Medications and Falls
Part -1

Introduction with General Principles and Risk Evaluation for Cardiovascular Medications

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Saint Francis Hospital and Medical Center
Hartford, CT
December 14, 2018

Dennis J Chapron reports no real or potential conflicts of interest relevant to this lecture.
Learning Objectives:
1. Review the epidemiological data on falls and the elderly.
2. Discuss some general principles as they apply to an analysis of medication use and falls.
3. Review the various classes of antihypertensive medications and their relative risk for causing falls in the elderly.
4. Define postural hypotension, discuss the physiological mechanisms for upright blood pressure control and explain how medications can compromise these mechanisms.
5. Discuss some cases of medication-induced falls related to the use of antihypertensive medications or medications with secondary blood pressure lowering effects.

Some Facts
Centers for Disease Control (CDC)
Falls Statistics for Older Adults (≥65yrs)

- During 2014 approximately 27,000 older adults died because of falls.
- Nearly 3 million older adults were treated in the ED for fall-related injuries, including fractures and head trauma, and about 800,000 of these patients required hospitalization.
Medicare currently will not pay to treat an injury resulting from a fall in a hospital.
### Appendix C. Connecticut Adverse Events in 2016

#### Most Frequently Reported Events

<table>
<thead>
<tr>
<th>NQF List (1A-7D) and Connecticut-Specific List (CT1 &amp; CT2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Description</td>
</tr>
<tr>
<td>4F Unstageable, stage 3 or 4 pressure ulcers acquired after admission to a healthcare facility</td>
</tr>
<tr>
<td>4F Patient death or serious injury associated with a fall while being cared for in a healthcare facility</td>
</tr>
<tr>
<td>CT1 Perforations during open, laparoscopic and/or endoscopic procedures resulting in death or serious disability</td>
</tr>
<tr>
<td>7C Sexual abuse or assault on a patient or staff member</td>
</tr>
<tr>
<td>1D Retention of a foreign object in a patient after surgery or other procedure</td>
</tr>
<tr>
<td>1A Surgery performed on the wrong body part</td>
</tr>
<tr>
<td>CT2 Death or serious injury associated with surgery</td>
</tr>
<tr>
<td>Total All other reported adverse events</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
### Some Other Important Adverse Events

#### Appendix B. Counts of Adverse Event Codes 2012-2017 (half year)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>CT 1</td>
<td>Perforations during open, laparoscopic and/or endoscopic procedures resulting in death or serious injury</td>
<td>55</td>
<td>79</td>
<td>71</td>
<td>49</td>
<td>58</td>
<td>NA</td>
</tr>
<tr>
<td>CT 2</td>
<td>Patient death or serious injury as a result of surgery</td>
<td>14</td>
<td>13</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>NA</td>
</tr>
<tr>
<td>NQF 4E</td>
<td>Patient death or serious injury associated with a fall while being cared for in a healthcare setting</td>
<td>76</td>
<td>90</td>
<td>78</td>
<td>90</td>
<td>72</td>
<td>53</td>
</tr>
</tbody>
</table>

#### Medication Errors

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>NQF 4A</td>
<td>Patient death or serious injury associated with a medication error, errors involving the wrong drug, wrong dose, wrong patient, wrong time, wrong rate, wrong preparation or wrong route of administration</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

