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INSIDE

Financial Disclosure:
Internal Medicine Alert's editor, Stephen Brunton, MD, is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Endo, EXACT Sciences, and Astra-Zeneca, and serves on the speaker's bureau of McNeil, Sanofi-Aventis, and Ortho-McNeil. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

Antipsychotics in Alzheimer's Patients: The CATIE-AD Study

ABSTRACT & COMMENTARY

By Norman R. Relkin, MD, PhD

Associate Professor, Clinical Neurology and Neuroscience, New York Presbyterian Hospital, Cornell Campus

Dr. Relkin is on the speaker's bureau for Pfizer, Eisai, and Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: *Because of adverse effects, special care should be used when prescribing the atypical antipsychotic drugs for patients with dementia.*

Source: Schneider LS, et. al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *New Engl J Med.* 2006;355:1533-1538.

AGITATION AND AGGRESSION ARE AMONG THE MOST dangerous and disruptive symptoms encountered in patients with Alzheimer's Disease (AD). Hallucinations and delusions can be extremely disturbing to patients and their care providers alike. Psychotic symptoms are often treated with medications such as quetiapine (Seroquel®), olanzapine (Zyprexa®) and risperidone (Risperdal®). However, these agents were not specifically tested or approved in the context of psychosis in Alzheimer's disease. A double blind, placebo-controlled multicenter study called CATIE-AD (Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's disease) examined the use of current-generation antipsychotics to determine whether these treatments offered real benefits relative to placebo effects in AD patients.

A total of 421 AD patients with an average MMSE score of 15 participated at 42 sites. All subjects had symptoms of psychosis, agitation and/or aggression at time of enrollment. Subjects were assigned either to placebo or to one of 3 antipsychotics at mean doses of 5.5 mg/d (olanzapine), 1 mg/d (risperidone) or 56.5 mg/day (quetiapine). The author acknowledged that the dose of quetiapine used in this study may have been less than optimal.

VOLUME 29 • NUMBER 2 • JANUARY 29, 2007 • PAGES 9-16

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The CATIE-AD study used an unusual "adaptive design" that was praised in an accompanying editorial in the *New England Journal of Medicine* as an exemplary method for evaluating the effectiveness of prescription medications. Participating physicians were not told which antipsychotic agent each patient would receive but were given the opportunity to change or discontinue the medication at any time. The primary outcome measure was the time until the treating physician made a change in the antipsychotic medication for any reason. The rationale for this design was that physicians most often change medications owing to lack of efficacy or side effects and that change was thought to provide less biased indication of real-world clinical utility than measures such as psychosis rating scales. The study also used the Clinical Global Impression of Change (CGIC), a physician-based assessment commonly used in AD pharmaceutical trials, as a 12-week secondary outcome measure.

The primary outcome (time to discontinuation for any reason) was not significantly different for placebo than any of the 3 antipsychotics. The time to discontinuation for perceived lack of efficacy was greater for risperidone and olanzapine than for placebo, whereas quetiapine was comparable to placebo. No significant difference relative to placebo was reported on the Global Assessment of Change (CGIC) for any of the treatment arms. Based on CGIC scores, 21% of placebo-treated patients were judged better at 12 weeks, compared to 32% on olanzapine, 26% on quetiapine and 29% on risperidone.

The overall rate of serious adverse events was lowest in patients receiving risperidone, but this difference did not reach statistical significance. Extrapyramidal side effects, including parkinsonism, were highest in patients receiving olanzapine (12%) or risperidone (12%), and only occurred in 1-2% of patients on quetiapine or placebo. Sedation was most problematic for patients on olanzapine (24%) and quetiapine (22%), but was also seen in patients on risperidone (15%) as well as a small percentage of those on placebo (5%). Cognitive disturbances (6%) and increased psychosis (7%) were most problematic in the olanzapine treated group, whereas increased agitation was reported in those receiving quetiapine (12%) or placebo (10%).

The authors' conclusion was that the adverse effects of these 3 antipsychotic medications "offset" the small treatment advantages they offered to patients with psychosis and AD. They did not conclude that antipsychotics were ineffective, nor did they recommend against their use in AD patients. They acknowledged that in light of the significant potential for adverse events it may be prudent to use these antipsychotics in patients who demonstrate good tolerance and observable benefits.

