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INSIDE

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Warning — proceed with caution: Rezulin can cause liver failure

Chances of complications can be reduced with monitoring

Physicians have been warned to monitor liver functions of Type II diabetics using Rezulin (troglitazone), easing the alarm over liver failure and even death among patients using the anti-insulin-resistance drug.

Richard Kahn, PhD, chief scientific and medical officer of the American Diabetic Association in Alexandria, VA, says new labeling included with the drug since July by its manufacturer, Parke-Davis, a division of Warner-Lambert Co. in Morris Plains, NJ, "minimizes the likelihood of adverse side effects and liver disease" from troglitazone. **(See box on manufacturer's warning label, p. 3.)**

"We think the benefits outweigh the risk, if the recommended testing is followed," Kahn says, echoing a statement issued by the U.S. Food and Drug Administration (FDA) in early December. He dismisses a Dec. 7 *Los Angeles Times* report highly critical of Rezulin, the approval and marketing tactics used for the drug, and the "potential conflict of interest" on the part of Richard C. Eastman, MD, the National Institutes of Health's top diabetes researcher. Kahn says, "It didn't raise anything we didn't know already."

Rezulin is currently being used by approximately 1 million Type II diabetics, with sales for Warner-Lambert approaching $1 billion, according to the *Los Angeles Times* article.

Troglitazone was hailed as a great new drug of our time when it first came on the market in March 1997. By December of that year, deaths began to be reported among troglitazone users in Great Britain, and

KEY POINTS

- Rezulin still best way to attack insulin resistance, researchers say.
- Vigilance to detect liver toxicity is necessary for patients using Rezulin.
- Other drugs currently under study may provide means of attacking insulin resistance.

Glaxo-Wellcome withdrew its application for European approval of the drug. Shortly thereafter, the U.S. FDA issued a warning about potential liver dysfunction among patients using the drug and recommended liver monitoring five times a year.

In June, the National Institutes of Health (NIH) removed troglitazone from a study of non-diabetics after the death of a patient who needed a liver transplant.

In July, the U.S. consumer advocacy group Public Citizen petitioned the FDA to withdraw troglitazone from the market after 26 deaths from liver failure and three reported liver transplants among troglitazone users. The same month, Parke-Davis issued a "Dear Health Care Professional" letter urging frequent liver monitoring for patients using the drug.

Parke-Davis now says serum transaminase levels should be checked before a patient begins taking Rezulin, and levels should be re-checked "monthly for the first eight months of therapy, every two months for the remainder of the first year, and periodically thereafter."

The manufacturer also states, "Rezulin should be added to, not substituted for," sulfonylureas or insulin or as an adjunct to diet and exercise control.

Parke-Davis: 'Data show it is safe'

The company's studies showed a 600 mg daily dosage of Rezulin plus glyburide was most effective in long-term glycemic control.

"Liver disease is not a problem from our perspective. The clinical data show it is safe," says **Howard Foyt**, MD, PhD, director of clinical research, diabetes, and metabolic disorders at Parke-Davis in Ann Arbor, MI. "We don't anticipate major future problems with liver dysfunction. We think the labeling took care of it."

In response to the withdrawal of troglitazone from the NIH study, Foyt says Parke-Davis is currently conducting a study of the same questions. "The NIH shut down our arm of the study because they questioned the risk in non-diabetic patients," he says. "To counteract that, we have instituted appropriate monitoring with the approval of the FDA."

Researchers hope that new insulin sensitizers currently under study may also target the underlying cause of diabetes without the risk present in troglitazone. SmithKline Beecham, the Philadelphia-based manufacturer of rosiglitazone, a TZD class drug, submitted the drug for FDA approval in late November. **(See definitions, above.)**

"It's an exciting future" for new drugs to treat Type II diabetics, says **Jerry P. Palmer**, MD, chief of endocrinology, metabolism, and nutrition at the Department of Veterans Affairs, Puget Sound Health Care System in Seattle, and director of diabetic and endocrinology research at the University of Washington, also in Seattle.

He says newer classes of drugs "will change how we treat the disease and identify people at risk earlier." Palmer, who is a diabetic, says he takes Rezulin and metformin. "I feel [Rezulin] is

How the Drugs Work

- ✔ **Sulfonylureas.**
  These drugs stimulate the pancreas to produce insulin. Long-term result may be pancreatic fatigue and increased insulin resistance.
- ✔ **Metformin.**
  Drug decreases sugar levels in the liver without increasing insulin demands.
- ✔ **Troglitazone.**
  In a class of drugs called thiazolidinediones, or TZDs, this drug turns insulin-resistant cells into insulin-sensitive cells, allowing more efficient use of the body's naturally produced insulin, sparing the pancreas from overwork. ■

COMING IN FUTURE MONTHS

- ■ Hypertension education: A neglected part of diabetes management
- ■ Overcoming cultural obstacles in diabetes management
- ■ Challenges and benefits of using telemedicine in diabetes management
- ■ Bringing physicians on board with your diabetes program
- ■ Special focus on age and diabetes: Pediatric, teen, adult, and geriatric issues

Warning from Rezulin package liner

"Rare cases of severe idiosyncratic hepatocellular injury have been reported during marketed use. **(See ADVERSE REACTIONS.)** The hepatic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported. Injury has occurred after both short- and long-term troglitazone treatment.

