

Oregon Data: Sense of Control Key at End of Life

BY JANE SALODOF MACNEIL
Southwest Bureau

SANTA ANA PUEBLO, N.M. — The key factor motivating the terminally ill to seek assisted suicide under Oregon's Death with Dignity Act—a sense of control—should prompt a rethinking of end-of-life care, Dr. Linda Ganzini said at the annual meeting of the Academy of Psychosomatic Medicine.

Studies of terminally ill patients in Ore-

gon showed that “some people want to leave this world in the driver's seat. That's their major goal,” said Dr. Ganzini, director of the geriatric psychiatry fellowship program at Oregon Health and Science University, Portland. “And we need to let this goal start driving how they should be cared for—whether they get assisted suicide or not.”

The findings gained new currency last month when the U.S. Supreme Court ruled that the Bush administration improperly

tried to use a federal drug law to stop physicians from prescribing lethal drugs to terminally ill patients under the Oregon law.

The studies, which also included physicians, nurses, hospice chaplains, and family members, showed that few of the factors cited in the political debate over the law were significant in determining who chose assisted suicide. Patients who requested lethal prescriptions were no more likely to be depressed, poor, poorly educated, from minority groups, or in worse

physical condition than patients who opted not to make such a request.

“These were individuals who wanted to control their lives,” Dr. Ganzini said. Relatively few people go through with assisted suicide, but those who do are determined to remain self-reliant until the end.

Many who requested assisted suicide had highly successful professional careers. Overcoming adversity early in life was another common experience.

Oregon's voters passed its Death with Dignity Act by a slim majority in 1994, making Oregon the first and only state to approve assisted suicide. The act was delayed by a legal injunction until 1997, when 60% of voters refused to repeal it.

Since 1997, Oregon has had 208 deaths by assisted suicide, said Dr. Ganzini, also a senior scholar at the university's center for ethics in health care. “For every 1,000 patients in Oregon who die, 100 will seriously consider assisted suicide, 10 will make an explicit request, and 1 will die by it.”

Compared with other patients, those with amyotrophic lateral sclerosis (ALS) in Oregon have an odds ratio above 20 for dying by assisted suicide. A sense of hopelessness was an important predictor of interest in obtaining a lethal prescription, Dr. Ganzini and her associates found in a study of 100 ALS patients.

Dr. Ganzini is now studying patients in the process of making legal requests. “They are really focused on what is coming down the road, how intolerable it will be, and how it will make their lives not worth living,” she said. Patients feared worsening of symptoms, but at the time of their requests, none complained of physical symptoms worse than 2 on a scale of 1-5.

In another study with cancer patients, growing dissatisfaction with medical care was a leading predictor of interest in assisted suicide, and perhaps the interest reflected hopelessness, she added.

In her current study, only 6 of 46 patients requesting assisted suicide met criteria for a major depressive disorder in structured clinical interviews. Even patients who felt hopeless were not depressed.

“I remain very perplexed. I still don't know why there are not more depressed people making a request,” Dr. Ganzini said. But she has a few theories: “I have no empirical data to support it, but people who go through this process have to be very physically fit, determined, convincing, and articulate. I think depressed people, particularly if they are physically ill people, may get left behind in this process.”

Another concern was that the Death with Dignity Act might undermine efforts to improve hospice or palliative care. Instead, 86% of assisted suicides occurred in hospice patients, Dr. Ganzini said.

Opposition to the law remains fairly strong. About 42% of hospice chaplains and a third of hospice nurses oppose the law, she said. Yet few said they would actively oppose it with a patient, and no chaplain would seek transfer of a patient who requested assisted suicide.

The Oregon experience highlights “a very rarefied group” of people whose needs are not generalizable but should not be ignored, Dr. Ganzini concluded. ■



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Brief Summary

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INDICATIONS AND USAGE: Cevimeline is indicated for the treatment of symptoms of dry mouth in patients with Sjögren's Syndrome.

CONTRAINDICATIONS: Cevimeline is contraindicated in patients with uncontrolled asthma, known hypersensitivity to cevimeline, and when miosis is undesirable, e.g., in acute iritis and in narrow-angle (angle-closure) glaucoma.

WARNINGS:

Cardiovascular Disease: Cevimeline can potentially alter cardiac conduction and/or heart rate. Patients with significant cardiovascular disease may potentially be unable to compensate for transient changes in hemodynamics or rhythm induced by EVOXAC®. EVOXAC® should be used with caution and under close medical supervision in patients with a history of cardiovascular disease evidenced by angina pectoris or myocardial infarction.

Pulmonary Disease: Cevimeline can potentially increase airway resistance, bronchial smooth muscle tone, and bronchial secretions. Cevimeline should be administered with caution and with close medical supervision to patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease.

