DIABETIC
Microvascular Complications
NEWS

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FDA Approves First Inhalable Insulin

The Food and Drug Administration (FDA) has approved the first inhalable insulin for the treatment of adults with type 1 or 2 diabetes. The approval came about 5 months after the Endocrinologic and Metabolic Drugs Advisory Committee voted 7 to 2 to back the delivery system.

Exubera is being marketed by Pfizer (New York, NY), which acquired the worldwide rights from Sanofi-Aventis (Bridgewater, NJ) in January. Exubera is a rapid-acting dry powder human insulin that is inhaled through the mouth into the lungs prior to eating, using a handheld inhaler, according to a Pfizer news release. The inhaler weights about 4 oz. and when closed is about the size of an eyeglass case.

"Until [this delivery system was approved] patients with diabetes who need insulin to manage their disease had only one way to treat their condition," said Steven Galson, MD, director of the FDA's Center for Drug Evaluation and Research, in a news release. "It is our hope that the availability of inhaled insulin will offer patients more options to better control their blood sugars."

Clinical trials demonstrated that inhaled insulin was as effective as injected short-acting insulin; however, some concerns were raised over pulmonary toxicity. The FDA said smokers or those who quit smoking in the previous 6 months should not use Exubera. Other contraindications include asthma, bronchitis or emphysema.

The efficacy and safety profile of inhaled insulin was studied in more than 2,500 patients for an average of 20 months in patients with type 1 or 2 diabetes.

"Many people who could benefit from insulin are fearful of injections, so they delay treatment 5 or 10 years, placing them at risk for serious complications. Now, for the first time, patients can improve blood sugar control with fewer or no painful injections," said William Cefalu, MD, chief of the division of nutrition and chronic diseases at Pennington Biomedical Research Center, Baton Rouge, La.

Pfizer said European regulators have also approved Exubera. Several other companies are developing inhaled insulin products, including Eli Lilly and Company (Indianapolis, Ind) and Alkermes Inc (Cambridge, Mass), which are partners in one project, and Mannkind Corp (Valencia, Calif), Kos Pharmaceuticals Inc (Cranbury, NJ) and Novo Nordisk (Bagsvaerd, Denmark).

Health Canada Advises Diabetic Patients Not to Use Gatifloxacin

Health Canada is advising diabetic patients not to use the antibiotic gatifloxacin (Tequin; Bristol-Myers Squibb, New York, NY) due to concerns about blood glucose disorders. The precaution is based on a recommendation made by the manufacturers submitted to the department. Health Canada is that country's federal department helping Canadians improve their health.

Gatifloxacin is an antibiotic prescribed for the treatment of respiratory infections, urinary tract and bladder infections and sexually transmitted diseases. Health Canada asked the manufactuer to submit revised product information for gatifloxacin, following evidence indicating a possible link between the antibiotic and blood glucose disorders. Health Canada is currently reviewing the information, and public and health professionals will be informed of the results once the review is completed.

Given the availability of other antibiotics, Health Canada recommends that patients with diabetes be prescribed alternative therapies as a precaution. Diabetic patients taking the agent should contact their physicians if they have any concerns.

Bristol-Myers Squibb has also recommended that doctors who prescribe gatifloxacin to their patients without diabetes take enhanced precautions and closely monitor patients, especially those aged ≥75 years, with kidney problems or who take diabetes medications.

The manufacturer, in conjunction with Health Canada, issued a health care provider letter and a public advisory about a possible link between the antibiotic and blood glucose disorders after serious cases of both hypoglycemia and hyperglycemia were reported in patients worldwide.

Are Sulfonylurea Dose and Mortality Linked in Diabetes?

Also out of Canada, a study that might fuel the fires of the controversial belief that sulfonylurea drugs increase mortality in diabetes patients. Even though a 1970 report suggested a link between sulfonylurea use and cardiovascular events, others since then have refuted this association.

