Transforming Care for Individuals Living with Psychosis

VIRTUAL CONFERENCE

OCTOBER 12, 2023

9:00AM to 12:00PM

Provided by:
Healthfirst and Albert Einstein College of Medicine—Montefiore Medical Center

healthfirst
Health Insurance for New Yorkers

Montefiore Einstein

Transforming Care for Individuals Living with Psychosis

PROGRAM OVERVIEW

Schizophrenia is a severe mental disorder characterized by positive, negative, and cognitive symptoms. The treatment of schizophrenia was revolutionized in the 1950's by the introduction of chlorpromazine. However, despite the evolving options of both first- and second-generation antipsychotics, some patients show little if any clinical response to many different antipsychotics.

This program aims to address common barriers to effective treatment of psychotic disorders including delayed onset of treatment, and lack of provider knowledge for when and how to initiate clozapine for individuals with treatment resistant schizophrenia and strategies for managing and mitigating common side effects of antipsychotics to improve adherence.

Participants will identify barriers to use/ optimal use of antipsychotic medications for persisting psychosis and expand their knowledge base of strategies for using FDA approved medications for treatment resistant schizophrenia to advance and improve clinical and quality of life outcomes among target population.

EDUCATIONAL OBJECTIVES

At the conclusion of the event, participants should be able to:

- Describe clinical and systemic barriers to early intervention of psychosis,
- Define treatment resistant schizophrenia (TRS) and understand the use case for a trial of FDA approved medication for TRS,
- Review best practices for initiation and management of antipsychotic medications including the management of predictable side effects,
- Consider ways to adopt clinical best practices within your practice setting (engagement, community, and effective use of antipsychotic medication) to promote meaningful recovery from persisting psychosis.

INTENDED AUDIENCE

This activity is designed for psychiatrists, psychiatric residents and psychiatric nurse practitioners in hospital and community settings.

ACCREDITATION STATEMENT

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, this activity has been planned and implemented by Albert Einstein College of Medicine—Montefiore Medical Center and Healthfirst. Albert Einstein College of Medicine—Montefiore Medical Center is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing (ANCC), to provide continuing education for the healthcare team.

CREDIT DESIGNATION STATEMENT

Albert Einstein College of Medicine–Montefiore Medical Center designates this live activity for a maximum of 3.0 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

FINANCIAL DISCLOSURE STATEMENT

The "Policy on Identification, Mitigation and Disclosure of Relevant Financial Relationships" of Albert Einstein College of Medicine-Montefiore Medical Center requires that any individual in control of content, including faculty, participating in CME/CE activities disclose to the audience all relevant financial relationships with ineligible companies* in the last 24 months. Any individual in control of content who refuses to disclose, or their disclosed relationships prove to create a conflict of interest, will be recused. Individuals with the absence of relevant financial relationships with ineligible companies will be disclosed to the audience.

All financial relationships of individual(s) in a position to control the content of this CME/CE activity has been identified and mitigated prior to this educational activity.

**The ACCME defines an ineligible company as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.*

DISCLOSURES

Dr. Carruthers has no relevant financial relationship with an ACCME-defined ineligible company in the past 24 months.

Dr. Forman has no relevant financial relationship with an ACCME-defined ineligible company in the past 24 months.

Dr. Laitman has no relevant financial relationship with an ACCME-defined ineligible company in the past 24 months.

REGISTRATION

If you need additional information or to register for the conference, please email Angela Sullivan, Manager, Provider Education, asullivan@health.org or call 917-748-8455.

DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed in this activity should not be used by clinicians without evaluation of patient conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

FUNDING ACKNOWLEDGMENT

This activity has not received any commercial support from an ineligible company.

AGENDA

Thursday, October 12, 2023

8:50AM–9:00AM	**Welcome** Donna Lynn Taylor, MSN, RN, CCM *Clinical Director, Behavioral Health Services* *Healthfirst* **Opening Remarks** Jay W. Carruthers, MD *Director of Suicide Prevention Center,* *New York State Office of Mental Health* *Assistant Professor, Department of Psychiatry, Albany Medical College* **Introduction to CME Activity** Howard L. Forman, MD *Behavioral Health Medical Director,* *CMO Montefiore Care Management* *Assistant Professor of Psychiatry, Albert Einstein College of Medicine*
LECTURE	
9:00AM–10:30AM	**Transforming Care for Individuals Living with Psychosis – Part 1** Robert Laitman, MD, MS
10:30AM–10:40AM	**10-minute Break**
10:40AM–11:45AM	**Transforming Care for Individuals Living with Psychosis – Part 2** Robert Laitman, MD, MS
11:45AM–12:00PM	**Question and Answer Session**
ADJOURN	

Course Director/Moderator

Howard L. Forman MD

Behavioral Health Medical Director, CMO Montefiore Care Management, Assistant Professor of Psychiatry, Albert Einstein College of Medicine

Howard L. Forman, MD, is Director of Addiction Consultation Service at Montefiore and Assistant Professor at our Albert Einstein College of Medicine. His clinical interests focus on the intersection of addiction, mental health, and physical illness. Dr. Forman is also a leading forensic expert who has been retained by state prosecutors, federal prosecutors, leading law firms across the country.

In addition to his areas of clinical focus, he is a nationally sought-after lecturer, and his research has been published in peer-reviewed journals and abstracts. He is also co-author of Prescription Drug Abuse, a book exploring the risks and controversies surrounding the issue of prescription drug abuse and misuse. He is the book review editor for the Psychiatric Times and his opinions have been featured in outlets as varied as the Rolling Stone Magazine and the New York Times. For several years, he was a columnist for US News and World Report. For more on Dr. Forman, please visit his profile here.

Faculty

Robert Laitman, MD, MS

Nephrology, Internal Medicine, Northwell Health

Robert Laitman, MD, MS has expertise in psychiatric internal medicine with a specialty in the optimal management of psychotic disorders with clozapine. He is co-author of Meaningful Recovery from Schizophrenia and Serious Mental Illness with Clozapine, a book which explores the gross underutilization of clozapine in America and its important role in treatment as the gold standard and only FDA approved medication for treatment resistant schizophrenia and suicidality. He is cofounder and copresident of Team Daniel Running for Recovery from Mental Illness, a nonprofit organization offering hope and help to individuals and families living with mental illness by organizing social and recreational events to bring them together and by helping them negotiate the healthcare system to find the best treatments available to them. In 2023, Dr. Laitman and his family were honored by Laurel House in Connecticut, for their advocacy and dedication to people and families struggling with Serious Mental Illness.

Dr. Laitman received a BA/MS from Northwestern University and an MD from Washington University in St. Louis. He is triple board certified in Internal Medicine, Nephrology, and Geriatrics.

For more information about Dr. Laitman, clozapine and Team Daniel please visit: Schizophrenia, Clozapine, Team Daniel Running, New York (teamdanielrunningforrecovery.org)

Transforming Care for Individuals Living with Psychosis

ROBERT LAITMAN, MD, MS

OCTOBER 12, 2023

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EINSTEIN Albert Einstein College of Medicine Montefiore

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DISCLOSURES

The following faculty have disclosed that they have no relevant financial relationships with ineligible companies in the past 24 months:

Jay W. Carruthers, MD

Howard Forman, MD

Robert Laitman, MD, MS

Donna Taylor, MSN, RN, CCM

Purpose and Objectives

PURPOSE	This program aims to address 1. common barriers to effective treatment of psychotic disorders 2. lack of provider knowledge for when and how to initiate clozapine 3. strategies for managing and mitigating common side effects of antipsychotics to improve adherence.

EDUCATIONAL OBJECTIVES

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1. Describe clinical and systemic barriers to early intervention of psychosis.
2. Define treatment resistant schizophrenia (TRS) and understand the use case for a trial of FDA approved medication for TRS.
3. Review best practices for initiation & management of antipsychotic medications & management of predictable side effects.
4. Consider ways to adopt clinical best practices within your practice setting to promote meaningful recovery from persisting psychosis

FINANCIAL DISCLOSURE	*None*

Agenda

1. Introduction
2. Clinician's Perspective: Schizophrenia Spectrum Disorders
3. Review Standard Treatment
4. Discuss Use Case for Alternative (Optimal) Treatment Approach for TRS
5. Management of Predictable Side effects
6. Break
7. Team Daniel Experience
8. Closing Comments
9. Discussion/ Question & Answer

Introduction

My son Daniel

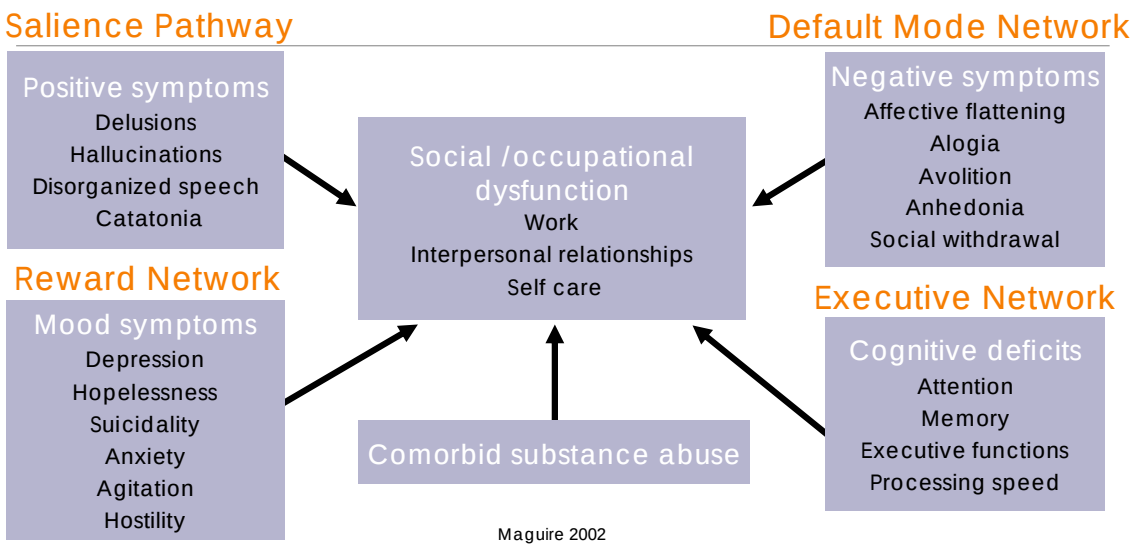
Daniel, 15 with family and voices

Daniel with his twin sisters

Our Daniel

Schizophrenia Spectrum Disorder A Clinician's View

Clinical Features of Psychosis



Maguire 2002

Harsh Realities

- Cerebral: A serious brain disease
- Common: 1.1% schizophrenia/2.2% severe bipolar of population
- Cognitive: Impairment is a central problem
- Costly: 2% of GNP, nearly $340 Billion in direct and indirect costs
- Chronic: Lifelong morbidity and increased mortality
  - 10 - 28 years shorter than the general population
  - 40% of this is due to suicide, with 10% - 15% lifetime completed suicide rates
- Crippling: One of 10 leading causes of disability in world (WHO)
- Circuitry Disorder: Neuro-circuitry due to a combination of genetic and environmental factors

5 Clinical Themes

Neurodevelopment

Development of Cognitive and Negative Symptoms, The Prodrome

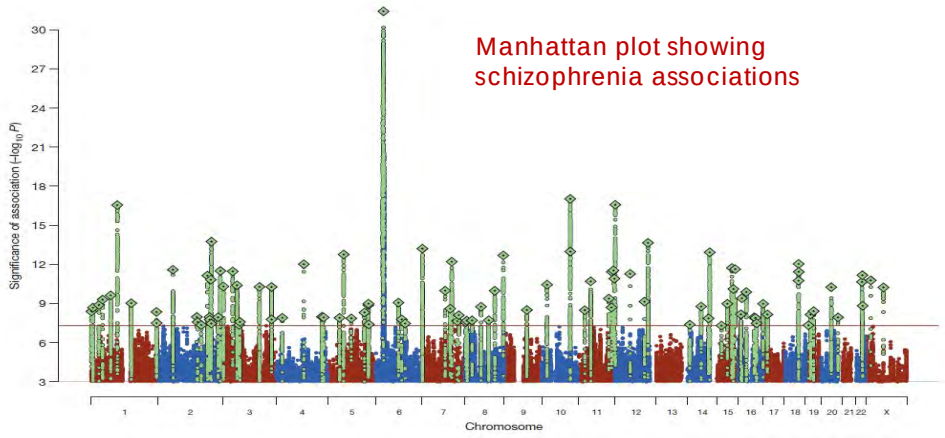
Onset of Psychosis

Current Treatments

The Future

Genetic and Early Environmental Risk Factors on Neurodevelopment

Schizophrenia Risk Associated with 108 Genomic Regions



Manhattan plot showing schizophrenia associations

Schizophrenia Working Group of the Psychiatric Genomics Consortium. Nature 2014; 511(7510):421–427.

Table. Association of Environmental Factors With the Risk of Schizophrenia[a]

Risk Factor	Odds Ratio (95% CI)
Obstetric complications	1.84 (1.25-2.70)
Winter birth in the northern hemisphere	1.04 (1.02-1.06)
Childhood trauma	2.87 (2.07-3.98)
Urban living	2.19 (1.55-3.09)
Migration (first generation)	2.10 (1.72-2.56)[b]
Cannabis use	5.17 (3.64-7.36)

[a] Odds ratios were taken from Radua et al.[49]

[b] An incidence rate ratio is reported, rather than an odds ratio.

Schizophrenia—An Overview
Robert A. McCutcheon, MRCPsych; Tiago Reis Marques, PhD; Oliver D. Howes, PhD
Published online October 30, 2019.

