

Management of Side Effects of Antipsychotics

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Disclosures

My spouse/partner and I have the following relevant financial relationships with commercial interests to disclose:

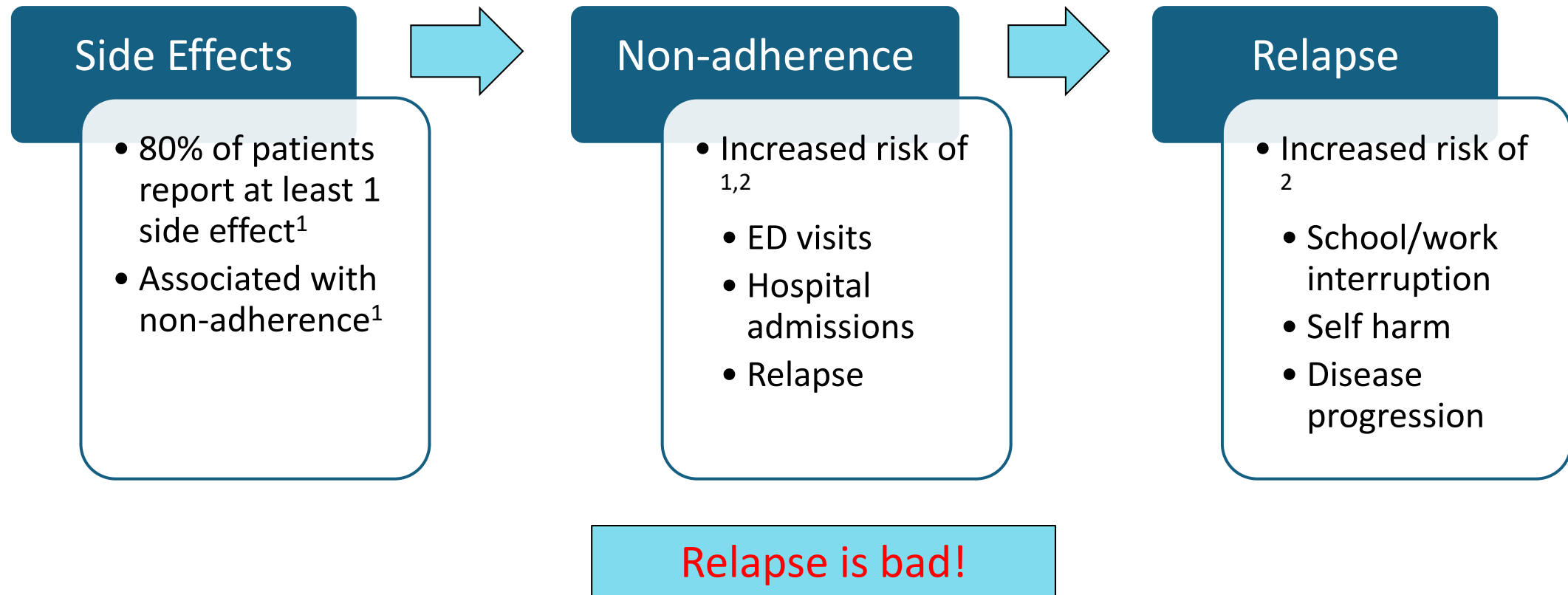
Artisan – Investor, Board Member (spouse)

Mirah – Investor (spouse)

Outline

- Antipsychotic pharmacology
- Emergent Side Effects
 - NMS
 - Prolonged QTc
 - GI side effects
 - Clozapine
- Non-Emergent Side Effects
 - Metabolic side effects
 - Motor side effects
 - Hyperprolactinemia
 - Sedation
- Framework for Side Effect Monitoring and Intervention

Why Do Side Effects Matter?



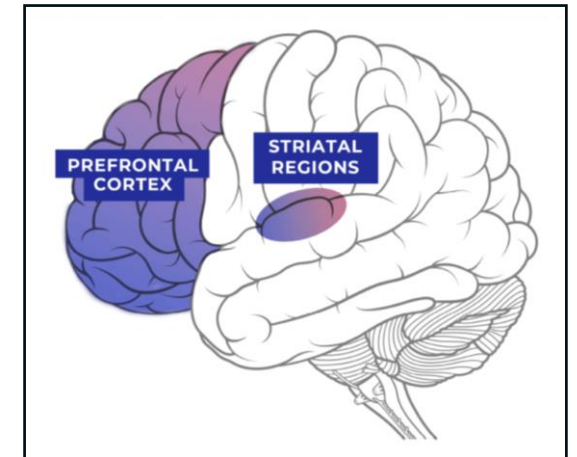
1. Dibonaventura M, et al. *BMC Psychiatry*. 2012;12:20. 2. Emsley R, et al. *BMC Psychiatry*. 2013;13:50.

