PainWeek®

It's a Pharmaceutical Festival!
Doing a deep Dive Into Drug Interactions!

Part 1

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Disclosure

- Nothing (so boring)

N O T H I N G

Learning Objectives

- At the conclusion of this presentation the participant will be to:
  - Define “drug interaction” and differentate between a pharmacokinetic and pharmacodynamic drug interaction.
  - Describe risk assessment, diagnosis and management of six common clinical syndromes caused by pharmacodynamic drug interactions.
  - Describe three example of a pharmacokinetic drug interaction.

Outline

- Drug interaction, pharmacodynamic, pharmacokinetic
- Anticholinergic, constipation, seizures, serotonin syndrome, CNS depression, QTc prolongation
- Pharmacokinetic drug interactions – absorption, distribution, **metabolism**, excretion

Drug Interactions

- Medications are used extensively to palliate symptoms
  - Patients with advanced illness take an average of 5 medications (range 0-13)
  - Increases risk for drug interactions
  - Risk increased due to patient fragility, co-morbid conditions, increased age

Defining a Drug Interaction

- "A measurable modification (in magnitude or duration) of the action of one drug by prior or concomitant administration of another substance."
  - Drug-drug (Rx, OTC, herbal)
  - Drug-food, drug-alcohol
  - Drug-lab, drug-disease, drug-chemical

Drug Interactions

- Pharmacodynamics
  - The study of the action and effects of medications on physiologic function
- Pharmacodynamic drug interactions can be:
  - Additive or synergistic (two or more analgesics)
  - Antagonistic (dexamethasone and glyburide)

Pharmacodynamic Drug Interactions in Palliative Care

- Anticholinergic effects
- Constipation
- Lowered seizure threshold
- Serotonin syndrome
- CNS depression
- QTc prolongation

Muscarinic Receptor Subtypes

Receptor Subtype	CNS Distribution	Non-CNS Location
M_1	Cerebral cortex, hippocampus, neostriatum	Salivary glands, sympathetic ganglia
M_2	Throughout the brain	Smooth muscle, cardiac muscle
M_3	Low levels throughout brain	Smooth muscle, salivary glands, eyes
M_4	Abundant in neostriatum, cortex and hippocampus	Salivary glands
M_5	Projection neurons of substantia nigra pars, compacta and ventral tegmental area and hippocampus	Eyes (ciliary muscle)

Antimuscarinic Pharmacologic Effects: Peripheral

- Dry eyes
- Urinary retention
- Dry mouth
- Constipation
- Heat intolerance
- Tachycardia
- Decreased sweating

Carnahan et al. J Clin Pharmacol 2006;46:1481-1486

Antimuscarinic Pharmacologic Effects: Central

- Forgetfulness
- Agitation / confusion
- Delirium
- Paranoia
- Dizziness
- Drowsiness
- Falls

Carnahan et al. J Clin Pharmacol 2006;46:1481-1486

Evoking Antimuscarinic Effects

Overactive bladder	• Oxybutynin (Ditropan) • Tolterodine (Detrol) • Trospium (Sanctura) • Solifenacin (Vesicare) • Darifenacin (Enablex)
Anticholinergic / Antiparkinson's	• Trihexyphenidyl (Artane) • Benztropine (Cogentin) • Amantadine (Symmetrel)
Antivertigo / antiemetic	• Meclizine (Antivert) • Scopolamine (TransDerm Scop)

Evoking Antimuscarinic Effects

Gastrointestinal / Antispasmodics	• Diphenoxylate (Lomotil) • Dicyclomine (Bentyl)
Antisecretory / Drying Agents	• Hyoscyamine (Levsin) • Atropine (ophthalmic given PO)
Bronchospasm	• Ipratroptium (Atrovent) • Tiotroptium (Spiriva)

Evoking Antimuscarinic Effects

Sedating Antihistamines	• Diphenhydramine (Benadryl) • Hydroxyzine (Vistaril)
Tricyclic Antidepressants	• Amitriptyline (Elavil) • Nortriptyline (Pamelor) • Desipramine (Norpramin) • Doxepin (Sinequan)
Antipsychotic Agents	• Chlorpromazine (Thorazine) • Olanzapine (Zyprexa) • Clozapine (Clozaril) • Thioridazine (Mellaril)

Evoking Antimuscarinic Effects

Phenothiazines	• Prochlorperazine (Compazine) • Promethazine (Phenergan)
Antiarrhythmic Agents	• Disopyramide (Norpace)
Muscle relaxants	• Cyclobenzaprine (Flexeril) • Orphenadrine (Norflex)

Cognitive Impact of Anticholinergics

- 27 studies reviewed
- Consistent correlation seen between SAA and worsening performance on cognitive testing
  - Acute (delirium)
  - Chronic (mild cognitive impairment)
- Deficits in processing, speed, psychomotor performance, concentration/attention, problem solving and language skills

Campbell et al. Clinical Interventions in Aging 2009;4:225-233.

