nonbizarre- can really occur
What are the psychotic disorders?

- Schizophrenia - 5 types
- Schizoaffective Disorder
- Delusional Disorder
- Brief Psychotic Disorder
- Shared Psychotic Disorder
- Psychotic Disorder due to Medical Cond.
- Substance-induced psychotic disorder
- Psychotic Disorder NOS (common in kids)
DSM Criteria for Schizophrenia

- Two or more of following for 1 month: (A Criterion)
- Delusions
- Hallucinations
- Disorganized speech
- Disorganized behavior
- Negative symptoms: flat affect, avolition, alogia
- Only 1 if delusions bizarre or voice keeping commentary or 2 voices conversing
DSM Criteria for Schizophrenia

- Social/occupational dysfunction
- Disturbance for at least 6 months with at least 1 month with criterion A
- Not due to substance, medical condition, mood disorder or PDD
Schizophrenia Subtypes

- Catatonic
- Paranoid
- Disorganized
- Undifferentiated
- Residual
Positive Symptoms

- Symptoms associated with distorted reality
  - Delusions
  - Hallucinations

Things present in those with schizophrenia as compared to those without.
Negative Symptoms

- Affective blunting
- Poverty of speech
- Thought blocking
- Poor grooming
- Lack of motivation-apathy
- Anhedonia
- Social withdrawal

Things absent from those with schizophrenia as compared to those without.
Epidemiology

- How common? 1% of world’s population
- Across cultures, races
- M:F, 1:1
- Age of onset is earlier in men
- M: onset late teens, early 20’s
- W: onset mid to late 20’s
- Studies show overdiagnosis in African Americans, not higher incidence
Course of Disease

- Chronic illness
- No cure
- Very treatable
- Without treatment-downhill course
Course of Disease

- Impacts morbidity and mortality
- Can be “lethal”
- 50% attempt suicide at least 1x
- 10-15% die in 20 yr f/u after diagnosis
- 75% smoke cigarettes
- 30-50% abuse alcohol
- 1/3-2/3 of homeless have schizophrenia
Cost of Schizophrenia

- 1990-accounted for 2.5% of health care expenditures+ nondirect costs($45 billion)
- 2002- $62.7 billion for direct and nondirect costs
- Unemployment rate is 70-80%
- 10% of those permanently disabled
Treatment prior to antipsychotics

- Talk therapy
- ECT
- Insulin induced seizures
- Frontal lobotomies
- Straight jackets
- Wet sheet wraps
Treatment

- Not just meds but definitely meds
- Psychosocial and cognitive rehab
- Clubhouse model-deinstitutionalization
- Supportive psychotherapy
- Family therapy
Now, let’s get to the meds

- Antipsychotics revolutionized treatment
- Chlorpromazine (Thorazine) – 1952
- 1st of the “Typical” antipsychotics
- First used as an anesthetic
Conventional Antipsychotics
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Dose (mg)</th>
<th>Common Dose Range</th>
<th>Relative Potency</th>
<th>EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
<td>100</td>
<td>200-900</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>Serentil</td>
<td>50</td>
<td>100-400</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Mellaril</td>
<td>100</td>
<td>200-800</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilatón</td>
<td>8</td>
<td>16-64</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine</td>
<td>5</td>
<td>5-40</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Prolixin</td>
<td>2</td>
<td>5-20</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>2</td>
<td>5-20</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Chlorprothixene</td>
<td>Taractan</td>
<td>75</td>
<td>100-600</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Navane</td>
<td>5</td>
<td>5-60</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Loxitane</td>
<td>15</td>
<td>25-250</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Molindone</td>
<td>Moban</td>
<td>10</td>
<td>50-225</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>
Neuroanatomy 101

- Neuron - brain cells, 100 trillion cells
- We lose them as we age
- Communicate with each other via chemical called neurotransmitters
- Psychotropic medications affect these neurotransmitters
How do these meds work?

- Target dopamanergic neurons
- Increase dopamine=psychosis
- Dopamine blockers
- Typical agents affect nigrostriatal tract and mesolimbic tract
- Nigrostriatal area also affects involuntary movements
- Reason for EPS
Extra Pyramidal Symptoms

- Akathesia - uncontrolled restlessness
- Dystonic reactions - muscle spasms, usually eyes, neck, back and tongue
- Parkinsonism - shuffling gait, stiffness, tremor, masked faces
- Can be intolerable, very frightening
- Common reason for medication noncompliance
Acetylcholine-Dopamine Balance

- Excess DA - psychosis
- Excess ACH - high EPS, decreased psychosis
EPS (Contd.)

- Higher incidence with higher potency
- Higher incidence at start of tx
- Risk factors for EPS: young age, male, IM administration
- Treat with anticholinergic or antihistaminergic
- Prevent with anticholinergic or antiparkinsonian drugs
### Treating EPS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dose (mg/day)</th>
<th>Duration of Action (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benztropine mesylate</td>
<td>Cogentin</td>
<td>0.5-6mg</td>
<td>24</td>
</tr>
<tr>
<td>Trihexyphenidyl hydrochloride</td>
<td>Artane</td>
<td>1-15</td>
<td>6-12</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Symmetrel</td>
<td>100-300</td>
<td>12</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Benadryl</td>
<td>25-150</td>
<td>8</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Inderal</td>
<td>20-120</td>
<td>8</td>
</tr>
</tbody>
</table>
Tardive Dyskinesia

