



Shedding A New Light On CHRONIC AILMENTS

Joanne Kaldy

Imagine an injection that could be administered once a year to treat osteoporosis or a compound that stimulates the body's own ability to produce red blood cells. These are a few of the innovations on the horizon to address some common geriatric syndromes seen in long term care facility patients. In fact, issues of aging are getting a growing amount of attention in medical literature, clinical trials, and new product development. Four conditions in particular—*anemia*, Parkinson's disease, osteoporosis, and depression—have been the subject of several significant studies, and new treatments and approaches for managing these conditions are showing promise.

TREATING ANEMIA

"Anemia of the elderly and anemia associated with cancer are big areas right now, and they're being targeted for both research and evidence-based guidelines for treatment," says John Adamson, MD, professor of medicine at the Medical College of Wisconsin, Milwaukee. "In fact, the National Institutes of Health has issued a request for grant applications for studies on aging and anemia, which is very good news for long term care," he says, because "there are gaps in knowledge that need to be filled. We don't really know whether correcting anemia in the elderly has any effect on long-term outcomes, including quality of life."

To date, most studies have established the relationship between anemia and survival. At least one study conducted by Chaves *et al.* (2002) has shown a link between anemia and functional dependence. Another study, conducted by Penninx *et al.* (2006), found that anemia can identify an elderly individual as being at risk for physical decline. This

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connection suggests the importance of recognizing and treating anemia in the elderly, as functional dependence affects patients' quality of life, adds cost to care, and increases burdens on facility staff.

New Treatment Opportunities

According to Adamson, an increased interest in treating anemia has led to the development of new drugs, which, in turn, could lead to more cost-effective management of chronic anemia. "With the appearance of competing agents coming on the market in the next couple of years, there may be an opportunity to bring down the cost of treating chronic anemia, and this could make treatment more accessible for long term care patients with this disease," he says.

A growing realization of anemia's potential consequences has triggered this new interest in treating the condition, says Adamson. "It is becoming more recognized as a complication of aging that affects morbidity and may affect mortality. Anemia also appears to be associated with shorter long-term survival," he says.

Anemia also is more common in the long term care setting than previously recognized. According to William Ershler, MD, director of the Institute for Advanced Study on Aging and senior investigator at the Clinical Research Branch, National Institutes of Health, 11 percent of people age 65 and over can be identified as having anemia. In the nursing facility setting, about 50 percent of patients meet these criteria.

"One thrust of research relates to determining if this is a marker of bad disease or a cause of functional decline," Ershler says, noting that this is important to know because the elderly often have numerous comorbidities, and it is difficult to tell, for example, if a patient's fatigue is being caused by cancer or anemia.

"We know that anemia is a problem, and we know that low hemoglobin is

problematic but can be corrected," says Ershler. "We think anemia is a cause of functional decline and adverse consequences. In studies with cancer and kidney failure patients, there are better cardiac and renal outcomes if you treat the anemia."

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At the same time, Lodovico Balducci, MD, professor of oncology and medicine at the University of South Florida College of Medicine in Tampa, notes that the most common cause of anemia in the elderly is iron deficiency. However, he says, in addition to treating the iron deficiency, it is essential to identify underlying causes for the iron loss and address those conditions.

"We know that even mild anemia in the elderly needs to be worked up aggressively, because it may indicate the presence of a serious underlying disease that needs to be corrected."

For residents in facilities, Ershler says, treatment may improve function "to the point that patients won't have to be hospitalized. A little erythropoietin goes a long way in treating ane-

mia." However, says Ershler, "We don't know what actual good it does, and it is not without risks [such as increased blood pressure]. It has to be closely monitored."

Promising Drugs

While research in the coming years likely will address questions of dosage, there already are some promising drugs on the horizon.

For instance, transdermal and oral versions of erythropoietin stimulators are being looked at for this application. "The limited data on these agents are very promising," says Ershler, noting that erythropoietin stimulators—which cause the bone marrow to produce more red blood cells, thereby decreasing the need for blood transfusions—are already being administered intravenously. The versions in development could simplify administration and make this product more practical in long term care settings, he says.

