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Antipsychotic Adverse Effects: Monitoring and Management

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2014 Fall Distance Learning Experience

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Objectives

1. Recommend strategies for managing the extrapyramidal symptoms associated with antipsychotics based on a patient's presenting symptoms.
2. Evaluate a patient's risk for QTc prolongation based on the antipsychotic they are taking, cardiac history, age, and concurrent medications.
3. Develop a monitoring plan for metabolic effects associated with second-generation antipsychotics according to the ADA/APA consensus document on antipsychotic drugs and obesity and diabetes.
4. Create evidence-based treatment regimens to clinically manage the adverse effects associated with clozapine therapy (e.g. seizures, constipation, sialorrhea, etc.) when presented with a patient case.
5. Describe the significant differences in adverse effects among the second-generation antipsychotics.

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First-Generation Antipsychotics (FGAs)

- Chlorpromazine (Thorazine®)
- Fluphenazine (Prolixin®)
- Haloperidol (Haldol®)
- Loxapine (Loxitane®)
- Perphenazine (Trilafon®)
- Thioridazine (Mellaril®)
- Thiothixene (Navane®)
- Trifluoperazine (Stelazine®)

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First-Generation Antipsychotics (FGAs)

Potency	Antipsychotics
Low	• Chlorpromazine • Thioridazine
Intermediate	• Perphenazine • Loxapine
High	• Trifluoperazine • Thiothixene • Haloperidol • Fluphenazine

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Second-Generation Antipsychotics (SGAs)

- Clozapine (Clozaril®)
- Risperidone (Risperdal®)
- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Ziprasidone (Geodon®)
- **Aripiprazole (Abilify®)**
- **Paliperidone (Invega®)**
- **Asenapine (Saphris®)**
- **Iloperidone (Fanapt®)**
- **Lurasidone (Latuda®)**

Bold indicates drug product is available in brand name only.

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Adverse Effects

- Agranulocytosis
- Anticholinergic
- Cardiac
- Enuresis
- Extrapyramidal symptoms
- Gastrointestinal (GI)
- Hepatic
- Hyperprolactinemia
- Metabolic
- Neuroleptic malignant syndrome (NMS)
- Ocular and skin deposits
- Orthostatic hypotension
- Osteoporosis
- Photo sensitivity
- Sedation
- Seizures
- Sexual dysfunction
- Venous thromboembolism

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Extrapyramidal Symptoms

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Extrapyramidal Symptoms (EPS)

- Akathisia
- Pseudoparkinsonism
- Dystonia
- Tardive dyskinesia

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Akathisia

- Symptoms
  - Inability to sit or stand still -Shifting
  - Restlessness -Tapping feet
  - Pacing -Marching in spot
- Monitoring
  - Barnes Akathisia Scale (BAS, BARS)

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Chen JJ. Drug-Induced Movement Disorders. *Ment Health Clin*. 2012;1(7):17. Available at: http://cpnp.org/resource/mhc/2012/01/drug-induced-movement-disorders. Accessed April 24, 2014.
Haddad P, Dursun S. Neurological complications of psychiatric drugs: clinical features and management. *Hum psychopharmacol* 2008; 23: 15-26.

Akathisia

- Treatment
  - Discontinue antipsychotic or reduce dose
  - Switch to SGA
  - Beta-blockers
    - Propranolol
    - Benzodiazepines

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Chen JJ. Drug-Induced Movement Disorders. *Ment Health Clin*. 2012;1(7):17. Available at: http://cpnp.org/resource/mhc/2012/01/drug-induced-movement-disorders. Accessed April 24, 2014.
Haddad P, Dursun S. Neurological complications of psychiatric drugs: clinical features and management. *Hum psychopharmacol* 2008; 23: 15-26.

Dystonia

- Symptoms
  - Torticollis - Trismus
  - Laryngospasm - Glossospasm
  - Oculogyric crisis - Blepharospasm
  - Retrocollis - Opisthotonus
- Monitoring
  - Modified Simpson Angus Scale (MSAS)

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Chen JJ. Drug-Induced Movement Disorders. *Ment Health Clin*. 2012;1(7):17. Available at: http://cpnp.org/resource/mhc/2012/01/drug-induced-movement-disorders. Accessed April 24, 2014.
Haddad P, Dursun S. Neurological complications of psychiatric drugs: clinical features and management. *Hum psychopharmacol* 2008; 23: 15-26.

Dystonia

- Treatment
  - Discontinue antipsychotic or reduce dose
  - Switch to SGA
  - Anticholinergics
    - Benztropine (po/IM/IV)
    - Trihexyphenidyl (po)
    - Diphenhydramine (po/IM/IV)
  - Benzodiazepines

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Chen JJ. Drug-Induced Movement Disorders. *Ment Health Clin*. 2012;1(7):17. Available at: http://cpnp.org/resource/mhc/2012/01/drug-induced-movement-disorders. Accessed April 24, 2014.
Haddad P, Dursun S. Neurological complications of psychiatric drugs: clinical features and management. *Hum psychopharmacol* 2008; 23: 15-26.

Pseudoparkinsonism

- Symptoms
  - Akinesia -Masked face
  - Bradykinesia -Shuffling gate
  - Resting tremor -Stooped posture
  - Cogwheel rigidity -Micrographia
- Monitoring
  - Modified Simpson Angus Scale (MSAS)

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Chen JJ. Drug-Induced Movement Disorders. *Ment Health Clin*. 2012;1(7):17. Available at: http://cpnp.org/resource/mhc/2012/01/drug-induced-movement-disorders. Accessed April 24, 2014.
Haddad P, Dursun S. Neurological complications of psychiatric drugs: clinical features and management. *Hum psychopharmacol* 2008; 23: 15-26.

