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Report recommends earlier treatment of hypertension

Pharmacists in unique role to assist with combination drug therapy

New clinical practice guidelines for the prevention, detection, and treatment of high blood pressure recommend earlier and more aggressive intervention for control of the disease. The guidelines also give non-physician practitioners, such as pharmacists, a better-defined opportunity to be an important part of therapy, says a pharmacist who participated in the development of the report.

In mid-May, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health announced the release of the "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7). A practical guide, called the "JNC 7 Express," was published first on the NHLBI web site. It also was included in the May 21 issue of the *Journal of the American Medical Association* (*JAMA*) and was posted on the *JAMA* web site. A full-length version of the report is set to appear in the July/August issue of the journal *Hypertension*.

The sixth report from the JNC, a coalition of 39 major professional, public, and voluntary organizations and seven federal agencies, was published in 1997. The decision to appoint a JNC 7 committee was based on four factors, the new report says: 1) the publication of many new hypertension clinical trials and observational studies; 2) the need for a new, clear, and concise guideline that would be useful for clinicians; 3) the need to simplify the classification of blood pressure; and 4) a clear recognition that the JNC reports were not being used to their maximum benefit. **(For a quick look at the key facts from the JNC 7 report, see p. 51.)**

"Since 1997, much more has been learned about the risk of high blood pressure levels and the course of the disease," said NHLBI director **Claude Lenfant**, MD, in a statement. "Americans' lifetime risk of developing hypertension is much greater than we'd thought."

The guidelines were prepared by an executive committee and five writing teams selected from the coordinating committee of the NHLBI's

National High Blood Pressure Education Program (NHBPEP), which represents 46 professional, voluntary, and federal organizations. The guidelines then were reviewed by 33 national hypertension experts and policy leaders and finally were approved by NHBPEP's full membership.

The group tried to streamline and simplify the guidelines to make them as applicable to practice as possible without limiting the science and the evidence they present, says **Mark J. Cziraky**, PharmD, FAHA, executive vice president of Health Core in Newark, DE. Representing the American Pharmacists Association in Washington, DC, Cziraky helped write the report and also helped develop JNC 7's tables of antihypertensive drug therapies, along with **Barry L. Carter**, PharmD, a professor at the University of Iowa College of Pharmacy in Iowa City and a representative of the American Society of Health-System Pharmacists in Bethesda, MD.

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A new classification system

One fundamental change in the guidelines is the new approach to categorizing blood pressure levels. The old system, which some clinicians claimed is confusing, classified blood pressure levels as optimal, normal, high-normal, or hypertensive stages 1, 2, or 3. JNC 7, however, has added the classification of prehypertension, and has combined stages 2 and 3 because their treatments were essentially the same. The JNC 7 categories are: normal (less than 120/less than 80 mmHg), prehypertension (120-139/80-89 mmHg), stage 1 hypertension (140-159/90-99 mmHg), and stage 2 hypertension (at or greater than 160/at or greater than 100 mmHg).

The classifications were changed because the relationship between blood pressure and risk of cardiovascular disease (CVD) events is continuous, consistent, and independent of other risk factors, the JNC 7 Express report explains. For individuals 40-70 years of age, each increment of 20 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure doubles the risk of CVD across the entire blood pressure range from 115/75 to 185/115 mmHg. "The new classification of 'prehypertension' recognizes this relationship and signals the need for increased education of health care professionals and the public to reduce blood pressure levels and prevent the development of hypertension in the general population."

The JNC 7 report does not recommend drug therapy for prehypertension unless patients have compelling indications such as kidney disease or diabetes. The report does recommend that these patients adopt lifestyle modifications, including weight reduction, adoption of the Dietary Approaches to Stop Hypertension eating plan, dietary sodium reduction, increased physical activity, and moderation of alcohol consumption. Patients also should stop smoking for overall cardiovascular risk reduction.

The change in classification became necessary because there is more evidence that patients are at risk and that many of these patients go on to develop hypertension by definition, Cziraky says.

"Identifying patients who are in a prehypertensive category, such as 125/85, is important, as these patients can benefit from intervention through lifestyle modifications, and the onset of hypertension can be potentially delayed."

According to Cziraky, it is important for patients and clinicians to understand that a person in the prehypertension stage may see benefit from early

Key facts from the JNC 7 report

The "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7) provides new clinical guidelines for hypertension prevention and management. Following are the report's key messages:

- In persons older than 50 years of age, systolic blood pressure greater than 140 mmHg is a much more important cardiovascular disease (CVD) risk factor than diastolic blood pressure.
- Beginning at 115/75 mmHg, the risk of CVD doubles with each additional increment of 20/10 mmHg. Individuals who are normotensive at age 55 have a 90% lifetime risk for developing hypertension.
- Individuals with a systolic blood pressure of 120-139 mmHg or a diastolic blood pressure of 80-89 mmHg should be considered as prehypertensive and require health-promoting lifestyle modifications to prevent CVD.
- Thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes. Certain high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium channel blockers).
- Most patients with hypertension will require two or more antihypertensive medications to achieve goal blood pressure (less than 140/90 mmHg, or less than 130/80 mmHg for patients with diabetes or chronic kidney disease).
- If blood pressure is more than 20/10 mmHg above goal blood pressure, consideration should be given to initiating therapy with two agents, one of which usually should be a thiazide-type diuretic.
- The most effective therapy prescribed by the most careful clinician will control hypertension only if patients are motivated. Motivation improves when patients have positive experiences with, and trust in, the clinician. Empathy builds trust and is a potent motivator.
- In presenting these guidelines, the committee recognizes that the responsible physician's judgment remains paramount. ■

intervention — not necessarily with medication, but at least with some discussions about lifestyle adjustments, such as salt restriction and weight reduction, he says.

Two or more drugs likely

For patients who need drug therapy to control their hypertension, the JNC 7 report recommends that thiazide-type diuretics be used as initial therapy for most patients with hypertension, either alone or in combination with one of the other classes demonstrated to be beneficial in randomized controlled outcome trials. The report also lists compelling indications that require the use of other antihypertensive drugs as initial therapy. If a drug is not tolerated or is contraindicated, then one of the other classes proven to reduce cardiovascular events should be used instead.

