

# EARLY ONSET SCHIZOPHRENIA

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# PRE-TEST

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# Question 1

- Prodromal symptoms of early-onset schizophrenia may include all of the following except?
  - A) Deficits in attention
  - B) Impaired language and verbal memory
  - C) Excellent coordination and motor skills
  - D) Dysphoria, anxiety and physical complaints
  - E) Social withdrawal and isolation



# Question 2

- All of the following clinical characteristics have been reported to be reliably diagnosed in children except:
  - A) Hallucinations
  - B) Delusions
  - C) Illogical thinking
  - D) Loosening of association
  - E) Incoherence

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# Question 3

- Neurobiological findings that have been associated with schizophrenia may include all of the following except:
  - A) Deficits in smooth eye pursuit movements
  - B) Impairments in autonomic responsivity
  - C) A progressive decrease in ventricular size
  - D) Smaller total cerebral volume
  - E) Frontal lobe dysfunction



# Question 4

- The two atypical antipsychotics approved by the FDA for treatment of schizophrenia in adolescents include:
  - A) Risperidone and Olanzapine
  - B) Quetiapine and Olanzapine
  - C) Ziprasidone and Quetiapine
  - D) Aripiprazole and Risperidone
  - E) Olanzapine and Aripiprazole



# Question 5

- Factors associated with a better prognosis in childhood onset schizophrenia include all except:
  - A) Earlier age of onset
  - B) Higher premorbid intelligence
  - C) More positive symptoms
  - D) Less negative symptoms
  - E) Family support and cooperation in treatment



# Case

- Raghav is a 10 year old boy who has come to the Child Mental Health Services for the first time with his mother, sent by his therapist for evaluation for Specific Learning Disability.
- On evaluation, you discover that Raghav lost his father 2 years ago. His father had alcohol dependence and induced psychosis. He ultimately committed suicide. His mother, a staff nurse, was terribly distressed about the same.
- You find him to be extremely withdrawn, talking in a low tone and not forthcoming about his symptoms. He refused admission, stating that he would rather be at home alone, where he usually is since his father's death, and since his mother works.
- He has been treated since 3 months by a private psychiatrist with Sertraline 100 mg with no improvement





# Clinical Examination

- Because children usually have no experience of knowledge of psychotic phenomena, they may misunderstand the questions during a psychiatric interview
- Questions regarding rare phenomena, such as psychotic symptoms, typically have the highest rates of false-positives in structured interviews
- Normal human thought and memory processes include hearing internal voices and experiencing false beliefs

# Clinical Examination (2)

- Collateral information is necessary
- Behavioral observations are often more useful than interpersonal observations and interview questions
  - e.g., does the child start fights with other children who are clearly much bigger and threatening (demonstrating consistent poor judgment)
- Projective Testing can be useful



# Assessing Hallucinations

*Sometimes children, when they are alone, hear voices or see things, or smell things and they don't quite know where they come from.*

*Has this ever happened to you? Tell me about it.*

*Has there ever been a time you heard voices when you were alone? What did you hear? Have you ever heard someone call your name when there was no one around? What kind of things did you hear? Did you ever hear music which other people could not?*

*Has there ever been a time when you saw things that were not there? What about shadows or other objects moving? Did you ever see ghosts?*

*When? Did this only happen at night while you were trying to sleep, or did it happen in the daytime too?*

*What did you see?*

*Has there ever been a time when you had an unusual smell about yourself?*



# Assessing Hallucinations (2)

*What did you think it was?*

*Did you think it is your imagination or real?*

*Did you think it was real when you (heard, saw, etc.) it?*

*What did you do when you (heard, saw, etc.) it?*

*These voices you heard (or other hallucinations), did they occur when you were awake or asleep? Could it have been a dream?*

*Did they happen when you are falling asleep? Waking up? Only when it was dark? Did they happen at any other time also?*

*Were you sick with fever when they occurred?*

*Have you ever been drinking beer, wine liquor?, or taking any drugs when it happened?*

*Was it like a thought or more like a voice (noise) or a vision?*



# Assessing Delusions

*Do you know what imagination is? Tell me.*

*Has there ever been a time your imagination played tricks on you?*

*What kinds of tricks?*

*Tell me more about them.*

*Did you have any ideas about things that you didn't tell anyone because you are afraid they might not understand?*

*What were they?*

*Did you believe in things that other people didn't believe in?*

*Like what?*

# Assessing Delusions (2)

*Has there ever been a time you felt that someone was out to hurt you? Who? Why?*

*Did you ever think you were an important or great person?*

*When you were with people you did not know, did you think that they are talking about you?*

*Was there ever a time when you felt something was happening to your body? Like did you believe it was rotting from the inside, or that something was very wrong with it?*

*Did you ever feel convinced that the world was coming to an end?*

*How often did you think about \_\_\_\_\_ ?*

# Clinical Characteristics

- Prodromal period is often prolonged in EOS:
  - Insidious onset is more common in children
  - Acute onset is more often in adolescents
- Prodromal symptoms often include:
  - Deficit in attention
  - Impaired language and verbal memory
  - Poor coordination and gross motor skills
  - Impaired academic performance
  - Limited Social skills
  - Social withdrawal and isolation
  - Some degree of functional impairment and aggression
  - Dysphoria, anxiety, physical complaints, sleep changes
  - Idiosyncratic or bizarre behaviors/preoccupations





# Clinical Characteristics

- In most series, majority of children have received a psychiatric diagnosis prior to the onset of psychotic symptoms
- Most common previous diagnoses:
  - Pervasive Developmental Disorders
  - ADHD
  - Depressive disorders
- Other diagnoses: ODD, CD, Early onset personality disorders





# Clinical Characteristics

- Once symptoms appear, phenomenology is similar to that seen in adults
- Most common characteristics:
  - Hallucinations: 80%, AH > VH
  - Delusions: 60%
  - Blunting of affect
  - Disorganized speech: less common
- Progressive increase in complexity as the child is getting older
- Illogical thinking and Loosening of Associations can be reliably diagnosed but not poverty of speech and incoherence; Catatonia is rare



# The Validity of Self-Report

The validity of psychotic symptoms should be questioned when:

- 1) The reports are inconsistent and there is no other documented evidence other than self-report
- 2) The qualitative nature of the reports is not typical of psychosis (e.g., greatly detailed descriptions or reports more suggestive of fantasy or imagination)
- 3) The reported symptoms occur only at specified times or are clearly reinforced by environmental circumstances (e.g., hearing voices only after a fight)



# Case

- So you have finished your preliminary enquiry of Raghav. And you realize you are not sure whether this is complicated grief, or depression or heading towards psychosis.
- What next would you like to do?
- How will you approach the case?
- What investigations are warranted?
- Give us the differentials.

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# Diagnosis and Differentials

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# What is Developmentally Normal?

- Most children who exhibit psychotic or psychotic-like symptoms do not have a true psychotic disorder
- Transient hallucinations are occasionally observed in preschool children (visual & tactile are most common) and are prognostically benign
  - Hypnagogic & hypnopompic hallucinations
- **Loosening of associations and illogical thinking decrease markedly after about age 6 – 7 years in children**



# Early Signs of Schizophrenia

- Children at increased risk for schizophrenia tend to have abnormalities of gait, posture, and muscle tone (e.g., neurologic soft signs)
- Hallucinations, thought disorder, and flattened affect are common in EOS
- Children with schizophrenia show 3 characteristic communication deficits:
  - Loose associations
  - Illogical thinking
  - Impaired discourse skills



# Dementia Praecox & Schizophrenia

- Emile Kraepelin, German psychiatrist, 1887
  - Distinguished DP from manic depression
- Paul Eugen Bleuler, Swiss psychiatrist, 1912
  - Renamed DP as Schizophrenia (from Greek, “to split the mind”) to emphasize the cognitive impairments
  - Believed that the “negative” symptoms were the defining characteristics
  - Identified the 4 As:
    - Affective blunting
    - Loosening of Associations
    - Autism
    - Ambivalence or indecisiveness



# Diagnosis

- Diagnostic criteria are the same for all ages with minimal modifications for Early Onset Schizophrenia (EOS; onset before age 18 years) and Very Early Onset Schizophrenia (VEOS; onset before age 13 years)
- Children should have at least two of the following characteristic symptoms for at least one month: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, negative symptoms



