

# United States Not Yet Ready For Gender-Blind T Scores

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SAN FRANCISCO — A trend toward using one set of parameters to diagnose osteoporosis in both men and women hasn't caught on in the United States, where sex-specific bone density scores are the norm, Eric S. Orwoll, M.D., said at a meeting on osteoporosis sponsored by the University of California, San Francisco.

Yet despite the ease of a gender-blind system and some persuasive data, using a sex-specific method is the way to go, at least until more data accumulate on bone loss and fracture risk in men, suggested Dr. Orwoll, professor of medicine at Oregon Health and Science University, Portland.

The evidence supporting the use of one set of parameters is mounting. Studies in recent years have shown, for example, that the 1-year risk for hip fracture overlaps in men and women with the same hip bone mineral densities. As the density gets lower, the risk for fracture increases at essentially the same rate in both sexes.

Such findings have led some bone experts to suggest that it would be easier and logical for clinicians to use just one reference range for diagnosing osteoporosis instead of using separate T scores for men and women. Bone densitometry machines in the United States currently calculate a sex-specific T score.

**‘There’s a little bit of incongruity in the application of the [international] recommendations, despite the fact that they’re scientifically reasonable.’**

The International Osteoporosis Foundation in 2000 noted that the same absolute values of bone density in men and women yield the same absolute risk of vertebral or hip fracture, suggesting that using one threshold for calculating risk makes sense. The data on men are scanty, according to the statement.

Those who favor using one set of parameters usually propose using T scores that report the number of standard deviations between current bone density and the mean peak density of a 30-year-old female.

But the problem with using such a strategy, Dr. Orwoll said, is that only about 3% of older men would be identified as osteoporotic, in comparison with a young female reference population, while 19% of older men would be deemed osteoporotic if their T scores came from reference to young male norms.

About 25%-30% of older men will have a fragility fracture, but if the female reference range were used, only a small percentage of them would be identified as osteoporotic.

“So there’s a little bit of incongruity in the application of the International Osteoporosis Foundation recommendations, despite the fact that they’re scientifically reasonable,” he said.

Dr. Orwoll encouraged clinicians to keep using the current system of sex-specific T scores from densitometry machines until better, long-term, prospective data on fracture risk in men become available.

He added that it’s also critical to include other clinical criteria besides T scores in identifying fracture risk in men. ■

estimates of relative fracture risk for a patient with below-average risk.

“In the unadjusted analysis, physicians who received augmented BMD reports were no more or less likely to recommend prescription medications for any of the vignettes,” Dr. Neuner said. In the adjusted model, however, 25% of the physicians who received the augmented BMD would have prescribed drug therapy for the below-average-risk 70-year-old, compared with 36% of the physicians who received the standard BMD report only—a statistically significant difference, she said.

Physicians in the standard BMD

group who correctly identified the woman as having a below-average risk of hip fracture based on age, weight, and hip BMD also were less likely to recommend drug therapy, she added.

The findings suggest that adding quantitative fracture risk estimates to BMD reports “has the potential to change physician prescribing behavior” for women at low risk for osteoporosis. Similarly, educating primary care providers about risk classification could change their perceptions about who should get preventive drug therapy, Dr. Neuner said. ■

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

No carcinogenic effect of meloxicam was observed in rats given oral doses up to 0.8 mg/kg/day (approximately 0.4-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) for 104 weeks or in mice given oral doses up to 8.0 mg/kg/day (approximately 2.2-fold the human dose, as noted above) for 99 weeks.

Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow.

Meloxicam did not impair male and female fertility in rats at oral doses up to 9 and 5 mg/kg/day, respectively (4.9-fold and 2.5-fold the human dose, as noted above). However, an increased incidence of embryolethality at oral doses  $\geq 1$  mg/kg/day (0.5-fold the human dose, as noted above) was observed in rats when dams were given meloxicam 2 weeks prior to mating and during early embryonic development.

**Pregnancy**

**Teratogenic Effects:** Pregnancy Category C.

Meloxicam caused an increased incidence of septal defect of the heart, a rare event, at an oral dose of 60 mg/kg/day (64.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) and embryolethality at oral doses  $\geq 5$  mg/kg/day (5.4-fold the human dose, as noted above) when rabbits were treated throughout organogenesis. Meloxicam was not teratogenic in rats up to an oral dose of 4 mg/kg/day (approximately 2.2-fold the human dose, as noted above) throughout organogenesis. An increased incidence of stillbirths was observed when rats were given oral doses  $\geq 1$  mg/kg/day throughout organogenesis. Meloxicam crosses the placental barrier. There are no adequate and well-controlled studies in pregnant women. MOBIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects:**

Meloxicam caused a reduction in birth index, live births, and neonatal survival at oral doses  $\geq 0.125$  mg/kg/day (approximately 0.07-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) when rats were treated during the late gestation and lactation period. No studies have been conducted to evaluate the effect of meloxicam on the closure of the ductus arteriosus in humans; use of meloxicam during the third trimester of pregnancy should be avoided.