In previous studies, Scot H. Simpson, MD, from the

University of Alberta in Edmonton, Canada, and colleagues had shown that metformin improves survival when compared with sulfonylureas. Researchers said it not clear if this was due to a protective effect of metformin or a potentially adverse effect from sulfonylureas.

In order to clarify this point, Dr. Simpson's team analyzed data on 5,795 patients entered in the Saskatchewan Health databases between 1991 and 1999. Patients were prescribed a first-ever oral antidiabetic agent. The researchers sought to determine if there was a dose-response relationship between sulfonylurea use and mortality. The findings were reported in the *Canadian Medical Association Journal.*

Patients were aged an average of 66.3 years, 56.6% were male, and they were followed for a mean of 4.6 years. Patients were taking first-generation sulfonylureas (n=120), glyburide (n=4,138) and metformin (n=1,537).

Investigators found that, at higher daily doses, sulfonylurea and to a lesser extent glyburide were associated with an increased risk of death. A dose-response relationship was not seen with metformin.

"This evidence, taken within the context of observations collected over the last 30 years, suggests that clinicians should carefully assess the need for sulfonylurea therapy in subjects at high risk of cardiovascular events — particularly now when several other classes of antidiabetic oral medications are available," the investigators conclude.

In an accompanying editorial, David S. H. Bell, MD, from the University of Alabama at Birmingham, said that sulfonylureas may raise the risk of death by directly affecting the myocardium. Even though these agents are still a popular treatment for diabetes, he said that they should be relegated to third-line therapy, which is consistent with recently published guidelines.

FDA Committee Recommends Orlistat for OTC Use

An FDA advisory committee voted 11 to 3 to recommend approval of orlistat (Alli; GlaxoSmithKline, Pittsburgh) for over-the-counter (OTC) use. The agent would be the only FDA-approved weight-loss medication available without a prescription. It is indicated for use by overweight adults along with a reduced calorie, low-fat diet (<30% calories from fat).

The joint Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committee recommended approval of the 60-mg capsules for OTC use. Orlistat 120-mg capsules (Xenical) will remain available by prescription for obesity management and for those who should be under the care of a physician.

The drug works by blocking fat absorption in the small intestines, and efficacy was demonstrated in 6-month clinic trials. On average, patients who took 3 doses per day lost 5.3 to 6.2 pounds. About 50% of the orlistat patients experienced the effect versus 26% of the placebo patients.

While the agent is generally viewed as safe, some panelists have concerns about the drug as an OTC option, worrying that patients may abuse the drug. Some panelists expressed concern about the fact that a high percentage of patients were not well informed of the side effects, which could cause problems in patients with certain conditions. For example, orlistat can interact with cyclosporine and warfarin. The drug may affect blood sugar control.

Other side effects include flatulence with discharge, oily discharge, increased number of bowel movements, oily spotting, oily or fatty stools, urgent need to have a bowel movement and inability to control bowel movements. About 50% of patients on orlistat experienced some side-effects and 7% lost bowel control.

Sidney M. Wolfe, MD, and Elizabeth Barbehenn, PhD, with Public Citizen's Health Research Group, testified before the FDA advisory committee. "The long-term effects of orlistat on morbidity or mortality associated with obesity have not been established. Although a statistically significant weight loss for orlistat 60 mg compared with placebo is seen, there is no evidence presented that a modest, transient weight loss due to orlistat will afford any long-term clinical benefit either through a change in behavior or a reduced risk of serious clinical disease manifest by being overweight," Drs. Wolfe and Barbehenn said in their testimony.

AMA, Congress Agree on Standards of Performance

The American Medical Association (AMA) has forged an agreement with Congress that promises to develop more than 100 standard measures of performance. Doctors will report on these measures to the federal government in an effort to improve the quality of health care in this country, according to a report in *The New York Times.*

The Bush Administration favors pay-for-performance arrangements with various health care providers and is working to bring this concept into the mainstream in order to link Medicare payment to quality. This initiative is underway in the private sector where consumer groups, insurance companies and large employers who pay for health care are demanding more feedback on the quality of care.

