# Psychopharmacology in the Physically III Child

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#### Introduction

- High rates of comorbidity between childhood psychiatric and physical disordersensure that psychopharmacological issues willpresent in pediatric settings ranging from the primary care clinician's office to the critical care unit.
- Little literature is available to guide psychotropicprescribing in physically ill children and adolescents

# DEVELOPMENTAL PHARMACOKINETICS AND PHARMACODYNAMICS

#### **Pharmacokinetics**

- Absorption
- Distribution: With the exception of lithium, methylphenidate, and venlafaxine, psychoactive drugs are 80%–95% bound to proteins, either abumin or α1-glycoprotein. Divalproex sodium and barbiturates tend to bind to albumin, whereas the TCAs, amphetamines, and benzodiazepines bind to globulins.
- <u>Metabolism</u>: water-soluble drugs are readily excreted by the kidneys, but fatsoluble drugs tend to accumulate until they are converted into water-soluble compounds or metabolized by the liver into inactive compounds
- <u>Elimination</u>

# Hepatic Disease

Elevations in liver transaminases

Hepato
-toxic
drugs

hepatocellular damage low albumin, high prothrombin time (PT), and high ammonia without much elevation in liver transaminases

Cholestasis without much hepatocellular injury or elevation in ALT or AST in pediatric patients, assay of γ-glutamyl transpeptidase is a better indicator of cholestasis and should be measured along with bilirubin

# Hepatic Disease

Hepatic disease may affect drug distribution due to changes in hepatic blood flow, effects on protein binding, and changes in volume of distribution due to peritoneal ascites. The effects are reduced medication availability for metabolism and a resultant increase in serum drug levels

# Acute vs chronic hepatitis

In acute hepatitis → no need to modify dosing because metabolism is only minimally altered and the change is transient.

In chronic hepatitis and cirrhosis → need to modify medication dosages.

In chronic hepatitis and cirrhosis → need to modify medication dosages.



# Hepatic Disease

- Reduction of albumin and α1-glycoprotein in <u>infectious and</u> <u>inflammatory hepatic disease</u>
- Elevation of protein levels in <u>surgery</u>, trauma, or cirrhosis

# changing in unbound active drug

Elevation of bilirubin levels in <u>acute viral hepatitis and primary</u>
 <u>biliary cirrhosis</u>: Bilirubin has a strong affinity for albumin binding sites and may displace medications

# Hepatic Disease

- It is often necessary to use lower dosages of medications in patients with hepatic disease. Initial dosing of medications should be reduced in patients with hepatic disease, and titration should proceed slowly. For drugs that have significant hepatic metabolism, intravenous administration may be preferred.
- Some medications like risperidone needs dose adjustments in both renal and hepatic impairment.

Medication class	Impact of hepatic disease on drug dosing	Potential drug effect on liver function	
Antidepressants	Antidepressants that are metabolized by phase I hepatic oxidative metabolism require an approximately 50% dosage reduction.  Doses of bupropion should not exceed 75 mg/day in patients with cirrhosis.  Trazodone requires dosage reduction due to prolonged clearance of trazodone in patients with hepatic disease.	TCAs may exacerbate hepatic encephalopathy by anticholinergic action.  Nefazodone use is contraindicated in hepatic disease.  Minor elevations in transaminases are common and usually benign.  Sertraline's short half-life and less potent inhibition of CYP 2D6 make it the preferred SSRI in hepatic disease.	
Antipsychotics	Atypical antipsychotics that are metabolized by phase I hepatic oxidative metabolism require dosage reduction.	Chlorpromazine is associated with intrahepatic cholestasis and obstructive hepatic disease.  Low-potency drugs may precipitate hepatic encephalopathy in patients with cirrhosis.  Discontinue clozapine in patients with marked transaminase elevations or jaundice.  Activate Windows	

# **Medication use in hepatic disease**

Medication class	Impact of hepatic disease on drug dosing	Potential drug effect on liver function
Anxiolytics/hypnotics	Benzodiazepine half-lives are increased in hepatic disease. Lorazepam, oxazepam, and temazepam require no dosage adjustment in hepatic disease because they are metabolized by phase II hepatic oxidative metabolism. Zaleplon and zolpidem require dosage reduction.	Avoid use of benzodiazepines in patients at risk of hepatic encephalopathy.
Mood stabilizers	Carbamazepine, divalproex, lamotrigine, and topiramate require dosage reduction and close monitoring.  No dosage adjustment is required for gabapentin or lithium.	Divalproex sodium is associated with hepatic failure in 1 in 40,000 cases. Carbamazepine is associated with hepatitis. Carbamazepine and valproic acid are contraindicated in patients with preexisting hepatic disease.
ADHD medication treatments	Atomoxetine requires 25%–50% reduction in dosage.	

