

P & T News

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MEDICATION USE IN OLDER ADULTS

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Older adults aged 65 years or more comprise about 15% of the United States population, but account for almost one-third of prescription drug use.¹ Thirty percent of hospitalizations in the older adult population are associated with drug-related problems or toxic effects of drug therapy.² It has been estimated that 21% of community-dwelling older adults and 40% of nursing home residents have received one or more inappropriate medications.³ Older adults are at high risk for medication side effects and adverse events due to a variety of reasons including both pharmacokinetic and pharmacodynamic age-related changes. Pharmacokinetic changes include alterations in drug absorption, distribution, metabolism and excretion, while pharmacodynamic changes refer to sensitivity to drug effects.

Pharmacokinetic Age-Related Changes

Absorption

Drug absorption is the uptake of medication into the bloodstream. In older adults, gastric pH increases, gut motility decreases, and splanchnic blood flow decreases by approximately 40%. Despite these changes, drug absorption remains generally unchanged with increasing age because most drug absorption occurs via passive diffusion in the duodenum which is not changed significantly with age. Calcium and iron require a low pH for absorption, and therefore, absorption of certain products may be reduced in older adults with increased gastric pH.

Distribution

Total body fat increases with age while total body water and lean muscle mass decrease. These age-related changes lead to effects on drug distribution. The volume of distribution of fat-soluble drugs (e.g., diazepam) is increased; therefore, the drug remains in the fatty tissues longer and the effect is prolonged. Alternatively, water-soluble drugs (e.g., NSAIDs) will reach therapeutic concentrations with lower doses. Reduced muscle mass results in higher levels of free drug for medications that bind to muscle (e.g., digoxin). Older adults may also have lower levels of albumin resulting in higher levels of free drug for agents that are highly protein bound (e.g., warfarin).



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Metabolism

With age, both hepatic blood flow and the number of functioning hepatocytes decrease. Overall, this results in a reduced capacity of the liver to metabolize drugs, and consequently, longer lasting drug effects. Some medications such as benzodiazepines, meperidine, and fluoxetine have active metabolites and the action of these medications can be significantly prolonged and contribute to adverse effects in older adults.

Excretion

For most drugs, elimination occurs primarily through the kidneys (as is the case with many antibiotics), and renal function may be reduced by up to 35-50% with age. Increased adverse effects are a risk in older adults due to accumulation of drug; therefore, medication doses need to be appropriately reduced according to renal function. Because serum creatinine levels reflect muscle mass and do not provide a reliable measure of renal function in older adults, an estimation of creatinine clearance should be used for dosing certain medications. An equation commonly used for calculating creatinine clearance (CrCl) is the Cockcroft-Gault equation:

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{weight (Kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for females})$$

Alternatively, the Modification of Diet in Renal Disease (MDRD) equation may be used. It appears to be associated with less bias and is a more accurate estimate of GFR compared to Cockcroft-Gault, but has only been validated in patients with renal failure.⁴

Pharmacodynamic Age-Related Changes

Pharmacodynamics refers to the sensitivity of an individual to drug effects at certain doses. Older adults exhibit increased receptor response to certain medications including benzodiazepines and antihistamines; thus, older adults are more likely to experience adverse effects with these medications at usual doses. Therefore, it is generally recommended that these medications be avoided in the older population.

The Beers Criteria

The Beers criteria are a list of medications considered potentially inappropriate for older adults. The list of medications was developed through literature review conducted by experts in pharmacology and geriatrics as well as questionnaires completed by experts in these fields. Initially published in 1991, the Beers criteria included medications inappropriate for nursing home residents greater than 65 years of age and were originally developed for the frailest elderly.⁵ The criteria were updated and expanded in 1997 with the goals of generalizing the criteria to the entire population over 65 years of age regardless of frailty or residence, assigning relative severity to each criterion and incorporating additional information considering medication use in certain diagnoses.⁶ The most recent update to the Beers criteria was published in 2003 and includes new products and information, reevaluated severity ratings, and new conditions or considerations not addressed in the 1997 update.² The current list is broken down into those medications which may be inappropriate for of any diagnosis or condition and medications which may be inappropriate depending on the circumstances for which they are being prescribed. Medications included in the Beers criteria are listed because their use in older adults poses an increased risk for adverse effects and events such as confusion, falls, and fractures.

