

Polypharmacy and It's Consequences

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Pharmacy Alternatives

Objectives

1. Describe the basic principles of how drugs work in the body and with one another.
2. Identify the four most important ways that drugs impact the body in both positive and negative ways.
3. Describe three reasons why individuals in vulnerable populations, particularly individuals with I/DD and or aging have increased risks for reactions to polypharmacy.

Definition and Statistics

- In a broad sense, polypharmacy describes individuals taking multiple medications
- Increased risk of inappropriate drug use, under use of effective medications, medication errors, poor adherence, drug-drug and drug disease interactions, and adverse drug reactions
- More frequently applied to seniors
 - 65-69: 14 medications on average
 - 80-84: 18 medications
- May be the appropriate course of action
- Dark side of polypharmacy:
 - Polypharmacy is responsible for 28% of hospital admissions
 - Polypharmacy is the fifth leading cause of death
 - Between 1998-2005, about 500,000 substantial adverse reactions causing death (tripled over previous years), birth defects, disabilities, hospitalization, life threatening situation or medical attention

Definition and Statistics

- Many polypharmacy problems stem from two sources:
 - A single patient receives meds from more than one doctor. (neurologist, internist, allergist, psychiatrist, etc)
 - A combination of drugs is prescribed with no prior research on how the drugs in question will interact, particularly in regard to each individual drug's side effects.

Drug Management Issues

- Drug ineffectiveness (FDA 1938)
- Adverse Drug Events
 - Over-sedation, falls, increased bleeding
- Over-dosage
- Under-dosage
- Drug Interactions
- Increased potential side effects
- Increased costs and hospitalizations

Challenges of Pharmacotherapy

- New drugs available each year
- FDA approved and off-label indications are expanding
- Changing managed-care formularies
- Advanced understanding of drug-drug interactions
- Increasing popularity of "nutritionals"
- Multiple co-morbid states
- Polypharmacy
- Medication compliance
- Effects of aging physiology on drug therapy
- Medication cost

Polypharmacy

- Doctors more likely to prescribe medications for older clients than young ones
- Altered response to medications: cumulative effect on physiology of aged:
 - Aging
 - Disease
 - Stress
 - Trauma

Polypharmacy


- Elderly rely on various medications to control or relieve a range of age-related problems
 - Cardiovascular disease
 - Diabetes
 - Degenerative joint disease
 - Autoimmune disorders
 - Neurological disorders

Polypharmacy

- Risks of problems:
 - Medication errors
 - Wrong drug, time, route
 - Adverse effects from each drug
 - Polypharmacy primary reason for adverse reactions
 - Adverse Interactions between drugs

The Aging Imperative

- Persons aged 65y and older constitute 13% of the population and purchase 33% of all prescription medications and 40% of all OTCs
- Most rapidly growing part of population (one in six)
- By 2040, 25% of the population will purchase 50% of all prescription drugs
- Process of aging involves changes in biological, functional, psychological, and social factors. It is accompanied by chronic disease, comorbidity, disability, frailty and social isolation



Main age related changes

- Body composition: reduction in body water and increase in fat stores
- Cardiac and peripheral vascular disease: stiffening, reduction in HR
- CNS: increased sensitivity, decreased blood flow, decline in receptors and pathways
- GI: decreased secretion of acid and pepsin, disjunction in motility, decreased GI blood flow, reduction in liver volume and blood flow
- Immune system: Decreased immunity to diseases, increased infections
- Musculoskeletal: loss of muscle tissue, osteoarthritis, osteoporosis
- Renal: reduction of renal mass and blood flow, decreased GFR
- Respiratory: vital capacity and FEV decreases, increased rigidity of chest wall, reduced thorax muscle strength and endurance
- Sensory: decreased visual, hearing, taste and smell

Polypharmacy and Medication related problems

- Elderly may be frail, highly sensitive to pharmacotherapy
 - Pharmacokinetic changes
 - Pharmacodynamics changes
- Inappropriate medication prescribing
 - High risk of intolerance related to drug disease interactions, drugs prescribed at too high dosages or for too long
 - Can lead to prescribing cascade
- Omission of appropriate medications
- Can negatively influence medication adherence
 - In elderly noncompliance 25-75% depending on number of drugs and daily doses

