



# The Relationship between Medication Use and Falls

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# Objectives for this morning

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- Provide a framework to more fully understand the role of medication-related falls
  - Highlight how drug pharmacology may potentiate falls
- Incorporate the recent literature and review how this information adds to our knowledge in this area
- Evaluate some strategies to limit excessive medication use in older adults

# Framework for Medication-related Falls

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- An interplay between falls and injuries from falls
  - Bone and muscle strength and integrity
  - Maintenance of balance and avoidance of dizziness
  - Prevention of psychomotor slowness
- Polypharmacy is an independent risk factor for falls

# Patient-vignette

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80 year-old female who lives in the community with her husband. Diagnoses include AD, hypercholesterolemia, HTN, allergies, anxiety, osteoporosis, osteoarthritis, cardiomyopathy with a murmur, and GERD.

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# Bone and muscle integrity

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- Commonly used medications that can alter calcium balance
  - Glucocorticosteroids
  - Excessive thyroid replacement
  - Phenytoin
  - Furosemide
  - Proton pump inhibitors

Drug	Pharmacologic Mechanism	Comments
Glucocorticosteroids	Decrease calcium absorption, decrease bone formation, increase bone resorption, and increase calcium excretion	Most common cause of secondary osteoporosis
Excessive thyroid replacement	Increases bone turnover and decreases bone remodeling; more severe in cortical bone	Maintain TSH within the normal range
Furosemide	Increases calcium excretion in the kidney	Thiazides increase calcium reabsorption in the kidney
Phenytoin	Long term use of anticonvulsants can lead to osteomalacia	Can be prevented with replacement of vitamin D
Proton pump inhibitors	Loss of stomach acidity leads to a decrease in absorption of calcium	

# FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors

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- In May 2010 caution was recommended by the FDA for those on long-term and or high-dose PPIs. In March of 2011, the FDA decided against adding a written caution statement to OTC PPIs because they are only intended for short term use.
  - In randomized clinical trials of PPIs for gastric disease treatment, bone fractures were not seen.
  - There are 7 well constructed epidemiological studies that show an association between PPI use and fracture
  - FDA plans to sponsor research that evaluates the RCT data of patients on bisphosphonates who also took PPIs (or not)

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# A word about calcium and vitamin D

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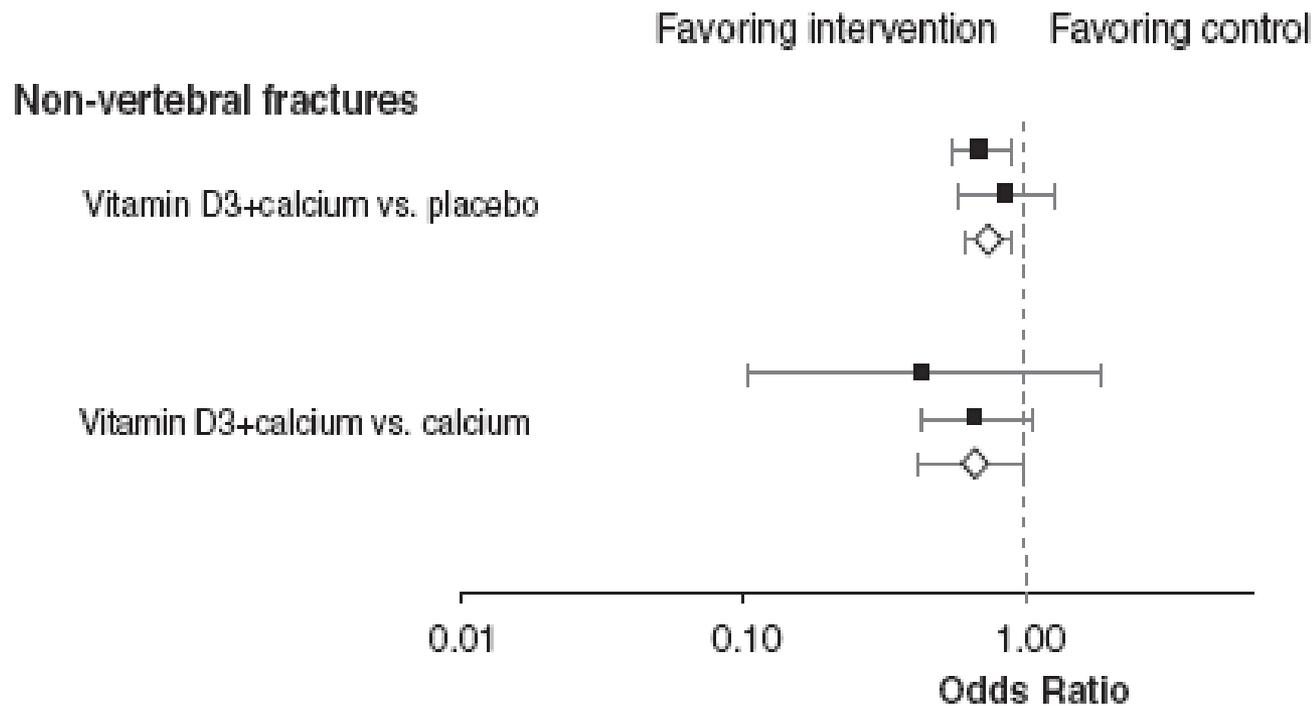
- Calcium preparations are formulated in a salt form and do not provide as much elemental calcium as one might think
  - In this patient, 1200 mg daily of calcium carbonate (40% calcium) provides about 480 mg elemental calcium.
  - 8 oz. of milk provides about 300 mg elemental calcium
- Many older people in this part of the country are Vitamin D deficient. Replacement with 800 units daily may not be sufficient.