Older adults are particularly sensitive to the adverse anticholinergic effects of many medications and anticholinergic side effects are a major determinant for the inclusion of many medications listed on the Beers criteria. Anticholinergic adverse effects are caused by a variety of medications including antihistamines, tricyclic antidepressants, muscle relaxants, gastrointestinal antispasmodics, and antipsychotics. The most common peripheral effects include dry mouth, blurry vision due to dry eyes, urinary retention, and constipation. Central effects include impaired concentration, confusion, reduced attention, and memory impairment.⁷

The updated Beers criteria include 48 medications/classes of medications that should be avoided and 20 diseases or conditions in which certain medications should be avoided. Table 1 lists a selection of specific medications that should be avoided. Table 2 includes conditions/disease states in which certain medications should be avoided.

Table 1. Specific Medications Which Should Generally Be Avoided in Older Adults

Medication	Concerns	Alternative(s)
Amitriptyline (Elavil®)	High risk of anticholinergic side effects due to active metabolite, confusion, increased risk of falls and fractures	Nortriptyline (Pamelor®), desipramine (Norpramin®)
Cimetidine (Tagamet®)	Confusion, increased fracture risk, drug interactions due to CYP3A4 inhibition	Famotidine (Pepcid®), lansoprazole (Prevacid®)
Diazepam (Valium®)	Prolonged half-life due to active metabolites, increased fall and fracture risk, delirium, confusion, memory disturbances	Taper and discontinue if possible, or use short-acting benzodiazepines (e.g., lorazepam [Ativan®]), although all benzodiazepines are strongly discouraged
Fluoxetine (Prozac®)	Long half-life, CNS stimulation, hyponatremia, weight loss	Citalopram (Celexa®), mirtazepine (Remeron®), sertraline (Zoloft®)
Meperidine (Demerol®)	Active metabolite (normeperidine) with long half-life, excitatory effects, confusion	Morphine, other analgesics
Antihistamines (diphenhydramine [Benadryl®], hydroxyzine [Vistaril®], etc.)	Potent anticholinergic side effects	Second-generation antihistamines (e.g., loratadine [Claritin®])
Muscle relaxants (cyclobenzaprine [Flexeril®], carisoprodol [Soma®], etc.)	Anticholinergic effects, sedation, weakness, lack of efficacy at tolerated doses	Exercise, physical therapy
Propoxyphene (Darvon®), propoxyphene-acetaminophen (Darvocet®)	Opioid side effects, no analgesic advantage over acetaminophen alone	Acetaminophen (Tylenol®)
Oxybutynin (Ditropan®)	Anticholinergic effects and lack of efficacy at tolerated doses	Extended-release formulations of oxybutynin (Ditropan XL®) or tolterodine (Detrol LA®)
Ketorolac (Toradol®)	High risk for asymptomatic but severe gastrointestinal adverse effects	Acetaminophen (Tylenol®)

A retrospective cohort study using the Beers criteria and a pharmacy benefits manager prescription claims database found that 21% of patients filled a prescription for at least one drug of concern, and almost 16% filled a prescription for two or more drugs of concern. The most commonly filled drugs of concern were amitriptyline and doxepin, which may be associated with anticholinergic side effects as well as confusion, falls, and fractures.¹

At UIHC, the most commonly prescribed drugs of concern include amitriptyline, cimetidine, diazepam, and fluoxetine. Nortriptyline and desipramine are tricyclic antidepressants that have fewer anticholinergic side effects than amitriptyline and are generally tolerated better in the older population. Alternatives to cimetidine include famotidine or lansoprazole. Generally, use of any benzodiazepine is discouraged in older adults; however, if a benzodiazepine must be used, intermediate- or short-acting benzodiazepines without active metabolites (such as lorazepam) are preferred. Fluoxetine (Prozac®) has a very long half-life and an active metabolite (norfluoxetine) that may cause CNS stimulation. Alternative antidepressants include citalopram, sertraline, and mirtazepine, with both citalopram and mirtazepine being available in a generic formulation.