Cognitive Impact of Anticholinergics

- Delirium - identified by disorientation, altered consciousness, disorganized thinking, fluctuating alertness
- Variable deficits in recalls identified
- Minimal changes in global measures of cognitive functioning with exposure to anticholinergics

Campbell et al. Clinical Interventions in Aging 2009;4:225-233.

Anticholinergics Conclusion

- Patients at risk
  - Older adults, advanced disease, fall risk
  - BPH, asthma
  - Taking other medications with similar adverse effects
  - Alzheimer's disease and other dementias (anticholinergics antagonize cholinesterase inhibitors)
- Consider non-drug interventions

Constipation

- 40% of all ADR affect the GI tract
- Drug-induced constipation occurs at therapeutics doses of drugs and is dose-related
- Medications most likely to cause constipation include:
  - Antispasmodics (11.6%)
  - Antihistamines (9.2%)
  - Antidepressants (8.2%)
  - Diuretics (5.6%)
  - Aluminum antacids (3.0%)
  - Opioids (2.6%)

Talley NJ et al. Amer J Gastroenterology 2003;98:1107-1111.

Drug-Induced Constipation

Therapeutic Category	Examples
Analgesics	Opioids (morphine), NSAIDs (ibuprofen)
Anticholinergics	TCA, antipsychotics (haloperidol), antiparkinsonian agents (benztropine), antihistamines (H1; diphenhydramine), antispasmodics (dicyclomine)
Cation-containing agents	Aluminum (antacids, sucralfate), calcium (antacids, supplements), bismuth, iron supplements, lithium
Chemotherapy	Vinca alkaloids (vincristine), alkylating agents (cyclophosphamide)
Antihypertensives	CCB (verapamil, nifedipine), diuretics (furosemide), centrally-acting (clonidine), antiarrhythmics (amiodarone), beta blockers (atenolol)
Bile acid sequestrants	Colestyramine, colestipol
$5HT_3$-receptor antagonists	Ondansetron
Laxatives	Chronic abuse

Branch RL, Butt TF. Drug-induced constipation. Adverse Drug Reaction Bulletin 2009;257.

Drug-Induced Constipation

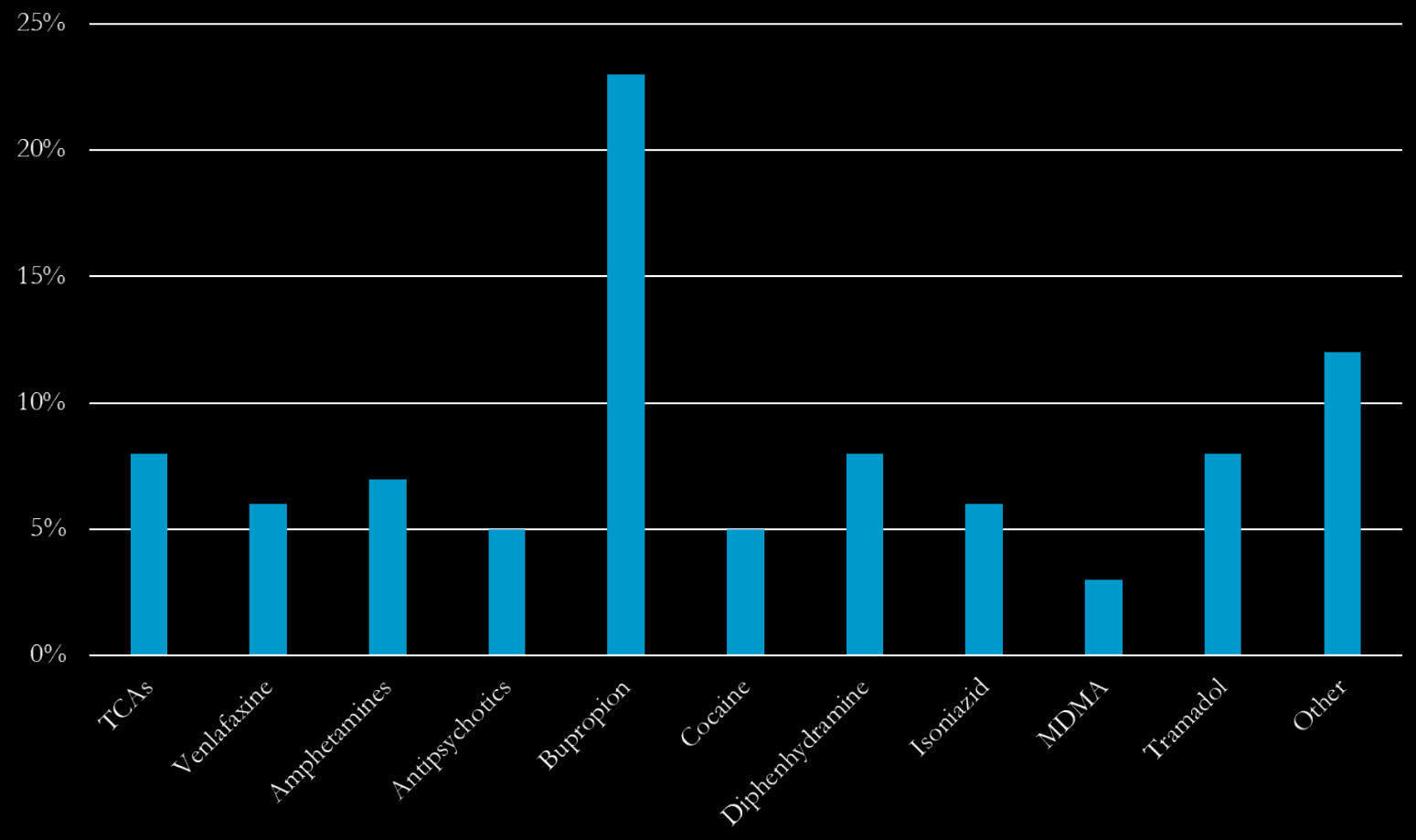
Therapeutic Category	Examples
Excess fiber	Dietary or prescribed
Other antidepressants	Monoamine amine oxidase inhibitors
Other antiparkinsonian agents	Dopamine agonists
Other antispasmodics	Peppermint oil
Anticonvulsants	Carbamazepine
Miscellaneous	Barium sulphate, octreotide, polystyrene resins, oral contraceptives
	Vitamin C tablets, ^{131}I thyroid ablation, erythropoietin, baclofen
	Pamidronate, alendronic acid, PPI and H_2 antagonists