# Vitamin D may reduce the risk of fracture

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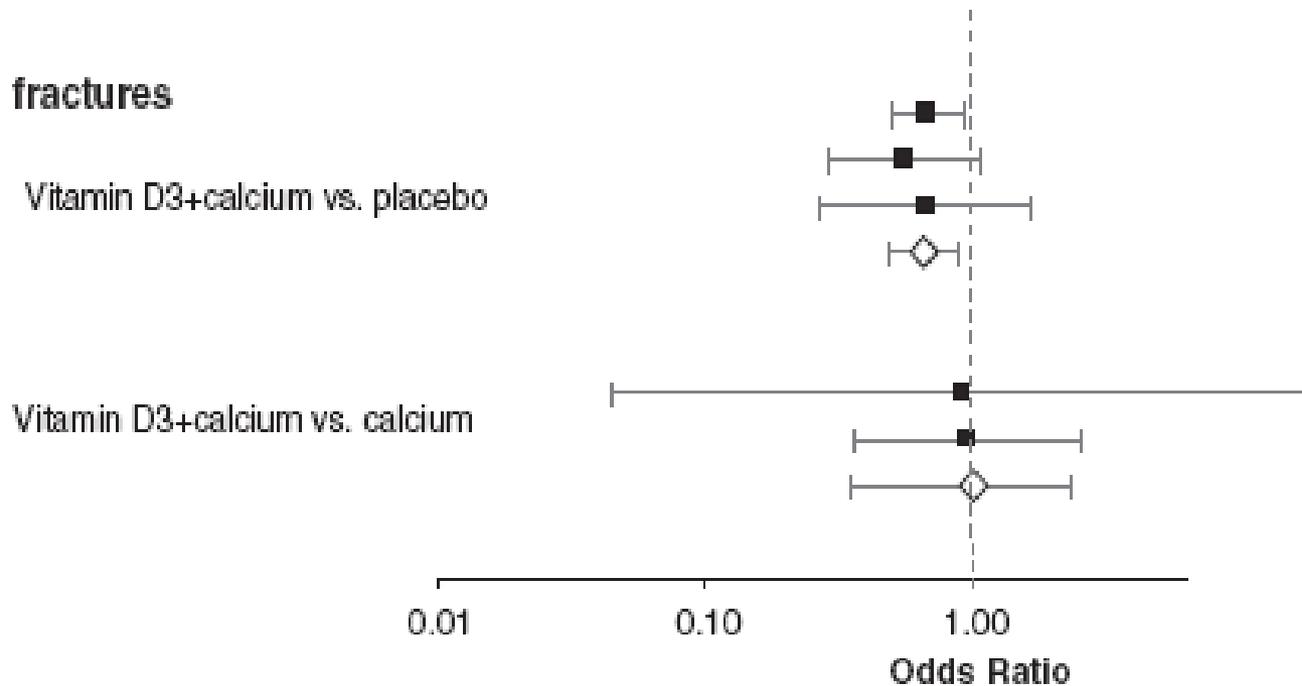
- ❑ Recent publication of a meta-analysis that included 8 controlled trials
  - More than 12,000 postmenopausal women
  - Evaluated the effects of vitamin D<sub>3</sub> versus placebo (with or without calcium in both groups)
- ❑ Concluded that daily supplementation of 800 units of vitamin D reduces non-vertebral, hip, and non-vertebral-non-hip fractures
- ❑ Supplementation of vitamin D with calcium is better than calcium alone for non-vertebral and non-vertebral-non-hip

Bergman GJD, et al. Efficacy of vitamin D<sub>3</sub> supplementation in preventing fractures in elderly women: A meta-analysis. *Curr Med Res Opin.* 2010;26:1193-1201.



