# Geriatric Giant Lecture Series
# Adverse Events and Adverse Drug Reactions in the Elderly

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**A. ADVERSE EVENTS**

**1. Definition of Adverse Event**
"Event that could or does result in unintended injury or complications arising from health care management, with outcomes that may range from death or disability to dissatisfaction, or require a change in care (such as prolongation of hospital stay)[1]

**2. Incidence of Adverse Events**

The elderly are at increased risk because of:
> Decreased homeostatic reserves
> Increased comorbidity
> Increased polypharmacy

The incidence in the USA is 5.3% in the elderly compared with 2.8% in the non-elderly. [2] In the Canadian Adverse Events Study the incidence of adverse events was 7.5% (similar to UK and Australian figures). In 36.9% of cases they were deemed to be preventable and this was the case in 20.8% of deaths.

Top two categories:
> Surgical procedures 34%
> Drug/fluid interventions 24%[3]

**3. Impact of Adverse Events**

To err is human but carries a high cost:
> Morbidity - 185,000 admissions/year[3]
> Mortality - 9,250-23,750 deaths[3] (3rd leading cause of death in USA).[4]
> Increased LOS in hospital
> Increased costs

**4. Types of Adverse Events**

This includes adverse consequences of:
> Medications – adverse drug events
> Investigations
> Procedures
> Prolonged hospitalisation and immobilisation
> Nosocomial infection
> Environmental hazards

These consequences may occur spontaneously or as the result of error. They include both acts of omission (failure to diagnose and treat) and act of commission (incorrect diagnosis or treatment, or poor performance).

## 5.  Immediate Management of Clinically Serious Adverse Event Algorithm[1]

- **R**espond to the patient's immediate needs
- **E**nvironment – provide a safe environment for other patients and staff
- **S**ecure and remove equipment/ medication/ supplies and/or products
- **P**rotect other patients and staff
- **O**ffer support to patient, family  and staff
- **N**otify the most responsible health practitioner
- **D**isclosure process initiated and event documented in the patient's health record and event reported in the AHS Reporting and Learning System for Patient Safety

## 6.  Limiting Adverse Events

Avoid unnecessary and risky diagnostic procedures.  Always obtain informed consent involving patient and families' agenda.

Limit hospitalization by beginning discharge planning from day 1 of the hospitalization.

Maximize function by engaging PT/OT early.

Always pay attention to infection control with washing hands and cleaning medical devices.

## B. ADVERSE DRUG EVENTS (ADE)

## 1.  Definition of Adverse Drug Event

An adverse drug event (ADE) is any unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use and suspected to be related to the drug. Adverse drug reactions can be divided into four types:

       **Type A (augmented)** reactions result from an exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose and are normally dose-dependent (e.g. low blood pressure with antihypertensives, low blood sugar with insulin). They also include reactions that are not directly related to the desired clinical action of the drug (e.g. dry mouth associated with tricyclic antidepressants). 80% of ADE's causing admission or occurring in hospital are type A in nature[5]

       **Type B (bizarre)** reactions represent a novel response not expected from the known pharmacological actions of the drug (e.g. anaphylaxis with penicillin, angioedema with angiotensin-converting enzyme-inhibiting drugs). They are not normally dependent on the dose and are often immune mediated.[6, 7]

       **Type C** reactions are associated with long term therapy (e.g. analgesic nephropathy)

       **Type D** reactions are delayed (e.g. carcinogenic, teratogenic).

## 2. Description of inappropriate prescribing in the elderly[8]

" . . a situation in which the pharmacotherapy does not  meet accepted medical standards".  Specifically it includes:

a) *overuse* (prescribing more drugs than clinically indicated  eg. antibiotics)
b) *underuse* (failure to prescribe drugs that are indicated for the treatment or prevention of a disease or condition eg. anticoagulation for atrial fibrillation, treatment for depression, pain and osteoporosis)

c) *misuse* (prescribing incorrectly a drug that is needed  eg. wrong dose, duration)
The 2010 CIHI report found that individuals older than 65 years of age consume ~ 40% of prescription drugs, despite the fact they represent ~14% of the total Canadian population.  It is estimated that the prevalence of potentially inappropriate prescribing (PIP) in this age group ranges from 11-65%.[9,10] With increased number of drugs consumed, the PIP risk rises.  With less than 4 drugs there is an associated 12% risk and with more than 5 drugs the risk increases to 40%.[11]