Ocular: Ophthalmic formulations of muscarinic agonists have been reported to cause visual blurring which may result in decreased visual acuity, especially at night and in patients with central lens changes, and to cause impairment of depth perception. Caution should be advised while driving at night or performing hazardous activities in reduced lighting.

PRECAUTIONS:

General: Cevimeline toxicity is characterized by an exaggeration of its parasympathomimetic effects. These may include: headache, visual disturbance, lacrimation, sweating, respiratory distress, gastrointestinal spasm, nausea, vomiting, diarrhea, atrioventricular block, tachycardia, bradycardia, hypotension, hypertension, shock, mental confusion, cardiac arrhythmia, and tremors.

Cevimeline should be administered with caution to patients with a history of nephrolithiasis or cholelithiasis. Contractions of the gallbladder or biliary smooth muscle could precipitate complications such as cholecystitis, cholangitis and biliary obstruction. An increase in the ureteral smooth muscle tone could theoretically precipitate renal colic or ureteral reflux in patients with nephrolithiasis.

Information for Patients: Patients should be informed that cevimeline may cause visual disturbances, especially at night, that could impair their ability to drive safely.

If a patient sweats excessively while taking cevimeline, dehydration may develop. The patient should drink extra water and consult a health care provider.

Drug Interactions: Cevimeline should be administered with caution to patients taking beta adrenergic antagonists, because of the possibility of conduction disturbances. Drugs with parasympathomimetic effects administered concurrently with cevimeline can be expected to have additive effects. Cevimeline might interfere with desirable antimuscarinic effects of drugs used concomitantly.

Drugs which inhibit CYP2D6 and CYP3A4 also inhibit the metabolism of cevimeline. Cevimeline should be used with caution in individuals known or suspected to be deficient in CYP2D6 activity, based on previous experience, as they may be at a higher risk of adverse events. In an *in vitro* study, cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 were not inhibited by exposure to cevimeline.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Lifetime carcinogenicity studies were conducted in CD-1 mice and F-344 rats. A statistically significant increase in the incidence of adenocarcinomas of the uterus was observed in female rats that received cevimeline at a dosage of 100 mg/kg/day (approximately 8 times the maximum human exposure based on comparison of AUC data). No other significant differences in tumor incidence were observed in either mice or rats.

Cevimeline exhibited no evidence of mutagenicity or clastogenicity in a battery of assays that included an Ames test, an *in vitro* chromosomal aberration study in mammalian cells, a mouse lymphoma study in L5178Y cells, or a micronucleus assay conducted *in vivo* in ICR mice.

Cevimeline did not adversely affect the reproductive performance or fertility of male Sprague-Dawley rats when administered for 63 days prior to mating and throughout the period of mating at dosages up to 45 mg/kg/day (approximately 5 times the maximum recommended dose for a 60 kg human following normalization of the data on the basis of body surface area estimates). Females that were treated with cevimeline at dosages up to 45 mg/kg/day from 14 days prior to mating through day seven of gestation exhibited a statistically significantly smaller number of implantations than did control animals.

Pregnancy: Pregnancy Category C.

Cevimeline was associated with a reduction in the mean number of implantations when given to pregnant Sprague-Dawley rats from 14 days prior to mating through day seven of gestation at a dosage of 45 mg/kg/day (approximately 5 times the maximum recommended dose for a 60 kg human when compared on the basis of body surface area estimates). This effect may have been secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Cevimeline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from EVOXAC®, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Although clinical studies of cevimeline included subjects over the age of 65, the numbers were not sufficient to determine whether they respond differently from younger subjects. Special care should be exercised when cevimeline treatment is initiated in an elderly patient, considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in the elderly.

ADVERSE REACTIONS: Cevimeline was administered to 1777 patients during clinical trials worldwide, including Sjögren's patients and patients with other conditions. In placebo-controlled Sjögren's studies in the U.S., 320 patients received cevimeline doses ranging from 15 mg tid to 60 mg tid, of whom 93% were women and 7% were men. Demographic distribution was 90% Caucasian, 5% Hispanic, 3% Black, and 2% of other origin. In these studies, 14.6% of patients discontinued treatment with cevimeline due to adverse events.

The following adverse events associated with muscarinic agonism were observed in the clinical trials of cevimeline in Sjögren's syndrome patients:

Adverse Event	Cevimeline 30 mg (tid) n = 533		Placebo (tid) n = 164		Adverse Event	Cevimeline 30 mg (tid) n = 533		Placebo (tid) n = 164	
Excessive Sweating	18.7%	2.4%	Urinary Frequency	0.9%	1.8%				
Nausea	13.8%	7.9%	Asthenia	0.5%	0.0%				
Rhinitis	11.2%	5.4%	Flushing	0.3%	0.6%				
Diarrhea	10.3%	10.3%	Polyuria	0.1%	0.6%				
Excessive Salivation	2.2%	0.6%							