### Appendix D. Adverse Event Reports by Event Type

#### Acute Care Hospitals, Connecticut 2016

| Hospital             | 1A 1B 1C 1D 1E 2A 2B 2C 2D 2E 3A 3B 3C 3D 3E 4A 4B 4C 4D 4E 5F 5G 5H 5I 5J 5K 5L 6A 6B 6C 6D 6E 6F 6G 6H 6I 6J 6K 6L 7A 7B 7C 7D 7E 7F 7G 7H 7I 7J 7K 7L | 1A 1B 1C 1D 1E 2A 2B 2C 2D 2E 3A 3B 3C 3D 3E 4A 4B 4C 4D 4E 5F 5G 5H 5I 5J 5K 5L 6A 6B 6C 6D 6E 6F 6G 6H 6I 6J 6K 6L 7A 7B 7C 7D 7E 7F 7G 7H 7I 7J 7K 7L | 1A 1B 1C 1D 1E 2A 2B 2C 2D 2E 3A 3B 3C 3D 3E 4A 4B 4C 4D 4E 5F 5G 5H 5I 5J 5K 5L 6A 6B 6C 6D 6E 6F 6G 6H 6I 6J 6K 6L 7A 7B 7C 7D 7E 7F 7G 7H 7I 7J 7K 7L | 1A 1B 1C 1D 1E 2A 2B 2C 2D 2E 3A 3B 3C 3D 3E 4A 4B 4C 4D 4E 5F 5G 5H 5I 5J 5K 5L 6A 6B 6C 6D 6E 6F 6G 6H 6I 6J 6K 6L 7A 7B 7C 7D 7E 7F 7G 7H 7I 7J 7K 7L | 1A 1B 1C 1D 1E 2A 2B 2C 2D 2E 3A 3B 3C 3D 3E 4A 4B 4C 4D 4E 5F 5G 5H 5I 5J 5K 5L 6A 6B 6C 6D 6E 6F 6G 6H 6I 6J 6K 6L 7A 7B 7C 7D 7E 7F 7G 7H 7I 7J 7K 7L | 1A 1B 1C 1D 1E 2A 2B 2C 2D 2E 3A 3B 3C 3D 3E 4A 4B 4C 4D 4E 5F 5G 5H 5I 5J 5K 5L 6A 6B 6C 6D 6E 6F 6G 6H 6I 6J 6K 6L 7A 7B 7C 7D 7E 7F 7G 7H 7I 7J 7K 7L |
| Backus     | 1              | 1             | 1             | 2             | 3            | 10           | 1             | 4             | 1             | 4             |
| Bridgewater| 1              | 2             | 1             | 1             | 2            | 3            | 10           | 1             | 4             |
| Bristol    | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| CCMC       | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Danbury    | 3              | 10            | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Day, Kimbell| 2             | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Dempsey    | 1              | 4             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Greenwich  | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Griffin    | 1              | 3             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Hartford   | 2              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Holyoke    | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Johnson    | 4              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| L & M      | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Manchester | 1              | 2             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Middlesex  | 2              | 3             | 2             | 2             | 2             | 2             | 2             | 2             | 2             |
| Milford    | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Norwalk    | 1              | 2             | 4             | 6             | 4             | 6             | 4             | 6             | 4             |
| Rockville  | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| St. Francis| 3              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| St. Mary's | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| St. Vincent's|             | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Sharon     | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Stamford   | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Waterbury  | 3              | 6             | 4             | 6             | 4             | 6             | 4             | 6             | 4             |
| Windham    | 1              | 1             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |
| Yale New Haven | 5            | 3             | 1             | 1             | 1             | 1             | 1             | 1             | 1             |

Notes: Event categories changed between 2012 and 2013, e.g. old 5D is new 4E (falls); old 7A is new CT1 (perforations during surgery)
Appendix E. Adverse Event Reports by Event Type and Rates per 100,000 Inpatient Days, Chronic Disease Hospitals and Hospice, Connecticut, 2016

<table>
<thead>
<tr>
<th>Facility</th>
<th>Facility Type</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallery</td>
<td>Acute Care</td>
<td>2</td>
</tr>
<tr>
<td>Hop Special</td>
<td>Acute Care</td>
<td>2</td>
</tr>
<tr>
<td>Unnamed</td>
<td>Acute Care</td>
<td>1</td>
</tr>
<tr>
<td>Veterans</td>
<td>Acute Care</td>
<td>1</td>
</tr>
<tr>
<td>Hablon Home</td>
<td>Acute Care</td>
<td>0</td>
</tr>
<tr>
<td>Chronic Disease</td>
<td>Acute Care</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Event definitions and categories changed between 2012 and 2013. Old 5D is rev-B. Old TA is rev CT1 (perforations during surgery).

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Serious Reportable Events in 2016
Acute Care Hospitals, Non-Acute Care Hospitals and Ambulatory Surgical Centers

Katherine T. Fillo, Ph.D, RN-BC
Director of Clinical Quality Improvement
Bureau of Health Care Safety and Quality

Lauren B. Nelson, JD
Director of Policy and Regulatory Affairs
Bureau of Health Care Safety and Quality

Public Health Council
September 13, 2017

Health and Human Services
Departments & Divisions

Mass..gov

Health and Human Services
SRE Types

- Death or Serious Injury Associated with a Medication Error*
- Death or Serious Injury Associated with Unsafe Blood Product Administration
- Maternal Death or Serious Injury Associated with Low-Risk Pregnancy Labor or Delivery
- Death or Serious Injury of a Neonate
- Death or Serious Injury Associated with a Fall
- Stage 3 or Stage 4 of Unmeasurable Pressure Ulcer
- Artificial Insemination With Wrong Donor Sperm or Egg
- Death or Serious Injury from Irretrievable Loss of a Specimen*
- Death or Serious Injury from Failure to Follow Up on Test Result

* Definition changed in October 2012  ** New event in October 2012

Acute Care Hospital Data

Total Number of SREs in Acute Care Hospitals by Year

- 2012: 599  - 2013: 891*
- 2014: 821  - 2015: 1313 **
- 2016: 1012 **

* Significant increase in the # of SREs reported from 2012 to 2013 due to adoption of new NQF definitions
** Two events in 2015 and 2016 affected a large number of patients and is reflected in the increase in SREs Slide 12 reported
In 2016 there were 285 fall-related SREs in Mass vs 74 events in CT
Falls and Medications

Traditional Risk Factors for Falls

- Cognitive impairment
- Stroke history
- History of falls
- Failed “Get up and go test” (decreased proximal muscle strength)
- Walking difficulty – gait/balance or arthritis
- Visual impairment
- Postural hypotension (Orthostasis)
- Urinary incontinence
- Selected medications or Polypharmacy
Traditional Risk Factors for Falls

- Cognitive impairment
- Stroke history
- Previous fall(s)
- Failed “Get up and go test” (decreased proximal muscle strength)
- Walking difficulty
- Visual impairment
- Orthostasis
- Urinary incontinence

Some pharmacology principles related to a fall investigation
Drug Administration And Clearance Issues
Peak plasma drug concentrations after oral administration occurs in about 2 hrs when fasted and later when fed.