Typically, these performance measures focus on diagnos-

tic tests and treatments that are known to produce better patients outcomes. According to federal officials, tracking how well and efficiently doctors or hospitals treat illnesses like diabetes, pneumonia and myocardial infarctions (MI) could provide consumers with useful information.

Congress strongly supports the initiative, as does the American Association of Retired People (AARP). Some medical specialists, however, said they were surprised by the deal, according to *The New York Times.* Many doctors fear that the government might use the information to justify cutting their Medicare fees.

"We are concerned that the push to measure quality will become a smoke screen to cut costs and to reduce the resources devoted to health care," said Frederick C. Blum, MD, president of the American College of Emergency Physicians.

AMA leaders said they agreed to help develop uniform quality of care measures because otherwise doctors would have dozens of disparate measures forced on them by insurance companies, health plans and government programs, the *The New York Times* article said. Under the accord physician groups are to develop "a total of approximately 140 physician performance measures covering 34 clinical areas" by the end of this year.

According to the agreement, by 2007 doctors will voluntarily report to the federal government on at least three to five quality measures per physician. Doctors should receive some additional payment to offset the costs of collecting and reporting the data, the agreement says.

"By the end of 2007," the pact says, "physician groups will have developed performance measures to cover a majority of Medicare spending for physician services." Medicare spent more than $57 billion under its physician fee schedule last year.

The agreement was signed by Duane M. Cady, MD, chairman of the AMA, and by three Republican members of Congress responsible for Medicare legislation: Sen. Charles E. Grassley (Iowa), Rep. Bill Thomas (Calif) and Rep. Nathan Deal (Ga).

Medical specialists said they wanted to improve the quality of care and were already developing performance measures. But they objected to the confidential pact and its ambitious timetable for assessing doctors' performance, according to the *The New York Times* article. In a letter to Dr. Cady, the presidents of seven medical specialty groups said they had not been consulted or informed. "The AMA acknowledged the existence of this agreement only after we uncovered it. The AMA agreed to the imposition of a pay-for-performance system without getting an assurance that doctors would be adequately paid for treating Medicare patients."

Medicare payments for physician service was frozen this year. As the law stands now, physicians are looking at cuts of >4.5% in each of the next 8 years. Congress often intervenes to prevent or delay such cuts, and it could easily stipulate that doctors must report measures of clinical performance as a condition of getting even a small increase in Medicare fees, *The New York Times* report said.

Ten national physician's groups sent separate letters to Congressional leaders that said: "We are dismayed that an agreement was reached on issues that are critical to the future of our specialties and our patients without our participation or knowledge. The [AMA] cannot be the sole representative for the groups who are paramount to the development and implementation of quality measures."

Quality measures are supposed to expose whether or not doctors follow the best accepted practices in treating patients. Examples of quality measures given by federal officials include: the proportion of diabetic patients with blood sugar and cholesterol at the recommended levels; the percentage of surgical patients who receive medications to prevent blood clots; the proportion of patients with pneumonia who receive antibiotics within a few hours of diagnosis; and the percentage of MI patients who receive beta-blockers when they arrive at a hospital.

AARP board member Thomas Thames told the *The New York Times* that his group supported efforts to measure performance and link Medicare payment to quality because "rewarding quality can improve results. We support moving to pay-for-performance on an aggressive timetable."

In a news briefing, administrator of the Centers for Medicare and Medicaid Services, Mark B. McClellan, MD, said Medicare should reward doctors for "efficiency and high-quality care, not simply pay for more services."

But Stuart L. Weinstein, MD, a University of Iowa professor and president of the American Academy of Orthopaedic Surgeons, said the timetable endorsed by the AMA and Congressional leaders was unrealistic. "Performance measures need to be developed by specialty societies, then tested and validated, to confirm that they really affect patient care in a positive way," he said in a news release.

Premenopausal Diabetic Women Have More Fractures, Lower Bone Density

Premenopausal women who have type 1 diabetes should strongly consider preventive screening for osteo-

porosis, the researchers of a study on bone density concluded in *Diabetes Care*.

