MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Management of side effects of antipsychotics

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Disclosures

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Outline

- Antipsychotic side effect summary
- Critical side effect management
  - NMS
  - Cardiac side effects
  - Gastrointestinal side effects
  - Clozapine black box warnings
- Routine side effect management
  - Metabolic side effects
  - Motor side effects
  - Prolactin elevation
- The man-in-the-arena algorithm

Receptor profile and side effects

- Alpha-1
  - Hypotension: slow titration
- Dopamine-2
  - Dystonia: prophylactic anticholinergic
  - Akathisia, parkinsonism, tardive dyskinesia
  - Hyperprolactinemia
- Histamine-1
  - Sedation
  - Weight gain
- Muscarinic-1-5
  - Anticholinergic side effects including cognition

Stroup TS and Gray N. World Psychiatry. 2018;17(3):341-56. [Clinical Update]
McCutcheon RA et al. JAMA Psychiatry. 2020;77(2):201-210. [Schizophrenia Review]

Antipsychotic side effects – NMA

- **[Efficacy]**
- **Side effects – TOP 3 (available in US)**
  - Akathisia
    - Highest: lurasidone, haloperidol, cariprazine
    - Lowest: clozapine, quetiapine, olanzapine
  - Weight gain
    - Highest: olanzapine, iloperidone, quetiapine
    - Least: ziprasidone, lurasidone, aripriprazole
  - QTc prolongation
    - Highest: ziprasidone, iloperidone, asenapine
    - Lowest: lurasidone, brexpiprazole, cariprazine
  - Prolactin elevation
    - Highest: paliperidone, risperidone, haloperidol
    - Lowest: clozapine, aripiprazole, cariprazine
  - Sedation
    - Highest: clozapine, quetiapine, ziprasidone
    - Lowest: cariprazine, paliperidone, iloperidone
- Elderly more likely to experience short-term toxicity*

Network meta-analysis (NMA): Ranking antipsychotics

Huhn M et al. Lancet 2019;394(10202):939-951.
Correll CU and Kane JM. JAMA Psychiatry. 2020;7(3):225-226. [Opinion]
***Schneider-Thoma J et al. Lancet Psychiatry. 2019 Sep;6(9):753-765.**
Geriatric patients: Krause M et al. Eur Neuropsychopharmacol. 2018 Dec;28(12):1360-1370.

Summary of antipsychotic side effects

Antipsychotic	Weight gain	Somnolence	Akathisia
Aripiprazole	++	++	+++
Brexpiprazole	++	++	0
Cariprazine	++	0 (NNH 100)	+++
Risperidone	+++	+++	+++
Paliperidone	++	++	++
Olanzapine	+++ (NNH 6)	+++ (NNH 7)	+
Quetiapine ER	+++	+++ (NNH 7)	0
Ziprasidone	+	++	+
Asenapine	++	+++	++
Iloperidone	+++	++	0
Lurasidone	+ (NNH 67)	+++	+++ (NNH 10)

Anticholinergic: olanzapine, quetiapine (could be adrenergic)
Orthostatic hypotension: risperidone/paliparidone, iloperidone
NNH = Number Needed to Harm
Based partially on: Citrome L. Clin Schizophr Related Psychoses. Summer 2016.

CRITICAL SIDE EFFECT MANAGEMENT

Neuroleptic malignant syndrome (NMS)

- Onset within 2 weeks of starting antipsychotic
- Tetrad
  - **Fever**
  - **Rigidity**: lead pipe rigidity, tremor, other
  - Mental status changes*: agitation, confusion
  - Autonomic instability: tachycardia; diaphoresis
- Elevated serum CK: >1000 IU/L
  - Leukocytosis, low iron (sensitive, not specific), myoglobinuria
- Differential diagnosis
  - Related disorders with fever/rigidity/dysautonomia
    - Serotonin syndrome
    - Malignant hyperthermia
    - Malignant catatonia
  - Other
    - CNS infection, systemic infection, seizures, drug intoxication (PCP), catatonia

Always consider forme fruste!

http://www.nmsis.org/
(Neuroleptic Malignant Syndrome Information Service)

Cardiac side effects – QTc prolongation

- QTc prolongation
  - Risk factor model: low potassium; long QTc syndrome
- Mechanism
  - hERG (human Ether-à-go-go-Related Gene)
    - Regulates potassium ion channel repolarization current
  - QTc prolongation increases risk for torsades de pointes
- Increased risk
  - Thioridazine : black box warning; 2D6; brand withdrawn
  - Pimozide: calcium channel blocker; 3A4 and 2D6; citalopram/escitalopram contraindicated
  - IV haloperidol (other risk factors!)
  - Ziprasidone
  - Iloperidone: similar to ziprasidone

Wenzel-Seifert K et al. Dtsch Arztebl Int. 2011 Oct; 108(41):687–93.
Potkin SG et al. J Clin Psychopharmacol. 2013;33(1):3-10.
Updated Review: Beach SR et al. Psychosomatics. 2018;59(2):105-122.
APA Resource document: Funk MC et al. Am J Psychiatry. 2020;177(3):273-274.

Ziprasidone and QTc – a case study

- Modest effect
  - ZODIAC[1] and pre-and post-approval studies[2]
    - Average increase of QTc of 6 msec for each 100 ng/mL increase in ziprasidone blood levels
    - No signal for an increased risk of ziprasidone-associated cardiac death
- Clinical dilemma
  - Minimal evidence about real-world relevance[3]
  - Antipsychotics as **component cause** for development of torsades de pointes

ZODIAC=Ziprasidone Observational Study of Cardiac Outcomes

[1]Strom BL et al. Am J Psychiatry 2011;168:193. [2]Camm AJ et al. CNS Drugs. 2012;26:351. [3]Beach SR et al. Psychosomatics. 2018;59(2):105-22.

Gastrointestinal side effects

- Gastrointestinal hypomotility
  - Constipation, ileus, ischemic bowel disease
  - Constipation 30%
- National cohort study (Taiwan)[1]
  - Constipation: quetiapine, clozapine
  - Ileus: high-potency antipsychotics, clozapine
  - Ischemic bowel disease
- Treatment
  - High index of suspicion
  - Prophylactic bowel regimens[2]

[1]Chen HK and Hsieh CJ. Schizophr Res. 2018;195:237-244. [2]Cruz A and Freudenreich O. Current Psychiatry. 2018;17(8):44.
See also new FDA guidance for clozapine: https://www.fda.gov/drugs/drug-safety-and-availability/fda-strengthens-warning-untreated-constipation-caused-schizophrenia-medicine-clozapine-clozaril-can

Clozapine: 5 black box warnings

1. Agranulocytosis
2. Seizures
3. Myocarditis
4. Orthostatic hypotension (with syncope or cardiorespiratory arrest)
5. Increased mortality in elderly patients with dementia-related psychosis (class warning for all antipsychotics)

Clozapine and agranulocytosis

- Clozapine can cause agranulocytosis
  - Led to complicated path to FDA-approval, including mandated registry-based prescribing (REMS)
  - Mandated, registry-based prescribing, with regular ANCs
- Severe neutropenia (ANC < 500/µL) is rare
  - 9/1000 people started on clozapine
  - Case fatality rate of 2.1%
- Severe neutropenia has peak incidence in the first several months after starting clozapine
  - Metabolite toxicity or hapten-based immune-mediated mechanism
  - Negligible incidence after 1 year

Myles N et al. Acta Psychiatr Scand. 2018;138(2):101-9.

