

# What's new in treating older adults?

## ABSTRACT

Clinical trials in the past few years have yielded findings that are relevant for clinical practice, not just for geriatricians but for all physicians who have elderly patients.

## KEY POINTS

Exercise has newly discovered benefits, such as preserving cognition and boosting the response to vaccination.

Vitamin D supplementation has been found to prevent fractures, but yearly megadoses had the opposite effect.

Denosumab (Prolia) has been approved for preventing fractures. It acts by inhibiting the receptor activator of nuclear factor kappa B (RANK) ligand.

The outlook for elderly patients starting hemodialysis is bleak, with loss of function and a high risk of death.

Dabigatran (Pradaxa), a direct thrombin inhibitor, may prove to be a safer alternative to warfarin (Coumadin).

Cholinesterase inhibitors for Alzheimer disease are associated with higher risks of hospitalization for syncope, hip fractures, bradycardia, and pacemaker insertion.

The Clinical Dementia Rating should be estimated when prescribing a cognitive enhancer and when advising a patient with memory impairment on driving safety.

Delirium often accelerates dementia; interventions for hospitalized elderly patients may reduce its incidence.

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NEW CLINICAL TRIALS and observational studies are shedding light on ways to improve the health of elderly patients. Here is a brief summary of these trials and how they might influence your clinical practice.

## EXERCISE HAS NEWLY DISCOVERED BENEFITS

According to government data,<sup>1</sup> exercise has a dose-dependent effect on rates of all-cause mortality: the more hours one exercises per week, the lower the risk of death. The difference in risk is most pronounced as one goes from no exercise to about 3 hours of exercise per week; above 3 hours per week, the curve flattens out but continues to decline. Hence, we advise patients to engage in about 30 minutes of moderate-intensity exercise every day.

Lately, physical exercise has been found to have other, unexpected benefits.

### Exercise helps cognition

ERICKSON KI, PRAKASH RS, VOSS MW, ET AL. AEROBIC FITNESS IS ASSOCIATED WITH HIPPOCAMPAL VOLUME IN ELDERLY HUMANS. *HIPPOCAMPUS* 2009; 19:1030–1039.

ETGEN T, SANDER D, HUNTGEBURTH U, POPPERT H, FÖRSTL H, BICKEL H. PHYSICAL ACTIVITY AND INCIDENT COGNITIVE IMPAIRMENT IN ELDERLY PERSONS: THE INVADE STUDY. *ARCH INTERN MED* 2010; 170:186–193.

The hippocampus is a structure deep in the brain that is involved in short-term memory. It atrophies with age, more so with dementia. Erickson<sup>2</sup> found a correlation between aerobic fitness (as measured by maximum oxygen consumption), hippocampal volume, and spatial memory performance.

Etgen and colleagues<sup>3</sup> studied nearly 4,000 older adults in Bavaria for 2 years. Among those reporting no physical activity, 21.4% had cognitive impairment at baseline, compared with 7.3% of those with high activity at baseline. Following those without cognitive impairment over a 2-year period, they found

the incidence of new cognitive impairment was 13.9% in those with no physical activity at baseline, 6.7% in those with moderate activity, and 5.1% in those with high activity.

### Exercise boosts the effect of influenza vaccine

WOODS JA, KEYLOCK KT, LOWDER T, ET AL. CARDIOVASCULAR EXERCISE TRAINING EXTENDS INFLUENZA VACCINE SEROPROTECTION IN SEDENTARY OLDER ADULTS: THE IMMUNE FUNCTION INTERVENTION TRIAL. *J AM GERIATR SOC* 2009; 57:2183–2191.

In a study in 144 sedentary but healthy older adults (ages 60 to 83), Woods et al<sup>4</sup> randomized the participants to undergo either flexibility or cardiovascular training for 10 months, starting 4 months before their annual influenza shot. Exercise extended the duration of antibody protection, with more participants in the cardiovascular group than in the flexibility group showing protection at 24 weeks against all three strains covered by the vaccine: H1N1, H3N2, and influenza B.