# Diagnosis

- Hallucinations and delusions are less complex than in adults
- Failure to achieve expected levels of interpersonal, academic, or occupational achievement
- Some symptoms must be present for 6 months
- Other psychotic conditions must be ruled out



# Epidemiology

- VEOS occurs predominantly in males
- Ratio M/F: 2/1
- Prevalence rates have not been established
- In a longitudinal patient study: of 312 patients over 13 years, only 4 were VEOS and 28 EOS (Thomsen, 1996)
- Youngest cases:
  - 3 years of age (Russel et al., 1989)
  - 5.7 years of age (Green and Padron-Gayol, 1986)
- No sufficient evidence to justify categorizing EOS, VEOS as a separate subcategory

# Very Early Onset Schizophrenia

- Defined as developing before age 13 years
- 0.1-1% schizophrenia presents prior to age 10 yrs (“very, very rare” before 6 y/o)
- Male preponderance in early years (about 2:1 < 14 years of age) but not beyond
- Early onset = poor prognosis
- Premorbid personality abnormalities (e.g., unusual personality styles, neurodevelopmental abnormalities, language problems, motor problems and a preponderance of negative symptoms) spells poor prognosis
- There may be at least two clinical phenotypes of schizophrenia: one characterized by longstanding neurobehavioral difficulties of early onset, and the other type develops in a previously “normal” person



# Early Onset Schizophrenia (EOS)

- Early-Onset Schizophrenia (develops after puberty to 18 years)
- 4% presents prior to age 15 yrs
- The content of delusions and hallucinations in this age group often reflects developmental concerns (e.g., hallucinations may have to do with monsters, pets, or toys and delusions revolve around aspects of identity and are less complex and systematic than in adults)
- Hallucinations are relatively common
- Auditory hallucinations are most frequent (somatic and visual hallucinations less so)
- Delusions are present in about 50% of cases
- Irrational or magical thinking and loosening of associations are relatively common
- Both preschool (very early) and childhood (early) onset are commonly insidious; acute in only about 25% of cases



# Adolescent Onset Schizophrenia

- The frequency of onset of psychotic illness increases markedly and symptomatology is similar to that of adults
- The male predominance extends into adolescence
- Could be accompanied with substance use



# Cognitive Delays

- 10-20% have an IQ in the borderline to mentally retarded range
- Actual numbers may be higher because some studies have excluded patients with mental retardation
- Language and communication deficits are common
- Neuropsychological testing:
  - Difficulties with complex information processing
  - Consistent with the adult literature

(Arasnow et al., 1994)



# Neurobiological Deficits

- Deficits in smooth eye pursuit movements
- Impairments in autonomic responsivity
- Neuroimaging findings:
  - A progressive increase in ventricular size
  - Smaller total cerebral volume
  - Decrease in cortical grey matter
  - Frontal lobe dysfunction
- No diagnostic value for laboratory evaluations and neuroimaging techniques
- Essential to rule out other medical disorders





# Psychological and Social Factors

- There is no evidence that psychological or social factors cause schizophrenia
- Environmental factors may potentially interact with biological risk factors to mediate the timing, the course, and severity of the disorder
- Psychosocial stressors influence the onset and/or exacerbation of acute episodes and relapse rates
- The relationship between schizophrenia and SES is unclear: predominance of sample inpatient





# Familial Pattern

- Increased family history of schizophrenia and schizophrenia spectrum disorders
- Increased family history of affective disorders, primarily depression
- Communications deficits are often found in families of children with VEOS



# Differential Diagnosis

- Thorough review of presenting symptoms, course, and premorbid functioning
- Adherence to DSM-5 criteria
- Clinician must have familiarity with normal development, general psychopathology, and how psychotic symptoms present in children:
- Determination of family psychiatric history



# General Medical Conditions

- Thorough pediatric and neurologic evaluation
- Delirium, seizure disorders, CNS lesions (brain tumors, congenital malformation), neuro-degenerative disorders (Huntington's chorea, lipid storage diseases) , metabolic diseases (endocrinopathies, Wilson's disease), DD (VCF), toxic encephalopathies (PCP, THC), and infectious (HIV).
- Laboratory tests:
  - CBC, Thyroid Function Tests, Serum chemistry, UA, toxicology
  - Chromosomal analysis, HIV
  - Neuroimaging studies, EEG



# Mood Disorders

- Both schizophrenia and psychotic mood disorders present with a variety of affective and psychotic symptoms
- In VEOS negative symptoms may be mistaken for depression
- Mania often presents with florid psychosis
- Psychotic depression may present with mood-congruent or incongruent psychotic features
- One half of children with VEOS or EOS with bipolar disorder may be originally misdiagnosed with schizophrenia
- Longitudinal reassessment is crucial



# Nonpsychotic Behavioral and/or Emotional Disorders

- PTSD: dissociative episodes with depersonalization and/or derealization, anxiety phenomena
- Lower rates of negative symptoms, bizarre behavior, and thought disorder
- N=209 children with schizophrenia → 21% personality disorders at 10 year follow-up (Thomsen, 1996)



# Schizoaffective Disorder

- Early onset schizoaffective disorder has not been well defined
- Follow-up studies have found low rates persisting
- 28% of EOS had schizoaffective psychoses at follow-up (Eggers, 1989)
- Better outcome than VEOS



# Pervasive Developmental Disorders

- Absence or transitory nature of psychotic symptoms
- Predominance of the characteristic deviant language pattern
- Aberrant social relatedness
- Early age of onset < 3 years of age for autism versus > 5 years for VEOS

# Schizophrenia vs. PDD

- Much of the early work on childhood “schizophrenia” was really about autism
- Individuals with autism do not appear to be at increased risk for schizophrenia
- There does seem to be an increased risk of psychosis among those with Asperger’s
- In the presence of PDD, schizophrenia is diagnosed only if prominent delusions or hallucinations have been present





# Other disorders

- OCD: Intrusive thoughts and repetitive ritualistic behaviors may be difficult to differentiate from psychosis in children
- Developmental Language Disorders: speech abnormalities mistakenly diagnosed as being thought disorder
- Schizotypal and schizoid personality disorders
- Multidimensionally Impaired: deficits in attention, impulse control, affect regulation, and transient or subclinical psychotic symptoms → Risk for schizophrenia versus a distinct disorder?



# Neuro-imaging



# Neuroimaging Studies in Children

- The most consistent findings from neuroimaging studies are ventricular enlargement and reduced total brain volume
- Longitudinal studies of patients with EOS have demonstrated progressive ventricular enlargement
- Siblings of patients with EOS have smaller total cerebral volume and total frontal and parietal gray matter volumes than volunteers (suggesting a possible genetic trait marker)
- Measurable differences in glucose metabolism, irregular ANS arousal, and problems with visual tracking of moving objects have also been demonstrated in children with schizophrenia



# Gray Matter Loss

- MRI brain scans of adolescents reveal fluid filled cavities in the middle of the brain enlarging abnormally between ages 14 and 18 in teens with early onset schizophrenia, suggesting shrinkage in brain tissue volume. These children lose 4-5x as much gray matter in their frontal lobes as normal teens.
- This gray matter loss engulfs the brain in a progressive wave from back to front over 5 years, beginning in rear structures involved in attention and perception, eventually spreading to frontal areas responsible for organizing, planning, and other "executive" functions impaired in schizophrenia. The final loss pattern is consistent with that seen in adult schizophrenia.

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# Gray Matter Loss cont' d

- While the healthy teens lose an average of 1 percent of gray matter per year, the schizophrenic patients lose up to 5 percent a year, with loss greatest among individuals with the most severe symptoms (e.g., hallucinations, delusions, bizarre and psychotic thoughts, and depression) and spreading to areas controlling sensory and motor functions.
- By 18, the teenagers in one study had lost 25 percent of their gray matter in certain brain areas.
- In another study, siblings of EOS patients had significantly thinner gray matter in left prefrontal and bilateral temporal areas beginning at age 8 with less significant thinning in right prefrontal and inferior parietal areas. These deficits were no longer present by age 20. Higher global functioning was associated with the lessening of GM thinning in the sibling group. These findings support the hypothesis that GM development is mostly genetically driven in frontal and temporal areas and more environmentally based in the less-affected parietal domains.
- In the pictures you will now see, red/pink areas indicate gray matter cell loss; while blue/green areas indicate cell stability.

