Gastric Bypass Helpful in Nonalcoholic Fatty Liver

BY MICHELE G. SULLIVAN

Mid-Atlantic Bureau

CAMBRIDGE, MD. — Gastric bypass surgery can improve liver pathology in patients who have been diagnosed with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, Dr. Kris V. Kowdley said at a hepatobiliary update sponsored by Johns Hopkins University.

Some researchers have expressed concerns that the dramatic and rapid weight loss associated with gastric bypass surgery could actually exacerbate nonalcoholic fatty liver disease (NAFLD), but that "clearly is not the case," said Dr. Kowdley of the University of Washington, Seattle.

Two recent studies support the beneficial effect of gastroplasty on this spectrum of liver pathology. A 2004 study included 23 patients with nonalcoholic steatohepatitis (NASH) and 12 with simple steatosis. Liver biopsies were obtained from all patients about 2 years after surgery. There were major improvements in lobular steatosis, necroinflammatory changes, and fibrosis; only four patients still fulfilled the criteria for NASH. Improvements were most pronounced in those with metabolic syndrome (Hepatology 2004;39:1647-54).

A 2005 study examined the results of gastric bypass in 16 patients whose mean presurgery weight was 334 pounds. A follow-up liver biopsy was performed about 1 year later. Steatosis had improved in 15 patients, with resolution in 13. Of 15 patients who had inflammation at baseline, 12 showed improvement, and 12 of 14 showed less ballooning. Six of 14 patients with perisinusoidal fibrosis and 6 of 13 with portal fibrosis showed improvement. No patient had worsening of steatosis, inflammation, ballooning, or fibrosis (Obes. Res. 2005;13:1180-6).

NAFLD is part of a histopathologic spectrum of liver injury that ranges from simple steatosis to necroinflammatory changes that may progress to cirrhosis. NASH is associated with increased risk of hepatocellular cancer and liver-related death.

The etiology of these disorders is poorly understood but is thought to be a "twohit" process beginning with fat accumulation in the liver, most often in the presence of obesity, insulin resistance, or type 2 diabetes. "The 'second hit' is presumed to be any number of processes that contribute to oxidative injury in the liver," Dr. Kowdley said, and could include ox-

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idative stress that interferes with mitochondrial function.

Most patients with NAFLD are asymptomatic; their disease is discovered screening tests identify abnormal liver function. Many are obese; studies

suggest that about 30% of patients who undergo gastric bypass have the disease. But the pattern of fat deposition is perhaps more important than the patient's weight, Dr. Kowdley said; NAFLD is highly associated with truncal obesity.

On ultrasound, the fatty liver typically appears diffusely hyperechoic in relation to the spleen and kidneys. Computed tomography and magnetic resonance imaging may show focal fat deposits. However, a liver biopsy is the most sensitive and specific means of diagnosis and can differentiate simple steatohepatitis from more advanced stages of the disease in which fibrosis may be present.

There are no approved pharmacologic therapies for NAFLD. Several drugs are under investigation, including metformin and thiazolidinediones.

Weight loss is one highly recommended method of dealing with NAFLD," Dr. Kowdley said. "Even a modest amount of weight loss, say 20 pounds, significantly decreases the fasting insulin level and improves liver enzymes, and those improvements are maintained as long as weight loss is maintained. A 40% reduction from initial alanine aminotransferase levels can

All patients with NAFLD should be counseled to lose weight through a combination of diet and exercise. Those with a body mass index (BMI) greater than 30 kg/m² or greater than 27 with additional liver disease risk factors, might benefit from the addition of orlistat (Xenical) or sibutramine (Meridia).

Lunesta

INDICATIONS AND USAGE
LUNESTA is indicated for the treatment of insomnia. In controlled outpatient and sleep
laboratory studies, LUNESTA administered at bedtime decreased sleep latency and

WARNINGS
Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including LUNESTIA. Beasuse some of the important adverse effects of LUNESTA appear to be dose-related, it is important to use the lowest possible effective dose, sepecially in the elderly (see DOSAGE AND ADMINISTRATION in the Full Prescribing Information).