"During all clinical studies in North America, a total of 48 of 2,510 (1.9%) Rezulin-treated patients and three of 475 (0.6%) placebo-treated patients had alanine transaminase (ALT) levels greater than three times the upper limit of normal.

"Twenty of the Rezulin-treated and one of the placebo-treated patients were withdrawn from treatment. Two of the 20 Rezulin-treated patients developed irreversible jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction.

"An additional Rezulin-treated patient had a liver biopsy which was also consistent with an idiosyncratic drug reaction. **(See ADVERSE REACTIONS, Laboratory Abnormalities.)**

"Serum transaminase levels should be checked at the start of therapy, monthly for the first eight months of therapy, every two months for the remainder of the first year of Rezulin therapy, and periodically thereafter. Rezulin therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT> 1.5 times the upper limits of normal).

"Liver function tests should also be obtained for all patients at the first symptoms suggestive of hepatic dysfunction, e.g. nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

"If serum transaminase levels are moderately increased (ALT> 1.5 to two times the upper limit of normal), liver function tests should be repeated within a week and then weekly until the levels return to normal. If at any time a patient has jaundice or ALT rises above three times the upper limit of normal, Rezulin should be discontinued." ■

pretty safe. There are concerns, but if you do the safety checks, including liver function studies, I wouldn't worry too much. The instance of severe liver function problems is one in 60,000. There is no perfectly safe medication. It is a wonderful medication and works well."

Insulin resistance is spreading like wildfire with 2,000 new cases being diagnosed daily, according to **Kathy Mulcahy**, CDE, RN, president of the American Association of Diabetes Educators and director of the INOVA Diabetes Center in Fairfax, VA.

While Mulcahy confirms the cost of the newer drugs is high, she adds, "The therapy to achieve near-normal blood glucose levels is cost-effective in comparison to the cost of complications at about $20 billion a year."

For further information, contact Howard Foyt, MD, PhD, Director of Clinical Research, Diabetes, and Metabolic Disorders, Parke-Davis, Ann Arbor, MI. Telephone: (734) 622-3618. ■

Laser monitor approved for home use by diabetics

Skin patch monitor may not be far away

The pain of blood glucose monitoring could soon be a thing of the past, providing a boon to diabetics and a boost for compliance.

A laser perforator has been approved by the U.S. Food and Drug Administration (FDA), and a non-invasive transdermal patch, which is paired with a glucose monitor, is entering final clinical trials and could be available by the end of the year.

A 'nearly painless' method

The Lasette, developed by Cell Robotics International Inc. of Albuquerque, NM, is advertised as a "nearly painless" method of drawing blood for glucose testing purposes. The Lasette, approved by the FDA in early December, according to **Ronald Lohrding**, PhD, president and CEO of Cell Robotics, directs a small beam of laser light on the long wave length through the skin at a very high speed.

"It leaves a small hole," says Lohrding. "You feel a tap, and you next to never feel pain. Many

people with diabetes avoid conducting daily glucose tests because of the pain associated with the needle sticks necessary to draw adequate blood, resulting in a deterioration of health." The company hopes the Lasette will encourage more frequent monitoring and, consequently, improve the health of diabetic patients.

The device uses an Erbium:YAG laser, runs on a battery, and is similar in size and shape to a VCR tape. It is adjustable to skin type and produces one drop of blood.

The FDA says clinical trials show "adequately trained patients can perform the finger pricks with the laser device as easily and accurately as with lancets." In addition, the FDA says the laser device may be particularly helpful for diabetic children who have difficulty using lancets.

Lohrding says there has been an unexpectedly large demand for the device despite its price (about $2,000). He thinks the strong response from physicians is in answer to a demand for increased testing compliance.

Cell Robotics is working on a smaller model with a somewhat lower price tag, Lohrding says. He hopes it will be available by mid-1999. The current device is available through ChroniMed Inc. of Minneapolis.

Patch works in tandem with monitor

The skin patch monitor is now undergoing final clinical trials at three university medical centers for submission to the FDA later this year. The device is composed of a single-use skin patch, similar to those that deliver nicotine or pain medication, and is placed on the user's forearm for five minutes.