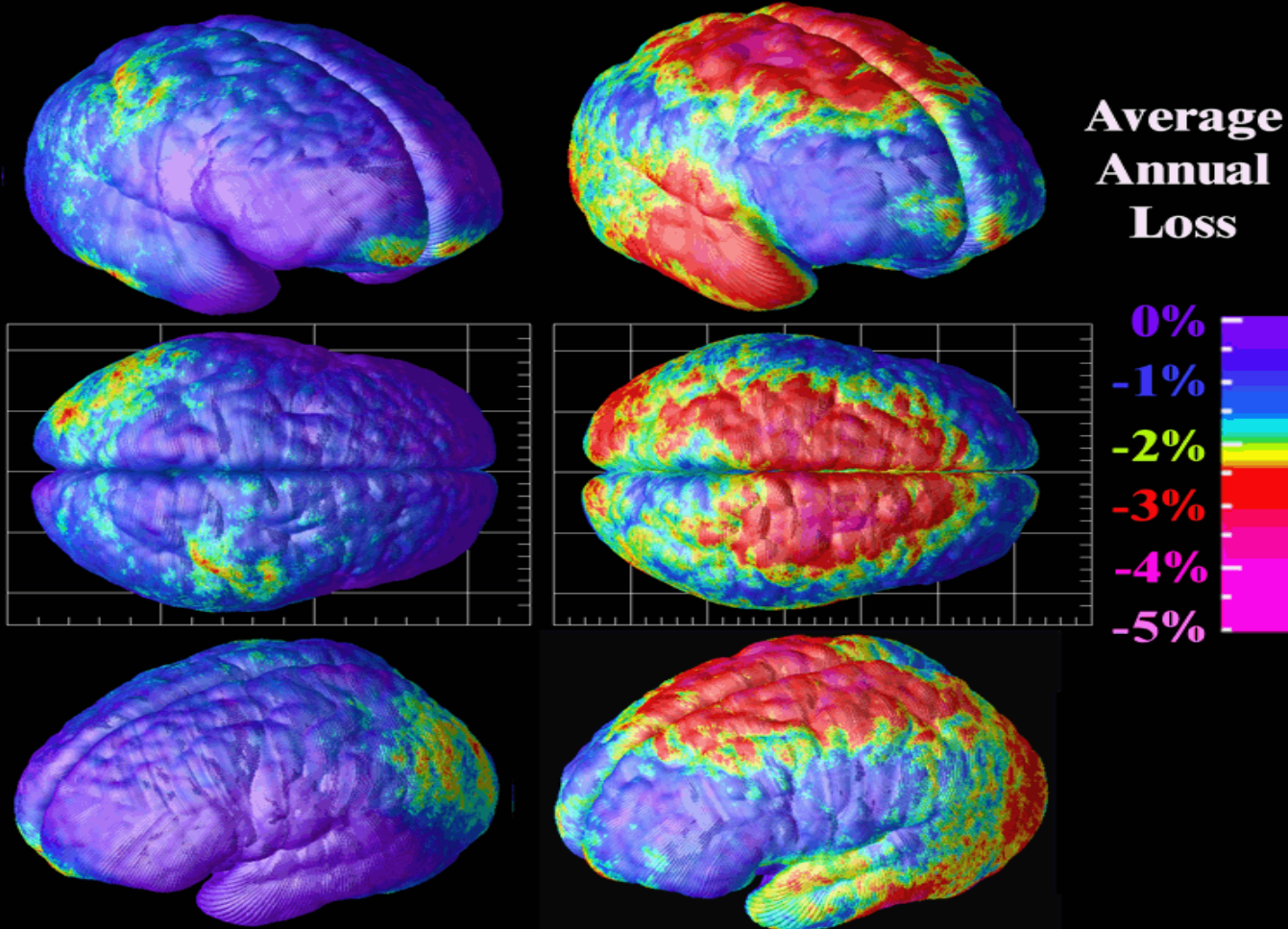




# Rate of Gray Matter Loss

**Normal  
Adolescents**

**Schizophrenic  
Subjects**



*Thompson et al., 2000*

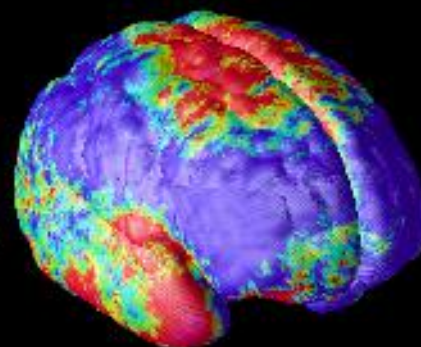
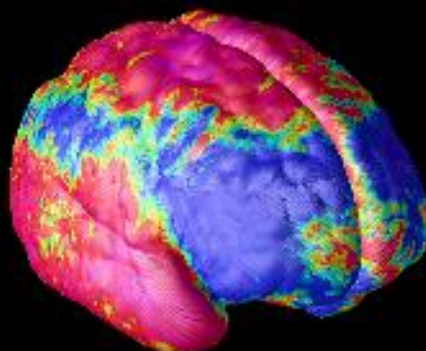
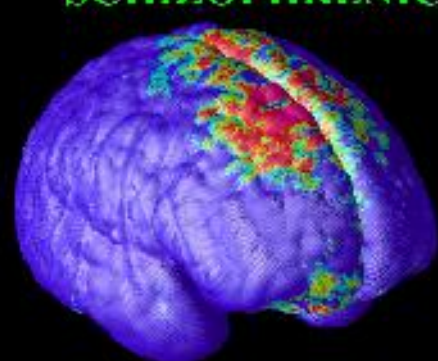
# Ruling out Medication Effects