### PREVENTING FRACTURES

Each year, about 30% of people age 65 or older fall, sustaining serious injuries in 5% to 10% of cases. Unintentional falls are the main cause of hip fractures, which number 300,000 per year. They are also a common cause of death.

### Vitamin D prevents fractures, but can there be too much of a good thing?

BISCHOFF-FERRARI HA, WILLETT WC, WONG JB, ET AL. PREVENTION OF NON-VERTEBRAL FRACTURES WITH ORAL VITAMIN D AND DOSE DEPENDENCY: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. *ARCH INTERN MED* 2009; 169:551–561.

SANDERS KM, STUART AL, WILLIAMSON EJ, ET AL. ANNUAL HIGH-DOSE ORAL VITAMIN D AND FALLS AND FRACTURES IN OLDER WOMEN: A RANDOMIZED CONTROLLED TRIAL. *JAMA* 2010; 303:1815–1822.

Bischoff-Ferrari<sup>5</sup> performed a meta-analysis of 12 randomized controlled trials of oral supplemental vitamin D<sub>3</sub> for preventing nonvertebral fractures in people age 65 and older, and eight trials for preventing hip fractures in the same age group. They found that the higher the daily dose of vitamin D, the lower the relative risk of hip fracture. The threshold dose at which supplementation significantly reduced the risk of falling was about 400 units per day. Higher doses of vitamin D reduced both falls and hip fractures by about 20%. The maximal effect was seen with studies using the maximum daily doses, ie, 770 to 800 units per day—not mega-

doses, but more than most Americans are taking. The threshold serum level of vitamin D of significance was 60 nmol/L (24 ng/mL).

Of interest, the effect on fractures was independent of calcium supplementation. This is important because calcium supplementation over and above ordinary dietary intake may increase the risk of cardiovascular events.<sup>6,7</sup>

Despite the benefits of vitamin D, too much may be too much of a good thing. Sanders et al<sup>8</sup> performed a double-blind, placebo-controlled trial in 2,256 community-dwelling women, age 70 or older, who were considered to be at high risk for fractures. Half received a large oral dose (500,000 units) once a year for 3 to 5 years, and half got placebo. Their initial serum vitamin D level was 49 nmol/L; the level 30 days after a dose in the treatment group was 120 nmol/L.

Contrary to expectations, the incidence of falls was 15% higher in the vitamin D group than in the placebo group ( $P = .03$ ), and the incidence of fractures was 26% higher ( $P = .047$ ). The falls and fractures tended to cluster in the first 3 months after the dose in the active treatment group, when serum vitamin D levels were highest.

**Comments.** Unless future studies suggest a benefit to megadoses of vitamin D or prove calcium supplementation greater than 1,000 mg is safe, the optimal daily intake of vitamin D is likely 1,000 units, with approximately 200 units from diet and 800 units from supplements. A diet rich in low-fat dairy products may not require calcium supplementation. In those consuming a low-calcium diet, supplements of 500 to 1,000 mg/day are likely adequate.

### Denosumab, a new drug for preventing fractures

CUMMINGS SR, SAN MARTIN J, MCCLUNG MR, ET AL; FREEDOM TRIAL. DENOSUMAB FOR PREVENTION OF FRACTURES IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS. *N ENGL J MED* 2009; 361:756–765.

SMITH MR, EGERDIE B, HERNÁNDEZ TORIZ N, ET AL; DENOSUMAB HALT PROSTATE CANCER STUDY GROUP. DENOSUMAB IN MEN RECEIVING ANDROGEN-DEPRIVATION THERAPY FOR PROSTATE CANCER. *N ENGL J MED* 2009; 361:745–755.