The patch permits dermal glucose to be drawn and causes a chemical reaction and color change in the patch's membrane, which is read by a monitor the size of a small flashlight. The "smart meter" runs on a 9-volt battery and contains a 32K processor that can store up to 120 days of readings by day, date, and time as many as six times a day. Data are downloadable to disks or over the telephone.

The device, called the TD Glucose Meter, paired with the TD Glucose Patch, was developed by Technical Chemicals and Products Inc. (TCPI) of Pompano Beach, FL. The system requires complex algorithms to calibrate it to each individual patient, according to **Howard Goldman**, TCPI's vice president of investor relations. The devices will be calibrated by the individual's physician.

"This means that patients will test themselves more often, and more times a day means better compliance," he says.

Goldman says the monitor will cost about $100, and the patches will cost about 80 cents each.

For further information, contact Ronald Lohrding, PhD, President and CEO, Cell Robotics International Inc., Albuquerque, NM. Telephone: (800) 866-1633. Howard Goldman, Vice President of Investor Relations, Technical Chemicals and Products Inc., Pompano Beach, FL. Telephone: (954) 979-0400. ■

Cardiologists recommend bypass over angioplasty

Bypass is treatment of choice for revascularization

Cutting-edge research shows that diabetic patients with myocardial infarctions (MIs) can be revascularized most successfully through bypass surgery using the left internal mammary artery. Furthermore, American and Belgian researchers discovered that patients undergoing the procedures and using sulfonylureas had significantly worse outcomes than those on metformin.

The study, involving 15,809 patients (9,600 in Leuven, Belgium and 6,209 at the Mid America Heart Institute in Kansas City, MO — 1,938 of them diabetics at baseline) was published in the *European Heart Journal* in November.

Only slightly more than half (51%) of the patients achieved complete revascularization through angioplasty, but 82% achieved complete success through bypass surgery, according to the study's lead author **James H. O'Keefe**,

KEY POINTS

- Study shows diabetics with myocardial infarction (MI) have better survival rates with bypass surgery than with angioplasty.
- Use of left internal mammary in bypass surgery improves outcomes for diabetic patients.
- Experts recommend avoiding sulfonylureas for patients with MI.

MD, professor of medicine at the University of Missouri in Kansas City and director of preventive cardiology at the Mid America Heart Institute.

In addition, the study shows that the 10-year survival rate for pharmacologically treated patients was better after bypass surgery (60%) than for angioplasty patients (46%). **(See box, at left.)**

All the U.S. diabetic angioplasty patients involved in the study who used oral agents were using sulfonylureas, while among the Belgian diabetics who had bypass surgery, 248 were using sulfonylureas, 35 metformin, and 11 both drugs. Metformin was not available in the United States at the time of the study and was used by only a small number of the Belgian bypass patients. Troglitazone was not available then in either country.

O'Keefe says, "There's no question that patients do worse with sulfonylureas after angioplasty. In general, risk-adjusted long-term survival of diabetic patients was worse after angioplasty than after surgery. This was especially true for diabetics treated with oral agents, where the surgical survival advantage was importantly magnified."

He says explanations for the worse outcomes on sulfonylureas are "speculative." A body of evidence beginning decades ago with the University Group Diabetes Program in the 1970s concluded that tolbutamide increased death from cardiovascular disease. O'Keefe concedes that the findings of the University Group study were largely dismissed because there was a lack of a suitable alternative therapy for Type II diabetics at the time.

One theory for the outcomes, according to O'Keefe, is sulfonylureas close down potassium ion channels, prolonging myocardial refractoriness, "possibly predisposing the dysrhythmias and also exacerbating the consequences of myocardial ischemia and infarction by mitigating ischemic preconditioning."

In a current study still in draft form, he further speculates that sulfonylureas may "increase atherogenesis and its complications" regardless of the level of glycemic control because they are vasoconstrictors and they worsen vascular reactivity. "Anybody who has high-risk coronary disease, ischemia, and multivessel involvement should opt for bypass surgery."

