Why does clozapine work in Treatment Resistant Schizophrenia?

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What are the characteristics of people with first episode psychosis who go on to become treatment resistant?

**Systematic review** of prospective longitudinal studies identifying predictors of treatment-resistant schizophrenia from the first episode. 12 published studies identified

**Results:** Younger age of onset was the most consistent predictor.

Poor premorbid adjustment, being male, lower level of education, longer duration of untreated psychosis, poorer functioning, and worse psychopathology were also reported.
What are the **biological** characteristics of people with FEP who go on to become treatment resistant?

1. Copy number variants
2. More abnormalities on MRI scan
3. Neuropsychological deficits
Non-responders show no excess in dopamine synthesis

Demjaha et al, 2011
TRS patients seem to have normal dopamine synthesis and release?

Potkin et al, 2020
Treatment-resistant patients: normal dopamine but elevated glutamate in anterior cingulate

Some TRS patients may have a neurodevelopmental and predominantly glutamatergic disorder.
Putative Neurodevelopmental Form of Treatment Resistance from Onset

- Normal pre-synaptic dopamine
- Increased glutamate
- Family History of schizophrenia
- Obstetric complications
- Treatment Resistant Schizophrenia
- Premorbid functioning
- Age of onset
- Negative symptoms

Arsime Demjaha
There are two types of TRS.
1. The majority are resistant from first onset, and have characteristics suggestive of neurodevelopmental impairment

2. A minority respond initially but then become resistant. They are similar to responders at onset

Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses

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Essentially confirmed Demjaha findings in the GAP Cohort
But what causes later (secondary) treatment-resistance?

Either there is some progressive change which makes them become resistant

Or some external factor impacts on some patients to produce psychosis in the face of normal striatal dopamine?
“Long-term antipsychotic treatment causes the proliferation of dopamine receptor sites, accompanied by an exaggerated response to DA agonists and a decreased response to antipsychotics i.e. “the dopamine receptor population is supersensitive”\(^1\)

Subsequently confirmed by many others including **Dopamine Royalty**

“Breakthrough” Dopamine Supersensitivity during Ongoing Antipsychotic Treatment Leads to Treatment Failure over Time \(^2\)

Anne-Noël Samaha,\(^1\) Philip Seeman,\(^2,3\) Jane Stewart,\(^4\) Heshmat Rajabi,\(^4\) and Shitij Kapur\(^1,2\)

Dopamine Receptor Supersensitivity

**a. Dopamine supersensitivity**

**Before antipsychotic treatment**

**After treatment: dopamine supersensitivity**

**Presynaptic**

**Postsynaptic**

Potkin et al, 2020
Neuroleptic-Induced Supersensitivity Psychosis: Clinical and Pharmacologic Characteristics

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

Tardive dyskinesia is thought to result from neostriatal dopaminergic receptor supersensitivity induced by chronic treatment with neuroleptics. The authors suggest that dopaminergic supersensitivity also occurs in the mesolimbic region after chronic neuroleptic exposure. There is evidence from studies in both animals and humans which supports the theory of mesolimbic supersensitivity. In animal pharmacologic studies CNS tolerance to neuroleptic effect is well documented, and prolonged exposure to neuroleptics leads to increased drug requirements to block the behavioral effects of dopamine.

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Dopamine supersensitivity in treatment-resistant schizophrenia

Tomotaka Suzuki a,b, Nobuisa Kanahara a, Hiroshi Kimura a, Hiroyuki Watanabe a,c, Toyoaki Hirata b, Makoto Asano b, Masaomi Iyo a

Impact of dopamine supersensitivity psychosis in treatment-resistant schizophrenia: An analysis of multi-factors predicting long-term prognosis

Hiroshi Yamanaka a,b, Nobuisa Kanahara a,c, Tomotaka Suzuki a,d, Masayuki Takase a, Toshihiro Moriyama b, Hiroyuki Watanabe a,c, Toyoaki Hirata b, Makoto Asano b, Masaomi Iyo a
John Kane’s demonstration that clozapine is superior to chlorpromazine in Treatment Resistant Schizophrenia

![Graph showing mean change from baseline in total score on Brief Psychiatric Rating Scale (BPRS) for patients treated with clozapine (solid line, n = 126) or chlorpromazine and benztrapine mesylate (broken line, n = 139). P < .001 during each week of study.]

**Table 6.**—No. of Patients Whose Condition Improved*

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. (%) of Patients Whose Condition Improved</th>
<th>All Others, No. (%)</th>
<th>Total, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>38 (30)</td>
<td>88 (70)</td>
<td>126 (100)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>5 (4)</td>
<td>136 (96)</td>
<td>141 (100)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>43 (16)</strong></td>
<td><strong>224 (84)</strong></td>
<td><strong>267 (100)</strong></td>
</tr>
</tbody>
</table>

*The categorization is based on the last evaluation completed for each patient. P < .001 by two-tailed Fisher’s exact test.

Clozapine is a weak $D_2$ blocker but has multiple other actions
Anxiolytic effects

Partly GABAergic, partly antihistaminic and partly 5HT$_{1a}$
Antidepressant - clozapine was based on the imipramine molecule and was originally developed as an antidepressant.

$5\text{-HT}_{2A}$ antagonism is associated with antidepressant effect. $5\text{-HT}_{1A}$ agonism also has antidepressant effects.
Some apparently TRS patients abuse drugs, and many smoke tobacco – these are known to cause $D_2$ supersensitivity.

Clozapine has been shown to decrease craving and drug/nicotine use.
None of these characteristics are unique to clozapine.
Clozapine doesn't work better than other antipsychotics at first episode


Figure 2 Kaplan–Meier remission survival plots for time to first remission for CPZ (broken line) and CLZ (solid line) groups. The median time to remission in the CLZ group was 8 and 12 weeks in the CPZ group.
A drug which doesn’t work especially well in first episode cases but does so in resistant cases – very odd!

How can this be?

Clozapine must be targeting some change that has taken place
Clozapine is an effective treatment for tardive dyskinesia, a supersensitivity disorder of the motor areas.

“Clozapine produces lower and more transient D2/D3 receptor occupancy than most other antipsychotics. This allows the dopamine supersensitivity of the motor system to gradually resolve, and tardive dyskinesia to slowly fade. Is it possible that the effectiveness of clozapine for some patients with TRS relies on a similar mechanism?”

Is this why clozapine works in TRS?

Psychother Psychosom
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Reversal of Dopamine Supersensitivity as a Mechanism of Action of Clozapine

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Prior to the trial, all patients received at least 60 mg haloperidol daily for 6 weeks to ensure resistance. This is likely to have induced D2 supersensitivity if they did not already have it.
Why does clozapine work in TRS?

- Clozapine has anxiolytic and antidepressant actions
- Clozapine has anti-craving effects on illicit drugs and smoking
- Clozapine may have useful glutamatergic actions
- Clozapine doesn’t make negative symptoms worse

Clozapine’s unique fast-on/fast-off effects on the D$_2$ receptor may enable D2 supersensitivity to normalize, and thus reverse the iatrogenic complications which we have caused.