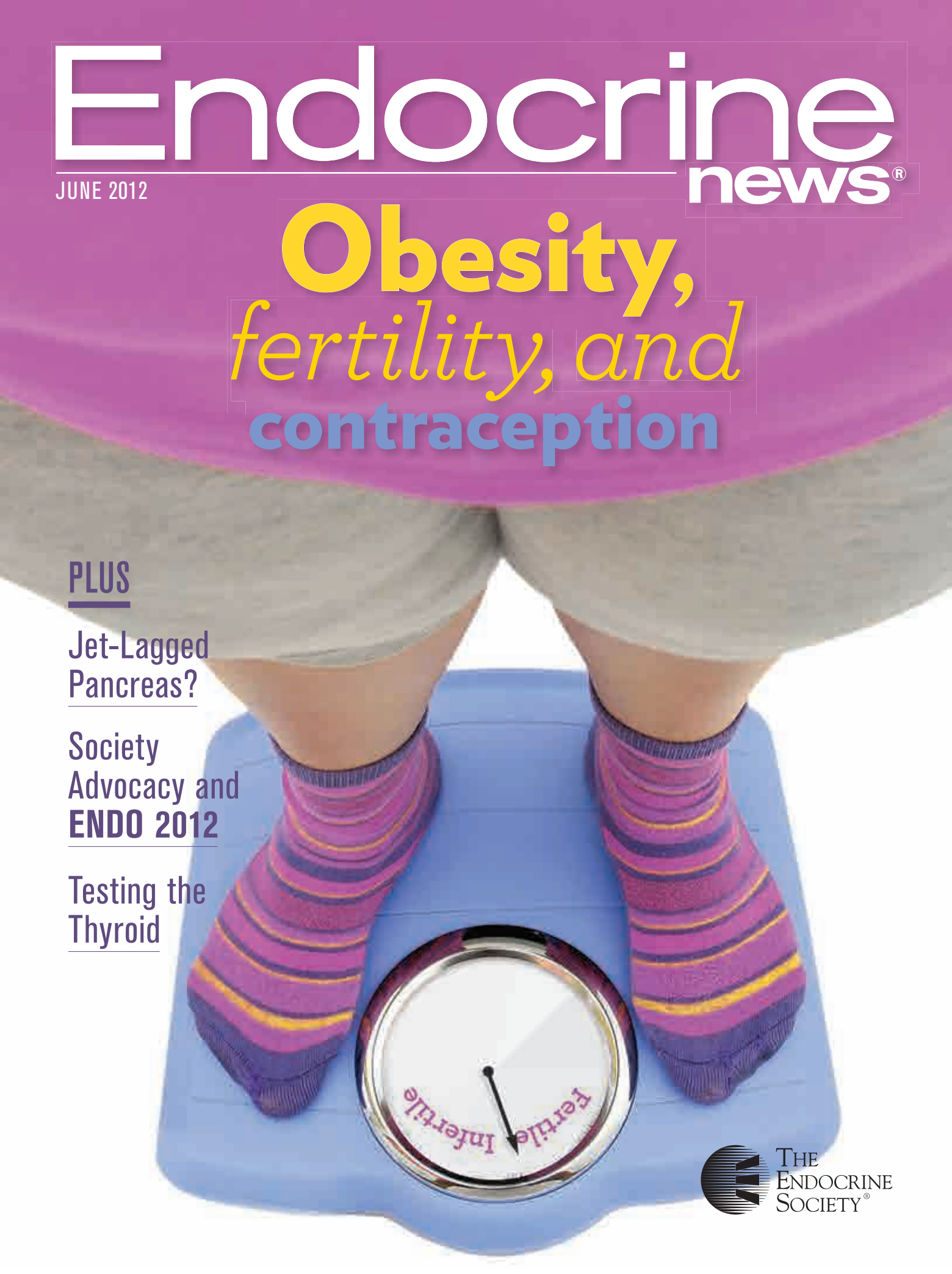
Endocrine news®
JUNE 2012

Obesity, *fertility, and* contraception



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NEWS & INSIGHTS FOR THE ENDOCRINE COMMUNITY

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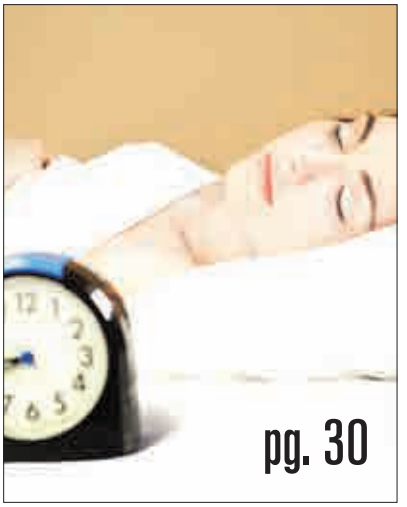

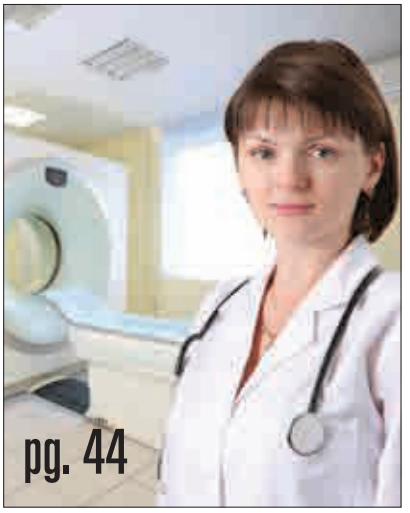

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Glucocorticoid-Induced Osteoporosis

Take a look at The Hormone Foundation's bilingual fact sheet on Glucocorticoid-Induced Osteoporosis (pages 45, 46).

Scan this QR code with your smartphone/mobile device for ***Endocrine News*** *Online.*

Presidential Farewell

Dear Colleagues:

Janet E. Hall, M.D.

It has been a great honor and a humbling experience to serve as your President during this past year. I have been fortunate to follow in Kelly Mayo's footsteps in year one of the Society's Strategic Plan 3 (SP3), which was developed under Kelly's outstanding leadership. I am extremely proud of the Society's accomplishments this year, none of which would have happened without the tireless efforts of our dedicated volunteers and the work of our talented and committed staff.

Health Disparities Initiatives

One of the key initiatives during my presidency has been to focus on health disparities in endocrine diseases. Under this initiative, two special projects were developed this year. First, the Scientific Statement Task Force has developed a statement on this issue. I would like to thank Sherita Golden who led the writing group that prepared this outstanding document, and Past President Bob Carey for his leadership of the Scientific Statement Task Force. The statement is being released during the Annual Meeting in Houston to further enhance the impact of disparities-related programming at ENDO 2012.

The Society is planning an international Summit on Health Disparities in Endocrinology that will highlight successful research- and community-based programs to reduce health disparities and inform a long-term strategy for how the Society will make an impact in this field. I would like to thank the Minority Affairs Committee members and its chair, Steve Festin, for the work they did to tee up the work of the Inter-Committee Work Group and the entire group for their efforts to make this issue one that the whole Society can embrace.

Basic Science Task Force

To address the challenges facing our basic science members and to improve their recruitment and retention in The Endocrine Society, a task force chaired by Basic Science Vice President, Ursula Kaiser, was constituted last fall. Vice President Kaiser will present the recommendations to Council at the June meeting.

ENDO Task Force Phase II

The ENDO Task Force was created to look at the Annual Meeting from the perspective of all the constituencies (basic, clinical science, clinician-in-practice, trainee, international) and of SP3, and to create new venues for evaluative feedback. This task force is also reporting its recommendations to Council in June and implementing the approved recommendations for the planning of **ENDO 2013.**

Advocacy and Outreach

The Advocacy and Public Outreach Core Committee, in conjunction with the Research Affairs and Clinical Affairs Core Committees, continued to advance the Society's advocacy agenda, which includes federal funding for research, physician reimbursement, health disparities, workforce issues, diabetes, and obesity. Through these efforts, the Society has enhanced its influence with key policy makers and raised the visibility of the field of endocrinology.

Additionally, 2011–2012 has been a tremendous year for the Society in terms of media outreach, response to breaking news, and overall media coverage. The fourth Science Writers Conference was held this year, with reporters attending from highly respected outlets including the *New York Times*, *Newsweek*, *Scientific American*, WebMD, and *Readers Digest*.

Education and Trainee Activities

I would like to thank the Annual Meeting Steering Committee chairs (Lynnette Nieman, Joel Elmquist, and Anthony McCall) and the committee members for planning an excellent ENDO 2012 program with outstanding content for each of our constituencies.

I commend the committees and staff who, under the direction of the Scientific & Educational Programs Core Committee, work so diligently to produce an amazing collection of high quality educational programs, such as *ESAP 2011*, *ESAP-ITE*, the *Endocrine Self-Assessment Program-Maintenance of Certification*, and the *Pediatric Endocrine Self-Assessment Program*.

The Society offers a variety of activities focusing on our trainees and young professionals. The opportunities at ENDO begin with the Endocrine Trainee Day, and continue with the Career Development Workshops, the Trainee Exchange and Reception, and the Presidential poster competition. Other opportunities include the Mentor Exchange and the Early Investigators Workshop. Additionally, the Society offers trainee awards and travel grants to help foster the career growth of young endocrinologists.

Hormone Health Network

As mentioned in last month's letter, the Hormone Foundation is launching a new brand—the Hormone Health Network. The goal is to ensure that the Society's investment in patient education is widely recognized, trusted, and broadly used by

Dear Readers,

At some point, women of reproductive age have to factor in whether they would like to have children. The decision is most difficult for those who are overweight or obese, because their body type impedes fertility and contraception. Three experts size up the clinical and laboratory evidence for these patients (page 22).

Burning the midnight oil burns out the body, leaving it prone to metabolic disorders such as type 2 diabetes and obesity. Epidemiological experiments have backed up this hypothesis, but now further evidence from biological experiments strengthens the link (page 30).

Before you order an imaging test for your patient, you may want to think again. Using iodinated contrast medium may put your patient at risk for a variety of thyroid dysfunctions (page 44).

For those attending **ENDO 2012,** welcome and enjoy. For those who are not, ***Endocrine News*** will highlight the meeting in upcoming issues. As always, feel free to email us at *endocrinenews@endo-society.org* to tell us how we're doing or to suggest story ideas. ■

Sincerely,

Jacqueline Ruttimann, Ph.D.
Interim Editor
Endocrine News

Viewpoint cont.

clinicians, and to engage patients and physicians in more effective dialogues about hormones, health, and endocrine diseases and conditions.

Publications

The Publications Core Committee has been busy monitoring and developing new forms of content delivery. A new journals app was launched, containing abstracts from the Society journals and the Annual Meeting abstracts for iPhone. Other enhancements in the publications area have been the move to a 2.0 platform on HighWire, offering easier user interface and ability to add new features, the Web page redesign, and the implementation of a new manuscript peer-review system.

International Activities

The Society's new Strategic Plan calls for enhanced collaborations with other international societies and establishing stronger ties with the international endocrine community. With this goal in mind, we hosted a reception at the ICE/ECE 2012, in Florence, Italy, with the leaders of all the international organizations in attendance and a Global Leadership Exchange dinner at ENDO in June.

In closing, I would like to thank the Society's leadership, committee chairs, and members, for their hard work, dedication, and passion. I leave the office of president in the excellent hands of Bill Young, who will continue to lead us through these challenging yet exciting times. I look forward to helping our Society in other ways in the future. ■

Sincerely,

Janet E. Hall, M.D.
President, The Endocrine Society

The Endocrine Society

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Janet E. Hall, M.D.
President
hall.janet@mgh.harvard.edu

William F. Young, Jr., M.D.
President-Elect
young.william@mayo.edu

Kelly Mayo, Ph.D.
Past-President
k-mayo@northwestern.edu

John C. Marshall, M.D., Ph.D.
Secretary-Treasurer
jcm9h@virginia.edu

Scott Hunt
Executive Director & CEO
shunt@endo-society.org

Eleanore Tapscott
Senior Director of Publications
etapscott@endo-society.org

Doug Byrnes
Director of Publications
dbyrnes@endo-society.org

Jacqueline Ruttimann, Ph.D.
Interim Editor
jruttimann@endo-society.org

Cynthia Richardson
Product/Production Manager
crichardson@endo-society.org

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Androgens Have Sex-Specific Effects on Adipose Tissue

➤ It's hard to figure out a hormone's workings when it has opposite actions in men and women—such as androgens' sex-specific metabolic effects. In men, androgen deficiency is linked to insulin resistance and obesity, and treatment with testosterone improves insulin sensitivity and reduces fat content. In women, the androgen excess of polycystic ovary syndrome correlates with insulin resistance and obesity.

Rodents do not seem to share this dichotomy, so researchers led by Charles T. Roberts Jr., Ph.D., of the Oregon National Primate Research Center in Beaverton, employed a nonhuman primate model to determine if androgens' sex-specific effects occur in fat tissue itself. They tested the effects of gonadectomy and hormone replacement on white adipose tissue in Japanese macaque males and rhesus macaque females.

In the males, in vivo androgen deprivation did not result in overt obesity or insulin resistance, possibly due to the relatively short period of androgen deficiency, but it did induce the appearance of very small, multilocular white adipocytes. Testosterone replacement restored normal cell size and improved insulin sensitivity in the adipose tissue.

The researchers used a novel ex vivo methodology to study the sex-specific properties and regulation of white adipose tissue under controlled culture conditions. Although ex vivo dihydrotestosterone treatment did not improve the insulin sensitivity of male white adipose tissue, in vivo testosterone replacement in androgen-deficient males had the effects described above, suggesting that androgens regulate male adipose insulin sensitivity. Female adipose tissue treated with androgens displayed elevated basal fatty acid uptake but reduced insulin-dependent fatty acid uptake. Androgen-stimulated basal uptake was greater in the adipose tissue of ovariectomized females than in that of intact females.

In an upcoming ***Endocrinology**** paper, the researchers say their results demonstrate that androgens are essential for normal adipogenesis in males and can impair essential adipocyte functions in females, strengthening the evidence that androgens have sex-specific effects at the level of white adipose tissue. ■

* Varlamov O, White AE, Carroll JM, et al. Androgen effects on adipose tissue architecture and function in nonhuman primates. *Endocrinology*, doi:10.1210/en.2011-2111.

Cancer Risk Increases with Insulin Levels in Type 2 Diabetes

➤ Insulin therapy is crucial in treating type 2 diabetes mellitus, but high insulin levels have their own danger. Gathering data from Taiwan's National Health Insurance Database and the National Cancer Research Registry, researchers at the National Taiwan University found high rates of cancer incidence associated with use of insulin and oral insulin secretagogues.

Risk of various cancers such as liver, stomach, and pancreas were elevated when insulin supplement was the primary treatment. Breast and prostate cancer, however, showed no increased risk. Cancer risk is lower with the use of sulfonylureas and glinides, designed to increase insulin expression, but remains high enough that carcinogenesis is a significant result of high serum insulin levels.

The study, to be published in ***The Journal of Clinical Endocrinology & Metabolism,**** finds cancer risk decreasing with use of insulin sensitizers like metformin and thiazolidinediones (TZDs). Showing up mostly in colorectal cancer, cancer incidence is 8% lower with metformin and 10% lower for TZDs. To explain this, the researchers posit that insulin-sensitizing drugs have anti-cancer properties inhibiting growth and inducing cell death.

In the delicate balance of managing diabetes, hyperinsulinemia can tip the scales toward even greater health risks. A greater emphasis on metformin and similar anti-diabetic medications might restore that balance, reducing the risk of cancer associated with insulin therapy. ■

* Chang C-H, Lin J-W, Wu L-C, Lai M-S, Chuang L-M. Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. *J Clin Endocrinol Metab*, doi:10.1210/jc.2012-1162.

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2012-00085 June

Thyroid Cancer Type Tied to Genomic Instability

➤ Evidence is building that a body's instability at its most basic level—the genome—could tip it toward some cancers by accentuating the genetic abnormalities that underlie them.

One potential source of this instability is defects in telomeres, the specialized nucleoprotein structures that protect chromosome ends from damage by erosion, end-to-end fusion, and other threats. Several studies have reported evidence that abnormally short telomeres play an important role in the early development of cancer and chromosome instability.

A team of researchers led by Furio Pacini, M.D., at the University of Siena, Italy, now report genomic instability's role in familial papillary thyroid cancer (PTC). The researchers used conventional and molecular cytogenetic approaches to verify whether familial PTC patients show a predisposition toward three indicators of genomic instability—telomere associations, telomere fusions, and spontaneous chromosome fragility. They analyzed these cytogenetic features in phytohemagglutinin-stimulated T lymphocytes from familial PTC patients, unaffected family members, sporadic PTC patients, and healthy subjects.

The familial PTC patients had significantly more spontaneous telomeric associations and telomeric fusions than healthy subjects and sporadic PTC patients. The familial PTC patients also had a spontaneous chromosome fragility frequency slightly higher than that of healthy subjects and sporadic PTC patients, with many acentric fragments carrying telomeric sequences resulting from sub-telomeric chromosomal breakage. Tests of telomere length by quantitative fluorescence in situ hybridization found a statistical difference between healthy subjects and the other groups, with healthy subjects having longer sequences.

The researchers conclude in an article slated for publication in ***The Journal of Clinical Endocrinology & Metabolism**** that telomere instability could be a factor underlying the predisposition of patients to develop this familial form of cancer. ■

* Cantara S, Pisu M, Frau DV, et al. Telomere abnormalities and chromosome fragility in patients affected by familial papillary thyroid cancer. *J Clin Endocrinol Metab*, doi:10.1210/jc.2011-2096.

Low Doses of BPA Affect Neural System

➤ The U.S. Food and Drug Administration recently denied a request from an environmental group to ban the ubiquitous chemical bisphenol A (BPA) from food and beverage containers—but evidence of BPA's endocrine-disrupting effects continues to mount. The latest comes from a study whose results suggest that BPA exerts a powerful impact on neural systems, including the estrogen-mediated brain functions of memory and learning.

Researchers led by Victoria Luine, Ph.D., of City University of New York, used ovariectomized rats to study the effects on recognition memory of BPA alone and of BPA in combination with doses of estrogens (17β-estradiol and 17α-estradiol) known to have effects.

They found that acute exposure to BPA altered estradiol-induced enhancements of spatial and nonspatial memory in adult female rats. BPA blocked enhancement of memory consolidation by both 17β-estradiol and 17α-estradiol in a task-specific and dose-specific manner. In contrast, in the absence of estradiol, BPA did not affect memory performance.

The researchers also investigated dendritic spines as a mechanism for the memory effects, because chronic changes in estradiol alter both recognition memory and spine density in the medial prefrontal cortex and hippocampus. The effects were complex, and depended on the dose, timing, and duration of treatment. In the prefrontal cortex, BPA did not alter estradiol-dependent increases. In the hippocampus, BPA's effect was additive with that of estradiol at times of memory consolidation (after 30 minutes), but blocked estradiol-caused increases in basal spines at times of memory retention (after 4 hours).

In an article accepted for publication in ***Endocrinology,**** the authors say their results raise important additional concerns about the chemical because these effects on estrogen-mediated cognitive function were caused by BPA at levels below the safe daily limit set by the U.S. Environmental Protection Agency. ■

* Inagaki T, Frankfurt M, Luine V. Estrogen-induced memory enhancements are blocked by acute bisphenol A in adult female rats: Role of dendritic spines. *Endocrinology*, doi:10.1210/en.2012.1121.

Gasping for Hypothalamic-Pituitary-Adrenal Function

➤ A hot topic in current research is transgenerational effects of prenatal interventions. Administration of synthetic glucocorticoids such as betamethasone to mothers at risk for preterm delivery to hasten fetal lung maturation is a prime example. Although this treatment is highly effective in decreasing respiratory distress syndrome in the newborn, there may be long-term consequences, especially following exposure to multiple treatments. In animal models, these have been shown to include disruptions in renal, cardiovascular, and neurologic system function and, particularly, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. This dysregulation not only persists in the long term, but also contributes to earlier development of metabolic conditions and hypertension. But what of the effects down the generational line?

Led by Stephen G. Matthews, Ph.D., at the University of Toronto, Canada, scientists previously demonstrated that HPA down-regulation due to changes in gene expression happens in the hippocampus, hypothalamus, and the pituitary gland in male guinea pig first-generation offspring and in female offspring during the luteal phase of the reproductive cycle. Their current study investigates whether these effects carry through to the next generation and whether they are still sex specific. In their upcoming paper in ***Endocrinology,*** * the researchers report that the second-generation offspring of grandmaternal guinea pigs given betamethasone prenatally show significant differences compared to controls born to offspring of guinea pig mothers given saline. Males showed increased negative feedback in response to dexamethasone challenge (i.e., cortisol suppression), and young males exhibited less activity—a tendency to avoid open areas, possibly due to anxiety. In females, pituitary function was impaired, and they showed decreased negative feedback to dexamethasone challenge (i.e., no suppression).

The researchers conclude that HPA function is affected in successive generations of guinea pig mothers treated with synthetic glucocorticoids and that given the link between HPA function and anxiety, stress behavior is likewise significantly altered. Perhaps it's time to reexamine that cost/benefit ratio. ■

* Iqbal M, Moisiadis VG, Kostaki A, Matthews SG. Transgenerational effects of prenatal synthetic glucocorticoids on hypothalamic-pituitary-adrenal function. *Endocrinology,* doi:10.1210/en.2012-1054.

Androgen Receptor Mutation Linked with Hereditary Polyglutamine Disorder

➤ Although the etiology of neurodegeneration was thought to involve abnormal protein aggregation, that hypothesis has recently been scrutinized. In diseases involving androgen receptor (AR) dysregulation, such as spinobulbar muscular atrophy (SMBA), also known as Kennedy disease, motor neuron loss does not seem to correlate with nuclear inclusion protein accumulation. Prior studies have shown that polyglutamine tract elongation disrupts AR transcription insofar as a membrane-associated AR induces nongenomic signaling in certain pathways with androgen stimulation. A new study puts these two findings together to explore a novel mechanism of SMBA pathogenesis.

Using NSC34, a cell line resembling motor neurons but lacking endogenous AR, scientists led by Norbert Bakalara, Ph.D., at the École Nationale Supérieure Chimie Montpellier, in France, induced expression of two AR mutants—one with a polyglutamine expansion (AR51Q) and loss of transcriptional activity and the other lacking the polyglutamine chain (AR0Q)—to examine effects on the c-*jun* signaling pathway. AR20Q was used as the control. An important mediator of apoptosis, c-*jun* is also implicated in neuronal foot process outgrowth. In their paper, to be published soon in ***Molecular Endocrinology,*** * the researchers report that AR51Q impairs cell viability by failing to activate the c-*jun* signaling pathway necessary to mount the appropriate response to cell stress and by diminishing astrocyte outgrowth.

The researchers conclude that down-regulation of nongenomic AR signaling may contribute to SBMA onset. Because classic AR behaves differently—even paradoxically—than does membrane-bound AR in the presence of steroid hormone, potential new therapeutic approaches should consider both, they add. ■

* Schindler M, Fabre C, de Weille J, Carreau S, Mersel M, Bakalara N. Disruption of nongenomic testosterone signaling in a model of spinal and bulbar muscular atrophy. *Mol Endocrinol,* doi:10.1210/me.2011-1367.

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INDICATIONS AND USAGE

- FORTEO® (teriparatide [rDNA origin] injection) is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, and for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture.
- High risk for fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

FORTEO is administered as a 20 microgram once daily dose and is available in a 2.4 mL prefilled delivery device for subcutaneous injection over 28 days.

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

See the Important Safety Information for Complete Boxed Warning.

