ADVERSE EFFECTS AND SAFETY OF ANTIPSYCHOTICS

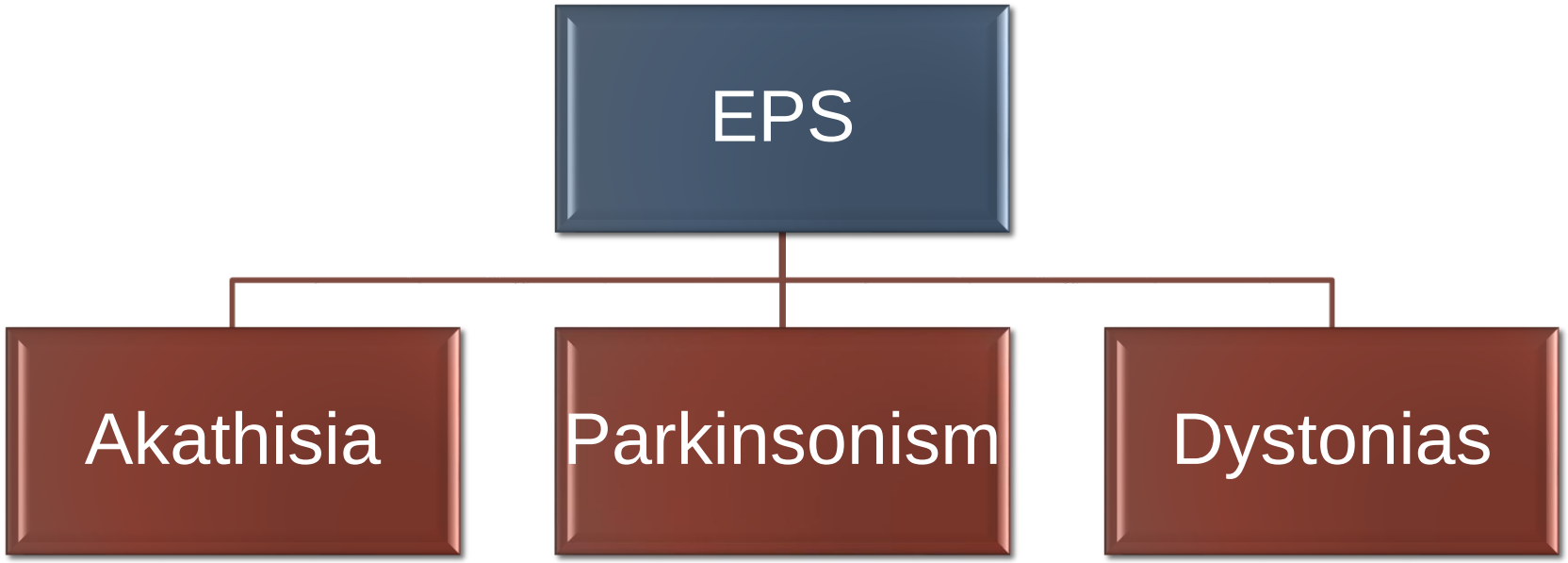
Casey Gallimore, PharmD, MS

Learning Objectives

1. Compare and contrast common adverse effects of 1) first versus second generation antipsychotics, and 2) among agents within the second generation class
2. Describe options for minimizing/managing adverse effects of antipsychotic agents (i.e. EPS, TD, metabolic effects, prolactin elevation, QT prolongation)
3. List parameters that should be evaluated when initiating or increasing a dose of an antipsychotic agent to monitor safety (including timing intervals for monitoring each parameter)
4. Provide a recommendation to manage adverse effects related to antipsychotic use in an individual patient
5. Discuss the safety of antipsychotic use in pediatric and geriatric patients, and during pregnancy
6. Select an antipsychotic agent to treat schizophrenia in an individual patient based on side effect profile and patient specific factors

Shared Adverse Effects of Antipsychotics

- Sedation
- Orthostatic hypotension
- Anticholinergic
- QT prolongation
- Extrapyramidal symptoms (EPS)
- Tardive dyskinesia
- Metabolic effects
- Hyper-prolactinemia
- Neuroleptic malignant syndrome



Extrapyramidal Symptoms (EPS): Dysfunction in extrapyramidal system (motor system involved in coordinated movements)

Tardive Dyskinesia (TD)

