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Management of Side Effects of Antipsychotics

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Disclosures

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

Artisan – Investor, Board Member (spouse)

Carney, Gaudet & Carney – Expert testimony

Mirah – Investor

Outline

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

Why Do Side Effects Matter?

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Side Effects

- 80% of patients report at least 1 side effect[1]
- Associated with non-adherence[1]

Non-adherence

- Increased risk of [1,2]
  - ED visits
  - Hospital admissions
  - Relapse

Relapse

- Increased risk of [2]
  - Self harm
  - School/work interruption
  - Disease progression

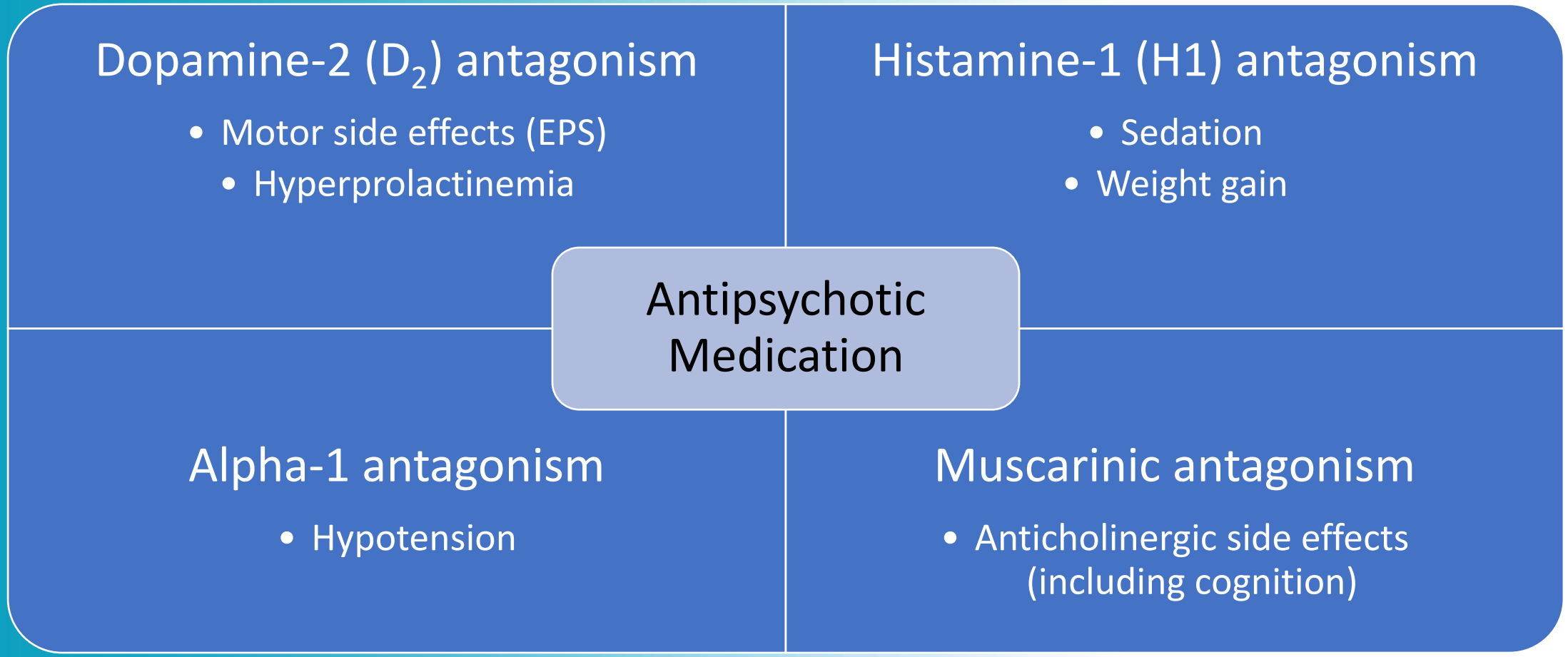
Relapse is bad!

