Pharmacotherapy for Schizophrenia

บรรยายในการประชุมเชิงปฏิบัติการเภสัชกรรมคลินิกครั้งที่ 3/2555 วันที่ 10 มกราคม พ.ศ. 2555 เวลา 13.00-14.00 น. ณ โรงแรมพูลแมน ถนนแยงซาคคิด จังหวัดขอนแก่น

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Scope

- What is schizophrenia
- Neurobiology in schizophrenia
- Pharmacological treatment
  - Mechanisms of each drugs: FGA, SGA
  - Adverse effects and management
What is Schizophrenia?

- A syndrome of impaired reality testing ability, symptoms include:
  - **Thought***- form (loosening of association), process (T. control, T. broadcasting), content (delusion)
  - **Perception** – hallucination esp. auditory
  - **Emotion** – ☄️ responsiveness, inappropriate
  - **Cognition** – attention, executive function
  - **Behavior** – bizarre, agitate, impulsive & violent, catatonia
Epidemiology

• Lifetime prevalence 1%
• Annual incidence 0.5-5 : 10000
• Male = Female
• Peak onset Male 10-25, Female 25-35
• Risk:
  • Environmental: prenatal infection, OB complication, immigration, drug use – LSD, amphetamines, cannabis
  • Genetic: family history, genetic syndromes, specific genes
Clinical Symptoms

Positive symptoms
• Delusion
• Hallucination
• Abnormal behavior
• Abnormal motor

Negative symptoms
• ↓ emotional response
• Restricted affect
• ↓ speech
• ↓ interest
• ↓ social drive
• ↓ sense of purpose
Age onset of Schizophrenia
Pathophysiology

• ‘Brain disease’
• Dopamine hypothesis ‘Dopamine overactivity’
• Present
  • Dopamine dysregulation
  • Glutamate involvement – NMDA receptor hypofunction – PCP
  • Serotonin involvement
Review of the Brain Regions

- Raphe nuclei – 5-HT
- Locus ceruleus – NE
- VTA – DA
- Substantia nigra – DA
1. **Mesolimbic Tract**
   - Hyperactive in Schizophrenia
   - Positive Symptoms

- Delusion
- Hallucination
- Pleasure
- Interest
- Libido
- Fatigue
- Euphoria
- Reward
- Motivation
Dopaminergic Tract

2. Mesocortical Tract
   - Hypoactive in Schizophrenia
   - D1 Play major role

DLPFC
   Executive Function
   Attention
   Concentration
   Impulse
   Obsession
   Compulsion
   Motor

VMPFC
   Emotion
   Fatigue
   Worry
   Pain
   Negative Symptoms
   Guilt
   Suicidal
3. **Nigrostriatal Tract**

- Normal in Schizophrenia
- D2 play major role
4. Tubuloinfundibular Tract
   - Negative control of Prolactin by Dopamine
   - Normal in Schizophrenia
GLUTAMATE PATHWAY

1. Cortical Brainstem Glutamate Projection
2. Cortico-striatal / accumbens
3. Cortico – Thalamic
4. Thalamo - Cortical

From pyramidal neuron layer 5 of PFC
1. Cortical Brainstem Glutamate Projection
2. Cortico-striatal / accumbens
3. Cortico – Thalamic
4. Thalamo - Cortical
5. Cortico - Cortical
Role of Glutamate in Mesolimbic Tract

Cortico-brainstem Glutamate Projection

− ‘BREAK’ Mesolimbic tract via GABA interneuron

Glutamate

Mesolimbic DA

Positive symptoms
Glutamate in Mesocortical Tract

Cortico-brainstem Glutamate Projection
– ‘accelerate’ Mesocortical tract directly

Glutamate \(\downarrow\)
Mesocortical DA \(\downarrow\)

Negative Cognitive Affective Symptoms

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5HT1A Receptor Action

- 5HT1A receptor >> DA accelerator

➤ via 5HT inhibition
- 5HT2A receptor >> DA break

- direct or via GABA interneuron

5HT2A Antagonist

▲ DA release
5HT & Cortical Glutamate Release

- 5HT1A >> Glutamate break
- 5HT2A >> Glutamate accelerator
Dx Schizophrenia: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR),

Three diagnostic criteria must be met
Characteristic symptoms: Two or more of the following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).

