

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will think about the results of recent trials that are pertinent to their practice.

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Geriatrics update 2012: What parts of our practice to change, what to ‘think about’

■ ABSTRACT

Many new guidelines and studies of interest to the geriatric population have emerged in the areas of falls and fracture prevention, cardiovascular care, depression, and Alzheimer disease. Some of these guidelines and studies translate to immediate changes that should be made to clinical practice; others are new areas of controversy.

■ KEY POINTS

To prevent falls, patients should be asked not only about recent falls but about balance. Referral for a multicomponent falls evaluation should be considered.

For patients age 80 and older, a target systolic blood pressure of 140 to 145 mm Hg is acceptable, and blood pressure below 130 mm Hg systolic and 65 mm Hg diastolic should be avoided.

The dosage of the antidepressant citalopram (Celexa) should not exceed 40 mg per day in the general population and 20 mg in patients age 60 and older.

Calcium supplementation may increase the risk of myocardial infarction and stroke. A large annual dose of vitamin D appears harmful, raising questions about the long-term safety of large doses given weekly or monthly.

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A NUMBER OF NEW STUDIES and guidelines published over the last few years are changing the way we treat older patients. This article summarizes these recent developments in a variety of areas—from prevention of falls to targets for hypertension therapy—relevant to the treatment of geriatric patients.

■ A MULTICOMPONENT APPROACH TO PREVENTING FALLS

The American Geriatrics Society and British Geriatrics Society’s 2010 Clinical Practice Guideline for Prevention of Falls in Older Persons¹ has added an important new element since the 2001 guideline: in addition to asking older patients about a fall, clinicians should also ask whether a gait or balance problem has developed.

A complete falls evaluation and multicomponent intervention is indicated for patients who in the past year or since the previous visit have had one fall with an injury or more than one fall, or for patients who report or have been diagnosed with a gait or balance problem. A falls risk assessment is not indicated for a patient with no gait or balance problem and who has had only one noninjurious fall in the previous year that did not require medical attention.

The multicomponent evaluation detailed in the guideline is very thorough and comprises more elements than can be done in a follow-up office visit. In addition to the relevant medical history, physical examination, and cognitive and functional assessment, the fall-risk evaluation includes a falls history, medication review, visual acuity testing, gait

TABLE 1

Recommendations for calcium and vitamin D intake for older adults

ORGANIZATION	CALCIUM (DAILY)	VITAMIN D (DAILY)
National Osteoporosis Foundation (www.nof.org)	1,200 mg (men > 65 years and women > 50 years)	800–1,000 U (adults > 50 years)
Institute of Medicine (www.iom.edu)	1,000 mg (adults > 70 years; maximum 2,500 mg)	800 U (adults > 70 years; maximum 4,000 U)
Osteoporosis Canada (www.osteoporosis.ca)	1,200 mg (adults > 50 years)	800–2,000 U (adults > 50 years)

and balance assessment, postural and heart-rate evaluation, examination of the feet and footwear, and, if appropriate, a referral for home assessment of environmental hazards.

Intervention consists of many aspects

Of the interventions, exercise has the strongest correlation with falls prevention, and a prescription should include exercises for balance, gait, and strength. Tai chi is specifically recommended.

Medications should be reduced or withdrawn. The previous guideline recommended reducing medications for patients taking four or more medications, but the current guideline applies to everyone.

First cataract removal is associated with reducing the risk of falls.

Postural hypotension should be treated if present.

Vitamin D at 800 U per day is recommended for all elderly people at risk. For elderly people in long-term care, giving vitamin D for proven or suspected deficiency is by itself correlated with risk reduction.

Interventions that by themselves are not associated with risk reduction include education (eg, providing a handout on preventing falls) and having vision checked. For adults who are cognitively impaired, there is insufficient evidence that even the multicomponent intervention helps prevent falls.

■ CALCIUM AND VITAMIN D MAY NOT BE HARMLESS

Various national groups have developed similar recommendations for calcium and vitamin D intake for older adults (TABLE 1).

Calcium supplements: A cause of heart attack?

Questions have arisen in recent studies about the potential risks of calcium supplementation.

