

Vasomotor Symptoms May Predict Bone Density

BY KATE JOHNSON
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NEW ORLEANS — Premenopausal vasomotor symptoms, particularly night sweats, are a previously unrecognized risk factor for low bone mineral density, according to Dr. Lubna Pal from the Albert Einstein College of Medicine, New York. Her study won the prize paper from the Society for Reproductive Endocrinology and Infertility at the annual meeting of the

American Society for Reproductive Medicine. Based on these data, “I would advise providers to specifically ask about vasomotor symptoms in premenopausal women and, for those who are symptomatic, to focus on unmasking additional factors that may enhance their fracture risk, such as low body mass; family or personal history of fractures; or smoking,” she said in an interview. “I don’t think we are there yet in terms of recommending bone

density screening for this population ... but these women need to be advised that a further deterioration in their bone density parameters is likely to occur in the postmenopausal period.” The cross-sectional study included 86 premenopausal infertile women aged 42 years or younger without premature ovarian failure or oophorectomy. A questionnaire was used to ask about the presence and frequency of vasomotor symptoms, including hot flashes and night sweats.

The study also measured subjects’ bone mineral density (BMD) and levels of serum N-telopeptide (NTx), a marker of bone turnover. A total of 12% of respondents reported one or both vasomotor symptoms, and 21% of respondents had evidence of low BMD, reported Dr. Pal. There was a significant correlation between vasomotor symptoms and low BMD, with 62.5% of symptomatic women showing evidence of low BMD, compared with 14% of asymptomatic women (odds ratio 10.18). Similarly, 36% of women with low BMD reported vasomotor symptoms, compared with 5% of those with normal BMD. After controlling for age, body mass index, menstrual regularity, race, and smoking, the study found that vasomotor symptoms (night sweats and/or hot flashes) were independent predictors of low bone density in the study population. The magnitude of this association was most robust for night sweats, with an adjusted odds ratio (AOR) of 52.47, followed by both symptoms combined (AOR 24.10), and then hot flashes alone (AOR 15.10). The presence of night sweats was also an independent predictor of bone turnover, with higher levels of serum NTx seen in symptomatic compared with asymptomatic women, she said. And finally, levels of inhibin B, a marker of ovarian reserve, were also significantly lower in women with night sweats compared with asymptomatic women, “suggesting that declining ovarian reserve may be a unifying physiologic mechanism tying vasomotor symptoms to both increased bone turnover and low bone density in this young population,” she said. ■

Colposcopy Referral May Not Be Needed For Mild Dyskaryosis

SANTA MONICA, CALIF. — It may not be necessary to refer women for colposcopy after a single, mildly dyskaryotic cervical smear, according to a poster presentation by A.S. Ahmed at the biennial meeting of the International Gynecologic Cancer Society. In a retrospective analysis of 375 patients who had a single smear positive for mild dyskaryosis and were followed for 4 years, Mr. Ahmed of King’s College, London, and his colleagues found that 50% of the follow-up smears were negative in the first year, and 87% stayed negative over the full 4 years. In all, 791 follow-up smears were performed and 477 (60%) were negative. After those negative smears, only 61 (13%) smears in 54 patients (14%) reverted to low-grade abnormalities. Of the 375 patients, 70 (19%) required an excisional biopsy. The prevalence of high-grade cervical intraepithelial neoplasia (CIN) was 11%, and no cases of cancer were detected. The authors said a single mildly abnormal cervical smear need not trigger a referral to colposcopy.

—Robert Finn



BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: FLOMAX® (tamsulosin HCl) capsules are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). FLOMAX capsules are not indicated for the treatment of hypertension.

CONTRAINDICATIONS: FLOMAX (tamsulosin HCl) capsules are contraindicated in patients known to be hypersensitive to tamsulosin HCl or any component of FLOMAX capsules.

WARNINGS: The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in FLOMAX (tamsulosin HCl) capsule treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents there is a potential risk of syncope (see **ADVERSE REACTIONS**).

Patients beginning treatment with FLOMAX capsules should be cautioned to avoid situations where injury could result should syncope occur.

Rarely (probably less than one in fifty thousand patients), tamsulosin, like other alpha₁ antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients must be advised about the seriousness of the condition (see **PRECAUTIONS, Information for Patients**).

PRECAUTIONS: General: 1. *Carcinoma of the prostate:* Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Patients should be evaluated prior to the start of FLOMAX (tamsulosin HCl) capsules therapy to rule out the presence of carcinoma of the prostate.

