Management of side effects of antipsychotics

Oliver Freudenreich, MD, FAACLCP
Co-Director,
MGH Schizophrenia Program
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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

• Alpha1
  – Hypotension: slow titration

• Dopamine2
  – Dystonia: prophylactic anticholinergic
  – Akathisia, parkinsonism, tardive dyskinesia
  – Hyperprolactinemia

• Histamine1
  – Sedation
  – Weight gain

• Muscarinic1-5
  – Anticholinergic side effects including cognition

Stroup TS and Gray N. World Psychiatry. 2018;17(3):341-56. [Clinical Update]
### Summary of antipsychotic side effects

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Weight gain</th>
<th>Somnolence</th>
<th>Akathisia</th>
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</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>+++</td>
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<tr>
<td>Brexpiprazole</td>
<td>+</td>
<td>++</td>
<td>0</td>
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<tr>
<td>Cariprazine</td>
<td>+</td>
<td>0 (NNH 100)</td>
<td>+++</td>
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<tr>
<td>Risperidone</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Paliperidone</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Olanzapine</td>
<td>+++ (NNH 6)</td>
<td>+++ (NNH 7)</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine ER</td>
<td>+++</td>
<td>+++ (NNH 7)</td>
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</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Asenapine</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>+ (NNH 67)</td>
<td>+++</td>
<td>+++ (NNH 10)</td>
</tr>
</tbody>
</table>

**Anticholinergic:** olanzapine, quetiapine (could be adrenergic)

**Orthostatic hypotension:** risperidone/paliparidone, iloperidone

**NNH = Number Needed to Harm**

Antipsychotic choice – meta-analysis

- **[Efficacy]**
- **Side effects – TOP 3 (available in US)**
  - EPS
    - Highest: haloperidol, lurasidone, risperidone
    - Lowest: clozapine, quetiapine, olanzapine
  - Weight gain
    - Highest: olanzapine, clozapine, iloperidone
    - Least: haloperidol, ziprasidone, lurasidone
  - QTc prolongation
    - Highest: ziprasidone, iloperidone, asenapine
    - Lowest: lurasidone, aripiprazole, palipideridone
  - Prolactin elevation
    - Highest: paliperidone, risperidone, haloperidol
    - Lowest: aripiprazole, quetiapine, asenapine
  - Sedation
    - Highest: clozapine, ziprasidone, quetiapine
    - Lowest: paliperidone, iloperidone, aripiprazole

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

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

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
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.
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)
Agranulocytosis

• Highest risk: first 6 months
  – Monitoring prevents deaths from agranulocytosis
• Mandated registry-based prescribing
  – “No blood, no drug”
  – Weekly ANC for 6 months, then every other for 6 months, then monthly thereafter
  – Cut-offs
    • ANC at least 1,500/microL to start
    • Discontinue if moderate or severe neutropenia
    • Different cut-offs for BEN population
• Interrupt clozapine if fever and check ANC
• Rechallenge only if benefit outweighs risk
• Ongoing treatment during chemotherapy feasible

https://www.clozapinerems.com/
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.
Myocarditis

• Clinical features
  – Non-specific!
• Highest risk period is four weeks¹
• Management
  – High index of suspicion
  – Increased case detection with monitoring²
  – No agreed-upon monitoring scheme
    • Consider adding inflammatory markers for 4 weeks
  – Consultation with cardiology
• Rechallenge discouraged in clear cases³
  – Slow titration may be protective

²Neufeld NH and Remington G. Schizophr Res. 2019;206:462-3.
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 (SMR, 7.0; 95% CI, 6.7-7.4)\(^2\)
  – Aspiration pneumonia underappreciated\(^3\)

• Management
  – Speech and swallowing evaluation
  – Glycopyrrolate 2 mg at night\(^4\)
  – Sublingual atropine 2 drops three times daily\(^5\)

\(^{2}\)Olfson M et al. JAMA Psychiatry. 2015;72(12):1172-81.
ROUTINE SIDE EFFECT MANAGEMENT
The day the music died
# CATIE – baseline cardiovascular risk factors

