VITALS

Major Finding: A majority (57%) of adults taking insulin for diabetes said they intentionally skipped an insulin injection occasionally and 20% did so regularly.

Data Source: Online survey with 502 participants in a sample weighted to be representative of insulin-using U.S. adults with diabetes.

Disclosures: Patton Medical Devices, which makes an insulin injection device, funded the study. Some of the investigators own stock in and have been advisers to the company.

Half of Adults With Diabetes Intentionally Skip Insulin Injections

BY SHERRY BOSCHERT

Most adults with type 1 or type 2 diabetes intentionally skip insulin injections, and 20% skip them regularly, according to an online survey of 502 diabetic adults.

The study is one of the first to identify factors that were associated with a greater likelihood of purposefully omitting insulin shots at least occasionally, as 57% of respondents reported doing. The 388 respondents with type 2 diabetes were more likely to report intentional omissions of insulin, compared with the 114 with type 1 diabetes, according to the report published online Jan. 26 (Diabetes Care 2010;33:240-5).

Respondents who were more likely to skip insulin injections were younger, were students, had lower household incomes, had higher education levels, or did not eat a healthy diet. Skipping insulin also was more likely among those who either had to take more daily injections, said the injections interfered with daily activities, or reported pain

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TWYNSTA®
(telmisartan/amlodipine) tablets
40/5 • 40/10 • 80/5 • 80/10 mg

WARNING: AVOID USE IN PREGNANCY
When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, TWYNSTA tablets should be discontinued as soon as possible. *See Warnings and Precautions.*

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Twynsta® (telmisartan/amlodipine) tablets are indicated for the treatment of hypertension, alone or with other antihypertensive agents.

TWYNSTA tablets may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

Base the choice of TWYNSTA tablets as initial therapy for hypertension on an assessment of potential benefits and risks including whether the patient is likely to tolerate the starting dose of TWYNSTA tablets.

Consider the patient's baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared with monotherapy when deciding whether to use TWYNSTA tablets as initial therapy.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Fetal/Neonatal Morbidity and Mortality

Telmisartan

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, discontinue TWYNSTA tablets as soon as possible [*see Boxed Warning*].

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Inform mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester that most reports of fetal toxicity have been associated with second or third trimester exposure. Nonetheless, when patients become pregnant or are considering pregnancy, physicians should have the patient discontinue the use of TWYNSTA tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, TWYNSTA tablets should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Hypotension

Telmisartan

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with TWYNSTA tablets. Either correct this condition prior to administration of TWYNSTA tablets, or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Amlodipine

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, observe patients with severe aortic stenosis closely when administering amlodipine, as one should with any vasodilator.

Hyperkalemia

Telmisartan

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

Patients with Impaired Hepatic Function

Telmisartan

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients.

Amlodipine

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine at 2.5 mg in patients with hepatic impairment. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in hepatically impaired patients.

Renal Function Impairment

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function.

The ONTARGET trial enrolled 25,620 patients ≥55 years old with atherosclerotic disease or diabetes with end-organ damage, randomized them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of telmisartan and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of telmisartan and ramipril is not recommended.

Risk of Myocardial Infarction or Increased Angina

Amlodipine

Uncommonly, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Heart Failure

Amlodipine

Closely monitor patients with heart failure.

Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsening of heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. In the PRAISE-2 study, 1654 patients with NYHA class III (80%) or IV (20%) heart failure without evidence of underlying ischemic disease, on stable doses of ACE inhibitor (99%), digitalis (99%), and diuretics (99%) were randomized 1:1 to receive placebo or amlodipine and followed for a mean of 33 months. While there was no statistically significant difference between amlodipine and placebo in the primary endpoint of all cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine), there were more reports of pulmonary edema in the patients on amlodipine.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

TWYNSTA Tablets

The concomitant use of telmisartan and amlodipine has been evaluated for safety in more than 3700 patients with hypertension; approximately 1900 of these patients were exposed for at least 6 months and over 160 of these patients were exposed for at least one year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

In the placebo-controlled factorial design study, the population treated with a telmisartan and amlodipine combination had a mean age of 53 years and included approximately 50% males, 79% were Caucasian, 17% Blacks, and 4% Asians. Patients received doses ranging from 20/2.5 mg to 80/10 mg orally, once daily.

The frequency of adverse reactions was not related to gender, age, or race.

The adverse reactions that occurred in the placebo-controlled factorial design trial in ≥2% of patients treated with TWYNSTA and at a higher incidence in TWYNSTA-treated patients (n=789) than placebo-treated patients (n=46) were peripheral edema (4.8% vs 0%), dizziness (3.0% vs 2.2%), clinically meaningful orthostatic hypotension (defined as a decrease in DBP >10 mmHg and/or decrease in SBP >20 mmHg) (6.3% vs 4.3%), and back pain (2.2% vs 0%). In addition, other adverse reactions that occurred in more than 1% of the patients treated with TWYNSTA tablets (n=789) were dizziness (2.0% vs 2.2% on placebo) and headache (1.4% vs 4.3% on placebo).

In the placebo-controlled factorial design trial, discontinuation due to adverse events occurred in 2.2% of all treatment cells of patients in the telmisartan/amlodipine-treated patients and in 4.3% in the placebo-treated group. The most common reasons for discontinuation of therapy with TWYNSTA tablets were peripheral edema, dizziness, and hypotension (each ≤0.5%).

