Hormone Therapy
A Woman’s Dilemma

PLUS

The Election and Health Care
Mum on Menopause
Benevolent Jellyfish
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THE EARLIER YOU RENEW THE MORE CHANCES YOU HAVE TO WIN.
AND REMEMBER, THERE IS NO INCREASE IN MEMBERSHIP DUES FOR 2013.
Mealtime insulin therapy matters inside the body.

But it first needs to fit your patient’s life.

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 Pump.

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

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.
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 (e.g., 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.

HI HCP ISI 08JUN2011

Humalog® isopro 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 Medronic MiniMed Paradigm pump. Medronic 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 their insulin dosages.

Hypoglycemia—Hypoglycemia is the most common adverse effect associated with the use of 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 the patient’s 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).

Maltung 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%)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Lispro (n=51)</th>
<th>Regular human insulin (n=86)</th>
<th>Total (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu syndrome</td>
<td>25 (48.8)</td>
<td>28 (32.6)</td>
<td>53 (38.6)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>21 (41.2)</td>
<td>29 (33.7)</td>
<td>50 (36.4)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>20 (39.2)</td>
<td>25 (29.1)</td>
<td>45 (32.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>25 (48.8)</td>
<td>19 (21.9)</td>
<td>43 (31.1)</td>
</tr>
<tr>
<td>Pain</td>
<td>16 (31.3)</td>
<td>14 (16.3)</td>
<td>30 (21.6)</td>
</tr>
<tr>
<td>Cough increased</td>
<td>14 (27.5)</td>
<td>15 (17.4)</td>
<td>29 (18.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>11 (21.6)</td>
<td>18 (20.9)</td>
<td>29 (17.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (9.8)</td>
<td>13 (15.1)</td>
<td>18 (10.8)</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>7 (13.7)</td>
<td>10 (11.6)</td>
<td>17 (10.2)</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>5 (9.8)</td>
<td>12 (14.0)</td>
<td>17 (10.2)</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (9.8)</td>
<td>10 (11.6)</td>
<td>15 (9.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (11.8)</td>
<td>7 (8.1)</td>
<td>13 (7.8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (11.8)</td>
<td>7 (8.1)</td>
<td>13 (7.8)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6 (11.8)</td>
<td>6 (7.0)</td>
<td>12 (7.2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7 (13.7)</td>
<td>5 (5.8)</td>
<td>12 (7.2)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>5 (9.8)</td>
<td>6 (7.0)</td>
<td>11 (6.6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (11.8)</td>
<td>5 (5.8)</td>
<td>11 (6.6)</td>
</tr>
<tr>
<td>Urinary tract infection &amp; 4 (7.4)</td>
<td>9 (5.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Lispro (n=714)</th>
<th>Regular human insulin (n=709)</th>
<th>Total (n=1423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>63 (16.4)</td>
<td>66 (16.7)</td>
<td>149 (10.5)</td>
</tr>
<tr>
<td>Pain</td>
<td>77 (10.8)</td>
<td>71 (10.0)</td>
<td>148 (10.4)</td>
</tr>
<tr>
<td>Injection</td>
<td>72 (10.1)</td>
<td>54 (7.6)</td>
<td>126 (8.9)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>47 (6.6)</td>
<td>58 (8.2)</td>
<td>105 (7.4)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>58 (8.1)</td>
<td>47 (6.6)</td>
<td>105 (7.4)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>44 (6.2)</td>
<td>58 (8.2)</td>
<td>102 (7.2)</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>53 (7.4)</td>
<td>48 (6.8)</td>
<td>101 (7.1)</td>
</tr>
</tbody>
</table>

Insulin infusion 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 lipatrophy (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 (CSI)
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).
INDICATIONS AND USAGE

Brief Summary:
HUMALOG should be drawn into the syringe first. Injection should occur immediately after all insulin products, including HUMALOG, cause a shift in potassium as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers, and particular close monitoring.

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 excitant in HUMALOG [see Contraindications].

Antibody Production

In 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 during the initial 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 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.

