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NOVEMBER 2012



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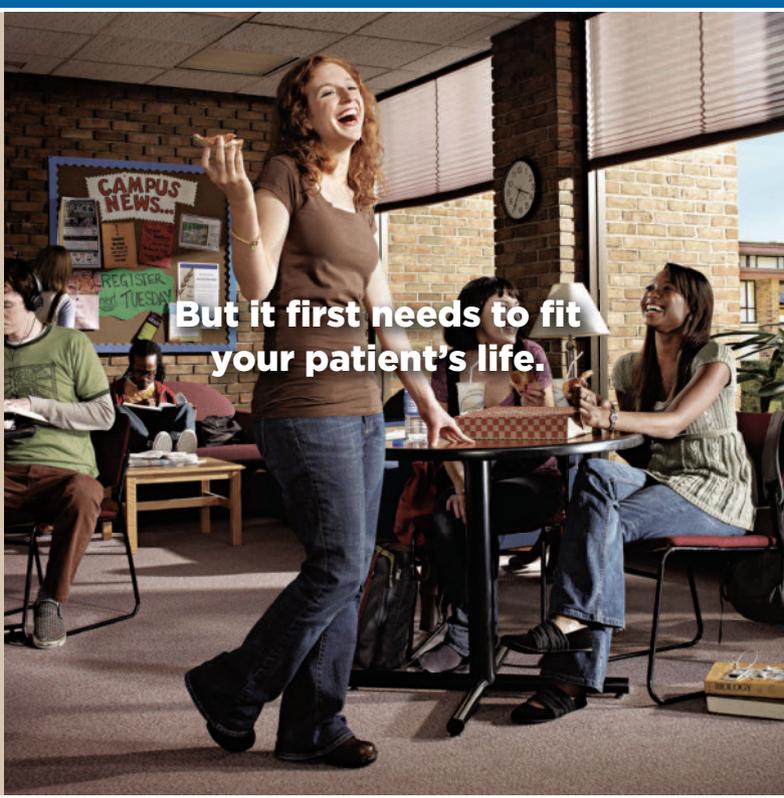


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Mealtime insulin therapy matters inside the body.



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Choose Humalog and the MiniMed Paradigm® REAL-Time Revel™ Insulin Pump

For adult patients with type 1 diabetes ready to have a conversation about using an insulin pump

- Humalog® (100 units /mL) can be used in a Paradigm Revel Insulin Pump¹

Indication for Humalog

- Humalog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

Select Safety Information for Humalog

- Humalog is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.
- Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously.
- Hypoglycemia is the most common adverse effect of Humalog therapy. The risk of hypoglycemia increases with tighter glycemic control. Severe hypoglycemia may be life threatening and can cause seizures or death.
- Humalog should be given within 15 minutes before or immediately after a meal.



Select Safety Information for Humalog, continued

- Humalog should not be diluted or mixed when used in an external insulin pump. Change Humalog in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days.
- Catheter occlusions and infusion-site reactions have been reported in patients receiving Humalog as a continuous subcutaneous infusion.

Reference

1. Paradigm® REAL-Time Revel™ User Guide. Starting on Insulin. ©2009 Medtronic MiniMed, Inc. 4.7.

Please see Important Safety Information on next page and Brief Summary of Full Prescribing Information for Humalog on following pages.

For more information about Humalog, please call The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979), or visit www.Humalog.com. For more information about Paradigm® REAL-Time Revel™, please call Medtronic at 1-888-350-3199, or visit www.medtronicdiabetes.com.

Humalog

insulin lispro injection, USP (rDNA origin)

Paradigm REAL-Time
Revel
MINIMED

 **Medtronic**

Lilly

Important Safety Information for Humalog

Contraindications

- Humalog® is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.

Warnings and Precautions

- **Dose Adjustment and Monitoring:** Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously. Concomitant oral antidiabetic treatment may need to be adjusted.

The time course of action for Humalog may vary in different individuals or at different times in the same individual and is dependent on many conditions, including delivery site, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require insulin dose adjustment.

- **Hypoglycemia:** Hypoglycemia is the most common adverse effect of Humalog. The risk of hypoglycemia increases with tighter glycemic control. Educate patients to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may vary for each person and may change over time. Early warning symptoms of hypoglycemia may be different or less pronounced under conditions such as long-standing diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. These situations may result in severe hypoglycemia and possibly loss of consciousness prior to the patient's awareness of hypoglycemia. Severe hypoglycemia may be life threatening and can cause seizures or death.

Use caution in patients with hypoglycemia unawareness and who may be predisposed to hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value.

Timing of hypoglycemia usually reflects the time-action profile of administered insulins. Other factors such as changes in food intake, injection site, exercise, and concomitant medications may alter the risk of hypoglycemia.

- **Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with Humalog.
- **Hypokalemia:** Humalog can cause hypokalemia, which, if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (eg, patients using potassium-lowering medications or medications sensitive to serum potassium concentrations).

Important Safety Information for Humalog, continued

Warnings and Precautions, continued

- **Renal or Hepatic Impairment:** Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.
- **Mixing of Insulins:** Humalog for subcutaneous injection should not be mixed with insulins other than NPH insulin. If Humalog is mixed with NPH insulin, Humalog should be drawn into the syringe first. Injection should occur immediately after mixing.
- **Subcutaneous Insulin Infusion Pump:** Humalog should not be diluted or mixed when used in an external insulin pump. Change Humalog in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days.

Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with Humalog may be required. Train patients using an insulin pump to administer insulin by injection and to have alternate insulin therapy available in case of pump failure.
- **Drug Interactions:** Some medications may alter glucose metabolism, insulin requirements, and the risk for hypoglycemia or hyperglycemia. Signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs. Particularly close monitoring may be required.

Adverse Reactions

- Adverse reactions associated with Humalog include hypoglycemia, hypokalemia, allergic reactions, injection-site reactions, lipodystrophy, pruritus, rash, weight gain, and peripheral edema.

Use in Specific Populations

- **Pediatrics:** Humalog has not been studied in children with type 1 diabetes less than 3 years of age or in children with type 2 diabetes.

Dosage and Administration

- Humalog should be given within 15 minutes before or immediately after a meal.

Please see following pages for Brief Summary of Full Prescribing Information for Humalog.

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Paradigm REAL-Time™
Revel
MINIMED

insulin lispro injection, USP (rDNA origin)

MiniMed Paradigm® REAL-Time Revel™ Insulin Pump Indications for Use

Pump

- The Paradigm Revel insulin pump is indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin.

MiniMed Paradigm REAL-Time Revel Insulin Pump Important Safety Information

Contraindications

- Pump therapy is not recommended for people who are unwilling or unable to perform a minimum of four blood glucose tests per day and to maintain contact with their healthcare professional. Successful insulin pump therapy requires sufficient vision or hearing to allow recognition of the pump signals and alarms.

Warnings

- The pump is not suitable for use in the presence of a flammable anesthetic mixture with air, oxygen, or nitrous oxide.
- Standard Luer sets are not compatible with the Medtronic MiniMed Paradigm pump. Medtronic Paradigm reservoirs and Paradigm-compatible infusion sets are specifically designed for use with the pump.
- Do not modify your Paradigm reservoir or Paradigm-compatible infusion set.
- Do not put any other drugs/medications inside your reservoir to use with this pump. Only insulin that has been prescribed by your physician can be used in this pump.
- Do not use pump cases that have a magnetic clasp.
- Do not expose your insulin pump to MRI equipment or other devices that generate very strong magnetic fields. The magnetic fields in the immediate vicinity of these devices can damage the part of the pump's motor that regulates insulin delivery, possibly resulting in over-delivery and severe hypoglycemia. Your pump must be removed and kept outside the room during magnetic resonance imaging (MRI) procedures.
- If your pump is inadvertently exposed to a strong magnetic field, discontinue use and contact our 24-Hour HelpLine for further assistance.

Please visit <http://www.medtronicdiabetes.com/about/safety.html> for complete safety information.

Humalog® is a registered trademark of Eli Lilly and Company and is available by prescription only.

MiniMed® is a registered trademark of Medtronic MiniMed, Inc.

Paradigm® is a registered trademark of Medtronic MiniMed, Inc.

Revel™ is a trademark of Medtronic MiniMed, Inc.

CareLink® is a registered trademark of Medtronic MiniMed, Inc.

The MiniMed Paradigm Revel Insulin Pump is Continuous Glucose Monitoring (CGM) ready. Optional glucose sensor and MiniLink® REAL-Time transmitter are available separately from Medtronic.

For information on the MiniMed Paradigm Revel Insulin Pump integrated with CGM, please contact your Medtronic representative.

Please see Important Safety Information for Humalog on opposite page.



Humalog®

(insulin lispro injection, USP [rDNA origin])

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

INDICATIONS AND USAGE

HUMALOG is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

CONTRAINDICATIONS

HUMALOG is contraindicated:

- during episodes of hypoglycemia
- in patients who are hypersensitive to HUMALOG or to any of its excipients.

WARNINGS AND PRECAUTIONS

Dose Adjustment and Monitoring—Glucose monitoring is essential for patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose. Concomitant oral antidiabetic treatment may need to be adjusted.

As with all insulin preparations, the time course of action for HUMALOG may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages.

Hypoglycemia—Hypoglycemia is the most common adverse effect associated with insulins, including HUMALOG. The risk of hypoglycemia increases with tighter glycemic control. Patients must be educated to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may be different for each person and may change from time to time. Severe hypoglycemia can cause seizures and may be life-threatening or cause death.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia [see *Drug Interactions*].

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers [see *Drug Interactions*], or intensified diabetes control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

Hypersensitivity and Allergic Reactions—Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including HUMALOG [see *Adverse Reactions*].

Hypokalemia—All insulin products, including HUMALOG, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Renal or Hepatic Impairment—Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

Mixing of Insulins—HUMALOG for subcutaneous injection should not be mixed with insulin preparations other than NPH insulin. If HUMALOG is mixed with NPH insulin, HUMALOG should be drawn into the syringe first. Injection should occur immediately after mixing.

Do not mix HUMALOG with other insulins for use in an external subcutaneous infusion pump.

Subcutaneous Insulin Infusion Pumps—When used in an external insulin pump for subcutaneous infusion, HUMALOG should not be diluted or mixed with any other insulin. Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days. HUMALOG should not be exposed to temperatures greater than 98.6°F (37°C).

Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with HUMALOG may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure [see *Dosage and Administration and How Supplied/Storage and Handling*].

Drug Interactions—Some medications may alter insulin requirements and the risk for hypoglycemia or hyperglycemia [see *Drug Interactions*].

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia [see *Warnings and Precautions*].
- Hypokalemia [see *Warnings and Precautions*].

Clinical Trial Experience—Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared with those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of Treatment-Emergent Adverse Events during HUMALOG clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (adverse events with frequency ≥5%)

Events, n (%)	Lispro (n=81)	Regular human insulin (n=86)	Total (n=167)
Flu syndrome	28 (34.6)	28 (32.6)	56 (33.5)
Pharyngitis	27 (33.3)	29 (33.7)	56 (33.5)
Rhinitis	20 (24.7)	25 (29.1)	45 (26.9)
Headache	24 (29.6)	19 (22.1)	43 (25.7)
Pain	16 (19.8)	14 (16.3)	30 (18.0)
Cough increased	14 (17.3)	15 (17.4)	29 (17.4)
Infection	11 (13.6)	18 (20.9)	29 (17.4)
Nausea	5 (6.2)	13 (15.1)	18 (10.8)
Accidental injury	7 (8.6)	10 (11.6)	17 (10.2)
Surgical procedure	5 (6.2)	12 (14.0)	17 (10.2)
Fever	5 (6.2)	10 (11.6)	15 (9.0)
Abdominal pain	6 (7.4)	7 (8.1)	13 (7.8)
Asthenia	6 (7.4)	7 (8.1)	13 (7.8)
Bronchitis	6 (7.4)	6 (7.0)	12 (7.2)
Diarrhea	7 (8.6)	5 (5.8)	12 (7.2)
Dysmenorrhea	5 (6.2)	6 (7.0)	11 (6.6)
Myalgia	6 (7.4)	5 (5.8)	11 (6.6)
Urinary tract infection	5 (6.2)	4 (4.7)	9 (5.4)

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (adverse events with frequency ≥5%)

Events, n (%)	Lispro (n=714)	Regular human insulin (n=709)	Total (n=1423)
Headache	63 (11.6)	66 (9.3)	149 (10.5)
Pain	77 (10.8)	71 (10.0)	148 (10.4)
Infection	72 (10.1)	54 (7.6)	126 (8.9)
Pharyngitis	47 (6.6)	58 (8.2)	105 (7.4)
Rhinitis	58 (8.1)	47 (6.6)	105 (7.4)
Flu syndrome	44 (6.2)	58 (8.2)	102 (7.2)
Surgical procedure	53 (7.4)	48 (6.8)	101 (7.1)

Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Lipodystrophy

Long-term use of insulin, including HUMALOG, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy [see *Dosage and Administration*].

Weight gain

Weight gain can occur with insulin therapy, including HUMALOG, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Peripheral Edema

Insulin, including HUMALOG, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Adverse Reactions with Continuous Subcutaneous Insulin Infusion (CSII)

In a 12-week, randomized, crossover study in adult patients with type 1 diabetes (n=39), the rates of catheter occlusions and infusion site reactions were similar for HUMALOG and regular human insulin treated patients (see Table 3).

Table 3: Catheter Occlusions and Infusion Site Reactions

	HUMALOG (n=38)	Regular human insulin (n=39)
Catheter occlusions/month	0.09	0.10
Infusion site reactions	2.6% (1/38)	2.6% (1/39)

In a randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes, adverse event reports related to infusion-site reactions were similar for insulin lispro and insulin aspart (21% of 100 patients versus 17% of 198 patients, respectively). In both groups, the most frequently reported infusion site adverse events were infusion site erythema and infusion site reaction.

Allergic Reactions

Local Allergy—As with any insulin therapy, patients taking HUMALOG may experience redness, swelling, or itching at the site of the injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of HUMALOG. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy—Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin, including HUMALOG. Generalized allergy to insulin may cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis.

In controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving regular human insulin (n=2969) and 30 patients receiving HUMALOG (n=2944).

Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in HUMALOG [see Contraindications].

Antibody Production

In large clinical trials with patients with type 1 (n=509) and type 2 (n=262) diabetes mellitus, anti-insulin antibody (insulin lispro-specific antibodies, insulin-specific antibodies, cross-reactive antibodies) formation was evaluated in patients receiving both regular human insulin and HUMALOG (including patients previously treated with human insulin and naive patients). As expected, the largest increase in the antibody levels occurred in patients new to insulin therapy. The antibody levels peaked by 12 months and declined over the remaining years of the study. These antibodies do not appear to cause deterioration in glycemic control or necessitate an increase in insulin dose. There was no statistically significant relationship between the change in the total daily insulin dose and the change in percent antibody binding for any of the antibody types.

Postmarketing Experience—The following additional adverse reactions have been identified during post-approval use of HUMALOG. 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.

Medication errors in which other insulins have been accidentally substituted for HUMALOG have been identified during postapproval use.

DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

Following are some of the examples:

- **Drugs That May Increase the Blood-Glucose-Lowering Effect of HUMALOG and Susceptibility to Hypoglycemia:** Oral antidiabetic agents, salicylates, sulfonamide antibiotics, monoamine oxidase inhibitors, fluoxetine, pramlintide, disopyramide, fibrates, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, and somatostatin analogs (e.g., octreotide).
- **Drugs That May Reduce the Blood-Glucose-Lowering Effect of HUMALOG:** corticosteroids, isoniazid, niacin, estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), somatropin, atypical antipsychotics, glucagon, protease inhibitors, and thyroid hormones.
- **Drugs That May Increase or Reduce the Blood-Glucose-Lowering Effect of HUMALOG:** beta-blockers, clonidine, lithium salts, and alcohol. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
- **Drugs That May Reduce the Signs of Hypoglycemia:** beta-blockers, clonidine, guanethidine, and reserpine.

USE IN SPECIFIC POPULATIONS

Pregnancy—Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking HUMALOG.

Although there are limited clinical studies of the use of HUMALOG in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome.

In a combined fertility and embryo-fetal development study, female rats were given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) from

2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was produced at the 20 units/kg/day-dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

In an embryo-fetal development study in pregnant rabbits, insulin lispro doses of 0.1, 0.25, and 0.75 unit/kg/day (0.03, 0.08, and 0.24 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) were injected subcutaneously on Gestation days 7 through 19. There were no adverse effects on fetal viability, weight, and morphology at any dose.

Nursing Mothers—It is unknown whether insulin lispro is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HUMALOG is administered to a nursing woman. Use of HUMALOG is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

Pediatric Use—HUMALOG is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. HUMALOG has not been studied in pediatric patients younger than 3 years of age. HUMALOG has not been studied in pediatric patients with type 2 diabetes.

As in adults, the dosage of HUMALOG must be individualized in pediatric patients based on metabolic needs and results of frequent monitoring of blood glucose.

Geriatric Use—Of the total number of subjects (n=2834) in eight clinical studies of HUMALOG, twelve percent (n=338) were 65 years of age or over. The majority of these had type 2 diabetes. HbA1c values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of HUMALOG action have not been performed.

OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

DOSE AND ADMINISTRATION

Dosage Considerations—When given subcutaneously, HUMALOG has a more rapid onset of action and a shorter duration of action than regular human insulin.

The dosage of HUMALOG must be individualized. Blood glucose monitoring is essential in all patients receiving insulin therapy.

The total daily insulin requirement may vary and is usually between 0.5 to 1 unit/kg/day. Insulin requirements may be altered during stress, major illness, or with changes in exercise, meal patterns, or coadministered drugs.

Subcutaneous Administration—HUMALOG should be given within 15 minutes before a meal or immediately after a meal.

HUMALOG given by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.

HUMALOG administered by subcutaneous injection should be given in the abdominal wall, thigh, upper arm, or buttocks. Injection sites should be rotated within the same region (abdomen, thigh, upper arm, or buttocks) from one injection to the next to reduce the risk of lipodystrophy [see Adverse Reactions].

Continuous Subcutaneous Infusion (Insulin Pump)—HUMALOG may be administered by continuous subcutaneous infusion by an external insulin pump. Do not use diluted or mixed insulins in external insulin pumps. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy [see Adverse Reactions]. Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days.

The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Although there is significant variability among patients, approximately 50% of the total dose is usually given as meal-related boluses of HUMALOG and the remainder is given as a basal infusion. HUMALOG is recommended for use in pump systems suitable for insulin infusion such as MiniMed, Disetronic, and other equivalent pumps.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HUMALOG 100 units per mL (U-100) is available as:

10 mL vials	NDC 0002-7510-01 (VL-7510)
3 mL vials	NDC 0002-7510-17 (VL-7533)
5 x 3 mL cartridges ¹	NDC 0002-7516-59 (VL-7516)
5 x 3 mL prefilled pen	NDC 0002-8725-59 (HP-8725)
5 x 3 mL Humalog KwikPen (prefilled)	NDC 0002-8799-59 (HP-8799)

Storage

Do not use after the expiration date.

Unopened HUMALOG should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use HUMALOG if it has been frozen. In-use HUMALOG vials, cartridges, pens, and HUMALOG KwikPen[®] should be stored at room temperature,

below 86°F (30°C) and must be used within 28 days or be discarded, even if they still contain HUMALOG. Protect from direct heat and light. See table below:

	Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature, (Below 86°F [30°C])
10 mL vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL vial	28 days	Until expiration date	28 days, refrigerated/room temperature.
3 mL cartridge	28 days	Until expiration date	28 days, Do not refrigerate.
3 mL prefilled pen	28 days	Until expiration date	28 days, Do not refrigerate.
3 mL Humalog KwikPen (prefilled)	28 days	Until expiration date	28 days, Do not refrigerate.

Use in an External Insulin Pump — Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days or after exposure to temperatures that exceed 98.6°F (37°C). A HUMALOG 3 mL cartridge used in the D-Tron® pumps should be discarded after 7 days, even if it still contains HUMALOG. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion set insertion site should be selected at least every 3 days.

Diluted HUMALOG for Subcutaneous Injection — Diluted HUMALOG may remain in patient use for 28 days when stored at 41°F (5°C) and for 14 days when stored at 86°F (30°C). Do not dilute HUMALOG contained in a cartridge or HUMALOG used in an external insulin pump.

Preparation and Handling

Diluted HUMALOG for Subcutaneous Injection — HUMALOG may be diluted with Sterile Diluent for HUMALOG for subcutaneous injection. Diluting one part HUMALOG to nine parts diluent will yield a concentration one-tenth that of HUMALOG (equivalent to U-10). Diluting one part HUMALOG to one part diluent will yield a concentration one-half that of HUMALOG (equivalent to U-50).

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling and Patient Counseling Information section of the Full Prescribing Information.

¹ 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® Memoir™ and HumaPen® Luxura™ HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3-mL insulin delivery device and Disetronic D-TRON® and D-TRON® Plus pumps.

Autopen® is a registered trademark of Owen Mumford, Ltd.

Humalog®, Humalog® KwikPen™, HumaPen®, HumaPen® Memoir™, HumaPen® Luxura™ and HumaPen® Luxura™ HD are trademarks of Eli Lilly and Company.

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Other product and company names may be the trademarks of their respective owners.



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Additional information can be found at www.humalog.com.

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By Erin Wayman

Ten years after the Women's Health Initiative study, experts reevaluate the risks of hormone therapy.

30 Mum on Menopause

From *The Hormone Health Network*

Recent surveys show that despite experiencing menopausal symptoms, patients are reluctant to bring them up with their doctor.

44 U.S. Health Care on the Ballot

By Sarah Zielinski

U.S. voters are not only voting for their President. They also will decide the fate of the current health care system.

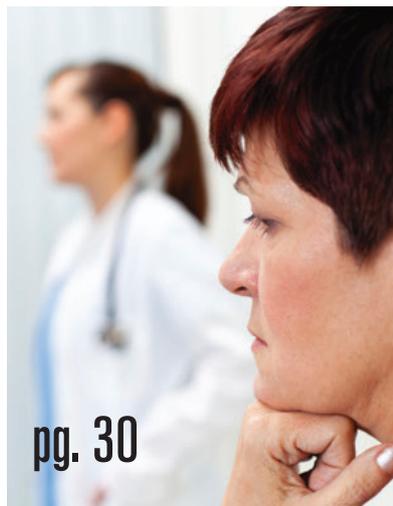
62 Jellies in the Spotlight

By Aleta George

Although reviled for their stings, jellyfish are having a positive impact on medical science.



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What Are the Effects of High Triglycerides?

Read the Hormone Health Network's patient guide on assessment and treatment (pages 50,51).



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



What's in Store for Endo 2013?

Dear Colleagues:

The Endocrine Society's annual meeting, **ENDO**, fosters the dissemination of basic, translational, and clinical science and practice across the entire field of endocrinology.

The opportunity to hear and present the latest science and practice advances, and to network with other endocrinologists, has made ENDO a fixture on our members' calendars. The Society's Annual Meeting Steering Committee (AMSC) met in August to plan the scientific program for **ENDO 2013**, which will take place June 15–18 in San Francisco. The AMSC co-chairs—Didi Robins (overall chair), Dan Marks (basic science chair), and Mike Tuttle (clinical science chair)—led the committee in developing a spectacular program, with outstanding content for each of our constituencies.

