# Psychosis and Schizophrenia in Clinical Practice

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## Psychosis in Practice

- Schizophrenia
- Mania
- Depression
- Brief Psychotic Episodes
- Substance Abuse
- FASD and other Neurodevelopment Disorders

# Schizophrenia

- Late Adolescent/Early Adult Age of Onset
- Life-Long Condition and Chronic Medication
  - Typical Antipsychotic drugs – introduced in 50's -60's
  - Atypical Antipsychotic drugs – introduced in later 80's 90's
  - Clozapine is the only ADP with demonstrated superiority
  - Market For Antipsychotic Drugs : Peak $16B /year US
- 1% of World Population
- Common "Complex" Disorder
  - Pathophysiology
  - Genetics
  - Variable Phenotype
- Positive and Negative Symptoms and Cognitive Deficits
- 10% Completed Suicide

# Prevalence and Treatment Rates

- **8.1 million** adults with schizophrenia or bipolar disorder mental illness (3.3% of the population)[+]
- **5.4 million** – approximate number with severe bipolar disorder (2.2% of the population), 51% untreated[+]
- **2.7 million** – approximate number with schizophrenia (1.1% of the population), 40% untreated[+]
- **3.9 million** – approximate number untreated seriously mentally ill patients in any given year (1.6% of the population)[+]

# Positive and Negative Symptom Scale (PANSS) Positive Symptoms

- *7 Items, (minimum score = 7, maximum score = 49)*
- Delusions
- Conceptual disorganization
- Hallucinations
- Excitement
- Grandiosity
- Suspiciousness/persecution
- Hostility

# PANSS
# Negative Symptoms

- *7 Items, (minimum score = 7, maximum score = 49)*
- Blunted Affect
- Emotional withdrawal
- Poor rapport
- Passive/apathetic social withdrawal
- Difficulty in abstract thinking
- Lack of spontaneity and flow of conversation
- Stereotyped thinking

# PANSS
# General Psychopathology

*16 Items, (minimum score = 16, maximum score = 112)*

Somatic concern
Anxiety
Guilt feelings
Tension
Mannerisms and posturing
Depression
Motor retardation
Uncooperativeness
Unusual thought content
Disorientation
Poor attention
Lack of judgment and insight
Disturbance of volition
Poor impulse control
Preoccupation
Active social avoidance

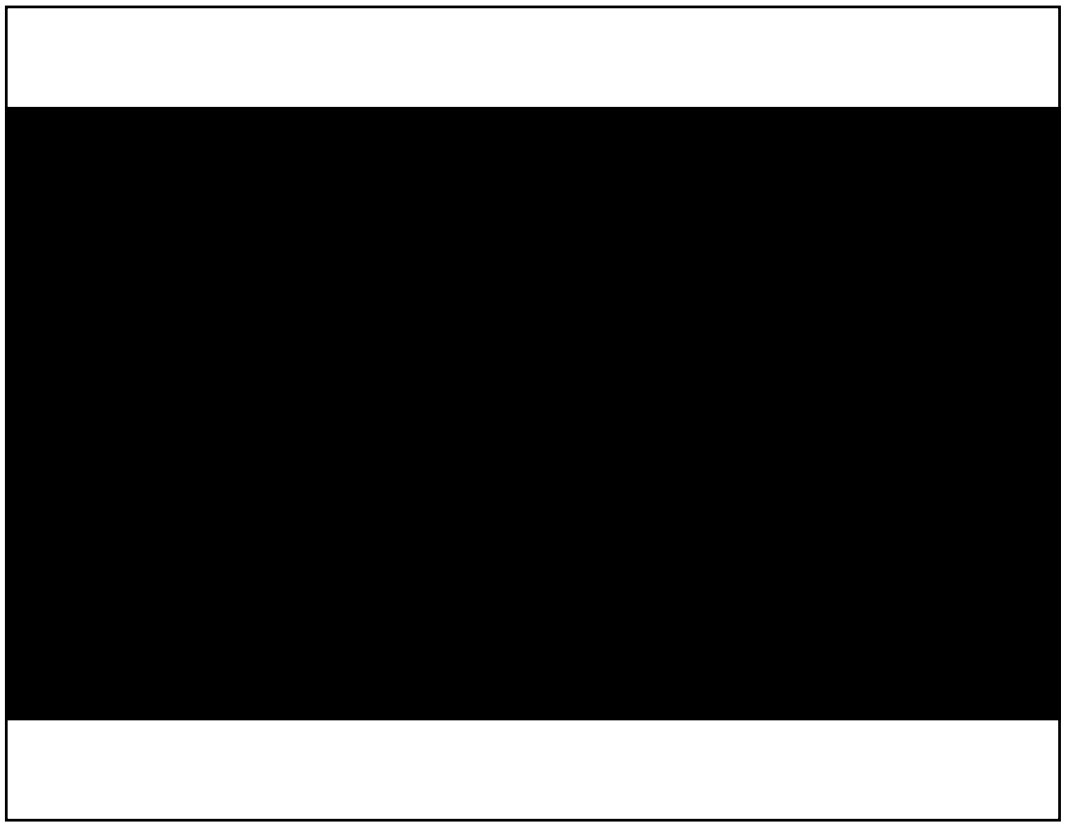
## More Mentally Ill Patients are in Jails or Prisons than Hospitals

