Schizophrenia: Diagnosis, Treatment Options and Outcomes

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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 Equiv.(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>Trilafon</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>Thiothixene</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 dopaminergic 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

- Akathisia-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 0.5-6mg</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidyl hydrochloride</td>
<td>Artane 1-15</td>
<td>6-12</td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>Symmetrel 100-300</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Benadryl 25-150</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Inderal 20-120</td>
<td>8</td>
<td></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>Paliperidone</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
<table>
<thead>
<tr>
<th>General Side Effects of Atypicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Less likely to cause EPS or TD</td>
</tr>
<tr>
<td>- Prolactin elevation-galactorhea, gynecomastia</td>
</tr>
<tr>
<td>- Sedation</td>
</tr>
<tr>
<td>- Anticholinergic</td>
</tr>
<tr>
<td>- Weight gain</td>
</tr>
<tr>
<td>- Also seen with typicals</td>
</tr>
</tbody>
</table>
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
Olanzipine (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><strong>Prolactin</strong></td>
<td>+ to ++</td>
<td>0</td>
<td>0 to +</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Elev</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>++</td>
<td>+++</td>
<td>0 to+</td>
<td>+++</td>
<td>+ to +</td>
<td>++</td>
<td>0 to +</td>
</tr>
<tr>
<td><strong>Gain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anticholinergic</strong></td>
<td>+ to +++</td>
<td>+++</td>
<td>+/−</td>
<td>+/−</td>
<td>+</td>
<td>+/−</td>
<td>+/−</td>
</tr>
<tr>
<td><strong>Sedation</strong></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.
Atypical use

- 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