As always, **ENDO 2013** will offer opportunities to hear cutting-edge science and current advances in the diagnosis and treatment of endocrine diseases. With more than 75 symposia on breakthroughs in endocrinology and with more than 80 clinical *Meet-the-Professor* sessions, the **ENDO 2013** program will cover the spectrum of endocrine research and its applications to patient care. In addition, **ENDO 2013** will continue to offer the popular *Master Clinicians Sessions*, on topics such as type 2 diabetes, osteoporosis, and adrenal masses. The format of these sessions features two topic experts fielding questions from highly experienced clinicians for in-depth discussions of difficult cases. **ENDO 2013** will also include basic and clinical *Year In* sessions. Basic *Year In* topics include "G Protein-Coupled Receptors (GPCRs)" and "Neuroendocrinology" and Clinical *Year In* topics include "Thyroid Cancer" and "Clinical Implications of Whole Genome Sequencing." For a second year in a row, a half-day forum on GPCRs will be held in conjunction with **ENDO 2013** to offer additional opportunities for detailed discussion of these important signaling molecules in endocrinology.

"Poster Preview Sessions" will debut this year to uniquely highlight research submitted in the form of abstracts. The posters will be selected from among the highest scoring abstracts and displayed as posters in each of the categories. Presenters will be invited to the podium to deliver a concise and compelling description of their work, with the goal of directing traffic to poster sessions.



William F. Young, Jr.
M.D., M.Sc.

The pre-**ENDO** *Diabetes Diagnosis & Management Workshop* will also be held in 2013. In addition to the outstanding scientific program, we will continue to take advantage of the opportunity **ENDO** offers to provide career development and networking for our students, fellows, and junior faculty. Special programming includes *Endocrine Trainee Day: Class of 2013*, *Career Development Workshops*, and the *Presidential Poster Competition*. In addition, selected junior investigators will be highlighted in *Presidential Symposia* that intermingle new with more established presenters. Providing a broad scope of late-breaking developments in endocrinology, **ENDO 2013** is the must-attend meeting of the year. I look forward to seeing you in San Francisco for a very successful 95th Annual Meeting and Expo!

As always, I welcome your comments at president@endo-society.org. ■

Sincerely,

William F. Young, Jr., M.D.
President, The Endocrine Society





Dear Readers,

Ten years ago, millions of women stopped taking hormone replacement therapy after the Women's Health Initiative clinical trial showed that the treatment put them at risk for breast cancer, strokes, and heart attacks. Now with additional research, medical experts are reassessing the risks and benefits and recommending a more reasonable individualized approach to taking hormones, writes Erin Wayman in our cover story on the controversy (page 22).

An eye-opening related story is The Endocrine Society and Hormone Health Network's recent surveys of women and doctors about menopause. The results show that a majority of women are suffering menopausal symptoms but are receiving no treatment. Many of the women know little about hormone therapy and are confused about their options, but most are not talking openly to their health providers about menopause problems (page 30).

The U.S. Presidential election is just days away, and much is at stake when

it comes to health care. The cost of medical treatment continues to rise, and many Americans have no health insurance. With the Republicans vowing to rescind the Democrats' new Affordable Care Act, Washington, D.C.-based writer Sarah Zielinski sheds light on some of the hot-button issues (page 44).

Although some scientists debate whether or not jellyfish are really taking over the oceans, others are exploring ways these beach menaces can serve humankind. In the last decades, according to writer Aleta George, who was recently mesmerized by the creatures' water ballet at the Monterey Bay Aquarium in California, jellies have become the basis of important medical science and research (page 62). ■

Sincerely,

Marian Smith Holmes
Managing Editor
Endocrine News

ENDOCRINE NEWS ONLINE EXCLUSIVES

The following articles are housed online only. See *Endocrine News Online* to read them and find related links (www.endo-society.org/endo_news).



Oil Have What She's Having

The Mediterranean diet works wonders not only for the waistline, but also for bones.



Better Health after Bariatric Surgery?

Bariatric surgery may be cost-effective, but only after the first six years, research suggests.



World's First Mother-to-Daughter Uterus Transplant

Two Swedish women receive wombs donated by their mothers.



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

Teresa K. Woodruff, Ph.D.
President-Elect
tkw@northwestern.edu

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

Marian Smith Holmes
Managing Editor
mholmes@endo-society.org

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

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

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Short Sprints Stave off Hypoglycemia during Exercise

► To avoid the low drop in blood sugar that can occur after a session of moderate-intensity exercise, people with type 1 diabetes mellitus (T1DM) should perform short sprints before exercising, suggests a recent article in *The Journal of Clinical Endocrinology & Metabolism* [*jcem.endojournals.org*].

For T1DM patients, the risk of hypoglycemia while exercising can discourage adding physical activity to their lifestyles. The new study

shows that starting with a 10-second sprint can reduce the risk, according to Paul A. Fournier, Ph.D., a professor in the School of Sport Science, Exercise and Health at the University of Western Australia, who led the study.

“We found in two separate studies that a 10-second sprint performed before or after moderate-intensity exercise reduces the risk of post-exercise hypoglycemia for 30 minutes to two hours,” Fournier said. “However, sprinting before moderate-intensity exercise has no effect on the rate of fall in blood glucose levels during exercise.”

The team of Australian researchers studied eight young adults with T1DM who averaged 22.9 years of age and a body mass index of 26.7. All were on insulin pump therapy. A second group of young adults without diabetes served as

controls. Before the exercise sessions, the participants with T1DM underwent insulin treatment and the investigators measured their glucose levels. Both groups then pedaled stationary bikes as hard as possible for 10 seconds. After different time intervals of exercise and rest, the investigators again took blood samples and measured glucose levels in both groups.

In the T1DM group, blood glucose levels increased significantly by 1.2 ± 0.2 mmol/L after the sprint and remained even during the rest period. In the group without diabetes, blood glucose levels increased significantly less than those of the T1DM patients. ■

Glenda Fauntleroy



Hyperthyroidism Increases Death Risk

► Hyperthyroidism is an all-too-common condition, and one that often occurs with other conditions, some fatal. Individuals with hyperthyroidism have a 21 percent higher mortality rate than people who do not have it.

Frans Brandt, M.D., at the Odense University Hospital, Denmark, led a team to find out whether the higher mortality rate derives from the hyperthyroidism itself or is because of associated conditions or genetics. Using a standardized evaluation system, they studied 4,850 singletons

from Denmark with hyperthyroidism and 926 twin individuals from 625 same-sex pairs discordant for hyperthyroidism.

In their paper, to be published soon in *The Journal of Clinical Endocrinology & Metabolism* [*jcem.endojournals.org*], the researchers report that individuals without pre-existing comorbidity at the time of hyperthyroidism diagnosis had an increased rate of death. This suggests an independent association between hyperthyroidism and mortality. In dizygotic twins, whose genomes are

about as similar as those of non-twin siblings, this association persisted. The twin with hyperthyroidism had an increased risk for death. However, in monozygotic twins, whose genomes are identical, the association did not hold up.

The researchers conclude that hyperthyroidism confers a higher risk of death, separate from coexisting conditions, and that genetic confounders are also at work, predisposing certain individuals with hyperthyroidism to death. Future studies should clarify whether severity of hyperthyroidism influences the risk of death, they add. ■

Kelly Horvath

High Triglycerides in First-Trimester Affects Pregnancy

► High maternal triglyceride and total cholesterol levels in the second and third trimesters are linked to both short- and long-term complications for the mother and the infant, including preterm birth, pregnancy-induced hypertension, preeclampsia, large-for-gestational age infants, and infant death. A new study seeks to discover what effects elevated lipids have during early pregnancy to eliminate factors associated with more advanced pregnancies such as problems with the placenta or the pregnancy itself.

Tanja Vrijkotte, Ph.D., at the Academic Medical Center in Amsterdam, the Netherlands, led a team of scientists analyzing lipid profiles from 4,008 healthy pregnant women in their 12th to 14th weeks of pregnancy who participated in the Amsterdam Born Children and their Development (ABCD) cohort study. In their paper, to be published soon in *The Journal of Clinical Endocrinology & Metabolism* [jcem.endojournals.org], the researchers report that serum triglyceride level correlated with hypertension, preeclampsia,

preterm birth, and large infant size, but had no effect on infant death. Total cholesterol level did not associate with adverse outcomes.

“Increasing evidence suggests that elevated plasma lipids may induce endothelial dysfunction by enhancing oxidative stress, leading to placental dysfunction,” says Vrijkotte. The researchers conclude that elevated triglycerides in early pregnancy are toxic for mother and child. Whether preconception screening could be useful to counsel for lifestyle modifications like diet and exercise remains to be studied, they add. ■

Kelly Horvath

Ingredient in Anti-Bacterial Products Affects Muscle Contraction

► Triclosan, the active ingredient in household products commonly marketed as “anti-bacterial,” has been shown to affect cardiac output and grip strength in mice and the swimming performance of fathead minnows—findings that have researchers at the University of California at Davis questioning how the substance may affect human and environmental

health. In a three-pronged study published in the July 13, 2012, issue of the *Proceedings of the National Academy of Sciences*, researchers found that triclosan impaired muscle contraction by interfering with how muscle cells communicate with each other.

First, the team injected anesthetized mice with triclosan at a dose equivalent to 12.5 mg/kg body weight. Within 10 minutes, the mice experienced a 25 percent reduction in cardiac function as

measured by the amount of blood pumped through their hearts.

Next, the researchers gave conscious mice a 40 mg/kg dose of triclosan and administered a grip-strength test. Over the next 60 minutes, grip strength in the mice dropped an average of 18 percent.

Finally, the team exposed fathead minnow larvae to triclosan at a concentration of 0.52 μ M for seven days, and observed inhibited swimming ability, predator avoidance, and endurance in the larvae.

Although mice and minnows are not men and women, the findings could indicate that triclosan poses a risk to human and environmental health, said Isaac Pessah, Ph.D., professor and chair in the Department of Molecular Biosciences, School of Veterinary Medicine.

“The doses in the mice relate to blood levels of triclosan we see in humans,” he said. “Although a normal, healthy person wouldn’t really be fazed by a temporary 10 percent, or even a 30 percent decrease in cardiac output, especially if they are not exercising or exerting themselves, it can raise a concern about what could happen for people with heart or skeletal muscle disease.”

The results in the minnow segment of the study have implications for the environment, he added. “Millions of pounds of triclosan have been produced, and it is well documented that waste treatment plants can’t remove all of it. It’s in sediment and our drinking water.”

Household products containing triclosan include hand soap, shampoo, cleaning supplies, bedding, shoes, clothes, and carpets. ■

Terri D’Arrigo



Neuropeptide Linked to Renal Damage

► Hypertension has been estimated to affect 30 percent of U.S. adults and is a risk factor for the development of cardiovascular and renal diseases. Homing in on potential proteins to counter this condition, Donna Wang, M.D., at Michigan State University, and her research group focused on substance P (SP), a neuropeptide that activates neurokinin 1 (NK1) receptors and affects cardiovascular and renal function. Their findings will appear in an upcoming article in *Endocrinology* [endo.endojournals.org].

The group created a mouse model to replicate renal injury dur-

ing hypertension by removing one kidney from C57BL/6 male mice and treating the animals with deoxycorticosterone (DOCA) and salt, with or without selective NK1 receptor antagonists L-733,050 and RP-67580. Renal physiology was determined five weeks following treatment. Mean arterial pressure increased in DOCA-salt-treated mice. The absence or addition of NK1 receptor antagonists had no effect on blood pressure.

The DOCA-salt-treated mice also experienced renal hypertrophy, increased urinary 8-isoprostane levels, elevated albumin excretion, and increased plasma SP levels.

In addition, renal damage (glomerulosclerosis and tubuloint-

erstitial injury in the renal cortex), renal collagen levels, and interstitial monocyte/macrophage infiltration were more pronounced in DOCA-salt-treated mice than control animals. Co-administration of the NK1 receptor antagonists alleviated all of these.

The authors noted that during experimental DOCA-salt-induced hypertension, SP levels were elevated and contributed to renal injury, a phenomenon that was blunted by NK1 receptor antagonists. However, because the DOCA-salt mouse hypertension model is not caused by excessive dietary salt intake alone, more studies are needed to examine the role of SP-mediated renal injuries in humans with salt-sensitive hypertension. ■

Joanne McAndrews, Ph.D.

STATS

By 2030, obesity rates for U.S. adults could reach or exceed

44%

in every state and exceed 60% in 13 states.

Source: Trust for America's Health and the Robert Wood Johnson Foundation report, September 2012. *F as in Fat: How Obesity Threatens America's Future*. <http://healthyamericans.org/assets/files/TFAH2012FasInFat18.pdf>.

Obesity Increases Men's Risk of Osteoporosis

► A new study shows that obese men should add bone loss to the already long list of health problems caused by carrying excess body weight.

"Obesity does not protect against bone loss as previously thought and obese men are at risk for osteoporosis," explained lead author Miriam Bredella, M.D., associate

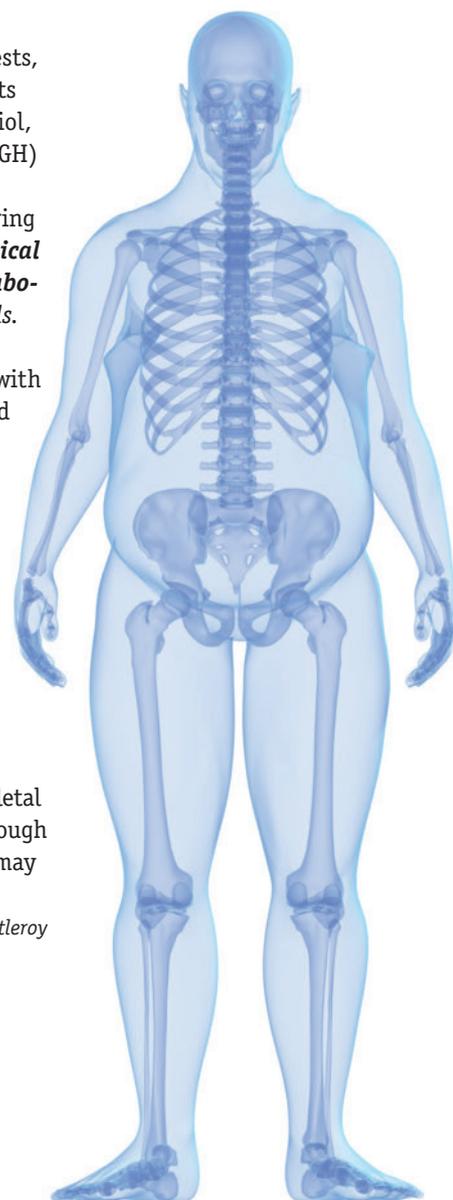
professor of radiology at Harvard Medical School in Boston. "[This is] through the accumulation of visceral fat and associated decreased growth hormone secretion and low testosterone levels."

The researchers studied 35 obese men with an average body mass index of 36.5. To determine the effect of visceral adipose tissue (VAT), or body fat, on bone microarchitecture and mechanical properties, computed tomography (CT) was used to divide the men into two groups. Men with VAT below the group's median were grouped into a low VAT group and those with VAT greater than the median were placed into a high VAT group. Each participant then underwent three-dimensional CT

scans and endocrine tests, including measurements of testosterone, estradiol, and growth hormone (GH) levels.

In the study appearing in *The Journal of Clinical Endocrinology & Metabolism* [jcem.endojournals.org], Bredella and her team found that men with high VAT had weakened bone health compared with those in the low VAT group. The researchers also concluded that decreased GH, insulin-like growth factor-1, and testosterone—all characteristics of male obesity—may cause harmful damage to skeletal microarchitecture, although higher estradiol levels may offer protection. ■

Glenda Fauntleroy



Breast Cancer Risk Higher in Night Shift Workers

► A new study may bring worrisome news to those who work at night. According to its findings, excessive use of artificial light during the night may be linked to an increased risk of breast cancer in industrialized countries where night shift work is common.

Researchers led by Lulu Mao, Ph.D., and Steven M. Hill, Ph.D., of the Tulane University School of Medicine in New Orleans investigated the molecular reasons that disruption of the body's natural circadian rhythms may be linked to breast cancer

invasion and metastasis. According to the study, the incidence of breast cancer is five times higher in nations where people are exposed to "light-at-night" than in underdeveloped countries. The World Health Organization has designated night-shift work and light-at-night exposure as a potential carcinogen.

The study suggested that the association between the disruption of circadian rhythms by exposure to light at night and the increased breast cancer risk resulted from the disruption of the circadian rhythm of glycogen synthase kinase 3 β (GSK3 β). GSK3 β is an enzyme critical in metab-

olism, cell proliferation, and invasion/metastasis. Disruption of its circadian rhythm perturbs the nocturnal surge of pineal melatonin (MLT), the biological timing signal.

The researchers report in *Molecular Endocrinology* [mend.endojournals.org]

that this disruption of the MLT circadian rhythm by light at night "has significant and far-reaching biological consequences." ■

Glenda Fauntleroy



Age-Based Reference Ranges Proposed for Androgens

► Sometimes treatment guidelines that sound straightforward can be hard to follow in practice. For example, current guidelines recommend that men with symptomatic androgen deficiency and low testosterone levels are candidates for testosterone supplementation. However, because testosterone levels decline with age, particularly after 40, it's been hard to pin down what constitutes an age-appropriate normal level and one that is low enough to justify supplementation.

A research team led by Bu Beng Yeap, M.B.B.S., Ph.D., of the School of Medicine and Pharmacology, University of Western Australia, Fremantle Hospital Unit, in Fremantle, Australia, attempted to establish reference ranges in healthy men age 70 years or older for testosterone and two of its downstream products: dihydrotestosterone (DHT), an even

more potent ligand for stimulating action at the androgen receptor, and estradiol, which exerts action via the estrogen receptor. The researchers measured early morning samples from 3,690 community-dwelling men aged 70–89 years in the Western Australia city of Perth.

Levels of all three steroids declined with age. Lower testosterone and lower DHT were associated with higher body mass index, higher waist-to-hip ratio, dyslipidemia, and diabetes. Lower estradiol was associated with diabetes. An apparent association of low testosterone with cardiovascular disease was attenuated after adjustment for other variables.

When the 2.5th percentiles for testosterone, DHT, and estradiol in 394 very healthy older men were used as thresholds, low testosterone or DHT was associated with frailty,

diabetes, and cardiovascular disease in the cohort as a whole. Based on their findings, the researchers proposed that levels at the 2.5th percentile or lower provided an age-appropriate threshold for defining a low level of each androgen. For their reference group, this percentile represented levels of 6.4 nmol/L for testosterone (184 ng/dL), 0.49 nmol/L for DHT, and 28 pmol/L for estradiol.

In an upcoming article in *The Journal of Clinical Endocrinology & Metabolism* [jcem.endojournals.org], the researchers suggest that additional studies could test the applicability of their proposed thresholds to improving the treatment of older men. ■

Eric Seaborg

Infant Antibiotic Use Could Raise Obesity Risk

► Treating infants with antibiotics in their first few months of life could raise



their risk of obesity later, a new study indicates.

U.S. farmers routinely give low-dose antibiotics to cattle and chickens to hasten fattening them for market. The earlier in life that the exposure begins, the greater the weight gain, so a research team led by Leonardo Trasande, M.D., M.P.P., of New York University School of Medicine in New York City, inquired whether antibiotics could have the same effect in humans.

Using data from more than 11,000 children in the United Kingdom's Avon Longitudinal Study of Parents and Children, the researchers examined the association of antibi-

otic exposure during three time periods during the first two years of life with increases in body mass over the first seven years.

They found that exposure to antibiotics during the first 6 months was associated with increases in body mass from 10 to 38 months, when the effect peaked. By age seven, the increase had largely disappeared. Exposure in the period of 6–14 months showed no association. Those exposed in the 15- to 23-month time-frame did not show consistently higher BMI until age seven, when exposure was associated with a small body mass index increase.

The researchers note that the size of the increase was modest in most individuals, but spread over the population,

the effect could be another factor contributing to the obesity epidemic.

The findings echo the results of a recent analysis of the Danish National Birth Cohort, which found that children of normal-weight mothers exposed to antibiotics during their first six months had an increased risk of being overweight at age seven.

The findings give another indication of the importance of intestinal bacteria in maintaining a healthy metabolism, and in their article in the *International Journal of Obesity*, the researchers point to the first six months of life as a window of special vulnerability to disruption. ■

Eric Seaborg

Aspirin Use, Bleeding Risk, and Diabetes

► A daily, low-dose aspirin may help keep the cardiologist away, but it is more likely to send users to the hospital with a hemorrhage in the gut or the brain than previously thought, say researchers in Italy. After comparing nearly 6 years of records from 186,425 patients who took low-dose aspirin daily with records from an equal number of patients who did not, the researchers found that daily aspirin use increased the risk of gastrointestinal bleeding 55 percent and the risk of intracranial bleeding 54 percent. These findings, published in the June 6, 2012, issue of *JAMA* suggest that major bleeding events, with or without aspirin use, prompt hospitalization five times more often than found in previous studies, an indication that

the real-life risk is much greater than indicated in clinical trials.

The team also observed that diabetes increases the risk of bleeding 36 percent, regardless of aspirin use. When analyzing data only from patients who did not take aspirin, the team found that diabetes increased the risk of gastrointestinal bleeding 59 percent and intracranial bleeding 64 percent.

Doctors must weigh the benefits of daily aspirin therapy against the risks when discussing treatment with their patients who are at risk for heart disease or stroke. The Italian team determined that for people who already have a 10- to 20-percent risk of having a heart attack in the next 10 years, the risks and benefits of taking low-

dose aspirin daily are roughly equal. For every 1,000 people treated each year, aspirin therapy was associated with two excess cases of bleeding, but it also prevented two cardiovascular events such as heart attack.

In their conclusion, the Italian researchers write: "diabetes might represent a different population in terms of both expected benefits and risks associated with antiplatelet therapy." ■

Terri D'Arrigo



Ghrelin Receptor Reverses Cardiomyopathy

► Restriction and restoration of blood to the heart—ischemia and reperfusion, respectively—reduce cardiomyocyte action potential (AP) amplitude, possibly by affecting intracellular calcium, sodium, and potassium levels, and augment reactive oxygen species (ROS), stress, and cell death. Among in vitro models of blood flow, the growth hormone secretagogue (GHS) ghrelin, which is prevalent in cardiomyocytes, and its synthetic analog hexarelin have been shown to be cardioprotective.

Led by Chen Chen, M.D., Ph.D., at the University of Queensland, Brisbane, Australia, scientists set out

to determine whether the protection from ghrelin and hexarelin derives from their influence on ion channels and APs and to identify their role in the apoptosis pathway. The team induced a 20-minute ischemia in adult mice hearts and then reperused the hearts with a solution containing either ghrelin or hexarelin for 30 minutes (controls were reperused for 70 minutes), either before or after the ischemic episode. A subset of reperused hearts also received ghrelin receptor 1a (GHS-R1a) antagonist. In their paper to be published soon in *Endocrinology* [endo.endojournals.org], the

researchers report normal APs in treated cardiomyocytes, except those given the GHS-R1a antagonist.