- **In rats, teriparatide caused an increase in the incidence of osteosarcoma, a malignant bone tumor.**
- **Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO only for patients for whom potential benefits outweigh potential risk.**
- **FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma (eg, those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).**

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FORTEO SELECT SAFETY INFORMATION

Prescribe FORTEO only for patients for whom the potential benefits are considered to outweigh the potential risks. FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma, including those with Paget's disease of bone, unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy. Additionally, patients with bone metastases or a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or pre-existing hypercalcemia should not receive FORTEO.

Use of FORTEO for more than 2 years during a patient's lifetime is not recommended.

Please see Important Safety Information, including Boxed Warning regarding osteosarcoma, and Brief Summary on following pages. See Full User Manual that accompanies the delivery device.

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INDICATIONS AND USAGE

- FORTEO® (teriparatide [rDNA origin] injection) is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, and for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture.
- High risk for fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

FORTEO is administered as a 20 microgram once daily dose and is available in a 2.4 mL prefilled delivery device for subcutaneous injection over 28 days.

IMPORTANT SAFETY INFORMATION

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® (teriparatide [rDNA origin] injection) only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

CONTRAINDICATIONS

Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

The following categories of patients have increased baseline risk of osteosarcoma and therefore should not be treated with FORTEO: Paget's disease of bone, pediatric populations and young adults with open epiphyses, or prior external beam or implant radiation therapy.

Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org.

Osteosarcoma occurs in about 4 out of every million older adults each year. Cases of bone tumor and osteosarcoma have been reported rarely in people taking FORTEO in the post-marketing period. The causality to FORTEO use is unclear.

Use of FORTEO for more than 2 years during a patient's lifetime is not recommended.

Patients with the following conditions also should not receive FORTEO: bone metastases or a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or hypercalcemic disorders.

FORTEO may increase serum calcium, urinary calcium, and serum uric acid.

Use with caution in patients with active or recent urolithiasis because of risk of exacerbation. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered.

Transient orthostatic hypotension may occur with initial doses of FORTEO. In short-term clinical pharmacology studies, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. FORTEO should be administered initially under circumstances where the patient can sit or lie down if symptoms of orthostatic hypotension occur.

Patients receiving digoxin should use FORTEO with caution because FORTEO may transiently increase serum calcium and hypercalcemia may predispose patients to digitalis toxicity.

ADVERSE REACTIONS

The most common adverse reactions in clinical trials include: arthralgia (10.1 FORTEO vs. 8.4 placebo), pain (21.3 FORTEO vs. 20.5 placebo), and nausea (8.5 FORTEO vs. 6.7 placebo). Other adverse reactions include: dizziness, leg cramps, joint aches, and injection site reactions.

USE IN PREGNANCY/NURSING MOTHERS

FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal studies, FORTEO may cause fetal harm.

It is not known whether teriparatide is excreted in human milk. Breastfeeding mothers should discontinue nursing or FORTEO, taking into account the importance of treatment to the mother.

INSTRUCTIONS FOR FORTEO USE

FORTEO is provided as a fixed-dose, prefilled delivery device that can be used for up to 28 days, including the first injection. The delivery device contains 28 daily doses of 20 mcg each. Do not transfer the contents of the delivery device into a syringe. The FORTEO Delivery Device should be stored under refrigeration at 36° to 46° F (2° to 8° C) at all times. Do not use FORTEO if it has been frozen.

For more safety information, please see Brief Summary of Prescribing Information, including Boxed Warning regarding osteosarcoma, on following pages. See Full User Manual that accompanies the delivery device.

TE HCP ISI 07Apr2011

FORTEO™
teriparatide (rDNA origin) injection
ANABOLIC ACTION FOR NEW BONE

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Lilly

FORTEO® (teriparatide [rDNA origin] 20 mcg for injection)

Brief Summary. Consult the package insert for complete prescribing information.

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

INDICATIONS

FORTEO is indicated: for the treatment of postmenopausal women with osteoporosis at high risk for fracture; to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy at high risk for fracture.

CONTRAINDICATIONS

Do not use FORTEO in patients with Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

Osteosarcoma In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. FORTEO should not be prescribed for patients at increased baseline risk of osteosarcoma. These include Paget's disease of bone (unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone); pediatric and young adult patients with open epiphyses; prior external beam or implant radiation therapy involving the skeleton. Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org. **Treatment Duration** The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patients' lifetime is not recommended. **Bone Metastases and Skeletal Malignancies** Patients with bone metastases or a history of skeletal malignancies should not be treated with FORTEO. **Metabolic Bone Diseases** Patients with metabolic bone diseases other than osteoporosis should not be treated with FORTEO. **Hypercalcemia and Hypercalcemic Disorders** FORTEO has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with FORTEO because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO. **Urolithiasis or Pre-existing Hypercalciuria** In clinical trials, the frequency of urolithiasis was similar in patients treated with FORTEO and placebo. However, FORTEO has not been studied in patients with active urolithiasis. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered. FORTEO should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition. **Orthostatic Hypotension** FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies with teriparatide, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. Typically, an event began within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment. **Drug Interactions** Hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, patients receiving digoxin should use FORTEO with caution.

ADVERSE REACTIONS

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 practice. *Treatment of Osteoporosis in Men and Postmenopausal Women* The safety of FORTEO in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo-controlled trials of 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years). The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to FORTEO and 691 patients to placebo. All patients received 1000 mg of calcium plus at least 400 IU of vitamin D supplementation per day. The incidence of all cause mortality was 1% in the FORTEO group and 1% in the placebo group. The incidence of serious adverse events was 16% in FORTEO patients and 19% in placebo patients. Early discontinuation due to adverse events occurred in 7% of FORTEO patients and 6% of placebo patients. **Percentage of Patients with Adverse Events Reported by at Least 2% of FORTEO-Treated Patients and in More FORTEO-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality(FORTEO, N=691, Placebo, N=691):** *Body as a Whole:* Pain (21.3%, 20.5%), Headache (7.5%, 7.4%), Asthenia (8.7%, 6.8%), Neck Pain (3.0%, 2.7%); *Cardiovascular:* Hypertension (7.1%, 6.8%), Angina Pectoris (2.5%, 1.6%), Syncope (2.6%, 1.4%); *Digestive System:* Nausea (8.5%, 6.7%), Constipation (5.4%, 4.5%), Diarrhea (5.1%, 4.6%), Dyspepsia (5.2%, 4.1%), Vomiting (3.0%, 2.3%), Gastrointestional disorder (2.3%, 2.0%), Tooth disorder (2.0%, 1.3%); *Musculoskeletal:* Arthralgia (10.1%, 8.4%), Leg cramps (2.6%, 1.3%); *Nervous System:* Dizziness (8.0%, 5.4%), Depression (4.1%, 2.7%) Insomnia (4.3%, 3.6%), Vertigo (3.8%, 2.7%); *Respiratory System:* Rhinitis (9.6%, 8.8%), Cough increased (6.4%, 5.5%), Pharyngitis (5.5%, 4.8%), Dyspepsia (3.6%, 2.6%), Pneumonia (3.9%, 3.3%); *Skin and Appendages:* Rash (4.9%, 4.5%), Sweating (2.2%, 1.7%). Immunogenicity In the clinical trial, antibodies that cross-reacted with teriparatide were detected in 3% of women (15/541) receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions or allergic reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response. *Laboratory Findings* **Serum Calcium:** FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after FORTEO administration was increased from 2% of women and none of the men treated with placebo to 11% of women and 6% of men treated with FORTEO. The number of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men. **Urinary Calcium:** FORTEO increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with FORTEO and placebo. **Serum Uric Acid:** FORTEO increased serum uric acid concentrations. In clinical trials, 3% of FORTEO patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis. **Renal Function:** No clinically

FORTEO® (teriparatide [rDNA origin] 20 mcg for injection) PA 097 FSAM00

important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment. *Studies in Men and Women with Glucocorticoid-Induced Osteoporosis* The safety of FORTEO in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥ 5mg per day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO and 214 patients exposed to oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day. The incidence of all cause mortality was 4% in the FORTEO group and 6% in the active control group. The incidence of serious adverse events was 21% in FORTEO patients and 18% in active control patients, and included pneumonia (3% FORTEO, 1% active control). Early discontinuation because of adverse events occurred in 15% of FORTEO patients and 12% of active control patients, and included dizziness (2% FORTEO, 0% active control). Adverse events reported at a higher incidence in the FORTEO group and with at least a 2% difference in FORTEO-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively. **Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of FORTEO. 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. **Osteosarcoma**: Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing. **Hypercalcemia**: Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use. Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following: *Allergic Reactions*: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria; *Investigations:* Hyperuricemia; *Respiratory System*: Acute dyspnea, chest pain; *Musculoskeletal*: Muscle spasms of the leg or back; *Other*: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C. There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At doses ≥ 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings. In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses ≥120 times the human dose (based on surface area, mcg/m2). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively. Exposure multiples were normalized based on body surface area (mcg/m2). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day). **Nursing Mothers:** It is not known whether teriparatide is excreted in human milk. Because of the potential for tumorigenicity shown for teriparatide in animal studies, 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:** The safety and efficacy of FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses. **Geriatric Use:** Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and 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. **Hepatic Impairment:** No studies have been performed in patients with hepatic impairment. **Renal Impairment:** In 5 patients with severe renal impairment (CrCl<30 mL/min), the AUC and T1/2 of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased.

OVERDOSAGE

Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur. In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) of the FORTEO delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported. Overdose Management There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

DOSAGE FORMS AND STRENGTHS

Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg.

PATIENT COUNSELING INFORMATION

Patients should read the FDA-approved *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with FORTEO and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

12/13/2010

PLEASE SEE FULL PRESCRIBING INFORMATION FOR ADDITIONAL INFORMATION.

Literature revised December 13, 2010

Manufactured by Lilly France – F-67640 Fegersheim, France
for Eli Lilly and Company – Indianapolis, IN 46285, USA
www.forteo.com

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Exercise After Liposuction Prevents Fat Regain

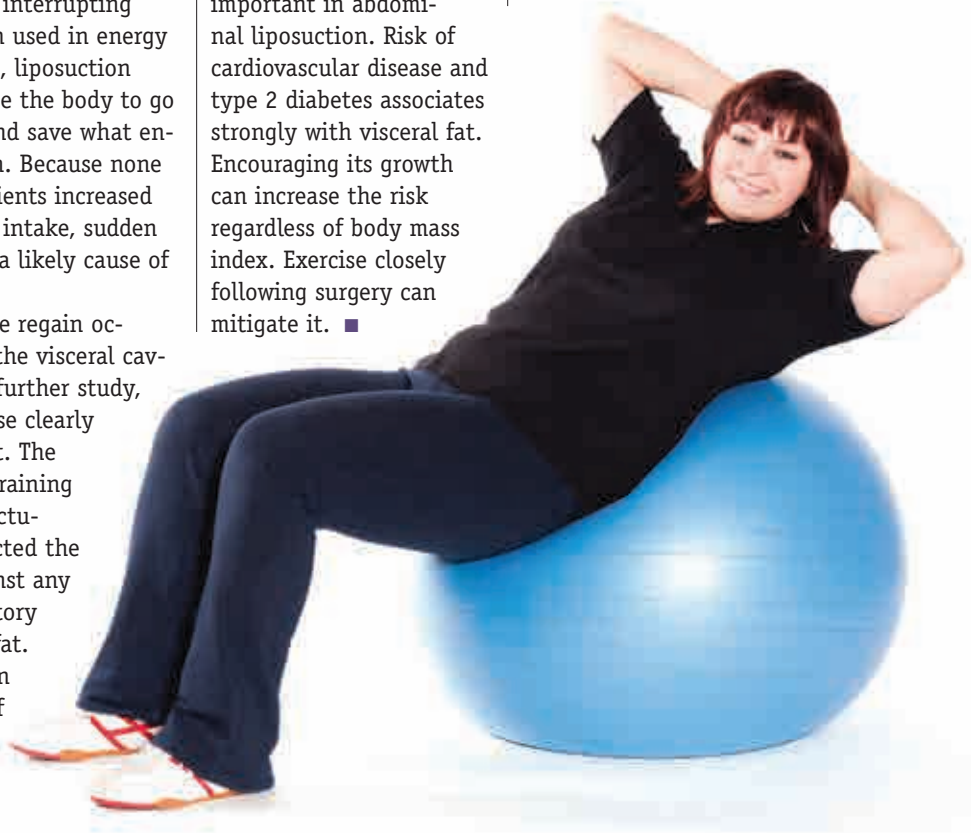
➤ Liposuction is touted as a third weapon in weight loss after diet and exercise, but it can be a double-edged sword. Regrowth of fat and increased risk for cardiovascular disease have been observed. In a recent 6-month trial at the University of São Paulo, Brazil, 36 "normal-weight" women had a small amount of abdominal fat removed through liposuction. Then, 18 of them underwent a 4-month exercise program and the other 18 had no exercise training. Only the latter group regained fat, but not where the researchers thought.

Instead of fat regrowth at the surgery site, the regain occurred in the visceral cavity between the internal organs. The study, to be published in ***The Journal of Clinical Endocrinology & Metabolism****, suggests that a compensatory regain of fat might come from a decrease in the total energy expenditure. By interrupting the system used in energy regulation, liposuction might force the body to go on alert and save what energy it can. Because none of the patients increased their food intake, sudden fat loss is a likely cause of fat regain.

Why the regain occurred in the visceral cavity needs further study, but exercise clearly prevents it. The 4-month training program actually protected the body against any compensatory regain of fat. The sudden increase of energy used during exercise or a longer-term rise in resting metabolic rate perhaps counteracted the body's post-surgery response.

This is particularly important in abdominal liposuction. Risk of cardiovascular disease and type 2 diabetes associates strongly with visceral fat. Encouraging its growth can increase the risk regardless of body mass index. Exercise closely following surgery can mitigate it. ■

* Benatti F, Solis M, Artioli G, et al. Liposuction induces a compensatory increase of visceral fat which is effectively counteracted by physical activity: A randomized trial. *J Clin Endocrinol Metab.* doi:10.1210/jc.2012-1012.



Epigenetic Changes Play Role in Diabetes Development

➤ The mechanisms underlying diabetes are complex and multifactorial, and researchers who are breaking down their many components to make sense of them have identified another transcription factor that hyperglycemia can play havoc with.

Pancreatic duodenal homeobox 1 (PDX-1) is a homeodomain-containing transcription factor that plays a key role in pancreatic development and function. Mutations in PDX-1 can cause a monogenic form of diabetes in humans; silencing of the *Pdx-1* gene in the pancreatic β-cells of mice causes diabetes. In the mature pancreas, it is mainly expressed in islet beta cells, where it plays an important role in glucose-dependent regulation of insulin gene expression.

Charlotte Ling, Ph.D., of Lund University Diabetes Center in Malmö, Sweden, led a team that compared DNA methylation and mRNA expression of PDX-1 in pancreatic islets of 55 nondiabetic donors and 9 type 2 diabetes mellitus (T2DM) patients.

PDX-1 expression was lower in the pancreatic islets of diabetes patients than in those from nondiabetic donors and correlated positively with insulin expression and glucose-stimulated insulin secretion in the islets. DNA methylation of *PDX-1* correlated negatively with its expression in the islets. Methylation of the *PDX-1* promoter and enhancer regions suppressed reporter gene expression in clonal β-cells.

Hyperglycemia decreased gene expression and increased *PDX-1* methylation. In mouse clonal beta-cells exposed to high glucose, *Pdx-1* expression decreased and *Pdx-1* methylation increased.

The researchers say that their findings demonstrate that epigenetic modifications of *PDX-1* can reduce its expression in human islets, which may lead to impaired insulin expression and secretion, and that hyperglycemia may be a factor behind increased DNA methylation and decreased expression of PDX-1. They conclude, in a paper coming out soon in ***Molecular Endocrinology,***** that epigenetic modifications may play a role in T2DM development ■

* Yang BT, Dayeh TA, Volkov P, et al. Increased DNA methylation and decreased expression of *PDX-1* in pancreatic islets from patients with type 2 diabetes. *Mol Endocrinol,* doi:10.1210/me.2012-1004.

Start a smart partnership

For patients not at goal on insulin glargine, adding BYETTA® can deliver a complementary approach to glycemic control

Indication and usage

BYETTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

- Not a substitute for insulin and should not be used in patients with type 1 diabetes or diabetic ketoacidosis.
- Concurrent use with prandial insulin cannot be recommended.
- Has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYETTA; consider other antidiabetic therapies for these patients.

Important Safety Information

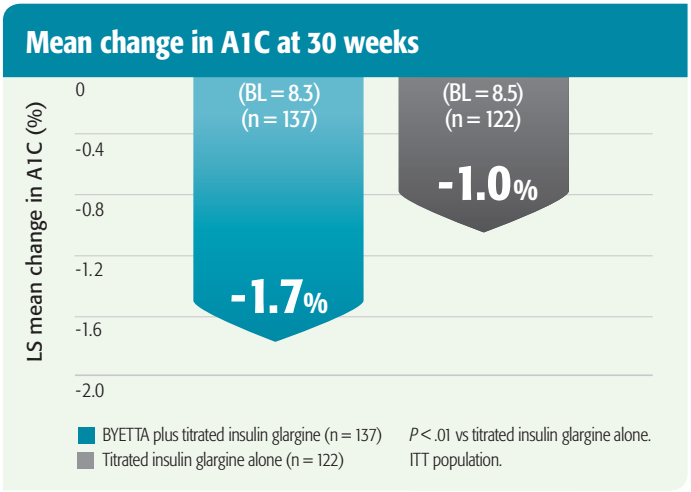
Contraindications

- BYETTA is contraindicated in patients with prior severe hypersensitivity reactions to exenatide or to any of the product components.

Warnings and precautions

- **Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation and dose increases of BYETTA, observe patients carefully for pancreatitis (persistent severe abdominal pain, sometimes radiating to the back, with or without vomiting). If pancreatitis is suspected, BYETTA should be discontinued promptly. BYETTA should not be restarted if pancreatitis is confirmed.**
- Increased risk of hypoglycemia when used in combination with glucose-independent insulin secretagogues (eg, sulfonylureas); reduction of the sulfonylurea dose may be needed. When used with insulin, evaluate and consider reducing the insulin dose in patients at increased risk of hypoglycemia.
- Postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis and kidney transplantation. BYETTA should not be used in patients with severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or when initiating or escalating the dose in patients with moderate renal failure.
- Not recommended in patients with severe gastrointestinal disease (eg, gastroparesis).
- Patients may develop antibodies to exenatide. In 3 registration trials, antibody levels were measured in 90% of patients, with up to 4% of patients having high-titer antibodies and attenuated glycemic response. If worsening of or failure to achieve adequate glycemic control occurs, consider alternative antidiabetic therapy.
- Postmarketing reports of serious hypersensitivity reactions (eg, anaphylaxis and angioedema). If this occurs, patients should discontinue BYETTA and other suspect medications and promptly seek medical advice.

BYETTA added to titrated insulin glargine achieved a significantly greater A1C reduction vs titrated insulin glargine alone



Abbreviations: LS, least squares; BL, baseline; ITT, intent to treat.

Patients with type 2 diabetes on insulin glargine alone or in combination with oral agents (metformin, thiazolidinedione, or both) were enrolled in a 30-week, randomized, double-blind, placebo-controlled clinical study to receive either BYETTA (5 mcg BID for 4 weeks then 10 mcg BID) or placebo in addition to titrated insulin glargine. In both arms, under investigator guidance, insulin was titrated to achieve a targeted fasting glucose level of <100 mg/dL using the Treat-to-Target algorithm.

- BYETTA did not increase the risk of hypoglycemia over that seen with insulin glargine alone and provided the potential benefit of weight loss (on average, 4.0 lb over 30 weeks).* Consider reducing the dose of insulin glargine in patients at increased risk for hypoglycemia.

***BYETTA is not indicated for the management of obesity, and weight change was a secondary endpoint.**

Warnings and precautions (cont'd)

- No clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.

Adverse reactions

- Most common adverse reactions in registration trials associated with BYETTA vs placebo (PBO): nausea (44% vs 18%), vomiting (13% vs 4%), and diarrhea (13% vs 6%). Other adverse reactions ≥5% and more than PBO: feeling jittery, dizziness, headache, and dyspepsia. With a thiazolidinedione (TZD), adverse reactions were similar; as monotherapy, most common was nausea (8% vs 0%). With insulin glargine: nausea (41% vs 8%), vomiting (18% vs 4%), diarrhea (18% vs 8%), headache (14% vs 4%), constipation (10% vs 2%), dyspepsia (7% vs 2%), asthenia (5% vs 1%).
- Hypoglycemia incidence, BYETTA vs PBO, with metformin (MET): 5.3% (10 mcg) and 4.5% (5 mcg) vs 5.3%; with SFU, 35.7% (10 mcg) and 14.4% (5 mcg) vs 3.3%; with MET + SFU, 27.8% (10 mcg) and 19.2% (5 mcg) vs 12.6%; with TZD, 10.7% (10 mcg) vs 7.1%; as monotherapy, 3.8% (10 mcg) and 5.2% (5 mcg) vs 1.3%; with insulin glargine, 24.8% (10 mcg) vs 29.5%.
- Withdrawals: as monotherapy, 2 of 155 BYETTA patients withdrew due to headache and nausea vs 0 PBO; with MET and/or SFU vs PBO, nausea (3% vs <1%) and vomiting (1% vs 0); with TZD ± MET, nausea (9%) and vomiting (5%), with <1% of PBO patients withdrawing due to nausea; with insulin glargine vs PBO, nausea (5.1% vs 0), vomiting (2.9% vs 0).

Drug interactions

- BYETTA slows gastric emptying and can reduce the extent and rate of absorption of orally administered drugs. Use with caution with medications that have a narrow therapeutic index or require rapid gastrointestinal absorption. Medications dependent on threshold concentrations for efficacy should be taken at least 1 hour before BYETTA.
- Postmarketing reports of increased international normalized ratio (INR) sometimes associated with bleeding with concomitant use of warfarin. Monitor INR frequently until stable upon initiation or alteration of BYETTA.

Use in specific populations

- Based on animal data, BYETTA may cause fetal harm and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Caution should be exercised when administered to a nursing woman.
- Safety and effectiveness have not been established in pediatric patients.

To learn more, visit www.ByettaHCP.com.

For additional safety profile and other important prescribing considerations, please see the adjacent pages for Brief Summary of Prescribing Information.

†SDI data, December 2009.

Byetta® exenatide injection

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BYETTA® (exenatide) injection

Brief Summary: For complete details, please see full Prescribing Information.

INDICATIONS AND USAGE

Type 2 Diabetes Mellitus

BYETTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use

BYETTA is not a substitute for insulin. BYETTA should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of BYETTA with prandial insulin has not been studied and cannot be recommended.

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYETTA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYETTA. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

DOSAGE AND ADMINISTRATION

Recommended Dosing

Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). Initiate at 5 mcg per dose twice daily; increase to 10 mcg twice daily after 1 month based on clinical response. Do not mix with insulin. Do not transfer BYETTA from the pen to a syringe or vial.

CONTRAINDICATIONS

Hypersensitivity

BYETTA is contraindicated in patients with prior severe hypersensitivity reactions to exenatide or to any of the product components.

WARNINGS AND PRECAUTIONS

Acute Pancreatitis

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYETTA, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYETTA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYETTA should not be restarted. Consider antidiabetic therapies other than BYETTA in patients with a history of pancreatitis.

Use with Medications Known to Cause Hypoglycemia

The risk of hypoglycemia is increased when BYETTA is used in combination with a sulfonylurea. Therefore, patients receiving BYETTA and a sulfonylurea may require a lower dose of the sulfonylurea to reduce the risk of hypoglycemia.

When BYETTA is used in combination with insulin, the dose of insulin should be evaluated. In patients at increased risk of hypoglycemia consider reducing the dose of insulin. The concurrent use of BYETTA with prandial insulin has not been studied and cannot be recommended. It is also possible that the use of BYETTA with other glucose-independent insulin secretagogues (e.g. meglitinides) could increase the risk of hypoglycemia.

