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.

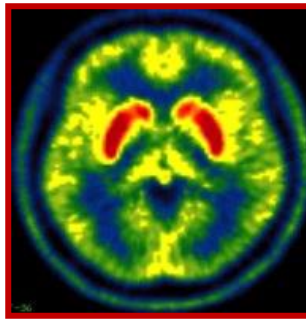
Poor premorbid adjustment, being male, lower level of education, longer duration of untreated psychosis, poorer functioning, and worse psychopathology were also reported.

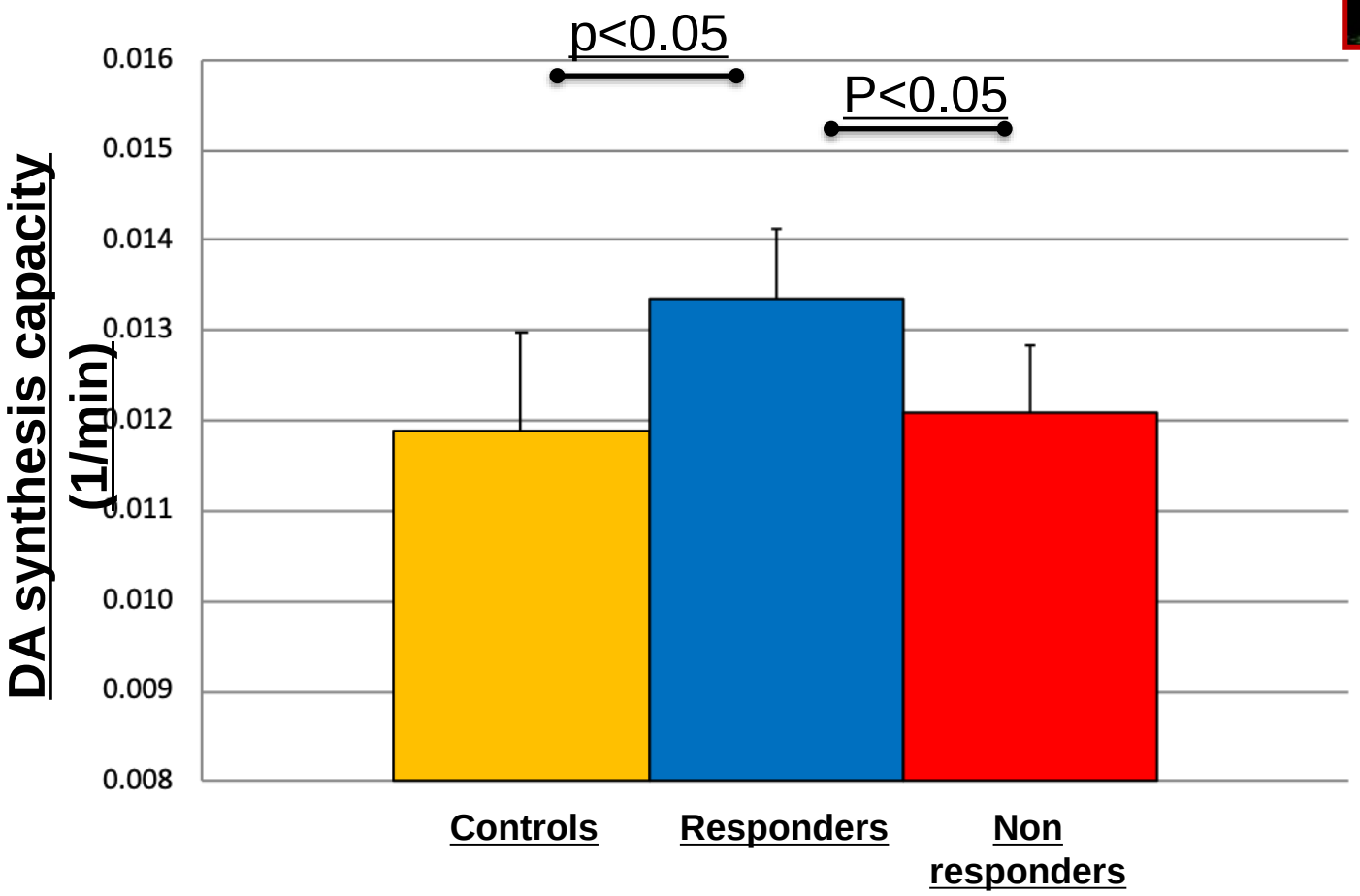
S E Smart, A P Kępińska, R M Murray, J H MacCabe
Psychological Medicine 2019 Aug 29;1-10.