400,000

Number of US Adults with Untreated Mental Illness in Jails or Prisons

## Violence and Serious Mental Illness

- 10% - estimated percentage of homicides involving an offender with serious mental illness
- 29% - estimated percentage of family homicides associated with serious mental illness
- 50% - estimated percentage of mass killings associated with serious mental illness.



# Assisted Outpatient Treatment in New York State

74% Reduction in Homelessness

87% Reduction In Incarceration

## Mandatory Treatment Laws in Maryland

"Like every state, Maryland has civil commitment laws that establish criteria for determining when involuntary treatment is appropriate for individuals with severe mental illness who cannot seek care voluntarily. Maryland is one of only five states that do not authorize involuntary treatment in the community, often called "assisted outpatient treatment (AOT)" or "outpatient commitment."

Treatment Advocacy Center

# ANTIPSYCHOTIC DRUGS

## *Second Generation Antipsychotics*

| | ***Daily Oral Dose (mg)*** |
|---|---|
| *clozapine (Clozaril)* | *100-900 (BID)* |
| *risperidone (Risperdal)** | *1.5-6.0* |
| *olanzapine (Zyprexa)** | *7.5-30* |
| *quetiapine (Seroquel)* | *200-800(BID)* |
| *ziprasidone (Geodon)** | *40-160 (BID)* |
| *aripiprazole (Abilify)** | *15-30* |
| *asenapine (Saphris)** | *5-10 SL (BID)* |
| *lurasidone (Latuda)* | *40-160* |
| *iloperidone (Fanapt)* | *6-12* |
| *brexipiprazole (Rexulti)* | *2-4* |
| *cariprazine (Vraylar)* | *1.5 mg – 6 mg* |

**approved for mania/mood disorder*

# "New" Antipsychotics

- Vraylar (cariprazine) (2015) – schizophrenia
  - antagonist to D2, 5HT1 and 5HT2
- Rexulti (brexpiprazole) (2015) – depression and schizophrenia.
  - partial agonist/antagonist at D2; 5HT2Antagonist
- Latuda (lurasidone) (2010) – schizophrenia, bipolar
  - antagonist D2, 5HT2
- Fanapt (Iloperidone) (2009) – schizophrenia
  - D2 and 5HT2 antagonism
  - QT prolongation
- Saphris (asenapine) (2009) –
  - D2 and 5HT2A antagonism