### 3.  Barriers to Optimal Drug Utilization
a)  Patient factors: increased comorbidities (hepatic, renal, cardiac) , consumer expectations, atypical disease presentation, functional limitations, cost concerns, fears to side effects/ dependency, number of drugs prescribed
b)  Physician factors: time committed to med review, reluctance to stop drugs, usage of the prescribing cascade to treat symptoms induced by other medications,
c)  System factors: multiple prescribers/ pharmacies, limited clinical pharmacy interaction

### 4.  Sequelae of inappropriate prescribing
Adverse drug events occur 2-3 times as frequently in older persons.
Patients taking:
> < 3 drugs have a 1-2% risk of ADE
> > 6 drugs have a 13% risk of ADE

30% of admissions to hospital are because of adverse drug events.  ADE's increase hospital length of stay, increase costs and increase mortality.  Drug-related morbidity annual costs are estimated to be $177 billion US in 2000 and ~11 billion in Canada.[12]  In nursing homes $1.33 is spent on adverse reactions for every $1 spent on medications. Other sequelae include reduced quality of life and decreased function

### 5.  Implicit and Explicit Criteria for appropriate Drug prescribing

This can occur by two methods – implicit (judgment-based) or explicit (criteria-based, using pre-determined standards).[13,8]  In general, a combined approach using a structured approach and clinical judgment with consideration of individual needs/ circumstances likely the most effective.
Implicit criteria rely on a clinician's judgment applied to an individual's clinical information and existing literature.  One such instrument to be used in this way is the Medication Appropriateness Index (MAI), developed in 1992 by Hanlon.[14] The use of this instrument has been used in outpatient, inpatient, long term care settings and is likely the best one for evaluation of geriatric psychiatry prescribing. The original MAI requires rating 10 weighted criteria for each drug prescribed, resulting in a score per drug and a summated score per patient.  A medication with a higher score indicates the drug is less suitable for a senior to have. The 10 questions MAI covers include:
Indication – is there sufficient reason for the use of the drug (curative, palliative and preventative)
Effectiveness – is the drug capable of being effective for the indication in a population of patients

Dosage – total amount of med taken per 24 hours; should be adjusted for renal function

Correct directions – assesses the route of administration, relationship to food and liquid, the schedule and time of the day

Drug-drug interactions – interaction affecting pharmacokinetics or pharmacodynamics when combining drugs

Drug-disease interactions – effect the drug has on a pre-existing and/or concomitant disease or condition.

Directions practical – applicable to patient's life

Unnecessary duplication – non-beneficial or risky combination of drugs with the same mechanism of action

Duration acceptable – evidence exists for the benefit and safety of the med

Expense – how the cost of the drug compares to other agents or equal efficacy and safety

Issues with the implicit criteria include differences with physician judgment (thus lowering reliability/ practical utility), and it is time consuming.  It does not explicitly refer to specific drugs or drug classes that are problematic in older people and does not capture underuse issues. This criteria is more transferrable across countries and does not need updates regularly but application requires more extensive professional skills.