COMMENTARY

Psychotic behaviors pose a real threat to the well-being of patients with AD and to those around them. Treatment-unresponsive agitation and aggression are among the reasons frequently cited for institutionalization of AD patients. The use of antipsychotic medications, as well as other psychotropic medications and non-pharmacologic interventions can be life-saving in some cases and can make the difference between a good outcome and a worst-case scenario.

While several criticisms can be made about design of the CATIE study, there is one major limitation that warrants special mention. The appropriate care of an agitated, psychotic AD patient is not simply a matter of writing a prescription for an antipsychotic drug. It is an interactive process that requires multiple types of parallel interventions, including identification and treatment of exacerbating physical precipitants, adjustments in psychotropic and non-psychotropic medications,

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

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United States
1 year *with* free AMA Category 1 credits: $289
(Student/Resident rate: $125).

Multiple Copies
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Questions & Comments

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attempted normalization of the sleep-wake cycle and nutrition, maintenance of a supportive environment and appropriate caregiver education. Ideally these interventions are made by physicians and allied health professionals with expertise in this area working as a team, with the cooperation and support of the patient's caregivers and family. However innovative the design of CATIE-AD may have been, it did not control for these critical co-factors.

Currently available antipsychotic medications may not be the drug of choice in every case, but they can play an extremely important role in the management of some AD patients with psychosis. The CATIE-AD study has been misinterpreted in the lay press as proof that novel antipsychotics lack efficacy and are unacceptably toxic in dementia patients. A closer look at the trial's design and actual outcomes contradicts these claims. The study's authors have publicly stated that these agents should still be tried in AD patients with psychosis and do work well in some cases. This study should not be accepted as justification for denying these medications to dementia patients with psychosis. CATIE-AD reminds us that all antipsychotics are potentially dangerous medications and that even the newest generation of these agents must be used judiciously. ■

Dr. Google, I Presume

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Dr. Wilke is Residency Program Director, Associate Professor of Family Medicine; University of Alabama at Birmingham School of Medicine—Huntsville Regional Medical Campus, Huntsville

Dr. Wilke reports no financial relationship to this field of study.

Synopsis: *Searching Google yielded a correct diagnosis in greater than half of cases.*

Source: Tang H, Ng JH. Googling for a diagnosis—use of Google as a diagnostic aid: internet based study. *BMJ*. 2006;333:1143-1145.

After the appearance of anecdotal reports of physicians and patients coming up with obscure diagnoses by use of the internet search engine Google, Tang and Ng decided to study its accuracy. They took the entire *New England Journal of Medicine*'s case records for 2005 (excluding management cases) and chose three to five terms that described the essence of each case. They then searched Google with these descriptors and chose its top three diagnoses. Comparing Google's "differential diagnosis" with the diagnosis as presented in *NEJM*, Google got it right in 15 of 26 cases (58%). As an example, in one case, an 80-year-old man presented with fatigue, unsteady gait, confusion, and insomnia, leading to death. The authors searched on the terms ataxia, confusion, insomnia, and death. Google suggested spongiform encephalopathy; the diagnosis in NEJM was Creutzfeldt-Jakob disease.

COMMENTARY

When I first began teaching in the mid-1980s, I played around with an "expert system" called DXplain. In 1984, when it was developed at the Massachusetts General Hospital Laboratory of Computer Science, it was DOS-based, "knew" 500 diseases, and was available only over dial-up on AMANET. So 20th century! It eventually migrated to the World Wide Web and joined many other proprietary, web-based, decision support tools (DST). Why are there so many DSTs on the Web, on your desktop computer, in your PDA, or integrated into your electronic health record? Because there are just too darn many facts and connections linking those facts for us to remember! We have become, of necessity, information masters, and the practice of medicine, art plus science, has changed forever. The promise of DSTs, as yet unfulfilled, is to make the science instantly available, allowing more time for the art. Why has Google overshadowed other DSTs? One factor is it's free, and they are proprietary. The other is its breadth; Tang and Ng report that it has access to three billion articles! However, at this time Google can't make a diagnosis; it can find articles that include the search terms that you give it. The better the search terms, the better the match. It still requires the skills of a physician to sort though the articles to find those that make the most clinical sense. It's about to get better (or worse), depending on your stance in the humanity-vs-machine debate. An editorialist discusses the development of the "semantic web," a melding of technologies "which aims to create a universal medium for information exchange by putting documents with computer processable meaning on the worldwide web." The future is so bright, we'll all need sunglasses!