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seem out of character, similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, halluciations, and depersonalization. Annesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

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can rarely be determined with certainty whether a particular instance of the abnoral behaviors listed above are drug-induced, spontaneous in origin, or a result of an
aderying psychiatric or physical disorder. Nonetheless, the emergence of any new
ehavioral sign or symptom of concern requires careful and immediate evaluation.

Following rapid dose decrease or abrupt discontinuation of the use of sedative/hyp notics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see **DRUG ABUSE AND DEPENDENCE**)

Ing known CNS-depressant effects.

Uses In Patients With Depression: Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time. Information For Patients: Patient information is printed in the complete prescribing

information.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions

CNIS-Active Drugs

Ethanot. An additive effect on psychomotor performance was seen with coadministration of eszopicione and ethanol 0.70 g/kg for up to 4 hours after ethanol administration. tion of eszopiclone and ethanol 0.70 g/kg for up to 4 hours after ethanol administration. Paroxetine: Coadministration of single doses of eszopiclone 3 mg and paroxetine 20 mg dally for 7 days produced no pharmacokinetic or pharmacodynamic interaction. Lorazepam: Coadministration of single doses of eszopiclone 3 mg and lorazepam are mg did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of either drug.

Olanzapine: Coadministration of eszopiclone 3 mg and olanzapine 10 mg produced a decrease in DSST scores. The interaction was pharmacodynamic; there was no alteration in the pharmacokinetics of either drug.

Drugs That Inhibit CYP3A4 (Retoconazole): CYP3A4 is a major metabolic pathway for elimination of eszopiclone. The AUC of eszopiclone was increased 2.2-fold by coadministration of ketoconazole, a potent inhibitor of CYP3A4, 40 mg dally for 5 days. C_{mg} and t₁₀ were increased 1.4-fold and 1.3-fold, respectively. Other strong inhibitors of CYP3A4 (g., litraconazole, clanithromycin, nelazodone, troleandomycin, ritonavir, nelfinavir) would be expected to behave similarly.

Purgs That Induce CYP3A4 (Rifiampicin): Racemic zopiclone exposure was

Drugs That Induce CYP3A4 (Ritamplician): Racemic zopiclone exposure was decreased 80% by concomitant use of ritampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone.

Infinite intervention to expected with exaceptations in a not highly bound to plasma proteins (52-59% bound); therefore, the disposition of eszopiclone is not expected to be sensitive to alterations in protein binding. Administration of eszopiclone 3 mg to a patient taking another drug that is highly protein-bound would not be expected to cause an alteration in the free concentration of either drug.

In 25 mg daily for the next 6 days.

rdarin: Eszopiclone 3 mg administered daily for 5 days did not affect the pharmainetics of (R)- or (S)-warfarin, nor were there any changes in the pharmaonic profile (prothrombin time) following a single 25-mg oral dose of warfarin.

cinogenesis: Mutagenesis, Impairment of Fertillity

cinogenesis: In a carcinogenicity study in Sprague-Dawley rats in which eszopine was given by oral gavage, no increases in tumors were seen; plasma levels

(G) of eszopiclone at the highest dose used in this study (16 mg/kg/day) are estited to be 80 (females) and 20 (males) times those in humans receiving the maxum recommended human dose (MRHD). However, in a carcinogenicity study in

Sprague-Dawley rats in which racemic zopicione was given in the diet, and in which plasma levels of eszopicione were reached that were greater than those reached in the above study of eszopicione, an increase in mammary gland adenocarcinomas in males were seen at the highest dose of 100 mg/kg/dsy, Plasma levels of eszopicione at this dose are estimated to be 150 (females) and 70 (males) times those in humans receiving the MRHD. The mechanism for the increase in mammary adenocarcinomas is unknown. The increase in thyroid tumors is thought to be due to increased levels of TSH secondary to increased metabolism of circulating thyroid hormones, a mechanism that is not considered to be relevant to humans.

