

# TREATMENT RESISTANT SCHIZOPHRENIA

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# DISCLOSURE

- No financial disclosure

# OUTLINE

- Discuss case of patient with treatment resistant Schizophrenia (TRS)
- Definitions and epidemiology
- Factors contribute for treatment resistance
- Treatment options
- Clozapine efficacy and augmentation Strategies
- Revisiting Loxapine
- Efficacy of Loxapine as an adjuvant in this case

# CASE DETAILS

- 18 years old African American Female brought to Emergency Department by grandmother for disorganized behavior
- Agitated
- Assaulted staff
- Endorsed-
  - married to Jesus
  - having devil's baby
  - raped by several hip-hop artists.

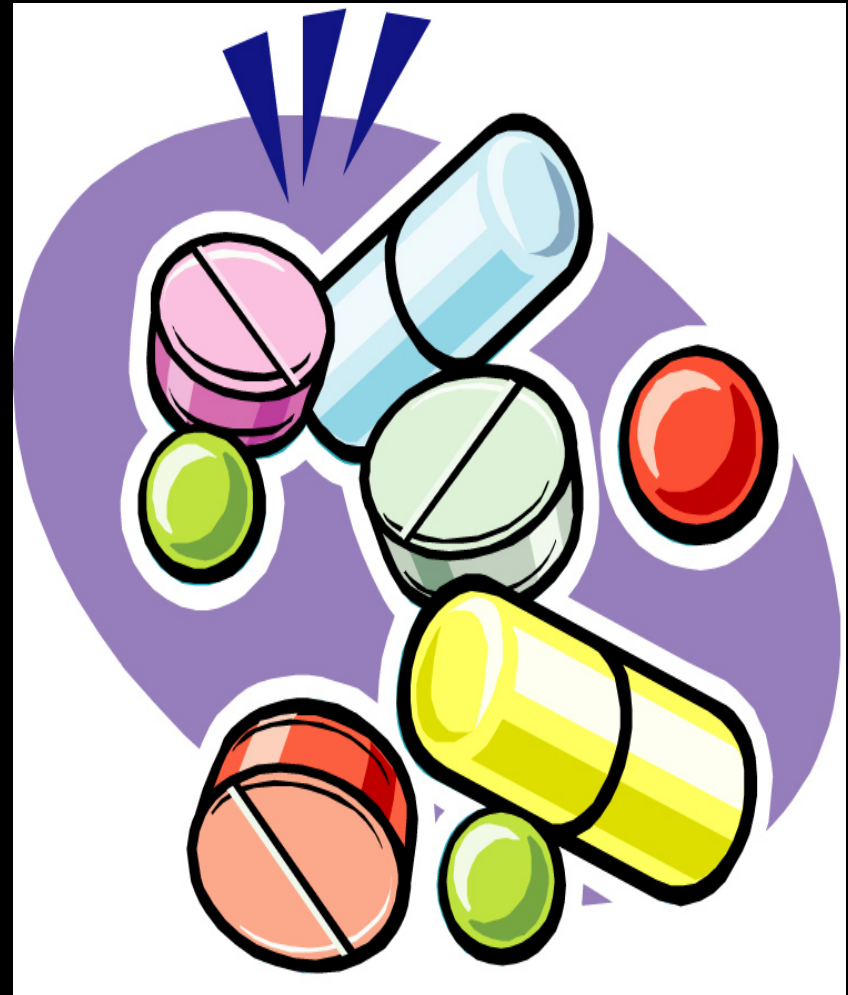
# PAST PSYCH HISTORY

- **Diagnosed** with Schizophrenia, Paranoid type at age 12
- **Social History:** Raised by Grandmother, Father incarcerated, mother possible substance use, in high school, no specialized education
- **Trauma-** per pt, starved by grandmother, raped by male family members while growing up, Grandmother denies, unable to confirm
- No brain injuries or seizures in past, no imaging available
- **Substance Abuse-** negative
- **Family History-** not significant
- **Multiple** Hospitalizations & failed antipsychotic trials including,

# MEDICATION TRIALS

- **Meds**

- Olanzapine 10 mg
  - Chlorpromazine 400 mg
  - Lurasidone 40mg
  - Quetiapine unknown dose
  - Lithium unknown dose
  - Valproic Acid 2000 mg
- 
- On **Clozapine 300 mg**,
    - d/c ed after ANC – 1.9→1.4



# HOSPITAL COURSE

- ALL LABS within normal limits
- Constant 1:1 –
  - hypersexual
  - agitated
  - delusional
  - responding to internal stimuli
- Poor hygiene

# INTERVENTIONS~12 MONTHS

Medications/Procedures	Max Daily Dose
Olanzapine	40 mg
Valproic Acid	1500 mg
Haloperidol	10 mg
Temazepam	30 mg
Clonazepam	4 mg
Propranolol	75 mg
Gabapentin	1200 mg
Quetiapine	500 mg
Ziprasidone	160 mg
Risperidone	1 mg – (EPS)
Lithium	900 mg
Loxapine	100 mg
<b>ECT</b>	12 sessions



# DISCHARGED

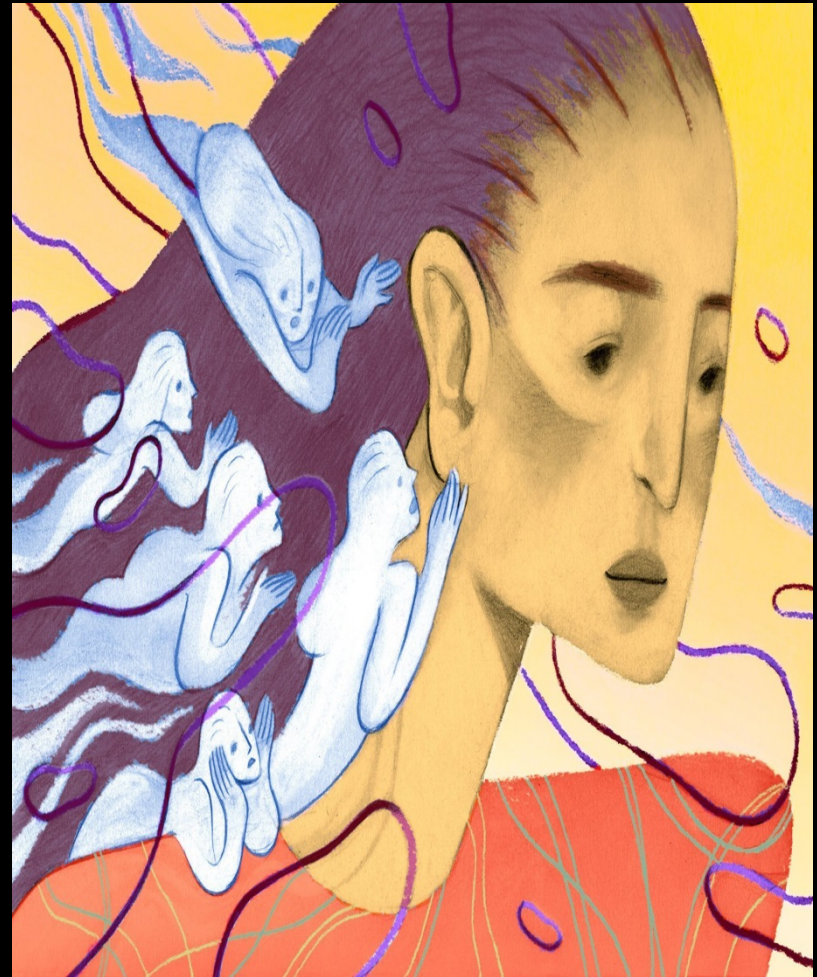
- 60-70% improvement in behavior
- Discharge meds:
  - Lithium 450 mg twice a day (level 0.59)
  - Loxapine 50 mg twice a day
  - Propranolol 20 mg three times a day
  - Trazodone 100 mg at night
  - Benztropine 0.5 mg daily

# WITHIN HOURS

- Brought Back for hitting grandmother

## Endorsing:

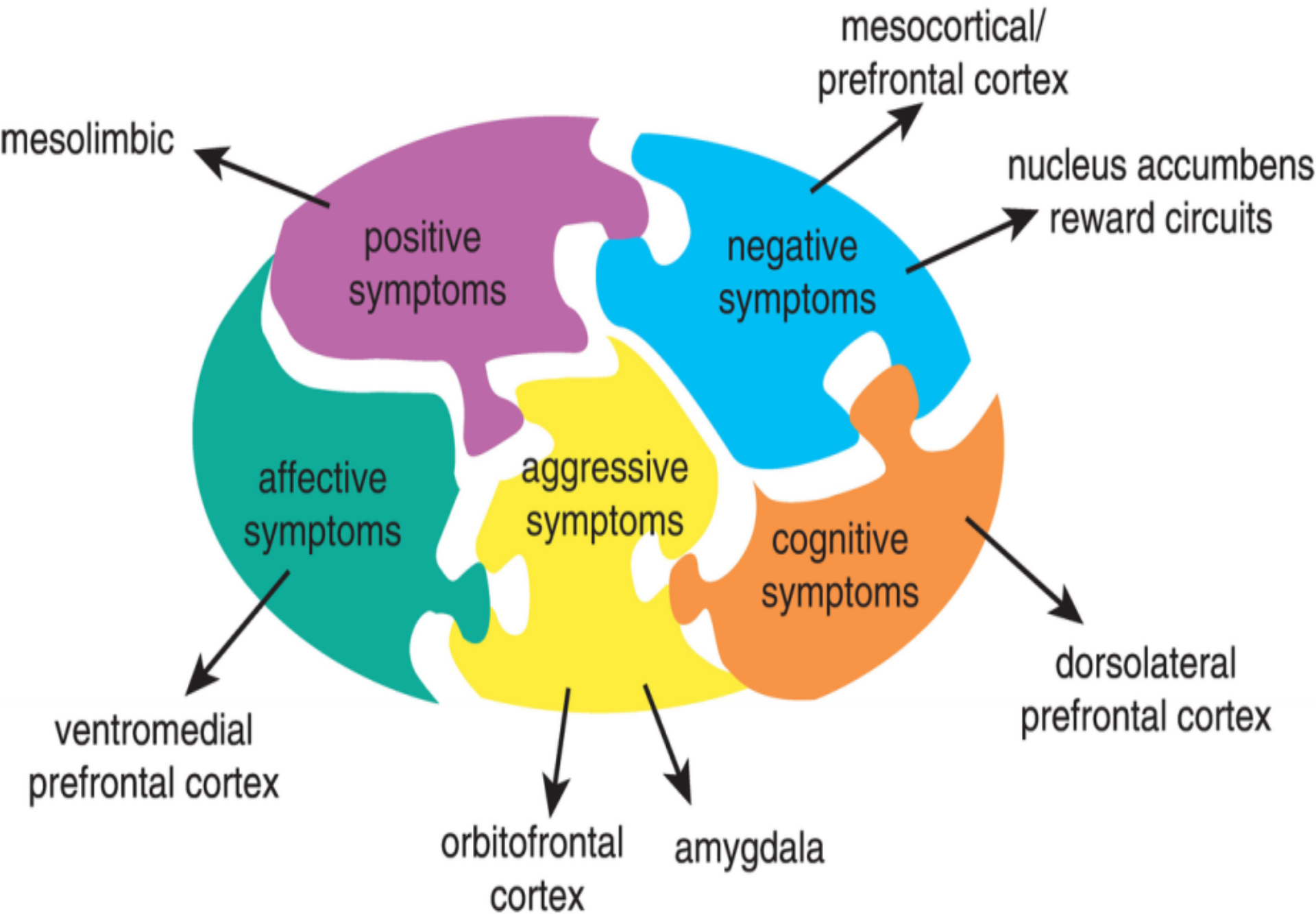
- Angels talking to her
- claimed to be hip hop artist
- have lots of money