# Dopaminergic Synapse

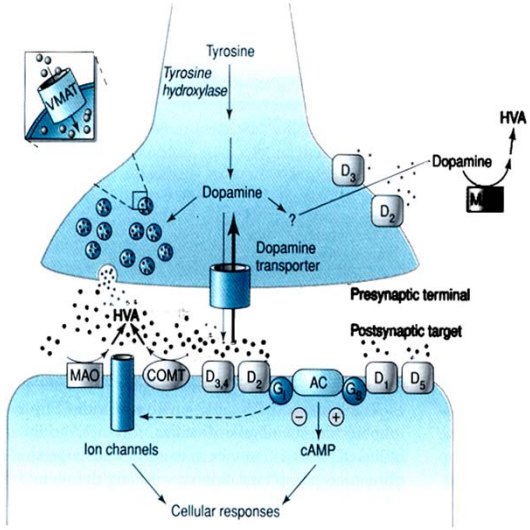



**Figure 8–7.** Model of a dopaminergic synapse. Presynaptic and postsynaptic molecular entities associated with the synthesis, release, signaling, and reuptake of dopamine are shown. Note that tyrosine hydroxylase (TH) is transported to the synaptic terminal so that dopamine may be synthesized on site. Also note that the $D_2$ receptor resides in both presynaptic and postsynaptic locations; in the former it functions as an autoreceptor and in the latter it assists in intercellular signaling. The $D_3$ receptor is also present on the presynaptic terminal, but its function is unclear. The question mark in the dopamine nerve terminal refers to persisting controversy as to whether MAO is expressed in dopaminergic neurons or whether most dopamine metabolism occurs in other cells, particularly glia. VMAT, vesicular monoamine transporter; $G_i$ and $G_s$, inhibitory and stimulatory guanine nucleotide-binding proteins; MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; AC, adenylyl cyclase.

## Nuplazid (pimvanserin) 2016

- Hallucinations and Delusions in Parkinson's disease
- Antagonist to 5HT2A and 5HT2C Receptors

## Tardive Dyskinesia: Ingrezza (valbenazine)

- '17 First FDA approved treatment for tardive dyskinesia
- Start: 40 mg PO qd x1wk, then incr. to 80 mg PO qd; Info: consider decr. dose in poor CYP2D6 metabolizers or if tolerability concern
- exact mechanism of action unknown; selectively and reversibly inhibits human vesicular monoamine transporter type 2 (VMAT2), decreasing monoamine uptake into synaptic vesicles and depleting monoamine stores
-

## *Black Box: Dementia-Related Psychosis*

- *Not approved for dementia-related psychosis*
- *Increased mortality risk in elderly dementia patients on conventional or atypical antipsychotics.*
- *Most deaths due to cardiovascular or infection events*
- *Extent to which increased mortality attributed to antipsychotic vs some patient characteristics is not clear*

## Best Prevention of Relapse in Schizophrenia

Clozapine and Long Acting Antipsychotic Injections

Tihonen et al, 2017 JAMA Psychiatry

## Long Acting Anitpsychotics by Injection

- Aripiprazole (Ablify Maintena)
- Aripiprazole lauroxil (Aristada)
- Fluphenazine (Prolixin Decanoate)
- Haloperidol (Haldol Decanoate)
- Olanzapine pamoate (Zyprexa Relprevv)
- Paliperidone (Invega Sustenna, Invega Trinza* - 4x/year)
- Risperidone (Risperdal Consta)

## Clozapine: The only Antipsychotic with Superior Efficacy

- First “atypical” antipsychotic
- Approved for Treatment Resistant Patients
  - Useful in presence of TD
- First used in the 70’s but not FDA approved until ’92
  - Requires CBC monitoring do to risk of agranulocytosis
  - Clozapine REMS

# Treatment Resistance

- Treatment Resistance – Little improvement after 2 or 3 antipsychotic trials
- 15% First Break Patients
- 30-35% Chronic Patients

# CNS Dopaminergic Pathways

Every Known Antipsychotic is an Antagonist to the $D_2$ Receptor Located in Subcortical DA Systems