Pseudoparkinsonism

- Treatment
  - Discontinue antipsychotic or reduce dose
  - Switch to SGA
  - Anticholinergics
  - Dopamine agonists
    - Amantadine

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Chen JJ. Drug-Induced Movement Disorders. *Ment Health Clin*. 2012;1(7):17. Available at: http://cpnp.org/resource/mhc/2012/01/drug-induced-movement-disorders. Accessed April 24, 2014.
Haddad P, Dursun S. Neurological complications of psychiatric drugs: clinical features and management. *Hum psychopharmacol* 2008; 23: 15-26.

Tardive Dyskinesia (TD)

- Incidence
  - Approximately 5% per year
  - Approximately 20-25% with long-term treatment
- Risk factors
  - Long-term antipsychotic use - FGA
  - High dose antipsychotic - Increasing age
  - Occurrence of acute EPS - Female gender
  - Organic mental disorder

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Bhidayasiri R, Fahn S, Weiner W, et al. Evidence based guideline: Treatment of tardive syndromes: Report of the guideline development subcommittee of the American Academy of Neurology. *Neurology* 2013; 81: 463-469.
Pierre J. Extrapyramidal symptoms with atypical antipsychotics. *Drug Saf* 2005; 28: 191-208.

Tardive Dyskinesia (TD)

- Prevention
  - Confirm indication for antipsychotic
  - Use SGA
  - Use minimum effective dose
  - Discontinue anticholinergics
  - Assess for signs using rating scales

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Caroff S, Miller D, Dhopesh V, Campbell E. Is there a rational management strategy for tardive dyskinesia? *Current Psychiatry* 2011; 10: 23-32.
Kaspar R, Ellingrod V. Strategies for managing drug-induced tardive dyskinesia. *Current Psychiatry* 2014; 13: 44-46.

Tardive Dyskinesia (TD)

- Monitoring
  - Abnormal Involuntary Movement Scale (AIMS)
  - Dyskinesia Identification System - Condensed User Scale (DISCUS)
    - Administer at least every 3 to 6 months

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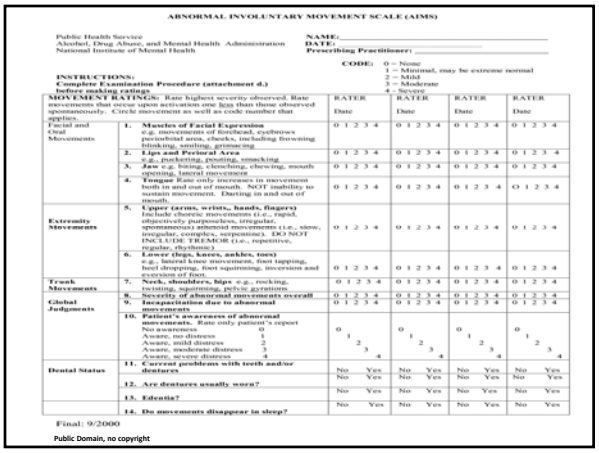
Caroff S, Miller D, Dhopesh V, Campbell E. Is there a rational management strategy for tardive dyskinesia? *Current Psychiatry* 2011; 10: 23-32.



ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration
National Institute of Mental Health

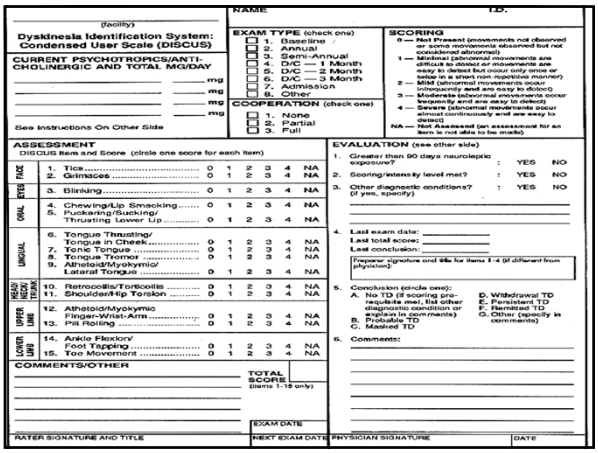
NAME:
DATE:
Prescribing Practitioner:

CODE: 0 – None
1 – Minimal, may be extreme normal
2 – Mild
3 – Moderate
4 – Severe

INSTRUCTIONS:
Complete Examination Procedure (attachement d.)
before making ratings

			RATER Date	RATER Date	RATER Date	RATER Date
MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.						
Facial and Oral Movements	1.	**Muscles of Facial Expression** e.g. movements of forehead, eyebrows periorbital area, cheeks, including frowning blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2.	**Lips and Perioral Area** e.g., puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3.	**Jaw** e.g. biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4.	**Tongue** Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Extremity Movements	5.	**Upper (arms, wrists,, hands, fingers)** Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (i.e., repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6.	**Lower (legs, knees, ankles, toes)** e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of feet.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Trunk Movements	7.	**Neck, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Global Judgments	8.	**Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9.	**Incapacitation due to abnormal movements**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10.	**Patient's awareness of abnormal movements.** Rate only patient's report No awareness 0; Aware, no distress 1; Aware, mild distress 2; Aware, moderate distress 3; Aware, severe distress 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Dental Status	11.	**Current problems with teeth and/or dentures**	No Yes	No Yes	No Yes	No Yes
	12.	**Are dentures usually worn?**	No Yes	No Yes	No Yes	No Yes
	13.	**Edentia?**	No Yes	No Yes	No Yes	No Yes
	14.	**Do movements disappear in sleep?**	No Yes	No Yes	No Yes	No Yes

Final: 9/2000



(facility)

Dyskinesia Identification System: Condensed User Scale (DISCUS)

CURRENT PSYCHOTROPICS/ANTI-CHOLINERGIC AND TOTAL MG/DAY

_____ mg
_____ mg
_____ mg
_____ mg

See Instructions On Other Side

NAME I.D.

