For Nausea at End of Life, Think Mechanistically

BY BRUCE JANCIN
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DALLAS — Haloperidol is, perhaps surprisingly to many, the drug of choice for nausea and vomiting caused by stimulation of the chemoreceptor trigger zone—the No. 1 mechanism for nausea in patients nearing the end of life, Dr. Steven Pantilat said at the annual meeting of the Society of Hospital Medicine.

"Haloperidol is the most potent dopamine-2 antagonist at the chemoreceptor trigger zone. We don't think of it that way. We don't think of it for this purpose. But it actually is a terrific drug, and it's the one we use now as our first-line agent," said Dr. Pantilat, director of the palliative care program at the University of California, San Francisco.

He advocated selecting antiemetics for palliative care patients based on the probable mechanism underlying the symptoms. Clues as to the likely mechanisms come from the history, along with an evaluation that may involve an oral inspection, an abdominal exam, a rectal exam to rule out fecal impaction, laboratory tests, and in some cases brain or abdominal imaging.

Here are the chief mechanisms for nausea and vomiting in end-of-life patients, and the drugs of choice for each:

► **Chemoreceptor trigger zone.** This can be activated by drugs including opioids, digoxin, NSAIDs, and antibiotics. It can also be activated by metabolic derangements including hypercalcemia and hepatic failure, or by chemotherapy. Dopamine and serotonin are the main mediators.

The dosing of haloperidol is 0.5-2 mg intravenously every 6 hours. Oral prochlorperazine at 10 mg every 6 hours works well, too, provided a patient can take it.

For chemotherapy-induced nausea and vomiting, the 5-HT3 antagonists ondansetron and granisetron are very effective. Good data support their use in this setting as well as in postoperative nausea, but patients seem to get these drugs for all sorts of other types of nausea, too. Dr. Pantilat said he used to frown on this practice because it's not evidence based and the drugs are very expensive; however, he has seen so many anecdotal good results that he has recently become more open to turning to ondansetron and granisetron when first-line drugs for various forms of nausea aren't working.

Lorazepam is effective for prevention of anticipatory nausea in patients preparing to return to the chemotherapy infusion center. But it won't help unless it is given before the anticipatory nausea has set in.

► **Vagal afferent nerve.** This prominent mechanism for nausea and vomiting is mediated by histamine receptors in the brain. Common underlying causes include GI stretch due to constipation or bowel obstruction, mucosal irritation due to thrush, and peritoneal carcinomatosis or other external causes of nerve irritation.

Dr. Pantilat considers the drug of choice to be promethazine at 12.5-25 mg every 6 hours intravenously, orally, or rectally. It's a highly potent binder of the histamine receptor but is also quite sedating, so caution is warranted in giving it to patients who might vomit. Metoclopramide is useful when the underlying cause of vagal afferent nerve irritation is gastroparesis or partial bowel obstruction.

► **Higher cortical structures.** When metastases, infection, or edema press on the brain, directly stimulating the medullary vomiting center, the treatment of choice is dexamethasone at a typical starting dose of 2-4 mg intravenously or orally every 6 hours to reduce swelling. If necessary, Dr. Pantilat will go as high as 10 mg.

Dexamethasone is also the drug of choice for intractable, unrelenting nausea and vomiting unresponsive to other antiemetics, although that's not common in palliative care.

"Many palliative care programs use steroids very freely to make people feel good, to try to stimulate appetite, for pain—particularly in the setting of metastases, and for nausea. There are a lot of good reasons, particularly at the end of life, to see this as a drug that can make people feel better in a lot of ways," he said. ■

Resources on Palliative Care

Here are several resources on palliative care that Dr. Pantilat recommends as particularly helpful:

► **Fast Facts.** One-page reports for clinicians on roughly 175 palliative care issues including dyspnea management, running a family conference, and how to use methadone. Available free for downloading onto a PDA through the Medical College of Wisconsin at www.eperc.mcw.edu/ff_index.htm.

► **Primer of Palliative Care, fourth edition.** Available for purchase from the American Academy of Hospice and Palliative Medicine at www.aahpm.org. "That's a wonderful little pocket guide. I carry it with me all the time. It covers everything from pain management to psychosocial issues," Dr. Pantilat said.

► **Perspectives on Care at the Close of Life.** An ongoing JAMA series coedited by Dr. Pantilat available free online at http://jama.ama-assn.org/cgi/collection/endoflife_care_palliative_medicine.