Liquid preparations given in a fasted state can peak in 30 minutes.

Example

Clinical pharmacology and pharmacokinetics of clonidine

A 300-μg oral dose of clonidine was administered to 5 normal volunteers and measurements of plasma concentration and effects upon blood pressure, heart rate, circulatory reflexes, sedation, and dry mouth were made for the following 8 hr. The plasma concentration rose to a peak of 1.02 ± 0.52 ng/ml (SD) at 90 min and fell with a mean half-life of 12.7 hr. Blood pressure of the group fell from 111.0/77.0 to 87.2/60.4 after 3 hr and was 95.2/62.2 mm Hg at 8 hr. Heart rate in recumbency was slowed. Marked sedation and a fall in salivary flow followed the same time-course as the plasma concentration. The cold pressor response was reduced but the Valsalva overshoot was little affected.


London, England
Department of Clinical Pharmacology, Royal Postgraduate Medical School
Clonidine plasma levels and effects on BP

Fig. 2. Mean plasma concentration of clonidine (upper panel) in 5 normal subjects who had an oral dose of 300 μg of clonidine with the mean change in their systolic blood pressure (●–●) and diastolic pressure (○–○) (lower panel).

Flow of saliva, g/min

Fig. 4. Mean and standard error of mean flow of saliva in 5 subjects for 8 hr after 300 μg of clonidine by mouth.
Patient fell on 2-17-2010 at 00:15

Fig. 5. Mean and standard error of mean sedation rated using a visual analog scale in 5 subjects for 8 hr after 300 μg of clonidine.
Patient fell on 2-17-2010 at 00:15

Drug Administration And Clearance Issues
Standard doses of medications may produce more intense effects in the elderly
An acute change in renal function (AKI) may prolong the half-life of a medication, making it more toxic if a dosage adjustment is not done. A toxic effect may include gait and balance disturbances leading to a fall.

86 yo woman admitted to ED for weakness and abdominal pain. Given contrast 120 mL of iohexol 350 on Oct 4th at 14:30
If a patient falls shortly after having an episode of AKI, check for a medication that should have been adjusted or stopped during that period.
For Many Medications Exaggerated Responses are Observed in the Elderly

- Sedative / hypnotics
- Blood pressure lowering agents
- Anticoagulants
- Antipsychotic medication
- Lithium
- Diuretics
- Anti-inflammatory drugs

Medication debridement is a key component to a falls reduction program

Consider

Discontinue or dosage reduction
Orthostatic Hypotension
aka Postural Hypotension:

An adverse effect common with many medications

In order to standardize the assessment and diagnosis of orthostatic hypotension (OH), the American Autonomic Society and the American Association of Neurology define OH as a decrease in systolic blood pressure of \( \geq 20 \) mm Hg or diastolic blood pressure of \( \geq 10 \) mm Hg within 3 minutes of standing.

Orthostatic Hypotension

• Common in the elderly
• May be symptomatic or asymptomatic
• Symptoms include dizziness, lightheadedness, and fainting
• Symptoms due to transient decreased cerebral perfusion
• Most common underlying causes include dehydration, autonomic dysfunction and medications.
• Vascular compliance or autonomic reflexes are sites of dysfunction leading to orthostatic hypotension.
• Risk factors from population studies include advanced age, hypertension and its treatment, diabetes and use of sedative and hypnotic medications.

Miller and Appel, Circulation 2015

The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension

Christopher H. Gibbons1, Peter Schmidt2, Italo Biaggioni3, Camille Frazier-Mills4, Roy Freeman5, Stuart Isaacson6, Beverly Karabin7, Louis Kuritzky7, Mark Lew8, Phillip Low9, Ali Mehdizad8, Satish R. Raj11, Steven Vernino12, Horacio Kaufmann13

DOI 10.1007/s00415-016-8375-4

CrossMark
Patients in the following five categories need to be routinely screened for OH:

(1) Patients suspected of, or diagnosed with any neurodegenerative disorder associated with autonomic dysfunction, including Parkinson’s Disease (PD), Multiple System Atrophy (MSA), Pure Autonomic Failure (PAF), or Dementia with Lewy Bodies (DLB);

(2) Patients who have reported an unexplained fall or have had an episode of syncope;

(3) Patients with peripheral neuropathies known to be associated with autonomic dysfunction (e.g., diabetes, amyloidosis, HIV);

(4) Patients who are elderly (≥70 years of age) and frail or on multiple medications;

(5) Patients with postural (orthostatic) dizziness or nonspecific symptoms that only occur when standing.

