

Discontinuing Hormone Therapy Disturbs Sleep

VITALS

Major Finding: Radiological Evaluation and Breast Density (READ) trial analysis predicts 2 months of disturbed sleep after stopping hormone therapy.

Data Source: Sample size of 1,405 from the READ trial database randomized to three arms: HT (518), 1-month cessation (452), 2-month cessation (435).

Disclosures: None reported. The trial was sponsored by the Department of Defense, the National Institute on Aging, and the nonprofit Group Health Research Institute.

BY RICHARD HYER

FROM THE ANNUAL MEETING
OF THE NORTH AMERICAN
MENOPAUSE SOCIETY

CHICAGO – Almost 40% of women report sleep problems in midlife, and since hormone therapy benefits sleep, cessation of that therapy might have the opposite effect. A study of

1,704 women from the Group Health Research Institute of Seattle confirms that it does.

“Sleep problems were related to the suspension of hormone therapy for 1 or 2 months,” investigator Sarah E. Tom, Ph.D., formerly of the institute, said of the study’s findings.

“Women who are discontinuing hormone therapy may

benefit from alternative sleep management strategies immediately following discontinuation,” she said.

This was a secondary analysis of data from the READ (Radiological Evaluation and Breast Density) study, a trial designed to test whether short-term suspension of hormone therapy resulted in better screening mammography performance. The trial recruited women aged 45-80 years from Group Health, a nonprofit health care system based in Washington state. The recruits were due for a screening mammography, and reported on use of hormone therapy for 2 years. They were randomized to continue hormone therapy or to suspend it for either 1 or 2 months prior to mammography.

The survey used a questionnaire that asked about the number of days subjects had sleep complaints, including trouble falling asleep and waking while sleeping.

Various confounding variables, including alcohol consumption, body mass index, age, race, and ethnicity, were considered, Dr. Tom said.

Of the 1,704 women, 1,405 had complete information on all variables. Of this group, 518 were randomized to continue hormone therapy, 452 to suspend therapy for 1 month, and 435 to suspend it for 2 months.

Demographic profiles were similar across all randomization groups. In the group continuing hormone therapy, for example, more than 90% were white and more than 50% used estrogen only. Sleep problems were comparable in the groups suspending therapy for 1 month or 2 months.

The group randomized to a 2-month suspension had an increase of about 0.7 days in trouble with their sleep, compared with women who continued therapy, Dr. Tom said. Waking while sleeping was frequently reported, and about 35% of women in the two hormone cessation groups reported using sleep aids in the previous week.

The study concluded that sleep problems were related to suspension of hormone therapy for 1 or 2 months. Differences were modest but persistent across sleep items, and were similar for the 1- and 2-month suspension groups. ■

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Brief Summary: Consult package insert for complete Prescribing Information.

prolia™
(denosumab)injection

Clinical Trials Experience. Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Treatment of postmenopausal women with osteoporosis

The safety of Prolia in the treatment of postmenopausal osteoporosis was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 7808 postmenopausal women aged 60 to 91 years. A total of 3876 women were exposed to placebo and 3886 women were exposed to Prolia administered subcutaneously once every 6 months as a single 60 mg dose. All women were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day. The incidence of all-cause mortality was 2.3% (n = 90) in the placebo group and 1.8% (n = 70) in the Prolia group. The incidence of nonfatal serious adverse events was 24.2% in the placebo group and 25.0% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 2.1% and 2.4% for the placebo and Prolia groups, respectively. Adverse reactions reported in ≥ 2% of postmenopausal women with osteoporosis and more frequently in the Prolia-treated women than in the placebo-treated women are listed in the table below.

Table 1. Adverse Reactions Occurring in ≥ 2% of Patients with Osteoporosis and More Frequently than in Placebo-Treated Patients

SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 3886) n (%)	Placebo (N = 3876) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	129 [3.3]	107 [2.8]
CARDIAC DISORDERS		
Angina pectoris	101 [2.6]	87 [2.2]
Atrial fibrillation	79 [2.0]	77 [2.0]
EAR AND LABYRINTH DISORDERS		
Vertigo	195 [5.0]	187 [4.8]
GASTROINTESTINAL DISORDERS		
Abdominal pain upper	129 [3.3]	111 [2.9]
Flatulence	84 [2.2]	53 [1.4]
Gastroesophageal reflux disease	80 [2.1]	66 [1.7]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Edema peripheral	189 [4.9]	155 [4.0]
Asthenia	90 [2.3]	73 [1.9]
INFECTIOUS AND INFESTATIONS		
Cystitis	228 [5.9]	225 [5.8]
Upper respiratory tract infection	190 [4.9]	167 [4.3]
Pneumonia	152 [3.9]	150 [3.9]
Pharyngitis	91 [2.3]	78 [2.0]
Herpes zoster	79 [2.0]	72 [1.9]
METABOLISM AND NUTRITION DISORDERS		
Hypercholesterolemia	280 [7.2]	236 [6.1]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	1347 [34.7]	1340 [34.6]
Pain in extremity	453 [11.7]	430 [11.1]
Musculoskeletal pain	297 [7.6]	291 [7.5]
Bone pain	142 [3.7]	117 [3.0]
Myalgia	114 [2.9]	94 [2.4]
Spinal osteoarthritis	82 [2.1]	64 [1.7]
NERVOUS SYSTEM DISORDERS		
Sciatica	178 [4.6]	149 [3.8]
PSYCHIATRIC DISORDERS		
Insomnia	126 [3.2]	122 [3.1]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	96 [2.5]	79 [2.0]
Pruritus	87 [2.2]	82 [2.1]

Hypocalcemia. Decreases in serum calcium levels to less than 8.5 mg/dL were reported in 0.4% women in the placebo group and 1.7% women in the Prolia group at the month 1 visit. The nadir in serum calcium level occurs at approximately day 10 after Prolia dosing in subjects with normal renal function.