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## Hip fractures

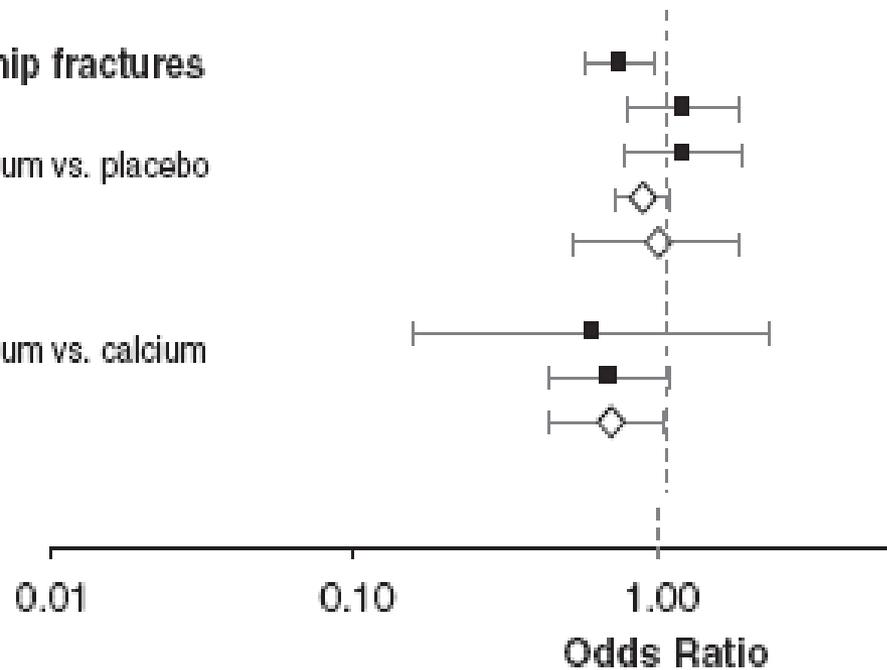


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## Non-vertebral-non hip fractures

Vitamin D3+calcium vs. placebo

Vitamin D3+calcium vs. calcium



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# Bisphosphonates and Atypical Femur Fracture

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- ❑ Bisphosphonates prevent bone resorption by inhibiting osteoclast activity
- ❑ Recent reports of concern about excessive inhibition of bone turnover predisposing to fracture
  - Atypical femur fractures are subtrochanteric and tend to be atraumatic
- ❑ Recent evaluation of patients treated in RCTs with bisphosphonates for 3-10 years showed a possible rate of 2.3/10,000 patient years.
- ❑ Confirmed in 2011:  $\cong$  5/10,000 pt years

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# PPIs, calcium absorption, and fracture

- Calcium dosage forms are in a salt form and require acid to split the salt from the  $\text{Ca}^{++}$
- The following table shows a typical result from this area of research

Gastro-enterology	Corley, 2009
<ul style="list-style-type: none"><li>•33,752 cases with fractures</li><li>•130,471 matched controls</li><li>•Ages <math>\geq 18</math> years</li><li>•Data source: KPNC/California, USA</li></ul>	<ul style="list-style-type: none"><li>•Risk of fracture with <math>\geq 2</math> years of PPI use and 1 other risk factor Odds Ratio (OR) = 1.30 (95% CI, 1.21–1.39)</li><li>•Risk of fracture increased with higher PPI dose: (<i>dose = number of pills per day &gt; 1.5</i>) OR = 1.41 (95% CI, 1.21-1.64)</li></ul>

# Framework for Medication-related Falls

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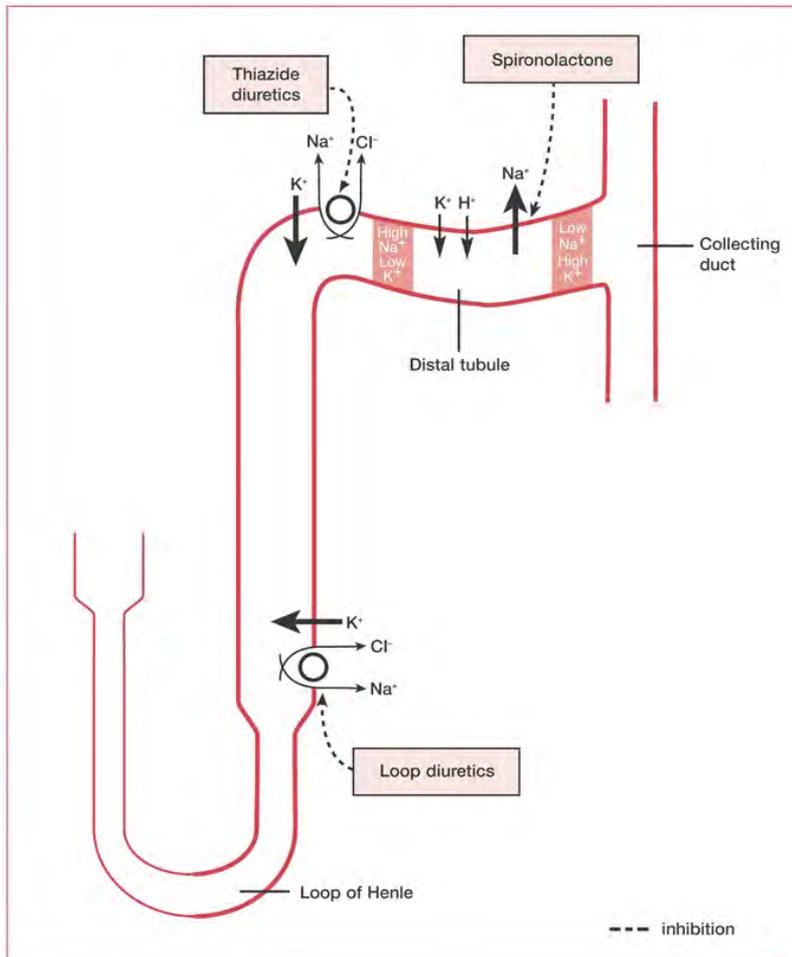
- An interplay between falls and injuries from falls
  - ✓ Bone and muscle strength and integrity
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# Role of cardiovascular drugs and falls