EXAM TYPE (check one)
1. Baseline
2. Annual
3. Semi-Annual
4. D/C — 1 Month
5. D/C — 2 Month
6. D/C — 3 Month
7. Admission
8. Other

COOPERATION (check one)
1. None
2. Partial
3. Full

SCORING
0 — Not Present (movements not observed or some movements observed but not considered abnormal)
1 — Minimal (abnormal movements are clinical questionable; movements occur only once or twice in a short non-repetitive manner)
2 — Mild (abnormal movements occur infrequently and are easy to detect)
3 — Moderate (abnormal movements occur frequently and are easy to detect)
4 — Severe (abnormal movements occur almost continuously and are easy to detect)
NA — Not Assessed (an assessment for an item is not able to be made)

ASSESSMENT
DISCUS Item and Score (circle one score for each item)

FACE	1. Tics	0	1	2	3	4	NA
	2. Grimaces	0	1	2	3	4	NA
EYES	3. Blinking	0	1	2	3	4	NA
ORAL	4. Chewing/Lip Smacking	0	1	2	3	4	NA
	5. Puckering/Sucking/ Thrusting Lower Lip	0	1	2	3	4	NA
LINGUAL	6. Tongue Thrusting/ Tongue in Cheek	0	1	2	3	4	NA
	7. Tonic Tongue	0	1	2	3	4	NA
	8. Tongue Tremor	0	1	2	3	4	NA
	9. Athetoid/Myokymic/ Lateral Tongue	0	1	2	3	4	NA
HEAD/ NECK/ TRUNK	10. Retrocollis/Torticollis	0	1	2	3	4	NA
	11. Shoulder/Hip Torsion	0	1	2	3	4	NA
UPPER LIMB	12. Athetoid/Myokymic Finger-Wrist-Arm	0	1	2	3	4	NA
	13. Pill Rolling	0	1	2	3	4	NA
LOWER LIMB	14. Ankle Flexion/ Foot Tapping	0	1	2	3	4	NA
	15. Toe Movement	0	1	2	3	4	NA

COMMENTS/OTHER

TOTAL SCORE (items 1-15 only)

EXAM DATE

RATER SIGNATURE AND TITLE | NEXT EXAM DATE | PHYSICIAN SIGNATURE | DATE

EVALUATION (see other side)

1. Greater than 90 days neuroleptic exposure? : YES NO
2. Scoring/severity level met? : YES NO
3. Other diagnostic conditions? (if yes, specify) : YES NO
4. Last exam date: _____ Last total score: _____ Last conclusion: _____
   Preparer signature and title for items 1-4 (if different from physician)
5. Conclusion (circle one):
   A. No TD (if scoring pre-requisite met, list other diagnostic condition or explain in comments)
   B. Probable TD
   C. Masked TD
   D. Withdrawal TD
   E. Persistent TD
   F. Remitted TD
   G. Other (specify in comments)
6. Comments:

Tardive Dyskinesia (TD)

- Symptoms
  - Orofacial movements
    - Tongue thrusting
    - Tongue rolling
    - Chewing or lateral jaw movements
    - Lip smacking
    - Grimacing
    - Frequent blinking
    - Brow arching
    - Blepharospasm
  - Extremity movements
    - Choreiform
    - Athetoid
    - Ballistic
    - Axial hyperkinesia

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Caroff S, Miller D, Dhopesh V, Campbell E. Is there a rational management strategy for tardive dyskinesia? *Current Psychiatry* 2011; 10: 23-32.

Tardive Dyskinesia (TD)

- Treatment
  - May be irreversible
  - No FDA-approved medications
    - Taper or discontinue antipsychotic if appropriate
      - Withdrawal dyskinesia
    - Switch antipsychotics
      - More or less potent agent
      - Clozapine
    - Discontinue anticholinergic medications
    - Trial of antidyskinetic medication

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Kaspar R, Ellingrod V. Strategies for managing drug-induced tardive dyskinesia. *Current Psychiatry* 2014; 13: 44-46.

Tardive Dyskinesia (TD)

- Antidyskinetic medications

Should be considered	Might be Considered	Should Not be Considered
Clonazepam	Amantadine	Diltiazem
Ginkgo biloba	Tetrabenazine	Galantamine
		Eicosapentaenoic acid

Insufficient Evidence to Support or Refute Use				
Acetazolomide	Bromocriptine	Thiamine	Baclofen	Vitamin E
Vitamin B_6	Selegiline	Melatonin	Nifedipine	Levetiracetam
Buspirone	Yi-gan san	Botulinum toxin	Reserpine	Methyldopa
ECT	Deep brain stimulation			

Bhidayasiri R, Fahn S, Weiner W, et al. Evidence based guideline: Treatment of tardive syndromes: Report of the guideline development subcommittee of the American Academy of Neurology. *Neurology* 2013; 81: 463-469.

