10 Things I’ve Learned About Schizophrenia

Gary Remington, MD, PhD, FRCP
Schizophrenia Lead
Division of Brain & Therapeutics
Departments of Psychiatry and Psychological Clinical Science
Institute of Medical Science
School of Graduate Studies
University of Toronto

Chief, Schizophrenia Division
Lead, Subspecialty Clinics
Campbell Family Mental Health Research Unit
Centre for Addiction & Mental Health (CAMH)

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Industry
Consultant
Neurocrine Biosciences
Synchroneuron

Research
Novartis

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Learning Objectives
To consolidate and review some of the more substantial changes in terms of how we conceptualize schizophrenia.

1. D₂ antagonism is necessary (mostly), but not sufficient, for the treatment of the illness’ psychosis domain
Classification of Antipsychotics

First Generation
- D₂ Antagonism
  - Low Potency
    - Chlorpromazine
    - Thioridazine
    - Meso-derazine etc
  - High Potency
    - Haloperidol
    - Fluphenazine
    - Remoxipride etc

Second Generation
- 5-HT₂/D₂ Antagonism
  - Asenapine
  - Clozapine
  - Lurasidone
  - Olanzapine
  - Quetiapine
  - Risperidone
  - Sertindole
  - Ziprasidone
  - Zotepine
  - Amisulpride
  - Sulpiride
  - Remoxipride

Third Generation
- Partial Dopamine Agonism
  - Aripiprazole
  - Dissociation (Koff) 🌐

D₂ Occupancy, Clinical Response & EPS

Brain Kinetics of Clozapine on D₂ Receptors


Clozapine: Concomitant 5-HT₂/D₂ Antagonism

2. Schizophrenia is not a disorder of too much dopamine.

Prodrome: Most Common Features

- decreased concentration, attention
- decreased drive, motivation; anergia
- depression
- sleep disturbance
- anxiety
- social withdrawal
- suspiciousness
- deteriorated social functioning
- irritability

3. First episode psychosis represents the end of the illness

4. Schizophrenia is both neurodevelopmental and neuropgressive
Early Influences

Morel (1853)

Kraepelin (1896)

Neurodevelopmental vs. Neuroprogressive

Insel TR. Nature 2011; 468:187-193

Antipsychotic Re-challenge

Responsive to first AP trial and restarted on same medication at same dose (N=38)
5. Antipsychotics act sooner than later

Antipsychotic Depolarization Block

...antipsychotics must be administered repeatedly to schizophrenics before therapeutic benefits are produced...chronic antipsychotic drug treatment results in the time-dependent inactivation of dopamine neuron firing via over-excitation, or depolarization block.

Grace A. J Neural Transm 1992

Heterogeneity: Outcome


Weekly BPRS/PANSS Improvement

Agid et al. Archives of General Psychiatry 2003
6. Schizophrenia is characterized by subtypes mediated by different mechanisms

![Graph showing treatment response to subtype schizophrenia]


Treatment Response to Subtype Schizophrenia

Three Subtypes of Schizophrenia

![Diagram illustrating three subtypes of schizophrenia]

7. Treatment resistance has at least 2 forms


Antipsychotic Responsive, Clozapine Responsive, Clozapine Resistant

Response

AP 1 + 2 (N = 70 + 5)
Clozapine (N = 13)
Other (N = 12)
Ultraresistant Schizophrenia (URS) or Clozapine-Resistant Schizophrenia

<table>
<thead>
<tr>
<th>Published criteria</th>
<th>Proposed criteria for clozapine resistance</th>
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<tbody>
<tr>
<td>Adequate dose</td>
<td>Plasma levels &gt; 350 ng/mL for oral daily dose or &gt; 250 ng/mL for oral divided daily dose, or oral dose &gt; 400 mg/day</td>
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<tr>
<td>Adequate duration, weeks</td>
<td>8</td>
</tr>
<tr>
<td>No significant improvement</td>
<td>&lt;20% decrease on BPRS (URS) or CSID-SCH-positive change &gt; 2 (m = much improved)</td>
</tr>
<tr>
<td>Current illness severity</td>
<td>BPRS &gt; 48, CGI-S &gt; 6, and 4 or more of the 12 out of 4 positive items on the BPRS</td>
</tr>
<tr>
<td>Duration of illness with no good</td>
<td>5</td>
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</tbody>
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BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression—Severity; CSID-SCH = Clinical Global Impression—Schizophrenia

* Plasma levels should be taken after 5 days of unchanged clozapine dosing and 12 hours from last clozapine dose.


8. There are no effective treatments for cognitive and negative symptoms

Tolerance

Cognition in Schizophrenia

Harvey & Keefe. AJP 2001
Hagan & Jones. Schizophr Bull 2005

The advantages for these new medications (second generation antipsychotics) may have been overestimated...although there is some evidence that newer antipsychotics are effective for improving cognition, it is unclear that this advantage is sufficient to affect functional outcomes.

Negative Symptoms: Treatment

Comb – Combination; AD – Antidepressants; SGA – Second Generation Antipsychotics; FGA – First Generation Antipsychotics; BS – Brain Stimulation; Psych – Psychological; Glut – Glutamatergic agents

Fusar-Poli P et al. Schizophren Bull 2015

9. Clinical and functional recovery are not parallel events

Symptomatic vs Functional Outcome

Robinson et al. Am J Psychiatry 2004
Schooler J Clin Psychiatry 2006
10. Amongst well established side effects...
Conventional antipsychotics also carry substantial metabolic risk.

Glucose dysregulation is multi-factorial and, in part, independent of weight.

FSIGTT and Bergmann’s Minimal Model

- Overnight fast
- Glucose and insulin sampled at −20, −10 and −5 min
- Bolus of 50% glucose IV at 0 min
- IV insulin at 20 mins.
- Glucose and insulin sampled via indwelling catheter at 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 22, 24, 35, 37, 38, 40, 50, 60, 70, 80, 100, 120, 140, 160, 180 mins.
- Computer analysis of glucose disappearance and insulin kinetics
- Measure of insulin sensitivity (SI) and Acute Insulin Response to Glucose (AIRG)
And the good news....

- Numerous new doors open (e.g. TRS/URS, different symptom domains)
- Personalized medicine

- response subtype
- family history
- trajectory
- genetics
- symptoms
- prodrome
- values
- premorbid functioning
- substance abuse
- biomarkers
- adherence
- supports
- resilience
- onset
- premorbid symptomology