CLINICAL

Benefits of Moderate Drinking

Moderate alcohol consumption is associated with an approximately 30% reduction in the risk of type 2 diabetes in women and men, regardless of body mass index, reported Lando L.J. Koppes, Ph.D., of the Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam.

In a metaanalysis of 15 prospective cohort studies of 11,959 incident cases of type 2 diabetes among 369,862 adults, light drinkers (<6 g/day of alcohol) had a 0.87 relative risk (RR) of type 2 diabetes, similar to the

CAPSULES

1.04 RR of heavy drinkers >48 g/day of alcohol). Moderate drinkers fared better (0.70 for 6-12 g/day of alcohol, 0.69 for 12-24 g/day, 0.72 for 24-48 g/day).

The researchers found no sex differences in RR for diabetes, except for alcohol consumption of 6-12 g/day (0.80 for men, 0.59 in women). In the six studies that reported body mass index, it was not related to RR for diabetes (Diabetes Care 2005;28:719-25).

Decline in Life Expectancy?

Life expectancy may decline because of the

obesity epidemic, with important implications for the solvency of age-entitlement programs, said S. Jay Olshansky, Ph.D., of the University of Illinois at Chicago.

Obesity prevalence in adults increased by about 50% per decade in the 1980s and 1990s, the investigators reported. Today, two-thirds of adults are obese or overweight, with 34% of women, 28% of men, and nearly 50% of black women classified as obese. Evidence suggests that disabilitv rates have risen as fitness levels have declined, and this has occurred at younger ages they added (N. Engl. J. Med. 2005:352:1138-45).

Obesity has been shown to reduce life

expectancy by an estimated 5-20 years, Dr. Olshansky said. "If left unchecked, the rising prevalence of obesity that has already occurred in the past 30 years is expected to lead to an elevated risk of a range of fatal and nonfatal conditions for these cohorts as they age." If the trend continues, especially at younger ages, the negative effect on longevity "could be much worse."

The obesity epidemic's impact could improve the solvency of Social Security, but the cost of treating related illnesses may increase the burden on Medicare, they said.

Relatives of Type 2 Diabetics

Lifestyle interventions can significantly improve risk factors associated with insulin resistance and cardiovascular disease in healthy first-degree relatives (FDRs) of patients with type 2 diabetes, according to Hilde K. Brekke of Sahlgrenska Academy at Göteburg University, Sweden.

In a 16-week study of 72 nondiabetic FDRs aged 25-55 years, 25 patients were assigned to the diet-only group, 25 were in the diet-and-exercise group, and 22 controls were told to continue their current lifestyle. Group nutrition counseling was given twice, with telephone follow-up every 10 days, to the two groups with a diet component. The exercise goal was to increase physical activity for at least 30 minutes, 4-5 times per week.

In the diet-only group, total cholesterol was reduced significantly by 0.31 mmol/L, LDL cholesterol was reduced by 0.22 mmol/L, and apolipoprotein B was reduced by 9.5 mg/dL on average, compared with controls. The diet-and-exercise group had significant reductions in body weight (2.1%) and waist circumference (3.0 cm), compared with controls (Diabetes Res. Clin. Pract. 2005;68:18-28).

The diet-and-exercise group also had a significant 13% reduction in fasting insulin, compared with controls, but both the diet-only and diet-and-exercise groups showed no significant changes in fasting glucose, insulin or insulin sensitivity index. A subgroup of 13 patients who were particularly compliant with dietary goals and exercise targets had significantly improved insulin sensitivity index and lipid profiles.

Leukemia Drug and Diabetes

Imatinib (Gleevec), an antineoplastic agent used to treat chronic myeloid leukemia, may help to put type 2 diabetes mellitus in regression, according to Dino Veneri, M.D., of the University of Verona (Italy).

The investigators reported on a 70-yearold woman with an 8-year history of type 2 diabetes who was diagnosed with chronic myeloid leukemia. She began imatinib 400 mg/day, which resulted in hematologic remission 2 months later. Her blood glucose levels declined during treatment, and insulin was discontinued 3 months after her leukemia was diagnosed. Regression of diabetes was confirmed over the following months. "During the past year, the patient's diet, physical activity, and weight have not changed, and she has not taken any medication known to affect glucose metabolism," Dr. Veneri said (N. Engl. J. Med. 2005;352:1049-50).

Imatinib inhibits phosphorylation, which may improve signaling and the function of effectors such as enzymes; this may enhance insulin sensitivity.