- Often irreversible involuntary movements
  - Blinking
  - Lip smacking
  - Movements of face, neck, back, trunk, extremities

- Monitoring and prevention are important
  - Utilize lowest effective dose for shortest duration
  - Consider switching from FGA to SGA, or lower risk agent
  - AIMS (abnormal involuntary movement scale) assessment
    - Q6mo- FGA, Q12 mo SGA, Q3-6mo if abnormal movements noted
    - http://www.cqaimh.org/pdf/tool_aims.pdf

Tardive Dyskinesia Treatment

- **Discontinue problematic agent**
- **Switch from FGA to SGA, or lower risk agent**

- Benzodiazepines
- Botulinum toxin injections
- Anticholinergics

- **Vesicular monoamine transporter 2 inhibitors (VMAT2)**
  - Tetrabenazine
  - Valbenazine (Ingrezza®)
  - Deutetrabenazine (Austedo™)

Neuroleptic Malignant Syndrome (NMS)

- Clinical syndrome characterized by fever, mental status changes, autonomic dysfunction, and rigidity
- 5 - 20% mortality rate
- Treatment
  - discontinuation of antipsychotic
  - supportive care
  - DA agonist (bromocriptine)
- Can rechallenge but CAREFULLY!
  - ~1/3 of NMS cases develop subsequent NMS if re-challenged

ECG Monitoring for QT Prolongation

- Recommended prior to starting antipsychotic in patients with existing risk factors for QT prolongation:
  - Older age (>70 yo)
  - Baseline electrolyte disturbances (hypokalemia or hypomagnesemia)
  - Congenital long QT syndrome
  - Family history of sudden death
  - Personal history of heart murmur, SOB with exertion, tachycardia at rest, irregular heartbeat, syncope, bradycardia
  - Known cardiac disease (MI, heart failure, arrhythmias)
  - Concurrent use of other QT prolonging medications or medications known to inhibit antipsychotic metabolism

Metabolic Changes

obesity, diabetes, hyperlipidemia,
cardiovascular disease
↓
morbidity and mortality

Antipsychotic	Absolute Weight Gain (kg)
Clozapine	5.3
Olanzapine	1.03 – 4.3
Iloperidone	0.7 – 0.8
Paliperidone	0.63 – 1.4
Quetiapine	0.39 – 1.7
Risperidone	2.5
Aripiprazole	-3.6 – 0.13
Asenapine	-1.4 – 1.2
Lurasidone	-0.8 – 1.3
Ziprasidone	-1.25 – -0.16

Joyce Wei Xin Chong et al. Atypical antipsychotics: A review on the prevalence, monitoring, and management of their metabolic and cardiovascular side effects. MHC. 2016;6:178-184.

Antipsychotic Monitoring

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes; 2004

	Baseline	Week 4	Week 8	Week 12	Q 3 months	Q 6 months	Q 12 months	Q 5 years
Personal/ Family History	X					X		
Weight & Height (BMI)	X	X	X	X	X			
Waist Circumference	X					X		
Blood Pressure	X			X		X		
Fasting Glucose	X			X		X		
Fasting Lipid Panel	X			X			X (high risk agents)	X

Managing metabolic changes

- Diet and exercise management
- Drug therapy (follow evidence-based cardiovascular and diabetes care)
  - Statin for elevated lipids
  - Antihypertensive for hypertension
  - Diabetes medication for elevated blood glucose
  - Metformin
- Switch to antipsychotic with lower potential for adverse metabolic effects (metabolic changes may be reversible)

Prolactin Elevation (hyperprolactinemia)

- Abnormal menstruation (women)
- Gynecomastia (men)
- Galactorrhea (lactation)
- Sexual dysfunction
- Decreased bone mineral density, osteoporosis, fracture

- Monitor prolactin levels in patient with above symptoms
  - Normal level 5 – 20 ng/mL
- Management options:
  - Dosage reduction
  - Switching to antipsychotic with less potential to elevate prolactin
  - Augmentation with aripiprazole or a full/partial dopamine agonist

Antipsychotics

First Generation (Typical)

- High D2 antagonism, low 5HT-2a antagonism

Second Generation (Atypical)

- 5HT-2a antagonism > D2 antagonism

Variable blocking of muscarinic, histaminergic, and alpha-1 receptors

First Generation Antipsychotics (FGA)