Renal Impairment

BYETTA should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation. In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well-tolerated due to gastrointestinal side effects. Because BYETTA may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of BYETTA from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min).

There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status, such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including BYETTA. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

Gastrointestinal Disease

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because BYETTA is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYETTA is not recommended in patients with severe gastrointestinal disease.

Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYETTA. Antibody levels were measured in 90% of subjects in the 30-week, 24-week and 16-week studies of BYETTA. In 3%, 4% and 1% of these patients, respectively, antibody formation was associated with an attenuated glycemic response. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered.

Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with BYETTA. If a hypersensitivity reaction occurs, the patient should discontinue BYETTA and other suspect medications and promptly seek medical advice.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.

ADVERSE REACTIONS

Clinical Trial Experience

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

Hypoglycemia

Table 1: Incidence (%) and Rate of Hypoglycemia When BYETTA was Used as Monotherapy or With Concomitant Antidiabetic Therapy in Six Placebo-Controlled Clinical Trials*

	BYETTA		
	Placebo twice daily	**5 mcg twice daily**	**10 mcg twice daily**
Monotherapy (24 Weeks)			
N	77	77	78
% Overall	1.3%	5.2%	3.8%
Rate (episodes/patient-year)	0.03	0.21	0.52
% Severe	0.0%	0.0%	0.0%
With Metformin (30 Weeks)			
N	113	110	113
% Overall	5.3%	4.5%	5.3%
Rate (episodes/patient-year)	0.12	0.13	0.12
% Severe	0.0%	0.0%	0.0%
With a Sulfonylurea (30 Weeks)			
N	123	125	129
% Overall	3.3%	14.4%	35.7%
Rate (episodes/patient-year)	0.07	0.64	1.61
% Severe	0.0%	0.0%	0.0%
With Metformin and a Sulfonylurea (30 Weeks)			
N	247	245	241
% Overall	12.6%	19.2%	27.8%
Rate (episodes/patient-year)	0.58	0.78	1.71
% Severe	0.0%	0.4%	0.0%
With a Thiazolidinedione (16 Weeks)			
N	112	not evaluated	121
% Overall	7.1%	not evaluated	10.7%
Rate (episodes/patient-years)	0.56	not evaluated	0.98
% Severe	0.0%	not evaluated	0.0%
With Insulin Glargine (30 Weeks) †			
N	122	not evaluated	137
% Overall	29.5%	not evaluated	24.8%
Rate (episodes/patient-years)	1.58	not evaluated	1.61
% Severe	0.8%	not evaluated	0.0%

* A hypoglycemic episode was recorded if a patient reported symptoms of hypoglycemia with or without a blood glucose value consistent with hypoglycemia. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose value consistent with hypoglycemia or prompt recovery after treatment for hypoglycemia.

† When BYETTA was initiated in combination with insulin glargine, the dose of insulin glargine was decreased by 20% in patients with an $HbA_{1c} \leq 8.0$ % to minimize the risk of hypoglycemia. See Table 9 for insulin dose titration algorithm.

N = The number of Intent-to-Treat subjects in each treatment group.

Immunogenicity

Antibodies were assessed in 90% of subjects in the 30-week, 24-week and 16-week studies of BYETTA. In the 30-week controlled trials of BYETTA add-on to metformin and/or sulfonylurea, antibodies were assessed at 2- to 6-week intervals. The mean antibody titer peaked at week 6 and was reduced by 55% by week 30. Three hundred and sixty patients (38%) had low titer antibodies (<625) to exenatide at 30 weeks. The level of glycemic control (HbA_{1c}) in these patients was generally comparable to that observed in the 534 patients (56%) without antibody titers. An additional 59 patients (6%) had higher titer antibodies (≥625) at 30 weeks. Of these patients, 32 (3% overall) had an attenuated glycemic response to BYETTA; the remaining 27 (3% overall) had a glycemic response comparable to that of patients without antibodies.

In the 16-week trial of BYETTA add-on to thiazolidinediones, with or without metformin, 36 patients (31%) had low titer antibodies to exenatide at 16 weeks. The level of glycemic control in these patients was generally comparable to that observed in the 69 patients (60%) without antibody titer. An additional 10 patients (9%) had higher titer antibodies at 16 weeks. Of these patients, 4 (4% overall) had an attenuated glycemic response to BYETTA; the remaining 6 (5% overall) had a glycemic response comparable to that of patients without antibodies.

In the 24-week trial of BYETTA used as monotherapy, 40 patients (28%) had low titer antibodies to exenatide at 24 weeks. The level of glycemic control in these patients was generally comparable to that observed in the 101 patients (70%) without antibody titers. An additional 3 patients (2%) had higher titer antibodies at 24 weeks. Of these patients, 1 (1% overall) had an attenuated glycemic response to BYETTA; the remaining 2 (1% overall) had a glycemic response comparable to that of patients without antibodies.

Antibodies to exenatide were not assessed in the 30-week trial of BYETTA used in combination with insulin glargine.

Two hundred and ten patients with antibodies to exenatide in the BYETTA clinical trials were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon. No treatment-emergent cross reactive antibodies were observed across the range of titers.

Other Adverse Reactions

Monotherapy

Adverse reactions (excluding hypoglycemia) for the 24-week placebo-controlled study of BYETTA BID (N = 155) when used as a monotherapy, with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo BID-treated patients (N = 77): nausea (8% vs 0%), vomiting (4% vs 0%), and dyspepsia (3% vs 0%).

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite, diarrhea, and dizziness. The most frequently reported adverse reaction associated with BYETTA, nausea, occurred in a dose-dependent fashion.

Two of the 155 patients treated with BYETTA withdrew due to adverse reactions of headache and nausea. No placebo-treated patients withdrew due to adverse reactions.

Combination Therapy

Add-on to metformin and/or sulfonylurea

Adverse reactions (excluding hypoglycemia) in the three 30-week controlled trials of BYETTA BID (N = 963) add-on to metformin and/or sulfonylurea, with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo-treated patients (N = 483): nausea (44% vs 18%), vomiting (13% vs 4%), diarrhea (13% vs 6%), feeling jittery (9% vs 4%), dizziness (9% vs 6%), headache (9% vs 6%), dyspepsia (6% vs 3%), asthenia (4% vs 2%), gastroesophageal reflux disease (3% vs 1%), and hyperhydrosis (3% vs 1%).

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite. Nausea was the most frequently reported adverse reaction and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased over time in most of the patients who initially experienced nausea. Patients in the long-term uncontrolled open-label extension studies at 52 weeks reported no new types of adverse reactions than those observed in the 30-week controlled trials.

The most common adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (3% of patients) and vomiting (1%). For placebo-treated patients, <1% withdrew due to nausea and none due to vomiting.

Add-on to thiazolidinedione with or without metformin

Adverse reactions (excluding hypoglycemia) for the 16-week placebo-controlled study of BYETTA BID (N = 121) add-on to a thiazolidinedione, with or without metformin, with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo-treated patients (N = 112): nausea (40% vs 15%), vomiting (13% vs 1%), dyspepsia (7% vs 1%), diarrhea (6% vs 3%), and gastroesophageal refiux disease (3% vs 0%).

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite. Chills (n = 4) and injection-site reactions (n = 2) occurred only in BYETTA-treated patients. The two patients who reported an injection-site reaction had high titers of antibodies to exenatide. Two serious adverse events (chest pain and chronic hypersensitivity pneumonitis) were reported in the BYETTA arm. No serious adverse events were reported in the placebo arm.

The most common adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (9%) and vomiting (5%). For placebo-treated patients, <1% withdrew due to nausea.

Add-on to insulin glargine with or without metformin and/or thiazolidinedione

Adverse reactions (excluding hypoglycemia) for the 30-week placebo-controlled study of BYETTA BID (N = 137) as add-on to insulin glargine with or without oral antihyperglycemic medications with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo-treated patients (N = 122): nausea (41% vs 8%), vomiting (18% vs 4%), diarrhea (18% vs 8%), headache (14% vs 4%), constipation (10% vs 2%), dyspepsia (7% vs 2%), asthenia (5% vs 1%), abdominal distension (4% vs 1%), decreased appetite (3% vs 0%), flatulence (2% vs 1%), gastroesophageal reflux disease (2% vs 1%).

The most frequently reported adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (5.1%) and vomiting (2.9%). No placebo-treated patients withdrew due to nausea or vomiting.

Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of BYETTA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergy/Hypersensitivity: injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema, anaphylactic reaction.

Drug Interactions: International normalized ratio (INR) increased with concomitant warfarin use sometimes associated with bleeding.

Gastrointestinal: nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

Neurologic: dysgeusia; somnolence

Renal and Urinary Disorders: altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis), kidney transplant and kidney transplant dysfunction.

Skin and Subcutaneous Tissue Disorders: alopecia

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of BYETTA use in pregnant women. In animal studies, exenatide caused cleft palate, irregular skeletal ossification and an increased number of neonatal deaths. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Female mice given SC doses of 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7 had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 390 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

In developmental toxicity studies, pregnant animals received exenatide subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given SC doses of 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 12 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC. Moreover, fetuses from pregnant mice given SC doses of 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate and skeletal effects at systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

Lactating mice given SC doses of 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

Pregnancy Registry

Amylin Pharmaceuticals, Inc. maintains a Pregnancy Registry to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling 1-800-633-9081.

Nursing Mothers

It is not known whether exenatide is excreted in human milk. However, exenatide is present at low concentrations (less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing) in the milk of lactating mice. Many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in nursing infants from exenatide, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account these potential risks against the glycemic benefits to the lactating woman. Caution should be exercised when BYETTA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of BYETTA have not been established in pediatric patients.

Geriatric Use

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide. BYETTA was studied in 282 patients 65 years of age or older and in 16 patients 75 years of age or older. No differences in safety or effectiveness were observed between these patients and younger patients. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function.

OVERDOSAGE

In a clinical study of BYETTA, three patients with type 2 diabetes each experienced a single overdose of 100 mcg SC (10 times the maximum recommended dose). Effects of the overdoses included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations. One of the three patients experienced severe hypoglycemia requiring parenteral glucose administration. The three patients recovered without complication. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

Manufactured for Amylin Pharmaceuticals, Inc., San Diego, CA 92121

This product and its use are covered by US Patent Nos. 5,424,286, 6,858,576, 6,872,700, 6,902,744, 6,956,026, 7,297,761, 7,521,423, 7,741,269, and other patents pending.

1-800-868-1190

http://www.BYETTA.com

Literature Revised December 2011

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Pituitary Gland Regeneration Grows on Researchers

➤ The mutability of pituitary gland cells in the context of fluctuating endocrine needs led scientists to propose that stem cells participate in such adaptations. Recently, they pinpointed the location of these cells and found that they express Sox2, a transcriptional factor common to many stem cells. Scientists have also demonstrated both that stem cells contribute to the restoration of some adult organs after tissue injury and that dividing (i.e., immature) cells such as the growth hormone (GH)-producing pituitary somatotrophs are capable of regeneration at early-postnatal age. Taken together, these findings beg the question—can pituitary gland cells also regenerate in the adult?

Led by Hugo Vankelecom, Ph.D., at the University of Leuven, Belgium, scientists established a transgenic mouse model of pituitary tissue damage. After injecting adult GH/Cre-inducible diphtheria toxin receptor (iDTR) mice and control mice (not expressing the iDTR) with diphtheria toxin for 3 consecutive days, they used immunofluorescence to examine pituitaries 1 day and 1 week later to confirm somatotroph ablation. In their paper, to be published soon in ***Endocrinology,**** the researchers report that pituitary stem cells respond keenly to adult injury to contribute to somatotroph restoration, as evidenced by expansion of the stem cell locus and proliferation of stem cells. Remarkably, the stem cells reveal both Sox2, as expected, but also GH, which was not found in control pituitary stem cells.

The researchers concluded that stem cells repair adult pituitary tissue that has sustained injury. The next step is determining whether the stem cells morph into GH-producing cells or if surviving somatotrophs instead "de-differentiate" to a stem-cell state in the regenerative process. This future research will require more sophisticated GH-cell lineage tracking but will potentially unlock pathways that can be exploited clinically, they add. ■

* Fu Q, Gremeaux L, Luque RM, et al. The adult pituitary shows stem/progenitor cell activation in response to injury and is capable of regeneration. *Endocrinology,* doi:10.1210/en.2012-1152.

STATS

When Mexican university students were asked to estimate their body size,

3 out of 4

obese students considered themselves to be merely overweight.

Source: Andrade FCD, Raffaelli M, Teran-Garcia M, Jerman JA, Garcia, CA, Up Amigos 2009 Study Group. Weight status misperception among Mexican young adults. *Body Image,* January 2012; 9(1):184–188.

Testosterone Builds Bone and Raises Cholesterol in Transsexual Men

➤ The making of a man is in his blood. Testosterone dictates the advance of puberty in boys, generally developing larger bone and muscle mass than estrogen does in girls. Under cross-sex hormonal therapy in adulthood, the bodies of female-to-male transsexual persons (transsexual men) change in much the same way. Researchers at the University of Ghent, Belgium, measured increased bone and muscle mass in 50 transsexual men continuing testosterone substitution sex-reassignment surgery (SRS) and compared them with 50 age-matched women.

Their upcoming paper in ***The Journal of Clinical Endocrinology & Metabolism,**** suggests that greater bone formation and resorption in transsexual men might actually be in response to the increase of muscle. They had no risk of low bone mass despite the lack of estrogen. Their periosteum, a membrane enveloping bone just under the skin, was larger compared to the female control group, perhaps due in part to low estrogen levels that inhibit periosteal growth.

An additional group of 16 transsexual men not yet undergoing testosterone substitution or SRS showed none of these changes. Their bodies were similar to a control group of 16 age-matched women.

Physical exercise made little difference in either transsexual group except in the periosteal circumference of those receiving testosterone.

Testosterone substitution was also associated with less fat mass in the larger group of transsexual men. Their fat distribution was more central, collecting more at the waist and in the visceral cavity. Total cholesterol, however, increased. Although transsexual men might not experience risk of bone loss during cross-hormonal therapy, their risk of metabolic complications may rise under the influence of testosterone. ■

* Van Caenegem E, Wierckx K, Taes Y, et al. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab,* doi:10.1210/jc.2012-1187.

SMART MOVES

developments in the endocrinology world

*** Pinchas Cohen, M.D.,** a former pediatric endocrinologist at the University of California, Los Angeles (UCLA), was named dean of the Davis School of Gerontology at the University of Southern California in Los Angeles. He will also hold the William and Sylvia Kugel Dean's Chair in Gerontology and act as executive director of the Ethel Percy Andrus Gerontology Center. Previously, Dr. Cohen was previously vice chair of the David Geffen School of Medicine at UCLA.

Gary H. Gibbons, M.D., was selected as the new director of the National Heart, Lung, and Blood Institute at the National Institutes of Health (NIH). Dr. Gibbons is the founder and current director of the Cardiovascular Research Institute, chairperson of the Department of Physiology, and professor of physiology and medicine at the Morehouse School of Medicine, in Atlanta, Ga.

*** John Kopchick, Ph.D.,** received the 2012 Ohio Patent Impact Award for his co-discovery of the acromegaly drug Somavert (pegvisomant). The award honors "inventors with patents that have significantly impacted the state of Ohio through positive changes measured by economic, social change, health benefits, growth of new industries, jobs, and other factors." Dr. Kopchick is the Goll-Ohio Professor of Molecular Biology in the Department of Biomedical Sciences at Ohio University in Athens.

Rajesh Ranganathan, Ph.D., was named director of the Office of Translational Research at the National Institute of Neurological Disorders and Stroke, NIH. Dr. Ranganathan was formerly a senior adviser in the Office of the Director, where he helped create the NIH National Center for Advancing Translational Sciences.

M. Roy Wilson, M.D., M.S., was named deputy director of strategic planning and program coordination at the National Institute on Minority Health and Health Disparities (NIMHD) at the NIH. Prior to joining the NIMHD, Dr. Wilson served as chancellor of the University of Colorado Denver, president of the Texas Tech University Health Sciences Center in Amarillo, and dean of the Creighton University School of Medicine in Omaha, Neb. His international research has focused on the epidemiology of low vision and blindness in populations from the Caribbean to West Africa.

Share Your News

If you or others you know change jobs, receive a promotion, are granted an award, or otherwise make endocrinology-related career news, please don't hesitate to let us know at *endocrinenews@endo-society.org*.

Maternal Diabetes Fits with Offspring Autism

➤ Autism incidence has steadily risen over the past several decades, inciting a riot of investigation into its etiology in direct proportion to the abundance of theories about its cause and the number of questions as yet unanswered. With epigenetics recently showing promise among these hypotheses, one more piece of the autism puzzle may have clicked into place.

Previous studies have demonstrated links between maternal metabolic conditions, such as diabetes and impaired neurodevelopment, probably due to the fetal biologic response to high maternal glucose levels. Fetal hyperinsulinemia leads to greater oxygen use, which in turn causes hypoxia and, ultimately, iron deficiency. Both conditions are known to harm human hippocampal development. Moreover, maternal cytokines produced in response to some metabolic conditions can cross the placenta, wreaking havoc in several neurogenerative processes and possibly causing development of seizure disorders.

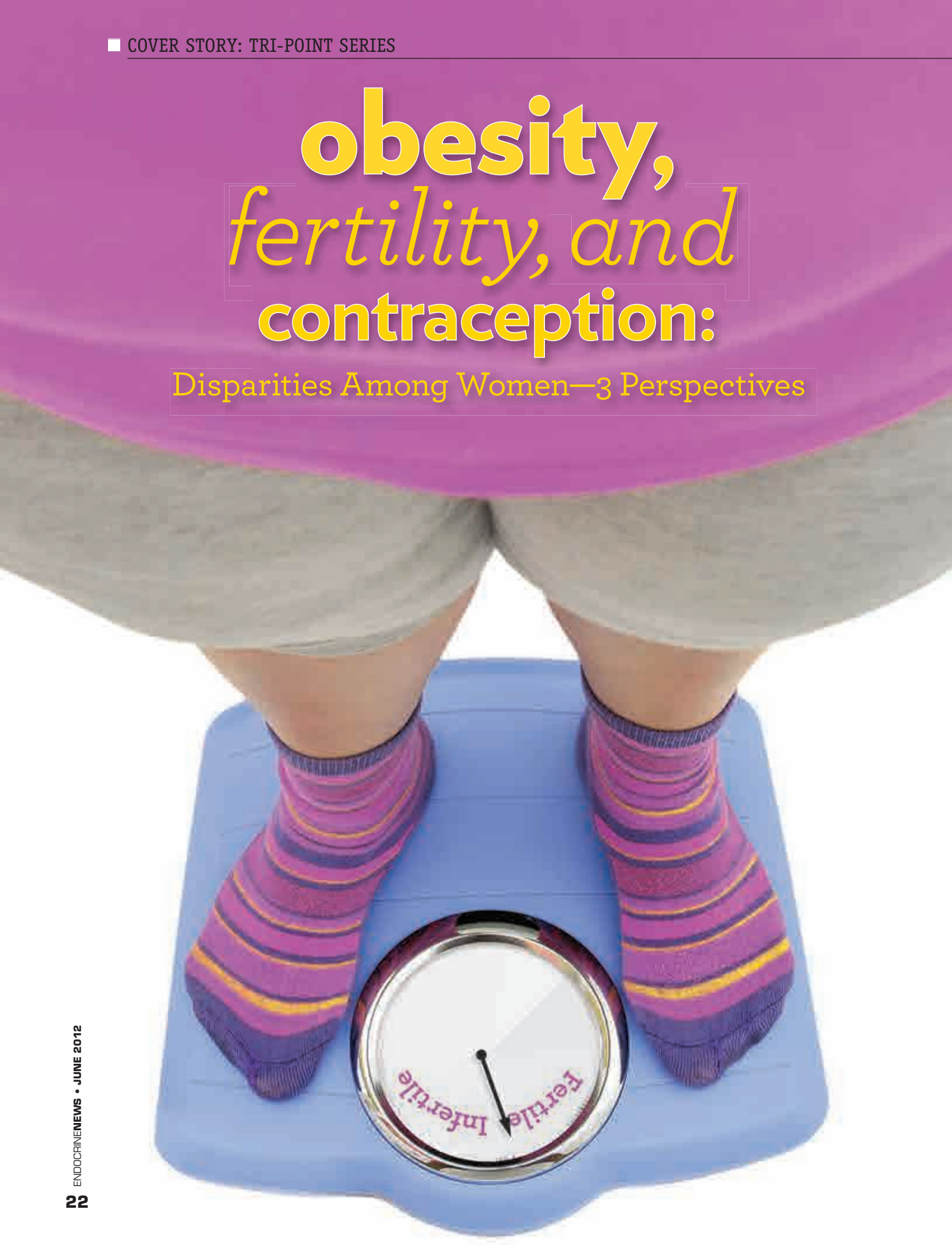
Led by Paula Krakowiak, M.S., at the University of California, Davis, scientists analyzed data from 1,004 children ages 2–5 years who participated in the Childhood Autism Risks from Genetics and the Environment (CHARGE) study. The purpose was to determine relationships between maternal metabolic conditions—primarily type 2 diabetes and gestational diabetes but also hypertension and obesity—and fetal neurodevelopmental impairments. Among these children, 517 had been previously diagnosed with autism spectrum disorders (ASDs), 172 with developmental delays, and 315 with typical development (control group). In their paper, to be published soon in ***Pediatrics,*** * the researchers report that children with an ASD (28.6%) or a developmental delay (34.9%) were more likely than children in the control group (19.4%) to have a mother with a metabolic condition. Additionally, the ASD children of mothers with diabetes were also more likely to exhibit poorer expressive language skills. Hypertension did not seem to play a role here.

The researchers conclude that metabolic conditions, particularly diabetes, and obesity are associated with developmental deficits ranging from language impairments to communication and socialization dysfunction. With the prevalence of diabetes and obesity rising among reproductive-aged women, the significance of this finding is staggering. ■

* Krakowiak P, Walker CK, Bremer AA, et al. Maternal metabolic conditions and risk for autism and other disorders. *Pediatrics,* in press.

obesity, *fertility, and* contraception:

Disparities Among Women—3 Perspectives



From The Endocrine Society's Research Affairs Core Committee
Edited by Cecilia Wang, M.D. and Kerry Burnstein, Ph.D.

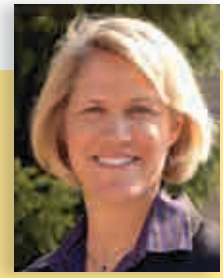
Introduction

Approximately 55% of American women of childbearing age are overweight or obese and approximately 5% suffer from extreme or morbid obesity. The overweight and obesity epidemic has significantly affected risks in obstetrics and gynecology. Increased antenatal and perinatal complications in overweight and obese pregnancy women include (but are not limited to) gestational diabetes mellitus, stillbirth, fetal anomalies, fetal macrosomia, and cesarean delivery. The focus of the current review is on the implications of overweight and obesity on fertility and contraception.

Basic Researcher Perspective

By Kelle H. Moley, M.D.

Dr. Moley is the James P. Crane Professor of Obstetrics and Gynecology Vice Chair and division director of basic science research at Washington University School of Medicine, St. Louis, Mo.



Highlights

- Obesity alters the hypothalamic, pituitary, gonadal, and uterine components of female reproductive physiology.
- Excess energy availability in the form of obesity affects the regulation of most neuropeptides, specifically kisspeptin and leptin.
- Maternal obesity and availability of excess fatty acids directly and/or indirectly impacts the mitochondria within oocytes and adversely affects oocyte quality.
- In obese rodent models, increased inflammation and abnormal lipid localization impairs implantation.
- A multi-targeted approach to infertility is needed to effectively reverse the poor reproductive capacity experienced by obese females.