Pharmacotherapeutics

- Definition: The use of drugs to treat disease
- Examples:
 - Replacement therapy: to replenish or substitute for missing substances in the body (insulin, iron)
 - Excite or depress cells (brain neurons)
 - Alter tissues or cells (chemotherapy)

Pharmacokinetics (PK)

- Absorption
 - bioavailability: the fraction of a drug dose reaching the systemic circulation
- Distribution
 - locations in the body a drug penetrates expressed as volume per weight (e.g. L/kg)
- Metabolism
 - drug conversion to alternate compounds which may be pharmacologically active or inactive
- Elimination
 - a drug's final route(s) of exit from the body expressed in terms of half-life or clearance

Pharmacokinetics (PK)


- Half Life: The time it takes for half the drug to be eliminated from the body
- Protein Binding: Binding to blood protein, albumin. Only free drug is available for clinical activity
 - Total drug load
 - Bound
 - Unbound
- Onset: Time interval that starts when the drug is administered and ends when therapeutic effects actually begins
- Peak: Highest level of blood concentration
- Duration: Length of time drug produces its therapeutic effect
- Steady State: Occurs when the rate of drug administration equals the rate of drug elimination. Occurs after five half lives

Effects of Aging on Rx use (Absorption)

- Reduced gastric acid production
 - Raises gastric pH
 - May alter solubility of some drugs (ASA etc)
- Longer gastric emptying
 - Delay or reduce absorption
- Impaired active transport system
- Decreased esophageal motility
 - decreased gastric and parietal cells makes it difficult to swallow
 - Capsules more difficult to swallow
- Loss of subcutaneous fat
 - Increased rate of absorption of topical medications
- Increased fragility of veins
 - IV administration more difficult

Effects of Aging on Absorption

- Rate of absorption may be delayed
 - Lower peak concentration
 - Delayed time to peak concentration
- Overall amount absorbed (bioavailability) is unchanged



Factors Affecting Absorption

- Route of administration
- What it taken with the drug
 - Divalent cations (Ca, Mg, Fe)
 - Food, enteral feedings
 - Drugs that influence gastric pH
 - Drugs that promote or delay GI motility
- Comorbid conditions
- Increased GI pH
- Decreased gastric emptying
- Dysphagia

Effects of Aging on Rx use (Distribution)

- Decreased cardiac output/circulation changes
 - May delay onset or extend effect of medications
- Decrease of lean body mass/increase of fatty tissue where medications are stored
 - Prolong medication's action
 - Increase sensitivity
 - Increase toxic effects
- Higher plasma levels/more erratic distribution
- Plasma protein binding issues

Effects of Aging on Volume of Distribution (Vd)

Aging Effect	Vd Effect	Examples
↓ body water	↓ Vd for hydrophilic drugs	ethanol, lithium
↓ lean body mass	↓ Vd for drugs that bind to muscle	digoxin
↑ fat stores	↑ Vd for lipophilic drugs	diazepam, trazodone
↓ plasma protein (albumin)	↑ % of unbound or free drug (active)	diazepam, valproic acid, phenytoin, warfarin
↑ plasma protein (α ₁ -acid glycoprotein)	↓ % of unbound or free drug (active)	quinidine, propranolol, erythromycin, amitriptyline

Effects of Aging on Rx use (Metabolism)

- Difficult to predict, depends on
 - General health & nutritional status
 - Use of alcohol, medications
 - Long term exposure to environmental toxins/pollutants
- Aging causes decreased liver mass/ hepatic blood flow
 - Delayed/reduced metabolism of drugs
 - Higher plasma levels
- Lower serum protein levels
 - Loss of protein binding
- Idiosyncratic reactions

Hepatic First-Pass Metabolism

- For drugs with extensive first-pass metabolism, bioavailability may increase because less drug is extracted by the liver
- The first-pass effect (or first-pass metabolism) is a phenomenon of drug metabolism. After a drug is swallowed, it is absorbed by the digestive system and enters the portal circulation. The absorbed drug is carried through the portal vein into the liver.