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

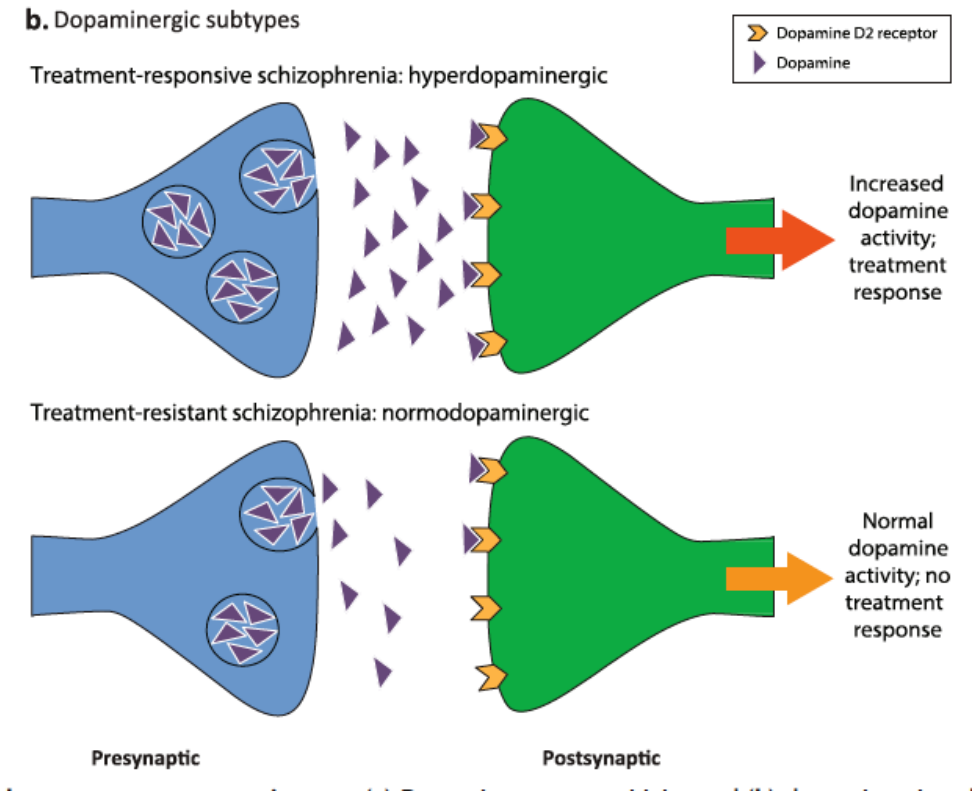
Non-responders show no excess in dopamine synthesis





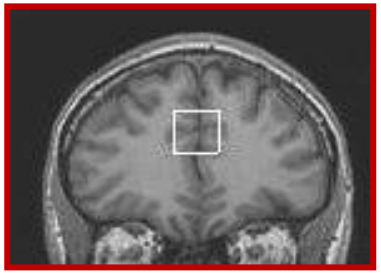
Demjaha et al, 2011

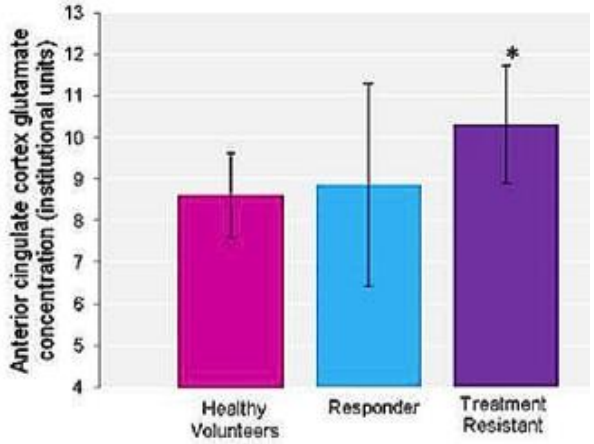
TRS patients seem to have normal dopamine synthesis and release?