O'Keefe's results take the five-year BARI (Bypass Angioplasty Revascularization Investigation) results to the next level. However, the EAST (Emory Angioplasty vs. Surgery Trial) study showed no difference in survival for diabetics following angioplasty or bypass surgery. "Neither of these studies included comparative outcomes after revascularization in diabetics as a pre-specified end-point, and both studies involved

Diabetic Patient Outcomes: James H. O'Keefe Study

- **15,809 total patients in study:**
  9,600 with bypass surgery in Belgium
  6,209 with angioplasty in United States
- **1,938 diabetics at baseline (12%):**
  1,056 with bypass surgery in Belgium (11% of total)
  882 with angioplasty in U.S. (14% of total)
- **Complete revascularization achieved:**
  Angioplasty: 51%
  Bypass: 82%
- **Drug treatment of diabetic patients:**
  - **Diet only:**
    Angioplasty: 201 (3%)
    Bypass: 475 (5%)
  - **Oral agents:**
    Angioplasty: 360 (6%)
    Bypass: 294 (3%)
  - **Insulin:**
    Angioplasty: 314 (5%)
    Bypass: 287 (3%)
- **10-year survival rate for patients treated pharmacologically:**
  Angioplasty: 46%
  Bypass: 60%
- **Risk-adjusted 10-year survival for diabetics treated with oral agents:**
  Angioplasty: 62%
  Bypass: 75%
- **Risk-adjusted 10-year survival for diabetics treated with diet only:**
  Angioplasty: 81%
  Bypass: 84%
- **Risk-adjusted 10-year survival for diabetics treated with insulin:**
  Angioplasty: 64%
  Bypass: 63%

Source: James H. O'Keefe, MD, University of Missouri, Kansas City.

a relatively small number of diabetic patients," he notes.

The BARI-II trial comparing angioplasty and bypass surgery in diabetic patients is currently under way.

Some diabetics, mainly those at high risk, may do as well with angioplasty as with bypass surgery, O'Keefe says, including the very young, who are likely to have discrete disease and the very old, who are at increased risk of perioperative morbidity. He also found the use of the internal mammary artery for grafting to the left anterior descending artery provided a "significant survival benefit" for patients receiving vessel grafts only or angioplasty.

It is important to note that the study took place before metformin and troglitazone were available in the United States and before stent procedures were in general use, says **Sanjay Kaul**, MD, attending cardiologist at Cedars-Sinai Medical Center in Los Angeles.

Kaul says since intimal hyperplasia or scarring of the arteries is "more luxuriant" in diabetics, angioplasty tends to be less successful than bypass surgery. He says that vein grafts obstruct more easily than arterial grafts, which explains the success rate of the mammary-arterial grafts.

Kaul is an advocate of stenting and says more research needs to be done along these lines. "About 70% of my coronary patients undergo stenting, and the re-stenosis rate is lower [than in angioplasty] at about 50%," Kaul says. "But there is evidence the outcome for diabetic patients is not as great, convincing, or compelling as for non-diabetic patients."

For more information, contact James H. O'Keefe, MD, Professor of Medicine at the University of Missouri in Kansas City and Director of Preventive Cardiology at the Mid America Heart Institute. Telephone: (816) 931-1883. ■

The virtual approach to diabetic neuropathy

Virtual reality and biofeedback may hold key

Virtual reality, until very recently the kingdom of video game buffs and the sci-fi fringe, has become the stuff of solid scientific research.

Paired with biofeedback, a '70s tool of the meditation and mantra crowd, virtual reality may soon provide diabetics with a means of eliminating the crippling effects of neuropathy and perhaps preventing the amputations so often coupled with the disease.

Researchers at Eastern Virginia Medical School in Norfolk are conducting preliminary studies aimed at teaching patients to prevent nerve damage by helping them visualize blood vessels feeding the nerves and to focus on relaxing to help improve circulation.

A team led by **Aaron Vinik**, MD, director of research at Strelitz Diabetes Institutes at Eastern Virginia, devised a series of tests to study blood flow to the nerves. "We used laser doppler techniques, which we applied to skin at different parts of the body to measure blood flow," he says. "Through a series of provocative tests, we have shown that diabetics have this as one of the earliest abnormalities. In fact, they have the decreased blood flow long before you can see other evidence of nerve damage."

Vinik and his team used a variety of tests such as heating and cooling parts of the body, mental arithmetic, and "everything that will try and activate the nervous system that will change the diameter of blood vessels and alter the flow."

He notes that diabetics respond poorly to all the provocateur's maneuvers. "I've always said if you want somebody to rob a bank and pass a lie detector test, use a diabetic. Basically what you are measuring with lie detector tests are changes in skin resistance and sweating and blood vessel reactivity, and [diabetics] don't have that."

The research soared to the stratosphere when Vinik hooked up with NASA researcher and virtual reality inventor, **Alan Pope**, PhD, who had

KEY POINTS

- Researchers look at virtual reality and biofeedback as possible methods of treating and preventing diabetic neuropathy.
- Patients can visualize opening blood vessels and can learn the sensation that accompanies blood vessel constriction.
- Through use of a virtual reality program designed by NASA, patients can see the results of their efforts to relax blood vessels in real time.

modeled how blood vessels react. "We said it would be very nice if we could actually get a model where we could see blood vessels in real time. So they went back and built a computer and software that does that," Vinik says.