The researchers conclude that ghrelin and hexarelin restore intracellular ion handling and act as ROS scavengers to protect cardiomyocytes both pre- and post-ischemia via GHS-R1a activation. “Ischemic heart disease is a leading cause of mortality, but has no effective drug treatment,” says Dr. Chen. “Our laboratory is now in the process of demonstrating the protective effect of hexarelin among in vivo disease models, in view of developing effective drug treatment for this disease.” ■

Kelly Horvath

Gene Linked to Dwarfism Disorder

► Researchers have tied a particular gene and gene product to a form of dwarfism, and have even found evidence in zebrafish that backs up their finding of a disrupted developmental pathway.

Microcephalic primordial dwarfism (MPD) is a rare and severe disorder in which growth failure begins in utero. It is associated with defects in single genes involved in fundamental cellular processes, including the functions of centrosomes. These genes encode the cytoplasmic microtubule-organizing centers integral to cell division, cell polarity, and cell cycle control.

Researchers led by Andrew Dauber, M.D., M.M.Sc., of Children’s Hospital Boston and Harvard University, and Vivian Hwa, Ph.D., of Oregon

Health & Science University in Portland, searched for the genetic origin of MPD in two sisters with a subtype of the disorder that included severe intellectual disabilities. They performed a whole exome sequence analysis, which they cross-referenced with a growth plate gene expression data set. This approach led them to focus on mutations in the *NIN* gene on chromosome 14q22.1. The *NIN* gene product is ninein, a key centrosomal protein important to the process of asymmetric cell division.

The researchers then studied zebrafish in which they had engineered the genetic knockdown of ninein function. This knockdown showed that ninein

is essential for the early formation and patterning of the brain. In fact, knockdown in the fish led to specific, MPD-like deficiencies of brain and skull development, including a

tial role for ninein during neural development.

In an article to be published in *The Journal of Clinical Endocrinology & Metabolism* [jcem.endojournals.org], the research-



deformed cranium with a small, squared skull reminiscent of the phenotype in humans. The results indicate a developmental role for ninein apart from its role in cell division, a finding consistent with evidence from mouse knockdown experiments that also show an essen-

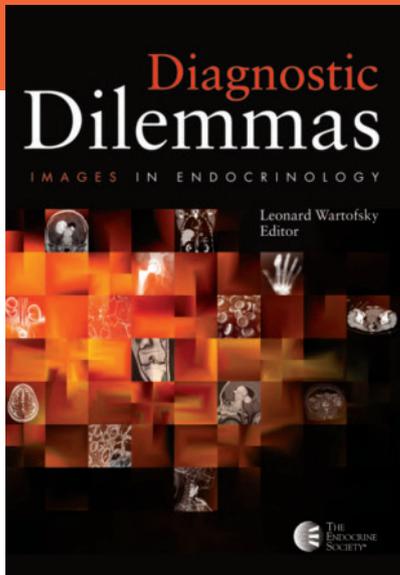
ers say this role of *NIN* in the development of MPD provides important clues for further research on the role of this and related genes in human growth and development. ■

Eric Seaborg

“Diagnostic Dilemmas certainly delivers and leads

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— Lewis E. Braverman, MD



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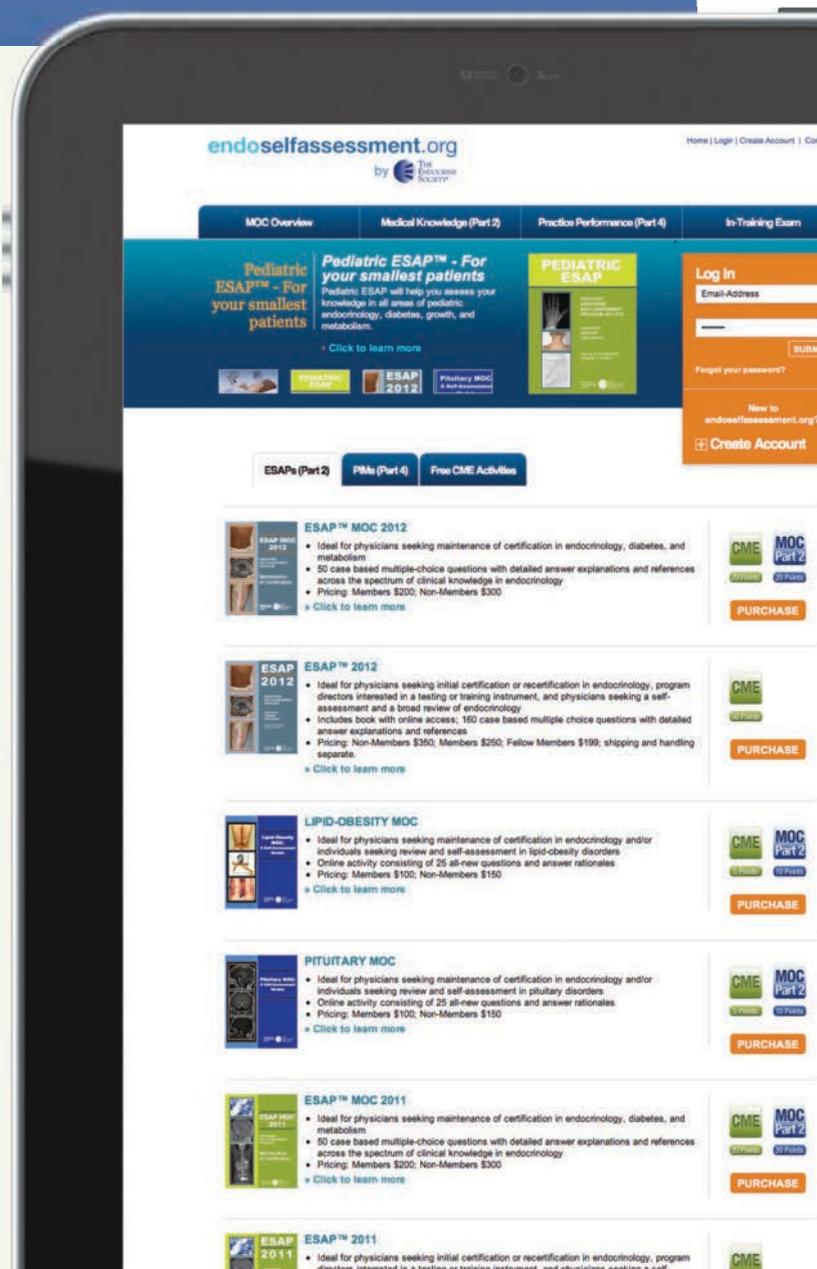
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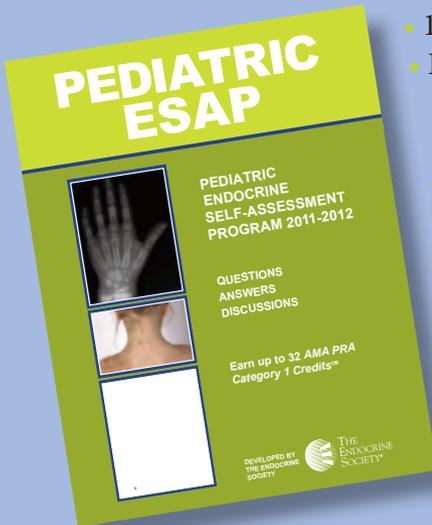
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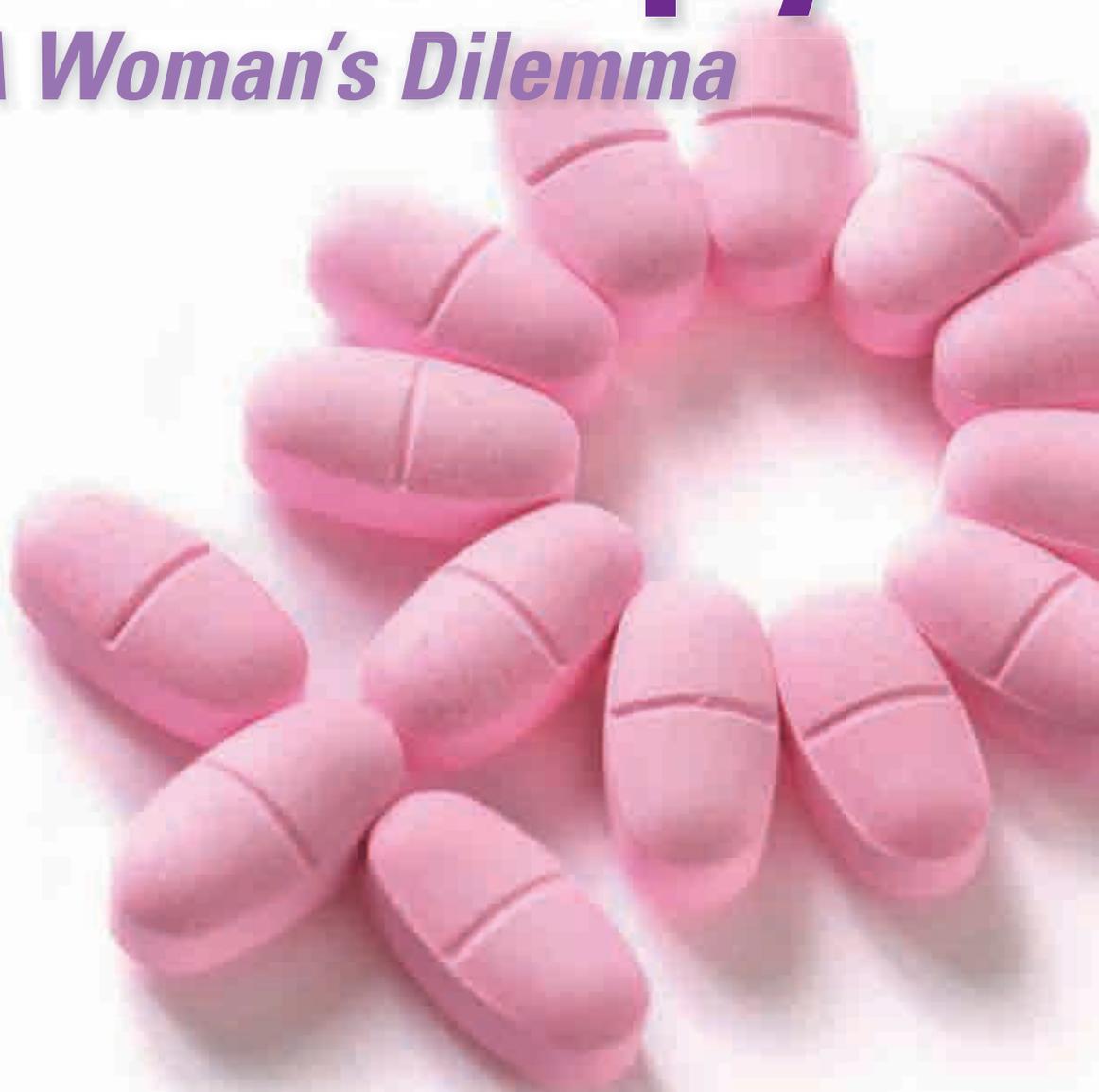
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Hormone Therapy

A Woman's Dilemma



By Erin Wayman

**“Death by Hormones.” “Alarm Over Hormone Replacement Therapy Cancer Risk.”
“Study Says Halt Hormone Therapy.”**

These were the headlines women woke up to on the morning of July 10, 2002. It was the day after researchers at the National Heart, Lung and Blood Institute (NHLBI) announced that they had stopped the largest randomized clinical trial of one of the most popular prescribed forms of hormone replacement therapy. Part of the NHLBI’s Women’s Health Initiative (WHI), the trial ended early because women taking the hormones had an increased risk of developing breast cancer compared to women on placebo.

The response was swift: Menopausal women ditched their hormones. In 1999, U.S. doctors wrote 90 million prescriptions for hormone replacement therapy. Within a year after the trial ended, that number dropped by a third and continued to fall. In 2010, about 30 million prescriptions were filled.

Yet not all of those women needed to give up the medication, according to experts. In 1941, the U.S. Food and Drug Administration (FDA) approved hormone replacement therapy—estrogen for women whose uteruses had been surgically removed or estrogen plus progesterone (to protect against endometrial cancer) for women with uteruses—and calls it the “most effective FDA approved medicine” to alleviate hot flashes, night sweats, and vaginal dryness, which frequently occur during menopause. The WHI, however, was investigating whether the drugs could also prevent cardiovascular disease in older women who were on average 63 years old and 12 years past menopause.

These are two very different uses of the drugs, but that subtlety was lost in the original media reports, says Robert Langer, M.D., M.P.H., medical

director of the Jackson Hole Center for Preventative Medicine in Wyoming. “Doctors as well as women got really confusing, mixed messages,” he says.

Over the past decade, with the release of additional follow-up data, doctors now have a better picture of the risks and benefits of hormone replacement therapy, now called menopause hormone therapy or MHT.

Highlights

- Hormone therapy is not recommended as a treatment to prevent chronic conditions such as heart disease or dementia.
- Hormone therapy is generally safe to treat menopausal symptoms in young, healthy women who are in their 50s or within 10 years of menopause, but should be used for the shortest period possible.
- Individual risk factors should be considered before prescribing hormone therapy or determining how long a woman can safely stay on the treatment.

“In the past 10 years, after the initial alarm, a much more reasonable approach is being taken,” says Virginia Miller, Ph.D., a professor of surgery and physiology at the Mayo Clinic College of Medicine.

Medical associations like The Endocrine Society and the North American Menopause Society (NAMS) agree that menopause hormone therapy is an effective treatment for menopausal symptoms. Adverse effects are low for relatively

Hormone Therapy Effects on Chronic Conditions *(Events per 10,000 women per year)*

Risks

Estrogen or Estrogen-plus-Progestin Therapies

- Stroke (9–11+)
- Deep venous thrombosis (7–12+)
- Gallbladder disease (20–23+)
- Urinary incontinence (872–1,271+)

Estrogen-plus-Progestin Therapy

- Dementia (22+)
- Pulmonary Embolism (9+)
- Invasive breast cancer (8+)



Benefits

Estrogen or Estrogen-plus-Progestin Therapies

- Spine and hip fractures (-46–56)

Estrogen-only Therapy

- Invasive breast cancer (-8)
- Breast cancer deaths (-2)

From the U.S. Preventive Services Task Force’s review of studies and trials since 2002.

young, healthy women, so these organizations recommend prescribing the therapy to women in their 50s, or those within 10 years of menopause. However, women with certain medical histories are not good candidates for treatment. According to NAMS, "If you have had blood clots, heart disease, stroke, or breast cancer, it may not be in your best interest to take hormone therapy."

In general, these medical societies advise that women stay on the treatment for the shortest period possible. For example, no more than three to five years for estrogen plus progesterone. However, because the Women's Health Initiative evaluated an older population of women, the risks of long-term hormone use in younger menopausal women are unclear.

"What the trials didn't answer is if a woman started in her 50s and took it into her 70s that the risk would go up,"

randomized clinical trial of the treatment. In 1993 to 1998, 16,608 women between the ages of 50 and 79 years enrolled in the estrogen-plus-progestin (a synthetic progesterone) trial and 10,739 women enrolled in the estrogen-only trial. These trials were supposed to run for 8.5 years, but the estrogen-plus-progestin trial ended about five years early, in 2002, after the researchers determined the treatment group had a 26 percent increased risk of developing breast cancer. The estrogen-only trial continued until 2004, when an increased risk of stroke was found in the group taking the hormone.

Recently the U.S. Preventive Services Task Force, an independent panel of experts, reviewed the original Women's Health Initiative studies, follow-up data, and other clinical trials investigating menopause hormone therapy since 2002. The task force published its preliminary

findings in July in the *Annals of Internal Medicine*. The panel considered menopause hormone therapy's effects on a range of chronic conditions. For many ailments, the treatment either had no effect or raised the risk of developing the condition. Only in some instances did hormones offer some preventive benefits.

"It's kind of a mixed bag about which risk factors are pulling in different directions," says task force leader Heidi Nelson, M.D., M.P.H., a research professor of medical informatics and clinical epidemiology and medicine at the Oregon Health and Science University.

Both forms of therapy led to a statistically significant increased risk of stroke, deep venous thrombosis,

gallbladder disease, and urinary incontinence. Estrogen plus progestin also raised the risk of dementia, pulmonary embolism, and invasive breast cancer.

However, both forms of treatment protected against spine and hip fractures due to bone loss. Estrogen-only therapy actually lowered the risk of invasive breast cancer and breast cancer deaths.

Although it might be tempting to conclude the progestin explains the difference between the two groups, other factors, such as the women's risks for breast cancer and cardiovascular disease, also differed, Nelson says.

Even though the absolute risk of developing breast cancer or suffering a stroke because of menopause hormone therapy was low (less than 1 case per 1,000 women)—and no higher than cholesterol-lowering statins, Hodis notes—the results indicate that neither therapy offered any cardiovascular benefits. "There's no need for women to take estrogen therapy to prevent a heart attack," Nelson says.

Some doctors theorize that the women in the WHI study did not experience cardiovascular benefits because they missed the "window of opportunity" when taking estrogen can help

On Point

The Endocrine Society's Scientific Statement on Postmenopausal Hormone Therapy

"The data suggest that for menopausal women ages 50 to 59 yr or younger than age 60 yr, the benefits of MHT outweigh the risks in many instances and particularly for relief of symptoms due to estrogen deficiency. Judgments about treatment require assessment of the needs in an individual patient and her potential for risks [such as breast cancer, coronary heart disease, fracture, stroke, and deep venous thrombosis]. . . . Current guidelines suggest use of MHT with the lowest effective dose and for the shortest duration possible."

Published in *The Journal of Clinical Endocrinology & Metabolism*, July 2010

To view the statement in its entirety, go to www.endo-society.org/journals/ScientificStatements/upload/jc-2009-2509v1.pdf.

says Howard Hodis, director of the Atherosclerosis Research Unit at the University of Southern California Keck School of Medicine. "There are no data in the Women's Health Initiative that can say that." In fact, no data from any randomized clinical trial are available to answer that question.

Some doctors think there's still a chance that the long-term use of menopause hormone therapy, started when a woman is young enough, may be not only safe but beneficial. "There are observational studies where women have taken these things for 20, 30, or 40 years and clearly still have reduced [coronary] events and mortalities," Hodis says. But this belief remains one of the most controversial aspects of menopause hormone therapy.

Risks versus Benefits

Menopause hormone therapy for the treatment of chronic conditions is not an FDA-approved use of the drugs. The Women's Health Initiative chose to look at the potential preventive benefits of the treatment because of the dozens of observational studies that indicated hormones might protect the heart. There had never been a large, long-term



Women's Attitudes toward Menopause Hormone Therapy

62% express concern about side effects of hormone therapy.

66% have not talked to their primary health care provider or OB/GYN about hormone therapy.

From an April 2012 survey commissioned by The Endocrine Society's Hormone Health Network.

prevent coronary heart disease. Estrogen is thought to help maintain proper blood flow. After the decline of the hormone at menopause, the lining of the carotid arteries thickens and arteries harden, leading to blockages and heart attacks.

"Once established, you can't prevent it or change it," Hodis says. "But if you can prevent it before it gets a foothold, you can potentially prevent progression and maybe even [coronary] events."

Furthermore, Langer says, starting estrogen within that window may prevent some of the risks associated with menopause hormone therapy. After menopause, the body's cell receptors that latch on to estrogen become misshapen with disuse. If estrogen is reintroduced later, the hormones won't fit properly with those receptors, causing damaging inflammation, Langer adds.

Hormones and Heart Trial

A recent randomized clinical trial investigated how starting menopause hormone therapy early affects cardiovascular disease and other chronic conditions. The Kronos Early Estrogen Prevention Study (KEEPS), sponsored by the Kronos Longevity Research Institute in Phoenix, was a four-year study of nearly 730 healthy women, ages 42 to 58 years. The results, announced in October, show no adverse effects, such as increased incidences of breast cancer, stroke, heart attack, or decline in cognitive function, associated with menopause hormone therapy, which suggests younger, healthy women can safely take the drugs for at least four years. In addition to treating typical menopausal symptoms, the researchers found other benefits such as higher levels of high-density lipoproteins ("good" cholesterol) and reported improvements in depression, anxiety and memory. But the therapies had no effect on the progression of the hardening of the carotid arteries.

"What we can't say is that estrogen is going to protect women against heart disease," says Kronos Director Mitch Harmon, M.D., Ph.D.

Another study—Early Versus Late Intervention Trial With Estradiol (ELITE), funded by the National Institute on Aging—concludes at the end of the year. The ELITE trial is looking at 643 women for an average of five years and comparing the effects of starting hormone therapy early (six years within menopause) or late (10 years after menopause). Like KEEPS, ELITE is monitoring the thickness and hardening of the arteries and cognitive function.

However, even these trials are not big or long enough to demonstrate whether menopause hormone therapy actually reduces the number of heart attacks or deaths. "Even if you show changes in coronary artery calcium, that doesn't mean there's a reduction in risk," says Jacques Rossouw, M.D., chief of the Women's Health Initiative. The question of estrogen's heart-protective benefits may never be answered to everyone's satisfaction.

Even short-term use to relieve menopausal symptoms may not be appropriate for all women, says Margery Gass, M.D., executive director of the North American Menopause Society. "Hormone therapy will always be a mixed picture of benefits and risks, and that's why it's important for a woman to work with her provider to determine what's in her particular best interest." ■

'Hormone therapy will always be a mixed picture of benefits and risks, and that's why it's important for a woman to work with her provider to determine what's in her particular best interest.'

Wayman is a Washington D.C.-based science writer.



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CYCLOSET[®]: First-in-class therapy for type 2 diabetes in adults



Important Safety Information

CYCLOSET is contraindicated in patients with hypersensitivity to ergot-related drugs, bromocriptine, or any of the excipients in CYCLOSET. Do not use in patients with syncopal migraines. It may precipitate hypotension. Do not use in nursing women. It may inhibit lactation. There are postmarketing reports of stroke in this patient population.

CYCLOSET can cause orthostatic hypotension and syncope, particularly upon initiation or dose escalation. Use with caution in patients taking antihypertensive medications. CYCLOSET may exacerbate psychotic disorders or reduce the effectiveness of drugs that treat psychosis. Use in patients with severe psychotic disorders is not recommended. CYCLOSET may cause somnolence. Advise patients not to operate

heavy machinery if symptoms of somnolence occur. Concomitant use with dopamine antagonists such as neuroleptic agents is not recommended.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with CYCLOSET or any other antidiabetic drug. CYCLOSET does not increase the risk of macrovascular events.

In controlled clinical trials, adverse reactions reported in $\geq 5\%$ of patients treated with CYCLOSET, and reported more commonly than in patients treated with placebo, included nausea, fatigue, dizziness, vomiting, and headache.

Safety and effectiveness have not been established in pediatric patients.

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

Please see adjacent Brief Summary of Prescribing Information.

