Schizophrenia and psychosis related disorders

Statement of disclosure
I do NOT have any relevant relationship with any commercial interests.

Objectives
1. To understand the clinical course of schizophrenia
2. Discuss neurobiology of schizophrenia
3. To understand first episode psychosis and early warning signs
4. Discuss evidence based treatment solutions.

Psychosis
- It includes hallucinations, delusions and thought disorder
- Psychosis can be caused by a variety of conditions that affect the functioning of the brain

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Substance-induced Psychosis

- High dose steroids
- L-Dopa
- PCP/ketamine
- Amphetamine
- Cannabis
- Synthetic cannabinoids

Differential Diagnosis

- Medical/surgical/substance-induced
  - Psychotic d/o due to GMC
  - Dementias
  - Delirium
  - Medications
  - Substance induced
- Personality disorders
  - Schizoid
  - Schizotypal
  - Paranoid
  - Borderline
  - Antisocial
- Mood disorders
  - Bipolar disorder
  - Major depression with psychotic features
- Miscellaneous
  - PTSD
  - Dissociative disorders
  - Malingering
  - Culturally specific phenomena
  - Religious experiences
  - Meditative states

Workup for new onset psychosis

- Good clinical history, physical exam, ROS
- URINE DRUG SCREEN
- Serum Alcohol, Thyroid profile, RPR, HIV
- CT or MRI brain
- +/- Lumbar Puncture, EEG (only if strong clinical suspicion for psychosis due to GMC)

Brain activation during sampling of auditory hallucinations

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Natural history of schizophrenia

Schizophrenia is associated with cognitive impairments

Comorbid disorders

- Up to 50% of patients with schizophrenia have a lifetime diagnosis of substance abuse or dependence
Impairment: Depression and Suicide

10-14% of patients with schizophrenia kill themselves

Young males, and perhaps especially those with good premorbid function, are at greatest risk

Genetic risks of developing schizophrenia

Perinatal risk factors

- Spring births (winter maternal infections)
- Obstetric hazards (prematurity, low weight, hypoxia)
- Starvation or stress during pregnancy (the 1944 Dutch famine and the 1939 Finnish winter war)
- Older father (de novo mutations)

Cannabis

- The longer the use, the more the picture resembles that of schizophrenia-like psychosis (Manrique-García et al., 2012)
- People using higher potency cannabis on a daily basis are five times more likely than non-users to suffer from a psychotic disorder (Di Forti et al., 2015)

Synthetic Cannabinoids

- Over 200 synthetic cannabinoids are available on the internet
- Because each has a slightly different molecular structure, side effects are unpredictable
- The latest ones cannot be detected by routine drug tests
Epidemiologic Risk

<table>
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<th>Factors</th>
<th>Odds Ratio</th>
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The dopamine hypothesis of schizophrenia

- All known antipsychotic drugs are dopamine D2 antagonists
- Excessive striatal dopamine in response to an amphetamine challenge

PET receptor occupancy studies

- Increase dopamine release in schizophrenia vs. healthy control following an amphetamine challenge

The glutamate hypothesis of schizophrenia

- PCP and ketamine, both NMDA antagonists, can induce symptoms that mimic the symptoms of schizophrenia

Magnetic Resonance Spectroscopy
Glutamate levels are elevated in unmedicated patients

Kraguljac et al, JAMA Psychiatry, 2013

The dysconnectivity hypothesis

Structural connectivity is abnormal in schizophrenia

White matter tracts in the brain
Functional Connectivity (FC): A Measure of The Coherence of Neural Activity between Brain Regions
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Schizophrenia before medication

“The snake pit”

The treatment of schizophrenia

There are no treatments for cognitive and negative symptoms!

First generation APD

- In clinical use since the 1950s
- Potent antagonism of the dopamine D2 receptor
- Liability to cause extrapyramidal (EPS) sxs, akathisia, acute dystonia, acute oculogyric crisis.
- Long term use associated with tardive dyskinesia (TD)
- Neuroleptic malignant syndrome

Second generation APD

- Broad receptor blockade (Olanzapine)
- Selective combinations of receptor blockade (Risperidone)
- Associated with the development of the metabolic syndrome: increase in weight and plasma glucose and lipids
FDA-Approved Pediatric Age Ranges and Indications for Atypical Antipsychotics

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Schizophrenia, bipolar I disorder: manic or mixed, irritability with autistic disorder

CMS, MIG report, July 2014

The pivotal role of primary care in treating patients with schizophrenia.

- Patients with schizophrenia die earlier than the general population
- Higher rates of cardiovascular, respiratory, infectious, and endocrine disease are seen in patients with schizophrenia

Viron et al, Schizophrenia for Primary Care

The duration of untreated psychosis (DUP)

Lahti & Reid, Neuropsychopharmacology, 2011
THE PIVOTAL ROLE OF PRIMARY CARE IN REDUCING DUP

- Pediatricians play an important role in assessing the mental health and behavioral problems of children
- Most people who have psychosis live in the community and are registered with a general practitioner
- 30 to 50% people with severe mental illness are seen only in primary care settings

Can children develop schizophrenia and what do they look like?