The first effort was like a 50-year-old cartoon. "The blood vessel looked like a tube, and we said to them, 'No, that's not what it looks like in reality,'" he says. "So we re-drew the tube to show them the arteries and capillaries, so they modeled them like that."

Now a subject wearing the headgear and an input cuff on the finger can "get inside the blood vessels. You don't just look at them from outside, but it's a model, so you can come right inside the model and you can walk around inside your blood vessels if you wish. Our studies on diabetics so far show that lot of the change was functional; it wasn't structural," Vinik says. "The vessels weren't permanently damaged; they were just overreactors. So we think that we ought to be able to train people to stop their vessels from being overreactors and we could then reduce the likelihood of developing ulcers and so forth."

"Sure this works. We've seen it all over the place. This is great for anything involving the autonomic nervous system. Eventually, we could create nerve entrainment through virtual reality."

Virtual reality may be slightly removed from the medical mainstream, but highly respected researchers like Vinik and many other colleagues are traveling the virtual road for answers to some age-old questions.

One of those travelers is **David Warner**, MD, PhD, a perceptual psychologist and founder of the Institute for Interventional Informatics at Syracuse (NY) University, whose work on a variety of fronts — including using virtual reality for paraplegics and for children with attention deficit disorder — has gained national attention.

"Virtual reality is an extra-strength placebo," he explains. "Sure this works. We've seen it all over the place. This is great for anything involving the autonomic nervous system. Eventually, we could create nerve entrainment through virtual reality."

Warner, Vinik, and their colleagues stop short of saying that diabetics could cure their own neuropathy through virtual reality and biofeedback. "If diabetics can unintentionally shut off circulation to an area of the body where it shouldn't be shut off, like to the extremities, patients can also restore the circulation," Warner says. "Eventually, they'll also be able to do it without virtual reality; that's just a tool to help them."

"In some future time, probably within our life span, we can learn to turn the pancreas back on," he concludes.

For more information, contact: Aaron Vinik, MD, Director of Research at Strelitz Diabetes Institutes, Eastern Virginia Medical School, Norfolk. Telephone: (757) 446-5910. David Warner, MD, PhD, Institute for Interventional Informatics at Syracuse (NY) University. Telephone: (800) 950-0849. E-mail: davew@well.com. ■

Two drugs may give relief from neuropathic pain

New uses for old drugs

Physicians may soon have two new weapons available in their arsenal against the sometimes excruciating pain of diabetic neuropathy that affects an estimated 45% of all diabetic patients during the course of their disease:

1. The effectiveness of gabapentin, long used to control seizures, has been established in a study from the University of Wisconsin Medical School at the University of Wisconsin at Madison, which was reported in the *Journal of the American Medical Association*.

2. Phase IIb human clinical trials are now under way in the use of Memantine, a drug used in Germany for AIDS dementia syndrome for the past 10 years.

Researchers studying the drugs believe they offer relief from the chronic and often debilitating pain suffered by an estimated 800,000 diabetics in the United States. Of particular concern is the night pain that disturbs sleep and extracts an enormous price in terms of quality of life.

The University of Wisconsin study shows gabapentin, an anticonvulsive drug available in the United States for four years, can be a first-line agent for diabetic peripheral neuropathy

KEY POINTS

- Study finds gabapentin, long used to control seizures, is effective in reducing pain of diabetic neuropathy.
- Neurobiological Laboratories begins human clinical trials on Memantine, used in Europe to treat dementia syndrome.
- New uses for the drugs may improve quality of life for 800,000 U.S. diabetics suffering from neuropathy.

because its action is "more rapid" than tricyclic antidepressants, says **Miroslav Backonja**, MD, associate professor of medicine at the University of Wisconsin and lead author of the Gabapentin study.

Backonja's double-blind study included 165 diabetic patients at 20 medical centers, average age 53, who had experienced neuropathy for one to five years and had an average pain score of 4 or more on an 11-point scale.

His results were as follows:

• Gabapentin significantly reduced pain and reduced sleep disturbances, improved mood and improved the patients' quality of life.

• At least 60% of patients on gabapentin reported at least a moderate improvement in pain, compared to 33% of the placebo group.

"This is the first time in more than a decade we've found another promising agent for treatment of nerve pain from diabetes, Backonja says. "Gabapentin is a welcome addition to our options for pain control. It is well-tolerated by most patients and doesn't interact negatively with other medications."

Gabapentin is likely to be used as an "off-label" medication as a result of the study, he says, since the new use is not likely to be presented for U.S. Food and Drug Administration (FDA) approval. "This is proven, but not FDA approved," Backonja says.