—Kevin Folev

BONIVA® (ibandronate sodium) TABLETS BRIEF SUMMARY CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

- CONTRAINDICATIONS

 Known hypersensitivity to BONIVA or to any of its excipients

 Uncorrected hypocalcemia (see PRECAUTIONS: General)

 Inability to stand or sit upright for at least 60 minutes
 (see DOSAGE AND ADMINISTRATION)

WARNINGSBONIVA, like other bisphosphonates administered orally may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see **PRECAUTIONS**). PRECAUTIONS: General

PRECAUTIONS: General

Mineral Metabolism: Hypocalcemia and other disturbances of bone and mineral
metabolism should be effectively treated before starting BONIVA therapy. Adequate
intake of calcium and vitamin D is important in all patients.

Upper Gastriontestinal Effects: Bisphosphonates administered orally have been
associated with dysphagia, esophagitis, and esophageal or gastric ubers. This
association has been reported for bisphosphonates in postmarketing experience but
has not been found in most preapproval clinical trials, including those conducted
with BONIVA. Therefore, patients should be advised to pay particular attention to and
be able to comply with the dosing instructions to minimize the risk of these effects
(see DOSAGE AND ADMINISTRATION).

Severe Renal Impairment. BONIVA is not recommended for use in patients with
severe renal impairment (creatinine clearance <30 mL/min).

Jaw Ostrongerosis: Ostrongerosis indireative in the law bas been reported in

severe renal impairment (creatinine clearance <30 mL/min).

Jaw Osteonerosis: Osteonerosis, primarily in the jaw, has been reported in patients treated with bisphosphorates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonerosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteriotis), and co-morbid disorders (e.g., anetic, capquiporativ, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated vally. For patients who develop osteonerosis of the jaw (ONJ) while on bisphosphorate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphorate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefityrisk assessment.

patient based on individual benefit/risk assessment.

Musculoskeletal Pain: In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoprorsis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of trugs include BONIVA (ibandronate sodium) Tablets. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. In placebo-controlled studies with BONIVA, the percentages of patients with these symptoms were similar in the BONIVA and placebo groups.

order to maximize absorption and clinical benefit.

BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day and before taking any oral medications containing multivalent cations (including antacids, supplements or vitamins).

To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, BONIVA tables should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA.

Plain water is the only drink that should he taken with BONIVA.

Plain water is the only drink that should be taken with BONIVA. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used. Patients should not chew or suck the tablet because of a potential for

oropharyngeal ulceration.

-The BONIVA 150-mg tablet should be taken on the same date each month (ie, the patient's BONIVA day).

-The BONIVA 150-mg tablet should be taken on the same date each morth (i.e. unpatients BONIVA day).

If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is more than 7 days away, the patient should be instructed to take one BONIVA 150-mg tablet in the morning following the date that it is remembered (see DOSAGE AND ADMINISTRATION). The patient should then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.

The patient must not take two 150-mg tablets within the same week. If the patient's next scheduled BONIVA day to take their tablet. The patient hould then return to taking one BONIVA 150-mg tablet every month in the morning of their chosen day, according to their original schedule.

absorption of boruld.

Physicians should be alert to signs or symptoms signaling a possible esophageal reaction during therapy, and patients should be instructed to discontinue BONIVA and seek medical attention if they develop symptoms of esophageal riritation such new or worsening dysphagia, pain on swallowing, retrostemal pain, or hearthum.

urug interactions Calcium Supplements/Anlacids: Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of BONNA BONNA should be taken at least 60 minutes before any oral medications containing multivalent cations (including antacids, supplements or vitamins) (see PREGAUTIONS: Information for Patients).

containing multivalent cations (including antacids, supplements or vitamins) (see PRECAUTIONs: Information for Patients).

42 Blockers and Proton Pump Inhibitors (PPIs): Of over 3500 patients enrolled in the BONIVA osteoporosis Treatment and Prevention Studies, 15% used anti-peptic agents (primarily Hz blockers and PPIs). Among these patients, the incidence upper gastrointestinal adverse experiences in the patients treated with BONIVA was similar to that in placebo-treated patients. Similarly, of over 1600 patients enrolled in a study comparing once-monthly with daily dosing regimens of blandronate, 14% of patients used anti-peptic agents. Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients treated with BONIVA 150 mg once monthly was similar to that in patients treated with BONIVA 150 mg once monthly was similar to that in patients treated with BONIVA 2.5 mg once daily. Aspirin/Nonsteroidal Antiinflammatory Drugs (NSAIDs): In the large, placebo-controlled osteoporosis Treatment Study, aspirin and nonsteroidal antiinflammatory drugs were taken by 62% of the 2946 patients. Among aspirin or NSAID users, the incidence of upper gastrointestinal adverse events in patients treated with ibandronate 2.5 mg daily (28.9%) was similar to that in patients treated with ibandronate 2.5 mg daily (29.9%) was similar to that in patients concomitantly taking aspirin or NSAIDs was similar in patients concomitantly taking aspirin or NSAIDs was similar in patients concomitantly taking aspirin or NSAIDs was similar in patients concomitantly taking aspirin or NSAIDs was similar in patients concomitantly taking aspirin or nSAIDs was similar in patients concomitantly taking aspirin or NSAIDs was similar in patients concomitantly taking aspirin or nSAIDs was similar in patients or not interfere with the use of bone-imaging agents. Specific studies with ibandronate have not been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: In a 104-