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

* National Cholesterol Education Program (NCEP) criteria

NHANES = National Health and Nutrition Examination Survey III
# NCEP ATP III Metabolic Syndrome

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td></td>
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<tr>
<td>Men</td>
<td>Waist circumference</td>
</tr>
<tr>
<td></td>
<td>&gt;40 in (&gt;102 cm) (IDF-94 cm)</td>
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<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;35 in (&gt;88 cm) (IDF-80 cm)</td>
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<tr>
<td>Triglycerides</td>
<td></td>
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<tr>
<td></td>
<td>&gt;150 mg/dL (1.7 mmol/L)</td>
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<tr>
<td>HDL cholesterol</td>
<td></td>
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<tr>
<td>Men</td>
<td></td>
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<tr>
<td></td>
<td>&lt; 40 mg/dL (1.03 mmoI/L)</td>
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<tr>
<td>Women</td>
<td></td>
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<tr>
<td></td>
<td>&lt;50 mg/dL(1.29 mmoI/L)</td>
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<tr>
<td>Blood pressure</td>
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<tr>
<td></td>
<td>≥130/85 mm Hg</td>
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<tr>
<td>Fasting blood glucose</td>
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<tr>
<td></td>
<td>&gt;100 mg/dL (5.6 mmoI/L)</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein
IDF = International Diabetes Federation
Antipsychotic-induced weight gain I

- Most robust predictor: H1 receptor affinity; 5HT2C polymorphisms
- Melanocortin 4 receptor (MC4R) gene in obesity (GWAS)\(^1\)
- Common variants near MC4R gene associated with severe antipsychotic-induced weight gain\(^2\)
- Muscarinic 3 receptor key role in insulin secretion\(^3\)
- Dopamine, striatum, reward systems\(^4\)

GWAS=Genome-Wide Association Study; PORT=Patient Outcomes Research Team; FGA=first-generation antipsychotic.

\(^1\)Farooqi IS et al. New Engl J Med. 2003;348:1085
\(^3\)Nurjono M et al. Schizophr Res. 2014; 157: 244.
Antipsychotic-induced weight gain II

• Almost all antipsychotics show weight gain after extended use
  • Weight gain more pronounced in antipsychotic naïve patients
  • Not clearly dose-dependent

• Meta-analysis in first-episode patient
  ✓ 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

Metabolic prevention

A. Choose wisely, if you can - prevent
B. Screen and monitor - detect
C. Prevent/blunt weight gain - mitigate
  • Switch
  • Add behavioral management
  • Add weight loss medications
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

• 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.
Guideline-concordant screening

**Possible BENCHMARK**

80% glucose monitoring (40% lipid monitoring)

**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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-treatment Baseline</th>
<th>1 month</th>
<th>2 month</th>
<th>3 month</th>
<th>6 month</th>
<th>9 month</th>
<th>12 month</th>
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<tbody>
<tr>
<td>Height (cm)&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Height percentile</td>
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<td>Weight (kg)&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Weight percentile</td>
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<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
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<tr>
<td>BMI percentile</td>
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<tr>
<td>Waist circumference (All the level of the umbilicus)&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Waist circumference percentile</td>
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<tr>
<td>Blood pressure (mmHg)&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Blood pressure percentile</td>
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</tbody>
</table>

**Possible BENCHMARK**

80% glucose monitoring (40% lipid monitoring)

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Switching to aripiprazole (CAMP)

CAMP study = comparison of antipsychotics for metabolic problems
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

Role of individual lifestyle intervention?