The liver is responsible for metabolizing many drugs. Some drugs are so extensively metabolized by the liver that only a small amount of unchanged drug may enter the systemic circulation, so the bioavailability of the drug is reduced. Alternative routes of administration (e.g., intravenous, intramuscular, sublingual) avoid the first-pass effect.

- Essentially giving an overdose if use normal doses of medication

Aging Effects on Hepatic Metabolism

- Metabolic clearance of drugs by the liver may be reduced due to:
 - decreased hepatic blood flow
 - decreased liver size and mass
- **Examples:** morphine, meperidine, metoprolol, propranolol, verapamil, amitriptyline, nortriptyline
- Significant reduction in clearance of drugs affected by Phase 1 pathways: SSRI, bupropion

Other Factors Affecting Drug Metabolism

- Gender
- Comorbid conditions
- Smoking
- Diet
- Drug interactions
- Race
- Frailty

Metabolic Pathways

Pathway	Effect	Examples
Phase I: oxidation, hydroxylation, dealkylation, reduction	Conversion to metabolites of lesser, equal, or greater	diazepam, quinidine, piroxicam, (Feldene) theophylline
Phase II: glucuronidation, conjugation, or acetylation	Conversion to inactive metabolites	lorazepam, oxazepam, temazepam (Restoril)

▶ NOTE: Medications undergoing Phase II hepatic metabolism are generally preferred in the elderly due to inactive metabolites (no accumulation)

Effects of Aging on Rx use (Excretion)

- Reduction in number of functioning nephrons/decreased glomerular filtration rate
 - Longer half-life of medications
 - Increased side effects
 - Increased potential for toxicity

Concepts in Drug Elimination

- Half-life
 - time for serum concentration of drug to decline by 50% (expressed in hours)
- Clearance
 - volume of serum from which the drug is removed per unit of time (mL/min or L/hr)
- Reduced elimination ⇒ drug accumulation and toxicity

Effects of Aging on the Kidney

- Decreased kidney size
- Decreased renal blood flow
- Decreased number of functional nephrons
- Decreased tubular secretion
- Result: ↓ glomerular filtration rate (GFR)
- Decreased drug clearance: atenolol, gabapentin, H2 blockers, digoxin, allopurinol, quinolones (Cipro, Floxin, Levaquin)

Pharmacodynamics (PD)

- Definition: the time course and intensity of pharmacologic effect of a drug
- Age-related changes:
 - ↑ sensitivity to sedation and psychomotor impairment with benzodiazepines
 - ↑ level and duration of pain relief with narcotic agents
 - ↑ drowsiness and lateral sway with alcohol
 - ↓ HR response to beta-blockers
 - ↑ sensitivity to anti-cholinergic agents
 - ↑ cardiac sensitivity to digoxin

Pharmacodynamic Definitions

- **Tolerance:** Decreased response to a drug over time, requiring an increase in drug dosage to achieve the same therapeutic effect (pain medications)
- **Additive effect:** Two drugs with similar actions administered together. The effects are equivalent to the sum of either drug administered alone at higher dosages.
- **Antagonism:** Drug interaction which occurs when the combined response of two drugs is less than the response produced by either alone.

Pharmacodynamic Definitions

- **Synergism:** Two drugs that produce the same effect are given together and one enhances the effect of the other drug. This produces greater effects than either drug given alone.
- **Protein Binding:** When two drugs are given together they can compete for protein binding sites, leading to an increase in the effect of one drug as that drug is displaced from the protein and become a free unbound drug.

PK and PD Summary

- PK and PD changes generally result in decreased clearance and increased sensitivity to medications in older adults and those with I/DD
- Use of lower doses, longer intervals, slower titration are helpful in decreasing the risk of drug intolerance and toxicity
- Careful monitoring is necessary to ensure successful outcomes

Consequences of Overprescribing


- Adverse drug events (ADEs)
- Drug interactions
- Duplication of drug therapy
- Decreased quality of life
- Unnecessary cost
- Medication non-adherence

Optimal Pharmacotherapy

- Balance between overprescribing and under prescribing
 - Correct drug
 - Correct dose
 - Targets appropriate condition
 - Is appropriate for the patient
 - Avoid "a pill for every ill"
 - Always consider non-pharmacologic therapy


Adverse Drug Events (ADEs)

