

Improving Drug Safety in Oklahoma in CMS' 9th SoW

The SPOkE Project

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Discussion Points

- America's "Other" Drug Problem
- Effects of Aging
- Medication Classes Requiring Special Consideration in the Elderly
- PIMS-Potentially Inappropriate Medications
- DDIs- Drug on Drug Interactions
- Drug Safety in CMS 9th Scope of Work
- SPOkE Project



America's "Other" Drug Problem



The Problem

- The elderly, with multiple co-morbidities, complex chronic conditions, and, often, on “poly-pharmacy”, are at increased risk for Adverse Drug Events (ADEs)
- ADEs have been linked to potentially preventable problems in elderly patients :
 - Depression, constipation, falls, immobility, confusion, hip fractures, etc.



The Magnitude of the Problem

- 30% of hospital admissions in elderly patients can be linked to drug-related problems or toxic effects from drugs
- 35% of ambulatory older patients have ADEs
- 29% of ADEs require health care services
- Up to 66% of NH Residents, over time, have ADEs, with 1/7 requiring hospitalization



* See References & Resources

The Magnitude of the Problem

Estimate of 106,000 medication related deaths annually

Cost estimates are \$76.6 billion for ambulatory care.
\$20 billion for hospitals, and \$4 billion for nursing homes



* See References & Resources

The Magnitude of the Problem

**If ranked as a disease, medication related problems
would be the 5th Leading Cause of Death in the US !**

Lazarou, JAMA 98



Contributors to “America’s Other Drug Problem”

- Polypharmacy (Rx and OTC)
- Consequences of drug-drug interactions
- Pharmacokinetic changes of aging
- Pharmacodynamic changes of aging
- Effects of co-morbidity on kinetics and dynamics
- Compliance problems



Polypharmacy

- Over 30% of prescription medications are taken by those over the age of 65 (13% of population)
 - An estimated 40 to 50% of OTC medications are consumed by older people
- Over 80% of older people take at least one medication per day
 - Community living elders take 3 to 4 different medications per day
 - Nursing home living elders take 7 to 9 different medications per day



* See References & Resources

Polypharmacy

- An estimated 25% of all prescribed medications for older people are inappropriately selected or dosed (Beer's List)
- Pre-Part D data from Oklahoma revealed that 42% of Medicaid recipients and 34% of state retirees were on a potentially inappropriate medication
- An estimated 30% of all medications for older people are considered of questionable necessity



* See References & Resources

Drug-Drug Interactions

- Increased likelihood of clinically significant drug-drug interactions with increased number of medications used
ex: Coumadin, omeprazole(Prilosec),
fluoxetine(Prozac),levothyroxine(Synthroid), prednisone,
Metoprolol, furosemide(Lasix)
- Increased morbidity and mortality associated with drug-drug interactions in the elderly due to decreased physiologic reserve



Pharmacokinetics of Aging

- Absorption
 - Though numerous structural and physiological age-related changes in the GI tract exist, they are of minimal clinical significance in the absence of gastrointestinal pathology
 - Decreased first-pass
- Distribution (volume of distribution)
 - Body Composition Changes
 - Lean-to-fat ratio altered – digoxin (Lanoxin*)
 - Decreased total body water - lithium
 - Protein concentration changes – phenytoin (Dilantin*) and warfarin (Coumadin*)



Pharmacokinetics of Aging

- Metabolism (clearance)
 - Liver size, blood flow and some metabolic pathways decline with age
 - Some Phase I metabolic pathways performed by CYP (oxidation, reduction, hydrolysis) diminish with age
 - Diazepam (Valium*), chlordiazepoxide (Librium*), alprazolam (Xanax*), flurazepam (Dalmane*)
 - Phase II metabolic pathways do not appear to diminish with age
 - Lorazepam (Ativan*), oxazepam (Serax*), triazolam (Halcion*), temazepam (Restoril*)



Pharmacokinetics of Aging

- Elimination (clearance)
 - Majority of people over the age of 50 lose 10% of renal function per decade
 - Digoxin, aminoglycosides, vancomycin, penicillins, cephalosporins, salicylate metabolites