\(^3\)Bartels SJ et al. Psychiatr Serv 2013;64:729.
FDA-approved weight loss medications

• Withdrawn 1997: fen-phen
• Withdrawn 2010: sibutramine (Meridia)
• Orlistat (Xenical, OTC Alli)
• Lorcaserin (Belviq) - CIV
• *Phentermine plus topiramate (Qsymia) – CIV
• Bupropion plus naltrexone (Contrave)
• *Liraglutide (Saxenda; lower-dose: Victoza)
• NEW: Superabsorbent hydrogel (Gelesis100)\(^a\)

Weight loss medications and schizophrenia

• Metformin\textsuperscript{1,2,3}
• Topiramate\textsuperscript{4}
• Amantadine\textsuperscript{5}
• Liraglutide\textsuperscript{6}

\textsuperscript{1}Wang M et al. *Schizophr Res.* 2012;138:54-7.
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\(^2\)
• Safety
  – Rare lactic acidosis: more likely with excessive alcohol use
  – May be associated with vitamin B12 deficiency\(^3\)
  – Safe for cognition\(^4\)
  – Most common side effects: GI (N/V 14%, diarrhea 7%)\(^5\)
• Dosing
  – Target total daily dose 2,000 mg (with food)

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.
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*

Clinical scheme of movement disorders

HYPERKINETIC

rhythmic

Medication tremor

Tremor

Tics

Myoclonus

Tardive dyskinesia

Choreo-athetoid

dystonic

Myoclonus

Speed

HYPOKINETIC

too much

Tics

Choreo-athetoid

dystonic

bradykinetic

akinetic

too little

Parkinsonism

Catatonia

ADR
Antipsychotic-induced motor side effects

ALL PATIENTS IN COHORT

No antipsychotic motor side effects

Tardive dyskinesia

Akathisia

Parkinsonism

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.
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

Tardive dyskinesia (TD) - Numbers

• **Incidence**¹
  – FGA 6.5% per year
  – SGA 2.6% per year

• **Prevalence**²
  – Global: 25%
  – Current SGA: 20%; never FGA: 7%
  – Current FGA: 30%

• **Reversibility**³
  – Remission rate: 2% (!)

TD – risk factors

- **Risk factors**¹
  - FGA>SGA>clozapine
  - Age (over age 45)
    - 26% year 1; 52% year 2; 60% year²
  - 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

TD – clinical features

• Delayed onset ("tardive")
• Repetitive, involuntary, purposeless movements ("choreiform")
• Grimacing, tongue protrusion, lip smacking, puckering and pursing, and rapid eye blinking; rapid movements of the arms, legs, and trunk; involuntary movements of the fingers
• Pay attention to: mouth openings, lateral jaw movements
• Less likely: any rapidly evolving syndrome, vivid piano player movements only, localized dystonia only, lower extremities only

http://www.ninds.nih.gov
TD - differential diagnosis

- Spontaneous movements in schizophrenia
- Old age (edentulous; orobuccal dyskinesias)
- Drug-induced dyskinesias
  - “Crack dance”
  - L-DOPA
- Chorea
  - Huntington’s disease
  - Sydenham’s chorea
  - Chorea gravidarum
- Blepharospasm and Meige syndrome
- Tourette’s and other tic disorders
- Tumors or strokes
- Systemic lupus erythematosus

Management of TD

PREVENT

Clear indication for antipsychotic

Short term treatment, if possible

Lowest-risk choice and lowest dose

MONITOR

Baseline motor exam

Longitudinal follow-up

At least annual AIMS*

TREAT

Slowly taper antipsychotic, if possible

Switch to quetiapine or clozapine**, if possible

Treat TD symptomatically

Stop anticholinergics***

*In low-risk patients; more frequent monitoring in higher risk patients
Abnormal involuntary movement scale (AIMS)

Severity scores
- Total score (sum of 1 to 7)
- Global severity score
- Incapacitation
- Insight into movements
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

Tardive dyskinesia - treatment

First-line
- Dopamine-depleting agents
  - 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.
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

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

- Indications
  - FDA-approved (2008) for Huntington’s disease
  - Off-label for tic disorders and treatment of choice for TD

- Mechanism of action
  - VMAT-2 inhibitor

- Side effects
  - Significant: poor tolerability
    - Somnolence, insomnia, akathisia, depression
    - Parkinsonism
  - Short half-life: frequent dosing (TID)
  - DDI: 2D6
  - QTc prolongation