# STATE UNIT

- Married to Angels, Husband-President Obama
- Hearing Angels talking to her, asking her not to take bath
- Seeing Demons in Room & Shower
- Isolative in room





# MINIMAL IMPROVEMENT

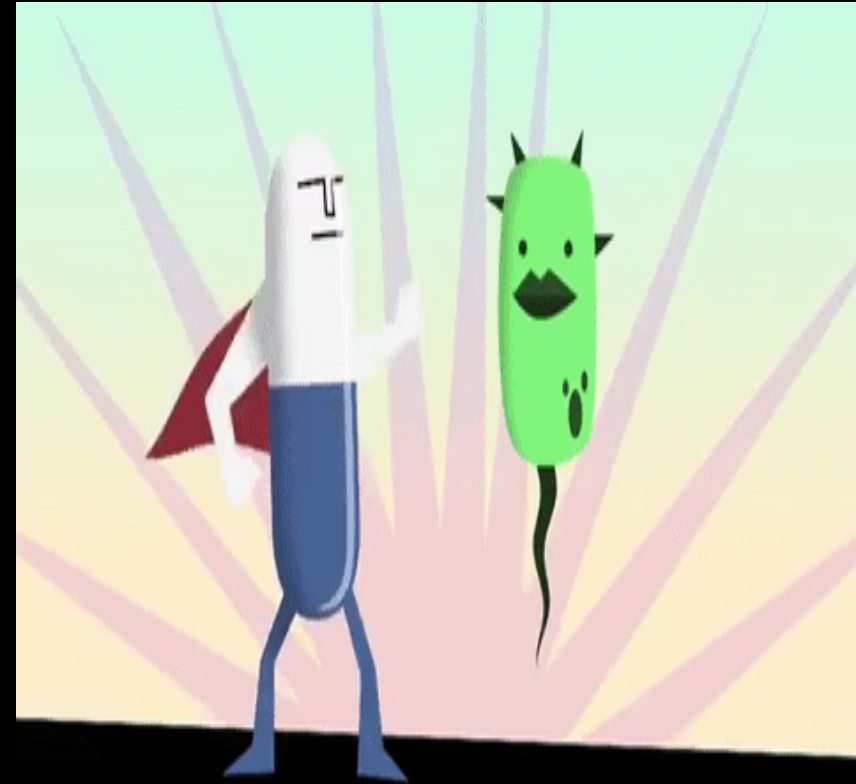
Medications	Highest Dose/Day
 Fluphenazine; fluphenazine decanoate	15 mg, 75 mg IM q2wks
Clozapine	Titration Protocol – ANC 1.4 (d/c)
 Haloperidol; haloperidol decanoate	15 mg, 300 mg IM q4 wks
Lurasidone	80 mg
Risperidone	6 mg
 paliperidone palmitate	156 mg x q4 weeks
Ziprasidone	160 mg
Quetiapine	600 mg
Olanzapine	45 mg
Aripiprazole	30 mg
Valproic Acid	1500 mg
Lithium	1350 mg

# AUGMENTED WITH

Other Medications	Highest Dose/Day
Lorazepam	3 mg
Clonazepam	1 mg
Fluoxetine	20 mg
Sertraline	50 mg
Propranolol	160 mg

# TREATMENT RESISTANT SCHIZOPHRENIA

- 1/3 (20-60%) of patients with schizophrenia
- Since introduction of Chlorpromazine
- Criteria first used by Kane et al (1988)
- $\geq 2$  different chemical classes,  $\geq 3$  periods of Tx each for 6 weeks (4-10), at dosages  $\geq 1000$  mg/day of chlorpromazine, in last 5 years
- each without significant symptomatic relief or good functioning; or  $<20\%$  improvement in BPRS scores



# BRENNER'S CRITERIA (1990)

Levels	Resistance	Symptoms	BPRS (18/24 item)
1	Clinical Remission	None	None >2
2	Partial remission	Mild Residual	None >3
3	Slight resistance	Incomplete Reduction	Only 1 item >4
4	Moderate resistance	Some reduction	2 items>4, Total 45/60
5	Severe resistance	Mild reduction	1>5 or 3>4; Total 50/67
6	Refractory	Slight Reduction	1>6 or 2>5; Total 50/67
7	Severely refractory	No Reduction	1>7; Total >50/67



**Table 1. Guidelines for Defining Treatment-Resistant Schizophrenia**

Guidelines	Prior AP Treatment Failure	Treatment Duration	Failure Criteria
APA (2004) <sup>9</sup>	≥ 2 Failures ≥ 1 Second-generation AP	≥ 6 wk	Little or no symptomatic response to a trial of adequate duration and dose (therapeutic range)
NICE (2014) <sup>2</sup>	≥ 2 Sequential failures ≥ 1 Nonclozapine second-generation AP	4–6 wk	Illness has not responded adequately despite established adherence to AP medication, prescribed at an adequate dose and for the correct duration
WFSBP (2012) <sup>18</sup>	≥ 2 Failures ≥ 2 Different chemical classes ≥ 1 Atypical AP	2–8 wk	No significant improvement in the psychopathology and/or target symptoms; ensured treatment adherence
TRRIP <sup>a</sup> (2017) <sup>17</sup>	≥ 2 Different APs ≥ 1 Prior treatment with long-acting injectable AP (≥ 4 mo)	≥ 6 wk (at therapeutic dose)	At least moderate disease severity and < 20% symptom reduction during a prospective trial or observation of ≥ 6 weeks; at least moderate functional impairment based on a validated scale; adherence (≥ 80% of prescribed doses) confirmed using trough serum AP levels

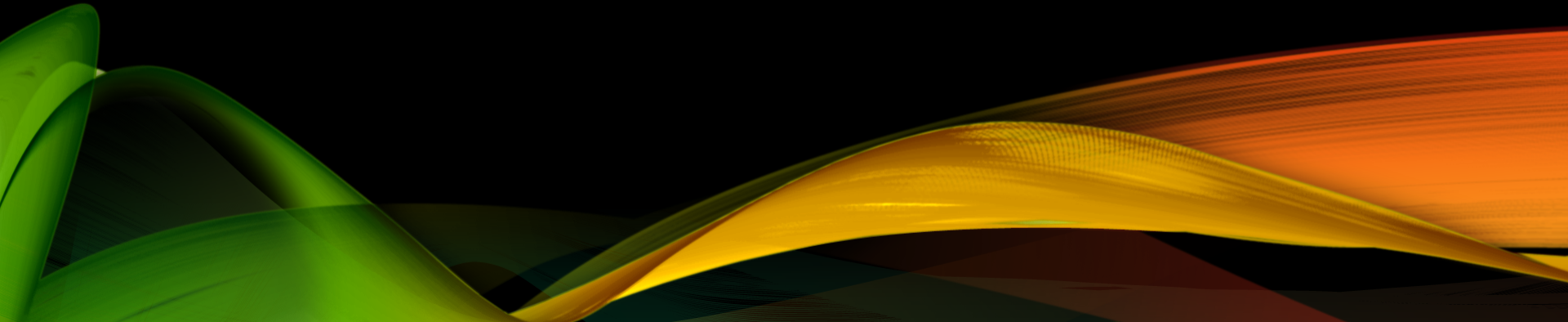
<sup>a</sup>Based on recommendations for optimum requirements.

Abbreviations: AP = antipsychotic, APA = American Psychiatric Association, NICE = National Institute for Health and Care Excellence, TRRIP = Treatment Response and Resistance in Psychosis, WFSBP = World Federation of Societies of Biological Psychiatry.

## Table 2. Burden of Treatment-Resistant Schizophrenia

Patient	Treatment Team	Family/Caregiver
<ul style="list-style-type: none"><li>• More severe positive and negative symptoms<sup>33</sup></li><li>• Worse neurocognitive functioning<sup>34</sup></li><li>• Higher health care costs<sup>35</sup></li><li>• Lower employment rates</li><li>• Lower quality of life</li><li>• Lower levels of community functioning<sup>33</sup></li></ul>	<ul style="list-style-type: none"><li>• Pessimism</li><li>• Therapeutic nihilism</li><li>• Lack of intellectual curiosity</li><li>• No specialized treatment teams</li></ul>	<ul style="list-style-type: none"><li>• Substantial amounts of time and income devoted to patient care-related activities<sup>36</sup></li><li>• Negative impact on the family/dissolution of the family<sup>37</sup></li></ul>

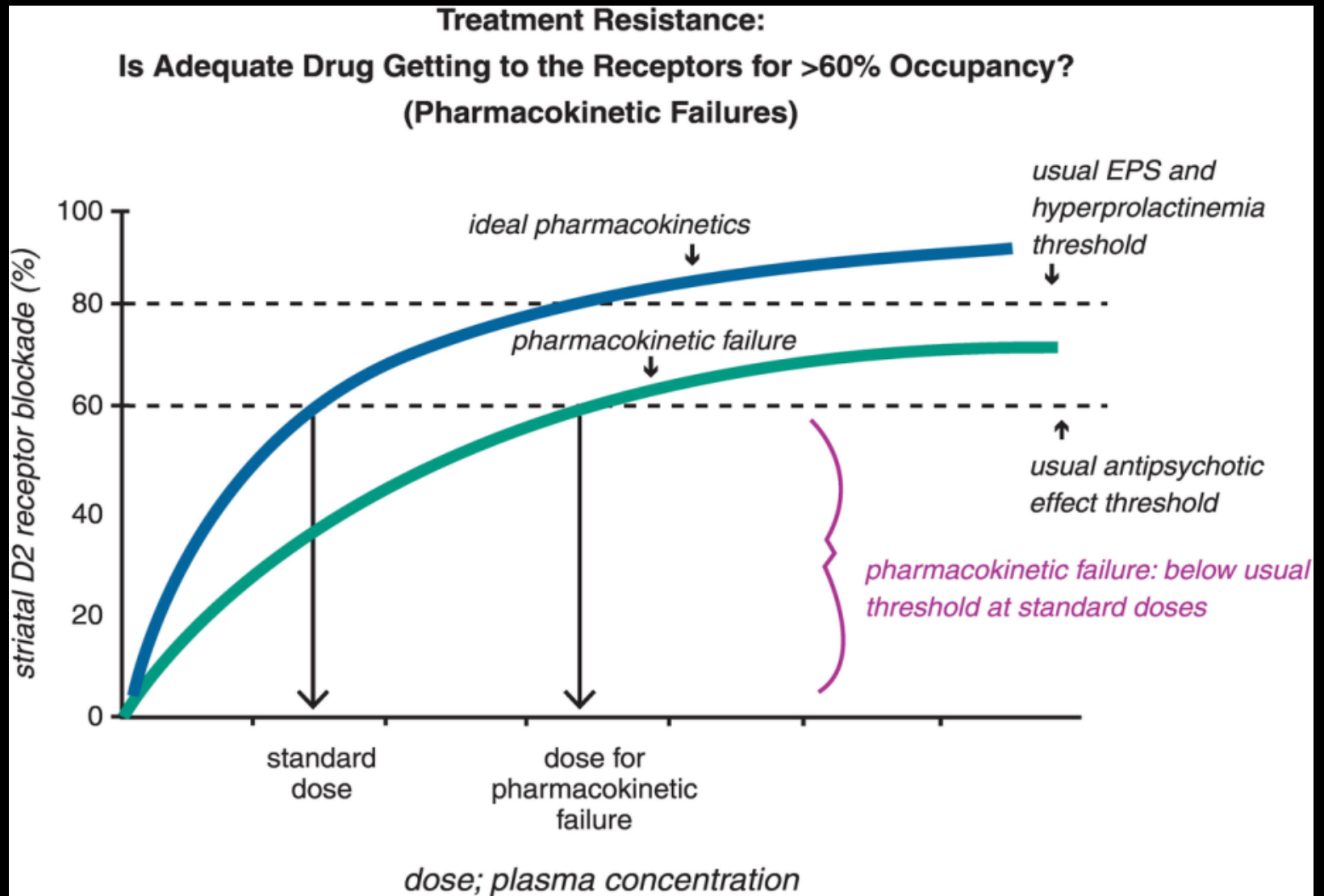
# **FACTORS CONTRIBUTING TO RESISTANCE**




# TWO PLAUSIBLE HYPOTHESIS

- 1) Dopamine (D2) receptors super sensitivity to dopamine
  - prolonged blockade of postsynaptic dopamine receptors by treatment leads to upregulation of receptors
  - increased psychotic symptoms (**breakthrough psychosis**) and motor side effects such as abnormal involuntary movements (eg, **tardive dyskinesia**) in treated patients.
- 2) “normodopaminergic” hypothesis
  - other neurotransmitter systems contribute to the symptoms
  - **High** concentrations of anterior cingulate **glutamate metabolite**
  - Another potential pathway, **N-methyl-D-aspartate (NMDA) antibody psychosis**, diagnosed with a positive antibody titer to the NR1 subunit of the NMDA receptor.

