Schizophrenia: causes and treatment

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PGC SCZ wave3

65,205 cases and 87,919 controls

256 genome wide significant sites
Loci implicated include

- **DRD2** - antipsychotics
- Glutamate and GABA genes – which influence dopamine release
- Neurodevelopmental/cognitive genes
- Immune genes – response to infection/stress

**The Polygenic Risk Score**

Estimate any individual’s liability to schizophrenia by summing together their risk SNPs

Examine relationship to environmental factors
Striatal Dopamine Synthesis is Elevated in schizophrenia

Jauhar et al JAMA Psychiatry Dec 2017
Dopamine (DA) as the “Wind of Psychotic Fire”

When individuals are acutely psychotic, they show an excessive release of DA.

DA normally mediates the attachment of salience to ideas and objects.

Heightened DA transmission leads to aberrant assignment of salience to external and internal stimuli.

Delusions arise from attempts to explain this abnormal salience.

4. Maher, 1983
How can we make sense of schizophrenia?

“
“Meaningful connections are created between temporary coincident external impressions ... or perceptions with thoughts that happen to be present, or events and recollections happening to occur in consciousness at the same time”

Social factors that increase the risk of Psychosis.

Childhood adversity

Migration/ethnic minority

Bullying

Adverse life events/stress
If the Final Common Pathway to Psychosis is Striatal Dopamine Excess, can social factors cause this?
Increased Stress-Induced Dopamine Release in Psychosis

Romina Mizrahi, Jean Addington, Pablo M. Rusjan, Ivonne Suridjan, Alvina Ng, Isabelle Boileau, Jens C. Pruessner, Gary Remington, Sylvain Houle, and Alan A. Wilson

Biological Psychiatry, 2012, 71, 561-567

12 Ultra-high risk subjects (6.9%) and 10 drug-naïve schizophrenic patients (11.44%) showed greater release of dopamine* in Associative Striatum in response to Montreal Stress Test compared to 12 controls

* measured using (11C)-(+) - PHNO binding
Drug Use can also increase risk of psychosis by impacting on striatal dopamine
Risk of psychosis in relation to extent of cannabis use

OR = 4

Marconi et al. Schiz Bull 2016
The Final Common Pathway to Psychosis is Dopamine Dysregulation, **Social Factors and Drug Abuse** can cause this.

Stress, childhood abuse, Migration, and drug abuse all impact on striatal Dopamine

*Howes and Murray, Lancet, 2014*
Does the incidence of psychosis vary across Europe, and if so what causes this?
EUGEI study: 2011-2013
Incident First Episode Psychosis cases N=1130 & population controls N=1499
What is the explanation for the low rates in Italy/Spain?

Migration

Families v social isolation?

High Potency Cannabis
The effect of daily use of high-potency cannabis on the odds for psychotic was particularly visible in **London and Amsterdam**

*Adjusted for age, gender, ethnicity, level of Ed, employment status and other drugs (tobacco, alcohol, stimulants, Ketamine, Legal highs, Hallucinogenics).

Prevalence of daily cannabis use in population controls (%)

Adjusted psychosis incidence (rate per 100,000)

$r=0.8, p=0.0109$
Population Attributable Fraction

If nobody smoked high potency cannabis, 12% of all cases of first episode psychosis across Europe would be prevented, rising to 32% in London and 50% in Amsterdam

Drug Treatment:

- Dopamine synthesis capacity
- Dopamine release
- Antipsychotic
- Psychosis

Diagram shows the relationship between dopamine synthesis capacity, dopamine release, antipsychotic drug treatment, and the occurrence of psychosis.
But people need more than drugs

Psychological and social treatments are important
Cognitive Behaviour Therapy

Randomised controlled trials have shown that cognitive behavioural therapy (CBT) can be useful not just for anxiety and depression in patients with psychosis but also for modifying positive symptoms especially delusions.
Sensitised dopamine system

Dopamine release

Aberrant processing of stimuli

Paranoid interpretation

Psychosis

Acute Stress

Drug abuse

Reduce stress or drug use

Block dopamine

Biased cognitive schema

CBT

New Psychological Therapies eg Avatar

Howes & Murray *Lancet* 2014
Analysis

Should psychiatrists be more cautious about the long-term prophylactic use of antipsychotics?