times, respectively, human exposure at the recommended daily oral dose of 2.5 mg, and cumulative exposures up to 3.5 and 2 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5.2 or 40 mg/kg/day were administered by oral gavage to male and female MMRI mice (exposures up to 475 and 70 times, respectively, human exposure at the recommended daily oral dose of 2.5 mg and cumulative exposures up to 135 and 20 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice (cumulative monthly exposures in males and females up to 70 and 115 times, respectively, human exposure at the recommended dose of 150 mg, based on AUC comparison). A dose-related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day 220 to 400 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). The relevance of these findings to humans is unknown.

Mutagenesis: There was no evidence for a mutagenic or clastogenic potential of bandronate in the following assays: in vitro bacterial mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the in vivo mouse micronucleus tests for chromosomal damage.

Impairment of Fertility. In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea, and implantation sites were observed at an oral dose of 150 mg and 13 times human exposure at the recommended once-monthl

gestation, decreases in fertility, copyora lutea, and implantation sites were observed at an oral dose of 15 mg/kg/day (45 times human exposure at the recommended daily oral dose of 2.5 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison).

Pregnancy: Pregnancy Category C: In female rats given oral doses of 1, 4, or 16 mg/kg/day beginning 14 days before mating and continuing through lactation, matemal deaths were observed at the time of delivery in all dose groups (33 times human exposure at the recommended daily oral dose of 2.5 mg or 21 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Perinatal pup loss in dams given 16 mg/kg/day (45 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). was likely related to matemal dystoca. In pregnant rats given oral doses of 6, 20, or 60 mg/kg/day during gestation, calcium supplementation (32 mg/kg/day by subcutaneous injection from gestation day 18 to parturition) did not completely prevent dystocia and periparturient mortality in any of the treated groups (116 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). A low incidence of postimplariation loss was observed in rats treated from 14 days before mating throughout lactation or during gestation, only at doses causing matemal dystocia and periparturient mortality, in regnant rats dosed orally with 1, 5, or 20 mg/kg/day from gestation day 21 (following dosure of the hard palate through weaning), matemal doxicity, including dystocia and mortality, felta perinatal and opsthatal mortality, were observed at doses 3.5 mg/kg/day (equivalent to human exposure at the recommended daily oral dose of 2.5 mg and 3.4 times human exposure at the recommended dolloy and dose of 3.5 mg and 3.4 times human exposure at the recommended dolloy and dose of 3.5 mg and 3.4 times human exposure at the recommended dolloy and dose of 3.5 mg and 3.4 t

potential risk to the mother and fetus.

Nursing Mothers: In lactating rats treated with intravenous doses 0.0.8 mg/kg, bandronate was present in breast milk at concentrations of 8.1 to 0.4 ng/ml. from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations: it is not known whether BONNA is excreted in human milk, Because many drugs are excreted in human milk, caution should be exercised when BONNA is administered to a nursing woman.

Pediatric 18x Sefety and 4.5.

Pediatric Use: Safety and effectiveness in pediatric patients have not beer

Content use: safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the patients receiving BONIVA 2.5 mg daily in postmenopausal osteoporosis studies, 52% were over 65 years of age, and 10% were over 75 years of age. Of the patients receiving BONIVA 150 mg once monthly in the postmenopausal osteoporosis 1-year study, 52% were over 65 years of age, and 9% were over 75 years of age, No overall differences in effectiveness or safety were observed between these patients and younger patients but greater sensitivity in some older individuals cannot be ruled out.

ADVERSE REACTIONS

Daily Dosing: Daily treatment with oral BONIVA was studied in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of BONIVA 2.5 mg once daily in these studies was similar to that of placebo.

event, prome or burviva 2.5 mg once daily in these studies was similar to that of placebo.

Treatment and Prevention of Postmenopausal Osteoporosis: Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIVA 2.5 mg daily group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily group and the placebo group. Overall, and according to body system, there was no difference between BONIVA and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

Table 1 lists adverse events from the Treatment and Prevention Studies reported in £2% of patients and in more patients treated daily with BONIVA than patients treated with placebo. Adverse events are shown without attribution of causality.