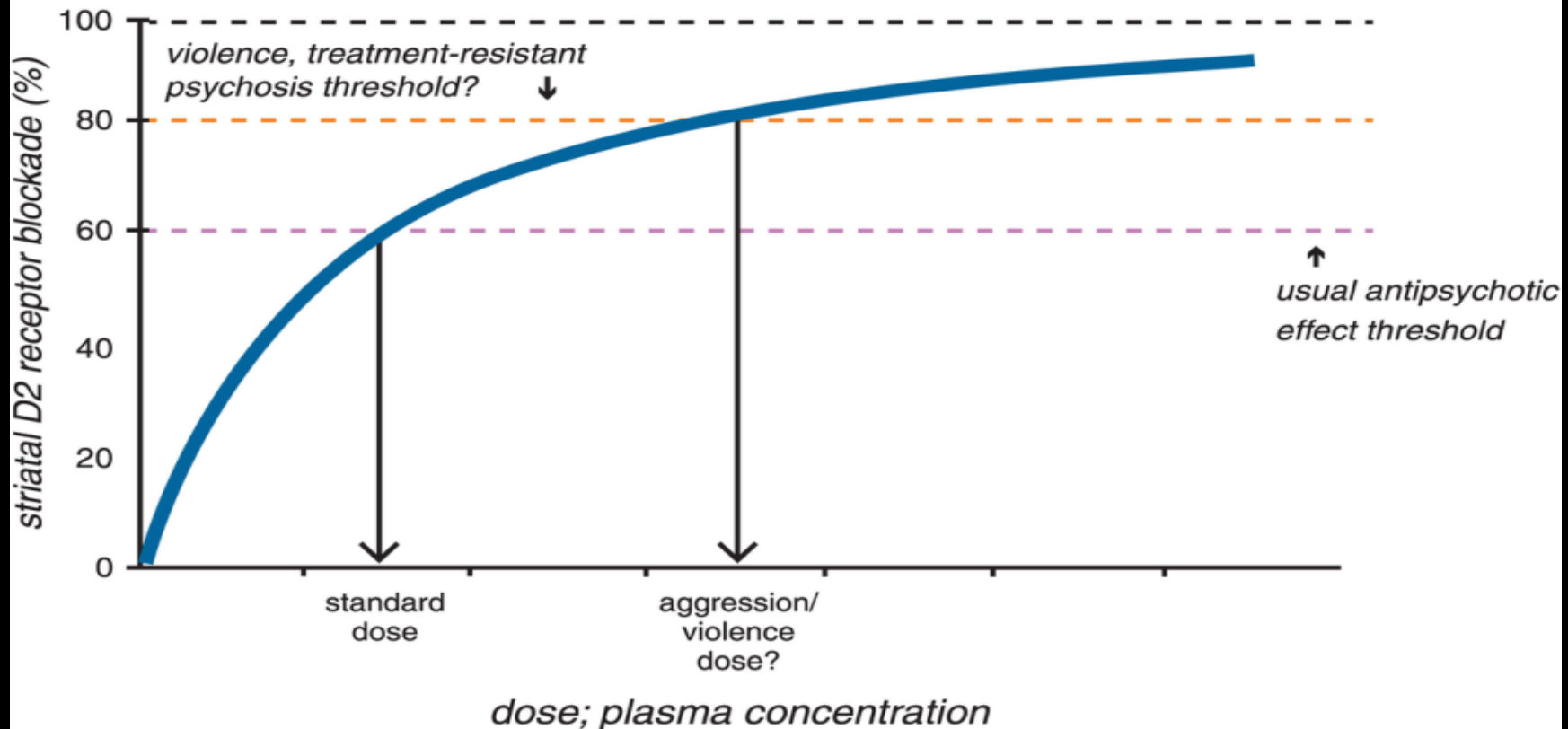
# PHARMACOKINETIC FAILURE



- 
- Poor drug absorption
  - Certain CYP450 variants- rapid metabolizers
  - Suspect- No Effect & no Side Effect
  - Confirm- Therapeutic drug levels

# PHARMACODYNAMIC FAILURE

## Violence and Treatment-Resistant Psychosis: Are Hypothetical Thresholds for Atypical Antipsychotic Drug Effects Altered? (Pharmacodynamic Failure?)

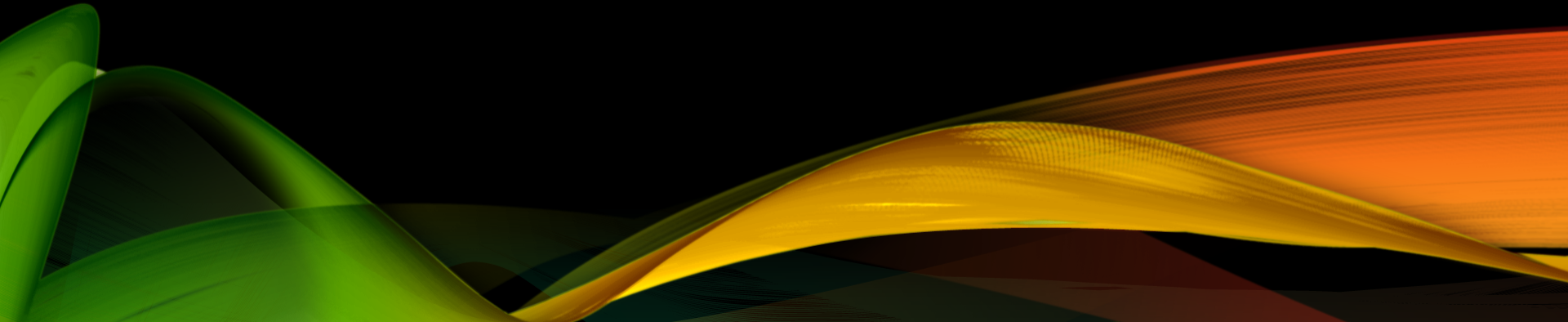


- **Slow responders**, late onset responders
- “time as a drug” and **treat for many weeks** – hoping to get a good outcome
- No way to predict
- **trial and error.**





# TREATMENT OPTIONS FOR RESISTANT SCHIZOPHRENIA



# Randomized controlled trials of antipsychotic monotherapy in treatment-refractory schizophrenia

Author and year	Study duration (weeks)	Number randomized	Antipsychotic	Efficacy*
Kane 1988 [11]	6	268	Clozapine	Clozapine > chlorpromazine
Pickar 1992 [12]	Varied	21	Clozapine	Clozapine > fluphenazine or placebo
Breier 1994 [13]	10	39	Clozapine	Clozapine > haloperidol
Kumra 1996 [14]	6	21 children	Clozapine	Clozapine > haloperidol
Hong 1997 [15]	12	40	Clozapine	Clozapine > chlorpromazine
Rosenheck 1997 [16]	1 year	423	Clozapine	Clozapine > haloperidol
Buchanan 1998 [17]	10	75	Clozapine	Clozapine > haloperidol
Kane 2001 [18]	29	71	Clozapine	Clozapine > haloperidol
Volavka 2002 [10]	14	157	Clozapine, olanzapine or risperidone	Clozapine ~ olanzapine > risperidone > haloperidol
McEvoy 2006 [9]	NA	99	Clozapine	Clozapine ~ olanzapine >

# Randomized controlled trials of antipsychotic monotherapy in treatment-refractory schizophrenia

Author and year	Study duration (weeks)	Number randomized	Antipsychotic	Efficacy*
Bondolfi 1998 [19]	8	86	Risperidone	Risperidone ~ clozapine
Wirshing 1999 [20]	8	67	Risperidone	Risperidone > haloperidol (at 4 weeks but not 8 weeks)
Breier 1999 [21]	6	29	Risperidone	Risperidone < clozapine
Wahlbeck 2000 [22]	10	19	Risperidone	Risperidone ~ clozapine
Azorin 2001 [23]	12	273	Risperidone	Risperidone < clozapine
Zhang 2001 [24]	12	78	Risperidone	Risperidone > haloperidol
Liberman 2002 [25]	8	36	Risperidone	Risperidone ~ haloperidol
Conley 2005 [26]	12	38	Risperidone or quetiapine	Risperidone ~ quetiapine ~ fluphenazine

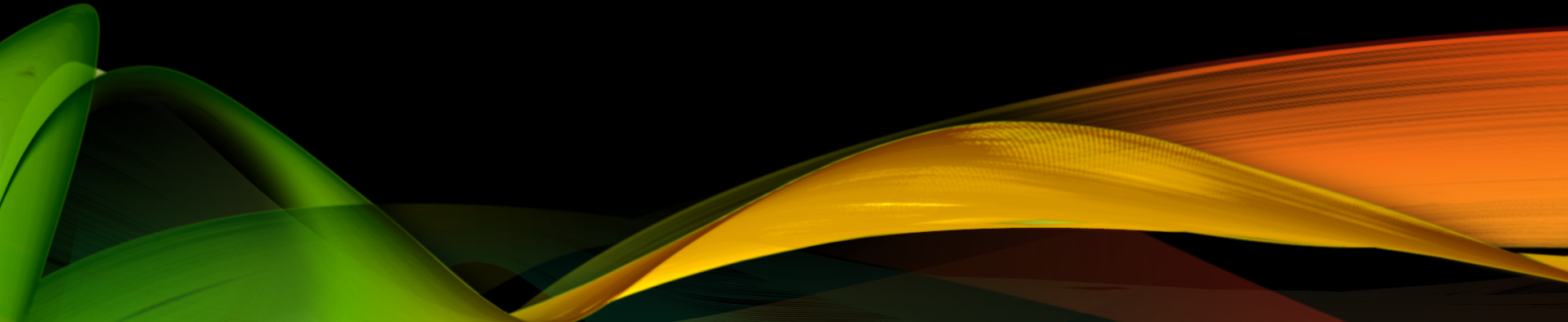
## Randomized controlled trials of antipsychotic monotherapy in treatment-refractory schizophrenia

Author and year	Study duration (weeks)	Number randomized	Antipsychotic	Efficacy*
Conley 1998 [27]	6	84	Olanzapine	Olanzapine ~ chlorpromazine
Breier 1999 [28]	6	526	Olanzapine	Olanzapine > haloperidol
Tollefson 2001 [29]	18	180	Olanzapine	Olanzapine ~ clozapine
Conley 2003 [30]	16	13	Olanzapine	Olanzapine < clozapine
Bitter 2004 [31]	18	147	Olanzapine	Olanzapine ~ clozapine
Buchanan 2005 [32]	16	63	Olanzapine	Olanzapine ~ haloperidol
Shaw 2006 [33]	8	25 children	Olanzapine	Olanzapine < clozapine
Meltzer 2008 [34]	6 months	40	Olanzapine	Olanzapine ~ clozapine
Kumra 2008 [35]	12	39 children	Olanzapine	Olanzapine < clozapine