Peripheral edema is a known, dose-dependent adverse reaction of amlodipine, but not of telmisartan. In the factorial design study, the incidence of peripheral edema during the 8 week, randomized, double-blind treatment period was highest with amlodipine 10 mg monotherapy. The incidence was notably lower when telmisartan was used in combination with amlodipine 10 mg.

Table 1: Incidence of Peripheral Edema during the 8 Week Treatment Period

		Telmisartan		
		Placebo	40 mg	80 mg
Amlodipine	Placebo	0%	0.8%	0.7%
	5 mg	0.7%	1.4%	2.1%
	10 mg	17.8%	6.2%	11.3%

Telmisartan

Telmisartan has been evaluated for safety in more than 3700 patients, including 1900 treated for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20-160 mg) monotherapy for up to 12 weeks, an overall incidence of adverse events was similar to the patients treated with placebo.

Adverse events occurring at an incidence of ≥1% in patients treated with telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 2.

Table 2: Adverse Events Occurring at an Incidence of ≥1% in Patients Treated with Telmisartan and at a Greater Rate than Patients Treated with Placebo

	Telmisartan (n=1455) %	Placebo (n=380) %
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to the adverse events in the table, the following events occurred at a rate of ≥1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy due to adverse events was required in 2.8% of 1455 patients treated with telmisartan tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in >0.3% of 3500 patients treated with telmisartan monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to telmisartan tablets: *Autonomic Nervous System:* impotence, increased sweating, flushing; *Body as a Whole:* allergy, fever, leg pain, malaise; *Cardiovascular:* palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; *CNS:* insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia; *Gastrointestinal:* flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders; *Metabolic:* gout, hypercholesterolemia, diabetes mellitus; *Musculoskeletal:* arthritis, arthralgia, leg cramps; *Psychiatric:* anxiety, depression, nervousness; *Resistance Mechanism:* infection, fungal infection, abscess, otitis media; *Respiratory:* asthma, bronchitis, rhinitis, dyspnea, epistaxis; *Skin:* dermatitis, rash, eczema, pruritus; *Urinary:* micturition frequency, cystitis; *Vascular:* cerebrovascular disorder; and *Special Senses:* abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings

In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan tablets.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

or embarrassment from the injections.

Physicians should work with patients to discover their issues around injecting insulin and give them the information or tools they need to overcome some of these barriers, suggested Mark Peyrot, Ph.D., of the department of sociology, Loyola University Maryland, Baltimore, and his associates.

Insulin pens, finer-gauge needles, injection ports, needle-free injectors, and other device-related strategies can reduce pain or embarrassment. "However, we have found that patients do not feel that their health care providers are giving them adequate assistance in managing these problems, even when they raise the issue with their providers," the investigators wrote.

Risk factors for intentionally skipping insulin injections differed for patients with type 1 and type 2 diabetes, separate analyses found. In respondents with type 1 diabetes, lack of a healthy diet, the number of daily insulin injections, and interference with daily activities were significantly associated with skipping insulin. In those with type 2 diabetes, age, education, income, pain, and embarrassment played greater roles in the risk for skipping insulin.

The investigators noted that insulin is used by more than 25% of people in the United States who have diabetes. Non-adherence with insulin regimens has been associated with higher hemoglobin A_{1C} levels and higher rates of hospitalization for diabetes-related complications.

Race and ethnicity were not associated with a likelihood of skipping insulin, contrary to findings in other studies, perhaps because the study controlled for the effects of income and education, or perhaps because the study did not have enough nonwhite participants. Whites comprised 73% of survey respondents, who were recruited by e-mail from the Harris Interactive Chronic Illness Panel.

Also contrary to some previous studies of adherence to insulin regimens, the current study found no significant association between omission of insulin and a history of depression, which surprised the investigators. This may be because the survey did not assess current depression.

Disabled respondents were less likely to skip an insulin injection, perhaps because they get more assistance with care or make a greater effort to attend to their health, the investigators speculated. They were not surprised that poor adherence with a healthy diet was associated with skipping insulin, as this has been reported before.

The survey's results suggest that intentional omission of insulin is a sub-

Patients in the United States are less convinced of insulin's effectiveness and more likely to blame themselves for needing it, compared with patients in other countries.

stantial problem, Katie Weinger, Ed.D., and Elizabeth A. Beverly, Ph.D., wrote in an editorial accompanying the report (Diabetes Care 2010;33:450-2).

The findings support previous studies that reported low levels of adherence to insulin regimens—intentional or not—in 59%-77% of patients with diabetes.

U.S. physicians are more likely than are doctors in other countries to delay prescribing insulin, and U.S. patients are less convinced of insulin's effectiveness and more likely to blame themselves for needing it, compared with patients in other countries, Dr. Weinger and Dr. Beverly noted. Physicians need to examine their own reluctance to initiate insulin and work with patients around these factors and the ones identified in Dr. Peyrot's study to minimize omission of insulin when needed, they suggested.

The few previous studies of reasons that patients skip insulin injections have focused mainly on patients with type 1 diabetes, especially on an association between eating disorders and insulin omission. The current study shows that not all insulin omission is motivated by desire to lose weight in patients with type 1 diabetes. It's unclear whether patients with type 2 diabetes think that skipping insulin will reduce weight.

Weight concerns were not addressed in the study. Neither were some other important issues, said Dr. Weinger, a researcher in the department of psychiatry at Harvard University, Boston, and Dr. Beverly, a researcher at the Joslin Diabetes Center, Boston. These issues include self-care behaviors, and the impact of insulin delivery systems. Nonetheless, the study provides an important look at the avoidance of insulin therapy. ■