

Benzodiazepines: Pharmacology to Co-Prescribing Risks and Concerns

Role of Benzodiazepines in the Elderly

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Estimated time to complete: 60 minutes

There are no prerequisites for participation.

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This educational program is designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation.

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Learning Objectives

At the conclusion of this session, attendees should be able to:

- Describe various conditions benzodiazepines are used for in the elderly
- Risks of benzodiazepines in the elderly
- Describe alternatives to benzodiazepines in the elderly

Target Audience

Physicians, physician assistants, advanced practice pharmacists, APRNs, residents, & fellows who prescribe controlled substances.

CME Accreditation

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Benzodiazepines and the Elderly

Dr. Angela Haliburda



We are a pill taking society.
It's a cultural, learned behavior.
70% of all Americans are taking Rx medications.
The elderly account for **13%** of the population,
yet, consume **40%** of all prescriptions drugs.



What is the definition of *Elderly*?

Descriptives for young age: Descriptives for old age:

Infant
Toddler
Little ones
Young child
Preschooler
Youngster
Elementary schooler
Middle schooler
Preteen
Juvenile
Minor
Adolescent
Teen
High schooler
Young man/young lady
Young adult

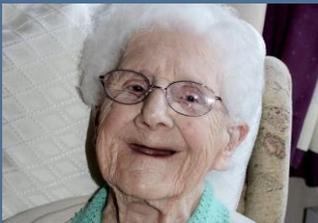
Elderly
Senior citizen
Old man or old woman





Elderly by age:
Low comorbidity
Active
Overall, healthy





Elderly by age & health:
Multiple comorbidities
Debilitated
End stage of life



Why do we consider benzodiazepine use in the elderly *separately*?

- ❖ The *highest use* occurs among the elderly
- ❖ The elderly have the *greatest risk of AE's*

Benzodiazepine use in older adults:

Of all the psychotropic drugs Rx'd for those 65+ yrs, ~40% are BZD's

BZD Rx's increase steadily with age:

4X more Rx's for 65+ yrs than all younger

Beyond 65 yrs, an additional **2X** more for those >75+ yrs

Elderly women receive **2X** as many BZD Rx's than men

BZD Rx's are increased in the institutionalized elderly

Of the drug-associated hospital admissions for those 65+ yrs, 10% are due to BZD adverse effects

The far majority of BZD Rx's for the elderly are written by non-psychiatrists

The elderly are more sensitive to the effects of benzodiazepines because of age-related changes in *cerebral responses*, *pharmacokinetics*, and *pharmacodynamics*.

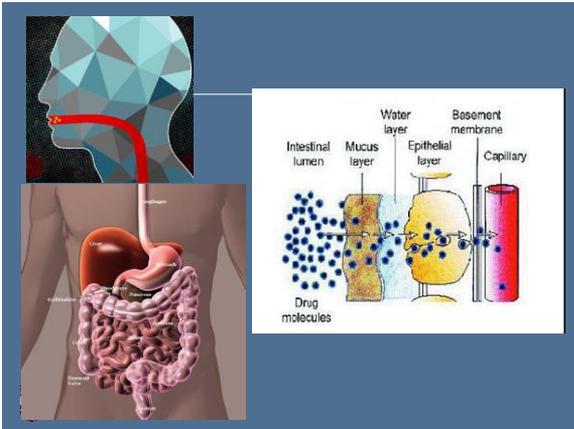
Negative effects related to benzodiazepines, such as *cognitive* and *psychomotor impairment*, *toxicity*, *dependence*, and *withdrawal* are proportionally greater among the elderly, who can least afford these risks

Aging is characterized by a progressive decline in the functional reserve of multiple organs and systems, which can influence the effects of the drug.

Pharmacokinetic changes related to aging affect:

- ✓ *Absorption*
- ✓ *Distribution*
- ✓ *Metabolism*
- ✓ *Elimination*

Overall, the altered pharmacokinetics observed in most elderly patients significantly affect the particular pharmacokinetics of most drugs.



Absorption

Aging changes that affect GI absorption:

- Decreased gastric acid secretion
- Decreased intestinal epithelium surface area = less absorptive surface area
- Decreased carrier-mediated transport mechanisms
- Decreased intestinal motility = increased transit time
- Decreased mesenteric blood flow
- Decreased tissue blood perfusion

All the above lead to slowing of GI absorption

Hepatic Metabolism

With aging, both blood flow to the liver and metabolic activity are reduced. This leads to an overall reduction in metabolic liver capacity in the elderly.