The study found that these women exhibited lower bone density and more fractures than women who did not have diabetes, even though those with diabetes were more likely to take bone-active osteoporosis medications and vitamin D supplements. Both groups of women exercised similar hours per week.

Researchers found one-third of premenopausal women (aged 35 to 55 years) with type 1 diabetes reported having a fracture after age 20 years compared to fewer than one-quarter of those who did not have diabetes. Women with type 1 diabetes also exhibited substantially lower overall bone density as well as in the hip and heel bone.

Lead researcher Elsa Strotmeyer, PhD, said it is still unclear why type 1 diabetes affects bone density, however, "it is also likely that even subclinical changes in the cardiovascular system, kidney or nervous system, which are often associated with a longer duration of disease, are influencing bone," she said.

The researchers, from the University of Pittsburgh's Department of Epidemiology in the Graduate School of Public Health and Department of Health Promotion and Development in the School of Nursing, concluded that early osteoporosis screening and fracture prevention efforts should be considered for women with type 1 diabetes prior to menopause.

Controlled Glucose May Improve Memory

Taking medication to control blood glucose levels may also improve memory in diabetes patients, according to a study in *Diabetes Care*.

Older adults with type 2 diabetes often have difficulty with their memory. To determine whether different types of medication would improve learning and memory, 145 adults with type 2 diabetes who were already taking metformin were randomized to additional treatment with either rosiglitazone or glyburide. Patients were followed for 6 months and completed a series of learning and memory tests at the beginning and end of the study.

The research team found that both rosiglitazone and glyburide improved fasting plasma glucose values an average of 21% to 24%, and both produced equivalent improvements on a cognitively demanding measure of working memory. The strong relationship between improved fasting blood glucose and memory scores indicated that efforts to reduce blood glucose levels may substantially improve memory in many older adults with diabetes.

The authors concluded that further testing is necessary to determine whether these effects are long-lasting and also whether greater benefit would be seen in people with more severe diabetes and greater cognitive impairment.

Lifestyle Intervention Decreased Urinary Incontinence in Women With Prediabetes

An analysis from the Diabetes Prevention Program (DPP) found that intensive lifestyle intervention in overweight, prediabetic women was associated with a lower prevalence of urinary incontinence when compared with metformin therapy or placebo.

Diabetes is associated with an increased risk of urinary incontinence, and weight loss improves the condition, investigators wrote in *Diabetes Care*. Often, however, exercise can worsen incontinence.

The DPP is a randomized controlled trial of 27 US centers. Included in this analysis were 660 women assigned intensive lifestyle therapy, 636 to metformin and 661 placebo. The main outcome measure was incontinence symptoms by frequency and type, validated by questionnaire completed at a mean of 2.9 years.

The prevalence of total weekly incontinence was 38.3% among those randomized to lifestyle intervention compared with 48.1% among the metformin women and 45.7% among the placebo group. Changes in weight accounted for most of the protective effect of the intensive lifestyle intervention on stress incontinence, according to researchers.

Typical Diabetes Risk Scores Developed in Whites Cannot be Applied to All Ethnicities

Risk scores based on phenotypic characteristics to identify patients at high risk of having undiagnosed diabetes have been developed in white populations. These typical risk scores cannot be applied to other populations of diverse ethnic origins, according to a report in *Diabetes Care*.

The impact of known risk factors of having undiagnosed type 2 diabetes differs between populations of different ethnic origins. The researchers used data from the worldwide DETECT-2 project. The database includes population-based surveys with information on at least 500 people with unknown diabetes having a 75-g oral glucose

tolerance test. There are 52 centers that have contributed data on 190,000 individuals from 34 countries.

"In this analysis, nine cross-sectional studies were selected representing diverse ethnic and reginal backgrounds," the investigators wrote. "The risk score assessed used information on age, sex, blood pressure treatment and body mass index."