Seizures

- Clozapine had highest seizure rate in drug safety program[1]
  - 0.18% versus others (0.03% – 0.05%)
- Dose-related seizure risk[2]
  - High cumulative seizure risk: 10% over 3.8 years (!)
- Most are tonic-clonic
- Prevention
    - Titration!
    - Therapeutic drug monitoring!
    - Pay attention to clinical comorbidities that increase seizure risk
    - Note red flags: myoclonus
- Treatment
  - Depakote is good choice
  - Carbamazepine is poor choice

[1]Druschky K et al. World J Biol Psychiatry. 2018;1-29.
[2]Devinsky O et al. Neurology 1991;41:369.
Clinical review: Varma S et al. Ther Adv Psychopharmacol. 2011;1(2):47-66.

Myocarditis

- Clinical features
  - Non-specific!
- Highest risk period is four weeks[1]
- Management
  - High index of suspicion
  - Increased case detection with monitoring[2]
  - No agreed-upon monitoring scheme
    - Consider adding inflammatory markers for 4 weeks
  - Consultation with cardiology
- Rechallenge discouraged in clear cases[3]
  - Slow titration may be protective

Freudenreich O. Acta Psychiatr Scand 2015;132:240.
[1]Ronaldson KJ et al. Aust N Z J Psychiatry. 2011;45:458-65.
[2]Neufeld NH and Remington G. Schizophr Res. 2019;206:462-3.
[3]Noël MC. J Clin Psychopharmacol. 2019;39(4):380-5.

Orthostatic hypotension

- Clozapine needs to be titrated
  - New patient
    - Establish sensitivity with test dose of 12.5 mg
    - No one titration scheme set in stone
      - Inpatient: increase 25 to 50 mg/d until you reach 300 to 440 mg per day (divided doses)
      - Take into account the patient when choosing a titration schedule
      - Consider TDM after reaching 100 mg/d
  - Established patient (!) after two missed doses
    - Start with 12.5 mg bid, then adjust more quickly

Clozapine-associated aspiration pneumonia

- Sialorrhea
  - Paradoxical
  - "Pool and drool hypothesis"
  - Most common side effect: almost 100%[1]
- Pneumonia
  - Influenza and pneumonia mortality (SMR, 7.0; 95% CI, 6.7-7.4)[2]
  - Aspiration pneumonia underappreciated[3,4]
- Management
  - Speech and swallowing evaluation
  - Glycopyrrolate 2 mg at night[5]
  - Sublingual atropine 2 drops three times daily[6]

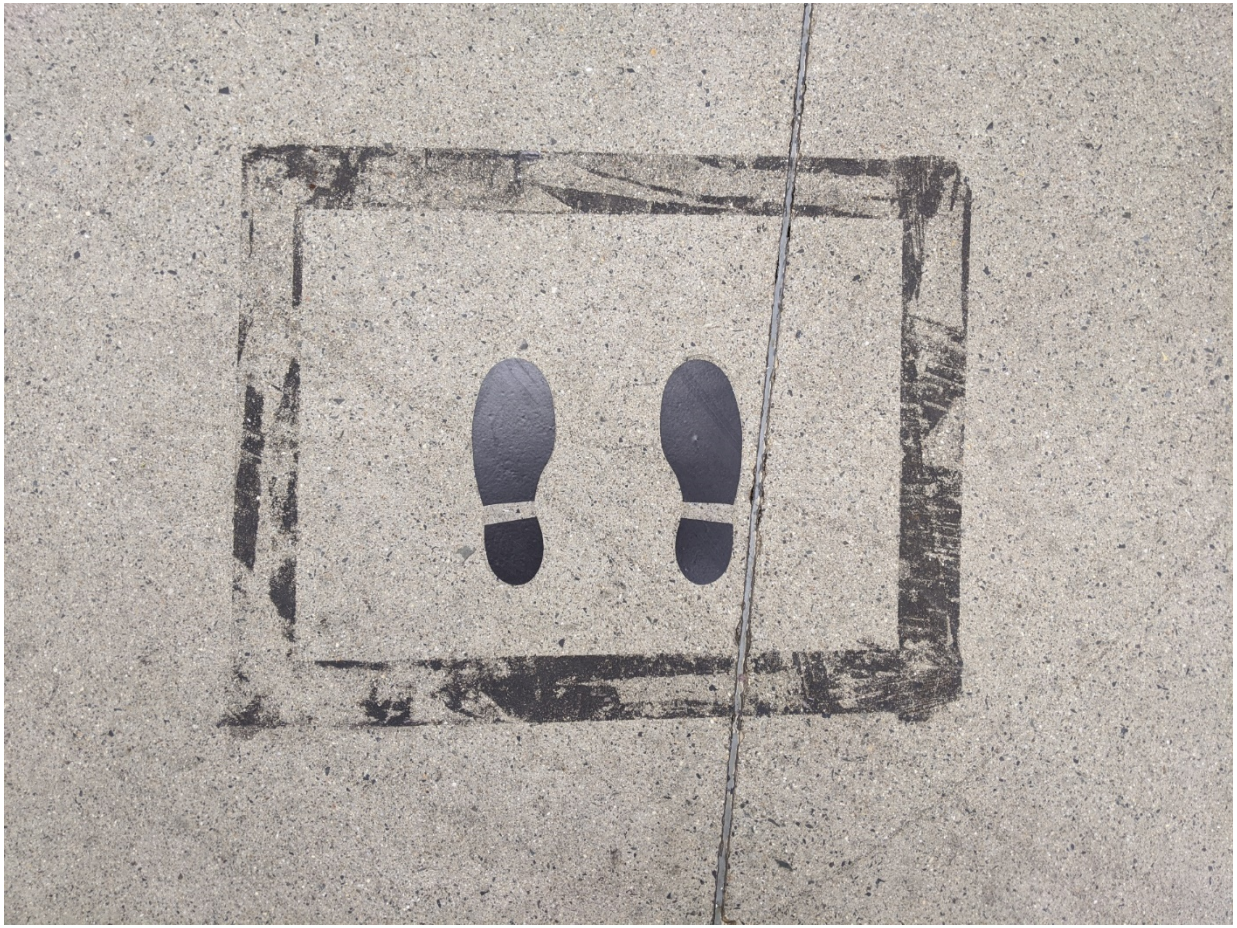
[1]Maher S et al. Ther Adv Psychopharmacol. 2016; 6(3): 178–84. [2]Olfson M et al. JAMA Psychiatry. 2015;72(12):1172-81. [3]Kaplan J et al. Psychosomatics. 2018;59(2):199-203. [4]De Leon H et al. World Psychiatry. 2020;19(1):120-1. [5]Man WH et al. J Clin Psychopharmacol. 2017;37(2):155-61. [6]van der Poorten T, De Hert M. Tijdschr Psychiatr. 2019;61(6):403-10.