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- Majority of the concern in this area relates to:
  - Postural hypotension
  - Drug-induced dizziness
  - Bradycardia
- Of particular concern in older people because
  - Decreased responsiveness of baroreceptors
  - Prescribing habits

# Thiazide and Loop Diuretics



- Thiazide diuretics inhibit sodium and chloride transport in the distal convoluted tubule which will lead to a decrease in peripheral vascular resistance after 6-8 weeks of therapy
- Loop diuretics inhibit sodium potassium chloride symport in the Loop of Henle which decreases sodium resorption

# Both types of diuretics cause orthostasis

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## □ Loops

- More likely to cause hypokalemia
- Also reduces circulating plasma volume

## □ Thiazides

- More likely to cause hyponatremia
- Also reduces peripheral resistance making it more difficult for the body to vasoconstrict upon standing
- A frequent cause of OH

# Other CV classes of drugs

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## □ Sympatholytics

- B-blockers decrease heart contractility and lower cardiac output
- Alpha-blockers are known to cause hypotension with administration of the first dose

## □ Calcium channel blockers

- Lowers peripheral vascular resistance resulting in vasodilatation; also can increase natriuresis

## □ ACE inhibitors/ARBs

- In patients who are volume contracted or in CHF, addition of an ACE or ARB can result in hypotension

## □ Vasodilators

- Nitrates and hydralazine can cause marked OH

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# Evaluation

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- ❑ Not unusual to use multiple CV drugs in an older patient
- ❑ Screen for postural hypotension
- ❑ Monitor electrolytes
  - Even a mild degree of hyponatremia is a risk factor for falls in older people; furosemide may be a better choice if fluid management is needed
- ❑ Monitor heart rate
- ❑ Be very careful about concomitant use of nitrates and phosphodiesterase inhibitors such as sildenafil (Viagra)

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# Bradycardia in an older person

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- ❑ This woman is using multiple medications that could slow her heart rate and lead to syncope
- ❑ Cholinesterase inhibitors
  - Increase vagal influences on the heart and can cause a type of 'neurocardiogenic' syncope
  - Important publication that evaluated the relationship between CIs and syncope-related outcomes like ED visits for bradycardia or syncope, pacemaker insertion, and hip fractures

Outcome	Hazard ratio (95% CI)
Syncope	
unadjusted	1.71 (1.49-1.96)
adjusted	1.81 (1.57-2.10)
Bradycardia	
unadjusted	1.72 (1.27-2.32)
adjusted	2.08 (1.47-2.96)
Permanent Pacemaker Insertion	
unadjusted	1.57 (1.10-2.23)
adjusted	1.72 (1.17-2.54)
Hip Fracture	
unadjusted	1.20 (1.03-1.39)
adjusted	1.21 (1.03-1.43)

Gill SS, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors. Arch Intern Med 2009;169(9):867

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- An interplay between falls and injuries from falls
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# Drugs that cause psychomotor slowness

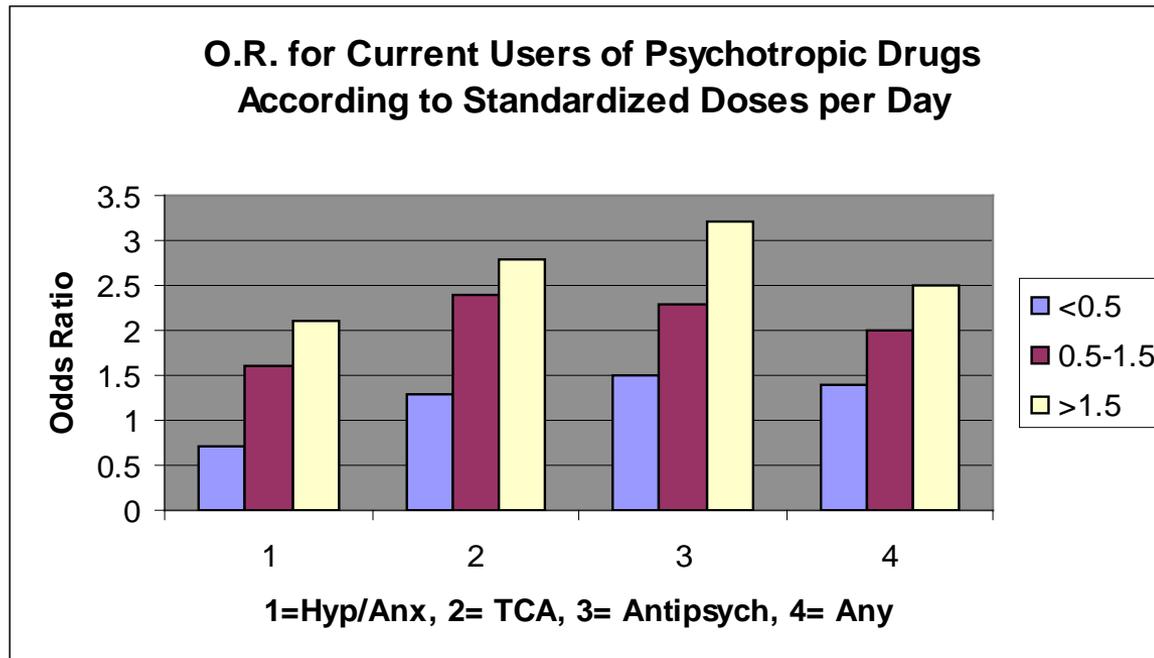
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- ❑ Sedative hypnotics
- ❑ Benzodiazepines
- ❑ Antipsychotics
- ❑ Antidepressants
- ❑ Narcotics
- ❑ Inappropriate medications (Beer's drugs)
  - Skeletal muscle relaxants
  - Anticholinergics