Antipsychotic Pharmacology

- All anti-dopaminergic antipsychotics block D₂ receptors, but with different affinities and selectivities
- First-generation (FGAs): high affinity D₂ antagonists
 - High/mid/low potency FGAs
- Second-generation (SGAs): lower affinity D₂ antagonists, 5-HT_{2a} antagonists
- Partial D₂ agonist/antagonists: D₂ agonists (low dopamine), D₂ antagonists (high dopamine)
- Xanomeline/trospium: muscarinic agonist + peripheral muscarinic antagonist

Xanomeline + Trospium

- Xanomeline:
 - Muscarinic agonist: M_1 & M_4 activity (prefrontal cortex & ventral striatum)
 - Treats psychosis by modulating cholinergic tone
 - Upstream from where FGAs & SGAs work
 - Peripheral muscarinic agonist:
 - Salivation, sweating, nausea, vomiting, diarrhea, urination
- Trospium:
 - Peripheral muscarinic antagonist
 - Reduces side effects



Emergent Side Effects



Neuroleptic Malignant Syndrome

- Classic tetrad:
 - Fever
 - Rigidity
 - Mental status changes
 - Autonomic instability
- Elevated CK (>1000 IU/L), leukocytosis
- Onset within 2 weeks of starting antipsychotic, rapid progression
- Differential: CNS/systemic infections, serotonin syndrome, malignant catatonia, malignant hyperthermia
- Treatment: stop antipsychotic, send to ED

Maintain a high level of suspicion- presentations can be atypical

QTc Prolongation

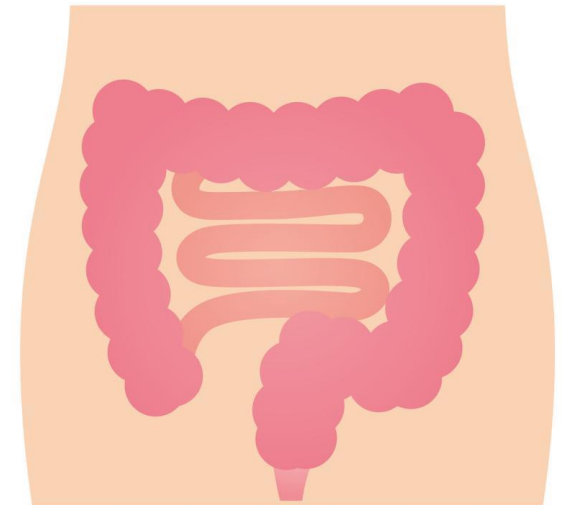
- Increases risk of Torsades de Pointes (life threatening)
- Risk factors: cardiac disease, low Mg or K, age¹
- Highest risk: FGAs, ziprasidone, iloperidone
- Baseline EKG when possible, personal & family history of cardiac disease
- Patients on high doses or multiple QT prolonging meds need closer monitoring



1. Beach SR, et al. *Psychosomatics*. 2018;59(2):105-122.

Gastrointestinal side effects

- Gastrointestinal hypomotility
 - Constipation, ileus, ischemic bowel disease → obstruction, toxic megacolon, sepsis & death
- 30-60% of patients experience antipsychotic-induced constipation¹
 - Clozapine, quetiapine are high risk
- Monitor at each visit
- Intervene (prophylactically)
 - Use stool softeners, osmotic laxatives, stimulant laxatives
 - Do NOT use bulking agents



1. Chen HK, et al. *Schizophr Res*. 2018;195:237-244.

Clozapine

- The only antipsychotic FDA approved for treatment-resistant schizophrenia
- 5 FDA Boxed Warnings
 - Know how to mitigate them
- Ileus and pneumonia are more common and more strongly associated with an increased risk of death¹
- Clozapine is still associated with lower all-cause mortality compared to other antipsychotics²

1. Partanen JJ, et al. *Am J Psychiatry*. 2024;181:879-892. 2. Vermeulen JM, et al. *Schizophr Bull*. 2019;45(2):315-329.

Clozapine FDA Boxed Warnings

1. Agranulocytosis

- Monitor ANC, weekly x 18w, monthly x 2y, then annual CBC¹

2. Myocarditis, pericarditis, cardiomyopathy

- EKG baseline, 2-4w, weekly CBC, CRP, hs-troponin x 8 weeks

3. Seizures

- Dose related, therapeutic drug monitoring

4. Orthostatic hypotension, bradycardia, syncope

- Slow titration

5. Increased mortality in elderly with dementia

- Class warning

1. Donovan AL, et al. *Psychiatr Serv.* 2026;77(5):470-3.

Clozapine Side Effect Interventions

Metabolic Side Effects

- Monitoring, lifestyle measures, metformin, GLP-1 agonists

Constipation

- Diet, hydration, senna, docusate, NO bulking agents

GERD

- Small meals, weight loss, raise head of bed, PPI, avoid omeprazole

Sialorrhea

- Towel on pillow, raise head of bed, ipratropium spray, atropine SL, glycopyrrolate

Urinary Incontinence/ Nocturnal Enuresis

- Desmopressin, treat constipation, aripiprazole

Tachycardia

- Slow titration, propranolol, atenolol, cardiology consult

Pneumonia

- Raise head of bed, treat sialorrhea, keep vaccinations up to date

Siskind D, et al. *Lancet Psychiatry*. 2025. Jul 1:S2215-0366(25)00098-7.