Researchers at the Neurobiological Technologies Inc. of Richmond, CA, say they hope to find similar results in its trial of Memantine. **Lisa Carr**, MD, PhD, Neurobiological Technologies' director of medical affairs, says earlier animal and laboratory evidence showed "trends toward efficacy, particularly in the reduction of nocturnal pain."

The eight-week double-blind placebo-controlled study includes 375 patients at 22 sites.

Memantine is an oral medication researchers theorize restores the function of impaired neurons by modulating activity of the NMDA receptors. "Memantine is an excellent NMDA receptor modulator," Carr says.

By restoring function, Carr says, injured or damaged neurons may be inhibited from firing abnormally. That process is linked to a number of neurological conditions, including neuropathy, Alzheimer's disease, shingles, herpes zoster, and a variety of types of dementia.

There have been no known serious complications from the use of Memantine. "There's a long body of knowledge we can draw on because it has been in use in Europe for a long time," Carr says.

While Memantine is believed to have analgesic effects on neuropathy, she cautions, "The drug does not act directly on vessels. It would not repair vessels. It should not replace adequate sugar control, which is still paramount."

For more information, contact: Miroslav Backonja, MD, Associate Professor of Medicine at the University of Wisconsin at Madison. Telephone: (608) 263-5420. Lisa Carr, MD, PhD, Director of Medical Affairs, Neurobiological Technologies. Telephone: (510) 215-8000. ■

Early glucose screening means early diagnosis

ADA says it's a good idea for those at risk

Researchers at the Centers for Disease Control and Prevention (CDC) speculate that someday soon a blood glucose screening will become as much a part of the routine doctor's office visit as taking blood pressure and weight measurements.

A recent study from the CDC in Atlanta shows that early opportunistic screening for Type II diabetes will not only permit early diagnosis but can be cost-effective as well.

The study published in the Nov. 25 *Journal of the American Medical Association* shows that early screening can be most helpful in ferreting out the earliest symptoms of the disease in young African-Americans, who are at high risk, as well as among other patients at risk, including those who are obese or who have a family history of the disease.

KEY POINTS

- Early opportunistic glucose screening for young adults may result in early diagnosis, according to a study by the Centers for Disease Control and Prevention.
- Early diagnosis may help prevent complications.
- The American Diabetes Association concurs that diabetes screening, as part of routine medical care, may be appropriate for young adults with one or more risk factors.

The CDC study states that early opportunistic screening for younger at-risk Americans "may be an appropriate public health strategy." This targets that nebulous group, estimated at 3.2% of the American population between the ages of 20 and 74, who are unaware they have diabetes and who may have the disease for nine to 12 years before it is diagnosed, resulting in an increased rate of complications. Early screening would result in a diagnosis of diabetes an average of 5.5 years earlier than under current practice, the study shows.

Early detection improves quality of life

The complex computerized projections of the lifetime cost effectiveness (in 1995 dollars) for one-time screening between the ages of 25 and 34 show modest savings in actual cost and almost no increase in longevity, but an enormous improvement in quality of life for those diagnosed early.

"The study is unique in that it gives us solid information on costing," says **Michael M. Engelgau**, MD, a medical epidemiologist in the CDC's Division of Diabetes Translation in Atlanta and lead author of the study. "And the cost effectiveness is more favorable among younger people and higher-risk populations."

A cheap and simple finger stick to measure fasting blood glucose with a standard monitor during a routine visit to a doctor's office could save money and pain in the long term.

Using a range of epidemiological and clinical research studies to simulate the natural progression of the disease from onset to death, Engelgau followed a hypothetical group of 10,000 patients. He measured lifetime health care costs per patient after early screening during a routine visit to a health care provider and compared the costs if the same group was screened according to current practices that recommend screening beginning at age 45. A cutoff value of 110 mg / dl fasting blood glucose was used as an indicator of diabetes, and an oral glucose tolerance test was used to provide a positive diagnosis.

Engelgau found the average person's life would be extended only about one week through early diagnosis, and early screening would save $1,275 in health care costs over the lifetime of the average patient — but $5,539 per African-American patient diagnosed early.

Engelgau discovered, however, early screening can postpone or even prevent the deterioration in quality of life due to diabetic complications like kidney failure, neuropathy, and blindness. In addition, it can potentially save enormous costs associated with those complications.

Those who were diagnosed early, Engelgau's study shows, have a 26% reduction in the development of end-stage renal disease, a 35% reduction in the incidence of blindness, and a 22% lesser chance of a lower extremity amputation over their lifetimes.

In addition, they would live longer free of these complications:

- ❒ .27 years longer without blindness;
- ❒ .15 years without lower-extremity amputation;
- ❒ .08 years without end-stage renal disease.