Neuroleptic Malignant Syndrome

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Neuroleptic Malignant Syndrome

- Incidence: ~0.01-0.02%
- Onset: Usually within 30 days
- Risk factors
  - High potency FGAs
  - Parenteral administration
  - Higher doses
  - Faster titration rates
  - Prior episode of NMS
  - -Agitation
  - -Restraint
  - -Dehydration
  - -Antipsychotic naïve

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Strawn J, Keck P, Caroff S. Neuroleptic Malignant Syndrome. *Am J Psychiatry* 2007; 164: 870-876.
Bienvenu O, Neufeld K, Needham D. Treatment of four psychiatric emergencies in the intensive care unit. *Crit Care Med* 2012; 40: 2662-2670.

Neuroleptic Malignant Syndrome

- Signs/Symptoms
  - Hyperthermia -Mental status changes
  - Muscle rigidity -Autonomic instability
  - Elevated creatine kinase
- Non-Pharmacologic Treatment
  - Discontinue all dopamine antagonists
  - Supportive care
    - Hydration
    - Correct electrolyte abnormalities
    - Cooling measures

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Strawn J, Keck P, Caroff S. Neuroleptic Malignant Syndrome. *Am J Psychiatry* 2007; 164: 870-876.
Bienvenu O, Neufeld K, Needham D. Treatment of four psychiatric emergencies in the intensive care unit. *Crit Care Med* 2012; 40: 2662-2670.

Neuroleptic Malignant Syndrome

- Pharmacologic Treatment
  - Benzodiazepines – lorazepam 1 to 2mg IV every 4 to 6 hours
  - Amantadine 200 to 400mg/day po or NG in divided doses
  - Bromocriptine 2.5mg po or NG BID or TID (may increase to 45mg/day)
  - Dantrolene 1 to 2.5mg/kg IV followed by 1mg/kg every 6 hours
- Electroconvulsive therapy 6 to 10 treatments

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Strawn J, Keck P, Caroff S. Neuroleptic Malignant Syndrome. *Am J Psychiatry* 2007; 164: 870-876.
Bienvenu O, Neufeld K, Needham D. Treatment of four psychiatric emergencies in the intensive care unit. *Crit Care Med* 2012; 40: 2662-2670.

QT_c Prolongation

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Relationship between QTc and Torsades de Pointes (TdP)

QTc Increase (msec)	Risk
≤ 5	Does not appear to cause TdP
>5 and <20	Inconclusive
>20	Increased risk for TdP

- QTc prolongation >500 msec or a change in baseline >30-60 msec are of particular concern

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US Department of Health and Human Services, FDA, CDER, CBER. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. 2005. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf. Accessed May 13, 2014.

Risk Factors for QTc Prolongation

- Female
- Advanced age
- Congenital long QT syndrome (LQTS)
- Electrolyte abnormalities
- Anorexia nervosa
- Malnutrition
- Diuretics
- Bradycardia
- Heart disease
- Renal and hepatic dysfunction
- Hypothyroidism
- CNS injury
- Diabetes
- Medications
- Drug-drug interactions

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Beach S, Celano C, Noseworthy P, et al. QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics* 2013; 54: 1-13.
Nachimuthu S, Assar M, Schussler J. Drug-induced QT interval prolongation: mechanisms and clinical management. *Ther Adv Drug Saf* 2012; 3: 241-253.
Mackin P. Cardiac side effects of psychiatric drugs. *Hum Psychopharmacol Clin Exp* 2007; 23: 3-14.

Risk of QTc Prolongation with Antipsychotics

Medication (n)	Dose (mg/day)	Mean Duration of Treatment (days)	Mean Change in Baseline QTc (msec)
Haloperidol (27)	15	18	7.1
Ziprasidone (31)	160	15	15.9
Quetiapine (27)	750	17	5.7
Olanzapine (24)	20	20	1.7
Risperidone (25)	6-8	25	3.9
Thioridazine (30)	300	16	30.1

No patient had a QTc interval ≥500 msec during the study.

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Harrigan E, Miceli J, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharm* 2004; 24: 62-69.

Risk of QTc Prolongation with Ziprasidone

- Modest effect on QTc interval
  - Does not appear to be dose-related
- Incidence of QTc prolongation ≥500 msec is ~0.06%
  - No episodes of TdP among 4571 patients treated
  - Rates of rapid and unexpected deaths comparable with other antipsychotics
  - No reports of significant cardiac events with overdose

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FDA. Briefing Document for Zeldox capsules (ziprasidone). New York: Pfizer Inc, 2000; 116.

TABLE 3. QTc-Prolongation Risk Stratification for Commonly Used Antipsychotic Medications*

	Association with QTc Prolongation	Association with Torsades de Pointes
High risk		
Thioridazine	+++	+++
Haloperidol (IV)	+++	+++
Ziprasidone	+++	+
Moderate risk		
Fluphenazine	++	–
Haloperidol (PO/IM)	++	++
Iloperidone	++	–
Paliperidone	++	–
Risperidone	+	+
Low risk		
Asenapine	+	–
Lurasidone	+	–
Olanzapine	+	+
Quetiapine	+	+
Minimal risk		
Aripiprazole	–	–

IV = intravenous; PO = orally; IM = intramuscularly.
* The relative risks for QTc prolongation may vary depending on dose, concomitant medications, and other medical illnesses.

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This table was published in Psychosomatics; Vol 54; Beach S, Celano C, Noseworthy P, et al; QTc prolongation, torsades de pointes, and psychotropic medications; pages 1-13; Copyright Elsevier (2013).