Clozapine-associated constipation

- FDA strengthens warning
- Untreated constipation can progress to serious bowel problems
- Risk increases with higher doses and with concomitant anticholinergics
- Clinician guidance
  - Evaluate bowel habits prior to clozapine
  - Monitor bowel function throughout treatment
  - Educate patients about constipation prevention
  - Consider prophylactic bowel treatment

https://www.fda.gov/drugs/drug-safety-and-availability/fda-strengthens-warning-untreated-constipation-caused-schizophrenia-medicine-clozapine-clozaril-can

Clozapine and COVID-19



Clozapine use during COVID-19

- Consensus statement on the use of clozapine during the COVID-19 pandemic[1]
  - REC #1: Criteria for up to 90-day clozapine supply
  - REC #2: Evaluate for any new infection
  - REC #3: Consider reducing clozapine dose during infection
- Consistent with FDA guidance[2]
- Endorsed by many states including MA and countries

[1]Siskind D et al. J Psychiatry Neurosci. 2020 Apr 3;45(4):200061. doi: 10.1503/jpn.200061.
[2]https://www.fda.gov/media/136317/download

Recommendation #1

- Prescribe up to 90-day clozapine supply during public health emergency, if indicated
  - Criteria for up to 90-day clozapine supply
    - Continuous clozapine treatment for > 1 year
    - Never had an ANC < 2000/µL (or < 1500/µL if history of BEN
    - No safe or practical access to ANC testing
  - 6 to 12 months case-by-case basis
  - Under 6 months country-specific guidelines

Discuss any change in customary management with patient and caregivers.

Recommendation #2

- Evaluate for any new infection
  - Fever, cough, sore throat, flu-like symptoms
    - Note overlap agranulocytosis and COVID-19 symptoms
  - Draw ANC
- Higher pneumonia risk in clozapine-treated patients[1]
  - Sialorrhea and aspiration pneumonia
  - High rates of smoking (COPD)

Don't automatically assume symptoms are COVID-19.

[1]de Leon J et al. World Psychiatry 2020;19(1):120-1.

Recommendation #3

- Consider reducing clozapine dose during infection
  - Clozapine level increase in admitted patients
    - Signs of clozapine toxicity: sedation, myoclonus, seizures
    - Mechanism via 1A2 inhibition
      - Cessation of smoking during admission
      - Cytokine-mediated inhibition of clozapine metabolism
  - Could prophylactically reduce by up to 50% during fever
  - Titrate back up after 3 days without fever
  - Consider TDM if possible in your setting

ROUTINE SIDE EFFECT MANAGEMENT

The day the music died

CATIE – baseline cardiovascular risk factors

	Males			Females		
	CATIE	**NHANES**	***P***	**CATIE**	**NHANES**	***P***
	N = 509	N = 509		N = 180	N = 180	
Metabolic Syndrome Prevalence*	36.0%	19.7%	.0001	51.6%	25.1%	.0001
Waist Circumference Criterion	35.5%	24.8%	.0001	76.3%	57.0%	.0001
Triglyceride Criterion	50.7%	32.1%	.0001	42.3%	19.6%	.0001
HDL Criterion	48.9%	31.9%	.0001	63.3%	36.3%	.0001
BP Criterion	47.2%	31.1%	.0001	49.6%	26.8%	.0001
Glucose Criterion	14.1%	14.2%	.9635	21.7%	11.2%	.0075

***National Cholesterol Education Program (NCEP) criteria**
NHANES = National Health and Nutrition Examination Survey III
McEvoy JP, et al. *Schizophr Res.* 2005;80:19-32.

Antipsychotic-induced weight gain

- Most robust predictor: H1 receptor affinity; 5HT2C polymorphisms
- Almost all antipsychotics show weight gain after extended use
  - Weight gain more pronounced in antipsychotic naïve patients[1]
  - Not clearly dose-dependent
- Meta-analysis in first-episode patient[2]
  - ✓ Short-term (3 months or less) weight gain: 3.22 kg
  - ✓ Long-term (over 3 months) weight gain: 5.3 kg
  - ✓ More weight gain in Western samples
  - ✓ Only antipsychotic that did not cause weight gain: ziprasidone
- Decreased insulin sensitivity develops rapidly in 12 weeks
  - More pronounced in olanzapine vs. risperidone or aripiprazole[3]

[1]Bak M, *PLoS One* 2014; 9: e94112.
[2]Tek C et al. Early Interv Psychiatr. 2016;10:193-202.
[3]Nicole GE et al. JAMA Psychiatry. 2018;75(8):788-796.

Metabolic prevention

A. Choose wisely, if you can - prevent
B. Screen and monitor – detect
   - Very frequent monitoring early[1]
C. Prevent/blunt weight gain - mitigate
   - Add behavioral management
   - Switch antipsychotics
   - Add prophylactic metformin
   - Add weight loss medications

[1]Zhang Y et al. J Clin Psychiatry. 2020;81(3):19m12785.

Choose wisely, if you can

Relative risk (Schizophrenia PORT 2009)[1]

Clozapine=olanzapine
low-potency FGAs
risperidone=paliperidone=quetiapine
medium-potency FGAs
high-potency antipsychotics=molindone*=aripiprazole=ziprasidone

***discontinued**

Newer antipsychotics

- Lurasidone[2,3]
  - Pooled analysis from 6 clinical trials, mean change at month 12[3]
    - -0.4 kg with lurasidone; +2.6 kg with risperidone; +1.2 kg with quetiapine XR.
- Cariprazine[4]
  - 1.9 kg weight gain from lead-in to end of 48-week open-extension
- Brexpiprazole[5]
  - 1.1 kg weight gain in short- and long-term studies

PORT = Patient Outcomes Research Team [1]Buchanan RW et al. *Schizophr Bull*. 2010;36(1):71-93.
[2]de Hert et al. *CNS Drugs*. 2012 Sep 1;26(9):733-59 [3]Meyer JM et al. *Int Clin Psychopharmacol*. 2015 Nov;30(6):342-50.
[4]Durgam S et al. *Psychopharmacology (Berl)*. 2017;234(2):199-209. [5]Kane JM et al. *Schizophr Res*. 2016;174(1-3):93-8.

Guideline-concordant screening

CAMESA GUIDELINE

Evidence-Based Recommendations for Monitoring Safety of Second Generation Antipsychotics in Children and Youth

Tamara Pringsheim, Constadina Panagiotopoulos, Jana Davidson, and Josephine Ho for the CAMESA guideline group

The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) Guideline Project

Perfect is the enemy of good.

- Population-based management
- Keep it simple
- Do it regularly (enough)
- Get non-fasting results

Table 4. A practical tool for metabolic monitoring of children & youth treated with second-generation antipsychotics

Parameter		Pre-treatment Baseline	1 month	2 month	3 month	6 month	9 month	12 month
Assessment date								
Height (cm)[1]								
Height percentile								
Weight (kg)[1]								
Weight percentile								
BMI: (kg/m^2)[1]								
BMI percentile								
Waist circumference (At the level of the umbilicus)[2]								
Waist circumference percentile								
Blood pressure (mm/Hg)[3]								
Blood pressure percentile								
Neurological examination[4]		☐ completed	☐ completed	☐ completed	☐ completed	☐ completed	☐ completed	☐ completed
Laboratory evaluations:	Normal values							
Fasting plasma glucose	≤ 6.1 mmol/L[5]		NR	NR			NR	
Fasting insulin[6]	≤ 100 pmol/L[7]		NR	NR			NR	
Fasting total cholesterol	< 5.2 mmol/L		NR	NR			NR	
Fasting LDL-C	< 3.35 mmol/L		NR	NR			NR	
Fasting HDL-C	≥ 1.05 mmol/L		NR	NR			NR	
Fasting triglycerides	< 1.5 mmol/L		NR	NR			NR	
AST			NR	NR	NR		NR	
ALT			NR	NR	NR		NR	
TSH (Quetiapine ONLY)			NR	NR	NR	NR	NR	
Prolactin[8]			NR	NR	NR	NR	NR	
Other_____ (e.g. Amylase, A1C, OGTT etc.)[9]								
Physician Initials: →								