Elsewhere, FibroGen has an oral preparation for treating anemia in clinical development. Based on the company's hypoxia-induced factor stabilization technology, this agent is designed to restore the oxygen-carrying capacity of the blood by stimulating the body's natural erythropoietic processes, including the induction of endogenous erythropoietin and the mobilization and utilization of iron stores, essential to the formation of new oxygen-carrying red blood cells. The product represents a potential first-in-class oral therapy for anemia.

Study of the drug is aimed at treatment for anemia of chronic kidney disease, chemotherapy-induced anemia, and anemia of chronic disease.

Another promising innovation is a new drug called deferasirox, a once-daily, drinkable preparation that could be an alternative to deferoxamine.

At the same time, Amgen has announced results from a Phase 2 study that showed that treating anemia with Aranesp (darbepoetin alfa) in patients with symptomatic heart failure

was well-tolerated, effectively raised hemoglobin, and improved patients' symptoms as measured by the Kansas City Cardiomyopathy Questionnaire. This is potentially important because anemia is a well-recognized comorbidity in many chronic conditions, although its role in heart failure has

been recognized only recently, according to Paul and Paul (2004). Of course, no innovation can be expected to have a widespread impact on outcomes for elderly patients if it is cost-prohibitive. Fortunately, Ershler says, "FibroGen is very sensitive to the pricing issue. One of the company's strategies is to make

an inexpensive alternative." He adds that Medicare Part D prescription drug plans (PDPs) do have anemia medications on their formularies.

"We have been treating Medicare patients, and they are getting the medications they need through the formularies," Ershler says.

TREATING PARKINSON'S DISEASE

"We don't really have a better understanding of Parkinson's disease (PD) in terms of genetic markers. Nor have we had any major advances from a biochemical standpoint," says Charles Cefalu, MD, professor and director of geriatric program development at the Louisiana State University Health Sciences Center in New Orleans. "From a radiological standpoint, however, we have had some advances. These have come with better medications that have fewer side effects and a better understanding of medication management for PD patients," Cefalu says.

Increasingly, clinicians are giving careful consideration to whether and when to initiate levodopa. As Cefalu notes, "We don't use levodopa anymore as a primary agent. We tend to use a combination of levodopa-carbidopa. There also are newer dopamine agonists."

New Approach Validated

This change in approach has been validated to some degree by recent studies such as the ELLDOPA study, which called into question the use of levodopa to treat PD. Conducted by the Parkinson's Study Group, this was a placebo-controlled, parallel-group, multisite clinical trial, designed to determine whether levodopa alters the natural course of PD.

The main outcome variables were changes in severity as measured by the total Unified Parkinson's Disease

Rating Scale. Participants received placebo or dosages of levodopa ranging from 150 to 600 mg.

The study found no evidence that levodopa treatment is harmful or promotes PD progression. But data did not prove that levodopa is protective either. There were a few adverse events, including "a little more" headache in the 600-mg/day group and slightly increased muscle tone and dystonia. In the higher dosage groups, some nausea and vomiting occurred, and there was more leg pain in the placebo and low-dose groups.

Dopaminergic adverse events included dyskinesias (defect in voluntary movement) and wearing off in the 600-mg/day group. Freezing was more prevalent in the lower-dose groups.

Catechol *O*-methyltransferase (COMT) "inhibitors are newer, and we should be using this class of drugs—which has fewer side effects—earlier," Cefalu says. COMT inhibitors enable a larger amount of levodopa to reach the brain, and this raises dopamine levels there. These agents help provide a more stable, constant supply of levodopa, and this makes for a longer-lasting benefit, he says.

Increasingly, physicians are starting to prescribe one COMT inhibitor, entacapone, along with levodopa, more often at the beginning of therapy. At the same time, there is a new combination medication (Stalevo) that contains entacapone, levodopa, and carbidopa, which may be more convenient for dosing in the long term care setting.