Drug	EPS	Anticholinergic	Orthostatic Hypotension	Sedation
Haloperidol	+++	-	-	++
Fluphenazine	+++	-	-	+
Loxapine	++	+	+	++
Perphenazine	++	-	-	++
Pimozide	+++	+	+	+
Trifluoperazine	+++	-	+	+
Thiothixene	+++	-	+	+
Chlorpromazine	+	+++	+++	+++
Thioridazine	+	++++	++++	+++

High Potency

Low Potency

EPS = extrapyramidal symptoms (movement disorders)

		D2	D3	5HT1A	5HT2A	5HT2C	5HT7	α 1	M1	M3	H1
Pines	Clozapine	+	+	+	++	++	++	+++	+++	++	+++
	Olanzapine	++	++		+++	++	+	++	++	++	+++
	Quetiapine	+	+	+	++	+	++	+++	++	++	+++
	Asenapine	+++	+++	++	+++	+++	+++	+++	+		+++
Dones	Risperidone	+++	+++	+	+++	++	+++	+++			++
	Paliperidone	+++	+++	+	+++	++	+++	+++			++
	Iloperidone	+++	++	++	+++	+	++	+++			++
	Ziprasidone	+++	+++	++**	+++	++	+++	++			++
	Lurasidone	+++	?	+++*	++	+	+++	++			
Azoles	Aripiprazole	+++*	+++	+++*	++	++	+++	++			++
	Brexpiprazole	+++*	++*	+++*	+++		++	+++	+		++
	Cariprazine	+++*	+++*	+++*	++	+	+	+			++
	Lumateperone	++		+++				++	+	+	+

D=dopamine, 5HT=serotonin, α=alpha adrenergic, M=muscarinic, H=histaminergic, * = partial agonist, ** = agonist

Binding affinity: + weak, ++ moderate, +++ strong

Adapted from Table 15 in: Stahl SM et al. Meta-guidelines for the management of patients with schizophrenia. CNS Spectrums. 2013;18:150-162.

Receptor	Therapeutic Effects	Side Effects
D2 Ant	↓ positive symptoms	EPS, hyperprolactinemia, ↑ negative symptoms, cognitive deficits, sedation
D2 PA	↓ positive symptoms	Lower EPS risk
D3	↓ positive symptoms, ↓ negative symptoms, pro-cognitive, antidepressant	Unknown
5HT1A	↓ EPS, ↓ hyperprolactinemia, antidepressant, anxiolytic	Unknown
5HT2A	↓ EPS, ↓ hyperprolactinemia	Unknown
5HT2C	Antidepressant	Cardiometabolic
5HT7	↓ circadian rhythm dysfunction, ↓ negative symptoms, pro-cognitive, antidepressant	Unknown
α1	↓ nightmares	Dizziness, sedation, hypotension
M1	↓ EPS	Constipation, sedation, dry mouth, blurred vision
M3	↓ EPS	Cardiometabolic, constipation, sedation, dry mouth, blurred vision
H1	Hypnotic	Cardiometabolic, sedation

D2 ant=full antagonist at D2 receptor, D2 PA=partial agonist at D2 receptor, D=dopamine, 5HT=serotonin, α=alpha adrenergic, M=muscarinic, H=histaminergic

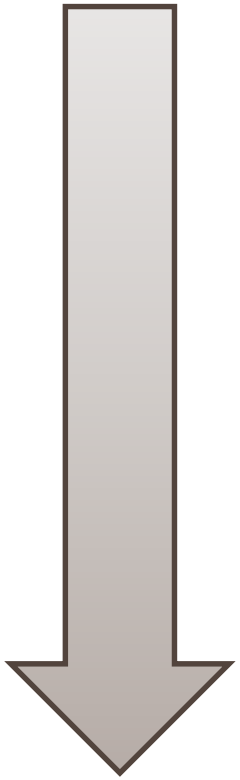
Adapted from Table 15 in: Stahl SM et al. Meta-guidelines for the management of patients with schizophrenia. CNS Spectrums. 2013;18:150-162.