When I interviewed residency candidates during this recruitment season, I asked them, "How do you want to be remembered, as a great diagnostician or a great healer?" With Google they could have it all. ■

Reference

1. Tang H, Ng JH. Googling for a diagnosis—use of Google as a diagnostic aid: internet based study. *BMJ*. 2006;333:1143-1145.

How Much Do Those Nutrients Really Help You?

ABSTRACT & COMENTARY

By Eileen C. West, MD

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Dr. West reports no financial relationship to this field of study.

Synopsis: This study addresses the role of nutritional status in the disablement process. Low serum concentrations of vitamins B6, B12 and selenium seem to predict subsequent disability in activities of daily living (ADLs) in older women living in the community.

Source: Bartali B, et al. Low Micronutrient Levels as a Predictor of Incident Disability in Older Women. *Arch Int Med.* 2006;166:2335-2340.

Community-dwelling women aged 65 and older who were enrolled in the Women's Health and Aging Study were followed every six months for three years with bloodwork and standardized questionnaires designed to measure functional capacity. The objective was to determine whether low concentrations of nutrients predict eventual physical demise. The nutrients measured were: total carotenoids, retinol, 25-hydroxyvitamin D, Vitamin B6, Vitamin B12, folate, selenium, and zinc. At the beginning of the trial, women were screened to identify self-reported trouble in several domains: mobility, upper extremity function, higher functioning household management, and self-care. Those with difficulties in 2 or more domains but who could still perform all ADLs were enrolled in the study. The selected women were then given a standardized questionnaire at home by trained interviewers. Two weeks later a trained RN came to the home to examine each participant with physical performance measures and a physical exam. Follow-up was every six months, and progress or decline was self-reported after the initial physical exam.

After three years of follow-up, 208 of 643 (32.3%) of participants had progressed to ADL disability. Of those who progressed, the incidence rates were worst among women who fell in the lowest quartile vs those in the upper 3 quartiles of serum nutrient concentrations. Selenium, Vitamin B6, and Vitamin B12 were found to be significant and independent predictors of ADL disability. Furthermore, high levels of homocysteine at baseline predicted the development of ADL disability ($P < 0.001$).

COMMENTARY

The beginning stages of research are seen in the above population-based study, and more research is needed. As with any study of this type, it is difficult to make assumptions about whether it is the low serum level of a nutrient or another factor which is responsible for a patient's deterioration in physical capacity. Also, serum levels do not necessarily predict response to supplementation, so making a leap to the concept that supplements (often at no small cost) provide benefit remains a risky affair. I have heard the old adage, "More than $20 per year spent on vitamins is a waste of money." Much more information is needed to determine the story for the nutrients studied here, and I am inclined to stick with the adage until we have more data.

Unfortunately, many studies using simple vitamins will not be completed as there is often no major financial incentive to doing them. Recent work regarding Vitamin E supplementation came out of the Women's Health Study subanalysis. The verdict? Some may be good, more may be harmful. Research analyzing Vitamin C supplementation did not prove clear superiority with supplementation (megadoses > 1 gram per day or otherwise). Such is the case with many of these trials. Omega-3 fatty acid supplementation appears currently on the "in demand" list, and there is some data to support the claims that it does have antioxidant and cholesterol-improving properties.

The finding for 25-hydroxyvitamin D (ie, no clear association) was surprising considering the discussion in the past 18 months implicating low levels of Vitamin D in gait disturbances, bone health, and falls.

This study offers a necessary first step to determine a simple association between low blood levels of specific nutrients and decline in physical function. If low serum levels of nutrients are normalized with a healthful diet, good nutrition alone, even in the absence of supplements, can prove to play a large role in slowing decline. Hopefully, the study will pave the way to more detailed study and valuable clinical results. ■

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1. Lee IM, et al. *JAMA.* 2005 Jul 6;294(1):56-65.
2. Gerdhem P, Ringsberg KA. *Osteoporos Int.* 2005;11:1425.

Long-Term Proton Pump Inhibitor Therapy and Risk of Hip Fracture

ABSTRACT & COMMENTARY

By Malcolm Robinson, MD, FACP, FACG

Emeritus Clinical Professor of Medicine; University of Oklahoma College of Medicine, Oklahoma City.