- Responsible for 5-28% of acute geriatric hospital admissions
- Greater than 95% of ADEs in the elderly are considered predictable and approximately 50% are considered preventable
- Most errors occur at the ordering and monitoring stages



Most Common Medications Associated with ADEs in the Elderly

- Opioid analgesics
- NSAIDs
- Anticholinergics
- Benzodiazepines
- Also: cardiovascular agents, CNS agents, and musculoskeletal agents



Adverse Drug Reaction Risk Factors in Older Outpatients Am J Ger Pharmacotherapy 2003;1(2):82-89

Beers Criteria/List

- List of potentially inappropriate medications for the elderly
- Many classes of medications and particular drugs
 - Anticholinergics
 - Antispasmodics
 - Anti-infectives
 - Cardiac
 - Antidepressants
 - Antipsychotics
 - Benzodiazepines
 - etc

The Beers Criteria

High Potential for Severe ADE	High Potential for Less Severe ADE
Amirtripyline (Elavil)	Antihistamines
Digoxin >0.125mg/d	diphenhydramine
Disopyramide (Norpace)	Dipyridamole (Persantine)
GI antispasmodics	Indomethacin
Meperidine	Muscle relaxants
Pentazocine (Talwin)	

Troublesome Medications

- Antacids
 - Acid-base imbalance (sodium bicarbonate)
 - Constipation (aluminum hydroxide)
- Anti-arrhythmics
 - Confusion
 - Slurred speech
 - Light-headedness, seizures
 - hypotension

Troublesome Medications

- Anticoagulants:
 - Bleeding
 - Watch food interactions
- Corticosteroids
 - Sodium retention (may worsen HTN & CHF)
 - Insomnia
 - Psychotic behavior
 - osteoporosis

Troublesome Medications

- Antipsychotics
 - Jaundice
 - Extrapyramidal symptoms
 - Sedation, dizziness (can lead to falls)
 - Orthostatic hypotension
 - Scaling skin on exposure to sunlight (phenothiazines)

Troublesome Medications

- Anxiolytics
 - Confusion, lethargy
 - Slurred speech
 - Ataxia, falls
 - Blurred vision

Troublesome Medications

- Laxatives
 - Intestinal malabsorption
 - Reduced absorption of fat-soluble vitamins (if taking mineral oil)
 - Magnesium toxicity (clients with renal insufficiency taking magnesium)

Troublesome Medications

- Narcotic analgesics
 - Respiratory depression
 - Constipation
 - Urinary retention
 - Demerol:
 - Hypotension, dizziness
 - confusion

Troublesome Medications

- NSAIDs
 - Prolong bleeding
 - Gastric discomfort, bleeding
 - Increased risk of toxicity (with impaired renal function)
 - Avoid with Lithium

Troublesome Medications

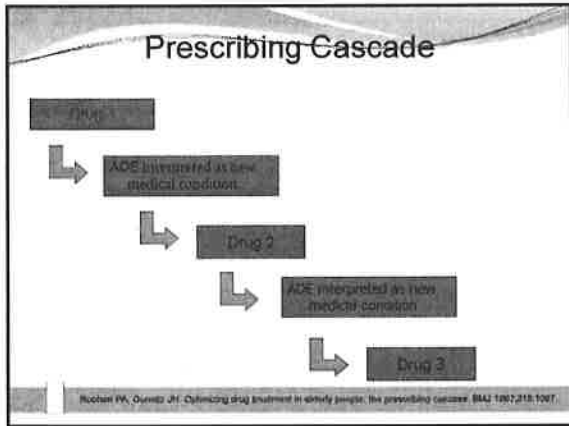
- Respiratory agents
 - Restlessness, nervousness
 - Confusion
 - Blood pressure disturbances
 - Palpitations, tachycardia
 - Chest pain

Troublesome Medications

- Tricyclic antidepressants
 - Dry mouth
 - Constipation
 - Blurred vision
 - Postural hypotension
 - Dizziness
 - Tachycardia
 - Urinary retention

Patient Risk Factors for ADEs

- Polypharmacy
- Multiple co-morbid conditions
- Prior adverse drug event
- Low body weight or body mass index
- Age > 85 years
- Estimated CrCl <50 mL/min