Potkin et al, 2020

Treatment-resistant patients: normal dopamine but elevated glutamate in anterior cingulate

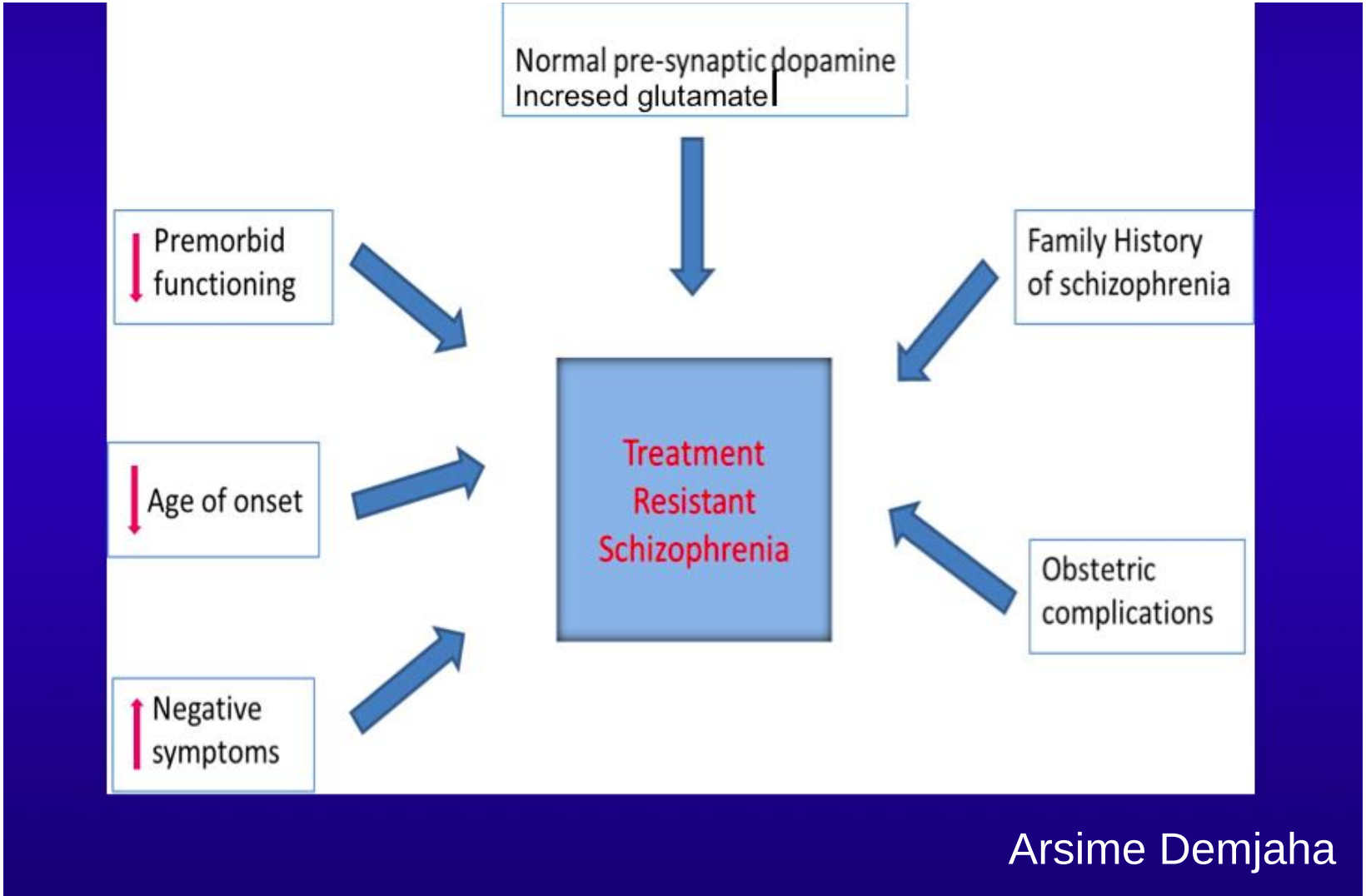




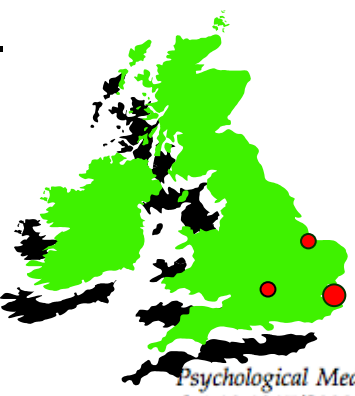
Demjaha A, *et al. Am J Psychiatry* 2012;**169**:1203–10;
Egerton A, *et al. Biol Psychiatry* 2013;**74**:106–12.