*n is the total number of patients exposed to the dose at any time during the study

EVOXAC® Capsules (cevimeline hydrochloride)

In addition, the following adverse events (≥3% incidence) were reported in the Sjögren's clinical trials:

Adverse Event	Cevimeline 30 mg (tid) n = 533		Placebo (tid) n = 164		Adverse Event	Cevimeline 30 mg (tid) n = 533		Placebo (tid) n = 164	
Headache	14.4%	20.1%	Conjunctivitis	4.3%	3.6%				
Sinusitis	12.3%	10.9%	Dizziness	4.1%	7.3%				
Upper Respiratory Tract Infection	11.4%	9.1%	Bronchitis	4.1%	1.2%				
Dyspepsia	7.8%	8.5%	Arthralgia	3.7%	1.8%				
Abdominal Pain	7.6%	6.7%	Surgical Intervention	3.3%	3.0%				
Urinary Tract Infection	6.1%	3.0%	Fatigue	3.3%	1.2%				
Coughing	6.1%	3.0%	Pain	3.3%	3.0%				
Pharyngitis	5.2%	5.4%	Skeletal Pain	2.8%	1.8%				
Vomiting	4.6%	2.4%	Insomnia	2.4%	1.2%				
Injury	4.5%	2.4%	Hot Flashes	2.4%	0.0%				
Back Pain	4.5%	4.2%	Rigors	1.3%	1.2%				
Rash	4.3%	6.0%	Anxiety	1.3%	1.2%				

*n is the total number of patients exposed to the dose at any time during the study

The following events were reported in Sjögren's patients at incidences of <3% and ≥1%: constipation, tremor, abnormal vision, hypertonia, peripheral edema, chest pain, myalgia, fever, anorexia, eye pain, sarcosis, dry mouth, vertigo, salivary gland pain, pruritus, influenza-like symptoms, eye infection, post-operative pain, vaginitis, skin disorder, depression, hiccup, hyporeflexia, infection, fungal infection, sialoadenitis, otitis media, erythematous rash, pneumonia, edema, salivary gland enlargement, allergy, gastroesophageal reflux, eye abnormality, migraine, tooth disorder, epistaxis, flatulence, toothache, ulcerative stomatitis, anemia, hypoesthesia, cystitis, leg cramps, ascensus, eructation, ironiiasis, palpitation, increased amylase, xerophthalmia, allergic reaction.

The following events were reported rarely in treated Sjögren's patients (<1%): Causal relation is unknown:

Body as a Whole Disorders: aggravated allergy, precordial chest pain, abnormal crying, hematoma, leg pain, edema, periorbital edema, activated pain trauma, pallor, changed sensation to temperature, weight decrease, weight increase, choking, mouth edema, syncope, malaise, face edema, substernal chest pain

Cardiovascular Disorders: abnormal ECG, heart disorder, heart murmur, aggravated hypertension, hypotension, arrhythmia, extrasystoles, t wave inversion, tachycardia, supraventricular tachycardia, angina pectoris, myocardial infarction, pericarditis, pulmonary embolism, peripheral ischemia, superficial phlebitis, purpura, deep thrombophlebitis, vascular disorder, vasculitis, hypertension

Digestive Disorders: appendicitis, increased appetite, ulcerative colitis, diverticulitis, duodenitis, dysphagia, enterocolitis, gastric ulcer, gastritis, gastroenteritis, gastrointestinal hemorrhage, gingivitis, glossitis, rectum hemorrhage, hemorrhoids, ileus, irritable bowel syndrome, melena, mucositis, esophageal stricture, esophagitis, oral hemorrhage, peptic ulcer, periodontal destruction, rectal disorder, stomatitis, tenesmus, tongue discoloration, tongue disorder, geographic tongue, tongue ulceration, dental caries

Endocrine Disorders: increased glucocorticoids, goiter, hypothyroidism

Hematologic Disorders: thrombocytopenic purpura, thrombocytopenia, thrombocytopenia, hypochromic anemia, eosinophilia, granulocytopenia, leucopenia, leukocytosis, cervical lymphadenopathy, lymphadenopathy

Liver and Biliary System Disorders: cholelithiasis, increased gamma-glutamyl transferase, increased hepatic enzymes, abnormal hepatic function, viral hepatitis, increased serum glutamate oxaloacetic transaminase (SGOT) (also called AST-aspartate aminotransferase), increased serum glutamate pyruvate transaminase (SGPT) (also called ALT-alanine aminotransferase)

Metabolic and Nutritional Disorders: dehydration, diabetes mellitus, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, thirst

Musculoskeletal Disorders: arthritis, aggravated arthritis, arthropathy, femoral head avascular necrosis, bone disorder, bursitis, costochondritis, plantar fasciitis, muscle weakness, osteomyelitis, osteoporosis, synovitis, tendinitis, tenosynovitis