"Diuretics enhance the antihypertensive efficacy of multidrug regimens, can be useful in achieving blood pressure control, and are more affordable than other antihypertensive agents. Despite these findings, diuretics remain underutilized," the report says.

The report doesn't say diuretics are appropriate in all cases, but rather that they always should at least be considered, Cziraky says. "When patients are on multiple drug therapies, diuretics are usually in that mix or should be strongly considered for that mix. That was a big point that came out in JNC 7 and has been coming out in more of the literature."

All the major studies published prior to the publication of JNC 7 were addressed and interpreted in the guidelines, Cziraky adds. "They were applied directly where they could be. If not, they were taken together as a group of literature."

Some health care specialists have said they believe the report might recommend diuretics too strongly, he says. "I know from discussions with the group and from knowing how the guidelines were developed that consideration of diuretics is appropriate, especially with combination therapies, and that there is a lot of room for clinical judgment."

The key is making sure to identify patients who are in prehypertensive states as well as those in hypertensive states, Cziraky says. "Once that

happens, put the patients on the therapy and get them controlled in a relatively short period of time," he advises.

Another point emphasized in the JNC 7 report is that most patients will need two or more drugs to get to the desired blood pressure control levels, he says. "When blood pressure is more than 20/10 mmHg above goal, consideration should be given to initiating therapy with two drugs, either as separate prescriptions or in fixed-dose combinations," the report says.

The report makes a careful effort to support every recommendation for drug therapy with citations in the literature, Cziraky says. "If the clinicians want to look at those articles in more depth, the references are there, too. They have the ability to go back and do their own interpretations."

How can pharmacists help?

The JNC 7 report emphasizes the importance of physician judgment. The report, however, also recognizes the value of all members of the health care team, including pharmacists, working together to control hypertension.

"Failure to titrate or combine medications, despite knowing the patient is not at goal blood pressure, represents clinical inertia and must be overcome," the report says. "Decision support systems (i.e., electronic and paper), flow sheets, feedback reminders, and involvement of nurse clinicians and pharmacists can be helpful."

To assist in this goal, pharmacists need to be able to classify each of their patients according to the categories given in the new guidelines, Cziraky says. Pharmacists then can make recommendations either directly to the patient or to providers and practitioners about choice of agents based on the categorization.

Information about appropriate combinations of drug therapies is especially helpful, because most patients will be taking several drugs, he says. "Make sure your patients are aware of the importance of taking their medications and why taking two agents for the same abnormality makes sense because they work by different mechanisms."

Lifestyle changes, however, should not be neglected as an important part of the treatment mix. "It takes a lot of education and discussion with the patients to make them aware of the importance of intervening with their high blood pressure," Cziraky says.

Overall, the JNC 7 report is an excellent tool pharmacists can use to help them control their patients' blood pressure, he adds. Pharmacists play a significant role in control of hypertension because they often see these patients most frequently and are thus in a good position to determine whether the patients are adhering to therapy. "There is a lot of opportunity for pharmacists to play a critical role in getting better control rates on elevated blood pressures in this country," Cziraky says. "They have a great chance to intervene and hopefully make an impact." ■

Dementia rates increase for older women on HRT

No change yet in FDA-approved uses

Older women taking combination hormone therapy had dementia twice as often as women not taking the therapy, according to a recently published study.

The results of the Women's Health Initiative Memory study (WHIMS) were published in the May 28 issue of the *Journal of the American Medical Association*. WHIMS, a substudy of the Women's Health Initiative program (WHI), was funded by Wyeth Pharmaceuticals. Wyeth produces Prempro, a form of estrogen plus progestin hormone therapy.

Women ages 65 or older at greater risk

WHIMS studied about 4,500 women who were between 65 and 79 years of age. Once they were initially judged not to have dementia, the women were randomly assigned to take one pill per day of Prempro (conjugated equine estrogen, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg) or a placebo. Researchers evaluated the women's cognitive status annually, and any of the women who showed signs of decline were evaluated in greater depth.

The findings showed that over a five-year period:

• The risk for dementia among women taking estrogen and progestin was twice that of women taking placebo pills. This represents an increase per year from 22 women per 10,000 at risk of dementia in the placebo group to 45 women per 10,000 in the combination therapy group. Sixty-one cases of dementia were diagnosed among the

women participating in the study; 66% of those cases occurred among women on combination therapy, while 34% occurred in women taking placebo.

• Most of the dementia found among women participating in the study was classified as probable Alzheimer's disease, with vascular dementia ranking second. There were 20 cases of Alzheimer's disease among the 40 dementia cases in women in the combination therapy group (50% of the cases); in women on placebo, 12 of the 21 cases of dementia (57%) were deemed Alzheimer's disease.

• There was no significant difference between the groups in the risk of being diagnosed with mild cognitive impairment.

The Alzheimer's Association in Chicago expressed disappointment with the results. "This clinical trial was prompted by a wide range of observational and laboratory data that suggested HRT [hormone replacement therapy] reduced women's risk of developing dementia, including Alzheimer's," said **Marilyn Albert**, PhD, in a statement. Albert is professor of neurology at Johns Hopkins University School of Medicine in Baltimore and is the chair of the Alzheimer's Association Medical and Scientific Advisory Council. "No one anticipated this outcome."

Researchers, however, advise practitioners to keep the study results in perspective. The risk of dementia is significant when viewed over a large population of women, but the risk to individual older women is relatively small. In addition, Wyeth points out that the applicability of these findings to the typical current user — a younger, symptomatic woman taking hormone therapy to relieve menopausal symptoms — is unclear. This study evaluated women who were, on average, age 71 at enrollment, a population at higher baseline risk than the average woman entering menopause, who is age 51, the company says. There also is a question regarding whether the timing of therapy initiation relative to the onset of menopause may be an important factor.

No labeling changes yet

Although the latest results from the WHI study indicate an increased incidence of dementia and memory impairment in older women, the U.S. Food and Drug Administration (FDA) announced in late May that there was no need to modify the approved uses of these drug therapies. The FDA says it is reviewing the new information and will determine whether labeling should be updated so women and prescribers are more fully informed about use of these therapies.