Table 2. Conditions/Disease States in Which Certain Medication Should Be Avoided

Diagnosis	Medication (s) of Concern	Effects
Hypertension	Pseudoephedrine	May elevate blood pressure
Bladder outflow obstruction	Any anticholinergic medication	Causes urinary retention
Chronic constipation	Calcium channel blockers and anticholinergics	Worsen/cause constipation
Parkinson's disease	Metoclopramide, conventional antipsychotics	Antidopaminergic/cholinergic effects
Cognitive impairment	Anticholinergics, CNS stimulants	CNS altering effects
SIADH/hyponatremia	Selective serotonin reuptake inhibitors (SSRIs)	Exacerbate/cause SIADH hyponatremia
Insomnia	Pseudoephedrine, Monoamine oxidase inhibitors (MAOIs), methylphenidate (Ritalin®)	CNS stimulation
Gastric or duodenal ulcers	Non-steroidal antiinflammatory drugs (NSAIDs), Aspirin >325 mg/day	May cause or exacerbate ulcers
Receiving anticoagulant therapy	Aspirin, NSAIDs, Dipyridamole (Persantine®), Clopidogrel (Plavix®)	Inhibition of platelet aggregation, increased risk of bleeding

SIADH = Syndrome of Inappropriate Antidiuretic Hormone Secretion

CNS = Central Nervous System

Initiatives to Reduce Use of Beers Criteria Medications at UIHC

UIHC received benchmarking data from the University HealthSystem Consortium (UHC) for patients over 65 years of age who received discharge medications that were considered inappropriate for use in older adults based on the Beers criteria. A task force was created to evaluate the data and make recommendations to decrease the use of inappropriate medications at UIHC. Several interventions are planned or already underway. The primary medications being addressed are amitriptyline, cimetidine, diazepam, fluoxetine, and meperidine. Preprinted doctors' order forms are being evaluated for elimination of problematic medications, educational initiatives for health care professionals are being provided, and pharmacists are receiving notifications when an older adult is prescribed a medication that is considered inappropriate so that follow-up with the health care team can occur.

Summary

In summary, older adults over 65 years of age are at high risk for drug-related problems. Certain medications should be avoided or used with extreme caution in older adults due to the potential for side effects and adverse drug reactions. When using medications in older adults, the risks and benefits of the medication should continually be assessed throughout therapy. Medications should generally be initiated at low doses and titrated slowly as needed. The Beers criteria should be used to determine which medications may be inappropriate in the older adult population.

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References

1. Arch Intern Med. 2004; 164: 1621-5.
2. Arch Intern Med. 2003; 163: 2716-24.
3. Am J Health-Syst Pharm. 2005; 62: 626-9.
4. Ann Intern Med. 1999; 130: 461-70.
5. Arch Intern Med. 1991; 151: 1825-32.
6. Arch Intern Med. 1997; 157: 1531-6.
7. Prim Care Companion J Clin Psychiatry. 2004; 6(suppl 2): 20-3.

Restricted Prescribing of Iron Dextran Due to Safety Issues

Parenteral iron therapy is occasionally necessary for patients receiving erythropoietin therapy, patients who are intolerant or unresponsive to oral iron therapy, or for use in treating functional iron deficiency. Three parenteral iron products are available in the United States: sodium ferric gluconate (Ferrlecit®), iron sucrose (Venofer®), and iron dextran (InFeD®). The use of these parenteral iron products is associated with adverse events ranging from mild to extreme severity. Adverse events to iron dextran, iron sucrose, and sodium ferric gluconate have been reported to occur in up to 50%, 36%, and 35% of patients, respectively.¹ The most common adverse events include hypotension, hypertension, bradycardia, chest pain, nausea, vomiting, diarrhea, abdominal pain, headache, fever, allergic reactions, pruritus, malaise, arthralgias, myalgias, and back pain. **In particular, iron dextran, has been associated with fatal anaphylactoid reactions.** Post-marketing data report hypersensitivity rates for iron sucrose and ferric gluconate to be 2.6 episodes per million doses; however, the rate for iron dextran is 8.7 episodes per million doses. To date, fatal hypersensitivity reactions have not been reported with ferric gluconate or iron sucrose; however, **the incidence of serious life threatening anaphylactoid reactions associated with iron dextran is reported to be between 0.6 to 0.7%.¹**