Synopsis: *Evaluation of a large United Kingdom (UK) database supports a dose-related association with hip fracture. There appears to be a correlation between PPI use, including dosage and chronicity, and occurrence of hip fractures in patients over age 50.*

Source: Yu-Xiao Yang, et al. *JAMA.* 2006;296:2947-2953

More than 47,000 hip fractures occur annually in the UK, usually related to osteoporosis. Known factors predisposing to osteoporosis include low calcium consumption and calcium malabsorption. Calcium absorption decreases with age and urinary calcium excretion increases. One-year mortality following hip fracture is 20%, and a similar percentage of hip fracture patients require nursing home care. Health care costs associated with hip fracture are immense. Proton pump inhibitors (PPIs) are very widely utilized, often chronically.

The authors speculate that elderly patients may already have hypochlorhydria, possibly exacerbated by *H. pylori* infection. Elderly patients also might exhibit decreased PPI clearance. Low gastric acidity might impair calcium absorption, a phenomenon seen in a few animal and human studies. Conversely, PPIs also may decrease bone resorption (thereby potentially averting osteoporosis) by inhibiting osteoclastic vacuolar hydrogen-potassium-ATPase. Data from the UK General Practice Research Database were utilized in this study. There are 9.4 million patients in the database. Exclusions for this study included less than 365 days of follow-up (2.3 million) and age less than 50 (6.9 million). Other exclusions were very short term PPI use and prevalent hip fractures. A total of 1.8 million patients remained in the final study group. Of these, 192,028 patients received at least 1 PPI prescription, 187,686 patients received H2RA prescriptions but no PPIs, and 1.4 million patients received neither form of acid suppressive therapy. Hip fracture cases were defined as occurring at least 1 year after beginning acceptable follow-up. Ten controls were selected for each case, matched for age, index date, year of birth, and duration of follow-up. Periods of PPI or H2RA use were cumulated along with an estimate of "high dosing" (defined as > 1.75 x the standard dose/day). GERD was the most prominent diagnosis within this selected patient group. A variety of pertinent co-morbidities were tabulated including congestive heart failure, CVA's, celiac sprue, and inflammatory bowel disease (and many more). Multiple additional drug exposures were considered including corticosteroids, thyroxine, thiazide diuretics, and bisphosphonates (among other exposures such as smoking).

As would be expected, most of the drugs and co-morbidities expected to have an association with hip fractures were indeed more commonly present in the hip fracture patient group vs. controls. PPIs were found to be associated with an increased risk of hip fracture with statistically significant adjusted odd ratios of 1.2 for one year ranging up to about 1.6 for 4 years of PPI therapy. Higher doses (> 1.75 times the normal dose per day) of either PPIs or H2RAs seemed to increase the relative risk of hip fracture. The authors ultimately speculated that calcium malabsorption could be the mechanism for this effect. In a previously reported but shorter duration Danish observational study, similar increases in hip fractures associated with PPIs were observed although no dose effect or effect of H2RAs were demonstrated in Denmark. The authors admit that their study may not have captured all possible co-morbidities, and they had no information regarding the utilization of over-the-counter calcium by either the patients or the control population. Despite these admitted deficiencies, the authors recommend that PPI users should increase calcium intake in the form of dairy products or co-ingestion of insoluble calcium supplements with presumably reltively acidic meals.

COMMENTARY

PPIs have had extensive pre-clinical testing including evaluation of their effects on nutrient absorption (including calcium). The degree of acid inhibition attained with oral PPIs is actually quite modest. Indeed, even when dosing PPIs multiple times daily, gastric pH cannot be held above 6.0. With smaller PPI doses, acid will be present in the stomach during large

segments of the 24-hour day in most individuals. As the authors point out in this study, the hip fracture patients are suffering from many other medical conditions and taking many other medications that are associated with hip fracture. Although they have attempted to adjust for all of these variables, it seems likely that many additional unmonitored medications and conditions also varied between groups. This article has already raised great concern among patients, and it is likely that many patients have independently discontinued their use of PPIs based on these speculative results. In the mind of this reviewer, this article and its data do not substantiate the modification of PPI use for otherwise appropriate indications. Although adequate calcium and vitamin D intake are known to be important in prophylaxis against osteoporosis and fractures, there are insufficient data to recommend any new additional dietary maneuvers in our patients who are taking acid suppressive medication. Patients should be advised to continue needed anti-secretory medications despite potential alarm raised by publications like this one. Statistical associations are often interesting, but we must always remember that association does not prove causality. ■

Pharmacology Update

Paliperidone Extended-Release Tablets (Invega™)

By William T. Elliot, MD, FACP, and James Chan, PhD, PharmD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

The FDA has approved a new atypical antipsychotic agent. Paliperidone is the active metabolite of risperidone. The drug is formulated in an osmotic drug delivery system (OROS) developed by ALZA. Invega is manufactured by ALZA Corp and marketed by Janssen.

