First Episode Schizophrenia

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Learning Objectives

• Recognize the first episode of schizophrenia
• Understand options for treatment for the first episode of schizophrenia
• Understand interventions for comorbid health problems
Epidemiology of Schizophrenia

- Lifetime prevalence of 1%
- Average age of onset 16-25 years old
  - Earlier in men, later in women
- Childhood onset schizophrenia:
  - Onset before age 13
  - <1% of all patients with schizophrenia
- Adolescent onset schizophrenia:
  - Onset before age 18
  - 30% of all patients with schizophrenia
DSM 5: Schizophrenia

- Two Criterion A symptoms for one month:
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Disorganized behavior
  - Negative symptoms
- One must be a “core symptom”
- Functional decline
- Total duration of symptoms: 6 months
Cognition in Schizophrenia

- Cognitive performance is 1-2 SD below age matched controls\(^1\)
- Affected areas include: attention, executive fn, memory, processing speed, social cognition\(^2\)
- Cognitive decline is nearly universal, present before the onset of psychosis, and worsens during the illness\(^3\)
- Chronic cognitive impairment is specific to schizophrenia- not seen in bipolar disorder or depression\(^4\)

Cognition in Schizophrenia

• Antipsychotic treatment leads to very small improvements in cognitive subtests\(^1\)
• Cognitive function is a critical determinant of global functional outcome\(^2\)

Acute Psychosis: Case Example

• 18 yo, freshman in college, no prior psych history
• Stopped attending class due to poor concentration, grades now Ds
• Not socializing at all, rarely leaves dorm room
• Not showering or changing clothes
• Told parents he was hearing voices
• MSE: disheveled and malodorous, guarded, not engaged, self dialoging but denies hallucinations
Acute Psychosis: Treatment Questions

- When do you start treatment?
- Which antipsychotic is first-line treatment?
- What dose do you use?
- How long do you treat before you switch?
- How long do you treat the first episode?
Treat ASAP

• Minimize duration of untreated psychosis (DUP)
• Early intervention is associated with:
  – Improved clinical outcomes at 2 years\(^1\) and 5 years\(^2\)
  – Higher GAF, improved social functioning, fewer symptoms at 20 years\(^3\)
• Early intervention increases the chances of achieving initial remission\(^4\)

What antipsychotic to use?

• Café Trial\(^1\)  SGAs only
  – Olanzapine, quetiapine and risperidone had comparable efficacy

• EUFEST\(^2\)  FGAs and SGAs
  – Haloperidol, quetiapine, ziprasidone, amisulpride, olanzapine had comparable efficacy
  – SGA’s were more well tolerated: 33-53% vs 72% FGA discontinuation rate

• TEOSS\(^3\)  FGAs and SGAs, children only
  – Molindone, olanzapine, risperidone had comparable efficacy and comparable discontinuation
  – Olanzapine had significant weight gain

Newer Antipsychotic Medications

- **Paliperidone**: 3-12 mg QD, approved 12-17 yo
  - Active metabolite of risperidone, similar SE profile
- **Lurasidone**: 40-160 mg QD, w/ food, approved 13-17 yo
  - Akathisia, less weight gain, more EPS?
- **Asenapine**: 2.5-10 mg BID SL, approved for bipolar only
  - Sedation, EPS, weight gain
- **Iloperidone**: 1-12 mg BID, not approved in children
  - Sedation, weight gain
- **Brexpiprazole**: 2-4mg QD, not approved in children
  - Partial D2 agonist, akathisia, less weight gain
- **Cariprazine**: 3-6 mg QD, not approved in children
  - Partial D2 agonist, akathisia, less weight gain
Comparative Efficacy Meta-Analysis

- Meta-analysis, 15 antipsychotics: FGAs, SGAs, Clozapine
- Clozapine was significantly more effective
- Olanzapine and risperidone were more effective than most (small effect size); all others had similar efficacy
- Haloperidol had highest all cause discontinuation

Bottom Line

• Given that efficacy is generally similar between agents, start with any antipsychotic, except olanzapine or clozapine (PORT Guidelines\textsuperscript{1})

• To make initial choice, consider individual side effect profiles and patient preferences

• Encourage patients to consider a long acting injectable (LAI) antipsychotic early on

Role of LAIs in FEP

- LAIs: risperidone, paliperidone, aripiprazole, olanzapine, haloperidol, fluphenazine
- LAIs increase adherence & allow for easier detection of non-adherence
- May be especially beneficial for early episode patients:
  - Improved positive symptoms
  - Fewer relapses
  - Fewer hospitalizations

What dose to use?

- First-episode patients are more responsive to medication
- FEP patients require lower doses of antipsychotics than multi-episode patients
- First-episode patients are more sensitive to side effects than multi-episode patients

What dose to use?