# **Medication use in hepatic disease**

- Gastrointestinal disease primarily affects drug absorption: diseases affecting gastrointestinal motility, surgical alteration of the gastrointestinal tract (e.g., bypass surgery, G-tube andJ-tube placement), short bowel syndrome, and celiac disease.
- Any conditions that divert blood away from the gastrointestinal tract, for example, congestive heart failure or shock, may also affect absorption.
- Administration of antacid medications may similarly reduce gastric absorption.

- Gastric motility may be affected by a number of general medical conditions and by specific medications. For example, gastric motility is delayed in patients with diabetes mellitus, gastritis, and pyloric stenosis. Anticholinergic medications delay gastric motility.
- Slowed gastrointestinal motility results in better absorption of poorly soluble drugs, and viceversa.
- Enteric-coated preparations of medications are likely to have increased rates of drug absorption patients with reduced gastric acidity.

- Orally administered drugs may be poorly absorbed in patients with malabsorption syndromes. If absorptionis an issue, liquid formulations of drugs and alternative routes of administration, including sublingual, intramuscular, and intravenous, may be preferred.
- Gastrointestinal disease affecting the large intestines generally has little effect because most medications are absorbed more proximally.

- SSRIs increase gastric motility and may cause diarrhea
- SSRIs have the potential to increase the risk of gastrointestinal bleeding, especially when coadministered with NSAIDs
- Using extended- or controlled-release preparations of medications may reducegastrointestinal side effects, particularly where gastric distress is related to rapid increases in plasma drug concentrations.

 Renal insufficiency may result in decreased drug absorption from the small intestine due to the gastric-alkalinizing effects of increased ammonia levels that develop in the presence of excess urea

- Renal insufficiency may increase the volume of distribution of water-soluble or protein-bound drugs with a consequent reduction in plasma levels.
- Plasma protein binding may be reduced in nephrotic syndrome as a result of decreases in albumin.
- Displacement of highly protein-bound drugs may result in increased availability of these drugs for renal filtration and excretion

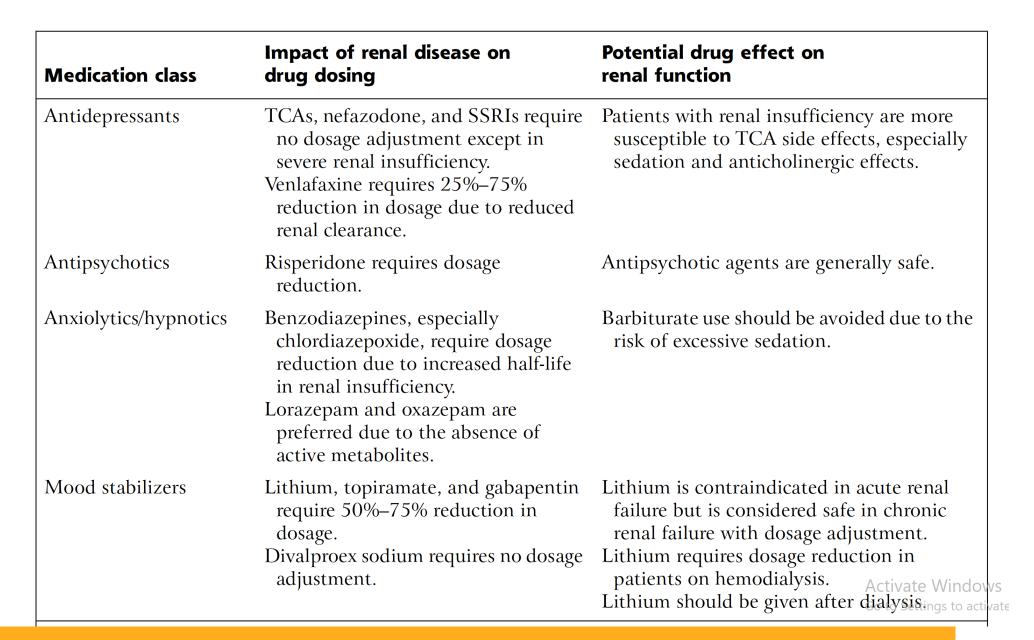
Renal excretion or clearance is reduced in renal failure and is significant for drugs that are cleared primarily by renal excretion.
 Renal blood flow may be altered by changes in glomerular vasculature, severe dehydration, and conditions affecting other organ systems (e.g., cirrhosis)