Denosumab (Prolia) is the first of a new class of drugs for the treatment of osteoporosis. It is a monoclonal antibody and member of the tumor necrosis factor superfamily that binds to the receptor activator nuclear factor kappa

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**We advise patients to engage in about 30 minutes of moderate exercise every day**

B (RANK) ligand. It has an antiresorptive effect, preventing osteoclast differentiation and activation. It is given by subcutaneous injection of 60 mg every 6 months; it is cleared by a nonrenal mechanism.

In a randomized controlled trial in 7,868 women between the ages of 60 and 90 who had osteoporosis, Cummings et al<sup>9</sup> reported that denosumab reduced the 3-year incidence of vertebral fractures by 68% ( $P < .001$ ), reduced the incidence of hip fractures by 40% ( $P = .01$ ), and reduced the incidence of nonvertebral fractures by 20% ( $P = .01$ ). In a trial in men receiving androgen deprivation therapy for prostate cancer, Smith et al<sup>10</sup> reported that denosumab reduced the incidence of vertebral fracture by 62% ( $P = .006$ ).

**Comment.** Denosumab was approved by the US Food and Drug Administration (FDA) on June 1, 2010, and is emerging in specialty clinics at the time of this publication. Its potential impact on clinical care is not yet known. It is costly—about \$825 (average wholesale price) per injection—but since it is given by injection it may be easier than a yearly infusion of zoledronic acid (Reclast). It has the potential to suppress immune function, although this was not reported in the clinical trials. It may ultimately have a role in treating osteoporosis in men and women, prostate cancer following androgen deprivation, metastatic prostate cancer, metastatic breast cancer, osteoporosis with renal impairment, and other diseases.

## ■ DIALYSIS IN THE ELDERLY: A BLEAK STORY

KURELLA TAMURA M, COVINSKY KE, CHERTOW GM, YAFFE K, LANDEFELD CS, MCCOLLOCH CE. FUNCTIONAL STATUS OF ELDERLY ADULTS BEFORE AND AFTER INITIATION OF DIALYSIS. *N ENGL J MED* 2009; 361:1539–1547.

JASSAL SV, CHIU E, HLAUNETH M. LOSS OF INDEPENDENCE IN PATIENTS STARTING DIALYSIS AT 80 YEARS OF AGE OR OLDER (LETTER). *N ENGL J MED* 2009; 361:1612–1613.

Nursing home residents account for 4% of all patients in end-stage renal disease. However, the benefits of dialysis in older patients are uncertain. The mortality rate during the first year of dialysis is 35% in patients 70 years of age and older and 50% in patients 80 years and older.

Is dialysis helpful in the elderly, ie, does it improve survival and function?

Kurella Tamura et al<sup>11</sup> retrospectively identified 3,702 nursing home residents starting dialysis in whom functional assessments

had been done. The numbers told a bleak story. Initiation of dialysis was associated with a sharp decline in functional status, as reflected in an increase of 2.8 points on the 28-point Minimum Data Set–Activities of Daily Living (MDS-ADL) scale (the higher the score, the worse the function). MDS-ADL scores stabilized at a plateau for about 6 months and then continued to decline. Moreover, at 12 months, 58% of the patients had died.

The MDS-ADL score is based on seven components: eating, bed mobility, locomotion, transferring, toileting, hygiene, and dressing; function declined in all of these areas when patients started dialysis.

Patients were more likely to decline in activities of daily living after starting dialysis if they were older, were white, had cerebrovascular disease, had a diagnosis of dementia, were hospitalized at the start of dialysis, or had a serum albumin level lower than 3.5 g/dL.

The same thing happens to elders living in the community when they start dialysis. Jassal and colleagues<sup>12</sup> reported that, of 97 community-dwelling patients (mean age 85), 46 (47%) were dead 2 years after starting dialysis. Although 76 (78%) had been living independently at the start of dialysis, only 11 (11%) were still doing so at 2 years.

**Comment.** These findings indicate that we do not know if hemodialysis improves survival. Hemodialysis may buy about 3 months of stable function, but it clearly does not restore function.