Some TRS patients may have a neurodevelopmental and predominantly glutamatergic disorder

Putative Neurodevelopmental Form of Treatment Resistance from Onset



Arsime Demjaha



Psychological Medicine, Page 1 of 9. © Cambridge University Press 2017
doi:10.1017/S0033291717000435

ORIGINAL ARTICLE

Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors

A. Demjaha[1]*†, J. M. Lappin[2]†, D. Stahl[3], M. X. Patel[1], J. H. MacCabe[1], O. D. Howes[1,4], M. Heslin[5], U. A. Reininghaus[1], K. Donoghue[6], B. Lomas[1], M. Charalambides[1], A. Onyejiaka[1], P. Fearon[7], P. Jones[8], G. Doody[9], C. Morgan[1,10]‡, P. Dazzan[1,2]‡ and R. M. Murray[1]‡

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

Demjaha A, *et al. Psychol Med* 2017;**47**:1981–9

Psychological Medicine (2016), **46**, 3231–3240. © Cambridge University Press 2016
doi:10.1017/S0033291716002014

ORIGINAL ARTICLE

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

J. Lally[1,2,3]*†, O. Ajnakina[1]†, M. Di Forti[4], A. Trotta[1], A. Demjaha[1], A. Kolliakou[6], V. Mondelli[5,6], T. Reis Marques[1], C. Pariante[5,6], P. Dazzan[1,5], S. S. Shergil[1,2,5], O. D. Howes[1,7], A. S. David[1,5], J. H. MacCabe[1,2], F. Gaughran[1,2]‡ and R. M. Murray[1,2]‡

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]

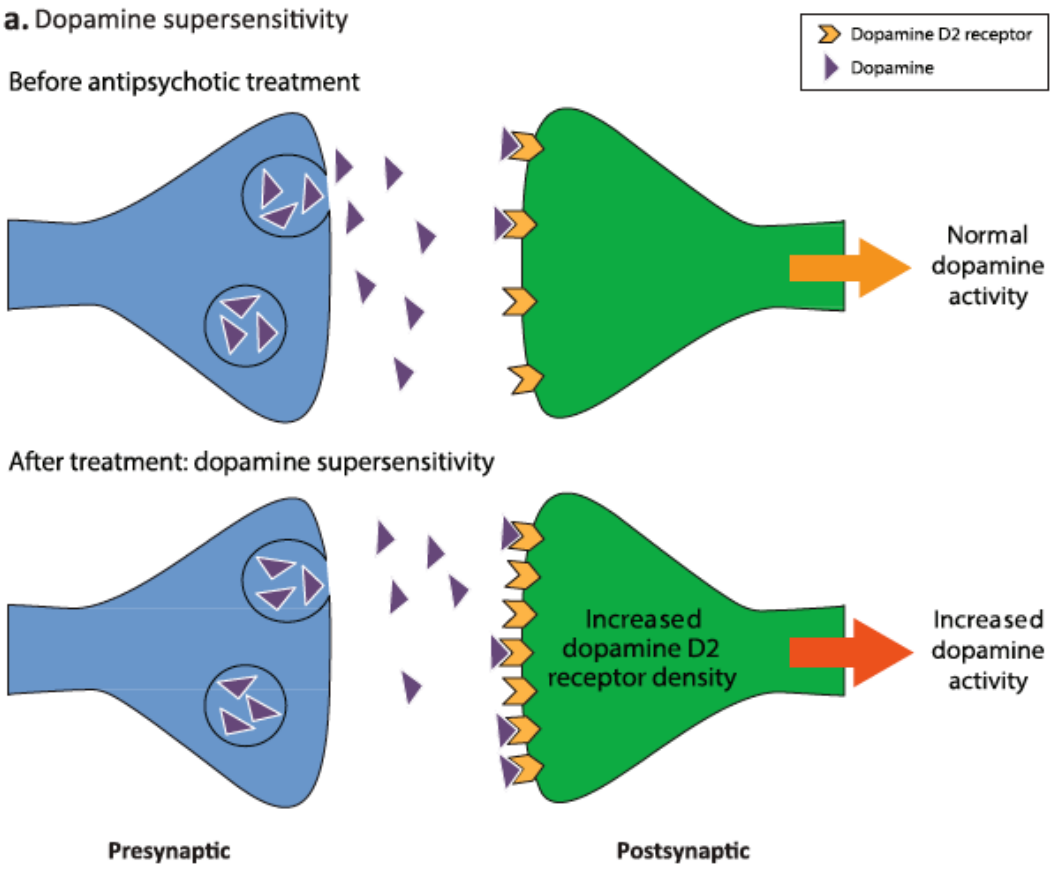
Subsequently confirmed by many others including **Dopamine Royalty**