For a given oral dose, the elderly have higher circulating drug levels = higher risk of toxicity.

First-pass metabolism (metabolism that occurs before a drug reaches systemic circulation) decreases by 1% per year > age 40.

Hepatic clearance of drugs metabolized by phase I reactions (oxidation, reduction, hydrolysis) is prolonged in the elderly.

The cytochrome P450 system affects BZDs metabolized by oxidation. Drugs that inhibit the P450 system, such as fluoxetine, ketoconazole, itraconazole, azithromycin, erythromycin and clarithromycin can decrease the rate of clearance of these BZD's and in turn increase their half-life and plasma concentrations. Use caution when prescribing BZDs with these drugs.

Distribution

Aging changes that affect distribution:

- ❖ Increased total body fat
- ❖ Decreased muscle mass
- ❖ Decreased total body water
- ❖ Decreased integrity of the blood-brain barrier
- ❖ Decreased albumin

These changes increase the volume of distribution of lipophilic drugs = they stay in the body longer = increased elimination half-life = longer interval to reach steady-state levels = longer time to evaluate drug effect = more adverse side effects

Elimination

Effects of Aging on the Kidney:

- Decreased renal blood flow
- Decreased kidney size
- Decreased number of functional nephrons
- Decreased tubular secretion
- Decreased glomerular filtration rate
- Decreased total clearance



Result: Decreased elimination

One of the most important pharmacokinetic changes associated with aging is decreased renal elimination of drugs leading to drug **toxicity**

Pharmacodynamic changes:

- The increased response of the elderly to BZD's is due to age-related alterations in the central nervous system receptors.
- The elderly have fewer brain cells and less cortical reserve than younger adults.
- BZD receptors in the brain become more sensitized (less metabolism = higher circulating levels = longer drug effects) and cause increased:
 - Sedation
 - Unsteadiness
 - Memory loss
 - Disinhibition

Alterations in pharmacodynamics, in addition to pharmacokinetics, helps explain the altered response of elderly to benzodiazepines.

The metabolism and excretion of most BZD's decrease in the elderly, so dose adjustment is usually required.

Toxicity may develop slowly because levels of chronically used drugs increase for 5 to 6 half-lives, until a steady state is achieved.

The highly lipophilic BZDs - Diazepam, Flurazepam, Chlordiazepoxide - have half lives of up to 96 hrs in the elderly, so signs of toxicity may not appear until days/wks after therapy starts.

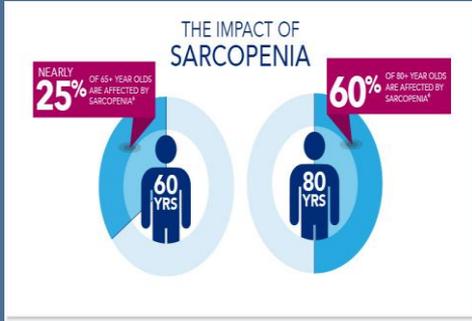
Half life increases are corrected by decreased dosage and reduced frequency of dosing.

Patients with hypoalbuminemia or chronic renal failure have > risk of sedation with BZDs. Maintenance doses will need adjustment when patients become ill or dehydrated or have recently recovered from dehydration.

The pharmacokinetics of Oxazepam and Lorazepam do not show clinically significant changes with age.

The complexity of interactions between comorbidity, polypharmacy, and age-related changes in pharmacokinetics justify the old adage "start low, go slow" with benzodiazepines for the elderly.

Sarcopenia is a natural age-related loss of muscle mass



Sarcopenia + Osteoporosis = increased risks of falls and fractures

Benzodiazepines can cause sedation. Sedation decreases mobility. Decreased mobility = increased risks of falls



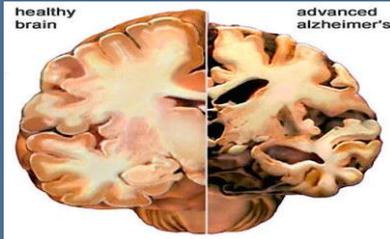
Take what's common in the elderly = sarcopenia and osteoporosis, and add in a benzodiazepine = recipe for greater risk of falls and fractures



The greatest risk of stroke is in women over age 75 from a clot to heart and/or brain after a fall and fracture.