The FDA continues to emphasize that combined estrogen and progestin is effective for treating moderate-to-severe symptoms of hot flashes and night sweats and for treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy. When intended for prevention of osteoporosis, approved non-estrogen treatments should be considered. Estrogen, and estrogen with progestin, also have never been approved for prevention of cognitive disorders, such as Alzheimer's disease or memory loss.

If physicians advise that estrogen- and progestin-containing products are appropriate for their patients, the products should be used at the lowest dose for the shortest duration to reach treatment goals. ■

Beware of counterfeit atorvastatin calcium

The U.S. Food and Drug Administration (FDA) is warning pharmacists and consumers to beware of counterfeit atorvastatin calcium (Lipitor).

The FDA originally issued its alert on the counterfeit cholesterol-lowering drug on May 23, when the agency's investigation turned up three lots of 90-count bottles. The agency announced that Albers Medical Distributors of Kansas City, MO, was voluntarily recalling 100,000 bottles. On June 3, the FDA announced the discovery of three additional lots (30,000 bottles) of the counterfeit drug.

The counterfeit product labels say "Repackaged by: MED-PRO, Inc. Lexington, Neb." in the lower left-hand corner. Pharmacists also should look for these lot numbers and notify consumers if they might have received the counterfeit drug:

• 20722V — 90-tablet bottles, 10 mg, expiration 09-2004

• 04132V — 90-tablet bottles, 10 mg, expiration 01-2004
• 16942V — 90-tablet bottles, 10 mg, expiration 09-2004
• 20842V — 90-tablet bottles, 10 mg, expiration 09-2004
• 16092V — 90-tablet bottles, 10 mg, expiration 07-2004
• D270481 — 90-tablet bottles, 20 mg, expiration not available

Pfizer, the manufacturer of atorvastatin, announced June 3 that it was suing Med-Pro and Albers to ensure they immediately stop the distribution of the counterfeit atorvastatin. Pfizer says it does not distribute the drug to Med-Pro and has no relationship with the company or with Albers Medical Distributors. Albers and Med-Pro deny involvement in the counterfeiting of atorvastatin.

According to Pfizer's analysis, tablets from Med-Pro packages purporting to contain Lipitor 10 mg and 20 mg bear a close resemblance to the authentic drug, though they may be slightly thicker. Consumers have reported that the counterfeit tablets dissolve more quickly and have a bitter taste. ▼

Injunction lifted against discount drug program

The U.S. Supreme Court has ruled that Maine can continue with its efforts to implement its "Maine Rx" program, which was designed primarily to provide discounted prescription drugs to Maine's uninsured residents. The 6-3 decision, however, does not "finally determine the validity" of the program, the court says.

"The District Court did not conduct an evidentiary hearing and did not resolve any factual disputes raised by the affidavits filed by the parties," the court said in its decision. "Accordingly, no matter how we answer the question whether petitioner's showing was sufficient to support the injunction, further proceedings in this case may lead to a contrary result."

Under the program, the state serves as a pharmaceutical benefits manager, negotiating discounts with drug manufacturers. These discounts come in the form of rebates paid by the drug manufacturers directly to the state. Maine residents enrolled in the program pay the reduced drug prices to their pharmacies, which then are reimbursed the discounted amount by the state, plus an administrative fee. If a manufacturer does not provide a rebate, that manufacturer's products may be placed on the Medicaid program's list of drugs that require preauthorization for payment.

The Maine Rx program was enacted in 2000 but never took effect because the Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington, DC, filed a lawsuit asking the federal district court in Maine to enjoin the program's implementation. PhRMA argued that the program was pre-empted by the federal Medicaid statute and violated the negative Commerce Clause. The federal court ruled in favor of PhRMA and issued the injunction. An appellate court in Boston reversed that decision in May 2001 but left the injunction in place. The Supreme Court then issued its ruling.

The fate of programs such as Maine's may lie in the hands of the Department of Health and Human Services (HHS), which supervises state implementation of Medicaid. One justice in the majority, **Stephen G. Breyer**, said, "Institutionally speaking, that agency [HHS] is better able than a court to assemble relevant facts (e.g., regarding harm caused to present Medicaid patients) and to make relevant predictions (e.g., regarding furtherance of Medicaid-related goals)." A spokesman for HHS told media outlets that the Supreme Court decision validated the Bush administration's position that states should seek federal approval before implementing such programs. ▼

Status of postmarketing studies to be posted

The FDA has announced two measures to inform the public about the status of manufacturers' commitments to carry out further clinical studies following the FDA's approval of certain drugs and biological products.

One of the measures, the publication of the FDA's first annual *Federal Register* (*FR*) report on these postmarketing studies, covers commitments that are required by the FDA as well as

those voluntarily accepted by the manufacturers. In addition to the *FR* report, which is mandated by the FDA Modernization Act of 1997, the FDA is posting on its web site a searchable database with most of the same information (www.fda.gov/cder/pmc).

The database includes open postmarketing study commitments that have been made with the FDA's Center for Biologics Evaluation and Research, and commitments concluded with the Center for Drug Evaluation and Research since Jan. 1, 1991. Both the *FR* notice and the web site list study commitments addressing clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology. Not included are certain other postmarketing commitments, such as those concerning chemistry, manufacturing, and controls, and there is no listing of proprietary information.

The web site, which lists only commitments that have been reviewed by the FDA for accuracy, will be updated with new postmarketing commitments each July, October, January, and April. Additional information about this site is available on the search page and in "Frequently Asked Questions (FAQs)." ▼

FDA, NCI plan to streamline cancer drug development

The U.S. Food and Drug Administration (FDA) and the National Cancer Institute (NCI) have recently announced that they will share knowledge and resources to facilitate the development of new cancer drugs and speed their delivery to patients. The planned agreement will enhance existing programs and add new joint programs to the existing close cooperative relationship between NCI and FDA, both of which are part of the Department of Health and Human Services (HHS).