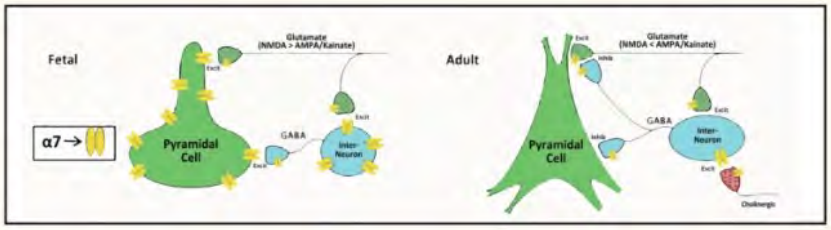
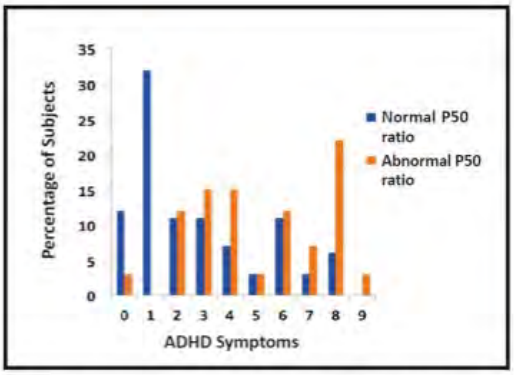


Figure 2.

Activation of alpha-7 nicotinic receptors in fetus and adults

During fetal development (left panel), cerebral alpha-7 nicotinic receptors are found on both pyramidal cells and interneurons. Choline in the extracellular fluid, rather than synpatic release of acetylcholine from cholinergic synapses (which have not yet reached the cerebrum), activates these fetal receptors. Postnatally (right panel), when cholinergic innervation has developed, acetylcholine activates the receptors, which are then restricted to interneurons. The activation of alpha-7 nicotinic receptors is required for the conversion of GABA from excitatory in fetal life to inhibitory in adult life and for the conversion of excitatory glutamate neurotransmisson from slower NMDA-type receptors to faster AMPA/kainate-type receptors.

Prenatal choline and the development of schizophrenia
Robert Freedman and Randal G. ROSS
Published April 25, 2015



Relationship of cerebral inhibition assessed by auditory evoked P50 ratio during the first month of life with the number of attentiondeficit hyperactivity symptoms at 40 months of age (reprinted with permission from Hutchison et al.[50])

Fifty children were included in the study. The Child Behavior Checklist, completed by the parents, was used to assess the number of ADHD symptoms at 40 months of age. Inhibition at one month was a significant predictor of the number of attention deficit-hyperactivity symptoms at 40 months ($F_{1,46} = 5.40$, $p = 0.025$).

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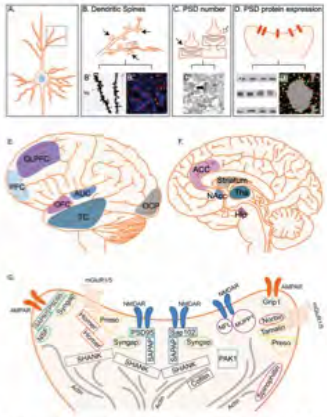
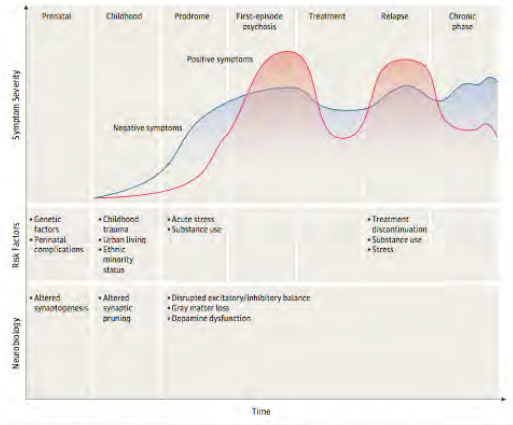


Fig. 1. Schematic representation of postsynaptic element measurements and brain regions included in the meta-analysis. Panel (A)–(D) show measurements that are used to quantify postsynaptic elements in postmortem brain tissue. (A) shows a neuron with its dendritic tree. The enlargement in (B) shows that each dendrite contains numerous dendritic spines (arrows), which can be quantified using Golgi staining (B′ from Glantz and Lewis, 2000[74]) or immunohistochemistry (B″ from Shelton et al, 2015[75]). In (C), presynaptic terminals innervate postsynaptic densities (PSD) on a dendritic spine (white arrow), forming an axospinous synapse, or directly on the dendrite (black arrow), forming an axodendritic synapse. The number of these PSD can be measured with electron microscopy (C′ from Roberts et al, 2015). The PSD in (D) is an accumulation of many postsynaptic proteins at the postsynaptic membrane, which can be quantified by western blot (D′ from Clinton et al, 2006) or immunohistochemistry (D″ from Chung et al, 2016). (E)–(G) provide a simplified representation of brain regions and proteins in the PSD that are assessed in studies included in our meta-analysis: PFC, prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; OC, olfactory cortex; AC, auditory cortex; TC, temporal cortex; OCP, occipital cortex; ACC, anterior cingulate cortex; Nacc, nucleus accumbens; Tha, thalamus; Hip, hippocampus.

Synapse Pathology in Schizophrenia: A Meta-analysis of Postsynaptic Elements in Postmortem Brain Studies
Amber Berdenis van Berlekom, Cita H. Muflihah, Gijsje J. L. J. Snijders, Harold D. MacGillavry, Jinte Middeldorp, Elly M. Hol, René S. Kahn and Lot D. de Witte
Published June 13, 2019

Cortical-Excitatory Imbalance and The Development of Cognitive and Negative Symptoms

Figure 1. The Clinical Course of Schizophrenia



People who go on to develop schizophrenia may show subtle motor and cognitive deviation in childhood but do not show the marked developmental delays associated with autism and intellectual disabilities. During late adolescence or early adulthood, a prodromal phase characterized by attenuated psychotic, negative, and cognitive symptoms and functional impairment often precedes the first psychotic episode. The first psychotic episode occurs when symptoms meet the threshold for a clinical diagnosis, as opposed to the subthreshold symptoms seen in the prodrome (although these may still be debilitating). The first psychotic episode is frequently the first contact with services, although patients are increasingly seeking help in the prodromal period. The positive symptoms generally respond well to antipsychotic medication, but negative and cognitive symptoms show less response and may even be exacerbated by antipsychotic medication in some cases. Most patients will relapse after stopping antipsychotic treatment, and the risk of relapse is reduced by continued antipsychotic treatment even when psychotic symptoms have fully resolved. This Figure also highlights some key risk factors for the development of schizophrenia together with neurobiological changes thought to be relevant to the development of symptoms. Note that altered synaptogenesis and synaptic pruning have not been clearly demonstrated in vivo, and the precise timing regarding all the changes listed remains unclear.

Schizophrenia—An Overview, Robert A. McCutcheon, MRCPsych; Tiago Reis Marques, PhD; Oliver D. Howes, PhD
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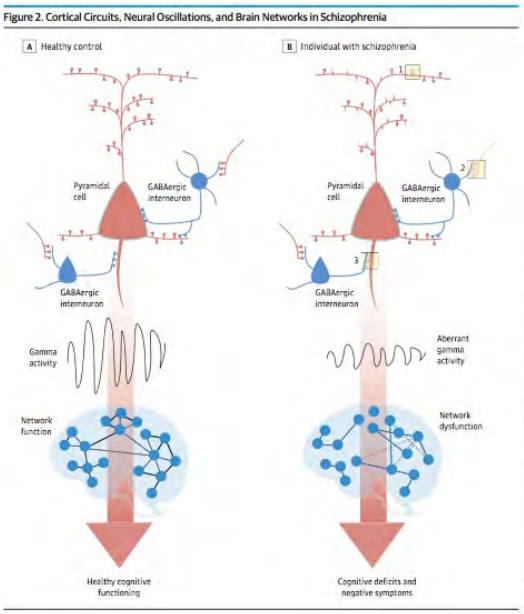

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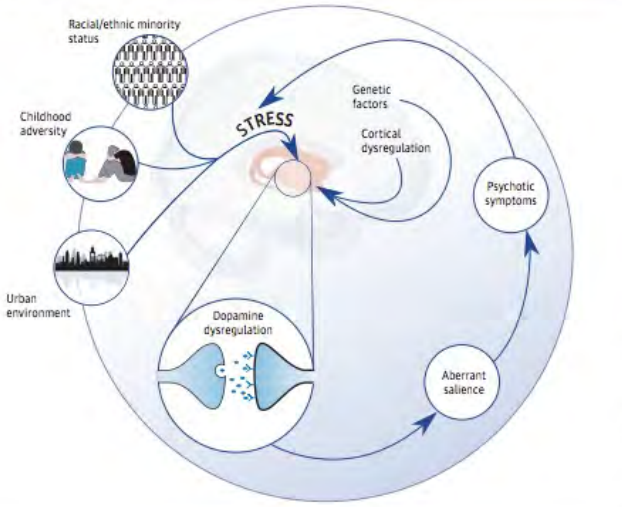
Onset of Psychosis

SUBCORTICAL DOPAMINE DYSREGULATION

Figure 3. Stress, Dopamine, and Psychosis



Psychosocial stressors sensitize the subcortical dopamine system to increase the response to subsequent triggers, while cortical deficits mean that regulatory control is also impaired. Later triggers, such as stress, then lead to inappropriate striatal dopamine release. This leads to the aberrant assignment of salience to stimuli and the development of psychotic symptoms. Psychosis itself is stressful, and this in turn may provide feedback that further dysregulates the system.

Schizophrenia—An Overview
Robert A. McCutcheon, MRCPsych; Tiago Reis Marques, PhD; Oliver D. Howes, PhD
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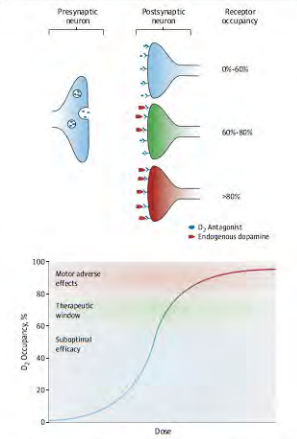
Figure 4. Dopamine Receptor Blockers, Treatment Response, and Adverse Effects



Positron emission tomography studies of D_2-antagonist antipsychotic drugs have shown that striatal D_2-receptor occupancy greater than 60% is generally required for a patient to have a high likelihood of improving but that occupancy levels greater than 80% are associated with a high likelihood of motor adverse effects. This suggests there is a therapeutic window of about 60% to 80% D_2-receptor occupancy by antipsychotic drugs that balances a high likelihood of improvement with a low risk of motor adverse effects. Fortunately, the licensed dosages for most recently licensed antipsychotic drugs generally correspond to this occupancy range. There are exceptions to this therapeutic window, for example, people with rapid metabolism may require higher dosages, partial agonists occupy a higher proportion of D_2 receptors, and clozapine generally leads to lower levels of D_2 occupancy. Positron emission tomography studies have also shown that high D_2 occupancy does not guarantee response, indicating that while D_2 occupancy is necessary in most patients, it is not sufficient in some patients.

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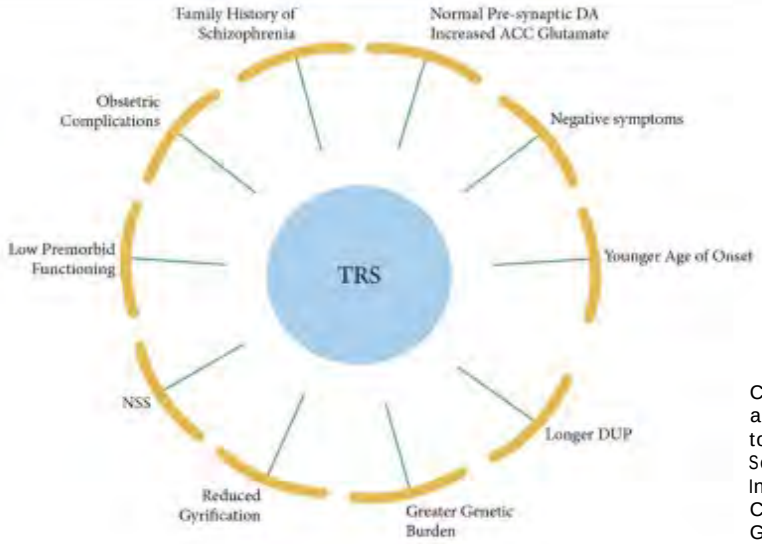
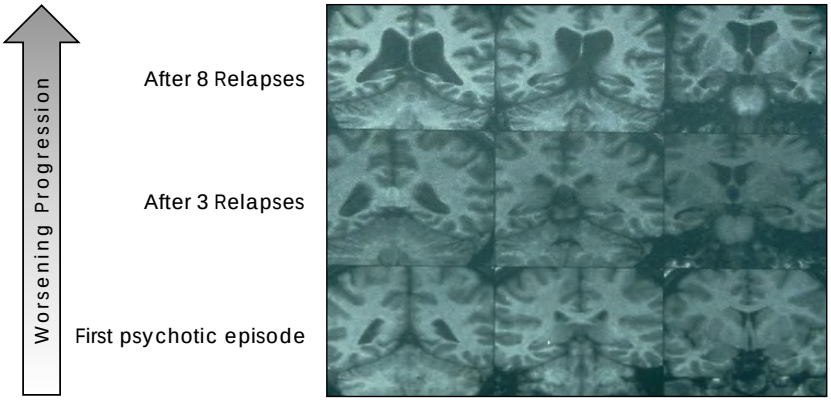


TRS- Treatment Resistant Schizophrenia, DA- Dopamine, DUP- Duration of Untreated Psychosis, PRS- Polygenic Risk Score, NSS- Neurological Soft Signs

FIGURE 3 | Putative model integrating factors that are associated with treatment resistance in schizophrenia.