Orthostatic Hypotension

- Dehydration
- Medications
- Autonomic Neuropathy

J Neurol (2017) 264:1567-1582
Upright posture
  ↓
Venous pooling
  ↓
Decreased cardiac output
  ↓
Decreased blood pressure
  ↓
Activation of baroreceptors
  ↓
Stimulation of brainstem vasomotor center
  ↓
Increased sympathetic outflow (norepi and epi)
  ↓
Increase heart rate and force of contraction
  ↓
Arteriolar and venous constriction
  ↓
Increased blood pressure (maintained)

Principles of Blood Pressure Control in the Upright Position

Seated vs Supine
Blood Pressure and Falls

• Sustained hypotension

• Orthostatic hypotension

Cardiovascular Medications

Some General Comments
The Risk of Hip Fracture After Initiating Antihypertensive Drugs in the Elderly

Debra A. Butt, MD, MSc, CCFP, FCFP; Muhammad Mamdani, PharmD, MPH; Peter C. Austin, PhD; Karen Tu, MD, MSc, CCFP, FCFP; Tara Gomes, MHS; Richard H. Glazier, MD, MPH, CCFP, FCFP

Conclusions: Antihypertensive drugs were associated with an immediate increased hip fracture risk during the initiation of treatment in hypertensive community-dwelling elderly patients. Caution is advised when initiating antihypertensive drugs in the elderly.


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Original Investigation

Antihypertensive Medications and Serious Fall Injuries in a Nationally Representative Sample of Older Adults

Mary E. Tinetti, MD, Ling Han, MD, PhD; David S. H. Lee, PharmD, PhD; Gail J. McAlary, PhD; Peter Peduzzi, PhD; Cary P. Gross, MD; Bingqing Zhou, PhD; Haoyun Lin, PhD

Conclusions and Relevance: Antihypertensive medications were associated with an increased risk of serious fall injuries, particularly among those with previous fall injuries. The potential harms vs benefits of antihypertensive medications should be weighed in deciding to continue treatment with antihypertensive medications in older adults with multiple chronic conditions.

2014 American Medical Association. JAMA Internal Medicine
The Concept of Trade-offs in Health Outcomes

Use of antihypertensive medications in a patient with fall risks*

- Decreased CV complications (stroke, MI, HF)
- Increased risk of fall complications (fractures and TBI)
- Medications-related symptoms (dizziness, fatigue)

*Fall in the previous year, use of a cane or walker, balance or walking difficulty, one or more ADL dependencies, postural hypotension, visual impairment, depressive symptoms, at least 4 meds

Tinetti, ME et al JAGS 2008;
Intensive vs standard blood pressure control

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults
Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Recommendation 1
In the general population aged 60 years or older, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) of 150 mm Hg or higher or diastolic blood pressure (DBP) of 90 mm Hg or higher and treat to a goal SBP lower than 150 mm Hg and goal DBP lower than 90 mm Hg.
Strong Recommendation – Grade A

JNC 8 Published online December 18, 2013.
Dosage adjustment was based on a mean of 3 blood pressure measurements at an office visit while the patient was seated and after 5 minutes of quiet rest. The measurements were made using an automated system (Omron Healthcare Model 907).
Orthostatic Hypotension

A drop in systolic blood pressure of at least 20 mm Hg or in diastolic pressure of at least 10 mm Hg at 1 minute after the patient stood up, as compared with the value obtained when the patient was seated.

Sprint Trial - NEJM November 26, 2015

<table>
<thead>
<tr>
<th>Event</th>
<th>Int Tx (%)</th>
<th>Std Tx (%)</th>
<th>Haz Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>2.4</td>
<td>1.4</td>
<td>1.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>2.3</td>
<td>1.7</td>
<td>1.33</td>
<td>0.003</td>
</tr>
<tr>
<td>Lyte abn</td>
<td>3.1</td>
<td>2.3</td>
<td>1.35</td>
<td>0.02</td>
</tr>
<tr>
<td>AKI</td>
<td>4.1</td>
<td>2.5</td>
<td>1.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fall-Inj</td>
<td>2.2</td>
<td>2.3</td>
<td>0.95</td>
<td>0.71</td>
</tr>
</tbody>
</table>
# Classes of Cardiovascular Medications And Relative Fall Risk

<table>
<thead>
<tr>
<th>Higher Risk</th>
<th>Lower Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha Blockers</td>
<td>ACEI</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>ARBs</td>
</tr>
<tr>
<td>Diuretics (vol/dep,abn lyte)</td>
<td>CCB</td>
</tr>
<tr>
<td>Nitrates</td>
<td>K⁺ sparing diuretics</td>
</tr>
</tbody>
</table>

3 or more antihypertensive agents – high risk
Alpha Blockers/Antagonists

- Alfuzosin (UroXatal)*
- Doxazosin (Cardura)
- Prazosin (Minipress)
- Terazosin (Hytrin)
- Tamsulosin (Flomax)*

Falls Associated ADE: postural hypotension, dizziness, weakness,

* Selective for the prostate gland
The risk of fall and fracture with the initiation of a prostate-selective α antagonist: a population based cohort study

Blayne Welk,1,2,3 Eric McArthur,2 Lisa-Ann Fraser,4 Jade Hayward,3 Stephanie Dixon,2,3 Y Joseph Hwang,3 Michael Ordon6

WHAT THIS STUDY ADDS
Prostate-specific α antagonists are associated with a small but significant increased risk of fall, fracture, and head trauma, probably as a result of induced hypotension.