• Drugs That May Increase the Blood-Glucose-Lowering Effect of HUMALOG and Susceptibility to Hypoglycemia: Oral antidiabetic agents, salicylates, sulfonamide antibiotics, monooxygenase inhibitors, fluoxetine, pramlintide, diisopropylamine, librates, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blockers, and sulfonylurea analogs (e.g., octreotide).

• Drugs That May Reduce the Blood-Glucose-Lowering Effect of HUMALOG: corticosteroids, isoniazid, niacin, estrogen, oral contraceptives, phenothiazines, diazepam, dluretics, 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 hypoglycemia 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 intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

DOSAGE 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 illnesses, 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 Insulin 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 (L-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 Cartridges1 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:

<table>
<thead>
<tr>
<th>Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])</th>
<th>Not In-Use (Unopened) Refrigerated</th>
<th>In-Use (Opened) Room Temperature, (Below 86°F [30°C])</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mL vial</td>
<td>28 days</td>
<td>28 days, refrigerated/room temperature.</td>
</tr>
<tr>
<td>3 mL vial</td>
<td>28 days</td>
<td>28 days, refrigerated/room temperature.</td>
</tr>
<tr>
<td>3 mL cartridge</td>
<td>28 days</td>
<td>28 days, Do not refrigerate.</td>
</tr>
<tr>
<td>3 mL prefilled pen</td>
<td>28 days</td>
<td>28 days, Do not refrigerate.</td>
</tr>
<tr>
<td>3 mL Humalog KwikPen (prefilled)</td>
<td>28 days</td>
<td>28 days, Do not refrigerate.</td>
</tr>
</tbody>
</table>

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 99.6°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-100). 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 Dieteronic D-TRON® and D-TRON® Plus pumps.

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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).
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 END0 2013 program will cover the spectrum of endocrine research and its applications to patient care. In addition, END0 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. END0 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 END0 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.

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 END0 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, END0 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
FROM THE EDITOR

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.
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.

“‘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.

Kelly Horvath
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 µM 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
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

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 during 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 tubulointerstitial 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.
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 3β (GSK3β). GSK3β is an enzyme critical in metabolism, 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](mend.endojournals.org)) that this disruption of the MLT circadian rhythm by light at night “has significant and far-reaching biological consequences.”

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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](jcem.endojournals.org)), the researchers suggest that additional studies could test the applicability of their proposed thresholds to improving the treatment of older men.

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**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 antibiotic 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 timeframe 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*

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**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*
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 reperfused the hearts with a solution containing either ghrelin or hexarelin for 30 minutes (controls were reperfused for 70 minutes), either before or after the ischemic episode. A subset of reperfused 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 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 essential role for ninein during neural development.

In an article to be published in The Journal of Clinical Endocrinology & Metabolism [jcem.endojournals.org], the researchers 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.
“Diagnostic Dilemmas certainly delivers and leads readers on a step by step discovery process as they unravel puzzling cases along with the authors. I would recommend this book to anyone seeking a current self-assessment resource relevant to their everyday practice challenges.”

— Lewis E. Braverman, MD

This one-of-a-kind authoritative guide will test your knowledge and diagnostic skills with carefully selected medical images previously published in *The Journal of Clinical Endocrinology & Metabolism* (*JCEM*). The patient presentations have been revised and updated by the original authors, and reflect rare disorders, unusual presentations of common disorders, and fascinating images. This four-color volume also includes detailed explanations of diagnostic work-ups, and diagnoses and treatments for complex endocrine disorders.

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Hormone Therapy
A Woman’s Dilemma

By Erin Wayman
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

<table>
<thead>
<tr>
<th>Risks</th>
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<tr>
<td><strong>Estrogen or Estrogen-plus-Progesterin Therapies</strong></td>
<td><strong>Estrogen or Estrogen-plus-Progesterin Therapies</strong></td>
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<tr>
<td>Stroke (9–11+)</td>
<td>Spine and hip fractures (-46–56)</td>
</tr>
<tr>
<td>Deep venous thrombosis (7–12+)</td>
<td></td>
</tr>
<tr>
<td>Gallbladder disease (20–25+)</td>
<td><strong>Estrogen-only Therapy</strong></td>
</tr>
<tr>
<td>Urinary incontinence (872–1,271+)</td>
<td>Invasive breast cancer (-8)</td>
</tr>
<tr>
<td><strong>Estrogen-plus-Progesterin Therapy</strong></td>
<td>Breast cancer deaths (-2)</td>
</tr>
<tr>
<td>Dementia (22+)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Embolism (9+)</td>
<td></td>
</tr>
<tr>
<td>Invasive breast cancer (8+)</td>
<td></td>
</tr>
</tbody>
</table>

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,” 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 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 progesterin 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
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 onto 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.’

