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New Concepts Emerge for Treatment of IC

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SAN ANTONIO — Highly effective treatments for interstitial cystitis remain elusive, but new concepts are enlivening the field, Deborah R. Erickson, M.D., said at the annual meeting of the American Urological Association.

Some of the concepts build on old ones, while others are completely new. But all are off-label, and with two exceptions they have not been subjected to placebocontrolled trials, cautioned Dr. Erickson, of the University of Kentucky (Lexing-

Here is a rundown of some interstitial cystitis (IC) treatment concepts she presented at the meeting:

Finding ways to restore the deficient bladder epithelium is an old approach; several drugs are being developed with this in mind, but none is yet available.

► Another old concept focuses on mast

cells—either inhibiting mast cell activation or blocking mast cell mediators. Ketotifen, a mast cell stabilizer, has proved effective when used topically in the eye and may be developed for IC. Montelukast, a leukotriene receptor blocker, has been the subject of one open-label trial in IC. Among 10 patients with IC and detrusor mastocytosis who had at least 28 mast cells per square millimeter of muscle tissue, 3 months of treatment with montelukast was associated with significant improvements in nocturia, day voids, and pain scores (J. Urol. 2001;166:1734-7).

▶ Immunosuppression is another old concept that's getting a fresh look. Until now, immunosuppression has not been popular for treating IC because it's too risky to apply to all patients, it's unclear which patients would do best with this strategy, and it's unclear when treatment can be stopped.

Patients with evidence of inflammation or autoimmune involvement may do best on immunosuppression. Such patients include those with the ulcer type of IC, those with evidence of inflammation on bladder biopsy, and those with high levels of urine mediators such as interleukin-6. High levels of nitric oxide gas also suggest inflammation, but special equipment is needed to measure gas levels.

In several recent open-label trials of patients selected for at least one of these signs, prednisone, prednisolone, and lowdose cyclosporine all have shown evidence

"The current status of immunosuppression in 2005 is [that] it's a valid concept, it's not a standard treatment, and the best drugs and doses are not well defined," Dr. Erickson said. "The best patients are the ones who have failed conventional treatment, are well-informed and compliant, and have some evidence for the autoimmune or inflammatory type of IC."

Another concept is to focus on nerves.

- ► Some patients with IC may have neuropathic pain, and gabapentin and pregabalin, which are well-studied treatments for neuropathic pain, may help. Several small open-label trials of gabapentin in IC have seemed to demonstrate efficacy.
- ► Many physicians have put lidocaine into the bladders of IC patients, but often this doesn't help, possibly because the acidic form of lidocaine is ionized and doesn't penetrate the epithelium very well. Two different formulations of alkalinized lidocaine appear to reduce bladder pain, but one of those forms seems to cause urethral pain on voiding.
- ► Sacral nerve stimulation has been approved by the Food and Drug Administration for significant symptoms of urgency/frequency. Some IC patients have this symptom. Three short-term studies and three longer-term studies appear to demonstrate efficacy in some patients.
- ▶ Lumbar epidural injections, typically with bupivacaine, have shown promise in three small trials. The methods varied widely, as did the duration of the effect (ranging from 0 to 75 days), so Dr. Erickson said more research clearly is needed.
- ▶ The only two drugs that have performed well in randomized, placebo-controlled trials are cimetidine and amitriptyline. Their mechanisms of action are unclear, and as a result neither fits into one of Dr. Erickson's concept categories.

In one study of 36 patients, cimetidine 400 mg b.i.d. resulted in significant improvements in suprapubic pain, nocturia, and total symptom score. The drug may work through histamine₂ receptors on mast cells or on T cells, or through reduced stomach acid secretion, which may translate into less acid excreted in

Lunesta

INDICATIONS AND USAGE LUNESTA is indicated for the t laboratory studies, LUNESTA

WARNINGS

Because sleep disturbances may be the presenting manifestation of a physical and/or spychiatric 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 LUNESTA Because some of the important adverse effects of LUNESTA appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly (see DOSAGE AND ADMINISTRATION in the Full Prescribing Information).

INATION 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 charactery, 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.