Women ages 65 - 70 who break a hip are 5 X more likely to die within a year than women of the same age who don't break a hip.

A study in JAMA Psychiatry found an association between benzodiazepine use in the elderly and increased risk of Alzheimer's disease. The association was stronger with increasing length of use; the risk was nearly doubled for those using benzodiazepines for more than 180 days.



Changes in the aging body that affect and are affected by drugs:

As we age, body functions slow down = drugs stay in the body longer = causing increased side effects = the need for decreased dosing pharmacokinetics and pharmacodynamics of aging

Changes in the aging body that lead to more use of drugs:

As we age, we have more pain, more sleep problems, a general decline in health that leads to taking more drugs. Lifestyle changes related to loss of independence, bereavement, loneliness and immobility, which increase anxiety and depression and often lead to the intentional overuse of drugs to cope with and escape from the difficulties of old age.

Benzodiazepines are frequently prescribed for the elderly to treat generalized anxiety and insomnia.

Fact: the prevalence of anxiety disorders declines with age. Yet, more Rx's for BZD's to treat anxiety are written for the elderly than the young. The reason? BZD's are effective and take effect quicker than antidepressants, which also treat anxiety.

Insomnia increases with age

But, current guidelines promote behavioral interventions as first-line treatment over benzodiazepines. However, behavioral interventions take time and more effort than it takes to prescribe benzodiazepines.

When used over long periods, BZD's can lead to dependence and withdrawal symptoms when discontinued.



Chronic Pain and Aging

Oww, Ahh.....The aches and pains of the aging body.

Benzodiazepines are often prescribed to help with neck and low back pain, muscle aches and spasms, restless legs, difficulty falling asleep or staying asleep during the night and generalized frustration and anxiety related to chronic pain.

What also helps with generalized pain? Alcohol!

Alcohol potentiates the effects of benzodiazepines and vice versa.

Alcohol and benzodiazepines are often used together

Alcohol abuse is on the rise in the elderly.

Widowers > 75 have a **high rate of alcoholism**

~ 50% of nursing home residents have alcohol related problems

Older adults are hospitalized almost as often for alcoholic related problems as for heart attacks.

>10% hospital admissions, 15% emergency room admissions, and 20 % of psychiatric hospital admissions are a result of alcohol and drug problems in the elderly.

Women and Alcohol:

If a man and a woman of the same body weight have the same drink over the same time period, the women will have a higher blood alcohol content and get drunk faster. Why?

Women have less enzyme (alcohol dehydrogenase) in their stomach to break down alcohol

Women have more fat and less muscle

Women have less total body water
= less dilutional effect



Telescoping:

If a man and a woman drink the same amount of alcohol for the same period of time, the woman will develop alcohol related health problems much faster and more severe than the man.



Not surprisingly, alcoholism and drug dependence occurs frequently in the elderly as a means of coping, an escape. But, it is often hidden, overlooked and misdiagnosed.

>20 % of patients aged 65+ admitted to a psychiatric unit have a diagnosis of substance dependence and a majority of these may have a diagnosis of benzodiazepine dependence.

It is important to screen for substance dependence among elderly persons, particularly benzodiazepine dependence, given that unrecognized substance abuse can lead to inappropriate and inefficient treatment.

Women are at greater risk of misdiagnosis and undertreatment: benzodiazepine dependence goes unrecognized in 75 % of the women, often because women tend to use benzodiazepines rather than alcohol, which more often alerts the physician to the possibility of substance dependence.

In 2011 there were over 423,000 ER visits in the US involving nonmedical use of benzodiazepines, of which 40% also involved alcohol.

There is an unspoken but pervasive assumption that it's not worth treating older adults for substance use disorders.

Behavior considered a problem in younger adults does not inspire the same urgency for care among older adults.

Along with the impression that alcohol or substance abuse problems cannot be successfully treated in older adults, there is the assumption that treatment for this population is a waste of health care resources.

"What difference does it make; he won't be around much longer anyway."

Other factors responsible for the lack of attention to alcoholism and benzodiazepine and other drug dependence among the elderly include stigma and shame about use and misuse of substances, a reluctance to seek professional help for what many in this age group consider a private matter.