Table 1: Adverse Events Occurring at a Frequency £2% and in More Patients Treated with BONIVA than in Patients Treated with Placebo Daily in the Osteoporosis Treatment and Prevention Studies

Body System	Placebo	BONIVA 2.5 mg		
	%	%		
	(n=1134)	(n=1140)		
Body as a Whole				
Back Pain	12.2	13.5		
Pain in Extremity	6.4	7.8		
Infection	3.4	4.3		

1.5	2.0
9.8	11.9
5.0	6.8
2.3	3.5
2.1	2.7
1.9	2.2
orders	
4.2	4.8
5.1	5.7
3.3	3.6
2.7	3.2
5.8	6.5
2.6	3.7
2.5	3.0
1.9	2.2
33.2	33.7
6.8	10.0
4.3	5.9
1.5	2.5
4.2	5.5
	ble-blind, multicenter study comparin
IO BUNIVA	150 mg once monthly in women wit
e uverali sai	ety and tolerability profiles of the two ora
	of serious adverse events was 4.8% in the RONIVA 150 mg once-month
	9.8 5.0 2.3 1.9 0rders 4.2 5.1 3.3 2.7 5.8 2.6 2.5 1.9 33.2 6.8 4.3 1.5 4.2

Table 2: Adverse Events with an Incidence of at Least 2% in Patients Treated with BONIVA 150 mg Once Monthly or 2.5 mg Daily			
Body System/Adverse Event	BONIVA	BONIVA	
204) 0,000	2.5 mg daily	150 mg monthly	
	%	%	
	(n=395)	(n=396)	
Vascular Disorders			
Hypertension	7.3	6.3	
Gastrointestinal Disorders			
Dyspepsia	7.1	5.6	
Nausea	4.8	5.1	
Diarrhea	4.1	5.1	
Constipation	2.5	4.0	
Abdominal Pain ^a	5.3	7.8	
Musculoskeletal and Connective	Tissue Disorders		
Arthralgia	3.5	5.6	
Back Pain	4.3	4.5	
Pain in Extremity	1.3	4.0	
Localized Osteoarthritis	1.3	3.0	
Myalgia	0.8	2.0	
Muscle Cramp	2.0	1.8	
Infections and Infestations			
Influenza	3.8	4.0	
Nasopharyngitis	4.3	3.5	
Bronchitis	3.5	2.5	
Urinary Tract Infection	1.8	2.3	
Upper Respiratory Tract Infection	2.0	2.0	
Nervous System Disorders			
Headache	4.1	3.3	
Dizziness	1.0	2.3	
General Disorders and Administra			
Influenza-like Illness ^b	0.8	3.3	
Skin and Subcutaneous Tissue Di		0.0	
Rash ^c	1.3	2.3	
Psychiatric Disorders Insomnia	0.8	2.0	
mounilla	U.0	2.0	

*Combination of abdominal pain and abdominal pain upper

erythematous, dermatitis, dermatitis allergic, dermätitis medicamentosa, erythema and exanthem. Patients with a previous history of gastrointestinal disease, including patients with peptic uler without recent bleeding or hospitalization and patients with dyspessia or reflux controlled by medication, were included in the once-monthly treatment study. For these patients, there was no difference in upper gastrointestinal adverse events with the 150 mg once-monthly regimen compared to the 2.5 mg once-daily regimen. Ocular Adverse Events: Reports in the medical literature indicate that bisphosphonates may be associated with ocular inflammation such as uveitis and sciertis. In some cases, these events did not resolve until the bisphosphonate was discontinued. There were no reports of ocular inflammation in studies with BONIVA 2.5 mg daily. Two patients who received BONIVA once monthly experienced ocular inflammation, one was a case of uveitis and the other scientis.

Laboratory Test Findings: the 3-year treatment study with BONIVA 2.5 mg daily, there were no clinically significant changes from baseline values or shifts in any laboratory variable for each of the treatment groups. As expected with sphosphonate treatment, a decrease in total alkaline phosphatase levels was seen in the active treatment groups compared to placebo. There was no difference compared with placebo for laboratory administration in the 1-year study.

OVERDOSABE: No specific information is available on the treatment of overdosage.

OVERDOSAGE: No specific information is available on the treatment of overdosage with BONIVA. However, based on knowledge of this class of compounds, oral overdosage may result in hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, dyspepsia, esophagitis, gastritis, or ulcer. Milk or antacids should be given to bind BONIVA. Due to the risk of esophageal irritation, vomiting should not be induced, and the patient should remain fully upright. Dialysis would not be beneficial.

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