1 To determine height, weight and BMI percentiles, use age and sex specific growth charts at http://www.cdc.gov/growthcharts/.
2 To determine age and sex specific percentiles, go to http://www.idf.org/webdata/docs/Mets definition children.pdf (pages 18-19).
3 To determine age and sex specific percentiles, go to http://pediatrics.aappublications.org/cgi/content/full/114/2/S2/555.
4 Tools available for monitoring extrapyramidal symptoms include: Abnormal Involuntary Movement Scale (AIMS), Simpson Angus Scale, Extrapyramidal Symptom Rating Scale, Barnes Akathisia Rating Scale.
5 For FPG values of 5.6-6.0 mmol/L, consideration should be given to performing an oral glucose tolerance test (OGTT).
6 Note that this assessment is NOT recommended for aripiprazole or ziprasidone, but IS appropriate for all other SGAs.
7 For fasting insulin levels >100pmol/L, consideration should be given to performing an OGTT. Normal reference range may vary between centres.
8 Assessment of prolactin levels should be completed according to protocol except when the patient is displaying clinical symptoms of hyperprolactinemia (i.e. menstrual irregularity, gynecomastia, or galactorrhea), in which case more frequent monitoring may be warranted. Please also note that risperidone has the greatest effect on prolactin.
9 It is recommended that amylase levels be monitored in case where the patient presents with clinical symptoms of pancreatitis (i.e. abdominal pain, nausea, vomiting).
NR = not recommended

Pringsheim T et al. J Can Acad Child Adolesc Psychiatry. 2011;20:218.
Morrato EH et al. JAMA Psychiatry. 2016;73:721-30.
Vanderlip ER et al. Am J Psychiatry 2016; 173(7):658-63.
See Taking Issue: Mangurian C. Psych Serv. 2017;68(3):213.

Behavioral interventions for SMI

- Evidence-based practice
  - ACHIEVE[1]
  - STRIDE[2]
  - In SHAPE[3]
- STRIDE core interventions
  - Increasing awareness through monitoring
  - Creating personalized diet and exercise
  - Reducing calories
  - Improving diet
  - Increasing physical activity
  - Graphing progress

Weight loss is possible for patients with SMI[4]

Long-term support might be needed

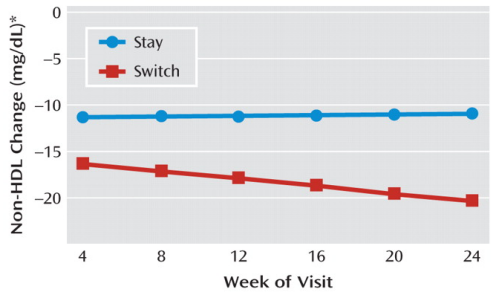
Consider behavioral-educational groups*

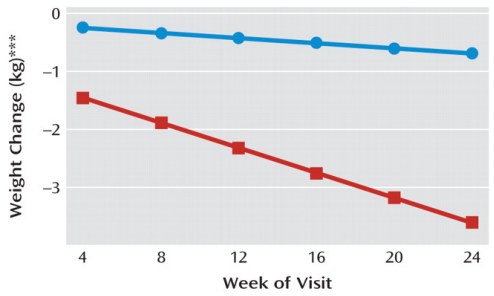
Use multifaceted interventions**

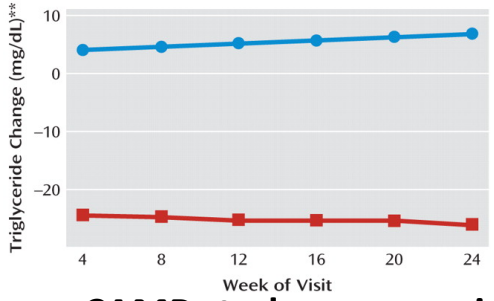
[1]Daumit GL et al. N Engl J Med 2013;368:1594. [2]Green CA et al. Am J Psychiatry 2015;172:71. [3]Bartels SJ et al. Psychiatr Serv 2013;64:729. [4]Bartels SJ. Am J Psychiatry 2015;172:9. (editorial) Speyer H. et al. World Psychiatry 2016;15:155. *Schnitzer K et al. Psychiatr Serv. 2020;71(7):730-733. **Daumit GL et al. JAMA Network Open. 2020;3(6):e207247

Switching to aripiprazole (CAMP)

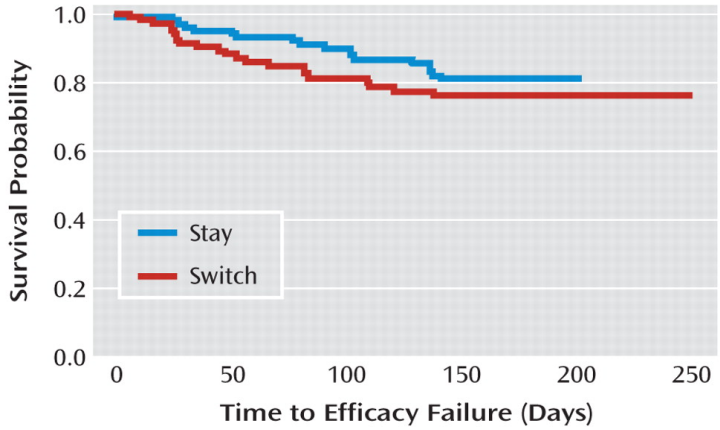
Metabolic Changes

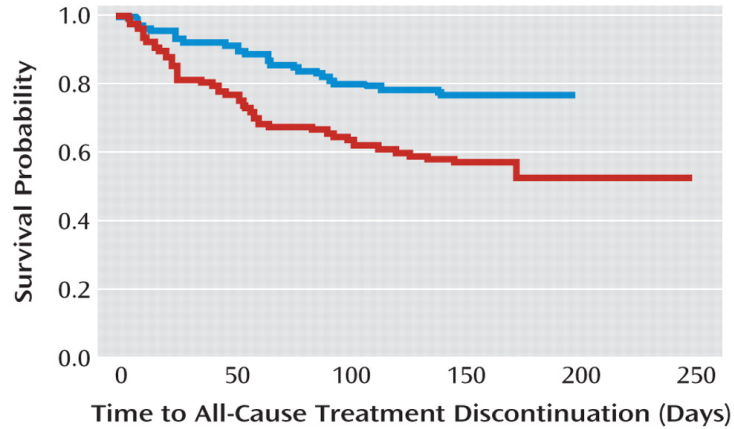






Efficacy Outcomes





CAMP study = comparison of antipsychotics for metabolic problems

Stroup et al. Am J Psychiatry. 2011;168:947.

Compare: Parabiaghi A et al. Acta Psychiatr Scand. 2016;133:63-75.

