Sexual Function Similar After Prostate Cancer Tx

BY JEFF EVANS Senior Writer

ORLANDO, FLA. — Posttreatment sexual function in prostate cancer patients differs initially between the various primary treatments, but becomes nearly equal among all modalities after 4 years, Joycelyn L. Speight, M.D., reported at a symposium on prostate cancer sponsored by the American Society of Clinical Oncology.

Still, some data on patients in a prostate cancer registry suggest that brachytherapy may offer modest advantages in preserving sexual function, at least for some patients, said Dr. Speight, of the University of California, San Francisco.

Sexual function after radiation- and brachytherapy (BT)-based treatment regimens tends to be highest immediately after treatment, then declines slowly during the ensuing 4 years. After radical prostatectomy, sexual function is lowest immediately after treatment and then slowly improves during the next 4 years, she reported.

"All of the treatments for prostate cancer can have an impact on health-related quality of life, and this often influences the patient's treatment choice," she said.

The findings were obtained from self-reports of sexual function and quality of life submitted by 2,903 patients in the CaP-SURE registry (Cancer of the Prostate Strategic Urologic Research Endeavor)

References: 1. Data on file, Sanofi-Synthelabo Inc. 2. IMS Health, National Prescription Audit Plus, MAT May 2004.

Ambien[®] 🕅 (zolpidem tartrate)

BRIEF SUMMARY

INDICATIONS AND USAGE Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia. Ambien has been shown to decrease skep latency and increase the duration of skep for up to 36 days in controlled dinical studies. Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks. Ambien should not be prescribed in quantities exceeding a 1-month supply (see Warninge)

CONTRAINDICATIONS

CONTRAINDICATIONS None Norw. Superimediate of the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initi-ated only after a careful evaluation of the patient. The failure of insomnia to remit the failure of insomnia to remit the failure of insomnia to remit and or psychiatric disorder, symptomatic treatment of insomnia to remit the disorder psychiatric or physical disorder. Such findings have emerged during the course of the important adverse effects of Ambien appear to be dose related (see Prezultions and Dosega and Administration), it is important to use the smallest possible effective dose, especially in the defaur-focur in association with the use of sedative/hypnotic changes have been reported to a by depressed by decreased and Administration. And the set of the simple resolution of the importance in the simple of the some and the set of a unrecequities when the some of the schwarder in the set of the simple the smallest possible effective dose, especially in the defaur-ing the course of the importance in the set of the simple of the set of the some of the set of the set of the simple of the set of the se

ated with withdrawal from other CNS-depressant drugs (see *Drug Abuse and Dependence*). Ambien, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onest of action, Ambien should only be ingested immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, includ-ing potential impairment of the performance of such activities that may occur the day following ingestion of Ambien. Ambien showed additive effects when com-bined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Ambien is administered with such agents because of the potentially additive effects. **PRECAUTONS** PRECAUTIONS

General Use in the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hyponcic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Ambien dosage is 5 mg in such patients (see Dosage and Administration) to decrease the possibility of side effects. These patients should be closely monitored.

Dosage and Administration) to decrease the possibility of side effects. These patients should be closely monitored. Use in patients with concomitant illness: Clinical experience with Ambien in patients with concomitant systemic illness is limited. Caution is advisable in using Ambien in patients with diseases or conditions that could affect metabo-lism or hemodynamic responses. Although studies did not reveal respiratory depresant effects at hypotic doses of Ambien in normals or in patients with mild to moderate chronic obstructive pulmonary disease (CDPD), a reduction in the Total Arousal Index together with a reduction in lowes toxygen saturation and increase in the times of oxygen desaturation below 80% and 90% was observed in Patients with mild-to-moderate sleep apnea when treated with Ambien 10 mg) when compared to placebo. However, precautions should be observed if Ambien is prescribed to patients with compromised respiratory func-tion, since sedative/hypnotics have the capacity to depress respiratory func-tion, since sedative/hypnotics have the capacity to depress respiratory func-dosage adjustment in renally impaired patients is required; however, these patients should be einsting respiratory impairment, have been received. Data in end-stage renal failure patients respeatedly treade with Ambien id not demon-strate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be einsteade with 5 mg in patients with hepatic compro-mise, and they should be closely monitored.

