Logistics Pose an Obstacle for Flu Antiviral Rx

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MONTREAL — Although influenza vaccination continues to be underutilized, it is a success story compared with the use of influenza antiviral medications, experts agreed at an international conference on community-acquired pneumonia.

Medications such as zanamivir and oseltamivir can prevent or greatly reduce the major symptoms and sequelae of influenza, including community-acquired pneumonia, yet they do not currently play a central role in influenza management.

"As long as the bean counters are practicing medicine without a license, this is not going to improve," said Dr. Grant Stiver, professor of medicine and head of infectious diseases at the University of British Columbia, Vancouver. "We put out money for heart transplants in 75-year-old men because we can see they are dying of heart failure, but to put out money for prophylaxis … seems to be a big stumbling block."

Besides lack of resources to promote the use of influenza antivirals, there is also a lack of awareness, both in the general public and within the medical community.

"Physicians are very reluctant to prescribe antivirals, and the message to patients has been don't go to the doctor if you have a virus," said Dr. Karl Weiss of the University of Montreal. "We have a long way to go to educate physicians and also the public," he said at the meeting, which was sponsored by the International Society of Chemotherapy.

"It's a different paradigm. We were all taught in school that there's nothing you can do for a viral infection, but these drugs work, and the faster we use them after symptom onset the better they work," Dr. Stiver agreed in an interview. And although clinical trials suggest minimal benefits if antivirals are administered more than 36 hours after symptom onset, the window is likely even shorter.

"There are very significant differences between using them at 36 hours and using them at 12 hours or even 24 hours," he said, noting that a 3-day reduction in symptoms has been shown when the medications are administered within 12 hours. This tight window of opportunity is a major barrier to the medications' widespread use, he said. "Most patients who develop an acute febrile illness, unless they're very, very sick, don't see a doctor for 48 or 36 hours, so it's a matter of education of the public that there is something available."

He suggested that in the event of an influenza epidemic, a better system needs to be in place to help patients access antivirals quickly. "You can't do this through doctors' offices. There must be some kind of algorithm set up whereby in major epidemics patients can receive the medication through pharmacies with some prearranged prescription from their physician." This would have to be directed by a public health alert to prevent patients from stockpiling or self-prescribing to treat other noninfluenza viruses, he said. ■

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 ß5% 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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ALTERNATIVE MEDICINE

AN EVIDENCE-BASED APPROACH

American Ginseng for Prevention of Respiratory Illness

History and Rationale for Use

Nearly 300 years ago, the first descriptions of Asian *Panax ginseng* reached the West from China, and shortly thereafter another member of this genus, *Panax quinquefolius,* was identified in Canada. This plant was later found in many locales in eastern North America, especially n the Cumberland Gap region of Appalachia. It was widely used by Native Americans for childbirth, fertility, and shortness of breath. According to the American Botanical Council, it was listed in the United States Pharmacopeia from 1842 to 1882.

Extracts of the roots of *P. quinquefolius* have immunomodulatory effects, including enhancing the production of interleukin (IL)-1, IL-6, and tumor necrosis factor–α, as well as of the major T-cell and natural killer cell cytokines IL-2 and interferon-gamma (J. Altern. Complement. Med. 2006;12:153-7). The plant's polysaccharide and oligosaccharide fractions are thought to be responsible for these effects.

Clinical Trials

One two-phase seasonal prophylaxis study compared a standardized proprietary formulation (CVT-E002, COLD-fX, CV Technologies, Edmonton, Alta.), 200 mg twice daily, with placebo for preventing respiratory illnesses, including influenza and respiratory syncytial virus (RSV) infection, in institutionalized older adults. The first phase enrolled 89 patients aged 60 years and older from assisted living or nursing homes during February and March 2000; the second phase enrolled 109 patients beginning in December 2000. During both phases of the double-blind trial, documented influenza was circulating in the community. One patient in the first study who was asymptomatic at the time of randomization subsequently developed culture-confirmed RSV infection.

About 90% of subjects received influenza vaccine. The primary end point was clinically confirmed acute respiratory illness; secondary end points included severity and duration of illness and laboratory-confirmed influenza or RSV infection. The likelihood of acute respiratory illness, based on the primary end point of symptoms, was not significantly lower in the treatment group. For the secondary end point of laboratory-confirmed influenza or RSV, there was an 89% lower relative risk with treatment (J. Am. Geriatr. Soc. 2004;52:13-9).

► *Extracts of the root of* Panax quinquefolius *have demonstrated various immunomodulatory effects.*
► *A proprietary formulation, CVT-E002, has shown benefits for the prevention of colds and influenza in clinical trials.*

In a recent multicenter study, the primary end point was laboratory-confirmed respiratory illness, said Dr. Janet E. McElhaney of the Center for Immunotherapy of Cancer and Infectious Diseases, University of Connecticut, Farmington, who was lead investigator for the first trial. "I'm more interested in reducing actual laboratory-diagnosed respiratory illness, because one of the things we ran into with the first trial was symptom overlap with some of the seasonal allergies seen in the spring," she said.

More than 90% of patients in both groups reported adverse events. The most common events were gastrointestinal, and all were judged to be unrelated to the study medication. Serious adverse events occurred in 11% and 6% of the placebo and active study groups, respectively. All serious adverse events were considered unrelated to the study drug.

Another study tested CVT-E002 for preventing respiratory tract infections in 43 community-dwelling adults aged 65 years and older. They were randomized in double-blind fashion to receive placebo or 200 mg twice daily of the ginseng extract for 16 weeks.

During the first 8 weeks, a similar proportion of patients in the two groups reported respiratory symptoms; during the last 8 weeks, 32% of patients in the active treatment group and 62% of those in the placebo group reported symptoms. This statistically significant difference represented a 48% relative risk reduction (J. Altern. Complement. Med. 2006;12:153-7).

During the first 8 weeks, the mean duration of symptoms was not significantly different between the groups, but in the last 8 weeks, the duration of symptoms was 55% shorter in the treatment group.

A third randomized, double-blind study analyzed data from 279 subjects aged 18-65 years recruited from the general population of Edmonton. They received 200 mg of CVT-E002 twice daily or placebo for 4 months starting in November 2003. The mean number of colds per person was less in the ginseng group (0.68) than in the placebo group (0.93), but the difference was not significant. But use of the ginseng extract was associated with a 12.8% absolute risk reduction of recurrent colds and 31% lower total symptom scores. Total number of days of symptoms was 34.5% lower in the treatment group (CMAJ 2005;173:1043-8).

One Expert's View

"I will be interested in seeing the results of the latest larger trial, but for now, based on its safety profile, I think that COLD-fX definitely has merit in terms of taking it during the winter months for prevention of respiratory illness, especially for the older population," said Dr. McElhaney, who is also a professor of medicine at the University of British Columbia, Vancouver.

All three trials were sponsored by CV Technologies.

—Nancy Walsh