MEDICATION-MATCHED

NON-SCHIZOPHRENIC

SCHIZOPHRENIC

DIFFERENCE



$p$ -value

0.00002

0.0001

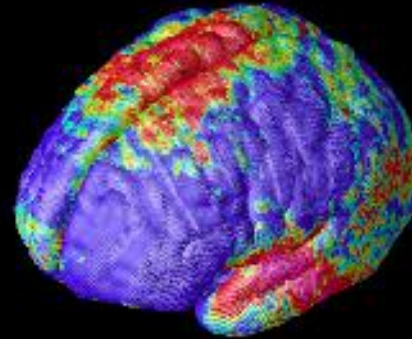
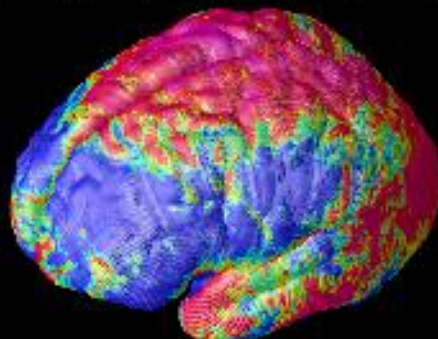
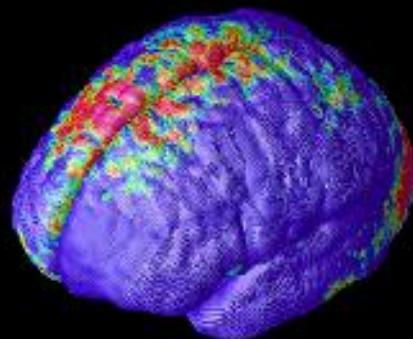
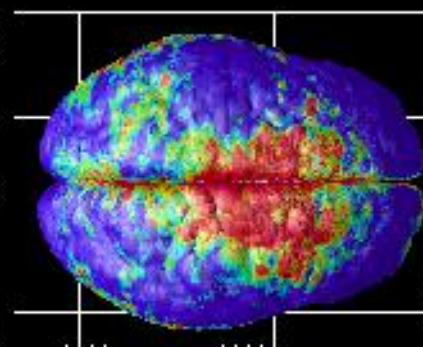
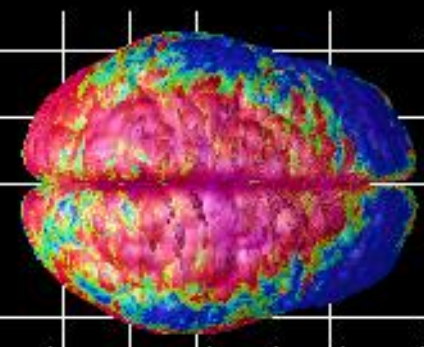
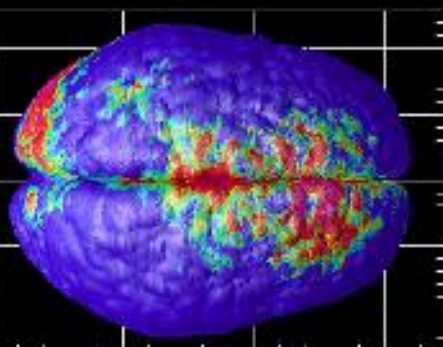
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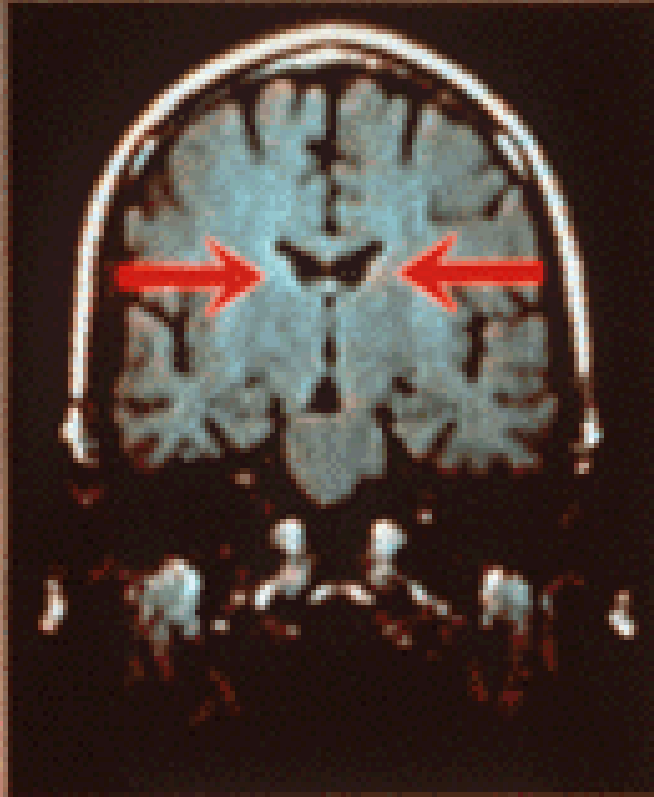
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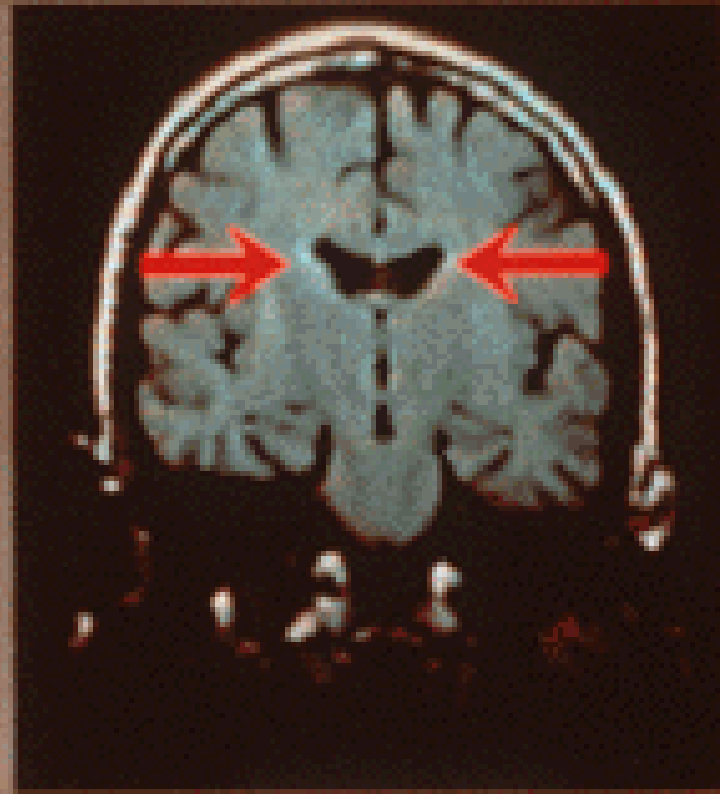


# SCHIZOPHRENIA IN MONOZYGOTIC TWINS

Pair no. 2: 44 year old males



UNAFFECTED



AFFECTED

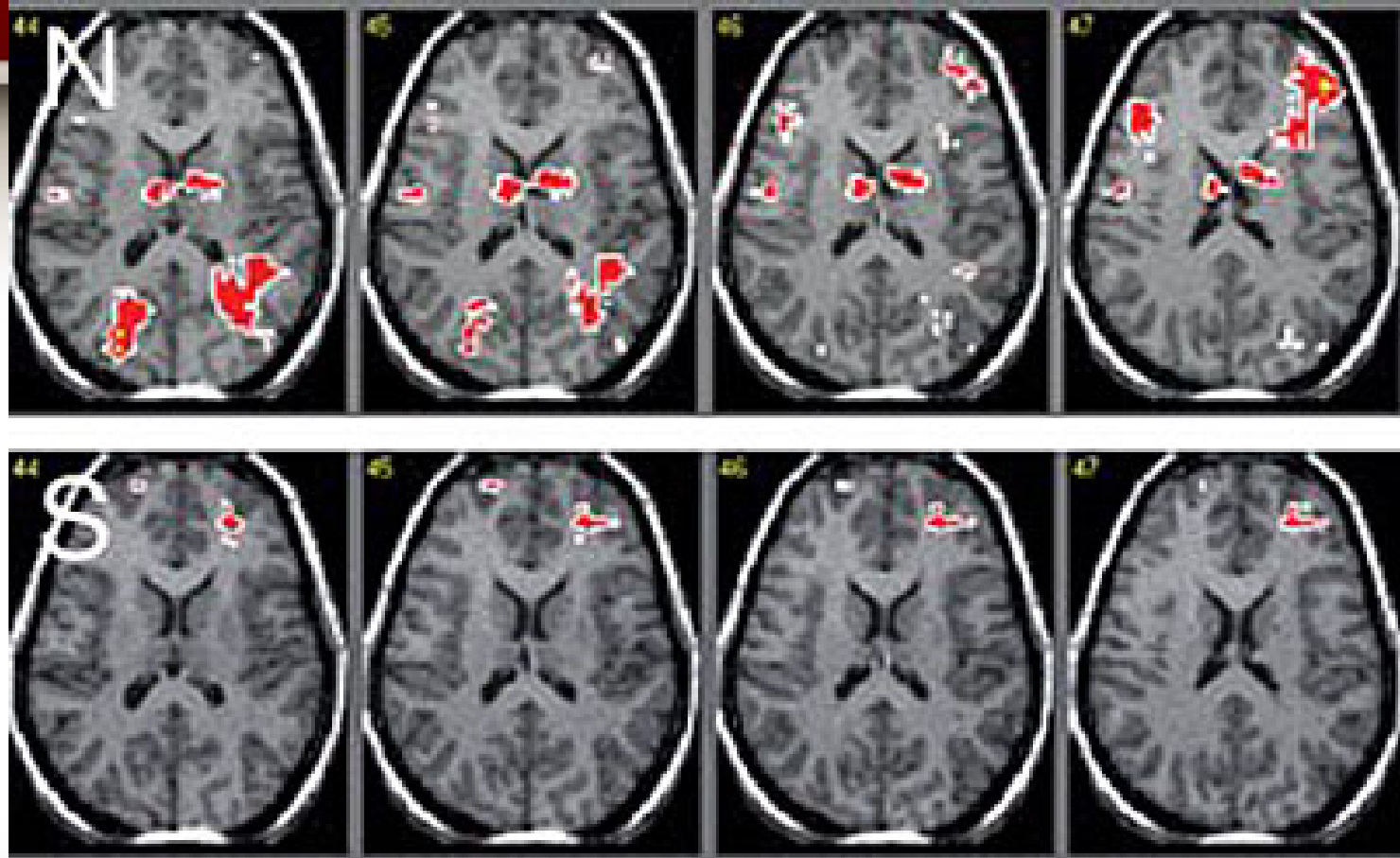
MRI imaging showing differences in brain ventricle size in twins - one schizophrenic, one not





Coronal MR scans from a normal comparison subject (left), and chronic schizophrenic (right). Note increase in CSF, ventricular enlargement, decreased gray matter volume.

# Brain Activity in Schizophrenia



Decreased brain activity in schizophrenia subjects compared to normal controls (N) in an fMRI study examining

Which mean gene?



