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UNDERSTANDING SIDE EFFECTS OF NEUROLEPTICS

Neuroleptics are major tranquilizers that reduce psychotic symptoms, such as hallucinations, delusions, and paranoia. All old, first generation neuroleptics, such as Haldol and Prolixin, work by blocking the dopamine system. New or second generation antipsychotics (SGA's), such as Risperdal and olanzapine, work by altering multiple transmitter systems, including serotonin and dopamine, while some neuroleptics also affect cholinergic and adrenergic systems (See Section 2, Tables 2-1 and 2-2). This mixture of neuro-chemical effects explains the range of side effects seen with each drug in patients. Medication toxicity is often dose-dependent and clinicians should use the minimum dose required to achieve therapeutic goals (See Section 2, Tables 2-3 and 2-4).

There are five major types of side effects with antipsychotic medications in the elderly: (1) motor side effects, (2) autonomic changes, (3) psychiatric complications, (4) medical complications, and (5) falls. The prescribing physician should be familiar with the side effects and the nursing staff should monitor residents for these changes.

1. MOTOR SIDE EFFECTS

Extra-pyramidal side effects (EPS) refer to dysfunction of the extra-pyramidal motor system that is affected by neuroleptics (See Table 3-1). Motor system abnormalities are common complications with old antipsychotics, as up to half of elders develop tardive dyskinesia after three years of continuous use. Newer medications produce far less EPS.

Table 3-1. Common Motor Side Effects of Antipsychotic Medications

Type	Symptoms	Monitoring Method
Tardive dyskinesia-	Abnormal involuntary movement	AIMS Scale
Parkinsonism-	Slow, stiffness of limbs and neck, rigid	Clinical Evaluation
Dystonia-	Spasm of axial muscles, such as neck	Clinical Evaluation
Akathisia-	Restlessness; especially in legs	Clinical Evaluation

The brain has two motor systems: (1) the voluntary or pyramidal motor system that moves your muscles under the direction of the mind, and (2) the extra-pyramidal systems that control muscle tone, posture and motor activity without conscious thought. The voluntary or pyramidal motor system is located in the cerebral cortex. The extra-pyramidal motor system, centered in the basal ganglia, relies on dopamine to maintain proper muscle tone and motor stability. All old, first generation antipsychotic medications block dopamine receptors, i.e., D₂ subtype. Cholinergic receptors in the extra-pyramidal system balance dopamine. Four major types of symptoms that occur from malfunction or imbalance of the extra-pyramidal motor systems are: (1) tardive dyskinesia, (2) dystonic reactions, (3) drug-induced Parkinsonism, and (4) akathisia. These symptoms should be familiar to the nursing staff, physician, and pharmacist.

(a). Tardive Dyskinesia (TD)

Tardive Dyskinesia is the most common side effect of long-term antipsychotic medication and occurs in one-third to two-thirds of elderly patients who use old medications for prolonged periods of time (See

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Table 3-2). Tardive dyskinesia is manifested by unwanted movements of the lips, face, hands, arms, and feet as well as rocking of the pelvis and jerking motions of the diaphragm. The risk of tardive dyskinesia is related to the type, duration, and dose of neuroleptic. Clinicians cannot predict the patient’s vulnerability to developing tardive dyskinesia although minorities and depressed women are at higher risk. There is no proven prevention or treatment for tardive dyskinesia except for neuroleptic dose reduction or changing to second generation antipsychotic medications. Anticholinergic agents, e.g., Cogentin and Artane, do not reduce tardive dyskinesia. Complications of tardive dyskinesia include patient discomfort and difficulty with motor tasks like eating or talking. About 5% of untreated elderly patients who are not receiving neuroleptics have spontaneous tardive dyskinesia. Staff should document pre-existing tardive dyskinesia to avoid patients or family blaming the medication for a natural disease. A quick, easy screening instrument, the Abnormal Involuntary Movement Scale (AIMS), can document most manifestations of tardive dyskinesia. The AIMS does not assess Parkinsonism.

