Overview of Clinical Symptoms and Medication Treatment in Early Psychosis

Christian Kohler, M.D.
Phenomenology of Schizophrenia

All psychotic disorders are referenced to schizophrenia

Diagnostic and Statistical Manual of Mental Disorders DSM-V (2013)
A. Characteristic Symptoms ($\geq 2$) $\geq 1$ month
   - delusions
   - hallucinations
   - disorganized speech
   - disorganized behavior
   - negative symptoms

B. Social/Occupational Dysfunction during A

C. Duration: prodrome/acute/residual symptoms $\geq 6$ months
Health Costs

- 3% of all health expenditures (Knapp et al, *Schiz Bull* 2004)
- 22% of all mental health costs (Theida et al, *Psych Serv* 2003)

20-30% live independently

<20% work 20 hours per week or more

Life expectancy: 20% lower than average
Prevalence of Schizophrenia

Lifetime Prevalence
ranges between 0.5% (rural regions) - 2.5% (urban settings)
across US ~4 Mill
Phila area ~50 000

similar to epilepsy, more than DAT and Parkinsonism

similar rates across different cultures
WHO study incl. US, South America, Japan, India, Africa and Europe
2 yr outcome better in developing countries
Course/Outcome with Treatment

- complete, prolonged recovery of psychosis with minimal/no negative sx;s
- partial recovery of psychosis or recurrent psychotic episodes
- no significant recovery of psychosis

Prognosticators for better outcome

- later and abrupt onset
- level of premorbid functioning
- brief duration of untreated psychosis
- prominent affective symptoms or disorganized behavior
- paucity of negative symptoms
Phenomenology of Schizophrenia

Phases of Illness

- Pre-Illness
- Prodromal
- Psychosis
- Remission
- Relapse

Function

First symptoms
Onset of First Episode
Onset of relapse

Adapted from Knowles, 2004
Clinical Challenge of Early Identification
Figure 1: The trajectory to schizophrenia showing the evolution of symptoms and the main risk factors.
Neurobiology and Genetics:

- pervasive disorder affecting most brain regions without gross alteration in brain structure

Limbic areas of the brain
- cingulate gyrus
- amygdala
- hippocampus
- prefrontal areas
Risks
- Genetic
- Pregnancy/birth
- Early childhood
- Early adolescence

Heterogenous causes producing common phenotype

(Source: Gottesman, 1991)
FIGURE 3.
NMDA receptor hypofunction hypothesis and positive symptoms of schizophrenia²

A. NMDA Receptor Regulation of Mesolimbic Dopamine Pathway: Tonic Inhibition

B. NMDA Receptor Hypofunction in Cortico Brainstream Projections: Hyperactivity of Mesolimbic Dopamine Pathway


NMDA= N-methyl-D-aspartate; DA= dopamine; GLU= glutamate; GABA= γ-aminobutyric acid; VTA= ventral tegmental area.

Treatment Considerations

- Antipsychotic Treatment
- Other Medications (antidepressants, mood stabilizers)
- Psychotherapy
- Comprehensive Interventions
• Positive Symptoms: Hallucinations, delusions, disordered thinking and behavior

• Mood Symptoms: Depression, anxiety, mania

• Negative Symptoms: Lack of motivation, initiative, emotional expression

• Cognitive dysfunction
  - temporal lobe functions (memory, language)
  - frontal lobe functions (attention, mental flexibility)
First-episode Treatment

- Highest chance of response/recovery
- Lack of effects of chronic illness
- Challenge of illness acceptance

Duration of untreated psychosis leads to increased

- Negative symptoms
- Cognitive dysfunction associated with functional impairment
About 12 First-episode studies in the last 40 years

- 60-85% response rates based on positive symptoms
- Time to remission: mean=35 weeks, median 11 weeks
- No superiority of SGA
- Relapse rates 60-80%
- 80% associated with medication nonadherence (Robinson 1999)
- Duration untreated psychosis: worse outcome (Perkins 2005)
- Duration of persisting psychosis
First-Generation Antipsychotics: e.g., haloperidol, perphenazine, chlorpromazine

Second-Generation Antipsychotics: e.g., clozapine, olanzapine, risperidone, quetiapine, ziprasidone, ariprazole

Effect: reduce positive symptoms within several days to months

Difference between First- and Second-Generation Antipsychotics
- effect on pathways
- improvement in depression, anxiety
- improvement in negative symptoms
- side effects s. a. acute dystonia, neuroleptic malignant syndrome (NMS), Parkinsonian symptoms, tardive dyskinesia
### Antipsychotics

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<th>g(95% CI)</th>
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<td>97201</td>
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<td>3005</td>
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<td>0.44 (0.37, 0.51)</td>
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</table>
Treatment: dependent on patient’s insight into symptom

- management of psychotic symptoms but not others
- relapse prevention: at least 1-2 years after first episode

Antipsychotic Medications: affect dopaminergic transmission in pathways projecting from the brainstem to the frontal and temporal brain areas

3 major pathways from brainstem to
- basal ganglia
- temporal lobes
- frontal lobes
How to decide on which antipsychotic medication?