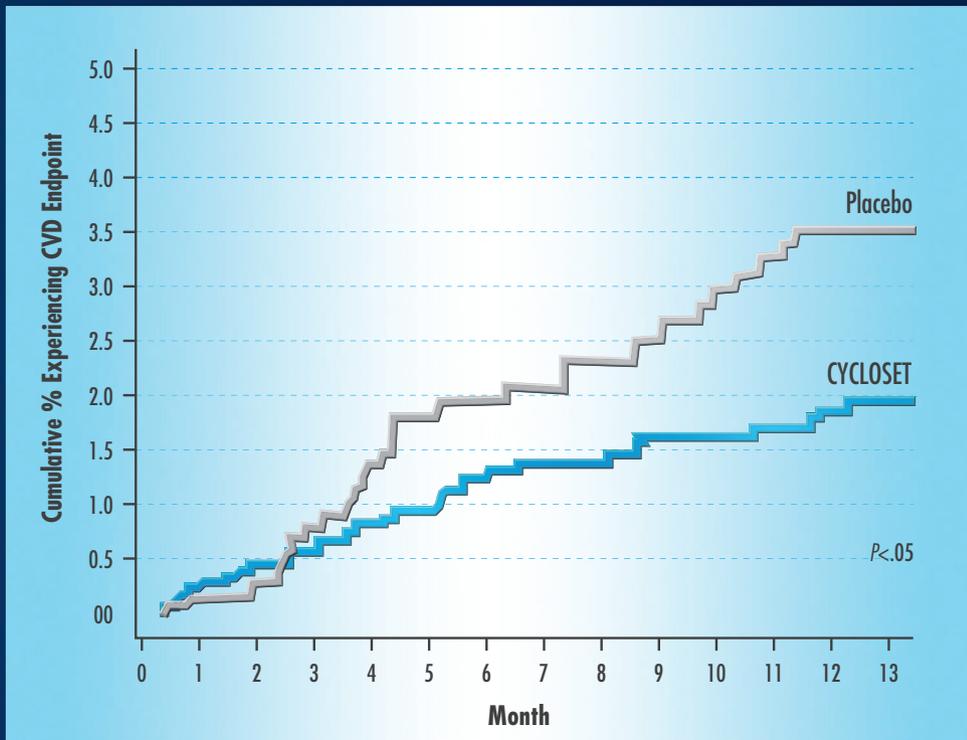
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• 0.6% to 0.9% A1C reductions seen when added to other oral agents†

Demonstrated CV safety profile‡

• 42% relative risk reduction for composite CVD endpoint§ vs placebo.
Hazard ratio=0.58 (95% CI, 0.35-0.96); $P < .05$



CYCLOSET is a dopamine receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

*Preclinical studies suggest that appropriately timed daily administration of bromocriptine, the active ingredient of CYCLOSET, may positively affect hypothalamic activities associated with insulin resistance and glucose intolerance. In clinical studies, morning administration of CYCLOSET improved glycemic control in adults with type 2 diabetes without increasing plasma insulin concentrations. The precise mechanism of action of CYCLOSET is unknown.

†Findings from a 52-week, randomized controlled trial to evaluate the safety and efficacy of CYCLOSET. Data shown are from a prospective 24-week assessment for treatment differences in the change from baseline to Week 24 in A1C among subjects with a baseline A1C $\geq 7.5\%$ (average baseline A1C of 8.3%), taking 1 or 2 OADs, and completing 24 weeks of therapy. In the intent-to-treat, LOCF population, A1C reductions in the CYCLOSET arm vs placebo were 0.5% for patients failing any OAD, 0.5% for patients failing metformin \pm OAD, 0.5% for patients failing metformin + SU \pm OAD, and 0.6% for patients failing TZD \pm OAD.

‡In a 52-week, randomized clinical trial of 3,070 patients, CYCLOSET was not associated with an increased risk for adverse cardiovascular events.

§Prespecified composite CVD endpoint of time to first MI, stroke, coronary revascularization, hospitalization for unstable angina, or hospitalization for CHF.

Reference: Data on File. Santarus, Inc.

CV=cardiovascular; CVD=cardiovascular disease; OAD=oral antidiabetic therapy; LOCF=last observation carried forward; SU=sulfonylurea; TZD=thiazolidinedione; MI=myocardial infarction; CHF=congestive heart failure.

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Please visit www.cycloset.com for more information.



Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Type 2 Diabetes Mellitus

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

1.2 Important Limitations of Use

- CYCLOSET should not be used to treat type 1 diabetes or diabetic ketoacidosis.
- Limited efficacy data in combination with thiazolidinediones
- Efficacy has not been confirmed in combination with insulin.

4 CONTRAINDICATIONS

CYCLOSET is contraindicated in

- Patients with known hypersensitivity to bromocriptine, ergot-related drugs, or any of the excipients in CYCLOSET.
- Patients with syncope/migraine. Bromocriptine increases the likelihood of a hypotensive episode among patients with syncope/migraine. Loss of consciousness during a migraine may reflect dopamine receptor hypersensitivity. CYCLOSET is a dopamine receptor agonist, and may, therefore, potentiate the risk for syncope in these patients.

• Women who are nursing their children. CYCLOSET may inhibit lactation. There are postmarketing reports of stroke in this patient population although causality has not been proven (*See Nursing Mothers (8.3)*).

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension: Hypotension, including orthostatic hypotension, can occur, particularly upon initiation of CYCLOSET therapy and with dose escalation. In a 52-week, randomized clinical trial of 3070 patients, hypotension was reported in 2.2% of patients randomized to CYCLOSET compared to 0.8% of patients randomized to placebo. Among CYCLOSET-treated patients reporting symptomatic hypotension, 98% were on at least one blood pressure medication compared to 73% on such medication in the total study population. In this trial, six CYCLOSET-treated patients (0.3%) reported an adverse event of orthostatic hypotension compared to 2 (0.2%) placebo-treated patients. All six patients were taking anti-hypertensive medications. Hypotension can result in syncope. In this trial, syncope due to any cause was reported in 1.6% of CYCLOSET-treated patients and 0.7% of placebo-treated patients (*See Adverse Reactions (6.1)*). As a precaution, assessment of orthostatic vital signs is recommended prior to initiation of CYCLOSET and periodically thereafter. During early treatment with CYCLOSET, patients should be advised to make slow postural changes and to avoid situations that could lead to serious injury if syncope was to occur. Use caution in patients taking anti-hypertensive medications.

5.2 Psychotic Disorders: In patients with severe psychotic disorders, treatment with a dopamine receptor agonist such as CYCLOSET may exacerbate the disorder or may diminish the effectiveness of drugs used to treat the disorder. Therefore, the use of CYCLOSET in patients with severe psychotic disorders is not recommended.

5.3 Somnolence: CYCLOSET may cause somnolence. In a 52-week, randomized clinical trial, 4.3% of CYCLOSET-treated patients and 1.3% of placebo-treated patients reported somnolence as an adverse event. None of these events were reported as serious and the majority of patients reported resolution of somnolence over time. Patients should be made aware of this potential side effect, particularly when initiating therapy with CYCLOSET. Patients experiencing somnolence should refrain from driving or operating heavy machinery.

5.4 Interaction with Dopamine Receptor Antagonists: Dopamine receptor antagonists, including neuroleptic agents that have dopamine D2 receptor antagonist properties (eg, Clozapine, Olanzapine, Ziprasidone), may reduce the effectiveness of CYCLOSET and CYCLOSET may reduce the effectiveness of these agents. CYCLOSET has not been studied in patients taking neuroleptic drugs. The concomitant use of CYCLOSET and dopamine receptor antagonists, including neuroleptic drugs, is not recommended.

5.5 Other Dopamine Receptor Agonists: Other dopamine receptor agonists are indicated for the treatment of Parkinson's disease, hyperprolactinemia, restless leg syndrome, acromegaly, and other disorders. The effectiveness and safety of CYCLOSET in patients who are already taking one of these other dopamine receptor agonists is unknown. Concomitant use is not recommended.

5.6 Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with CYCLOSET or any other anti-diabetic drug. In a 52-week, randomized clinical trial, CYCLOSET use was not associated with an increased risk for adverse cardiovascular events (*See Adverse Reactions (6.1)*).

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates reported in one clinical trial may not be easily compared to rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice. In the pooled CYCLOSET phase 3 clinical trials (CYCLOSET N = 2298, placebo N = 1266), adverse events leading to discontinuation occurred in 539 (24%) CYCLOSET-treated patients and 118 (9%) placebo-treated patients. This between-group difference was driven mostly by gastrointestinal adverse events, particularly nausea.

The CYCLOSET safety trial was a 52-week, placebo-controlled study that included patients treated only with diet therapy or with other anti-diabetic medications. A total of 3,070 patients were randomized to CYCLOSET (titrated to 1.6 to 4.8 mg daily, as tolerated) or placebo. The study population had a mean baseline age of 60 years (range 27-80) and 33% were 65 years of age or older. Approximately 43% of the patients were female, 68% were Caucasian, 17% were Black, 13% were Hispanic, and 1% were Asian. The mean baseline body mass index was 32 kg/m². The mean duration of diabetes at baseline was 9 years and the mean baseline HbA1c was 7.0% with a mean baseline fasting plasma glucose of 142 mg/dL. At baseline, 12% of patients were treated with diet only, 40% were treated with one oral anti-diabetic agent, 33% were treated with two oral anti-diabetic agents, and 16% were treated with insulin alone or insulin in combination with an oral anti-diabetic agent. At baseline, 76% of patients reported a history of hypercholesterolemia, 75% reported a history of hypertension, 11% reported a history of revascularization surgery, 10% reported a history of myocardial infarction, 10% reported a history of angina, and 5% reported a history of stroke. Forty-seven percent of the CYCLOSET-treated patients and 32% of the placebo-treated patients prematurely discontinued treatment. Adverse events leading to discontinuation of study drug occurred among 24% of the CYCLOSET-treated patients and 15% of the placebo-treated patients. This between-group difference was driven mostly by gastrointestinal adverse events, particularly nausea.

Table 1 summarizes the adverse events reported in ≥5% of patients treated with CYCLOSET in the phase 3 clinical trials regardless of investigator assessment of causality. The most commonly reported adverse events (nausea, fatigue, vomiting, headache, dizziness) lasted a median of 14 days and were more likely to occur during the initial titration of CYCLOSET. None of the reports of nausea or vomiting were described as serious. There were no differences in the pattern of common adverse events across race groups or age groups (<65 years old vs. ≥65 years old). In the 52-week, CYCLOSET safety trial, 11.5% of CYCLOSET-treated women compared to 3.6% of placebo-treated women reported vomiting. In this same trial, 5.4% of CYCLOSET-treated men compared to 2.8% of placebo-treated men reported vomiting.

Table 1:

Adverse Events Reported in Phase 3 Clinical Trials of CYCLOSET (≥5% of Patients and Numerically More Frequent in CYCLOSET-Treated Patients than in Placebo-Treated Patients, Regardless of Investigator Assessment of Causality*)

Monotherapy	CYCLOSET 1.6 mg – 4.8 mg	Placebo
	N (%)	N (%)
N = 159	N = 80	N = 79
Nausea	26 (32.5)	6 (7.6)
Rhinitis	11 (13.8)	3 (3.8)
Headache	10 (12.5)	7 (8.9)
Asthenia	10 (12.5)	5 (6.3)
Dizziness	10 (12.5)	6 (7.6)
Constipation	9 (11.3)	3 (3.8)
Sinusitis	8 (10.0)	2 (2.5)
Diarrhea	7 (8.8)	4 (5.1)
Amblyopia	6 (7.5)	1 (1.3)
Dyspepsia	6 (7.5)	2 (2.5)
Vomiting	5 (6.3)	1 (1.3)
Infection	5 (6.3)	4 (5.1)
Anorexia	4 (5.0)	1 (1.3)

continued

Table 1 (continued)
Adverse Events Reported in Phase 3 Clinical Trials of CYCLOSET (≥5% of Patients and Numerically More Frequent in CYCLOSET-Treated Patients than in Placebo-Treated Patients, Regardless of Investigator Assessment of Causality*)

Adjunct to Sulfonylurea (2 pooled 24 week studies)	N = 244	N = 250
Nausea	62 (25.4)	12 (4.8)
Asthenia	46 (18.9)	20 (8.0)
Headache	41 (16.8)	40 (16.0)
Flu syndrome	23 (9.4)	19 (7.6)
Constipation	24 (9.8)	11 (4.4)
Cold	20 (8.2)	20 (8.0)
Dizziness	29 (11.9)	14 (5.6)
Rhinitis	26 (10.7)	12 (4.8)
Sinusitis	18 (7.4)	16 (6.4)
Somnolence	16 (6.6)	5 (2.0)
Vomiting	13 (5.3)	8 (3.2)
Amblyopia	13 (5.3)	6 (2.4)

52-Week Safety Trial†	N = 2054	N = 1016
Nausea	661 (32.2)	77 (7.6)
Dizziness	303 (14.8)	93 (9.2)
Fatigue	285 (13.9)	68 (6.7)
Headache	235 (11.4)	84 (8.3)
Vomiting	167 (8.1)	32 (3.1)
Diarrhea	167 (8.1)	81 (8.0)
Constipation	119 (5.8)	52 (5.1)

*All randomized subjects receiving at least one dose of study drug

†The Safety Trial enrolled patients treated with diet or no more than 2 anti-diabetic medications (metformin, insulin secretagogues such as a sulfonylurea, thiazolidinediones, alpha glucosidase inhibitors, and/or insulin)

Hypoglycemia

In the monotherapy trial, hypoglycemia was reported in 2 CYCLOSET-treated patients (3.7%) and 1 placebo-treated patient (1.3%). In the add-on to sulfonylurea trials, the incidence of hypoglycemia was 8.6% among the CYCLOSET-treated patients and 5.2% among the placebo-treated patients. In the CYCLOSET safety trial, hypoglycemia was defined as any of the following: 1) symptoms suggestive of hypoglycemia that promptly resolved with appropriate intervention, 2) symptoms with a measured glucose <60 mg/dL or 3) measured glucose below 4.9 mg/dL regardless of symptoms. In the 52-week safety trial, the incidence of hypoglycemia was 6.9% among the CYCLOSET-treated patients and 5.3% among the placebo-treated patients. In the safety trial, severe hypoglycemia was defined as an inability to self-treat neurological symptoms consistent with hypoglycemia that occurred in the setting of a measured blood glucose <50 mg/dL (or evidence of prompt resolution of these symptoms with administration of oral carbohydrates, subcutaneous glucagon, or intravenous glucose if blood glucose was not measured). In this trial, severe hypoglycemia was reported among 0.5% of CYCLOSET-treated patients and 1% of placebo-treated patients.

Syncope

In combined phase 2 and 3 clinical trials, syncope was reported in 1.4% of the 2,500 CYCLOSET-treated patients and 0.6% of the 1,454 placebo-treated patients. Among the 3,070 patients studied in the 52-week safety trial, 33 CYCLOSET-treated patients (1.6%) and 7 placebo-treated patients (0.7%) reported an adverse event of syncope. The cause of syncope is not known in all cases (*See Warnings and Precautions (5.1)*). In this trial, electrocardiograms were not available at the time of these events, but an assessment of routine electrocardiograms obtained during the course of the trial did not identify arrhythmias or QTc interval prolongation among the CYCLOSET-treated patients reporting syncope.

Central Nervous System

In the 52-week safety trial, somnolence and hypoesthesia were the only adverse events within the nervous system organ class that were reported at a rate <5% and ≥1% and that occurred at a numerically greater frequency among CYCLOSET-treated patients (CYCLOSET 4.3% vs. Placebo 1.3% for somnolence; CYCLOSET 1.4% vs. Placebo 1.1% for hypoesthesia). **Serious Adverse Events and Cardiovascular Safety**
The primary endpoint of the 52-week safety trial was the occurrence of all serious adverse events. A secondary endpoint was the occurrence of the composite of myocardial infarction, stroke, coronary revascularization, hospitalization for angina, and hospitalization for congestive heart failure.

All serious adverse events and cardiovascular endpoints were adjudicated by an independent event adjudication committee. Serious adverse events occurred in 176/2054 (8.5%) CYCLOSET-treated patients and 98/1016 (9.6%) placebo-treated patients. The hazard ratio comparing CYCLOSET to placebo for the time to first occurrence of a serious adverse event was 1.02 (upper bound of one-sided 96% confidence interval, 1.27). None of the serious adverse events grouped by System-Organ Class occurred more than 0.3 percentage points higher with CYCLOSET than with placebo. The composite cardiovascular endpoint occurred in 31 (1.5%) CYCLOSET-treated patients and 30 (3.0%) placebo-treated patients. The hazard ratio comparing CYCLOSET to placebo for the time-to-first occurrence of the prespecified composite cardiovascular endpoint was 0.58 (two-sided 95% confidence interval, 0.35 – 0.96). Therefore, the incidence of this composite endpoint was not increased with CYCLOSET relative to placebo.

6.2 Postmarketing Experience

The active agent in CYCLOSET (bromocriptine mesylate) has been used in other formulations and often multiple times per day to treat hyperprolactinemia, acromegaly, and Parkinson's disease. The following adverse reactions have been identified during postapproval use of bromocriptine mesylate for these indications, generally at doses higher than those approved for the treatment of type 2 diabetes. Because these reactions 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.

Hallucinations

Hallucinations and mental confusion including delusions have been reported with bromocriptine. To date, there have been no reported cases of hallucinations or delusions among CYCLOSET-treated patients (N = 2500) in combined Phase 2 and 3 clinical trials of CYCLOSET.

Fibrotic-Related Complications

Fibrotic complications, including cases of retroperitoneal fibrosis, pulmonary fibrosis, pleural effusion, pleural thickening, pericarditis and pericardial effusions have been reported. These complications do not always resolve when bromocriptine is discontinued. Among several studies investigating a possible relation between bromocriptine exposure and cardiac valvulopathy, some events of cardiac valvulopathy have been reported, but no definitive association between bromocriptine mesylate use and clinically significant (moderate to severe) cardiac valvulopathy could be concluded.

To date, there have been no reported cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis or pericardial effusions among the CYCLOSET-treated patients (N=2500) in combined Phase 2 and 3 controlled clinical trials of CYCLOSET. There was one unconfirmed case (0.04% event rate) of an adverse event of pulmonary fibrosis classified as non-serious in a CYCLOSET-treated patient.

No cases of cardiac valvulopathy have been reported in any of the clinical studies to date with CYCLOSET.

Psychotic and Psychiatric Disorders

Psychotic disorders have been reported with bromocriptine. Additionally, pathological gambling has been reported with bromocriptine used to treat patients with Parkinson's disease. To date, there have been no reported cases of psychoses or pathological gambling among the CYCLOSET-treated patients (N=2500) in combined Phase 2 and 3 controlled clinical trials of CYCLOSET.

Stroke

The indication for use of bromocriptine for inhibition of postpartum lactation was withdrawn based on postmarketing reports of stroke. Causality of bromocriptine use and the occurrence of stroke in this patient population has not been proven. Based on the CYCLOSET clinical trials, there is no evidence of increased risk for stroke when CYCLOSET is used to treat type 2 diabetes.

Neuroleptic-like Malignant Syndrome

A neuroleptic-like malignant syndrome (manifested by high fever and increase in creatinine phosphokinase) has been reported upon cessation of bromocriptine treatment in patients with advanced Parkinson's disease or patients with secondary Parkinsonism. To date, there have been no reported cases of neuroleptic-like malignant syndrome in combined Phase 2 and 3 controlled clinical trials of CYCLOSET, including the Safety Trial (N = 2500). In the CYCLOSET Safety Trial, there were no reports of neuroleptic-like malignant syndrome during the 30 days of follow-up after cessation of CYCLOSET (N = 2054).

7 DRUG INTERACTIONS

The active ingredient in CYCLOSET, bromocriptine mesylate, is highly bound to serum proteins. Therefore, CYCLOSET may increase the unbound fraction of other concomitantly used highly

protein-bound therapies (eg, salicylates, sulfonamides, chloramphenicol and probenecid), which may alter their effectiveness and risk for side effects.

CYCLOSET is a dopamine receptor agonist. Concomitant use of dopamine receptor antagonists, such as neuroleptics (eg, phenothiazines, butyrophenones, thioxanthenes), or metoclopramide may diminish the effectiveness of CYCLOSET and CYCLOSET may diminish the effectiveness of these therapies. The concurrent use of CYCLOSET with these agents has not been studied in clinical trials and is not recommended (*See Warnings and Precautions (5.4)*).

CYCLOSET in combination with ergot-related drugs may cause an increase in the occurrence of ergot-related side effects such as nausea, vomiting, and fatigue, and may also reduce the effectiveness of these ergot therapies when used to treat migraine. The concurrent use of these ergot agents within 6 hours of CYCLOSET dosing is not recommended.

CYCLOSET is extensively metabolized by the liver via CYP3A4. Therefore, potent inhibitors or inducers of CYP3A4 may increase or reduce the circulating levels of CYCLOSET, respectively. Use caution when co-administering drugs that are strong inhibitors, inducers, or substrates of CYP3A4 (eg, azole antimycotics, HIV protease inhibitors) (*See Pharmacokinetics (12.3)*).

There are postmarketing reports of hypertension and tachycardia when bromocriptine was co-administered with sympathomimetic drugs (eg, phenylpropanolamine and isometheptene) in postpartum women. There are limited clinical trial data supporting the safety of co-administering sympathomimetic drugs and CYCLOSET for more than 10 days. Therefore, concomitant use of these agents with CYCLOSET for more than 10 days duration is not recommended. Also, there are limited clinical trial data supporting the safety of selective 5-hydroxytryptamine1B (5-HT1B) agonists (eg, sumatriptan) used concurrently with CYCLOSET and the concomitant use of these agents with CYCLOSET should be avoided.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Two strains of pregnant rats were dosed orally with 3, 10, and 30 mg/kg/day (up to 72 times the human 4.8 mg daily dose, based on mg/m² comparison) from gestation day 6-15 and with a single dose of 10 mg/kg on gestation day 5. Implantation was inhibited at 10 and 30 mg/kg/day (2.4 and 7.2 times the human 4.8 mg daily dose, based on mg/m² comparison). When rats were dosed with 3, 10, and 30 mg/kg/day from gestation day 8-15 there was an increase in resorptions at 10 and 30 mg/kg. These effects were probably due to the dependence of implantation and the maintenance of gestation on prolactin in the rat and are not relevant for humans in which these events are not dependent on prolactin but on luteinizing hormone. There was no evidence of teratogenic effects in the rat.

In a small study in macaque monkeys given oral doses of 2 mg/kg/day (10 times the human 4.8 mg daily dose, based on mg/m² comparison) during organogenesis no embryotoxic or teratologic effects were observed.

When male rats given oral doses of 2, 10 or 50 mg/kg/day (up to 120 times the human 4.8 mg daily dose, based on mg/m² comparison) were mated with untreated females, there was a slight increase in pup loss in the 10 and 50 mg/kg/day groups (24-120 times the human 4.8 mg daily dose, based on mg/m² comparison).

In two strains of pregnant rabbits treated from gestation day 6-18 with oral doses of 3, 10, 30, 100, and 300 mg/kg/day (up to 1400 times the human 4.8 mg daily dose, based on mg/m² comparison) there was maternal toxicity and embryolethality at doses ≥10 mg/kg/day (48 times the human 4.8 mg daily dose, based on mg/m² comparison). Low incidences of fetal abnormalities were observed at maternally toxic doses of 100-300 mg/kg/day (480-1400 times the human 4.8 mg daily dose, based on mg/m² comparison). There were no treatment-related fetal abnormalities at doses ≤30 mg/kg/day (140 times the human 4.8 mg daily dose, based on mg/m² comparison). Implantation was not affected in rabbits treated from gestation day 1-6 with oral doses of 100-300 mg/kg/day (480-1400 times the human 4.8 mg daily dose, based on mg/m² comparison).