**Labor and Delivery**

Studies in rats with meloxicam, as with other drugs known to inhibit prostaglandin synthesis, showed an increased incidence of stillbirths, increased length of delivery time, and delayed parturition at oral dosages  $\geq 1$  mg/kg/day (approximately 0.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion), and decreased pup survival at an oral dose of 4 mg/kg/day (approximately 2.1-fold the human dose, as noted above) throughout organogenesis. Similar findings were observed in rats receiving oral dosages  $\geq 0.125$  mg/kg/day (approximately 0.07-fold the human dose, as noted above) during late gestation and the lactation period.

**Nursing Mothers**

Studies of meloxicam excretion in human milk have not been conducted; however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. Because of the potential for serious adverse reactions in nursing infants from MOBIC, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

**Geriatric Use**

Caution should be exercised in treating the elderly (65 years and older).

**ADVERSE REACTIONS**

The MOBIC phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with MOBIC 7.5 mg/day, 3505 OA patients and 1351 RA patients treated with MOBIC 15 mg/day. MOBIC at these doses was administered to 661 patients for at least 6 months and to 312 patients for at least one year. Approximately 10,500 of these patients were treated in ten placebo and/or active-controlled osteoarthritis trials and 2363 of these patients were treated in ten placebo and/or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across MOBIC trials.

A 12-week multicenter, double-blind, randomized trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of MOBIC with placebo and with an active control. Two 12-week multicenter, double-blind, randomized trials were conducted in patients with rheumatoid arthritis to compare the efficacy and safety of MOBIC with placebo.

**The following adverse events (%) occurred in  $\geq 2\%$  of MOBIC 7.5 mg daily (n=154) and 15 mg daily (n=156) patients, respectively, in a 12-week osteoarthritis placebo- and active-controlled trial:** abdominal pain, 1.9%, 2.6%; diarrhea, 7.8%, 3.2%; dyspepsia, 4.5%, 4.5%; flatulence, 3.2%, 3.2%; nausea, 3.9%, 3.8%; accident household, 4.5%, 3.2%; edema<sup>1</sup>, 1.9%, 4.5%; fall, 2.6%, 0.0%; influenza-like symptoms, 4.5%, 5.8%; dizziness, 2.6%, 3.8%; headache, 7.8%, 8.3%; pharyngitis, 0.6%, 3.2%; upper respiratory tract infection, 3.2%, 1.9%; rash<sup>2</sup>, 2.6%, 0.6%.

**The following adverse events (%) occurred with MOBIC 7.5 mg daily in  $\geq 2\%$  of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials:** abdominal pain, 2.7%, 4.7%; constipation, 0.8%, 1.8%; diarrhea, 1.9%, 5.9%; dyspepsia, 3.8%, 8.9%; flatulence, 0.5%, 3.0%; nausea, 2.4%, 4.7%; vomiting, 0.6%, 1.8%; edema<sup>1</sup>, 0.6%, 2.4%; pain, 0.9%, 3.6%; dizziness, 1.1%, 2.4%; headache, 2.4%, 3.6%; anemia, 0.1%, 4.1%; arthralgia, 0.5%, 5.3%; back pain, 0.5%, 3.0%; insomnia, 0.4%, 3.6%; coughing, 0.2%, 2.4%; upper respiratory tract infection, 0.2%, 8.3%; pruritus, 0.4%, 2.4%; rash<sup>2</sup>, 0.3%, 3.0%; micturition frequency, 0.1%, 2.4%; urinary tract infection, 0.3%, 4.7%.

**The following adverse events (%) occurred with MOBIC 15 mg daily in  $\geq 2\%$  of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials:** abdominal pain, 2.3%, 2.9%; constipation, 1.2%, 2.6%; diarrhea, 2.7%, 2.6%; dyspepsia, 7.4%, 9.5%; flatulence, 0.4%, 2.6%; nausea, 4.7%, 7.2%; vomiting, 0.8%, 2.6%; edema<sup>1</sup>, 2.0%, 1.6%; pain, 2.0%, 5.2%; dizziness, 1.8%, 2.6%; headache, 2.7%, 2.6%; anemia, 0.0%, 2.9%; arthralgia, 0.0%, 1.3%; back pain, 0.4%, 0.7%; insomnia, 0.0%, 1.6%; coughing, 0.8%, 1.0%; upper respiratory tract infection, 0.0%, 7.5%; pruritus, 1.2%, 0.0%; rash<sup>2</sup>, 1.2%, 1.3%; micturition frequency, 0.4%, 1.3%; urinary tract infection, 0.4%, 6.9%.