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

Antipsychotic Pharmacology

- All antipsychotics block D_2 receptors, but with different affinities and selectivities
- First-generation (FGAs): high affinity D_2 antagonists
  - High/mid/low potency FGAs
- Second-generation (SGAs): lower affinity D_2 antagonists, 5-HT_{2a} antagonists
- Partial D_2 agonist/antagonists: D_2 agonists (low dopamine), D_2 antagonists (high dopamine)

Predicting Side Effects: Receptor Activity



Emergent Side Effects

Neuroleptic Malignant Syndrome (NMS)

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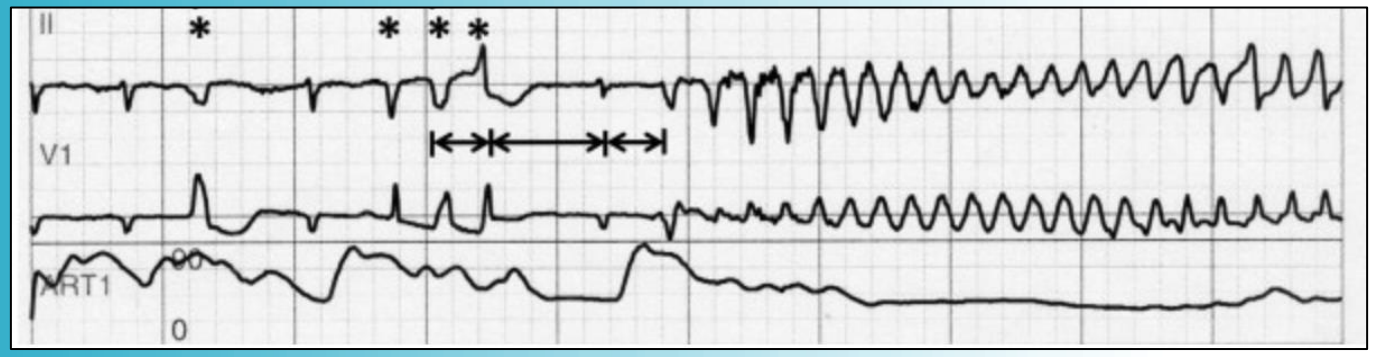
- Classic tetrad:
  - Fever
  - Rigidity
  - Mental status changes
  - Autonomic instability
- Elevated CK (>1000 IU/L), leukocytosis
- Onset within 2 weeks of starting antipsychotic, rapid progression
- Differential: CNS/systemic infections, serotonin syndrome, malignant catatonia, malignant hyperthermia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

Maintain a high level of suspicion- presentations can be atypical

QTc Prolongation

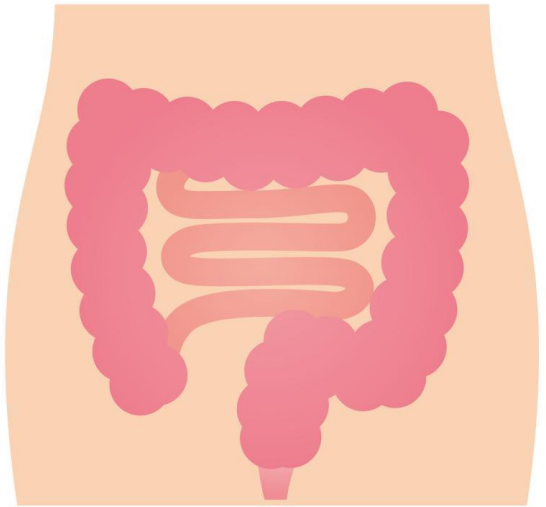
- Increases risk of Torsades de Pointes
- Risk factors: cardiac disease, low Mg or K, age[1]
- Highest risk: FGAs, ziprasidone, iloperidone
- Baseline EKG when possible, personal & family history of cardiac disease
- Patients on high doses or multiple QT prolonging meds need closer monitoring



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 constipation[1]
  - 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 Black Box Warnings
  - Know how to mitigate them
- Clozapine is still associated with lower all-cause mortality compared to other antipsychotics[1]

1. Vermeulen JM, et al. *Schizophr Bull.* 2019;45(2):315-329.

Clozapine Black Box Warnings

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1. Agranulocytosis
   - REMS
2. Myocarditis
   - Baseline EKG, weekly CRP, troponin x 8 weeks
3. Seizures
   - Dose related, therapeutic drug monitoring
4. Orthostatic hypotension
   - Slow titration
5. Increased mortality in elderly
   - Class warning