Is this the best we can do? Standard hemodialysis may have flaws, and nocturnal dialysis and peritoneal dialysis are used more in other countries. These dialysis techniques require more study in our older population. The lesson from these two publications on dialysis is that we should attend more carefully to slowing the decline in renal function before patients reach end-stage renal disease.

## ■ DABIGATRAN: AN ALTERNATIVE TO WARFARIN FOR ATRIAL FIBRILLATION

CONNOLLY SJ, EZEKOWITZ MD, YUSUF S, ET AL; RE-LY STEERING COMMITTEE AND INVESTIGATORS. DABIGATRAN VERSUS WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION. *N ENGL J MED* 2009; 361:1139–1151.

Atrial fibrillation is common, affecting 2.2 million adults. The median age of people who have atrial fibrillation is 75 years, and it is

**Most older vulnerable patients are either insufficient or deficient in vitamin D; supplements are reasonable**

the most common arrhythmia in the elderly. Some 20% of ischemic strokes are attributed to it.<sup>13-15</sup>

Warfarin (Coumadin) is still the mainstay of treatment to prevent stroke in patients with atrial fibrillation. In an analysis of pooled data from five clinical trials,<sup>16</sup> the relative risk reduction with warfarin was about 68% in the overall population (number needed to treat 32), 51% in people older than 75 years with no other risk factors (number needed to treat 56), and 85% in people older than 75 years with one or more risk factors (number needed to treat 15).

But warfarin carries a risk of bleeding, and its dose must be periodically adjusted on the basis of the international normalized ratio (INR) of the prothrombin time, so it carries a burden of laboratory monitoring. It is less safe in people who eat erratically, resulting in wide fluctuations in the INR.

Dabigatran (Pradaxa), a direct thrombin inhibitor, is expected to become an alternative to warfarin. It has been approved in Europe but not yet in the United States.

Connolly et al,<sup>17</sup> in a randomized, double-blind trial, assigned 18,113 patients who had atrial fibrillation to receive either dabigatran 110 or 150 mg twice daily or adjusted-dose warfarin in an unblinded fashion. At 2 years, the rates of stroke and systemic embolism were about the same with dabigatran 110 mg as with warfarin but were lower with dabigatran 150 mg (relative risk 0.66, 95% confidence interval [CI] 0.53–0.82,  $P < .001$ ). The rate of major bleeding was lower with dabigatran 110 mg than with warfarin (2.71% per year vs 3.36% per year,  $P = .003$ ), but it was similar with dabigatran 150 mg (3.11% per year). Rates of life-threatening bleeding were 1.80% with warfarin, 1.22% with dabigatran 110 mg ( $P < .05$ ), and 1.45% with dabigatran 150 mg ( $P < .05$ ).

**Comment.** I suspect that warfarin's days are numbered. Dabigatran 110 or 150 mg was as safe and as effective as warfarin in clinical trials, and probably will be more effective than warfarin in clinical practice. It will also probably be safer than warfarin in clinical practice, particularly in challenging settings such as long-term care. On the other hand, it will likely be much more expensive than warfarin.

## DEMENTIA

### Adverse effects of cholinesterase inhibitors

GILL SS, ANDERSON GM, FISCHER HD, ET AL. SYNCOPE AND ITS CONSEQUENCES IN PATIENTS WITH DEMENTIA RECEIVING CHOLINESTERASE INHIBITORS: A POPULATION-BASED COHORT STUDY. ARCH INTERN MED 2009; 169:867–873.

Cholinesterase inhibitors, eg, donepezil (Ari-cept), galantamine (Razadyne), and rivastigmine (Exelon), are commonly used to treat Alzheimer disease. However, these drugs carry risks of serious adverse effects.

Gill et al<sup>18</sup> retrospectively reviewed a database from Ontario, Canada, and identified about 20,000 community-dwelling elderly persons admitted to the hospital who had been prescribed cholinesterase inhibitors and about three times as many matched controls.