An NCI/FDA Oncology Task Force, which comprises senior staff from both agencies, will oversee implementation of the specific components of the agreement. Areas of collaboration should include the following:

- developing markers of clinical benefit (biomarkers) for evaluating new cancer medicines;
- creating a cancer bioinformatics infrastructure to improve data collection, integration, and analysis for preclinical, preapproval, and post-approval research across all the sectors involved in the development and delivery of cancer therapies;
- addressing joint technology development issues;
- advancing the development and evaluation process for cancer chemoprevention agents, including the development of clinically meaningful endpoints;
- conducting a systematic review of current policies to identify other ways in which FDA-NCI collaborations can enhance the development and regulatory process for cancer technologies;
- improving consumer awareness of the consequences of choices about diet and nutrition for cancer prevention;
- enhancing staff capabilities through collaborative training, joint rotations, and joint appointments. ■

New FDA Approvals

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

- *Bortezomib injection (Velcade) by Millennium Pharmaceuticals.* The FDA has approved bortezomib injection (Velcade) as a new treatment

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for multiple myeloma. The FDA reviewed the application for this drug in less than four months. Bortezomib injection is the first in a new class of anticancer agents known as proteasome inhibitors.

Bortezomib injection is indicated for patients whose disease has relapsed after two prior treatments and who have demonstrated resistance to their last treatment. The FDA evaluated the safety and efficacy of bortezomib injection based on a study of 202 patients who had received at least two prior therapies and demonstrated disease progression on their most recent therapy. Altogether, out of 188 patients evaluated for response, 28% showed a response to bortezomib injection. The response lasted a median time of one year. Another trial in 54 patients with relapsed multiple myeloma showed similar responses.

There are no controlled trials yet of bortezomib injection demonstrating clinical benefit, such as improvement in survival. The drug's developer will perform additional studies after approval to address this issue.

The most commonly reported adverse events reported in clinical trials include nausea, fatigue, diarrhea, constipation, headache, decreased appetite, decreased platelets and red cells in the blood, fever, vomiting, and peripheral neuropathy.

• *New indication for imatinib mesylate (Gleevec) by Novartis.* The FDA has approved imatinib mesylate (Gleevec) tablets for the treatment of pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase. Imatinib mesylate is indicated for children whose disease has recurred after stem-cell transplant or who are resistant to interferon alpha therapy.

This drug was approved under the accelerated approval program. It is the first approval of a new pediatric cancer drug treatment in more than a decade. In addition to its original approved indication for CML refractory to other treatments in adults and its expansion to use as a first-line treatment for CML, imatinib mesylate also was previously granted accelerated approval for the treatment of gastrointestinal stromal cancer. As a condition of approval, Novartis has agreed to conduct pediatric studies to gain greater insight into the drug's use in children.

The most frequently reported adverse events reported with the use of imatinib mesylate are nausea, vomiting, diarrhea, edema (sometimes severe), and muscle cramps. A considerable reduction in white blood cells and platelets also has been reported.

The recommended dosage for pediatric populations is 260 mg/m^2/day. In children, imatinib mesylate treatment can be given as a once-daily dose or, alternatively, the daily dose may be split in two—once in the morning and once in the evening.

• *New indication for levofloxacin (Levaquin) by Ortho-McNeil Pharmaceutical.* The FDA has approved levofloxacin (Levaquin) tablets/injection and levofloxacin in 5% dextrose injection for the treatment of chronic bacterial prostatitis due to *Escherichia coli*, *Enterococcus faecalis*, or *Staphylococcus epidermidis*. With this indication, the drug becomes the only once-daily fluoroquinolone indicated to treat chronic bacterial prostatitis. Chronic bacterial prostatitis is the tenth indication for Levaquin since the FDA first approved it in 1997. ■

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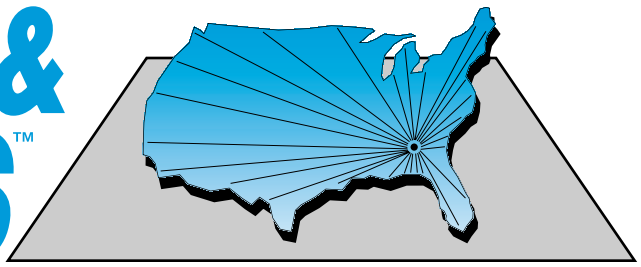

Urokinase (Abbokinase) formulary evaluation

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Written while on clinical rotation
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Introduction

Due to manufacturing problems, the U.S. Food and Drug Administration (FDA) took urokinase (Abbokinase) off the market in December 1998. During inspection of the manufacturing facility in October and November of 1998, urokinase production was found to differ from Good Manufacturing Practice regulations. The FDA suggested that the manufacturer, Abbott Laboratories, not release any of the product until the FDA reviewed the inspection findings. The FDA issued a warning in January 1999 stating that products such as urokinase, which is made from human source materials, have the potential to transmit infectious agents. Even though Abbott had procedures in place to reduce such risks, the FDA inspection revealed deficiencies in certain procedures.

Since then, Abbott has corrected its manufacturing problems, and urokinase recently returned to the market. Its place in therapy is now being re-evaluated. This evaluation will focus on thrombolytic use in peripheral arterial occlusion and pulmonary embolism.

Thrombolytics compared

- **Urokinase** — an enzyme produced by the kidneys and excreted in urine
- **Alteplase** — a recombinant DNA form of the enzyme human-tissue-type plasminogen activator
- **Reteplase** — a recombinant DNA form of the enzyme human-tissue-type plasminogen activator

Background/mechanism of action

When a vessel is occluded, the body signals the release of tissue plasminogen activator (t-PA) from endothelial cells. Plasminogen is an inactive precursor that is converted to plasmin. Plasmin, an enzyme, dissolves intravascular fibrin clots and other plasma proteins, including several coagulation factors.

T-PA binds to fibrin and converts plasminogen (which also is bound to fibrin) to plasmin. T-PA has little effect on circulating plasminogen because it is rapidly cleared from blood or inhibited by circulating inhibitors, plasminogen activator inhibitor-1, and plasminogen activator inhibitor-2. Alpha2-antiplasmin inactivates plasmin by forming a stable complex with it. In healthy people, the fibrinolytic system is in balance such that unwanted fibrin thrombi are removed, while fibrin in wounds persists.

Thrombolytics act like tissue plasminogen activators, converting plasminogen to plasmin. Alpha2-antiplasmin plasma concentrations are sufficient to inhibit about 50% of plasmin activity. However, when thrombolytics are used, massive activation of plasminogen occurs and the inhibitor is overwhelmed, so much so that free plasmin causes a systemic lytic state. Thrombolytic drugs dissolve both pathological thrombi and fibrin deposits at sites of vascular injury.