<sup>1</sup>WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined. <sup>2</sup>WHO preferred terms rash, rash erythematous and rash maculo-papular combined.

**The following adverse events (%) occurred respectively with MOBIC 7.5 and 15 mg daily in  $\geq 2\%$  of patients treated in two 12-week rheumatoid arthritis placebo controlled trials:** abdominal pain NOS<sup>3</sup>, 2.9%, 2.3%; diarrhea NOS<sup>3</sup>, 4.8%, 3.4%; dyspeptic signs and symptoms<sup>1</sup>, 5.8%, 4.0%; nausea<sup>2</sup>, 3.3%, 3.8%; influenza like illness<sup>3</sup>, 2.9%, 2.3%; upper respiratory tract infections-pathogen class unspecified<sup>1</sup>, 7.0%, 6.5%; joint related signs and symptoms<sup>1</sup>, 1.5%, 2.3%; musculoskeletal and connective tissue signs and symptoms NEC<sup>1</sup>, 1.7%, 2.9%; headaches NOS<sup>2</sup>, 6.4%, 5.5%; dizziness (excl vertigo)<sup>2</sup>, 2.3%, 0.4%; rash NOS<sup>2</sup>, 1.0%, 2.1%.

<sup>1</sup>MedDRA high level term (preferred terms): dyspeptic signs and symptoms (dyspepsia, dyspepsia aggravated, eructation, gastrointestinal irritation), upper respiratory tract infections-pathogen unspecified (laryngitis NOS, pharyngitis NOS, sinusitis NOS), joint related signs and symptoms (arthralgia, arthralgia aggravated, joint crepitation, joint effusion, joint swelling), and musculoskeletal and connective tissue signs and symptoms NEC (back pain, back pain aggravated, muscle spasms, musculoskeletal pain).

<sup>2</sup>MedDRA preferred term: diarrhea NOS, abdominal pain NOS, influenza like illness, headaches NOS, dizziness (excl vertigo), and rash NOS.

Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events; therefore the daily dose of MOBIC should not exceed 15 mg.

The following is a list of adverse drug reactions occurring in <2% of patients receiving MOBIC in clinical trials involving approximately 16,200 patients. Adverse reactions reported only in worldwide post-marketing experience or the literature are shown in italics and are considered rare (<0.1%).

**Body as a Whole:** allergic reaction, *anaphylactoid reactions including shock*, face edema, fatigue, fever, hot flushes, malaise, syncope, weight decrease, weight increase. **Cardiovascular:** angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis. **Central and Peripheral Nervous System:** convulsions, paresthesia, tremor, vertigo.

**Gastrointestinal:** colitis, dry mouth, duodenal ulcer, eructation, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage, hematemesis, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis. **Heart Rate and Rhythm:** arrhythmia, palpitation, tachycardia. **Hematologic:** agranulocytosis, leukopenia, purpura, thrombocytopenia. **Liver and Biliary System:** ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis, jaundice, liver failure. **Metabolic and Nutritional:** dehydration. **Psychiatric Disorders:** abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence. **Respiratory:** asthma, bronchospasm, dyspnea. **Skin and Appendages:** alopecia, angioedema, bullous eruption, erythema multiforme, photosensitivity reaction, pruritus, *Stevens-Johnson syndrome*, sweating increased, *toxic epidermal necrolysis*, urticaria. **Special Senses:** abnormal vision, conjunctivitis, taste perversion, tinnitus. **Urinary System:** albuminuria, BUN increased, creatinine increased, hematuria, *interstitial nephritis*, renal failure.

**OVERDOSAGE**

There is limited experience with meloxicam overdose. Four cases have taken 6 to 11 times the highest recommended dose; all recovered. Cholestyramine is known to accelerate the clearance of meloxicam.

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse, and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed with symptomatic and supportive care following an NSAID overdose. In cases of acute overdose, gastric lavage followed by activated charcoal is recommended. Gastric lavage performed more than one hour after overdose has little benefit in the treatment of overdose. Administration of activated charcoal is recommended for patients who present 1-2 hours after overdose. For substantial overdose or severely symptomatic patients, activated charcoal may be administered repeatedly. Accelerated removal of meloxicam by 4 gm oral doses of cholestyramine given three times a day was demonstrated in a clinical trial. Administration of cholestyramine may be useful following an overdose. Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

**Rx only**

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