Huse, and uney should be closely monitored. Use in depression: As with other sedative/hypnotic drugs, Ambien should be administered with caution to patients exhibiting signs or symptoms of depres-sion. Suicidal tendencies may be present in such patients and protective meas-ures may be required. Intentional overdosage 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. nformation for patients: Patient information is printed in the complete presong information.

ratory tests: There are no specific laboratory tests recommended.

Interactions active drugs: Ambien was evaluated in healthy volunteers in single-dose ction studies for several CNS drugs. A study involving haloperiol and tem revealed no effect of haloperiod on the pharmacokinetics or pharma-namics of zolpidem. Imipramine in combination with zolpidem produced no nacokinetic interaction other than a 20% decrease in peak levels of amine, but there was an additive effect of decreased alertness. Similarly, promazine in combination with zolpidem produced no pharmacokinetic cition, but there was an additive effect of decreased alertness and psy-totor performance. The tack following chronic administration. additive effect on psychomotor performance between alcohol and zolpi-was demonstrated.

In additive effect on psychomotor performance between alcohol and zolpi-n was demonstrated. Single-dose interactions of the solution of the s

ed by zolpidem. The systematic evaluations of Ambien in combination with other CNS-rugs have been limited, careful consideration should be given to the sology of any CNS-active drug to be used with zolpidem. Any drug with reseant effects could potentially enhance the CNS-depressant effects of

Drugs that affect drug metabolism via cytochrome P450: A randomized, double-blind, crossover interaction study in ten healthy volunteers between itraconazole (200 mg one daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in AUC_{0-mo} of zolpidem. There were no significant pharmacodynamic effects of zolpidem on subjective drowiness, postural away, or psychomotor performance. A randomized, placebo-controlled, crossover interaction study in eight healthy female voluments between 5 consecutive daily doses of rifampin (600 mg) and a single dose of zolpidem (20 mg) given 17 hours after the last body of rifampin todwed significant reductions of the AUC (-75%), cmm, (-55%), dam (T₁₀ - 35%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem.

clopidem.
Obter drugs: A study involving cimetidine/zolpidem and ranitidine/zolpicombinations revealed no effect of either drug on the pharmacokinetics or nacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics ar to affect portiorombin time when given with wafarin in normal sub Zolpidem's sedative/hypnolic effect was reversed by flumazenti; however, n ificant alterations in zolpidem pharmacokinetics were found.

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cocaine, cannabinoids, or amphetamines in two standard urine drug screens. Carcinogenesis, mutagenesis, impairment of fertility Carcinogenesis: Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4.18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10-mg human dose on a mg/kg or mg/m basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the maximum 10-mg human dose on a mg/kg or mg/m basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the esen in 4/100 rtats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipora mas observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipo-ma and liposaroma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous ocurrence.

controls and the turnor findings are thought to be a spontaneous occurrence. Mutagenesis: Capidam did not have mutagenic activity in several tests includ-ing the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes in vitro, and the micronucleus test in mice. Impairment of fertility: In a rat reproduction study, the high dose (100 mg basek(a) of coljedim resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4 to 100 mg basek(a) of 5 to 130 times the recommended human dose in mg/m. No effects on any other fertility parameters were noted.

regnancy repagnancy reratogenic effects: Category B. Studies to assess the effects of zolpidem on uman reproduction and development have not been conducted. Teratology studies were conducted in rats and rabbits. In rats, adverse maternal and fetal effects occurred at 20 and 100 mg base/kg nd included dose-related maternal lethargy and ataxia and a dose-related trend o incomplete ossification of fetal skull bones. In rabbits, dose-related maternal sedation and decreased weight gain curred at all doses tested. At the high dose, 16 mg base/kg, there was an crease in postimplantation fetal loss and underossification of sternebrae in iable fetuses.

rerease in postimplantation fetal loss and underossincauou or ster-iable fetuses. This drug should be used during pregnancy only if clearly needed. Anierstagenic effects: Studies to assess the effects on children whose me took zolpidem during pregnancy have not been conducted. However, ch born of mothers taking sedative/hyponic durgs may be at some risk for drawal symptoms from the drug during the postnatal period. In addition, n tal flaccidity has been reported in infants born of mothers who received sed hypnotic drugs during pregnancy. Labor and delivery: Ambien has no established use in labor and delivery.