Branch RL, Butt TF. Drug-induced constipation. Adverse Drug Reaction Bulletin 2009;257.

Drug-Induced Seizures

- 6-9% of seizures are drug-induced
- Drugs can cause seizures directly
  - At or above therapeutic concentrations
- Drugs can cause seizures indirectly
  - Reducing the effectiveness of AED
  - Hypoglycemia, hyponatremia, hyperpyrexia
  - Due to adverse effects (hypoxia, arrhythmia or cerebral edema

Drug-Induced Seizures



Thundiyil JG et al. J Medical Tech 2007;3:15-19.

Drug-Induced Seizures

- Cases involving TCAs, cocaine and theophylline have shown a marked decrease
- Newer causes of drug-induced causes have emerged including:
  - Bupropion, tramadol, and venlafaxine

Drug Withdrawal-Induced Seizures

- Anticonvulsant agents
- Benzodiazepines
- Barbiturates
- Opioids
- Baclofen

Serotonin Syndrome

- A potentially life-threatening condition caused by excess serotonergic stimulation of the central nervous system.
- Caused by:
  - Drug interactions
  - Intentional overdose
- Symptoms occur within minutes to hours after starting a second drug

Serotonin Syndrome

- Classic triad of symptoms
  - Altered mental status
  - Neuromuscular hyperactivity
  - Autonomic hyperactivity
- All three features are not always present together

Clinical Features of Serotonin Syndrome

- Neuromuscular hyperactivity
  - Akathisia
  - Tremor
  - Clonus
  - Myoclonus
  - Rigidity
  - Nystagmus
- Autonomic hyperactivity
  - Diaphoresis
  - Fever
  - Tachycardia
  - Tachypnea
- Altered mental status
  - Agitation
  - Excitement
  - Confusion

Sun-Edelstein. Expert Opin Drug Safe 2008;7:587-596

Drug-Induced Serotonin Syndrome

Therapeutic Category	Examples
SSRIs	Paroxetine, sertraline, fluoxetine, fluvoxamine, citalopram
SNRIs	Venlafaxine, milnacipran, duloxetine, sibutramine
TCAs	Clomipramine, imipramine
Misc Antidepress	Mirtazapine, trazodone, St. John's Wort
Maoist	Trancylcpromine, phenelzine, isocarboxazid
Antiparkinsons	Selegilene
Anti-infectives	Linezolid, furazolidone
Opioids	Meperidine, fentanyl, methadone, tramadol, pentazocine, dextromethorphan
Antihistamines	Chlorpheniramine, brompheniramine
CNS stimulants / Psychedelics	Amphetamine, sibutramine, methylphenidate, cocaine, MDMA (ectasy), LSD
Triptans (+/-)	Sumatriptan, zolmitriptan, rizatriptan, almotriptan, frovatriptan