- Delusions
- Hallucinations
- Disorganized speech, which is a manifestation of formal thought disorder
- Grossly disorganized behavior (e.g. dressing inappropriately, crying frequently) or catatonic behavior
- Negative symptoms: Blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)

If the delusions are judged to be bizarre, or hallucinations consist of hearing one voice participating in a running commentary of the patient’s actions or of hearing two or more voices conversing with each other, only that symptom is required above. The speech disorganization criterion is only met if it is severe enough to substantially impair communication.
Dx Schizophrenia: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR),

Social or occupational dysfunction:

one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.

Significant duration: Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if symptoms remitted with treatment).

If signs of disturbance are present for

more than a month but less than six months, the diagnosis of schizophreniform disorder is applied.

Psychotic symptoms lasting less than a month may be diagnosed as brief psychotic disorder

If psychotic signs and symptoms occur with mood symptoms: schizoaffective disorder

If previous pervasive developmental disorder, schizophrenia could be an additional Dx if prominent delusions or hallucinations are also present
Course of Schizophrenia

Baseline function
25% full recovery
50% Residual symptoms & Social deficit
Some deficit
Significant deficit
25% very poor outcome

Acute psychotic episode
Treatment

Acute phase

Exacerbation

Psychiatric stabilization
Initiation of APs

Community-based treatment

Response

Maintenance phase

Maintenance treatment

Remission
(Symptoms free 6 mo)

Recovery
(Functional recovery)

Relapse

Residual signs & symptoms

Recovery

May be
- Cognitive impairment
- Psychiatric co-morbidity
- Medical co-morbidity

Non-adherence
Co-morbidity

Response

Resistant
Pharmacological Treatment

• Target symptoms
  1. Positive symptoms
  2. Agitation & irritability
  3. Negative symptoms

1° Negative Symptoms
“Deficit Syndrome of Schizophrenia”
• Prevalence
  – 15%(1st episode)
  – 30%(chronic)
• Significant & persistent > 12 mo
• Treat with ssris, psychosocial

2° Negative Symptoms
• Positive symptoms
• Depression
• Drug effects – parkinsonism, sedation
• Social anxiety
• Social deprivation
• Apathy – cognitive impairment, brain damage
Acute Phase Treatment

1. Hospitalization
2. Biological treatment
   1. Pharmacotherapy
   2. Electroconvulsive therapy
   3. Transcranial magnetic stimulation
3. Psychosocial treatment
Acute Phase Treatment: pharmacotherapy

Antipsychotics = the main stay: either atypical or typical
Now with the generic antipsychotics available: atypical antipsychotic drugs may be preferred for both acute and long term treatment over the older typical antipsychotics

Augment strategies:
1. Little firm evidence that adding adjunctive agents to standard neuroleptics will dramatically change the somatic treatment of schizophrenia.
2. The most promising adjunctive agents are benzodiazepines, lithium, and carbamazepine, as well as antidepressants and ECT for affective symptoms.
What is the first line pharmacotherapy

- **First generation APs (FGAs)**
  - Equivalent efficacy, differ in potency and side effects
  - 65% occupancy of striatal D2 receptor → antipsychotics efficacy
  - > 80% occupancy → extrapyramidal side effects (EPS)
  - Low potency FGAs:
    - Low affinity & less selective to D2
    - Require higher doses (~50X of haloperidol)
    - Associated with wide range of side effect
## FGAs Doses