Nursing mothers: Studies in lactating mothers indicate that between 0.004 and 0.01% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown. The use of Ambien in nursing mothers is not recommended.

Pediatric use: Safety and effectiveness in pediatric patients below the age have not been established.

have not been established. Geriatric use: A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. chinical trials who received zolpidem were >80 years of age. For a pool of U.S. patients receiving zolpidem at doese of >10 mg or placebo, there were three adverse events occurring at an incidence of at least 3% for zolpi-dem and for which the zolpidem incidence was at least twice the placebo inci-dence (ie, they could be considered drug related).

Adverse Event	Zolpidem	Placebo
Dizziness	3%	0%
Drowsiness	5%	2%
Diarrhea	3%	1%

A total of 30/1,959 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 28/30 (93%) who were \geq 70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem doess >10 mg. A total of 24/1,959 (1.2%) non-U.S. patients receiving zolpidem reported confusion, including 18/24 (75%) who were \geq 70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doess >10 mg.

>10 mg. Associated with discontinuation of treatment: Approximately 4% of 1,701 Patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse clinical event, Events most commonly associated with discontinuation from U.S. trials were daytime drowsings (0.5%), dizziness (0.4%), headache (0.5%), nause (0.5%).

urumeness (u.37%), fuzziness (u.47%), headache (0.5%), naussa (0.6%), and vomit-ing (0.5%). Approximately 4% of 1,959 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drownises (1,11%), dizzinass/vertigo (0.3%), annesia (0.5%), nau-sea (0.5%), headache (0.4%), and falls (0.4%). Data from a clinical study in which selective serotonin reuptake inhibitor. (SSRI) treated patients were given zolpidem revealed that four of the seven dis-continuations during double-blind treatment with zolpidem (n-95) were associ-ated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=97) was discontinued after a natempted suicide.

ncidence in controlled clinical trials Most commonly observed adverse of

idence in controlled clinical trials st commonly observed adverse events in controlled trials: During short-ti atment (up to 10 nights) with Ambien at dosses up to 10 mg, the most c nhy observed adverse events associated with the use of zolpidem and see stically significant differences from placebo-treated patients were dror ing longe-term treatment (28 to 35 nights) with zolpidem at doses up t , the most commonly observed adverse events associated with the us , the most commonly observed adverse events associated with the pidem and seen at statistically significant differences from placebo-treat ients were dizziness (5%) and drugged feelings (3%). eatmen nonly obser stically

patients were dizziness (5%) and drugged tealings (3%). Treatment-mergent adverse experiences in placebo-controlled clinica The following are treatment-emergent adverse events from U.S. placet trolled clinical trials. Data are limited to data from doses up to and incluu mg. In short-term trials, events seen in zolpidem patients (in-655) at an inc equal to 1% or greater compared to placebo (n=473) were: headache (7% for placebo), drowinses (2% vo 1%), dizziness (1% vo 9%), anusea (2%) diarrhea (1% vo 9%), and myalgia (1% vo 2%). In long-term clinical trials, sen in zolpidem patients (in-152) at an incidence of 1% or greater comp placebo (n=161) were: dry mouth (3% vs 1% for placebo), allergy (4% v

back pain (3% vs 2%), influenza-like symptoms (2% vs 0%), chest pain (1% vs 0%), fatigue (1% vs 2%), palpitation (2% vs 0%), headache (19% vs 22%), drowsines (8% vs 5%), dizziness (5% vs 1%), lethardy (3% vs 1%), dragotf eeling (3% vs 0%), inghtheadedness (2% vs 1%), dapression (2% vs 1%), abnormal dreams (1% vs 0%), anmoist (1% vs 0%), anmoist (1% vs 1%), ancorval routenss (3% vs 2%), dabomial pain (2% vs 2%), constipation (2% vs 1%), dabomial pain (2% vs 2%), constipation (2% vs 1%), anisti (1% vs 3%), dargots (3% vs 2%), das (2% vs 2%), and urinary tract infection (2% vs 2%). pharyngitis (3% vs i infection (2% vs 2%).