Obesity is the result of a prolonged mismatch between energy intake and expenditure, leading to an excess of stored body lipids. This condition has significant and long-lasting effects on fertility. Our understanding of the possible mechanisms responsible for the reproductive sequelae come from animal studies, mostly in rodents, using both genetic and diet-induced obesity models.

Obesity results in central, gonadal, and uterine effects, impacting ovulation, oocyte quality, and implantation. This discussion supports the hypothesis that obesity affects all three sites.

Central Pathways and Neuropeptides

Hypothalamic reproductive function is regulated by neurons and their secreted neuropeptides, and these neurons can sense not only total nutritional availability but also changes in diet.[1, 2] Reduced reproductive function and ovulatory dysfunction have been clearly linked to nutritional restriction in humans and animal models.[3, 4] Most studies demonstrate decreased secretion of neuropeptides such as kisspeptin, galanin, leptin, and neuropeptide Y, and thus conclude that decreases in accessible energy substrates either directly or indirectly perturb signaling via the master regulator, the gonadotropin-releasing hormone neurons. Surprisingly, overnutrition in the form of obesity or chronic high-fat feeding leads to a hypothalamic hypogonadism phenotype, more similar to a low-energy balance state such as starvation. This phenomenon has been linked in high-fat fed mice to a decrease in kisspeptin-producing neurons in these neurons in the hypothalamus, resulting in a 60% reduction in pregnancy rates.[5] Although these central events appear to be directly connected, genetic mouse models have emphasized the complexities of these pathways and suggest that other indirect mechanisms may be responsible for the integration of the reproductive and energy balance axes.[6, 7]

Oocyte Quality

Mice fed a high-fat diet demonstrate decreased ovulation and fertility whereas fetuses of these mice have impaired embryonic development and growth restriction.[8] Oocytes from obese mice are significantly smaller, exhibiting delayed meiotic maturation and increased follicular apoptosis. The inciting metabolic factor is not clear; however, abnormal circulating and follicular fluid levels of free fatty acids have been associated with poor oocyte quality and decreased pregnancy rates in women undergoing in vitro fertilization (IVF).[9]

One proposed mechanism for compromised oocyte quality and poor reproductive outcomes in obese females includes altered mitochondrial activity at the oocyte stage. Oocytes have the largest number of mitochondria of any cell in the body and thus are vulnerable to many different metabolic stressors. Abnormal mitochondrial structure and function have been reported in oocytes from diet-induced obese mice resulting in poor fertilization rates and abnormal embryo development.[8, 10, 11] Oocytes from high-fat fed obese mice experience uneven mitochondrial distribution, altered mitochondrial DNA copy number, and abnormal mitochondrial metabolism. These events appear to be linked to higher rates of spindle defects and chromosome misalignment in the maturing oocytes of diabetic animals.[12] This higher rate of aneuploidy may be responsible for the increased miscarriage rates in obese women.[13]

Since the fertilized zygote inherits only the maternal mitochondria, oocyte abnormalities and aberrant mitochondria carry over to the zygote stage and manifest even after transfer to non-obese recipients, thus suggesting a programming event that occurs during the periovulatory period.

Implantation

The process of implantation and uterine receptivity is adversely affected by obesity and a high-fat diet in mice. This phenomenon may be associated with inflammation and abnormal lipid metabolism. First, global transcriptome profiling of a rat uterus following a high-fat diet reveals distinct signatures for genes regulating inflammation and lipid metabolism. Gene-set enrichment and pathway analysis suggest upregulation of uterine nuclear factor–κB and c-Jun-*N*-terminal kinase signaling. This induction is accompanied by a pattern of increased cytokines and other inflammatory process regulators.[12] Second, high-fat feeding may result in morphological evidence of abnormal lipid accumulation in the uterine endometrium of rats.[12] This ectopic localization of stored lipids has been linked to increased mRNA expression of several lipid metabolism genes such as *FABP4, CD36,* and *lipoprotein lipase*. Lipid accumulation in the uterine endometrium has also been described in the genetic obesity models, *db/db* and *ob/ob*.[13] Although the data suggest that extensive pro-inflammatory gene expression together with uterine lipid accumulation occur in maternal obesity at the time of implantation, it is not clear how these observations affect uterine receptivity. Recent studies show that adiponectin and its receptors have distinct expression patterns during the peri-implantation and decidualization processes.[14] Such events may interfere with attachment of the blastocyst or differentiation of the endometrial stroma leading to decidualization. Implications of these studies remain unexplored.

Health Disparities from an Animal Perspective

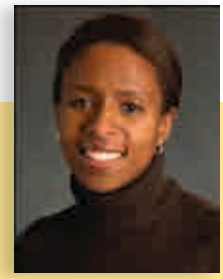
Although a seemingly odd pairing, two recent basic science studies in mice have informed clinical studies related to women's health. These studies tested the hypothesis that the observed social and ethnic disparities in breast cancer incidence and mortality might be related to higher levels of social stress in vulnerable populations.[9, 10] Both types of studies examined social isolation as a biological stressor in a female mouse model predisposed to develop mammary tumors. Peri-pubertal female mice were caged either individually or group-housed in the usual fashion of five mice to a cage, with all other parameters controlled. In the first study, 14 weeks of social isolation was associated with up-regulation of lipid synthesis and glycolytic pathway gene expression, which led to the development of a significantly larger mammary gland tumor burden than in group-housed mice.[10] This study identified putative biomarkers and targets for preventive intervention in breast cancer. Although the second study did not show a difference in tumor growth, the investigators determined that social isolation resulted in hypothalamic differences in kisspeptin expression associated with reduced duration of estrous cycles.[9] Both studies modeled a potential cause of health disparity, namely social isolation, to inform the mechanism of disease. The same type of approach could be adapted to studies in obesity, because social and ethnic disparities play a key role.

The process of implantation and uterine receptivity is adversely affected by obesity and a high-fat diet in mice.

Clinical Practitioner Perspective

By Samantha F. Butts, M.D., M.S.C.E.

Dr. Butts is the assistant professor of obstetrics and gynecology, Division of Infertility and Reproductive Endocrinology at the Perelman School of Medicine, University of Pennsylvania, Philadelphia.



Highlights

- Racial and ethnic disparities in reproductive outcomes occur across the female life-course from puberty to infertility, encompassing obstetric risks and beyond; elevated prevalence of obesity in African Americans and Latinas represents one important factor contributing to these disparities.
- Obesity is associated with challenges to fertility including ovulatory dysfunction (most notably demonstrated in women with PCOS), and elevated risk of miscarriage.
- In PCOS patients treated with clomiphene citrate for induction of ovulation, obesity is also a risk factor for diminished odds of live birth; obesity is a risk factor for diminished odds of live birth in ART cycles except in donor egg IVF.
- Concern exists that hormonal contraceptives fail more frequently in obese women than non-obese women. Proposed mechanisms include rapid drug metabolism/clearance and sequestration of lipophilic drugs in fat stores. The actual association between obesity and hormonal contraceptive efficacy is a matter of current debate. More studies are needed to explore comparative effectiveness of OCPs and other hormonal delivery systems.
- Weight loss, even modest amounts (2%–10% of total body weight), improves ovulation frequency in obese women with PCOS. Dramatic weight loss that occurs with bariatric surgery also improves ovulatory function in PCOS and diminishes perinatal risks in women who conceive.

A growing body of research has emerged acknowledging the presence of differences in reproductive outcomes across racial and ethnic groups, with a goal of isolating basic determinants to improve outcomes for women at risk. One of the prevailing, modifiable correlates of reproductive risk that has high prevalence in ethnic and racial minorities (African Americans and Latinas compared to women of European descent) is the presence of obesity.[1] Obesity is linked to many reproductive problems that are disparate between racial and ethnic groups including early puberty, infertility, assisted reproductive technology (ART) outcomes, and perinatal risks (i.e., stillbirth and preeclampsia). Although it has been hypothesized that racial and ethnic reproductive disparities have numerous environmental and genetic underpinnings, obesity as a link between disparities and reproductive challenges will be the focus of this review.

Overweight, Obesity, and Diminished Fecundity: Anovulation and Beyond

Multiple reports demonstrate that risk of early pregnancy loss increases both after unassisted conception and after conception with infertility treatments in overweight and obese women.[2] Mechanisms of impaired fecundity in obese women are unclear, but Study of Women's Health Across the Nation (SWAN) investigators found that women with a BMI greater than 25 kg/m^2 have decreased luteinizing hormone (LH) amplitude and mean serum LH levels, with a longer follicular phase and a shortened luteal phase.[3,4] LH alterations likely have an impact on follicular development and ovulation, with implications for endometrial development and embryo implantation. Several reports of large cohorts have noted an adverse impact of obesity on ART outcomes, with respect to attenuated response to gonadotropins, increased cycle cancellation rates, diminished clinical pregnancy rates, and diminished live birth rates.[5,6] In contrast, the majority of reports suggest that donor egg IVF pregnancy rates are not affected when the donor egg recipient is obese.[5,6]

Polycystic ovary syndrome (PCOS) affects 5%–10% of reproductive-age women.[6] Overweight and obesity are most notably associated with disordered ovulation and menstrual cycle irregularity, in women with this disorder. Anovulation is the primary defect leading to infertility in obese women with PCOS. The Cooperative Multicenter Reproductive Medicine Network Trial of Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome demonstrated that independent of assigned treatment (clomiphene citrate, metformin, or the treatments combined), subjects with a body mass index (BMI) greater than 30 kg/m^2 had a significantly lower rate of live birth than those with BMI less than 30 kg/m^2.[7]

Overweight, Obesity, and Contraceptive Efficacy

Oral contraceptive pill (OCP) failure rates in the general population are higher than in clinical trials, which tend to enroll subjects who are close to ideal body weight.[8] This discrepancy has led to a concern that hormonal contraceptive failures in general are increased in overweight and obese women compared to normal weight women. Proposed mechanisms for diminished effectiveness of hormonal contraception in overweight and obese women include rapid hepatic drug metabolism/clearance and sequestration of lipophilic drugs in fat stores.[9] Observational studies have reported an increased risk of OCP failures in overweight and obese women—even when restricting the analysis to consistent users—who had greater than double the risk of pregnancy compared to normal weight

women.[9] Conversely, a randomized trial comparing ovarian suppression in normal weight and obese women who were consistent OCP users found no difference in ovarian suppression between groups.[8] The results of several current studies have been contradictory, making the final answer to this question elusive. A Cochrane Review has addressed the issue of hormonal contraceptive efficacy in obese and non-obese women across drug delivery types. At present, and based on only one trial referenced, it is possible that Depo-Provera has comparable efficacy in normal weight and overweight women. However, the authors conclude that a limited number of heterogenous studies using varied anthropomorphic measures, some excluding women over a certain body-size category, limits a definitive conclusion regarding whether hormonal contraception is less effective in overweight and obese women.[10]

Impact of Weight Loss on Fertility in Overweight and Obese Women

Weight loss should be a first-line approach to addressing infertility in overweight and obese women who are anovulatory.[6] A number of short-term clinical trials have demonstrated that weight loss in the range of 2%–10% of starting body weight restores menstrual cyclicity and/or ovulation in 44%–72% of anovulatory subjects.[6, 11] Medical and surgical therapies for weight loss are recommended when obesity is associated with comorbidities or when lifestyle approaches have not been successful.[6]

Bariatric Surgery and Reproductive Outcomes

Bariatric surgery results in the most profound and long-lasting weight loss of any method currently available. Weight loss for patients with a starting BMI of 40 kg/m^2 or greater averages 20–40 kg over 2 years, with weight loss maintenance described for up to 10 years.[6] Such weight loss has been demonstrated to confer significant improvement in ovulatory dysfunction in obese women with PCOS. In one series of obese women with PCOS, menstrual regularity was noted in all participants between 6 and 12 months after weight loss surgery and was associated with reduced hyperandrogenism and improved insulin sensitivity.[12]

Pregnancy is not recommended for at least 1 year after bariatric surgery—when weight loss is the most rapid. No significant pattern of adverse perinatal outcomes has been associated with pregnancies occurring after bariatric surgery. However, patients who conceive after bariatric surgery should be followed by a nutritionist and those with adjustable laparoscopic gastric bands should consult with their surgeon during pregnancy if new onset gastrointestinal symptoms arise.[6]

Conclusions

Approximately 55% of American women of childbearing age are overweight or obese and approximately 5% suffer from extreme or morbid obesity.[13] This epidemic has significantly impacted risks in obstetrics and gynecology especially in African American and Latina women in whom obesity is most prevalent. It is recommended that women who are overweight or obese be extensively counseled by providers about associated early pregnancy, antenatal, and perinatal risks and that this counseling occur prior to conception (if feasible) or early in pregnancy. Supervised weight loss is critical for reducing obesity-related reproductive risks. Whether or not obesity is definitively associated with hormonal contraceptive failure remains a matter of ongoing investigation. Although the results of future reports are forthcoming, it is critical to reinforce the basic principles of contraceptive efficacy to our patients and to select approaches that minimize their risk.

Clinical Researcher Perspective

By Alex J. Polotsky, M.D., M.Sc.

Dr. Polotsky is an assistant professor, Department of Obstetrics and Gynecology at the University of Colorado Denver, Anschutz Medical Campus, Aurora.

Highlights

- Obesity affects over 30% of the U.S. population. Impact on reproduction is consistently observed even in **ovulatory obese** women with regular menstrual periods.
- Important pathophysiologic features distinguish PCOS and obesity, most notably the opposing effects on LH pulsatility: PCOS is characterized by markedly increased serum LH, while simple obesity is generally associated with decreased overall serum LH and decreased indices of LH pulsatility.
- CLI of obesity is an under-appreciated phenomenon, which may explain the association of obesity with subfertility. Corrective measures for CLI in obesity have not been investigated.
- Obesity is not associated with decreased sexual activity. Thus affected women are in need of contraceptive, sexually transmitted diseases prevention, and preconception services that may be underappreciated by providers.
- Considerable gender and ethnic differences in prevalence of obesity and their impact of fertility remain under-investigated.

The obesity pandemic is predicted to precipitate a decline in life expectancy in the 21st century. Over 32% of all U.S. adults are now obese as defined by a BMI of greater than 30 kg/m^2.[1] By 2015, 75% of all US adults are projected to be overweight or obese with BMI of greater than 25 kg/m^2.[2] The reproductive consequences of female

Table 1. PCOS vs. Non-Syndromic Obesity

	PCOS	Non-Syndromic Obesity
Menstrual regularity	Oligomenorrhea*	Variable
Body mass	Variable (up to 50% not obese)	Defined by body mass index > 30 kg/m^2
Mean serum LH	↑	↓
LH pulsatility	↑ LH pulse frequency	Normal LH pulse frequency ↓ LH pulse amplitude
Androgens	Hyperandrogenism*	Variable
Onset	Often starts at menarche	Variable

* Mandatory by 1990 NIH criteria, variable by 2003 Rotterdam criteria.

obesity are manifested by a variety of disturbances, including menstrual cycle irregularities, oligo-ovulation, higher risk of miscarriage and subfertility, decreased chances of success after fertility treatments, and higher risk of failure with some methods of contraception. On a population level, a compounded loss of fertility is likely, because obese women with an overweight or obese male partner have up to a two-fold further loss in fertility than their obese counterparts with normal weight partners. This report will concentrate on published clinical research studies devoted to the impact of female obesity on reproduction.

Impact of Female Obesity on Reproduction Should be Considered Distinctly from Evaluating Polycystic Ovary Syndrome

Traditionally, reproductive effects of female adult obesity were attributed to increases in anovulation, amenorrhea, and hyperandrogenism. Most of the existing body of literature concerning obesity and reproduction involves women with PCOS, a condition characterized by androgen excess and irregular menses and, frequently, accompanying obesity. This is understandable, because PCOS is regarded as one of the most common endocrinopathies in the general population, with an estimated 5%–8% prevalence among reproductive age women. However, simple obesity (also referred to as non-syndromic or "garden variety") is considerably more prevalent than PCOS and affects every third woman in the United States. Importantly, several pathophysiologic features distinguish PCOS from obesity, most notably the opposing associations with indices of LH pulsatility. PCOS is characterized by increased serum LH, whereas simple obesity is generally associated with decreased overall serum LH and decreased LH pulse amplitude (see Table 1). Thus, it is imperative to avoid indiscriminate grouping of women in clinical studies of obesity and reproduction because inadequate characterization of research subjects could lead to misinterpreting the impact of adiposity per se.

Subfertility in Ovulatory Obese Women

Non-obstetric effects of female adult obesity on fertility are largely attributed to increased prevalence of anovulation. The impact of adiposity on reproductive outcomes in ovulatory obese women with preserved menstrual regularity is only recently coming to the forefront of investigative attention. Large body mass prolongs the time to pregnancy and is associated with sub-fecundity in women with regular menstrual cycles. An increase in waist-hip ratio by as little as 0.1 unit was associated with a 30% decrease in the per-cycle probability of conception in a study of 500 fertile women undergoing donor sperm insemination.[3] In a cohort of over 3,000 subfertile couples in whom the female partner was confirmed to be ovulatory, the probability of spontaneous conception declined with a BMI over 29 kg/m^2.[4] Multivariate analysis from the same study indicated that an increase in BMI by one unit resulted in a 4% reduction in the likelihood of conception. Data from SWAN, which included mostly ovulatory women, indicated that adolescent obesity was associated with a 3-fold increased risk of lifetime nulliparity and a 4-fold increased risk of lifetime nulligravidity, further underscoring the impact of obesity on lifetime childbearing potential.[5] Although association of obesity with subfertility is well documented in population studies, our understanding of the pathophysiological phenomena underpinning these observations is limited.

Relative Hypogonadotropic Hypogonadism and Corpus Luteum Insufficiency Are Potential Mechanisms to Explain Obesity-Related Reproductive Phenotype

Since the 1970s, obesity has been associated with longer follicular phases and decreased serum gonadotropins and luteal progesterone. More recently, a detailed evaluation of daily hormones from 836 ovulatory cycles indicated that women with BMI over 25 kg/m^2 excreted significantly less urinary LH, FSH, and progesterone metabolites.[6] This relative hypogonadotropic hypogonadism of obesity could conceivably be explained by either central (hypothalamic or pituitary) or peripheral defects within the hypothalamic-pituitary-ovarian (HPO) axis. Several distinct lines of evidence implicate a defect in the central part of the HPO axis in obesity, specifically, a selective deficiency in the LH pulse amplitude. Notably, decreased LH pulse amplitude but unaffected LH pulse frequency has been reported in obese men. Studies from ovulatory morbidly obese women indicate a significant reduction in LH pulse amplitude, yet no change in LH pulse frequency compared to normal weight

controls.[7] One of the potential pathophysiologic mechanisms for this association is altered or exaggerated sensitivity to estrogen negative feedback in obesity, a hypothesis that is being actively investigated in clinical studies.

There are considerable gender and ethnic differences in regard to prevalence of obesity in the United States.

Female Obesity Is Not Associated with Decreased Sexual Activity

Reduced exposure to sexual encounters either by decreased likelihood of finding a partner or by rare sexual intercourse may potentially explain the association of female obesity with subfertility. Research on frequency of sexual intercourse among women with large body mass yielded conflicting results. A study from 101 German adults suggested a significant negative correlation between the body size and frequency of vaginal intercourse.[8] However, several recent reports from larger studies demonstrated no differences in frequency of sexual activity by BMI. A report of 626 women in a Reproductive Medicine Network trial, found no difference by body mass in the frequency of timed sexual intercourse when instructed to do so for conception.[9] Similar results were observed by the investigators from the 2002 National Survey of Family Growth.[10] The analytic sample included 6,690 women aged 15–44 years who were surveyed about a variety of health outcomes. The study found that for most of the parameters describing sexual behavior, there was no appreciable difference in frequency of sexual activity by body mass. Compared to normal weight women, both obese and overweight women had significantly higher likelihood of ever having had a heterosexual intercourse (77% and 56%, respectively). The main conclusion of this large study should not be ignored: Obese and overweight women do not report decreased frequency of sexual encounters compared to their leaner counterparts, and thus are in need of related contraceptive, sexually transmitted diseases prevention, and preconception services. This finding may be underappreciated by providers.

Obesity, Fertility, and Contraception: Disparities among Women

There are considerable gender and ethnic differences in regard to prevalence of obesity in the United States. The prominent paradigm of considerably higher female vis-à-vis male obesity in many countries has not been adequately explained. In the United States, African American women are reported to have the highest prevalence of high BMI. The latest National Health and Nutrition Examination Survey data reported a drastic disparity as age-adjusted prevalence of obesity was found to be 58.6% for non-Hispanic black women as compared with 32.2% for non-Hispanic white women.[11] Data on health disparities among women in regard to obesity and fertility are sparse, but female obesity and its link with subfertility are beginning to be cited as a problem in the developing world. Of note, obesity is thought to influence the data on ethnic differences in epidemiology of PCOS, as illustrated by a recent report from South China where a relatively small 2.2% prevalence was reported among 915 women presenting for their annual physical.[12] More studies are needed to explain why nations fluctuate in the male-female obesity gap and why vast ethnic differences exist in prevalence of obesity in U.S. women and the impact of these disparities on fertility studies. ■

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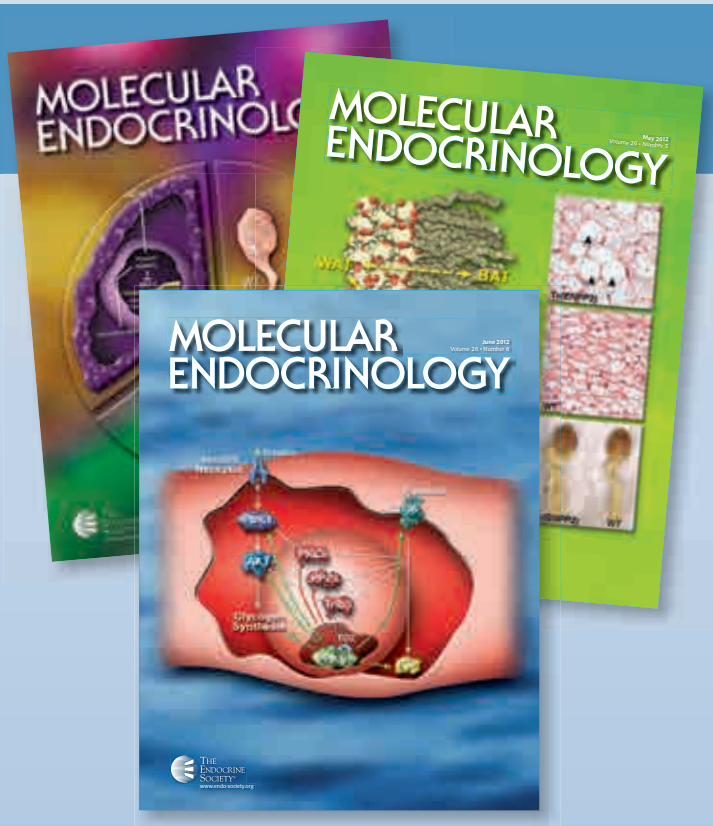

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SLEEP AND ADDLE METABOLIC

CIRCADIAN DISRUPTIONS PROCESSES

Is a jet-lagged pancreas to blame?

By Eric Seaborg*

Mom always told you to get a good night's rest. Here's another reason why she might be right: A new study implicates a jet-lagged pancreas in the pathology linked to increased obesity and type 2 diabetes mellitus (T2DM). Published in *Science Translational Medicine,* the study says the two diseases gang up to hit the metabolism high and low, with sleep restriction increasing insulin resistance and circadian disruption decreasing insulin secretion.[1]

The evidence from epidemiological research linking sleep disruption with metabolic perturbations is growing, but these studies do not answer the question of causality. For example, a study published in December in *PLoS Medicine* followed almost 180,000 female nurses. The investigators found that rotating night shift work was strongly associated with an increased T2DM risk.[2] However, the affected women also gained more weight, ate a less healthful diet, and exercised less than their peers, muddying the contributions of night and rotating shift work schedules alone.