Prophylactic metformin to prevent antipsychotic-associated glucose intolerance

- Shown in first-episode and chronic patients on antipsychotic to re-sensitive insulin receptors[1]
- MOA: does not cause hypoglycemia[2]
- Meta-analysis: total cholesterol, TGs, weight, HbA1c; not WC, LDL[3]
- Safety
  - Rare lactic acidosis: more likely with excessive alcohol use
  - May be associated with vitamin B12 deficiency[4]
  - Safe for cognition[5]
  - Most common side effects: GI (N/V 14%, diarrhea 7%)[6]
- Dosing
  - Target total daily dose 2,000 mg (with food)

QA:
S&S of metformin toxicity

[1]Zheng W et al. J Clin Psychopharmacol. 2015;35(5):499-509.
[2]Ferrannini E. N Engl J Med 2014; 371(16):1547-8. 3Jiang W-L et al. Transl Psychiatry. 2020;10(1):117.
[4]Aroda VR, et al. J Clin Endocrinol Metab. 2016;101(4):1754-61.
[5]Luchsinger JA, et al. Diabetes Care. 2017;40(7):958-65. [6]Zheng W, et al. J Clin Psychopharmacol. 2015;35(5):499-509.

IMPACT trial for youth SMI

Improving Metabolic Parameters in Antipsychotic Child Treatment

- Obese youth
  - Being overweight in youth predicts later CAD
- IMPACT compared three strategies
  - Healthy lifestyle education (HLE)
  - HLE plus metformin
  - HLE plus switch to aripiprazole or molindone/perphenazine*
- Results
  - N=127
  - Age 8 to 19 (mean 13.7)
  - BMI improved after 24 weeks for MET and SWITCH
    - ES MET 0.68; ES SWITCH 0.81
    - Weight loss 55% MET, 47% SWITCH, 10% CONTROL
  - High rate of discontinuation with perphenazine
  - HLE ineffective in this age group

Correll CU et al. World Psychiatry. 2020;19(1):69-80.

***Chosen based on TEOSS results; molindone replaced by perphenazine**

FDA-approved weight loss medications

- Withdrawn 1997: fen-phen
- Withdrawn 2010: sibutramine (Meridia)
- Orlistat (Xenical, OTC Alli)
- WITHDRAWN 02/13/20 lorcaserin (Belviq) – CIV
- ***Phentermine plus topiramate** (Qsymia) – CIV
- Bupropion plus naltrexone (Contrave)
- ***Liraglutide** (Saxenda; lower-dose: Victoza)
- *NEW*: Superabsorbent hydrogel (Gelesis100)[a]

See critique: Woloshin S and Schwartz LM. JAMA Intern Med. 2014;174:615-9.
See LIGHT study: Sharfstein JM and Psaty BM. JAMA. 2016;315:984-6.
***Best comparative effectiveness: Khera R et al. JAMA. 2016;315:2424-34.**
[a]Greenway FL et al. Obesity. 2019; 27(2):205-216.

Topiramate and weight loss

- Topiramate (23/46/69/92 mg) + phentermine
  - FDA-approved for weight loss in obesity [brand name QSYMIA]
  - Most effective medication in a meta-analysis[1]
    - 75% achieved at least 5% weight loss
    - 8.8 kg (95% CrI, -10.20 to -7.42 kg) weight loss over one year
- Topiramate in schizophrenia[2]
  - Meta-analysis of 8 add-on trials (N=439)
  - Results
    - Dose range 100 to 400 mg/d
    - Improved psychopathology
    - **Reduced weight**
  - "Larger studies are needed"

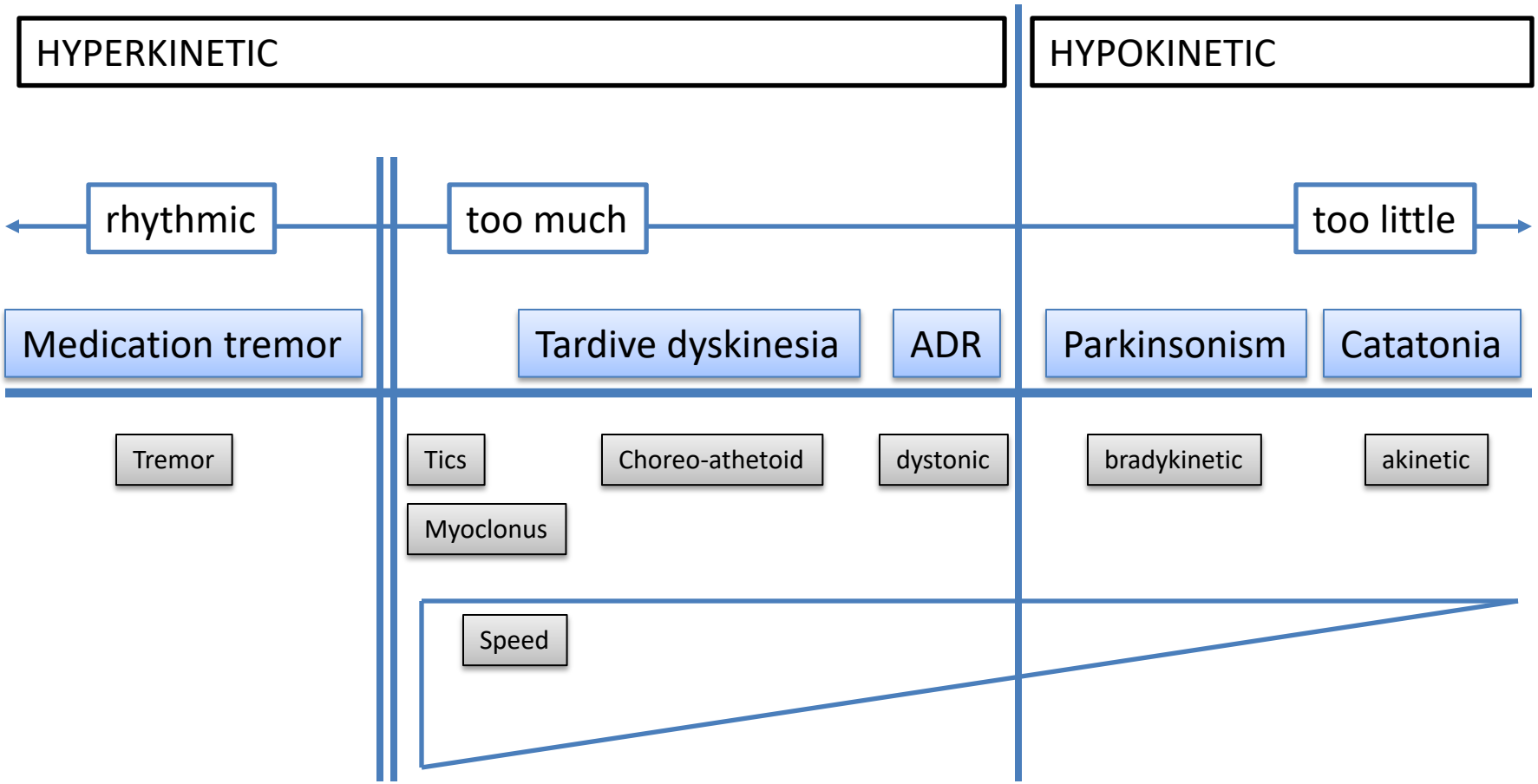
[1]Khera R et al. JAMA. 2016;315(22):2424-34.
[2]Correll CU et al. J Clin Psychiatry. 2016;77(6):e746-e756.