- In general, initial dosages of medications should be reduced or dosing intervals lengthened in patients with renal failure.
- with the exception of lithium and gabapentin, psychotropic medications do not require significant dosing adjustments in patients with renal failure

- Lithium may be given to renal transplant recipients; however, cyclosporin may elevate serum lithium levels by decreasing lithium excretion, necessitating a dosage adjustment.
- Patients with renal failure and those on dialysis appear to be more sensitive to TCA side effects, possibly due to the accumulation of hydroxylated tricyclic metabolites

# Hemodialysis

- Most psychotropic medications are highly protein bound and not significantly cleared by dialysis
- lithium, gabapentin, and topiramate are completely removed by dialysis, with the common practice being to administer these medications after dialysis
- Drugs with a narrow therapeutic index should be avoided wherever possible in dialysis patients
- Dialysis → risk of dehydration → neuroleptic malignant syndrome being more likely



#### Medication use in renal disease

#### Cardiac disease

- Cardiac disease may influence the pharmacokineticsof medications. For example, congestive heart failure may result in decreased perfusion of drug absorption sites both in the gastrointestinal tract and in skeletal muscle, affecting drugs given both orally and by intramuscular injection
- Sympathetic activity may redistribute blood flow to the brain and heart, reducing perfusion of the liver, kidneys, and other organs, with the potential to affect drug distribution

#### Cardiac disease

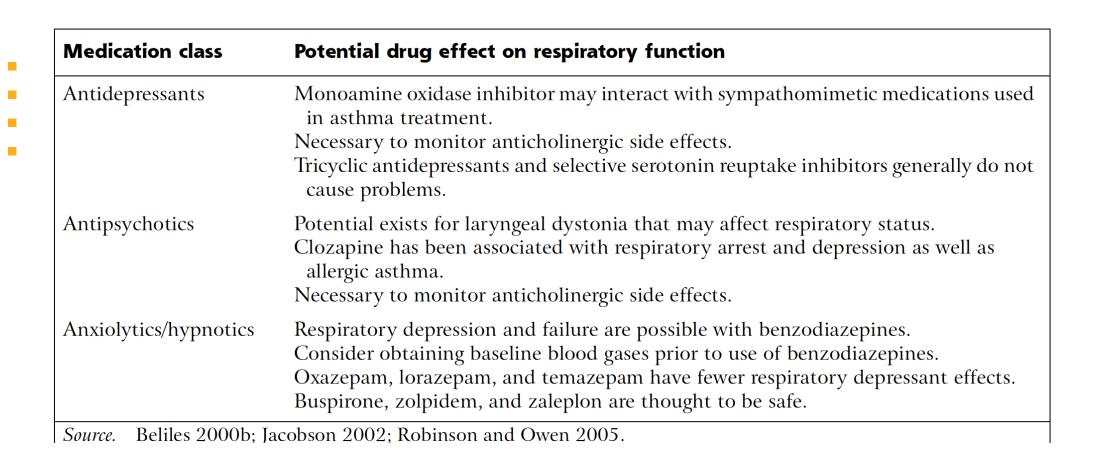
- Orthostatic hypotension: TCAs, Trazodone
- SSRIs and bupropion are preferred as antidepressant agents in patients with cardiac disease.
- Conduction disturbances: Thioridazine and pimozide
- Arrhythmias: haloperidol, Quinidine-like effects of TCAs, antipsychotic agents may lead to prolongation of the QTc
- Patients with Wolff-Parkinson-White syndrome who have a short P-R interval (less than 0.12 seconds) and widened QRS interval associated with paroxysmal tachycardia are at high risk of life-threatening ventricular tachycardia that **may be exacerbated by the use of a TCA**