In clinical studies, subjects with impaired renal function were more likely to have greater reductions in serum calcium levels compared to subjects with normal renal function. In a study of 55 patients with varying degrees of renal function, serum calcium levels < 7.5 mg/dL or symptomatic hypocalcemia were observed in 5 subjects. These included no subjects in the normal renal function group, 10% of subjects in the CrCL 50 to 80 mL/min group, 29% of subjects in the CrCL < 30 mL/min group, and 29% of subjects in the hemodialysis group. These subjects did not receive calcium and vitamin D supplementation. In a study of 4550 postmenopausal women with osteoporosis, the mean change from baseline in serum calcium level 10 days after Prolia dosing was -5.5% in subjects with creatinine clearance < 30 mL/min vs. -3.1% in subjects with CrCL ≥ 30 mL/min.

Serious Infections. Receptor activator of nuclear factor kappa-B ligand (RANKL) is expressed on activated T and B lymphocytes and in lymph nodes. Therefore, a RANKL inhibitor such as Prolia may increase the risk of infection. In the clinical study of 7808 postmenopausal women with osteoporosis, the incidence of infections resulting in death was 0.2% in both placebo and Prolia treatment groups. However, the incidence of nonfatal serious infections was 3.3% in the placebo group and 4.0% in the Prolia group. Hospitalizations due to serious infections in the abdomen (0.7% placebo vs. 0.9% Prolia), urinary tract (0.5% placebo vs. 0.7% Prolia), and ear (0.0% placebo vs. 0.1% Prolia) were reported. Endocarditis was reported in no placebo patients and 3 patients receiving Prolia. Skin infections, including encephalitis and cellulitis, leading to hospitalization were reported more frequently in patients treated with Prolia (< 0.1% placebo vs. 0.4% Prolia). There was no imbalance in the reporting of opportunistic infections.

Dermatologic Reactions. A significantly higher number of patients treated with Prolia developed epidermal and dermal adverse events (such as dermatitis, eczema, and rashes), with these events reported in 8.2% of placebo and 10.8% of Prolia group (p < 0.0001). Most of these events were not specific to the injection site [see Warnings and Precautions].

Osteonecrosis of the Jaw. ONJ has been reported in the osteoporosis clinical trial program in patients treated with Prolia [see Warnings and Precautions].

INDICATIONS AND USAGE:
Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture. Prolia is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures [see Clinical Studies [14.1] in Full Prescribing Information].

DOSAGE AND ADMINISTRATION: Recommended Dosage. Prolia should be administered by a healthcare professional. The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Prolia via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily [see Warnings and Precautions].

If a dose of Prolia is missed, administer the injection as soon as the patient is available. Thereafter, schedule injections every 6 months from the date of the last injection.

CONTRAINDICATIONS: Hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia [see Warnings and Precautions].

WARNINGS AND PRECAUTIONS: Hypocalcemia and Mineral Metabolism. Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g., history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis), clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended. Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis. Instruct all patients with severe renal impairment, including those receiving dialysis, about the symptoms of hypocalcemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation. Adequately supplement all patients with calcium and vitamin D [see Dosage and Administration, Contraindications, Adverse Reactions, and Patient Counseling Information [17.1] in Full Prescribing Information].

Serious Infections. In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group [see Adverse Reactions]. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with Prolia. Endocarditis was also reported more frequently in Prolia-treated subjects. The incidence of opportunistic infections was balanced between placebo and Prolia groups, and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis. Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. Consider the benefit-risk profile in such patients before treating with Prolia. In patients who develop serious infections while on Prolia, prescribers should assess the need for continued Prolia therapy.

Dermatologic Adverse Reactions. In a large clinical trial of over 7800 women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the Prolia group compared to the placebo group. Most of these events were not specific to the injection site [see Adverse Reactions]. Consider discontinuing Prolia if severe symptoms develop.

Osteonecrosis of the Jaw. Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. ONJ has been reported in patients receiving denosumab [see Adverse Reactions]. A routine oral exam should be performed by the prescriber prior to initiation of Prolia treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with Prolia in patients with risk factors for ONJ such as invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). Good oral hygiene practices should be maintained during treatment with Prolia. For patients requiring invasive dental procedures, clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit-risk assessment. Patients who are suspected of having or who develop ONJ while on Prolia should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia therapy should be considered based on individual benefit-risk assessment.

Suppression of Bone Turnover. In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry [see Clinical Pharmacology [12.2] and Clinical Studies [14.1] in Full Prescribing Information]. The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

ADVERSE REACTIONS: The following serious adverse reactions are discussed below and also elsewhere in the labeling:

- Hypocalcemia [see Warnings and Precautions]
- Serious Infections [see Warnings and Precautions]
- Dermatologic Adverse Reactions [see Warnings and Precautions]
- Osteonecrosis of the Jaw [see Warnings and Precautions]

The most common adverse reactions reported with Prolia are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions leading to discontinuation of Prolia are breast cancer, back pain, and constipation. The Prolia Postmarketing Active Safety Surveillance Program is available to collect information from prescribers on specific adverse events. Please see www.proliasafety.com or call 1-800-772-6436 for more information about this program.

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