Iron sucrose, sodium ferric gluconate, and iron dextran are available at UIHC. Iron sucrose is most commonly prescribed; however, because iron dextran can be given in large doses of 1000 mg to 2000 mg at one time, it is occasionally prescribed at UIHC for total dose infusions. Unfortunately, **based on adverse drug reaction reporting at UIHC between December 2004 and November 2005, 8.9% of patients who received iron dextran experienced a severe anaphylactoid reaction, consisting of shortness of breath, throat tightening, chest tightness, and/or tachycardia.** Due to the risk of fatal hypersensitivity reactions associated with iron dextran and the availability of safer alternatives, such as sodium ferric gluconate and iron sucrose, the Pharmacy and Therapeutics Subcommittee has decided that **iron dextran should be restricted to use in patients who require a one time total dose infusion of iron and who meet the specified criteria for use** (see Table 1). A preprinted A1a Doctors' Order form will be available to check the appropriate criteria for use of iron dextran, choices for pre-medications, orders for iron dextran, and to help minimize adverse effects of total dose iron dextran infusion, the medications that must be kept at bedside in the event of a severe anaphylactoid reaction. In addition, an informed consent document must be reviewed with the patient and signed by the patient prior to starting the infusion. The prescriber must complete the preprinted A1a Doctors' Order form and the patient must sign the informed consent document before pharmacy will dispense the dose.

Table 1. Criteria for Use of Total Dose Iron Dextran Infusion

<p>Patient requires a total dose infusion with iron dextran* because he/she is:</p> <ol style="list-style-type: none">1) Unable to receive multiple infusions of sodium ferric gluconate or iron sucrose locally.2) Historically non-compliant with follow up infusions.3) Unable to return to UIHC (due to transportation issues) to receive multiple infusions of iron sucrose (Venofer®) or sodium ferric gluconate (Ferrlecit®).4) Unable to use iron sucrose (Venofer®) or sodium ferric gluconate (Ferrlecit®) due to a previous severe anaphylactoid adverse reaction to one of these agents. <p>*As safer alternatives, iron sucrose may be given in doses up to 500 mg IV over 4 hours and sodium ferric gluconate may be given in doses up to 250 mg over 1 hour.</p> <p><i>One of the above criteria for use must be met, AND the patients must sign an informed consent document.</i></p>

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Reference:

1. *Am J Hematol* 2004; 76:74-8.

PHARMACY AND THERAPEUTICS SUBCOMMITTEE ACTIONS

DRUGS ADDED TO STOCK

ABATACEPT

Abatacept (Orencia® - BMS) is an inhibitor of T-cell activation used for the treatment of moderate to severe rheumatoid arthritis in patients who have not responded to disease-modifying drugs.

Note: The prescribing of abatacept is restricted to Rheumatology.

AMINOLEVULINIC ACID

Aminolevulinic acid (Levulan® Kerastick® - Berlex) topical solution is indicated for the treatment of actinic keratosis of the face and scalp.

Note: Prescribing is restricted to Dermatology.

CONIVAPTAN

Conivaptan (Vaprisol® - Astellas) injection is indicated for the treatment of euvoletic hyponatremia in hospitalized patients.

Note: Prescribing of conivaptan is restricted to Nephrology.

ETHYLENE VINYL ALCOHOL COPOLYMER IN DMSO

This urethral implant (Tegress® - Bard) is indicated for the treatment of women with stress urinary incontinence due to sphincter deficiency.