Effectiveness/Acuity of Illness: psychosis as primary target

Associated clinical symptoms, i.e., depression/anxiety, insomnia, restlessness/agitation.

Side effects: EPS, weight gain
Texas Treatment Algorithm

No History of Typical Antipsychotic Failure

Stage 1
- Use Olanzapine or Quetiapine or Risperidone
  - Use in any order
  - Nonresponse to one

Stage 2
- Use Another
  - Nonresponse to two
  - Use the Third
    - Nonresponse to three
    - Typical Antipsychotic
      - Nonresponse

Stage 3
- Use the Third
  - Nonresponse
  - Partial response
  - Clozapine

Stage 5
- Clozapine + Augmenting Agent (typical or atypical antipsychotic, mood stabilizer, ECT, antidepressant)
  - Nonresponse or clozapine refused

Stage 5a
- Atypical + Typical Combination of Atypicals, Typical or Atypical + ECT

(Any stage[s] can be skipped depending on the clinical picture)

Acute Exacerbation
- First presentation or not nonresponders to olanzapine, quetiapine, or risperidone

Stage 2
- Use Olanzapine or Quetiapine or Risperidone
  - Use in any order
  - Nonresponse to one

Stage 3
- Use Another
  - Nonresponse to two
  - Use the Third
    - Nonresponse to three
    - Typical Antipsychotic
      - Nonresponse

Stage 4
- Use the Third
  - Nonresponse
  - Partial response
  - Clozapine

Stage 5
- Clozapine + Augmenting Agent (typical or atypical antipsychotic, mood stabilizer, ECT, antidepressant)
  - Nonresponse or clozapine refused

Stage 6
- Atypical + Typical Combination of Atypicals, Typical or Atypical + ECT

History of Typical Antipsychotic Failure

Stage 2
- Use Olanzapine or Quetiapine or Risperidone
  - Use in any order
  - Nonresponse to one

Stage 3
- Use Another
  - Nonresponse to two
  - Use the Third
    - Nonresponse to three
    - Typical Antipsychotic
      - Nonresponse

Stage 4
- Use the Third
  - Nonresponse
  - Partial response
  - Clozapine

Stage 5
- Clozapine + Augmenting Agent (typical or atypical antipsychotic, mood stabilizer, ECT, antidepressant)
  - Nonresponse or clozapine refused

Stage 6
- Atypical + Typical Combination of Atypicals, Typical or Atypical + ECT

Source: Am J Health Syst Pharm © 2003 American Society of Health-System Pharmacists
Person
I cannot believe what anyone is saying or trust anyone.
The voices are too much!
I am scared, my feelings are gone.
I cannot think, I cannot sleep.
… why has my world changed?

Provider
Take this medicine…
But which one??

- CBT
- Behavior Therapy
- Supportive
- Family
- Motivational
- Dynamic
- Group
- Gestalt or Existential or Primal Scream???
Psychotherapy

Situation

Thoughts

Actions  Feelings
Applied to persons with
  • acute and chronic schizophrenia
  • targeting negative, depressive and positive symptoms

Cochrane Review (2013)
  • Likely most effective on symptoms of depression
  • No superiority regarding relapses, hospitalization rates, symptom changes compared to other psychotherapies, group therapy
  • Superiority to med trials re drop-out rates
Most effective

- Symptom oriented
- Normalizing experience
- Supportive/ motivational
- Setting clear goals
- Involving family as care provider
b. **Supportive Psychotherapy**
   - focus on coping with symptoms
   - social and occupational functioning

c. **Cognitive Psychotherapy** (recent application to schizophrenia)
   - identification of symptoms
   - cognitive redirection

d. **Cognitive Remediation**: to improve difficulties with memory & attention

e. **Family Education**: supportive limit setting
   - referral to National Alliance for Mentally Ill (NAMI)

f. **Combination Treatments**: RAISE, PIER, schizophrenia PORT
Initiatives over past 20 years in Australia, Scandinavia, UK, Germany

Recent US projects (RAISE, NAPLS, PIER/RWJ Foundation)

- No single, specific intervention
- Multidisciplinary

Community Mental Health Services Block Grant
2014-2015 SAMHSA 5% set aside funds
Allowed us to offer comprehensive multicomponent treatment effort

- Clinical assessment
  - Diagnostic
  - Development/functional
  - Family assessment

- Personalized treatment plan

- Recovery oriented CBT with family involvement

- Medication management

- Family support and information group

- Cognitive remediation