# disease cardiac use Medication

Medication class	Potential drug effect on cardiac function	
Tricyclic antidepressants (TCAs)	Increased cardiac morbidity and mortality due to arrhythmias.  Side effects in healthy individuals are limited to orthostatic hypotension.  Nortriptyline is preferred TCA due to lower likelihood of hypotension.  Potential for delayed cardiac conduction, increased heart rate, and heart block.  Prolonged P-R interval, QRS duration, and QTc interval.  Potential for torsades de pointes in persons with preexisting conduction disturbances.  Potential for ventricular tachycardia or fibrillation in Wolff-Parkinson-White syndrome.	
Selective serotonin reuptake inhibitors	Isolated reports of bradycardia and atrial fibrillation with fluoxetine.  Citalopram and escitalopram are not recommended in cardiac disease involving prolonged conduction times.	
Antipsychotics	Orthostatic hypotension is associated with use of clozapine, quetiapine, and low-potency antipsychotics. Pimozide, thioridazine, mesoridazine, droperidol, sertindole, ziprasidone, and high-dosage intravenous haloperidol carry risk of prolonged QTc interval.	
Anxiolytics/hypnotics	Benzodiazepines and buspirone are thought to be free from cardiovascular effects.	
Mood stabilizers	Lithium may cause sinus node dysfunction or first-degree atrioventricular block.  Carbamazepine is associated with atrioventricular conduction disturbances.  Lamotrigine is associated with QTc interval prolongation.  Divalproex sodium is thought safe.	
Psychostimulants	U.S. Food and Drug Administration warns against use of psychostimulants in patients with structural and other serious cardiac disorders. Although methylphenidate and amphetamines may be safe at low dosages, consultation with a cardiologist is recommended.	

# Respiratory Disease

- Benzodiazepines → risk of respiratory depression → concern in patients with pulmonary disease
- SSRIs and buspirone are **good alternative** medications for thetreatment of anxiety.
- Consideration should be given to possible airway compromise due to acute laryngospasm when dopamine-blocking agents are used.
- Nonselective  $\beta 1/\beta 2$ -adrenergic blockers such as propranolol can precipitate bronchial constriction and are contraindicated in persons with asthma.



### Medication use in respiratory disease

# Neurological Disease

- Central nervous system side effects of psychotropic medications can mimic the signs and symptoms of neurological disorders, confound diagnostic assessment, and influence treatment decisions
- Care must be taken to differentiate symptoms of a primary neurological disorder and medication side effects when psychopharmacological treatment occurs in the presence of neurological disease



# Epilepsy

- Comorbidity rates of psychiatric disorders and epilepsy have been estimated to run as high as 60%, with ADHD, depression, and anxiety being the most commonly associated comorbidities.
- Psychotropic medications can be used safely in the presence of epilepsy following consideration of potential interactions between the psychotropic agent of choice, the seizure disorder, and the indicated anticonvulsant treatment.

# **Epilepsy**

- Antipsychotics are known to lower seizure threshold, with low-potency agents and clozapine possessing more proconvulsant properties.
- Stimulants are purported to be safe and effective for many patients to treat ADHD in the context of epilepsy; however, they can also exacerbate seizures in some patients. Methylphenidate: Caution
- Clomipramine, maprotiline, and bupropion possess significant
   seizure-inducing properties and should be avoided when the risk of
   seizures is present

# Acute Agitation

- Unfortunately, there are no published studies that compare psychopharmacological treatments of the acutely agitated child seen in emergency department setting
- Most common categories of psychiatric medications include antipsychotics and benzodiazepines, either alone or in combination.

# Benzodiazepines

- Although the benzodiazepines differ in potency, speed of onset of action, and route of administra-tion, there are no data to support the use of one spe-cific benzodiazepine over another in terms of ther-apeutic efficacy.
- Lorazepam is the most frequently used benzodiazepine for treatment of acute agitation, and one study in adults has shown that it had comparable efficacy with intramuscular haloperidol.
- Intramuscular midazolam also has been used to treat acute agitation with superior results compared with both haloperidol and lorazepam, although midazolam's short duration of action may limit its utility.
- Limitations on the use of benzodiazepines inpediatric patients may occur as a result
   of both excessive sedation and behavioral or emotional disinhibition.