## Randomized controlled trials of antipsychotic monotherapy in treatment-refractory schizophrenia

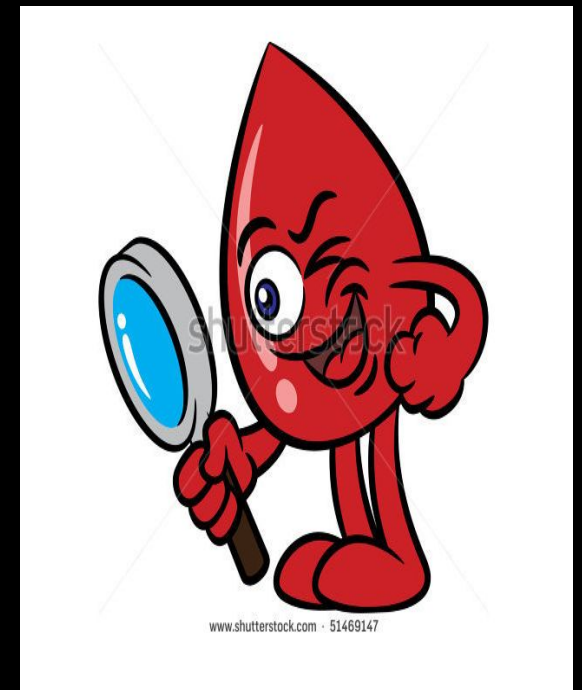
Author and year	Study duration (weeks)	Number randomized	Antipsychotic	Efficacy*
Emsley 2000 [36]	8	288	Quetiapine	Quetiapine > haloperidol
Kane 2006 [37]	12	306	Ziprasidone	Ziprasidone > chlorpromazine
Sacchetti 2009 [38]	18	147	Ziprasidone	Ziprasidone ~ clozapine
Kane 2007 [39]	6	300	Aripiprazole	Aripiprazole ~ perphenazine

# HOW ABOUT CLOZAPINE FOR OUR PATIENT



- Hematology Consult to reconsider Clozapine

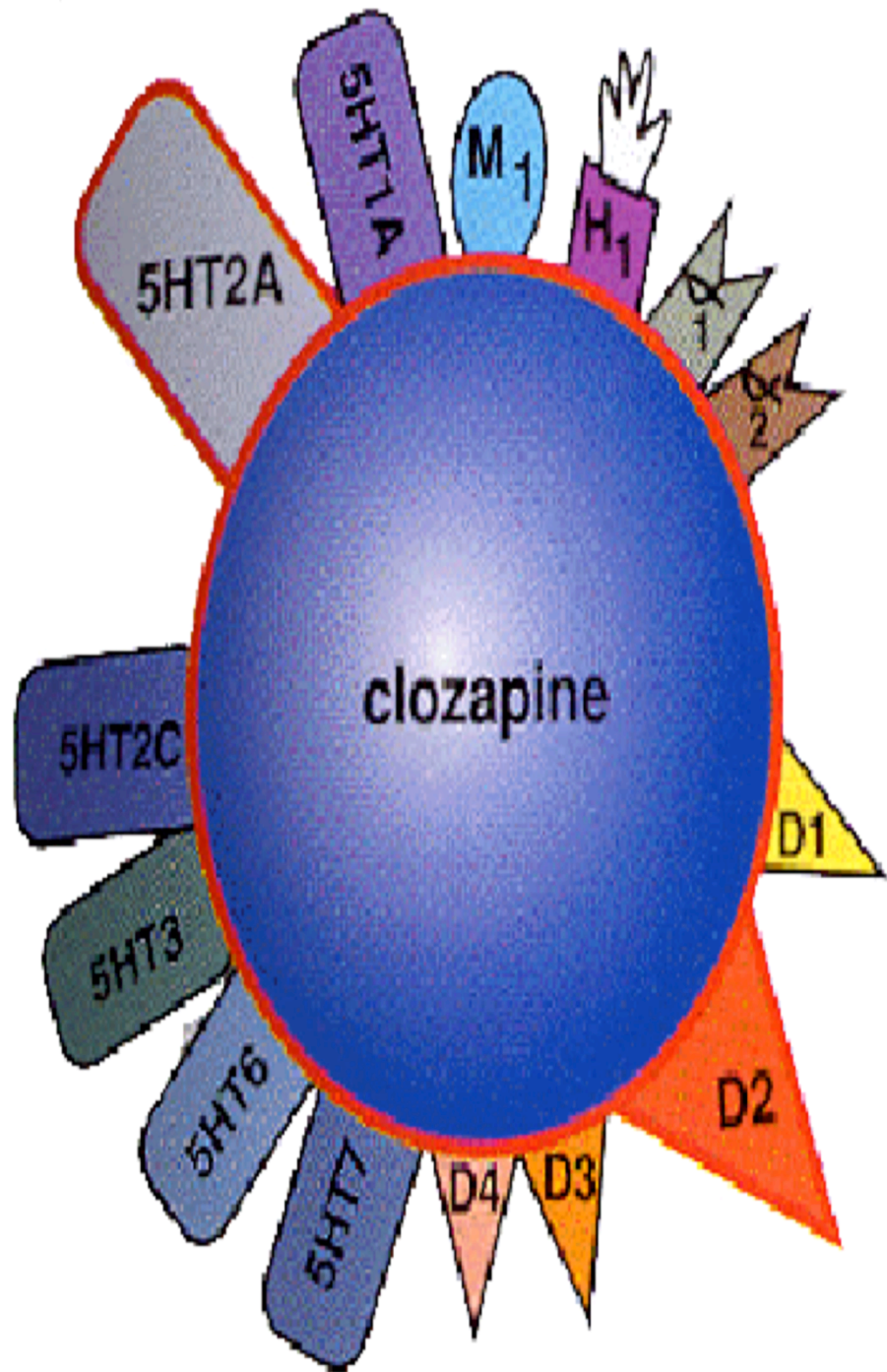
- Benign Ethnic Neutropenia

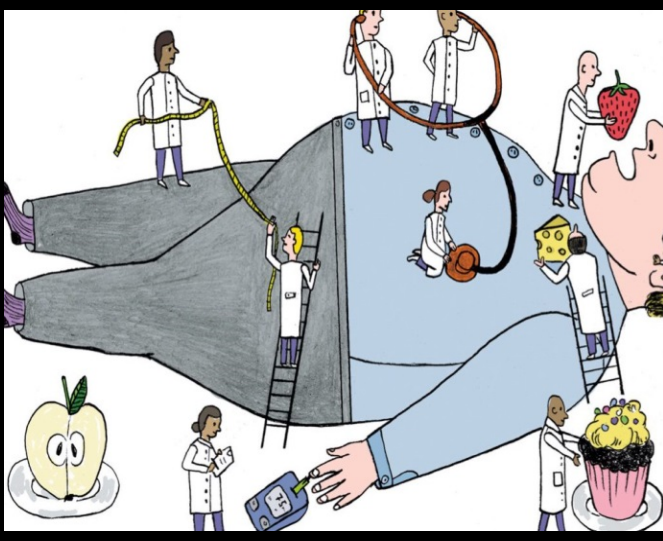
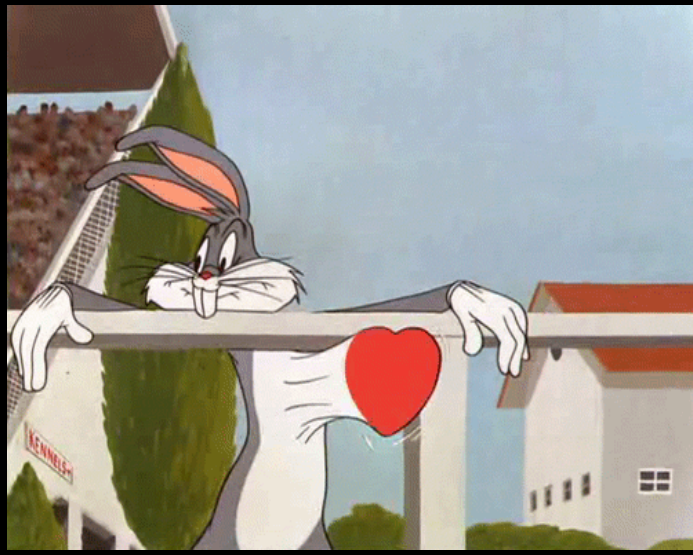
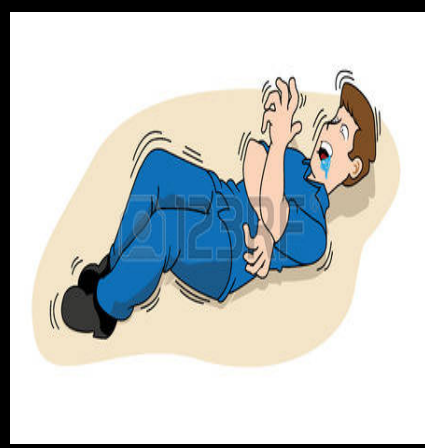
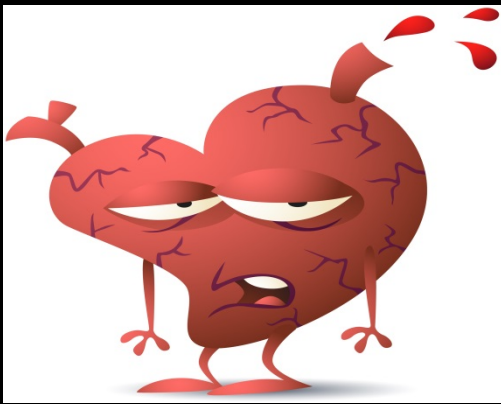
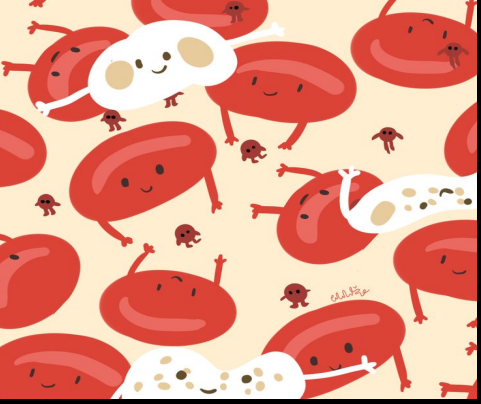