Clinical Course, Neurobiology and Therapeutic Approaches to Treatment Resistant Schizophrenia. Toward an Integrated View. Cheryl Cheuk-Yan Leung, Romayne Gadelrab, Chukwuma Uchenna Ntephe, Philip K. McGuire and Arsime Demjaha
Published 03 September, 2019

PROGRESSIVE MRI CHANGES OVER THREE RELAPSES IN A MALE WITH SCHIZOPHRENIA



Nasrallah, HA. personal files

Rethinking of Schizophrenia

Classifying as "neurological illness" is profoundly new view from past centuries:

- Offers best potential to shift from discrimination into action for millions of lives
- Provides new Roadmap for comprehensive and integrated care, treatment and acceptance
- New hope for prevention and cure over the next two decades

Key Realities:

- These illnesses begin in prenatal or perinatal life, not adolescence
- Early diagnosis and treatment is critical
- There's a massive gap between established clinical/scientific knowledge and the inadequacies in existing systems of care

Potential to Improve Millions of Lives

Prevalence and Treatment Rates*

8.3 million adults with schizophrenia or bipolar disorder brain illness (3.3% of the population)+
5.5 million – approximate number with severe bipolar disorder (2.2% of the population), 51% untreated+
2.8 million – approximate number with schizophrenia (1.1% of the population), 40% untreated+
3.9 million – approximate number untreated in any given year (1.6% of the population)+

Consequences of Non-treatment*

169,000 homeless people with serious mental illness**
383,000 inmates with mental illness in jails and prisons
50% – estimated percentage of individuals with schizophrenia or bipolar who attempt suicide during their lifetimes
44,193 suicide deaths in 2015
10% – estimated percentage of homicides involving an offender with serious mental illness (approximately 1,425 per year at 2014 homicide rates)
29% – estimated percentage of family homicides associated with serious mental illness
50% – estimated percentage of mass killings associated with serious mental illness

* Numbers and percentages of US adults
+National Institute of Mental Health, 2016
**2015 Annual Homeless Assessment Report

Medications
Standard Treatment of Schizophenia/Psychotic Illnesses (including TRS)

First Generation ((typical)	Second Generation (atypical)
Chlorpromazine (Thorazine)	Aripiprazole (Abilify)
Fluphenazine (Prolixin)	Asenapine (Secuado)
Haloperidaol (Haldol)	Brexpiprazole (Rexulti)
Loxapine (Adusuve)	Cariprazine (Vraylar)
Molindone (Moban)	lioperidone Ifanapt)
Perphenazine (Trilafon)	Lumateperone (Caplyta)
Pimozide (Orap)	Lurasidone (Latuda)
Prochlorperazine (Compazine,Compro)	Olanzapine (Zyprexa)
Thiothixene (Navane)	Quetiapine (Seroquel)
Thoridazine (Mellaril)	Paliperidone (Invega)
Trifluoperazine (Stelazine)	Risperidone (Risperdal)
	Ziprasidone (Geodone)

"Good Enough"

Current treatment approach does not address the most disabling symptoms

We can do better, we have the evidence

Standard Treatment

Clozapine: An Historical Perspective

Clozapine has always challenged the mental health system

1953: FDA approved first Pharma "Blockbuster" Thorazine.

1958: Clozapine Synthesized by Schmutz.

1960: Clozapine was patented; patients and family loved it.

Unfortunately, psychiatry avoided clozapine; most were preoccupied with the dopamine model for psychosis.

1989: Clozapine was FDA approved but held to an unprecedented standard.

- Demonstrated marked improvement in treatment refractory population when compared to standard of care.
- Sandoz bundled clozapine with the required blood monitoring; significantly increasing costs.
- Clozapine was heavily restricted and rationed.

Clozapine Risks

- Agranulocytosis - Dangerously low neutrophils (white blood cells)
- Seizures
- Intractable weight gain in over 80% and diabetes
- Unremitting sedation
- Drooling
- Intractable constipation
- Myocarditis and heart failure
- Rebound psychosis if withdrawn
- Venous Thromboembolism (VTE)
- Pulmonary Infection

Clozapine Benefits

- FDA indicated for treatment-resistant schizophrenia, however:

  IT IS THE MOST EFFECTIVE MEDICATION IN ALL SETTINGS.
- Reduces suicide (FDA indicated).
- Reduces violent behavior.
- Reduces substance abuse
- Allows patients to robustly participate and succeed in physical, social and cognitive rehabilitation.
- Best acceptance, lowest discontinuation, and best survival.

Major Benefit: Lowers Risk of Death

First year of psychotic illness the risk of death 24 to 89 times for ages 16-30.

Suicide risk in psychotic spectrum illness:

- 50% attempt, 10% completion (3-5 % in the first year).
- Clozapine reduces this risk by 70-90% compared to other antipsychotics.
- 380 to 900 more survive for every 10,000 treated with clozapine.

Agranulocytosis risks, for comparison:

- Only 0.3% to 0.8% occurrence, with overall mortality of 1 to 2.5 per 10,000.
- 90- 95% of this risk occurs in the first 18 weeks.
- After 6 months the risk of death is no more than other antipsychotics.
- Context: Iceland does not monitor;1/10 of this 2/10,000.

Psychosis cuts life short by 20-25 years, mostly due to cigarette and drug use.

- Clozapine significantly reduces smoking and substance use disorders.

FDA's Mini-Sentinel Distributed Database: Query

Description	Code*
Diseases of white blood cells	288
Neutropenia	288.0
Neutropenia, unspecified	288.00
Congenital neutropenia	288.01
Cyclic neutropenia	288.02
Drug induced neutropenia	288.03
Neutropenia due to infection	288.04
Other neutropenia	288.09
Genetic anomalies of leukocytes	288.2
Hemophagocytic syndromes	288.4
Decreased white blood cell count	288.5
Leukocytopenia, unspecified	288.50
Other decreased white blood cell count	288.59
Unspecified disease of white blood cells	288.9

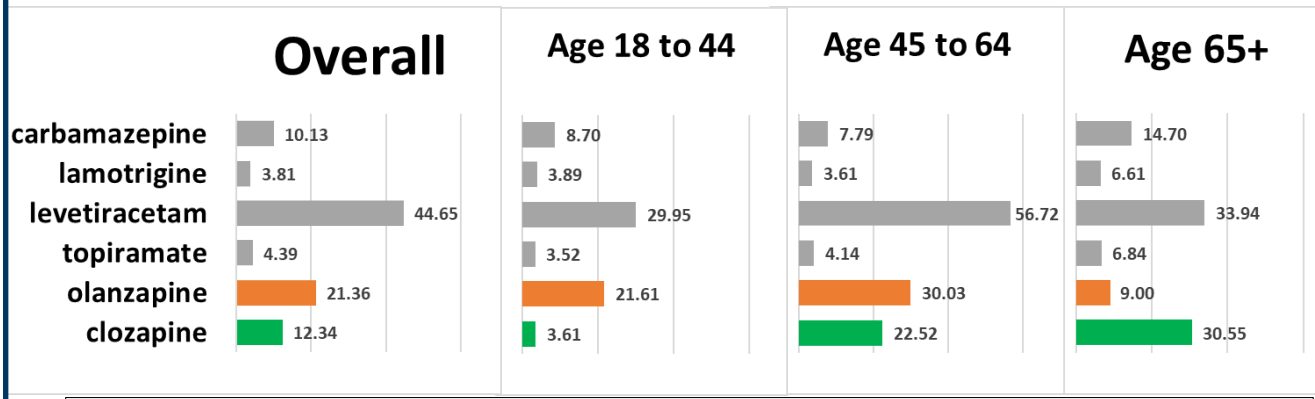
Note: "agranulocytosis" is not a named condition in the ICD-9-CM

The FDA's Database of 94M insurance plan subscribers from 2000 to 2013:

All *EVENTS* with primary diagnoses of neutropenia and related conditions

FDA's Mini-Sentinel Distributed Database: Results

Neutropenia Events per 10k Years at Risk (2000 – 2013)



In the age group 18 to 44 the incidence is FIVE TIMES HIGHER for olanzapine than clozapine

Characterization of Agranulocytosis (Taylor, 2022)

A 14-year study of ~3500 patients in clozapine registry

- 16 events of ANC falling below 0.5 were reported (0.46%)
- 7 of the 16 were excluded (4 normal on repeat, 1 was off clozapine, 1 on chemo, 1 lab error)
- 9 events in 8 patients considered life-threatening agranulocytosis (LTA) (0.23%)
- 6 of the 8 had previous neutropenia
- 0 deaths (0%)
- Mean duration of clozapine: 48 days, with a range of 21 to 105 days.
- Median age at initiation of treatment: 51 years, with a range of 25 to 72 years.
- *No events beyond that time frame.*

Taylor, D et al. Distinctive pattern of neutrophil count change in clozapine-associated, life-threatening agranulocytosis. *Schizophrenia* 8, 21 (2022).

Characterization of Agranulocytosis (Taylor, 2022)

- Most cases of agranulocytosis are not life-threatening
- May not even be clozapine-related
- Association with neutropenia is a result of surveillance bias
- Intensive blood monitoring reveals random, clinically silent, and non-pathological episodes of neutropenia

Mandatory Monitoring Causes More Harm Than Good.

Taylor, D et al. Distinctive pattern of neutrophil count change in clozapine-associated, life-threatening agranulocytosis. *Schizophrenia* 8, 21 (2022).

Live Longer on Clozapine

A Finnish 20-year Study of >62,000 Patients with Schizophrenia

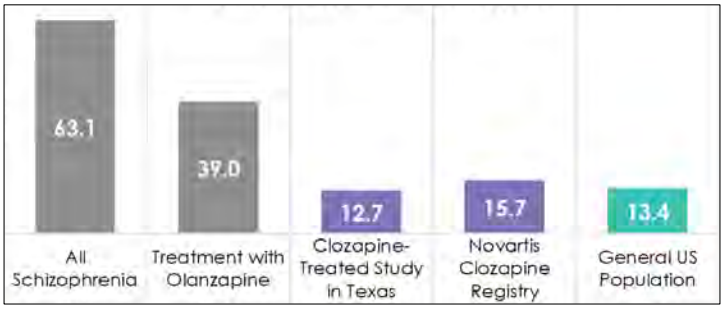
65% less likely to die than untreated patients with schizophrenia

25% to 50% less likely to die compared patients on other antipsychotics.

45% reduction in cardiovascular deaths

(Vermeulen JM, et al, 2019; Taipale H, et al (FIN20), 2020; Hayes RD, et al, 2015; Wimberley T, et al, 2017)

70% - 90% Reduction in Suicide



CLOZAPINE REDUCES SUICIDE RATE IN PATIENTS WITH SCHIZOPHRENIA

Annual Suicides Per 100,000

(Reid WH, et al, 1998; Meltzer HY, et al. 2003)

Optimal Treatment Approach for Clozapine in Treatment Resistant Schizophrenia & other Persisting Psychotic Disorders

EASE Method

A set of general principles that constitute the correct approach

E Early intervention with clozapine

A Assertive monitoring (TDM) & managing predictable side effects

S Slow titration

E Engage the patient and the family to provide support

Early Intervention with Clozapine

1. APA Guidelines: 2 antipsychotic trials of 2-4 weeks given in an adequate dose with minimal or no response, or Persistent risk of suicide, or Persistent risk of aggressive behavior.
2. TRRIP Working Group Consensus Guidelines for Clozapine: 2 antipsychotic trials of 6-week duration with doses equivalent to 600 mg chlorpromazine with documented 80% adherence documented by pill count and therapeutic drug monitoring.
3. Clozapine is the only effective antipsychotic for treatment-resistant schizophrenia. The response rate is <5% for all US available antipsychotics except Olanzapine which is 7%.
4. Delay in starting clozapine has Sequela: Delay in Clozapine initiation over 2.8 years predictor of failure to adequately respond.
5. First year of Psychotic illness associated with up to 5 % mortality of suicide and 50-fold mortality risk. Clozapine use here could reduce risk 90%.
6. There are no studies demonstrating that clozapine is inferior so the argument could be made that using it first is the best approach. Decrease duration of psychosis with the most effective and best patient accepted antipsychotic.

Assertive Monitoring & Management

1. Assertive monitoring allows you to confirm medication compliance.
2. Assertive Monitoring with Therapeutic drug monitoring(TDM) optimizes treatment affect as there is a clear dose response for both efficacy and side effects.
3. Threshold TDM 350 ng/ml. This is not optimal dose increased response seen with levels up to 1000 ng/ml but side effect management often more problematic over 700 ng/ml
4. Rational Polypharmacy “Doing the Medicine” can manage the side effects so that constipation, weight gain, excessive sialorrhea, tachycardia and other cardiac issues, seizure risk, and nocturnal enuresis can be dramatically mitigated.

Slow Careful Titration of Clozapine

1. Clozapine rarely first antipsychotic used so current antipsychotic must be slowly cross tapered off as clozapine is slowly initiated to avoid a rebound psychosis.
2. Slow titration dramatically improves side effects and overall tolerability leading to a decrease in discontinuation from over 50% to less than 10% secondary to afore mentioned side effects.
3. Slow titration minimizes risk for myocarditis and neutropenia
4. Slow titration allow you to find the optimal dose for any individual and minimizes the risk of dramatic overshoot.
5. For this reason, we start our stable outpatients at 12.5 mg at bed and only increase by 12.5 mg every 3 days. Standard to maintain current antipsychotic until clozapine is at 100 mg and then start cross taper.