2. *Intraoperative Floppy Iris Syndrome:* Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients treated with alpha-1 blockers. Most reports were in patients taking the alpha-1 blocker when IFIS occurred, but in some cases, the alpha-1 blocker had been stopped prior to surgery. In most of these cases, the alpha-1 blocker had been stopped recently prior to surgery (2 to 14 days), but in a few cases, IFIS was reported after the patient had been off the alpha-1 blocker for a longer period (5 weeks to 9 months). IFIS is a variant of small pupil syndrome and is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions. The patient’s ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances. The benefit of stopping alpha-1 blocker therapy prior to cataract surgery has not been established.

3. *Sulfa Allergy:* In patients with sulfa allergy, allergic reaction to FLOMAX has been rarely reported. If a patient reports a serious or life threatening sulfa allergy, caution is warranted when administering FLOMAX.

4. *Drug-Drug Interactions:* The pharmacokinetic and pharmacodynamic interactions between FLOMAX capsules and other alpha-adrenergic blocking agents have not been determined. However, interactions may be expected and FLOMAX capsules should NOT be used in combination with other alpha-adrenergic blocking agents.

The pharmacokinetic interaction between cimetidine and FLOMAX capsules was investigated. The results indicate significant changes in tamsulosin HCl clearance (26% decrease) and AUC (44% increase). Therefore, FLOMAX capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Results from limited *in vitro* and *in vivo* drug-drug interaction studies between tamsulosin HCl and warfarin are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX capsules.

Information for Patients: Patients should be told about the possible occurrence of symptoms related to postural hypotension such as dizziness when taking FLOMAX capsules, and they should be cautioned about driving, operating machinery or performing hazardous tasks.

Patients should be advised not to crush, chew or open the FLOMAX capsules.

Patients should be advised about the possibility of priapism as a result of treatment with FLOMAX capsules and other similar medications. Patients should be informed that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction (impotence).

Laboratory Tests: No laboratory test interactions with FLOMAX capsules are known. Treatment with FLOMAX capsules for up to 12 months had no significant effect on prostate-specific antigen (PSA).

Pregnancy: Teratogenic Effects, Pregnancy Category B. Administration of tamsulosin HCl to pregnant female rats at dose levels up to 300 mg/kg/day (approximately 50 times the human therapeutic AUC exposure) revealed no evidence of harm to the fetus. Administration of tamsulosin HCl to pregnant rabbits at dose levels up to 50 mg/kg/day produced no evidence of fetal harm. FLOMAX capsules are not indicated for use in women.

Geriatric Use: Of the total number of subjects (1,783) in clinical studies of tamsulosin, 36% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and the other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Nursing Mothers: FLOMAX capsules are not indicated for use in women.

Pediatric Use: FLOMAX capsules are not indicated for use in pediatric populations.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Rats administered doses up to 43 mg/kg/day in males and 52 mg/kg/day in females had no increases in tumor incidence with the exception of a modest increase in the frequency of mammary gland fibroadenomas in female rats receiving doses $\geq$ 5.4 mg/kg (P<0.015). The highest doses of tamsulosin HCl evaluated in the rat carcinogenicity study produced systemic exposures (AUC) in rats 3 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

Mice were administered doses up to 127 mg/kg/day in males and 158 mg/kg/day in females. There were no significant tumor findings in male mice. Female mice treated for 2 years with the two highest doses of 45 and 158 mg/kg/day had statistically significant increases in the incidence of mammary gland fibroadenomas (P<0.0001) and adenocarcinomas (P<0.0075). The highest dose levels of tamsulosin HCl evaluated in the mice carcinogenicity study produced systemic exposures (AUC) in mice 8 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

The increased incidences of mammary gland neoplasms in female rats and mice were considered secondary to tamsulosin HCl-induced hyperprolactinemia. It is not known if FLOMAX capsules elevate prolactin in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is not known.

Tamsulosin HCl produced no evidence of mutagenic potential *in vitro* in the Ames reverse mutation test, mouse lymphoma thymidine kinase assay, unscheduled DNA repair synthesis assay, and chromosomal aberration assays in Chinese hamster ovary cells or human lymphocytes. There were no mutagenic effects in the *in vivo* sister chromatid exchange and mouse micronucleus assay.