# Genetics of Schizophrenia

- Concordance: averages 46% for monozygotic twins, as high as 60% in some studies; 14% for dizygotic twins
- Siblings (1<sup>st</sup> degree relatives) of schizophrenics have a 10% chance of developing the disease
- Risk increases to 17% for persons with one sibling and one parent with the disease; and 46% for children of two schizophrenic parents
- Children with one schizophrenic parent have a 5-6% chance of developing the disease



# Etiology and risk factors of childhood psychosis

## Genetics:

- Copy Number variations (CNVs): Are alterations in DNA, causing there to be an abnormal number of copies of DNA sections (i.e. a component may be deleted or duplicated). Deletions at the 22q11.2 section of DNA is a well accepted genetic subtype of schizophrenia.(VCF)
- A number of CNVs have been examined as possible predictors of schizophrenia, no one alone has been conclusive as a predictor of schizophrenia.
- Velo-cardio-facial syndrome 22q11 deletion-25%



# Etiology and risk factors of childhood psychosis

Family and Twin studies:

Families of children with COS indicate that first-degree relatives and other relatives have similar neurocognitive difficulties. 30% of non-psychotic parents of children with COS showed neurocognitive impairments.

Higher correlations of psychotic symptoms in children between monozygotic twins compared with dizygotic twins, similar to patterns in adults with psychosis

Children with psychosis symptoms are more likely than children w/out psychosis symptoms to have mothers who have a psychosis spectrum disorder



# Etiology and risk factors of childhood psychosis



- Environmental risk factors:
  - Urban area
  - Disadvantaged family
  - Parent-child relationship:
    - Studies suggest that children with psychotic symptoms tend to have parents who exhibit more negative expressed emotion.
- Stress and trauma:
  - Maltreatment and abuse
  - Chaotic household
- Birth complications:
  - Perinatal complications and lower birth weights more commonly seen in children with psychotic symptoms compared to controls.

(Husted, Ahmed, Chow, Brzustowicz, & Bassett, 2011; Boman, Wynn, & Cannon, 2011; Cannon & Arseneault, 2010)





# To treat or not?

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# Treatment: To Treat or Not to Treat

- The interval between onset of psychosis and initiation of treatment varies in studies between 0.4 – 3.2 years
- Prolonged untreated psychosis may lead to neurotoxicity and poorer clinical outcomes
- Accumulating evidence linking earlier treatment and better prognosis
- No clear relationship between duration of untreated psychosis and the risk of relapse as yet
- Mixed data regarding untreated psychosis and cognitive deterioration



# Treatment

- Must involve both the child and the family
- Combination of psychosocial and pharmacological treatment approaches
- Developing a support system: siblings, friends, peers, and teachers
- Most recommended treatments are based on trials in adults with schizophrenia
- Risperidone and Aripiprazole recently approved for treatment of schizophrenia in adolescents



# Psychosocial Therapies

- Social skills training
- Intensive in home therapy:
  - Mobile therapy
  - Family Based Service Unit
- Individualized educational program
- Targeting high emotional expression and identifying and addressing environmental stressors
- Psychoeducational programs
- Day treatment, partial hospitalization programs, after school, and summer programs
- Inpatient treatment for stabilization



# Pharmacological Approaches

## Special considerations

- Children metabolize medications faster than adults: may need to consider multiple daily doses; plasma half-life versus brain half-life
- Higher density of D2 receptors in children compared to adults
- Likely more sensitive to side effects than adults
- Low body fat
- Long-term side effects unclear



# Treatment of Early Onset Schizophrenia Spectrum Disorders Study (TEOSS)

- Publicly funded clinical trial
- To compare efficacy, safety and tolerability of risperidone, olanzapine, and molindone in youth
- Randomized, double-blind, parallel-group design at four sites
- Youth with EOSS (8-19 years): 8-week acute trial of risperidone (0.5-6.0 mg/d), olanzapine (2.5-20 mg/d), or molindone (10-140 mg/d)

McClellan, et al. JAACAP 2007



# Treatment of Early Onset Schizophrenia Spectrum Disorders Study (TEOSS)

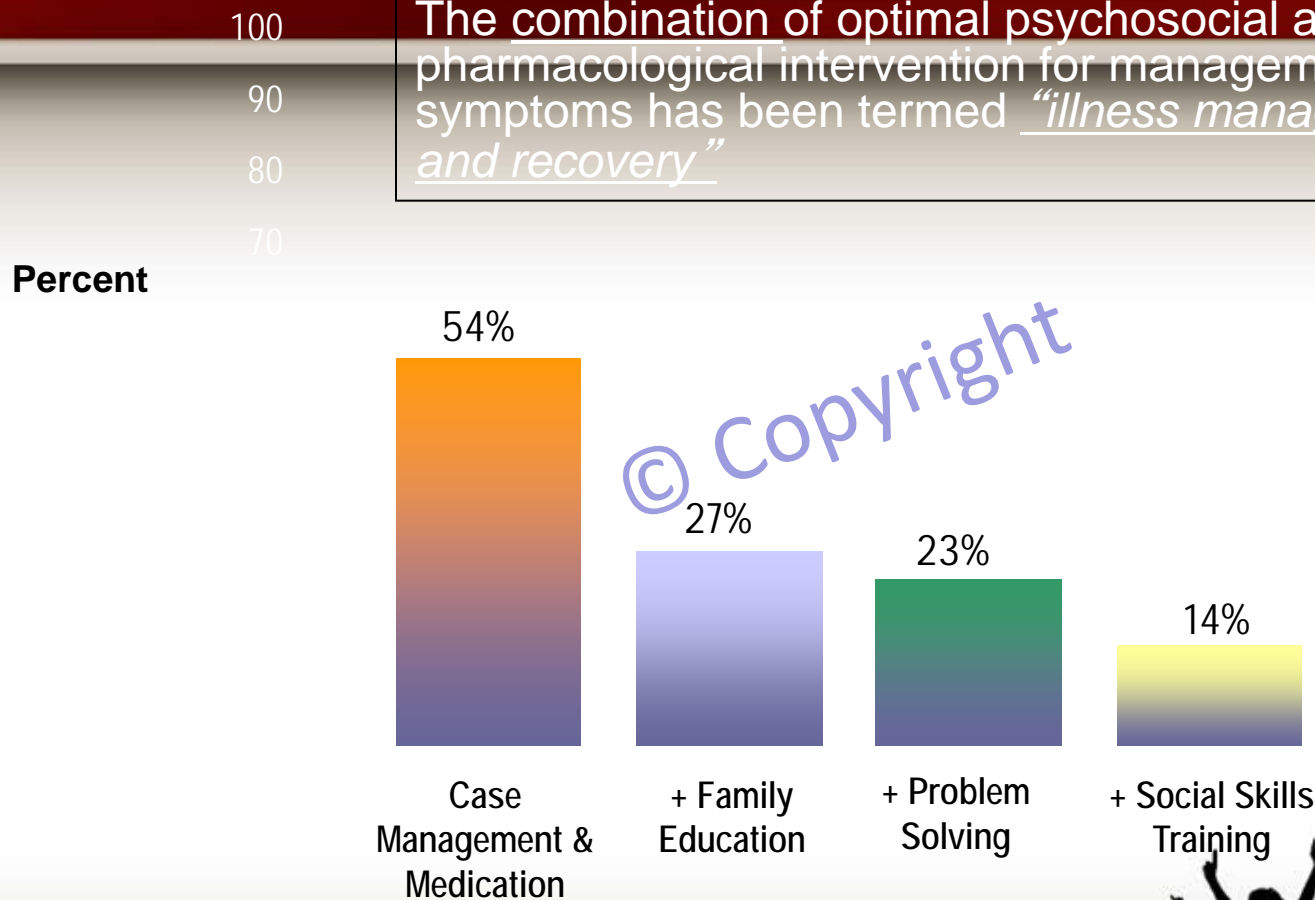
- Primary outcome measure: Responder status at 8 weeks (20% reduction in baseline PANSS scores + significant improvement on CGI)
- 476 youths screened, 173 further evaluated, and 119 randomized.
- Responders continued double-blind treatment for 44 weeks.