For additional links related to this feature, please visit Endocrine News Online at www.endo-society.org/endo_news.

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.
**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 ≥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®: First-in-class therapy for type 2 diabetes in adults

**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.

**Improved glycemic control**
- 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); \( P < .05 \)

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**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 ≥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 ± OAD, 0.5% for patients failing metformin + SU ± OAD, and 0.6% for patients failing TZD ± 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.

CYCLOSET is a registered trademark of VeroScience, LLC, Tiverton, RI 02878.
Manufactured for: VeroScience, LLC, Tiverton, RI.
Distributed and Marketed by: Santarus, Inc., San Diego, CA.
Please visit www.cycloset.com for more information.
5.3 Contraindications

- Pregnancy: CYCLOSET is contraindicated in women who are or may become pregnant. There is a risk of fetal harm if CYCLOSET is administered to a pregnant woman. Therefore, CYCLOSET should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- Nursing: Breastfeeding is not recommended during treatment with CYCLOSET. Breastfeeding is not recommended during treatment with CYCLOSET.

5.4 Lactation

- Breastfeeding is not recommended during treatment with CYCLOSET. Breastfeeding is not recommended during treatment with CYCLOSET.

5.5 Children

- Children: The safety and effectiveness of CYCLOSET in children have not been established.

5.6 Macrovascular Outcomes

- CYCLOSET may reduce the effectiveness of these agents. CYCLOSET has not been studied in combination with insulin.

5.7 Antihypertensive Medications

- Patients taking antihypertensive medications should be observed closely when using CYCLOSET, as antihypertensive medications may diminish the effectiveness of CYCLOSET and CYCLOSET may diminish the effectiveness of these ergot therapies when used to treat migraine.

5.8 Other Medications

- The concurrent use of CYCLOSET with other medications may alter the effect of CYCLOSET or the concomitant medication.

5.9 Use in Specific Populations

- Pregnancy

- Nursing

- Lactation

- Children

- Geriatric Use

- Patients with Severe Renal Impairment

- Patients with Severe Hepatic Impairment

- Other Contraindications

- Adverse Reactions

- Drug Abuse

- Overdosage

- Precautions

- Drug Interactions

- Laboratory Tests

- Other Clinical Studies

- Use in Specific Populations

6.1 Clinical Trials Experience

- Clinical trials of 3070 patients treated with CYCLOSET showed that there were no serious effects seen during treatment with CYCLOSET.

7.1 Adverse Events Reported in Placebo-Controlled 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)

- Table 1: Adverse Events Reported in Placebo-Controlled 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)

8.1 Administration

- Administration of CYCLOSET should be initiated at low doses and increased as necessary until the desired effect is achieved or side effects are observed.

8.2 Postmarketing Experience

- CYCLOSET has been associated with a variety of adverse events, including somnolence, dizziness, and headache. It is recommended that CYCLOSET be used with caution in patients with a history of hypotension or those who are taking antihypertensive medications.

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8.4 Pediatric Use

- The safety and effectiveness of CYCLOSET in children have not been established.

8.5 Geriatric Use

- Geriatric patients may require a lower starting dose and closer monitoring than younger adults.

8.6 Patients with Severe Renal Impairment

- Patients with severe renal impairment may require a lower starting dose and closer monitoring than patients with normal renal function.

8.7 Patients with Severe Hepatic Impairment

- Patients with severe hepatic impairment may require a lower starting dose and closer monitoring than patients with normal hepatic function.

8.8 Other Contraindications

- Contraindications to the use of CYCLOSET include pregnancy, breastfeeding, and certain medical conditions such as heart failure, conduction disturbances, and recent myocardial infarction.

8.9 Adverse Reactions

- Adverse reactions to CYCLOSET are generally mild to moderate in severity and include somnolence, dizziness, headache, and gastrointestinal effects.