"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]

Rupniak NMJ, *et al. Life Science* 1983;**32**:2289–31;
Samaha, *et al. J Neurosci* 2007;**27**:2979–86

Dopamine Receptor Supersensitivity



Potkin et al, 2020

Neuroleptic-Induced Supersensitivity Psychosis: Clinical and Pharmacologic Characteristics

BY GUY CHOUINARD, M.D., M.SC. (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 a supersens

There is evidence from studies in both animals and humans which supports the theory of mesolimbic su persensitivity. In animal pharmacologic studies CNS tolerance to neuroleptic effect is well documented, and prolonged exposure to neuroleptics leads to increased dosage requirements to block the behavioral effects of

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Dopamine supersen
in treatment-resist

Tomotaka Suzuki [a,b], Nob
Hiroshi Kimura [a], Hiroyu

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

Hiroshi Yamanaka [a,b], Nobuhisa 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

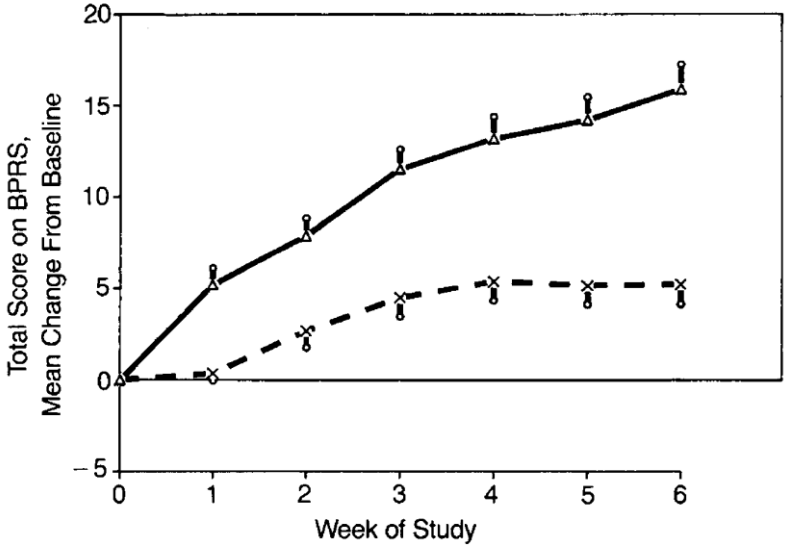


Fig 2.—Mean change from baseline in total score on Brief Psychiatric Rating Scale (BPRS) for patients treated with clozapine (solid line, n = 126) or chlorpromazine and benztropine mesylate (broken line, n = 139). $P < .001$ during each week of study.