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In a carcinogenicity study in B6GSF mice in which racemic zopiclone was given in the diet, an increase in pulmonary carcinomas and carcinomas plus adenomas in females and an increase in skin fibromas and sarcomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 8 (females) and 20 (males) times those in humans receiving the MRHD. The skin tumors were due to skin lesions induced by aggressive behavior, a mechanism that is not relevant to humans. A carcinogenicity study was also performed in which CD-1 mice were given eszopiclone at doses up to 100 mg/kg/day by oral gavage; although this study did not reach a maximum tolerated dose, and was thus inadequate for overall assessment of carcinogenic potential, no increases in either pulmonary or skin tumors were seen at doses producing plasma levels of eszopiclone estimated to be 90 times those in humans receiving the MRHD—i.e., 12 times the exposure in the racemate study.

Eszopiclone did not increase tumors in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

Mutagenesis: Eszopiclone was positive in the mouse lymphoma chromosomal aberration assay and produced an equivocal response in the Chinese hamster ovary ell chromosomal aberration assay, it was not mutagenic or clastogenic in the bacterial Arnes gene mutation assay, in an unscheduled DNA synthesis assay, or in an in vivo mouse bone marrow micronucleus assay.

micronucleus assay.

Impairment Of Fertility: Eszopicione was given by oral gavage to male rats at doses up to 45 mg/kg/day from 4 weeks premating through mating and to female rats at doses up to 180 mg/kg/day from 2 weeks premating through day 7 of pregnancy. An additional study was performed in which only females were treated, up to 180 mg/kg/day. Eszopicione decreased fertility, probably because of effects in both males and females, with no females becoming pregnant when both males and females were treated with the highest dose; the no-effect dose in both sexes was 5 mg/kg (16 times the MRHD on a mg/m² basis). Other effects included increased preimplantation loss (no-effect dose 25 mg/kg), ahnormal estrus cycles (no-effect dose 25 mg/kg), and decreases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

function in the offspring.
There are no adequate and well-controlled studies of eszopiclone in pregnant women.
Eszopiclone should be used during pregnancy only if the potential benefit justifies the
potential risk to the fetus.
Labor And Delivery: LUNESTA has no established use in labor and delivery.
Mursing Mothers: It is not known whether LUNESTA is excreted in human milk.
Because many drugs are excreted in human milk, caution should be exercised when
LUNESTA is administered to a nursing woman.

Positistic like Scales and Affectiveness of eszopichora in children below the area of 18

Pediatric Use: Safety and effectiveness of eszopiclone in children below the age of 18 have not been established.

trolled clinical trials who received eszopicione were 65 to 86 years of age. The over-all pattern of adverse events for elderly subjects (median age = 71 years) in 2-week studies with injoittime dosing of 2 mg eszopicione was not different from that seen in younger adults. LUNESTA 2 mg exhibited significant reduction in sleep latency and improvement in sleep maintenance in the elderly population. ANYERS FRACTIONS

weginis, lauviatily arialyses, and tock. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tabulations that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while the patient was receiving therapy following baseline evaluation.

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Adverse Findings Observed in Placebo-Controlled Trials

Adverse Events Resulting in Discontinuation of Treatment: In placebo-controlled, parallel-group clinical trials in the elderly, 3.8% of 208 patients who received placebo, 2.3% of 215 patients who received 2 mg LUNESTA, and 1.4% of 72 patients who received 1 mg LUNESTA discontinued treatment due to an adverse event. In the 6-week parallel-group study in adults, no patients in the 3 mg arm discontinued because of an adverse event. In the long-term 6-month study in adult insomnia patients, 7.2% of 195 patients who received placebo and 12.8% of 593 patients who received 3 mg LUNESTA discontinued due to an adverse event. No event that resulted in discontinuation occurred at a rate of greater than 2%.