Engagement of the Treated Individual and Family

1. Voluntary: Patients not experiencing anosognosia (less than 40%) may be receptive, especially since the typical journey to clozapine involves multiple failed antipsychotics and years of inadequate care. For patients with less pervasive anosognosia use LEAP. Amador's approach of reflective listening, followed by empathy and ultimately agreement and partnering toward a common goal.
2. Involuntary: Use the courts - Medication over objection as an inpatient and Assisted outpatient Treatment (AOT) to compel use.
3. NY AOT criteria (Kendra's Law) 2 or more admissions with documented non-adherence in a 3-year period and or violence in the setting of non-adherence.
4. Family must be involved as it is difficult to impossible to sustain a clozapine regimen without caregiver support. Train caregivers to observe patient symptoms and adherence. Never let Health Information Portability and Accountability act (HIPAA) interfere with this. 0 prosecution for "violating HIPAA" when best judgement is used.
5. Community: We have Team Daniel in-person gatherings in a non-medical setting, and we have weekly zoom sessions for both the patients and family. We encourage NAMI.

Clozapine Dosing for Positive Symptoms vs Negative Symptoms

1. Split the dose when positive symptoms need to be controlled.
2. When giving the first dose of clozapine wait until the patient has woken up fully “clozapine haze”. Frequent technique is first dose at lunch.
3. Patients with minimal positive symptoms and mostly negative symptoms can have their dose at bedtime to minimize daytime sedation.
4. Clozapine dosing when compliance can be assured may be split up to 4 times a day to minimize side effects such as sedation and improve efficacy at controlling positive symptoms.

Therapeutic Range and Efficacy

1. 350 ng/ml is the threshold where you start to see a response in greater than 60% of patients with resistant schizophrenia.
2. Typically, in other psychotic disorders, the threshold response has not been established but is usually significantly lower.
3. Individualize treatment and slowly explore higher therapeutic drug levels as most patients demonstrate improved response up to levels of 1000 ng/ml and 1500 ng/ml when fluvoxamine is used.
4. Levels of over 700 ng/ml often are associated with increased side effects.
5. Balance risk and benefits and manage side effects to get efficacy.

Major Side Effects and Treatment

1. Constipation
2. Sialorrhea
3. Weight Gain and Metabolic Derangements
4. Sedation
5. Seizure risk
6. Cardiology of Clozapine: sinus tachycardia, orthostatic hypotension, Qtc prolongation, risk of myocarditis and cardiomyopathy
7. Nocturnal enuresis/bladder issues/sexual function
8. Neutropenia and Eosinophilia

Managing Predictable Side-Effects

Constipation

1. Clozapine causes gastrointestinal hypomotility and slow gastrointestinal transit which can lead to ileus, bowel obstruction and bowel ischemia. The mechanism is secondary to clozapine's anticholinergic effects, 5-HT3 antagonism, and alpha-2 adrenergic receptor antagonism. Constipation is a predictable side effect and worsens with higher therapeutic levels. It always needs to be monitored and always needs to be treated.
2. Bristol Stool Chart monitor daily and ask and adjust regimen for goal daily Bristol 4 stool.
3. Stool softener use Docusate 100 mg daily to 200 mg twice a day.
4. Laxative use either Senna or Bisacodyl 8.6 mg daily to 17.2 mg twice daily for Senna and 5 mg daily to 10 mg twice daily for Bisacodyl.
5. Osmotic laxative use Polyethylene glycol (Miralax) 17 grams in 12 ounces of water daily to every 2 hours until constipation resolves.
6. Intestinal secretogogues use either linactolide 72 micro to 290 micro daily, or lubiprostone 8 micro bid to 24 micro bid.
7. Avoid other anticholinergic or other constipating agents.
8. Bulk-forming laxatives i.e., psyllium fiber must be avoided as they further slow transit time and can cause inspissation.
9. Magnesium products prn, as well as suppositories, and enemas and manual dis-impaction may be needed.

Sialorrhea & Risk for Aspiration Pneumonia

Problematic excessive salivation mechanism involves excessive production of saliva secondary to alpha 2 adrenergic receptor blockade and clozapine's major metabolite's norclozapine's partial M1 agonism. Excessive pooling occurs secondary to impaired gag and esophageal dysmotility. The excessive saliva, the sedation, and esophageal dysmotility and reduced bronchial secretions can lead to aspiration pneumonia.

1. Elevate the head of the bed.
2. Topical anticholinergic agents either ipratropium nasal spray 0.6 % 1-4 puff sublingual or 1 % Atropine ophthalmic solution 1 gtt -4 gtt sl both qhs or bid.
3. Glycopyrrolate 1-4 mg at bed NB will worsen constipation and tachycardia. This is an anticholinergic agent that unlike benztropine does not cross the blood –brain barrier.
4. Consider clonidine and guanfacine alpha-2 agonists but need care because of hypotension and sedation.
5. Botulinum Toxin –B injected directly into the parotid and submandibular glands.
6. N acetyl cysteine (NAC) 1200 mg twice a day can be an effective expectorant.
7. Consider metoclopramide 5-10 mg at bed.

Weight Gain and Metabolic Derangements

People with SMI often have lifestyle factors that contribute to poor metabolic health including sedentary behavior, and poor diet. Clozapine causes hypothalamic appetite dysregulation secondary to Histamine H1 and serotonin 5-HT2c antagonism. Insulin resistance via decreased in GLP-1 further contributes to truncal obesity and serious metabolic issues.

1. Start with diet and exercise
2. Metformin
3. Sodium Glucose Transort-2 (SGLT-2) inhibitors
4. Glucagon like peptide-1 (GLP-1) weekly injections
5. Appetite suppressants: High dose famotidine, low dose topiramate
6. Statins, fibrates and omega 3 fatty acids

Seizure Risk

Clozapine in a dose dependent manner lowers the seizure threshold. Doses over 600 mg without seizure prophylaxis are associated with a risk of seizure greater than 5%. Rapid escalations of dose and therefore levels further increases this risk.

1. Type of seizure seen: Tonic-clonic focal and generalized, Myoclonic, Tonic.
2. Preferred drugs: Lamotrigine, Levetiracetam, and Lacosamide.
3. Sodium Valproate very effective but we try to avoid because of increased sedation, weight gain and risk of neutropenia and Myocarditis.

Cardiac Issues

Clozapine, because of its potent anticholinergic actions, predictably causes a resting tachycardia and orthostatic hypotension. QTc prolongation is often cited but much less common than most other antipsychotics.

1. Tachycardia treat with Beta blockers either propranolol, metoprolol or atenolol.
2. Orthostatic hypotension treat with a high salt and fluid intake and if needed Fludrocortisone and midodrine.
3. Myocarditis almost always first 8 weeks thought to be immunologically based slow titration and avoid valproic acid.
4. Cardiomyopathy thought secondary to untreated persistent tachycardia. Treat with Beta blockers.

Nocturnal Enuresis and Sexual function

Clozapine causes sedation and will increase urgency and frequency as it increases bladder wall tone and decreases bladder-urethral sphincter tone.

1. Avoid caffeine
2. Behavioral approach: Avoid drinking close to bed and urinate before sleep
3. Oral DDAVP (desmopression) 0.1 to 0.6 mg
4. Myrbetriq
5. Of all antipsychotics, clozapine has the least affect on sexual function since no prolactin increase but retrograde ejaculation common but does not affect potency.

Sedation * Alertness * Cognition *

Clozapine soporific nature is felt to be primarily antihistaminic and anticholinergic. Pharmacologic treatment must be deferred until positive symptoms are well controlled. All pharma agents can worsen psychosis.

1. Cognitive Enhancement Therapy and Cognitive Behavioral Therapy
2. Physical exercise
3. Acetylcholinesterase Inhibitor Donepezil
4. Histamine 3 blockade increasing intracerebral histamine Famotidine
5. NMDA manipulation Memantine
6. Indirect dopamine agonists Modafanil and Armodafanil
7. Nicotinic receptors: Bupropion

Catatonia

1. Malignant catatonia ECT
2. Non-malignant benzodiazepines either lorazepam or clonazepam as much as 30mg in divided doses daily
3. Avoid antipsychotics that are anti-dopaminergic
4. For psychosis associated catatonia, use Clozapine

Neutropenia and Eosinophilia

The severe neutropenia (ANC <500) occurs in less than 0.26%. After 18 weeks it is reduced by 90%. At 1 year the risk is greater in other antipsychotics.

1. The minimal risk can be reduced to essentially 0 by a slow titration since the mechanism is immunologic (tolerance).
2. The risk of neutropenia in age less than 44 is 5 X greater for olanzapine.
3. In patients who develop clozapine induced agranulocytosis (NC <500) mortality is less than 3%.
4. REMS is a problem with more false positives than true positive leading to patients suffering. Mandatory monitoring needs to be eliminated.
5. REMS as it stands monitoring weekly for 26 weeks and every 2 weeks for 26 weeks, and then every 4 weeks for life. If ANC 1000-1500 continue and monitor 3 times a week, 500-1000 3 times a week and stop, less than 500 and stop. Benign ethnic neutropenia (BEN) start over 1000 weekly, 500-1000 3 times a week and continue, less than 500 daily and stop.
6. Treatment of neutropenia Lithium and Granulocyte colony –stimulating factor.
7. Downward trends and elevations are not issues. Lowish counts tricks: Exercise and afternoon draw.
8. One of the primary reasons there is cloza-phobia and PITA factor can be minimized Athelas device.
9. Lone eosinophilia is very common and by itself should never be a reason to discontinue clozapine.

What to do with an Inadequate Response?

Electrical Convulsive therapy: It is the seizure quality and duration not the electricity that provides benefit. It is the electricity that causes side effect. Unilateral less side effect (STM), bilateral more effective. Need skilled practitioner, 3 times a week. After 15-20 treatments, state of art, all need maintenance.

Adding a potent D2 antipsychotic, evidence is not evidence-based.

TMS: Experimental but getting better; SAINT protocol, State matters.

Consider Fluvoxamine

Clozapine & Fluvoxamine With TDM

Clozapine metabolizes into clozapine and norclozapine with CYP1A2

Fluvoxamine: Blocks the CYP1A2 enzyme to increase ratio of clozapine/norclozapine for better efficacy and less side effects.

- Baseline ratio of clozapine/norclozapine: about 1.3
- After adding fluvoxamine: 2.6

Benefits: Improve sedation, sleep time, weight, sialorrhea (over-salivation), positive and negative symptoms.

Risks: Higher levels of clozapine can cause seizures. Worsen GI side effects ALL patients on the fluvoxamine-clozapine combo are maintained on Lamotrigine or other seizure prophylaxis.

CAUTION: Fluvoxamine must be added VERY slowly with TDM at each increase!

Start slowly at 6.25mg per day at bedtime!

Break

Robert Laitman, M.D. *of*

TEAM DANIEL

presents

Optimal Treatment of Psychotic Disorders: Clozapine/Engagement/Community

TEAM DANIEL
Running for Recovery from Mental Illness

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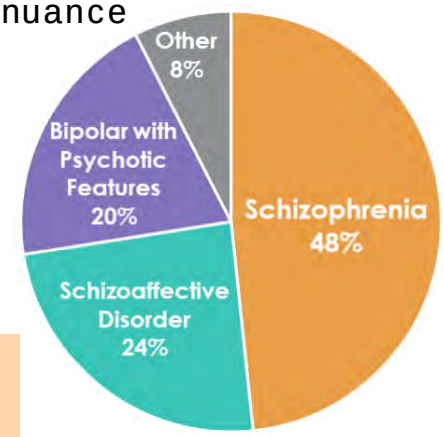
The "Team Daniel" Practice – Clozapine Centered

Over 180 clozapine patients with 94% rate of continuance
Not a "first episode clinic"
(Only 5% are truly "clozapine first")

54% are already on clozapine at intake
46% are new to clozapine



Dr. Robert Laitman and Dr. Ann Mandel specialize in both "treatment-resistant" and clozapine-resistant patients.

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The "Team Daniel" Cohort

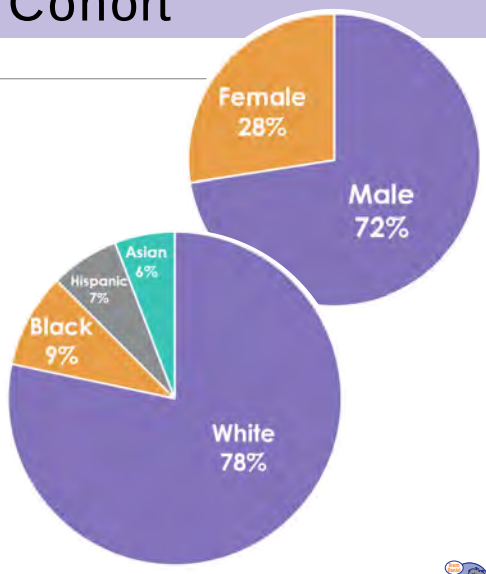
120 patients that have received a clozapine-centered treatment approach for 1 year or longer

- Average age: 34 years old
- Youngest: 17
- Oldest: 75

Longest patient on clozapine:

- 31 years (and counting)
- 59% with anosognosia (poor insight)
- 9 patients on Assisted Outpatient Treatment (AOT)

"Team Daniel Extended Family" represents hundreds of families that we consult and that join our weekly zoom.



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Not Every Patient is a "Clozapine Success"

18 Refused or never started treatment; unable to obtain an AOT (8%)
- Anosognosia is a significant barrier, representing 8% of patients.

10 Discontinued treatment or transitioned to other medications.
- Other antipsychotic, mood stabilizer or cognition medications.
- 1 clozapine adverse effect: cardiomyopathy in an elderly transplant patient.

2 Deaths
- 1 elderly patient
- 1 suicide

24 Lost to follow up, dismissed or transferred to another practice (11% attrition).

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How is Team Daniel Different?

- We use Clozapine First… NOT as a last resort!
- We believe patients have a Right to Be Well and encourage the use of LEAP and if needed court-ordered Assisted Outpatient Treatment (AOT).
- We do not tolerate side effects, including weight gain, and we aggressively use adjunctive medications, ultra-slow titrations, diet and exercise to treat and prevent them.
- Our goal is Meaningful Recovery and returning patients to their pre-illness baseline level of functioning and well-being.
- We promote a sense of community and engage and communicate with the patient's Family. After learned helplessness and hopelessness we restore optimism.

