

Old Drug Combo Prevents Colorectal Adenomas

BY BETSY BATES

Los Angeles Bureau

SAN DIEGO — Small doses of two historic drugs administered in tandem profoundly reduced the development of colorectal adenomas in patients with prior adenoma formation, heralding a “mid-game home run” in secondary chemoprevention, investigators reported at the annual meeting of the American Association for Cancer Research.

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia (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 \geq Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed injury, anxiety. *Primarily ejaculatory delay. †Denominator used was for males only (N=225 Lexapro; N=188 placebo). ‡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: Headache (24% and 17%); Paresthesia (2% 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[†] (14% and 2%); Anorgasmia[‡] (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 \geq Lexapro: inflamed injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). †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 $\geq 2\%$ 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 (2%, 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 experiences 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 1429 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, lightness of chest, leg pain, asthenia, syncope, malaise, anapylaxis, 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 spasm, 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, 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, anioedema, 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, prothrombinemia, 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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Rev. 07/07

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Dr. Frank L. Meyskens Jr., professor of medicine and biological chemistry at the University of California, Irvine, presented late-breaking results from a phase III trial of difluoromethylornithine (DFMO), a synthetic inhibitor of ornithine decarboxylase, and sulindac (Clinoril), an NSAID, in 375 patients.

Patients were recruited following resection of at least one adenoma (3 mm or larger) discovered on colonoscopy—a history placing them at significant risk of recurrence.

Oral doses of DFMO (500 mg) and sulindac (150 mg) daily were given to 191 randomized patients, while 184 were assigned to placebo. Low-dose aspirin was used by approximately 40% of patients in each group.

At 3 years' follow-up, total adenomas detected by colonoscopy were reduced by 70%, advanced adenomas by 92%, and multiple adenomas by 95%.

Specifically, an adenoma was found in 42 of 97 patients who received placebo and completed the trial (43%), compared with 12 of 107 on the DFMO/sulindac combination (11%). Advanced adenomas—large, intramucosal or invasive adenomas with histologic features linked with conversion to colorectal cancer—were seen in nine (9.3%) patients in the placebo group and one patient receiving combination chemoprevention. More than one adenoma was found in 15 patients receiving placebo and 1 patient in the chemoprevention arm.

“These are absolutely stunning findings,” Dr. Scott M. Lippman told meeting attendees in a formal discussion of the phase III results. “I would consider this a mid-game home run.”

The research culminates a “long quest” by Dr. Meyskens and coinvestigator Dr. Eugene W. Gerner of the University of Arizona, Tucson, to fight the development of cancer by targeting ornithine decarboxylase, a key polyamine pathway that acts as an instigator of growth.

DFMO, long abandoned as chemotherapy because of inefficacy and hearing-related toxicity, was known to prevent many forms of cancer in preclinical and in vitro models. The researchers conducted novel “de-escalation” dose-finding trials, determining in the mid-1990s that a 500-mg dose (one-fiftieth of the therapeutic dose and one-quarter of the ototoxic dose) could reduce the polyamine content of colonic flat mucosa.

The decision was made to combine the drug (approved for African sleeping sickness and, more recently, as a topical depilatory) with sulindac, an NSAID in use for a half-century, to maximize each drug's efficacy at the smallest possible doses.

Sulindac has multiple mechanisms of action and was used in the trial at a 150-mg dose daily, half the dose used in the treatment of arthritis.

Adverse events were carefully monitored, with particular attention given to cardiovascular and otologic side effects previous-

ly associated with NSAIDs and DFMO.

At least one serious adverse event requiring hospitalization was seen in 31 patients receiving placebo and 42 patients in the DFMO/sulindac group. No significant difference was seen in the number of patients experiencing a serious adverse event.

Serious cardiovascular side effects occurred in 16 patients receiving active treatment versus 9 in the placebo arm. This difference, while not statistically significant, may indicate a “worrisome trend” and deserves more study, according to Dr. Lippman of the M.D. Anderson Cancer Center, Houston, a formal discussant of the study.

No hearing loss was perceived in patients receiving DFMO and sulindac, although a 1- to 2-dB difference was found in precise hearing tests. This difference is “a sound equivalent to rubbing your two fingers together,” Dr. Meyskens said. The hearing loss was reversible with discontinuation of the drug.

The DFMO/sulindac drug combination also has shown “very promising” results in early studies of prostate cancer and is being studied as a topical agent in skin cancers.

Future research may investigate its chemopreventive potential in patients with “cured” low-stage colorectal cancer, and a larger group of patients with prior advanced adenomas detected at colonoscopy.

However, because DFMO has gone off patent, creative solutions are being sought to finance future studies of the drug combination's potential as a chemopreventive agent, Dr. Meyskens said.

The study was published online simultaneously with the presentation at AACR (Cancer Prev. Res. 2008 April [Epub doi: 10.1158/1940-6207.CAPR-08-0042]). ■

Patient Preference May Affect Adherence to Referrals for Colorectal Cancer Screening

BY KATE JOHNSON

Montreal Bureau

MONTREAL — Primary care physicians referring patients for routine colorectal cancer screening may see better adherence, particularly among men, if they consider patient preference regarding screening modality, reported Maida Sewitch, Ph.D., from McGill University, Montreal. However, the picture is less clear for women.

In a study of 203 primary care patients referred for colorectal cancer screening (40% male, mean age 64 years), overall adherence was 52%, Dr. Sewitch reported in a poster at Canadian Digestive Diseases Week.

For both genders combined, the strongest predictor of adherence was a physician's referral that matched a patient's preferred screening modality (adjusted odds ratio 3.64), she said. However, the results looked quite different when analyzed according to patient gender.

“What we found was that the people for whom matched modality was important were the men—and that men who were matched on modality were 3.5 times more

likely to adhere to screening referral than men who were not matched. But women didn't care about modality. We didn't expect that at all,” Dr. Sewitch said in an interview.

The four choices of screening modality offered in the study were colonoscopy, double contrast barium enema, flexible sigmoidoscopy, and fecal occult blood testing (FOBT). The most commonly requested modality was FOBT, she said.

Although matching the referral modality to patient preference increased the odds of screening adherence in men (AOR 3.49), it only had a slight impact in women (AOR 1.24), she said. Instead, the predictor of female adherence to screening was past history of screening (AOR 2.1), she reported.

Women may “have more trust in their physician's recommendation, and a past history of screening may demystify the experience, whereas men want what they want,” Dr. Sewitch said. “It might have a lot to do with control.”

“Physicians should be speaking with patients about what they want. If they're going to recommend some kind of colorectal cancer screening, they can ask their patients what they want to do and give

their referral based on that,” she said.

A second poster presented at the meeting described an investigation of patient preference regarding the timing of a pre-colonoscopy consult with a gastroenterologist. A total of 125 average-risk patients (66% male, mean age 60 years) participated in the study, with 21% receiving a gastroenterology consult on a different day (DD) previous to their colonoscopy, and 79% receiving the consult on the same day (SD), just before their colonoscopy.

Patients were asked to complete a questionnaire after their colonoscopy regarding their preference for a DD or SD consult, reported Dr. Liliana Oliveira from the University of Ottawa. The study found that patient preferences appeared to be affected only by prior consultation experience. Among patients who had an SD consult, 86% indicated a preference for this practice, and among those who had a DD consult, 61.5% preferred this practice; these findings were significant.

She stressed that SD consultation is only intended for average-risk patients. Although SD consultation is common, she said it remains somewhat controversial. ■