Adverse Events Observed at an Incidence of ≥2% in Controlled Trials. The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from a Phase 3 placebo-controlled study of LUNESTA at doses of 2 or 3 mg in non-elderly adults. Treatment duration in this trial was 44 days. Data are illimited to adverse events that occurred in 2% or more of patients treated with LUNESTA at Mase greater than the incidence in placebo-treated patients (n=99)!

Body as a whole; headache (13%, 21%, 17%), viral infection (1%, 3%, 3%). Digestive system; dry mouth (3%, 5%, 7%), dyspepsia (4%, 4%, 5%), nausea (4%, 5%, 4%), 000; somnolence (3%, 10%, 8%), depression (0%, 4%, 1%), dizziness (4%, 5%, 7%), hallucinations (0%, 1%, 3%), librocomiting (1%, 3%, 4%), by Special senses: unpleasant taste (3%, 17%, 5%, 0%), somnolence (3%, 10%, 5%, 6%), Osperosion (0%, 4%, 1%), dizziness (4%, 5%, 7%), hallucinations (0%, 1%, 3%), librocomitial system. dysmenorrhea (0%, 3%, 0%, 0%), evenousness (3%, 5%, 0%), somnolence (3%, 10%, 5%, 6%), Special senses: unpleasant taste (3%, 17%, 34%). Urgenital system.

*Gender-specific adverse event in females **Gender-specific adverse event in males

patients!

Body as a whole: accidental injury (1%, 0%, 3%), headache (14%, 15%, 13%), pair (2%, 4%, 5%), Digestive system: diarrhea (2%, 4%, 2%), dry mouth (2%, 3%, 7%) dyspepsia (2%, 6%, 2%), hervous system; abnormal treams (0%, 3%, 1%), dizzness (2%, 1%, 6%), nervousness (1%, 0%, 2%), neuralgia (0%, 3%, 0%), Skin and appendages; purifus: (1%, 4%, 1%). Special senses; unpleasant taste (0%, 8%, 12%), Urgential system; unpressent taste (0%, 8%, 12%), treaming the control of the cont

ins involving uniferial treatments, uses, and investigators. ited figures, however, do provide the prescribing physician with some basi ating the relative contributions of drug and non-drug factors to the ad-incidence rate in the population studied.

estiliating the relative contributions of utiling and innorming factors to the adverse event incidence rate in the population studied.

Other Events Observed During The Premarketting Evaluation Of LUNESTA. Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section and reported by approximately 1550 subjects treated with LUNESTA at doses in the range of 1 to 3.5 mg/day during Phase 2 and 3 clinical trials throughout the United States and Canada. All reported events are included except those already listed here or listed desewhere in labeling, minor events common in the general population, and events unlikely to be drug-related. Although the events reported occurred during treatment with LUNESTA, they were not necessarily caused by it.

Events are listed in order of decreasing frequency according to the following definitions: frequent adverse events are those that occurred in fewer than 1/100 patients; infrequent adverse events are those that occurred in fewer than 1/100 patients infrequent adverse events are actegorized based on their incidence for the appropriate gender.

Frequent: Chest pain, migraine, peripheral edema.

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LUNESTA or any other hypnotic.

Tolerance: Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use of these drugs for a few weeks. No development of tolerance to any parameter of sleep measurement was observed over six months. Tolerance to the efficacy of LUNESTA 3 mg was assessed by 4-week objective and 6-week subjective measurements of time to sleep onset and sleep maintenance for LUNESTA in a placebo-controlled 4-day study, and by subjective measurements of time to sleep onset and WASO in a placebo-controlled study for 6 months.

OVERDOSAGE

There is limited premarketing clinical experience under the controlled study for 6 months.

onen associated with overtuose with other CNS-depressant agents. Recommended Treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. The value of dialysis in the treatment of overdosage has not been determined.

Poison Control Center: As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdosage.

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