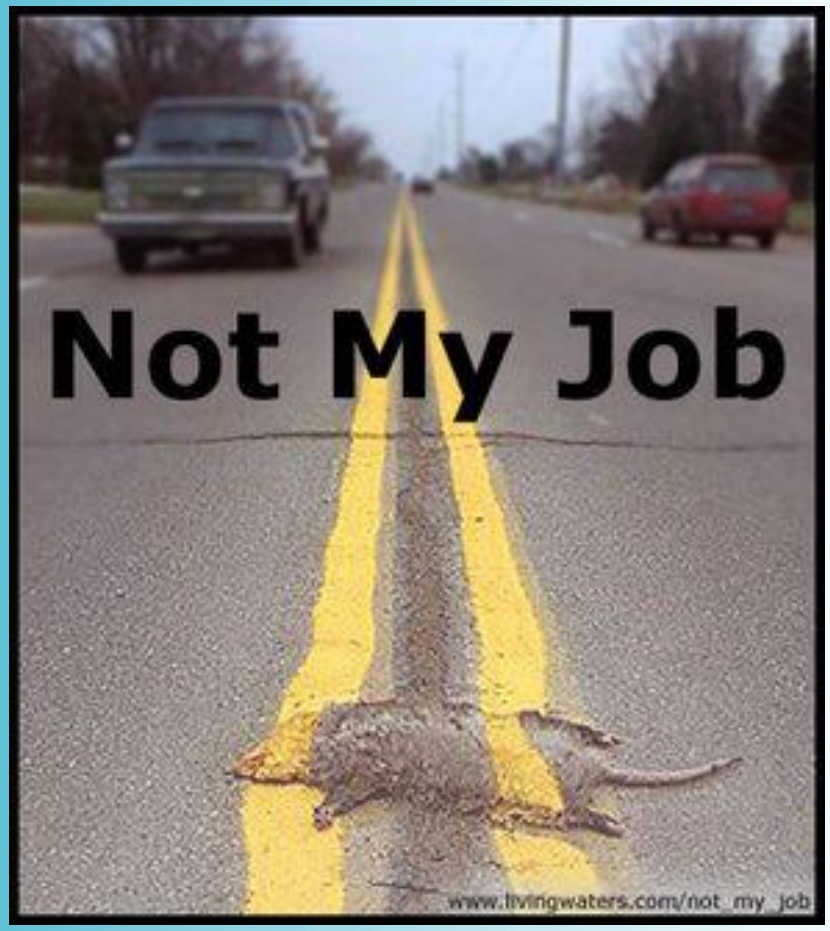
Non-Emergent Side Effects

Morbidity and Mortality

- Schizophrenia is associated with a 20-year decrease in life expectancy[1] & a 4-fold increase in mortality[2]
  - Mortality gap may be getting wider over time[3]
- 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.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IT'S MY JOB

Antipsychotic-Induced Weight Gain

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- Almost all antipsychotics show weight gain after extended use[1]
  - Weight gain more pronounced in antipsychotic-naïve patients[2]
  - Not universally dose dependent- individual antipsychotics have their own dose-response curves[3]
- Rapid early weight gain, plateaus over time (6 months-1 year)[1]
- Decreased insulin sensitivity & lipid changes develop rapidly (2-4 weeks)[4,5]
- 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. Sabe M, et al. *J Clin Psychiatry.* 2023.84(2):22r14490. 4. Cao H, et al. *J Psychiatr Res.* 2020;129:265-271. 5. Zhang Y, et al. *J Clin Psychiatry.* 2020;81(3):19M12785.

Prevention of Weight Gain

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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

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Long Term Metabolic Effects of Antipsychotics[1]

High	Med	Low	Very Low
• Clozapine • Olanzapine	• Risperidone • Paliperidone • Quetiapine	• Aripiprazole • Cariprazine • Asenapine	• Lurasidone • Ziprasidone • Lumateperone[2]

1. Burschinski A, et al. *World Psychiatry.* 2023;22:116-128. 2. McIntyre RS, et al. *Am J Psychiatry.* 2024;181:26-38.

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 acceptable[1]
- Telehealth requires innovative monitoring