# Some perspective in this area

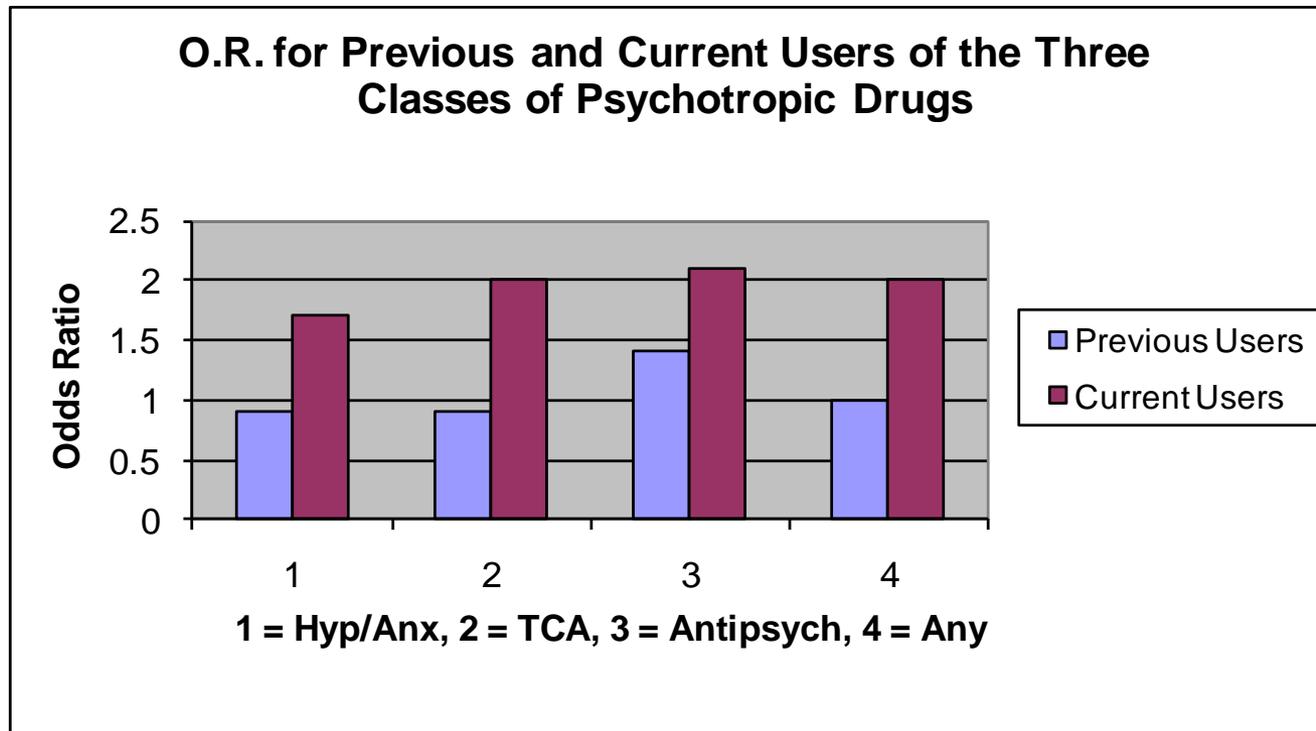
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A long publication history establishing the association between falls/hip fracture with the use of drugs that cause psychomotor slowing



# Risk for falls/hip fracture

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# Benzodiazepines – what do we know about the risk?

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- Long half life benzodiazepines carry greater risk than short half life agents
  - For instance, diazepam (Valium) has a half life of more than 24 hours vs. lorazepam (Ativan) of several hours
  - More lipophilic compounds carry greater risk due to accumulation in body fat stores
- Higher doses of benzodiazepines carry greater risk than lower doses
- Critical to evaluate the duration of use