Studies in pregnant women have not shown that bromocriptine increases the risk of abnormalities when administered during pregnancy. Information concerning 1,276 pregnancies in women taking bromocriptine has been collected. In the majority of cases, bromocriptine was discontinued within the first 8 weeks of pregnancy (mean 29 days); however, 8 patients received the drug continuously throughout pregnancy. The mean daily dose for all patients was 5.8 mg (range 1-40 mg). Of these 1,276 pregnancies, there were 1,088 full-term deliveries (4 stillborn), 145 spontaneous abortions (11.4%), and 28 induced abortions (2.2%). Twelve extrauterine gravidities and 3 hydatidiform moles (twice in the same patient) caused early termination of pregnancy. These data compare favorably with the abortion rate (11.25%) cited for pregnancies induced by clomiphene citrate, menopausal gonadotropin, and chorionic gonadotropin. Although spontaneous abortions often go unreported, especially prior to 20 weeks of gestation, their frequency has been estimated to be 10-15% in the general population. The incidence of birth defects in the general population ranges from 2% to 4.5%. The incidence of birth defects in 1,109 live births from patients receiving bromocriptine was 3.3%. There is no suggestion that bromocriptine contributed to the type or incidence of birth defects in this group of infants.

A review of 4 different multicenter surveillance programs analyzed 2,351 pregnancies of 2,185 women treated with bromocriptine. In 563 children born of these women and followed for a minimum of 3-12 months, there was no suggestion of any adverse effect of intrauterine exposure to bromocriptine on post-natal development. Most (675%) women had taken bromocriptine for 2-8 weeks and at 5-10 mg per day. Among 86 women having 93 pregnancies and treated with bromocriptine throughout pregnancy or from week 30 of pregnancy onwards (mostly for treatment of prolactinoma), there was only 1 spontaneous abortion. Similar results have been obtained in a Japanese hospital survey of 442 children born to 434 patients treated with bromocriptine during pregnancy and followed for at least one year. Because the studies in humans cannot rule out the possibility of harm, CYCLOSET should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

CYCLOSET is contraindicated in women who are nursing their children. CYCLOSET contains bromocriptine which inhibits lactation. The indication for use of bromocriptine for inhibition of postpartum lactation was withdrawn based on postmarketing reports of stroke in this setting (*See Contraindications (4) and Adverse Reactions (6.2)*).

8.4 Pediatric Use

The safety and effectiveness of CYCLOSET in pediatric patients have not been established.

8.5 Geriatric Use

In the two clinical trials of CYCLOSET add-on to sulfonylurea therapy and in the monotherapy trial, a total of 54 patients randomized to CYCLOSET were ≥65 years old. In the 52-week safety trial, 601 of the 2,054 CYCLOSET-treated patients (29%) were ≥65 years old. No overall differences in safety or effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. (*See Clinical Studies (14.1)*).

10 OVERDOSAGE

With another formulation of bromocriptine mesylate, the most commonly reported signs and symptoms associated with acute overdose were nausea, vomiting, constipation, diaphoresis, dizziness, pallor, severe hypotension, malaise, confusion, lethargy, drooping eyelids, delusions, hallucinations, and repetitive yawning. The lethal dose has not been established.

Treatment of overdose consists of removal of the drug by emesis (if conscious), gastric lavage, activated charcoal, or saline cathartics. Careful supervision and recording of fluid intake and output is essential. Hypotension should be treated by placing the patient in the Trendelenburg position and administering intravenous fluids. If satisfactory relief of hypotension cannot be achieved by using the above measures to their fullest extent, vasopressors should be considered.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 74-week dietary study in mice at doses up to 50 mg/kg/day (56 times the human 4.8 mg daily dose, based on mg/m² comparison) there was no evidence of tumorigenicity.

In a 100-week dietary carcinogenicity study in rats at doses of 1.8, 9.9 and 44.5 mg/kg/day (up to 106 times the human 4.8 mg daily dose, based on mg/m² comparison) there was a significant increase in the incidence of malignant uterine neoplasms in the mid- and high dose groups (24-106 times the human 4.8 mg daily dose, based on mg/m² comparison). The increase in uterine neoplasms was probably due to the inhibition of prolactin-stimulated progesterone secretion resulting in estrogen domination and endometrial stimulation in the aging rat. Because prolactin does not play a role in human progesterone production this finding is unlikely to be clinically relevant.

Mutagenicity

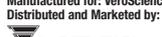
Bromocriptine was not mutagenic in the *in vitro* Ames bacterial mutation assay, the V79 Chinese hamster fibroblast mutagenicity test, in the *in vivo* bone marrow micronucleus test in mice and in the *in vivo* Chinese hamster bone marrow chromosomal aberration test.

Impairment of Fertility

In female rats treated with oral doses of 1 and 3 mg/kg (2 to 7 times the human 4.8 mg daily dose, based on mg/m² comparison) from 2 weeks prior to mating through 2 weeks post mating or throughout lactation there was no effect on fertility. Postnatal pup weight gain was reduced dose-dependently in treated groups probably due to lactation inhibition.

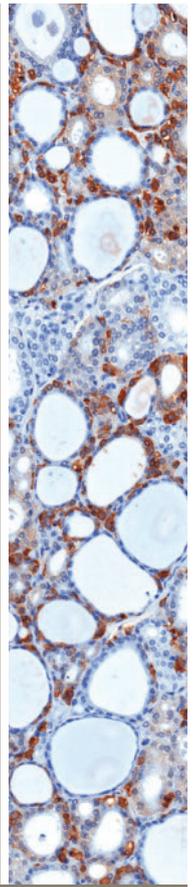
In male rats treated with oral doses of 2, 10, and 50 mg/kg/day (up to 120 times the human 4.8 mg daily dose, based on mg/m² comparison) there was no effect on mating or fertility.

Manufactured for: VerScience, LLC, Tiverton, RI. Distributed and Marketed by: Santarus, Inc., San Diego, CA.



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The first endocrine-specific Practice Improvement Module (PIM), is a Web-based, self-evaluation tool designed to assist you in evaluating your care of patients with thyroid nodules. Using data from your practice, including patient charts, our PIM allows you to:

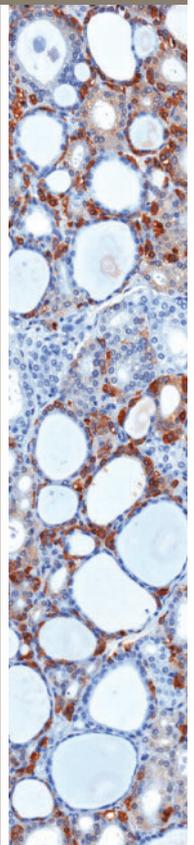
- 1) Evaluate your performance in evaluating thyroid nodules;
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Evaluation of Thyroid Nodules PIM Task Force

Erik Alexander, MD | Carol Greenlee, MD, FACP, FACE | Susan Mandel, MD, MPH

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Mum on

Menopause

New Surveys Show Many Women with Symptoms Are Not Receiving Treatment and Some Don't Even Want to Talk About It

Many women suffering from menopausal symptoms are miscommunicating with their doctors or not talking at all about possible treatments, according to recent surveys from The Endocrine Society's patient education resource, the Hormone Health Network. The nationally representative surveys of 810 women, ages 45 to 60 years, and of 424 primary care providers about menopause and related health issues were conducted in an effort to better understand how menopausal women are faring 10 years after researchers halted the Women's Health Initiative's clinical trials on hormone therapy.

According to the women's survey results, half of women in this age range are experiencing symptoms of menopause

and most say at least one symptom is moderate to severe. Of women experiencing menopausal symptoms, a majority, about 70 percent, say the symptoms have negatively affected their quality of life, and 7 percent regard the impact as serious. Yet, just over a quarter of those with symptoms report receiving any type of treatment. White women are twice as likely to be treated as African Americans.

The survey also finds that many women are not seeking advice from their health care providers about different options to treat their symptoms, even though they say they feel comfortable talking to their primary health care providers or gynecologists about menopause in general. Three percent of the women experiencing symptoms say their provider referred them to an endocrinologist for treatment. The comfort level of talking to doctors, however, varies across demographic groups. Women with a college degree and high incomes are significantly more likely to say they are very at ease with physicians than their non-college graduate



and lower-income counterparts. Eighty percent of the high earners say they are comfortable compared to 56 percent of the low-income women.

In the survey of OB/GYNs, family doctors, and internists, 90 percent of the physicians say they are comfortable talking to patients about menopause, but 20 percent fewer think the patients feel the same way. Data also suggest that women may not be talking about all of their symptoms with their doctors—particularly male physicians.

Although 55 percent of female physicians say it is very common

for women to talk to them about a lack of sexual desire as a result of menopause, only 38 percent of male physicians say the same. Nine in 10 doctors say women are more forthcoming when talking about hot flashes but shy away from talking about other symptoms.

“Most of us in this field pride ourselves on communicating well with patients,” says Cynthia Stuenkel, an endocrinologist specializing in menopause at the University of California, San Diego. “On the other hand, I know that some clinicians have intentionally washed their hands of

Only **27%**
have received treatment
for menopausal symptoms

survey. Women are uncomfortable with the risks and therefore unwilling to consider hormone treatment, according to doctors. More than half of them believe patients are confused about the therapy.

“Left with the impression that hormone therapy isn’t a safe option, far too many women are suffering in silence thinking they have no options for symptom relief,” says Stuenkel. “There are a number of lifestyle, over-the-counter, and non-hormonal prescription therapies. We know that for some women, however, hormonal therapy provides the most effective relief for severe menopausal symptoms.”

More than a third of the women surveyed get their information from TV, magazines, and other media, and another third from family and friends, followed by 20 percent who use the Internet. However, nearly half of the women say the information on menopause is often confusing and they don’t know which sources to trust.

At least 61 percent of the physicians surveyed say that consensus on the effectiveness of various treatments is sorely needed. Adds Stuenkel: “Women deserve to know that the experts do agree about the safety of hormone therapy for young, healthy women close in time to menopause when symptoms are likely most severe.”

Key Findings

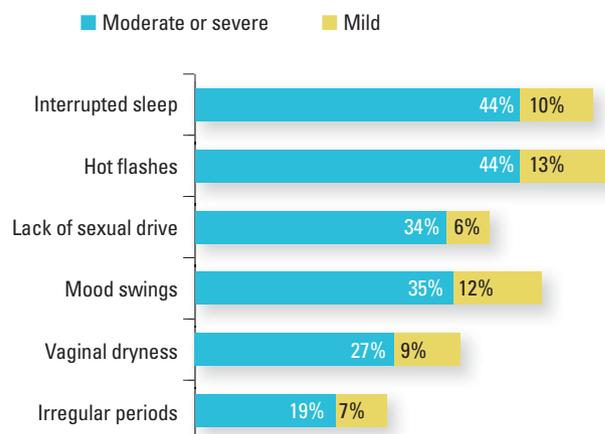
- Half of women 45 to 60 years old (50 percent) are experiencing symptoms of menopause such as hot flashes, interrupted sleep, mood swings, and lack of sexual desire. Among these women, 69 percent say menopausal symptoms negatively affect their quality of life.
- One-third of women 45 to 60 years of age are experiencing moderate-to-severe symptoms such as interrupted sleep (34 percent) and hot flashes (31 percent). More than one in four women (28 percent) are experiencing a moderate or severe lack of sexual desire.
- A majority of women currently experiencing symptoms (72 percent) have not received treatment for their symptoms. The majority say they have not talked with their doctor or provider about hormone therapy (62 percent) or other non-hormonal treatment options (61 percent) for their symptoms. Half have not spoken with their provider about lifestyle changes that could relieve symptoms.
- About half of women 45 to 60 years old are unfamiliar with hormone therapy. Only 1 in 10 (11 percent) have a positive impression of hormone therapy compared to 42 percent who have a negative impression.
- More than 4 in 10 say information about managing and treating symptoms of menopause is confusing or that they are not sure whom to trust.

Many Women Experience Moderate to Severe Symptoms of Menopause

Two-thirds of respondents say they have experienced symptoms of menopause, and half are currently suffering symptoms. Nearly half have hot flashes and interrupted sleep. A third experience mood swings and lack of sexual desire. About one-fourth report vaginal dryness and irregular periods.

Certain symptoms of menopause, such as interrupted sleep and hot flashes, are felt more severely than others. One-third of women say their symptom of interrupted sleep is severe or moderate; another third say the same about hot flashes. Twenty-eight percent of women describe their lack of sexual desire as severe or moderate.

Percentage of Women Currently Experiencing Menopause Symptoms

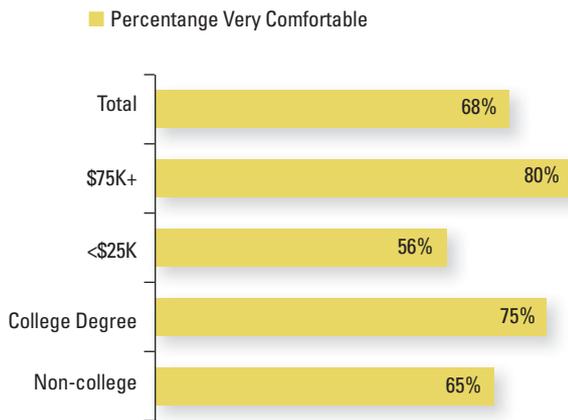


the entire menopausal symptom relief hormone therapy package because of frustration with the controversies about hormone therapy and conflicting expert opinions about the best approach to therapy.”

The women’s survey confirms that many women are unfamiliar with treatment options. Less than one-fourth of women had considered hormone therapy to treat symptoms. Just 17 percent reported receiving the therapy to relieve hot flashes and sleep disturbance. Nearly half of the participants had negative impressions of hormone therapy and 62 percent expressed concern about side effects such as breast cancer, blood clots, and heart disease.

Doctors expressed similar observations in the physicians’

How Comfortable Are Women Talking to their Primary Health Care Provider or OB/GYN about Menopause?

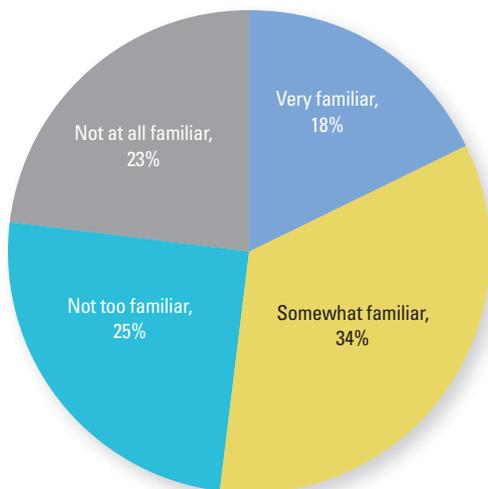


Lack of Familiarity with Hormone Therapy

Less than one-fourth of women (23 percent) have considered hormone therapy to treat menopausal symptoms, and 17 percent report having received the treatment. The most common reasons for using hormone therapy are to relieve hot flashes (66 percent of users) and sleep disturbances (50 percent of users).

Although 52 percent of women are very or somewhat familiar with hormone therapy, 48 percent are unfamiliar with the treatment. This lack of familiarity could be an impediment to starting conversations with their providers on the topic. Those with a high school degree or less education and lower incomes, under \$25,000, are more likely to be unfamiliar with hormone therapy than others.

How Familiar Are Women with Hormone Therapy?

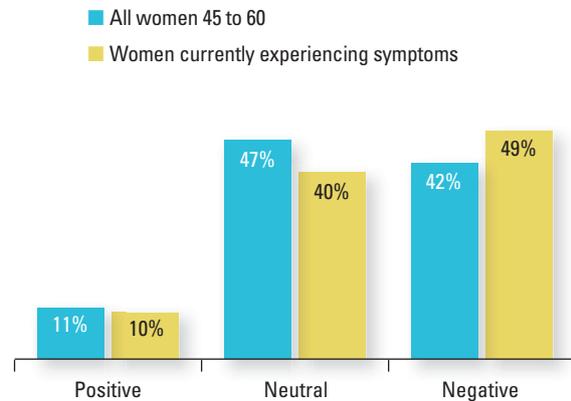


Mixed Impressions of Hormone Therapy

Almost half of women ages 45 to 60 years (47 percent) have a neutral impression of hormone therapy, probably due to a lack of familiarity. Among others, impressions of hormone therapy tend to be

negative, with 11 percent expressing a positive opinion of hormone therapy compared to 42 percent who have a negative impression.

Impression of Hormone Therapy



Many women (62 percent) express concern about side effects of hormone therapy. Seventeen percent say they are not concerned, and 20 percent do not know enough to form an opinion.

From The Endocrine Society and the Health Hormone Network.

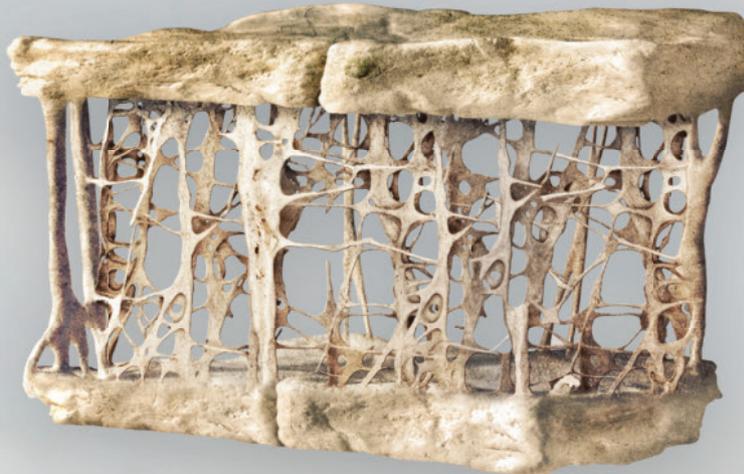
ON POINT: The Menopause Map

The Endocrine Society and the Hormone Health Network recently released the “Menopause Map,” a Web-based interactive tool designed to facilitate communication between women and their doctors about the options available to treat menopause symptoms. Patients can go online to www.hormone.org/MenopauseMap and answer a series of questions about their personal health history and menopausal symptoms. Based on a woman’s individual symptoms, medical history, and preferences, the tool guides her to a personalized page outlining treatment options that might be right for her. The Map also provides a list of focused questions that women can raise with their doctors.



**\$50/MONTH
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HER FIRST OSTEOPOROTIC FRACTURE COULD LEAD TO ANOTHER



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).

Find out how FORTEO helps form new bone at www.FORTEOhcp.com

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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.**

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
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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.rfi.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

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

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 AND USAGE

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. 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.

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%), Gastrointestinal 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 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 ≥ 5 mg 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 \geq 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 \geq 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 T_{1/2} 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.

06/15/2012

PLEASE SEE FULL PRESCRIBING INFORMATION OR WWW.FORTEOHCP.COM FOR ADDITIONAL INFORMATION.

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Society Recommends Revisions to 2013 Medicare Physician Fee Schedule

By Meredith Dyer

The Endocrine Society recently submitted comments to the Centers for Medicare & Medicaid Services (CMS) on the 2013 Medicare Physician Fee Schedule proposed rule. CMS recommends changes to physician payment policies for the upcoming year and sets the rates at which endocrinologists will be reimbursed for services provided to Medicare beneficiaries. The comment letter, which can be downloaded at www.endo-society.org/advocacy/legislative/letters/, focuses on several areas of particular importance to endocrinologists. Here we present an overview of the Society's comments on CMS' recommendations for the 2013 Medicare physician fee schedule.

Quality Measures

CMS recommends the inclusion of 264 individual quality measures and 26 measure groups in the 2013 Physician Quality Reporting System (PQRS), a reporting program that uses incentive payments and payment adjustments to encourage health care professionals to use quality measures to report information to the agency. CMS also proposes to align PQRS electronic health record-based reporting measures with those under the Electronic Health Records (EHR) incentive program, another initiative aimed at increasing adoption of health information technology. The Society supports efforts to align these quality reporting programs to reduce the administrative burden that physicians and staff face in reporting quality measures to multiple programs. The Society also supports new individual osteoporosis measures that endocrinologists can use to meet the PQRS requirements and recommends using

these as an osteoporosis measures group to encourage post-fracture care coordination.

Value-based Payment Modifier

CMS also provides details on the implementation of a value-based payment modifier (VBM), a payment policy included in the Affordable Care Act to reward physicians who improve quality and reduce costs and to penalize those who do not. To be applied to group practices of 25 or more, the first VBM payments would be made in 2015 and would be based on quality and cost measures reported in 2013. To avoid a penalty in 2015, groups would need to successfully participate in a PQRS group reporting option in 2013. Groups that do not participate in PQRS in 2013 would receive a 1 percent payment reduction in 2015. Groups that successfully meet the PQRS requirements could opt out of the VBM and receive neither a positive nor a negative payment adjustment in 2015 or could choose to have the value-based payment modifier applied and potentially receive a payment increase.

The Society opposes basing the initial VBM on 2013 measures, recommending a delay until 2014 to allow physicians to become better educated about the VBM. This delay would also provide CMS with additional time to work out a number of details that remain unclear.

e-Prescribing

CMS proposes to include a new group practice reporting option under the e-prescribing quality improvement program that would apply to practices with 2 to 24 eligible professionals. To meet the e-prescribing

criteria, practices would need to report 225 electronic prescriptions to qualify for a 0.5 percent incentive payment and to avoid a 1.5 percent penalty on Medicare Part B claims. The Society believes that reporting 225 electronic prescriptions is too burdensome and recommends a tiered approach that would reduce the threshold for smaller practices and make it easier for providers to meet the program requirements.

CMS also proposes to add two new hardship exemptions for the e-prescribing program that would allow eligible professionals or group practices who demonstrate an intent to participate in the EHR quality improvement program, or who successfully do so, to avoid the 1.5 percent e-prescribing penalty in 2013. The Society appreciates CMS' willingness to include additional hardship exemptions that will allow providers to avoid the 2013 e-prescribing penalty, but believes that a reasonable amount of time to report these exemptions is necessary. In the comment letter, the Society requests that CMS provide at least 90 days for eligible professionals to report a new hardship exemption after the physician fee schedule has been finalized.

Transitional Care Management

CMS proposes to cover transitional care management services for the coordination of a patient's care in the 30 days following a discharge from a hospital or nursing facility. The Society supports payment for transitional care management services and other non-face-to-face care coordination services, and encourages CMS to evaluate additional opportunities to compensate physicians for the time they spend providing these necessary services.

CMS is expected to finalize the 2013 Medicare physician fee schedule in early November. An overview of the final rule will be detailed in a future edition of *Endocrine Insider*. ■

Dyer is the manager of health policy at The Endocrine Society.

RESEARCH BRIEFS

► The following studies will be published in Endocrine Society journals. Before print, they are edited and posted online in each journal's Early Release section. You can access the journals via www.endo-society.org.

Endocrinology

► **Pancreatic PYY is a VDR target gene, further linking vitamin D signaling and energy metabolism regulation.**

Choi M, Ozeki J, Hashizume M, Kato S, Ishihara H, Makishima M. *Vitamin D receptor activation induces peptide YY transcription in pancreatic islets.*

► **Three subpopulations of β cells are seen in mice expressing the green fluorescent protein under the control of the mouse insulin I gene promoter.**

Katsuta H, Aguayo-Mazzucato C, Katsuta R, et al. *Subpopulations of GFP-marked mouse pancreatic β -cells differs in size, granularity, and insulin secretion.*

► **Apo AIV uses a CCK-dependent system and vagal nerves to relay its satiation signal to the rodent hindbrain.**

Lo CC, Langhans W, Georgievsky M, et al. *Apolipoprotein AIV requires cholecystokinin and vagal nerves to suppress food intake.*

► **Serum and ovarian chemerin levels are elevated in a 5α -dihydrotestosterone-induced rat PCOS model.**

Wang Q, Kim JY, Xue K, Liu J-y, Leader A, Tsang BK. *Chemerin, a novel regulator of follicular steroidogenesis and its potential involvement in polycystic ovarian syndrome.*

► **Disruption of the leptin gene in Sprague Dawley rats leads to increased body weight, hyperinsulinemia, glucose intolerance, immunosuppression, and in-**

creased bone mass.