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

Selective Prevention: Therapeutic Lifestyle Intervention

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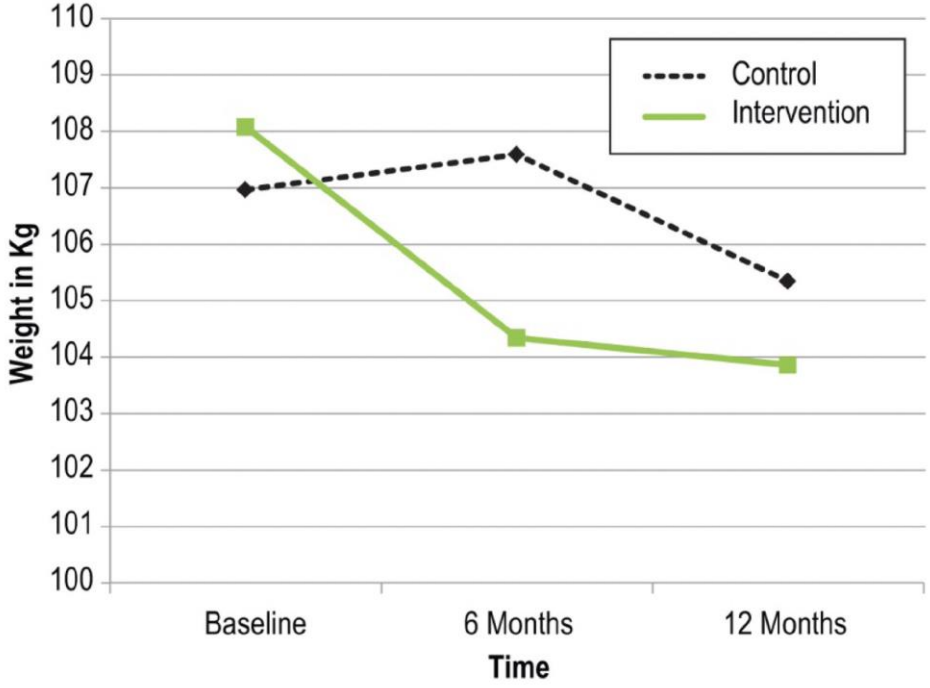
- Group intervention vs control
  - Nutrition education
  - Group exercise (20 mins weekly)
- Intervention group lost 4.4 kg more than the control group
  - ~ 4.5% of their body weight

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



Green CA, et al. *Am J Psychiatry.* 2015;172(1):71-81.

Metformin

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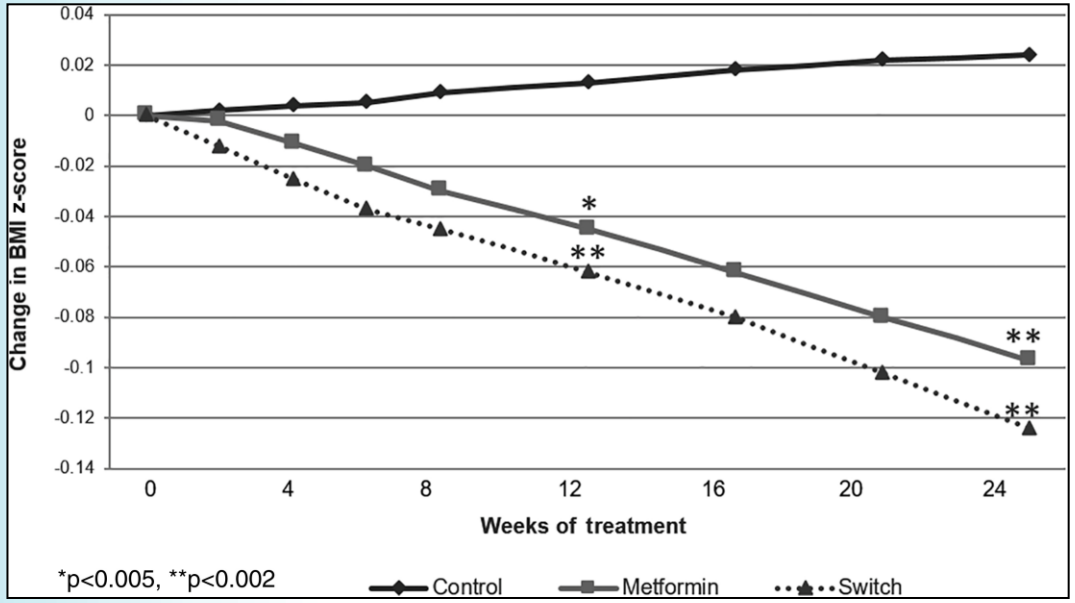
Safety	Dosing	Efficacy
• Rare lactic acidosis • May be associated with B12 deficiency[1]	• Target dose 2000 mg TDD • Give with food	• Significant decrease in weight, BMI, HbA1c[2] • Significant improvement in lipid profiles[2] • Most effective prior to development of obesity[3]