Problems of Causality

This muddled picture is always the case because night workers tend to be associated with less healthful lifestyle choices, especially diet options, said Orfeu M. Buxton, Ph.D., assistant professor in the division of sleep medicine at Harvard Medical School, associate neuroscientist at Brigham and Women's Hospital in Boston, and lead author of the *Science Translational Medicine* paper. Dr. Buxton and his colleagues are trying to tease out the causality underlying the associations.

In a previous study of healthy men aged 20–35 years, his team showed that 7 nights of sleep restriction significantly reduced their insulin sensitivity, as assessed by an intravenous glucose tolerance test and euglycemic-hyperinsulinemic clamp.[3]

A 28-Hour Day

The just-published study was much more ambitious. The team asked 21 healthy adults to spend 39 days under controlled laboratory conditions, in an individual suite with dim light and no time cues. After 6 days of a "sleep replete" condition, with sleep at a normal circadian time, the subjects spent up to 21 days with their sleep restricted to 5.6 hours during a circadian rhythm–disrupting 28-hour day schedule. They experienced feeding and sleep-wake cycles that were the equivalent of moving four time zones west every day. The subjects then had 9 days of recovery sleep opportunity of 10 hours per 24 hours at a normal circadian time. Their diet and activities were strictly prescribed. The researchers monitored a variety of metabolic parameters, such as resting metabolic rate, body temperature, blood glucose and insulin levels after a meal, and more.

Pancreatic Problem

Glucose elevations following a meal in the morning were much higher, and they were sustained for several hours afterward at a higher level than when the subjects were rested. "Much to our surprise, the pancreas secreted far less insulin when subjects were circadian disrupted than when subjects were well rested and in phase," Dr. Buxton told ***Endocrine News.*** "So, sleep restriction alone and circadian disruption both increase diabetes risk, but the difference is that sleep restriction does so by reducing insulin sensitivity without any change of insulin response, whereas circadian disruption does so by greatly decreasing the insulin response."

Another important finding was that the test subjects experienced a reduction in resting metabolic rate of about 8%. If such a reduction continued with no cut in caloric intake or increase in activity, it could lead to a weight gain of about 10 pounds in a year, which implies an obesity risk.

Of course, the researchers noted other metabolic perturbations. Glucose and cortisol concentrations rose above baseline levels; leptin levels were slightly lower, and ghrelin levels were slightly higher. The deviations returned to normal during the 9 days of recovery sleep. A surprise in the results was the lack of an age effect. The changes were no more pronounced in older subjects than in younger ones.

The Double Whammy

Some critics have complained that the researchers sacrificed clarity by combining circadian disruption with sleep restriction, but Dr. Buxton said the two are inseparable in the lives of night workers and rotating night workers. "Your circadian clock drives you to be alert during the biological day and asleep during the biological night. Most night workers have extreme difficulties getting the amount of sleep they would at night when they have to recover during the day," he said. Outside noise, light, and the phone interrupt sleep, and it's much harder to get back to sleep during the day.

"We know little about the biological mechansims through which sleep disturbance leads to metabolic changes," said Frank Hu, M.D., Ph.D., M.P.H., professor of nutrition and epidemiology at the Harvard School of Public Health. He added that the two studies by Dr. Buxton "provide strong evidence that sleep deprivation or shift work can actually decrease insulin sensitivity and decrease insulin secretion."

Sound sleep is actually as important as good diet and regular exercise.

Sleep as a Lifestyle Choice

Dr. Hu is the lead author of the previously mentioned epidemiological study linking shift work and diabetes in nurses. He also co-authored a prospective study on 4-year weight gain that found the effect of a short sleep period alone on weight gain to be small, but also found that short sleep was associated with other problems, such as skewing diet choices away from healthful items like yogurt and walnuts and toward sugary drinks and unhealthful snacks.[4]

Chronic sleep deprivation could be a factor contributing to the obesity epidemic. The average sleep duration in the United States has declined by more than an hour a night in the past 40 years, and has fallen below 7 hours per night. Studies show that the optimal amount of sleep for most individuals is in the range of 7–8 hours a night.

Dr. Hu said when clinicians talk to patients on combating metabolic syndrome by improving their diet and lifestyle, perhaps it's time to broaden lifestyle counseling to include tips on better sleep hygiene as well, like Mom's admonition to get to bed on time. "To a large degree, sound sleep is actually as important as good diet and regular exercise." ■

* Eric Seaborg is an award-winning free-lance writer, living in Charlottesville, Va.

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The Lowdown on Low Iodine: Diet Strategies for Thyroid Cancer Patients

CONFIRMED PANELISTS:

Susan J. Mandel, MD, MPH,
University of Pennsylvania

Shalimar Manuel, BScHE, MA,
Young Adult Cancer Canada

Norene Gilletz, Featured Chef

SUNDAY, JUNE 24

1:00–3:00 PM

Weighing in on Acromegaly: The Patient's Perspective

CONFIRMED PANELISTS:

Lisa B. Nachtigall, MD,
Massachusetts General Hospital

Wayne Brown, Acromegaly Community Inc.

Amy Riolo, Featured Chef

MONDAY, JUNE 25

1:00–3:00 PM

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Western Slope Endocrinology

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Endocrinology

Hepcidin inhibition by E_2 increases iron uptake, compensating for iron loss during menstruation; this mechanism may also contribute to increased iron stores in oral contraceptive users.
Yang Q, Jian J, Katz S, Abramson SB, Huang X. *17beta-estradiol inhibits iron hormone hepcidin through an estrogen responsive element half-site.*

Total α1AMPK deficiency in male mice affects androgen production and spermatozoa quality, leading to a decrease in fertility. Using an AMPK activator such as metformin could jeopardize human male fertility.
Tartarin P, Guibert E, Toure A, et al. *Inactivation of AMPK alpha1 induces asthenozoospermia and alters spermatozoa morphology.*

The intermediate filament vimentin moves cholesterol from the cytoplasm to the mitochondria for steroidogenesis.
Shen W-J, Zaidi SK, Patel S, et al. *Ablation of vimentin results in defective steroidogenesis.*

Nucleobindin-2 regulates epithelial growth factor–stimulated MEK/Erk signaling, cell proliferation, and adipocyte differentiation.
Tagaya Y, Miura A, Okada S, Ohshima K, Mori M. *Nucleobindin-2 is a positive modulator of EGF-dependent signals leading to enhancement of cell growth and suppression of adipocyte differentiation.*

The Journal of Clinical Endocrinology & Metabolism

SREs are just as common in thyroid cancer patients as in those with metastatic breast cancer, necessitating the need for antiresorptive therapy.
Farooki A, Leung V, Tala H, Tuttle RM. *Skeletal-related events due to bone metastases from differentiated thyroid cancer.*

LPO is linked to periodontal disease susceptibility in T2DM patients.
de Souza Bastos A, Graves DT, de Melo Loureiro AP, et al. *Lipid peroxidation is associated with the severity of periodontal disease and local inflammatory markers in patients with type 2 diabetes.*

***Steroidogenic factor-1* mutations are frequently found in 46, XY DSD individuals and manifest with a broad phenotype.**
Camats N, Pandey AV, Fernández-Cancio M, et al. *Ten novel mutations in the* NR5A1 *gene cause disordered sex development in 46,XY and ovarian insufficiency in 46,XX individuals.*

Down-regulation of a specific subset of miRNAs leads to pituitary tumorigenesis.
D'Angelo D, Palmieri D, Mussnich P, et al. *Altered microRNA expression profile in human pituitary GH adenomas: Downregulation of miRNAs targeting* HMGA1, HMGA2, *and* E2F1.

Molecular Endocrinology

Tsc22d3-2–deficient male mice are infertile, exhibit severe testis dysplasia, increases in apoptotic cells within seminiferous tubules, a heightened number of Leydig cells, and a significantly elevated follicle-stimulating hormone and testosterone levels.
Suarez PE, Rodriguez EG, Soundararajan R, et al. *The glucocorticoid-induced leucine zipper* (Gilz/Tsc22d3-2) *gene locus plays a crucial role in male fertility.*

Several genes are regulated by various tissue-selective estrogen complex combinations, but not by an estrogen or selective estrogen receptor modulator alone.
Wardell SE, Kazmin D, McDonnell DP. *Transcriptional profiling in a cellular model of breast cancer reveals functional and mechanistic differences between clinically relevant SERMs and between SERM/estrogen complexes.*

FOXO1 deregulation may contribute to macrovascular complications in poorly controlled diabetes.
Cifarelli V, Lee S, Kim DH, et al. *FOXO1 mediates the autocrine effect of endothelin-1 on endothelial cell survival.*

Hormones and Cancer

Loss of heterozygosity is the most prevalent second allele–inactivating event in both syndromic and sporadic pheochromocytomas.
Weber A, Hoffmann MM, Neumann HPH, Erlic Z. *Somatic mutation analysis of the* SDHB, SDBC, SDHD, *and* RET *genes in the clinical assessment of sporadic and hereditary pheochromocytoma.*

JUNE 2012 issue of *Endocrine Reviews*

Giannoulis MG, Martin FC, Nair KS, Umpleby AM, Sonksen P. *Hormone replacement therapy and physical function in healthy older men. Time to talk hormones?*

Vandenberg LN, Colborn T, Hayes TB, et al. *Hormones and endocrine-disrupting chemicals: Low-Dose effects and nonmonotonic dose responses.*

Rosen CJ, Adams JS, Bikle DD, et al. *The nonskeletal effects of vitamin D: An Endocrine Society scientific statement.* ■

Society Advocacy and Practice Management Initiatives to Be Highlighted at **ENDO 2012**

Whether you're a clinician or a researcher, you're bound to find something to interest you at **ENDO 2012.** The Society continues to advocate and develop resources for each of the key demographics comprising its membership. Below are examples of upcoming sessions that illustrate the initiatives the Society has undertaken to benefit endocrinology in these fields.

Transitioning Care for Type 1 Diabetes Patients

Endocrinologists who treat young adults with type 1 diabetes face a number of hurdles in coordinating care and providing optimum transitional guidance to their patients as they leave childhood. In an effort to close gaps in this transition process, the Society has been developing resources for pediatric and adult endocrinologists—and the patients they treat—specific to type 1 diabetes. At **ENDO 2012,** the Society will hold a practice management session on Sunday, June 24, from 2:45–3:30 p.m., with Drs. Carol Greenlee, Celeste Hart, and Katharine Garvey, to provide members with an overview of the difficulties likely to be encountered and the resources that have been developed.

Workforce Shortages

As the incidence of endocrine diseases such as diabetes and obesity increases, the demand for the services of an endocrinologist continues to grow. However, evidence suggests that there is a nationwide shortage of endocrinologists.

In 2000, the Society analyzed the projected supply of and demand for endocrinologists through 2020. The resulting data were the basis for a 2003 study in ***The Journal of Clinical Endocrinology & Metabolism*** titled, "A Model to Determine Workforce Needs for Endocrinologists in the United States Until 2020," and have also formed the groundwork for the Society's communications with policy makers. However, since the analysis was completed, many factors have changed, thereby bringing into question the applicability of the current projection model. Increasing the supply of endocrinologists is a top-tier advocacy issue for the Society, and without up-to-date data, the Society does not have a strong basis for its arguments.

ENDO 2012 Events Related to Society Advocacy

Endocrine Disruptors with NIEHS Director Linda Birnbaum—
Saturday, June 23, 3:45—5:15 p.m.

Managing The Transition of Care for Patients with Type 1 Diabetes—
Sunday, June 24, 2:45—3:30 p.m.

Endocrinologist Workforce: An Analysis of Supply & Demand—
Monday, June 25, 2:45—3:30 p.m.

The Society partnered with the Lewin Group to update the projections, and the new findings will be presented at **ENDO 2012.** Society members are encouraged to attend the session on Monday, June 25, from 2:45–3:30 p.m., to learn more about the factors affecting the supply of and demand for endocrinologists, projected workforce numbers through 2025, and implications for the Society's advocacy efforts.

Partnerships with NIH

Dr. Alan Guttmacher, director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), will discuss the future of the Institute and key scientific opportunities relating to endocrinology during the Saturday, June 23, morning Plenary Session. The Society recently participated in the development of the new NICHD Scientific Vision and provided recommendations on several endocrine-related topics supporting the Institute's mission. Society leadership met with Dr. Guttmacher earlier this month to discuss his vision for NICHD and potential collaborations with the Society.

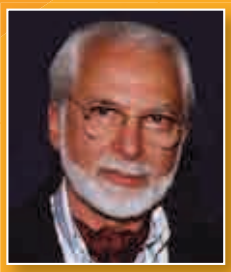
During the Saturday Presidential Symposia Session, Dr. Linda Birnbaum, director of the National Institute of Environmental Health Sciences (NIEHS), will discuss how environmental chemicals target multiple endocrine pathways. As part of the Society's advocacy efforts on issues involving endocrine-disrupting chemicals (EDCs), the Society has prepared a statement that outlines endocrine principles that should be incorporated into studies that inform the regulation of these hormone-altering compounds. The statement is an extension of concepts described in the 2009 Scientific Statement and Position Statement on EDCs and will help the Society implement the advocacy goals established in those documents. The Society has also hosted briefings and participated in conferences including the *Horizons@Heinz* environmental policy lectures last month, at which Dr. R. Thomas Zoeller spoke about the impacts of low-doses of EDCs on human health. The Society hosted a Capitol Hill briefing last August to discuss the impact of EDCs on human health and participated in the European Commission's EDC conference on the current challenges in science and policy earlier this month.

The Society will continue to represent its member clinicians and researchers through a variety of initiatives to benefit endocrinology. A comprehensive listing of the **ENDO 2012** programs can be accessed at *www.endosociety.org/endo2012/program/*. ■

The Endocrine Society 2012 Awards

The 2012 Laureate Awards

Since 1944, the Laureate Awards have recognized the highest achievement in the field of endocrinology. These distinguished recipients are the innovators, educators and practitioners who are transforming endocrinology. The dedication, commitment and achievements of these winners have earned them a place of distinction in endocrine history.



Fred Conrad Koch Award
Supported by the Fred Conrad Koch Memorial Fund
Samuel Refetoff, MD

Robert H. Williams Distinguished Leadership Award
Supported by The Endocrine Society
Leonard Wartofsky, MD, MACP

Distinguished Educator Award
Supported by The Endocrine Society
Francis S. Greenspan, MD
Clinical Professor Emeritus

Distinguished Physician Award
Supported by The Endocrine Society
John A. H. Wass, MA, MD, FRCP

Sidney H. Inbgar Distinguished Service Award
Supported by the Sidney H. Ingbar Memorial Fund
Alvin M. Matsumoto, MD

Clinical Investigator Award Lecture
Supported by The Endocrine Society
Gerald I. Shulman, MD, PhD

Edwin B. Astwood Award Lecture
Supported by The Endocrine Society
Keith R. Yamamoto, PhD

Gerald D. Aurbach Award Lecture
Supported by the Gerald D. Aurbach Memorial Fund
Evan Dale Abel, MBBS, DPhil

Roy O. Greep Award Lecture
Supported by the Roy O. Greep Memorial Fund
Carol A. Lange, PhD

Ernst Oppenheimer Award
Supported by The Endocrine Society
Tamas L. Horvath, DVM, PhD

Richard E. Weitzman Memorial Award
Supported by the Richard E. Weitzman Memorial Fund
Manuel Tena-Sempere, MD, PhD

THE ENDOCRINE SOCIETY®

Endocrine Trainee Day Travel Awards

The workshop represents a unique opportunity for medical and graduate students and clinical and postdoctoral fellows to discuss the breadth of endocrinology with their peers and the leaders in the field. The workshop is *supported by The Endocrine Society* and *Women in Endocrinology.*

The Endocrine Trainee Day Class of 2012 travel award winners are listed on The Endocrine Society website http://www.endo-society.ortg/awards/ENDOAwardsGrants/trainee_day.cfm
Travel awards are supported by The Endocrine Society, the Eunice Kennedy Shriver National Institute for Child Health and Human Development, and Women in Endocrinology.

Abstract Awards and Travel Grants

Clinical Fellows Travel Grants *

These are awarded to outstanding abstracts submitted by in-training clinical fellows with an interest in osteoporosis/bone. *Supported by Amgen.* http://www.endo-society.org/awards/ENDOAwardsGrants/Clinical-Fellows-Abstract-Award-Travel-Grants.cfm

Clinical Fellows Abstract Awards and Travel Grants *

These are awarded to outstanding abstracts submitted by in-training clinical fellows with an interest in women's health. *Supported by Pfizer, Inc.* http://www.endo-society.org/awards/ENDOAwardsGrants/PfizerClinicalFellowsTravel-Grant.cfm

Clinical Research Fellowship and Mentor Awards

These are awarded to outstanding abstracts submitted by in-training clinical fellows who are conducting research as a major investigator in clinically relevant aspects of women's health. The six recipients will compete in an oral presentation at ENDO 2012 and the mentor of the winning presentation will receive the *Clinical Research Mentor Award. Supported by Pfizer, Inc.*

Carolina Di Blasi, MD
Alexander Faje, MD
Grace Huang, MD
Pornpoj Pramyothin, MD
Chevon Rariy, MD
Lauren Roth, MD

Eugenia Rosemberg Abstract Travel Awards

These are awarded to outstanding abstracts submitted by junior faculty/early career professionals in the basic science abstract category. *Supported by the Eugenia Rosemberg Memorial Fund.*

Miao-Hsueh Chen, PhD
John Gill, PhD
Sheng Wu, PhD

Mara E. Lieberman Memorial Travel Grants

These are awarded to outstanding abstracts submitted by women. *Supported by the Mara E. Lieberman Memorial Fund.*

Jessicah Collins, MD
Joanna Klubo-Gwiezdzinska, MD, PhD

Promotion and Tenure Travel Awards *

The *How to Secure Promotion and Tenure Workshop* presents a unique opportunity for junior faculty and mid-career professionals to gain essential skills and knowledge that will help them navigate the promotion and tenure process. The workshop is *supported by The Endocrine Society and Novo Nordisk Inc.*

Travel Awards to attend the workshop are supported by The Endocrine Society. http://www.endo-society.org/trainees/tenuretrackworkshop.cfm

The Endocrine Society Outstanding Abstract Awards *

These are awarded to abstracts presented by in-training post-doctoral fellows, new faculty, or graduate students. *Supported by The Endocrine Society.* http://www.endo-society.org/awards/ENDOAwardsGrants/travelgrants.cfm

Conference Travel Grants

Early Investigators Workshop for Trainees Travel Grants *

Awarded to basic science and clinical fellows pursuing research careers to attend an exclusive seminar on hypothesis-driven research led by experts in the field. This workshop was held in October 2011. *Supported in 2011 by Amgen and Genzyme Corporation.* http://www.endo-society.org/eiw

* Award winners are listed on The Endocrine Society web site: http://www.endo-society.org

Research Fellowship Awards

Amgen Scholars Fellowship *

This one year fellowship is awarded to perform clinical research related to osteoporosis and/or bone disorders. *Supported by Amgen.* http://www.endo-society.org/awards/ResearchFellowships/amgenscholars.cfm

Clinical Research Fellowship Award *

This one year fellowship is awarded to perform clinical research related to women's health (including reproductive health, menopause and osteoporosis, and endometriosis. *Supported by Pfizer, Inc.* http://www.endo-society.org/awards/SocietyAwards/pfizerresearchfellowship.cfm

Lilly Endocrine Scholars Award

This one year fellowship is awarded to perform clinical research related to pituitary disorders, bone disorders, or diabetes mellitus (in vivo studies or in vitro studies with human tissue or human cell lines). *This activity is supported by a contribution from Lilly USA, LLC.* For further information concerning Lilly grant funding, visit www.lillygrantoffice.com.

Matthew Stenerson, MD

International Endocrine Scholars Program *

These awards promote the career development of young endocrinologists from around the globe. Recipients receive counsel through a unique mentorship that helps them find financial support, advice, and esteemed training opportunities. *Supported by The Endocrine Society.* http://www.endo-society.org/awards/SocietyAwards/international_endo/index.cfm

Minority Access Program Fellowships and Travel Awards *

These awards provide undergraduate students from under-represented minority groups with training in top-notch endocrine research labs and professional development activities designed to nurture the educational and career growth of future scientists. *Supported by The Endocrine Society and the National Institute of General Medical Sciences.* http://www.endo-society.org/minorityactivities/minority-access-program.cfm

Summer Research Fellowships *

These fellowships are awarded to encourage promising undergraduate students, medical students, and first-year graduate students to pursue careers in endocrinology. Recipients participate in research projects under the guidance of Society members for ten to twelve weeks during the summer. *Supported by The Endocrine Society.* http://www.endo-society.org/awards/research_fellowship/summer.cfm

Additional Awards

The Harold Vigersky Practicing Physician Travel Award

Awarded to a practicing physician dedicated to providing patient care in a small practice setting. The recipient must be less than 10 years out of their fellowship and receive no outside support or funding to attend scientific meetings and CME conferences. *Supported by Robert A. Vigersky, MD.*

Michael H. Shanik, MD

Delbert A. Fisher Research Scholar Award

Awarded to one recipient annually for scholarly work on the history of endocrinology. The scholar will deliver the Clark T. Sawin Memorial History of Endocrinology Lecture at ENDO and may submit an article to be considered for publication by The Endocrine Society. *Supported by Dr. and Mrs. Delbert A. Fisher*

Leonard Wartofsky, MD, MACP

The Early Investigators Awards

Awarded to outstanding early career investigators for their accomplishments in endocrine research. *Supported by Amgen.*

Kathleen Page, MD
Kevin Pfleger, PhD
Yvonne Ulrich-Lai, PhD
Qianben Wang, PhD
Daniel Winer, PhD

The Early Investigators Awards

Awarded to outstanding early career investigators for their accomplishments in endocrine research related to women's health. *Supported by Pfizer, Inc.*

Rodrigo Fernandez-Valdivia, PhD
Susan Krum, PhD
Elizabeth Lawson, MD
Cecilia Proietti, PhD
Varykina Thackray, PhD

Medical Student Achievement Awards *

Awarded to graduating senior medical school students and osteopathic school students who have shown exceptional ability and interest in endocrinology. *Supported by The Endocrine Society.* http://www.endo-society.org/awards/SocietyAwards/medical_Student/index.cfm

Intel International Science and Engineering Fair Awards *

Awarded annually to high school students who present the best endocrine-related science at the Intel International Science and Engineering Fair – the world's largest pre-college science exposition. *Supported by The Endocrine Society.* http://www.endo-society.org/awards/SocietyAwards/Intel/index.cfm

Annual Biomedical Research Conference for Minority Students Poster Awards

Awarded to minority students in recognition of outstanding endocrine-related poster presentations displayed at the Annual Biomedical Research Conference for Minority Students in November 2011. *Supported by The Endocrine Society.* http://www.endo-society.org/awards/SocietyAwards/biomedical.cfm

* Award winners are listed on The Endocrine Society web site: www.endo-society.org

The Endocrine Society Journal Awards

International Award for Publishing Excellence in *The Journal of Clinical Endocrinology & Metabolism* in 2011

Awarded to the 14 best clinical research papers published in 2011 of *The Journal of Clinical Endocrinology & Metabolism.* This activity is supported by a contribution from *Lilly USA, LLC.* For further information concerning Lilly grant funding, visit www.lillygrantoffice.com

"Impaired Regulation of the Incretin Effect in Patients with Type 2 Diabetes"
Vol. 96, No. 3, P. 737-745
Corresponding author: Tina Vilsbøll

"Action of Metformin on the Insulin-Signaling Pathway and on Glucose Transport in Human Granulosa Cells"
Vol. 96, No. 3, P. E427-E435
Corresponding author: Suman Rice

"Current Thyroglobulin Autoantibody (TgAb) Assays Often Fail to Detect Interfering TgAb that Can Result in the Reporting of Falsely Low/ Undetectable Serum Tg IMA Values for Patients with Differentiated Thyroid Cancer"
Vol. 96, No. 5, P. 1283-1291
Corresponding author: C. Spencer

"The Thyroid Epidemiology, Audit, and Research Study (TEARS): Morbidity in Patients with Endogenous Subclinical Hyperthyroidism"
Vol. 96, No. 5, P. 1344-1351
Corresponding author: Thenmalar Vadiveloo

"Effects of Once-Weekly Sustained-Release Growth Hormone: A Double-Blind, Placebo-Controlled Study in Adult Growth Hormone Deficiency"
Vol. 96, No. 6, P. 1718-1726
Corresponding author: Beverly M. K. Biller

"Adiposity, Inflammation, and Risk for Death in Black and White Men and Women in the United States: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study"
Vol. 96, No. 6, P. 1805-1814
Corresponding author: Susan G. Lakoski

"Socioeconomic Trajectories Affect Mortality in Klinefelter Syndrome"
Vol. 96, No. 7, P. 2098-2104
Corresponding author: Claus Højbjerg Gravholt

"Mammalian Target of Rapamycin Pathway Activation Is Associated to RET Mutation Status in Medullary Thyroid Carcinoma"
Vol. 96, No. 7, P. 2146-2153
Corresponding author: Marco Volante

"Combination of Niacin and Fenofibrate with Lifestyle Changes Improves Dyslipidemia and Hypoadiponectinemia in HIV Patients on Antiretroviral Therapy: Results of "Heart Positive," a Randomized, Controlled Trial"
Vol. 96, No. 7, P. 2236-2247
Corresponding author: Ashok Balasubramanyam

"Impact of Mutational Testing on the Diagnosis and Management of Patients with Cytologically Indeterminate Thyroid Nodules: A Prospective Analysis of 1056 FNA Samples"
Vol. 96, No. 11, P. 3390-3397
Corresponding author: Yuri E. Nikiforov

"Effect of Lifestyle Intervention on Features of Polycystic Ovarian Syndrome, Metabolic Syndrome, and Intima-Media Thickness in Obese Adolescent Girls"
Vol. 96, No. 11, P. 3533-3540
Corresponding author: Thomas Reinehr

"Iron Modifies Plasma FGF23 Differently in Autosomal Dominant Hypophosphatemic Rickets and Healthy Humans"
Vol. 96, No. 11, P. 3541-3549
Corresponding author: Erik A. Imel

"Urine Steroid Metabolomics as a Biomarker Tool for Detecting Malignancy in Adrenal Tumors"
Vol. 96, No, 12, P. 3775-3784
Corresponding author: Wiebke Arlt

"Cardiovascular Disease and Risk Factors in PCOS Women of Postmenopausal Age: A 21-Year Controlled Follow-Up Study"
Vol. 96, No. 12, P. 3794-3803
Corresponding author: Johanna Schmidt

Endocrinology Student Author Awards

Awarded to outstanding first authored student papers published in a 2011 issue of *Endocrinology.*
Supported by The Endocrine Society.