COMT inhibitors are not new, Cefalu says, noting that "three years ago we had COMT inhibitors, as well as MAO [monoamine oxidase] inhibitors and dopamine agonists, but we didn't use them as well as we should have. We should be utilizing these drugs and not others." He explains that a key issue is to educate primary care physicians about preferred drugs. "Physicians may feel uncomfortable with these because they aren't generally used for treating PD."

New Drug Approved

In May, a new drug to treat PD received Food and Drug Administration (FDA) approval. The drug, Azilect (rasagiline), blocks the breakdown of dopamine. It is approved as an initial single-drug therapy for early PD and as an addition to levodopa in patients with more advanced stages.

Azilect is not without potential adverse effect. It can cause dangerous interactions when patients consume food or beverages that contain tyramine, which is found in draft beer, red wine, aged cheeses, soy sauce, salamis, and other products. These interactions can cause sudden and severe blood pressure increase, resulting in stroke or death. Other side effects include involuntary movements, hallucinations, and lowered blood pressure. Azilect joins another rasagiline, Agilect, on the market.

According to at least one study, rasagiline is not more likely to cause side effects in the elderly than in

younger patients. This can help eliminate the need for special drug monitoring in this population, according to Goetz *et al.* (2006). The authors found that rasagiline was linked more frequently to adverse effects when it was used with levodopa. Although some side effects were more common in the elderly, such as very low blood pressure and hallucinations, the drug was determined not to be riskier for elders.

Other Studies Under Way

Elsewhere, the National Institute of Neurological Disorders and Stroke (NINDS) is conducting a number of studies regarding neuroprotection in a nationwide multi-center effort called Neuroprotection Exploratory Trials in Parkinson's Disease. According to Karl Kieburtz, MD, professor of neurology and community and preventive medicine, University of Rochester School of Medicine and Dentistry, NINDS is "looking at 59 agents—four in pilot studies—that might be of value. These studies are unusual because they look at things that don't work."

The studies are aimed at identifying agents that are useless so that "we can abandon these and focus on what might be useful," says Kieburtz.

One completed study involving 200 PD patients showed that creatine and minocycline may warrant further consideration for study in a larger trial,

according to Kieburtz. Study investigators caution that while the news is encouraging, the results do not demonstrate that these agents are effective in treating PD. Before these interventions can be recommended as a treatment, they must be tested in a larger trial with hundreds of patients.

Patients were randomly assigned to receive 200 mg/day minocycline, 10 g/day creatine, or placebo. Participants were then followed for 12 months. Researchers examined the safety and tolerability of the medications and the severity of the PD.

Although neither agent caused major side effects, minocycline was not as well-tolerated. Both creatine and minocycline appeared to modify the disease features as measured by a decline in clinical signs.

Based on the initial analyses of the pilot studies, creatine and minocycline have passed the first hurdle. However, further study is required before the researchers can conclude whether creatine or minocycline is, in fact, helpful, harmful, or has no significant impact.

Nonpharmacologic Advances

Some recent advances in PD treatment involve nonpharmacologic interventions. Experts outlined many of these at the World Parkinson Congress, held earlier this year in Washington, D.C. According to Andres Lozano, MD,

head of applied and interventional research at the Toronto Western Research Institute in Canada, much promising work is being done regarding deep brain stimulation, a technique that suppresses tremor by delivering mild electrical stimulation to block brain signals that cause the uncontrollable shaking.

"[Deep brain stimulation] increases the amount of time patients have good motor function, and, subsequently, it improves patients' quality of life," says Lozano, noting that the greatest benefit is for involuntary movement and tremor. In most cases, he observes, patients are able to reduce the use of levodopa for at least a period of time.

Gait and postural problems respond much less to deep brain stimulation, and the treatment doesn't help problems in other spheres. "Our challenge now is to understand what causes other problems and develop novel treatments to address them," Lozano says.

Deep brain stimulation also is being used to treat depression in some PD patients, and "it is possible that we may be able to target different areas of the brain to handle different problems," says Lozano, who also points out a downside to the treatment: "Of course, this intervention is brain surgery, and, therefore, it is not without risks. The bleeding could cause strokes or even death."