Vaira S, Yang C, McCoy A, et al. *Creation and preliminary characterization of a leptin knockout rat.*

The Journal of Clinical Endocrinology & Metabolism

► **Maternal height, adiposity, and serum vitamin D directly predict fetal femur size.**

Ioannou C, Javaid MK, Mahon P, et al. *The effect of maternal vitamin D concentration on fetal bone.*

► **In boys with Klinefelter syndrome, CNP production and clearance are increased, which may explain their overgrowth.**

Olney RC, Prickett TCR, Espiner EA, Ross JL. *C-type natriuretic peptide (CNP) levels are altered in boys with Klinefelter syndrome.*

► **Male-to-female transsexuals have a female-typical infundibular NKB system.**

Taziaux M, Swaab DF, Bakker J. *Sex differences in the neurokinin B system in the human infundibular nucleus.*

► **The BRAF V600E mutation is associated with lymph node metastases, stage, extrathyroidal extension, tumor size, male gender, multifocality, absence of capsule, classic PTC, and tall cell variant PTC.**

Li C, Lee KC, Schneider EB, Zeiger MA. *BRAF V600E mutation and its association with clinic-pathologic features of papillary thyroid cancer: A meta-analysis.*

► **As with seasonally obese animals, human BMI is linked with the time difference between the peak releases of prolactin and cortisol.**

Roelfsema F, Pijl H. *Phase difference between serum prolactin and cortisol rhythms is related to body mass index in humans.*

Molecular Endocrinology

► **Computational screening platforms can be used to create AR antagonists that can be used in CRPC.**

Shen HC, Shanmugasundaram K, Simon NI, et al. *In silico discovery of androgen receptor antagonists with activity in castration-resistant prostate cancer.*

► **The plasma membrane expression level of gonadotropin-releasing hormone receptor regulates the interpretation of the GnRH signal by gonadotropes.**

Stewart MD, Deng JM, Stewart CA, et al. *Mice harboring Gnrhr E90K, a mutation that causes protein misfolding and hypogonadotropic hypogonadism in humans, exhibit testis size reduction and ovulation failure.*

► **In utero exposure to high fat alters the fetal thyroid axis and sets the stage for obesity in adulthood.**

Suter MA, Sangi-Haghpeykar H, Showalter L, et al. *Maternal high fat diet modulates the fetal thyroid axis and thyroid gene expression in a non-human primate model.*

► **Lowering glucose substrate and inhibiting pyruvate dehydrogenase may augment adjuvant therapies for ER-positive breast cancer.**

O'Mahony F, Razandi M, Pedram A, Harvey BJ, Levin ER. *Estrogen modulates metabolic pathway adaptation to available glucose in breast cancer cells.*

► **20-hydroxyeicosatetraenoic acid may be a potential new drug target for hypertension and hyperglycemia.**

Lai G, Wu J, Liu X, Zhao Y. *20-HETE induces hyperglycemia through the cAMP/PKA-PhK-GP pathway.* ■

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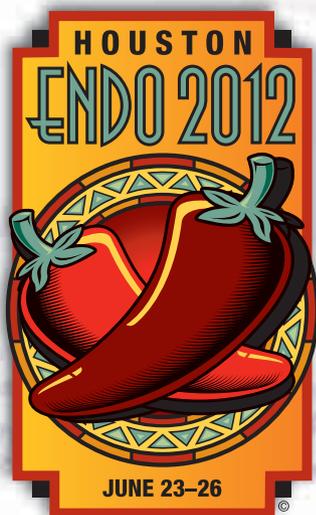
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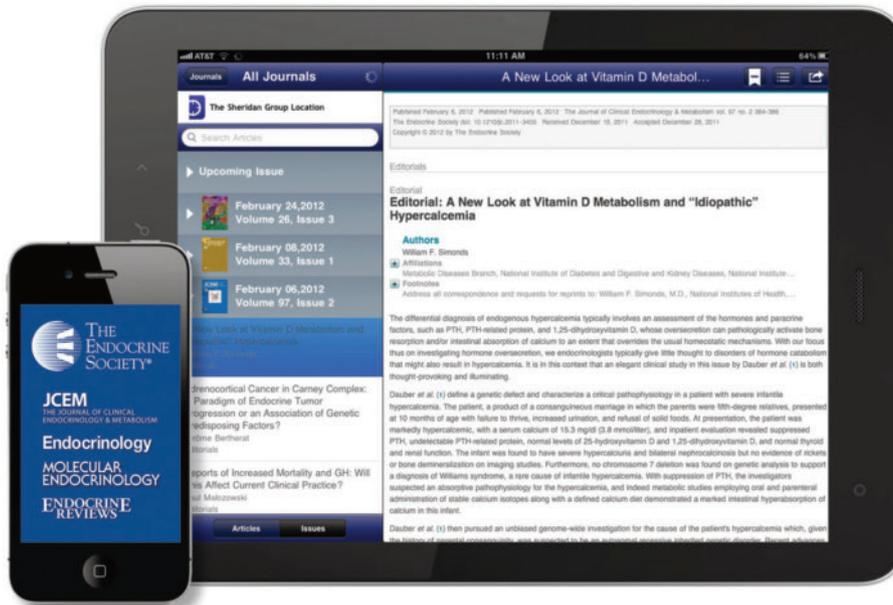


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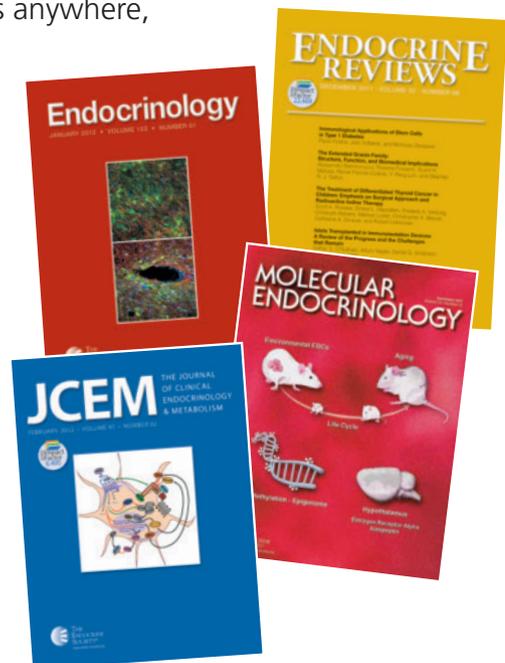
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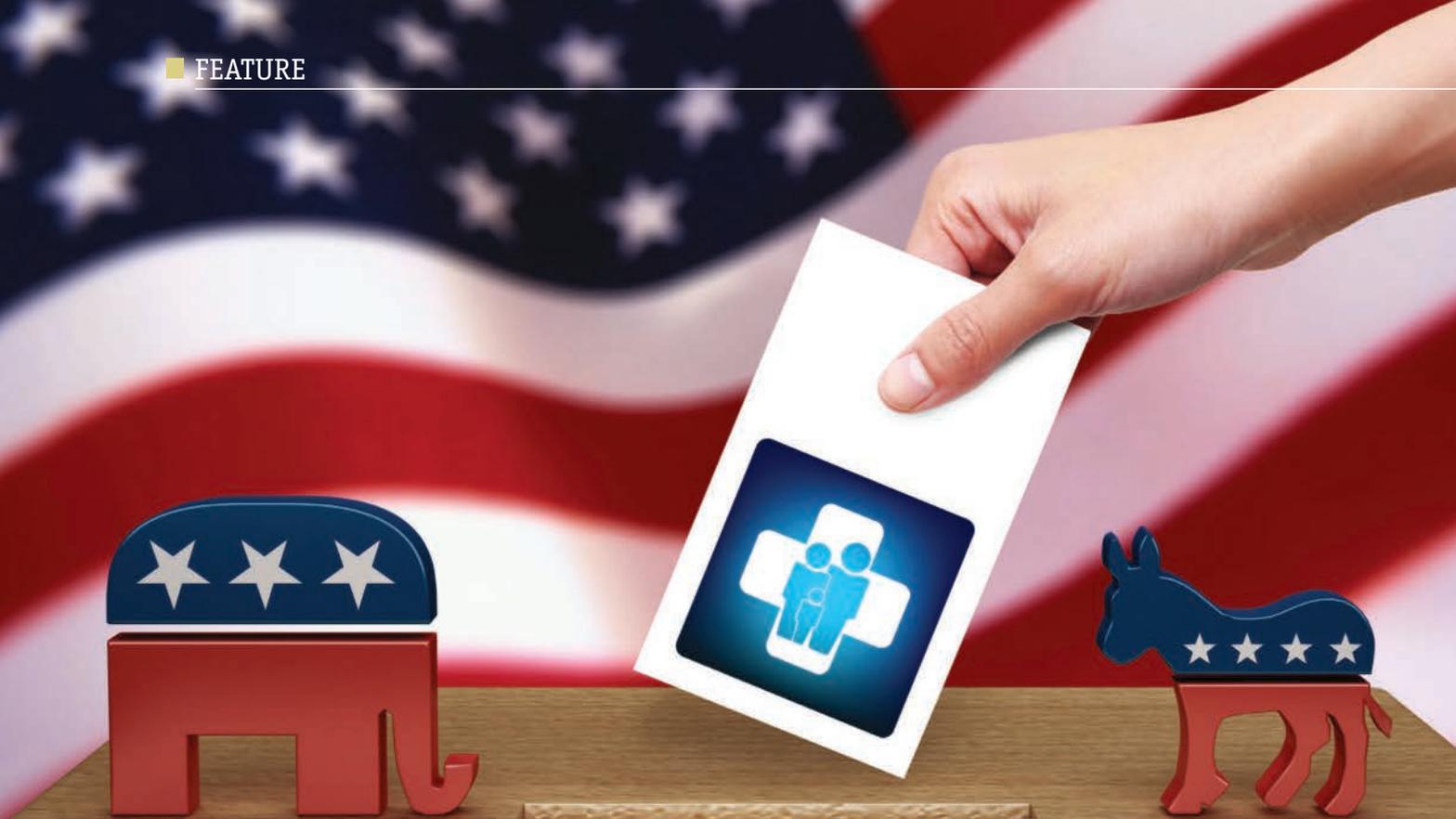
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Casting Your VOTE for Quality Health Care

By Sarah Zielinski

As the country's electorate prepares to cast ballots for the U.S. President, some health care advocates may still be weighing which political party would best serve their needs. Health spending accounted for nearly a fifth of the U.S. gross domestic product (GDP) in 2010 and costs have been rising faster than inflation for years, yet 48.6 million Americans lack health insurance.

Endocrinologists and other health care practitioners are concerned about how to balance rising costs while providing quality health care, but a political path based on such issues is "not clear cut," according to William Applegate, consultant to The Endocrine Society and director of Health Care Government Relations Practice at Bryan Cave law firm in Washington, D.C.

"We tend to have friends on both sides of the aisle," he says, acknowledging that his firm "cultivates bipartisan support." This election is complicated by the fact that the Mitt Romney camp has not put forth a "comprehensive clear plan," Applegate says, and President's Barack Obama's landmark Affordable Care Act (ACA), passed in 2010, "simultaneously has support and opposition depending on the various provisions and pieces of the law." Much of the ACA has yet to be implemented and people "are waiting to see how it all gels."

Although the full extent of ACA's impact on the health care system can't be known yet, health care coverage has slowly ticked upward in the last year due to young adults gaining health insurance under their parents' plans. Cover-

age is expected to increase in 2014, with the end of health insurance discrimination for pre-existing conditions and gender, the implementation of state health insurance exchanges, and the expansion of Medicaid, the federal plan for low-income families.

The American College of Physicians, the largest medical-specialty organization in the country and a longtime advocate of universal health care, supports the initiatives of the Affordable Care Act. Team-based care and preventive provisions of the ACA are particularly attractive, says endocrinologist Dennis Cope, a member of the ACP's Board of Regents and Chair of Internal Medicine at UCLA Medical Center. Access to screening and preventive care can reduce and alleviate chronic diseases such as thyroid disorders and diabetes, he says.

"Right now we're having an epidemic of obesity, which can lead to type 2 diabetes. Early treatment would be beneficial," he says. "But currently, there is not much reimbursement if you don't do procedures, and endos typically don't do procedures. The Affordable Care Act pays for integrative care. If we start paying more for cognitive information and integration of material, we can save a lot on procedures and have a better outcome."

William F. Young, Jr., president of The Endocrine Society and chair of the Division of Endocrinology, Metabolism, and Nutrition at the Mayo Clinic College of Medicine in Rochester, Minnesota, agrees: "The Affordable Care Act encourages integration of health services." But Young has reservations. "In an ideal world it would result in more effective hand-offs between primary care physicians and endocrinologists. However, it has also encouraged the newly integrated systems to limit provider choice as a means of coordinating care. These closed systems, or narrow networks, may discourage the referral of patients for subspecialist consultations in a timely fashion," he adds.

Under the ACA, the Centers for Medicare & Medicaid Services created the Medicare Shared Savings Program and established 33 quality measures for patient care coordination and safety; six of the measures directly relate to diabetes care.

"That positions endocrinologists to play a very important role in working with primary care physicians and patient-centered medical homes and accountable care

organizations to help achieve those targeted metrics," says David Longworth, chairman of the Medicine Institute at Cleveland Clinic.

Usha Srinivasan, who has practiced endocrinology in Bel Air, Maryland, for 30 years, says she likes some features of the ACA, mainly the contraception provision for women, coverage for young people on their parents policy until age 26, acceptance of patients with pre-existing conditions and removal of the lifetime cap for coverage, but "we don't have the infrastructure for it," she says. "As an endocrinologist, I am already overworked. You need time with your patients. ACA is going to increase the number of patients, but it will decrease the quality of care."

Relying on the premium contributions of healthy young people to pay for the expansion of coverage is not realistic, she says. "Type 2 diabetes and other endocrine diseases are occurring in young people, so they can't bear the [financial] burden for others."

Another questionable aspect of the ACA is the documentation required by "the gatekeepers," Srinivasan adds. "It's extensive and the electronic recording-keeping is already subject to fraud." She, however, dismisses Romney on the issue of health care: "He doesn't have a health care plan."

Like Srinivasan, other health care experts have expressed concerns about the far-reaching impact of the ACA. The

Obama and Romney on Science and Health

STEM CELL RESEARCH

Obama: Issued an executive order in March 2009 that rescinded the limits on federal funding of stem cell research. The National Institutes of Health (NIH) now lists some 160 approved stem cell lines and more than a dozen active funding opportunities for stem cell research.

Romney: Does not support embryonic stem cell research; as governor of Massachusetts, he attempted to ban the research. Instead supports research on adult stem cells and cell lines derived from sources other than human embryos.

RESEARCH FUNDING

Obama: Has proposed increasing federal spending on research to 3 percent of GDP. NIH received an influx of money for research in 2010 under the American Recovery & Reinvestment Act, but spending has since returned to previous levels.

Romney: Has stated his strong support for federally funded research but also promised to cap spending on non-defense agencies including NIH and cut their budgets by 5 percent on his first day in office.

REGULATION OF ENDOCRINE-DISRUPTING CHEMICALS

Obama: Under Obama, the Food and Drug Administration banned bisphenol A from baby bottles and children's drinking cups in July; in 2011, the Environmental Protection Agency announced plans to regulate the amount of perchlorate allowed in tap water.

Romney: Has promised to reform environmental regulation, requiring that all new regulations account for cost, allow companies multiple years to come into compliance with new regulations, and require Congressional approval all new "major" regulations.

Supreme Court decision that upheld the legislation allows states to opt out of the expansion of Medicaid. If states choose not to participate—and most Republican governors have said they will not expand their Medicaid programs — hospital funding will be decreased and benefits to millions of low-income people will be reduced. “The cuts could have devastating effects on hospitals,” says Dave Dillon, a Missouri Hospital Association spokesman. “We’re very worried about the viability of Medicaid.”

Other health care watchers have raised concerns about cuts in Medicare funding to private insurers. “The Affordable Care Act will significantly decrease Medicare reimbursements to all physicians,” contends Richard Dolinar, a clinical oncologist in Phoenix and a senior fellow on health care policy for the Heartland Institute, a conservative think tank. “Medicare rates will eventually be less than Medicaid rates. More than 40 percent of Medicare providers will go out of business or stop seeing Medicare patients.

Mitt Romney promises to work with Congress to repeal the ACA. “I’m replacing it with my own plan,” the candidate said on “Meet the Press” in September. Though the details of Romney’s replacement plan have yet to be released, he is known to favor a free-market approach he says would create competition that in turn improves efficiency and effectiveness in health care.

Romney has also promised major changes to Medicare

and Medicaid that he claims would cut costs while keeping physician payments at current levels. Individuals already in retirement or near retirement age would see no change to their Medicare, but the system would be repackaged for younger people, who would be given a fixed-amount benefit to purchase insurance. In addition, Medicaid would be transformed into a block grant program for states, which would receive a lump sum amount that would grow by inflation plus one percent each year, controlling spending on the program.

A recent analysis from the Kaiser Family Foundation, a non-partisan health policy organization, however, concluded that repeal of the ACA could result in increases in Medicare premiums and prescription drug payments for current retirees. A 2011 Kaiser analysis found that repealing the ACA and converting Medicaid into a block grant program would save the federal government \$1.4 trillion over a 10-year period but also result in tens of millions of people losing their health insurance.

Whoever wins the White House will have to contend with costly and critical health care issues, notes Longworth. “The trend of escalating health care costs, despite the relatively poor quality outcomes that we get when compared to other developed countries, is an unsustainable combination of events.” ■

Zielinski is a Washington, D.C.-based writer.

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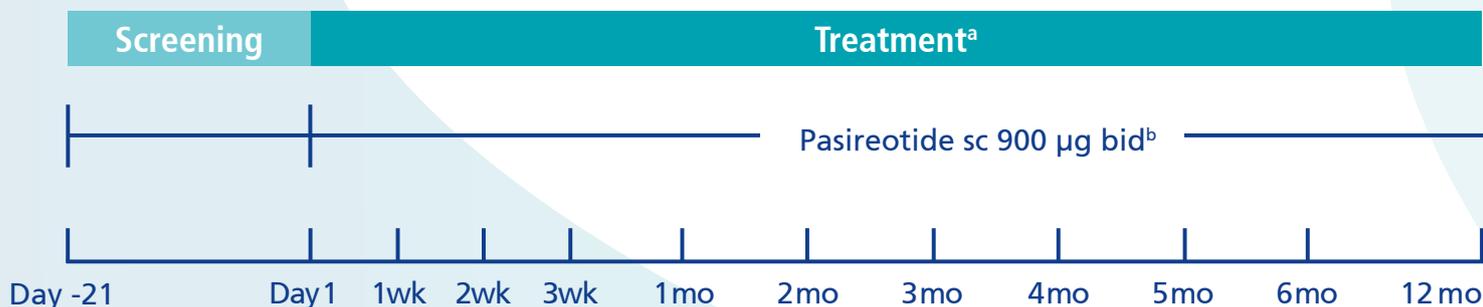


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^aPatients will be followed at 12-week intervals between Months 6 and 12.

^bDose may be reduced to 600 µg bid and 300 µg bid upon sustained disease control, or in the case of tolerability concerns. The starting dose for patients with impaired glucose metabolism will be 600 µg bid.

ELIGIBLE PATIENTS:

- Adult patients with a confirmed diagnosis of Cushing's disease
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 - Morning plasma ACTH within or above the normal range
 - MRI confirmation of pituitary adenoma (≥0.6 cm) or positive inferior petrosal sinus gradient for patients with a microadenoma <0.6 cm
 - Histopathological confirmation of an ACTH-staining adenoma in postsurgical patients
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PRIMARY END POINT:

- The proportion of patients with drug-related grade 3 or 4 AEs or serious AEs



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Abbreviations: ACTH, adrenocorticotropic hormone; AEs, adverse events; bid, twice a day; MRI, magnetic resonance imaging; SC, subcutaneous; UFC, urinary free cortisol; ULN, upper limit of normal.

ClinicalTrials.gov Identifier: [NCT01582061](https://clinicaltrials.gov/ct2/show/study/NCT01582061)

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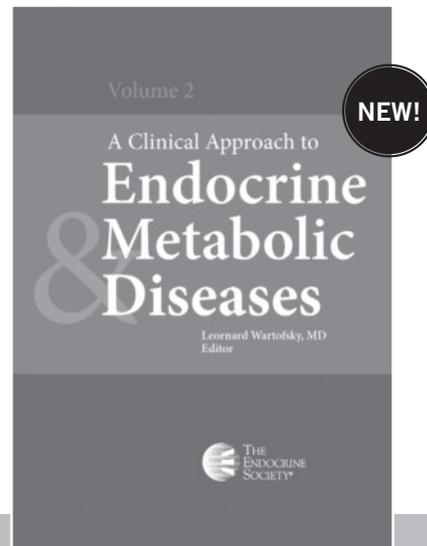
Editor, Leonard Wartofsky, MD

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A 63-year-old Hispanic woman who has been under your care for 10 years was diagnosed with type 2 diabetes (T2DM) 6 years ago. In addition to long-standing hypertension and hypercholesterolemia, she has a BMI (body-mass index) of 31 kg/m² and a family history of cardiovascular disease. However, she has never had a cardiovascular event and does not report any cardiac symptoms.

She monitors her fasting glucose level twice a week. Her morning fasting glucose levels have ranged between 140 and 160 mg/dl. She is taking metformin (1,000 mg b.i.d.) and extended-release glipizide (10 mg b.i.d.). You have been seeing her every six months since her diagno-

Concerned about her inability to reach her glycemic goal (HbA1c of 7.0 percent), she seeks advice about whether a change in medications might help her manage her T2DM more effectively.

sis of T2DM. Her hypertension has been successfully controlled with hydrochlorothiazide (25 mg daily) and lisinopril (20 mg daily) and her hypercholesterolemia with simvastatin (20 mg daily). Additionally, she takes aspirin (81 mg daily).

The patient has struggled to manage her weight and has been counseled about lifestyle changes. Even though she has lost weight on various diets (approximately 10–15 pounds), she regains all of the weight lost. She tries to walk 30 minutes three times a week. Her BMI has fluctuated between 30 and 32 kg/m² for the past decade.

A recent blood test showed her HbA1c level to be 8.0 percent. Her other laboratory tests have con-

Two Orals Fail in a T2DM Patient

sistently shown normal results for liver, renal, and thyroid function. Physical examination shows normal blood pressure (118/78 mm Hg) and normal cardiorespiratory, abdominal, and neurologic findings.

The patient has health insurance through her employer, which includes prescription drug coverage. Concerned about her inability to reach her glycemic goal (HbA1c of 7.0 percent), she seeks advice about whether a change in medications might help her manage her T2DM more effectively.

Treatment Options

Which one of the following treatment options do you think would be most appropriate for this patient?