Cortical DA Modulates Subcortical Activity via Glutamatergic Connections

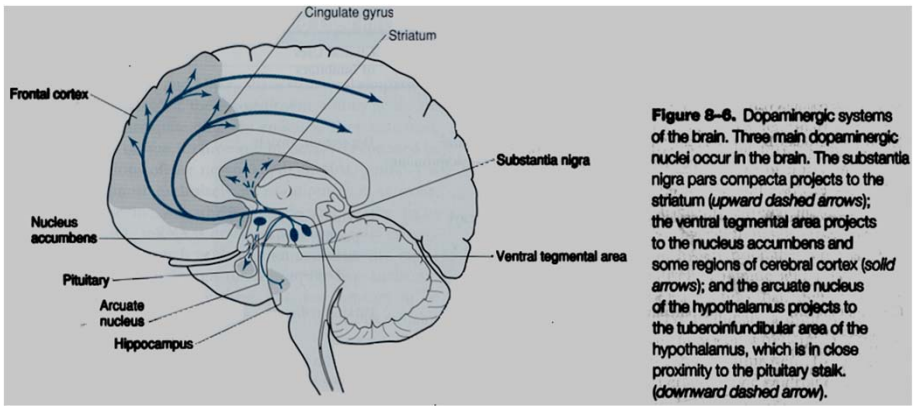
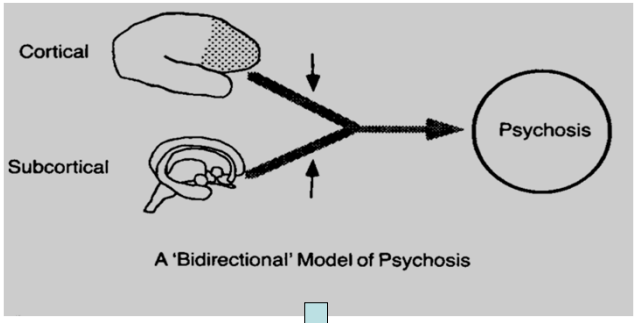



**Figure 8–6.** Dopaminergic systems of the brain. Three main dopaminergic nuclei occur in the brain. The substantia nigra pars compacta projects to the striatum (*upward dashed arrows*); the ventral tegmental area projects to the nucleus accumbens and some regions of cerebral cortex (*solid arrows*); and the arcuate nucleus of the hypothalamus projects to the tuberoinfundibular area of the hypothalamus, which is in close proximity to the pituitary stalk. (*downward dashed arrow*).

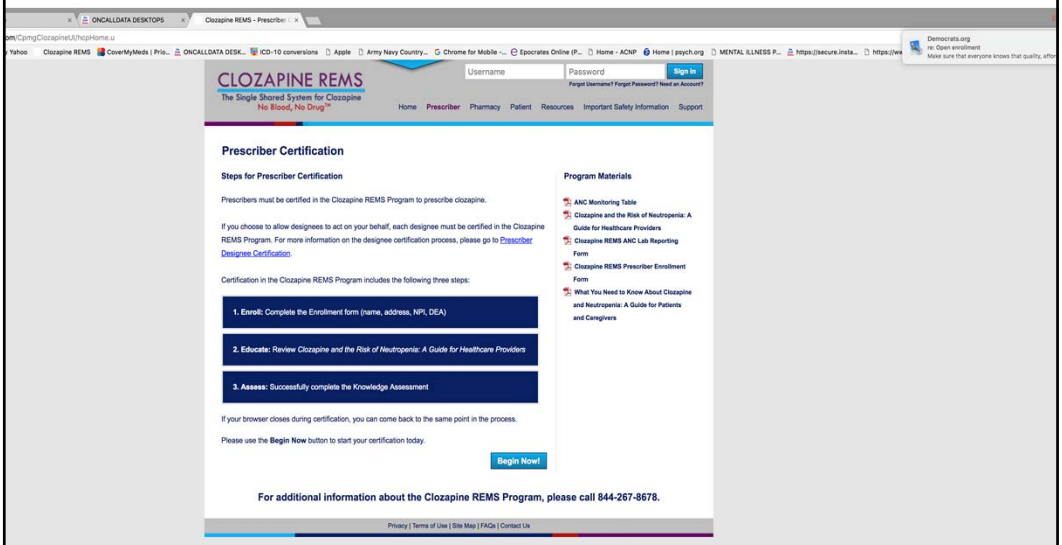
# Regional Dopamine Dysfunction




**Targeted Drug Effect**

1. Enhance Cortical Dopamine Release
2. Modulate Subcortical Systems

# Clozapine Risk Evaluation and Mitigation Strategy (REMS)



Article

## Effect Size of Symptom Status in Withdrawal of Typical Antipsychotics and Subsequent Clozapine Treatment in Patients With Treatment-Resistant Schizophrenia

David Pickar, M.D.