Johanna Barclay, PhD
Mentor: Michael J. Waters, PhD
Erik R. Nelson, PhD
Mentor: Donald P. McDonnell, PhD

Molecular Endocrinology Student Author Awards

Awarded to outstanding first authored student papers published in a 2011 issue of *Molecular Endocrinology.*
Supported by The Endocrine Society.

Tyler B. Moran, PhD
Mentor: Lori T. Raetzman, PhD
Giulia Grimaldi, PhD
Mentor: Jan J. Brosens, MD, PhD

Introducing BYDUREON

The first and only once-weekly treatment for type 2 diabetes

Indication and Usage

BYDUREON is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

- Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe only to patients for whom potential benefits are considered to outweigh potential risk.
- Not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- Not a substitute for insulin, should not be used in patients with type 1 diabetes or diabetic ketoacidosis, and cannot be recommended for use with insulin.
- BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and should not be used together.
- Exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, based on postmarketing data. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYDUREON; consider other antidiabetic therapies for these patients.

BOXED WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

For additional safety profile and other important prescribing considerations, please see the adjacent pages for Brief Summary of Prescribing Information.

To learn more about once-weekly BYDUREON, visit www.BYDUREONHCP.com

Once-weekly

BYDUREON™

exenatide extended-release for injectable suspension

AMYLIN®

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BYETTA is a registered trademark of Amylin Pharmaceuticals, Inc.

BYDUREON™ (exenatide extended-release for injectable suspension)

Initial U.S. Approval: 2012

Brief Summary: For complete details, please see full Prescribing Information

WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications* and *Warnings and Precautions*].

INDICATIONS AND USAGE

BYDUREON is an extended-release formulation of exenatide, administered as an injection once every seven days (weekly).

Type 2 Diabetes Mellitus

BYDUREON is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

Important Limitations of Use

Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe BYDUREON only to patients for whom the potential benefits are considered to outweigh the potential risk.

BYDUREON is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

BYDUREON is not a substitute for insulin. BYDUREON should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of BYDUREON with insulin has not been studied and cannot be recommended.

BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and therefore should not be used together.

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYDUREON has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYDUREON. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

CONTRAINDICATIONS

Medullary Thyroid Carcinoma

BYDUREON is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Hypersensitivity

BYDUREON is contraindicated in patients with a prior serious hypersensitivity reaction to exenatide or to any of the product components.

WARNINGS AND PRECAUTIONS

Risk of Thyroid C-cell Tumors

In both genders of rats, exenatide extended-release caused a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures compared to controls. A statistically significant increase in malignant thyroid C-cell carcinomas was observed in female rats receiving exenatide extended-release at 25-times clinical exposure compared to controls and higher incidences were noted in males above controls in all treated groups at ≥2-times clinical exposure. The potential of exenatide extended-release to induce C-cell tumors in mice has not been evaluated. Other GLP-1 receptor agonists have also induced thyroid C-cell adenomas and carcinomas in male and female mice and rats at clinically relevant exposures. It is unknown whether BYDUREON will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies. Serum calcitonin was not assessed in the clinical trials supporting the approval of BYDUREON [see *Boxed Warning*].

Serum calcitonin is a biological marker of MTC. Patients with MTC usually have calcitonin values >50 ng/L. Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with BYDUREON. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

Acute Pancreatitis

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYDUREON, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYDUREON should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYDUREON should not be restarted. Consider antidiabetic therapies other than BYDUREON in patients with a history of pancreatitis.

Hypoglycemia

The risk of hypoglycemia is increased when exenatide is used in combination with a sulfonylurea. Therefore, patients receiving BYDUREON and a sulfonylurea may require a lower dose of the sulfonylurea to minimize the risk of hypoglycemia. It is also possible that the use of BYDUREON with other glucose-independent insulin secretagogues (e.g. meglitinides) could increase the risk of hypoglycemia.

Renal Impairment

BYDUREON should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation. In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well tolerated due to gastrointestinal side effects. Because BYDUREON may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min). BYDUREON has not been studied in patients with end-stage renal disease or severe renal impairment.

There have been postmarketing reports of altered renal function with exenatide, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including exenatide. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

Gastrointestinal Disease

Exenatide has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because exenatide is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYDUREON is not recommended in patients with severe gastrointestinal disease.

Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYDUREON. Anti-exenatide antibodies were measured in all BYDUREON-treated patients in the five comparator-controlled 24-30 week studies of BYDUREON. In 6% of BYDUREON-treated patients, antibody formation was associated with an attenuated glycemic response. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered.

Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with exenatide. If a hypersensitivity reaction occurs, the patient should discontinue BYDUREON and other suspect medications and promptly seek medical advice.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON or any other antidiabetic drug.

ADVERSE REACTIONS

Clinical Trial Experience

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

The safety of BYDUREON was assessed in five comparator-controlled trials, in patients who entered the studies not achieving adequate glycemic control on their current therapy. In a double-blind 26 week trial, patients on diet and exercise were treated with BYDUREON 2 mg once every seven days (weekly), sitagliptin 100 mg daily, pioglitazone 45 mg daily, or metformin 2000 mg daily. In a double-blind 26 week trial, patients on metformin were treated with BYDUREON 2 mg once every seven days (weekly), sitagliptin 100 mg daily, or pioglitazone 45 mg daily. In an open-label 26 week trial, patients on metformin or metformin plus sulfonylurea were treated with BYDUREON 2 mg once every seven days (weekly) or optimized insulin glargine. In two open-label 24 to 30 week studies, patients on diet and exercise or metformin, a sulfonylurea, a thiazolidinedione or combination of oral agents were treated with BYDUREON 2 mg once every seven days (weekly) or BYETTA 10 mcg twice daily.

Withdrawals

The incidence of withdrawal due to adverse events was 4.9% (N=45) for BYDUREON-treated patients, 4.9% (N=13) for BYETTA-treated patients and 2.0% (N=23) for other comparator-treated patients in the five comparator-controlled 24-30 week trials. The most common adverse reactions leading to withdrawal for BYDUREON-treated patients were nausea 0.5% (N=5) versus 1.5% (N=4) for BYETTA and 0.3% (N=3) for other comparators, injection site nodule 0.5% (N=5) versus 0.0% for BYETTA and 0.0% for other comparators, diarrhea 0.3% (N=3) versus 0.4% (N=1) for BYETTA and 0.3% (N=3) for other comparators, injection site reaction 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators and headache 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators.

Hypoglycemia

The incidence (% of subjects) and rate (episodes/subject year) of minor hypoglycemia in the five comparator-controlled 24-30 week trials of BYDUREON used as monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione or combination of these oral antidiabetic agents were as follows. In these trials, an event was classified as minor hypoglycemia if there were symptoms of hypoglycemia with a concomitant glucose <54 mg/dL and the patient was able to self-treat.

In the 26-week monotherapy trial: BYDUREON, 2.0% (0.05) [N = 248]; sitagliptin, 0.0% (0.00) [N = 163]; pioglitazone, 0.0% (0.00) [N = 163]; and metformin, 0.0% (0.00) [N = 246]. In the 26-week add-on to metformin trial: BYDUREON, 1.3% (0.03) [N = 160]; sitagliptin, 3.0% (0.12) [N = 166]; and pioglitazone, 1.2% (0.03) [N = 165]. In the 26-week add-on to metformin or metformin plus sulfonylurea trial: with concomitant sulfonylurea, BYDUREON, 20.0% (1.11) [N = 70] and titrated insulin glargine, 43.9% (2.87) [N = 66]; without concomitant sulfonylurea, BYDUREON, 3.7% (0.11) [N =163] and titrated insulin glargine, 19.1% (0.64) [N = 157]. Insulin glargine was dosed to a target fasting glucose concentration of 72 to 100 mg/dL. The mean dose of insulin glargine was 10 Units/day at baseline and 31 Units/day at endpoint.

In the 24-30 week trials of BYDUREON as monotherapy or add-on to metformin, sulfonylurea, thiazolidinedione or any combination of these oral agents, incidence (% of subjects) and rate (episodes/subject year) of minor hypoglycemia were as follows. In the 24-week trial: with concomitant sulfonylurea, BYDUREON, 12.5% (0.72) [N = 40] and BYETTA, 11.8% (0.31) [N = 34]; without concomitant sulfonylurea, BYDUREON, 0.0% (0.00) [N = 89] and BYETTA, 0.0% (0.00) [N = 89]. In the 30-week trial: with concomitant sulfonylurea, BYDUREON, 14.5% (0.55) [N =55] and BYETTA, 15.4% (0.37) [N = 52]; without concomitant sulfonylurea, BYDUREON, 0.0% (0.00) [N = 93] and BYETTA, 1.1% (0.02) [N = 93].

There were no reported events of major hypoglycemia in these five comparator-controlled 24-30 week trials. Major hypoglycemia was defined as loss of consciousness, seizure or coma (or other mental status change consistent with neuroglycopenia in the judgment of the investigator or physician) which resolved after administration of glucagon or glucose or required third party assistance to resolve because of severe impairment in consciousness or behavior. Patients were to have a concomitant glucose <54 mg/dL.

Immunogenicity

Anti-exenatide antibodies were measured at prespecified intervals (4-14 weeks) in all BYDUREON-treated patients (N=918) in the five comparator-controlled studies of BYDUREON. In these five trials, 452 BYDUREON-treated patients (49%) had low titer antibodies (≤125) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers. An additional 107 BYDUREON-treated patients (12%) had higher titer antibodies at endpoint. Of these patients, 50 (6% overall) had an attenuated glycemic response to BYDUREON (<0.7% reduction in HbA_{1c}); the remaining 57 (6% overall) had a glycemic response comparable to that of patients without antibodies. In the 30-week trial in which anti-exenatide antibody assessments were performed at baseline and at 4-week intervals from week 6 to week 30, the mean anti-exenatide antibody titer in the BYDUREON-treated patients peaked at week 6 then declined by 56% from this peak by week 30.

A total of 246 patients with antibodies to exenatide in the BYETTA and BYDUREON clinical trials were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon. No treatment-emergent cross reactive antibodies were observed across the range of titers.

Other Adverse Reactions

Monotherapy

In a 26-week trial, treatment-emergent adverse reactions reported in ≥5% of BYDUREON-treated patients (N = 248) vs sitagliptin (N = 163), pioglitazone (N = 163) and metformin (N = 246), respectively, were nausea (11.3% vs 3.7%, 4.3%, and 6.9%), diarrhea (10.9% vs 5.5%, 3.7%, and 12.6%), injection-site nodule (10.5% vs 6.7%, 3.7%, and 10.2%), constipation (8.5% vs 2.5%, 1.8%, and 3.3%), headache (8.1% vs 9.2%, 8.0%, and 12.2%), and dyspepsia (7.3% vs 1.8%, 4.9%, and 3.3%). Patients in the sitagliptin, pioglitazone, and metformin arms received weekly placebo injection.

Combination therapy

26-week add-on to metformin

Treatment-emergent adverse reactions reported in ≥5% of BYDUREON-treated patients (N = 160) vs sitagliptin (N = 166) and pioglitazone (N = 165), respectively, were nausea (24.4% vs. 9.6% and 4.8%), diarrhea (20.0% vs 9.6% and 7.3%), vomiting (11.3% vs 2.4% and 3.0%), headache (9.4% vs 9.0% and 5.5%), constipation (6.3% vs 3.6% and 1.2%), fatigue (5.6% vs 0.6% and 3.0%), dyspepsia (5.0% vs 3.6% and 2.4%), decreased appetite (5.0% vs 1.2% and 0.0%), and injection-site pruritus (5.0% vs 4.8% and 1.2%). Patients in the sitagliptin and pioglitazone arms received weekly placebo injection.

26-week add-on to metformin or metformin plus sulfonylurea

Treatment-emergent adverse reaction reported in ≥5% of BYDUREON-treated patients (N = 233) vs titrated insulin glargine (N = 223), respectively, were nausea (12.9 vs 1.3), headache (9.9 vs 7.6), diarrhea (9.4 vs 4.0), and injection-site nodule (6.0 vs 0.0).

24-30 week monotherapy or as add-on to metformin, sulfonylurea, thiazolidinedione or combination of oral agents

In the 24-week trial, treatment-emergent adverse reactions reported in ≥5% of BYDUREON-treated patients (N = 129) vs BYETTA (N = 123), respectively, were nausea (14.0% vs 35.0%), diarrhea (9.3% vs 4.1%), and injection-site erythema (5.4% vs 2.4%). In the 30-week trial, treatment-emergent adverse reactions reported in ≥5% of BYDUREON-treated patients (N = 148) vs BYETTA (N = 145), respectively, were nausea (27.0% vs 33.8%), diarrhea (16.2% vs 12.4%), vomiting (10.8% vs 18.6%), injection-site pruritus (18.2% vs 1.4%), constipation (10.1% vs 6.2%), gastroenteritis viral (8.8% vs 5.5%), gastroesophageal reflux disease (7.4% vs 4.1%), dyspepsia (7.4% vs 2.1%), injection-site erythema (7.4% vs 0.0%), fatigue (6.1% vs 3.4%), headache (6.1% vs 4.8%), and injection-site hematoma (5.4% vs 11.0%).

Nausea was the most common adverse reaction associated with initiation of treatment with BYDUREON, and usually decreased over time.

Injection Site Reactions

In the five comparator-controlled 24-30 week trials, injection site reactions were observed more frequently in patients treated with BYDUREON (17.1%) than in patients treated with BYETTA (12.7%), titrated insulin glargine (1.8%) or those patients who received placebo injections (sitagliptin (10.6%), pioglitazone (6.4%), and metformin (13.0%) treatment groups). These reactions for patients treated with BYDUREON were more commonly observed in antibody-positive patients (14.2%) compared with antibody-negative patients (3.1%), with a greater incidence in those with higher titer antibodies. Incidence of injection site reactions for patients treated with BYETTA was similar for antibody positive patients (5.8%) and antibody negative patients (7.0%). One percent of patients treated with BYDUREON withdrew due to injection site adverse reactions (injection site mass, injection site nodule, injection site pruritus, and injection site reaction).

Small, asymptomatic subcutaneous injection site nodules are seen with the use of BYDUREON. In a separate 15-week study in which information on nodules were collected and analyzed, 24 out of 31 subjects (77%) experienced at least one injection site nodule during treatment; 2 subjects (6.5%) reported accompanying localized symptoms. The mean duration of events was 27 days. The formation of nodules is consistent with the known properties of the microspheres used in BYDUREON.

Post-Marketing Experience

BYETTA

The following additional adverse reactions have been reported during post-approval use of BYETTA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergy/Hypersensitivity: injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema; anaphylactic reaction.

Drug Interactions: increased international normalized ratio (INR), sometimes associated with bleeding, with concomitant warfarin use.

Gastrointestinal: nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

Neurologic: dysgeusia; somnolence

Renal and Urinary Disorders: altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis), kidney transplant and kidney transplant dysfunction.

Skin and Subcutaneous Tissue Disorders: alopecia

DRUG INTERACTIONS

Orally Administered Drugs

Exenatide slows gastric emptying. Therefore, BYDUREON has the potential to reduce the rate of absorption of orally administered drugs. Use caution when administering oral medications with BYDUREON.

In patients with type 2 diabetes, BYDUREON did not affect the absorption of orally administered acetaminophen to any clinically relevant degree.

Warfarin

BYDUREON has not been studied with warfarin. However, in a drug interaction study, BYETTA did not have a significant effect on INR. There have been postmarketing reports for BYETTA of increased INR with concomitant use of warfarin, sometimes associated with bleeding. In patients taking warfarin, the INR should be monitored more frequently after initiating BYDUREON. Once a stable INR has been documented, the INR can be monitored at the intervals usually recommended for patients on warfarin.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of BYDUREON use in pregnant women. In rats, exenatide extended-release administered during the major period of organogenesis reduced fetal growth and produced skeletal ossification deficits in association with maternal effects; exenatide extended-release was not teratogenic in rats. In animal developmental studies, exenatide, the active ingredient of BYDUREON, caused cleft palate, irregular skeletal ossification and an increased number of neonatal deaths. BYDUREON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fetuses from pregnant rats given subcutaneous doses of exenatide extended-release at 0.3, 1 or 3 mg/kg on gestation days 6, 9, 12 and 15 demonstrated reduced fetal growth at all doses and produced skeletal ossification deficits at 1 and 3 mg/kg in association with maternal effects (decreased food intake and decreased body weight gain). There was no evidence of malformations. Doses of 0.3, 1 and 3 mg/kg correspond to systemic exposures of 3, 7 and 17-times, respectively, the human exposure resulting from the recommended dose of 2 mg/week, based on area under the time-concentration curve (AUC).

Female mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7, had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

In developmental toxicity studies, pregnant animals received exenatide, the active ingredient of BYDUREON, subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given subcutaneous doses of exenatide at 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 4 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. Fetuses from pregnant mice given subcutaneous doses of exenatide at 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate and skeletal effects at systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

Lactating mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

Pregnancy Registry

Amylin Pharmaceuticals, Inc. maintains a Pregnancy Registry to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling (800) 633-9081.

Nursing Mothers

Exenatide is present in the milk of lactating mice at concentrations less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing. It is not known whether exenatide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for exenatide extended-release in animal studies, a decision should be made whether to discontinue nursing or to discontinue BYDUREON, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of BYDUREON have not been established in pediatric patients. BYDUREON is not recommended for use in pediatric patients.

Geriatric Use

In the five comparator-controlled 24-30 week trials, BYDUREON was studied in 132 patients (16.6%) who were at least 65 years old and 20 patients who were at least 75 years old. No differences in safety (N = 152) and efficacy (N = 52) were observed between these patients and younger patients, but the small sample size for patients ≥75 years old limits conclusions.

In separate trials, BYETTA was studied in 282 patients at least 65 years old and in 16 patients at least 75 years old. No differences in safety and efficacy were observed between these patients and younger patients, but the small sample size for patients ≥75 years old limits conclusions.

Because elderly patients are more likely to have decreased renal function, use caution when initiating BYDUREON in the elderly.

Hepatic Impairment

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic impairment is not expected to affect blood concentrations of exenatide.

OVERDOSAGE

There were no reports of overdose in the five comparator-controlled 24-30 week trials of BYDUREON. Effects of overdoses with BYETTA in clinical studies included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations, including severe hypoglycemia requiring parenteral glucose administration. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

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1-877-700-7365
http://www.bydureon.com
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Iodides from Imaging Studies Linked to Thyroid Dysfunction

*By Eric Seaborg **

There's more evidence that clinicians and patients should think twice about that imaging study. A new analysis finds that a higher risk of thyroid dysfunction is strongly associated with the iodide exposure involved in CT scans and cardiac catheterizations.[1]

Some 80 million doses of iodinated contrast media are given for imaging studies worldwide each year, exposing patients to high levels of potentially thyroid-damaging iodide. A typical dose contains 15–60 million µg of bound iodine. About 13,500 µg is in the form of free iodide even before injection, and more becomes unbound while in the body. Depending on how much is freed, the exposure represents an acute iodide load of 90 times to several hundred-thousand times the recommended daily intake of 150 µg, according to a paper in *Archives of Internal Medicine*.

Given the huge numbers of patients receiving iodine doses large enough to cause thyroid damage, the research team was stunned to find a dearth of studies asking the obvious question about what effect it is having, said lead author Steven M. Brunelli, M.D., M.S.C.E. Dr. Brunelli is director of inpatient dialysis services and an epidemiologist in the renal and pharmacoepidemiology divisions at Brigham and Women's Hospital in Boston. He is also an assistant professor at Harvard Medical School.

The researchers performed a nested case-control study of some 2,000 patients who did not have a pre-existing thyroid condition treated at two Boston hospitals over a 20-year period. They matched 178 incident hyperthyroid cases with 665 euthyroid controls and 213 incident hypothyroid cases with 779 controls.

"We found that the risk of hyperthyroidism following iodinated contrast media exposure was increased about twofold. The risk of more severe forms of hyperthyroidism was increased about 2.5-fold. There wasn't a clear statistical association with new hypothyroidism, but if you looked at more severe forms of hypothyroidism, the risk was about 3-fold, and that was very statistically significant, as were the two hyperthyroid findings. It appears that these agents really may have profound effects on thyroid function," Dr Brunelli told ***Endocrine News.*** He cautioned that the study was observational, so causality has yet to be firmly established.

Dr. Brunelli said that clinicians and patients should take these findings into account when considering whether a nonessential imaging study is needed: "In testing that is discretionary, this is one more piece of information that informs the risk/benefit equation."