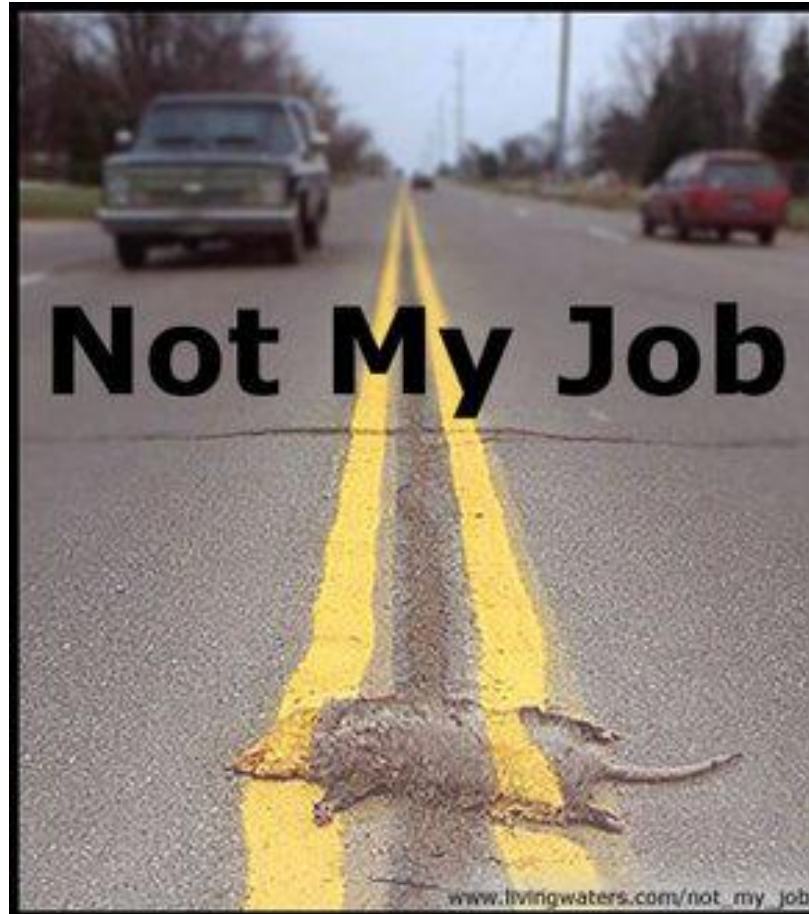
Non-Emergent Side Effects

Morbidity and Mortality

- Schizophrenia is associated with a 20-year decrease in life expectancy¹ & a 4-fold increase in mortality²
 - Mortality gap may be getting wider over time³
- Premature mortality is due to cardiovascular disease (#1), respiratory disease, infections and cancers^{3,4}

We MUST be part of closing the mortality gap

1. Druss BG, et al. *Med Care*. 2011;49(6):599-604. 2. Revier CJ, et al. *J Nerv Ment Dis*. 2015;203(5):379-386. 3. Ward MC, et al. *JAMA Psychiatry*. 2019;76(7):759-760. 4. Olfson M, et al. *JAMA Psychiatry*. 2015;72(12):1172-1181.





Antipsychotic-Induced Weight Gain

- Almost all FGA/SGA antipsychotics show weight gain after extended use¹
 - Weight gain more pronounced in antipsychotic-naïve patients² and patients with schizophrenia³
 - Not universally dose dependent- individual antipsychotics have their own dose-response curves⁴
- Rapid early on, plateaus over time (6 months-1 year)¹
- Decreased insulin sensitivity & lipid changes are rapid (2-4 weeks)^{5,6}
- Early monitoring is key

1. Burschinski A, et al. *World Psychiatry*. 2023;22:116-128. 2. Bak M, et al. *PLoS One*. 2014;9(4):e94112. 3. Stogios N, et al. *Focus*. 2025;23:407-418. 4. Sabe M, et al. *J Clin Psychiatry*. 2023.84(2):22r14490. 5. Cao H, et al. *J Psychiatr Res*. 2020;129:265-271. 6. Zhang Y, et al. *J Clin Psychiatry*. 2020;81(3):19M12785.

Prevention of Antipsychotic-Induced Weight Gain (AIWG)

Universal

- Metabolically lowest-risk antipsychotic
- Baseline monitoring: BMI, waist circumference, glucose, HbA1c, lipids
- Ongoing monitoring: weight, HbA1c and lipids

Selective

- Therapeutic lifestyle interventions
- Metformin

Indicated

- Switch to metabolically lower risk antipsychotic
- Weight loss medications

**Practice
universal and
selective
prevention
simultaneously**

Antipsychotic Selection

Long Term Metabolic Effects of Antipsychotics¹

High	Med	Low	Very Low
• Clozapine • Olanzapine	• Risperidone • Paliperidone • Quetiapine	• Aripiprazole • Cariprazine • Asenapine	• Lurasidone • Ziprasidone • Lumateperone² • Xanomeline / Trospium³

1. Burschinski A, et al. *World Psychiatry*. 2023;22:116-128. 2. McIntyre RS, et al. *Am J Psychiatry*. 2024;181:26-38. 3. Kaul I, et al. *JAMA Psychiatry*. 2024;81(8):749-756.