Add a thiazolidinedione (TZD)
Zachary T. Bloomgarden, M.D., Mount Sinai School of Medicine, New York City

The durable glucose lowering and improved insulin sensitivity associated with the TZDs, and their several noteworthy non-glycemic effects, make them attractive options as additions to the treatment regimen of this patient. The wise clinician, however, must also be cognizant of potential adverse effects and contraindications, particularly if this patient, known to be at risk for cardiovascular disease, has any signs of peripheral vascular disease or systemic fluid retention. The clinician should also assess this 63-year-old for fracture risk, because a woman at even moderately high risk of fracture might better be given a different agent.



Add a glucagon-like peptide-1 (GLP-1) agonist
Carol H. Wysham, M.D., Washington State University, Spokane, Washington

Compared to insulin glargine or pioglitazone, GLP-1 receptor agonists have similar potential to improve this patient's glucose levels. These agents are available as easy-to-use pens and, unlike the other options presented, the patient will likely experience satiety and weight loss. In my experience, GLP-1 agonists are very well received by patients. Once the overall glycemic and non-glycemic effects (especially weight loss potential) are described to patients, the need for injection does not present itself as a barrier.

Add insulin

Charles F. Shaefer, M.D., FACP, FCCP, Medical College of Georgia, Augusta, Georgia

Currently, more than 90 percent of T2DM cases are managed by the primary care community. It should be within the scope of expertise for every primary care provider to recognize the need for and institute basal insulin therapy, when appropriate. When there is failure to maintain goal HbA1C with one or two oral agents, basal analog insulin is a well-studied, effective, and cost-efficient way to advance therapy with a minimum of treatment-related side-effects or safety issues. ■

For references and additional discussion of this case study and to vote or comment on treatment options, please go to www.betacellsindiabetes.org/casestudy.

Hormone Health Network's Patient Guide to the Assessment and Treatment of Hypertriglyceridemia (High Triglycerides)

Having high levels of triglycerides, or *hypertriglyceridemia*, is a common problem. Triglycerides are fats in the blood (also called lipids). Your body needs some blood fats for energy. But when your triglyceride levels are too high, these fats may put you at risk for heart disease, stroke, and other health problems.

Most often, having high triglycerides has no warning signs. The good news, though, is there is a simple test to find high triglycerides, and treatments are available.

This guide for patients comes from The Endocrine Society's practice guidelines for physicians about the detection and treatment of hypertriglyceridemia.

What are the effects of high triglycerides?

It is unclear if high triglycerides alone are a risk factor for cardiovascular disease (heart disease and stroke). Triglycerides do not directly cause the plaque that can block your heart's arteries (*atherosclerosis*) and lead to a heart attack. Yet, cholesterol in triglyceride-rich particles in the blood may add to plaque formation.

Also, many people with high triglycerides have other lipid problems or other risk factors for heart disease. A high triglyceride level is one part of the metabolic syndrome, a cluster of risk factors that increase the risk for heart disease and diabetes.

High triglycerides can affect more than your heart and blood vessels. Very high triglycerides raise the risk for *pancreatitis*, an inflammation of the pancreas. The pancreas is large gland behind the stomach that makes key hormones like insulin. It helps your body maintain healthy blood glucose (sugar) levels. Pancreatitis can cause stomach pain and digestive problems. It can damage the pancreas and, over a long time, can lead to diabetes.

What raises the risk for high triglycerides?

Triglycerides normally increase with age. They may become too high for one or more reasons.

Risk factors include

- Lifestyle factors
 - Being overweight or obese
 - Not getting enough exercise
 - Drinking too much alcohol
- Familial (inherited) disorders
- Type 2 diabetes or the metabolic syndrome
- Pregnancy

- Medications
 - Some “water” pills (thiazide diuretics)
 - Beta-blockers
 - Estrogen (birth control pills, hormone therapy)
 - Isotretinoin for acne
 - Corticosteroids for conditions such as asthma and arthritis
 - Certain cholesterol-lowering drugs
 - Protease inhibitors for HIV
 - Immune suppressants (such as sirolimus)
 - Some antipsychotics (mental health medicines)



Most often, having high triglycerides has no warning signs. The good news, though, is there is a simple test to find high triglycerides, and treatments are available.

The most common reasons for high triglycerides include being overweight, lack of exercise, the metabolic syndrome, type 2 diabetes, and *familial combined hyperlipidemia*. The latter is a genetic disorder that runs in the family. It results in high triglycerides, high “bad” (low-density lipoprotein, or LDL) cholesterol, and low “good” (high-density lipoprotein, or HDL) cholesterol.

How are high triglycerides found?

A blood test called a *lipid panel* measures triglycerides and cholesterol. You should have this test after fasting (not eating or drinking anything but water) for at least 12 hours.



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NETWORK



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Adults should get this screening test every five years or sooner. If you have diabetes, a family history of high triglycerides, or other risk factors, you may need screening more often, according to the National Cholesterol Education Program (NCEP) Guidelines.



The first step for lowering triglycerides is to lose weight if you are overweight, exercise often, and eat a healthy diet low in saturated (bad) fat and sugar. Besides these lifestyle changes, you may also need drug treatment.

The NCEP defines borderline-high triglycerides as 150 to 199 milligrams per deciliter (mg/dL) and high triglycerides as 200 to 499 mg/dL. Very high triglycerides are 500 mg/dL or higher. The Endocrine Society instead defines hypertriglyceridemia by its disease risk (see chart below). Most people with high triglycerides have levels from 150 to 999 mg/dL, which puts them at risk for heart disease. Above 2,000 mg/dL poses a high risk for pancreatitis.

Triglyceride Test Results and Disease Risk

Level	Severity of hypertriglyceridemia	Raised risk
Less than 150 mg/dL	Normal	None
150–199 mg/dL	Mild	Heart disease
200–999 mg/dL	Moderate	Heart disease
1,000–1,999 mg/dL	Severe	Very severe hypertriglyceridemia
2,000 mg/dL or higher	Very severe	Pancreatitis

If your triglycerides are above normal, your doctor will find out if the cause is primary (genetic) or secondary (e.g., due to hormonal disease or medications). Untreated secondary causes need treatment. If the cause is a medication, ask your doctor if you can switch to a medicine that does not raise triglycerides.

Your health care providers may check you for other risk factors for heart disease, such as high blood pressure, high blood glucose, and too much fat around your waist. They also may ask about your family history of abnormal lipids and heart disease. This helps to assess your future risk for having a heart attack or a stroke.

What is the treatment for high triglycerides?

The goal of treatment is to lower your triglycerides. Patients with very severe hypertriglyceridemia should try to lower their triglycerides below 1,000 mg/dL, to reduce their risk for pancreatitis.

Lifestyle changes. The first step for lowering triglycerides is to lose weight if you are overweight, exercise often, and eat a healthy diet low in saturated (bad) fat and sugar. Also, limit the amount of refined, processed grains you eat, such as white bread, rice, and pasta. Follow your doctor's advice about limiting intake of alcohol, which raises triglycerides in some people.

Medications. Besides lifestyle changes, you may also need drug treatment. For mildly or moderately high triglycerides, your doctor may prescribe one of these types of drugs:

- *Fibrates*, which greatly lower triglycerides and sometimes raise HDL (good) cholesterol. In the U.S., these prescription drugs include gemfibrozil and fenofibrate.
- *Niacin*, or vitamin B3, at doses of 1,000 to 3,000 mg per day, lowers triglycerides and LDL cholesterol and raises HDL cholesterol. These doses apply to immediate-release (released into the body right away) niacin, available by prescription or as a supplement. The dose of sustained-release (released into the body over time) niacin, which is only available as a supplement, shouldn't exceed 2,000 mg per day because of the risk of liver damage.
- *Omega-3 (n-3) fatty acids* eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) lower triglycerides. These polyunsaturated (good) fats are found in fatty fish such as salmon. In high doses, they can treat high triglycerides. You can get high doses of omega-3 fatty acids in a fish oil supplement or by prescription.

Your doctor may add a statin to your other drug treatment. Though statins mainly lower LDL cholesterol, they also can decrease triglycerides. Some studies show that statins reduce the risk of heart attacks and strokes. It is unclear if fibrates and niacin prevent heart attacks and strokes.

If your triglycerides are above 1,000 mg/dL, though, the first choice of medicine is a fibrate. You may need a statin, too, but experts advise against treatment with statins alone if your high triglycerides are severe or very severe. Fibrates are better than statins at lowering triglycerides. However, people with liver disease or gallbladder disease should not take fibrates.

Talk to your doctor about the risks and benefits of all these drugs. Medications do not cure the problem of high triglycerides, so you will need to take them long term. However, weight loss and other lifestyle changes can lower high triglycerides enough to eliminate the need for medication.

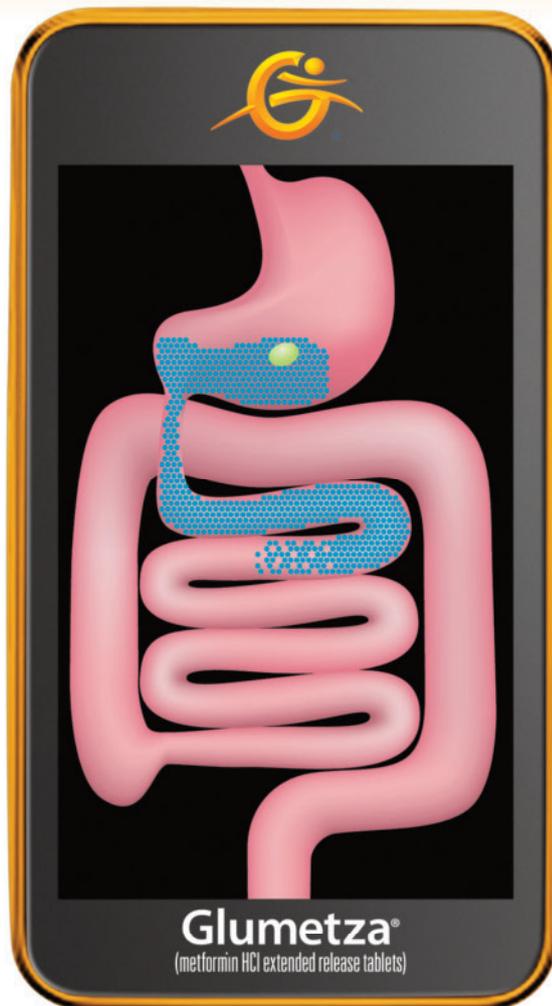
Ask your doctor if you should see an endocrinologist. This physician specialist can find and treat hormonal causes of high triglycerides.

EDITORS

Lars Berglund, MD, PhD
John Brunzell, MD
Frank M. Sacks, MD

September 2012

GLUMETZA®: Unique, controlled delivery may improve



IMPORTANT SAFETY INFORMATION ABOUT GLUMETZA

WARNING: LACTIC ACIDOSIS

*See full prescribing information
for complete boxed warning*

- Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. (5.1)
- Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. (5.1)
- If acidosis is suspected, discontinue GLUMETZA and hospitalize the patient immediately. (5.1)

GLUMETZA is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see **WARNINGS and PRECAUTIONS** (5) of the Full Prescribing Information).
 - Known hypersensitivity to metformin hydrochloride.
 - Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those

tolerability and help more patients get to A1C goal

▶ TECHNOLOGY

GLUMETZA provides a unique, advanced polymer technology* that may help reduce GI adverse events in your patients

- GLUMETZA targets the upper GI tract for slow delivery over 8-9 hours,¹ providing consistent 24-hour control

▶ TOLERABILITY

Well tolerated, with no significant increase in adverse events at higher doses

- <1% of GLUMETZA patients discontinued due to GI adverse events in Week 1^{2†}; starting dose was 1000 mg

▶ A1C CONTROL

Improved tolerability[‡] may help more patients reach A1C goal

- More patients reached goal with GLUMETZA 2000 mg QD versus Glucophage[®] 1500 mg/day^{1,3§}

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with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

In clinical trials, the most common side effects with GLUMETZA monotherapy were diarrhea, nausea, dyspepsia, and upper abdominal pain. In clinical trials of GLUMETZA combined with a sulfonyleurea, the most common side effects included hypoglycemia, diarrhea, and nausea.

*GLUMETZA 500 mg utilizes patented AcuForm[®] gastric retention technology. GLUMETZA 1000 mg utilizes patented Smartcoat[®] gastric retention technology.⁴

[†]Findings from a 24-week, noninferiority clinical trial comparing different GLUMETZA dosing regimens vs Glucophage[®] (metformin hydrochloride tablets). GLUMETZA patients were initiated with 1000 mg (2 X 500 mg OD) for 1 week, then titrated to their randomly assigned dose over 2 to 3 weeks, and remained on this dose for the remainder of the study unless discontinuation was warranted.

[‡]The overall incidence of drug-related adverse events was similar with GLUMETZA dosed up to 2000 mg/day vs Glucophage 1500 mg/day: 33% vs 35%, respectively.^{2§}

[§]From a supplementary analysis of the findings from a 24-week, 4-arm, noninferiority trial comparing different GLUMETZA dosing regimens vs Glucophage. Note: 40.6% of patients (n=182) reached A1C goal with GLUMETZA 1500 mg BID (dosed 500 mg AM; 1000 mg PM).

[¶]Some restrictions apply. Please see the eVoucherRx[™] and Savings Card Program Brochure for Terms and Conditions. Santarus reserves the right to modify or cancel these offerings at any time.

References: 1. Foster RH, Keam SJ. Metformin extended release. *Am J Drug Deliv.* 2006;4(3):1-11. 2. Schwartz S, Fonseca V, Berner B, Cramer M, Chiang YK, Lewin A. Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. *Diabetes Care.* 2006;29(4):759-764. 3. Glumetza [package insert]. San Diego, CA. Santarus, Inc. 2011. 4. Data on file. Santarus, Inc.

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Glumetza[®]
(metformin HCl extended release tablets)

GLUMETZA®

(metformin hydrochloride extended release tablets)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

BEFORE PRESCRIBING, CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USE—GLUMETZA (metformin hydrochloride extended release tablets) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

GLUMETZA is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia. (See **WARNINGS AND PRECAUTIONS**)
- Known hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

WARNINGS AND PRECAUTIONS

Lactic Acidosis

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUMETZA and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate concentrations (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 μ g/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years. In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUMETZA. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. GLUMETZA treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, GLUMETZA should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUMETZA should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking GLUMETZA, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, GLUMETZA should be temporarily discontinued prior to any intra vascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis (In controlled trials, 32% and 67% for adjunctive treatment in adults and pediatric patients, respectively, and 15 to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adults and pediatric patients, respectively, and 1 to 2% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis. (See Drug Interactions and Clinical Pharmacology) The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis.

Patients should be educated to promptly report these symptoms should they occur. If present, GLUMETZA should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUMETZA, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUMETZA do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly-controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUMETZA, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See **CONTRAINDICATIONS**)

Monitoring of Renal Function

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore GLUMETZA is contraindicated in patients with renal impairment.

Before initiation of GLUMETZA and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and GLUMETZA discontinued if evidence of renal impairment is present. Metformin treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis.

Use of concomitant medications that may affect renal function or metformin disposition — Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **DRUG INTERACTIONS**), should be used with caution.

Radiological studies and surgical procedures:

Radiological studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, GLUMETZA should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been re-evaluated and found to be normal.

GLUMETZA therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUMETZA therapy, the drug should be promptly discontinued.

Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving GLUMETZA.

Impaired Hepatic Function

Because impaired hepatic function has been associated with some cases of lactic acidosis GLUMETZA should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B₁₂ Levels

In controlled, 29-week clinical trials of immediate release metformin, a decrease to subnormal levels of previously normal serum Vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUMETZA or Vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUMETZA and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B₁₂ levels. In these patients, routine serum Vitamin B₁₂ measurements at two- to three-year intervals may be useful.

Hypoglycemia

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as

sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLUMETZA or any other oral anti-diabetic 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 clinical practice.

In clinical trials conducted in the U.S., over 1000 patients with type 2 diabetes mellitus have been treated with GLUMETZA 1500-2000 mg/day in active-controlled and placebo-controlled studies with the 500 mg dosage form.

In the 24-week monotherapy trial comparing GLUMETZA to immediate-release metformin, serious adverse reactions were reported in 3.6% (19/528) of the GLUMETZA-treated patients compared to 2.9% (5/174) of the patients treated with immediate-release metformin. In the add-on to sulfonylurea study, patients receiving background glyburide therapy were randomized to receive add-on treatment of either one of three different regimens of GLUMETZA or placebo. In total, 431 patients received GLUMETZA and glyburide and 144 patients received placebo and glyburide. A serious adverse reaction was reported in 2.1% (9/431) of the GLUMETZA and glyburide-treated patients compared to 1.4% (2/144) of the placebo and glyburide-treated patients. When the data from the monotherapy and add-on to sulfonylurea clinical trials were combined, the most frequently (incidence $\geq 0.5\%$) reported serious adverse reactions classified by system organ class were gastrointestinal disorders (1.0% of GLUMETZA-treated patients compared to 0% of patients not treated with GLUMETZA) and cardiac disorders (0.4% of GLUMETZA-treated patients compared to 0.5% of patients not treated with GLUMETZA). Only 2 serious adverse reactions (unstable angina [n=2] and pancreatitis [n=2]) were reported in more than one GLUMETZA-treated patient.

Adverse reactions reported in greater than 5% of patients treated with GLUMETZA that were more common in the combined GLUMETZA and glyburide group than in the placebo and glyburide group are shown in Table 1.

In 0.7% of patients treated with GLUMETZA and glyburide, diarrhea was responsible for discontinuation of study medication compared to no patients in the placebo and glyburide group. Table 1: Adverse Reactions Occurring in 1% or More of Patients on Omeprazole Therapy from U.S. Studies

Table 1: Treatment-Emergent Adverse Reactions Reported By $>5\%$ of Patients for the Combined GLUMETZA Group Versus Placebo Group

Adverse Reaction	GLUMETZA + Glyburide (n = 431)	Placebo + Glyburide (n = 144)
Hypoglycemia	13.7%	4.9%
Diarrhea	12.5%	5.6%
Nausea	6.7%	4.2%

*AE's that were more common in the GLUMETZA-treated than in the placebo-treated patients.

Laboratory Tests

Vitamin B₁₂ concentrations

Metformin may lower serum vitamin B₁₂ concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on GLUMETZA and any apparent abnormalities should be appropriately investigated and managed. (See **WARNINGS AND PRECAUTIONS**)

DRUG INTERACTIONS

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorophenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with metformin, as the risk of lactic acidosis may increase.

Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUMETZA and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving GLUMETZA, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving GLUMETZA, the patient should be observed closely for hypoglycemia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category B

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which represent 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, Metformin HCl should not be used during pregnancy unless clearly needed.

Labor and Delivery

The safety and effectiveness of GLUMETZA used during labor and delivery has not been evaluated in human studies.

Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Thus, the potential for hypoglycemia in nursing infants after Metformin HCl Oral Solution may exist.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. GLUMETZA is not recommended in pediatric patients below the age of 18 years.

Geriatric Use

Clinical studies of GLUMETZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. (See **WARNINGS AND PRECAUTIONS**)

OVERDOSAGE

No cases of overdose were reported during GLUMETZA clinical trials. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea, and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded.

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. (See **WARNINGS AND PRECAUTIONS**) Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdose is suspected.

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Society update

Society Member Robert J. Lefkowitz Wins 2012 Chemistry Nobel

The Royal Swedish Academy of Sciences awarded the 2012 Nobel Prize in Chemistry jointly to Robert J. Lefkowitz, M.D., and Brian K. Kobilka, M.D., for their groundbreaking discoveries that reveal the inner workings of G-protein-coupled



Dr. Lefkowitz

receptors, a family of receptors that enables cells to sense their environment and adapt accordingly. Lefkowitz, an Endocrine Society member, is an investigator at the Howard Hughes Medical Institute and a professor of medicine at Duke University Medical Center, Durham, North Carolina. Kobilka is a professor of medicine and of molecular and cellular physiology at Stanford University School of Medicine, Stanford, California.

For many years, scientists suspected that cells contained some kind of recipient for hormones, but what these receptors actually consisted of and how they worked remained a mystery. Lefkowitz used radioactivity to identify several receptors and gained an initial understanding of how they worked. Kobilka, who worked in Lefkowitz's lab as a postdoctoral fellow, isolated the gene for the β -adrenergic receptor. The duo then discovered that this gene was similar to a receptor in the eye that captures light, rhodopsin. In time, they discovered

a whole family of receptors that look and work in a similar manner. More than a thousand genes code for these receptors, which play key roles in sight, smell, taste, and other physiological functions such as heart rate, blood pressure, and glucose metabolism. About half of all medications achieve their effect through G-protein-coupled receptors.

"Robert Lefkowitz is a hero in the field of endocrinology and his Nobel Prize is well-deserved," said William F. Young, Jr., M.D., president of The Endocrine Society. "His research has helped us understand the chemistry of cell communication and carries great potential in helping develop new and more effective treatments for many diseases and disorders."

Dr. Lefkowitz has received numerous awards for his research, including three of The Endocrine Society's prestigious laureate awards: the 2001 Fred Conrad Koch Award, the 1995 Gerald D. Aurbach Award Lecture, and the 1982 Ernst Oppenheimer Award.

The Visiting Professorship Program Awards Recipients Announced

Supported by The Endocrine Society and Pfizer, Inc., the Visiting Professorship Program in Growth Hormone Regulation and Disorders (VPGH) provides financial support to U.S. academic centers to invite distinguished faculty studying growth hormones for educational exchanges, such as seminars, lab visits, grand rounds, journal clubs, and lunch/dinner with stu-

dents. The VPGH promotes greater awareness of cutting-edge growth hormone research, encourages young investigators to enter specialized endocrine research, and fosters research collaborations among academic centers. The Endocrine Society congratulates the 2012 VPGH Award-

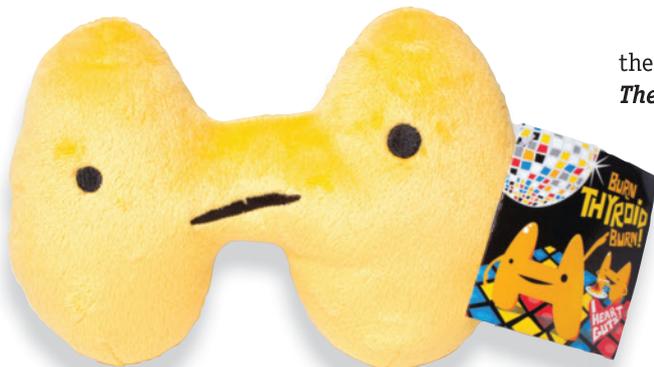


ees: the University of Colorado Denver, which will host Dr. Shlomo Melmed of Cedars-Sinai Medical Center, Los Angeles, and the University of Puerto Rico, which will host Dr. Beverly Biller of Massachusetts General Hospital, Boston.

Thyroid and Pregnancy Fact Sheets from The Hormone Health Network

Thyroid disorders, which are more prevalent in women than men, are of particular concern during pregnancy. Left untreated, hyperthyroidism and hypothyroidism pose a risk to both mother and baby. The possibility of malignancy may also be of concern to pregnant women with thyroid nodules. The Hormone Health Network's updated series of three patient guides, based on The Endocrine Society's revised clinical practice guideline on maternal thyroid dysfunction, address hyperthyroidism, hypothyroidism, and thyroid nodules and cancer before, during, and after pregnancy. Visit www.hormone.org to read and download the patient guides.





the September issue of *The Journal of Clinical Endocrinology & Metabolism*. The 60-minute, interactive webinar includes discussions of the diagnosis and definitions of hypertriglyceridemia, the causes of elevated triglycerides, and secondary causes of hyperlipidemia. The guideline also recom-

mends treatment goals in patients with moderate hypertriglyceridemia. The guideline is now available through the Society's Web site for free download (www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm). Bound copies will be available for purchase at the Society's online store (www.endo-society.org/custom_apps/publication/online_store.cfm?).