# Patient-vignette

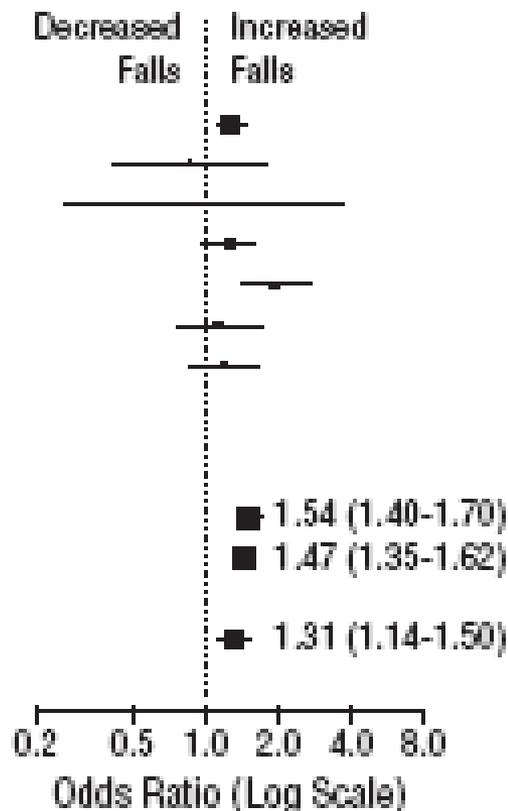
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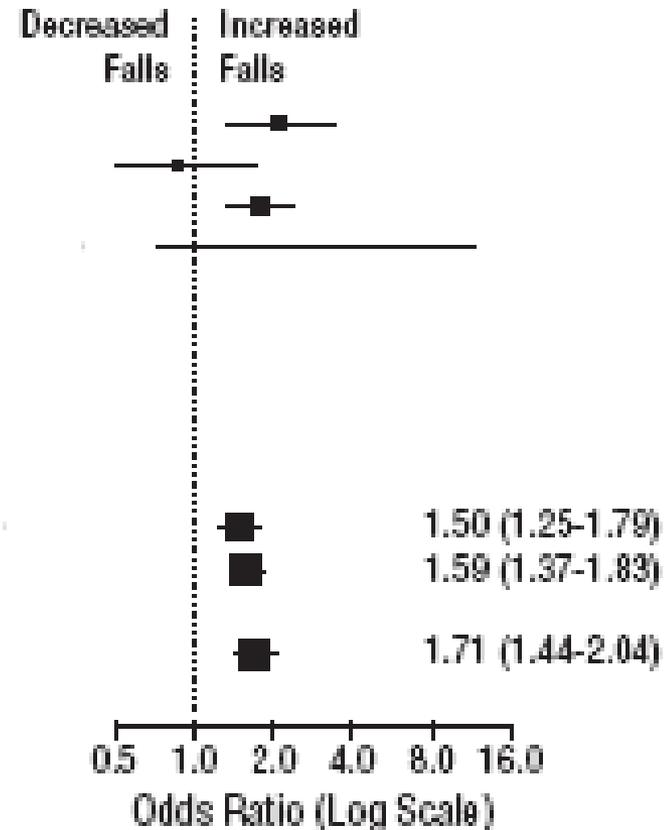
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# Meta-analysis of 9 medication classes

## Sedative/hypnotics



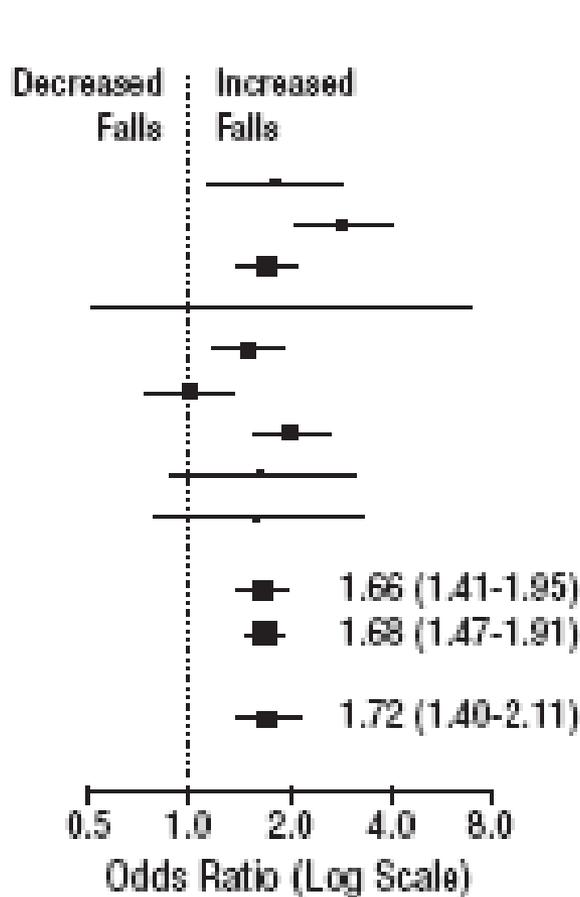
## Antipsychotics



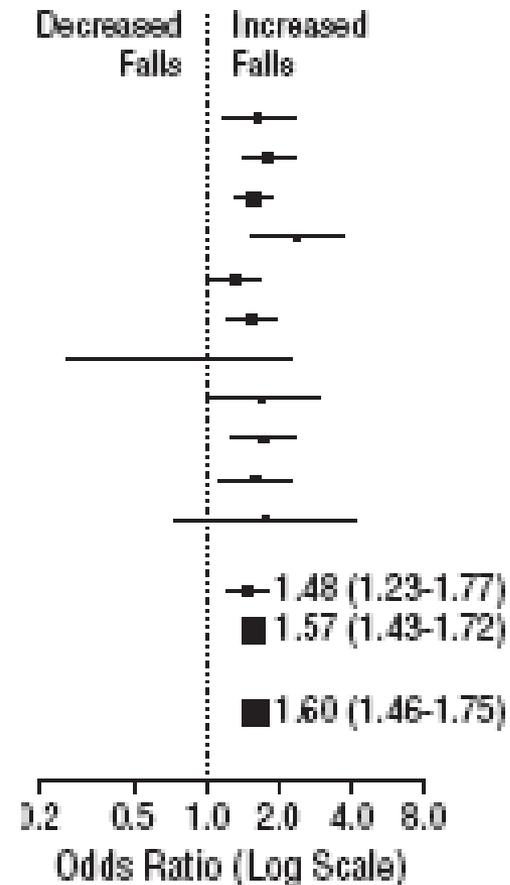
Woolcott JC. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 2009;169:1952-60.