Monitoring

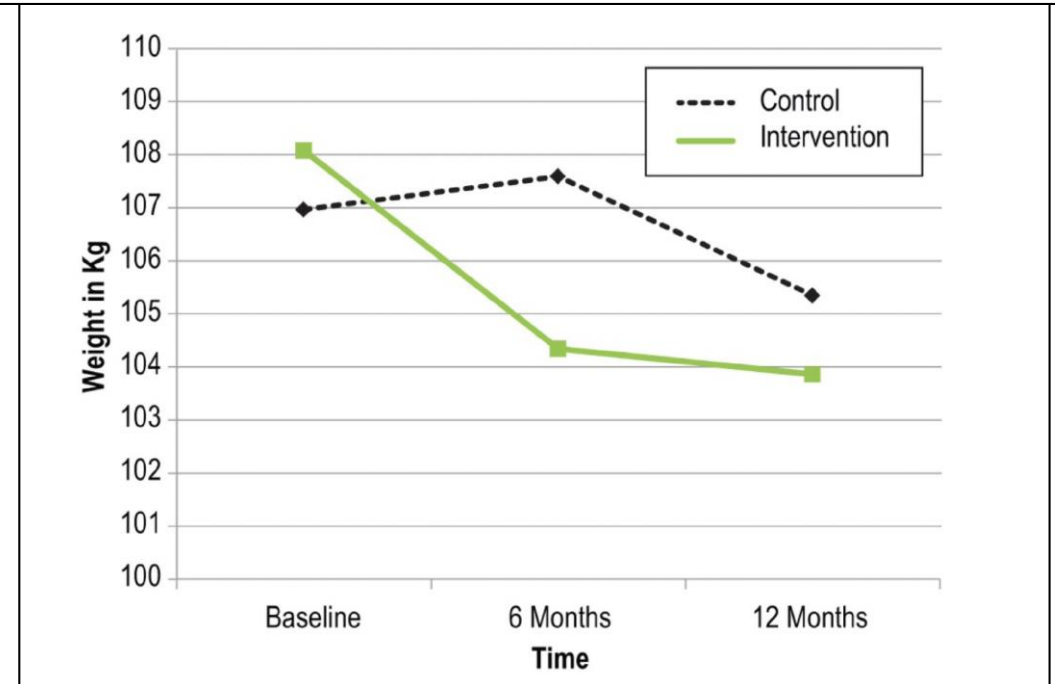
- Baseline monitoring: BMI, waist circumference, glucose, HbA1c, lipids
- Ongoing monitoring:
 - Weight at every visit
 - HbA1c and lipids at regular intervals, particularly early on, annually thereafter
- “Perfect is the enemy of good enough”
 - Non-fasting labs are acceptable¹
- Telehealth requires innovative monitoring

1. Mora S, et al. *JAMA Intern Med.* 2019;179(7):898-905.

Selective Prevention: Therapeutic Lifestyle Intervention

- Lifestyle counseling, psychoeducation, exercise¹
- Group exercise intervention²
 - Intervention group lost 4.4 kg more than the control group
- Greater impact with low-risk antipsychotics³
- Several null studies⁴
 - Important for general physical health, may not be sufficient alone for AIWG

The STRIDE Weight Loss and Lifestyle Intervention for Individuals Taking Antipsychotic Medications: A Randomized Trial



1. Vancampfort D, et al. *World Psychiatry*. 2019;18:53-66. 2. Green CA, et al. *Am J Psychiatry*. 2015;172(1):71-81. 3. Sampogna G, et al. *J Psychiatr Res*. 2025;181:570-578. 4. Stogios N, et al. *Focus*. 2025;23:407-418.

Metformin

Safety

- Rare lactic acidosis
- May be associated with B12 deficiency

Dosing

- Target dose 2000 mg TDD¹
- Give with food

Efficacy

- Significant decrease in weight, BMI, HbA1c, lipids²
- Most effective prior to development of obesity³

Initiation

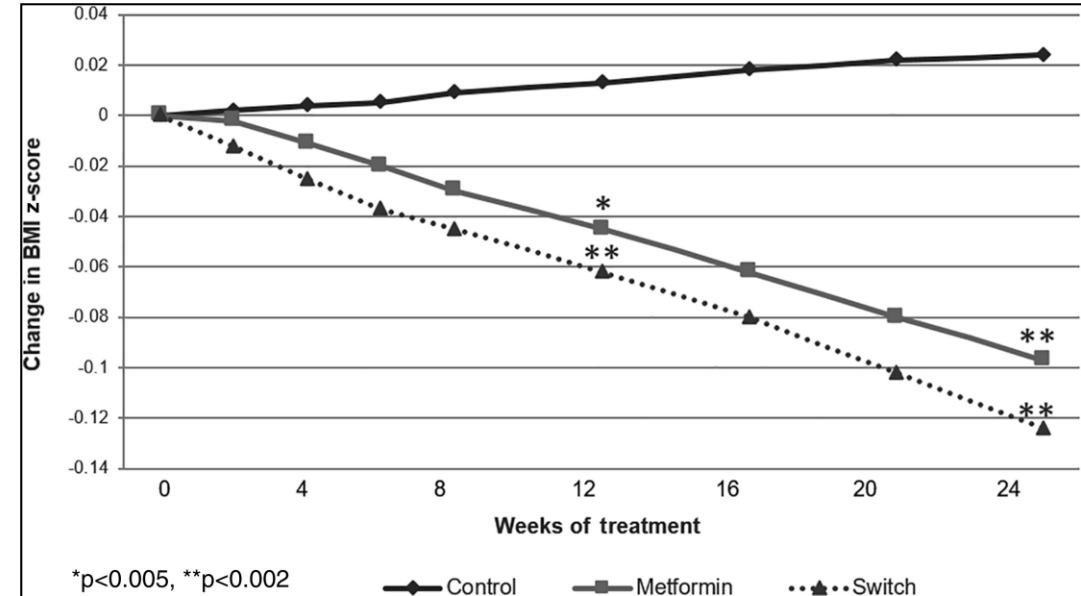
- Co-initiation:⁴
 - High-risk antipsychotic
 - Moderate-risk antipsychotic + health risk factor

1. McCutcheon RA, et al. *Lancet Psychiatry*. 2025;12:384-394. 2. Zheng W, et al. *J Clin Psychopharmacol*. 2015;35(5):499-509. 3. Chen H, et al. *J Clin Psychiatry*. 2024;85(1):23M14894. 4. Carolan A, et al. *Schizophr Bull*. 2024. Dec 9:sbae205.

