

Data Sought on Alternative for PCOS Infertility

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PHILADELPHIA — The jury is still out on whether aromatase inhibitors could offer an alternative to clomiphene in the treatment of infertility associated with polycystic ovary syndrome, said endocrinologist Andrea D. Coviello of Boston University.

Aromatase inhibitors have been approved for use in breast cancer but are still experimental for ovulation induction, Dr. Coviello

said at Endocrinology in the News, sponsored by Boston University, INTERNAL MEDICINE NEWS, and FAMILY PRACTICE NEWS.

Instead of blocking the receptors centrally in the hypothalamus and the pituitary, aromatase inhibitors block estradiol production. Like clomiphene, aromatase inhibitors are used during the follicular phase.

The rationale for moving to aromatase inhibitors is that this class of drugs is thought to have fewer antiestrogenic side effects, including a lower risk of ovarian hyperstim-

ulation syndrome and a lower risk of multiple gestation. But there are also significant concerns about fetal development problems in the babies conceived using aromatase inhibitors, she said. A definitive study to help physicians assess how aromatase inhibitors stack up to clomiphene has yet to be done. Current data are from small studies, said Dr. Coviello, who said she has no commercial support to disclose.

In a prospective, randomized trial of 74 patients, there was no significant difference

in pregnancy rates between those receiving clomiphene and those receiving the aromatase inhibitor, letrozole (Fertil. Steril. 2006;86:1447-51). But estrogen levels were significantly lower in the letrozole group on the day of human chorionic gonadotropin administration, indicating potential for a better side-effect profile with letrozole.

INTERNAL MEDICINE NEWS, FAMILY PRACTICE NEWS, and this newspaper are published by the International Medical News Group, a division of Elsevier. ■

occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo were: **Cardiac Disorders**—palpitations; **Eye Disorders**—vision blurred; **Gastrointestinal Disorders**—nausea, dry mouth, diarrhea, constipation*, abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain), vomiting; **General Disorders and Administration Site Conditions**—fatigue (includes asthenia); **Investigations**—weight decreased*; **Metabolism and Nutrition Disorders**—decreased appetite (includes anorexia); **Nervous System Disorders**—dizziness, somnolence (includes hypersomnia and sedation), tremor; **Psychiatric Disorders**—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), anxiety, decreased libido (includes loss of libido), orgasm abnormal (includes anorgasmia), abnormal dreams (includes nightmare); **Reproductive System and Breast Disorders**—erectile dysfunction, ejaculation delayed, ejaculation disorder (includes ejaculation failure and ejaculation dysfunction); **Respiratory, Thoracic, and Mediastinal Disorders**—yawning; **Skin and Subcutaneous Tissue Disorders**—hyperhidrosis; **Vascular Disorders**—hot flush. *Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

The most commonly observed adverse reactions in duloxetine-treated MDD/GAD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were nausea, dry mouth, constipation, somnolence, decreased appetite, and hyperhidrosis.

Diabetic Peripheral Neuropathic Pain—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPN placebo-controlled trials (N=225 Cymbalta 60 mg BID; N=228 Cymbalta 60 mg QD; N=115 Cymbalta 20 mg QD; N=223 placebo) with an incidence greater than placebo were: **Gastrointestinal Disorders**—nausea, constipation, diarrhea, dry mouth, vomiting, dyspepsia, loose stools; **General Disorders and Administration Site Conditions**—fatigue, asthenia, pyrexia; **Infections and Infestations**—nasopharyngitis; **Metabolism and Nutrition Disorders**—decreased appetite, anorexia; **Musculoskeletal and Connective Tissue Disorders**—muscle cramp, myalgia; **Nervous System Disorders**—somnolence, headache, dizziness, tremor; **Psychiatric Disorders**—insomnia; **Renal and Urinary Disorders**—pollakiuria; **Reproductive System and Breast Disorders**—erectile dysfunction; **Respiratory, Thoracic and Mediastinal Disorders**—cough, pharyngolaryngeal pain; **Skin and Subcutaneous Tissue Disorders**—hyperhidrosis.

The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence ≤ placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia.

Effects on Male and Female Sexual Function—Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. Physicians should routinely inquire about possible sexual side effects. See Table 5 in full PI for specific ASEX results.

Vital Sign Changes—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure [see **Warnings and Precautions**].

Duloxetine treatment, for up to 13-weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3 beats per minute.

Weight Changes—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

Laboratory Changes—Cymbalta treatment in placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients [see **Warnings and Precautions**].

Electrocardiogram Changes—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13-weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg BID, no prolongation of the corrected QT interval was observed.

Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine—Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 23,983 patients were treated with duloxetine. Of these, 6,702 took duloxetine for at least 6 months, and 3,006 for at least one year. The following listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. **Cardiac Disorders**—Frequent: palpitations; Infrequent: myocardial infarction and tachycardia; **Ear and Labyrinth Disorders**—Frequent: vertigo; Infrequent: ear pain and tinnitus; **Endocrine Disorders**—Infrequent: Hypothyroidism; Eye Disorders—Frequent: vision blurred; Infrequent: diplopia and visual disturbance; **Gastrointestinal Disorders**—Frequent: flatulence; Infrequent: eructation, gastritis, halitosis, and stomatitis; Rare: gastric ulcer, hematochezia, and melena; **General Disorders and Administration Site Conditions**—Frequent: chills/rigors; Infrequent: feeling abnormal, feeling hot and/or cold, malaise, and thirst; Rare: gait disturbance; **Infections and Infestations**—Infrequent: gastroenteritis and laryngitis; **Investigations**—Frequent: weight increased; Infrequent: blood cholesterol increased; **Metabolism and Nutrition Disorders**—Infrequent: dehydration and hyperlipidemia; Rare: dyslipidemia; **Musculoskeletal and Connective Tissue Disorders**—Frequent: musculoskeletal pain; Infrequent: muscle tightness and muscle twitching; **Nervous System Disorders**—Frequent: dysgeusia, lethargy, and paresthesia/hypoesthesia; Infrequent: disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; Rare: dysarthria; **Psychiatric Disorders**—Frequent: abnormal dreams and sleep disorder; Infrequent: apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; Rare: completed suicide; **Renal and Urinary Disorders**—Infrequent: dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal; **Reproductive System and Breast Disorders**—Frequent: anorgasmia/orgasm abnormal; Infrequent: menopausal symptoms, and sexual dysfunction; **Respiratory, Thoracic and Mediastinal Disorders**—Frequent: yawning; Infrequent: throat tightness; **Skin and Subcutaneous Tissue Disorders**—Infrequent: cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; Rare: ecchymosis; **Vascular Disorders**—Frequent: hot flush; Infrequent: flushing, orthostatic hypotension, and peripheral coldness.

Postmarketing Spontaneous Reports—The following adverse reactions have been identified during postapproval use of Cymbalta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

DRUG INTERACTIONS: Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2—When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine t_{1/2} was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin [see **Warnings and Precautions**].

Inhibitors of CYP2D6—Concomitant use of duloxetine (40 mg QD) with paroxetine (20 mg QD) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine) [see **Warnings and Precautions**].

Dual Inhibition of CYP1A2 and CYP2D6—Concomitant administration of duloxetine 40 mg BID with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and C_{max}.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)—Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued [see **Warnings and Precautions**].

Lorazepam—Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam—Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption [see **Warnings and Precautions**].

Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg BID).