Schizophrenia

- Incidence of COS is approximately 1 in 40,000
- Incidence of EOS is approximately 1 in 10,000
- 50% of children with COS have at least one first degree family member with schizophrenia
- Chromosomal abnormalities are more common in COS than in adult onset schizophrenia


What symptoms do children show before the onset of psychosis?
Childhood antecedents of schizophrenia and affective illness

- Maladjusted social behavior in some children could be an early sign of psychotic illness in adulthood.
- Even at age 7, subjects who will later develop schizophrenia differ from their school mates in the eyes of their teachers.

Done et al, BMJ, 1994

Can we predict who among high risk individuals will progress to full blown psychosis?

- A Danish study found that the risk of schizophrenia spectrum disorders was highly elevated, particularly within the first year after onset of a child and adolescent psychiatric disorder and remained significantly elevated > 5 years with an incidence rate ratio of 4.93.
- The risk was highly elevated in group diagnosed with anxiety disorders, affective disorders and OCD

Maibing et al Schizophrenia bulletin 2014

Can we predict who among high risk individuals will progress to full blown psychosis?

- Children aged 11 years who reported psychotic symptoms were shown to be at 5 to 16 fold increased risk of schizophrenic spectrum disorder in adulthood
- Heritability varies by type of psychotic experience, being highest for paranoia and parent rated negative symptoms and lowest for hallucinations

Kelleher et al Psychological medicine 2011

NIH-funded study highlights need for increased early intervention programs

NIH: National Institute of Mental Health

HIGHER DEATH RATE AMONG YOUTH WITH FIRST EPISODE PSYCHOSIS

NIH-funded study highlights need for increased early intervention programs

April 6, 2017 • Press Release
### Differential Diagnosis

- Children who are victims of abuse may report hearing voices or seeing visions of their abuser
- Often confused with autism because symptoms overlap. In COS symptom onset is later than for autism

### Differential Diagnosis

- Transient hallucinations observed in preschool children
  - Hypnogogic and hypnopompic hallucinations
  - Invisible Friends
- Looseness of associations and illogical thinking decrease markedly after age 6-7 in children

### First Episode Psychosis Clinic

- Patients between the ages of 8 to 42 who present with recent onset (<2-4 years) affective or non-affective psychosis
- Patients can have a history of substance provided this is not a bona fide drug-induced psychosis
- Medicaid, BCBS, VIVA and other private insurances
- Uninsured patients provided they are from Jefferson County. Those patients can be approved by Cooper Green to be seen in the clinic.
- UAB Access Team (205-934-7008)

### WHY A FIRST EPISODE PSYCHOSIS CLINIC

- To develop therapeutic alliance with patients who have poor insight
- To use evidence-based therapeutic interventions
- To move swiftly when treatment fails
- To educate patients and families
- Between 2 and 3 percent of the U.S. population is at risk for psychosis
  

### Cannabis as risk factor

- Twofold increase in relative risk for later schizophrenia
- Fourfold increase among the heaviest users compared to nonusers.
**Cannabis**

- The proportion of tetrahydrocannabinol (THC) was 3% or less in the 1960s
- In the US, potency reached an average of 12% by 2014
- Sudden high consumption can induce an acute intoxication that can be rapidly resolved
- The longer the use, the more the picture resembles that of schizophrenia-like psychosis (Manrique-Garcia et al., 2012)

- A meta-analysis showed that the more extensive the cannabis use, the greater the risk of psychosis (Marconi et al., 2016)
- People using higher potency cannabis on a daily basis are five times more likely than non-users to suffer from a psychotic disorder (Di Forti et al., 2015)

**Synthetic Cannabinoids**

- In the late 2000s, synthetic compounds often termed “spice” started to be used. In general, synthetics cannabinoids are more potent than cannabis.
- More chronic psychotic disorders can occur in persistent users of synthetic cannabinoids

- Over 200 synthetic cannabinoids are available on the internet
- Because each has a slightly different molecular structure, side effects are unpredictable
- The latest ones cannot be detected by routine drug tests
- UAB ER routine drug screen does not detect synthetic cannabinoids

**The dopamine hypothesis of schizophrenia**

- All known antipsychotic drugs are dopamine D2 antagonists
- Amphetamine challenge can induce paranoid symptoms
- Excessive striatal dopamine in response to an amphetamine challenge

**Gray matter loss during the early stage of the illness**

[Image: Gray matter loss in adolescents with schizophrenia]
Longitudinal loss of gray matter volume in first episode psychosis (FEP)

- At baseline, FEP has significantly smaller GM volume compared to healthy controls in superior temporal gyrus.
- On rescan after 1.5 years, FEP showed volume reductions in STG and widespread brain neocortical regions (frontal, parietal, limbic regions).

Asami et al., Neuroimage, 2010