TREATING OSTEOPOROSIS

According to Felicia Cosman, MD, clinical director, National Osteoporosis Foundation, "The whole last decade has been one of many therapeutic options to treatment of osteoporosis. There are more on the horizon that we expect to be available in the next two to three years."

Improved Diagnosis, Prevention

Diagnostic technology also has improved dramatically. "Not long ago, there were few bone-density machines

and no Medicare reimbursement for testing," says Cosman. "Now just about everyone has access to bone-density testing equipment, and we know that this is the best way to diagnose osteoporosis in the absence of a fracture. We also have honed in on research for universal measures. We now know about nutritional modifications and exercise that can be preventative. We also know that consuming some alcohol is fine and may even benefit bones, but excessive alcohol use

and smoking are detrimental." One recent study has even suggested that chest X-rays may help spot osteoporosis in older people. Researchers studied a random sample of 459 patients over age 60 and found that undetected osteoporosis in this population may be discovered if X-ray images are examined for vertebral fractures, according to Majumdar *et al.* (2006).

One important diagnostic advance was the recognition of absolute risk. The National Osteoporosis Risk

Assessment (NORA) study (2006) showed that absolute risk of fracture increased with age for all fracture sites. This was most evident for hip fractures, where the incidence of risk for women with low bone mineral density (BMD), the primary indicator of osteoporosis, increased at least twofold for each decade increase in age. The study concluded that—at any given BMD—the absolute as well as the excess fracture risk increased with age.

The NORA study is key, says Mary Beth Elliott, associate professor, School of Pharmacy, University of Wisconsin-Madison, “because we now know that people with lower bone density at the heel and forearm are most likely to experience fractures.”

Advance Has Drawbacks

Teriparatide (Forteo) “has been another enormous advance,” according to Cosman. “It can help patients who are pretty far gone. It actually can repair some of the defects seen in aging menopausal patients,” she says. Forteo is a man-made form of the naturally occurring hormone parathyroid. It forms new bone and increases bone mineral density and bone strength.

However, this drug, too, is not without its disadvantages. Not only does it have a high price tag, but the once-daily injection required places a burden on facility nursing staff.

As Elliott explains, “This is a good product, but it is extremely expensive, and we are unlikely to see it often in nursing facilities.”

Fortunately, there are other products in the works that would require less frequent dosing. Currently in the testing phase is AMG 162 from Amgen, an osteoporosis therapy for bone loss that requires only twice yearly injections. Preliminary findings suggest that the treatment significantly decreased bone loss at the total hip compared with placebo at 12 months. At all doses, it also increased total hip BMD, similar to or greater than alendronate (a bisphosphonate).

Cosman says that bisphosphonates are still the main drugs used to treat osteoporosis in the elderly, and, to date, there have been both positive and negative developments regarding these medications.

In another study, yearly intravenous injection of a strong bisphosphonate,

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zoledronic acid, strengthened the bones of osteoporosis patients as well as daily oral dosing with other bisphosphonates. The study drew no conclusion about the drug’s effectiveness in preventing bone fractures. However, while more study is necessary, the authors concluded that an annual infusion of zoledronic acid might be an effective osteoporosis treatment.

Drug Combinations

One study showed that the bisphosphonate Fosamax is more effective when taken with another drug. Researchers gave postmenopausal women parathyroid hormone (PTH), a bone-building drug for one year, followed by another year on Fosamax. The results showed that women who took both drugs had approximately a

30 percent increase in bone density. This compared to 14 percent for those who took just PTH and 7 percent for those who only took Fosamax.

At the same time, a potentially serious problem recently has come to light regarding Fosamax. At least 300 Americans are suing the drug’s manufacturers for developing osteonecrosis, or breakdown of bone, in the jaw after taking Fosamax. “This is a rare but pretty nasty side effect. The individuals most likely to experience this are those who have cancer or a dental infection of some kind,” says Elliott.

A common problem for frail elders is that many can’t stand or sit up for an hour after taking bisphosphonates. These individuals are at high risk for serious gastroesophageal side effects and are inappropriate candidates for these medications.