- ### Concepts in Drug-Drug Interactions
- Absorption may be ↑ or ↓
 - Drugs with similar effects can result in additive effects
 - Drugs with opposite effects can antagonize each other
 - Drug metabolism may be inhibited or induced

- ### Drug-Drug Interactions (DDIs)
- May lead to adverse drug events
 - Likelihood ↑ as number of medications ↑
 - Most common DDIs:
 - cardiovascular drugs
 - psychotropic drugs (antipsychotics, antidepressants, anti-anxiety medications)
 - Depend largely on mechanism of action (seizures, psychosis, depression, Alzheimer's Disease)
 - Most common drug interaction effects:
 - confusion
 - cognitive impairment
 - hypotension
 - acute renal failure

Common Drug-Drug Interactions

Combination	Risk
ACE inhibitor + potassium	Hyperkalemia
ACE inhibitor + K sparing diuretic	Hyperkalemia, hypotension
Digoxin + antiarrhythmic	Bradycardia, arrhythmia
Digoxin + diuretic	Electrolyte imbalance; arrhythmia
Antiarrhythmic + diuretic	
Diuretic + diuretic	Electrolyte imbalance; dehydration
Benzodiazepine + antidepressant	Sedation; confusion; falls
Benzodiazepine + antipsychotic	
CCB/nitrate/vasodilator/diuretic	Hypotension

Dunne J, Choudhury P, Towse C, et al. Drug-drug interactions related to hospital admission in the USA: a prospective study of 1000 patients. J Am Geriatr Soc 1996; 44:101-104

- ### Drug-Disease Interactions
- Obesity alters Vd of lipophilic drugs
 - Ascites alters Vd of hydrophilic drugs
 - Dementia may ↑ sensitivity, induce paradoxical reactions to drugs with CNS or anticholinergic activity
 - Renal or hepatic impairment may impair metabolism and excretions of drugs
 - Drugs may exacerbate a medical condition

Common Drug-Disease Interactions

Combination	Risk
NSAIDs + CHF	Fluid retention; CHF exacerbation
Thiazolidinediones + CHF	
BPH + anticholinergics	Urinary retention
Narcotics + constipation	Exacerbation of constipation
Anticholinergics + constipation	
Metformin + CHF	Hypoxia; increased risk of lactic acidosis
NSAIDs + gastropathy	Increased ulcer and bleeding risk
NSAIDs + HTN	Fluid retention; decreased effectiveness of diuretics

Medication related Problems and Suggestions

- Polypharmacy:
 - Are all drugs prescribed indicated?
 - Are they effective?
 - Which could be d/c'd?
- Inappropriate prescribing:
 - Check benzodiazepines, anticholinergic, NSAIDs, ACE Inhibitors in patients with DM and proteinuria, ACE inhibitors and beta blockers
- Dose and administration frequency:
 - Should adjustments take place?
 - Frequency?
 - Dose?
 - Drug formulation?
- ADRs: what is the risk and are we monitoring?
 - Drowsiness, EPS, bleeding with NSAIDs, bradycardia, hypotension, constipation with verapamil, diltiazem
 - Hypoglycemia with sulfonylurea antidiabetics
 - Drowsiness and constipation after opioids
 - Increase risk of falls after benzodiazepines, hypnotics, antipsychotics, antidepressants, anticholinergic agents and diuretics

Medication related Problems and Suggestions

- Drug-drug interactions:
 - Loss of renal function after ACE inhibitors and NSAIDs or K sparing diuretics
 - Risk of serious hemorrhage after coumadin and SSRIs
 - Digoxin intoxication
 - Hyponatremia and GI bleeding after SSRIs and diuretics or NSAIDs
 - Postural hypotension and falls after antihypertensive meds and vasodilators, antipsychotics or tricyclic antidepressants
 - Decreased antihypertensive effect after co-administration of HTN and antidepressants
 - Bradycardia after beta agonists and some SSRIs (Prozac and Paxil)
 - Increased phenytoin toxicity when co-administered with verapamil, diltiazem, amiodorone, fluconazole, miconazole, ketoconazole, erythromycin, clarithromycin, sulfonamides, cimetidine, ciprofloxin, grapefruit juice

Medication related Problems and Suggestions

- Compliance:
 - Depression, cognitive changes, dysphagia
- Changes in medications after admission/discharge from hospital:
 - Check the drug history as this is the time medication errors and polypharmacy issues can arise
 - Critical assessment of drugs at this time. Which medications are really needed or can be stopped?