Frazier, et al. JAACAP 2007



# Good Treatment is ***Sufficiently Comprehensive***: One Year Relapse Rates With Integrated Services for People with Schizophrenia

The combination of optimal psychosocial and pharmacological intervention for management of symptoms has been termed “illness management and recovery”



Falloon, IRH, Held, T, Coverdale, JH, Roncone, R, Laidlaw, TM. (1999) Psychosocial Interventions for Schizophrenia: A Meta-analysis of international studies. *Psychiatric Rehabilitation Skills*, 3, 268-290





# Use of Antipsychotics

- The number of children prescribed antipsychotics increased 5x between 1995 and 2003 to an estimated 2.5 million each year
- Antipsychotic use saw a 73% increase between 2001 – 2005 in those under 18 y/o vs. adults who experienced a 13% increase during this same time.
- Total use of atypical antipsychotics is accounted for by 85% adults and 15% children
- This translates to an increase from 3.81/1000 in 2001 to 6.6/1000 in 2005; by contrast 11/1000 adults use an atypical antipsychotic (Medco, 2005)
- Rates appear to be slowing, however: 22% growth in 2003, 14% in 2004, and 3.4% in 2005
- Over 50% of the prescriptions are for children with ADHD and other non-psychotic illness
  - Cooper et al, Journal of Ambulatory Pediatrics, 2006





# Conventional Antipsychotics

- Double-blind, controlled trials have shown that haloperidol and loxitane are effective for treating children with schizophrenia
  - Haloperidol found to be effective in reducing symptoms of thought disorder, hallucinations and persecutory ideation
  - Loxitane and haloperidol superior to placebo
- Single-blind trials support the effectiveness of thiothixene and thioridazine with improvement in psychotic symptoms in about 50% in youth with chronic schizophrenia
- Same side effect profile as in adults: EPS ( $\downarrow$  in children,  $\uparrow$  in adolescents), sedation, TD and NMS



# 2<sup>nd</sup> Generation Antipsychotics in Kids

- State Medicaid study, 2001 – 2005
- 41% of kids treated with an antipsychotic did not have a diagnosis for which antipsychotics are supported
- Indications: ADHD, MDD, CD, ODD, Adj D/O
- Evidence by medication:

<u>Evidence</u>	<u>Aripiprazole</u>	<u>Olanzapine</u>	<u>Quetiapine</u>	<u>Risperidone</u>	<u>Ziprasidone</u>
Strong	10.8	21.6		64.2	
Plausible			16.2		3.6
Weak	22.9	29.1	45.9	1.7	56.9
None	77.1	43.9	32.6	30.6	43.1



# Duration of Untreated Psychosis

- The Duration of Untreated Psychosis (DUP) prior to first psychiatric admission adversely affects acute treatment response and short-term outcome in schizophrenia.
- In one recent study, 58 schizophrenic patients were assessed at their first psychiatric admission and after a 15-year course of the illness. The 15-year outcome in different domains was compared between patients with different DUPs prior to the first psychiatric admission.
- A longer DUP was associated with more pronounced negative, positive and general psychopathological symptoms, as well as lower global functioning, 15 years after the first psychiatric admission, even after effects of other factors possibly related to the long-term outcome were controlled for.
- The findings underline the importance of establishing health service programs for the early detection and treatment of schizophrenic patients with the aim of shortening the DUP and improving the course and outcome of schizophrenic patients.

--Bottlender et al, 2003



# Medication Side Effects (2)

- Children are more vulnerable to EPS
  - This has long been known for children who were exposed to conventional antipsychotics
  - EPS is related to D2 receptor occupancy in adults and children have a greater density of D1 and D2 receptors than adults
- Chart reviews to date indicate probably less vulnerability when children are treated with atypical antipsychotics



# Medication Side Effects (3)

Additional concerning side effects of atypical antipsychotics include:

- 1) Sedation
- 2) Prolactin elevation
- 3) Weight gain
- 4) Cardiac toxicity



# Prolactin Meta-Analysis

- Meta-analysis of 29 studies of antipsychotics from 1965 – 2008, including haloperidol, pimozide, risperidone, olanzapine, clozapine, ziprasidone, and quetiapine
- All antipsychotics, except clozapine, ziprasidone, and quetiapine, increase the mean prolactin level from baseline values of 8.0 ng/mL to 25-28 ng/mL after 4 weeks of treatment
- The most and best data are available for risperidone. Five risperidone studies (n = 577) show an increase of prolactin level from 7.8 ng/mL to 17.7 ng/mL after 1 year of treatment, and two risperidone studies (n = 60) show an increase from 7.4 ng/mL to 24.9 ng/mL after 2 years of treatment.
- Aggregated over all antipsychotics, prolactin-related side effects, such as gynecomastia, galactorrhea, irregular menses, and sexual dysfunction, were reported by 4.8% of the children and adolescents.
- No data are available on bone mineral density in relation to antipsychotic-induced hyperprolactinemia in children and adolescents.



# Metabolic Side Effects

- A study of South Carolina Medicaid claims data retrospectively compared 4140 children & adolescents (<18 years) who were prescribed conventional or atypical antipsychotics from 1998 through 2003 and 4500 children who did not receive psychotropic medication.
- Compared with controls, children treated with antipsychotics had significantly higher rates of obesity (OR = 2.13), type 2 diabetes (OR = 3.23), cardiovascular conditions (OR = 2.70), and orthostatic hypotension (OR = 1.64), but not hypertension, dyslipidemia, or cerebrovascular events.
  - McIntyre & Jerrell, 2008





# Monitoring Glucose

- Medicaid claims data study of 5,370 children aged 6 – 17 years prescribed antipsychotic medications from July 1, 2004 – June 30, 2006
- Researchers found that glucose screening was performed in only 31.6% and lipid testing in only 13.4%.