Woolcott JC, et al. Arch Intern Med 2009;169:1952-60.

## Antidepressants



## Benzodiazepines



# Inappropriate medication use and falls

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- ❑ 3C study utilized a prospective cohort design in France over 4 years
- ❑ 6343 community dwelling older men and women
- ❑ Face to face interviews with trained clinicians without defining “fall” to the subject
- ❑ Evaluated all of the Beer’s drugs

# Inappropriate meds with anticholinergic properties

Medication	Odds Ratio	Adjusted OR	P value
Anticholinergics			
Occasional use	1.29 (1.01-1.65)	1.21 (0.93-1.58)	0.15
Regular use	1.83 (1.40-2.40)	1.57 (1.18-2.10)	0.002
Long-acting Benzo			
Occasional use	1.58 (1.26-1.98)	1.40 (1.10-1.79)	0.006
Regular use	1.65 (1.32-2.04)	1.41 (1.12-1.79)	0.004

Berdot S, et al. Inappropriate medication use and risk of falls – A prospective study in a large community-dwelling elderly cohort. BMC Geriatrics 2009;9:30

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# Polypharmacy as an independent risk factor for falls

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- When evaluated, most studies report that the number of medications used is an independent risk factor for falls
  - How many is too many?
  - Will frequently see 4 prescription drugs cited
- As a society, we take more medications and the rate of increase of medication use is increasing

Figure 1. Trends in the percentage of persons using prescription drugs: United States, 1999–2008