infection (2% vs 2%). **Dose relationship for adverse events:** There is evidence from dose compan trials suggesting a dose relationship for many of the adverse events associ with zolpidem use, particularly for certain CNS and gastrointestinal adv

events. Adverse events are further classified and enumerated in order of decr frequency using the following definitions: frequent adverse events are definitions: frequent adverse events are definitionse focuring in 1/100 to 1/1,000 patients; rare events are those occurring in 1/100 to to 1/1,000 patients.

Jess than 1/1,000 patients. Frequent: abdominal pain, abnormal dreams, allergy, amnesia, anoxis, anxi-ety, arthralgia, asthenia, ataxia, back pain, chest pain, confusion, constipation, depression, diarrhea, diplopia, dizziness, drowsiness, drugged feeling, dry, mouth, dyspepsia, euphoria, fatigue, headache, hiccup, infection, influenza-like symptoms, insomnia, lethargy, lightheadedness, myagia, nausea, nervousness, palpitation, seep disorder, vertigo, vision abnormal, vomiting.

palpitation, sleep disorder, vertigo, vision abnormal, vomiting. Infrequent: abnormal hepatic function, agitation, arthritis, bronchitis, ce brovascular disorder, coughing, cystitis, decreased cognition, detached, diffic ty concentrating, dysarhina, dysphaeja, dyspnea, edema, emotional lability, e irritation, eye pain, falling, fever, flatulence, gastroenteritis, hallucination, hypy glycemia, hypertension, hypoesthesia, illusion, increased SQF1, increase sveating, leg cramps, malaise, menstrual disorder, migraine, pallor, paresthese postural hypotension, pruritus, sderitis, sleeping (after daytime dosing), spee disorder, stupor, syncope, tachtycardia, taste perversion, thirst, tinnitus, traun tremor, urinary incontinence, vaginitis.

disorder, stupor, syncope, tachycardia, taste perversion, thirst, tinnitue, trauma, tremor, urinary incontinence, vaginitia, Rere: abdominal body sensation, abnormal accommodation, abnormal gait, abnormal thinking, abscess, acne, acute renal failure, aggressive reaction, aller-gic reaction, allery aggravated, altered saliva, anaphylactic shock, anemia, angi-na pectoris, apathy, appetite increased, arrhythmia, arteritis, arthrosis, bilru-niemai, breast fibroadenosis, breast neoplasm, breast pain, bronchospasm, bullous eruption, circulatory failure, conjunctivitis, corneal ukeration, decreased libido, delusion, dementia, depersonalization, dermatitis, epistaxis, eructation, esophagospasm, extrasystoles, face edema, feel-ing strange, flushing, furunculosis, gastritis, glaucoma, gout, hemorrhoids, her-pes simplex, herpes zoster, hot flashes, hypercholesteremia, hypertemsjol-niemia, hyperhigidemia, hypertension aggravated, hypoknesia, hypotension, hypotonia, hypoxia, hysteria, impotence, increased alkaline phosphatase, inflammation, intestinal obstruction, intoxicated feeling, lacrimation abnormal, alynotis, neuropathy, neurosis, contrain, ottis externa, ottis media, pain, panio attacks, paresis, parosmia, periorbital edema, personality disorder, phlebitis, tenes-mus, tetany, throbitosensitivity reaction, neuronia, polytina, julimonary edema, putmonary embolism, purpura, pyelonephritis, rectal hemorrhage, renal pain, puticaria, variorose veisny, ventricular tachycardia, weight decrease, yanving. DRUG ABUSE AND DEPENDENCE Controlled substance: Schedivel N