Urokinase is slightly different from alteplase and reteplase because it directly activates plasminogen to plasmin. Urokinase can bind to plasminogen directly; however, alteplase and reteplase activate plasminogen that is bound to fibrin. Plasminogen is present in thrombi and emboli; therefore, activation by urokinase occurs within, as well as on the surface of, thrombi and emboli.

Alteplase and reteplase have similar mechanisms of action. Both preferentially activate plasminogen that is bound to fibrin, which theoretically confines fibrinolysis to the formed thrombus and avoids systemic activation.

Clinical uses (*FDA-labeled use)

Urokinase

- peripheral arterial occlusion
- acute pulmonary embolism*
- acute myocardial infarction
- catheter occlusion

Alteplase

- peripheral arterial occlusion
- acute pulmonary embolism *
- acute myocardial infarction*
- acute ischemic stroke*
- catheter occlusion

Reteplase

- peripheral arterial occlusion
- pulmonary embolism
- acute myocardial infarction*

Dosing of urokinase — adults

• Peripheral arterial occlusion

— The most common initial dose is 240,000 international units/hour (IU/hr) for two to four hours or until blood flow is restored.

— The most common maintenance regimens are: 1) 120,000 IU/hr to a maximum of 48 hours or 2) 120,000 IU/hr for two hours, then 60,000 IU/hr until lysis is complete. The dose is administered intra-arterially in close proximity to the thrombus or intra-thrombus (directly in the thrombus). The intravenous route is not used.

Several different regimens have been used in studies, including:

— A bolus dose of 60,000 IU administered into the thrombus, followed by 240,000 IU/hr for two hours, 120,000 IU/hr for two hours, and 60,000 IU/hr for up to a maximum of 20 hours.

— An initial dose of 150,000 IU over one-half to two hours, followed by continuous infusion of 50,000 IU/hr. The average time to clot lysis was 26 hours.

— An initial dose of 240,000 IU/hr until blood flow was restored, followed by a maintenance dose of 60,000 IU/hr or 120,000 IU/hr until clot lysis was achieved.

• Pulmonary embolism

— A loading dose of 4,400 IU/kg of urokinase is administered over a period of 10 minutes, followed by continuous infusion of 4,400 IU/kg/hr of urokinase for 12 hours. No other medications should be added to the urokinase solution.

• Acute myocardial infarction

— The optimal dose of urokinase for intracoronary thrombolysis is 6,000 IU/min for up to two hours.

• Catheter clearance

— The recommended dose is 5,000 IU × one dose intra-catheter (IC).

— A second injection of urokinase may be necessary.

Dosing of urokinase — children

Urokinase is not FDA-approved for children. The safety and efficacy of urokinase therapy has not been established in pediatric patients.

• Catheter clearance

— The recommended dose is 5,000 IU × one dose IC.

— A second injection of urokinase may be necessary.

• Central thrombosis

Urokinase was used in neonates to treat four cases of central thrombosis via umbilical artery catheter into the abdominal aorta. The dose used was a 4,400 IU/kg loading dose followed by a 4,000 to 20,000 IU/kg/hr maintenance dose. The duration of therapy ranged from three to nine days.

Dosing of alteplase — adults

• Peripheral arterial occlusion

The literature provides data on weight-based and non-weight-based dosing regimens ranging from 0.02 to 0.1 mg/kg/hr and 0.25 to 10 mg/hr. The risk of bleeding is increased with higher doses. In one study, for example, patients received a 10 mg bolus, followed by 5 mg/hr for up to 24 hours. In this study, the t-PA patients experienced more major bleeding episodes than the urokinase group; however, both drugs demonstrated similar efficacy. In another study, patients received an average dose of 0.86 ± 0.5 mg/hr. This study used the lower dosage range and found that urokinase and alteplase had similar safety and efficacy. Thus, in studies in which the patients received doses of t-PA > 2.0 mg/hr, there was a greater incidence of bleeding in the t-PA group than in the studies that gave doses of < 2.0 mg/hr. The Society of Cardiovascular and Interventional Radiology (SCVIR) dosing guidelines recommend the following doses:

— The dose is 0.001-0.02 mg/kg/hr (weight-based) or 0.12-2.0 mg/hr (non-weight-based); dose should not exceed 2 mg/hr.

— The total dose is < 40 mg for catheter-directed therapy. A single bolus dose should not exceed 10 mg.

— The dose of concurrent heparin therapy is

2,500 units (U) bolus followed by 500 U/hr. Activated partial thromboplastin time (aPTT) should be monitored.

• **Acute pulmonary embolism**

The dose is 100 mg over two hours.

• **Acute myocardial infarction, front-loading dose (weight-based)**

— For patients who weigh more than 67 kg, the total dose is 100 mg over 1.5 hours; infuse 15 mg over one to two minutes. Infuse 50 mg over 30 minutes. Begin heparin 5,000-10,000 U bolus followed by continuous infusion of 1,000 U/hr. Infuse the remaining 35 mg of alteplase over the next hour.

— For patients who weigh less than 67 kg, the total dose is 1.25 mg/kg; infuse 15 mg IV bolus over one to two minutes. Then infuse 0.75 mg/kg (not to exceed 50 mg) over the next 30 minutes, followed by 0.5 mg/kg over the next 60 minutes (not to exceed 35 mg). Begin heparin 5,000-10,000 U bolus followed by continuous infusion of 1,000 U/hr.

• **Acute ischemic stroke**

The dose should be given within the first three hours of the onset of symptoms. The loading dose is 0.09 mg/kg as a bolus, followed by 0.81 mg/kg as a continuous infusion over 60 minutes. The maximum total dose should not exceed 90 mg.

• **Central venous catheter occlusion**

For patients who weigh 10-30 kg, the dose is 2 mg (1 mg/1 mL) instilled into the occluded catheter. The solution should be allowed to stay in the catheter for 30 minutes. Then catheter function should be assessed by attempting to aspirate blood and catheter contents. If catheter function is not restored, allow the solution to stay in the catheter for 90 additional minutes (120 minutes total). The catheter's functioning should be reassessed after a total of 120 minutes. If catheter function restoration fails, this entire process may be repeated one additional time.