John J. Bartko, Ph.D.

**Objective:** In light of the efficacy of newer antipsychotic agents and the possibility that drug withdrawal may negatively affect subsequent drug response, concern has arisen that the use of placebo in schizophrenia research may be unethical. This study examines the effect size of symptom exacerbation during drug washout with placebo and the effects of drug washout on the efficacy of subsequent drug treatment.

**Method:** Fifty patients with treatment-resistant schizophrenia hospitalized on a research unit participated in a double-blind longitudinal study of the effects of drug washout after chronic treatment with a typical antipsychotic and before prospective treatment with clozapine. Brief Psychiatric Rating Scale (BPRS) scores were analyzed to examine drug effects and effect sizes for baseline treatment with a typical antipsychotic (>6 months treatment), drug washout with placebo (mean=34 days), early treatment with clozapine (mean=42 days, mean dose=345.0 mg/day), and optimal clozapine treatment (mean=83 days, mean dose=450.5 mg/day).

**Results:** Patients' BPRS total, positive, and negative symptom scores significantly increased during placebo washout, compared with baseline treatment, and significantly decreased with administration of clozapine, compared with placebo washout and baseline treatment. However, 30% of patients showed some symptom improvement during placebo washout. The effect sizes for the BPRS total score were 0.63 for baseline treatment versus placebo washout, 1.10 for optimal clozapine treatment versus placebo washout, and 0.82 for optimal clozapine treatment versus baseline treatment.

**Conclusions:** Symptom exacerbation induced by drug withdrawal in patients with treatment-resistant schizophrenia did not impede subsequent responsiveness to clozapine. The effect size for clozapine, compared with typical antipsychotics, suggests that the drug-washout longitudinal design is useful for establishing a drug-free baseline and for investigating drug response, while requiring relatively few subjects.

*(Am J Psychiatry 2003; 160:1133–1138)*

Two trends of the past decade have had a major influence on clinical trials of new drugs to treat schizophrenia: 1) increasing concerns about whether the use of drug anisms and clinical outcome in schizophrenia (7), although this thesis remains controversial (8–12). Whereas it is untenable to argue that psychotic exacerbation brought

29

# *NIMH MATRIC Initiative*

*The National Institute of Mental Health (NIMH) Initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), was designed to stimulate the development of psychopharmacological agents to improve cognition in schizophrenia*

MATRICS Assessment Inc.

- *The MCCB includes ten tests that measure seven cognitive domains.*
- *Speed of processing*
- *º BACS: Symbol Coding*
- *º Category Fluency: Animal Naming*
- *º Trail Making Test: Part A*
- *Attention/vigilance*
- *º CPT-IP*
- *Working memory*
- *º WMS®-III: Spatial Span*
- *º Letter-Number Span*
- *Verbal learning*
- *º HVLT-RTM*
- *Visual learning*
- *º BVMT-RTM*
- *Reasoning and problem solving*
- *º NAB®: Mazes*
- *Social cognition*
- *º MSCEITTM: Managing Emotions*

## Matrics Cognitive Battery

- Processing Speed
- Attention Vigilance
- Working Memory
- Verbal Learning
- Visual Learning
- Working Memory
- Social Cognition
- Reasoning and Problem Solving

## No Treatment – new or old – has shown effectiveness with Matric Battery

PANSS Negative Symptoms are responsive to Clozapine and some antipsychotic treatment in association with positive symptom reduction

# *Off Label Use for Treatment of Schizophrenia*

- *Antipsychotic monotherapy is the only approved treatment for schizophrenia.*
- *No Drug Combinations are approved for the treatment of schizophrenia*
- *Off-Label use is legal and may be of benefit to the patient*
- *Liability – community standards*