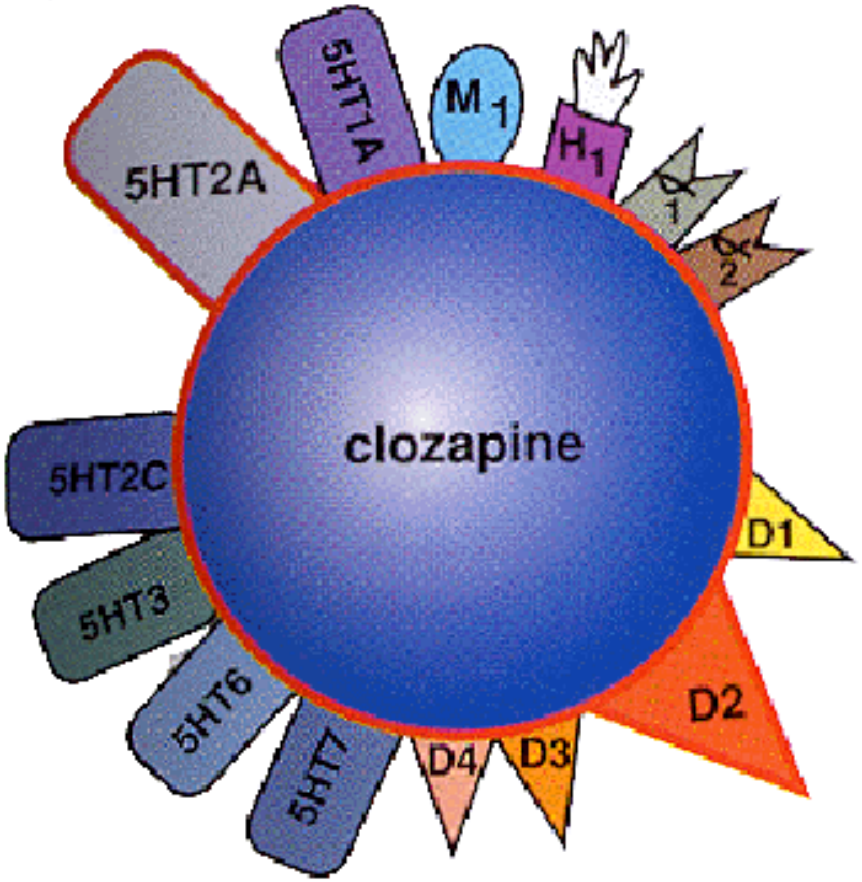
Table 6.—No. of Patients Whose Condition Improved*

Drug	No. (%) of Patients Whose Condition Improved	All Others, No. (%)	Total, No. (%)
Clozapine	38 (30)	88 (70)	**126 (100)**
Chlorpromazine	5 (4)	136 (96)	**141 (100)**
Total	**43** (16)	**224** (84)	**267 (100)**

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

Kane J, Honigfeld G, Singer J et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988; 45: 789-796

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-HT_{2A} antagonism is associated with antidepressant effect. 5-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 doesnt work better than other antipsychotics at first episode

Lieberman JA, Phillips M, Gu H, et al.
Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. Neuropsychopharmacology 2003; **28**:995-1003.