TEAM DANIEL®

Why Clozapine First?

- Early treatment leads to best outcomes: Including survival.
- Shorten the duration of untreated psychosis (DUP) by early treatment with clozapine; the earlier it is used the better.
- Better compliance and faster and more robust recovery.
- Decrease early suicide (24X increased mortality the first year).
- Decrease early aggression (12% serious violence.)
- Superior in adherence, quality of life, and patient satisfaction.
- Reduces drug and cigarette abuse.
- Patients respond better to psychosocial support.
- Patients achieve robust Meaningful Recovery.

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Our "Meaningful Recovery" Definition

Employed or Engaged for 20 hours per week or more:

- Attending school full-time, or part-time with other activities.
- Responsibly maintaining a homemaker and/or parenting role.
- Participating in a vocational rehabilitation program.
- Engaged in consistent volunteer activity

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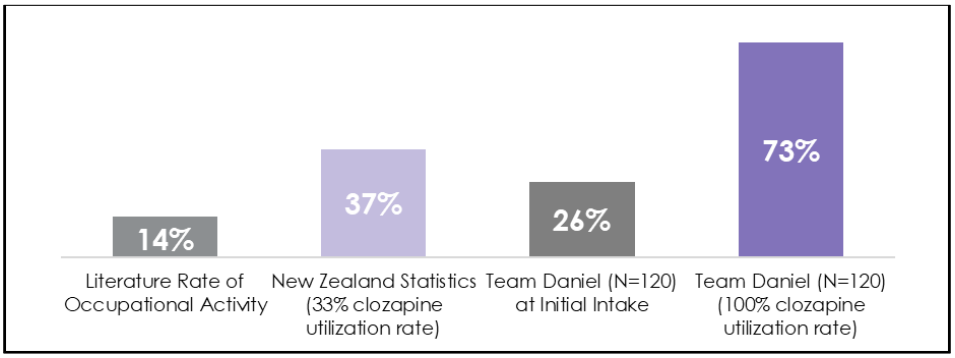
Rate of Meaningful Recovery

Meaningful Rate of Recovery

20+ Hours Per Week of School, Work or Meaningful Activity



Increased Clozapine Utilization = More Meaningful Recovery

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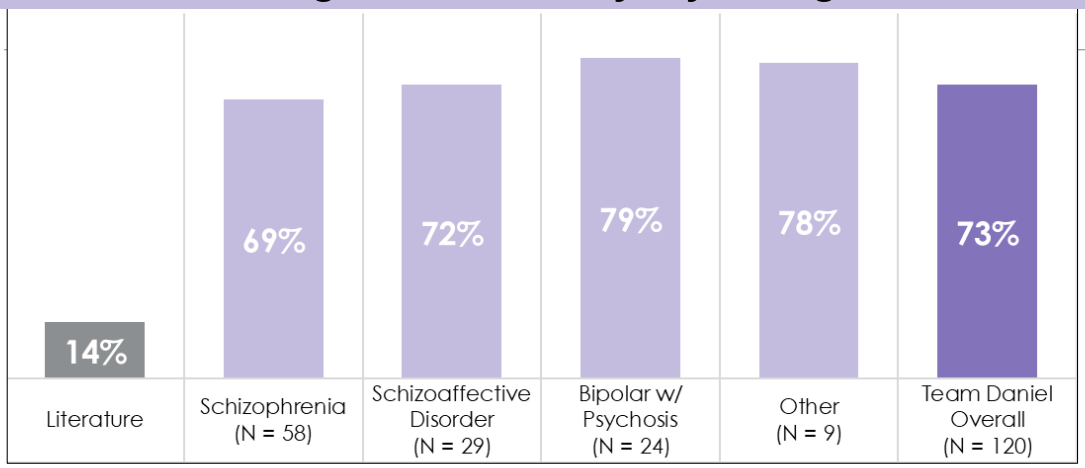
Meaningful Recovery By Diagnosis



Rate of Meaningful Recovery

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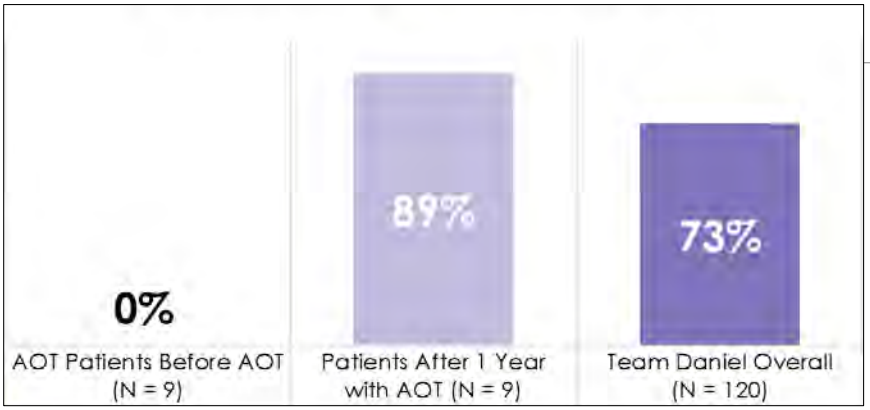
"AOT" Saves Lives and Livelihoods



100% Significant Improvement in Quality of Life.

No hospitalizations!

MEANINGFUL RECOVERY WITH ASSISTED OUTPATIENT TREATMENT (AOT)

"AOT" may be called "COT" for Court-Ordered Treatment or "MOT" for Mandatory Outpatient Treatment. The intent is court-mandated participation in treatment, with hospitalization enforced for non-compliance.

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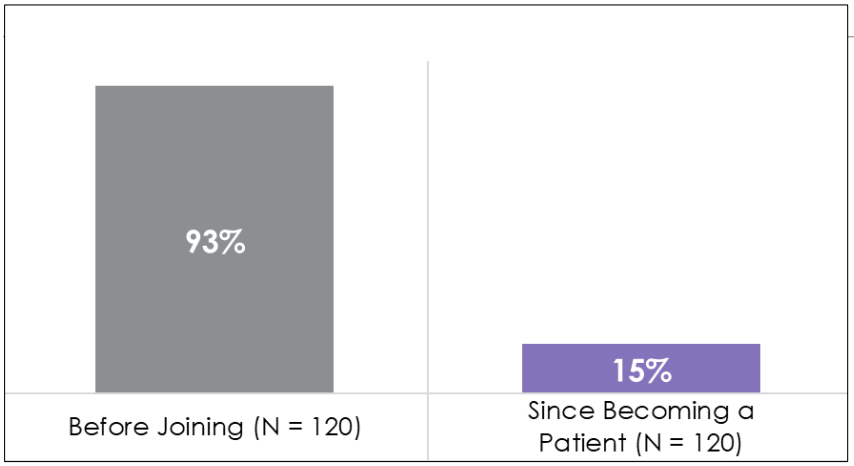
85% Have Not Returned to the Hospital



18 Hospitalizations:

9 patients for mental health
1 for Substance Use
4 for Adverse effect:
- 2 Seizures
- 1 Pneumonia
- 1 Lithium toxicity

3 for Medical reasons
1 Age-related decline

% OF PATIENTS WITH ONE OR MORE HOSPITALIZATIONS

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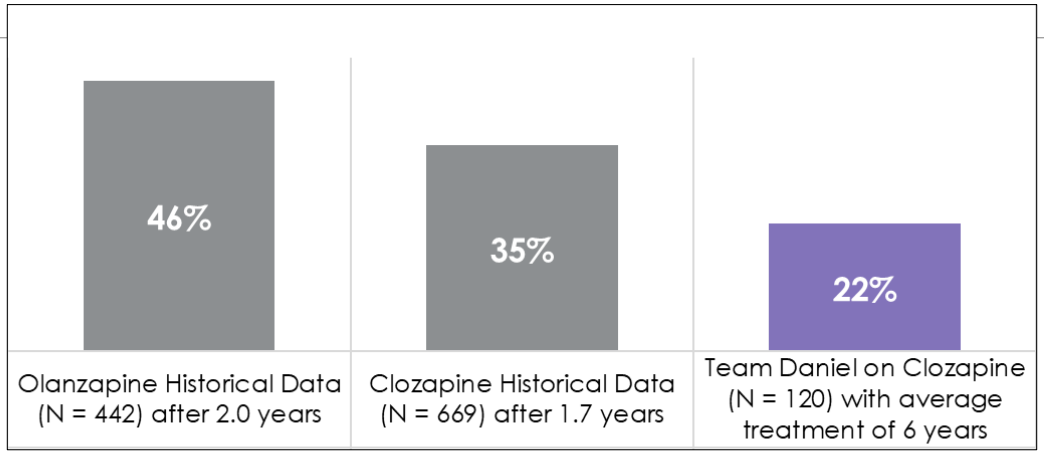
Less Weight Gain



PROPORTION OF PATIENTS WITH MORE THAN 7% INCREASE IN BODY WEIGHT

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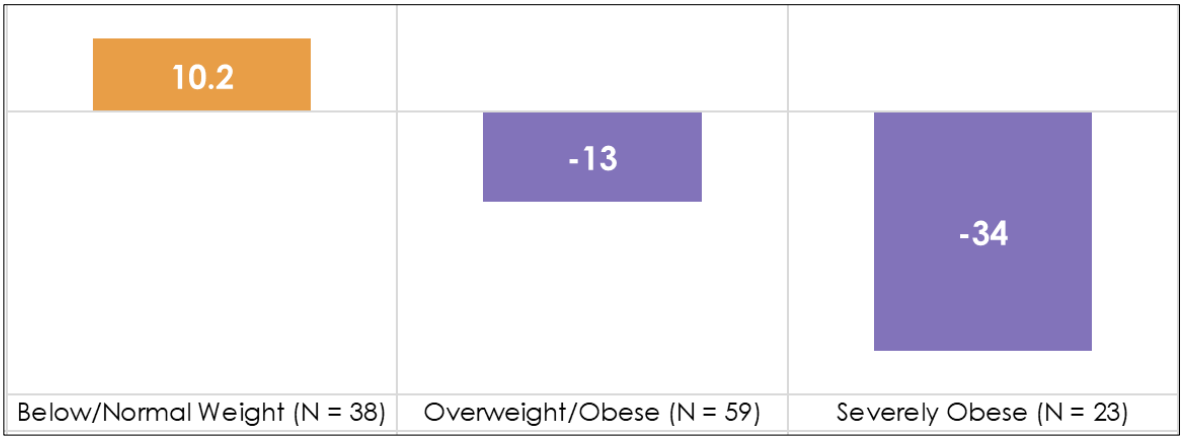
Impressive Weight Change



Team Daniel Weight Change (lb) by BMI Class at Initial Intake

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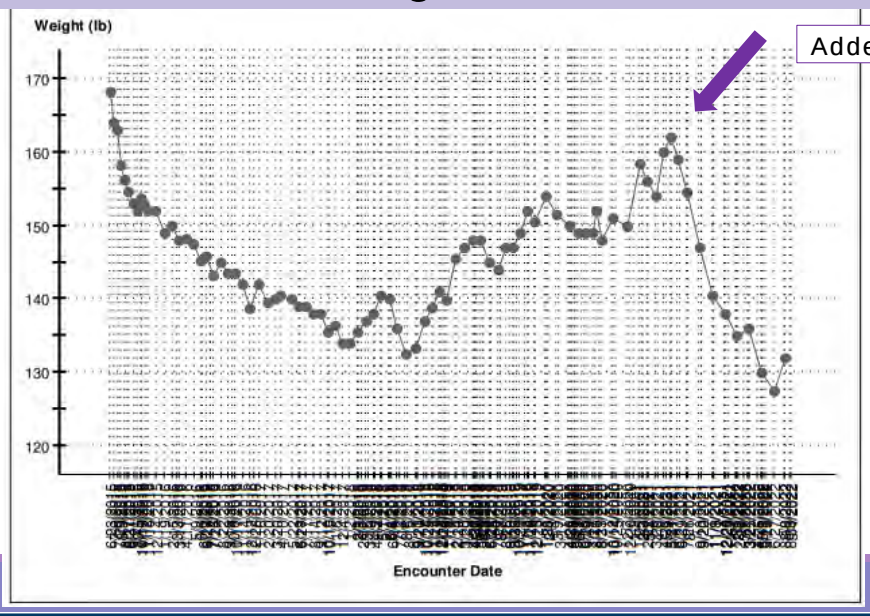
Patient Weight Over Time: GLP-1 Agonists



Female Patient

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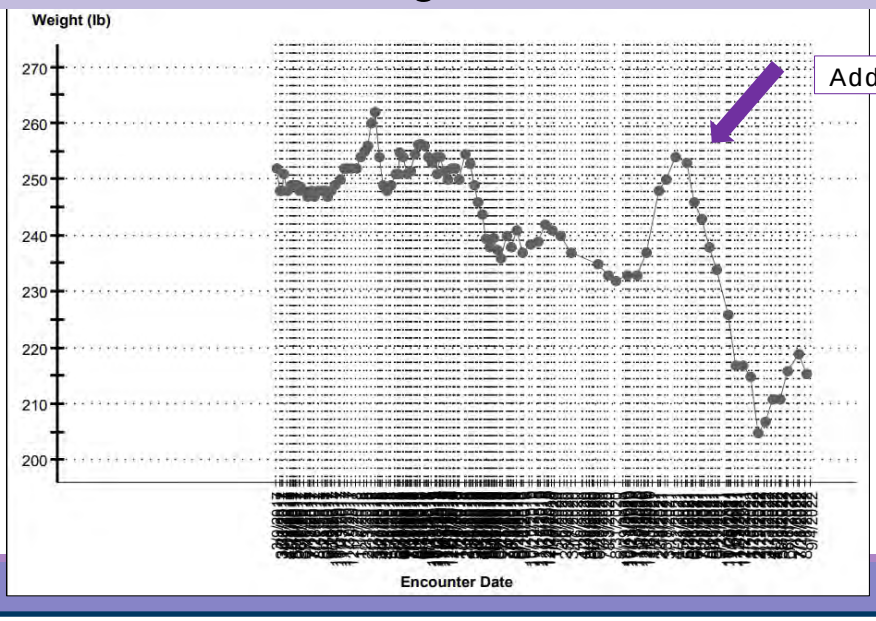
Patient Weight Over Time: GLP-1 Agonists