# Antipsychotic Agents

- Antipsychotic agents are widely used in the treatment of <u>acute agitation</u>, <u>delirium</u>, <u>mania</u>, and <u>psychosis</u>.
- Traditionally, haloperidol (IV/ Intra nasal) has been one of the most commonly used antipsychotic agents.
- Generally, current adult emergency department practices tend to favor risperidone or olanzapine for patients who are willing to take oral medications, due to the more favorable side-effect profile.
- For patients requiring intramuscular administration, both ziprasidone and olanzapine have become widely acceptable alternatives to the use of haloperidol.

# Anxiety

- ✓ Generalized anxiety disorder (GAD)
- ✓ Separation anxiety disorder
- ✓ Posttraumatic stress disorder (PTSD)
- ✓ Specific phobias
- ✓ Anxieties related to the medical treatment environment

# Benzodiazepines

- there are very few data for children.
- alprazolam and clonazepam for children with <u>school refusal</u>, <u>GAD</u>, and <u>separation</u> anxiety disorder.
- Benzodiazepine use however, may be indicated in specific situations in which there are concomitant physical symptoms such as nausea or muscle spasms that may be responsive to this category of medications.
- side effects of benzodiazepines include sedation, disinhibition, and behavioral dyscontrol.

# **Antidepressants**

- GAD.....sertraline, fluoxetine (alternative: venlafaxine)
- Social phobia.....paroxetine , fluoxetine
- Separation anxiety disorder......fluoxetine
- PTSD.....TCA

# **Propranolol**

• There are some data to support the use of propranolol in both adult and pediatric patients with PTSD.

#### Buspirone

- Buspirone is an azapirone anxiolytic with a primary indication for chronic generalized anxiety.
- It has little potential for abuse or physical dependency and is considered an agent of choice when risk for substance abuse accompanies a need to treat anxiety.
- The anxiolytic effects of Buspirone can take weeks to be felt, thus requiring adjunctive treatments when acute anxiety must be addressed.
- Buspirone metabolism and clearance are decreased in hepatic and renal disease.

## Depression

✓ Treatment for moderate to severe depression or impaired function.

#### **Antidepressants**

- SSRIs have become choice for depression due to their effectiveness, safety, and sideeffect profiles
- For patients on multiple medications for their physical illness, where drug interactions are a concern, **escitalopram** may have benefits over other SSRIs commonly recognized as first-line agents, including fluoxetine.
- studies of the TCAs have shown no greater efficacy compared with placebo, and they are not currently recommended due to their unfavorable side-effect profile and risk of lethality following overdose.
- Bupropion for children with comorbid major depression and ADHD.
- in children with chronic pain syndromes, venlafaxine may have dual benefits in terms
- of its demonstrated antidepressant and analgesic actions.

#### **Psychostimulants**

- including dexamphetamine, methylphenidate, methamphetamine, pemoline, and modafinil
- The available literature, primarily from studies with adults, suggests that psychostimulants have useful antidepressant properties and may be used as adjuncts to standard antidepressants in refractory depression, particularly in physically ill patients or those with terminal illness.
- Three studies suggested that psychostimulants used as monotherapy significantly reduced short-term depressive symptoms as well as symptoms of fatigue.

### Fatigue

✓ The prevalence of cancer-related fatigue ranges from 4% to 91%

#### **Psychostimulants**

 the findings were significant enough to support the use of methylphenidate, dexmethylphenidate and modafinil to treat HIV and cancer-related fatigue. (in adults)

 Side effects of psychostimulants, including irritability, anorexia, insomnia, labile mood, nausea, and tachycardia

#### **Antidepressants**

 Paroxetine may show benefit for fatigue, but primarily when it is a symptom of clinical depression.

 Bupropion which has psychostimulant-like effects, showing benefits for the treatment of cancer-related fatigue.

#### Insomnia

- ✓ Medical ?
- ✓ Complication of treatment ?

- 1) Non-pharmacological and sleep hygiene
- 2) Pharmacological approaches

#### Phamacological approaches:

#### 1-Diphenhydramine

its usefulness in decreasing both sleep latency times and nighttime awakenings.

Infants ages 6-15 months found no benefit.

#### 5-Benzodiazepines

not recommended for children with insomnia unless they are being used concomitantly for other primary psychiatric conditions or as part of treatment for other physical symptoms, such as nausea.

#### 2-Chloral Hydrate

Respiratory compromise in children with obstructive sleep apnea, wheezing, brain stem disorder and in overdose.

#### 3-Melatonin

a reduction in initial insomnia and enhanced total sleep time.