Indicated Prevention

- Switch to lower risk antipsychotic
- IMPACT Trial: Randomized to metformin, switch to lower risk antipsychotic or continue current antipsychotic
- Metformin and switch were equally effective for decreasing BMI

The IMPACT Trial



Correll CU, et al. *World Psychiatry*. 2020;19:69-80.

Switching Antipsychotics

- Does switching antipsychotics increase relapse risk?
- In stable patients, switching antipsychotics may not increase risk of relapse¹
- Patients with <6 months stability or high PANSS scores are more likely to relapse with a switch²
- Must engage in shared decision making

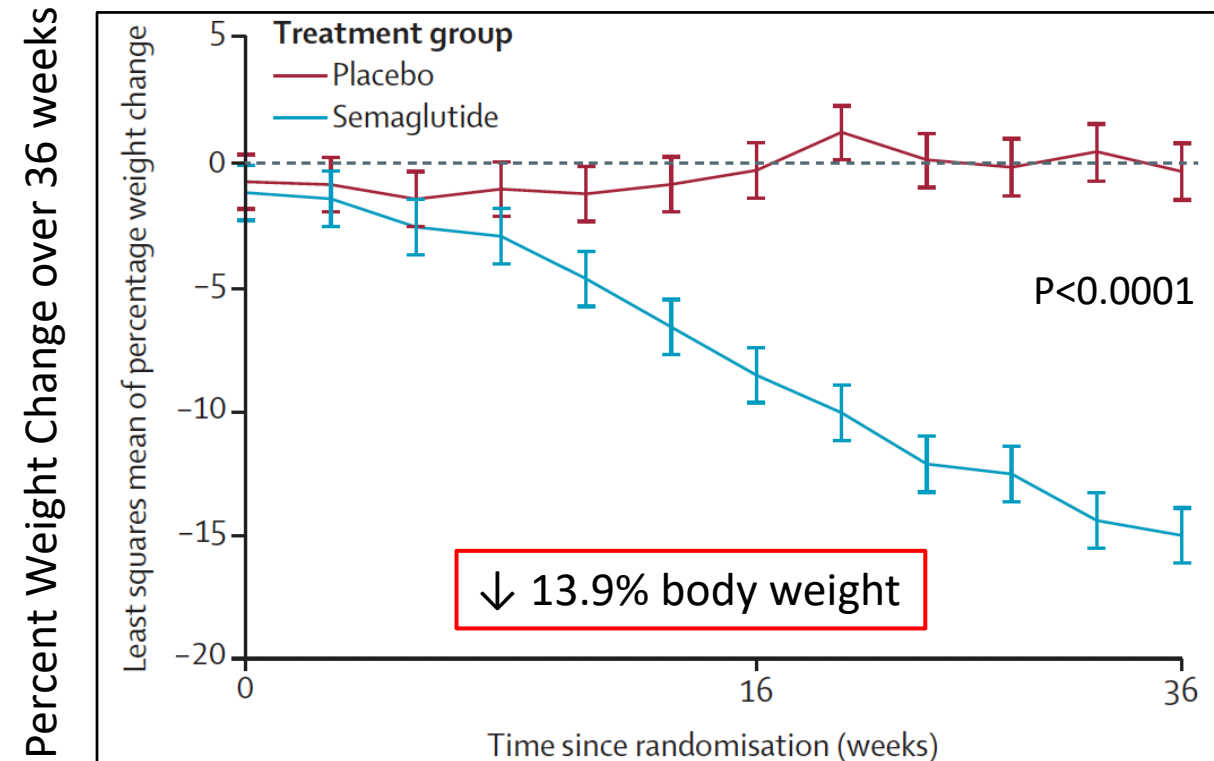


1. Ostuzzi G, et al. *Lancet Psychiatry*. 2022;9(8):614-624. 2. Cai J, et al. *Psychiatry Res*. 2023;322:115138.

GLP-1 Agonists

- Slow gastric motility, decrease appetite
- Semaglutide, liraglutide
- Insurance coverage limited: requires BMI >27 & comorbidity or BMI >30
- Very effective¹
- Also associated with decreased mortality, hospitalizations and suicidal behavior²

Semaglutide vs. Placebo¹



1. Siskind D, et al. *Lancet Psychiatry*. 2025;12;493-503. 2. Liu TH, et al. *Eur Neuropsychopharmacol*. 2026; 103:112739.

Additional Strategies

Topiramate¹

- 100-200 mg/day
→ ↓ weight/BMI
- Cognitive dulling

SGLT2 Inhibitors²

- Sodium-glucose co-transporter-2 inhibitors
- Increase renal glucose excretion
- More research needed in SMI

GLP/GIP Co-Agonist³

- Tirzepatide
- Improvements in obesity-related morbidity
- May also improve attention
- More research needed in SMI

Naltrexone/bupropion⁴

- Mediates food reward
- More research needed in SMI

1. Correll CU, et al. *J Clin Psychiatry*. 2016;77(6):e746-e756. 2. Vasiliu O. *Experimental Ther Med*. 2023;25(3):125. 3. McIntyre RS, et al. *Am J Psychiatry*. 2024;181(1):26-38. 4. Tham M, et al. *Obes Res Clin Pract*. 2021;15(1):49-57.