Male Patient

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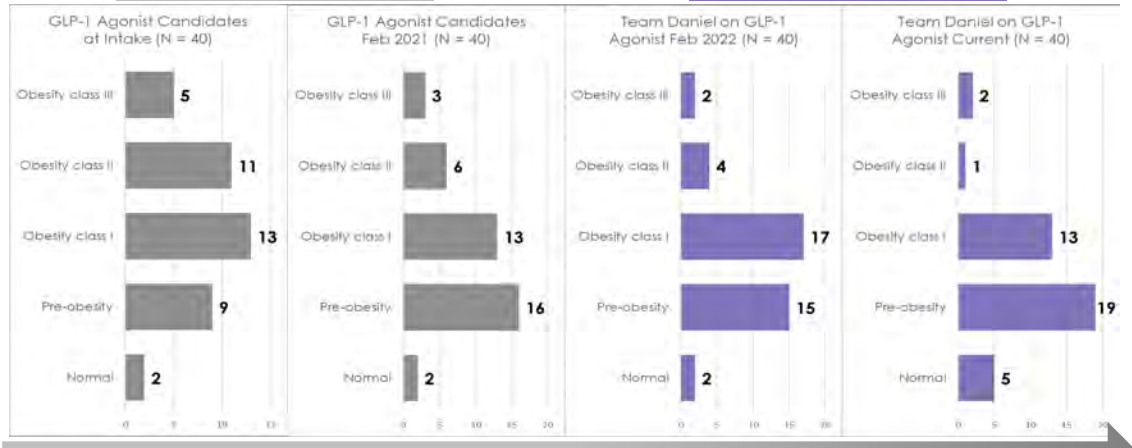
Team Daniel on GLP-1 Agonist BMI Class Distribution Progress

Before GLP-1 Agonist | GLP-1 Agonist Added



Intake	*Year 1*	*Year 2*	*Current*
73% Obese	*55%Obese*	*58%Obese*	*40%Obese*

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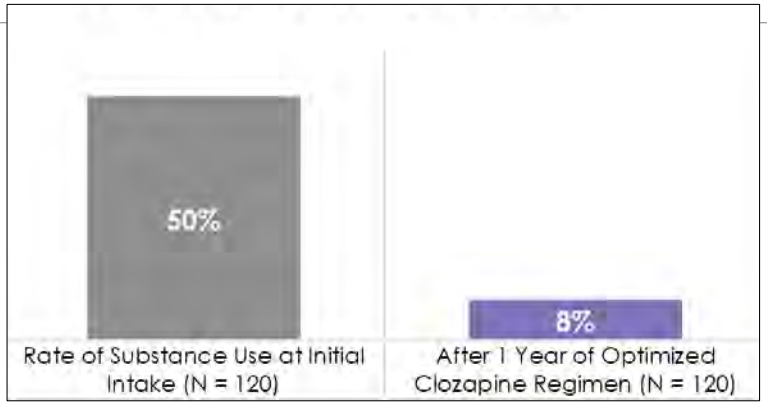
SUD Recovery Rate Unprecedented



82% Recovery from Substance Use

82% Recovery from Cannabis Use Alone

RATE OF SUBSTANCE USE DISORDER

Cannabis was the primary drug in 85% of patients

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Cessation Rate Beats the Odds

31 of 46 Smokers Quit

Most used combination therapy:

87% Chantix
50% NRT
63% Bupropion

RATE OF TOBACCO CESSATION

(N=46 Team Daniel Smokers)

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Team Daniel Notable Adverse Events (N=120*)

Pneumonia	17	5 due to Covid-19 2 patients hospitalized High rate of detection
Seizures	6	2 patients of Asian descent 1 abruptly stopped smoking 2 patients hospitalized
Lithium Toxicity	1	Resolved with lowering lithium dose The patient was hospitalized
Cardiomyopathy	1	This occurrence in an elderly transplant patient is our only case of discontinuing clozapine due to adverse effects*
Suicide	1	Tragic and unexpected*
Stevens-Johnsons Syndrome	1	Discontinued Lamotrigine
• Agranulocytosis • Embolus • Myocarditis	0	No cases observed in hundreds of patients among the Team Daniel cohort and extended family

*The suicide death and cardiomyopathy patient are not included among the 95 patients being characterized in the Team Daniel cohort

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Team Daniel Notable Adverse Events (N=120)

Neutropenia	4	3 resolved after 1 instance 1 resolved with lithium
Substantial Weight Gain	11	7 cases are tied to poor compliance with weight control medications 3 New to the weight control regimen
Severe orthostasis	2	Improved with fludrocortisone
Severe secondary narcolepsy	2	Using various strategies (splitting the dose, medications)
Urinary difficulties	3	Improved with desmopressin
Movement Disorders	1	1 rare case of clozapine-related dystonia observed at a very high dose, resolved with lowering dose 3 patients with tardive dyskinesia from previous antipsychotic use resolved with clozapine

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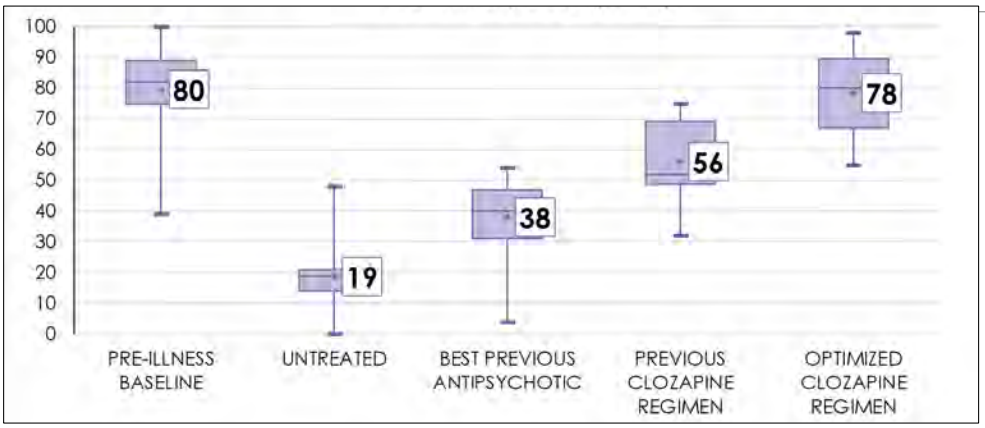
Most Patients Return to Baseline



TEAM DANIEL Returns to Baseline Functioning & Well-being

GLOBAL ASSESMENT OF FUNCTIONING SCORES
Preliminary Data (N=14)

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Achieving Goals

Critical first step: Know the sufferer and hopefully engage family.

- Often patients are in a lot of pain - no barriers - hugs help.
- Be an active cheerleader and be a friend.
- Use Xavier Amador's LEAP approach for patients with anosognosia (unawareness of Illness):

  Listen – Empathize – Agree – Partner

- Engage the patient in every way possible, using AOT if necessary.
- Ensure the patient feels safe and accepted; we have few boundaries.

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Achieving Goals - 2

- Acknowledge the road to recovery will always have a few detours.
  - This helps everyone relax and know that even if they "screw up" you will never abandon them.
- Always be available and make sure patient has information.
  - All patients and families get our cell phone #'s and e-mail.
- Compassion and Availability really goes a long way.
- Everyone leaves our office with the treatment note. We also share with the family.

Optimism is essential: Your belief combats learned hopelessness.

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Clozapine Routine Monitoring

- Therapeutic Drug Monitoring (TDM) is critical!
  - Blood serum levels of clozapine and norclozapine to guide dosing.
- Thorough physical with a body mass index (BMI) and orthostatic blood pressures.
- Baseline echo, EKG, HSCRP, troponin (periodically follow up), serum BNPs in patients with tachycardia (elevated heart rate).
- Baseline and follow CBC with absolute neutrophil counts, chem panels including renal and liver function test, lipids, thyroid function, Glyco-hgb, and urine toxicology, immune/infection workup.
- Dual diagnosis: urine and serum tox screens and cotinine levels every visit.

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Avoid Predictable Side Effects (a review)

Weight Gain: Add diet and Metformin early; consider SGLT2 inhibitors and Incretin mimetics. (GLP-1 receptor agonists)

High Triglycerides: Statins, omega 3 and fibrates (fenofibrate).

Metabolic Syndrome and Diabetes: Metformin, SGLT2 inhibitors, high-dose ranitidine or famotidine, plant-based diet, exercise and Incretin mimetics.

Sinus Tachycardia: Add Beta Blocker (Propranolol) or in those with pulmonary disease Metoprolol or atenolol (if anxiety is already well controlled).

Seizure Prevention: Lamotrigine, Gabapentin, Topiramate or Valproate (if violent).

Drooling: Add .06% Ipratropium Nasal Spray, or 0.1% atropine eye drops under the tongue. Consider Glycopyrrolate and Botox. Elevate the head of the bed.

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Avoid Predictable Side Effects (review continued)

Constipation: Hydrate! Cathartics (Dulcolax and Senna), stool softeners (Colace), laxatives (MOM, lactulose, Miralax), Linaclotide (Linzess), and Acarbose.

Remedy the problem: Clozapine causes a slow transit time!

Neutropenia:

- Draw blood in the afternoon and exercise beforehand.
- Consider adding lithium and granulocyte colony stimulating factor (CSF).
- Recognize Benign Ethnic Neutropenia (BEN) and confirm with genetic testing.

Nighttime Urination: Behavior changes, DDAVP or Myrbetriq.

Hypotension: Florinef (fludrocortisone), midodrine in severe cases.

Nausea and Vomiting: Early use of ondansetron (Zofran).

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Enhancing Clozapine

Cognitive enhancement: donepezil, bupropion, famotidine, memantine, modafinil, armodafinil, amantadine, and consider fluvoxamine.

Presently investigating pitolisant (Wakix).

Concomitant mood disorder and OCD: SSRI (i.e., escitalopram)and cognitive behavioral therapy(CBT), carefully consider fluvoxamine or bupropion.

Support: Socialization skills, educational, vocational, psychosis-informed CBT, dialectical behavioral therapy (DBT), family therapy, speech therapy and cognitive enhancement programs.

Treat co-occurring addictions

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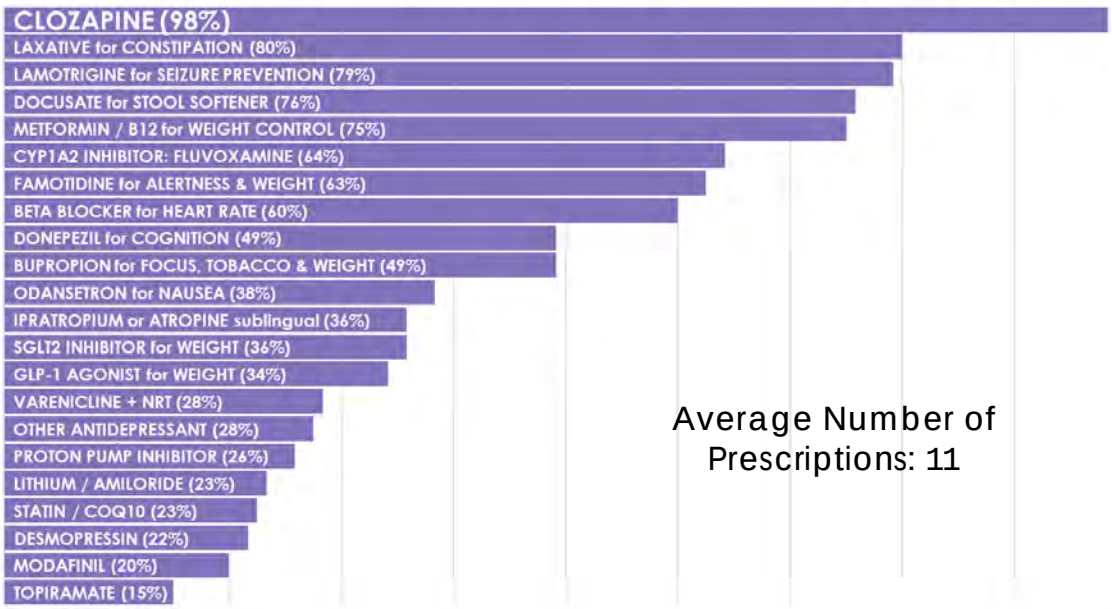
TEAM DANIEL OPTIMIZED REGIMEN (N=120)



Average Number of Prescriptions: 11

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Other Common Medications

LORAZEPAM OR ALPRAZOLAM	14%	
KLONOPIN	14%	
LINZESS OR TRULANCE	13%	
SYNTHROID	11%	
WAKIX (PITOLISANT) Investigational		10%
MEMANTINE		8%
OTHER ANTIPSYCHOTIC		7%
GABAPENTIN		6%
BENZTROPINE		5%
NALTREXONE		5%
DEPAKOTE	4%	
HYDROXYZINE		4%
GLYCOPYRROLATE		3%
FLUDROCORTISONE	3%	
BUSPIRONE	2%	
AMANTADINE		2%

- Supplements: CoQ10, B12, Vitamin D3, Fish Oil, melatonin, caffeine

Never:
Stimulants / ADHD medications

Rare:
Depakote
Benztropine
Hydroxyzine
Multiple antipsychotics

Only As Needed:
Benzodiazepines

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Exercise and Engagement

SMI is a team sport.