"What we're gaining from early screening is improvement to the quality of life, not in length of life," Engelgau says.

Quite simply, this means that for every year a diabetic patient lives free of amputation, blindness, or other painful and debilitating complication, life is better, he explains.

Data for African-Americans were used in the minority component of the study because they were readily available from other studies, Engelgau says, but researchers estimate the effect would be similar in other at-risk populations, including Hispanics and Native Americans.

He writes: "Opportunistic screening of all adults aged 25 years or older for Type II diabetes would cost $236,449 per life-year gained and $56,649 per QALY [quality-adjusted life-year] gained. In comparison, screening mammography for women aged 50 years or older costs from $3,400 to $83,830 per life-year gained, annual screening screening for cervical cancer for women aged 21 years or older costs $50,000 per life-year gained, and hypertension screening for asymptomatic men and women 20 years old costs $48,000 and $87,000 respectively."

Engelgau acknowledges that the American

Diabetes Association (ADA) recommendations for routine screening begin at age 45, but says, "These results suggest that screening is more cost-effective at younger ages."

The ADA is not ready to revise its recommendation for routine screenings beginning at the age of 45, according to **Richard Kahn**, PhD, the ADA's chief scientific and medical officer in Alexandria, VA, but says, he sees "no conflict whatsoever with the recommendation for early screening for high-risk individuals." He also says the finger stick and glucose monitoring in a doctor's office is "our preferred way to go. It's simple and cheap."

"It's an interesting and useful piece of information," Kahn says while he raises a question not answered by the Engelgau study: "What is the frequency with which they should be measured?"

An ADA statement on Engelgau's findings states, "This study underscores the association's general recommendations that screening for diabetes as part of routine medical care may be appropriate if patients, including a young adult, have one or more risk factors. . . . However, it may be too soon to assess if this single study will have any impact on the American Diabetes Association's overall guidelines to begin testing for diabetes at age 45, and, if normal, to be repeated at three-year intervals."

For further information, contact Michael Engelgau, MD, Medical Epidemiologist, Centers for Disease Control and Prevention, Atlanta. Telephone: (770) 488-5842. ■

Pharmacists help diabetic patients manage better

City of Asheville says educational tool is a success

Has the position of pharmacist devolved into nothing more than a glorified pill counter and pusher of buttons who makes computers spit out patient instruction forms?

Some pharmacists think so.

But not several professionals in Asheville, NC, who say they've found a new lease on life by giving diabetic patients a new approach to their disease self-management. It's a unique method of diabetes management, experts agree, but it's one that had a stunning affect shortly after its inception. And it's gaining national attention as a new pathway in patient education.

The recipe is simple:

- ✔ Take a group of Asheville city employees, retirees, and their dependents covered under the municipal self-insurance program.
- ✔ Add a city risk management director who is not only concerned with reducing the cost of treating diabetics but with improved quality of life for the 46 diabetic plan members, 43 of them on oral agents, insulin, or a combination of the two.
- ✔ Add a handful of independent pharmacists willing to take a risk in terms of time and money to work directly with patients.
- ✔ Stir in the incentive for patients: new glucose monitoring equipment and zero co-pay for all diabetes-related drugs and supplies.

The outcome? An impressive reduction in the HbA1c levels of the patients and dramatic improvements in terms of sick time, emergency department visits, and hospitalizations.

The numbers were so impressive to **John Miall**, risk management director for the City of Asheville, that he agreed to pay the pharmacists for their efforts nine months ahead of schedule. In fact, the pharmacist-based diabetes education program was so successful that the city has begun a similar program for asthma patients and the city's health care partner, Mission-St. Joseph's Hospital, decided to offer similar services to its employees beginning this year. **(See results, p. 11.)**

Three months into the diabetes study, the city's nurse-educator noticed patients were taking better care of themselves in terms of diet, sleep, and exercise. Some patients had already begun to

KEY POINTS

- The city of Asheville, NC, agrees to try pharmacist-based diabetes education program proposed by state pharmacists association.
- Training for pharmacists was provided by Diabetes Center of Mission-St. Joseph's Hospital in Asheville.
- Pharmacists monitor prescriptions, counsel patients, and report back to doctors.
- Benefits become apparent almost immediately in terms of reduced number of sick days and quality-of-life assessments from patients.
- Long-term benefits of reduced HBA1c and total cholesterol levels are expected to prevent complications and reduce costs.

think of their pharmacist as their "coach."

"I'm convinced that having someone knowledgeable to talk to made a big difference to them," Miall says. Six months into the project, the city had begun to save money, even though one of the diabetic patients had been diagnosed with leukemia and had already incurred expenses of $9,000 unrelated to diabetes. "We were already seeing improvements in emotional, physical, and mental health as well as improvements in cholesterol, triglyceride, and hemoglobin levels," he says.