Tamsulosin (Flomax) = selective α antagonist

BMJ 2015;351:h5398 | doi: 10.1136/bmj.h5398

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Beta Blockers

- Acebutolol (Sectral)
- Atenolol (Tenormin)
- Betaxolol (Kerlone)
- Bisoprolol (Zebeta)
- Carvedilol (Coreg)
- Labetalol (Trandate)
- Metoprolol (Lopressor)
- Nadolol (Corgard)
- Nebivolol (Bystolic)
- Pindolol (Visken)
- Propranolol (Inderal)
- Timolol (Blocadren)

Falls Associated ADE: bradycardia, fatigue, additive with other AHDs, OH-synergistic with alpha blockers
Upright posture
Venous pooling
Decreased cardiac output
Decreased blood pressure
Activation of baroreceptors
Stimulation of brainstem vasomotor center
Increased sympathetic outflow (norepi and epi)
Beta blocker
Increase heart rate and force of contraction
arteriolar and venous constriction
Increased blood pressure

Common Diuretics

**Loop Type**
- Bumetanide
- Ethacrynic acid
- Furosemide
- Torsemide

**Thiazide Type**
- Chlorothiazide
- Chlorthalidone
- Hydrochlorothiazide
- Indapamide
- Methyclothiazide
- Metolozone

Falls Associated ADE: Volume and electrolyte abnormalities (K⁺ and Na⁺)
Diuretics = Dehydration
Orthostatic BP changes

New loop diuretic prescriptions may be an acute risk factor for falls in the nursing home

Sarah D. Berry, Murray A. Mitelman, Yuqing Zhang, Daniel H. Solomon, Lewis A. Lipsitz, Elizabeth Mostofsky, Dana Goldense and Douglas P. Kiel

1 Hebrew SeniorLife Institute for Aging Research and Beth Israel Deaconess Medical Center Division of Gerontology, Boston, MA, USA
2 Department of Medicine, Beth Israel Deaconess Medical Center Cardiovascular Epidemiology Research Unit, Boston, MA, USA
3 Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, USA
4 Department of Medicine, Brigham and Women’s Hospital, Boston, MA, USA

Results: During a mean follow-up of 8.4 months, 1181 participants experienced an incident fall. Nine participants experienced a diuretic change on the day before the fall. The odds of falling one day following a change in a diuretic was elevated (OR = 2.88; 95%CI = 0.89, 4.66). The association was stronger and reached nominal statistical significance when loop diuretics were examined separately (OR = 2.46; 95%CI = 1.02, 5.82). We estimated that, for every 271 loop diuretic drug changes, one excess fall occurred.

Conclusions: Nursing home residents are at an increased risk of falls in the day following a new prescription or increased dose of a loop diuretic drug. Extra precautions should be taken immediately following a loop diuretic drug change in an effort to prevent falls. Copyright © 2012 John Wiley & Sons, Ltd.

PHARMAÇCOEPIDEMIOLOGY AND DRUG SAFETY 2012; 21: 560–563
Furosemide Bolus vs Infusion Dosing

Figure 2. The mean hourly urine volumes. The open circles indicate the bolus group, and the closed circles indicate the infusion group. Asterisks indicate significant differences between the groups (hour 5, p < 0.01).

Falls and Electrolyte disturbances

Relative risk of hypokalemia or hyponatremia with daily dosing

Chlorthalidone > Hydrochlorothiazide > Furosemide
Sodium (mEq/L)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>&lt;135</td>
</tr>
<tr>
<td>Normonatremia</td>
<td>135-145</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>&gt;145</td>
</tr>
</tbody>
</table>

Signs and Symptoms of Hyponatremia

- Acute presentation: early (125-130 mEq/L)-nausea and malaise; later (115-120 mEq/L)-headache, lethargy, obtundation, seizures, coma, respiratory arrest.
- Chronic presentation: fatigue, nausea, dizziness, gait disturbance (falls), forgetfulness, confusion, lethargy, muscle cramps
Potassium (mEq/L)

- Hypokalemia      <3.5
- Normokalemia    3.5 - 5.5
- Hyperkalemia     >5.5

Signs and Symptoms of Hypokalemia

- Muscle: weakness ascending legs to trunk and arms that can progress to frank paralysis; muscle cramps, rhabdomyolysis, myoglobinuria; respiratory muscle weakness and GI involvement causing ileus
- ECG: ST segment depression, decreased T wave amplitude, increased U wave amplitude, and prolonged QT interval.
- Cardiac arrhythmias: Premature atrial and ventricular beats, sinus bradycardia, junctional tachycardia, AV block, and ventricular tachycardia/fibrillation.
The risk of thiazide-induced hyponatremia is 3-fold higher in patients ≥70 years old and higher in women possibly because of smaller body size and lower sodium intake.