Indications

Paliperidone is indicated for the treatment of schizophrenia.[1]

Dosage

The recommended dose is 6 mg once daily, taken in the morning. Dose titration is generally not required. Doses above 6 mg should be evaluated based on balancing potential benefit and adverse events. Increases of 3 mg/day should be made at intervals of greater than 5 days. The maximum dose is 12 mg daily. Tablets should be taken whole, not chewed or crushed and without regard to meals.[1] No dosage adjustment of mild to moderate hepatic dysfunction. Dose reduction is recommended for moderate to severe renal dysfunction.

Paliperidone is available as 3 mg, 6 mg, and 9 mg tablets.

Potential Advantages

The combination of the active metabolite and extended-release technology of the OROS system minimizes fluctuation in the plasma level of the drug. This may facilitate treatment initiation. Since paliperidone does not undergo hepatic metabolism, drug-drug interactions involving hepatic enzyme systems are unlikely. Paliperidone also has minimal effect on p-glycoprotein.

Potential Disadvantages

Paliperidone shares the adverse effects associated with atypical antipsychotics in general and risperidone in particular. These include increased mortality in elderly patients with dementia related psychosis, prolonged QTc, neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia and diabetes mellitus, hyperprolactemia, esophageal dysmotility, and orthostatic hypotension. Most common adverse events are tachycardia or palpitation (12% vs 7% placebo). Less frequent adverse events include akathisia and extrapyramidal side effects. Due to the extended drug delivery system, it should be avoided in patients with rapid gastrointestinal transit time.[1] Treatment greater than 6 weeks has not been studied.

Comments

Paliperidone is the primary active metabolite of isperidone. After administration of risperdone, levels of paliperidone are about 22 times higher than the parent compound. The efficacy of paliperidone was demonstrated in three 6-week, placebo-controlled, multinational trials (n = 1665).[1] In a published study, 628 subjects were randomized to paliperidone 6 mg, 9 mg, 12 mg, placebo, and olanzapine 10 mg daily (active control).[3] Primary endpoints were a decrease in the Positive and Negative Syndrome Scale (PANSS) that includes 5 factors (positive symptoms, negative symptoms, disorga-

nized thought, uncontrolled hostility/excitement and anxiety/depression) and clinician rating of personal and social functioning (PSP). Paliperidone 6 mg reduced PANSS by 17.9 22.2 compared to -4.1 23.2 for placebo and -19.9 10 for olanzapine. A 30% or greater reduction was achieved with 56% of the paliperidone 6 mg arm, 52% for olanzapine and 30% for placebo. Improvement was observed at day 8 of therapy. For change in PSP, 60.5% of the paliperidone 6 mg arm had a 10-point improvement (on a 100-point scale) compared to 32.5% for placebo and 62.7% for olanzapine. All treatments were statistically better than placebo. The 6 mg dose appears to be the optimal dose. The 12 mg dose was associated with a marginal gain in efficacy (12 mg) but with a greater incidence of movement disorder related adverse effects as well as other adverse events. Frequency of gain of 7% of body weight occurred in 2% of placebo, 5% for paliperidone 6 mg, and 13% for olanzapine. Somnolence was more common with olanzapine. Increase in prolactin levels occurred with paliperidone but decreased with placebo and olanzapine. The 30-day wholesale cost of paliperidone 6 mg is $292.80.