Principles of Prescribing in the Elderly and Individuals with I/DD

- Avoid prescribing prior to diagnosis
- Start with a low dose and titrate slowly
- Avoid starting 2 agents at the same time
- Reach therapeutic dose before switching or adding agents
 - When do you switch?
 - When do you augment?
- Consider non-pharmacologic agents/treatments
 - Diet, exercise, smoking cessation, physical therapy

Prescribing Appropriately

- Determine therapeutic endpoints and plan for assessment
 - Decisions based on patient's age, life expectancy, goals of therapy (curative or palliative), treatment target (tx of acute illness, prevention of morbidity and mortality, life prolongation, maintenance of current functional or health state, quality of life)
- Consider risk vs. benefit
- Avoid prescribing to treat side effect of another drug
- Use 1 medication to treat 2 conditions
- Consider drug-drug and drug-disease interactions
- Use simplest regimen possible
- Adjust doses for renal and hepatic impairment
- Avoid therapeutic duplication
- Use least expensive alternative

Preventing Polypharmacy

- Review medications regularly and each time a new medication started or dose is changed
- Maintain accurate medication records (include vitamins, OTCs, and herbals)
- Care should be provided according to best practice, and when possible should be evidence based
 - If not possible, identify reliable and realistic targets for therapy and monitor patient to assess target achievement or ADRs

Preventing Polypharmacy

- Discontinuance should be guided by a review of medication-related problems, and the pharmacological characteristics of drugs to be stopped in order to avoid adverse events related to d/c of the drug
 - Ex: agitation, anxiety, confusion, delirium or insomnia after d/c of a benzodiazepine
 - Anxiety, insomnia, hallucinations, or depression after d/c of baclofen

Preventing Polypharmacy

- Coordination among clinician and caregivers
 - Use of electronic health records
- Communication and transparency between all providers
 - Emergency room visits
 - Doctor visits
 - hospitalizations

Polypharmacy in Individuals with I/DD

- Lack of safety and efficacy studies
- Increase in the use of psychotropic medications in this group
- Individuals with dual diagnosis
 - 62% prescribed psychotropic meds
 - More likely to be prescribed antipsychotics
 - Not as many experiences physicians
 - More likely to "treat" behavior rather than investigate why it occurred

Polypharmacy in Individuals with I/DD

- If assault or severe self abuse, antipsychotic medications are first choice (up to 85%)
- Common side effects: agitation, aggressive behavior, anxiety, difficulty concentrating, insomnia, blurred vision, difficulty speaking, tics. Normally attributed to diagnosis rather than side effects
- Economic impact
- Developing risk of DM and hyperglycemia

I/DD population and Drug Dynamics

- I/DD population:
 - Age earlier and differently
 - More incidence of multiple disease states
- Assault on liver and kidneys due to lifetime use of medications
 - Anti-seizure medications
 - Few medications extensively excreted in kidneys ex: gabapentin
- Not as many functioning brain neurons
 - Affects psychotropic medications ex: antipsychotics, antidepressants

I/DD population and Drug Dynamics

- I/DD population:
 - Non-ambulatory status slows metabolism
 - Oral dosing slowed
 - May be incomplete
 - GERD and hyper acidic states
 - Swallowing issues and g-tube absorption issues
 - What can be crushed
 - Adherence to g tube
 - Medications administered alone vs together

If Client Taking > Five Meds Regularly

- Suggest physician prescribe combination drugs or long-acting forms
 - Fewer pills to remember
- Suggest re-evaluation of medications periodically
- New medications
 - Good information
 - Encourage follow up

Potential Benefits of Drug Review

- Individuals diverted from ERs and inpatient treatment
- Reduction in polypharmacy can lead to less physical symptoms and complaints
- Cost reduction
- Research is needed

Summary

- Successful pharmacotherapy means using the correct drug at the correct dose for the correct indication in an individual patient
- Age alters PK and PD
- ADEs are common among the elderly
- Risk of ADEs can be minimized by appropriate prescribing