BEST CHOICE

WORST CHOICE

Metabolic Changes	Sedation	EPS	Anticholinergic
Ziprasidone Lurasidone Aripiprazole Brexpirazole Cariprazine Lumateperone Pimavanserin	Aripiprazole Brexpiprazole Cariprazine Lumateperone Pimavanserin	Clozapine Quetiapine Iloperidone Lumateperone Pimavanserin	Asenapine Paliperidone Ziprasidone Lurasidone Aripiprazole Brexipraxole Cariprazine Lumateperone Pimavanserin
Asenapine Iloperidone Paliperidone Risperidone Quetipatine	Iloperidone Lurasidone Paliperidone Risperidone Ziprasidone Asenapine Olanzapine	Aripiprazole Brexpiprazole Cariprazine Asenapine Olanzapine Ziprasidone	Risperidone Illoperidone
Clozapine Olanzapine	Clozapine Quetiapine	Paliperidone Risperidone Lurasidone	Clozapine Olanzapine Quetiapine

BEST CHOICE



WORST CHOICE

Prolactin Elevation
Clozapine Quetiapine Iloperidone Lurasidone Aripiprazole Brexiprazole Cariprazine Lumateperone Pimavanserin
Olanzapine Asenapine Ziprasidone
Risperidone Paliperidone

Orthostatic Hypotension
Aripiprazole Brexpiprazole Cariprazine Lumateperone
Olanzapine Quetiapine Asenapine Risperidone Paliperidone Lurasidone Ziprasidone Pimavanserin
Iloperidone Clozapine

QT Prolongation
Lurasidone Aripiprazole Brexpiprazole Cariprazine Lumateperone Pimavanserin
Clozapine Olanzapine Quetiapine Asenapine Risperidone Paliperidone
Iloperidone Ziprasidone

Clozapine (Clozaril®) Adverse Effects

- First approved second generation AP
- Reserved for refractory patients
- Use-limiting ADEs:
  - Agranulocytosis (1-2%)
    - Strict monitoring of WBC and ANC required
  - Dose dependent seizure risk
  - Hypotension (slow titration)
  - Excessive salivation (sialorrhea)
  - Urinary incontinence (alpha-adrenergic blocking)
  - Constipation (anticholinergic effects)

WBC = white blood cell count
ANC = absolute neutrophil count

Clozapine Risk Evaluation & Mitigation Strategy (REMS)

- All prescribers and pharmacies must be certified within Clozapine REMS Program
- Compliance with WBC and ANC monitoring required for patient to receive clozapine

- Patients and monitoring tracked in REMS registry:
  - Weekly: First 6 months of therapy
  - Every other week: 6-12 months of therapy
  - Every 4 Weeks: after 12 months, for duration of therapy

Clozapine Monitoring

- **Mild neutropenia (ANC: 1000 - 1499):** Continue clozapine, increase monitoring to 3x per week

- **Moderate neutropenia (ANC: 500 - 999):** Monitor daily, hold clozapine until ANC is ≥ 1000/microL

- **Severe neutropenia/agranulocytosis (ANC: <500):** Discontinue clozapine

Note: *Clinicians can elect to continue or re-challenge with clozapine despite moderate or severe neutropenia if they determine psychiatric benefit outweighs the medical risk*

Safety in Special Populations

	Risk	Recommendations
Pediatrics	▪ Trend of increasing prescription of AA for disruptive behaviors ▪ Particularly susceptible to hyperprolactinemia and metabolic effects of AA	▪ Only use for specific indication and with clearly documented goals ▪ Regular monitoring of metabolic parameters
Pregnancy	▪ No major congenital malformations observed—risk likely less compared to mood stabilizers (lithium, valproic acid, carbamazepine) ▪ FGA use associated with low birth weight, preterm delivery, transient EPS and withdrawal with 3rd trimester use ▪ SGA use associated with maternal weight gain, gestational diabetes, increased infant size, neurodevelopment delays that resolve by 12 months ▪ Risk of relapse / recurrence with discontinuation	▪ More data for FGA vs SGA ▪ For FGA, high potency preferred over low potency (lower anticholinergic, hypotensive, antihistamine ADE burden) ▪ Clozapine may be more problematic than other SGAs (floppy baby syndrome, need for monitoring of WBC) ▪ Close metabolic monitoring during pregnancy ▪ Ultrasound monitoring for fetal size