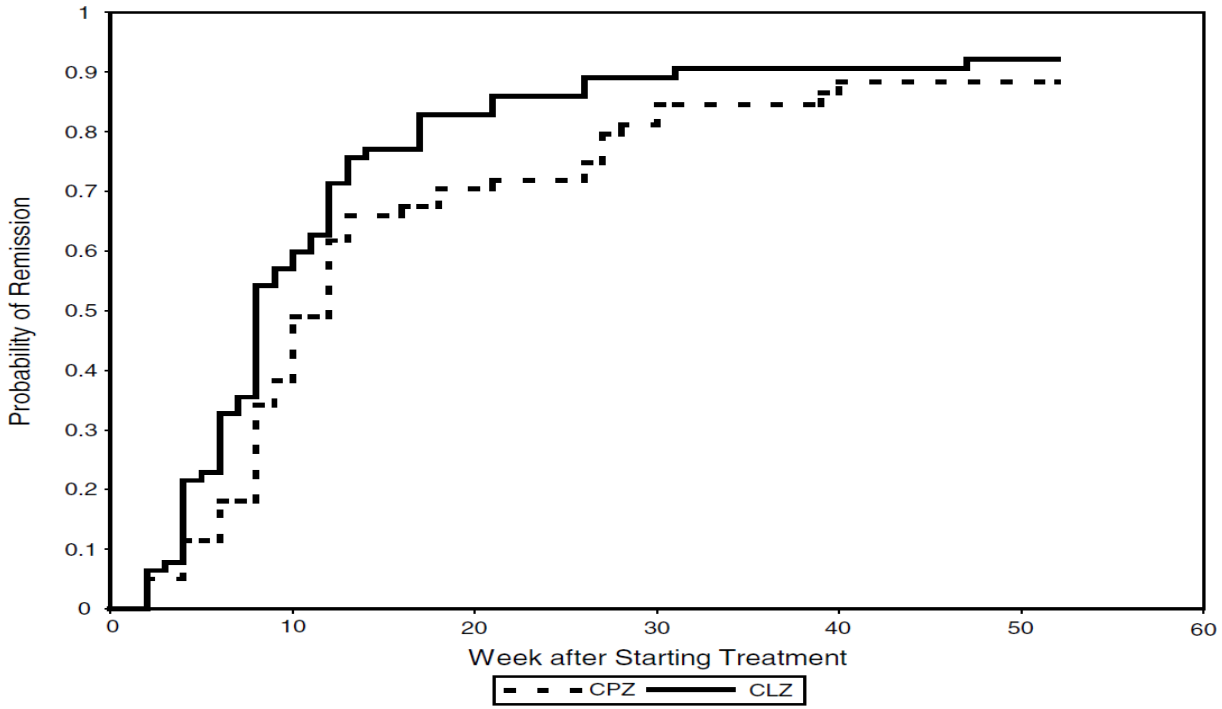


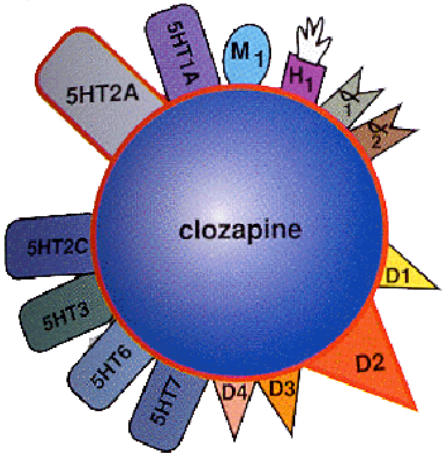
Figure 2 Kaplan–Meier remission survival plots for time to first remission for CPZ (broken line) and CLZ (solid line) groups. The median time to remission in the CLZ group was 8 and 12 weeks in the CPZ group.

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?"

Murray et al British Journal of Psychiatry , 2016, 209 , pp. 361 - 365

Is this why clozapine works in TRS?

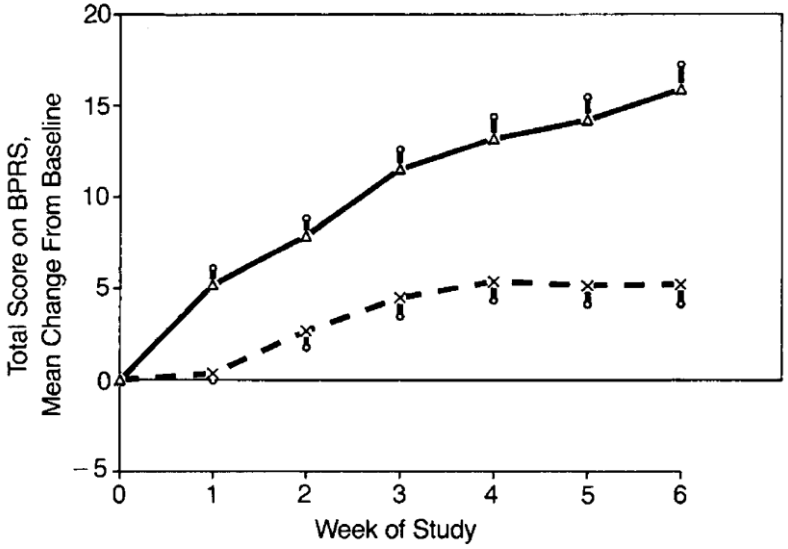
Psychother Psychosom
DOI: 10.1159/000491700

Reversal of Dopamine Supersensitivity as a Mechanism of Action of Clozapine

David D. Kim[a] *Alasdair M. Barr*[a] *William G. Honer*[b] *Ric M. Procyshyn*[b]

[a]Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada; [b]Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada

Kane J, Honigfeld G, Singer J et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988; 45: 789-796



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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