Several adverse events were more frequent in people receiving cholinesterase inhibitors. Findings (events per 1,000 person-years):

- Hospital visits for syncope: 31.5 vs 18.6, adjusted hazard ratio (HR) 1.76, 95% CI 1.57–1.98
- Hip fractures: 22.4 vs 19.8, HR 1.18, 85% CI 1.04–1.34
- Hospital visits for bradycardia: 6.9 vs 4.4, HR 1.69, 95% CI 1.32–2.15
- Permanent pacemaker insertion: 4.7 vs 3.3, HR 1.49, 95% CI 1.12–2.00.

**Comment.** This study adds to the concerns that cholinesterase inhibitors, which have only modest cognitive benefits, may increase the risk of falls, injury, and need for pacemaker placement in demented patients. A low threshold to stop medications in this class should be considered when a patient on a cholinesterase inhibitor presents with bradycardia, falls, and syncope.

### The importance of 'staging' dementia

IVERSON DJ, GRONSETH GS, REGER MA, ET AL. STANDARDS SUBCOMMITTEE OF THE AMERICAN ACADEMY OF NEUROLOGY. PRACTICE PARAMETER UPDATE: EVALUATION AND MANAGEMENT OF DRIVING RISK IN DEMENTIA: REPORT OF THE QUALITY STANDARDS SUBCOMMITTEE OF THE AMERICAN ACADEMY OF NEUROLOGY. NEUROLOGY 2010; 74:1316–1324.

The Clinical Dementia Rating (CDR) is a simple scale that should be applied by clinicians to describe stage of dementia in patients with Alzheimer disease. This scale can be useful in a variety of settings, from prescribing antidementia drugs to determining whether a patient should still drive. Although research

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**Vitamin D  
1,000 U/day  
plus calcium  
500–1,000 mg  
in those with  
minimal dietary  
intake reduces  
falls, fracture  
risk**

protocols utilize a survey or semistructured interview to derive the stage, the clinician can estimate the stage easily in the office, particularly if there is an informant who can comment on performance outside the office.

There are four stages to the CDR<sup>19</sup>:

- 0: No dementia
- 0.5: Mild memory deficit but intact function
- 1.0: Moderate memory loss with mild functional impairment
- 2.0: Severe memory loss, moderate functional impairment
- 3.0: Severe memory loss, no significant function outside of the house.

**Comment.** The first stage (0.5, mild memory deficit but intact function) corresponds to “mild cognitive impairment.” In the clinic, these patients tend to take more notes. They come to the appointment with a little book and they write everything down so they don’t forget. They do arrive at their appointments on time; they are not crashing the car; they are paying their bills.

Patients with CDR stage 1.0 dementia (moderate memory loss with mild functional impairment) may miss appointments, they may confuse their medications, and they may have problems driving. They are still taking care of their basic needs, and they show up for appointments acceptably washed and dressed. However, they are likely having trouble shopping and managing their finances.

Patients with severe memory loss and moderate functional impairment (CDR stage 2.0) may not realize they haven’t bathed for a week or have worn the same clothes repeatedly. They are having trouble with basic activities of daily living, such as bathing and toilet hygiene. However, if you were to encounter them socially and didn’t talk to them for too long, you might think they were normal.

Those with severe memory loss and no significant function outside the house (CDR stage 3.0) are the most severely disabled. Dementia in these individuals is recognizable at a glance, from across the room.

Alzheimer patients progress through the stages, from CDR stage 0.5 at about 1 year to stage 1 by about 2 years, to stage 2 by 5 years, and to stage 3 at 8 or 9 years.<sup>20</sup>

**In prescribing antedementia medications.** The CDR can help with prescribing antedementia drugs. No medications are approved by the FDA for stage 0 or 0.5. Cholinesterase inhibitors are approved for stages 1, 2, and 3; memantine (Namenda) is approved for stages 2 and 3.