<table>
<thead>
<tr>
<th>Equivalent dose (mg)</th>
<th>Typical dose (mg/d)</th>
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<tbody>
<tr>
<td><strong>Low potency</strong></td>
<td></td>
</tr>
<tr>
<td>• Chlorpromazine</td>
<td>100*</td>
</tr>
<tr>
<td>• Thioridazine</td>
<td>90</td>
</tr>
<tr>
<td><strong>Medium potency</strong></td>
<td></td>
</tr>
<tr>
<td>• Perphenazine</td>
<td>10</td>
</tr>
<tr>
<td><strong>High potency</strong></td>
<td></td>
</tr>
<tr>
<td>• Trifluoperazine</td>
<td>5</td>
</tr>
<tr>
<td>• Fluphenazine</td>
<td>5</td>
</tr>
<tr>
<td>• Haloperidol</td>
<td>2</td>
</tr>
<tr>
<td>• Pimozide</td>
<td>1</td>
</tr>
</tbody>
</table>
Side Effects associated with FGAs

<table>
<thead>
<tr>
<th>Low potency FGAs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sedation</td>
</tr>
<tr>
<td>• Hypotension</td>
</tr>
<tr>
<td>• Weight gain</td>
</tr>
<tr>
<td>• Anticholinergic symptoms (dry mouth, urinary retention, constipation, blurred vision)</td>
</tr>
<tr>
<td>• Impaired heat regulation (hypo or hyperthermia)</td>
</tr>
<tr>
<td>• Pigmentary retinopathy (thioridazine &gt; 800 mg/d)</td>
</tr>
<tr>
<td>• Cardiac conduction effects (pimozide, chlopromazine, thioridazine)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>High potency FGAs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Less above SEs but more EPS, NMS</td>
</tr>
</tbody>
</table>
Extrapyramidal Side Effects

**Dystonia**

- Acute muscle spasm – neck, tongue, back, opisthonus (lateral eye deviation), stridor (laryngeal spasm)
- Usually within first 4 days after starting drug/ dose
- Risk: young, Hi-potency FGAs
- Mx: prophylaxis with anticholinergics, SGAs

**Parkinsonism**

- Tremor, bradykinesia, rigidity, mask face – confused with ve symptoms, depression
- Risk: Hi-potency FGAs, Hi-doses, young & old
- Max: dose, anticholinergics, SGAs (clozapine, quetiapine)
## Extrapyramidal Side Effects

### Akathisia

- Restlessness in lower extremities – often pacing, leg discomfort commonly confused with psychotic agitation
- Dose dependent
- Mx: ↓dose, propranolol 10-20 mg tid-qid, SGAs

### Tardive Dyskinesia (TD)

- Involuntary choreiform movement of tongue, oral-buccal, upper extremities (some tardive dystonia)
- > 6 mo FGAs, ↓ 5%/yr of exposure, lifetime risk 50-60%
- Unclear whether influenced by dose or potency
- Risk: old, history of parkinsonian side effect, DM
- Mx: SGAs (↓risk), switching to clozapine

* Beware ‘withdrawal dyskinesia’ – resolve in 6 wks
Neuroleptic Malignant Syndrome (NMS)

- < 1% of pt. receiving FGAs (subsyndromal may be more common)
- Can be associate with clozapine, SGAs – non-rigid NMS
- Onset may be gradual, usually in following order
  - Confusion & fluctuating level of consciousness
  - Rigidity
  - Diaphoresis
  - Mutism
  - Autonomic instability
  - Hyperthermia
  - CPK
- Differential from lethal catatonia (absence APs treat^n)
- Mx: STOP APs, Hydration, cooling
  Bromocriptine or Dantrolene
  Reinstitutuion APs 2 wks after resolve
What is the first line pharmacotherapy