Neoplasms: basal cell carcinoma, squamous carcinoma

Nervous Disorders: carpal tunnel syndrome, coma, abnormal coordination, dysesthesia, dyskinesia, dysphonia, aggravated multiple sclerosis, involuntary muscle contractions, neuralgia, neuropathy, paresthesia, speech disorder, agitation, confusion, depersonalization, aggravated depression, abnormal dreaming, emotional lability, manic reaction, paroniria, somnolence, abnormal thinking, hyperkinesia, hallucination

Miscellaneous Disorders: fall, food poisoning, heat stroke, joint dislocation, post-operative hemorrhage

Resistance Mechanism Disorders: cellulitis, herpes simplex, herpes zoster, bacterial infection, viral infection, genital moniliasis, sepsis

Respiratory Disorders: asthma, bronchospasm, chronic obstructive airway disease, dyspnea, hemoptysis, laryngitis, nasal ulcer, pleural effusion, pleurisy, pulmonary congestion, pulmonary fibrosis, respiratory disorder

Rheumatologic Disorders: aggravated rheumatoid arthritis, lupus erythematosus rash, lupus erythematosus syndrome

Skin and Appendages Disorders: acne, alopecia, burn, dermatitis, contact dermatitis, lichenoid dermatitis, eczema, furunculosis, hyperkeratosis, lichen planus, nail discoloration, nail disorder, onychia, onychomycosis, paronychia, photosensitivity reaction, rosacea, scleroderma, seborrhea, skin discoloration, dry skin, skin exfoliation, skin hypertrophy, skin ulceration, urticaria, verruca, bulbous eruption, cold clammy skin

Special Senses Disorders: deafness, decreased hearing, motion sickness, parosmia, taste perversion, blepharitis, cataract, corneal opacity, corneal ulceration, diplopia, glaucoma, anterior chamber eye hemorrhage, keratitis, keratoconjunctivitis, mydriasis, myopia, photopsia, retinal deposits, retinal disorder, scleritis, vitreous detachment, tinnitus

Urogenital Disorders: epididymitis, prostatic disorder, abnormal sexual function, amenorrhea, female breast neoplasm, malignant female breast neoplasm, female breast pain, positive cervical smear test, dysmenorrhea, endometrial disorder, intermenstrual bleeding, leukorrhea, menorrhagia, menstrual disorder, ovarian cyst, ovarian disorder, genital pruritus, uterine hemorrhage, vaginal hemorrhage, atrophic vaginitis, albuminuria, bladder disorder, increased blood urea nitrogen, dysuria, hematuria, micturition disorder, nephrosis, nocturia, increased nonprotein nitrogen, pyelonephritis, renal calculus, abnormal renal function, renal pain, stranguary, urethral disorder, abnormal urine, urinary incontinence, decreased urine flow, pyuria

In one subject with lupus erythematosus receiving concomitant multiple drug therapy, a highly elevated ALT level was noted after the fourth week of cevimeline therapy. In two other subjects receiving cevimeline in the clinical trials, very high AST levels were noted. The significance of these findings is unknown.

Additional adverse events (relationship unknown) which occurred in other clinical studies (patient population different from Sjögren's patients) are as follows:

cholinergic syndrome, blood pressure fluctuation, cardiomegaly, postural hypotension, aphasia, convulsions, abnormal gait, hyperesthesia, paralysis, abnormal sexual function, enlarged abdomen, change in bowel habits, gum hyperplasia, intestinal obstruction, bundle branch block, increased creatine phosphokinase, electrolyte abnormality, glycosuria, gout, hyperkalemia, hyperproteinemia, increased lactic dehydrogenase (LDH), increased alkaline phosphatase, failure to thrive, abnormal platelets, aggressive reaction, amnesia, apathy, delirium, delusion, dementia, illusion, impotence, neurosis, paranoid reaction, personality disorder, hyperhemoglobinemia, apnea, atelectasis, yawning, oliguria, urinary retention, distended vein, lymphocytosis

Post-Marketing Adverse Events: cholecystitis

MANAGEMENT OF OVERDOSE: Management of the signs and symptoms of acute overdose should be handled in a manner consistent with that indicated for other muscarinic agonists: general supportive measures should be instituted. If medically indicated, atropine, an anti-cholinergic agent may be of value as an antidote for emergency use in patients who have had an overdose of cevimeline. If medically indicated, epinephrine may be of value in the presence of severe cardiovascular depression or bronchoconstriction. It is not known if cevimeline is dialyzable.

DOSE AND ADMINISTRATION: The recommended dose of cevimeline hydrochloride is 30 mg taken three times a day. There is insufficient safety information to support doses greater than 30 mg tid. There is also insufficient evidence for additional efficacy of cevimeline hydrochloride at doses greater than 30 mg tid.

Rx Only

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www.daiichius.com

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