Approximately 3 in 10 patients exposed to thiazide diuretics develop hyponatremia.
Common Nitrates

- Isosorbide dinitrate (Isordil)
- Isosorbide mononitrate (Imdur)
- Nitroglycerine (ointment, TDD, spray, SL tabs)

Falls Associated ADE: Hypotension and postural hypotension (dizziness, lightheadedness) – probably most prevalent during pretolerance period.
Combinations of Cardiovascular Drugs That Have an Increased Risk for Hypotension

- Alpha blockers with beta blockers
- Three or more antihypertensive drugs
- Loop diuretics with metolozone
- Diuretics and ACEI (initiation)
- Amiodarone with clonidine
- Verapamil/Diltiazem with a beta blocker or clonidine

Cardiovascular Medications

- Higher Risk
  - Alpha Blockers
  - Beta Blockers
  - Diuretics (volume dep)
  - Nitrates
- Lower Risk
  - ACEI
  - ARBs
  - CCB
  - K+ sparing diuretics

3 or more antihypertensive agents – high risk
## Angiotensin Converting Enzyme Inhibitors

- Benazepril (Lotensin)
- Captopril (Capoten)
- Enalapril (Vasotec)
- Fosinopril (Monopril)
- Lisinopril (Zestril)
- Moexipril (Univasc)
- Perindopril (Aceon)
- Quinapril (Accupril)
- Ramipril (Altace)
- Trandolapril (Mavik)

Falls Associated ADE: low incidence (dizziness, fatigue), mostly additive with other AHDs.

## Angiotensin Receptor Blockers (ARBs)

- Candesartan (Atacand)
- Eprosartan (Teveten)
- Irbesartan (Avapro)
- Losartan (Cozaar)
- Olmesartan (Benicar)
- Telmisartan (Micardis)
- Valsartan (Diovan)

Falls Associated ADE: low incidence (dizziness, fatigue), mostly additive with other AHDs.
Calcium Channel Blockers

- Amlodipine (Norvasc)
- Diltiazem (Cardizem)
- Felodipine (Plendil)
- Isradipine (DynaCirc)
- Nicardipine (Cardene)
- Nifedipine (Procardia, Adalat)
- Nisoldipine (Sular)
- Verapamil (Isoptin)

Falls Associated ADE: low incidence (dizziness fatigue), mostly additive with other AHDs.

Potassium Sparing Diuretics

- Amiloride (Midamor)
- Eplerenone (Inspira)
- Spironolactone (Aldactone)
- Triamterene (Dyrenium)

Falls Associated ADE: Hyperkalemia (conduction problems/bradycardia)
Hyperkalemia and Falls

• Muscle weakness
• Cardiac arrhythmias

Cases
Table 2  Medications Frequently Associated with Falls by Class

<table>
<thead>
<tr>
<th>Class</th>
<th>Specific Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Chlordiazepoxide, diazepam, alprazolam</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, nortriptyline, fluoxetine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Fluphenazine, chlorpromazine, haloperidol, risperidone</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Phenytoin, phenobarbital</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Diphenhydramine, hyoscyamine, tolterodine, oxybutynin</td>
</tr>
<tr>
<td>Sedative hypnotics</td>
<td>All barbiturates, zolpidem, zaleplon</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>Cyclobenzaprine, metaxalone, methocarbamol</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Diuretics, doxazosin, terazosin, clonidine, digoxin</td>
</tr>
<tr>
<td>medications</td>
<td></td>
</tr>
</tbody>
</table>

American Journal of Medicine (2007) 120, 493-497

76 y.o. man admitted for:

Near syncope
Fall noted 10/11 at 5:10 am
Tizanidine (first dose) given at 22:20 with terazosin, tramadol and metoprolol

Pulse low 90 minutes post med admin falling episode on 10/11 at 5:10 am

Low blood pressure x 3

Tizanidine = a clonidine derivative with issues of hypotension and bradycardia.
Hypotension and bradycardia associated with concomitant tizanidine and lisinopril therapy

Susan W. Publow and Donald L. Branam

Conclusion

The addition of tizanidine in a patient receiving long-term treatment with lisinopril was associated with severe hypotension and bradycardia.

Am J Health-Syst Pharm—Vol 67  Oct 1, 2010
Comments

• Pt with history of hypertension on background tx with beta blocker and alpha blocker was given 4 mg of the muscle relaxant tizanidine, a clonidine derivative known to cause bradycardia and hypotension. Reaction was temporally related to tizanidine administration.

• Not sure why this muscle relaxant with CV ADEs was chosen for a pt with background antihypertensive medications and an admitting dx of “near syncope”. Terazosin should be replaced by tamsulosin (Flomax®).

Another fall case
85 y.o. woman admitted to the CV service from the ED for syncope with falls. Discovered to be in AV block with bradycardia and hypotension.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Sig</th>
<th>Start Date</th>
<th>End Date</th>
<th>Taking?</th>
<th>Authorizing Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>amlodipine (Norvasc) tablet 10 mg</td>
<td></td>
<td>8/3/16</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>atenolol (Tenormin) tablet 50 mg</td>
<td></td>
<td>8/3/16</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>atorvastatin (Liptor) tablet 40 mg</td>
<td></td>
<td>8/3/16</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Bimatoprost 0.5% ophthalmic solution</td>
<td>Place 1 drop into both eyes 3 (daily)</td>
<td>4/13/16</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>calcium-vitamin D (Calcium 500/200 D-3) 500 -200 mg-unit per tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>captopril (Prinivil) 100 mg capsule</td>
<td></td>
<td>10/18/07</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>glimepiride (Amaryl) tablet 4 mg</td>
<td></td>
<td>8/3/16</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>insulin aspart (NovoLog) 100 units/mL</td>
<td></td>
<td>1/8/16</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Combigan® = Brimonidine and Timolol
Bimatoprost = Timolol
Comment