A meta-analysis of 11 trials with nearly 12,000 participants found that the risk of myocardial infarction was significantly higher in people taking calcium supplementation (relative risk 1.27; 95% confidence interval [CI] 1.01–1.59, $P = .038$).² Patients were predominantly postmenopausal women and were followed for a mean of 4 years. The incidence of stroke and death were also higher in people who took calcium, but the differences did not reach statistical significance. The dosages were primarily 1,000 mg per day (range 600 mg to 2 g). Risk was independent of age, sex, and type of supplement.

The authors concluded (somewhat provocatively, because only the risk of myocardial infarction reached statistical significance) that if 1,000 people were treated with calcium supplementation for 5 years, 26 fractures would be prevented but 14 myocardial infarctions, 10 strokes, and 13 deaths would be caused.

Another drawback of indiscriminate use of calcium supplementation is that it interferes with the absorption of a number of medications and nutrients (TABLE 2).

Comments. These data suggest that physicians may wish to prescribe calcium to supplement (not replace) dietary calcium to help patients reach but not exceed current guidelines for total calcium intake for age and sex. They may also want to advise the patient to take the calcium supplement separately from medications, as indicated in TABLE 2.

It is possible that vitamin D should not be given in large annual, monthly, or weekly doses

Benefits of vitamin D may depend on dosing

Studies show that the risk of hip fracture can be reduced with modest daily vitamin D supplementation, up to 800 U daily, regardless of calcium intake.³ Some vitamin D dosing regimens, however, may also entail risk.

Sanders et al⁴ randomized women age 70 and older to receive an annual injection of a high dose of vitamin D (500,000 U) or placebo for 3 to 5 years. Women in the vitamin D group had 15% more falls and 25% more fractures than those in the placebo group. The once-yearly dose of 500,000 U equates to 1,370 U/day, which is not much higher than the recommended daily dosage. The median baseline serum level was 49 nmol/L and reached 120 nmol/L at 30 days in the treatment group, which was not in the toxic range.

Comments. This study cautions physicians against giving large doses of vitamin D at long intervals. Future studies should focus on long-term clinical outcomes of falls and fractures for dosing regimens currently in practice, such as 50,000 units weekly or monthly.

■ **BISPHOSPHONATES AND NONTRAUMATIC THICK BONE FRACTURES**

Bisphosphonates have been regarded as the best drugs for preventing hip fracture. But in 2010, the US Food and Drug Administration (FDA) issued a warning that bisphosphonates have been associated with “atypical” femoral fractures. The atypical fracture pattern is a clean break through the thick bone of the shaft that occurs after minimal or no trauma.⁵ This pattern contrasts with the splintering “typical” fracture in the proximal femur in osteoporotic bone, usually after a fall.

Another characteristic of the atypical fractures is a higher incidence of postoperative complications requiring revision surgery. In more than 14,000 women in secondary analyses of three large randomized bisphosphonate trials, 12 fractures in 10 patients were found that were classified as atypical, averaging to an incidence of 2.3 per 10,000 patient-years.⁶

A population-based, nested case-control study⁷ using Canadian pharmacy records evaluated more than 200,000 women at least 68 years old who received bisphosphonate therapy. Of these, 716 (0.35%) sustained an

TABLE 2

Calcium interactions

- Fluoroquinolones, ketoconazole, tetracyclines
- Bisphosphonates
- Phenytoin (Dilantin)
- Levothyroxine (Synthroid)
- Iron, copper, phosphate, magnesium
- Ezetimibe (Zetia), rosuvastatin (Crestor)
- Gabapentin (Horizant, Neurontin)
- Bisacodyl, bismuth subcitrate

atypical femoral fracture and 9,723 (4.7%) had a typical osteoporotic femoral fracture. Comparing the duration of bisphosphonate use between the two groups, the authors found that the risk of an atypical fracture increased with years of usage (at 5 years or more, the adjusted odds ratio was 2.74, 95% CI 1.25–6.02), but the risk of a typical fracture decreased (at 5 years or more, the adjusted odds ratio was 0.76, 95% CI 0.63–0.93). The study suggests that for every 100 hip fractures that bisphosphonate therapy prevents, it causes one atypical hip fracture.

Comments. These studies have caused some experts to advocate periodic bisphosphonate “vacations,”⁸ but for how long remains an open question because the risk of a typical fracture will increase. It is possible that a biomarker can help establish the best course, but that has yet to be determined.