8.10 Drug Interactions

- CYCLOSET is a CYP3A4 substrate and is metabolized by CYP3A4. Other medications that are substrates of CYP3A4 may affect the metabolism of CYCLOSET.

8.11 Laboratory Tests

- Laboratory tests should be performed periodically to monitor the effectiveness of CYCLOSET.

8.12 Other Clinical Studies

- Other clinical studies have shown that CYCLOSET is effective in the treatment of type 2 diabetes.

8.13 Nonclinical Toxicology

- Nonclinical studies have shown that CYCLOSET is safe and well-tolerated in animals.

Table 1: Adverse Events Reported in Placebo-Controlled 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)

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Table 2: Components of the composite endpoint of interest were the occurrence of the primary endpoint, serious adverse events, and cardiovascular endpoints.

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are already taking one of these other dopamine receptor agonists is unknown. Concomitant use was 32 kg/m

adverse events leading to discontinuation occurred in 539 (24%) CYCLOSET-treated patients

rates reported in one clinical trial may not be easily compared to those rates reported in another

6.1 Clinical Trials Experience

patients taking neuroleptic drugs. The concomitant use of CYCLOSET and dopamine receptor

including neuroleptic agents that have dopamine D2 receptor antagonist properties (eg,

Dopamine receptor antagonists,

was reported in 1.6% of CYCLOSET-treated patients and 0.7% of placebo-treated patients

six CYCLOSET-treated patients (0.3%) reported an adverse event of orthostatic hypotension

medication compared to 73% on such medication in the total study population. In this trial,

majority of patients reported resolution of somnolence over time. Patients should be made

somnolence as an adverse event. None of these events were reported as serious and the

avoid situations that could lead to serious injury if syncope was to occur. Use caution in patients

• Limited efficacy data in combination with thiazolidinediones

HbA1c was 7.0% with a mean baseline fasting plasma glucose of 142 mg/dL. At baseline,

Nausea

26 (32.5) 6 (7.6)

9 (11.3) 3 (3.8)

2

. The mean duration of diabetes at baseline was 8 years and the mean baseline

Hypotension, including orthostatic hypotension, can occur, particularly

Hypoglycemia

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

Therefore, CYCLOSET may increase the unbound fraction of other concomitantly used highly

Hallucinations

bromocriptine mesylate for these indications, generally at doses higher than those approved

Psychotic disorders have been reported with bromocriptine. Additionally, pathological gambling

for humans in which these events are not dependent on prolactin but on luteinizing hormone.

Fibrotic complications, including cases of retroperitoneal fibrosis, pulmonary fibrosis, pleural

association between bromocriptine mesylate use and clinically significant (moderate to severe)

cardiac valvulopathy could be concluded.

considered.

symptoms associated with acute overdose were nausea, vomiting, constipation, diaphoresis,

but greater sensitivity of some older individuals cannot be ruled out.

8.4 Pediatric Use

CYCLOSET is contraindicated in women who are nursing their children. CYCLOSET contains

In two strains of pregnant rabbits treated from gestation day 6-18 with oral doses of 3, 10,

implantation and the maintenance of gestation on prolactin in the rat and are not relevant

for these indications, generally at doses higher than those approved

for these indications, generally at doses higher than those approved

Complete the PIM, either individually or as a part of a practice team, and earn 20 points toward

the Self-Evaluation of Practice Performance (Part 4) requirement of Maintenance of Certification

(MOC) and claim up to 20 AMA PRA Category 1 Credits™.
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 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’ 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.”

### 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 symptom of interrupted sleep and hot flashes as severe or moderate; another third say the same about hot flashes. Twenty-eight percent of women describe their symptom of interrupted sleep and hot flashes as severe or moderate; another third say the same about hot flashes. Twenty-eight percent of women describe their symptom of interrupted sleep and hot flashes as severe or moderate; another third say the same about hot flashes. Twenty-eight percent of women describe their symptom of interrupted sleep and hot flashes as severe or moderate; another third say the same about hot flashes. Thirty-five percent of women say their symptom of mood swings is severe or moderate; another third say the same about mood swings. Almost 27 percent of women describe their symptom of vaginal dryness as severe or moderate; another third say the same about vaginal dryness. Twenty percent of women say their symptom of irregular periods is severe or moderate; another third say the same about irregular periods.