**Table 3. Antipsychotic Usage.**

| Medication Abbreviaton | Treatment | Count | Percent |
|---|---|---|---|
| *FGA = First Generation Antipsychotic Drug* | SGA without FGA | 148 | 74 |
| *SGA = Second Generation Antipsychotic Drug* | FGA without SGA | 15 | 7.5 |
| | FGA+SGA | 28 | 14 |
| | No Antipsychotic Drug | 9 | 4.5 |
| | TOTAL | 200 | 100 |
| | Percent of FGA administration that also received SGA administration | 28 of 43 | 65 |
| | More than one SGA | 60 | 30 |
| | More than one FGA | 8 | 4 |
| | More than one APS | 85 | 42.5 |

doi:10.1371/journal.pone.0003150.t003

Pickar D, Vinik J, Bartko JJ (2008) Pharmacotherapy of Schizophrenic Patients: Preponderance of Off-Label Drug Use. PLOS ONE 3(9): e3150. https://doi.org/10.1371/journal.pone.0003150
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0003150

**Table 4. All Medication Class Combinations.**

| Medication Class | Treatment | Count | Percent |
|---|---|---|---|
| *AA = Anti-Anxiety* | No Medication | 5 | 2.5 |
| *AD = Antidepressant* | AA | 0 | 0 |
| *MS = Mood Stabilizer* | AD | 3 | 1.5 |
| *APS = Anti-Psychotic* | MS | 0 | 0 |
| | APS | 51 | 25.5 |
| | AD+AA | 0 | 0 |
| | MS+AA | 0 | 0 |
| | MS+AD | 0 | 0 |
| | MS+AD+AA | 1 | .5 |
| | APS+AA | 5 | 2.5 |
| | APS+AD+AA | 8 | 4 |
| | APS+AD | 38 | 19 |
| | APS+MS | 51 | 25.5 |
| | APS+MS+AA | 8 | 4 |
| | APS+MS+AD | 22 | 11 |
| | APS+MS+AD+AA | 8 | 4 |
| | TOTAL | 200 | 100 |

doi:10.1371/journal.pone.0003150.t004

Pickar D, Vinik J, Bartko JJ (2008) Pharmacotherapy of Schizophrenic Patients: Preponderance of Off-Label Drug Use. PLOS ONE 3(9): e3150. https://doi.org/10.1371/journal.pone.0003150
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0003150



**Table 5. Results of Linear Discriminant Function.**

| Clinical Predictor | APS+MS n = 89 | APS+AD n = 76 |
|---|---|---|
| DX | F = 15.69, p<.001 | |
| Total # hospitalizations | | F = 7.48, p = .006 |
| Ever Hurt Someone | F = 6.0, p = .015 | |
| Montgomery-Asberg Total | | F = 6.7, p = .01 |
| PANNS Gen Psych | F = 5.34, p = .022 | |

doi:10.1371/journal.pone.0003150.t005

Pickar D, Vinik J, Bartko JJ (2008) Pharmacotherapy of Schizophrenic Patients: Preponderance of Off-Label Drug Use. PLOS ONE 3(9): e3150. https://doi.org/10.1371/journal.pone.0003150
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0003150

PLOS ONE TENTH ANNIVERSARY

## Met-Analysis for Cotreatment added to Antipsychotic Monotherapy of Schizophrenia

Correll et al, 2017

- "No single strategy can be recommended for patients with schizophrenia based on current meta-analytic literature"
- Limitations due to poor quality meta-analyses

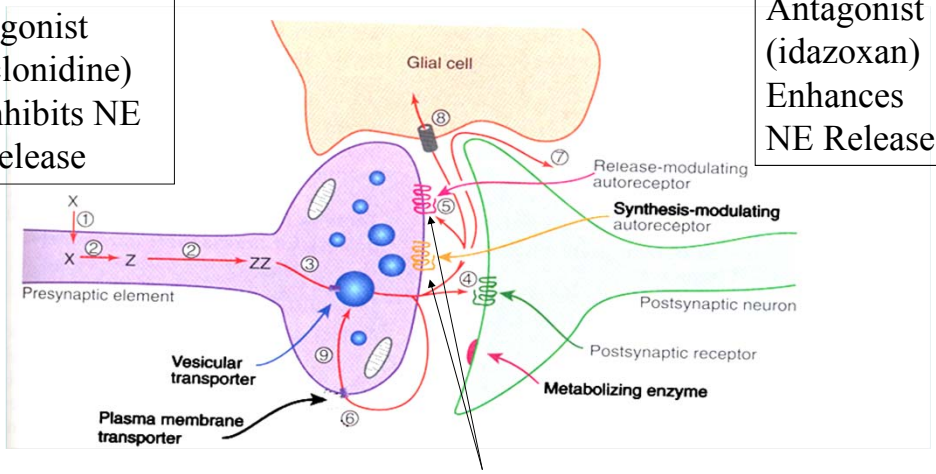
## NIMH Recovery After and Initial Schizophrenia Episode (RAISE)