- **Second generation APs (SGAs)**
  - Similar efficacy as FGAs for positive symptoms
  - Modestly greater than average in negative symptoms, cognition, depression, anxiety
  - Better tolerate and fewer EPS & probably less TD
  - Higher risk of Wt. gain
    - High - clozapine, olanzapine
    - Midium – quetiapine, risperidone, (and low-potency FGAs)
    - Low – Ziprasidone, aripiprazole, (haloperidal & mid-potency FGAs)
## Antipsychotics Side Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>EPS</th>
<th>TD</th>
<th>Prolactin</th>
<th>Antich. S/E</th>
<th>Sedation</th>
<th>Wt. gain</th>
<th>DM</th>
<th>DLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Perphenazine</td>
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<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clozapine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>-</td>
<td>?</td>
<td>-</td>
<td>+++*</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Ziprazidone</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

TD = Tardive Dyskinesia, Antich. S/E = Anticholinergic side effect, DLD = Dyslipidemia

* Elevate urinary hesitancy, dry mouth, constipation in CATIE study, probably not via muscarinic receptor
What is the first line pharmacotherapy

• **Second generation APs (SGAs)**
  
  – Hyperprolactinemia – risperidone, amisulpride
  
  – Insulin sensitivity – clozapine, olanzapine
  
  – Should monitor for DM esp. clozapine, olanzapine
  
  – Metabolic syndrome: ≥ 3 risk factors
    
    • Abdominal obesity >> waist Ø – M > 40 in, F > 35 cm.
    
    • Triglyceride ≥ 150 mg/dl
    
    • HDL >> M < 40 mg/dl, F < 50 mg/dl
    
    • BP ≥ 130/85 mmHg
    
    • FPG ≥ 110 mg/dl
Acute Phase Treatment

• Drug selection
  – Small differences in efficacy
  – General side effects profile & pt. characteristics
  – Evidence of prior response to the same drug
  – Avoid side effects experienced with a drug in the past
  – Pt.’s preference for a specific drug
  – Planned mode of administration
Acute treatment: response

• Response of symptoms to medication is variable;
• "Treatment-resistant schizophrenia" = failure to respond to 2 or more anti-psychotic medications given in therapeutic doses for 6 weeks or more.
• Patients in this category may be prescribed clozapine, a medication of superior effectiveness but several potentially lethal side effects including agranulocytosis and myocarditis
• Clozapine is the only medication proven to be more effective for persons who do not respond to other types of antipsychotics.
• It also appears to reduce suicide in people with schizophrenia. As clozapine suppresses the development of bone marrow, in turn reducing white blood cells which can lead to infection, blood tests are taken for the first six months on this medication.
Maintenance Treatment

- Antipsychotic medications reduce (not prevent) the risk of future (intense and frequent) psychotic episodes.
- Acute phase: higher dosage of antipsychotic than in maintenance phase.
- If symptoms reappear on a lower dosage, a temporary increase in dosage may prevent a full-blown relapse.
Maitenance treatment

Patients, their families and doctors should work together to have good adherence.

Reasons for poor adherence:

• Patients may have poor insight and deny the need for medication
• Disorganized thinking causes forgetting to take their daily doses.
• Family members or friends may not understand schizophrenia and may inappropriately advise the patient stop treatment when he or she is feeling better.
• Physicians (Dr, pharmacologist, nurse and any) may neglect to ask patients how often they are taking their medications, or may be unwilling to accommodate a patient’s request to change dosages or try a new treatment.
• Substance abuse can interfere with the effectiveness of treatment, leading patients to discontinue medications.
Maintenance phase

• Long-acting injectable forms that eliminate the need to take pills every day.
• Time duration of treatment may more than 5 years or life long
• No antipsychotic medication should be discontinued without talking to the doctor
• Patient and family education about schizophrenia, its symptoms, and the medications being prescribed to treat the disease is an important part of the treatment process and helps support the rationale for good adherence.
Maintenance treatment