Clinical Implications

Paliperidone is the primary metabolite of risperidone and is expected to share very similar pharmacological characteristics. This along with established drug delivery systems offers once daily dosing, more constant release of the drug, and lower potential for drug interactions. However, no clear clinical advantages have been demonstrated by direct comparisons to risperidone or other atypical antipsychotics. ■

References

1. Invega Product Information. December 2006. *Janssen.*
2. Zhu HJ, et al. *Neuropsychopharmacology*. 2006; Epub.
3. Kane J, et al. Schizophrenia Research. 2006; *Epub.*

CME Questions

3. In the CATIE study, the relative frequency of extrapyramidal side effects from antipsychotic medications was:
a. risperidone > quetiapine > olanzapine > placebo
b. olanzapine = risperidone = quetiapine > placebo
c. olanzapine = risperidone > quetiapine = placebo
d. risperidone > olanzapine > quetiapine > placebo

4. Which of the following is NOT one of the vitamins studied in which low levels showed an association with more rapid physical decline:
a. vitamin B6
b. zinc
c. vitamin B12
d. selenium

Answers: 3 (c); 4 (b)

CME Objectives

The objectives of *Internal Medicine Alert* are:
- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim. Dr. Kuritzky reports no financial relationship to this field of study.

Preventing Diabetes: Long Term Outlook

The Finnish Diabetes Prevention Study (FDPS) demonstrated that a program of diet and exercise was capable of reducing the incidence of diabetes by approximately 60% in persons with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), compared to placebo. These encouraging results were confirmed in a US program with similar design, both trials having at least 3 years follow up. Whether the impact of lifestyle changes persists beyond the initial intervention period was the focus of this publication by Lindstrom, et al.

At the conclusion of the FDPS, subjects who had not progressed from IFG/IGT to diabetes continued to be monitored for a total follow up of 7 years, and were compared with the original control population. At 7 years (mean) follow up, there was still a 36% relative risk reduction in diabetes.

It is not possible to determine how much of the beneficial long-term risk reduction is due to a "carry-over" effect from the original intervention vs adherence to favorable lifestyle continuation post-study. In any case, long-term benefits of exercise, diet, and maintenance of weight are apparent. ■

Lindstrom J, et al. Lancet. *2006;368:1673-1679*

Preventing Osteoporotic Fracture: Which Antiresorptive?

Since the relative demise of hormone replacement therapy as a routine tool for dealing with osteoporosis (OSPS), bisphosphonates-specifically alendronate (ALN), Risedronate (RIS) and Ibandronate (IBN)-have become the mainstay of treatment. Each bisphosphonate has at least one favorable data set, but it is difficult to choose between them in the absence of large head-to-head trials.

A meta-analysis was performed based upon combined trials of bisphosphonates as well as data from the Women's Health Initiative to seek a stronger data set from which to stratify osteoporotic fracture risk reduction with various therapies. Because the trial data for IBN is somewhat limited, analysis was based upon a single large trial (n = 2,946) which included fracture end points.

The most favorable outcomes were seen with ALN (49-55% risk reduction), followed by hormone replacement therapy (25-36% risk reduction), and then RIS (26-27% risk reduction). No conclusion could be reached in reference to IBN, calcitonin, or raloxifene due to insufficient and/ or inconsistent evidence. ■

Liberman UA, et al Int J Clin Pract. *2006;60(11):1394-1400*

Metformin + DPP-4: Safety and Efficacy

Metformin is the most commonly prescribed initial monotherapy for diabetes. Most diabetics will require additional pharmacotherapy to maintain glycemic goals. Dipeptidyl peptidase-4 inhibitors (DPP4) are a new group of pharmacotherapies that capitalize upon several favorable actions of glucagon-like-peptide (GLP): enhancement of glucose-mediated insulin secretion, blockade of glucagon release, and modulation of glucose delivery to the GI tract. Even though endogenous GLP provides these functions, it is a very short-lived agent. DPP4 inhibitors prevent the breakdown of GLP, enhancing its duration of action.

The DPP4 agents fall under a larger classification of "incretins" (pronounced "in-KREE-tin"). Sitagliptin (tradename Januvia) is the first approved agent of this class, although others are pending FDA approval.

This trial randomized patients on metformin who maintained an A1c > 8.0% to sitagliptin 100 mg QD or placebo for 6 months. At the end of the trial, sitagliptin produced a significant 0.65% reduction in A1c, and more patients had achieved their goal A1c with sitagliptin (47%) than with placebo (18%). Sitagliptin was well tolerated. Although the absolute impact of DPP4 inhibitors on A1c is not as prodigious as other classes of agents, it is sufficient to allow many uncontrolled patients to achieve glycemic goals. ■

Charbonnel B, et al Diabetes Care. *2006;29(12):2638-264*

In Future Issues: **Avoiding a Lawsuit in Primary Care**