<u>Explicit</u> criteria are drug or disease oriented and has high reliability and reproducibility.  They can be readily applied to large samples of people. The problems with relying solely on explicit criteria include the fact that the lists of drugs can become outdated.  At best, these criteria may be considered screening tools to identify and priorize problem areas in drug prescribing for high risk elderly. One example is the updated 2012 Beers criteria. It is useful to warn physicians of potential problems prior to prescribing.  It categorizes the medications / classes that should be avoided in those 65 +. It was developed from interdisciplinary panel of 11 experts who applied modified Delphi method to the systematic review and grading to reach consensus.  53 medications / or classes are divided into 3 categories: potentially inappropriate meds (PIM)/ classes to avoid, PIM to avoid with certain diseases/ syndromes and meds to be used with caution in older adults.  Some noteworthy additions of drugs to avoid in the 2012 criteria include all short acting BZ (regardless of dose), glyburide, megesterol, metoclopramide, sliding scale insulin.  Among new drug-disease interactions added include CI/syncope, SSRI/fall or fractures and pioglitazone/ rosiglitazone/ CHF.[15]  Limitations to the 2012 criteria include the evidence base, lack of dose-adjustment for renal function, drug-drug interactions, therapeutic duplication, special populations within geriatrics, list of alternatives.  The Beers criteria will be regularly updated every 3 years.[15] There are drugs listed like amiodarone, doxazosin, nitrofurantoin as inappropriate when they may be the most appropriate choices depending on the individual case.

In Europe, explicit criteria using the **S**creening **T**ool of **O**lder **P**erson's **P**rescriptions (STOPP) has been used.  STOPP 2006 includes 65 indicators for potentially inappropriate prescribing including drug-disease interactions, drug-drug interactions, therapeutic duplication and duration of therapy concerns.  An updated version of STOPP will be validated and published in 2012.  Differences between STOPP and Beers criteria include the following:  STOPP is organized according to physiological systems, emphasizes adverse drug-drug interactions and duplicate drug class prescription and

common instances of potentially PIM not included in the Beers.[16]  STOPP can be used not only as a screening tool but also as a method of ID potential ADEs.

Recurring drug categories to avoid, regardless of the consensus criteria used, include the following: [17,18]

a) Anticholinergics (eg. tertiary tricyclic antidepressants, GI anti-spasmodics, antimuscarinics,  antipsychotics, first-generation antihistamines) with concerns of CNS, GI, GU, cardiovascular side effects and fall risk
b) Sedative/hypnotics (eg. barbiturates, long and short acting benzodiazepines, Z-drugs should not be prescribed for chronic usage)
c) Anti-inflammatories (eg. non-COX NSAIDS – avoid chronic usage)
d) Opiate-related Analgesics (eg. pentazocine, meperidine)
e) Antiarrythmics Class Ia, Ic, III (eg. disopyramide with anticholinergic, negatively inotropic side effects; amiodarone, digoxin > 0.125 mg/d)
f) Cardiovascular (eg. alpha blockers, alpha agonists, IR nifedipine, spironolactone > 25 mg/d with risk of hyperkalemia)
g) Anti-infective (eg. nitrofurantoin with reduced CrCl/ pulmonary toxicity)
h) Endocrine (eg. dessicated thyroid /cardiac, testosterone /cardiac/ CA risk, GH, sliding scale/ hypoglycemia, megesterol/ DVT, OHA/glyburide with low BS)

