THE ABCs OF DIAGNOSING AND TREATING PEDIATRIC PSYCHOSIS
Learning Objectives

• Apply evidence-based strategies to the differential diagnosis of psychotic symptoms in pediatric patients

• Apply evidence-based treatment strategies in the management of pediatric patients diagnosed with psychosis
Overview

• Differential diagnosis
• Schizophrenia DSM-5
• Adolescent presentation
• Epidemiology and etiology
• Work up
• Treatment findings from both NIH and industry trials
• Summation
Differential Diagnosis
Differential Diagnosis

- Mood disorders with psychotic features
- PTSD
- OCD
- Other anxiety disorders
- Substance use disorder/intoxication
- Autism and other developmental disabilities
- Psychotic disorders including schizophrenia
- Delirium
- Dementia
- Medical illnesses-list is long and won’t cover except to mention NMDA receptor encephalitis
DSM-5
Schizophrenia *DSM-5*

- Two or more of the following present for most of 1 month:
  - **Delusions**: fixed, false idiosyncratic belief
  - **Hallucinations**: sensory perception without environmental stimulus
    - illusions are misperceptions (e.g., the bathrobe over a chair is a person sitting in the chair)
  - Disorganized speech incoherent/derailment
  - Grossly disorganized or catatonic behavior
  - Negative symptoms, affective flattening, alogia, avolition

Schizophrenia *DSM-5 II*

- Social and occupational dysfunction
- Duration of at least **6 months**
- Exclude schizoaffective and mood disorder
- Exclude substance/medical disorder
- Diagnose in autistic patients, only if they exhibit prominent delusions and hallucinations

Adolescent Presentation
Case A: Tan-Moy

- He had a few friends in elementary school, but as middle school approached, he stopped playing soccer and football.
- In the summer before sophomore year, he spent the entire vacation going to work with his father because he did not want to stay home alone.
- He started 10th grade and began to think that all the kids were picking on him and bullying him.
- The tech education teacher noticed that he would yell at the computer during the class.
- He stopped eating meals with his family and began losing weight.
Pediatric Presentation Schizophrenia

• Failure to achieve age-appropriate levels of interpersonal, academic, or occupational functioning

• Rare onset before age thirteen; incidence peaks ages 15-30

• Early onset occurs predominantly in males (2:1 ratio)
  • Age of onset for males is approximately 5 years before females

• Described cases by Kraepelin
Pediatric Presentation Schizophrenia II

• Patients with schizophrenia experience:
  • Delusions/firmly held idiosyncratic false beliefs
  • Hallucinations/false perceptions without sensory stimulus, any of 5 senses, most common auditory
  • Withdrawal from the outside world, negative symptoms
  • Disorganization of thoughts and behaviors
Pediatric Presentation Schizophrenia III

- Trouble telling dreams/television from reality
- **Seeing things and hearing voices**
- Vivid and *bizarre* thoughts and ideas
- Extreme moodiness, *anxiety*, and fearfulness
- Ideas that people are “out to get them”
- Problems with making and keeping *friends*
- Not eating due to fear that food is poisoned
- Rule out other causes of psychosis: drugs; delirium; medication; mood disorder
- **Family history** of schizophrenia or long stay in psychiatric hospital
Subtypes-No Longer in DSM-5 but in ICD-10

- **Paranoid** - preoccupation with delusions and auditory hallucinations, no disorganized speech, catatonic behavior, flat affect
- **Disorganized** - disorganized speech & behavior, flat/inappropriate affect
- **Catatonic** - >2 of motor immobility, excessive motor activity, extreme negativism or mutism, peculiar movements posturing, stereotyped movements, mannerisms or grimacing, echolalia or echopraxia
- **Undifferentiated** - meet first criteria, but does not fit into other three subtypes
- **Residual** - evidence of SZ disturbance in absence of complete set of active symptoms or sufficient number to meet another subset
Course