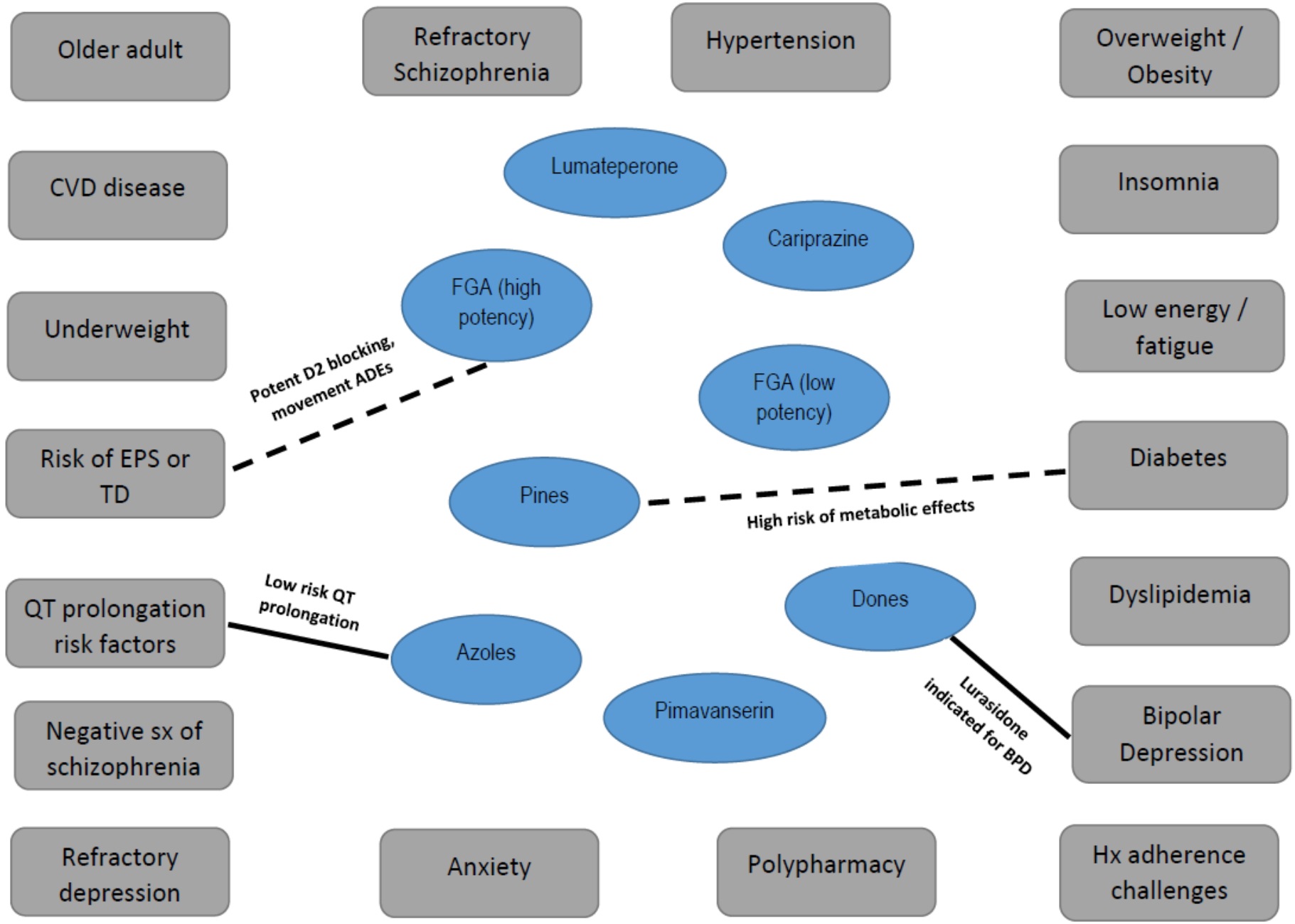
BMJ. 2015;351:h5918.

Black Box Warning

"Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death"

- Based on analyses of 17 placebo-controlled trials
  - 2.8% rate placebo group, 4.5% rate antipsychotic group
- Causes of death varied, most appeared to be cardiovascular (i.e. heart failure, sudden death) or infectious (i.e. pneumonia) in nature
- Observational studies suggest treatment with typical antipsychotic drugs may also increase mortality risk
- Avoid antipsychotic use for this indication if possible

Practice Assignment: Concept Map



Questions??

- Casey.Gallimore@wisc.edu