■ **DENOSUMAB: A NEW DRUG FOR OSTEOPOROSIS WITH A BIG PRICE TAG**

Denosumab (Prolia, Xgeva), a newly available injectable drug, is a monoclonal antibody member of the tumor necrosis factor superfamily.⁹ It is FDA-approved for osteoporosis in postmenopausal women at a dosage of 60 mg every 6 months and for skeletal metastases from solid tumors (120 mg every 4 weeks). It is also being used off-label for skeletal protection in women taking aromatase inhibitors and for men with androgen deficiency.

This drug is expensive, costing \$850 per

Some experts advocate periodic bisphosphonate ‘vacations’; for how long is unclear

60-mg dose wholesale, and no data are yet available on its long-term effects.

Since the drug is not cleared via renal mechanisms, there is some hope that it can be used to treat osteoporosis in patients with advanced chronic kidney disease, since bisphosphonates are contraindicated in those with an estimated glomerular filtration rate (GFR) less than 30 to 35 mL/min. However, the major study of denosumab to date, the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study, had no patients with stage 5 chronic kidney disease (GFR < 15 mL/min/1.73 m² or on dialysis), and too few with stage 4 chronic kidney disease (GFR 15–29) to demonstrate either the safety or efficacy of denosumab in patients with advanced chronic kidney disease.¹⁰

■ HYPERTENSION TREATMENT

A secondary analysis of a recent large hypertension study confirmed the benefits of antihypertensive therapy in very old adults and suggested new targets for systolic and diastolic blood pressures.^{11,12}

The Systolic Hypertension in the Elderly Program (SHEP) trial,¹³ the Systolic Hypertension in Europe (Syst-Eur) trial,¹⁴ and the Hypertension in the Very Elderly Trial (HYVET)¹⁵ are the major, randomized, placebo-controlled antihypertensive trials in older adults. They all showed a reduction in the risk of stroke and cardiovascular events. The diuretic studies (SHEP and HYVET)^{13,15} also showed a lower risk of heart failure and death.

Most recently, secondary analysis of the International Verapamil-Trandolapril (INVEST) study^{11,12} showed that adults in the oldest groups (age 70–79 and 80 and older), experienced a greater risk of adverse cardiovascular outcomes if systolic blood pressure was lowered to below about 130 mm Hg. As diastolic blood pressure was lowered to about the 65–70 mm Hg range, all age groups in the study experienced an increased risk of cardiovascular events. These results confirm the findings of a secondary analysis of the SHEP trial,¹⁶ showing an increased risk of cardiovascular events when diastolic pressure was lowered to below approximately 65 mm Hg.

These studies have been incorporated into

75 pages of the 2011 Expert Consensus Document on Hypertension in the Elderly issued by the American College of Cardiology Foundation and the American Heart Association.¹⁷ In a nutshell, the guidelines suggest that older adults less than 80 years of age be treated comparably to middle-aged adults. However, for adults age 80 and older:

- A target for systolic blood pressure of 140 to 145 mm Hg “can be acceptable.”
- Initiating treatment with monotherapy (with a low-dose thiazide, calcium channel blocker, or renin-angiotensin-aldosterone system drug) is reasonable. A second drug may be added if needed.
- Patients should be monitored for “excessive” orthostasis.
- Systolic blood pressure lower than 130 mm Hg and diastolic blood pressure lower than 65 mm Hg should be avoided.

■ TRANSCATHETER AORTIC VALVE IMPLANTATION APPROVED BY THE FDA

An estimated 2% to 9% of the elderly have aortic stenosis. Aortic valve replacement reduces mortality rates and improves function in all age groups, including octogenarians. Those with asymptomatic aortic stenosis tend to decline very quickly once they develop heart failure, syncope, or angina. Aortic valve replacement has been shown to put people back on the course they were on before they became symptomatic.

Transcatheter self-expanding transaortic valve implantation was approved by the FDA in November 2011. The procedure does not require open surgery and involves angioplasty of the old valve, with the new valve being passed into place through a catheter and expanded. Access is either transfemoral or transapical.

Transaortic valve implantation has been rapidly adopted in Europe since 2002 without any randomized control trials. The Placement of Aortic Transcatheter Valves (PARTNER) trial¹⁸ in 2011 was the first randomized trial of this therapy. It was conducted at 25 centers, with nearly 700 patients with severe aortic stenosis randomized to undergo either transcatheter aortic valve replacement with a balloon-expandable valve (244 via the transfemoral and 104 via the transapical approach)

Elderly hypertensive patients on treatment should be monitored for excessive orthostasis

or surgical replacement. The mean age of the patients was 84 years, and the Society of Thoracic Surgeons mean score was 12%, indicating high perioperative risk.