After one year, the city had saved $38,970 in inpatient hospital claims, while adding $2,988 in outpatient claims, adding $5,320 in pharmacists' fees, adding $2,465 for glucose monitors and adding $8,000 for patient education at the Mission-St. Joseph's Diabetes Center. The rather unexpected net savings to the city in the first year: $20,246.

While Miall is happy with the savings, he says the implications of this "drop in the bucket" in view of the city's $4 million health care benefit program are much larger. "If you're preventing one diabetic patient from facing an amputation in the future by improving his or her care now, [besides patient morbidity] you're saving between $30,000 and $50,000."

At a cost of approximately $6,000, the city's health partner, Mission-St. Joseph's Hospital Diabetes Center brought in 24 community pharmacists for a 32-hour intensive training program spread over two weekends. Physicians, dietitians, nurses, and other pharmacists provided up-to-date disease management information and educational techniques to the participating pharmacists.

Course participants took before and after tests to determine their absorption of the material. Then each patient's physician was notified of the patient's participation in the project, and physician input was invited.

Each patient was matched with a pharmacist who spent approximately one hour in an initial assessment session in which a history was taken, a one-page personality preference questionnaire was completed, and compliance goals were set. Patients also receive training in the use of their monitors and, if necessary, in mixing insulin.

Monthly follow-up visits and monitoring lasting 20 to 30 minutes also improved compliance. Study results showed an average of 5.8 patient visits with a pharmacist in a year.

A key to the success of the Asheville Project is making the pharmacist an important part of the team, says **Daniel G. Garrett**, MS, RPh, FASHP, president of the North Carolina Center for Pharmaceutical Care, a coalition of state pharmacy organizations in Chapel Hill, NC. He points out that patients see a pharmacist about five times as often as they see any other health care professional, so it makes sense that pharmacists can develop a relationship with a patient that encourages compliance.

Pharmacist-educators overcame initial resistance from physicians when they demonstrated they have information that can help all members of the team. For example:

❒ Pharmacists can let physicians know if a prescription was filled (15% are not).

❒ Pharmacists can let physicians know if patients are taking the medication (13% do not, even if they fill prescriptions).

❒ They can provide feedback about whether a medication is working.

❒ They can find out from the patient is there are problems and head off potentially serious consequences before the patient's next doctor appointment, which may be months away.

"What's really different about The Asheville Project," Garrett says, "is that we started with one employer and one pharmacist, and we made it

Asheville Project Results

Baseline HbA1c	7.6
After 8 months	7.0
After 14 months	6.2
Baseline total cholesterol	210
After 8 months	208
After 14 months	198
Baseline HDL	45
After 8 months	42
After 14 months	48
Baseline LDL	118
After 8 months	113
After 14 months	98
Baseline number of sick days for all diabetics per year	1,708
Number of sick days after 12 months of study	811
Baseline average number of sick days per diabetic patient	12.6
Average number of sick days after 12 months of study	6.2

work." Garrett and his association are expanding the program to include five more communities in North Carolina, and they've been deluged with requests for information since a 27-page series of articles on The Asheville Project was published in the October issue of *Pharmacy Times.*

Plus, two drug store chains have added weight to the program by jumping into The Asheville Project, "a little late because of corporate hierarchy," Miall says.

"Pharmacists are attracted to this program because it of the opportunity to do something more meaningful," says **Lucinda Maine**, PhD, RPh, senior vice president for professional and public affairs of the American Pharmaceutical Association, who calls The Asheville Project an "elegant, small-scale demonstration that this stuff really works. The Asheville Project got all this attention because of the power of the results and the power of the collaboration," she says.

Most importantly, the patients who participated in The Asheville Project are happy. "That's the most gratifying thing about it," Miall says, recalling a woman who came to a meeting early in the program. "She came up to me crying and grabbed my hand. She said, 'I can never tell you how much this means to me.'"

For more information, contact Daniel G. Garrett, MS, RPh, FASHP, President of the North Carolina Center for Pharmaceutical Care. Telephone: (800) 852-7343. ■

CE objectives

After reading this month's issue of *Diabetes Management*, the continuing education participant should be able to:

• Identify particular clinical, administrative, education, or managerial issues related to the disease management of diabetes patients.

• Describe how those issues affect diabetes patients, diabetes management programs, and diabetes costs.

• Cite practical solutions to disease management problems associated with diabetes, based on overall expert guidelines from the National Institutes of Health, the American Diabetes Association, the American Association of Diabetes Educators, or other authorities, or based on independent recommendations from clinicians at individual institutions. ■

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