Pharmacodynamics of Aging

- Alterations in receptor affinity
- Alterations in receptor number
- Enhanced or diminished post-receptor response
- Changes in homeostatic control mechanisms (baroreceptors)



Pharmacodynamics of Aging

- Central nervous system sensitivity
 - Increased receptor response
 - Reduced CNS dopamine
 - EPS symptoms
 - Reduced serotonin receptor function
 - Enhanced sensitivity to antidepressants
 - Altered GABA-benzodiazepine receptor function
 - Increased sensitivity to benzodiazepine, alcohol, barbiturate
 - Reduced CNS acetylcholine
 - Enhanced anti-cholinergic side effects
 - Sedation, confusion, psychosis, delirium
 - Urinary retention, constipation



Medication Classes Requiring Special Consideration in the Elderly



Diuretics

- Principles:
 - Increased likelihood of electrolyte disturbances
 - Start low (HCTZ 12.5 mg)
 - Cornerstone for hypertension management



Antihypertensives

- Principles:
 - Select agents which act peripherally and are not highly lipophilic
- Preferred:
 - ACE inhibitors, ARBs, CC blockers, atenolol
- Avoid:
 - Agents which act centrally or are highly lipophilic
 - Methyldopa, clonidine, propranolol
 - Short-acting nifedepine



Antiarrhythmics/ Digitalis Glycosides

- Principles:
 - Increased cardiosensitivity and altered kinetics
 - Pay attention to ECG. Watch for toxicity.



Antianxiety/ Sedative Agents

- Principles:
 - Select agents which are short-acting, without active metabolites
 - Lowest possible dose for the shortest possible time
 - Evaluate need for therapy frequently
- Preferred:
 - Oxazepam (Serax*), lorazepam (Ativan*), triazolam (Halcion*), temazepam (Restoril*)
 - Buspirone (Buspar*), Zolpidem (Ambien*)
 - Sonata*, Lunesta*, Rozerem* ???
- Avoid:
 - Diazepam (Valium*), chlordiazepoxide (Librium*), flurazepam (Dalmane*), alprazolam (Xanax*)



Antipsychotics

- **Principles:**
 - Use least sedating agents with minimal anticholinergic side effects and minimal orthostatic changes in blood pressure
- **Preferred:** (however, be aware of “black box” warning!)
 - Atypical antipsychotics
 - Risperidone (Risperdal*) – first choice amongst atypicals based on cost, effectiveness and side-effect profiles
 - Olanzapine (Zyprexa*)
 - Ziprasidone (Geodon*)
 - Quetiapine (Seroquel*)
 - Aripiprazole (Abilify*)
- **Avoid:**
 - Chlorpromazine, perphenazine, haloperidol (?)



Antidepressants

- Principles:
 - Use least sedating agents with minimal cardiotoxicity, minimal anticholinergic side effects and minimal orthostatic changes in blood pressure
 - Start low - go slow – but go
- Preferred:
 - SSRIs -- Sertraline (Zoloft*), paroxetine (Paxil*), citalopram (Celexa*), escitalopram (Lexapro*)
 - Mixed -- Bupropion (Wellbutrin*), Venlafaxine (Effexor*), Duloxetine (Cymbalta*)
 - Tricyclic Antidepressant -- Secondary amines: nortriptyline(Aventyl*), desipramine (Norpramin*)
 - Tetracyclics -- mirtazapine (Remeron*)
- Avoid:
 - Tertiary amine tricyclic antidepressants -- amitriptyline (Elavil*), imipramine (Tofranil*)



Anticoagulants

- Principles:
 - Be aware of increased sensitivity to warfarin, especially in patients with decreased protein
 - Be aware of interactions with other meds
 - Be aware of increased risk of bleeding
 - Re-evaluate need for therapy frequently
 - Start low - go slow