Drug-induced extrapyramidal symptoms (EPS)

- By time course
  - Peracute — Acute dystonic reaction (ADR)
  - Acute — Akathisia, NMS
  - Subacute — Parkinsonism
  - Chronic — Tardive dyskinesia (TD)
- Other syndromes
  - Pisa syndrome
  - Rabbit syndrome
  - See also: supersensitivity psychosis*

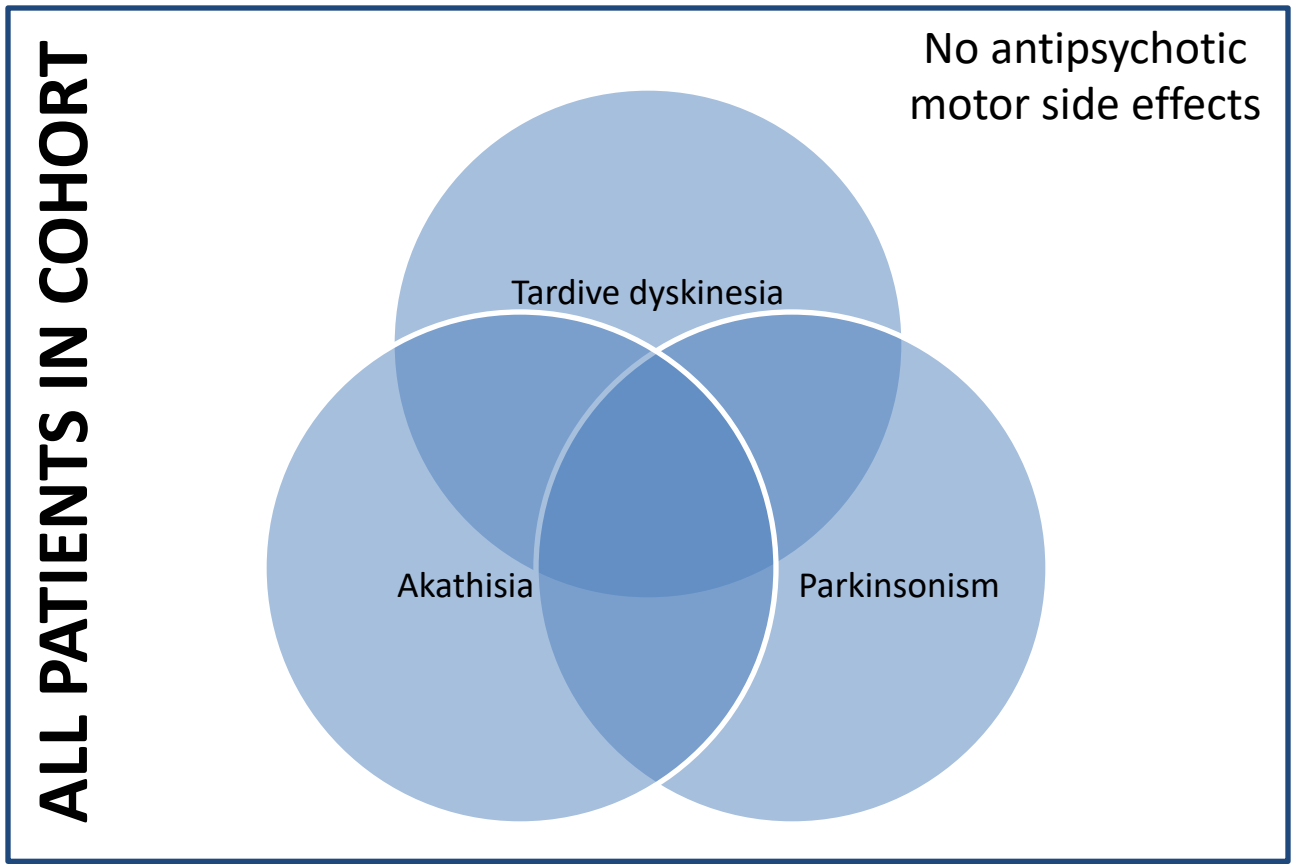
***Chouinard G et al. Psychother Psychosom. 2017;86(4):189-219.**

Clinical scheme of movement disorders



Freudenreich O. Psychotic Disorders. Springer, 2020.

Antipsychotic-induced motor side effects



Based on: Janno S et al. Am J Psychiatry 2004;161(1):160-3.

Akathisia - treatment

- Recognize
  - Differential diagnosis: psychotic agitation
- Change antipsychotic drug regimen
  - Reduce dose
  - Switch to low-risk antipsychotic
    - Iloperidone[1], quetiapine, clozapine
- If not possible add anti-akathisia medication
  - Benzodiazepines
  - Propranolol 40 to 80 mg per day
  - Serotonin 2A receptor antagonists[2]
    - Mirtazapine 15 mg per day
  - Anticholinergics ineffective (add only if Parkinsonism)

Poyurovski M. Br J Psychiatry. 2010;196(2):89-91. [REVIEW}
[1]Weiden PJ et al. CNS Drugs. 2016 Aug;30(8):735-47.
[2]Poyurovski M and Weizman A. J Clin Psychopharmacol. 2015;35(6):711-4.

Parkinsonism - treatment

- Anticholinergics
  - Avoid because of cognitive side effects
  - If used prophylactically, stop after one month
- Amantadine
  - Good alternative to anticholinergics
  - Dose: 100 mg twice daily
  - Possible benefit: weight loss

Graham KA et al. Am J Psychiatry. 2005;162:1744-6.

Tardive dyskinesia (TD) - Numbers

- **Incidence**[1]
  - FGA 6.5% per year
  - SGA 2.6% per year

TD is iatrogenic!

- **Prevalence**[2]
  - Global: 25%
  - Current SGA: 20%; never FGA: 7%
  - Current FGA: 30%

- **Reversibility**[3]
  - Remission rate: 2% (!)

[1]Carbon M et al. World Psychiatry. 2018; 17(3):330-340.
[2]Carbon M et al. J Clin Psychiatry. 2017;78(3):e264-e278.
[3]Bhidayasirir R et al. Neurology. 2013;81(5):463-469.

TD – risk factors

- **Risk factors[1]**
  - FGA>SGA>clozapine
  - Age (over age 45)
    - 26% year 1; 52% year 2; 60% year 3[2]
  - Dose and duration of treatment (cumulative dose)
  - Sensitivity to EPS (acute EPS)
  - Other:
    - Non-modifiable: female, African decent, brain damage, mood disorders, gene polymorphisms (Perlecan gene HSPG2)
    - Modifiable: alcohol/drugs, diabetes, smoking, anticholinergics

[1]Solmi M et al. J Neurol Sciences. 2018;389:21-7.
[2]Jeste DV et al. Arch Gen Psychiatry. 1995;52(9):756-65.