- Kane et al, 2016
  - Comprehensive multidisciplinary treatment vs community care for 2 years following initial psychotic episode
  - RAISE improved quality of life, function and some symptoms
  - Improvement related to shorter duration of initial episode
  - No difference between RAISE and community Care for subsequent hospitalizations.

# $\alpha_2$ NE Autoreceptor (Presynaptic Adrenoceptor)

Agonist (clonidine) Inhibits NE Release

Antagonist (idazoxan) Enhances NE Release

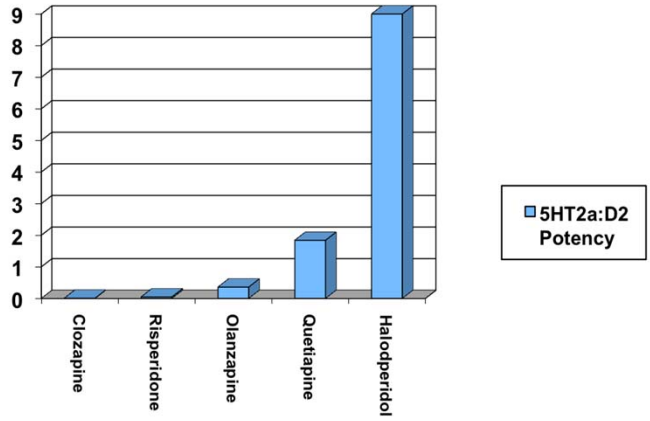



$\alpha_2$ Receptor

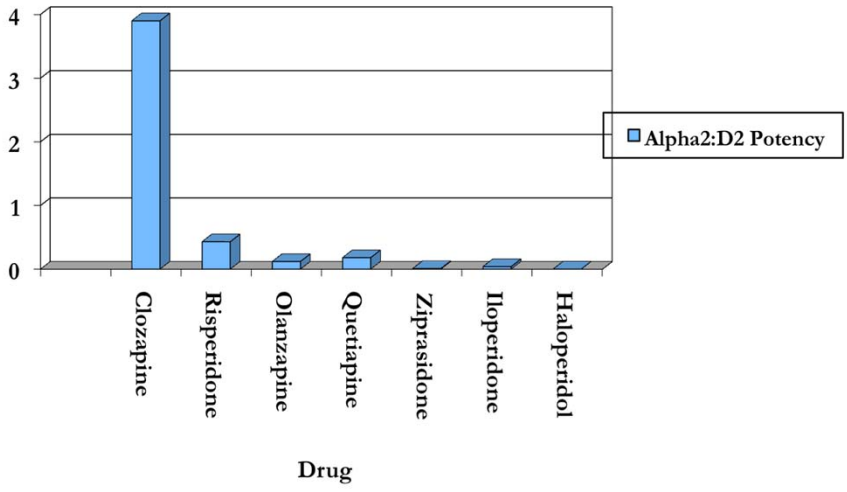
# Alpha2 Antagonist Augmentation of D2 blockers: Idazoxan