- Longer treatment duration lowers risk of psychotic relapse and psychiatric hospitalization
- Decrease patients' personal burden and lower the economic costs for acute care in the mental health system.
- Greater symptom improvement\(^{[28]}\) and better functional outcomes in the treatment of patients with schizophrenia.\(^{[29]}\)
- Clozapine, olanzapine, and risperidone, quetiapine and ziprasidone were found to be associated with significantly longer (in order from the longest) treatment duration compared to haloperidol with prophylactic anticholinergic agents.
- Treatment with clozapine requires periodic blood monitoring to assess the risk of developing agranulocytosis. In addition to the likely initial selection of more adherent patients for treatment with clozapine in usual care, the frequent monitoring may help increase treatment duration with clozapine
# Inhibitors and inducers of antipsychotic-metabolizing cytochrome P450 enzymes

<table>
<thead>
<tr>
<th>CYP 450 subtype and its substrate</th>
<th>Inhibitor</th>
<th>Inducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2/ clozapine, olanzapine</td>
<td>Fluvoxamine, Grape fruit juice in Large quatities</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>2D6/clozapine, olanzapine, risperidone, Aripiprazole (≥ 3A4)</td>
<td>SSRIs (especially Fluoxetine, paroxetine, High dose sertraline)</td>
<td></td>
</tr>
<tr>
<td>3A4/clozapine, quetiapine, ziprasdone, aripiprazole</td>
<td>Erythromycin and other macrolide antibiotics, Ketoconazole and other, Other antifungal drugs, Protease inhibitors</td>
<td>Barbiturates, Carbamazepine, Phenytoin, Rifampin, Glucocorticoids</td>
</tr>
</tbody>
</table>
Treatment of metabolic syndrome

• The five components of the metabolic syndrome are improved by even modest amounts of weight loss achieved with
• Life style change:
  • diet high fiber, low saturated fat diet and
  • exercise. Subjects who exercise the most, gain the most benefit.
• Some patients may require drug therapy: use of statins, fibrates, and niacin.
• Aspirin should be considered in those with at least a 10% risk of a coronary event over 10 years.
• Consider angiotensin converting enzyme inhibitor drugs or angiotensin receptor blockers, due to their effects on preventing complications of diabetes, such as progression of diabetic nephropathy and due to their effects on regression of left ventricular hypertrophy.
• Finally, three related conditions, nonalcoholic fatty liver disease, polycystic ovary syndrome and protease inhibitor associated lipodystrophy improve with therapeutic lifestyle change.
• Although metformin is shown to be useful with polycystic ovary syndrome, the data supporting drug therapy for the other syndromes is less convincing. More robust studies are needed before any firm recommendations can be made.
Psychosocial treatment: Important in both acute and maintenance phase

- Cognitive behavioral therapy (CBT) is used to target specific symptoms and improve related issues such as self-esteem, social functioning, and insight.
- More recent reviews clearly show CBT is an effective treatment for the psychotic symptoms of schizophrenia.
- Family Therapy or Education, which addresses the whole family system of an individual with a diagnosis of schizophrenia, has been consistently found to be beneficial, at least if the duration of intervention is longer-term.
- There is also some evidence for benefits from social skills training, although there have also been significant negative findings.
- Some studies have explored the possible benefits of music therapy and other creative therapies.
Course of Schizophrenia

- **Group 1**: One episode only—no impairment
  - 22%

- **Group 2**: Several episodes with no or minimal impairment
  - 35%

- **Group 3**: Impairment after the first episode with subsequent exacerbation and no return to normality
  - 8%

- **Group 4**: Impairment increasing with each of several episodes and no return to normality
  - 35%
เรารักษาผู้ป่วยโรคจิตต่ำนะคะเพื่อให้ผู้ป่วยครอบครัวและสังคมมีความสุขกันรักษาผู้ป่วยโรคจิตกันทั้งครอบครัวและสังคมมีความสุข

Department of Psychiatry
Suggested Reading


THANK YOU