Note: Prescribing is restricted to Urology and Urogynecology.

ROTAVIRUS VACCINE

Rotavirus oral vaccine (RotaTeq® - Merck) is indicated for the prevention of rotavirus gastroenteritis in infants and children.

SOLIFENACIN

Solifenacin (Vesicare® - Astellas/GSK) is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

ADDITIONAL ACTIONS

BRIMONIDINE 0.1% OPHTHALMIC SOLUTION

This product replaces the 0.15% Alphagan P® product. The Pharmacy and Therapeutics Subcommittee considers Alphagan® 0.2% and Alphagan P® 0.1% and 0.15% to be therapeutically equivalent and may be used interchangeably. Pharmacy will dispense the generic form of brimonidine unless prescriptions/orders for Alphagan P® are marked as "DAW" or "Dispense As Written", then the Alphagan P® product ordered will be dispensed.

CLEANSING RECTAL ENEMA

A pediatric formulation (Fleet Enema for Children®) has been added to stock.

DULOXETINE

Due to reports of hepatotoxicity, duloxetine should not be used in patients with liver disease or who use a substantial amount of alcohol.

Note: The prescribing of duloxetine is restricted to the Pain Medicine Service.

MEASLES, MUMPS, RUBELLA, AND VARICELLA VIRUS VACCINE

This combination vaccine (ProQuad®) has been added to stock.

DRUGS DELETED FROM STOCK

ACITRETIN (SORIATANE®) 10 mg CAPSULES

Discontinued due to low use. Acitretin 25 mg capsules are available.

ALUMINUM HYDROXIDE ORAL SUSPENSION 360 ml BOTTLES

Discontinued due to low use. Aluminum Hydroxide 400 mg capsules are available.

AMOXICILLIN-CLAVULANATE EXTENDED-RELEASE (AUGMENTIN® XR) TABLETS

Discontinued due to the availability of regular-release tablets and extra-strength tablets.

BRIMONIDINE 0.15% OPHTHALMIC SOLUTION

Replaced with 0.1% (Alphagan P®) ophthalmic solution.

CIMETIDINE

Discontinued due to low use. Famotidine tablets, injections, and oral liquid are available.

CLARITHROMYCIN EXTENDED-RELEASE TABLETS (BIAIXIN XL®)

Discontinued due to low use. Clarithromycin regular-release tablets are available.

DEXTRAN 70 6% IN 0.9% NaCl 500 ml

Discontinued due to low use.

DIPIVEFRIN (PROPINE®) 0.1% OPHTHALMIC SOLUTION

Discontinued due to low use. Brimonidine ophthalmic solution is available.

DURASPHERE®

Discontinued due to low use. Contigen® is available.

FLOXURIDINE (FUDR®) INJECTION

Discontinued due to low use. Other antineoplastic agents are available.

FLUOROURACIL (CARAC®) 0.5% TOPICAL CREAM

Discontinued due to low use. Fluorouracil 1% and 5% topical cream is available.

GADODIAMIDE (OMNISCAN®) INJECTION 50 ml

Discontinued due to low use. Gadodiamide injection 5, 10, 15, and 20 ml are available.

GADOTERIDOL (PROHANCE®) INJECTION

Discontinued due to low use. Gadodiamide injection is available.

GENTAMICIN 0.1% TOPICAL OINTMENT

Discontinued due to low use. Bacitracin topical ointment is available.

GONADORELIN (FACTREL®) 100 mcg INJECTION

Discontinued due to low use. Menotropins injection is available.

GRISEOFULVIN 125 mg ULTRAMICRONIZED TABLET

Discontinued due to low use. Griseofulvin 250 mg ultramicrosized tablet is available.

HYDROXYPROPYLMETHYLCELLULOSE 0.3% OPHTHALMIC GEL 10 ml

Discontinued due to low use. Hydroxypropylmethylcellulose 0.3% Ophthalmic Gel 3 ml is available.

P & S LIQUID TOPICAL SOLUTION

Discontinued due to low use.