Prevention of QTc Prolongation

- Confirm indication for antipsychotic
- Only use high doses when there is a clear therapeutic advantage
- Avoid administration with other QT prolonging medications
- Avoid QT prolonging drugs in patients with:
  - Pre-existing heart disease
  - Ventricular arrhythmias
  - Electrolyte abnormalities
- Monitor ECG in hospital setting if:
  - Initiation of drug known to cause TdP
  - Overdose on proarrhythmic agent
  - New-onset bradyarrhythmia
  - Severe hypokalemia or hypomagnesemia

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Nachimuthu S, Assar M, Schussler J. Drug-induced QT interval prolongation: mechanisms and clinical management. *Ther Adv Drug Saf* 2012; 3: 241-253.
Mackin P. Cardiac side effects of psychiatric drugs. *Hum Psychopharmacol Clin Exp* 2007; 23: 3-14.

Monitoring for QTc Prolongation

- No consistent data exist on how and when to monitor QT interval with antipsychotics
- Measure QT interval during peak plasma concentration of antipsychotic
- Assess QTc at baseline and intermittently post-initiation for patients with risk factors
- Monitor ECG at baseline and then at least daily with IV haloperidol

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Al-Khatib S, LaPointe N, Kramer J, Califf R. What clinicians should know about the QT interval. *JAMA* 2003; 289: 2120-2127.
Anderson M, Al-Katib S, Kramer J, et al. Cardiac repolarization: current knowledge, critical gaps, and new approaches to drug development and patient management. *Am Heart J* 2002; 144: 769-781.
FDA. Information for healthcare professionals: haloperidol. 2007. Available at : http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/drugsafetyinformationforhealthcareprofessionals/ucm085203.htm. Accessed May 13, 2014.
Beach S, Celano C, Noseworthy P, et al. QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics* 2013; 54: 1-13.

Monitoring for QTc Prolongation – LQTS Experts

- One third to one half of LQTS experts would check an ECG before and after starting an antipsychotic
- Check ECG before and after starting a drug if it has very probable, probable, or possible potential for causing QT prolongation

Very Probable	Probable	Possible
Thioridazine	Ziprasidone	Chlorpromazine Haloperidol Olanzapine Risperidone

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Al-Khatib S, LaPointe N, Kramer J, Califf R. What clinicians should know about the QT interval. *JAMA* 2003; 289: 2120-2127.

Orthostasis and Syncope

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Orthostasis and Syncope

- Risk factors
  - Treatment with clozapine, iloperidone, chlorpromazine and thioridazine
  - Rapid dose titration
  - Initial treatment period
  - Elderly
  - Dehydration
  - Alcoholic neuropathy
  - Concomitant medications that affect hemodynamic tone
  - Disorders of the autonomic nervous system

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Gugger J. Antipsychotic pharmacotherapy and orthostatic hypotension: Identification and management. *CNS Drugs* 2011; 25: 659-671.
Clozaril® Package Insert. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/Clozaril.pdf. Accessed May 13, 2013.

Orthostasis and Syncope

- Non-pharmacologic management
  - Rise slowly to standing position
  - Compression stockings
  - -Salt-containing diet
  - -Drink plenty of fluid
- Pharmacologic treatment
  - Switch antipsychotics
  - Titrate dose slowly
    - Specific dose titration schedule for iloperidone
    - Use initial iloperidone titration schedule if >3 days missed
  - Lower the dose
  - Fludrocortisone 0.2 to 2 mg daily (divided in 2-3 doses)

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Gugger J. Antipsychotic pharmacotherapy and orthostatic hypotension: Identification and management. *CNS Drugs* 2011; 25: 659-671.
Testani M. Clozapine-induced orthostatic hypotension treated with fludrocortisone. *J Clin Psychiatry* 1991; 55: 497-498.
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Hyperprolactinemia

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Hyperprolactinemia

- Risk factors
  - Treatment with FGAs, risperidone, or paliperidone
  - Children/adolescents
  - Premenopausal women
- Symptoms
  - Gynecomastia -Infertility
  - Galactorrhea -Sexual dysfunction
  - Amenorrhea -Osteoporosis

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Singh R, Deep G. Hyperprolactinemia in antipsychotic use. *Psychiatric Annals* 2012; 42: 389-392.
Bostwick J, Guthrie S, Ellingrod V. Antipsychotic-induced hyperprolactinemia. *Pharmacotherapy* 2009; 29: 64-73.

Hyperprolactinemia

- Monitoring
  - Obtain prolactin level at baseline, 3 months, or if any clinical feature appears
- Treatment
  - Reduce antipsychotic dose
  - Switch to a different antipsychotic
  - Adjunct dopamine agonist
    - Bromocriptine
    - Cabergoline
    - Amantadine
  - Adjunct aripiprazole

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Singh R, Deep G. Hyperprolactinemia in antipsychotic use. *Psychiatric Annals* 2012; 42: 389-392.
Bostwick J, Guthrie S, Ellingrod V. Antipsychotic-induced hyperprolactinemia. *Pharmacotherapy* 2009; 29: 64-73.

Metabolic Effects

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Metabolic Effects

Medication	Metabolic Syndrome	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+++	+	+
Risperidone	+	++	D	D
Olanzapine	+++	+++	+	+
Quetiapine	++	++	D	D
Ziprasidone*	+/-	+/-	-	-
Aripiprazole*	+/-	+/-	-	-

+ = increased effect, - = no effect; D = discrepant results
* = Newer drugs with limited long-term data

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American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27: 596-601.