Sun-Edelstein. Expert Opin Drug Safe 2008;7:587-596

Suspecting Serotonin Syndrome

- Was a serotonergic agent administered in the past five weeks?
  - –No – stop; Yes –continue
- Experienced one of the following:
  - –Tremor and hyperreflexia
  - –Spontaneous clonus
  - –Muscle rigidity, temperature > 38°C and either ocular clonus or inducible clonus
  - –Ocular clonus, and either agitation or diaphoresis
  - –Inducible clonus and either agitation or diaphoresis
- No – stop; Yes – possibly serotonin syndrome

Boyer EW et al. NEJM 352;1112-1

Drug-induced CNS depression

- Sedation, agitation, confusion
- May progress to respiratory depression
- Opioids, benzodiazepines
- Non-benzodiazepine sedative-hypnotics
- Barbiturates, alcohol, antipsychotics
- Antidepressants, antihistamines (H1)
- Antiemetics, anticonvulsants, illicit drugs

Drug-induced CNS depression

- Less obvious causes:
  - Cimetidine
  - Anticholinergic agents
  - Drugs that reduce GFR
    - NSAIDs
    - ACE inhibitors
- Fall risk increased with:
  - Sedatives, hypnotics, antidepressants, benzodiazepines

Opioid-Induced Sedation

- Occurs in 20-60% patients taking opioids
- Sedation is defined as “depression of brain functioning by a medication, manifested by sleepiness, drowsiness, fatigue, slowed brain activity, reduced wakefulness, and impaired performance.”
- Dose-dependent effect
- Tolerance within a few days
- Don’t confuse with “catch-up” sleep

Opioid-Induced Respiratory Depression

- Quantified by
  - Observed changes in breathing frequency
    - Severe respiratory depression considered to be breathing rate of less than 8-10 breaths/minute
  - And/or oxygen saturation
- Slowed and irregular respiration leads to hypercapnia and hypoxia

Factors that modulate opioid-induced respiratory depression

- Drug interactions
  - Propofol, midazolam
- Sleep – obstructive sleep apnea
  - Opioids increase stage 2 sleep (light sleep) and decrease stage 4 (deep sleep) and REM sleep
  - Methadone and benzodiazepines
- Pain – stimulated respiration

Pattinson KTS. Br J Anaesth 2008;100:747-758.

Factors that modulate opioid-induced respiratory depression

- Genetics
- Polymorphisms affecting MOP receptor activity and opioid bioavailability
- Polymorphisms affecting opioid metabolism

Pattinson KTS. Br J Anaesth 2008;100:747-758.

Atypical Opioids and Respiratory Depression

- Tramadol
  - Causes less respiratory depression than meperidine or oxycodone at equivalent doses
  - Reported in patients with renal failure
- Buprenorphine
  - Partial agonist; may cause less respiratory depression than conventional opioids at equivalent doses

Pattinson KTS. Br J Anaesth 2008;100:747-758.

Drug-Induced QTc Prolongation

- QT interval prolongation is an abnormality of the electrical activity of the heart that places individuals at risk for ventricular arrhythmias.
  - > 450 ms in men; > 470 ms in women
- Increase in QTc > 60 ms from baseline after medication administration, or
- QTc values > 500 ms after medication adminstration
  - Potential risk for arrhythmia, including Torsades de Pointes (TdP)

Risk Factors for Drug-Induced QTc Prolongation

- Female sex
- Hypokalemia
- Severe hypomagnesemia
- Bradycardia
- Recent conversion from atrial fibrillation
- Congestive heart failure
- Subclinical long QT syndrome (LQTS)
- Baseline QT interval prolongation
- Ion-channel polymorphisms
- Medications / high serum concentrations / rapid infusion

Drugs that may cause TdP

- Drugs commonly involved
  - Disopyramide, dofetilide, ibutilide
  - Procainamide, quinidine, sotalol, bepridil
- Other drugs
  - Amiodarone, arsenic trioxide, cisapride
  - Erythromycin, clarithyromycin, halofantrine, pentamidine, sparfloxacin, chloroquine
  - Domperidone, droperidol
  - Chlorpromazine, haloperidol, thioridazine
  - Methadone

Gupta A et all Am Heart J 2007;153:891-899.

Methadone and LQTS and TdP

- Increasingly prescribed for chronic pain
- Associated mortality rising disproportionately relative to other opioids
- Potent blocker of delayed rectifier potassium ion channel
- Results in QT-prolongation and TdP in susceptible individuals

Risk Factors for Methadone and Prolonged QTc

- Dose-related
- Inappropriate initial dosing (including drug diversion) or conversion calculation
- Sleep apnea, heart/lung/liver disease
- Use of other drugs that increase risk
- https://crediblemeds.org/

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