The archived sessions of these webinars can be accessed at www.endo-society.org/education/webinars/.

Refer a Member

Refer a new full member to The Endocrine Society. When your referred colleague or friend joins and mentions your name, you will receive a \$20 Starbucks Card! Refer someone today and learn more about the program at www.Endo-Society.org/Referral.



NIH Loan Repayment Program Deadline Nears

To encourage scientific investigators to remain in the biomedical research field, the National Institutes of Health is offering to pay annually up to \$35,000 of qualified researchers' student loans through its extramural loan repayment program. Individuals who commit two years to conducting government-funded research in

one of the following five fields are eligible: clinical research; pediatric research; health disparities research; contraception and infertility; and clinical research for individuals from disadvantaged backgrounds. All applications are due November 15. Visit www.lrp.nih.gov to learn more about the programs and to apply.

In Memoriam: Past President Seymour Lieberman, Ph.D., 1917–2012

Seymour Lieberman, Ph.D., a past president of The Endocrine Society (1975–1976) and professor emeritus of biochemistry at Columbia University in New York City, died on October 8. He was 95.

A leader in the field of endocrinology, Lieberman pioneered the study of the metabolism of steroid hormones. He was the first to suggest and provide evidence for the involvement of transient intermediates in steroid biosynthesis. He isolated cholesterol sulfate from natural resources and approximately 50 steroid metabolites and conjugates from human urine. He also created steroid-protein conjugates and antibodies to these hybrid molecules, many of which are now used in radioimmunoassay procedures for most of the steroid hormones. Finally, he developed a radioactive tritium-labeling procedure for peptides and proteins (such as ACTH, LH, and LHRF). At the time of his death, he was head of a research laboratory that focused on the role of steroids in hypertension—work he referred to as “my most important contribution.”

Born in Manhattan, Lieberman attended Brooklyn College, graduating at age 20. He received his Ph.D. in biochemistry from Stanford University in 1941. After World War II, he went to Basel, Switzerland, to



Dr. Lieberman

Society Online Store Receives Make-Over

Shopping at The Endocrine Society's online store just got better. In addition to its new look, the Web site is easier to navigate. Individuals can log on either as a guest or as a member. What's more, members will automatically have their discounts included in the final purchase price. Publications and new products are now available. Go now to view the new online store at www.endo-society.org/custom_apps/publication/online_store.cfm?

New Clinical Practice Webinars Now Available

The Endocrine Society recognizes a significant need for better care coordination to ensure that pediatric and adult providers—and their patients—are fully prepared for transitions of care. To meet this need, the Society recently spearheaded an initiative to develop transition of care resources specific to type 1 diabetes. The Society hosted a webinar in November to discuss these resources, which include a recommended approach to planning for pediatric practices, a clinical summary, a patient skill set, and more. To access copies of these resources, please go to www.endo-society.org/clinicalpractice/transition_of_care.cfm.

In October, the Society also hosted a webinar for its newest clinical practice guideline, *Evaluation and Treatment of Hypertriglyceridemia*, which was published in



study with Tadeus Reichstein, Ph.D., a 1950 Nobel Laureate. Lieberman returned to United States to work at the Sloan-Kettering Institute and then at Columbia University, where he remained for 61 years.

Lieberman was known as a mentor and educator. Numerous professors and chairmen of departments throughout the United States and Europe got their start in his Columbia laboratory. For more than 30 years, he organized and led a weekly journal club that was attended by physicians and scientists from around New York City. During his presidency at The Endocrine Society, he championed the cause of young researchers and academicians to obtain access to the organization. In 1953, he won the Ciba Award, the Society's award for young investigators under the age of 35. Lieberman also served as editor of *The Journal of Clinical Endocrinology & Metabolism*.

Later in his career, he was active in public health organizations related to reproduction and population control. He worked for the Population Council, the human reproduction unit of the World Health Organization, the Cancer Chemotherapy National Service Center, and the Ford Foundation.

Lieberman was also a member of the National Academy of Sciences and received the Roussel Prize, the Dale Medal from the United Kingdom Society for Endocrinology, the Distinguished Service Award from Columbia University, and the Boehringer Mannheim Award from the United Kingdom Association of Clinical Biochemists.

He was married to Sandra Spar, who died in 1993. He is survived by one son, Paul, and daughter-in-law, Genie Bailey, of Providence, Rhode Island, and two grandchildren, Jacob, of Cambridge, Massachusetts, and Alyson, of Philadelphia.

To learn more about Lieberman's role in endocrinology, please view the oral history he made for The Clark T. Sawin Memorial Library, at www.endo-society.org/about/sawin/lieberman-video.cfm.

SMART MOVES

developments in the endocrinology world



* **Richard T. Kloos, M.D.**, received the 2012 Distinguished Service Award from the American Thyroid Association for his "important and continuing contributions to the ATA." Dr. Kloos is currently senior medical director of Veracyte, Inc., a molecular diagnostics company that has recently produced a gene expression test to identify low-risk thyroid nodules.

* **Frederic Wondisford, M.D.**, was honored with the 2012 Sidney Inghar Distinguished Lectureship Award from the American Thyroid Association for his research on the biological behavior of thyroid hormone receptors, thyroid hormone feedback on the hypothalamic-pituitary axis, and thyroid hormone-resistant states. Dr. Wondisford is a professor of pediatrics, medicine and physiology at The Johns Hopkins University in Baltimore, and director of the JHU-UMD Diabetes Research and Training Center.

Antonio Di Cristofano, Ph.D., received the 2012 Van Meter Award from the American Thyroid Association for his research on the role of the phosphoinositol 3-kinase signaling pathway in the pathophysiology of thyroid cancer. Dr. Di Cristofano is an associate professor in the Department of Developmental and Molecular Biology at Albert Einstein College of Medicine in New York City.

* **Paul W. Ladenson, M.D.**, was honored with the 2012 Lewis E. Braverman Award from the American Thyroid Association for his mentorship skills and long history of thyroid research. A former Editor-in-Chief of *The Journal of Clinical Endocrinology & Metabolism*, Dr. Ladenson is director of the Division of Endocrinology and Metabolism, John Eager Howard Professor of Endocrinology, and professor of medicine, pathology, oncology, radiology, and radiological science at The Johns Hopkins University. His research interests include applications of thyroid hormone analogs for treatment of cardiovascular disease, novel approaches to thyroid cancer diagnosis and management, and health economic analyses related to thyroid patient care.

* Member of *The Endocrine Society*.

EndoCare Online

EndoCare Online connects clinician members to an array of free resources that are easy to search and order. You can order patient education materials, product coupons, samples and vouchers, product information, and a variety of patient-assistance programs for each product at no cost. **NEW for 2012: free ePrescribing!** Learn more about this useful member benefit at www.endo-society.org/clinicalpractice. ■

calendar

DEC 15–19: SAN FRANCISCO
American Society for Cell
Biology Annual Meeting.
www.ascb.org/meetings

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

CLASSIFIEDS

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

Endocrinologist

The Strelitz Diabetes Center and Division of Endocrinology and Metabolism, at the Eastern Virginia Medical School, are seeking an Endocrinologist at the Assistant or Associate Professor rank (tenure track). The candidate will participate in clinical and educational activities of the division, and will have completed an endocrinology fellowship and be BC/BE in Internal Medicine and Endocrinology. Opportunities for program development include diabetes education, inpatient glucometrics, and thyroid cancer management. We are seeking an individual to join our group with interests in quality and the development of innovative clinical programs focusing on early intervention. The successful candidate will become an integral part of a system of care, working with our primary care network and multiple specialties to enhance diabetes care. The position includes a faculty appointment, teaching opportunities and a competitive salary and benefit package. Previous experience with thyroid ultrasound preferred. The search committee will also consider applicants with an active research program focused on aspects related to diabetes or thyroid disease. There are excellent laboratory facilities available and possible start up package. The historic port city of Norfolk is centrally located in the 1.8 million person Hampton Roads area on the Chesapeake Bay, a short drive from the Virginia Beach oceanfront. Forward CV to: HRapps@evms.edu. EVMS is an Equal Opportunity/Affirmative Action Employer/M/F/D/V and a Drug and Tobacco Free workplace.

Endocrinology Opportunity Southern Illinois University School of Medicine, Springfield, Illinois

The Department of Internal Medicine, Division of Endocrinology at Southern Illinois University seeks an additional Endocrinologist. Interested candidates should be board certified in Internal Medicine, and be board certified / board eligible in Endocrinology. Currently, the division is led by Michael Jakoby, M.D., who also serves as the Director of the Center for Diabetes and Metabolic Health. In this position you will be involved with patient care and the teaching of fellows, residents, and medical students. A faculty appointment is available at the Assistant or Associate Professor Level based upon experience and track record. Opportunities for basic and clinical research are available based upon individual interests. This position offers a competitive salary, along with full and comprehensive benefits (including 5 weeks of vacation, CME and 11 state holidays). Southern Illinois University School of Medicine is located in beautiful Springfield, the state capital. With a service area of 500,000 in central Illinois, Springfield accounts for more than 25 percent of the total population. Local residents have access to a wide variety of social, educational, artistic, historic, and recreational activities that serve to enhance the quality of life. Springfield has had the unique opportunity to capture a surprisingly urban business and social climate. The SIU School of Medicine values a racially and culturally diverse workforce. Southern Illinois University is an affirmative action / equal opportunity employer. To learn more, contact Beth Briggs

at 800-678-7858 x64454 or ebriggs@cejkasearch.com ID#139880A15.

Suburban Philadelphia—100 percent Endocrinology

Established group of three endocrinologists seeks BC/BE endocrinologist for full-time position. Mix of outpatient office and inpatient consultative work at single community teaching hospital. 1:4 call. Contact Barbara Boyce at endocrinology@bmmsa.com, Telephone: 610-527-1604, Fax: 610-525-8018.

Search For Faculty Members: Harvard Search

The Reproductive Endocrine Unit of the Department of Medicine of the Massachusetts General Hospital and Harvard Medical School is seeking a faculty member at the Associate Professor level specializing in Reproductive Endocrinology and desiring an academic career in clinical investigation, teaching, and research. Candidates should be physicians or M.D./Ph.D.s and must be board certified/eligible in Internal Medicine and Endocrinology. Applicants should have prior evidence of excellence across the full spectrum of clinical research, conducting a referred practice in Endocrinology, and teaching in an academic health science center and seeking a long term career in academic medicine. Minority and women candidates are especially encouraged to apply for this position. The successful candidate will join the faculty of the Reproductive Endocrine Division of the Department of Medicine at the Massachusetts General Hospital as an Associate Professor at the Harvard Medical School. They will also participate fully in the Harvard Reproductive Endo-

crine Sciences Center, one of twelve National Centers of Excellence in Reproduction competitively funded by the National Institute of Child Health & Development (NICHD). This position occurs in an environment of a leading academic medical center with strong, stable funding, deep traditions of excellence in clinical care and research, and broad training programs for medical house officers and post-doctoral fellows in Endocrinology. While candidates are expected to be substantially supported by peer-reviewed sources, this position will be supported by an ensemble of outstanding core facilities and a strong genetic community at the Massachusetts General Hospital, Harvard Medical School, the Broad Institute, and the broader Harvard Medical communities and affiliated hospitals. Interested applicants should send letters of interest accompanied by a curriculum vitae to Dr. William F. Crowley, Jr., M.D., Chief of the Reproductive Endocrine Unit, MGH and Director, Harvard Reproductive Sciences Center, BHX 511, MGH, Boston, Massachusetts 02114. MGHReproductiveEndocrine@partners.org. ■

ENDOCRINOLOGIST



OCHSNER HEALTH SYSTEM in New Orleans is searching for a **BC/BE ENDOCRINOLOGIST to join our staff at Ochsner Baptist Medical Center.**

Candidates with experience or directly from training are welcomed to apply. Areas of interest should include general endocrine disorders, diabetes, and endocrine disorders as related to pregnancy. This position is mainly outpatient based, but will serve a large Ob/Gyn group with significant inpatient consultation. Salary is competitive and commensurate with experience and training.

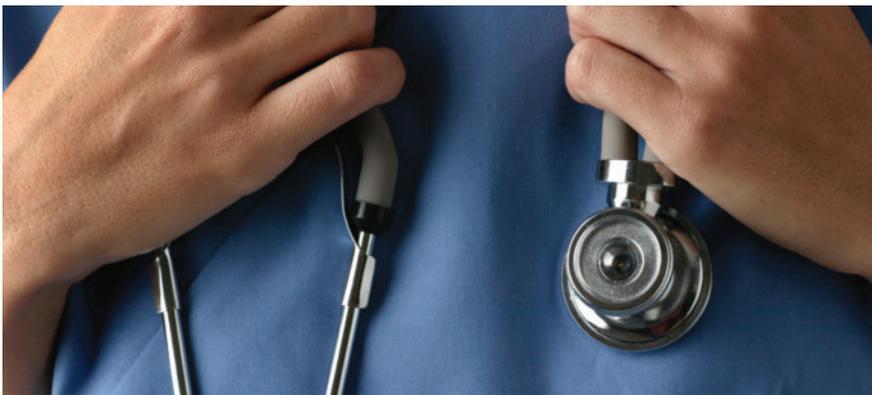
Ochsner Baptist Medical Center, with a deep-rooted history in Uptown New Orleans, is a fully accredited, full-service hospital staffed by more than 390 physicians. We have all private rooms, an ICU, 13 operating rooms, and a state-of-the-art imaging center. We are proud to be distinguished by our excellence in specialty care and high patient satisfaction scores. Our newly renovated 24-hour full-service emergency department is staffed by a team of board-certified ER physicians.

The Ochsner Health System comprises 8 hospitals and more than 38 clinics across southeast Louisiana with over 1.5 million clinic patient visits annually. Ochsner is a major provider of graduate medical education with 23 ACGME-accredited residency and fellowship programs, including our Endocrinology Fellowship Program. Please visit our Web site at www.ochsner.org.

New Orleans is a cosmopolitan, historic city with a pleasant climate, unique architecture, multiple medical schools and academic centers, professional sports teams, world-class dining and cultural interests, and world-renowned live entertainment and music.

Please email CV to: profrecruiting@ochsner.org, Ref. # ABENDO1 or call 800-488-2240 for more information. EOE.

Sorry, no J-1 visa opportunities available.



The Endocrine Society's EndoCareers resources have proven to be very useful for recruiting endocrinologists over the years. I recommend this option to anyone looking for good quality people!

— Physician Recruiter, Tucson, AZ

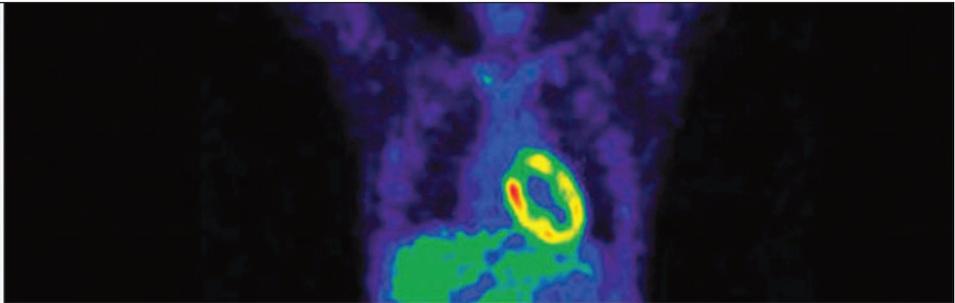
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The Hospital for Sick Children, Research Institute

Position Available: Obesity Scientist

The Program in Physiology and Experimental Medicine (PEM) at The Hospital for Sick Children is seeking to fill a faculty-level position of Scientist (Assistant/Associate Professor equivalent, but more senior candidates will also be considered). We seek an exceptional individual to establish and conduct an independent research program that would complement the current obesity, metabolism and nutrition research groups involved in evaluating mechanisms leading to cardiometabolic disorders, regulation of appetite in children, and clinical trials of prevention and treatment of childhood obesity. The position will be associated with a strong collaborative and multidisciplinary environment linking paediatric endocrinology, cardiology, general paediatrics and obesity research programs. This appointment will be located in our new state-of-the-art SickKids Research & Learning Tower, currently under construction.

Candidates must have a PhD degree or equivalent, have completed significant postdoctoral training, and have an outstanding record of research productivity. Candidates with experience in appetite regulation are preferred. The successful candidate will be cross-appointed to an appropriate academic department at the University of Toronto and receive a competitive salary and start-up package.

Applicants should e-mail their application (Curriculum vitae, description of past research and proposed research, and three representative publications), preferably in PDF format to palma.ottaviani@sickkids.ca by Nov 30th, 2012. Potential start date is August 2013. Candidates should also arrange to have three signed letters of recommendation sent by mail to: PEM Search, c/o Dr. Palma Ottaviani, The Hospital for Sick Children, 555 University Ave., Toronto, Ontario, Canada M5G 1X8.

All qualified candidates are encouraged to apply; however Canadian citizens and permanent residents will be given priority. The Hospital for Sick Children hires on the basis of merit and is committed to equity in employment.

SickKids

www.sickkids.ca

UNIVERSITY OF TORONTO



Now Available

Evaluation & Treatment of Hypertriglyceridemia: An Endocrine Society Clinical Practice Guideline

Developed independently by a team of experts, evidence based, and vetted through a rigorous, multi-step peer review process, the *Evaluation & Treatment of Hypertriglyceridemia* guideline addresses:

- Diagnosis and definitions of hypertriglyceridemia
- Causes of elevated triglycerides
- Secondary causes of hyperlipidemia
- Treatment goals in patients with moderate hypertriglyceridemia

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- Acromegaly
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- Pharmacological Management of the Obese Patient
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- Congenital Adrenal Hyperplasia
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- Pediatric Obesity
- CVD and Type 2 Diabetes in Patients at Metabolic Risk
- Patients with Primary Aldosteronism
- The Diagnosis of Cushing's Syndrome
- Hirsutism in Premenopausal Women
- Androgen Therapy in Women



To purchase available guidelines visit:

www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm.

To view patient guides (companion pieces to the clinical guidelines), visit The Hormone Health Network's Web site at www.hormone.org/public/patientguides.cfm.

Visit <http://www.guidelinecentral.com> to purchase pocket cards developed from select Endocrine Society guidelines.





Jellies in the Spotlight

By Aleta George

At the Monterey Bay Aquarium in California, a group of high school girls point their iPads at a tank of amber-colored sea nettle jellyfish, videotaping the pulsating parachute-shaped creatures. Although the gelatinous animals' rhythmic undulations induce calmness, I am grateful for the thick glass separating me from their lacy but stinging appendages, which can paralyze prey in a microsecond.

species are still being seen for the first time by humans." Jellyfish, or jellies (the term many scientists prefer), have no bones or brain and are older than dinosaurs. "They appear so simple in form, yet accomplish relatively sophisticated behaviors, like luring fish, mimicry, and bioluminescence."

The ability of some jellyfish species to produce light in their bodies has fascinated researchers and led to

discovered, and Shimomura spent many years studying its molecular structure.

In the 1990s, other scientists helped propel GFP into the limelight after biochemist Douglas Prasher cloned it at Woods Hole Oceanographic Institution in Massachusetts. Upon request, Prasher sent the clone to Martin Chalfie, a neurobiologist at Columbia University who discovered that GFP could be expressed in other living organisms. Prasher also sent the clone to Roger Tsien, a biochemist at the University of California, San Diego, who modified the protein to emit a spectrum of colors.

When the Nobel committee awarded the 2008 Nobel Prize to Shimomura, Chalfie, and Tsien for their work on GFP, the three laureates acknowledged Prasher's contribution and paid for him to attend the Stockholm ceremony. At the time, Prasher was working as a shuttle driver, but he has since returned to research at Tsien's Laboratory in San Diego.

"Successful innovation is a team sport," said surgeon Quyen Nguyen about the quartet's collaboration during a 2011 TED talk. Nguyen is a senior scientist in the Tsien Lab, which is taking the concept of fluorescent markers to new levels. They have designed a smart molecule to label tumors with fluorescent dye to show the surgeon in the operating room how far to cut without waiting for the tissue to be evaluated by a lab. The Tsien Lab also discovered a molecule that labels nerves. "Basically, we've come up with a way to stain tissue and color code the surgical field," says Nguyen. "I think it will change the way we do surgery."

Norman Maitland, a molecular biologist at the University of York, adapted the protein to help diagnose cancers deep in the body tissue and bone. "When a specially developed camera is switched on, the proteins just flare up and you can see where the cancer cells are," he told the *BBC News*.

Potential applications seem to



© Monterey Bay Aquarium/Randy Wilder

Over the centuries, how to get fast relief from jellyfish stings has dominated most discussions of them, but in recent decades scientific discoveries of their benefits have been making headlines.

"They are a fascinating area for further study," says Steve Haddock, a research scientist at the aquarium's research institute. "Many

groundbreaking scientific discoveries in fluorescence and bioluminescence. In 1962, chemist and marine biologist Osamu Shimomura discovered that a protein that bound to calcium ions made the jellyfish *Aequorea victoria* glow when he isolated and purified green fluorescent protein (GFP), a genetic marker. It was the first photoprotein ever

BACK STORY



be as varied as the ocean itself. Monterey's Haddock thinks one of the coolest applications for GFP is "Brainbow." By applying Tsein's spectrum of colors, Harvard scientists have developed a way to attach a rainbow of fluorescent proteins to the brain, which allows them to track neurological pathways.

Jellies for Arthritis

Jellyfish are turning up in labs across the country. Alabama's Auburn University holds a patent on a collagen from cannonball jellies, which researcher Peggy Hsieh theorizes will be beneficial in the treatment of rheumatoid arthritis. Hsieh's experiments have demonstrated that oral doses of jellyfish collagen have successfully suppressed arthritis in laboratory rats. The university is

Harvard scientists have developed a way to attach a rainbow of fluorescent proteins to the brain, which allows them to track neurological pathways.

looking for a partner to test this further in hopes of creating a safe and inexpensive protein supplement.

Another jellyfish protein already on the market is Prevagen apoequorin, a dietary supplement made by Quincy Bioscience. The synthetic Prevagen is based on the photoprotein isolated from *A. victoria*. Accord-

ing to founder and president Mark Underwood, the supplement keeps brain cells alive longer and improves concentration. Although Underwood claims that Prevagen might help us remember where we parked our cars while grocery shopping, the supplement is not FDA approved.

Massachusetts neuropsychologist Wayne L. Klein, who himself was a human guinea pig for the drug, says there is evidence that apoequorin is neuroprotective inside the brain. The glitch is that it needs to be injected into the brain with a needle, he adds. Klein insists that we'd be better off reducing stress physiologically rather than pharmacologically, which might be attained simply by visiting an aquarium and watching the graceful acrobatics of luminescent jellyfish. ■

George is a freelance writer in Suisun City, California.

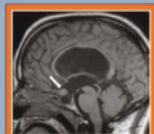


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Reference: 1. Polonsky KS, et al. *N Engl J Med*. 1988;318:1231-1239.

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