- Every Saturday morning, we have our willing patients and families come to our house for a run and seasonally swim.
- The House is magic in fostering acceptance, engagement, and trust. It has taken the therapeutic relationship to another level.
- Normalization, socialization, and befriending in a non-medical environment value cannot be overestimated.

Zoom Session's Every Saturday:

- A family/caregiver zoom led by Team Daniel Staff
- A zoom for patients led by Daniel Laitman (TEAM DANIEL'S inspiration).

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Exercise Benefits Meta-Analysis

In 29 studies, 1,109 patients statistically significant improvement in:

- Total symptom severity
- Positive symptoms
- Negative symptoms
- General psychopathology
- Quality of life
- Global functioning
- Depressive symptoms

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Teamwork

In July 2021, Team Daniel ran the Long Island Jovia Marathon: Michael Orth, *Commissioner at WC, DCMH;* Dr. Rob Laitman, Jasper Bresolin, Malachy Friel.

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The Diet

Eat 3 meals a day – Do NOT drink your calories

Avoid all simple processed carbohydrates:

- NO cookies, candy, chips, dips, cakes, ice cream, donuts
- Minimize bread, pasta (whole grain only)and rice (small portion brown rice only)

BREAKFAST

High fiber cereal *or*
Eggs, (Veg omelet) *or*
Oatmeal with raisins

Coffee *or* tea

Milks: Almond *or* Skim
Sweeteners: Stevia, Splenda

LUNCH

Non tropical fruit
Blueberries, strawberries, blackberries, apples, plums or pears.
Greek yogurt *100-160cal*

SNACK

Nuts *or* fruit
Blueberries, strawberries, blackberries, apples, plums or pears.

DINNER

Garden salad *with only vegetables & a light low salt dressing spritzed on.*

Vegetable *like broccoli, brussel sprouts, string beans, spinach, or cauliflower.*

Protein *6-8 ounce of fish, poultry, pork, tofu, setain, or a legume : lentils, chickpeas etc.*

Non tropical fruit

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Clozapine Initiation

Slow titration.

Get to therapeutic levels (using TDM).

See the patient every week.

Shift majority of dose to bedtime dosing,
once positive symptoms are better.

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Benefits of Ultra-Slow Titration

Identify lowest effective dose.

Minimize and proactively treat predictable early side effects:

- Sedation
- Constipation
- Weight gain
- Orthostasis (dizziness & low blood pressure)
- Tachycardia (rapid heart rate)
- Sialorrhea (over-salivation)

Reduced risk of cardiomyopathy and myocarditis.

Significantly more likely to have success and compliance.

Expect a long cross-taper from the previous antipsychotic.

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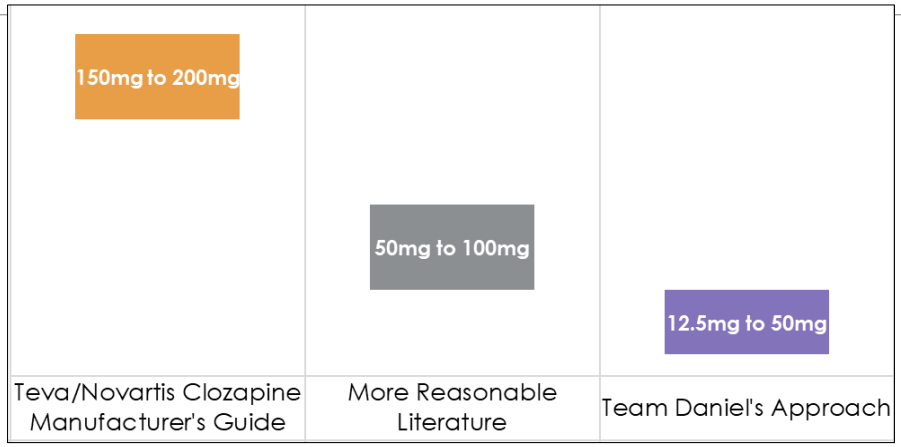
Clozapine Titration Schedule – Go Slow!



Total Daily Dose (mg) Increases Per Week

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Clozapine Metabolism Via CYP1A2

Cigarettes: dramatically lowers clozapine

- Stopping dramatically raises levels
- Hydrocarbons & coal tars stimulate metabolism
- Nicotine has no affect

Caffeine: increases the levels - Keep it steady!

Be aware of drug interactions!

- Some quinolones increase levels (Ciprofloxacin)

Inflammation dramatically increases levels.

- With serious illness, reduce dose by 67% until the fever resolves.

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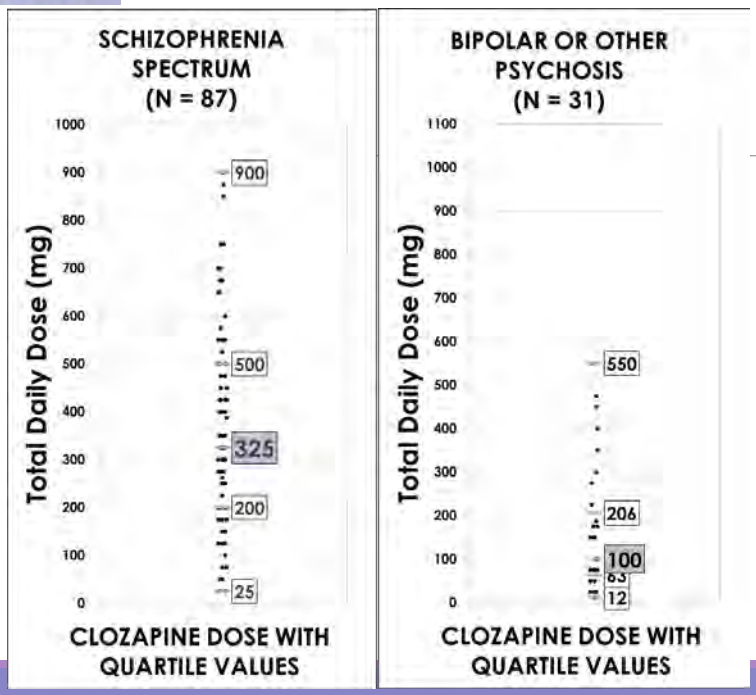

TOTAL DAILY CLOZAPINE DOSE (mg) AFTER 1 YEAR

(N = 118)*

*2 patients symptoms resolved

Note:

Many patients have clozapine levels augmented with fluvoxamine which allows a lower dose to be used.

There is no standard dose:

Use TDM and patient symptoms to determine dose.

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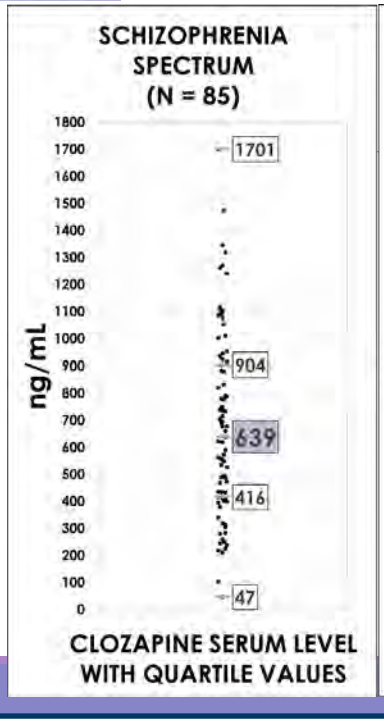

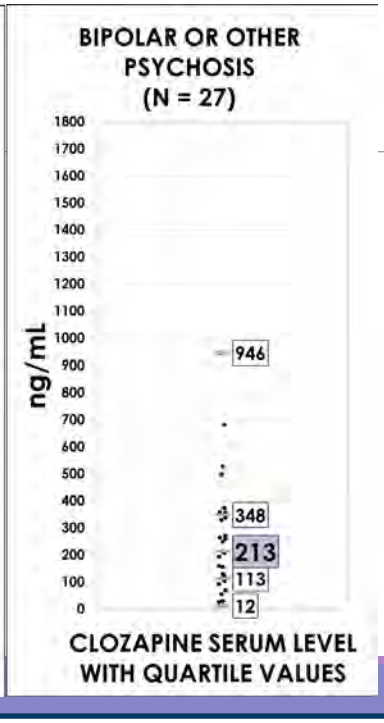

THERAPEUTIC CLOZAPINE SERUM LEVELS (ng/mL) AFTER 1 YEAR

IN PATIENTS WITH DETECTABLE LEVELS (N = 112)*

*8 patients with no detectable levels

Push Boundaries:

Literature therapeutic range:
350 to 650 ng/mL
Traditional Upper Limit:
1000 ng/mL

Most TEAM DANIEL patients are on anti-seizure medications.

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Rev. 2/2/2022

Team Daniel Clozapine Regimen Initiation Summary

		Clozapine	Initial PRN's	Colace (Constipation)	Metformin ER (Weight Control)	Lamotrigine ER (Seizure Prophylaxis)	Other Anti-psychotics	Substance Use	Smoking
MONTH 1	Week 1	12.5 mg PM	Zofran (nausea) 4 - 8 mg, up to 2X daily 1% Atropine drops sublingual (salivation) 1 - 3 drops at bedtime Up to 3 drops 3x daily Famotidine -H2 blocker (acid reflux) 20 mg 2X daily and/or omeprazole** once daily Beta Blocker i.e. propranolol (tachycardia) 10 mg up to 3X per day Use 10-20 mg PRN for anxiety Consider PRN clozapine 12.5 - 25 mg for daytime psychosis/anxiety Desmopressin (nocturnal enuresis/urinary urgency) 0.1 mg at bedtime to start Klonopin 0.5 mg 2X daily for catatonia that has not responded to therapeutic clozapine serum levels. **PPI's decrease clozapine level		Start within first month of treatment to prevent metabolic syndrome and weight gain.	Prophylactic seizure prevention for patients with seizure history, mood disorder, or clozapine serum level over 500 ng/mL. This is especially critical to establish if a patient may need fluvoxamine in the future.	Acute psychosis: temporarily consider Zyprexa, Abilify or risperidone; to be discontinued after a therapeutic clozapine level is reached. Slowly down-taper and discontinue sleeping pills, stimulants, ADHD medications, and all other antipsychotics: clozapine is most effective as a mono-therapy antipsychotic. Smokers will require higher doses of clozapine and a longer transition from previous medications.	No changes first 2-4 weeks; keep it level. Discuss dangers of marijuana/THC. Consider 50 mg naltrexone (PM) for SUD. As clozapine becomes effective discuss life goals and how to transition from harmful substances. Consider drug counseling, DBT, possibly 12-step programs. DO NOT PUSH. Avoid short-acting benzodiazepines like Xanax. PRN Ativan or klonopin (low dose) for acute symptoms only during initial clozapine titration; discontinue after acute symptoms subside.	Smoking decreases serum levels on average 50% Discuss transition to vape or ideally NRT which is preferred. Consider Chantix or bupropion and other means of reducing dependence on nicotine. Continue to explain the value of non-smoked forms.
	Week 2	25 mg PM							
	Week 3	50 mg PM (Start TDM)		100 mg PM					
	Week 4	75 mg PM		Customize bowel regimen per patient symptoms: - Colace up to 400 mg - Senna-S - Dulcolax - Miralax - Linzess if needed (no fiber supplements) Use Bristol Stool chart and communicate often - patients may not be forthcoming.	500 mg PM				
MONTH 2	Week 5	100 mg PM*			500 mg PM	25 mg AM			
	Week 6	125 mg PM*			500 AM/500 PM	25 mg AM			
	Week 7	150 mg PM*			500 AM/500 PM	50 mg AM			
	Week 8	175 mg PM*			500 AM/1000 PM	50 mg AM			
MONTH 3	Week 9	Increase 25 mg weekly or every two weeks per symptoms and Therapeutic Drug Monitoring (TDM). Therapeutic range begins when clozapine serum level reaches 350-500 ng/mL. Some patients need to go higher for adequate symptom control. Consider splitting dose for strong positive symptoms with 2:1 ratio bedtime to morning dose.			500 AM/1000 PM	Continue increasing lamotrigine 50 mg every two weeks up to 200 mg. If lamotrigine is not tolerated consult Dr. Laitman for the next best option: - Gabapentin - Keppra - Trileptal (check for Asian ancestry) - Topamax Depakote is NOT recommended due to increased risks / side effects. **Watch carefully for Stevens-Johnson rash.**			
	Week 10				1000 AM/1000 PM				
	Week 11				Consider Farxiga/Xigduo and Trulicity (or similar) in patients with continuing weight or metabolic concerns. Metformin depletes B12 - add 1000 mcg daily.				
	Week 12								
MONTH 4	Week 13								
	Week 14								
	Week 15								
	Week 16								

Dr. Robert Laitman mobile: 914-629-5130

*** Note: Slow clozapine titration reduces incidence of myocarditis, seizure, cardiomyopathy and pneumonia. Start TDM at 50 mg to confirm patient adherence.**

Cautions:

- **Consult Dr. Laitman for instructions on how to handle medications in previous regimen that are anticholinergic or antihistaminergic, or that may lower blood pressure, increase clozapine levels or increase seizure risk.**
- **For mild neutropenia (ANC < 1500 ug/mL or ANC < 500 ug/mL for a BEN patient) start 450mg of lithium ER (PM dose). Increase as needed to 1.2 mmol/L serum level until resolved.**
- **Indigenous/Asian/Native American descent are slow metabolizers and on average need 1/3 the dosage of European descent. Slower titration with frequent TDM is recommended.**
- **Baseline tests prior to initiating clozapine: EKG, metabolic panel, A1C, ANC, HSCRP lipid panel and where financially feasible EEG/Brain MRI.**