RECOMMENDED MONITORING FREQUENCY AND CLINICAL DECISIONS BY ANC LEVEL

ANC Level	Treatment Recommendation	ANC Monitoring
<p><b>Normal Range for a New Patient GENERAL POPULATION</b></p> <ul style="list-style-type: none"> <li>ANC <math>\geq</math> 1500/<math>\mu</math>L</li> </ul>	<ul style="list-style-type: none"> <li>Initiate treatment</li> <li>If treatment interrupted:                             <ul style="list-style-type: none"> <li>&lt; 30 days, continue monitoring as before</li> <li><math>\geq</math> 30 days, monitor as if new patient</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Weekly from initiation to six months</li> <li>Every 2 weeks from 6 to 12 months</li> <li>Monthly after 12 months</li> </ul>
<p><b>BEN POPULATION</b></p> <ul style="list-style-type: none"> <li>ANC <math>\geq</math> 1000/<math>\mu</math>L</li> <li>Obtain at least two baseline ANC levels before initiating treatment</li> </ul>	<ul style="list-style-type: none"> <li>Discontinuation for reasons other than neutropenia</li> </ul>	<ul style="list-style-type: none"> <li>See Section 2.4 of the full Prescribing Information</li> </ul>
<p><b>Mild Neutropenia (1000 - 1499/<math>\mu</math>L)*</b></p>	<p><b>GENERAL POPULATION</b></p> <ul style="list-style-type: none"> <li>Continue treatment</li> </ul>	<p><b>GENERAL POPULATION</b></p> <ul style="list-style-type: none"> <li>Three times weekly until ANC <math>\geq</math> 1500/<math>\mu</math>L</li> <li>Once ANC <math>\geq</math> 1500/<math>\mu</math>L return to patient's last "Normal Range" ANC monitoring interval**</li> </ul>
	<p><b>BEN POPULATION</b></p> <ul style="list-style-type: none"> <li>Mild Neutropenia is normal range for BEN population, continue treatment</li> <li>Obtain at least two baseline ANC levels before initiating treatment</li> <li>If treatment interrupted                             <ul style="list-style-type: none"> <li>&lt; 30 days, continue monitoring as before</li> <li><math>\geq</math> 30 days, monitor as if new patient</li> </ul> </li> <li>Discontinuation for reasons other than neutropenia</li> </ul>	<p><b>BEN POPULATION</b></p> <ul style="list-style-type: none"> <li>Weekly from initiation to six months</li> <li>Every 2 weeks from 6 to 12 months</li> <li>Monthly after 12 months</li> <li>See Section 2.4 of the full Prescribing Information</li> </ul>
<p><b>Moderate Neutropenia (500 - 999/<math>\mu</math>L)*</b></p>	<p><b>GENERAL POPULATION</b></p> <ul style="list-style-type: none"> <li>Recommend hematology consultation</li> <li>Interrupt treatment for suspected Clozapine induced neutropenia</li> <li>Resume treatment once ANC normalizes to <math>\geq</math> 1000/<math>\mu</math>L</li> </ul>	<p><b>GENERAL POPULATION</b></p> <ul style="list-style-type: none"> <li>Daily until ANC <math>\geq</math> 1000/<math>\mu</math>L, then</li> <li>Three times weekly until ANC <math>\geq</math> 1500/<math>\mu</math>L</li> <li>Once ANC <math>\geq</math> 1500/<math>\mu</math>L check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval**</li> </ul>
	<p><b>BEN POPULATION</b></p> <ul style="list-style-type: none"> <li>Recommend hematology consultation</li> <li>Continue treatment</li> </ul>	<p><b>BEN POPULATION</b></p> <ul style="list-style-type: none"> <li>Three times weekly until ANC <math>\geq</math> 1000/<math>\mu</math>L or <math>\geq</math> patient's known baseline.</li> <li>Once ANC <math>\geq</math> 1000/<math>\mu</math>L or patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval**</li> </ul>
<p><b>Severe Neutropenia (&lt; 500/<math>\mu</math>L)*</b></p>	<p><b>GENERAL POPULATION</b></p> <ul style="list-style-type: none"> <li>Recommend hematology consultation</li> <li>Interrupt treatment for suspected Clozapine induced neutropenia</li> <li>Do not rechallenge unless prescriber determines benefits outweigh risks</li> </ul>	<p><b>GENERAL POPULATION</b></p> <ul style="list-style-type: none"> <li>Daily until ANC <math>\geq</math> 1000/<math>\mu</math>L</li> <li>Three times weekly until ANC <math>\geq</math> 1500/<math>\mu</math>L</li> <li>If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC <math>\geq</math> 1500/<math>\mu</math>L</li> </ul>
	<p><b>BEN POPULATION</b></p> <ul style="list-style-type: none"> <li>Recommend hematology consultation</li> <li>Interrupt treatment for suspected Clozapine induced neutropenia</li> <li>Do not rechallenge unless prescriber determines benefits outweigh risks</li> </ul>	<p><b>BEN POPULATION</b></p> <ul style="list-style-type: none"> <li>Daily until ANC <math>\geq</math> 500/<math>\mu</math>L</li> <li>Three times weekly until ANC <math>\geq</math> patients established baseline</li> <li>If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC <math>\geq</math> 1000/<math>\mu</math>L or at patient's baseline</li> </ul>







# CLOZAPINE TRIAL

TITRATED UP TO 500 MG DAILY

TROUGH CLOZAPINE LEVEL  
~550 NG/ML (200-450 NG/ML)

## VERY MILD

↓ Positive symptoms,  
less incidents

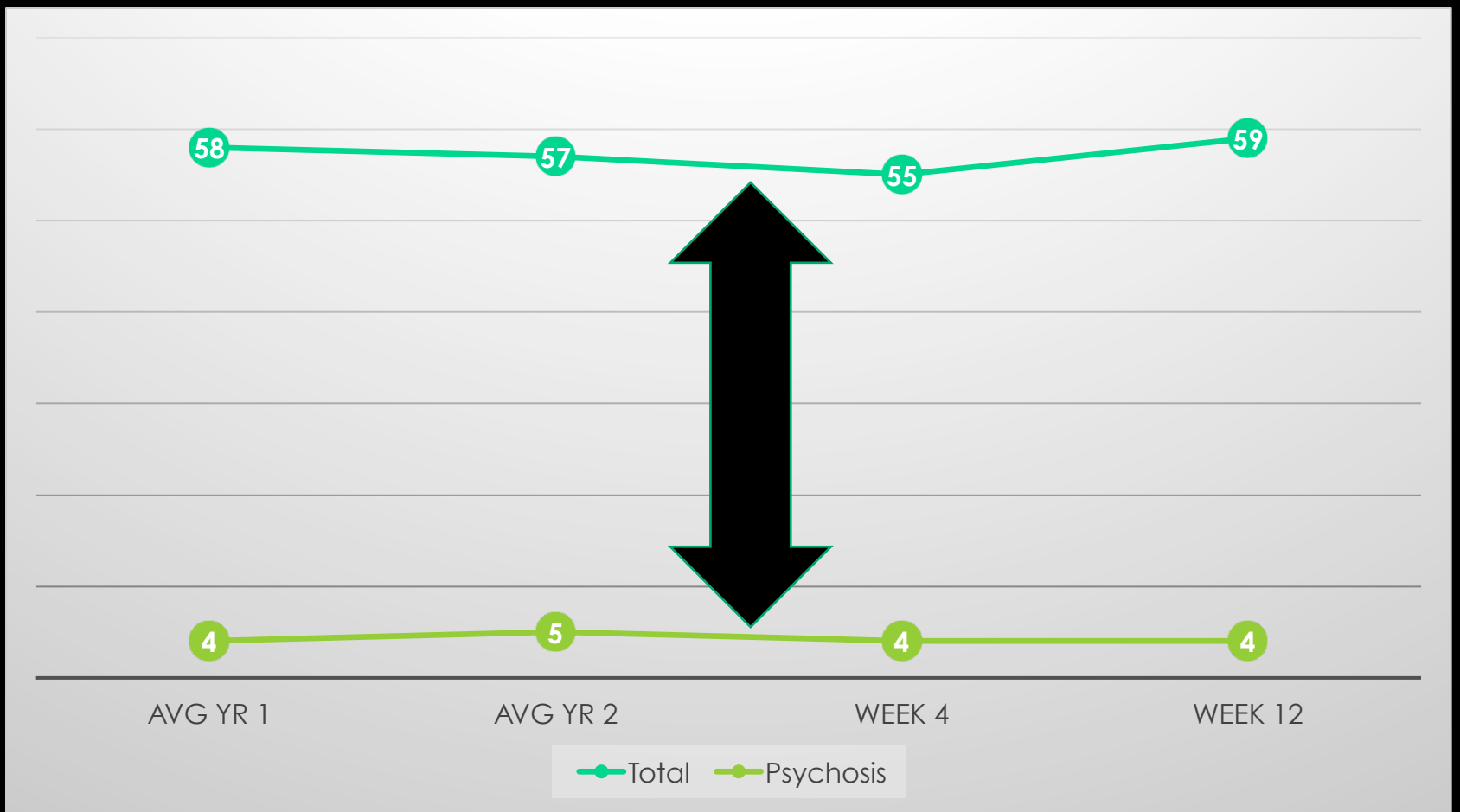
↑ Hygiene

↑ Therapy Group  
Attendance

↑ Cognition



# BPRS SCORES



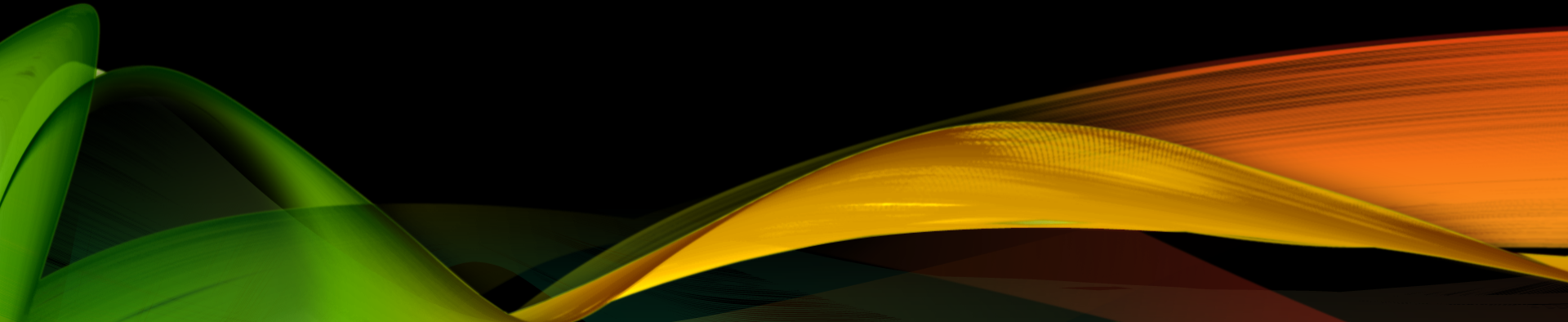


# **CLOZAPINE RESISTANT PSYCHOSIS**

- Present in about 40% - 70%
- Trough Clozapine levels **300-450 ng/ml**, trial at least 3 months, optimum threshold requirement
- Total levels **more than 1000 ng/ml** usually have less therapeutic value, increase seizure risk, differ by patients
- Can get **total levels** with clozapine and its metabolite norclozapine