Table 3-2. A Partial Summary of Common Side Effects Produced by Antipsychotic Medications in Persons with Dementia (45,46)

Category of Side Effect	Symptom of Side Effect	First Generation Antipsychotic Medications at Greater Risk	Risk Level	Second Generation Antipsychotic Medications at Greater Risk	Risk Level	Comments for All Types of Medications
COGNITIVE	Confusion	Low Potency, e.g., chlorpromazine	H	All equal	L	All medications at high dose
	Sedation	Low Potency, e.g., chlorpromazine	H	Quetiapine	L	All medications at high dose
NEUROLOGICAL	Parkinsonism	High potency haloperidol	H	Risperidone	L	Quetiapine quite low
	Dystonia	High potency haloperidol	H	All equal	R	
	Tardive Dyskinesia	All Medications	H	All equal	I	
	Akathisia	High potency, e.g., haloperidol	H	Aripiprazole	I	
METABOLIC	Obesity	Some reported in all medications	M	Olanzapine and Clozapine	M	Monitor Weight
	Hyperglycemia	Some reported in all medications	M	Olanzapine and Clozapine	M	Aripiprazole and ziprasidone with low risk
	Dyslipidemia	Some reported in all medications	I, M	Clozapine	M	Monitor lipids with all medications
AUTONOMIC	Orthostatic hypotension	Low potency, e.g., chlorpromazine	H	Quetiapine, Clozapine	L	---
	Tachycardia	Low potency	I	Clozapine	L	---
NEUROLEPTIC MALIGNANT SYNDROME	Hypertension, Tachycardia, Hyperthermia, Muscular Rigidity	All high potency, e.g., haloperidol	L	All equal	R	Rare in second generation medications
OTHER (drug-specific)	Cardiac QTc Prolongation	thioridazine	H	Ziprasidone	I	Most have minimal effect
	Agranulocytosis	All equal	L	Clozapine only	H	---
BLACK BOX	Black box for ↑ mortality in elderly with dementia	All Medications	L	All Medications	L	All drugs have a Black Box warning

H=high M=moderate L=low R=rare I=Inconclusive

(b). Drug-Induced Parkinsonism

Drug-induced Parkinsonism is sometimes called pseudo-parkinsonism, and includes stiffness, shuffling gait, masked faces, or difficulty in arising from sitting position. Pseudo-parkinsonism is caused by blockade of the dopamine receptor in contrast to Parkinson’s disease that is caused by death of dopamine producing neurons. One-third to one-half of elderly patients who receive old, first-generation antipsychotics will develop pseudo-parkinsonism. High-potency, old neuroleptics, e.g., Haldol and Prolixin, have the highest rate of parkinsonism. Treatment of parkinsonism includes using anticholinergic agents to correct the dopamine/acetylcholine imbalance in the basal ganglia, neuroleptic dose reduction or switching to second generation antipsychotic medications. Anticholinergic medications may increase confusion in many older dementia residents. Pseudo-parkinsonism is not measured by the AIMS and must be documented for OBRA compliance. Complications of psuedo-parkinsonism include patient

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discomfort, gait problems, falls, and weight loss. The slowness and reduced facial expressions may mimic depressive symptoms. Patients can be switched to new antipsychotics that produce less parkinsonism, e.g., olanzapine. Quetiapine has the lowest risk for producing pseudo-parkinsonism.

(c). Dystonia

Acute dystonic reactions involve spasm of neck, back and other axial skeletal musculature. These side effects are treated with anticholinergic agents, e.g., Cogentin or Benadryl. Although uncommon in the elderly, dystonic reactions are most common with use of high-potency, first generation neuroleptics in younger patients receiving antipsychotic medication for the first time. Some demented patients develop peculiar dystonic reactions with downward flexion of the neck, sometimes called the PISA syndrome.

(d). Akathisia

Akathisia is an inner sense of restlessness or an uncontrollable drive to move the extremities that resembles anxiety or agitation. Akathisia occurs in up to 40% of patients receiving high-potency older neuroleptics and frequently results in prescription of additional neuroleptic medication for “agitation”. The dose escalation only worsens the akathisia. Second generation medications produce far less akathisia, although aripiprazole may produce more than others. The cause of akathisia is unknown. Treatment for akathisia includes lowering neuroleptic dose, switching to low-potency neuroleptics, prescribing Inderal (10-30 mg b.i.d.), or low dose benzodiazepines, like Klonopin (0.25 mg po b.i.d). Anticholinergic agents have not been shown to be effective for akathisia. Complications of akathisia include non-compliance with medication and irritability, as well as inappropriate and excessive medication to treat misdiagnosed agitation.