Management of TD

PREVENT	MONITOR	TREAT
Clear indication for antipsychotic	Baseline motor exam	*Slowly* taper antipsychotic, if possible
Short term treatment, if possible	Longitudinal follow-up	Switch to quetiapine or clozapine**, if possible
Lowest-risk choice and lowest dose	At least annual AIMS*	Treat TD symptomatically

Stop anticholinergics***

***In low-risk patients; more frequent monitoring in higher risk patients**

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

*****Bergman H. and Soares-Weiser K. Cochrane Database Syst Rev. 2018 Jan 17;1:CD000204.**

Tips on using the AIMS

- A score on a the AIMS is not a diagnosis
  - There is no mention of TD in the AIMS
- Assessment
  - Look at 7 body areas
  - Severity for each
  - Functional relevance and insight
  - There is no single best interpretation of AIMS scores*
    - Not a linear scale
- Score what you see
  - Do not count tremor
  - Do not count gum chewing (!)
- Repeat every 6 months or more frequently if high risk

Severity scores
Total score (sum of 1 to 7)
Global severity score

Incapacitation

Insight into movements

See also: Munetz MR and Benjamin S. Hosp Community Psychiatry. 1988;39:1172-7.
***Kane JM et al. J Clin Psychiatry. 2018;79(3):11-21. [TD Assessment Working Group]**

Tardive dyskinesia - treatment

First-line

- Dopamine-depleting agents

VMAT-2 inhibitors

  - Reserpine
  - Tetrabenazine
  - **Deutetrabenazine***
  - **Valbenazine***

Second-line

- Amantadine
- Benzodiazepines
- Beta-blockers
- Branched-chain amino acids
- Clozapine – switch**
- Ginkgo biloba
- Vitamin B6 – but toxicity?
- Vitamin E – perhaps as prophylaxis
- Botox injections – for focal TD; orofacial TD
- Deep brain stimulation – for tardive dystonia

Waln O and Jankovic J. Tremor Other Hyperkin Mov 2013;3.
***Solmi M. Drug Des Devel Ther. 2018;12:1215-1238.**
****Mentzel TQ et al. J Clin Psychiatry. 2018;79(6). pii: 17r11852.**

Vesicular monoamine transporter (VMAT)

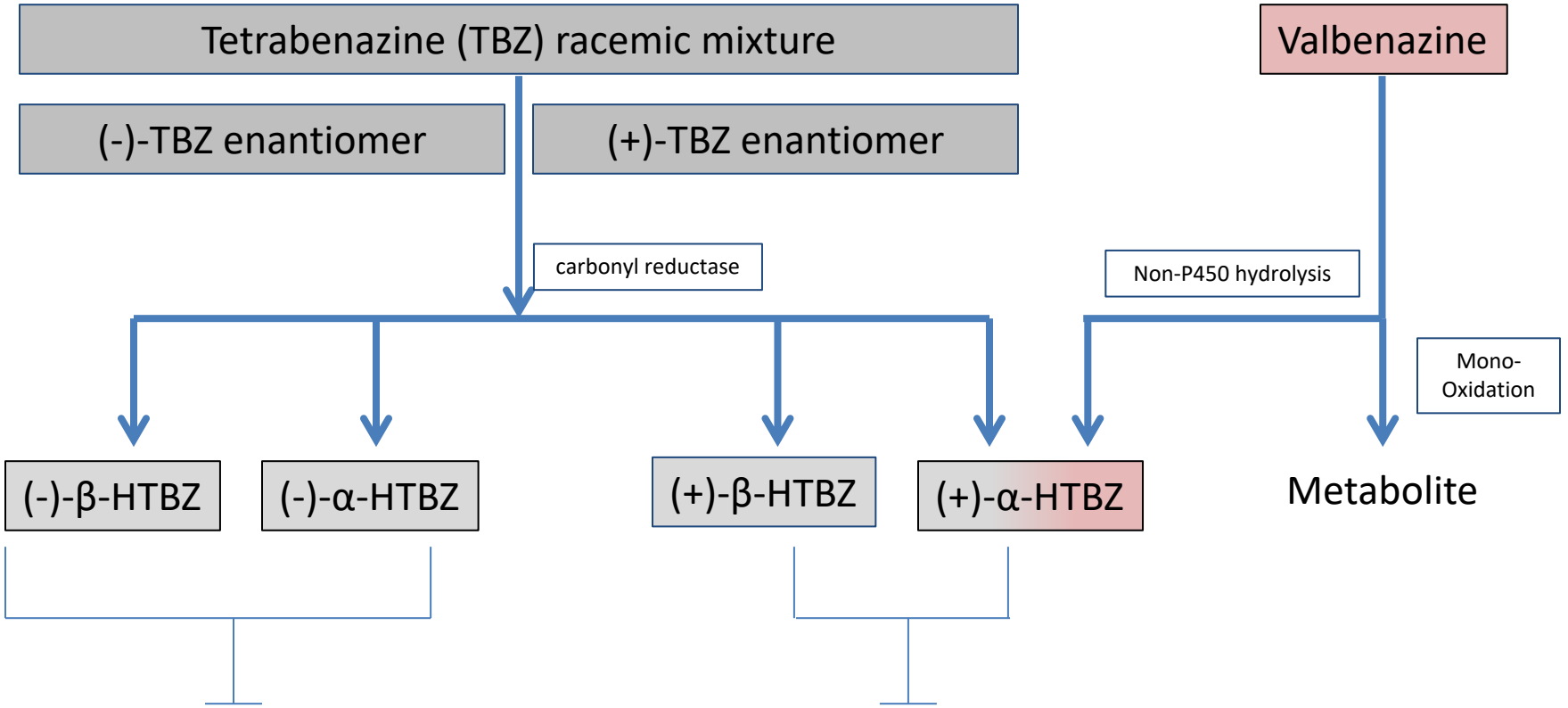
- Transport protein of synaptic vesicles
- Presynaptic neuron
- 2 types
  - VMAT2 for monoamine neurons
- Inhibition increases cytosolic neurotransmitter → vulnerable to MAO degradation → depletion
- 2 binding sites
  - Reserpine*
  - Tetrabenazine

Monoamine depleters

Wimalasena K. Med Res Rev. 2011;31(4):483-519.

***Also used in veterinary medicine as long-acting horse tranquilizer**

Tetrabenazine and valbenzine metabolism



VMAT-2
- Low affinity

Off-target effects
- Dopamine receptors
- Serotonin Receptors
- Adrenergic receptors

VMAT-2
- Potent inhibition

Off-target effects
- None or minimal

TBZ = Tetrabenazine
HTBZ = Dihydrotetrabenazine

Freudenreich O and Remington G. Clin Schizophr Rel Psychoses. 2017;11(2):113-9.

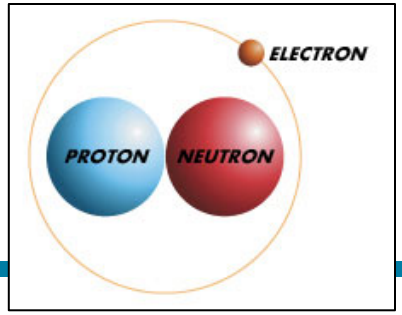
Valbenazine

- VMAT-2 inhibitor
- FDA-approved 2017 for adults with tardive dyskinesia
  - Clear efficacy

ES 0.90 for 80 mg dose

- Longer half-life (20 hours): QD dosing
- Dosing
  - Start 40 mg/d x 7 days, then 80 mg/d
- Minimal effect QTc
- Lower dose for poor metabolizers 2D6 or 3A4

Deutetrabenazine



- Deuterated tetrabenazine
- FDA-approval 2017 for Huntington's disease (brand name Austedo) and for TD
  - Start 6 mg twice daily, increase by 6 mg weekly
  - Twice daily dosing
  - Up to 24 mg twice daily (48 mg TDD)
  - Adjust dose for 2D6 status
  - Monitor QTc for doses above 24 mg per day
- Clinical trials
  - AIM-TD*
  - Ongoing RIM-TD (open-label, one-year safety study)

Huntington Study Group. JAMA 2016;316(1):40-50.
Cummings MA et al. Clin Schizophr Relat Psychoses. 2018;11(4):214-220.
***Anderson KE et al. Lancet Psychiatry. 2017;4(8):595-604.**

TD – best practices expert consensus

- Outdated practice guidelines
- Method
  - 29 TD experts
  - Modified Delphi procedure
  - Content area: screening, diagnosing, treating TD
- Consensus in 4 areas
  1) Brief, clinical assessment at every visit
  2) Even mild movements in one body area could be TD
  3) Management requires reassessment of antipsychotics and anticholinergis; VMAT-2
  4) Informed discussions with patient/caregiver essential

Caroff SN et al. J Clin Psychiatry. 2020;81(2):50-60.