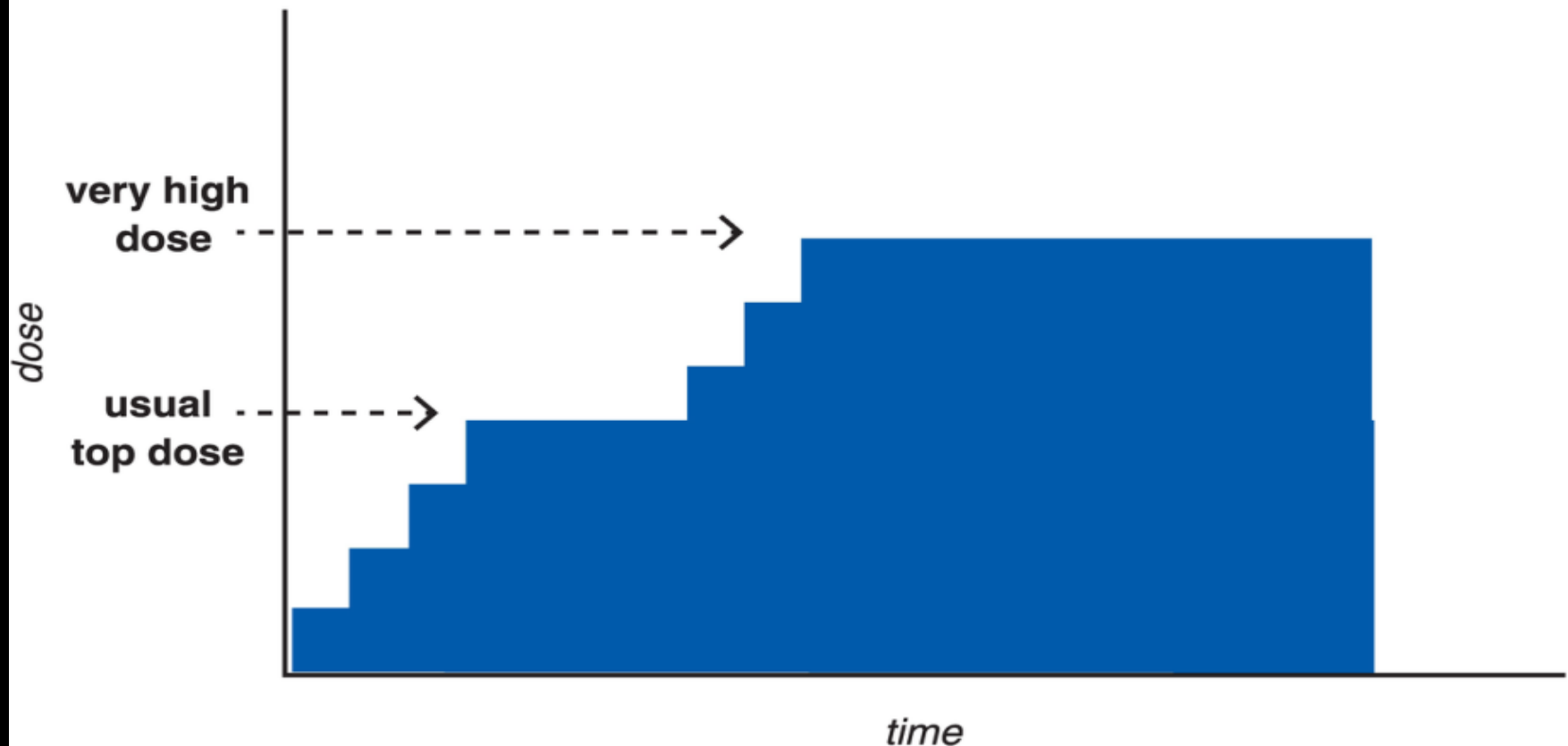
**WHAT CAN WE DO?**



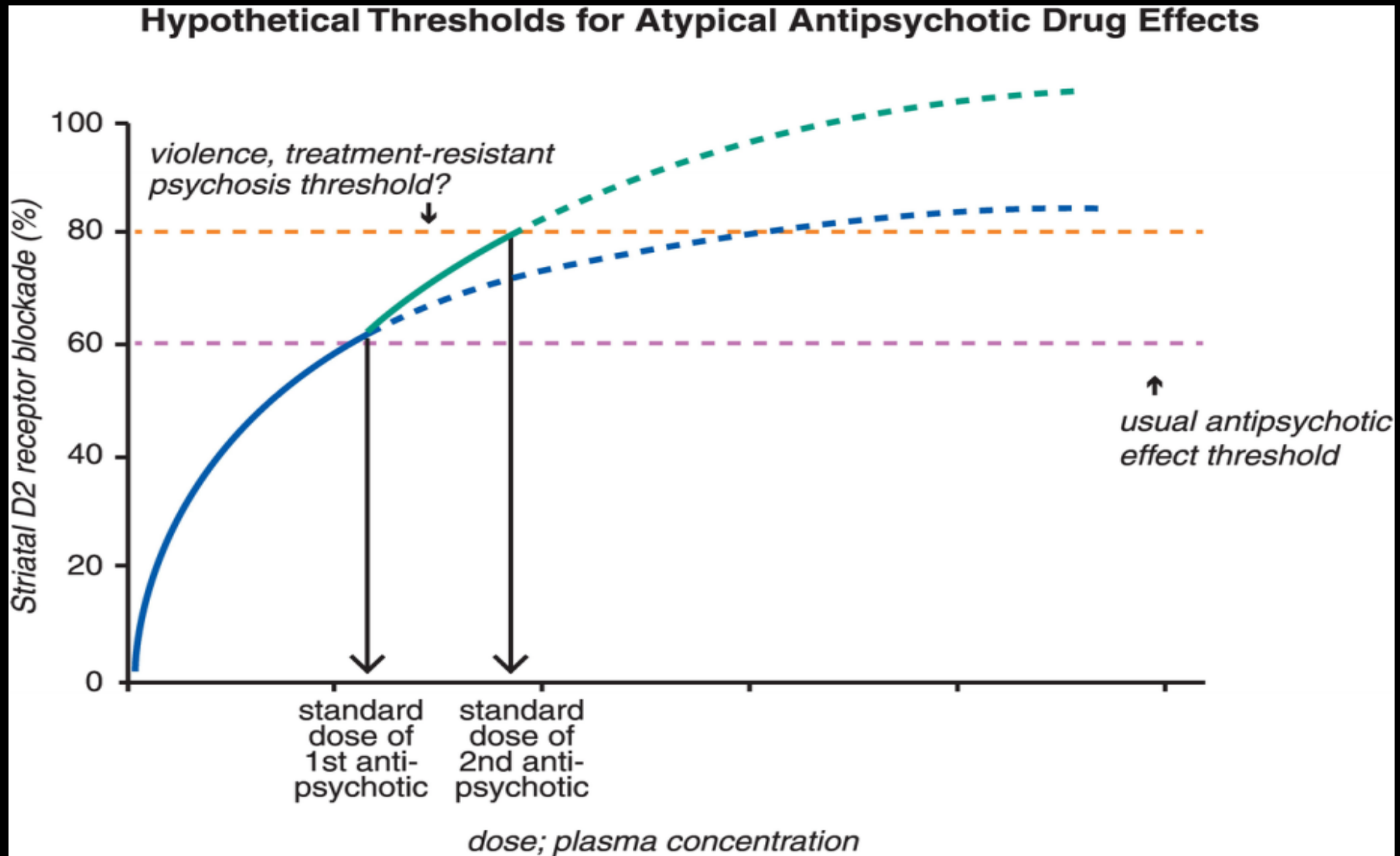


# 1) HIGH DOSE

**Novel Solution to Nonresponse/Violence:  
High to Very High Doses Beyond the Generally  
Recommended Range**



## 2) ADD ANOTHER ANTIPSYCHOTIC



# COMBINATION OF MEDICATIONS

- Achieving **optimal** receptor occupancy;
- Targeting **different receptors** with the added drug
- **Reducing** the dose-related side-effects



# BEFORE CONSIDERING CLOZAPINE AUGMENTATION

- **Diagnosis Reevaluation**
- r/o severe case of schizoaffective disorder or bipolar disorder with psychotic features
- **Potential Substance Abuse**
  
- **Medication Adherence**

# LITERATURE

- **Risperidone and lamotrigine** are the best studied - each has five placebo-controlled randomized trials.
- **No IMPRESSIVE** efficacy, reasonable tolerability
- **Topiramate** – efficacy for weight loss, many meta-analyses, **not consistent** improvement on psychopathology
- **ECT** – One RCT & case reports: positive, Another sham controlled study- no efficacy, **Moderate efficacy**

Tiihonen J, Wahlbeck K, Kiviniemi V. [The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis](#). Schizophr Res 2009;109: 10Y4

Weiner E, Conley RR, Ball MP, et al. [Adjunctive risperidone for partially responsive people with schizophrenia treated with clozapine](#). Neuropsychopharmacology 2010;35:2274Y83.

Petrides, G., et al (2014). [Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study](#). American Journal of Psychiatry, 172(1), 52-58.

Havaki-Kontaxaki, B. J., (2006). [Concurrent administration of clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia](#). Clinical neuropharmacology, 29(1), 52-56.

# RCTs- Adjunct Antipsychotics

Author and year	Study duration (weeks)	Number randomized	Combination	Efficacy*
Potter 1989	8	57	Chlorpromazine and clozapine	Chlorpromazine and clozapine ~ or > clozapine or chlorpromazine
Shiloh 1997	10	28	Sulpiride and clozapine	Sulpiride and clozapine > clozapine
Josiassen 2005	12	40	Risperidone and clozapine	Risperidone and clozapine > clozapine
Anil Yağcıoğlu 2005	6	30	Risperidone and clozapine	Risperidone and clozapine < clozapine
Honer 2006	8	68	Risperidone and clozapine	Risperidone and clozapine ~ clozapine
Freudenreich 2007	6	24	Risperidone and clozapine	Risperidone and clozapine ~ or > clozapine
Weiner 2010	16	69	Risperidone and clozapine	Risperidone and clozapine ~ or > clozapine

Krein in 2006 [59]	7	20	Amisulpride and clozapine	Amisulpride and clozapine ~ or > clozapine
Assion 2008 [60]	6	16	Amisulpride and clozapine	Amisulpride and clozapine ~ or > clozapine
Genç 2007 [61]	8	56	Amisulpride and clozapine	Amisulpride and clozapine > quetiapine and clozapine
Chang 2008 [62]	8	62	Aripiprazole and clozapine	Aripiprazole and clozapine ~ or > clozapine
Fleischhacker 2010 [63]	16	207	Aripiprazole and clozapine	Aripiprazole and clozapine ~ or > clozapine
Muscatello 2011 [64]	24	40	Aripiprazole and clozapine	Aripiprazole and clozapine > clozapine
Zink 2009 [65]	6	24	Ziprasidone and clozapine	Ziprasidone and clozapine ~ clozapine and risperidone
Kane 2009 [66]	16	323	Risperidone or quetiapine and aripiprazole	Risperidone or quetiapine and aripiprazole ~ risperidone or quetiapine
Henderson 2009 [67]	10	15	Aripiprazole and olanzapine	Aripiprazole and olanzapine ~ olanzapine
Shafti 2009 [68]	12	28	Fluphenazine decanoate and olanzapine	Fluphenazine decanoate and olanzapine ~ or > olanzapine
Kotler 2004 [69]	8	17	Sulpiride and olanzapine	Sulpiride and olanzapine ~ or > olanzapine
Takahashi 1999 [70]	8	24	Risperidone or mosapramine and one or more first-generation antipsychotics	Risperidone or mosapramine and one or more first-generation antipsychotics > one or more first-generation antipsychotics