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Team Daniel Clozapine Regimen Maintenance Summary TABLE 2

Suboptimal Clozapine Results (Most Resistant Schizophrenia)	Fluvoxamine	Depression & Alertness	Cognition Improvement	Metabolic Syndrome Weight Control	Hypersalivation & Pneumonia Prevention	Lithium Carbonate ER	Neutropenia & Clozapine Toxicity
TDM OF CLOZAPINE SERUM LEVELS: 75% of patients START responding at 400 ng/mL; the threshold for Bipolar is lower. Up to 1000 ng/mL should be pursued for efficacy. With adjunct fluvoxamine, levels up to 1500 ng/mL or higher may be considered. Median Team Daniel patient serum levels are 640 ug/mL at 1 year of treatment. Statistics represent clozapine levels only, not the sum of clozapine & norclozapine. **POSITIVE SYMPTOMS**: Split clozapine dosage 2-3x daily, largest dose before bed e.g., 50mg 9am / 75mg 2pm / 125 mg 7pm. If no positive symptoms, give entire dose at bedtime. **PREVIOUS ANTIPSYCHOTICS**: slowly taper & discontinued as clozapine is titrated to therapeutic levels. **ECT**: Most effective for depression. Consider for audio & visual hallucinations. **TMS**: for negative symptoms. **ANTIPSYCHOTIC AUGMENTATION**: 1st choice-Aripiprazole for low weight gain & low sedation profile. 2nd choice-Risperdal. There is no compelling evidence that antipsychotic augmentation provides greater efficacy. Concomitant antipsychotic use can impede clozapine's efficacy & increase adverse side effects. **MINOCYCLINE ANTIBIOTIC**: 100 mg 2x daily. **AVOID**: smoking (decreases clozapine serum levels), marijuana & CBD (increases psychosis risk), herbal supplements (Unknown medication interactions).	**SSRI / OCD**: (CYP1A2 inhibitor) increases clozapine serum levels without increasing norclozapine metabolite. Goal: achieve therapeutic clozapine serum levels for adequate symptom control with lower dosage & fewer side effects. Can dramatically improve sialorrhea. **CAUTION - Medication Interaction: Seizure risk increases as clozapine serum levels increase. Fluvoxamine can double or triple clozapine levels. Anti-seizure meds (preferably lamotrigine) must be given before initiating fluvoxamine.** Starting dose: 6.25 mg pm (1/4 of 25 mg). Titrate 6.25 mg every 2 weeks. Check clozapine serum levels with each fluvoxamine increase. Slowly taper clozapine while titrating fluvoxamine. clozapine: norclozapine ratios improve. Target: clozapine: norclozpine ratio: 2:1 (or better), e.g., 640:320	**DEPRESSION** -Antidepressant: Bupropion XL 150-450 mg daily. Aids in weight loss. reduces nicotine cravings. Initiate after psychosis is reduced due to increased risk of mania. Patients must be on sufficient seizure prophylaxis (Preferably lamotrigine) due to increased seizure risk. -ECT: treatment-resistant depression **ALERTNESS** -(narcolepsy treatment): Modafinil 100-200 mg am. Cut 100 mg into 1/4 & titrate slowly, may trigger psychosis & anxiety. ADD/ADHD: often psychosis illness prodrome & misdiagnosed. Stimulants can worsen psychosis. Optimized clozapine is the best treatment for focus & attention.	H2 BLOCKER: Famotidine 100 mg 2x daily. ACETYL-CHOLINESTERASE INHIBITOR: Donepezil 5-10 mg daily (may reduce clozapine-induced constipation). NMDA Antagonist: Memantine 5-10 mg 2x daily. GUANFACINE: 1-2 mg (indicated for hypertension & inattention) Caution: can cause drowsiness & hypotension. BrainHQ, Speech therapy, DBT, CBTP, & academic courses of interest. CETCLEVELAND: Formal Cognitive Enhancement Therapy (CET) AVOID, when possible (due to adverse cognitive effects): Haldol, diphenhydramine (Benadryl), benztropine (Cogentin), hydroxyzine, benzodiazepines, and divalproex sodium (Depakote). DAILY VITAMINS: B12, Folic Acid, D3, Omega 3, CoQ10, NAC, Phosphatidyl-Choline during pregnancy for prevention.	DON'T wait for diabetic criteria. Clozapine causes impairment in glucose tolerance. METFORMIN ER 1000 BID: (Use Extended Release), start at 500 mg pm, and titrate to 1000 mg am/pm for ANY increase in weight, appetite, lipids, and liver enzymes. Exceptions: underweight, & normal: weight, lipids, glucose, and liver enzymes. For GI side effects: lower dosage &/or limit to pm (<2000 mg daily may not produce weight loss). SGLT2 INHIBITORS: Jardiance (or similar) 10-25 mg daily. GLP-1 RECEPTOR AGONISTS: weekly dulaglutide (Trulicity or similar) or semaglutide (Ozempic or similar) subcutaneous injection. DUAL GIP/GLP-1 RECEPTOR AGONIST: tirzepatide (Mounjaro or similar) subcutaneous injection weekly. Naltrexone/bupropion (Contrave) 8/90 mg pm. Topiramate 25 mg - higher doses may worsen sedation. Surgical weight loss for extreme cases. Caution: weight loss surgery can impact clozapine absorption & serum levels. Therapeutic clozapine serum level is the most significant factor in patients' ability to understand the need for a consistent exercise program. Avoid sweets, carbs, and junk foods, and never drink your calories.	**HYPER-SALIVATION**: Prevent aspiration pneumonia - a dangerous complication of clozapine therapy, far surpassing risks of severe neutropenia. Elevate the head of the bed. No food 2 hours before bed. ANTI-CHOLINERGICS: 1% sublingual atropine drops or ipratropium bromide spray 1-3 drops/puffs under the tongue at bedtime, up to 3x daily. Glycopyrrolate 1-4 mg BID. Caution: high risk of constipation & tachycardia. Mitigate with Linzess & Propranolol beta-blocker. Guanfacine 1-2 mg at bedtime. Caution: hypotension risk NAC (N-acetylcysteine) 500-1200mg BID Resistant sialorrhea: Botox submandibular & parotid salivary gland injections every 3 months.	**MOOD STABILIZER**: Administer concurrently with clozapine for persistent mood disorders. Titrate 150-300 mg weekly to a therapeutic range of 0.8-1.2 mEq/L. **NEUTROPENIA**: ANC <1500/mcL. Titrate lithium carbonate ER 150-300 mg weekly to 0.8-1.2 mEq/L until resolved. For chronic neutropenia or levels <500/mcL, filgrastim 5-10 mcg/kg/weekly. To prevent kidney damage & improve renal clearance: Use extended-release and administer once daily before bed. For doses >450mg, add amiloride 5mg am to prevent diabetes insipidus. Therapeutic Drug Monitoring (TDM) monthly/quarterly & Thyroid panel. Hypothyroidism: Use levothyroxine.	**NEUTROPENIA**: affects <3% of clozapine patients. Drops or downward trends are not concerning unless the ANC count is <1500/uL or <1000/uL for Benign Neutropenia (BEN) patients. ANC results: <1500/uL repeat test immediately following exercise & in the afternoon when the neutrophil count is highest. <1500/uL persists; add lithium carbonate ER. Repeat ANC 3x weekly. <500/uL add filgrastim. BEN ANC: <1000/uL Repeat ANC 3x weekly. If clozapine must be discontinued, in 6 months, rechallenge with prophylactic lithium. Titrate 6.25 mg of clozapine weekly. **CLOZAPINE TOXICITY**: Toxic ranges are not well established. Serum levels >1500 ng/mL may cause Seizure, hypotension, cardiovascular abnormalities, confusion, choking, shallow breathing, and severe sedation - cut dose to ½ & check levels. As clinical symptoms improve, resume dosage. **MYOCARDITIS / TACHYCARDIA**: use ultra-slow titration, and avoid Depakote. Treat resting heart rate >100 with a beta blocker.

Dr. Robert Laitman 914-629-5130 Dr. Ann Mandel Laitman 914-841-2095

TEAM DANIEL®

The Clozapine Clinic

The General Model:

- Psychiatric MD or NP adept in medicine.
- Full time internist, or neurologist adept in clozapine.
- Psychologist or psychiatric social worker for P-CBT.
- Social workers for case management and housing and frequent legal interface.
- Peer specialist who is on clozapine.
- Work and social opportunities, befriending, normalizing: create a community!

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The Clozapine Clinic - 2

The General Model:

- Exercise training and nutrition support.
- Family support and education – the LEAP method.
- CBT-P, DBT, cognitive enhancement therapy and job training.
- Full supported therapeutic housing.
- Substance abuse intervention for cigarettes, drugs and alcohol.
- Pet therapy (dogs do matter).
- Full biopsychosocial model: The Goal is Meaningful Recovery.

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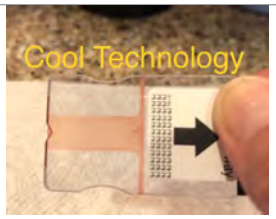
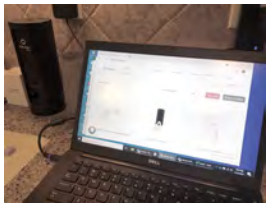
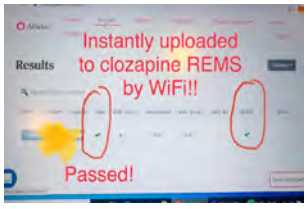
The Clozapine Clinic



Finger Prick Testing Real Photos from a Very Excited Patient!





Athelas

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What Team Daniel Families Are Saying…

"We were told to grieve, and that our child would never return to their former self - those doctors were wrong."

"Other than sleeping more hours than the average person, our child is recovered, perhaps even better than before the illness."

"Clozapine quieted my mind instead of deadening it."

"Kids on clozapine look normal and act normal."

"Clozapine turned the light back on in their eyes…"

"The Awakening Phenomenon" has been well-documented in observational studies of clozapine in patients with schizophrenia. Dr. Stephen Stahl called it "***the restoration of lost souls to near normal existence***"

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KD in Art School – Before Illness

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KD on olanzapine, nonclozapine-APs, and LAI's

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KD after 5 months on Clozapine

(still subtherapeutic)

Comments for the APA Guideline for Treatment: Surviving & Thriving with Schizophrenia

1. Need to increase access to treatment by promoting universal health care and expanding the number of providers.
2. Reclassify Schizophrenia as a neurobiological syndrome.
3. Change the treatment model to use comprehensive wrap around services and minimize the duration of untreated psychosis.
4. Use clozapine in an optimal fashion mitigating side effects and enhancing benefits.
5. Change the reimbursement structure for clozapine management to reflect the considerable amount of time and work appropriate management requires.

- Robert S. Laitman, M.D.

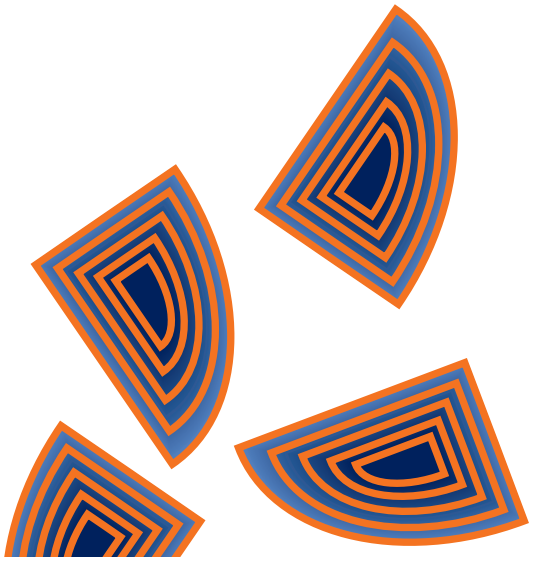
Comments for the APA Guideline for Treatment: continued..

6. Change clozapine REMS guidelines to reflect the actual risk of Agranulocytosis
7. Educate the psychiatric community about what is possible with appropriate treatment (optimal clozapine) to combat learned helplessness and hopelessness
8. Engage patients and their families by revising the HIPAA laws, expanding the AOT laws, and using LEAP
9. Treat the patient and not the disease. That means address co-occurring substance abuse, treat cigarette abuse, and emphasize diet and exercise.
10. Always be kind!

- Robert S. Laitman, M.D.

Summary and the Future

1. Meaningful recovery is possible with an optimal clozapine regimen.
2. The ideal clinic will provide wrap around services with vocational and educational services, case management, housing, and expert medical and psychological management. All this tied into a community. Education and involvement of the family will be stressed. You cannot do clozapine without adequate support.
3. Future eliminate REMS as a mandatory blood draw and change it to an educational site.
4. Develop weekly Intramuscular clozapine.



The System

1. It is broken and fragmented
2. People are suffering
3. We can do better
4. We just need the will

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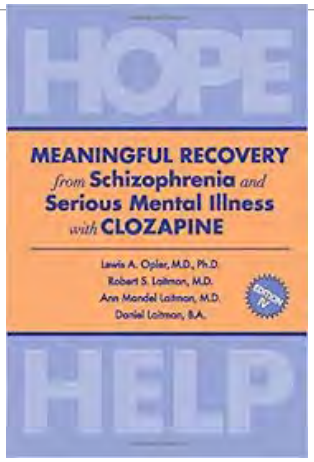
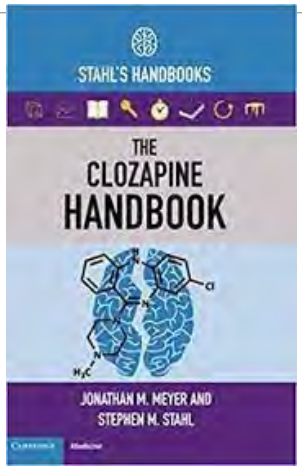
Important References





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