Medication	Weight, kg (≤12 weeks)	Weight, kg (≥24 weeks)	Total cholesterol, mg/dl (≤12 weeks)	Total cholesterol, mg/dL (≥24 weeks)	Triglycerides, mg/dL (≤12 weeks)	Triglycerides, mg/dL (≥24 weeks)	Fasting blood glucose, mg/dL (≤12 weeks)	Fasting blood glucose, mg/dL (≥24 weeks)
Asenapine	+1.1-1.3	+0.9	+0.4-1.1	-6	-3.5 - +3.8	-9.8	-0.6 - +3.2	+2.4
Aripiprazole	+0.3	-1.5	-	-	-	-	+4.4	+2.2
Clozapine	+0.9-2.8	-0.6 - +3.7	+13	-	+71	-	+11	-
Iloperidone	+2-2.7	-	+8.2	-3.9-23.2	-0.8	-8.9 - +35.4	+6.6	-18 - +0.54
Lurasidone	+0.43	-0.59- +0.73	-3.8 - +12.3	-2.5-3.8	-3.1 - +29.1	-4.8 – 15.1	-0.4 - +2.6	+0.8-2.3
Olanzapine	+2.6	+5.6	+5.3	5.6	+20.8	+18.7	+2.76	+4.2
Paliperidone	+0.6-1.1	+1.4-2.6	-2.4 - +5.3	-1.5	-10.6 - +18.3	-6.4 – 10.5	-0.7 - +4.3	+3.3-4.6
Quetiapine	-	-	-	-	-	-	+3.2	+5
Risperidone	+0.7-2.2	+4.3-5.3	1.8-6.9	+4.4-5.5	-4.9 - +8.3	+19.9	+0.6-0.8	+2.8-4.1
Ziprasidone	+0.5	+0-1.4	-	-	-	-	-	-

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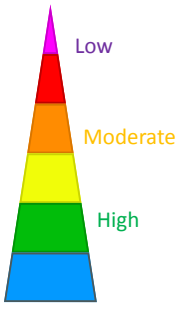
Adams KS. Toolbox: Metabolic Adverse Effects of Atypical Antipsychotics. *Ment Health Clin*. 2013;3(3):100. Available at: http://cpnp.org/resource/mhc/2013/09/toolbox-metabolic-adverse-effects-atypical-antipsychotics. Accessed May 20, 2014.

Relative Risk for Metabolic Syndrome



- Aripiprazole
- Ziprasidone
- Lurasidone
- Asenapine
- Iloperidone
- Paliperidone
- Risperidone
- Quetiapine
- Olanzapine
- Clozapine

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Monitoring Protocol for Metabolic Effects

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

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American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27: 596-601.

Treatment of Metabolic Effects

- Consider intervention if patient gains ≥ 5% of initial body weight
  - Diet and exercise
  - Switch to SGA with low metabolic liability
  - Medically treat metabolic side effects
  - Appetite suppressants or weight loss drugs
  - Metformin
  - Topiramate?

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American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27: 596-601.
Jarskog L, Hamer R, Catellier D, et al. Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder. *Am J Psychiatry* 2013; 170: 1032-1040.
Amiel J, Magurian C, Ganguli R, Newcomer J. Addressing cardiometabolic risk during treatment with antipsychotic medications. *Curr Opin Psychiatry* 2008; 21: 613-618.

Mortality in Elderly Patients with Dementia-Related Psychosis

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Mortality in Elderly Patients with Dementia- Related Psychosis

- Black box warning for all antipsychotics
  - Increased mortality in elderly patients with dementia-related psychosis
  - Most deaths are cardiovascular or infectious in nature
  - Prevention
    1. Determine underlying factors for behavior
    2. Eliminate precipitating factors
    3. Implement non-pharmacologic treatment
    4. Initiate pharmacotherapy if necessary
    5. Maintain lowest effective dose and reassess need for antipsychotic

Ihl R, Frolich L, Winblad B, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of Alzheimer's disease and other dementias. W J Biol Psychiatry 2011; 12: 2-32.
Jeste DV, Blazer D, Casey D et al. ACNP White Paper: Update on use of antipsychotics drugs in elderly persons with dementia. Neuropsychopharmacology 2008; 33: 957-970.
Thomas C. Antipsychotics in the Treatment of Neuropsychiatric Symptoms in Dementia. *Ment Health Clin.* 2012;1(11):12. Available at: http://cpnp.org/resource/mhc/2012/05/antipsychotics-treatment-neuropsychiatric-symptoms-dementia. Accessed May 20, 2014.

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Clozapine

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Clozapine – Highlighted Adverse Effects

- Agranulocytosis
- Seizures
- Myocarditis
- Cardiomyopthy
- Fever
- Gastrointestinal hypomotility
- Sialorrhea
- Enuresis
- Hepatic impairment

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Clozapine - Agranulocytosis

- Incidence: ~1%
- Onset: Usually within the first 8 weeks
- Risk factors
  - Elderly
  - Female gender
  - Cachectic
  - Between months 1 and 6 of therapy
- Symptoms
  - Sore throat
  - Fever
  - Erythema

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Clozaril® Package Insert. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/Clozaril.pdf. Accessed May 13, 2013.