Studies in rats revealed significantly reduced fertility in males dosed with single or multiple daily doses of 300 mg/kg/day of tamsulosin HCl (AUC exposure in rats about 50 times the human exposure with the maximum therapeutic dose). The mechanism of decreased fertility in male rats is considered to be an effect of the compound on the vaginal plug formation possibly due to changes of semen content or impairment of ejaculation. The effects on fertility were reversible showing improvement by 3 days after a single dose and 4 weeks after multiple dosing. Effects on fertility in males were completely reversed within nine weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day tamsulosin HCl (1/5 and 16 times the anticipated human AUC exposure) did not significantly alter fertility in male rats. Effects of tamsulosin HCl on sperm counts or sperm function have not been evaluated.

Studies in female rats revealed significant reductions in fertility after single or multiple dosing with 300 mg/kg/day of the R-isomer or racemic mixture of tamsulosin HCl, respectively. In female rats, the reductions in fertility after single doses were considered to be associated with impairments in fertilization. Multiple dosing with 10 or 100 mg/kg/day of the racemic mixture did not significantly alter fertility in female rats.

ADVERSE REACTIONS: The incidence of treatment-emergent adverse events has been ascertained from six short-term U.S. and European placebo-controlled clinical trials in which daily doses of 0.1 to 0.8 mg FLOMAX (tamsulosin HCl) capsules were used. These studies evaluated safety in 1783 patients treated with FLOMAX capsules and 798 patients administered placebo. Table 3 summarizes the treatment-emergent adverse events that occurred in $\geq$ 2% of patients receiving either FLOMAX capsules 0.4 mg, or 0.8 mg and at an incidence numerically higher than that in the placebo group during two 13-week U.S. trials (US92-03A and US93-01) conducted in 1487 men.

TABLE 3. TREATMENT EMERGENT* ADVERSE EVENTS OCCURRING IN $\geq$ 2% OF FLOMAX CAPSULES OR PLACEBO PATIENTS IN TWO U.S. SHORT-TERM PLACEBO-CONTROLLED CLINICAL STUDIES			
BODY SYSTEM/ ADVERSE EVENT	FLOMAX CAPSULES GROUPS		PLACEBO n=493
	0.4 mg n=502	0.8 mg n=492	
BODY AS WHOLE			
Headache	97 (19.3%)	104 (21.1%)	99 (20.1%)
Infection ²	45 (9.0%)	53 (10.8%)	37 (7.5%)
Asthenia	39 (7.8%)	42 (8.5%)	27 (5.5%)
Back pain	35 (7.0%)	41 (8.3%)	27 (5.5%)
Chest pain	20 (4.0%)	20 (4.1%)	18 (3.7%)
NERVOUS SYSTEM			
Dizziness	75 (14.9%)	84 (17.1%)	50 (10.1%)
Somnolence	15 (3.0%)	21 (4.3%)	8 (1.6%)
Insomnia	12 (2.4%)	7 (1.4%)	3 (0.6%)
Libido Decreased	5 (1.0%)	10 (2.0%)	6 (1.2%)
RESPIRATORY SYSTEM			
Rhinitis ³	66 (13.1%)	88 (17.9%)	41 (8.3%)
Pharyngitis	29 (5.8%)	25 (5.1%)	23 (4.7%)
Cough Increased	17 (3.4%)	22 (4.5%)	12 (2.4%)
Sinusitis	11 (2.2%)	18 (3.7%)	8 (1.6%)
DIGESTIVE SYSTEM			
Diarrhea	31 (6.2%)	21 (4.3%)	22 (4.5%)
Nausea	13 (2.6%)	19 (3.9%)	16 (3.2%)
Tooth Disorder	6 (1.2%)	10 (2.0%)	7 (1.4%)
UROGENITAL SYSTEM			
Abnormal Ejaculation	42 (8.4%)	89 (18.1%)	1 (0.2%)
SPECIAL SENSES			
Blurred vision	1 (0.2%)	10 (2.0%)	2 (0.4%)

*A treatment-emergent adverse event was defined as any event satisfying one of the following criteria:

- The adverse event occurred for the first time after initial dosing with double-blind study medication.
- The adverse event was present prior to or at the time of initial dosing with double-blind study medication and subsequently increased in severity during double-blind treatment; or
- The adverse event was present prior to or at the time of initial dosing with double-blind study medication, disappeared completely, and then reappeared during double-blind treatment.

²Coding preferred terms also include cold, common cold, head cold, flu, and flu-like symptoms.

³Coding preferred terms also include nasal congestion, stuffy nose, runny nose, sinus congestion, and hay fever.