It can rarely be determined with certainty whether a particular instance of the abnor mal behaviors listed above are drug-induced, spontaneous in origin, or a result of a underlying psychiatric or physical disorder. Nonetheless, the emergence of any behavioral 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**) withdrawal from other CNS-depressant drugs (see DRUG ABUSE AND DEPENDENCE). LUNESTA, like other hypnotics, has CNS-depressant effects. Because of the rajid onset of action, LUNESTA should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty failing asleep. Patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (e.g., operating machinery or driving a motor vehicle) after ingesting the drug, and be cautioned about potential impairment of the performance of such activities on the day following ingestion of LUNESTA. Like other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, antiournulsants, antibitstamines, ethanol, and other drugs that themselves produce CNS depression. LUNESTA should not be taken with alcohol. Dose adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents, because of the potentially additive effects.

General
Timing Of Drug Administration: LUNESTA should be taken immediately before bedtime. Taking a sedative/hypnofic while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.

Use In The Elderly And/Or Debilitated Patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. The recommended starting dose of LUNESTA for these patients is 1 mg (see DOSAGE AND ADMINISTRATION in the Full Prescribing Information).

Use In Patients With Concomitant Illness: Clinical experience with eszopiclone in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

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

Drug Interactions
CMS-Active Drugs
Ethanot. An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol 0.70 g/kg for up to 4 hours after ethanol administration.

The description of the descripti 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: and lorazepam: Davagamic ocadministration of single doses of eszopiclone 3 mg and lorazepamic Olarazapime: Coadministration of eszopiclone 3 mg and olarazapine 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 VP3A4. (90 mg dally for 5 days. Cyms and two were increased 1.4-fold and 1.3-fold, respectively. Other strong inhibitors of CYP3A4 (p. intraconazole, clanithromycin, nelazodone, triclandomycin, ritonavir, nelfinavir) would be expected to behave similarly.

Drugs That Induce CYP3A44 (Ritampicin): Racemiic zopiclone exposure was

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

Januar intervendual or expected with exacopticions in 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.

and 0.25 mg daily for the next 6 days. Warfarin: Escopicione 3 mg administered daily for 5 days did not affect the pharma-cokinetics of (R)- or (S)-warfarin, nor were there any changes in the pharmacody-namic profile (prothrombin time) following a single 25-mg oral dose of warfarin. Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis: In a carcinogenicity study in Sprague-Dawley rats in which escopi-cione was given by oral gavage, no increases in tumors were seen; plasma levels (AUC) of eszopicione at the highest dose used in this study (16 mg/kg/day) are esti-mated to be 80 (females) and 20 (males) times those in humans receiving the max-imum 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/day, 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 BEGSF1 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

(S)-N-desmethyl zopicione, a metabolite of eszopicione, was positive in the Chinese hamster ovary cell and human lymphocyte chromosomal aberration assays. It was negative in the bacterial Ames mutation assay, in an *in vito* P-postlabeling DINA adduct assay, and in an *in vivo* mouse bone marrow chromosomal aberration and 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), ahordmal estrus cycles (no-effect dose 25 mg/kg), and decreases in sperm number and motility and increases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

Pregnancy
Pregnancy Category C: Eszopicione administered by oral gavage to pregnant rats and Pregnancy Category C: Eszopicione administered by oral gavage to pregnant rats and rabbits during the period of organogenesis showed no evidence of teartogenicity up to the highest doses tested (250 and 16 mg/kg/day in rats and rabbits, respectively, these doses are 800 and 100 times, respectively, the maximum recommended human dose (MRHD) on a mg/m² basis). In the rat, slight reductions in fetal weight and evidence of developmental delay were seen at maternally toxic doses of 125 and 150 mg/kg/day, but not at 62.5 mg/kg/day (200 times the MRHD on a mg/m² basis). Eszopicione was also administered by oral gavage to pregnant rats throughout the pregnancy and lactation periods at doses of up to 180 mg/kg/day. Increased post-implantation loss, decreased postnatal pur weights and survival, and increased pup startle response were seen at all doses; the lowest dose tested, 60 mg/kg/day is 200 times the MRHD on a mg/m² basis. These doses did not produce significant maternal toxicity. Eszopicione had no effects on other behavioral measures or reproductive function in the offspin or an adequate and well-controlled studies of especiations in populations.

Intercent in the orispining.

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.

potential risk to the tetus. Labor And Delivery: LUNESTA has no established use in labor and delivery. Nursing 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.

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

Geriatric Use: A total of 287 subjects in double-blind, parallel-group, placebo-confound clinical trials who received eszopiclone were 65 to 86 years of age. The overall pattern of adverse events for elderly subjects (median age = 71 years) in 2-week studies with nighttime dosing of 2 mg eszopiclone 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.

AVERISE REACTIONS

weights, advokative attayses, 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.

'Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abnormal dreams, accidental injury, back pain, diarrhea, flu syndrome, myalgia, pain, pharyngitis, and rhinitis. Adverse events that suggest a dose-response relationship in adults include viral infection, dry mouth, dizzness, hallucinations, infection, rash, and unpleasant taste, with this relationship clearest for unpleasant taste. The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from combined Phase 3 placebo-controlled studies of LUNESTA at doses of 1 or 2 mg in elderly adults (ages 65-68). Treatment duration in these trials was 14 days. Data are limited to events that occurred in 2% or more patients treated with LUNESTA in mg (n=72) or 2 mg (n=215) in which the incidence in patients treated with LUNESTA was greater than the incidence in placebo-treated patients.

patients.¹

Body as a whole: accidental injury (1%, 0%, 3%), headache (14%, 15%, 13%), pain (2%, 4%, 5%). Digestive system: diarrhea (2%, 4%, 2%), dry mouth (2%, 3%, 7%), dyspepsia (2%, 6%, 2%), hervous system: abnormal dreams (9%, 3%, 1%), dizzness (2%, 1%, 6%), nervousness (1%, 0%, 2%), neuraliga (9%, 5%, 0%), Skin and appendages; prurflus: (1%, 4%, 1%). Special senses: unpleasant taste (0%, 8%, 12%), transpart asystem: unper varter infection (0%, 3%, 0%).

Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abdominal pain, asthenia, nausea, rash, and

cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contributions of drug and non-drug factors to the adverse event incidence rate in the population studied.

Other Events Observed During The Premarketing 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 1565 subjects treated with LUNESTA at osses in the range of 1 to 3.5 myday 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 elsewhere 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 definions: frequent adverse events are those that occurred on one or more occasions in at least 17,100 patients but in al least 17,100 patients. Gender-specific events are categorized based on their incidence for the appropriate gender.

Frequent: chest pain, migraine, peripheral edema.

becume in newer inridence for the appropriate gender.

Frequent: chest pain, migraine, peripheral edema.

Infrequent: cane, aglation, allegrior reaction, alopecia, amenorrhea, anemia, anorexia, apathy, arthritis, asthma, ataxia, breast engorgement, breast enlargement, breast encoplasm, breast pain, bronchilis, bursitis, cellulitis, cholelithiasis, conjunctivitis, contact dermattiis, cystitis, dry eyes, dry skin, dyspnea, dysuria, ezzema, ear pain, emotional lability, epistaxis, face dedma, female lacation, fever, halifosis, heat stroke, hematuria, hernia, hiccup, hostility, hypercholesteremia, hypertension, hypertonia, hypesthesia, incoordination, increased appetite, insomnia, joint disorder (mainly swelling, stiffness, and pain), kidney calculus, kidney pain, laryngitis, leg cramps, lymphadenopathy, malaise, mastilis, melena, memory impairment, menorrhagia, mouth ulceration, myasthenia, neck rigidity, neurosis, mystagnus, otitis externa, otitis media, paresthesia, photosensitivity, reflexes decreased, skin discoloration, sweating, thinking abnormal (mainly difficulty concentrating), thiris, inthis, bytiching, ulcerative stomatitis, urinary frequency, urinary incontinence, urticaria, uterine hemorrhage, vaginal hemorrhage, vaginitis, vertigo, vestibular disorder, weight gain, weight loss.

Rare: abnormal gait, arthrosis, collis, dehydration, dysphagia, erythema multiforme.

disorder, weight gain, weight loss.

Amera: abnormal gait, arthrosis, colitis, dehydration, dysphagia, erythema multiforme euphoria, furunculosis, gastritis, gout, hepatitis, hepatomegaly, herpes zoster hirsuitsm. hyperacusis, hyperesthesia, hyperilpemia, hypokalemia, hypokinsi iritis, liver damage, maculopapular rash, mydriasis, myopathy, neuritis, neuropathy oliguria, photophobia, ptosis, pyelonephritis, rectal henorrhage, stomach ulcer stomatitis, stupor, thrombophlebitis, tongue edema, tremor, urethritis vessiculobullous rash.

maximum recommended dose of escopicione). Signs And Symptoms: Signs and Symptoms of overdose effects of CNS depressants can be expected to present as exaggerations of the pharmacological effects noted in preclinical testing. Inpairment of consciousness ranging from somnolence to coma has been described. Pare individual instances of fatal outcomes following overdose with racemic zopicione have been reported in European postmarketing reports, most often associated with overdose with other CNS-depressant agents.

often associated with overdose 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. Funnazenil 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 hypototic drug oroduct overdosage.

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