- **Prodrome**: functional deterioration before onset of psychotic symptoms
- **Acute phase**: prominent positive symptoms and marked deterioration in functioning
- **Recoverative/Recovery**: several months; more negative and some positive symptoms, may have depression/dysphoria
- **Residual**: persistent impairment due to negative symptoms
- Most youth have a **chronic** course
Epidemiology and Etiology
Epidemiology

• 1% of population
• M:F 1.4:1
• Peak age of onset 15-30 years old
• Early onset (EOS) <18-year-old EOS males more frequent
• Childhood onset (COS) <13-year-old COS rare
• Misdiagnosis common in early onset, bipolar, psychotic mood disorder, personality disorder, OCD, developmental syndromes
Etiology

• Genetic: 5-20X the risk in first degree relatives of those with schizophrenia, 5-15% if sibling has it

• Velocardiofacial syndrome increased risk on chromosome 22

• Neuroanatomy includes increased size of ventricles, decreased gray matter, cortical thinning
Work Up
Work Up

• Need a good history of time course, family history, previous symptoms, and treatment
• Physical examination with special attention to neurologic exam
• Toxicology screen for substances of abuse
• MRI to rule out CNS lesion
• Neurology consult for possible other CNS illnesses associated with psychotic symptoms such as lupus, NMDA encephalitis, and others
Treatment
Practice Parameter AACAP

• Revised in 2013, covering literature 2004-2010

• Team of experts in child psychiatry made the review and recommendations

• Standard in the field of how to treat youth with schizophrenia

Recommendations

• Psychiatric assessments should include a screen for psychosis
• Diagnose based on adult DSM-5 criteria
• Suspected schizophrenia: evaluate for comorbid medical and psychiatric disorder and suicidality
• FDA-approved antipsychotic medication as primary treatment: aripiprazole, risperidone, paliperidone, olanzapine, quetiapine, lurasidone
• Treat long term to avoid relapse
Recommendations II

- Use adjunctive medication (glycopyrrolate) for side effects and comorbid illnesses
- Clozapine trial for treatment resistant schizophrenia
- Baseline and follow-up labs, symptoms, and side effects
- Psychotherapeutic interventions alongside medication: CBT, social skills, cognitive remediation, and family therapy plus psychoeducation
- ECT if other options fail
Schizophrenia Medications

• Second generation antipsychotics
• For treatment resistant schizophrenia, use clozapine
• Alternative treatment is first-generation antipsychotics, three FDA-approved in children:
  • Haloperidol for Tourette’s Disorder and psychosis
  • Chlorpromazine for severe behavior and psychosis
  • Pimozide for Tourette’s Disorder
APPENDIX
Positive Medication Trials
Aripiprazole Trial

• Findling AJP 2008 165(11) aripiprazole in schizophrenia

• 302 13-17-year-olds PBO100, 10 mg ARI 100, 30 mg ARI 102

• Reduction in PANSS at 6 weeks PBO 22.3, 10 mg ARI 30.6, 30 mg ARI 31.9

• Lead to FDA labeling for aripiprazole for 13-17 year olds
Improvement on the PANSS for Adolescents With Schizophrenia

mean PANSS=94.5. b=p<.05. c=p<.01
Olanzapine Trial

• L Kryzhanovskaya. JAACAP 2009; 48(1)

• 107 13-17-year-olds with schizophrenia, 6 week trial
  PBO 35, OLZ 72 2.5-20 mg, mean dose 11.1 mg

• Reduction in BPRS at 6 weeks PBO 9.3, OLZ 19.4,
  effect size 0.63

• Mean weight gain PBO 0.1 kg, OLZ 4.3 kg
Visit-wise Mean Least Squares Change in BPRS

Baseline 3.5 days 1 week 2 weeks 3 weeks 4 weeks 5 weeks 6 weeks

BPRS-C Mean Change from Baseline

- Olanzapine
- Placebo

p = .020
p = .004
p = .023
p = .010
p = .015
p = .015
NIMH TEOSS Treatment of Early Onset Schizophrenia Syndrome