• Very elderly woman with long history of syncope and falls at home.
• Found in ED to be in “heart block”.
• Patient orthostatic with symptoms in the ED.
• Home medications indicate excessive beta blockers, two as eye medications (timolol) and one oral (atenolol). Excessive beta blockage can produce AV block.
Another Case

76 y.o. / Man
Pt Loc: Medical-Tele Level 1
Patient Class: Inpatient
Admit Dx: BT (brain tumor) (HCC) [D49.6]
Admit Date: 09/30/2017
Allergies: Sulfa Antibiotics
Ht: 5' 10" (1.778 m)
Wt (kg): 77.1 kg (170 lb)
Last BSA: 1.95 m² CrCl: 64.9 mL/min
Scr: 0.9 MG/DL
Home meds include 3 antihypertensive agents and insulin

<table>
<thead>
<tr>
<th>Medication</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANLODIPINE (Norvasc) tablet 2.5 mg</strong></td>
<td>Take 1 tablet (2.5 mg total) by mouth daily.</td>
</tr>
<tr>
<td><strong>atenolol (Tenormin) capsule 50 mg</strong></td>
<td>Take 1 capsule (50 mg total) by mouth at bedtime.</td>
</tr>
<tr>
<td><strong>BEZONATE (Tessalon Perles) 150 mg capsule</strong></td>
<td>Take 2 capsules (200 mg total) by mouth 2 (two) times a day as needed for cough.</td>
</tr>
<tr>
<td><strong>carvedilol (Coreg) 6.25 mg tablet</strong></td>
<td>Take 1 tablet (6.25 mg total) by mouth 2 (two) times a day.</td>
</tr>
<tr>
<td><strong>Enalapril (Vasotec) capsule 6.25 mg - 8.25 mg. Orally 2 times daily. First dose on day 1. Oral dose then 2x daily at 1000 (x2).</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Coenzyme G100 (CO Q 10 PC)</strong></td>
<td>Take 50 mg by mouth daily.</td>
</tr>
<tr>
<td><strong>Coenzyme G100 (COQ10) 100 MG CAPS</strong></td>
<td>Take 100 mg by mouth daily.</td>
</tr>
<tr>
<td><strong>Insulin continuous subcutaneous pump (Outpatient)</strong></td>
<td>Inject under the skin continuously. Type of insulin: Norelco 100-unit Basal rate: 6am-8pm: 0.5 8pm-6am: 0.8 Rep: 0.5 mg/kg, max 500 mg/24h.</td>
</tr>
<tr>
<td><strong>Insulin Inulin 30 ml (Bigolin)</strong></td>
<td>Take 1 tablet (30 mg total) by mouth daily.</td>
</tr>
<tr>
<td><strong>Multiple Vitamins-Minerals (MULTIVITAMIN PC)</strong></td>
<td>Take by mouth daily.</td>
</tr>
<tr>
<td><strong>NOVOLG 100 UNIT/ML injection</strong></td>
<td>Inject under the skin continuously. 50 UNITS POUR DAY OR AS DIRECTED BY DR.</td>
</tr>
<tr>
<td><strong>Vitamin C (ASCORBIC ACID) 250 MG tablet</strong></td>
<td>Take 1,000 mg by mouth daily.</td>
</tr>
</tbody>
</table>

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**Fall on 10/13 at 2:40**

<table>
<thead>
<tr>
<th>Medication</th>
<th>N000</th>
<th>N001</th>
<th>N002</th>
<th>N003</th>
<th>N004</th>
<th>N005</th>
<th>N006</th>
<th>N007</th>
<th>N008</th>
<th>N009</th>
<th>N010</th>
<th>N011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atenolol (Tenormin) capsule 50 mg</strong></td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
</tr>
<tr>
<td><strong>Carvedilol (Coreg) 6.25 mg tablet</strong></td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
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<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
</tr>
<tr>
<td><strong>Enalapril (Vasotec) capsule 8.25 mg</strong></td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
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<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
</tr>
<tr>
<td><strong>Insulin (Novolin R) 20 ml</strong></td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
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<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
</tr>
<tr>
<td><strong>Insulin (Novolin R) 100 ml</strong></td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
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<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
</tr>
<tr>
<td><strong>Insulin continuous subcutaneous pump</strong></td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
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<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
</tr>
<tr>
<td><strong>Insulin Inulin 30 ml (Bigolin)</strong></td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
</tr>
</tbody>
</table>

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11/27/2018
Comment

- Patient admitted to the hospital for evaluation of a newly diagnosed brain tumor. Of note this patient was hyponatremic on admission, hyponatremia being an important risk factor for falls and fractures.
- This patient was admitted on 3 antihypertensive medications- carvedilol, amlodipine and lisinopril. This burden of antihypertensive drugs places this patient at a high risk for syncope with falls.
- As an inpatient, chlorpromazine was initiated for hiccups. This medication is well recognized for causing significant orthostatic drops in blood pressure, effects that will be potentiated by co-prescribed antihypertensive medications.
- Description of in hospital fall is consistent with syncope.