- Based on pharmacology of clozapine
- Without neutropenia
- Stay tuned

# $5HT_{2a}$:$D_2$ Receptor Affinities in Second Generation Antipsychotics



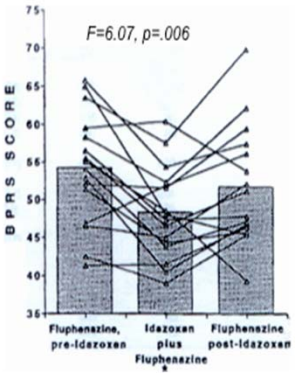

# Most Unique Facet of Clozapine Receptor Pharmacology: $\alpha_2$:$D_2$ Receptor Affinity Balance



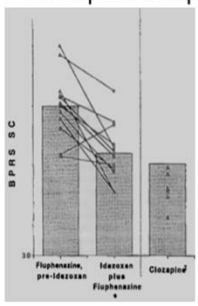
# Litman et al, Results

## Idazoxan + Fluphenazine (Prolixin)

IDAZOXAN AUGMENTS FLUPHENAZINE

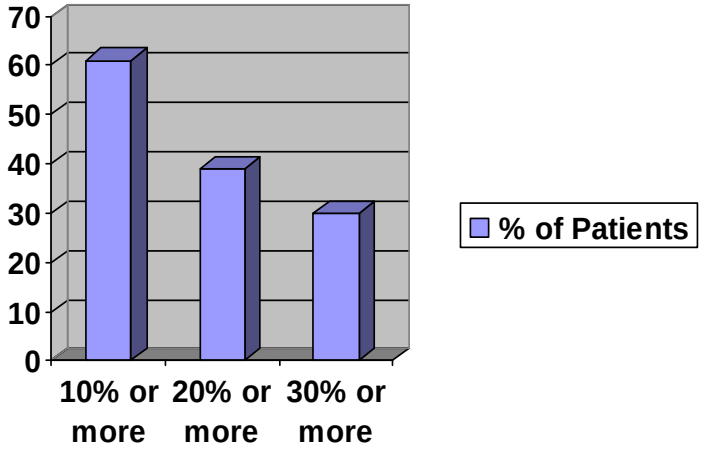



IDAZ + Fluph Is Comparable To Clozapine Response




Clozapine treatment Following 3 week drug washout

# Cumulative % of Patients with Reductions in Thought Disorder Cluster (n=23)



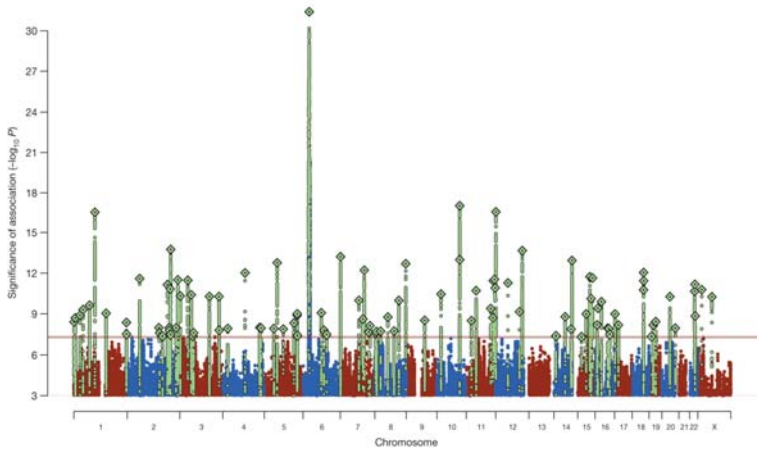
## Genetics and Schizophrenia

- YES
- 80% heritability base on monozygotic/dizygotic twins
- Environmental factors clearly exist

## Genome-Wide Association Studies (GWAS)

- GWAS scans the entire genome for differences between the disease groups
  - Very, very large datasets required ef, >30,000 Cases
  - Chromosome regions (loci) identified
  - Sophisticated statistical analysis to pick up even small increases in the number of specific genetic variants that might contribute to risk (SNP's, CNVs)
- No single gene appears to be key
  - 108 genetic loci have been linked to schizophrenia (Ripke et al, 2014)
  - C4 (complement component 4), GRM3 (glutamate metabolic receptor 3), DRD2 (receptor for D2 receptor) have signal

Manhattan plot showing schizophrenia associations.




S Ripke *et al. Nature* **000**, 1-7 (2014) doi:10.1038/nature13595

nature

# Candidate Gene Variants: On the Outs but Look For Return

- Clinical correlates with invidividual candidate genes
- Clinical information beyond diagnosis is critical
- Ultimately necessary to render CWAS relevant