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia[3] (2% and <1%).*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo B Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=225 Lexapro; N=188 placebo). [3]Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see **TABLE 3**). **TABLE 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Lexapro (N=429) and Placebo (N=427)): Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder[1,2] (14% and 2%); Anorgasmia[3] (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo B Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=182 Lexapro; N=195 placebo). [3]Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125): Insomnia** (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%).*Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials** [In Males Only: **Lexapro** (N=407) **and Placebo** (N=383)]: Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). [In Females Only: **Lexapro** (N=737) **and Placebo** (N=636)]: Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in **Tables 2 & 3**, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. Cardiovascular - *Frequent:* palpitation, hypertension. *Infrequent:* bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - *Frequent:* light-headed feeling, migraine. *Infrequent:* tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - *Frequent:* heartburn, abdominal cramp, gastroenteritis. *Infrequent:* gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - *Frequent:* allergy, pain in limb, fever, hot flushes, chest pain. *Infrequent:* edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - *Infrequent:* bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - *Frequent:* increased weight. *Infrequent:* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - *Frequent:* arthralgia, myalgia. *Infrequent:* jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - *Frequent:* appetite increased, lethargy, irritability, concentration impaired. *Infrequent:* jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female* - *Frequent:* menstrual cramps, menstrual disorder. *Infrequent:* menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only: N= 905 Respiratory System Disorders - *Frequent:* bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. *Infrequent:* asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - *Frequent:* rash. *Infrequent:* pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - *Frequent:* vision blurred, tinnitus. *Infrequent:* taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - *Frequent:* urinary frequency, urinary tract infection. *Infrequent:* urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

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Malnutrition Missed in Hospitalized Elderly

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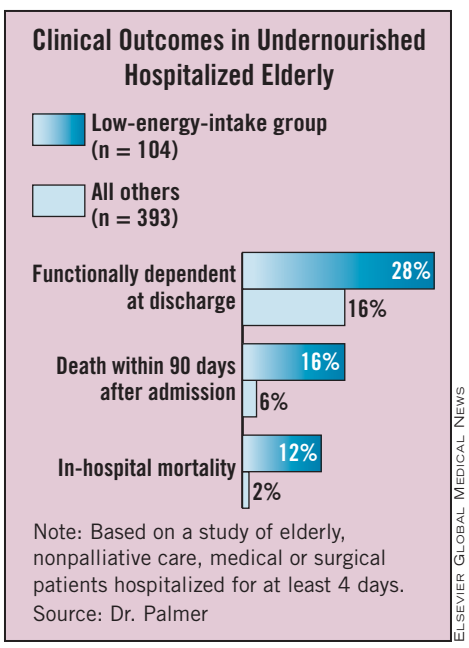
DALLAS — Nutritional deterioration in elderly hospitalized patients is very common, often unrecognized, and linked to negative consequences in terms of key hospital outcome measures.

"Let me say, for sure, malnutrition in elderly patients is associated with terrible outcomes in terms of length of stay, mortality, functional decline, and of course nursing home admission," Dr. Robert M. Palmer said at the annual meeting of the Society of Hospital Medicine.

Many studies indicate that about 40% of hospitalized elderly patients are either protein-calorie undernourished upon admission or become so before discharge.

"The interesting thing is it's really unusual to see malnutrition as a diagnosis in their medical record, and it's even more unusual to see that it's being adequately treated," observed Dr. Palmer, head of the section of geriatric medicine at the Cleveland Clinic Foundation.

The consequences of failure to address these deficits during the hospital stay were spelled out some years ago in a prospective Arkansas Veterans Affairs study.



The study involved 497 consecutive elderly, nonpalliative care, medical or surgical patients hospitalized for at least 4 days—in theory, long enough for them to undergo a nutritional assessment and have major deficiencies met. Their in-hospital nutrient intake was assessed daily. Those identified as having low energy intake were subsequently assessed more intensively at the bedside on a meal-by-meal basis.

A total of 21% of the seniors had an in-hospital average daily nutrient intake of less than 50% of their calculated maintenance energy requirement. At admission, their health status was comparable with and in some respects better than that of the other patients at the VA facility. For example, their body mass index, midarm muscle circumference, and subcutaneous fat stores were significantly greater. They were also more likely to consider their health to be good or excellent and to have been admitted electively (JAMA 1999;281:2013-9).

Nonetheless, there was a huge difference in outcomes between the two groups. (See box.) The investigators determined that the biggest contributing factor to the in-hospital malnutrition problem was attending physicians' practice of ordering patients to have nothing by mouth but not prescribing nutrients by another route.

One-quarter of patients in each group received canned nutritional supplements at some point during hospitalization. Those in the undernourished group were significantly less likely to consume theirs. Enteral and parenteral nutritional support were seldom employed. ■