1. Aroda VR, et al. *J Clin Endocrinol Metab.* 2016;101(4):1754-61. 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.

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.

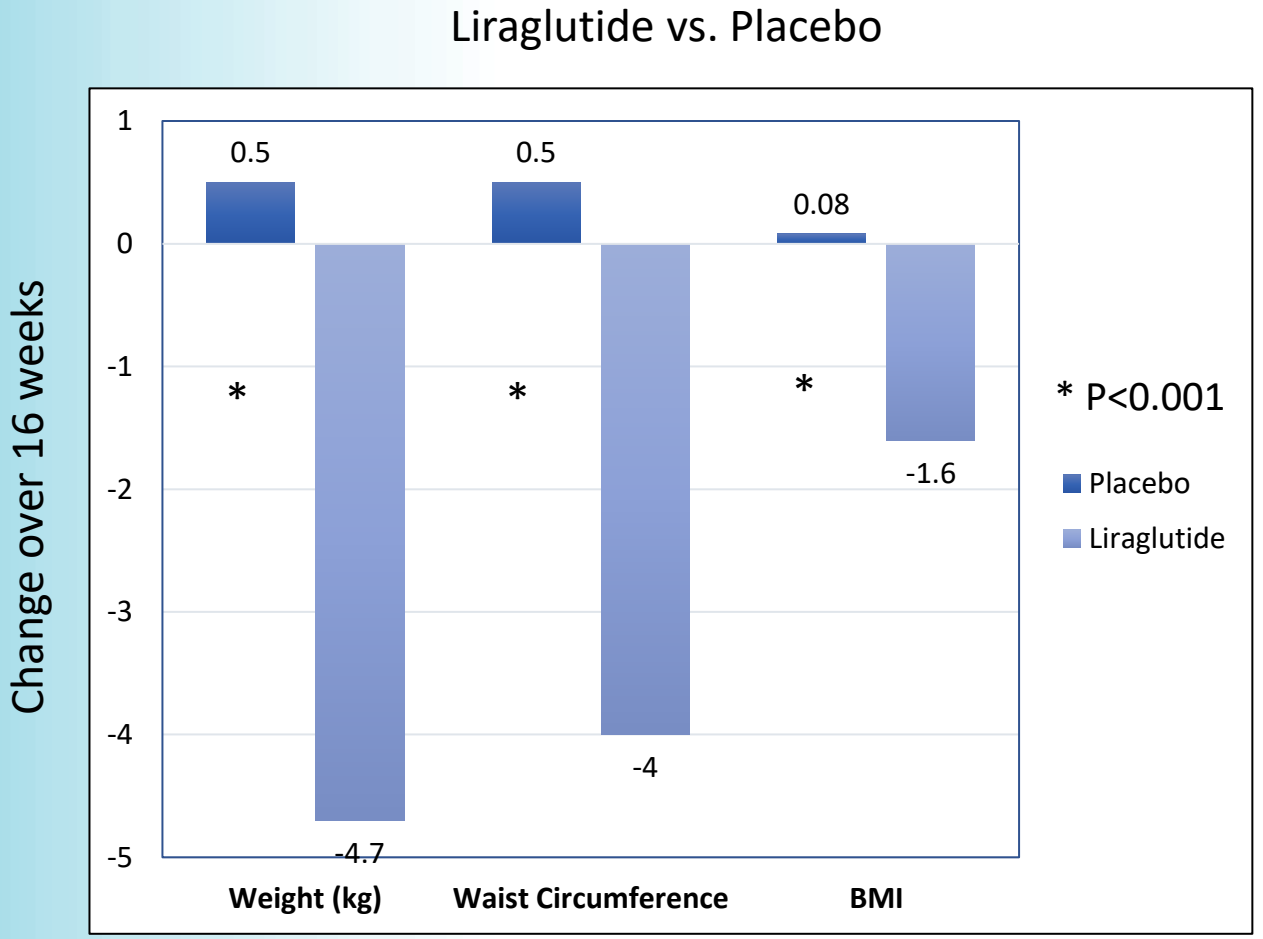
Switching Antipsychotics

- Does switching antipsychotics increase relapse risk?
- In stable patients, switching antipsychotics may not increase risk of relapse[1]
- Patients with <6 months stability or high PANSS scores are more likely to relapse with a switch[2]
- 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

- GLP-1 stimulates insulin secretion, inhibits glucagon secretion
- Slow gastric motility, decrease appetite
- Semaglutide, luraglutide
  - Approved for treatment of obesity and diabetes
- Side effects: nausea, constipation
- Insurance coverage requires BMI >27 & comorbidity or BMI >30



Larsen JR, et al. *JAMA Psychiatry.* 2017;74(7):719-728.

Additional Strategies

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Topiramtate[1]	SGLT2 Inhibitors[2]	GLP/GIP Co-Agonist[3]	Naltrexone/bupropion[4]
• 100-200 mg/day → ↓ weight/BMI • Cognitive dulling	• Sodium-glucose co-transporter-2 inhibitors • ↑ renal glucose excretion • More research needed in SMI	• Tirzepatide • Improvements in obesity-related morbidity • May also improve attention • More research needed in SMI	• 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 antipsychotic

Early

Late

Acute Dystonic Reaction

- 50% occur within 2 days of starting treatment, almost 100% within 1 week[1]
- 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

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* Associated with bad outcomes- non-adherence, suicide attempts[2]

- **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, cariprazine[1]
- 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
  - Iloperidone, quetiapine, clozapine[1]
- Treat symptomatically (even while switching)[1]
  - Beta blockers (propranolol)
  - 5-HT_{2a} antagonists: mirtazepine (low dose)[1], trazodone[2]
  - Benzodiazepines (time-limited)[3]
- Avoid anticholinergics[1,3]

1. Poyurovsky M, et al. *Drugs.* 2020;80:871-882. 2. Shams-Alizadeh N, et al. *J Clin Psychopharmacol.* 2020;40:611-614.
3. 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 dose[1]
  - Change to a different antipsychotic (SGA)[1]
  - Amantadine[2]
  - 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 domains[1]
- Can occur with all antipsychotics
  - FGAs: 6.5% incidence per year[2] SGAs: 2.6% incidence per year[2]
  - Prevalence: 25.3% overall[3]
  - Clozapine is lowest risk

