

Give Levothyroxine Separately for Best Absorption

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SAN FRANCISCO — A few hours' buffer between taking thyroxine and other medications can help ensure optimal absorption of the thyroid hormone, according to several researchers.

Many nutritional supplements and commonly prescribed medications interfere with thyroid absorption, the researchers said at the annual meeting of the Endocrine

Society. When taken together, some medications bind the hormone so completely that virtually none enters the bloodstream.

"In most cases, it's believed that malabsorption of levothyroxine is due to binding of the hormone to other medications in the gut lumen, forming an insoluble or nonabsorbable complex," Dr. Steven P. Weitzman said in a poster presented at the meeting. Even newer compounds, which were thought to result in less malabsorption, seem to be problematic.

Dr. Weitzman, an endocrinologist at Stony Brook University, New York, examined the interaction of levothyroxine with two relatively new drugs—colesevelam (Welchol), the newest bile acid sequestrant approved for hyperlipidemia and diabetes; and lanthanum carbonate (Fosrenol), a new phosphate binder used in end-stage renal disease. The study included six healthy, euthyroid subjects, who first took levothyroxine 1 mg alone, then levothyroxine with 3.8 g colesevelam, then levothyroxine with 500 mg lanthanum carbonate. A minimum of 3 weeks separated each dosing study.

Total serum T₄ and TSH were measured at regular intervals during the 6 hours after administration of the study medications. Results were reported as both the area under the curve response and serum T₄ concentration.

Within 1 hour of taking levothyroxine alone, subjects displayed a sharp increase in serum T₄ from a mean of 7 mcg/dL to 10 mcg/dL. Serum T₄ peaked at 4 hours, reaching a mean level of 13 mcg/dL. The area under the curve response was 1,692 g·min/mL.

T₄ concentrations were significantly lower after the subjects took the hormone with lanthanum carbonate. At 1 hour, the T₄ level had risen to a mean of 8.6 mcg/dL. At 6 hours, the peak level was 11 mcg/dL. The area under the curve response was 982 g·min/mL.

Colesevelam exerted the largest inhibitory response on serum T₄. By 1 hour after taking the hormone and the medication together, mean T₄ levels rose to 7.6

mcg/dL and peaked there after 2 hours. The area under the curve response was only 107 g·min/mL.

"Both colesevelam and lanthanum carbonate reduced the absorption of levothyroxine and blunted the rise in serum T₄ when given with levothyroxine," Dr. Weitzman said. "Colesevelam appeared to be a particularly potent inhibitor of T₄ absorption and nearly abolished the increase in serum T₄."

In a second study, Dr. Bandar Alshehri, an endocrinology fellow at the University of Toronto, and colleagues performed a chart review of 549 hospitalized patients treated with levothyroxine during a mean 11-day hospital stay. Most of these patients (67%) were also receiving supplements or drugs known to inhibit the absorption of T₄. The offending compounds were proton pump inhibitors (42%), calcium supplements (28%), iron supplements (15%), multivitamins (13%), psyllium fiber (12%), and magnesium-containing antacids or laxatives (1%).

Most of the patients (97%) received their levothyroxine during the daytime; the majority (88%) also got their other medications during the same period.

Ninety percent of patients were getting the hormone within 1 hour of the potentially interfering medications. Fewer than 1% received the medications at least 4 hours apart. A simple change—routine administration of levothyroxine at bedtime—could reduce the offending coadministration rate to around 19%, because the interfering medications are not usually administered at bedtime, Dr. Alshehri said. ■

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1%); Libido Decreased (3% and 1%); **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%); **Urogenital:** Ejaculation Disorder^{1,2} (9% and <1%); Impotence (3% and <1%); Anorgasmia¹ (2% and <1%). ¹Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. ²Primarily ejaculatory delay. ³Denominator used was for males only (N=225 Lexapro; N=188 placebo). ⁴Denominator 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 Disorder¹ (Percentage of Patients Reporting Event) Body System/Adverse Event (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%); Anorgasmia¹ (6% and <1%); Menstrual Disorder (2% and 1%). ¹Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. ²Primarily ejaculatory delay. ³Denominator used was for males only (N=182 Lexapro; N=195 placebo). ⁴Denominator 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 Events¹ in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=310).** **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%). ¹Adverse 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; Adverse Event: 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=698)]: Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priligis 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, disequilibrium, 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, lightheadedness, 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, attrition reaction, 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, bruising, 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. ¹% 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 spontaneous and clinical trial experience and were not observed during the premarketing evaluation of escitalopram: Blood and Lymphatic System Disorders: hemolytic anemia, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, cardiac failure, myocardial infarction, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma. Gastrointestinal Disorders: gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait. Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction. Investigations: electrocardiogram QT prolongation, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hypoglycemia, hypokalemia. Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis. Nervous System Disorders: akathisia, choreoathetosis, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hyposensitivity, myoclonus, neuroleptic malignant syndrome, nystagmus, seizures, serotonin syndrome, tardive dyskinesia. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, anger, delirium, delusion, nightmare, paranoia, visual hallucinations. Renal and Urinary Disorders: acute renal failure. Reproductive System and Breast Disorders: priapism. Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism. Skin and Subcutaneous Tissue Disorders: angioedema, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, hypotension, orthostatic hypotension, phlebitis thrombosis. Forest Pharmaceuticals, Inc. Subsidiary of Forest Laboratories, Inc. 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Subclinical Hyperthyroidism Elevates All-Cause Mortality

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SAN FRANCISCO — A diagnosis of subclinical hyperthyroidism significantly increases the risk of death from any cause in the subsequent 10 years, especially among elderly patients, according to Dr. Patrick Haentjens.

The increased risk of death starts low and increases up until about age 80, with an overall increased risk of 41%, Dr. Haentjens said at the annual meeting of the Endocrine Society. After age 80, competing causes of death eliminate the association with thyroid dysfunction.

When translated to an absolute risk of death, excess mortality for a white U.S. woman diagnosed at age 70 was only 1.5% at 2 years, but increased to almost 9% by 10 years, said Dr. Haentjens of the Center for Outcomes Research, University of Ziekenhuis, Brussels. Men seemed to fare worse; for a white U.S. man diagnosed at age 70, the excess mortality risk was 2% at 2 years, 6% at 5 years, and almost 11% at 10 years after the diagnosis.

However, Dr. Haentjens' meta-analysis found no significantly increased mortality risk associated with subclinical hypothy-

roidism. The study was published online in the *European Journal of Endocrinology* (doi:10.1530/EJE-08-0110).

The meta-analysis included nine papers, which reported data on seven cohorts with subclinical hyperthyroidism (290 patients) and nine cohorts with subclinical hypothyroidism (1,580 patients). The individual studies compared long-term outcomes among these patients and 13,000 euthyroid controls. Follow-up ranged from 2 to 20 years.

Among the seven cohorts with subclinical hyperthyroidism, the hazard ratio for all-cause mortality ranged from 0.84 to 2.22. Only one paper (*Lancet* 2001;358:861-5) found a significant increase. However, in the pooled analysis, the overall risk was significantly increased, with a hazard ratio of 1.41, compared with euthyroid controls. Among the nine cohorts that explored all-cause mortality in patients with subclinical hypothyroidism, the hazard ratio ranged from 0.49 to 2. Three studies found significant differences, but one of them reported a significantly decreased risk of all-cause mortality, while the other two reported a significantly increased risk. Overall, the pooled analysis did not show an increased all-cause mortality risk. ■