Dosing of alteplase — children

• For pediatric patients older than 2 years of age and weighing 10-29 kg, the dose to be given is 1 mg/1 mL (max dose of 2 mg/2 ml.)

• Pediatric patients older than 2 years of age and weighing 30 kg or more should receive 2 mg/2 mL.

• Alteplase has not been studied in children younger than 2 years of age or weighing less than 10 kg.

Dosing of reteplase — adults

• **Acute myocardial infarction**

— Reteplase is administered as two 10-unit bolus injections each over two minutes. The second dose should be given 30 minutes after initiation of the first injection.

— Reteplase should be given through a line in which no other medications are being administered. Reteplase is incompatible with heparin; therefore, if both drugs are being given to the patient, the line should be flushed before and after reteplase with either 0.9% sodium chloride or 5% dextrose solution.

• **Pulmonary embolism (not FDA-approved)**

Administer 10 U IV over two minutes, wait 30 minutes, and then repeat the dose.

Dosing of reteplase — children

Reteplase is not recommended in children.

Pharmacokinetics

A comparison of the pharmacokinetic parameters for urokinase, alteplase, and reteplase is presented in **Table 1, below**.

Monitoring parameters

• Before therapy begins, baseline levels of hematocrit, platelet count, thrombin time, aPTT, prothrombin time (PT), or fibrinogen should be evaluated.

• To avoid dislodgement of a deep-vein thrombosis, do not take lower-extremity blood pressure.

Table 1: Pharmacokinetic comparison

Kinetic parameter	Urokinase	Alteplase	Reteplase
Onset	Immediate	30 min	30 min
Half-life	10-20 min	26.5 to 46 min	13-16 min
Elimination	Cleared by the liver, with a small amount excreted in urine and bile	Primarily cleared by the liver	Hepatic and renal

• During the infusion, a decrease in plasminogen and fibrinogen (indicating a prolongation in clotting time of coagulation tests) and an increase in fibrinogen degradation products (FDP) generally confirm a lytic state. Therefore, a lytic state can be confirmed by checking fibrinogen (200-400 mg/dL), aPTT (22.5-38.7 seconds), and PT (10.9-12.2 seconds) approximately four hours after starting therapy.

• During therapy, the following should be monitored every eight to 12 hours: CBC, reticulocyte count, platelet count, DIC panel (fibrinogen, plasminogen, FDP, D-dimer, PT, PTT), and thrombosis panel (AT-III, protein C).

• During therapy, the patient should be monitored for signs of bleeding, such as hematuria, gastrointestinal bleeding, gingival bleeding, and stool guaiac.

Contraindications/warnings

Contraindications for thrombolytic therapy are relative, not absolute. Therefore, the benefits and risks of this therapy should be evaluated for each patient. Thrombolytics are contraindicated in the following situations:

• hypersensitivity to a thrombolytic product;
• active internal bleeding;
• surgery or trauma within 10 days;
• intracranial neoplasm;
• arteriovenous malformation, or aneurysm;
• severe uncontrolled hypertension (greater than 180/110 mmHg);
• recent stroke, serious head trauma, or intracranial/intraspinal surgery; and
• pregnancy.

Warnings

• If alteplase is administered three to four hours after a major ischemic stroke, it may cause cerebral edema with fatal brain herniation. Therefore, it is very important that alteplase is administered within three hours of symptom onset.

• If a serious bleed at a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occurs, immediately discontinue the thrombolytic and heparin.

Adverse drug reactions

• **Urokinase**

— More than 10%: Bleeding, arrhythmias, hypotension, periorbital swelling, and dyspnea.

— Less than 1%: Anaphylaxis, bronchospasm, chills, nausea, vomiting, rash, epistaxis, and anemia.

• **Alteplase**

— 1-10%: Bleeding, hypotension, fever, ecchymosis, and nausea and vomiting.

— Less than 1%: Epistaxis, gingival hemorrhage, intracranial hemorrhage, pericardial hemorrhage, retroperitoneal hemorrhage, and allergic reactions.

• **Reteplase**

— More than 10%: Bleeding.

— Less than 1%: Allergic reactions, intracranial hemorrhage, and cholesterol embolization.

Drug interactions

As expected, all three of these drugs interact with other drugs that potentiate the risk of bleeding, such as anticoagulants, antiplatelet agents (acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, dipyridamole, and GP IIb/IIIa inhibitors), low-molecular-weight heparins, and other thrombolytics.

Alteplase has an additional drug-drug interaction with nitroglycerin. Nitroglycerin increases hepatic blood flow, which may decrease alteplase plasma concentrations. This may decrease the efficacy of alteplase and increase the risk of reocclusion of the artery. Concomitant use of alteplase and nitroglycerin should be avoided if possible. If both drugs are necessary, the lowest effective dose of nitroglycerin should be used.

Ways to decrease potential medication errors with thrombolytics

There is a high risk for medication errors with the thrombolytics because each of the agents has a different dosing regimen, complex reconstitution instructions, and specific administration criteria. The following measures may prevent some of these errors:

• multidisciplinary education programs;
• education on differences in dosing;
• stressing that urokinase and reteplase are dosed in units and alteplase is dosed in milligrams;
• education on reconstitution procedures;
• stressing that these agents often are administered as a bolus dose followed by continuous infusion; and
• use of approved protocols.

Clinical trials

Meyerovitz MF, Goldhaber SZ, Reagan K, et al. Recombinant tissue-type plasminogen activator versus urokinase in peripheral arterial and graft occlusions: A randomized trial. *Radiology* 1990; 175:75-78.

Table 2: Results of the Meyerovitz MF, et al study

	No. of patients studied		Cumulative no. of patients with 95% lysis		
Time	rt-PA	Urokinase	rt-PA n = 16	Urokinase n = 16	P-value
Arteriogram at four hours	16	16	4	0	0.10
Arteriogram at eight hours	10	11	7	1	0.04
Arteriogram at 16 hours	1	4	7	3	0.25
Arteriogram at 24 hours	5	10	8	6	0.72

Objective: To compare intra-arterial administration of recombinant-human-tissue-type plasminogen activator (rt-PA) with urokinase in patients with peripheral arterial or bypass graft occlusions.