nuclea substance: Outdoor is a buse potential in former drug abusers found a the effects of single closes of zalpidem tartrate 40 mg were similar, but no entical, to diazepam 20 mg, while zalpidem tartrate 10 mg was difficult to dis

that the effects of single doese or zopuerin autore v mg versamilier identical, to diazepam 20 mg while zopidiem tartrate 10 mg was difficult to dis-tinguish from placebo. Sedative/hypontics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomine to a withdrawal syndrome that may include abdominal and mus-cle cramps, vomiting, sweating, tremors, and convulsions. The U.S. dinical tria syndrome, Neverthelaes, the following adverse events included in DSM-IIR for iteria for uncomplicated sadstire/hypontic withdrawal events included in DSM-IIR to dense of ≤1% during U.S. clinical trials following placebo substitution occurring within 48 hours following last zopidiem treatment; storage, nauses, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal disconfort. Rare posed, and withdrawal were been dependence and withdrawal have been received. Individuals with a history of addiction to, or abuse of, drugs or alcohol are at increased risk of habituation and dependence; they should be under careful sur-vellance when receiving any process.

increased risk of habituation and dependence; they should be under careful sur-veillance when receiving any hyporotic. OVERDOSAGE Signs and symptoms: In European postmarketing reports of overdose with zolpi-dem alone, impairment of consciousness has ranged from sommolence to light coma, with one case each of cardiovascular and respiratory compromise. Individuals have fully recovered from zolpidem tatrate overdoses up to 400 mg (40 times the maximum recommended dose). Overdose cases involving multiple CNS-depressant agents, including zolpidem, have resulted in more severe symptomatology, including tatal outcomes.

nptomatology, including fatal outcomes. commended treatment: General symptomatic and supportive vuld be used along with immediate gastric lavage where ap avenous fluids should be administered as needed. Flumazenil may spiration, pulse, blood pressure, and other appropriate signs should ed and general supportive measures employed. Sedating drugs held following zolojdem overdosage. Zolpidem is not tials/zable. The possibility of multiple drug ingestion should be considered.

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every 6 months for up to 4 years after treatment.

The validated questionnaires consisted of the Rand 36-item health survey, the UCLA prostate cancer index, and a 12item medical health checklist.

In patients who received 6 months or less of neoadjuvant androgen deprivation therapy (ADT), brachytherapy (BT) was associated with the least change and decline in sexual function and significantly better overall sexual function 4 years after treatment than other treatment modalities.

But in patients who received more than 6 months of neoadjuvant ADT, all therapies provided similar levels of sexual function 4 years after treatment.

Patients who received external beam radiotherapy (EBRT) alone, BT alone, or EBRT plus a BT boost were significantly older on average than were patients who received nerve-sparing or non-nerve-spar-

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ing radical prostatectomy (70 years vs. 63 years), and were significantly more likely to have at least one comorbid condition such as diabetes, hypertension, or coronary artery disease (82% vs. 53%). The group

treated with EBRT and/or BT also was significantly more likely to have received neoadjuvant ADT for more than 6 months prior to treatment, compared with the prostatectomy group (38% vs. 8%).

Regardless of treatment, all patients who received more than 6 months of neoadjuvant ADT showed clinically significant improvement in sexual function between treatment and year 1.

After the first year, sexual function levels reached a plateau for all groups that received more than 6 months of neoadjuvant ADT, Dr. Speight said at the symposium, which was cosponsored by the Society of Urologic Oncology and the American Society for Therapeutic Radiology and Oncology.

By year 4, patients who received EBRT, BT, or EBRT plus BT had the same level of sexual function regardless of whether they received more than 6 months of neoadjuvant ADT. But patients who received nerve-sparing or non-nerve-sparing radical prostatectomy with more than 6 months of neoadjuvant ADT had significantly better sexual function after 4 years than those who had 6 months or less of neoadjuvant ADT.

Sexual function was evaluated on a scale of 0 to 100, with higher scores meaning better function. At 4 years after treatment, no group scored higher than 34 on average.

Immediately after treatment, no group had an average score lower than 12. No data were available on sexual function prior to treatment.