According to this analysis of 29,758 individuals, 1,805 had undiagnosed diabetes. The risk score's accuracy varied widely, with sensitivity, specificity and percentage needing further testing ranging between 12% and 57%, 72% and 93%, and 2% and 25%, respectively. The worst performance of the risk score was in non-white populations.

Waist Circumference an Important Metabolic Syndrome Criteria

Waist circumference is a valuable component of metabolic syndrome, according to a report in *Diabetes Care*. The International Diabetes Federation (IDF) requirement of an elevated waist circumference warrants caution, the investigators wrote, given that a large number of men with normal waist circumference have multiple risk factors and an increased risk of mortality.

The prediction of mortality with the International Diabetes Federation (IDF) and National Cholesterol Education Panel (NCEP) metabolic syndrome criteria was comparable in men, according to this study of 20,789 white, non-Hispanic men aged 20 to 83 years from the Aerobics Center Longitudinal Study.

The study compared the NCEP, the revised NCEP (NCEP-R) and the IDF metabolic syndrome criteria for mortality risk and examined the effects of waist circumference on mortality within the context of these criteria. The main outcome measures were all-cause cardiovascular disease (CVD) mortality over 11.4 years of follow-up.

The proportions of men with metabolic syndrome at baseline were 19.7%, 27% and 30%, respectively, according to NCEP, NCEP-R and IDF criteria. A total of 632 deaths occurred and the relative risks for all-cause mortality were 1.36, 1.31 and 1.26 for the NCEP, NCEP-R and IDF definitions, respectively. The corresponding relative risks for CVD mortality were 1.79, 1.67 and 1.67, respectively. The investigators said there was a significant trend for a higher risk of CVD mortality across waist circumference categories among men with at least two additional metabolic syndrome risk factors (P=.01).

Major Genetic Risk Factor for Type 2 Diabetes Identified

A discovery of a variant in a gene on chromosome 10 that represents the most significant genetic risk factor for type 2 diabetes found to date has been reported in *Nature Genetics*. According to researchers from Decode Genetics (Reykjavik, Iceland), more than one-third of individuals in the populations studied carry one copy of the at-risk variant and are at an approximately 45% increased risk of the disease compared with controls; 7% carry two copies and are at a 141% greater risk. The original finding was made in Iceland and was subsequently confirmed in Danish and US studies.

"This is a milestone in human genetics. A common gene variant conferring elevated risk of type 2 diabetes has been earnestly sought by the genetics community for many years. We have found such a variant, which we estimate accounts for about 20% of type 2 diabetes cases. This discovery sheds new light on the biological causes of the disease. Importantly, virtually all of this risk can be captured by looking at a single-letter change in DNA — ideal for the development of a genetic test for assessing individual risk and developing more personalized and effective prevention strategies. This is also an exciting starting point for the discovery of new drugs, and we are actively pursuing the development of both diagnostic and therapeutic products to better prevent and treat type 2 diabetes," said Kari Stefansson, CEO of Decode Genetics and senior author on the study, in a news release.

The variant is located in a gene encoding a protein called transcription factor 7-like 2 (TCF7L2). Decode Genetics isolated the gene by following up on the results of a population-based, genome-wide linkage scan in Iceland that identified a promising region on chromosome 10. The Decode Genetics team genotyped 228 microsatellite markers — polymorphic signposts along the genome — in this region in a total of more than 2000 patients and controls. Analysis of the frequency of different alleles of these markers pinpointed a version of one marker within the gene encoding TCF7L2 that is approximately 1.5 times more common in patients than in controls. This corresponds to a 50% increase in risk of type 2 diabetes per copy carried.

This finding was replicated in Danish and US cohorts, where the at-risk version of the marker conferred an increased risk of 41% and 85%, respectively, per copy carried. For all of the cohorts combined, the at-risk allele conferred an increase in risk of approximately 45% for those carrying one copy and a 141% increase in risk for individuals carrying two copies. Utilizing data from the HapMap project, a single nucleaotide polymorphism was found that correlates nearly perfectly with the at-risk microsatellite. ■