Boniva, a new once-monthly bisphosphonate, has received much attention and holds promise for use with frail, elderly patients with limited mobility. Data have shown that Boniva is highly effective and well-tolerated. The drug has been shown to reduce spinal fractures by 62 percent in patients with postmenopausal osteoporosis.

In long term care settings, costs of osteoporosis treatments can be a barrier. However, Cosman suggested that costs are starting to come down. For example, she says, at least one generic bisphosphonate will be available in the next year or so.

Unresolved Issue

One issue that has not been resolved revolves around which frail elderly patients should be treated for osteoporosis and what treatment they should receive. “There are lots of opinions about this,” says Cosman, “but there are many individuals who I wouldn’t select for long-term therapy—such as patients who are wheelchair-bound, suffering from dementia, or have lots of other chronic illnesses. On the other hand, she says, she would recommend treating even very old

individuals who are ambulatory and cognitively intact. “These are the kinds of people who lose independence and functioning due to a fracture. This is a population with whom we should be very aggressive, and there is no upper age limit,” Cosman says.

There is little disagreement on another issue—the regular use of calci-

um and vitamin D. “Giving calcium and D on a regular basis is a win-win situation. We are talking about zero risk and low cost,” says Cosman, noting that a high-dose pill can be administered once weekly if daily dosing is too burdensome.

While there have been advances in osteoporosis treatment in the works, it

is unlikely that long term care patients will benefit from all of these. “Most PDPs probably cover some bisphosphonate, but the injectable products can be very expensive,” says Elliot. “In the long term care setting, it may be wise to start by looking at low-hanging fruit. Identify patients who aren’t getting regular calcium and vitamin D.”

TREATING DEPRESSION

In recent years, there have been relatively few new medications for treating depression in the elderly.

However, some significant studies suggest a new approach to treating depression in this population is important for better short- and long-term outcomes.

Employing A Team Model

One key study demonstrated that a team care model for treating depression in older adults was more cost-effective than standard treatment. The IMPACT (“Improving Mood-Promoting Access to Collaborative Treatment for Late Life Depression”) study indicated that not only does the team model improve depression but it also decreases pain and improves physical functioning and quality of life, according to principal investigator Jurgen Unutzer (2002).

For example, the study showed that effective depression treatment can improve problems related to arthritis. On examination of a subset of 1,001 patients who had both depression and arthritis, the researchers found that IMPACT care not only improved depressive symptoms but also lessened pain and impairment due to arthritis.

At 12 months, about one-half of patients receiving IMPACT care reported at least a 50 percent reduction in depressive symptoms, compared with a 19 percent reduction in patients who received the usual care (defined as medication, psychotherapy, or any

combination of the two). Among the key elements of the IMPACT model is assignment of a depression care manager, who can be a nurse, social worker, or psychologist (sometimes supported by a medical assistant). The care manager’s role includes:

- Educating patients about depression;
- Supporting antidepressant therapy prescribed by the patient’s primary care provider;
- Coaching patients in behavioral activation and pleasant events scheduling;
- Offering a brief course (six to eight sessions) of counseling, such as problem-solving treatment;
- Monitoring depression symptoms for treatment response; and
- Completing a relapse prevention plan.

The other elements of the IMPACT model involve a designated psychiatrist and collaborative care in which patients, care managers, and primary care providers work together to develop a treatment plan and the care manager and primary care provider consult with the psychiatrist when patients don’t improve.

Results of the study suggest that the IMPACT program contributed to positive outcomes after the services were discontinued.

After IMPACT services ended, patients who had received this team care experienced more than 100 additional depression-free days over a two-

year period than those who received usual care.

Implications For Long Term Care

While the IMPACT study was conducted in primary care settings with community-dwelling elderly, Unutzer believes that an IMPACT-like team approach to treating depression in the elderly can be utilized in long term care settings. In fact, he says, this is currently being studied, with results expected in two years. “I think that different levels of long term care staff could be taught core components of what these care managers do and to do some behavioral activation and pleasant event scheduling,” Unutzer says. He says that the care management approach to depression could provide facility patients with increased access to consultant psychiatrists.