Analgesics

- Principles:
 - Be aware of GI risk associated with NSAIDS
 - Be aware of increased sensitivity to narcotic analgesics
 - Be aware of additive CNS depressant effect of narcotics with other agents
- Preferred:
 - Non-narcotic – acetaminophen, NSAIDS as second line,
 - Narcotic like and narcotics – tramadol, codeine, hydrocodone, morphine, oxycodone, fentanyl
- Avoid:
 - Non-narcotic – ketoralac
 - Narcotic like and narcotic – propoxyphene, meperidine, pentzocine



Antiulcerants

- Principles:
 - Use H-2 antagonist carefully, use one-half the usual adult dose
 - Proton pump inhibitors appear safe
(? Calcium balance)
- Avoid:
 - Cimetidine



Hypoglycemic Agents

- Principles:
 - Be aware of altered kinetics and sensitivity
 - Be aware of altered glucose counterregulatory response to hypoglycemia. Be aware of altered presentations of hypoglycemic symptoms
 - Initiate therapy at one-half the usual adult dose
- Avoid:
 - Use first generation sulfonylureas (chlorpropamide)



OTC/Herbals

- DO
 - Be aware of increased sensitivity
 - Monitor for drug-drug interactions carefully



“PIMs” Potentially Inappropriate Medications



PIMs-Potentially Inappropriate Medications

- Different methods for defining medication-related problems in the elderly
 - Use of lists containing specific drugs to avoid or appropriateness indexes by clinicians
 - Systematic review of literature
 - Limited number of controlled studies in elderly
 - Develop consensus criteria
 - Beers Criteria and Canadian Criteria
 - Beers Criteria adopted by CMS in 1999 for nursing home regulation



Beers Criteria

- Based on expert consensus developed through an extensive literature review
- Most recent update includes 48 individual medications or classes to generally avoid
 - amitriptyline (Elavil)
 - muscle relaxants and antispasmodics including cyclobenzaprine (Flexeril)
 - diphenhydramine (Benadryl)
- 20 diseases or conditions and meds that should be avoided in those conditions

ORIGINAL INVESTIGATION

Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Results of a US Consensus Panel of Experts

Donna M. Fick, PhD, RN; James W. Cooper, PhD, RPh; William E. Wade, PharmD, FASHP, FCCP; Jennifer L. Waller, PhD; J. Ross Maclean, MD; Mark H. Beers, MD

Background: Medication toxic effects and drug-related problems can have profound medical and safety consequences for older adults and economically affect the health care system. The purpose of this initiative was to revise and update the Beers criteria for potentially inappropriate medication use in adults 65 years and older in the United States.

Methods: This study used a modified Delphi method, a set of procedures and methods for formulating a group judgment for a subject matter in which precise information is lacking. The criteria reviewed covered 2 types of statements: (1) medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available and (2) medications that should not be used in older persons known to have specific medical conditions.

Results: This study identified 48 individual medications or classes of medications to avoid in older adults and their potential concerns and 20 diseases/conditions and medications to be avoided in older adults with these conditions. Of these potentially inappropriate drugs, 66 were considered by the panel to have adverse outcomes of high severity.

Conclusions: This study is an important update of previously established criteria that have been widely used and cited. The application of the Beers criteria and other tools for identifying potentially inappropriate medication use will continue to enable providers to plan interventions for decreasing both drug-related costs and overall costs and thus minimize drug-related problems.

Arch Intern Med. 2003;163:2716-2724

TOXIC EFFECTS of medications and drug-related problems can have profound medical and safety consequences for older adults and economically affect the health care system. Thirty percent of hospital admissions in elderly patients may be linked to drug-related problems or drug toxic effects.¹ Adverse drug events (ADEs) have been linked to preventable problems in elderly patients such as depression, constipation, falls, immobility, confusion, and hip fractures.² A 1997 study of ADEs found that 33% of ambulatory older adults experienced an ADE and 29% required health care services (physician, emergency department, or hospitalization) for the ADE.³ Some two thirds of nursing facility residents have ADEs over a 4-year period.⁴ Of these ADEs, 1 in 7 results in hospitalization.⁴