# ADJUNCTIVE NON-ANTIPSYCHOTICS

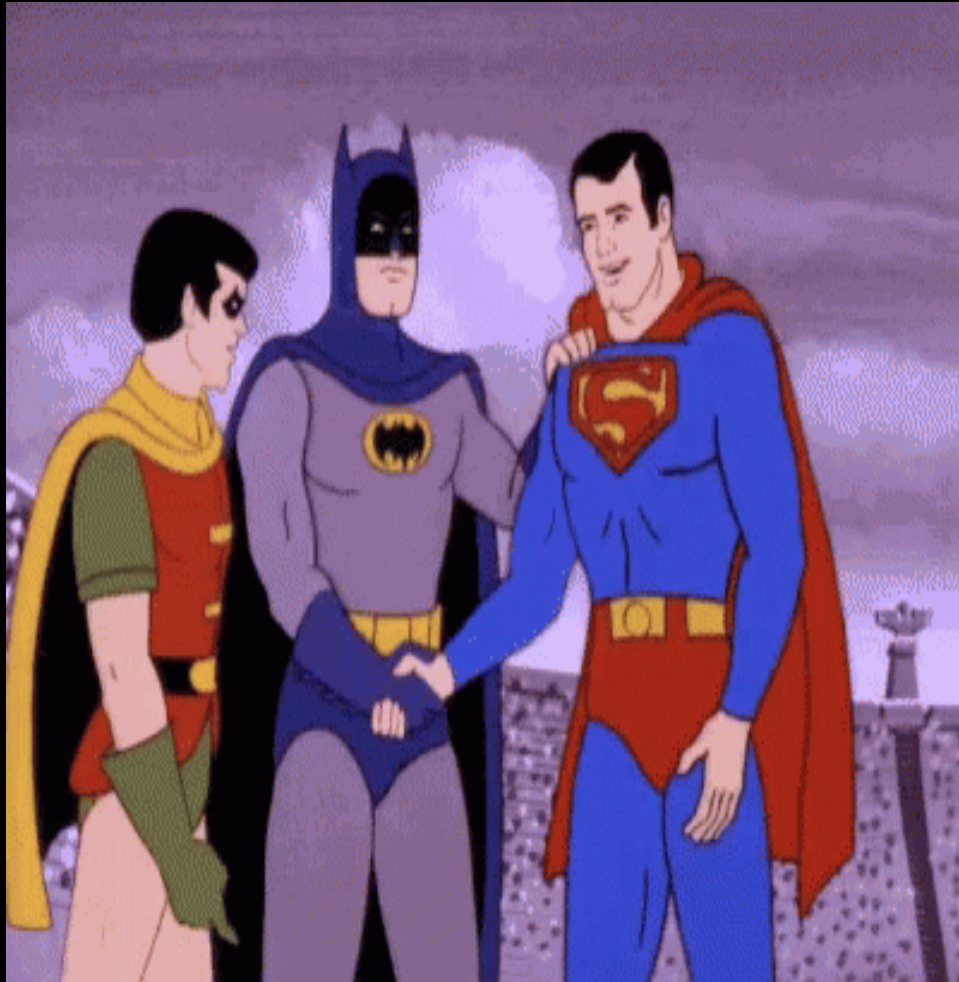
Intervention	# RCT	Duration (wk)	# subjects	Useful? (Y:N)
Antidepressants	36	4-24	1277	24:12
ACE inhibitors/AZ	20	8-52	843	5:15
Glutamate Rec	18	4-12	751	11:7
Neurosteroids/Hormones	10	4-12	443	10:0
NSAIDs	5	5-12	267	3:2
Antiglucocorticoids	2	4-6	35	0:2
ADHD Meds	4	2-8	99	0:4
B-blockers	2	3-6	64	2:0
GABA-A Rec	2	4	75	1:1
Omega-3 Fatty Acid	2	12-16	127	1:1
Opioid Antagonists	3	3-12	63	2:1
Peptides	2	3	41	1:1



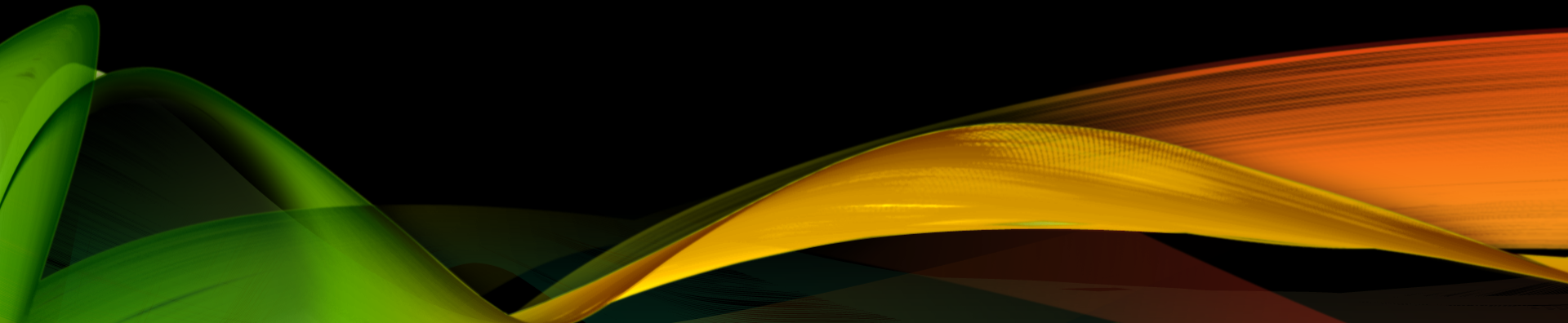
# ADJUNCTIVE NON-ANTIPSYCHOTICS

Intervention	# RCT	Duration (wk)	# subjects	Useful? (Y:N)
Purinergic Agents	5	6-8	220	5:0
5-HT <sub>1A</sub> Agonists	4	6-8	160	3:1
5-HT <sub>3</sub> Antagonists	2	12	151	2:0
Wakefulness Agents (eg. Modafinil)	4	4-8	139	0:4
Other Medications	12	3-22	532	9:3
CBT	3	21-24	124	2:1
ECT	2	4-6	76	1:1
r-TMS	11	1-4	291	6:5
Others (OT)	3	6-18 months	121	3:0

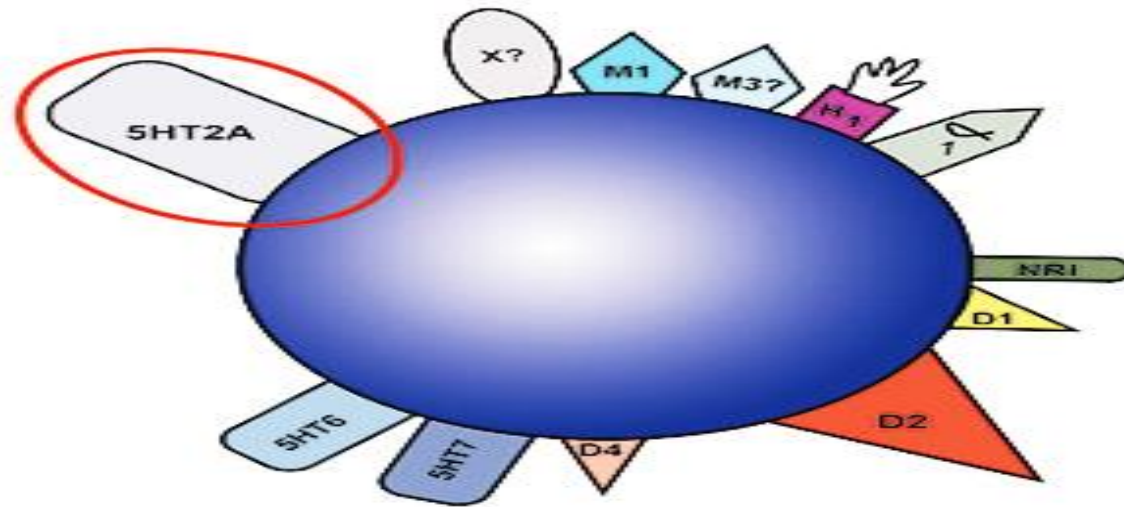
# RIGHT ADJUNCTIVE FOR OUR PT?



# REVISITING LOXAPINE



# Loxapine: Conventional or Low-Dose Atypical?



- Dibenzoxazepine tricyclic antipsychotic agent - **Similar to Clozapine** with **5HT2A/D2** antagonism
- Similar Conventional – **EPS & ↑ Prolactin**
- **Atypical** – Low doses <50mg/day
- **Amoxapine**- metabolite- TCA (CYP3A4, CYP2C19 & CYP2C8)



	D1	D2	D3	D4	H1	M1	α1	α2	5-HT 1	5-HT 2
Loxapine	++	+++	+++	+++	++	+	++	-	-	+++



+++ Very high, ++ high, + moderate, - low.


- Receptor **Binding: Similar affinity** as clozapine and olanzapine with a more potent 5-HT<sub>2A</sub> antagonism.
- Receptor **occupancy**: (10-100mg/day), PET Data,
  - D2 receptor - 43% to 90%
  - 5-HT<sub>2A</sub> receptor- 27% to >98%
- **Calming** effects and **suppression of aggressive** behavior with NR1, M1, H1



# SIDE EFFECTS





**Drowsiness**  


**Tachycardia**  

**Dry mouth** 

**Urinary retention**  

**Hypotension**  

**BP**

**Increased appetite** 



**Bradykinesia** 

**Postural instability** 



- Risk of **death in elderly**- comparable to others



- **Teratogenic?** – Paucity of Data
- **Three** reports- No direct correlation
  - Achondroplasia
  - Multiple unspecified malformations
  - Tremors at 15 weeks of age.

# LOXAPINE TRIAL-100 MG

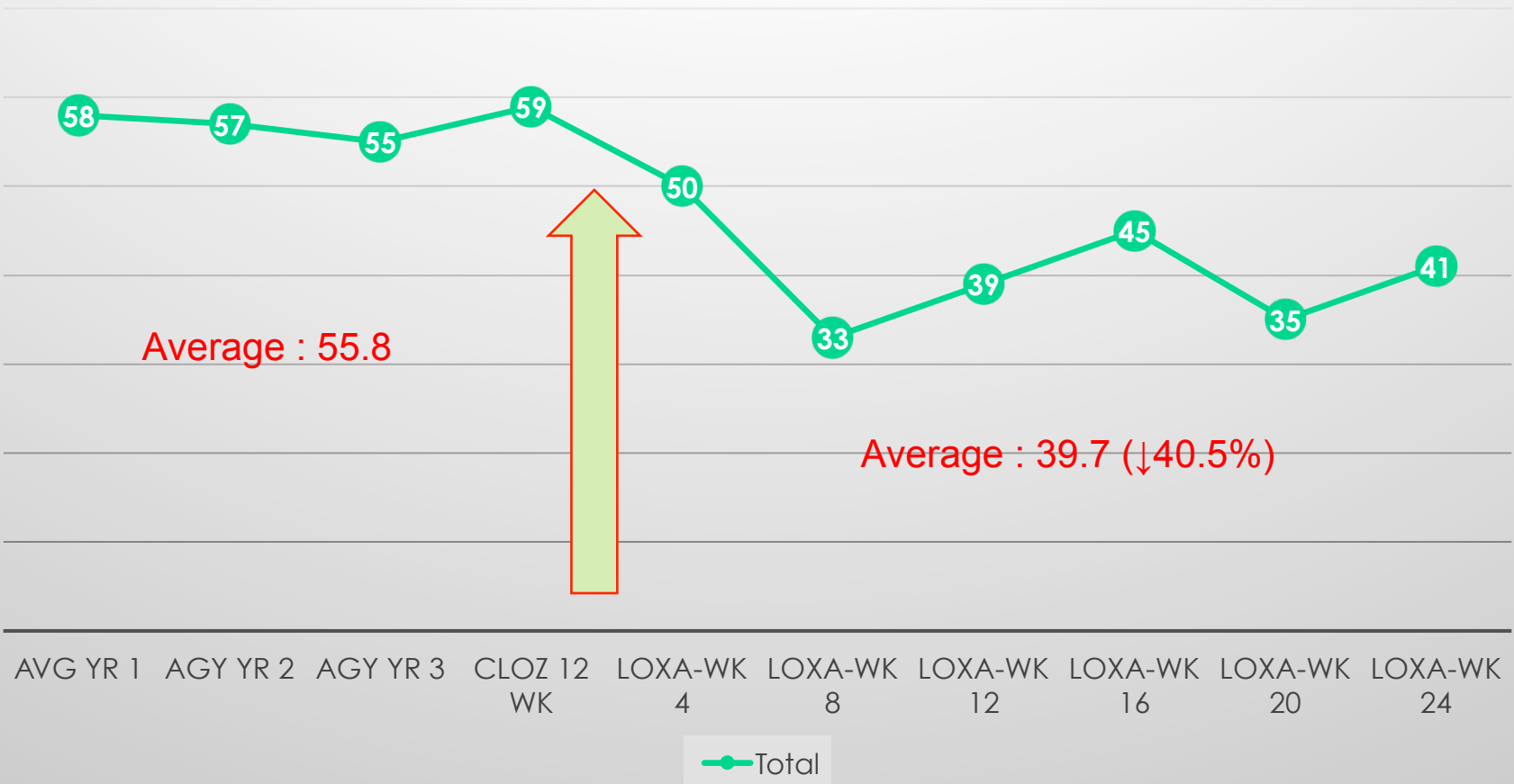
- ↓↓ Positive Symptoms
- ↓↓ Responding to internal stimulus
- ↑↑ hygiene  
(Taking baths more)
- ↑↑ Group attendance
- Ability to hold **linear** conversation
- **Brighter** Affect