» Arch Pediatr Adolesc Med 2010; 164:344-51





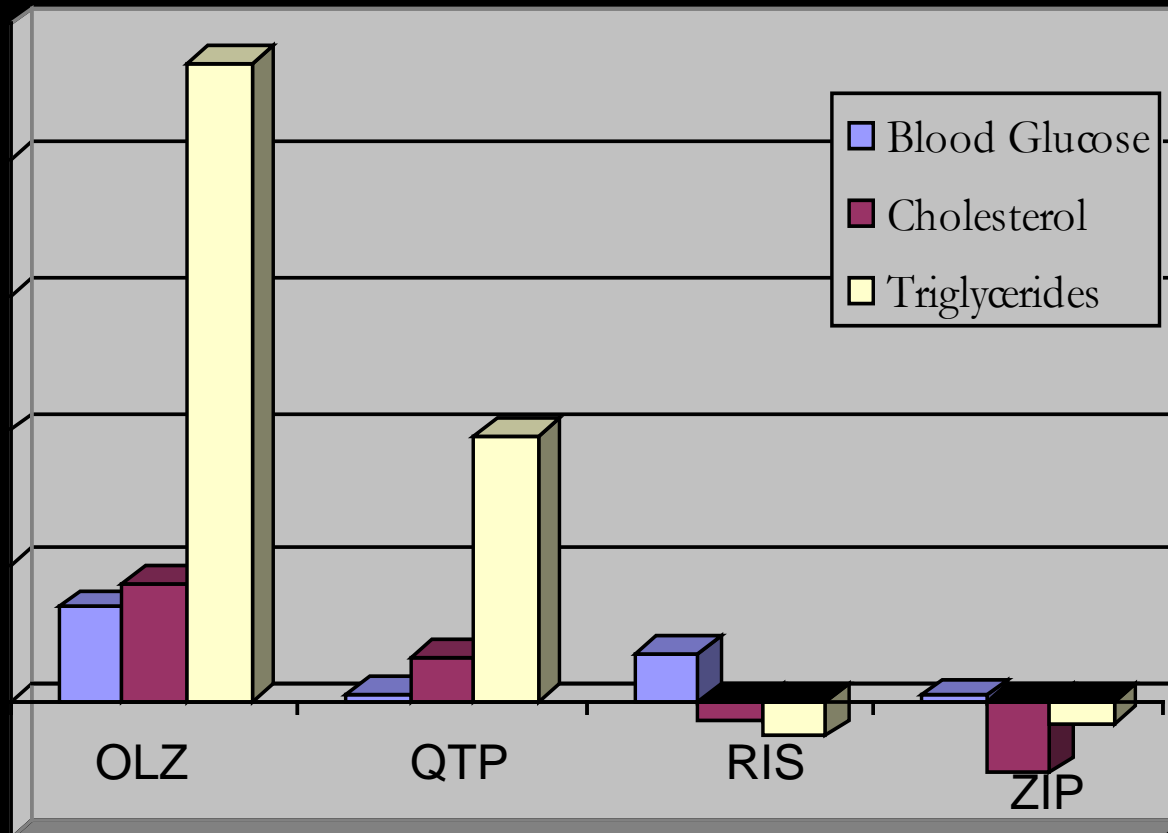
# SATIETY Study

- Nonrandomized SGA Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) cohort study, 2001 – 2007, at LIJ inpatient/outpatient
- N = 338, aged 4 to 19 years, with  $\leq 1$  week prior antipsychotic trmt
- Diagnoses: 130/47.8% had ASD, 82/30.1% had schizophrenia spectrum, 60/22.1% had disruptive or aggressive behavior disorders (small comparison group of 15 kids who refused participation)
- Intervention involved treatment with aripiprazole, olanzapine, quetiapine, or risperidone for 12 weeks
- After a median of 10.8 weeks of treatment, weight increased by 8.5 kg with olanzapine (n = 45), by 6.1 kg with quetiapine (n = 36), by 5.3 kg with risperidone (n = 135), and by 4.4 kg with aripiprazole (n = 41) compared with the minimal weight change of 0.2 kg in the untreated comparison group (n = 15).
- With olanzapine and quetiapine, respectively, mean levels increased significantly for total cholesterol (15.6 mg/dL and 9.1 mg/dL), triglycerides (24.3 mg/dL and 37.0 mg/dL), non–high-density lipoprotein (HDL) cholesterol (16.8 mg/dL and 9.9 mg/dL), and ratio of triglycerides to HDL cholesterol
- With risperidone, triglycerides increased significantly (mean level, 9.7 mg/dL)
- Metabolic baseline-to-end-point changes were not significant with aripiprazole or in the untreated comparison group.

• Correll et al, 2009



# Impact of Different Antipsychotics on Metabolic Measures



# ECG: QT Interpretation (1)

- QTc duration is the single best parameter for assessing unstable ventricular depolarization
  - Upper Limits:
    - Adults = 470 ms
    - Boys = 450 ms
    - Girls = 460 ms
- Medication induced increases in QTc by  $> 10\%$  suggests need for investigation



# ECG: QT Interpretation (2)

## Pretreatment Screening

- Congenital Risk Factors
  - Family/past h/o congenital deafness, palpitations, prolonged QT diagnosed by ECG, & "drop attacks," such as syncope or seizures (not dx as seizures)
- Acquired Risk Factors
  - Blood labs:  $Ca^{++}$ ,  $K^+$ ,  $Mg^{++}$ , LFTs, BUN/Cr (hypokalemia, hypermag, and hypercal can cause prolongation)
  - ECG
  - Physical exam: BP/HR
  - Review current medications



# ECG: QT Interpretation (3)

## Calculating QTc

- Leads II and V5 are most sensitive
- Measure QT from start of Q wave to end of T wave (if non-significant U wave); measure to end of U wave if present
- Bazett's Formula:  $QTc = \text{actual QT} / \text{square root of preceding R-R interval in seconds}$ 
  - Overestimates at rates  $> 100$  bpm
- Flattened T waves themselves tend to be innocuous in children & adolescents, but flattened T waves may reveal significant U waves (greater than 1/3 the height of the T wave) not previously visible, suggesting prolonged ventricular repolarization



# Monitoring Patients on Atypical Antipsychotics

Source: *Diabetes Care*, February 2004

Lab Value	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	Every 5 Years
Personal Family History	X					X	
Weight (BMI)	X	X	X	X	X		
Waist Circumference	X					X	
Blood Pressure	X			X		X	
Fasting Plasma Glucose	X			X		X	
Fasting Lipid Profile	X			X			



# Risperidone

- Treated patients had significantly greater reduction decrease in PANSS scores
- Treated patients had significant decrease in hallucinations, delusional thinking, and other symptoms of their illness.
- Drowsiness, fatigue, increase in appetite, anxiety, nausea, dizziness, dry mouth, tremor, and rash were the most common side effects noted in the studies



# Risperidone

- Recently approved by the FDA for schizophrenia for the age range 13-17 years.
- Based on two short-term (6 to 8 weeks), double-blind, controlled trials for patients with acute episode of schizophrenia
- 417 subjects in the two studies treated with Risperidone ranging from 0.15 mg/day to 6 mg/day



# Risperidone: Side Effects

- EPS: 5 of 16 patients in the series by Grcevich's group (1996)
- TD
- Weight gain (3.6-6.3 Kg)
- Fatigue/sedation
- Galactorrhea
- Hepatotoxicity: Association of weight gain, increased LFT and liver fatty infiltration?
- Others: photophobia, headache, insomnia, depression, anxiety, lightheadedness

# Olanzapine

- 8-week open-label trial (Kumra et al., 1998)
  - 8 youths with treatment resistant EOS
  - Results based on CGI:
    - 3 much improved
    - 1 minimally improved
- 15 children with VEOS (Sholevar et al., 2000)
  - 6 to 13 years of age
  - Results
    - 5 “great improvement”
    - 5 “moderate improvement”



# Olanzapine

- Pharmacokinetics:
  - Ages 10-18 years
  - Dose received 2.5-20 mg/day
  - Elimination half-life  $37.2 \pm 5.1$  hours
- Adverse effects:
  - Increased appetite: average weight gain  $3.4 \pm 4.1$  kg
  - Constipation
  - Nausea/vomiting
  - Headache
  - Somnolence
  - Transient elevation of liver function tests



# Olanzapine

- 1-year open-label trial of olanzapine for the treatment of COS: Positive symptoms improved after 6 weeks and negative symptoms showed improvement after 1 year of treatment. (Ross 2003)

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- Adverse effects reported in various studies: Increased appetite and weight gain, sedation, GI symptoms, headaches, agitation, liver function abnormalities, and sustained tachycardia



# Quetiapine

- No published controlled trials
- Pharmacokinetic study (McConville et al., 2000):
  - well tolerated up to the dose of 400 mg bid
  - No unexpected and serious side effects observed
  - Most common SE: insomnia, tachycardia, and decreased total thyroxine
  - No emergence of EPS
- Single case reports:
  - 14-year-old boy with schizophrenia (Szigethy et al., 1998)
  - 15-year-old girl with an acute psychosis (Healy et al., 1999)



# Ziprasidone

- Retrospective analysis in a State Hospital
- Children and adolescent who received ziprasidone for at least 10 days
- Chart reviewed for diagnoses, dose/duration, response, vital signs, EKGs, and side effects
- CGI-S were assigned retrospectively by the investigators
- Endpoint was defined as:
  - patient discharge from the hospital
  - discontinuation of ziprasidone therapy

» Patel et al., 2002





# Ziprasidone

- 8 males and 5 females; age range: 13 to 18 yo
- Diagnoses: MDD (4); schizophrenia (4); bipolar disorder (3); Psychotic disorder, NOS (2)
- Average endpoint dose was  $53.31 \pm 25.22$  mg/day
- 10 patients were considered as responders
- Limited side effects:
  - akathisia; agitation
  - gastrointestinal upset, sedation, and dizziness
  - EKGs
- Conclusion: Ziprasidone maybe effective and well tolerated as an acute treatment for children and adolescents



# Ziprasidone

- Sikich 2006: Ziprasidone beneficial in 13/40 patients with COS after 12 weeks of treatment
- Mean final dosage 118 mg/d.
- Over 1 year: 50% patients gained weight but no significant ECG changes occurred.
- Preliminary data suggest that ziprasidone may be useful in the treatment of COS.



# Aripiprazole

- October 2007: FDA approved aripiprazole for the treatment of childhood schizophrenia in patients aged 13-17 years.
- Initiation of treatment at 2mg/d and then titrated upwards for 5 days to a target dose of 10 mg/d
- Approval based on a randomized double-blind study of 302 ethnically diverse adolescents with an acute episode of schizophrenia requiring hospitalization at 101 centers in 13 countries.



# Aripiprazole

- Aripiprazole started at 2 mg/d and then up-titrated for 5 days to 10 mg/d or uptitrated for 11 days to 30 mg/d. Approximately 85% of patients completed the study
- At 6 weeks: Both doses achieved significant improvements from baseline relative to placebo
- 30 mg/d didn't show improved efficacy vs. 10 mg/d
- Adverse reactions: Incidence  $\geq 5\%$  ; at least twice that of placebo
- A/E were dose related and included extrapyramidal symptoms, somnolence and tremor.