Not recommend in immunosuppress patients.

#### 4-trazodone

antidepressant with sedating properties

#### 7-Mirtazapine

there have been no studies in pediatric patients but it may be a particularly effective treatment option in physically ill patients who have disease- or treatment related physical symptoms, including poor appetite and pruritus

#### 6-Nonbenzodiazepine Hypnotics

(zolpidem, eszopiclone, zaleplon)

in children is considered "off label," and therefore no official dosing guidelines are available.

# PSYCHIATRIC MEDICATIONS USED IN THE TREATMENT OF PAIN

migraine, peripheral neuropathies, phantom limb pain, fibromyalgia, and pain related to the invasion of nerves by tumors

#### **Antidepressants**

✓ TCAs (The effect of TCAs on pain reduction and improved sleep is more rapid (3–7 days) and occurs at lower dosages (0.1–0.2 mg/kg/day) than is expected in the treatment of depression).

Where sedation is problematic or the patient is particularly susceptible to anticholinergic side effects, **imipramine** and **nortriptyline** are alternate considerations.

- ✓ SNRIs (at least as effective as the TCAs with fewer side effects)
- ✓ SSRIs
- Mirtazapine

#### **Anticonvulsants**

- Carbamazepine, clonazepam, and phenytoin have been widely used in the treatment of migraine and neuropathic pain.
- Divalproex sodium has been used for migraine prophylaxis.
- Topiramate and Lamotrigine have been used for diabetic neuropathy and trigeminal neuralgia.
- Carbamazepine and Phenytoin have been helpful in managing cancer pain with dysesthetic components.

Start slowly and increased gradually

#### **Antipsychotic Agents**

• The phenothiazines are the most commonly employ antipsychotics for analgesia.

• Chlorpromazine and Haloperidol have been used to treat nausea associated with the use of opiates or pain.

#### Benzodiazepines

• they do decrease affective responses to acute pain and they may produce extended relief in chronic pain due to musculoskeletal disorders, perhaps as a result of their muscle-relaxant properties.

• Short-term use of benzodiazepines can be effective in postoperative pain and sickle cell crises.

#### **Antihistaminic Agents**

• Hydroxyzine is an antihistaminic agent with proven analgesic properties at high dosages (in adjunct with opioids).

#### **Psychostimulants**

• Methylphenidate and Dextroamphetamine have been found to be safe and effective adjuncts to opiate analgesia and have also been used in the treatment of spasmodic torticollis, spastic colon, and headaches (to reduce the dose of narcotics without diminution of their analgesic effect).

# MEDICATION CONSIDERATIONS IN THE CONTEXT OF **SURGERY** AND **ANESTHESIA**

They recommended consideration of the extent of the surgery, the patient's physical state, potential drug interactions, effects and side effects of psychotropic medications, risk of withdrawal symptoms, and risk of psychiatric recurrence or relapse when medication treatment is interrupted.







# NEUROPSYCHIATRIC SIDE EFFECTS & CATATONIA

#### Neuroleptic Malignant Syndrome

- Rare and potentially fatal.
- Prevalence: 0.2-1%
- With dopamine blocking agents
- Malnutrition and dehydration in the context of an organic brain syndrome and simultaneous treatment with lithium and antipsychotic agents may increase the risk.
- Dx : heatstroke, malignant hyperthermia, lethal catatonia, serotonin syndrome, anticholinergic toxicity

#### **Serotonin Syndrome**

- Caused by SSRIs, monoamine oxidase inhibitors (MAOIs), valproate, dextromethorphan, lithium, meperidine, and fentanyl.
- Serotonin syndrome is often self-limited and may resolve spontaneously after discontinuation of the serotonergic agents.
- Dx : NMS, anticholinergic toxicity

#### **Anticholinergic Syndrome**

- Central anticholinergic side effects include agitation or lethargy, hallucinations, respiratory depression, and coma.
- Peripheral: include tachycardia, mydriasis and associated blurring of vision, flushed skin, increased temperature, decreased or absent bowel sounds, urinary retention, and dry mucous membranes.
- ✓ **Physostigmine** may be used to control agitation and delirium symptoms.
- Symptoms of agitation associated with ACS may also be treated with benzodiazepines.