**Advising about driving.** The CDR is the only risk predictor with a quality-of-evidence rating of A. More than half of people with stage 0.5 memory impairment are safe drivers; fewer than half of those with stage 1.0 are still safe drivers; and patients with stage 2.0 dementia should not be driving at all.<sup>21</sup> An adverse rating by a caregiver carries a quality-of-evidence rating of B. Predictors of driving risk with a quality-of-evidence rating of C are decreased mileage due to self-restriction, agitation, or aggression; a crash in the past 1 to 5 years; a citation in the past 2 to 3 years; and a Folstein Mini-Mental State Examination score of 24 or less. Studies also show that a memory-impaired person’s self-rating of safe driving ability or of assurance that he or she avoids unsafe situations is not reliable.<sup>21</sup>

## ■ DELIRIUM

Delirium goes by a number of synonyms, eg, “sundowning,” acute confusional state, acute change in mental status, metabolic encephalopathy, toxic encephalopathy (psychosis), acute brain syndrome, and acute toxic psychosis.

Delirium is common in hospitalized elderly patients, occurring in 11% to 42% of elderly hospitalized patients overall, up to 53% of elderly surgical patients on regular hospital floors, 80% of elderly surgical patients in intensive care, and about half of elderly patients after undergoing coronary artery bypass grafting. Unfortunately, it is undiagnosed in 30% to 60% of cases.<sup>22–24</sup>

Many pathways can lead to delirium, including hypoxemia, metabolic derangement, drug effects, systemic inflammation, and infection.<sup>25</sup>

Outcomes can vary from full recovery to death. After 1 year, 50% of those who leave the hospital with some evidence of delirium have not regained their baseline function. Delirium also increases the cost of care and the risk of institutionalization.

**We should make more of an effort to slow the decline in renal function before older patients reach end-stage renal disease**



## Delirium can accelerate dementia

FONG TG, JONES RN, SHI P, ET AL. DELIRIUM ACCELERATES COGNITIVE DECLINE IN ALZHEIMER DISEASE. *NEUROLOGY* 2009; 72:1570–1575.

Delirium accelerates the course of dementia in patients who had some evidence of dementia before they entered the hospital. Often, the change is noticeable by the family.<sup>26</sup>

## Preventing delirium

INOUE SK, BOGARDUS ST JR, CHARPENTIER PA, ET AL. A MULTICOMPONENT INTERVENTION TO PREVENT DELIRIUM IN HOSPITALIZED OLDER PATIENTS. *N ENGL J MED* 1999; 340:669–676.

LUNDSTRÖM M, OLOFSSON B, STENVALL M, ET AL. POSTOPERATIVE DELIRIUM IN OLD PATIENTS WITH FEMORAL NECK FRACTURE: A RANDOMIZED INTERVENTION STUDY. *AGING CLIN EXP RES* 2007; 19:178–186.

Delirium can often be prevented. In a report published in 1999, Inouye et al<sup>27</sup> described the outcomes of a program to prevent delirium in hospitalized medically ill elderly patients. Interventions were aimed at optimizing cognitive function, preventing sleep deprivation, avoiding immobility, improving vision and hearing, and treating dehydration. The incidence of delirium was 9.9% in the interven-

tion group vs 15% in the control group, a 40% reduction ( $P < .05$ ).

Lundström et al<sup>28</sup> implemented a similar program for elderly patients with hip fractures. Interventions included staff education and teamwork; active prevention, detection, and treatment of delirium; transfusions if hemoglobin levels were less than 10 g/dL; prompt removal of indwelling urinary catheters, with screening for urinary retention; active prevention and treatment of constipation; and protein-enriched meals. The incidence of delirium was 55% in the intervention group vs 75% in the control group, a 27% reduction.

**Comment.** Although we have long known that the risk of delirium in medical and surgical patients can be reduced, most hospitals do not have systematic programs to detect delirium and reduce its incidence. Hopefully, reduction in delirium risk will also reduce its adverse consequences, including worsening of dementia and increased mortality. ■

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**Delirium in hospitalized patients can often be prevented, along with, we hope, its adverse consequences**

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