Relatives of older adults, particularly their adult children, are ashamed of the problem and choose not to address it.

Younger adults often assign different quality-of-life standards to older adults. Their attitudes are reflected in remarks like, "Grandmother's cocktails are the only thing that makes her happy."

Diagnosis is difficult because symptoms of alcoholism and drug dependency in the elderly can mimic symptoms of other medical and behavioral disorders that are common in this group, such as diabetes, dementia, and depression.

Many elderly patients live alone and experience bereavement and empty-nest syndrome. They are more likely to contemplate ending their own life as a means of dealing with anxiety, loneliness, depression and insomnia.



Adverse Reactions:

Adverse drug reactions may be experienced to a greater extent by benzodiazepine-dependent patients who use benzodiazepines over a prolonged period and use them frequently.

The use of benzodiazepines among elderly patients has been associated with intellectual and cognitive impairment, characterized by anterograde amnesia, diminished short-term recall, and increased forgetfulness. These symptoms are consistent with the early stages of dementia but are also characteristic of normal aging.

Cognitive impairment seems to develop insidiously as a late complication of benzodiazepine use and is most commonly associated with using long-acting benzodiazepines.

Elderly patients with cognitive impairment show improved functioning once the drug has been discontinued.

Changes in the aging body that affect and are affected by drugs

Changes in the aging body that lead to more use of drugs

Changes in society and our drug culture that affect the elderly:

The elderly are targets of family and friends trying to get pills, of all kinds, benzodiazepines included.

With the rise in prescription opioid abuse and the epidemic of heroin abuse, many addicts ping-pong between getting high on dope and going through withdrawal. Benzodiazepines are frequently used to decrease the severity of withdrawal symptoms when dope is not available.

Our hospital protocol uses clonidine and high dose diazepam to treat opioid w/drawal.

Although benzodiazepines generally don't have the high street value of opioids, such as oxycodone, they still have street value and in certain cases, when withdrawal is severe and no opioids are available, benzodiazepines can fetch a pretty penny.

Grandmother is.....



..... a target

Meet Patel



He likes to drive

The Pharmacist



She dispenses drugs & She pilfers drugs

This is Charlie



He helps others and he helps himself

Realtor: Every medicine cabinet has unused prescription pills



As providers, we fill the medicine cabinets. Food for thought.

Conclusions:

Benzodiazepines are frequently prescribed for elderly patients but opinion about their use is divided among experienced clinicians. A review of the literature leads to the conclusion that BZDs should be prescribed with caution, at low doses, and for short periods.

Short-half-life BZDs, such as oxazepam, alprazolam, and triazolam, are usually recommended for older adults because they do not accumulate in the blood, are rapidly cleared from circulation, and offer greater dosage flexibility.

Adverse reactions to BZDs are more common among elderly patients and occur more frequently with advancing age. Adjust dosage for renal and hepatic impairment. Monitor BZDs use in each follow up.

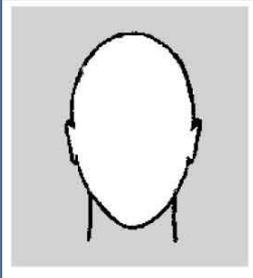
Avoid BZDs for conditions not indicated. Avoid BZDs together with psychotropic drugs having sedative properties.

Inquire about the possibility of abuse and dependence. Gradually taper in dependent patient to avoid withdrawal symptoms.

Duration of use should not exceed more than a few months.

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This is the *face* of a prescription drug abuser.....



.....It can be filled in by *any one among us!*

Errors Made in Prescribing for the Elderly

- ✓Polypharmacy: A drug for every complaint and the elderly have a lot of complaints; aches and pains, insomnia, depression, breathing and circulation difficulties.
- ✓Side effects are missed because they are interpreted as signs of getting old; sleepiness, ataxia, decreased cognition, lethargy.
- ✓The elderly see different providers for follow up visits and the provider of the day doesn't realize the patient was active and alert last month.
- ✓Providers often assume the patient is ill because they are not taking their meds, but the patient may be ill because they are taking the med and the dose prescribed for them is too much.
- ✓The elderly frequently have complicated comorbidities and there isn't enough time in the office visit to address them all, so many go unaddressed for quite some time.

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