• Sikich AJP 2008; 165 (11)

• NIMH study of 8-19-year-olds with schizophrenia spectrum
  35 OLZ 2.5-20 mg, 41 RIS 0.5-6 mg, 40 MOL 10-140 mg + 1 mg benztropine

• Response CGI-I 1 or 2+ >20% reduction in PANSS at 8 weeks

• Response rate OLZ 34%, RIS 46%, MOL 50%

• RIS and OLZ not superior to MOL
A. Time Course of Treatment Discontinuation

- **Molindone** (red line)
- **Olanzapine** (blue line)
- **Risperidone** (green line)

**Percent Survival**

**Weeks**

0 1 2 3 4 5 6 7 8
B. Observed PANSS Total Score by Week of Treatment

PANSS Total Score vs. Weeks

- **Molindone**
- **Olanzapine**
- **Risperidone**

Weeks range from 0 to 8.
A. Changes in Body Mass Index (BMI) Percentile

B. Metabolic Changes

- Molindone
- Olanzapine
- Risperidone

<table>
<thead>
<tr>
<th>Metabolic Parameter</th>
<th>Molindone</th>
<th>Olanzapine</th>
<th>Risperidone</th>
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<tbody>
<tr>
<td>Tot Chol</td>
<td>-5%</td>
<td>0%</td>
<td>-20%</td>
</tr>
<tr>
<td>LDL</td>
<td>-10%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>TRIG</td>
<td>-20%</td>
<td>-10%</td>
<td>-5%</td>
</tr>
<tr>
<td>AST</td>
<td>0%</td>
<td>-5%</td>
<td>5%</td>
</tr>
<tr>
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<td>-5%</td>
</tr>
<tr>
<td>Prolactin</td>
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<td>0%</td>
<td>-5%</td>
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<tr>
<td>Insulin</td>
<td>-5%</td>
<td>-10%</td>
<td>-20%</td>
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</table>
Risperidone Trial

• 6 week double-blind trial in 160 teens 13-17 years old with schizophrenia
• 3 groups placebo, 1-3 mg or 4-6 mg
• Change in PANSS
• Response >20% reduction in PANSS

Haas JCAP 2009
Risperidone Effect Evident at 8 Days

87% of Placebo, 82% of 1-3mg Risperidone & 84% of 4-6mg Risperidone Completed Study

Long Term Risperidone

• Follow-up of above trial and second high and very low dose trial (no placebo allowed in EU study)

• Teens, 390 total, 13-17 years old; 279 for 6 months; 111 for 12 months

• Dose of 2-6 mg daily; median modal dose 3.8 mg

• 75% completed 6 months and 50% completed 12 months
Change in PANSS on Risperidone Long-Term

Figure 2
Paliperidone Trial

- 6 week double-blind, placebo controlled trial
- 201 12-17-year-olds
- One of 3 weight-based dosing v placebo low medium high
  - 29-<51 kg 1.5, 3, or 6 mg
  - >51 kg 1.5, 6 or 12 mg
- Medium dose was effective
- PANSS change by dose 3mg -19.0, 6 -13.8 and 12 -16.3 compared with PBO -7.9

Singh Biological Psychiatry, 2011.
Paliperidone Change in PANSS by MG Dose

[Graph showing change in PANSS scores over days with different doses of paliperidone ER and placebo.]

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Baseline Mean [SD]</th>
<th>Endpoint Mean [SD]</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>51</td>
<td>90.6 [12.13]</td>
<td>82.7 [21.45]</td>
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<tr>
<td>Paliperidone ER 1.5 mg</td>
<td>54</td>
<td>91.6 [12.54]</td>
<td>81.9 [19.54]</td>
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<tr>
<td>Paliperidone ER 3 mg</td>
<td>16</td>
<td>92.1 [16.88]</td>
<td>73.1 [26.55]</td>
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<tr>
<td>Paliperidone ER 6 mg</td>
<td>45</td>
<td>90.8 [13.66]</td>
<td>77.0 [20.59]</td>
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<tr>
<td>Paliperidone ER 12 mg</td>
<td>34</td>
<td>91.0 [13.00]</td>
<td>74.7 [16.57]</td>
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</tbody>
</table>
Paliperidone v. Aripiprazole Trial