- Tardive dyskinesia
- Abnormal involuntary movements
- Dyskinetic
- Choreoathetoid
- Usually face, tongue, mouth
- Can involve trunk, arms
- Can occur after brief exposure
- Stop meds, lower dose
- Can be permanent
- Must get informed consent

- Risk increases with longer use (4%/yr tx)
- Risk increases with age, female gender, affective disorder, GMC, high doses
- Can be disfiguring
- Clozapine may help
- Vit E, lithium, amantadine
Atypical Agents

- Newer
- Affect D2 and 5HT(2A) receptors
- Reason for increased efficacy
- Affects positive (D2) and negative (5HT) symptoms
- Don’t effect nigrostriatal tract as much-less EPS
- Affect mesolimbic and mesocortical tracts
# Atypical Agents

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Daily Dosage (mg)</th>
<th>Forms available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>10-30</td>
<td>INJ, soln, tabs-D</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Clozaril</td>
<td>25-900</td>
<td>tabs-D</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>5-20</td>
<td>INJ, tabs-D</td>
</tr>
<tr>
<td>Paliparidone</td>
<td>Invega</td>
<td>6-12</td>
<td>tabs</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>300-800</td>
<td>tabs</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>1-12</td>
<td>tabs-D, soln, INJ</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
<td>40-160</td>
<td>tabs</td>
</tr>
</tbody>
</table>
How do we choose an atypical?

- Side effect profile - make them work for patient
- Any absolute contraindications or medical risks
- Other meds: drug-drug interactions
- Cost!!!
- Insurance
- Patient/family perceptions
- Doctor’s own perceptions about meds
General Side Effects of Atypicals

- Less likely to cause EPS or TD
- Prolactin elevation-galactorhea, gynecomastia
- Sedation
- Anticholinergic
- Weight gain
- Also seen with typicals
Risperidone (Risperdal)

- 1993
- Only depot form of atypical
- Depot form q 2 weeks
- Weight gain, sedation and high prolactin most common
- Above 6 mg daily—↑EPS
Olanzapine (Zyprexa)

- Very sedating
- Excessive weight gain
- Metabolic syndrome
Quetiapine (Seroquel)

- Moderate for weight gain
- Slit lamp eye exam recommended - cataracts, not often done
- Very sedating
- Used in low doses for sleep - off label
Ziprasidone (Geodon)

- 2001
- Short acting injectable available
- Can be used for acute agitation
- More weight neutral than other atypicals
- Lower incidence of metabolic syndrome
Aripiprazole (Abilify)

- Not a full DA agonist
- “Dopamine stabilizer”
- Agonist in areas of low activity
- More weight neutral
- Low incidence of metabolic syndrome
Clozapine (Clozaril)

- 1989
- Weight gain
- Agranulocytosis - serious, fatal
- Weekly WBC count
- Specific protocol - complex to manage
- Used in refractory cases
- Seizures
- Excessive salivation
Palipaeridone (Invega)

- 2007
- Active metabolite of risperidone
- Slow release over 24 hours
Comparison of Atypicals

<table>
<thead>
<tr>
<th></th>
<th>Typicals</th>
<th>Cloz</th>
<th>Arip</th>
<th>Olanz</th>
<th>Risp</th>
<th>Que</th>
<th>Zip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin Elev</td>
<td>+ to ++</td>
<td>0</td>
<td>0 to +</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>++</td>
<td>+++</td>
<td>0 to+</td>
<td>+++</td>
<td>++ to +++</td>
<td>++</td>
<td>0 to +</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>+ to +++</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Sedation</td>
<td>+ to ++</td>
<td>+++</td>
<td>0 to +/-</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>0 to +/-</td>
</tr>
</tbody>
</table>

Cloz=clozapine, Arip=aripiprazole, Olanz=olanzapine, Risp=risperidone, Que=quetiapine, Zip=ziprasidone
Are Atypicals Worth It?

- CATIE-Sept 2005
- NIMH study in NEJM
- Ground breaking
- Outcome stated typicals=atypicals in efficacy
- Cost of atypicals may not always be justified
- Patients stopped both meds at a high rate
### Cost of Meds

<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>$500</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>$400</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>$400</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>$200</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>$300</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>$400</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>$350</td>
</tr>
<tr>
<td>Haloperidol (Haldol)</td>
<td>$45</td>
</tr>
<tr>
<td>Perphenazine (Trilafon)</td>
<td>$25</td>
</tr>
</tbody>
</table>
Use of Atypicals in Children

- Controversial
- Mostly off label use
- Autism spectrum disorders
- Severe behavioral problems
- Hugh increase in RXs written for kids in last 5 years.
Atypicals-other uses

- Bipolar disorder - FDA approval
- OCD-severe, refractory
- Dementia- in past, black box warning
Treatment - 3 phases

- Phase I - acute phase
- Prevent harm
- Control disturbed behavior
- Reduce psychosis
- Return to best level of functioning
- Patient/family alliance
- Formulate short and long term treatment plans
- Connect with community aftercare
Phase II- Stabilization

- Minimize risk of relapse
- Maximize adaptation to return to community
- Continue symptom reduction
- Consolidate recovery
- Promote recovery
Phase III- Stable Phase

- Sustain remission
- Maintain or improve functioning and quality of life
- Promptly treat symptom exacerbation/relapse
- Monitor for side effects
Case Study
References

- Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision, American Psychiatric Association, 2000
- Physicians Desk Reference, 2008
- NIMH, Questions and Answers about the NIMH Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE), http://www.nimh.gov/healthinformation.catieqa.cfm
QUESTIONS?