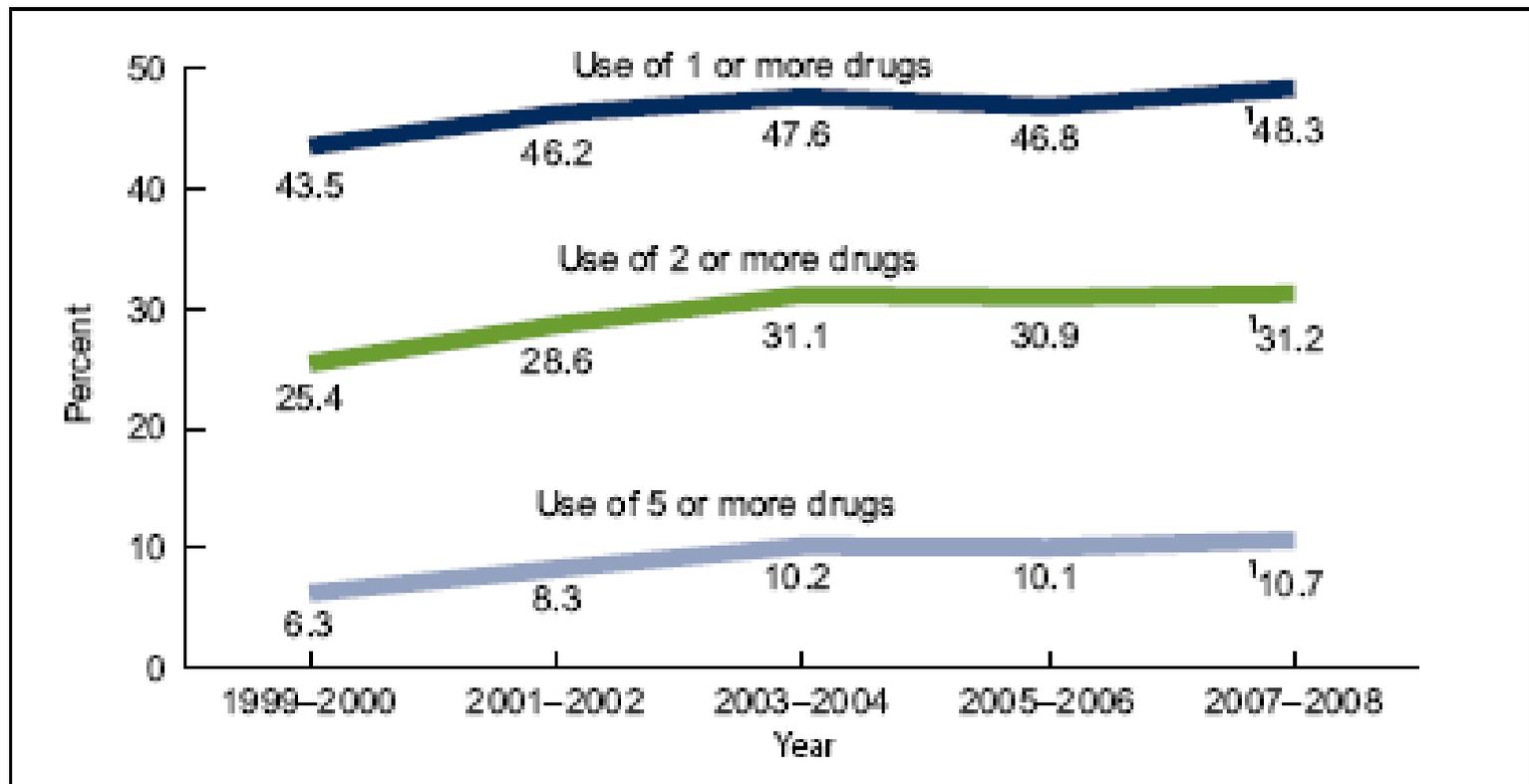
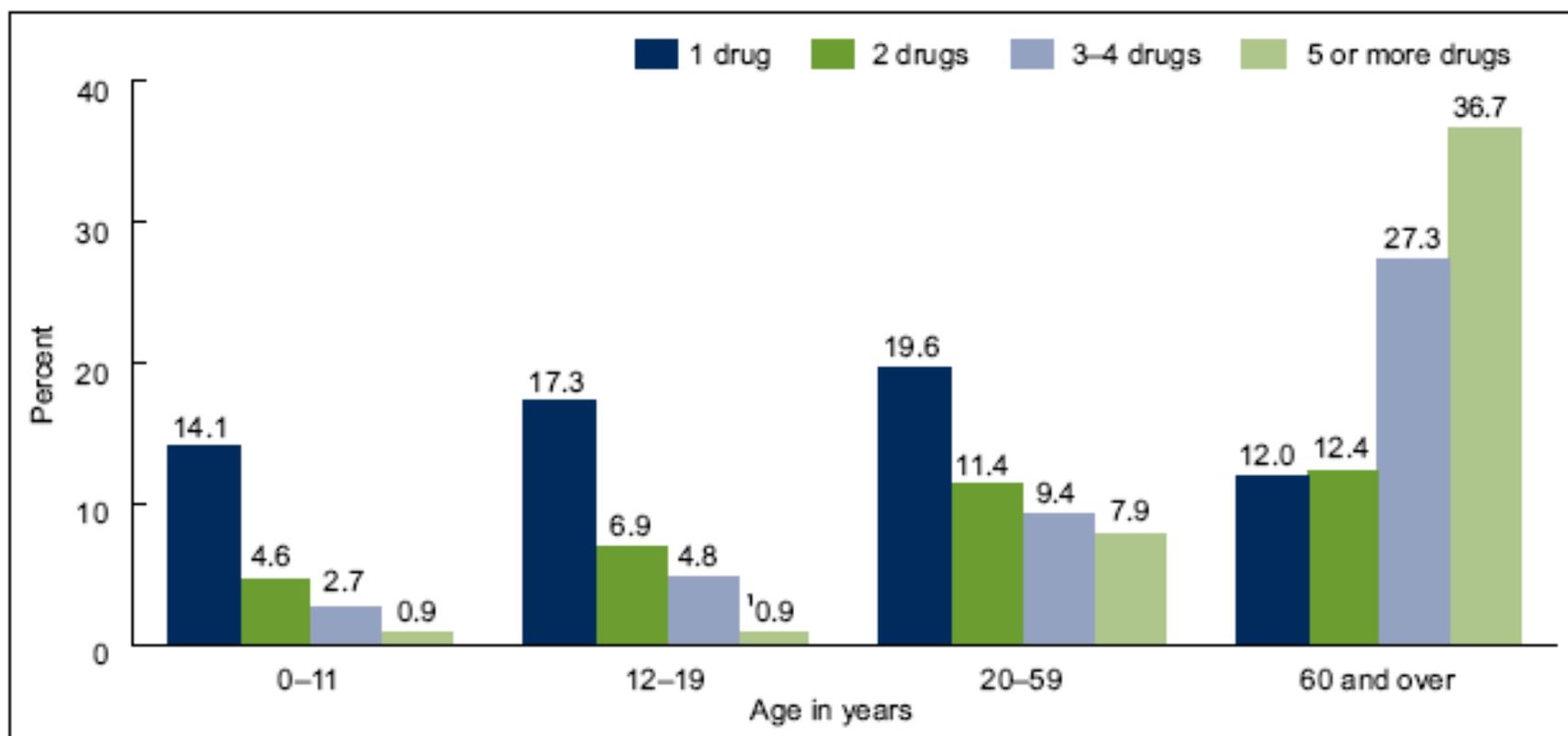


Figure 2. Percentage of prescription drugs used in the past month, by age: United States, 2007–2008



CDC; National Center for Health Statistics; data is from NHANES 2007-2008.

# In conclusion

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- Consider these interventions:
  - DC HCTZ
  - DC/↓ amlodipine
  - Aggressively monitor vital signs
  - ↑ calcium/vit D
  - DC omeprazole
  - DC/ ↓ zolpidem

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