Hyperprolactinemia

- Tuberoinfundibular pathway
  - Dopamine is PIF (prolactin-inhibiting factor)
- Gender-specific problems[1]
  - Females have higher prolactin elevations
  - Female side effects
    - (Secondary) amenorrhoea and infertility
    - Gynecomastia and galactorrhea
    - Loss of libido
  - Male side effects
    - Loss of libido, erectile dysfunction
    - Gynecomastia and galactorrhea
- Long-term effects
  - (Secondary) hyopogonadism → osteoporosis → fracture risk[2]
  - Increased breast cancer risk?[3]
  - No increased endometrial cancer risk[4]

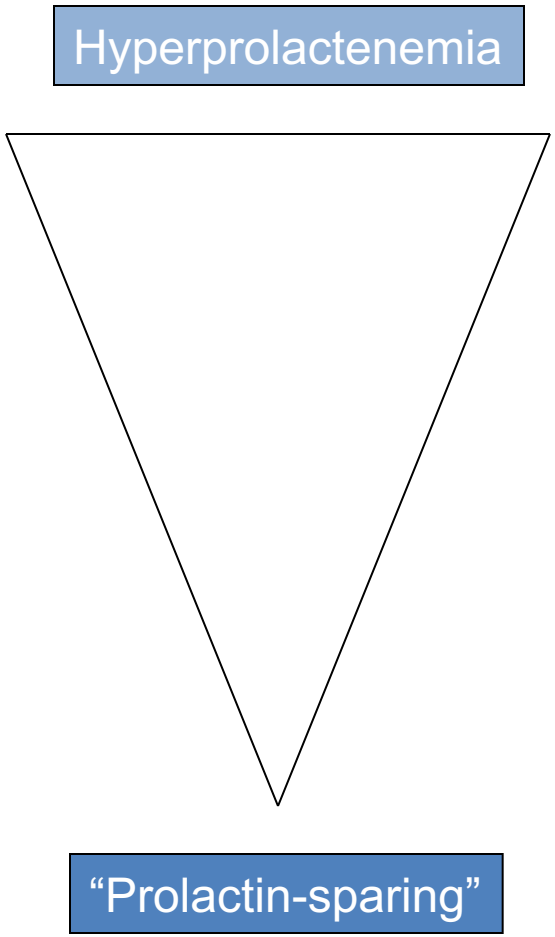
[1]Inder WJ and Castle D. Austr NZ J Psychiatry. 2011;45:830. [2]Bolton SM et al. JAMA Psychiatry. 2017;74(6):641-8.
[3]De Hert M et al. Acta Psychiatr Scand. 2016;133:5. [4]Klil-Drori AJ et al. J Clin Psychiatry. 2017;78(6):714-9.
Montejo AL et al. World Psychiatry. 2018;17(1):3-11. [Sexual dysfunction due to psychotropics]

Management of elevated prolactin

- Shared-decision making
  - Gender-specific side effects
  - Long-term risk (osteoporosis, breast cancer?)
- Decision points
  - Monitor prolactin
    - Baseline
    - Serial prolactin levels
  - Endocrinology referral
  - Take action
    - Stay the course
    - Switch to prolactin-sparing antipsychotic
    - Add aripiprazole

Labad J et al. Schizophr Res. 2020 (in press).

“Prolactin-sparing” antipsychotics



Paliperidone

Risperidone, first-generation AP

Olanzapine*

Lurasidone, asenapine

Ziprasidone

Iloperidone, quetiapine, clozapine

Aripiprazole and partial agonists**

*Usually transient

**Can lower prolactin levels

Huhn M et al. Lancet 2019;394(10202):939-951.

Citizenship in a republic

It is not the critic who counts; not the man who points out how the strong man stumbles, or where the doer of deeds could have done them better. **The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood;** who strives valiantly; who errs, who comes short again and again, because there is no effort without error and shortcoming; but who does actually strive to do the deeds; who knows great enthusiasms, the great devotions; who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement, and who at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who neither know victory nor defeat.

Sequential antipsychotic trials

- **Select**
  - Lowest-risk choice
  - Patient preference
    - LAI acceptable?
  - Early ancillary medical prevention
    - Behavioral interventions
    - Adjunctive metformin*
- **Monitor**
  - Clinical response
  - Follow antipsychotic monitoring guidelines**
- **Step-up**
  - Switch antipsychotics
    - Psychiatric: early use of clozapine for refractory patients
    - Medical: metabolically lower risk antipsychotic
  - Add psychological treatments
  - Treat medical morbidities

You need to be the man in the arena!

*Gerken AT et al. *Curr Psychiatry*. 2016;15(11):e1-2.

**Vanderlip ER et al. *Psychiatr Serv*. 2014;65(5):573-6.

Premature mortality in schizophrenia

There is no medical health without psychiatric health.[4]

- Causes of premature death[1]
  - Nontrivial amount due to suicide and accidents
  - Majority due to 5“natural causes”
    - Medication side effects
    - Suboptimal life style
    - Somatic comorbidity
    - Suboptimal treatment
    - Accelerated aging/genetic explanations
- Denmark (1995-2015)[2]
  - Overall improvements in life-years lost
  - Gap of 11 – 13 years in life-expectancy remains
  - General population gained three years due to natural causes
- Benefit for schizophrenia in unnatural causes offset by increased mortality from natural causes
- Inadequate detection throughout life-span[3]
- BUT: cardiovascular risk is lower in patients taking antipsychotics[4]

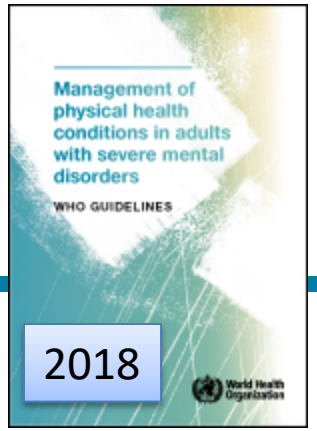
[1]Laursen TM. Curr Opin Psychiatry. 2019; 32(5):388-393. [Meta-analysis]
[2]Laursen TM et al. Schizophr Res. 2019;206:284-290.
[3]Brink M et al. Schizophr Res. 2019;206:347-354. [4]Taipale H et al. World Psychiatry 2020;19(1):61-68.

Need for med-psych integration ("reverse integration")

"All organizations are perfectly designed to get the results they get!"

- Don Berwick, MD (and others)

Beyond monitoring: need for action



- Physical health monitoring (screening) *alone* does not improve mortality
- Improving physical health through intervention[1]
  - Psychiatric stability
  - Dietary and exercise interventions
  - Choice and duration of antipsychotic prescribing
  - Pharmacological support for smoking cessation
  - Screening for health conditions
- Correct (*standard*) medical treatment saves lives[2]

[1]Ilyas A et al. Br J Psychiatry. 2017;211:194-96.
[2]Kugathasan P et al. JAMA Psychiatry. 2018;75:1234-40.
Ward MC and Druss BG. JAMA Psychiatry. 2019;76(7):759-60. [JAMA Network Insights]

THANK YOU!

John Umstead Hospital, Butner, NC, ca. 1995