Recent estimates of the overall human and economic consequences of medication-related problems vastly exceed the findings of the Institute of Medicine (IOM) on deaths from medical errors, estimated

to cost the nation \$8 billion annually.⁵ In 2000, it is estimated that medication-related problems caused 106,000 deaths annually at a cost of \$85 billion.⁶ Others have calculated the cost of medication-related problems to be \$76.6 billion to ambulatory care, \$20 billion to hospitals, and \$4 billion to nursing home facilities.^{7,8} If medication-related problems were ranked as a disease by cause of death, it would be the fifth leading cause of death in the United States.⁹ The prevention and recognition of drug-related problems in elderly patients and other vulnerable populations is one of the principal health care quality and safety issues for this decade.

CME course available at www.archinternmed.com

The aforementioned IOM report has focused increased attention on finding solutions for unsafe medication practices, polypharmacy, and drug-related problems in the care of older adults. There are many ways to define medication-related prob-

From the Department of Medicine, Center for Health Care Improvement (Drs Fick and Maclean); and Office of Biostatistics (Dr Waller), Medical College of Georgia, Augusta; Department of Veterans Affairs Medical Center, Augusta (Dr Fick); Department of Clinical and Administrative Pharmacy, College of Pharmacy, University of Georgia, Athens, (Dr Cooper and Wade); and Merck & Co Inc, West Point, Pa (Dr Beers). The authors have no relevant financial interest in this article.

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Potentially Inappropriate Medications

Table 1. 2002 Criteria for Potentially Inappropriate Medication Use in Older Adults: Independent of Diagnoses or Conditions

Drug	Concern	Severity Rating (High or Low)
Propoxyphene (Darvon) and combination products (Darvon with ASA, Darvon-N, and Darvocet-N)	Offers few analgesic advantages over acetaminophen, yet has the adverse effects of other narcotic drugs.	Low
Indomethacin (Indocin and Indocin SR)	Of all available nonsteroidal anti-inflammatory drugs, this drug produces the most CNS adverse effects.	High
Pentazocine (Talwin)	Narcotic analgesic that causes more CNS adverse effects, including confusion and hallucinations, more commonly than other narcotic drugs. Additionally, it is a mixed agonist and antagonist.	High
Trimethobenzamide (Tigan)	One of the least effective antiemetic drugs, yet it can cause extrapyramidal adverse effects.	High
Muscle relaxants and antispasmodics: methocarbamol (Robaxin), carisoprodol (Soma), chlorzoxazone (Paraflex), metaxalone (Skelaxin), cyclobenzaprine (Flexeril), and oxybutynin (Ditropan). Do not consider the extended-release Ditropan XL.	Most muscle relaxants and antispasmodic drugs are poorly tolerated by elderly patients, since these cause anticholinergic adverse effects, sedation, and weakness. Additionally, their effectiveness at doses tolerated by elderly patients is questionable.	High
Flurazepam (Dalmane)	This benzodiazepine hypnotic has an extremely long half-life in elderly patients (often days), producing prolonged sedation and increasing the incidence of falls and fracture. Medium- or short-acting benzodiazepines are preferable.	High
Amitriptyline (Elavil), chlordiazepoxide-amitriptyline (Limbitrol), and perphenazine-amitriptyline (Triavil)	Because of its strong anticholinergic and sedation properties, amitriptyline is rarely the antidepressant of choice for elderly patients.	High
Doxepin (Sinequan)	Because of its strong anticholinergic and sedating properties, doxepin is rarely the antidepressant of choice for elderly patients.	High
Meprobamate (Miltown and Equanil)	This is a highly addictive and sedating anxiolytic. Those using meprobamate for prolonged periods may become addicted and may need to be withdrawn slowly.	High
Doses of short-acting benzodiazepines: doses greater than lorazepam (Ativan), 3 mg; oxazepam (Serax), 60 mg; alprazolam (Xanax), 2 mg; temazepam (Restoril), 15 mg; and triazolam (Halcion), 0.25 mg	Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums.	High