(e). Combinations of Motor Symptoms

Patients may develop any or all of the motor side effects at any given time. After initiation of neuroleptic medication, the dystonic reaction and akathisia often develop first. In the subsequent weeks of treatment, patients may develop parkinsonism and finally, after months or years of medications, the patients develop tardive dyskinesia. Patients on high-potency medications, e.g., Haldol or Prolixin, are at higher risks to develop EPS although all neuroleptics can produce these symptoms. Patients can develop any combination of motor side effects. The treatment team should consider an AIMS (Abnormal Involuntary Movement Scale) for tardive dyskinesia, a brief motor assessment for parkinsonism, and a behavioral assessment for akathisia.

2. AUTONOMIC SIDE EFFECTS

Autonomic side effects of antipsychotic medications include orthostatic hypotension and tachycardia. Old, low-potency neuroleptics, e.g., Mellaril, Thorazine and Mobar, will lower blood pressure and raise heart rate secondary to effects on the autonomic system. Clozapine produces the worst orthostasis among the new medications. Many elderly persons have orthostatic hypotension and their supine/erect pressures should be evaluated prior to initiation of neuroleptics. Treatment for autonomic side effects includes switching to different antipsychotics or assessing other medications that lower blood pressure like antihypertensives. Complications of autonomic side effects include falls and light-headedness. Neuroleptics do not significantly impair respiratory function, except in high dosages or in combination with other sedating medications, like narcotics or benzodiazepines. Neuroleptics can cause constipation, urinary retention in males or sexual dysfunction. Most antipsychotics alter colonic function and increase risk for rectal impaction as well as producing constipation. Neuroleptics can occasionally produce hyperthermia.

Neuroleptic Malignant Syndrome (NMS) is a rare but sometimes fatal complication of neuroleptic usage. Symptoms include: (1) autonomic hyperactivity, (2) delirium, and (3) muscular rigidity. Patients may

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abruptly develop high fever, tachycardia, hypertension and frequently manifest an elevated white blood cell count. Motor symptoms include tremors and muscular rigidity. Central Nervous System (CNS) symptoms include delirium. Unrecognized NMS can be fatal. Clinicians often confuse NMS for sepsis; however, septic elderly patients rarely develop significant rigidity and muscle spasms resulting in elevated creatine phosphokinase (CPK). Treatment of NMS includes discontinuation of antipsychotic medication and supportive therapy until the episode passes. Patients can be restarted on antipsychotics if absolutely necessary and after consideration of alternative therapy but physicians should switch to a different medication and avoid first generation medications. NMS occurs with all antipsychotic medication but it is far more common with old, high-potency neuroleptics (See Table 3-2).

3. PSYCHIATRIC SIDE EFFECTS

The psychiatric side effects of antipsychotic medications include sedation, apathy, and confusion. Older, low-potency medications, e.g., Mellaril or Thorazine, have higher rates of sedation and confusion. Atypical antipsychotics can also sedate patients. Cognitive side effects include diminished activity and function in some demented residents. Interventions include switching neuroleptics or decreasing the dosage. Antipsychotics may slightly diminish cognitive function; however, appropriate doses rarely produce marked worsening of dementia (See Table 3-2).

4. MEDICATION-SPECIFIC MEDICAL COMPLICATIONS

All antipsychotic medications can produce medical complications including: 1) glucose and lipid intolerance, 2) cardiac conduction problems, 3) bone marrow alterations, and 4) alteration of metabolism of other medications. Many antipsychotic medications, e.g., Clozaril, Haldol, olanzapine, can elevate blood sugars (See Table 3-3). Never medicated, schizophrenic patients are at higher risk for diabetes (x2 to x4) when compared to normal individuals. Antipsychotic medications can be safe in diabetic patients; however, appropriate monitoring is required, e.g., blood sugar checks (See Table 3-4).

Some old and new medications can alter the QTc interval on EKG, which may increase the likelihood of fatal cardiac arrhythmias, i.e., torsades des pointes. EKG evaluation of QTc interval may be required to assure patient safety. The consulting pharmacist can advise you on the interaction of antipsychotic medications with the metabolism of other drugs.