- FEP patients respond to lower doses of antipsychotics\(^1,2\)

<table>
<thead>
<tr>
<th></th>
<th>FEP Daily Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>2.1 mg</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10 mg</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>11.7 mg</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2.4 mg</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

When to switch antipsychotics?

- Clinical improvement is slow
  - Positive symptoms take weeks to resolve
  - Negative symptoms and cognitive symptoms won’t resolve
- AACAP Guidelines: After 6 weeks, if there are insufficient effects while using adequate dosages, consider switching
Clozapine

• 20% of FEP patients will not respond to FGAs or SGAs

• Patients with 2 failed trials should be offered clozapine
  – The only antipsychotic agent for which there is established superiority over other agents

• For tx refractory schizophrenia, clozapine is more beneficial than haloperidol and high dose olanzapine (66% vs 33%)\(^1\)

• Clozapine can be used in adolescents, but adolescents are more sensitive to its side effects, especially\(^2\):
  • akathisia (15% vs 3%)
  • neutropenia (6% vs 1%)

How long to treat?

AACAP Guidelines 2013

• Most individuals need long term treatment and are at significant risk of relapse if medication is discontinued
• Maintain medication at the lowest effective dose to minimize adverse events
• After prolonged remission, a small number of individuals may be able to discontinue medication
• Change from 2001 guidelines- emphasized intermittent treatment or discontinuation
Relapse off Medication

- 3 year, open label trial
- All FEP patients, stable for 2 years
- All patients underwent gradual medication taper
- Relapse rates:
  - 79% at 1 year
  - 97% at 3 years

Bottom Line: Maintenance Treatment

- **Strongly** encourage long term treatment at the lowest effective dose
- Most patients ask for a trial off medication
  - They will do it with or without you
- After 1-2 years of stability, for **low risk** patients, after significant discussion, consider gradual taper, with **close** monitoring
- A **small** subgroup of patients may maintain remission/partial remission off medication\(^1\)
- Multi-episode patients will need indefinite maintenance treatment

All about meds?

- RAISE Study
- Comprehensive tx vs. usual care
- Comprehensive tx:
  - Med management, individual therapy, family psycho-ed, supp employment/ed
- Outcomes:
  - Time in treatment, functioning, QLS, PANSS, depression, hospitalizations

Not My Job
Morbidity and Mortality

• Schizophrenia is associated with a 20 year decrease in life expectancy\(^1\) and a 4 fold increase in mortality\(^2\)
• Premature mortality is due to cardiovascular dz, respiratory dz, infections and cancers\(^3\)
• Even in FEP, cardiac and metabolic abnormalities are present early on\(^4\)
• Related to underlying illness, unhealthy lifestyle, antipsychotic meds, inadequate medical care

Antipsychotics and Weight Gain

• Children may be particularly prone to weight gain

• Naturalistic study: At 12 weeks, antipsychotic naïve youth gained\textsuperscript{1}:
  – 4.4 kg on aripiprazole
  – 5.3 kg on risperidone
  – 6.1 kg on quetiapine
  – 8.5 kg on olanzapine

Monitoring

- **Baseline:**
  - BMI
  - Fasting glucose, lipids, BP
  - Family history of obesity, DM, CVD, HTN
- **BMI:** check at 4, 8, 12 weeks, every 3 months after
- **Fasting glucose, lipids, BP:** check at 3 months, then annually if normal
- **Intervene for abnormalities!**
Metformin

• Mechanism of action: does not cause hypoglycemia
  — Decreases hepatic production & GI absorption of glucose
  — Increases peripheral glucose utilization

• Safety
  — Rare lactic acidosis: more likely with excessive alcohol use
  — May be associated with B12 deficiency¹
  — Most common side effects: GI (N/V 14%, diarrhea 7%²)

• Dosing (adolescents, adults)
  — Target dose 2000 mg TDD (with food)

Metformin in Schizophrenia

- First episode patients, n=72
- Metformin 500 mg BID
- Weight loss (3.3 kg) & improved insulin sensitivity

![Graph showing weight changes over weeks for placebo and metformin groups.](image)

Summary

• Schizophrenia: positive symptoms, negative symptoms, cognitive changes

• Key treatment goals for the first episode
  – Treat early with low doses of antipsychotics
  – Consider LAIs early on
  – Encourage maintenance treatment for most patients

• Monitor and treat comorbid physical health conditions
Acknowledgements

MGH Schizophrenia Program

Oliver Freudenreich, MD
Daphne Holt, MD, PhD
Cori Cather, PhD
John Tyson, MD
Hannah Brown, MD
Yosh Kaneko, MD
Drew Coman, PhD
Alla Shapero, LICSW

THANK YOU!