Study design: A prospective randomized trial of 32 patients with peripheral arterial or bypass graft occlusions. Sixteen patients were randomized to receive rt-PA, and 16 to receive urokinase.

Inclusion criteria: Men or women 18 years of age and older who have a peripheral arterial or bypass graft occlusion as diagnosed by an arteriograph.

Exclusion criteria:

- Active internal bleeding within three weeks
- Recent (within one year) cerebrovascular accident, intracranial or intraspinal surgery, or intracranial neoplasm
- Internal surgery or organ biopsy within 10 days
- Open-heart surgery within three weeks
- "One plus" or more positive occult blood at stool exam
- Severe impairment of hepatic function
- Severe uncontrolled arterial hypertension or diabetic hemorrhagic retinopathy
- Pregnancy or lactation

Endpoints:

- Arteriograms were taken at baseline and at four, eight or 16, and 24 hours. The endpoint was 95% or greater clot lysis.

Treatment regimens:

- The rt-PA dose was given as a 10 mg bolus administered into the thrombus, followed by 5 mg/hr for up to 24 hours.
- The urokinase dose was given as a 60,000 IU bolus administered into the thrombus, followed by 240,000 IU/hr for two hours, 120,000 IU/hr for two hours, and 60,000 IU/hr for up to a maximum of 20 hours.
- Also, all patients received concomitant IV heparin (3,000-5,000 U loading dose followed by 600-1,000 U/hr).

Results: Lysis occurred more rapidly for the rt-PA group at eight hours (P = 0.04). Five rt-PA patients and two urokinase patients experienced major bleeding episodes (P = 0.39). Fibrinogen levels were similar in both groups at baseline (P = 0.79), four hours (P = 0.59), eight hours (P = 0.34), and 16 hours (P = 0.95). However, fibrinogen levels were significantly lower in the rt-PA group than in the urokinase group at 24 hours (P = 0.01).

After completing the study protocol of up to 24 hours of therapy, six urokinase patients and two rt-PA patients received additional therapy in an effort to successfully lyse their clots. The six urokinase patients received an additional 18-72 hours of therapy. Four of these patients achieved successful thrombolysis. The two rt-PA patients did not have successful lysis of their clots after an additional 1-36 hours of therapy.

There was no apparent difference in 30-day clinical success. Additional results of the study are summarized in **Table 2, above**.

Conclusions: The authors concluded that rt-PA and urokinase have similar efficacy at 24 hours of treatment. However, rt-PA did tend to cause more rapid lysis than urokinase. This study also demonstrated that rt-PA tended to cause more bleeding complications than urokinase, although this finding was not statistically significant. Overall, the authors concluded that rt-PA and urokinase yielded similar clinical outcomes.

Limitations and strengths: This unblinded study evaluated a small sample of patients and did not clearly define the inclusion criteria. However, the study was randomized and approved by the Institutional Review Board and the FDA. In addition, written informed consent was obtained from all patients, and baseline characteristics were similar.

Cina CS, Goh R, Chan J, et al. Intra-arterial catheter-directed thrombolysis: Urokinase versus tissue plasminogen activator. *Ann Vasc Surg* 1999; 13:571-575.

Objective: To evaluate whether t-PA and urokinase have similar efficacy and safety in the management of ischemic limbs.

Study design: This prospective cohort study compared catheter-directed fibrinolysis with urokinase and t-PA in the management of limb ischemia. Thirty-four patients received urokinase; 24 patients received t-PA.

Inclusion criteria: Patients with non-embolic limb ischemia of less than three months' duration caused by occlusion of native arteries or bypass grafts.

Exclusion criteria: Exclusion criteria were not included.

Endpoints:

- **Primary:** Angiographic recanalization of the occluded vessel.
- **Secondary:** Duration of the procedure.

Treatment regimens:

- The 150,000 IU bolus dose of urokinase was given over one-half to two hours, followed by continuous infusion of 50,000 IU/hr.
- The 5 mg bolus dose of t-PA was followed by an infusion of 1 mg/hr.
- Also, concomitant heparin was administered at 400 U/hr.

Results:

- **Primary endpoint — T-PA:** 18 of 24 patients had successful recanalizations.
- **Primary endpoint — Urokinase:** 27 of 34 patients had successful recanalizations.
- **Secondary endpoint:** Recanalization was established at an average time of 14.9 hr in the t-PA group and 25.5 hr in the urokinase group (P = 0.009).
- The lowest mean fibrinogen level was not statistically different between the groups (P = 0.3). Also, the risk of death was not significantly different between the groups (P = 0.29).
- There were significantly more major bleeds in the t-PA group than in the urokinase group. Major bleeds occurred in 11 t-PA patients and three urokinase patients (P = 0.0018).

Conclusions: The authors concluded that t-PA and urokinase have similar overall efficacy; however, time to lysis was shorter with t-PA. This study also demonstrated that t-PA had a higher incidence of bleeding complications.

Limitations and strengths: Although the baseline characteristics of this cohort study were similar, inclusion and exclusion criteria were not clearly defined and the sample size was small.

Sugimoto K, Hofmann LV, Razavi MK, et al. The safety, efficacy and pharmacoeconomics of low-dose alteplase compared with urokinase for catheter-directed thrombolysis of arterial and venous occlusions. *J Vasc Surg* 2003;37:512-517.

Objective: To compare the efficacy, complications, and costs associated with low-dose (less than 2 mg/hr) alteplase vs. urokinase for catheter-directed treatment of acute peripheral arterial occlusive disease and deep-vein thrombosis.

Study design: This retrospective review evaluated 89 patients with 93 involved limbs that were treated with either t-PA with subtherapeutic heparin or urokinase with full heparin at a single center.

Inclusion criteria:

- Acute limb ischemia (less than 14 days)
- Acute symptomatic deep-vein thrombosis (up through 30 days)

Exclusion criteria: Exclusion criteria were not defined.

Endpoints: Success rates, complications, infusion time, and costs were included as endpoints.

Treatment regimen:

- The urokinase dose was typically 120,000 IU/hr (range: 50,000-240,000 IU/hr). Full-dose heparin was given to maintain the partial thromboplastin time at 1.5-2 times the baseline.