# Clozapine

- Sporn et al, 2007: 54 children & adolescents participated in a double-blind (N=22) or open-label (N=32) clozapine trial.
- Clinical improvement as per Brief Psychiatric Rating Scale strongly correlated with N-desmethylclozapine/clozapine ratio at 6-weeks.
- Rate of side effects higher than typically seen in adults



# Clozapine

- NIMH study: N=21 with VEOS (Kumra et al., 1996):
  - Clozapine ( $176 \pm 149$  mg/day) superior to haloperidol ( $16 \pm 8$  mg/day)
  - Both positive and negative symptoms improved
  - In the clozapine group: 5 developed neutropenia and two had seizures, but no agranulocytosis
  - Tremor, akathisia, and EPS in 15%
- Case studies:
  - Types of side effects similar to what is seen in adults
  - One case of acute pancreatitis
  - Clozapine-induced obsessive compulsive symptoms
  - Dose: 50mg/day up to 900 mg/day



## Comparisons of Antipsychotics in COS

Antipsychotic	Type of study	N	Outcome	Mean daily dose ranges	Adverse effects
Olanzapine vs risperidone vs haloperidol <sup>18</sup>	Double-blind, randomized, 8 weeks	50	3 agents equally efficacious	Olanzapine: 12.3 ± 3.5 mg Risperidone: 4 ± 1.2 mg Haloperidol: 5 ± 2 mg	Atypicals: Parkinsonian symptoms, EPS Haloperidol: EPS, headache, blurred vision All: weight gain
Risperidone <sup>19</sup>	Open-label prospective study	11	Significant improvement on total PANSS score (28%), BPRS score (30%), and CGI severity score (31%)	Risperidone 3.14 ± 1.6 mg/d	EPS, somnolence, weight gain, depression
Risperidone vs olanzapine <sup>20</sup>	Open-label, randomized, comparative 12-week study	259	Both agents equally efficacious	Risperidone: 1.62 ± 1.02 mg/d Olanzapine: 8.18 ± 4.41 mg/d	EPS and weight gain; no difference between 2 groups
Olanzapine vs risperidone vs haloperidol <sup>21</sup>	8 weeks, open clinical trial	43	Significant improvement in both positive and negative symptoms in all 3 groups using PANSS	Olanzapine: 12.9 ± 3.1 mg/d Risperidone: 3.3 ± 1.1 mg/d Haloperidol: 8.3 ± 3.8 mg/d	Haloperidol: more severe EPS and depression Olanzapine and haloperidol: fatigability, sedation, and increased sleep duration
Haloperidol vs clozapine <sup>16</sup>	6-week double-blind trial	21	Clozapine: better efficacy	Haloperidol: 16 ± 8 mg/d Clozapine: 176 ± 149 mg/d	Clozapine: neutropenia, seizures, cardiac complications
Clozapine vs olanzapine <sup>17</sup>	Double-blind, randomized 8-week trial	25	Clozapine: significant improvement compared with olanzapine using medication-free baseline	Clozapine: 327 mg/d Olanzapine: 19.1 mg/d	Both groups: weight gain Clozapine: seizures, lipid abnormalities

COS, childhood-onset schizophrenia; EPS, extrapyramidal syndrome; PANSS, positive and negative symptom scale; BPRS, brief psychiatric rating scale; CGI, clinical global impression.

Khurana et al 2007

Allka A. Subramanyam -Early Onset Schizophrenia PG Training Series 2<sup>nd</sup> February, 2017





# Other Treatment approaches

- Evidence from the adult literature:
  - Lithium
  - Benzodiazepines
  - Anticonvulsants
  - ECT
- No data in children for Schizophrenia



# Course and Outcome

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# Course

- Acute phase: Predominance of positive symptoms; generally lasts 1 to 6 months; shift from positive to negative over time
- Recuperation/Recovery phase: significant impairment with negative symptoms
- Residual phase: Some youth with EOS may have prolonged periods between acute phases with limited symptoms. Most continue to be impaired with negative symptoms
- Chronically ill patients: Some patients will remain chronically ill → most severely impaired children will require the most comprehensive treatment resources



# Outcome

- Mostly retrospective studies: limitations
- Premorbid characteristics, treatment response and adequacy of therapeutic resources
- VEOS longitudinal study (Eggers, 1978, 1989):
  - 10 year follow-up study:
    - 57 patients, onset between 7 and 13 years of age
    - 28% had schizoaffective disorder
    - 50% significant impairment
    - 30% good social adaptation
    - 20% remission
    - Onset before age 10 (n = 11) → poor outcome
  - 42 year follow-up study:
    - 25% complete remission
    - 25% partial remission
    - 50% chronic impairment



# Outcome

- In general, the earlier the onset of COS, the poorer the prognosis.
- Predictors of better prognosis include higher premorbid intelligence, more positive than negative symptoms, and cooperation of family in treatment (Remschmidt 2002)
- Long-term follow-up over 6-40 years indicates that significant impairment persists into adulthood; only 7% of the sample were able to maintain a stable relationship; 59% were unmarried and living alone; 73% had some form of employment, 27% were unable to work (Eggers, 2002)

Outcome in COS							
Authors	F/U period (y)	Age at onset (y)	N	Female (%)	Male (%)	Criteria	Value (%)
Lay <sup>25</sup>	10	11 through 18	96	41 (43)	55 (57)	Social disability	No dysfunction: 8 (12) Minimum: 5 (8) Obvious: 9 (14)
Remschmidt <sup>27</sup>	42	5 through 14	38	15 (39)	23 (61)	Global assessment scale	Good: 6 (16) Moderate: 9 (24) Poor: 23 (60)
Eggers <sup>7</sup>	42	6 through 14	44	25 (57)	19 (43)	Course of illness	Complete remission: 11 (25) Partial remission: 11 (25) Poor: 22 (50)
Asarnow <sup>28</sup>	1 to 7	6 through 11	21	6 (29)	15 (71)	Course of illness	Remission: 6 (33) Chronic schizophrenia: 12 (67)
Werry <sup>26</sup>	4.3 ± 3.2	7 through 17	30	15 (50)	15 (50)	<i>DSM-III-R</i>	Serious social disability: 22 (55) Remission: 7 (23) Subchronic: 4 (13) Chronic: 19 (64)
Inoue <sup>30</sup>	3	10 through 17	19	9 (47)	10 (53)	Occupational situation	Fully employed: 3 (16) Same level: 4 (21) Below level: 3 (16) Limited ability: 5 (26) Hospitalized: 4 (21)
Kimura <sup>37</sup>	> 3	12 through 17	23	9 (39)	14 (61)	Course of illness	Remittent: 7 (30.5) Fading: 7 (30.5) Scanty: 6 (26) Persistent: 3 (13)

COS, childhood-onset schizophrenia; F/U, follow-up.

Khurana, et al. Feb 20



- EIP-Early Intervention Psychiatric Unit
- CAMHS
- ARMS-At Risk Mental Symptoms
- NSS-Neurological Soft Signs

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# POST-TEST

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# Question 1

- Prodromal symptoms of early-onset schizophrenia may include all of the following except?
  - A) Deficits in attention
  - B) Impaired language and verbal memory
  - C) Excellent coordination and motor skills
  - D) Dysphoria, anxiety and physical complaints
  - E) Social withdrawal and isolation



# Question 2

- All of the following clinical characteristics have been reported to be reliably diagnosed in children except:
  - A) Hallucinations
  - B) Delusions
  - C) Illogical thinking
  - D) Loosening of Associations
  - E) Poverty of speech

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# Question 3

- Neurobiological findings that have been associated with schizophrenia may include all of the following except:
  - A) Deficits in smooth eye pursuit movements
  - B) Impairments in autonomic responsiveness
  - C) A progressive decrease in ventricular size
  - D) Smaller total cerebral volume
  - E) Frontal lobe dysfunction



# Question 4

- The two atypical antipsychotics approved by the FDA for treatment of schizophrenia in adolescents include:
  - A) Risperidone and Olanzapine
  - B) Quetiapine and Olanzapine
  - C) Ziprasidone and Quetiapine
  - D) Aripiprazole and Risperidone
  - E) Olanzapine and Aripiprazole



# Question 5

- Factors associated with a better prognosis in childhood onset schizophrenia include all except:
  - A) Earlier age of onset
  - B) Higher premorbid intelligence
  - C) More positive symptoms
  - D) Less negative symptoms
  - E) Family support and cooperation in treatment



# Answers

- 1) C
- 2) E
- 3) C
- 4) D
- 5) A

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