• 8 week double blind trial of paliperidone, aripiprazole and placebo

• 12-17-year-olds placed on paliperidone titrated up from 3-9 mg and aripiprazole titrated up from 2-15 mg

• 75% of people completed the 8 week trial

• Change in PANSS Ari -19.3; Pali -19.8

• Side effects Pali akathisia, headache, somnolence, tremor, and weight gain, Ari worsening of schizophrenia and somnolence

• Extrapyramidal symptoms including dystonia and hyperkinesia occurred in>2% in paliperidone ER–treated versus aripiprazole treated patients

Savitz JAACAP 2015.
PANSS Change Ari and Pali

**Graph a**

Mean (+/-SE) Change from Baseline

<table>
<thead>
<tr>
<th>Days</th>
<th>N</th>
<th>Baseline Mean [SD]</th>
<th>Endpoint Mean [SD]</th>
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<tbody>
<tr>
<td>7</td>
<td>112</td>
<td>89.6 [12.22]</td>
<td>64.0 [17.61]</td>
</tr>
<tr>
<td>14</td>
<td>112</td>
<td>89.6 [12.22]</td>
<td>64.0 [17.61]</td>
</tr>
<tr>
<td>28</td>
<td>112</td>
<td>89.6 [12.22]</td>
<td>64.0 [17.61]</td>
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<td>56</td>
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<td>89.6 [12.22]</td>
<td>64.0 [17.61]</td>
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<td>98</td>
<td>112</td>
<td>89.6 [12.22]</td>
<td>64.0 [17.61]</td>
</tr>
<tr>
<td>140</td>
<td>112</td>
<td>89.6 [12.22]</td>
<td>64.0 [17.61]</td>
</tr>
<tr>
<td>182</td>
<td>112</td>
<td>89.6 [12.22]</td>
<td>64.0 [17.61]</td>
</tr>
</tbody>
</table>

- **Paliperidone ER**: N = 112, Baseline Mean = 89.6[12.22], Endpoint Mean = 64.0[17.61]
- **Aripiprazole**: N = 114, Baseline Mean = 92.0[12.09], Endpoint Mean = 65.2[18.72]
Lurasidone Trial

- 6 week double-blind placebo controlled trial
- 12-17-year-olds, 112 placebo; 110 on 40 mg and 104 on 80 mg
- Change in PANSS at week 8 was the primary outcome measure
- CGI-I was the primary secondary measure
- FDA approved for adolescent schizophrenia in January 2017
PANSS Total Score: Change From Baseline (MMRM, ITT)

*P<0.05; **P<0.01; ***P<0.001.
LS, least squares; MMRM, mixed model for repeated measures.
Negative Schizophrenia Trials
Ziprasidone Trial

- 6 week double-blind placebo controlled trial
- 2:1 ratio 40-160 mg daily, 283 total, 193:90
- Change in BPRS not significant -14.16 drug: -12.35 placebo

Findling JCAP 2013.
Change in BPRS on Ziprasidone

![Graph showing change in BPRS-A Total Score over weeks with mean change from baseline and 95% CI](image)
Asenapine Trial

- Trial of Asenapine v. placebo in three arms placebo, 2.5 mg bid, 5 mg bid for 8 weeks to look at reduction in PANSS at week 8

- Both on CGI and PANSS, the doses of active medication did not make clinical significance

- Average PANSS change PBO -17.1; 40 mg -21.8; 80 mg -22.7 p=.07

- Average CGI change: PBO -0.8; 40 mg -1.0; 80 mg -1.2 (significant for the 80 mg dose)

- 26-week extension study, people had an average improvement of 12.9 in those previously on asenapine and 16.1 points for those previously on placebo

Findling. JCAP 2015.