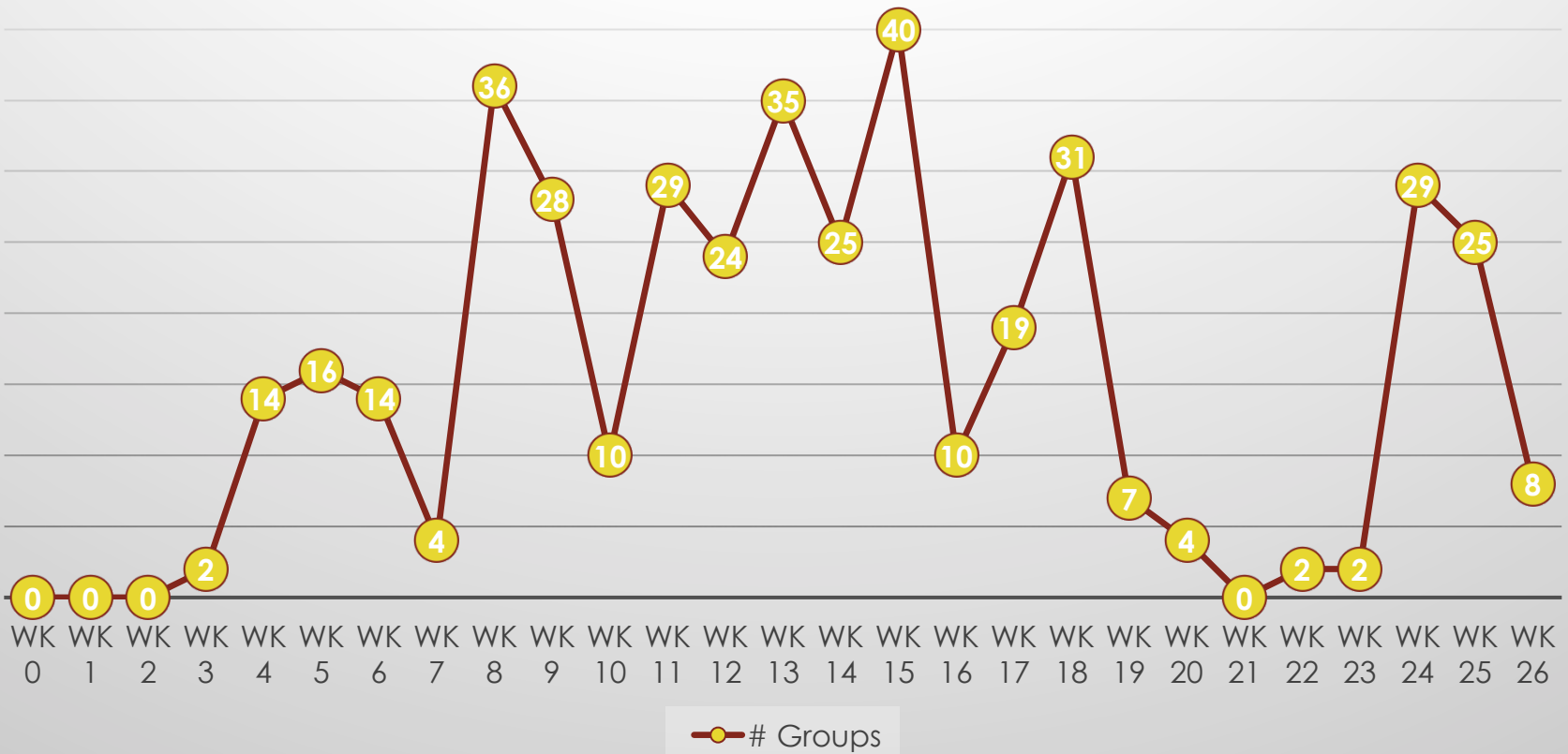


# BPRS SCORES

## Total



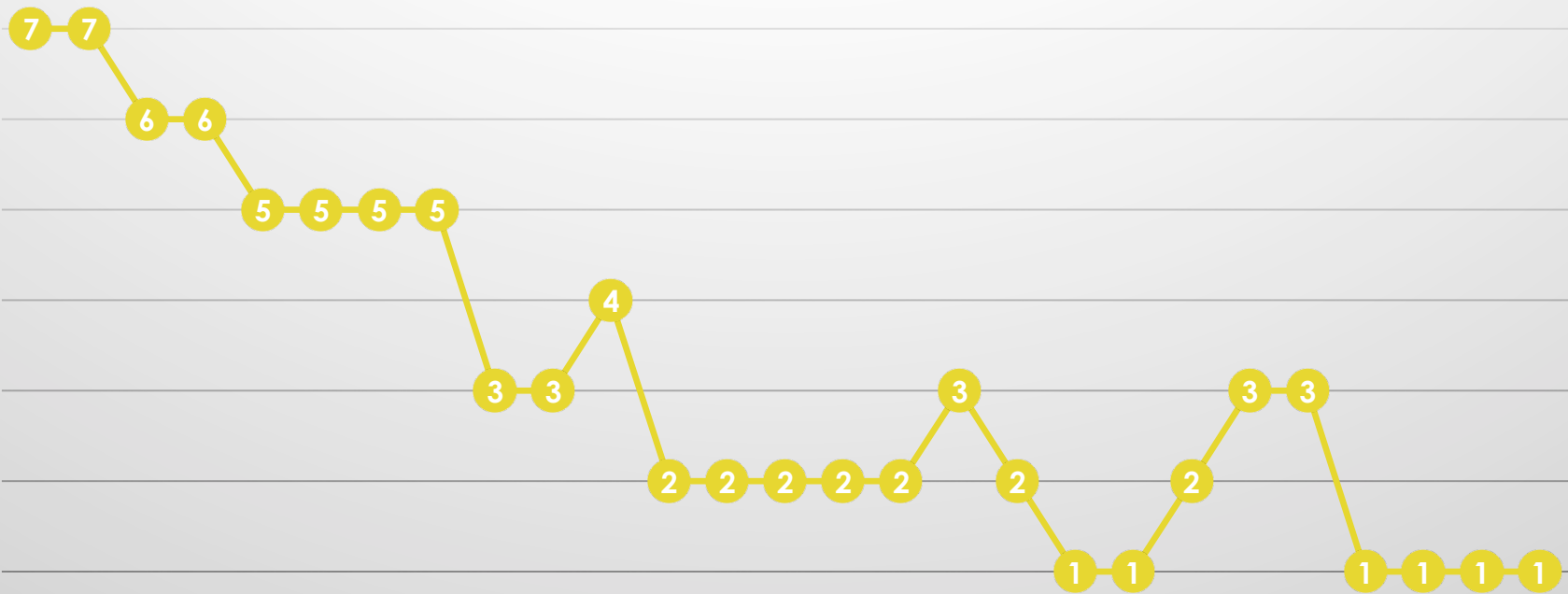
# THERAPY GROUPS ATTENDANCE



# CLINICAL GLOBAL IMPRESSION SCALE-IMPROVEMENT

Number	Interpretation
1	Very much improved
2	much improved
3	minimally improved
4	no change
5	minimally worse
6	much worse
7	very much worse

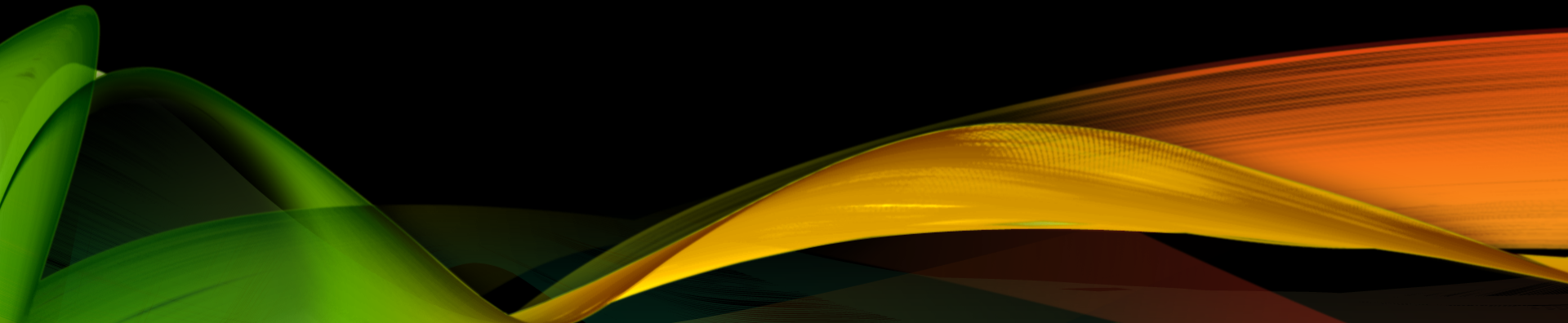
# CGI SCALE - IMPROVEMENT



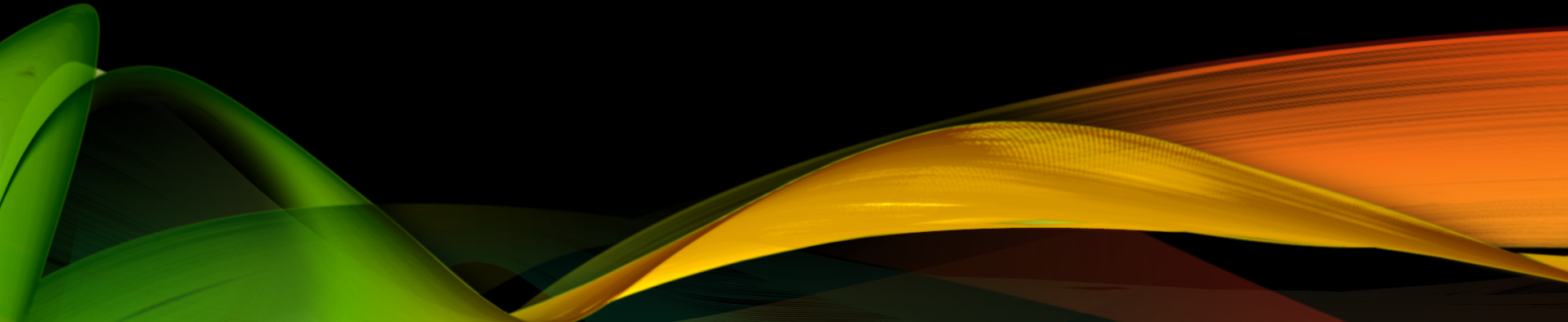
WK  
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

Overall

**OVERALL IMPROVEMENT IN  
QUALITY OF LIFE FOR THE  
LONGEST PERIOD SINCE  
DIAGNOSIS**



**WHAT HAVE WE LEARNED**



# SELECTING RIGHT MEDICATION & COMBINATION



- **No one size fits all** – individualized approach
- Drug interactions
- Side effect profile
- Cost
- Compliance
- Availability of data

# NON-PHARMACOLOGICAL APPROACHES

- Cognitive Behavioral Therapy
- Family and Social support
- Community treatment programs - eg. Vocational Rehabilitation
- Motivational therapies
- Cognitive remediation - attention, working memory and executive capacity

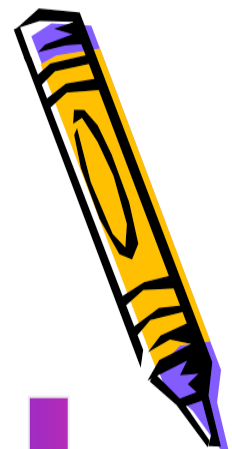




**TO CONCLUDE...**



THANK YOU



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