Motor Side Effects: Extrapyramidal Symptoms

Highest risk with high potency FGAs but can occur with any FGA/SGA antipsychotic

Early

Late

Dystonia

Akathisia

Parkinsonism

Tardive
Dyskinesia

Acute Dystonic Reaction

- 50% occur within 2 days of starting treatment, almost 100% within 1 week¹
- Distressing, but not typically life threatening
- Treatment
 - Stop antipsychotic
 - Parenteral anticholinergic (benztropine or diphenhydramine)
 - Continue brief course of oral anticholinergics for 2-3 days

1. Caroff SN, et al. *Neurol Clin.* 2011;29(1):127-viii.

Akathisia

* Associated with bad outcomes-
non-adherence, suicide attempts²

- **ακαθιζειν** = “not to sit”
- Subjective inner restlessness with objective physical manifestations
 - Early/mild akathisia, only the subjective component may be present
- Screen proactively*
- Highest risk: high potency FGAs, aripiprazole, lurasidone, cariprazine¹
- Differential diagnosis: psychotic agitation, agitated depression, anxiety, restless leg syndrome

1. Citrome L. *J Clin Psychopharmacol*. 2017;37(2):138-147. 2. Poyurovsky M, et al. *Drugs*. 2020;80:871-882.

Akathisia - Treatment

- Decrease the antipsychotic dose
- Switch to a different antipsychotic
 - Quetiapine, clozapine¹
- Treat symptomatically (even while switching)
 - Beta blockers (propranolol)^{1,2}
 - 5-HT_{2a} antagonists: mirtazepine (low dose)^{1,2}, trazodone^{2,3}
 - Benzodiazepines (time-limited)⁴
- Avoid anticholinergics^{1,3, 4}

1. McCutcheon RA, et al. *Lancet Psychiatry*. 2025;12:384-394. 2. Furukawa Y, et al. *Schizophr Bull*. 2026;52(2):1-8. 3. Shams-Alizadeh N, et al. *J Clin Psychopharmacol*. 2020;40:611-614. 4. Vanegas-Arroyave N, et al. *CNS Drugs*. 2024;38:239-54.

Parkinsonism

- Resembles Parkinson's disease (PD)
- Differential: negative symptoms, psychomotor retardation of depression, PD
- Treatment
 - Decrease the antipsychotic dose¹
 - Change to a different antipsychotic (SGA)¹
 - Amantadine²
 - Anticholinergic medication (temporarily)²

1. Shin HW and Chung SJ. *J Clin Neurol*. 2012;8:15-21. 2. Vanegas-Arroyave N, et al. *CNS Drugs*. 2024;38:239-54.

Motor Side Effects: Late

- Tardive Dyskinesia (TD)
- Involuntary, irregular choreiform movements
 - Often affecting face/mouth, can occur anywhere
- Iatrogenic
- Severe impact across physical, psychological and social domains¹
- Can occur with all FGAs & SGAs
 - FGAs: 6.5% incidence per year² SGAs: 2.6% incidence per year²
 - Prevalence: 25.3% overall³
 - Clozapine is lowest risk among FGAs/SGAs

Prevention is critical- TD is
often irreversible

1. Jain R, et al. *J Clin Psychiatry*. 2023;84(3):22m14694. 2. Carbon M, et al. *World Psychiatry*. 2018;17:330-340. 3. Carbon M, et al. *J Clin Psychiatry*. 2017;78(3):e264-e278.