- Expensive

Tetrabenazine and valbenazine metabolism

Tetrabenazine (TBZ) racemic mixture

(-)-TBZ enantiomer

(+)TBZ enantiomer

carbonyl reductase

(-)-β-HTBZ

(-)-α-HTBZ

Valbenazine

Non-P450 hydrolysis

Mono-Oxidation

(+)-β-HTBZ

(+)-α-HTBZ

Metabolite

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

TBZ = Tetrabenazine HTBZ = Dihydrotetrabenazine
Valbenazine

• VMAT-2 inhibitor
• FDA-approved April 11, 2017 for adults with tardive dyskinesia
• 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
Valbenazine

- Clinical trials
  - Phase II: KINECT 1, KINECT 2
  - Phase III: KINECT 3, KINECT 4 (one-year safety/tolerability study)
- KINECT 3 (6 week trial)\(^1\)
  - N=234
  - Blinded, central raters\(^2\)
  - Aims score improvements
    - 80 mg: 3.2 points (d=0.90)
    - 40 mg: 1.9 points (d= 0.52)
    - Placebo: 0.1 points
  - Side effects: akathisia, arthalgia, dry mouth, vomiting, dyskinesia
- KINECT 4\(^3\)
  - 95% response rate (none-to-mild after treatment)
- RE-KINECT\(^3\)
  - TD has impact on QOL

\(^3\)Posters presented at APA 2019 in San Francisco
Deutetrabenazine

- Deuterated tetrabenazine
- FDA-approval April 2017 for Huntington’s disease (brand name Austedo) and August 2017 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)

Hyperprolactinemia

- Tubero-infundibular pathway
  - Dopamine is PIF (prolactin-inhibiting factor)

- Gender-specific problems\(^1\)
  - Females have higher prolactin elevations
  - Female side effects
    - (Secondary) amenorrhea and infertility
    - Gynecomastia and galactorrhea
    - Loss of libido
  - Male side effects
    - Loss of libido, erectile dysfunction
    - Gynecomastia and galactorrhea

- Long-term effects
  - (Secondary) hypono- gonadism \(\rightarrow\) osteoporosis \(\rightarrow\) fracture risk\(^2\)
  - Increased breast cancer risk?\(^3\)
  - No increased endometrial cancer risk?\(^4\)

- Metformin for antipsychotic-induced hyperprolactinemia\(^5\)

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“Prolactin-sparing” antipsychotics

Hyperprolactenemia

- Paliperidone
- Risperidone, first-generation AP
- Olanzapine*
- Lurasidone, asenapine
- Ziprasidone

Iloperidone, quetiapine, clozapine

Aripiprazole** and partial agonists

*Usually transient
**Can lower prolactin levels

Antipsychotics and pregnancy

• Nationwide Medicaid database
  – First trimester exposure to antipsychotics
    • N=9258 exposures to atypical antipsychotics
    • N=733 exposures to typical antipsychotics

• Results
  – Congenital malformations
    • Not exposed: atypical:typical = 3.3% vs. 4.5% vs. 3.8%
  – Relative risks (after confounding adjustment)
    • Atypical RR, 1.05; (95% CI, 0.96-1.16)
    • Typical RR, 0.9; (95% CI, 0.62-1.31)
    • Risperidone RR, 1.26; (95% CI, 1.02-1.56)

• Systematic review
  – High relapse risk if abrupt discontinuation
  – Highest risk: maternal morbidity and untreated illness*


Quetiapine safety
Pooled risk ratio 1.03
Cohen et al. Am J Psychiatry; 175(12):1225-31

Gestational diabetes
Olanzapine
Quetiapine
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 errrs, 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
    - Early use of clozapine for refractory patients
    - Clozapine over polypharmacy
  - Add psychological treatments
  - Treat medical morbidities


**Perfect is the enemy of good.

You need to be the man in the arena!
Premature mortality in schizophrenia

• 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\(^3\)

\(^1\)Laursen TM. Curr Opin Psychiatry. 2019 [Epub ahead of print]. Meta-analysis
\(^3\)Brink M et al. Schizophr Res. 2019;206:347-54.
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
  – 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

Ward MC and Druss BG. JAMA Psychiatry. 2019;76(7):759-60. [JAMA Network Insights]
THANK YOU!

John Umstead Hospital, Butner, NC, ca. 1995