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

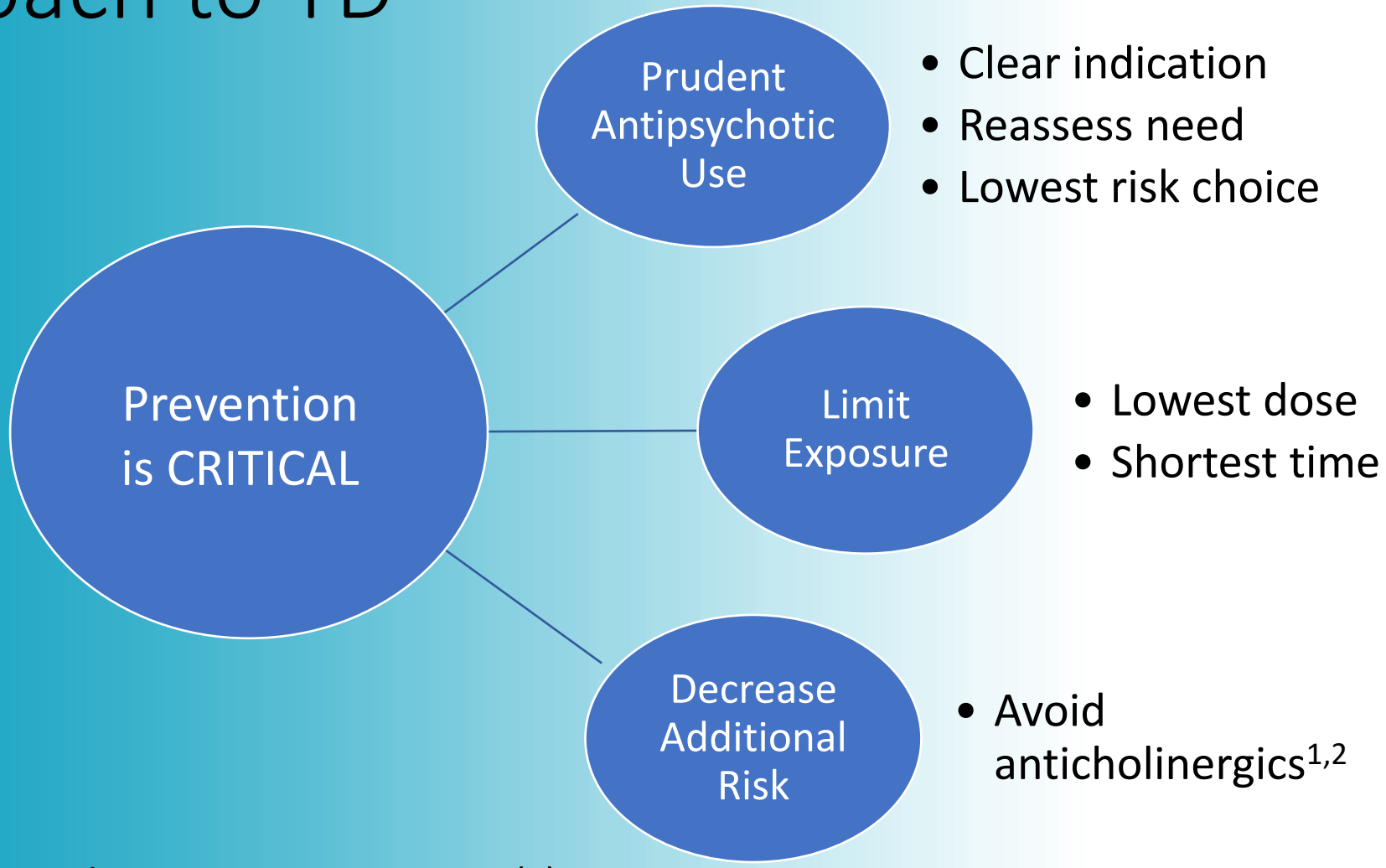
Non-modifiable

- 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



- Clear indication
- Reassess need
- Lowest risk choice

- Lowest dose
- Shortest time

- Avoid anticholinergics[1,2]

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

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

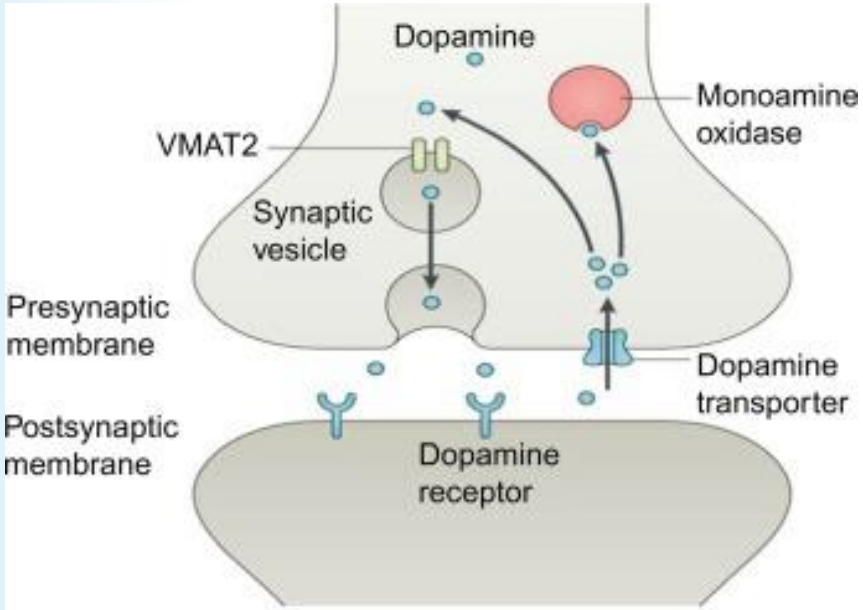
- Baseline motor exam
- Each visit, semi-structured assessment[1]
  - Patient & caregiver report, visual observation, brief psychomotor exam
- AIMS* at least annually
  - More frequently (Q3-6 months) if high risk
- Consensus guidelines for diagnosis[2]
  - Probable TD: score of 2+ in 2 areas or 3+ in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