Table3: Results

	Overall average hourly infused dose	Total dose	Infusion time*	Success rates	Cost*	Major/minor complications
t-PA	0.86 ± 0.50 mg/hr	21.2 ± 15.1 mg	24.6 ± 11.2 hours	89.4%	$466 ± $331	2.2%/6.9%
Urokinase	13.5 ± 5.6 (10^6) IU/hr	4.49 ± 2.39 (10^6) IU/hr	33.3 ± 13.3 hours	85.7%	$6,871 ± $3,867	2.1%/10.4%

* $P < 0.05$ for infusion time and cost

• The t-PA dose was typically 0.5 mg/hr for peripheral arterial occlusive disease and 1.0 mg/hr for deep-vein thrombosis (range: 0.25-2.0 mg/hr). Subtherapeutic heparin was administered to maintain the partial thromboplastin time at less than 1.5 times the baseline.

Results: Results of the Sugimoto et al study are presented in **Table 3, p. 6**.

Conclusions: The authors concluded that low-dose t-PA with sub-therapeutic heparin and urokinase with full-dose heparin are similar in safety and efficacy. However, t-PA was found to act significantly faster and was less expensive than urokinase.

Limitations: This retrospective review was neither blinded nor randomized and included a small sample size.

Studies comparing urokinase and alteplase

Recently, urokinase returned to the market, and its place in therapy must be re-established. Eleven trials were identified that have compared urokinase and alteplase for use in peripheral arterial occlusive disease. Most of these trials were small and not blinded. The majority of these trials demonstrated that urokinase and alteplase have similar efficacy and safety for the treatment of peripheral arterial occlusive disease. A number of trials have demonstrated similar rates of bleeding for both urokinase and alteplase. Some studies found that alteplase had a greater risk of bleeding than urokinase; however, these trials are small, and, in some cases, this finding could be due to the use of larger doses of alteplase. One trial reported more bleeding complications with urokinase than with alteplase; however, the statistical significance was not stated. Most of the studies found that alteplase acts more rapidly than urokinase.

Three trials evaluated the cost of thrombolytics, and all three found that alteplase is less expensive than urokinase. Two of the trials also evaluated length of stay and found that alteplase decreased length of stay and therefore decreased cost. Most of the trials comparing urokinase and alteplase have several limitations, including small sample size, lack of blinding and randomization, and vague inclusion and exclusion criteria.

The FDA has approved urokinase and alteplase for use in acute pulmonary embolism. Three randomized clinical trials have compared t-PA and urokinase for pulmonary embolism. All three of these trials demonstrated similar safety and efficacy between these two agents for pulmonary embolism. These studies also found that alteplase acts more rapidly; however, one study demonstrated that a novel dosing regimen of urokinase (3 million IU/2 hrs, with the initial 1 million IU given as a bolus over 10 minutes) resulted in no significant difference in lysis at two hours vs. alteplase. As in the studies conducted to evaluate peripheral arterial occlusive disease, these studies have several limitations, including small sample size and vague inclusion and exclusion criteria. To date, no large randomized blinded clinical trials exist to compare available thrombolytics for peripheral arterial occlusive disease or pulmonary embolism.

Conclusion

It is difficult to draw definite conclusions about the differences in safety and efficacy of alteplase and urokinase because the comparative trials are so dissimilar. The trials are hard to compare because they have inconsistent study designs, various dosing regimens and administration techniques, and different safety and efficacy endpoints. Nonetheless, the literature that is available appears to demonstrate similar efficacy and safety between low-dose alteplase and urokinase for peripheral arterial occlusive disease and pulmonary embolism. In the future, it would be beneficial to have larger randomized blinded trials to lend more support to this conclusion.

As for reteplase, at this time there are few studies available evaluating its use for peripheral arterial occlusion, and no literature is available for its use in the treatment of pulmonary embolism. One retrospective cohort study found that reteplase had a satisfactory efficacy and safety profile in the treatment of peripheral arterial occlusive disease. However, controlled clinical trials are needed to compare different regimens of reteplase and to compare reteplase to different thrombolytics.

Based on the available data, alteplase appears to be the best initial choice for treatment of peripheral arterial occlusive disease and pulmonary embolism, due to the advantages of more rapid lysis and decreased expense. If the maximum dose of alteplase recommended by the SCVIR for peripheral arterial occlusive disease fails, then urokinase is a viable alternative. Urokinase also is an alternative agent for pulmonary embolism.

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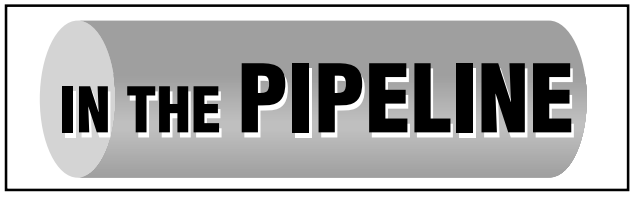

• Medarex has announced that its licensee, Novartis Pharma AG, has commenced Phase I clinical trials of a fully human antibody product candidate for the treatment of **autoimmune disease**.

• Oncolytics Biotech has resumed enrollment in the Phase I component of its clinical study examining the use of Reolysin, its formulation of the human reovirus, in the treatment of **recurrent malignant glioma**.

• Sangart has initiated its Phase Ib/II clinical trial for Hemospan (MP4), an **oxygen transport** agent, at the Karolinska Hospital in Stockholm, Sweden. This clinical trial will include 30 patients undergoing elective orthopedic surgeries.

• Repligen Corp. has announced plans to conduct a clinical trial to evaluate RG1068, synthetic human secretin, in patients with **schizophrenia**. The objective of the trial is to determine if the improvements in social interaction found in a Phase II study of secretin in autism can be replicated in patients with schizophrenia who have significant social deficits.

• Isis Pharmaceuticals has initiated a Phase I clinical trial of ISIS 113715 for **Type 2 diabetes**. ISIS 113715 is a second-generation antisense drug designed to improve defective insulin signaling by targeting the gene PTP-1B.

• The FDA has granted investigational drug VG1000, manufactured by Virogenomics, orphan drug status for the treatment of **multiple sclerosis**.

• Hybridon has initiated a Phase I clinical trial of HYB2055, the company's second-generation immunomodulatory oligonucleotide, in patients with **malignant solid tumors**.