TD Risk Factors

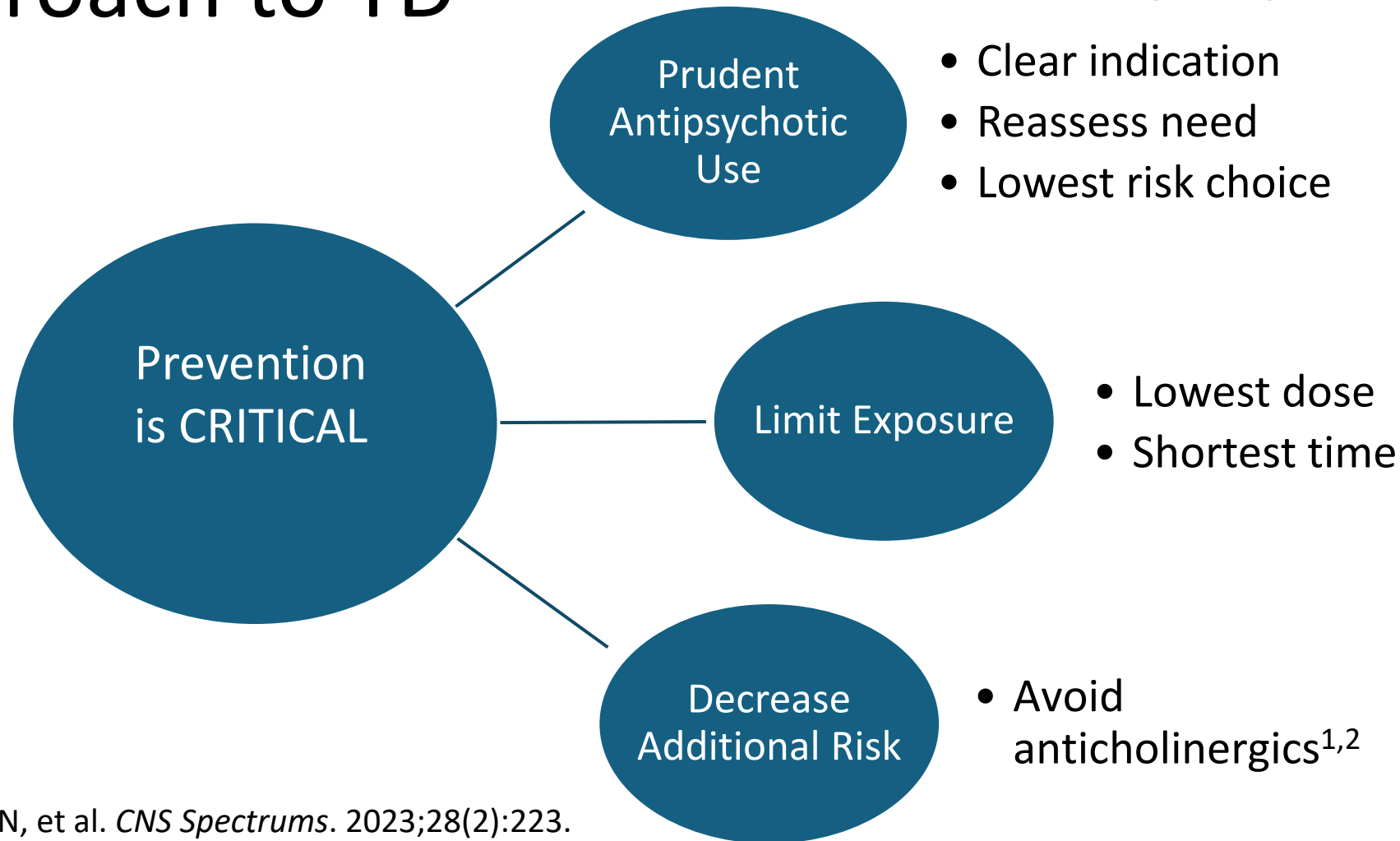
Non-modifiable

- Age (older)
- Female
- African-American
- Brain injury
- History of early EPS

Modifiable

- Diabetes
- Nicotine use
- Alcohol use
- **Anticholinergic medication**
- **Cumulative antipsychotic exposure**

Approach to TD



1. Vanegas-Arroyave N, et al. *CNS Spectrums*. 2023;28(2):223.

2. Vanegas-Arroyave N, et al. *CNS Drugs*. 2024;38:239-54.

Monitor

- Baseline motor exam
- Each visit, semi-structured assessment¹
 - Patient & caregiver report, visual observation, brief psychomotor exam
- AIMS* at least annually
 - More frequently (Q3-6 months) if high risk
- Consensus guidelines for diagnosis²
 - Probable TD: score of 2+ in 2 areas or 3+ in 1 area
- Broad differential: consult with neurology

AIMS*

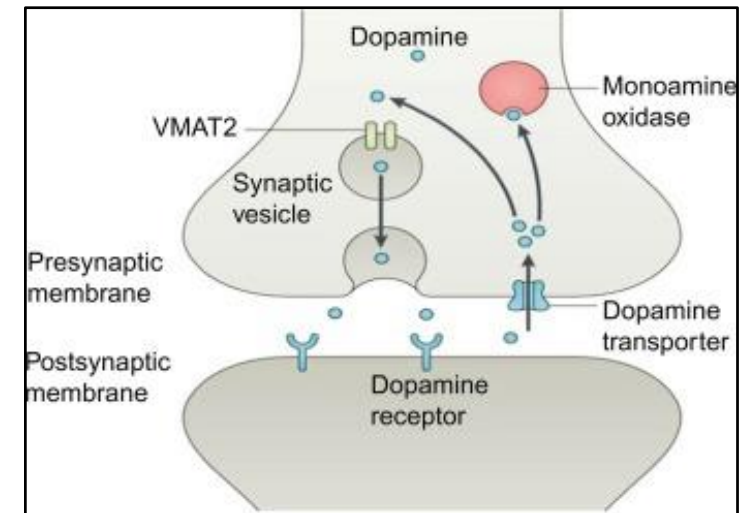
No gum, no candy, no mask
Tremor doesn't count
Must be in person

1. Caroff SN, et al. *J Clin Psychiatry*. 2020;81(2):19cs12983. 2. Schooler and Kane. *Arch Gen Psychiatry*. 1982;39:486-487.

TD Treatment

- If possible, taper antipsychotic slowly
- If possible, switch to quetiapine or clozapine¹
- Symptomatic treatment¹
 - First line: VMAT-2 inhibitors
 - **Valbenazine, deutetrabenazine**
 - Monitor QTc if risk factors
 - Lower dose for poor metabolizers/inhibiting drugs at CYP2D6 or 3A4

VMAT = Vesicular monoamine transporter



VMAT-2 inhibitors do not reverse TD

1. McCutcheon RA, et al. *Lancet Psychiatry*. 2025;12:384-394.

TD Treatment – Second Line

- Amantadine^{1,2,3}
- Benzodiazepines (clonazepam)^{1,3} – but risk of harm
- Beta-blockers¹
- Ginkgo biloba^{1,2}
- Branched-chain amino acids¹
- Vitamin B6^{2,3} – but risk of neuropathy
- Vitamin E^{2,3} – perhaps to prevent further decline?
- Botox injections⁴ – for focal TD, orofacial TD, tardive dystonia
- Deep brain stimulation^{1,3} - for tardive dystonia or treatment refractory TD
- TMS¹

1. Debrey SM and Goldsmith DR. *Focus*. 2021(19):14-23. 2. Artukoglu BB, et al. *J Clin Psychiatry*. 2020;81(4):19r12798. 3. Ricciardi L, et al. *Can J Psychiatry*. 2019;64(6):388-399. 4. Factor SA. *Neurother*. 2020;17(4):1694-1712.