## 3. Factors Associated with ADE

ADE's are increased in the elderly due to changes with drug handling that occur with aging, increased comorbidity, polypharmacy and non adherence.
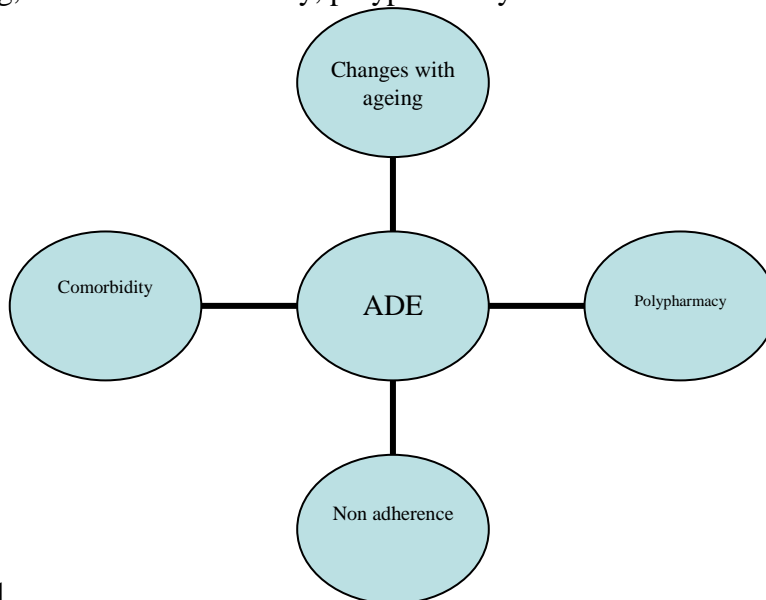


Fig 1

### i) Physiology of Aging

Body composition changes as we age which can alter the pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body).  With

aging there is decreased lean body mass, decreased albumin, increased adipose tissue and decrease in total body water. This leads to an increased volume of distribution of *lipid*-soluble drugs resulting in a longer half life and duration of action of those drugs affected e.g. benzodiazepines.

$$t\frac{1}{2} = \frac{\text{Vd (vol of distribution)}}{\text{clearance}}$$

Conversely, with the decreased volume of distribution seen with *water*-soluble medications such as digoxin, morphine, lithium and theophylline increased serum concentrations with rapid peak effects and potential for toxicity can be seen. Therefore, a lower loading dose should be considered.

There is a decrease in albumin with age (20% over the lifespan). This can result in larger unbound (active) drug being available which can lead to toxicity. Drugs that are protein-bound include warfarin, ASA, NSAIDS, phenytoin, antiepileptics and theophylline. In acutely ill or malnourished patients, protein binding may play a role in distribution.

Absorption of drugs with aging is minimally affected. Drugs that inhibit propulsive gut motility retard absorption. Calcium, iron and vitamins may be absorbed at slower rates due to active transport mechanisms. Note that with the transdermal route of administration there can be variable absorption.

In considering changes with drug metabolism there is a reduction in liver mass / blood flow and reduced first pass metabolism. This could result in increased bioavailability for some drugs such as verapamil or labetolol. Dose adjustments have been made in the formulation of these drugs to ensure adequate dose reaches the systemic circulation.

There is negligible difference in conjugation with age (phase II metabolism). There is however changes with phase I metabolism with oxidation/ reduction. The bulk of drug metabolism occurs via the cytochrome P450 (CYP) oxidation/reduction enzyme system. The extent of inhibition or induction varies with this enzyme system and can also be impacted by environmental, genetic or lifestyle factors such as smoking.

With aging there are renal physiological changes seen with a reduction in renal blood flow, number of functioning nephrons, tubular secretion and glomerular filtration rate. The result is that drugs reach higher blood levels and stay in the body longer. Serum creatinine is not a reliable indicator of renal decline. Typically renal function for drug *dose* adjustment utilizes the Cockcroft-Gault formula:

- CLCR= (140 – age) x weight (kg) x *constant*
         Serum Creatinine (µmol/L)
- For females the constant is 1.04
- For males the constant is 1.23

With slower drug clearance the half life of the drug and the duration of drug effect is longer.

Pharmacodynamics refers to a process where there is an interaction between a drug and an effector organ resulting in a change of functional status of the organ. As a result of pharmacodynamics there is increased sensitivity to: sedative hypnotics, neuroleptics, antidepressants, antihypertensives, anticoagulants, narcotcs and anticholinergic agents. Decreased sensitivity is seen with beta blockers. If using these agents in clinical practice, start with lower doses and titrate to effect carefully.

