

# First-Ever Depression Spikes in Perimenopause

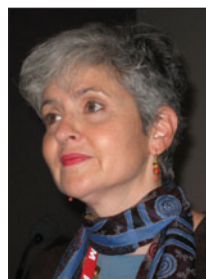
BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF  
THE AMERICAN SOCIETY FOR  
REPRODUCTIVE MEDICINE

DENVER – Women with no history of depression are at sharply increased risk of first-ever, clinically significant depressive symptoms during the menopausal transition, three major prospective longitudinal studies have shown.

It's a situation that requires clinicians to have their depression-detection radar fully powered up, according to Dr. Nanette F. Santoro.

"A very important thing to remember is that this type of depression is new to these women. This is their first episode. They may come into our offices clearly in distress, but they don't have the vo-



**'That late perimenopause is just a bummer. It almost doubles the risk' of new depression.**

DR. SANTORO

cabulary to tell you they're depressed because they don't know what that feels like," she said in a plenary lecture at the meeting.

Dr. Santoro presented highlights from the ongoing observational Study of Women's Health Across the Nation (SWAN), in which 3,302 African American, white, Hispanic, Japanese, and Chinese women at seven sites in the United States have been evaluated annually since their enrollment during 1996-1997 at age 42-52.

"We're now in our 14th year of SWAN, and we're still cranking out data," noted Dr. Santoro, professor and chair of the department of obstetrics and gynecology at the University of Colorado, Denver.

At baseline, when the women were premenopausal, 23% had clinically relevant depressive symptoms, as defined by a score of 16 or more on the Center for Epidemiologic Studies Depression Scale (CES-D).

The other 77% of women, those with low baseline CES-D scores and no lifetime history of depression, were hit particularly hard by depressed mood symptoms in the menopausal transition. In a multivariate analysis, a woman with a CES-D of less than 16 at baseline had a 30% higher odds of having a CES-D score of 16 or greater when she was in the early perimenopausal period, which is marked by increased menstrual irregularity but at least one menses within the past 3 months.

Women in the late perimenopausal period, as defined by 3-11 months of amenorrhea, had an adjusted 73% increased odds of significant depressive symptoms, compared with those who were still premenopausal.

The risk was elevated even more in

women with significant vasomotor symptoms (J. Affect. Disord. 2007; 103:267-72).

"That late perimenopause is just a bummer. It almost doubles the risk," Dr. Santoro observed.

The risk declines slightly to a 63% increased odds of significant depressive symptoms during the postmenopausal period.

Hormone therapy, which was used by

20% of the SWAN women, may have conferred modest relief from depressive symptoms, as hormone therapy users had a peak 64% increase in the odds of a CES-D of 16 or more during the menopausal transition.

The risk of new-onset depressive symptoms during menopause was independent of demographic, psychosocial, and behavioral factors, as well as comorbid conditions, all of which were fac-

tored into the multivariate regression analysis.

Chinese women had half the risk of depressive symptoms compared with white women, but the risk in the other ethnic groups didn't vary significantly from that in the white women.

Similar results have been reported from the Harvard Study of Moods and Cycles, in which Dr. Lee S. Cohen and his coworkers studied a cohort of pre-



Image of trabecular bone insert reproduced with permission from David W. Dempster, PhD.

## INDICATION

**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.**

## IMPORTANT SAFETY INFORMATION

❖ **Hypocalcemia:** Prolia® is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia®. Hypocalcemia may worsen, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels is highly recommended. Adequately supplement all patients with calcium and vitamin D.

❖ **Serious Infections:** In a clinical trial (N = 7808), serious infections leading to hospitalization were reported more frequently in the Prolia® group than in the placebo group. 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 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. In patients who develop serious infections while on Prolia®, prescribers should assess the need for continued Prolia® therapy.

❖ **Dermatologic Adverse Reactions:** 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. Consider discontinuing Prolia® if severe symptoms develop.

❖ **Osteonecrosis of the Jaw (ONJ):** ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia®. An oral exam should

menopausal women with no lifetime history of major depression. The investigators found that for these women, who were less racially diverse than the SWAN women, entry into perimenopause was associated with a doubled likelihood of developing significant depressive symptoms, compared with similar-age women who remained premenopausal.