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Clozapine - Agranulocytosis

- Prevention – Slowly titrate dose
  - Must restart titration is therapy is interrupted for ≥ 2 days

Day	Dose
1	12.5mg po in the AM and HS
2	25mg po in the AM
3	25mg po in the AM and HS
4	25mg PO in the AM and 50mg PO at HS
5	50mg PO in the AM and at HS
6	50mg PO in the AM and 75mg PO at HS
7	50mg PO in the AM and 100mg PO at HS
8	75mg PO in the AM and 100mg PO at HS
9	100mg PO in the AM and 100mg PO at HS
10	100mg PO in the AM and 125mg PO at HS
11	100mg PO in the AM and 150mg PO at HS
12	100mg PO in the AM and 175mg PO at HS
13 & 14	100mg PO in the AM and 200mg PO at HS

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- Prevention – WBC/ANC monitoring and registry

Hematologic Values for Monitoring	Frequency of WBC and ANC Monitoring
WBC ≥3500/mm^3 and ANC ≥ 2000/mm^3	• Do not initiate if WBC <3500/mm^3 or ANC <2000/mm^3 • Monitor weekly for the first 6 months • Monitor every 2 weeks from 6 months to 12 months of therapy • Monitor every 4 weeks after 12 months of therapy
WBC ≥ 3000-3500/mm^3 and/or ANC ≥ 1500-2000/mm^3	• May continue clozapine • Monitor twice weekly until WBC >3500/mm^3 and ANC >2000/mm^3
WBC ≥ 2000-3000/mm^3 and/or ANC ≥ 1000-1500/mm^3	• Hold clozapine • Monitor daily until WBC > 3000/mm^3 and ANC >1500/mm^3 • Monitor twice weekly WBC >3500/mm^3 and ANC >2000/mm^3 • May rechallenge when WBC >3500/mm^3 and ANC >2000/mm^3

WBC < 2000/mm^3 and/or ANC < 1000/mm^3	• Discontinue clozapine and do not rechallenge
	• Monitor until normal and for at least four weeks from day of discontinuation as follows:
	  • Daily until WBC > 3000/mm3 and ANC > 1500/mm3
	  • Twice weekly until WBC > 3500/mm3 and ANC > 2000/mm3
	  • Weekly after WBC > 3500/mm3

Clozaril® Package Insert. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/Clozaril.pdf. Accessed May 13, 2013.

Clozapine - Agranulocytosis

- Treatment
  - Discontinue clozapine
  - Supportive care
  - Antibiotics when indicated
  - Pharmacologic treatment
    - Granulocyte colony-stimulating factor (G-CSF)
    - Lithium

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Ojong M, Allen SN. Management and Prevention of Agranulocytosis in Patients Receiving Clozapine. *Ment Health Clin.* 2013;3(3):100. Available at: http://cpnp.org/resource/mhc/2013/09/management-and-prevention-agranulocytosis-patients-receiving-clozapine. Accessed May 13, 2014.
Gullion G, Yeh H. Treatment of clozapine-induced agranulocytosis with recombinant granulocyte colony-stimulating factor. *J Clin Psychiatry* 1994; 44: 401-405.
Paton C, Esop R. Managing clozapine-induced neutropenia with lithium. *Psychiatric Bulletin* 2005; 29: 186-188.

Clozapine - Seizures

- Dose related seizure activity
  - <300mg/day 1%
  - 300-600mg/day 2.7%
  - >600mg/day 4.4%
- Management
  - Reduce dose by 50%
  - Consider anticonvulsant if recurrent seizures

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Devinsky O, Honigfeld G, Patin J. Clozapine-related seizures. *Neurology* 1991; 41: 369-371.
Wong J and Delva N. Clozapine-Induced Seizures: Recognition and Treatment. Can J Psych 2007; 52(7):457-463.

Clozapine – Myocarditis and Cardiomyopathy

- Incidence: 0.015% to 0.188%
- Onset
  - Myocarditis – within 2 months
  - Cardiomyopathy – after 2 months
- Symptoms
  - Tachycardia -Fever
  - Dyspnea -Flu-like symptoms
  - Chest pain -Diarrhea/vomiting
  - Palpitations -Dysuria

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Merrill D, Dec G, Goff D. Adverse cardiac effects associated with clozapine. *J Clin Psychopharmacol* 2005; 25: 32-41.
Clozaril® Package Insert. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/Clozaril.pdf. Accessed May 13, 2013.
Ronaldson K, Fitzgerald P, Taylor A, et al. A new monitoring protocol for clozapine-induced myocarditits based on an analysis of 75 cases and 94 controls. *Aust NZ J Psychiatry* 2011: 45: 458-465.

Clozapine – Myocarditis and Cardiomyopathy

- Proposed monitoring
  - Vital signs, C-reactive protein (CRP), troponin
- Proposed management

Signs/Symptoms	Management Strategy
• Symptoms of unidentified illness OR • HR ≥ 120bpm or increased by >30bpm OR • CRP 50-100 mg/L OR • Troponin ≤ 2 ULN	• Continue clozapine • Check troponin and CRP daily until they normalize
• CRP > 100 mg/L OR • Troponin >2 ULN	• Discontinue clozapine • Obtain echocardiogram • Consult cardiology

Ronaldson K, Fitzgerald P, Taylor A, et al. A new monitoring protocol for clozapine-induced myocarditits based on an analysis of 75 cases and 94 controls. *Aust NZ J Psychiatry* 2011; 45: 458-465.

Clozapine - Fever

- Characteristics
  - Spiking with temperatures below 104°F
  - Lasts ~2.5 days
  - Not dose related
  - Associated with respiratory and GI symptoms
  - Occurs within the first month of therapy
- Management
  - Rule out NMS, agranulocytosis, and myocarditis
    - WBC with differential, troponin, CRP, urinalysis, blood cultures, creatine kinase
  - Acetaminophen

Lowe C, Grube R, Scates A. Characterization and clinical management of clozapine-induced fever. *Ann Pharmacother* 2007; 41: 1700-1704.
Nielsen J, Correll C, Manu P, Kane J. Termination of clozapine treatment due to medical reasons: When is it warranted and how can it be avoided. *J Clin Psychiatry* 2013; 74: 603-613.
Wong J and Delva N. Clozapine-Induced Seizures: Recognition and Treatment. Can J Psych 2007; 52(7):457-463.