### ii) Comorbidity

Numerous comorbidities increase the chance of <u>drug-disease</u> and <u>drug-drug</u> interactions. Examples of drug-disease interactions include: steroids usage affecting diabetic control, anticholinergics causing urinary retention, metoclopramide worsening the motor status of patients with Parkinson's disease. Drug-drug interactions include reduced blood pressure lowering effect of ACEI's with concomitant usage of NSAIDS and increased INR result with warfarin and Tylenol given together.

### iii) Non adherence

This may be *intentional.* The patient's compliance is dependent on how the drug regime fits with their beliefs and fears. Intentional non-adherence may be as high as 50% in elderly patients. There can be *non-intentional* factors contributing such as communication factors (ineffective instructions/advice regarding the drug, complex regimens, language barrier). There may be patient factors like poor vision/hearing, limited dexterity, cognitive impairment and mobility. Packaging of the drugs can impact adherence secondary to small labels, containers and generic naming. There may also be coordination factors secondary to multiple providers and lack of social support. Always rationalize medications. It has been shown that patients taking multiple daily doses of medication have a 75% rate of noncompliance.[19] Prescribers should try to utilize once or twice daily regimens.

### C. STRATEGIES FOR APPROPRIATE PRESCRIBING[20,21]

a)  Maintain an up-to-date drug list with explicit indications / objectives for all drugs prescribed;
    - consider nonpharmacologic options
    - regularly review need for the drug and stop the drug if possible; withdrawal of medications needs close attention also
b)  Know the actions, adverse effects, and toxicity profiles of meds prescribed; avoid and be vigilant of high-risk drugs as identified by Beers and STOPP criteria
    - consider adverse drug effect as a potential cause for any new symptom
c)  Start new medications at a low dose and titrate up based on tolerability and response; give time limited trial for new medications to determine if outcomes met
d)  Priorize medication prescribing – know life expectancy/ prognosis/ quality of life; time horizon to benefit; recommend how to modify treatment for the elderly in the context of life expectancy with these issues in mind[22]
e)  Avoid using one drug to treat the side effects of another (*prescribing cascade*)

f) Attempt to use one drug to treat two of more conditions
g) Avoid using drugs from the same class or with similar actions
h) Educate patient and/or caregiver about each medication;
   - know patient's cognitive / functional strengths / health literacy / access to care / financial concerns / cultural factors/ preferences
   - provide written information / engage in medication reconciliation ("teach me back" strategy)
   - may need to arrange home visit to review medications with transitional team member

   Educate prescribers/ MD
   -  know applicability and quality of evidence, outcomes, harms and burdens, time horizon to benefit
i) Maintain the simplest medication regimen regarding number of meds, routes, frequency of administration (once or twice daily dosing preferable)
j) Communicate with other prescribers (teamwork between MD and pharmacists leads to best outcomes); encourage one prescriber to be responsible primarily; transitions of care information to be clearly written / faxed in a timely manner
**k)** Engage in use of systems / technologies that support optimal prescribing behavior: [23,24]

   -drug utilization reviews
   -automated drug alerts providing info on potential drug interactions or dose problems
   -palmtop reference guides for drug-drug interactions tools
   -pharmacist-led interventions for med review
   -**Medication Reconciliation:** crucial for transitions of care.  It is a process that identify med discrepancies, informs prescribing decisions and prevents med errors.  The process has 3 steps: verification (med use history, accurate list), clarification  (meds and doses are accurate) and reconciliation (identify any discrepancies between what is ordered and patient list, making changes to orders, documenting changes, communicating updated list to next provider).  Process decreases med errors by 70% and ADE's by 15%.
   - **Structure Medication Review (SMR)[25]:** is a regularly scheduled discussion between a patient and their doctor/pharmacist/nurse to review ALL medications to address
   How each medication is working
   How each medication is taken
   Patient concerns
SMR should be done when the patient asks for a review, they have > 5 meds, > 3 comobidities, they have received meds from more than one physician and they have had a med change in the last 12 months

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