Historical Context

Measure	Population	# of drugs or changes
Beers, 1991	Nursing home patients	Expert consensus identifying 19 medications/classes
Beers, 1997	Community-dwelling elderly	Expert consensus identifying 28 medications/classes
Zhan, 2001	Community-dwelling elderly	Expert panel classified Beers Criteria into 3 categories (always avoid, rarely appropriate, and some indications)
Beers, 2003	Community-dwelling elderly	Expert consensus identifying 48 medications/classes
HEDIS, 2006	Community-dwelling elderly	Expert panel classified Beers into 3 categories; Always Avoid and Rarely Appropriate in 2006 HEDIS measures



Zhan List

- In 2001, Zhan & colleagues selected 33 drugs from the Beers Criteria and separated them into three categories

Always Avoid	Rarely Appropriate	Some Indications
Meperidine (Demerol)	Propoxyphene (Darvon)	Amitriptyline (Elavil)



PIM Studies

- Most studies on Beers Criteria or PIM are retrospective
 - Findings can only show an association or relationship between inappropriate medication use and healthcare outcomes...not a cause
- Need well-designed prospective studies to better evaluate health outcomes of inappropriate medication use
 - Can assist in strengthening predictive validity of Beers Criteria



Potentially Inappropriate Medications (PIM)

- **One study found PIM rate of 23% in Medicare managed care population (>65 yo)**
 - % of patients with at least 1 PIM based on Beers Criteria
 - Those receiving a PIM had higher total costs, higher provider and facility costs, and higher mean number of inpatient, outpatient, and ED visits
- **Majority of PIM used:**
 - Antihistamines, skeletal muscle relaxants, opiates (propoxyphene), and psychotropic meds
- **HHS Secretary Thompson called for national action plan to ensure appropriate use of therapeutic agents in elderly (2002)**

* See References & Resources



Impact on Care

- Regardless of existing discussions, Beers Criteria is being used in measures of quality
 - 2006 HEDIS measure assessing quality of care in managed healthcare plans
 - PDPs not required to cover benzodiazepines and barbiturates (both on Beers list) under Medicare Part D
 - CMS requesting QIOs assess PIM use in Medicare population



DDIs- Drug on Drug Interactions



Characteristics of Drugs with Clinically Relevant Interactions

- Narrow Therapeutic Window
(Warfarin, Digoxin, MAO Inhibitors, many Anticonvulsants, Theophylline)
- Dose Dependent (INR affected by Warfarin availability)
- Common Metabolism (CYP 450)
Amiodarone(Cordarone), Clarithromycin(Biaxin), Erythromycin, Fluconazole(Diflucan), Fluoxetine(Prozac), Paroxetine(Paxil)



DDIs- Classification

- Pharmacokinetic (Change of Delivery)
- Pharmacodynamic (Change in Response)
(Synergistic or Antagonistic)



Common Mechanisms of Pharmacokinetic Interactions

- Inhibition of Drug Metabolism
- Induction of Drug Metabolism
- Inhibition of Drug Absorption



Common Mechanisms of Pharmacodynamic Interactions

- Excessive Therapeutic Effect Due to Similar Clinical Indication (Excessive hypotensive effect with concurrent use of prazosin(Minipress) & metoprolol tartrate(Lopressor)
- Excessive Therapeutic Effect Due to Unintended Effect of Other Agent (Increased QT interval in patients on amiodarone(Cordarone) when levofloxacin(Levaquin) added)
- Blunted Effect Due to Opposite Effect of Other Agent (Impaired BP reduction with amlodipine(Norvasc) when vasoconstrictor added such as pseudoephedrine(Sudafed)
- Blunted Effect Due to Unintended Effect of Other Agent (hyperglycemia from steroid use while on hypoglycemics)
- Increased Complication Risk Due to Similar Adverse Effect (Increase hyperkalemia with ACEIs with potassium-sparing diuretics