Clozapine – GI Hypomotility

- May result in:
  - Constipation
  - Fecal impaction
  - Feculent vomiting
  - -Bowel necrosis
  - -Death
- Risk factors
  - High clozapine dose
  - Concomitant anticholinergic medications
  - Concomitant medical illness

Palmer S, McLean R, Ellis P, Harrison-Woolrych M. Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. J Clin Psychiatry 2008; 69:759-768.
Fowler JA. Clozapine-Induced Gastrointestinal Hypomotility: More Than Just Constipation. *Ment Health Clin.* 2011;1(5):29. Available at: http://cnp.org/resource/mhc/2011/11/clozapine-induced-gastrointestinal-hypomotility-more-just-constipation. Accessed May 15, 2014.

Clozapine – GI Hypomotility

- Symptoms
  - Abdominal pain
  - Abdominal distention
  - Constipation
  - Nausea
  - Vomiting
- Prevention/Treatment
  - No established guidelines
  - No clear consensus on best laxative
  - Try lifestyle modifications first
    - Exercise, dietary fiber, hydration

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Fowler JA. Clozapine-Induced Gastrointestinal Hypomotility: More Than Just Constipation. *Ment Health Clin*. 2011;1(5):29. Available at: http://cpnp.org/resource/mhc/2011/11/clozapine-induced-gastrointestinal-hypomotility-more-just-constipation. Accessed May 15, 2014.

Step	Management Strategies
1	• Fiber 2 scoops po BID • Docusate 100mg po BID
2	• Lactulose 15mL po BID • Docusate 100mg po BID
3	• Lactulose 30mL po BID • Docusate 200mg po BID
4	• Lactulose 45mL po BID • Docusate 200mg po BID
5	• Lactulose 45mL po BID • Docusate 200mg po BID • Bisacodyl 10mg po BID
6	• Polyethylene glycol 17grams po BID • Docusate 200mg po BID • Bisacodyl 20mg po BID • Milk of magnesia 30mL po daily
7	• Magnesium citrate 300mL po x 1 • Fleets enema BID x 3 days • Polyethylene glycol 4-8 liters per day until clean • Consult GI

Use milk of magnesia 30mL prn for steps 1-5

Hall B. Constipation Protocol. *Ment Health Clin* 2011. Available at: http://cpnp.org/sites/default/files/Constipation_Protocol.pdf. Accessed May 15, 2014.

Clozapine - Sialorrhea

- Mechanism
  - Agonist activity at muscarinic M4 receptors
  - Antagonist activity at alpha$_2$-adrenergic receptors
- Non-pharmacologic management
  - Chew sugarless gum
  - Cover pillow with a towel

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Lamba G and Ellison JM. Reducing clozapine-induced hypersalivation. *Current Psychiatry* 2011; 10:77-78.

Clozapine - Sialorrhea

- Pharmacologic treatment

Mechanism	Treatment Options
Muscarinic receptor antagonist (anticholinergic)	• Benztropine 0.5 to 6mg po daily • Trihexyphenidyl 2 to 15mg po daily • Amitriptyline 15 to 100 mg po daily • Scopolamine 1.5mg patch topically every 72 hrs • Atropine 1% eye drops – 1 to 6 drops sublingually daily • Ipratropium bromide nasal spray 0.03-0.06% - 2 to 6 sprays sublingually daily
Alpha$_2$-adrenergic receptor agonist	• Clonidine 0.05 to 0.1mg po daily or 0.1 to 0.2mg patch topically weekly • Guanfacine 1mg po daily
Inhibit acetylcholine release in salivary glands	• Botulinum toxin 150 units injected into parotid glands

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Reducing clozapine-induced hypersalivation. *Ment Health Clin*. 2011;1(5):12. Available at: http://cpnp.org/resource/mhc/2011/11/reducing-clozapine-induced-hypersalivation. Accessed May 16, 2014

Clozapine - Enuresis

- Non-pharmacologic management
  - Monitor fluid intake - Use toilet regularly
  - Avoid caffeine -Enuresis alarm
- Pharmacologic treatment
  - Desmopressin 0.2mg po QHS
  - Oxybutynin 5mg po daily
  - Imipramine 25mg po QHS

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Thiel J. Second Generation Antipsychotics & Nocturnal Enuresis in Children. *Ment Health Clin*. 2013;2(11):78. Available at: http://cpnp.org/resource/mhc/2013/05/second-generation-antipsychotics-nocturnal-enuresis-children. Accessed May 20, 2014.

Clozapine – Hepatic Impairment

- Ranges from LFT elevations to liver failure
- Occurs during first months of treatment
- Monitoring
  - Routine LFT measurement may lead to unnecessary discontinuation
  - Measure LFTs with clinical symptoms: jaundice, malaise, rash
  - Monitor more closely if LFTs are elevated
- Discontinue if LFTs >3 times the ULN

LFT = liver function test
ULN = upper limit of normal

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Nielsen J, Correll C, Manu P, Kane J. Termination of clozapine treatment due to medical reasons: When is it warranted and how can it be avoided. *J Clin Psychiatry* 2013; 74: 603-613.

Summary

- Antipsychotics are associated with multiple adverse effects that make adherence difficult for patients and monitoring/management difficult for providers.
- SGAs are often better tolerated than FGAs but are associated with more metabolic side effects.
- Clozapine demonstrates superior efficacy but has multiple adverse effects that limit its use.
- Pharmacists can play a large role in helping monitor and manage side effects associated with antipsychotics.

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