In an invited commentary that accompanied the article, Elizabeth Pearce, M.D., M.Sc., an endocrinologist with Boston University School of Medicine, suggested clinicians apply the findings to practice by giving thorough attention to patients "at high risk to develop thyroid dysfunction after the administration of iodinated contrast medium," with "palpation of the neck for the detection of goiter" a reasonable precaution before ordering the tests.[2] "Patients who may be particularly unable to tolerate thyroid dysfunction, such as those with underlying unstable cardiovascular disease, are also good candidates for monitoring of thyroid function after iodine exposure," she wrote.

In another comment that accompanied the article, Deborah Grady, M.D., M.P.H., of the University of California, San Francisco, wrote: "Given that exposure to iodinated contrast media is also associated with renal dysfunction, these data provide another reason for clinicians to think carefully about the value of imaging before ordering studies." ■

* Eric Seaborg is an award-winning free-lance writer living in Charlottesville, Va.

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Glucocorticoid-Induced Osteoporosis

PLEASE TEAR HERE

What is glucocorticoid-induced osteoporosis?

Glucocorticoid-induced osteoporosis (GIO) is a condition in which people who take medicines called glucocorticoids develop osteoporosis—weakening of the bones. Osteoporosis increases the risk of broken bones (fractures).

Glucocorticoids are synthetic (manufactured) hormones also known as steroids. They include medicines such as prednisone, cortisone, hydrocortisone, and dexamethasone.

Common conditions treated with glucocorticoids include:

- rheumatoid arthritis or lupus
- asthma or chronic obstructive pulmonary disease (COPD)
- inflammatory bowel disease
- psoriasis or other skin diseases
- organ transplant (to reduce the risk of rejection)

Glucocorticoids can be taken as a pill (by mouth), an injection under the skin or in a vein, a nasal spray or inhaler, or even as a skin ointment or cream.

What causes GIO?

Normally, your body continuously removes old bone and replaces it with new bone. However, glucocorticoids can increase the breakdown of bone and decrease the formation of new bone. This can cause your bones to weaken. Weak bones can break easily when you have a minor fall (called a fragility fracture). Some people break bones for no reason at all. Bone fractures can be serious and painful. They can affect your ability to move, walk, and care for yourself.

Glucocorticoids start to weaken your bones during the first 3 months of use. The rate of bone loss is greatest within the first 6 months of treatment, but continues as long as you take glucocorticoids. The higher your dose, the greater the risk of GIO. But even low doses can cause GIO over time. Therefore, experts recommend that doctors prescribe the smallest possible dose for the shortest period of time. Glucocorticoids given by mouth, by vein, or by skin injection are most likely to cause GIO.

Who is most at risk for GIO?

Some people who take glucocorticoids are at greater risk for GIO:

- Women who have gone through menopause
- Men age 50 or older
- Those who have had previous fractures
- People who have other risk factors for osteoporosis, including those who
  - Don't get enough calcium and vitamin D
  - Smoke cigarettes
  - Drink three or more alcoholic beverages per day
  - Have a family history of osteoporosis

How will you know whether your bones are weak?

A bone mineral density test (also called a DXA test) measures the strength of your bones. This simple, painless test uses low-dose x-rays to help predict your chances of having a fracture. Your doctor also may check your spine for fractures using x-rays or an MRI (magnetic resonance imaging) test.

How can you reduce your risk of GIO?

If you'll be taking glucocorticoids for 3 months or longer, you can lower your risk of GIO by following these steps:

- Do weight-bearing exercise such as walking, running, or dancing
- Quit smoking if you smoke
- Limit yourself to no more than two alcoholic beverages each day

Experts also suggest taking calcium and vitamin D supplements, even if you're taking glucocorticoids for less than 3 months. Your doctor can tell you how much to take. Your doctor also may check your risk of falling and provide advice about how to prevent falls. People who are especially at risk for osteoporosis will need medicine.

Who will need medicine to protect their bones?

Your doctor will review your medical history, current condition, and glucocorticoid dose to determine your risk. Experts recommend bone-protective medicine for certain people who are taking glucocorticoids for at least 3 months:

- Women who have gone through menopause
- Men age 50 or older

The following groups also might need medicine to protect their bones:

- Men and women at high risk for osteoporosis, even if they are taking glucocorticoids for less than 3 months
- Premenopausal women and men under the age of 50 who have had fragility fractures in the past

Which types of medicines help protect bones?

Two types of medicines are available. Your doctor will prescribe the type of medicine that's best for you.

- Bisphosphonates keep bones strong by slowing the breakdown of bone. They lower the risk of fractures of the hips and spine.
- Teriparatide helps the body build new bone and makes bones stronger. It also lowers the risk of fractures.

Ask your doctor if you need a DXA test and how much calcium and vitamin D you should take. If you need medicine to protect your bones, talk with your doctor about how long you should take it, what side effects you might have, and any other questions that concern you.

Resources

Find-an-Endocrinologist: *www.hormone.org* or call *1-800-HORMONE (1-800-467-6663)*

Hormone Foundation information:

About osteoporosis:
— *www.hormone.org/Resources/osteoporosis-and-bone-health.cfm*
— *www.hormone.org/Osteoporosis/treatment.cfm*

About bisphosphonates:
www.hormone.org/Resources/upload/Bisphosphonates-Web.pdf

National Osteoporosis Foundation: *www.nof.org*

National Institutes of Health (NIH) Osteoporosis and Related Bone Diseases National Resource Center: *www.niams.nih.gov/Health_Info/Bone/Osteoporosis/overview.asp or call 1-800-624-BONE*

EDITORS:
Jens Bollerslev, MD
Steven T. Harris, MD
Benjamin Z. Leder, MD

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Osteoporosis inducida por glucocorticoides

¿Qué es la osteoporosis inducida por glucocorticoides?

La osteoporosis inducida por glucocorticoides (OIG) es una enfermedad en la que las personas que toman medicamentos llamados glucocorticoides desarrollan osteoporosis o debilitamiento de los huesos. La osteoporosis aumenta el riesgo de fracturas de huesos.

Los glucocorticoides son hormonas sintéticas (fabricadas), también conocidas como esteroides. Incluyen medicamentos como la prednisona, cortisona, hidrocortisona y dexametasona.

Comúnmente, los glucocorticoides se usan en el tratamiento de:

- artritis reumatoide o lupus
- asma o enfermedad pulmonar obstructiva crónica
- enfermedad inflamatoria intestinal
- psoriasis u otras enfermedades de la piel
- trasplantes de órganos (para reducir el riesgo de rechazo)

Los glucocorticoides se pueden tomar a manera de pastilla (oralmente), inyección subcutánea (debajo de la piel) o a la vena, en aerosol nasal o inhalador, o incluso ungüento o crema para la piel.

¿Qué causa la OIG?

Comúnmente, el cuerpo elimina y reemplaza masa ósea continuamente. Sin embargo, los glucocorticoides pueden acelerar la desintegración de los huesos y disminuir la formación de masa ósea. Esto puede hacer que los huesos se debiliten. Los huesos débiles pueden fracturarse fácilmente en caídas leves (lo que se denomina fractura por fragilidad). Algunas personas tienen fracturas de huesos sin motivo alguno. Las fracturas óseas pueden ser graves y dolorosas. Pueden afectar su capacidad de moverse, caminar y cuidar de sí mismo.

Los glucocorticoides comienzan a debilitar los huesos durante los tres primeros meses de uso. La velocidad de la pérdida ósea es mayor en los primeros seis meses de tratamiento, pero continúa mientras se toman glucocorticoides. Cuanto mayor sea la dosis, mayor es el riesgo de OIG. Pero incluso dosis bajas pueden causar OIG con el tiempo. Por lo tanto, los expertos recomiendan que los médicos receten la menor dosis posible durante el período más breve posible. Los glucocorticoides usados oralmente y los inyectados a la vena o bajo la piel causan mayor propensión a OIG.

¿Quiénes corren mayor riesgo de desarrollar OIG?

Algunas personas que toman glucocorticoides corren mayor riesgo de desarrollar OIG:

- Las mujeres que han pasado por la menopausia
- Los hombres de 50 años de edad o más
- Las personas que han tenido fracturas anteriores
- Las personas que tienen otros factores de riesgo para la osteoporosis, entre ellas quienes
  - No consumen suficiente calcio o vitamina D
  - Fuman cigarrillos
  - Beben tres o más bebidas alcohólicas por día
  - Tienen antecedentes familiares de osteoporosis

¿Cómo puede averiguar si tiene huesos débiles?

Una prueba de densidad mineral ósea (también conocida como la prueba DXA) determina la fortaleza de los huesos. Esta prueba simple, que no causa dolor, utiliza una dosis baja de rayos x para ayudar a pronosticar la probabilidad de que sufra una fractura. Su médico también puede examinarle la columna vertebral en busca de fracturas utilizando rayos x o una prueba de exploración por resonancia magnética (MRI por sus siglas en inglés).

¿Cómo puede reducir el riesgo de desarrollar OIG?

Si va a tomar glucocorticoides durante tres meses o más, puede reducir el riesgo de desarrollar OIG siguiendo estos pasos:

- Haga ejercicio soportando peso como caminar, correr o bailar
- Si fuma, deje de hacerlo
- Limite su consumo de bebidas alcohólicas a no más de dos al día

Los expertos también sugieren tomar suplementos de calcio y vitamina D, incluso si lleva menos de tres meses tomando glucocorticoides. Su médico le puede decir en qué cantidad los debe tomar. Su médico también puede determinar el riesgo que corre de caerse y ofrecerle consejos sobre formas de evitar las caídas. Las personas con mayor riesgo de osteoporosis requieren medicamentos.

¿Quiénes necesitan medicamentos para protegerse los huesos?

Su médico examinará su historia médica, condición actual y dosis de glucocorticoides para determinar el riesgo que corre. Los expertos recomiendan medicamentos para proteger los huesos para ciertas personas que están tomando glucocorticoides por un periodo de por lo menos tres meses:

- Las mujeres que han pasado por la menopausia
- Los hombres de 50 años de edad o más

Es posible que quienes están en las siguientes categorías también necesiten medicamentos para protegerse los huesos:

- Los hombres y mujeres con un alto riesgo de osteoporosis, incluso si están tomando glucocorticoides por un periodo menor a tres meses
- Las mujeres premenopáusicas y hombres menores de 50 que han tenido fracturas por fragilidad

¿Qué tipos de medicamentos ayudan a proteger los huesos?

Hay dos tipos de medicamentos disponibles. Su médico le recetará el tipo de medicamento que es mejor para usted.

- Los bifosfonatos mantienen los huesos fuertes y detienen la desintegración de los huesos. Reducen el riesgo de fracturas de la cadera y espina dorsal.
- La teriparatida ayuda al cuerpo a producir masa ósea y fortalece los huesos. También reduce el riesgo de fracturas.

Pregúntele a su médico si necesita hacerse una prueba DXA y cuánto calcio y vitamina D debe tomar. Si necesita un medicamento para protegerse los huesos, pregúntele a su médico cuánto tiempo debe tomarlo, qué efectos secundarios puede tener y cualquier otra inquietud que tenga.

Recursos

Encuentre a un endocrinólogo: *www.hormone.org* o llame al *1-800-467-6663*

Información de la Hormone Foundation:

Acerca de la osteoporosis:
— *www.hormone.org/Resources/osteoporosis-and-bone-health.cfm*
— *www.hormone.org/Osteoporosis/treatment.cfm*

Acerca de los bifosfonatos:
www.hormone.org/Resources/upload/Bisphosphonates-Web.pdf

National Osteoporosis Foundation: *www.nof.org*

National Institutes of Health (NIH) Osteoporosis and Related Bone Diseases National Resource Center: *www.niams.nih.gov/Health_Info/Bone/Osteoporosis/overview.asp* o llame al *1-800-624-BONE*

EDITORES:
Jens Bollerslev, MD
Steven T. Harris, MD
Benjamin Z. Leder, MD

Febrero del 2012

Para mayor información sobre cómo encontrar un endocrinólogo, obtener publicaciones gratis en Internet, traducir esta hoja de datos a otros idiomas, o para hacer una contribución a la Fundación de Hormonas, visite a *www.hormone.org* o llame al 1-800-HORMONE (1-800-467-6663). La Fundación de Hormonas, la filial de enseñanza pública de la Sociedad de Endocrinología (*www.endo-society.org*), sirve de recurso al público para promover la prevención, tratamiento y cura de trastornos hormonales. Se permite la reproducción de esta página para fines no comerciales por profesionales e instructores médicos que deseen compartirla con sus pacientes y estudiantes.
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TRAINEE CORNER

Get Answers at The Endocrine Society's Early Investigators Workshop

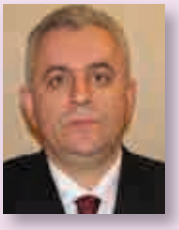
Are you currently a fellow who is taking steps to initiate your first research project? Have you been searching for advice on how to design your research study or develop an effective mentoring plan? Are you interested in learning how to identify and secure funding for your research? Even how to balance it all with your personal life? If your answer is yes to any of these questions, The Endocrine Society has a workshop that you won't want to miss, specifically designed to give you in-depth instruction on how to build a successful careers in research.

The Early Investigators Workshop (EIW) features hypothesis-driven clinical and translational research presentations, career development talks, small-group research presentations, and networking opportunities with peers and faculty. It is a valuable educational opportunity for fellows to grow their knowledge base and pick up essential skills that will help achieve their career goals. The 2012 EIW will be held on September 28 and 29 in the San Francisco Bay area.

Open to both basic science and clinical research fellows, the Workshop has been a rewarding experience for those who attend it. Participants from the 2011 Workshop talked to ***Endocrine News*** about their experiences.

I learned that mentorship was very important for anyone in an academic career, in particular at the early stages. It was also fascinating to hear the lecture on the relations between academia and industry. The grant-writing lecture and discussions were very helpful. The discussion sessions on fellows' presentations were useful and helped me learn how to write a funding proposal to NIH. The session on balancing academic and family life was very interesting because it presented challenges but also presented solutions.

Fellows in their second year should be certain to attend this workshop. There was obvious support from the faculty for further connections. It was a great meeting. Thanks to The Endocrine Society for showing excellent support to the fellows. Thanks to the great faculty members for their great effort.



Abdulkadir Omer, M.D., a second year clinical fellow at the University of Massachusetts, Worcester, attended the workshop to learn how to set up academic life as a fellow and to advance to the next stages of his career.

I think this workshop not only met my expectations but exceeded them. Professors not only shared steps and strategies that led them to succeed in their careers, but also cautioned us against mistakes they made in their careers.

I would strongly recommend the Early Investigators Workshop to anyone serious about making a career in this field. Early years of postdoc or research require proper guidance and this workshop provides a great platform to meet highly successful and accomplished people in this field. There were good opportunities to talk to them on various topics.

I would advise future participants to come prepared for this workshop by reading about the profile and area of research of the speakers to ensure better understanding about their fields, get their business cards in the meeting, actively network among peers and mentors, start writing grants early in their careers, and attend such meetings and conferences on a regular basis because this is very helpful in career growth.

Shilpi Mahajan, Ph.D., second year postdoctoral fellow at the University of California, San Francisco, attended the workshop to enhance her understanding and skill sets on various topics concerning basic and clinical research and also to meet accomplished professors in the field of endocrinology.

The Early Investigators Workshop is a must-attend event for any early career investigators wishing to advance their research careers. Nominations are now being accepted through July 17.

Space for this event is limited so apply today! Visit *www.endo-society.org/trainees/* and search "Early Investigators Workshop." ■

KEY DATES 2012

ENDOCRINE TRAINEE DAY *(www.endo-society.org/endo2012/audience/fellows.cfm)*
- General Registration Open
- Endocrine Trainee Day—June 22

ENDO 2012 HOW TO SECURE PROMOTION AND TENURE WORKSHOP
- General Registration Open
- How to Secure Promotion and Tenure Workshop—June 22

ENDO 2012, HOUSTON, TEX. *(www.endo-society.org/endo2012/)*
- Meeting Dates—June 23–26

ENDOCRINE BOARD REVIEW, MIAMI, FLA., *(www.endo-society.org/CEU/agenda.cfm)*
- Meeting Dates—September 11–13

2012 EARLY INVESTIGATORS WORKSHOP, SAN FRANCISCO, CALIF., *(www.endo-society.org/trainees/)*
- Meeting Dates—September 28–29
- Nomination Submission Opens
- Application Deadline—July 17

ENDOCRINE Society update

New *Endocrinology* Editor-in-Chief

Andrea C. Gore, Ph.D., is slated to become the next Editor-in-Chief of ***Endocrinology,*** from January 2013 through December 2017. She will take over from Jeffrey D. Blaustein, Ph.D. Dr. Gore is currently a member of the The Endocrine Society's Advocacy and Public Outreach Core Committee.

Dr. Gore is the Gustavus and Louis Pfeiffer Professor of Pharmacology and Toxicology at The University of Texas at Austin. Her research focuses on the neuroendocrine control of reproduction during postnatal development and aging. An internationally recognized expert on the biological actions of endocrine-disrupting chemicals on reproductive development, she is the lead author on the Society's scientific statement about endocrine-disrupting chemicals. She also served as the basic science chair of the 2007 Annual Meeting Steering Committee.

Society Announces 2012 Harold Vigersky Practicing Physician Travel Award Winner

The Endocrine Society is pleased to announce that the 2012 Harold Vigersky Practicing Physician Travel Award recipient is Michael H. Shanik, M.D., an endocrinologist practicing at Endocrine Associates of Long Island, P.C., in Smithtown, N.Y. Dr. Shanik attended medical school at New York Medical College and completed his residency at Long Island Jewish Medical Center. He will receive complimentary registration to **ENDO 2012** and a $1,500 stipend for travel and lost productivity.

The Harold Vigersky Practicing Physician Travel Award was established by former President Robert Vigersky, M.D., to help clinical practitioners in private practice offset the costs associated with attending ENDO or CEU meetings. Clinical practitioners interested in applying for the 2013 Harold Vigersky Practicing Physician Travel Award can learn more at *www.endo-society.org/vigerskyaward*.

The Endocrine Society Credit Card

The Endocrine Society has partnered with Capital One® to offer you three credit card options to fit your needs. Choose a card that earns great rewards, one with a low introductory APR, or another to build your credit. Plus, you can choose an image for your card that highlights your support for the Society. Apply today at *www.CapitalOneConnect.com/Endo*.

New Fact Sheet, Patient Guide from The Hormone Health Network

Neuropathies affect an estimated 60%–70% of patients who have had poorly controlled diabetes for 10 years or more. Most of these patients, however, have a slow progression of symptoms or no symptoms at all, so they may not be aware of a problem until considerable damage has been done. The Hormone Foundation's latest patient fact sheet, *Diabetic Neuropathy*, describes the two main nerve disorders caused by diabetes—distal polyneuropathy (DPN) and autonomic neuropathy—and the symptoms and health effects of each. The fact sheet encourages patients to discuss their symptoms with their doctor, get yearly screens for DPN, and pay particular attention to their feet. Patients are assured that they can prevent diabetic neuropathy or slow its progress with good blood glucose control, healthy lifestyle choices, and proper foot care.

Osteoporosis is not just a woman's disease: About 20% of the 44 million Americans who have osteoporosis or osteopenia are men. The Foundation's

Patient Guide to Osteoporosis in Men is based on The Endocrine Society's new clinical practice guideline on the same topic. The patient guide defines osteoporosis and identifies its potentially serious consequences. It helps men identify their individual risk factors and describes other diagnostic criteria. The guide explains bone density testing as a tool to detect osteoporosis, and recommends that men at increased risk of osteoporosis, and all men aged 70 years and older, have their bone mineral density measured. Men learn about available treatment options, including medication, and tips on osteoporosis prevention through dietary and lifestyle changes.

Visit *www.hormone.org* to read and download the fact sheet and patient guide.

Find the Funding You Need

The Society is pleased to announce a new member benefit: **EndoGrants Central.**

EndoGrants Central is a database of grant opportunities specifically of interest and relevance to the endocrine community, saving you time and effort.

Through EndoGrants Central you can find special, one-time Requests for Proposals (RFPs) from both federal and foundation funders, and opportunities for both U.S. and international researchers. Opportunities are also sorted by eligibility/career stage: all investigators, early-career investigators, and trainees.

The database is updated every Monday so you won't miss time-sensitive RFPs. Learn more at *www.endo-society.org/grants.* ■

Missed the Webinar on Osteoporosis in Men?

On Tuesday, June 5, 7:30 p.m. ET, leading bone expert Nelson B. Watts, M.D., F.A.C.P., M.A.C.E., facilitated a Webinar that complemented the Society's latest clinical practice guideline on Osteoporosis in Men. Webinar attendees earned *1.0 AMA PRA Category 1 Credit™* for participating in the session.

This is the third Webinar on an Endocrine Society clinical practice guideline. The previous Webinar was on hyperglycemia in non-critical care setting and discussed recommendations for safe glycemic targets. In this most recent Webinar, Dr. Watts discussed recommendations for the skeletal differences between men and women, ideal daily calcium intake, and pharmacologic therapy and treatment for a selection of men.

This 1-hour Webinar included 45 minutes of instructional content followed by 15 minutes of questions and answers.

To access this and other archived Society Webinars, see *www.endo-society.org/education/webinars/.*

calendar

JUN 23–26: HOUSTON, TEX.
ENDO 2012: The Endocrine Society's 94th Annual Meeting & Expo.
www.endo-society.org/endo.

SEPT 11–15: MIAMI, FLA.
Endocrine Board Review and Clinical Endocrinology Update.
www.endo-society.org/ceu.

See more events at *www.endosociety.org*, on the **Worldwide Endocrine Events Calendar.**

In Memoriam

Leonard D. Kohn, M.D.
Athens, Ohio
d. April 18, 2012

John C. Lowe, M.A., D.C.
Houston, Tex.
1946–2012

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Go to ***www.endo-society.org/endo_news*** or scan this QR Code with your smartphone's QR Reader to see the many new online features, headlines, news briefs, interactive text, photos, and links, among other enhancements.

If you are interested in submitting classified advertising to **Endocrine News**, *please contact Christine Whorton at* placement@endo-society.org *or 800-361-3906.*

Attractive Pediatric Endocrinology Position in the Midwest – Toledo, Ohio

Endocrine and Diabetes Care Center (EDCC), located in Toledo, Ohio, is recruiting a board certified/ board eligible Pediatric Endocrinologist. EDCC is the premier Endocrine group in the region of northwest Ohio and southeast Michigan that has been experiencing non-stop growth. This enables a new physician to rapidly build a successful practice in the community. EDCC is comprised of 7 endocrinologists: 5 adult and 2 pediatric specialists. Due to future retirement, EDCC is seeking a Pediatric Endocrinologist. Advantages: the first comprehensive diabetes and endocrine care center in northwest Ohio; the only care center in northwest Ohio that provides complete care for both adults and children; a comprehensive diagnostic, treatment, education, and support center for metabolic bone health and patients with diabetes, endocrine-related disorders, and thyroid disease; an American Diabetes Association (ADA)–recognized provider since 2000; large referral base—27 counties throughout northwest Ohio and southeast Michigan (population base of 1.8 million); affiliated with ProMedica Health System, ranked the nation's top most integrated health system; competitive compensation, signing bonus, and excellent benefits package; assistance with relocation. Please visit: *www.edcc.net* and *www.promedica.org/doctors*. For more information, please contact: Denise Johnston, In-House, Physician Recruiter, ProMedica Health System, Toll Free: 800-427-2755; Office: 419-824-7445; Email: *denise.johnston@promedica.org*.