As in SWAN, the risk of depression was even greater in women with self-reported significant hot flashes and night sweats. In the Harvard longitudinal study, the use of hormone therapy did

not affect the risk of developing depressive symptoms; there was a suggestion that it might have lessened the risk of severe depression arising during the menopausal transition, although the patient numbers were too small to draw firm conclusions (Arch. Gen. Psychiatry 2006;63:385-90).

Investigators at the University of Pennsylvania, Philadelphia, reported that women with no history of depression at enrollment in their longitudinal study were 4.3-fold more likely to post high CES-D scores during the menopausal transition than when they were pre-

menopausal. Formal diagnosis of a depressive disorder was 2.5 times more likely to occur in the menopausal transition (Arch. Gen. Psychiatry 2006; 63:375-82).

The Harvard group speculated that the increased risk for developing a first episode of depression when entering the perimenopause could be due in part to the marked sleep disruption caused by hot flashes, and/or to sensitivity to abrupt changes in the reproductive hormone milieu.

In keeping with that hypothesis, the SWAN investigators recently reported

that higher testosterone levels appear to contribute to depressive symptoms arising during the menopausal transition. No other hormones were associated with a CES-D score of 16 or more (Arch. Gen. Psychiatry 2010;67:598-607).

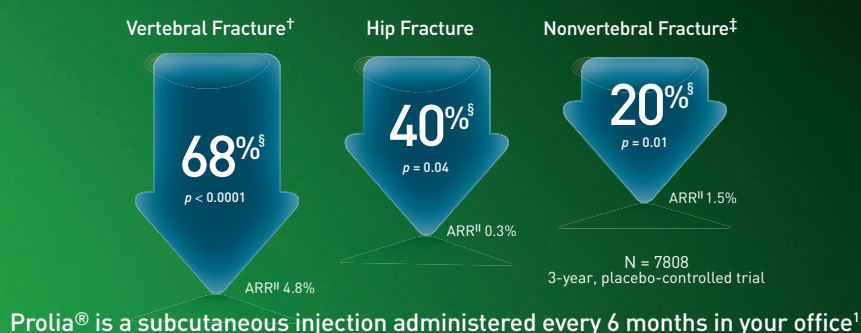
The SWAN study is cosponsored by the National Institute on Aging, the National Institute of Nursing Research, the National Institutes of Health Office of Research on Women's Health, and the National Center for Complementary and Alternative Medicine. Dr. Santoro said she had no relevant financial conflicts of interest. ■

In Treating Your Postmenopausal Osteoporosis Patients  
at High Risk for Fracture, Help . . .

## BE A FORCE AGAINST FRACTURE

Prolia® targets and binds to RANK Ligand, inhibiting osteoclast formation, function, and survival<sup>1</sup>

Prolia® significantly reduced fracture risk at key sites in a phase 3 trial\*<sup>1,2</sup>



Please see Brief Summary of Prescribing Information on the following page.

be performed by the prescriber prior to initiation of Prolia®. A dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with risk factors for ONJ. Good oral hygiene practices should be maintained during treatment with Prolia®.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia® should be considered based on individual benefit-risk assessment.

✚ **Suppression of Bone Turnover:** Prolia® resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment are unknown. Monitor patients for consequences, including ONJ, atypical fractures, and delayed fracture healing.

✚ **Adverse Reactions:** The most common adverse reactions (> 5% and more common than placebo) are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. Pancreatitis has been reported with Prolia®.

The overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia® groups. A causal relationship to drug exposure has not been established. Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

✚ **Prolia® Postmarketing Active Safety Surveillance Program:** The Prolia® Postmarketing Active Safety Surveillance Program is available to collect information from prescribers on specific adverse events. Please go to [www.proliasafety.com](http://www.proliasafety.com) or call 1-800-772-6436 for more information about this program.

\* Key sites: vertebral, hip, and nonvertebral.<sup>1,2</sup>

<sup>†</sup> Includes 7393 patients with a baseline and at least one post-baseline radiograph.<sup>1,2</sup>

<sup>‡</sup> Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the vertebrae, skull, face, mandible, metacarpals, fingers, and toes.<sup>1,2</sup>

<sup>§</sup> RRR = relative risk reduction.

|| ARR = absolute risk reduction.

References: 1. Prolia® (denosumab) prescribing information, Amgen. 2. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009;361:756-765.

For more information, visit [www.ProliaHCP.com](http://www.ProliaHCP.com)

 **prolia**  
(denosumab) injection

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