Robin M. Murray, Diego Quattrone, Sridhar Natesan, Jim van Os, Merete Nordentoft, Oliver Howes, Marta Di Forti and David Taylor

Summary
Patients who recover from an acute episode of psychosis are frequently prescribed prophylactic antipsychotics for many years, especially if they are diagnosed as having schizophrenia. However, there is a dearth of evidence concerning the long-term effectiveness of this practice, and growing concern over the cumulative effects of antipsychotics on physical health and brain structure. Although controversy remains concerning some of the data, the wise psychiatrist should regularly review the benefit to each patient of continuing prophylactic antipsychotics against the risk of side-effects and loss of effectiveness through the development of supersensitivity of the dopamine D₂ receptor. Psychiatrists should work with their patients to slowly reduce the antipsychotic to the lowest dose that prevents the return of distressing symptoms. Up to 40% of those whose psychosis remits after a first episode should be able to achieve a good outcome in the long term either with no antipsychotic medication or with a very low dose.

Declaration of interest
R.M.M. and J.v.O. have received honoraria from Bristol-Myers Squibb, Janssen, Lilly, Roche, Servier and Lundbeck for lectures, and M.D.F. has received honoraria from Janssen and Lundbeck. O.H. has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organised by Astra-Zeneca, Autifony, Bristol-Myers Squibb, Eli Lilly, Heptares, Janssen, Lundbeck, Leyden Delta, Otsuka, Servier, Sunovion, Rand and Roche.

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Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy
Long-term Follow-up of a 2-Year Randomized Clinical Trial

Lex Wunderink, MD, PhD; Roeline M. Nieboer, MA; Durk Wiersma, PhD; Sjoerd Sytema, PhD; Fokko J. Nienhuis, MA

**IMPORTANCE** Short-term outcome studies of antipsychotic dose-reduction/discontinuation strategies in patients with remitted first-episode psychosis (FEP) showed higher relapse rates but no other disadvantages compared with maintenance treatment; however, long-term effects on recovery have not been studied before.

**OBJECTIVE** To compare rates of recovery in patients with remitted FEP after 7 years of follow-up of a dose reduction/discontinuation (DR) vs maintenance treatment (MT) trial.

### Table 2. Recovery, Symptomatic Remission, and Functional Remission After 7 Years of Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DR (n = 52)</th>
<th>MT (n = 51)</th>
<th>Total Sample (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>21 (40.4%)</td>
<td>9 (17.6%)</td>
<td>30 (29.1%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>36 (69.2%)</td>
<td>34 (66.7%)</td>
<td>70 (68.0%)</td>
</tr>
<tr>
<td>Functional</td>
<td>24 (46.2%)</td>
<td>10 (19.6%)</td>
<td>34 (33.0%)</td>
</tr>
</tbody>
</table>

Abbreviations: DR, dose reduction/discontinuation; MT, maintenance treatment.
1. “dopamine supersensitivity and functional tolerance to antipsychotics are due in part to changes in striatal dopamine receptor function”

2. “breakthrough” supersensitivity during antipsychotic treatment undermines treatment efficacy”
Neuroleptic-Induced Supersensitivity Psychosis: Clinical and Pharmacologic Characteristics

BY GUY CHOUINARD, M.D., M.SC. (PHARMACOL), AND BARRY D. JONES, M.D.

Review article

Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse

Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse.

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Haloperidol D2 occupancy – implications for dose reduction
Switching paliperidone to placebo – effect of formulation

Kim et al.
Poster presented at the 15th International Congress on Schizophrenia Research; March 28 – April 1, 2015; Colorado Springs, Colorado, USA