Ohio Endocrinologists

The Cleveland Clinic seeks highly qualified board certified/board eligible endocrinologists to supplement our endocrine services. The duties of these predominantly clinical posts will be divided between our main campus in Cleveland and our regional facilities on the western and southern side of Cleveland. A clinical research interest will be welcomed, and the successful applicants will be expected to participate in the academic activities of the Endocrine Department. This position, at Associate or Staff level depending on experience, offers an attractive benefits pack-

For more information about

Community Health Network visit:

eCommunity.com

Community Health Network

Endocrinology Opportunity in Indianapolis, Indiana

Community Physician Network is seeking a motivated, BC/BE Endocrinologist to serve patients on the south side of Indianapolis due to system-wide growth and a rapidly growing patient population. The Endocrinologist will be employed and part of Community Physician Network's Endocrinology service line which includes 6 well established Endocrinologists and a nurse practitioner.

This opportunity offers:

- 100% Endocrinology, no Primary Care duties
- Limited call schedule
- Most inpatient Diabetes referrals managed by Hospitalists and Diabetologists
- Excellent compensation and benefit package and paid CME

Community Physician Network is a physician led organization that leads and manages with integrity, honesty and open communication and is a forward thinking, innovative organization positioned well to compete, leading to individual and group success. You can expect a competitive, fair and flexible compensation model that provides enhanced earnings potential for superior individual and group performance. Community Physician Network boasts an environment that fosters collegiality, professional security and the practice of high quality medicine.

Indiana is consistently ranked as one of the nation's top physician friendly states with low cost malpractice, a simplified licensing process and affordable cost of living. Indianapolis, the 14th largest city in the nation, offers big-city amenities in a convenient, friendly and inviting Midwest atmosphere.

For more information please contact:

Beth Kapsalis, Network Physician Recruiter

317-621-2141 | docjobs@ecommunity.com

www.eCommunity.com/PhysicianRecruitment

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age and a collegial and intellectually stimulating work environment. The melting pot culture that has helped establish Cleveland as a vibrant and versatile metropolitan area adds a unique flair to the lifestyle here. The Cleveland area is a very comfortable and affordable place to live with a variety of available activities, good school systems, and a great place to raise a family. Contact Jennifer Tonkli, Administrator, *tonklij@ccf.org;* tel 216-445-3784.

California Endocrinologist

Well-established solo practice in Los Angeles area, 100% endocrinology, seeking BC/BE endocrinologist for a position as an associate. Future partnership possible. Not a J1 or H1B visa opportunity. Send cover letter and CV to *socalendo2012@gmail.com*.

Academic Clinical Faculty Position

Quillen College of Medicine at East Tennessee State University (ETSU), Division of Endocrinology, Metabolism and Diabetes is seeking a full-time faculty member at the Asst./Assoc. Prof level on academic clinical track. Bring your passion for teaching and help build an Endocrinology fellowship program. We are seeking a physician interested in teaching and clinical practice, mainly outpatient care with occasional inpatient consultation. Requirements include ABIM certification in IM and BC/BE in Endocrinology. Salary and academic rank commensurate with qualifications and experience. ETSU is located in the beautiful mountains of northeast Tennessee. It is a family-oriented community, with an excellent school system and an abundance of year-round recreational and low cost of living. ETSU is an equal-opportunity, affirmative-action employer. Quillen was recently awarded the editors' choice by PreMedLife as one of the top 10 places in the US to attend medical school. All applicants must apply through eJobs at ETSU by completing an application and uploading a CV and 3 references. Inquiries can be directed to: Alan Peiris, M.D., Chief, Division of Endocrinology; *peiris@etsu.edu* or Renee McNeely at *mcneely@etsu.edu*.

Florida Endocrinologist

Well-established practice presents outstanding opportunity for J-1 or other endocrinologists interested in long term employment in Central Florida location. Performance based compensation system provides benefits similar to ownership without the hassle of administrative nightmares. Email CV to *janetecody@aol.com*.

Minnesota Endocrinologist

Join collegial group of 3 BC Endocrinologists, fellowship trained at Mayo Clinic and University of Iowa. Immediately busy, full-time practice! Focus of diabetes, thyroid disease, osteoporosis, obesity, and other endocrine disorders. Built in referral base with 150+ primary care physicians, excellent administrative support, EMR, and a systematic approach to quality. Call 1:4 Salary plus Quality and wRVU bonuses with comprehensive benefits. Employment with HealthEast Care System, the largest non-profit system in the East Metro Minneapolis/St. Paul area with 4 acute care hospitals, 15 clinics, 7,000 employees, and 1,400 physicians. Contact: Michael Griffin, Manager of Physician Recruitment: *mjgriffin@healtheast.org* or 651-232-2227.

Tennessee Endocrinologist

The Division of Endocrinology and Metabolism, Department of Medicine, University of Tennessee Health Science Center in Memphis, TN, has faculty openings, academic rank based on qualification, preferred BC/BE in Endocrinology; U.S. citizenship or permanent residency; clinical experience in diabetes and metabolism research. Send letter and CV to Samuel Dagogo-Jack, M.D., Chief of Endocrinology by email at *sdj@utmem.edu*. The University of Tennessee is an EEO/AA Title VI/Title IX, Section 504 ADA/ADEA institution in the provision of its education and employment programs and services.

Postdoctoral Research

NIH T32 sponsored 2–3 year postdoctoral research training track for M.D.s or Ph.D.s. Ph.D. trainees devote 100% time to research related efforts. M.D. trainees may integrate the research experience into clinical training. The program is divided into 4 main research groups from which the trainees can select an area of focus: 1) Diabetes, Metabolism, and Nutrition; 2) Metabolomics; 3) Male reproductive biology; and 4) Neuroendocrinology. Past trainees supported by this grant included many that remained in the academic environment. A number are now department chairpersons, division chiefs, and program directors. Positions are available for 2012 and 2013. Trainees must be United States citizens or permanent residents. Please apply at *http://huclaendo.labiomed.org*.

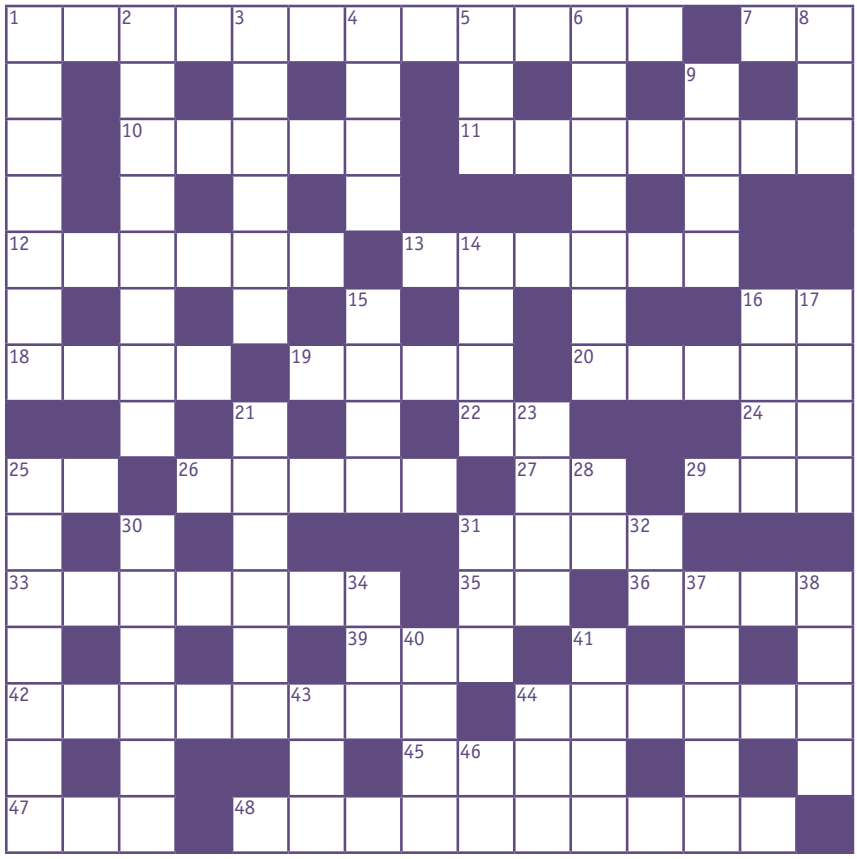
Texas Endocrinologist

Busy 1 Physician and 2 Nurse Practitioners: Endocrinology practice committed to patient care seeking a BC/BE physician. University town of 150,000 in Central Texas located 100 miles from Austin or Dallas. New facility, in house lab, DXA, thyroid ultrasound biopsy. ADA–approved Diabetic Education Program, and Research Center. Excellent salary and benefits with potential for growth. Send resume to The Diabetes & Endocrine Center, 333 Londonderry Dr., Suite 200, Waco, Texas, Phone: 254-751-9777, Fax: 254-751-9788, Email: *jgersbach@aactx.com*. At the June **ENDO 2012** meeting, at the Convention Center, contact number is 254-715-2233. ■

THE ENDOCRINE SOCIETY®

Crossword

By Myles Mellor



Across

1 Condition causing male breasts
7 Rare endocrine syndrome, ___-Fraumeni
10 Mushy
11 It speeds labor
12 Genetic abnormality in the X chromosome, _____ Syndrome
13 Sweetbreads
16 French, abbr.
18 Break off
19 It's used in flame retardants
20 Gleason, for one
22 Remove prefix
24 Light metal symbol
25 __OA, endocrine-disrupting chemical
26 Prader-___ Syndrome
27 Milliliter, abbr.
29 Kleinfelter Syndrome
31 Gallbladder fluid
33 Gland in the mouth
35 Place, abbr.
36 Western test
39 Differential thermal analysis, for short
42 Dangerous and unwanted material
44 2002–2003 Society president who recently passed, John ___
45 Gene ___
47 And the others, for short
48 Bone cell

Down

1 Hereditary
2 Kidney-shaped
3 Small region in the brain
4 Past Society President, Kelly ___
5 Weaken
6 Tissue connecting the right and left lobes of the thyroid gland
8 Electrical charge
9 Polychlorinated biphenyls
14 Pay attention to
15 Norwegian mathematician who invented group theory
16 WHO osteoporosis tool
17 Trust
21 Animal model rodent type
23 Nobelist, _____ Kocher
25 Compound with two or more amino acids linked in a chain
28 Lower left, for short
30 Hormone secreted from one tissue that affects the hormone secretion of another
31 It's banned from baby cups and toys
32 Eastbound, for short
34 Pesticide, endocrine-disrupting chemical
37 Meditation position
38 Period
40 _____1 (juvenile diabetes)
41 Society President, Janet ___
43 Identifies
44 Past Society President who met with Michelle Obama to discuss pediatric obesity, _____ Vigersky
46 ___cyte, female germ cell ■

Puzzler Page Answers:

You can find all Puzzler Page answers online via *www.endo-society.org/endo_news/index.cfm*. Printed answers will appear in the next issue.

Victoza® (liraglutide [rDNA origin] injection)

Rx Only

BRIEF SUMMARY. Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors *[see Contraindications and Warnings and Precautions].*

INDICATIONS AND USAGE: Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Important Limitations of Use:** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. In clinical trials of Victoza®, there were more cases of pancreatitis with Victoza® than with comparators. Victoza® has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza®. Use with caution in patients with a history of pancreatitis. Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Victoza® and insulin has not been studied.

CONTRAINDICATIONS: Victoza® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies *[see Boxed Warning, Contraindications].* In the clinical trials, there have been 4 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 1 case in a comparator-treated patient (1.3 vs. 0.6 cases per 1000 patient-years). One additional case of thyroid C-cell hyperplasia in a Victoza®-treated patient and 1 case of MTC in a comparator-treated patient have subsequently been reported. This comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Four of the five liraglutide-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One liraglutide and one non-liraglutide-treated patient developed elevated calcitonin concentrations while on treatment. Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~ 1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo and active control, respectively. Otherwise, Victoza® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza®-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza®-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza®. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza®. The clinical significance of these findings is unknown. Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. **Pancreatitis:** In clinical trials of Victoza®, there were 7 cases of pancreatitis among Victoza®-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years). Five cases with Victoza® were reported as acute pancreatitis and two cases with Victoza® were reported as chronic pancreatitis. In one case in a Victoza®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. One additional case of pancreatitis has subsequently been reported in a Victoza®-treated patient. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza® treatment. After initiation of Victoza®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Use with caution in patients with a history of pancreatitis. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia. In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients and in two comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea or other insulin secretagogues *[see Adverse Reactions].* **Renal Impairment:** Victoza® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza®-treated patients *[see Adverse Reactions].* Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration *[see Adverse Reactions].* Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza®. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

ADVERSE REACTIONS: Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Victoza® was evaluated in a 52-week monotherapy trial and in five 26-week, add-on combination therapy trials. In the monotherapy trial, patients were treated with Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, or glimepiride 8 mg daily. In the add-on to metformin trial, patients were treated with Victoza® 0.6 mg, Victoza® 1.2 mg, Victoza® 1.8 mg, placebo, or glimepiride 4 mg. In the add-on to glimepiride trial, patients were treated with Victoza® 0.6 mg, Victoza® 1.2 mg, Victoza® 1.8 mg, placebo, or rosiglitazone 4 mg. In the add-on to metformin + glimepiride trial, patients were treated with Victoza® 1.8 mg, placebo, or insulin glargine. In the add-on to metformin + rosiglitazone trial, patients were treated with Victoza® 1.2 mg, Victoza® 1.8 mg or placebo. *Withdrawals:* The incidence of withdrawal due to adverse events was 7.8% for Victoza®-treated patients and 3.4% for comparator-treated patients in the five controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza®-treated patients and 0.5% of comparator-treated patients. The most common adverse reactions leading to withdrawal for Victoza®-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials. Tables 1, 2 and 3 summarize the adverse events reported in ≥5% of Victoza®-treated patients in the six controlled trials of 26 weeks duration or longer.

Table 1: Adverse events reported in ≥5% of Victoza®-treated patients or ≥5% of glimepiride-treated patients: 52-week monotherapy trial

	All Victoza® N = 497	Glimepiride N = 248
Adverse Event Term	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Upper Respiratory Tract Infection	9.5	5.6
Headache	9.1	9.3
Influenza	7.4	3.6
Urinary Tract Infection	6.0	4.0
Dizziness	5.8	5.2
Sinusitis	5.6	6.0
Nasopharyngitis	5.2	5.2
Back Pain	5.0	4.4
Hypertension	3.0	6.0

Table 2: Adverse events reported in ≥5% of Victoza®-treated patients and occurring more frequently with Victoza® compared to placebo: 26-week combination therapy trials

Add-on to Metformin Trial			
	All Victoza® + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
Adverse Event Term	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4
Add-on to Glimepiride Trial			
	All Victoza® + Glimepiride N = 695	Placebo + Glimepiride N = 114	Rosiglitazone + Glimepiride N = 231
Adverse Event Term	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2

Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6
Add-on to Metformin + Glimepiride			
	Victoza® 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Event Term	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4
Add-on to Metformin + Rosiglitazone			
	All Victoza® + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175	
Adverse Event Term	(%)	(%)	
Nausea	34.6	8.6	
Diarrhea	14.1	6.3	
Vomiting	12.4	2.9	
Decreased Appetite	9.3	1.1	
Anorexia	9.0	0.0	
Headache	8.2	4.6	
Constipation	5.1	1.1	
Fatigue	5.1	1.7	

Table 3: Treatment-Emergent Adverse Events in 26 Week Open-Label Trial versus Exenatide (Adverse events with frequency ≥5% and occurring more frequently with Victoza® compared to exenatide are listed)

	Victoza® 1.8 mg once daily + metformin and/or sulfonylurea N = 235	**Exenatide 10 mcg twice daily + metformin and/or sulfonylurea** N = 232
Preferred Term	(%)	(%)
Diarrhea	12.3	12.1
Dyspepsia	8.9	4.7
Constipation	5.1	2.6

Gastrointestinal adverse events: In the five clinical trials of 26 weeks duration or longer, gastrointestinal adverse events were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse events occurred in 17% of comparator-treated patients. Events that occurred more commonly among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In a 26-week study of Victoza® versus exenatide, both in combination with metformin and/or sulfonylurea overall gastrointestinal adverse event incidence rates, including nausea, were similar in patients treated with Victoza® and exenatide. In five clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. Approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. In a 26 week study of Victoza® versus exenatide, both in combination with metformin and/or sulfonylurea, the proportion of patients with nausea also declined over time. *Immunogenicity:* Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza® may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza®-treated patients in the five clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza®-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza®-treated patients in the 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza®-treated patients in the 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the 26-week add-on combination therapy trials. Among Victoza®-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza®-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza®-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza®-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza® when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza® treatment. In clinical trials of Victoza®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. *Injection site reactions:* Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza®-treated patients in the five clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza®-treated patients discontinued due to injection site reactions. *Papillary thyroid carcinoma:* In clinical trials of Victoza®, there were 6 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.9 vs. 0.6 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. *Hypoglycemia:* In the clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 7 Victoza®-treated patients (2.6 cases per 1000 patient-years) and in two comparator-treated patients. Six of these 7 patients treated with Victoza® were also taking a sulfonylurea. One other patient was taking Victoza® in combination with metformin but had another likely explanation for the hypoglycemia (this event occurred during hospitalization and after insulin infusion) (Table 4). Two additional cases of hypoglycemia requiring the assistance of another person for treatment have subsequently been reported in patients who were not taking a concomitant sulfonylurea. Both patients were receiving Victoza®, one as monotherapy and the other in combination with metformin. Both patients had another likely explanation for the hypoglycemia (one received insulin during a frequently-sampled intravenous glucose tolerance test, and the other had intracranial hemorrhage and uncertain food intake).

Table 4: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

	Victoza® Treatment	**Active Comparator**	**Placebo Comparator**
Monotherapy	**Victoza®** (N = 497)	**Glimepiride** (N = 248)	**None**
Patient not able to self–treat	0	0	—
Patient able to self–treat	9.7 (0.24)	25.0 (1.66)	—
Not classified	1.2 (0.03)	2.4 (0.04)	—
Add-on to Metformin	**Victoza® + Metformin** (N = 724)	**Glimepiride + Metformin** (N = 242)	**Placebo + Metformin** (N = 121)
Patient not able to self–treat	0.1 (0.001)	0	0
Patient able to self–treat	3.6 (0.05)	22.3 (0.87)	2.5 (0.06)
Add-on to Glimepiride	**Victoza® + Glimepiride** (N = 695)	**Rosiglitazone + Glimepiride** (N = 231)	**Placebo + Glimepiride** (N = 114)
Patient not able to self–treat	0.1 (0.003)	0	0
Patient able to self–treat	7.5 (0.38)	4.3 (0.12)	2.6 (0.17)
Not classified	0.9 (0.05)	0.9 (0.02)	0
Add-on to Metformin + Rosiglitazone	**Victoza® + Metformin + Rosiglitazone** (N = 355)	**None**	**Placebo + Metformin + Rosiglitazone** (N = 175)
Patient not able to self–treat	0	—	0
Patient able to self–treat	7.9 (0.49)	—	4.6 (0.15)
Not classified	0.6 (0.01)	—	1.1 (0.03)
Add-on to Metformin + Glimepiride	**Victoza® + Metformin + Glimepiride** (N = 230)	**Insulin glargine + Metformin + Glimepiride** (N = 232)	**Placebo + Metformin + Glimepiride** (N = 114)
Patient not able to self–treat	2.2 (0.06)	0	0
Patient able to self–treat	27.4 (1.16)	28.9 (1.29)	16.7 (0.95)
Not classified	0	1.7 (0.04)	0

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events *[see Adverse Reactions]*, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. **Laboratory Tests:** In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use of Victoza®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Gastrointestinal: nausea, vomiting and diarrhea sometimes resulting in dehydration *[see Warnings and Precautions]*. Renal and Urinary Disorders: increased serum creatinine, acute renal failure or worsening of chronic renal failure, which may sometimes require hemodialysis *[see Warnings and Precautions]*.

OVERDOSAGE: In a clinical trial, one patient with type 2 diabetes experienced a single overdose of Victoza® 17.4 mg subcutaneous (10 times the maximum recommended dose). Effects of the overdose included severe nausea and vomiting requiring hospitalization. No hypoglycemia was reported. The patient recovered without complications. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available upon request.

For information about Victoza® contact: Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540, 1–877-484-2869

Date of Issue: May 18, 2011 **Version: 3**

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

Victoza® is a registered trademark of Novo Nordisk A/S. Victoza® is covered by US Patent Nos. 6,268,343; 6,458,924; and 7,235,627 and other patents pending. Victoza® Pen is covered by US Patent Nos. 6,004,297; 6,235,004; 6,582,404 and other patents pending.

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VICTOZA®
liraglutide (rDNA origin) injection

The #1 prescribed GLP-1 by endocrinologists*

Help adult patients grab type 2 diabetes by the roots.

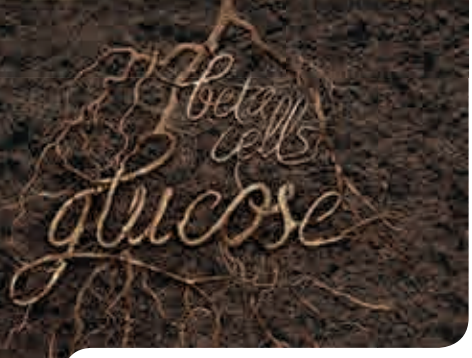
Powerful A1C reductions
—Lowered FPG and PPG

-0.8% to -1.5%†

Increased beta-cell function
—Improves insulin secretion

Low rate of hypoglycemia

May reduce weight
—Victoza® is not indicated for the management of obesity, and weight change was a secondary end point in clinical trials



90% of subjects found the Victoza® pen easy to learn how to use when demonstrating into a pillow.[1‡] Hear from Victoza® patients at **VictozaPro.com/Voices**.

novo nordisk®

VICTOZA®
liraglutide (rDNA origin) injection

Indications and usage

Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

In clinical trials of Victoza®, there were more cases of pancreatitis with Victoza® than with comparators. Victoza® has not been studied sufficiently in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using Victoza®. Use with caution in patients with a history of pancreatitis.

Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of Victoza® and insulin has not been studied.

Important safety information

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

If pancreatitis is suspected, Victoza® should be discontinued. Victoza® should not be re-initiated if pancreatitis is confirmed.

When Victoza® is used with an insulin secretagogue (e.g. a sulfonylurea) serious hypoglycemia can occur. Consider lowering the dose of the insulin secretagogue to reduce the risk of hypoglycemia.

Renal impairment has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration, which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment.

There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

The most common adverse reactions, reported in ≥5% of patients treated with Victoza® and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

Victoza® has not been studied in type 2 diabetes patients below 18 years of age and is not recommended for use in pediatric patients.

Victoza® should be used with caution in patients with hepatic impairment.

Please see brief summary of Prescribing Information on adjacent page.

Reference: 1. Data on file. Novo Nordisk Inc, Princeton, NJ.

*IMS Health Inc. LifeLink Longitudinal Prescription Database (LRx)™, April 2010-March 2011. Patients new to a GLP-1 agonist regimen from a previous regimen without a GLP-1 agonist.

†Victoza® 1.2 mg and 1.8 mg when used alone or in combination with OADs.

‡A randomized, multicenter, open-label, single-visit test to evaluate the usability of 3 Victoza® pens following subject review of the Victoza® Instructions for Use. Subjects with uncorrected visual impairment, limited manual dexterity, motor impairment, mental incapacity, or psychiatric disorder were excluded. Eligible subjects (N=90) were randomized to 1 of 6 pen/dose combinations and asked to read the Victoza® Instructions for Use and independently perform a specified injection into a foam pillow. After reading the Victoza® Instructions for Use and completing the task assigned, subjects completed the Victoza® Usability Questionnaire. The questionnaire included questions pertaining to how easy or difficult it was to prepare the pen, dial the dose and read the scale, deliver the dose, and learn to use the pen.

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