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 <u>slowly</u>
- If possible, switch to quetiapine or clozapine[1]
- Symptomatic treatment
  - First line: VMAT-2 inhibitors
  - Valbenazine, deutetrabenazine

VMAT = Vesicular monoamine transporter



1. Mentzel TQ, et al. *J Clin Psychiatry.* 2018;79(6):17r11852.

Harriot ND, et al. *Prog Med Chem*. 2018(57):87-111.

VMAT-2 Inhibitors

- Valbenazine
  - QD dosing
  - Monitor QTc if risk factors
  - Lower dose for poor metabolizers/inhibiting drugs at CYP2D6 or 3A4
- Deutetrabenazine IR and ER
  - BID (IR) & QD (ER) dosing
  - Monitor QTc if risk factors
  - Lower dose for poor metabolizers/inhibiting drugs at CYP2D6

VMAT-2 inhibitors do **not** reverse TD

TD Treatment – Second Line

- Amantadine[1,2,3]
- Benzodiazepines (clonazepam)[1,3] – but risk of harm
- Beta-blockers[1]
- Ginkgo biloba[1,2]
- Branched-chain amino acids[1]
- Vitamin B6[2,3] – but risk of neuropathy
- Vitamin E[2,3] – perhaps to prevent further decline?
- Botox injections[4] – for focal TD, orofacial TD, tardive dystonia
- Deep brain stimulation[1,3] - for tardive dystonia or treatment refractory TD
- TMS[1]

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

- Dopamine is Prolactin Inhibiting Factor (PIF)
- Blocking inhibition leads to increased prolactin levels
- Higher D_2 affinity → higher prolactin levels

Increase prolactin

FGAs, risperidone, paliperidone

Aripiprazole, all partial agonists, clozapine, quetiapine, iloperidone

Prolactin-Sparing

Hyperprolactinemia- Side effects

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Women:
- Decreased Libido
- Gynecomastia
- Galactorrhea
- Infertility
- Amenorrhea

Men:
- Decreased Libido
- Gynecomastia
- Galactorrhea
- Infertility
- Erectile dysfunction

- Long term side effects:
  - Hypogonadism → osteoporosis & fractures[1]
  - Increased risk of breast cancer (OR 1.47)[2]

1. Andrade C. *J Clin Psychiatry*. 2023;84(1):23fl4790. 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:[2]
  - Consider the differential diagnosis, consult with endocrine
  - Shared decision making with the patient
    - 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. Labad J, et al. *Schizophr Res*. 2020;222:88-96.

Sexual Side Effects

- Direct effect: D_2, alpha-1, 5-HT_{2a}, muscarinic receptor antagonism
- Decreased libido, anorgasmia, erectile dysfunction (ED)
- Up to 80% patients with schizophrenia have sexual dysfunction[1]
  - Ask directly
- Treatment[2]
  - Dose reduction
  - Switch to an SGA or prolactin-sparing antipsychotic
  - Treat ED with phosphodiesterase inhibitors

1. Souaiby L, et al. *J Ment Health.* 2020;29(6):623-630. 2. Downing L, et al. *J Psychiatry Neurosci.* 2019; 44(4):287-288.

Sedation

- Can be extremely severe
  - Worsens functional impairment from negative symptoms
- Highest risk: Clozapine, olanzapine, quetiapine[1]
- Treatment[2]
  - Lower total daily dose, split dose
  - Coffee (in small amounts)
  - Be careful with modafinil
  - Avoid stimulants (trigger relapse[3])

1. Citrome L. *J Clin Psychopharmacol.* 2017;37:138-147. 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.

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Framework: Side Effect Monitoring and Intervention

Side Effect Monitoring

- Enormous amount of monitoring to complete
- 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 reminders[1]
- Population-based patient registry[2]
- Dedicated medical screening nurse[3]
- 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 Integration[1]
  - 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

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Thank You

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