He says that some of the findings present an important message to long term care facilities in terms of the benefits of aggressively treating depression and using teams to provide this treatment. “One of the most surprising findings was that only one in five patients treated for depression with the usual care will get better,” says Unutzer. “We think that these numbers can be doubled with organized treatments.”

Unutzer notes that he and his group are looking at elements that might be predictors of which patients are most likely to benefit from an IMPACT program. “For example, we have found

that people with chronic pain got some benefit, but it was harder to improve their depression,” he says, adding that, “we now are looking at a model that addresses pain and depression in conjunction.”

While Unutzer acknowledges that the IMPACT model might not be optimal for all patients or settings, he says that changes are necessary in the way depression is treated in the elderly.

“Half of the people in the IMPACT study were on regular care of some kind for depression, but they never got better,” he says. “When this is happening, things need to change. We have too many people who are on minimally effective treatments.”

That the so-called “usual care” often fails when applied to the elderly is not surprising, says Unutzer, pointing, for example, to the PROSPECT study, which concluded that there is a link between the intensity of depression treatment and medical comorbidity and treatment outcomes for depression.

Yet another study that demonstrated the advantages of care for depression that goes beyond the “usual” is the RESPECT [“Re-Engineering for the Primary Care Treatment of Depression”] study, conducted by Dietrich *et al.* (2004). This study indicated that patients treated for depression showed significant improvement and increased satisfaction with care when clinicians utilized a quality improvement approach. Results showed that 60 percent of patients responded substantially to treatment within six months, while 90 percent rated their care as excellent.

“IMPACT, PROSPECT, RESPECT—these studies all reach the same conclusion: Care as usual no longer can be considered adequate,” says Richard Goldberg, professor of psychiatry and human behavior at Brown University, Division of Biology and Medicine, in Rhode Island. While these studies suggest that more could

WHAT'S AHEAD?

It is encouraging that the research and pharmaceutical communities are working diligently to develop better, more cost-effective approaches to recognizing and managing geriatric syndromes.

Some of these innovations are far from ready for regular use in long term care facilities. However, efforts to decrease costs and increase access hold promise that—in the near future—new diagnostic tools, treatments, and technologies will help patients with these illnesses enjoy higher levels of functioning and quality of life for longer periods of time.

be done to treat depression in the elderly, Unutzer notes that the studies also could be considered encouraging.

“They show us that depression is a common and disabling, but very treatable, condition,” says Unutzer. “When you treat depression effectively, you can have a good payoff in terms of health, functioning, and quality of life.”

Challenges Of Team Approach

Of course, Unutzer observes, a successful team approach to managing depression is not without its challenges. “The main challenge posed by this model is that the medical director may not have a systematic approach to follow through, and patients can fall through the cracks. Our study addresses this by adding interventions that go

well beyond prescribing of medications and include extensive behavioral activation,” he says.

Another challenge of initiating an ongoing team approach is the cost it adds in terms of staff time and other expenses, says Unutzer. However, he adds, while costs relating to treating depression go up initially, expenses associated with the cost of comorbid conditions and loss of independence and functioning decrease substantially over time.

Some other innovations may improve depression care or treatment for the elderly in the future. For example, “Increasing the recognition of vascular depression as an entity and how elderly depressive symptoms occur because of vascular changes in the brain is an important development,” says Goldberg. “This suggests that by treating conditions such as hypertension, high cholesterol, and carotid arteries, we can prevent the vascular damage that leads to depressive symptoms.”

The first line of pharmacologic therapies for treating depression in the elderly remains the selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors, says Goldberg. “However, we still have a lot to learn about what to do next if people don’t respond to these drugs.”

In a setting where medication cost is always an issue, new generics could be significant to some degree, and a generic version of Lexapro, a widely prescribed antidepressant, was approved by the FDA in May of this year.

“I wish I could be more optimistic about the future for depression in this population, but we still have work to do,” says Goldberg. “Antidepressants are not the entire treatment approach. We need to support dignity, activities, and social relationships.” ■

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