### Manifestations of severe serotonin, neuroleptic malignant, and anticholinergic syndromes

	Serotonin syndrome	Neuroleptic malignant syndrome	Anticholinergic syndrome
Medication	Serotonin agents	Dopamine antagonists	Anticholinergic agents
Time for condition to develop	<12 hours	1–3 days	<12 hours
Mental status	Agitation, coma	Alertness, stupor, mutism, coma	Agitated delirium
Vital signs	Hypertension	Hypertension	Hypertension
	Tachycardia	Tachycardia	Tachycardia
	Tachypnea	Tachypnea	Tachypnea
	>41.1°C	>41.1°C	<38.8°C
Pupils	Mydriasis	Normal	Mydriasis
Mucosa	Sialorrhea	Sialorrhea	Dry
Skin	Diaphoresis	Diaphoresis, pallor	Erythema
Neuromuscular tone	Increased (lower extremities)	"Lead-pipe" rigidity (all muscle groups)	Normal
Reflexes	Hyperreflexia	Bradyreflexia	Normal

#### Catatonia

- relatively rare
- primary psychiatric illness or secondary to physical illness or medication effects?
- incidence: 0.16 case per million in the pediatric population.
- Core features: mutism, stupor, motoric immobility, negativism, excitement, catalepsy, and posturing.
- Malignant catatonia ?
- Lethal catatonia?
- Dx: Parkinson's
- disease, stroke, malignant hyperthermia, and selective mutism, Hyperkinetic movement
- disorders (Tourette's syndrome and cerebral palsy), and hypokinetic movement disorders
  - (Huntington's disease and Wilson's disease).

#### Management of Catatonia

- 1) Treatment of any identifiable underlying etiological factors and maintenance of nutrition and homeostasis.
- 2) Benzodiazepines, including lorazepam, have been found to be beneficial, in particular for the motor and speech symptoms.
- 3) Other pharmacological agents include carbamazepine and bromocriptine. There are isolated case reports of the use of atypical neuroleptic medications (e.g., risperidone) to treat haloperidolinduced catalepsy.
- 4) Electroconvulsive therapy is cited as the single most efficacious treatment, including for pediatric patients.
- In severe cases, dantrolene has been administered with electroconvulsive therapy to control the
   signs of hyperthermia and muscular rigidity.

#### Causes of secondary catatonia

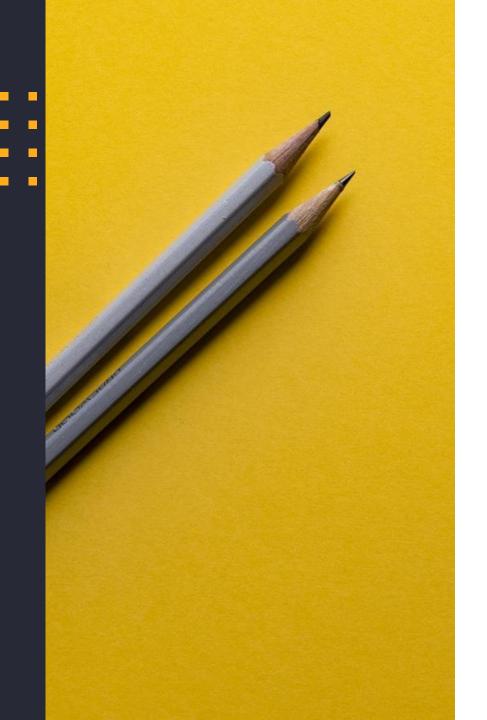
Neurological causes		
Angioma		
Basilar artery thrombosis		
Bilateral infarction of the anterior cingulate gyrus		
Bilateral infarction of the temporal lobes		
Cerebral anoxia		
Closed head injury		
Encephalitis or other central nervous system infection		
Glioma		
HIV encephalopathy		
Normal-pressure hydrocephalus		
Seizure disorders		
Surgery involving the hypothalamus		
Other medical causes		

Addison's disease

Cushing's disease

Bacterial sepsis

Hyperthyroidism Malaria Postoperative states Systemic lupus erythematosus Typhoid fever Uremia Viral hepatitis Vitamin deficiencies Medications and toxins Antipsychotic agents Corticosteroids Cyclobenzaprine 3,4-Methylenedioxymethamphetamine (MDMA) Phencyclidine (PCP) Sedative-hypnotic withdrawal Tetraethyl lead poisoning



# Thanks!

Any questions?

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