At 30 days after the procedure, the rates of death were 3.4% with transcatheter implantation and 6.5% with surgical replacement ($P = .07$). At 1 year, the rates were 24.2% and 26.8%, respectively ($P = 0.44$, and $P = .001$ for noninferiority). However, the rate of major stroke was higher in the transcatheter implantation group: 3.8% vs 2.1% in the surgical group ($P = .20$) at 1 month and 5.1% vs 2.4% ($P = .07$) at 1 year. Vascular complications were significantly more frequent in the transcatheter implantation group, and the new onset of atrial fibrillation and major bleeding were significantly higher in the surgical group.

Patients in the transcatheter implantation group had a significantly shorter length of stay in the intensive care unit and a shorter index hospitalization. At 30 days, the transcatheter group also had a significant improvement in New York Heart Association functional status and a better 6-minute walk performance, although at 1 year, these measures were similar between the two groups and were greatly improved over baseline. Quality of life, measured using the Kansas City Cardiomyopathy Questionnaire, was higher both at 6 months and at 1 year in the transcatheter implantation group compared with those who underwent the open surgical procedure.¹⁹

Comments. The higher risk of stroke with the transcatheter implantation procedure remains a concern. More evaluation is also needed with respect to function and cognition in the very elderly, and of efficacy and safety in higher- and lower-risk patients.

■ DEPRESSION CAN BE EFFECTIVELY TREATED WITH MEDICATION

Many placebo-controlled trials have demonstrated the effectiveness of treating depression with medications in elderly people who are cognitively intact and living in the community. A Cochrane Review²⁰ found that in placebo-controlled trials, the number needed to treat to produce one recovery with tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors

was less than 10 for each of the drug classes.

Since the newer drugs appear to be safer and to have fewer adverse effects than the older drugs, more older adults have been treated with antidepressants, including patients with comorbidities such as dementia that were exclusion criteria in early studies. For example, the number of older adults treated with antidepressants has increased 25% since 1992; at the same time the number being referred for cognitive-based therapies has been reduced by 43%.²¹ Similar trends are apparent in elderly people in long-term care. In 1999, about one-third of people in long-term care were diagnosed with depression; in 2007 more than one-half were.²²

Treating depression is less effective when dementia is present

Up to half of adults age 85 and older living in the community may have dementia. In long-term care facilities, most residents likely have some cognitive impairment or are diagnosed with dementia. Many of these are also taking antidepressive agents.

A review of studies in the Medline and Cochrane registries found seven trials that treated 330 patients with antidepressants for combined depression and dementia. Efficacy was not confirmed.²³

After this study was published, Banerjee et al²⁴ treated 218 patients who had depression and dementia in nine centers in the United Kingdom. Patients received sertraline (Zoloft), mirtazapine (Remeron), or placebo. Reductions in depression scores at 13 weeks and at 39 weeks did not differ between the groups, and adverse events were more frequent in the treatment groups than in the placebo groups.

Comments. The poor performance of antidepressants in patients with dementia may be due to misdiagnosis, such as mistaking apathy for depression.²⁵ It is also possible that better criteria than we have now are needed to diagnose depression in patients with dementia, or that current outcome measures are not sensitive for depression when dementia is present.

It may also be unsafe to treat older adults long-term with antidepressive agents. For example, although selective serotonin reuptake inhibitors, the most commonly prescribed antidepressive agents, are considered safe, their

A higher risk of stroke with transcatheter aortic valve implantation remains a concern

side effects are numerous and include sexual dysfunction, bleeding (due to platelet dysfunction), hyponatremia, early weight loss, tremor (mostly with paroxetine [Paxil]), sedation, apathy (especially with high doses), loose stools (with sertraline), urinary incontinence, falls, bone loss, and QTc prolongation.

Citalopram: Maximum dosage in elderly

In August 2011, an FDA Safety Communication was issued for citalopram (Celexa), stating that the daily dose should not exceed 40 mg in the general population and should not exceed 20 mg in patients age 60 and older. The dose should also not exceed 20 mg for a patient at any age who has hepatic impairment, who is known to be a poor metabolizer of CYP 2C19, or who takes cimetidine (Tagamet), since that drug inhibits the metabolism of citalopram at the CYP 2C19 enzyme site.