Orthostatic changes in blood pressure noted day before fall on 10/12

Fall on 10/13 at 2:40

<table>
<thead>
<tr>
<th>Time</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>Right Arm</th>
<th>Left Arm</th>
<th>Right Leg</th>
<th>Left Leg</th>
<th>Right ECG</th>
<th>Left ECG</th>
<th>Right Foot</th>
<th>Left Foot</th>
<th>Head Position</th>
<th>Bed Position</th>
<th>NAP Setting</th>
<th>Alarm Status</th>
<th>Alarm Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>0429</td>
<td>120/60</td>
<td>70</td>
<td>Sitting</td>
<td>Sitting</td>
<td>Standing</td>
<td>Automatic</td>
<td>Automatic</td>
<td>Automatic</td>
<td>Automatic</td>
<td>Automatic</td>
<td>Sitting</td>
<td>Standing</td>
<td>Automatic</td>
<td>Automatic</td>
<td>Automatic</td>
</tr>
</tbody>
</table>
Fall on 10/13 at 2:40 – no pressures recorded 20 minutes post fall

<table>
<thead>
<tr>
<th>Time</th>
<th>150/17</th>
<th>3:00</th>
<th>3:30</th>
<th>4:00</th>
<th>4:30</th>
<th>5:00</th>
<th>5:30</th>
<th>6:00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp</td>
<td>97.1 (36.2)</td>
<td>97.5 (36.3)</td>
<td>97.3 (36.3)</td>
<td>97.2 (36.1)</td>
<td>97.1 (36.1)</td>
<td>97.1 (36.1)</td>
<td>97.1 (36.1)</td>
<td>97.1 (36.1)</td>
</tr>
<tr>
<td>Pulse</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
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<tr>
<td>Heart Rate Source</td>
<td>Monitor</td>
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<tr>
<td>Rate</td>
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<td>14</td>
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<tr>
<td>BP Location</td>
<td>Right arm</td>
<td>Right arm</td>
<td>Right arm</td>
<td>Right arm</td>
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<td>Left arm</td>
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<td>Left arm</td>
</tr>
<tr>
<td>IV tubing</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IV Solution</td>
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<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<td>Normal</td>
</tr>
<tr>
<td>Vital Signs</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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</tr>
<tr>
<td>SPO2</td>
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<td>95</td>
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<td>95</td>
<td>95</td>
<td>95</td>
<td>95</td>
<td>95</td>
</tr>
</tbody>
</table>

Orthostatic changes noted 10 hrs post fall
Chlorpromazine discontinued

Upright posture
↓
Venous pooling
↓
Decreased cardiac output
↓
Decreased blood pressure
↓
Activation of baroreceptors
↓
Stimulation of brainstem vasomotor center
↓
Increased of sympathetic outflow (norepi and epi)

- Increase heart rate and force of contraction
- arteriolar and venous constriction
- Increased blood pressure

CPZ- α antagonist
Upright posture
→ Venous pooling
→ Decreased cardiac output
→ Decreased blood pressure
→ Activation of baroreceptors
→ Stimulation of brainstem vasomotor center
→ Increased sympathetic outflow (norepi and epi)

Beta blocker
→ Increase heart rate and force of contraction

CPZ-α antagonist
→ arteriolar and venous constriction
→ Increased blood pressure

Background treatment with 3 antihypertensive medications including a beta blocker (blocks reflex tachycardia) should have been considered when selecting a medication for hiccups.
Multiple Choice Questions

1. In 2016 Connecticut Department of Public Health Report on serious hospital events, falls ranked as
   a. The most common cause of death or injury.
   b. Second as a cause of death or injury.
   c. Third as a cause of death or injury.
   d. Almost equal to medication errors as cause of death or injury.

2. A consensus panel recommended screening for postural hypotension in all of the following patients except:
   a. Patients suspected of, or diagnosed with any neurodegenerative disorder associated with autonomic dysfunction
   b. Patients with peripheral neuropathies known to be associated with autonomic dysfunction
   c. Patients who are elderly (≥70 years of age) and frail or on multiple medications
   d. Patient’s with mild to moderate hypertension.

Multiple Choice Questions -continued

3. Which antihypertensive medication would NOT quality as high risk for falls?
   a. Doxazosin
   b. Lisinopril
   c. Isosorbide dinitrate
   d. IV furosemide

4. Blood pressure measurements in the Sprint Trial (intensive treatment vs standard treatment) were done as follows
   a. a single resting (1-3 minutes of rest) blood pressure determination.
   b. average of 2 resting (1-3 minutes of rest) blood pressure measurements
   c. single measurement of both resting and standing blood pressure after 10 minutes of rests
   d. after 5 minutes of quiet rest, the average of 3 blood pressure determinations

5. Which non-antihypertensive medication has a high risk for hypotensive episodes?
   a. diazepam
   b. cimetidine
   c. tizanidine
   d. methocarbamol