Hyperprolactinemia

- Higher D₂ affinity → higher prolactin levels
- Side Effects:
 - Decreased libido, erectile dysfunction
 - Gynecomastia
 - Galactorrhea
 - Infertility
 - Amenorrhea
- Long-term side effects:
 - Hypogonadism → osteoporosis & fractures¹
 - Increased risk of breast cancer (OR 1.47)²

Increase prolactin



FGAs,
risperidone,
paliperidone



Aripiprazole, all
partial agonists,
clozapine,
quetiapine,
iloperidone

Prolactin-Sparing

1. Andrade C. *J Clin Psychiatry*. 2023;84(1):23f14790. 2. Solmi M, et al. *Schizophr Bull*. 2024. doi:10.1093/schbul/sbae058.

Hyperprolactinemia: Monitoring & Treatment

- Monitoring:¹
 - Baseline prolactin, recheck early on, serially thereafter
 - Monitor symptoms regularly
- Treatment:
 - Consider the differential diagnosis, consult with endocrine
 - Shared decision making with the patient²
 - Monitor (especially for asymptomatic hyperprolactinemia)
 - Add a prolactin-sparing antipsychotic (aripiprazole)
 - Switch to a prolactin-sparing antipsychotic

1. Grigg J, et al. *Psychopharmacology*. 2017;234(22):3279-3297. 2. McCutcheon RA, et al. *Lancet Psychiatry*. 2025;12:384-394.

Sedation

- Worsens functional impairment from negative symptoms
- Most severe early in treatment¹
 - 50% resolve within 1 week, 75% within one month
- Treatment²
 - Tincture of time
 - Lower total daily dose, split dose
 - Coffee (in small amounts)
 - Be careful with modafinil
 - Avoid stimulants (trigger relapse,³ especially amphetamines⁴)

1. Nomura N, et al. *Lancet Psychiatry*. 2025;12:266-275. 2. APA: Practice Guideline on the Treatment of Patients With Schizophrenia, 3rd Edition. 2020. 3. Cressman AM, et al. *J Clin Psychopharmacol*. 2015;35(6):667-671. 4. Moran LV, et al. *Am J Psychiatry*. 2024;181:901-909.

Xanomeline-Trospium Side Effects

- Side Effects¹
 - GI: nausea, vomiting, diarrhea, dyspepsia, GERD, constipation
 - Headaches
 - Hypertension
 - Insomnia
- Xanomeline-Trospium does NOT cause¹
 - Weight gain, akathisia, EPS, somnolence
- MUST be taken on an empty stomach

1. Kaul I, et al. *JAMA Psychiatry*. 2024;81(8):749-756.

Framework: Side Effect Monitoring and Intervention

Side Effect Monitoring

- So much monitoring!
- Real world metabolic monitoring rates are ~40%¹
 - If those are monitoring rates, what are the intervention rates?
- Can't depend on memory and good intentions alone

At Each Visit	Q 6months-Annually
Weight	HbA1c
Motor exam	Lipid panel
Constipation	Prolactin level
Sedation	AIMS
Hyperprolactinemia	BP, pulse
Sexual side effects	Vaccines
Smoking, alcohol, drugs	Preventive health Care
Exercise	Infectious disease screening

1. Poojari PG, et al. *Clin Epidemiol Glob Health*. 2022;15:101035.

Framework Examples

- Automated EMR reminders¹
- Population-based patient registry²
- Dedicated medical screening nurse³
- Problem-based charting
 - Every side effect category becomes a “problem” to monitor at each visit
 - Weight Gain: current weight, recent labs & when due next, weight loss medications
 - Motor Side Effects, Hormonal Effects, Sedation....

Perfect is the enemy of good
enough

1. Delmonte MT, et al. *J Clin Pharm Ther*. 2012;37:668-673. 2. Manguarian C, et al. *Psychiatr Serv*. 2022;73(8):942-945. 3. Poojari PG, et al. *Clin Epidemiol Glob Health*. 2022;15:101035.

Intervention

- Monitoring is not enough, we must intervene
- Psychiatric clinics are the principal connection patients have to the health care system
 - Improving medical care starts in the psychiatric clinic
- Reverse Integration¹
 - Bring primary care into psychiatric care
 - Coaching behavioral change, preventive (not reactive) care, treatment algorithms, expert consultation & referral when needed
 - Improve screening and physical health outcomes^{1,2}

1. Ward MC and Druss BG. *Focus*. 2017;15(3):271-278. 2. Manguarian C, et al. *Psychiatr Serv*. 2022;73(8):942-945.

Summary

- Emergent side effects
- Non-emergent side effects
- Framework for monitoring
- The need for intervention

“Prevention is better than cure.”

Desiderius Erasmus

Thank You

MGH Psychosis Clinical and Research Program

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