Table 3-3. Medical Complications of Common Antipsychotics				Table 3-4 Basic Monitoring of Metabolic Effects In Persons Receiving Antipsychotic Medications							
Medications	Hyperglycemia	EKG Alterations (↑ QTc)	Elevated Lipids	Priority to therapy	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years ²	
Haldol	++	--	+	X					X		
Mellaril	++	+++	+	X	X	X	X	X			
Risperidone	++	--	--	X			X		X		
Quetiapine	++	+	--	X			X		X		
Olanzapine	+++	+	--	X			X			X	
Ziprasidone	+	++	--								
Aripiprazole	+	+	--	X							

+=reported in literature ++=multiple reports in literature +++=significant potential for complications

1. History for diabetes or hyperlipidemia¹
 2. If initial labs are negative²

Antipsychotic medications can produce weight loss in elderly patients through a variety of mechanisms. Excessively sedated patients will lose interest in eating. Drug-induced extra-pyramidal symptoms, including parkinsonism, i.e., stiffness and shaking may decrease the patient's ability to feed themselves. Patients who receive long-term antipsychotic medication may develop oral dyskinesia and dysarthria, i.e., oral coordination problems that lessen their ability to chew and swallow. Antipsychotic medications can

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also produce esophageal dysmotility and combinations of these oropharyngeal abnormalities can cause the patient to demonstrate choking behavior. The second generation antipsychotics produce fewer extrapyramidal symptoms and therefore are probably less problematic for feeding. Dietitians should be aware of the effect of psychotropic medications on nutrition. Anticholinergic medication produces dry mouth that can sometimes cause chewing and swallowing problems.

5. GAIT ABNORMALITIES AND FALLS

Falls are a common, serious problem in all elderly patients -- especially those with dementia. High-risk patients include those with a past history of falls or gait abnormalities. Antipsychotic medications can increase the fall risk by sedation, extrapyramidal symptoms, e.g., parkinsonism, orthostasis, or drug-drug interactions. Staff should monitor patients following initiation of neuroleptic medication and take appropriate actions to minimize the risk for accidental injury using falls evaluation, medication adjustment, physical therapy evaluation, etc.

6. POTENTIALLY LETHAL COMPLICATIONS OF ANTIPSYCHOTIC MEDICATIONS IN THE ELDERLY

A series of studies have examined the role of antipsychotic medications in producing dangerous complications in elderly patients with dementia. The common noteworthy side effects are listed in **Table 3-5**; although the data on many potential complications remains controversial. For instance, the long-term consequence of hyperprolactinemia in elderly patients is unknown.

Table 3-5. Important Side Effects Associated With Antipsychotic Medications In Older Patients with Dementia

Side Effect	Drug	Risk	Data	Ref.
Death	All	Slight	S	T1, T2
Stroke	All, but higher in old meds.	Slight	C	T3
Pulmonary embolism	All	Slight	C	T5
Hyperprolactinemia osteoporosis	Old > new	Unclear	C	T6, T7

Old=first generation S=substantial data C=controversial

7. FDA BLACK BOX ADVISORY FOR USE IN DEMENTIA

All antipsychotic medications carry a FDA Black Box advisory on increased mortality risk for a range of causes when these medications are used for treatment of behavioral problems in dementia. This risk is slight but significant (**See Table 3-6**). Patients are at greatest risk in the first six months of therapy. Families should be advised prior to initiation of therapy and documentation should confirm this advisory. Death is more likely during the initial six months of therapy (**See Tables 3-7**).

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Table 3-6. Meta-analysis of Relative Risk of Death in Elders with Dementia who Receive Antipsychotic Medication

- n= 15
 - t= 12 weeks
 - $N_1/N_2 = 3353 / 1757$
 - Death rate = 3.5% vs 2.3%
 - OR = 1.54
- N_1 = number receiving medication
 N_2 = number without medication

JAMA 2005;294(15):1934-42

Table 3-7. Relative Risk of Death in all Elderly During Initiation of Antipsychotic Medication Therapy

Days	Relative Risk (RR) for Death
180	1.37
<40	1.56
40 to 79	1.37
80 to 180	1.27

NEJM 2005;353:2335-2341

8. INFORMED CONSENT

All antipsychotic medications have powerful effects on the brain and other potentially significant side effects. These potential complications are summarized in Table 6. Demented patients often lack the ability to provide informed consent for psychotropic medications. Families should be consulted prior to initiation of antipsychotic therapy to explain the use of these powerful medications. Family education may lessen the likelihood that a patients' family will sue a facility over medication-induced complications like extra-pyramidal symptoms or falls.

The FDA Block Box warning must be explained to the responsible family and then documented in the record. Families can refuse the medications; however, the family then assumes responsibility for other adverse outcomes. A series of handouts are available to explain these complications to the family. Antipsychotic medications are considered to be a commonly standard of care for demented patients with psychosis or severe dangerous behaviors that fail to respond to behavioral interventions.

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