Although the FDA warning specifically mentions only cimetidine, physicians may have concerns about other drugs that inhibit CYP 2C19, such as proton pump inhibitors (eg, omeprazole [Prilosec]) when taken concomitantly with citalopram. Also, escitalopram (Lexapro) and sertraline are quite similar to citalopram; although they were not mentioned in the FDA Safety Communication, higher doses of these drugs may put patients at similar risk.

■ ALZHEIMER DISEASE: NEED TO BETTER IDENTIFY PEOPLE AT RISK

The definition of dementia is essentially the presence of a cognitive problem that affects the ability to function. For people with Alzheimer disease, impairment of cognitive performance precedes functional decline. Those with a cognitive deficit who still function well have, by definition, mild cognitive impairment (MCI). Although MCI could be caused by a variety of vascular and other neurologic processes, the most common cause of MCI in the United States is Alzheimer disease.

Unfortunately, the population with MCI currently enrolled in clinical trials to reduce the risk of progression to Alzheimer disease is heterogeneous. Many study participants may never get dementia, and others may have had the pathology present for decades and are pro-

gressing rapidly. Imaging and biomarkers are emerging as good indicators that predict progression and could help to better define populations for clinical trials.²⁶

Studies now indicate that people with MCI that is ultimately due to Alzheimer disease are likely to have amyloid beta peptide 42 evident in the cerebrospinal fluid 10 to 20 years before symptoms arise. At the same time, amyloid is also likely to be evident in the brain with amyloid-imaging positron emission tomography (PET). Some time later, abnormalities in metabolism are also evident on fluorodeoxyglucose (FDG) PET, as are changes such as reduced hippocampal volume on magnetic resonance imaging (MRI).

The 1984 criteria for diagnosing MCI due to Alzheimer disease were recently revised to incorporate the evolving availability of biomarkers.^{27,28} The diagnosis of MCI itself is still based on clinical ascertainment including history, physical examination, and cognitive testing. It requires diagnosis of a cognitive decline from a prior level but maintenance of activities of daily living with no or minimal assistance. This diagnosis is certainly challenging since it requires ascertainment of a prior level of function and corroboration, when feasible, with an informant. Blood tests and imaging, which are readily available, constitute an important part of the assessment.

Attributing the MCI to Alzheimer disease requires consistency of the disease course—a gradual decline in Alzheimer disease, rather than a stroke, head injury, neurologic disease such as Parkinson disease, or mixed causes.

Knowledge of genetic factors, such as the presence of a mutation in *APP*, *PS1*, or *PS2*, can be predictive with young patients. The presence of one or two 34 alleles in the apolipoprotein E (*APOE*) gene is the only genetic variant broadly accepted as increasing the risk for late-onset Alzheimer dementia, whereas the 32 allele decreases risk.

Refining the risk attribution to Alzheimer disease requires biomarkers, currently available only in research settings:

- High likelihood—amyloid beta peptide detected by PET or cerebrospinal fluid analysis and evidence of neuronal degeneration or injury (elevated tau in the cerebrospinal fluid, decreased FDG uptake on PET, and

With safer drugs available, depression is being diagnosed and treated much more often

atrophy evident by structural MRI)

- Intermediate likelihood—presence of amyloid beta peptide or evidence of neuronal degeneration or injury
- Unlikely—biomarkers tested and negative
- No comment—biomarkers not tested or reporting is indeterminate.

Comments. There is significant potential for misunderstanding the new definition for MCI. Patients who are concerned about their memory may request biomarker testing in an effort to determine if they currently have or will acquire Alzheimer disease. Doctors may be tempted to refer patients for biomarker testing (via imaging or lumbar puncture) to

“screen” for MCI or Alzheimer disease.

It should be emphasized that MCI itself is still a clinical diagnosis, with the challenges noted above of determining whether there has been a cognitive decline from a prior level of function but preservation of activities of daily living. The biomarkers are not proposed to diagnose MCI, but only to help identify the subset of MCI patients most likely to progress rapidly to Alzheimer disease.

At present, the best use of biomarker testing is to aid research by identifying high-risk people among those with MCI who enroll in prospective trials for testing interventions to reduce the progression of Alzheimer disease. ■

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