Signs and Symptoms of Orthostasis: In the two U.S. studies, symptomatic postural hypotension was reported by 0.2% of patients (1 of 502) in the 0.4 mg group, 0.4% of patients (2 of 492) in the 0.8 mg group, and by no patients in the placebo group. Syncope was reported by 0.2% of patients (1 of 502) in the 0.4 mg group, 0.4% of patients (2 of 492) in the 0.8 mg group and 0.6% of patients (3 of 493) in the placebo group. Dizziness was reported by 15% of patients (75 of 502) in the 0.4 mg group, 17% of patients (84 of 492) in the 0.8 mg group, and 10% of patients (50 of 493) in the placebo group. Vertigo was reported by 0.6% of patients (3 of 502) in the 0.4 mg group, 1% of patients (5 of 492) in the 0.8 mg group and by 0.6% of patients (3 of 493) in the placebo group.

Multiple testing for orthostatic hypotension was conducted in a number of studies. Such a test was considered positive if it met one or more of the following criteria: (1) a decrease in systolic blood pressure of $\geq$ 20 mmHg upon standing from the supine position during the orthostatic tests; (2) a decrease in diastolic blood pressure $\geq$ 10 mmHg upon standing, with the standing diastolic blood pressure <65 mmHg during the orthostatic test; (3) an increase in pulse rate of $\geq$ 20 bpm upon standing with a standing pulse rate $\geq$ 100 bpm during the orthostatic test; and (4) the presence of clinical symptoms (faintness, lightheadedness/lightheaded, dizziness, spinning sensation, vertigo, or postural hypotension) upon standing during the orthostatic test.

Following the first dose of double-blind medication in Study 1, a positive orthostatic test result at 4 hours post-dose was observed in 7% of patients (37 of 498) who received FLOMAX capsules 0.4 mg once daily and in 3% of the patients (8 of 253) who received placebo. At 8 hours post-dose, a positive orthostatic test result was observed for 6% of the patients (31 of 498) who received FLOMAX capsules 0.4 mg once daily and 4% (9 of 250) who received placebo (Note: patients in the 0.8 mg group received 0.4 mg once daily for the first week of Study 1).

In Studies 1 and 2, at least one positive orthostatic test result was observed during the course of these studies for 81 of the 502 patients (16%) in the FLOMAX capsules 0.4 mg once daily group, 92 of the 491 patients (19%) in the FLOMAX capsules 0.8 mg once daily group and 54 of the 493 patients (11%) in the placebo group.

Because orthostasis was detected more frequently in FLOMAX capsule-treated patients than in placebo recipients, there is a potential risk of syncope (see **WARNINGS**).

Abnormal Ejaculation: Abnormal ejaculation includes ejaculation failure, ejaculation disorder, retrograde ejaculation and ejaculation decrease. As shown in Table 3, abnormal ejaculation was associated with FLOMAX capsules administration and was dose-related in the U.S. studies. Withdrawal from these clinical studies of FLOMAX capsules because of abnormal ejaculation was also dose-dependent with 8 of 492 patients (1.6%) in the 0.8 mg group, and no patients in the 0.4 mg or placebo groups discontinuing treatment due to abnormal ejaculation.

Post-Marketing Experience: The following adverse reactions have been identified during post-approval use of FLOMAX capsules. 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. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to FLOMAX capsules. Allergic-type reactions such as skin rash, pruritus, angioedema of tongue, lips and face and urticaria have been reported with positive challenge in some cases. Priapism has been reported rarely. Infrequent reports of palpitations, hypotension, skin desquamation, constipation and vomiting have been received during the post-marketing period. During cataract surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported in association with alpha-1 blocker therapy (see **PRECAUTIONS, General**).

OVERDOSAGE: Should overdosage of FLOMAX (tamsulosin HCl) capsules lead to hypotension (see **WARNINGS** and **ADVERSE REACTIONS**), support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then administration of intravenous fluids should be considered. If necessary, vasopressors should then be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin HCl is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit.

One patient reported an overdose of thirty 0.4 mg FLOMAX capsules. Following the ingestion of the capsules, the patient reported a severe headache.

DOSAGE AND ADMINISTRATION: FLOMAX (tamsulosin HCl) capsules 0.4 mg once daily is recommended as the dose for the treatment of the signs and symptoms of BPH. It should be administered approximately one-half hour following the same meal each day.

For those patients who fail to respond to the 0.4 mg dose after two to four weeks of dosing, the dose of FLOMAX capsules can be increased to 0.8 mg once daily. If FLOMAX capsules administration is discontinued or interrupted for several days at either the 0.4 mg or 0.8 mg dose, therapy should be started again with the 0.4 mg once daily dose.

Keep FLOMAX capsules and all medicines out of reach of children.

Patients should be reminded to read and follow the "Patients' Instructions for Use," which should be dispensed with the product.

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