DDIs- Drug on Drug Interactions

Warfarin as a Model

- Warfarin- Vitamin K Antagonist, key cofactor in the synthesis of Coag Factors II, VII, IX, X
- No effect on activated factors, only synthesis of new ones (delayed onset)
- Elderly catabolize clotting factors more slowly, intensifying delay of onset / interactions
- S & R Warfarin Isomers have different drug interactions



Warfarin-Therapeutic Considerations

- Clinical effect measured by the International Normalized Ratio, (INR)
- Narrow Therapeutic Window
 - Risk for Intracerebral Bleed doubled with each increase of 1 in INR ⁽¹⁾
 - Risk for Stroke/DVT doubled with poor anticoagulation control for patients in lowest tertile ⁽²⁾
- (1) Hylek, Ann Intern Med 1994;120:897-902
- (2) White, Arch Intern Med 2007;167:239-45



Warfarin-Therapeutic Considerations

Influence of Increasing Age

- Age, an independent two fold risk factor for bleeding (1)
- Atrial Fibrillation / Valve Disease increase thromboembolic risk (15-25% of Strokes) (2)
- Many elderly have additional risk factors – co-morbidities, cognitive deficits, social barriers, transportation, etc

- (1) Hutton, Drugs Aging 1999;53:655-9
- (2) Singer CHEST 2008,133:546-592



Pharmacokinetic Drug Interactions with Warfarin

- Inhibition of CYP 450 Warfarin Metabolism (Increase of INR & Bleeding Risk)
 - sulfamethoxazole/trimethoprim(Bactrim), amiodarone(Cordarone), metronidazole(Flagyl), fluconazole(Diflucan),omeprazole(Prilosec), cimetidine (Tagamet)
 - Speed of onset/offset of interaction differs
 - Patient Variability
 - Management- alternative drug, INR monitoring, prophylactic Warfarin dose adjustment



Pharmacokinetic Drug Interactions with Warfarin

- Induction of CYP 450 Warfarin Metabolism (Decrease of INR & Increased Thromboembolic Risk)
 - (rifampin(Rifaden), carbamazepine(Tegretol), phenytoin(Dilantin), nafcillin(Unipen), dicloxacillin(Dynapen)
 - Speed of onset/offset of interaction often delayed
 - Patient Variability
 - Management- alternative med, alternative anticoagulation, INR monitoring, prophylactic dose adjustment



Pharmacokinetic Drug Interactions with Warfarin

- Drugs that Inhibit absorption of Warfarin
(Reduced INR & Increased Thromboembolic Risk)
 - cholestyramine(Questran), colestipol(Colestid), mesalamine(Asacol), sucralfate(Carafate)
 - Management- avoidance, timing of Warfarin dose, INR monitoring



Pharmacodynamic Drug Interactions with Warfarin

- Excessive Therapeutic Effect Due to Similar Clinical Indication (independent of INR)
 - independently increase hemorrhagic risk
 - aspirin(Bayer), clopidogrel(Plavix), NSAIDS, Heparin, fondaparinux(Arixtra)
- May be appropriate with mechanical heart valves, atrial fib, stents, hx of Stroke
- Risk Assessment / Counseling



Pharmacodynamic Drug Interactions with Warfarin

- Excessive Therapeutic Effect Due to Unintended Clinical Effect
 - levothyroxine(Synthroid) increases INR by increasing catabolism of clotting factors
 - Broad Spectrum Antibiotics may increase INR by reducing Vit K producing gut flora or conversion of Vit K to reduced KH₂
 - orlistat (Alli) may increase INR by reducing absorption of (fat soluble) Vit K



Pharmacodynamic Drug Interactions with Warfarin

- Blunted Therapeutic Effect Due to Opposite or Unintended Clinical Effect
 - Direct Increase of Thromboembolic Risk with no effect on INR or Warfarin kinetics
 - Oral Contraceptives, HRT



Pharmacodynamic Drug Interactions with Warfarin

- Increased Bleeding Risk due to Similar Adverse Effect Profile (Independent of INR & Warfarin)
 - NSAIDS, Steroids, Antiplatelet Agents