![Percentage of Women Currently Experiencing Menopausal Symptoms](image)

#### Percentage of Women Currently Experiencing Menopausal Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Moderate or severe</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interrupted sleep</td>
<td>44%</td>
<td>10%</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>44%</td>
<td>13%</td>
</tr>
<tr>
<td>Lack of sexual drive</td>
<td>34%</td>
<td>6%</td>
</tr>
<tr>
<td>Mood swings</td>
<td>35%</td>
<td>12%</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>27%</td>
<td>9%</td>
</tr>
<tr>
<td>Irregular periods</td>
<td>19%</td>
<td>7%</td>
</tr>
</tbody>
</table>

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.
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.

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.
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
NOW IS THE TIME FOR ANABOLIC ACTION

FORTEO CONNECT OFFERS PERSONALIZED SUPPORT TO HELP PATIENTS THROUGHOUT THEIR TREATMENT

- Patients can choose to sign up for an insurance investigation, injection training, and/or ongoing support for up to 24 months
- Now with the FORTEO Co-pay Card, eligible commercially insured patients will pay no more than a $50/month co-pay*

*This offer may be terminated, rescinded, revoked, or amended by Lilly USA, LLC at any time without notice. Patient should provide the card to his/her pharmacist, along with a valid prescription from the physician.

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.

• High risk for fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

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

IMPORTANT SAFETY INFORMATION

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

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

CONTRAINdications

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

WARNINGS AND PRECAUTIONS

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

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

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) which 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.

ADVERSE REACTIONS

Osteoporosis Trials in Women and Men Adverse Events

Osteoporosis Trials in Women and Men Adverse Events

Orthostatic Hypotension
Transient orthostatic hypotension may occur with initial doses of FORTEO. In short-term clinical pharmacology studies, transient episodes of symptomatic orthostatic hypotension were observed. Symptoms included dizziness, lightheadedness, presyncope, and syncope. In clinical trials, the incidence of symptomatic orthostatic hypotension was less than 1% in FORTEO patients. In postmarketing reports, symptomatic orthostatic hypotension has been observed with FORTEO.

Metabolic Bone Diseases
FORTEO has not been studied specifically in patients with metabolic bone disease or hyperparathyroidism. Therefore, the safety and efficacy of FORTEO were evaluated in clinical studies of patients with primary or hypogonadal osteoporosis or patients who have undergone total hip or total knee replacement surgery. In the clinical studies, the safety and efficacy of FORTEO were demonstrated in patients with osteoporosis at high risk for fracture.

In clinical trials, 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 1352 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: 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%); Immune System: In the clinical trial, antibodies that cross-react with teriparatide were detected in 3% of patients (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 hypercalcemia 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, urateria, 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 (16 men, 81 women) aged 22 to 89 years (mean 57 years) treated with ≥ 5mg per day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO and 214 patients exposed to oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day. The incidence of all cause mortality was 4% in the FORTEO group and 6% in the active
control group. The incidence of serious adverse events was 21% in FORTEO patients and 18% in active control patients, and included dizziness (2% FORTEO, 0% active control). Adverse events reported at a higher incidence in the FORTEO group and with at least a 2% difference in FORTEO-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of FORTEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Osteosarcoma: Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing.

Hypercalcemia: Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use. Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following: Allergic Reactions: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria; Investigations: Hyperuricemia; Respiratory System: Acute dyspnea, chest pain; Musculoskeletal: Muscle spasms of the leg or back; Other: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema.

USE IN SPECIFIC POPULATIONS

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

OVERDOSAGE

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

DOSAGE FORMS AND STRENGTHS

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

PATIENT COUNSELING INFORMATION

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

06/15/2012

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

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www.forteo.com

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RX only.

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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.
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.


Three subpopulations of β cells are seen in mice expressing the green fluorescent protein under the control of the mouse insulin 1 gene promoter.


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


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


Disruption of the leptin gene in Sprague Dawley rats leads to increased body weight, hyperinsulinemia, glucose intolerance, immunosuppression, and increased bone mass.


**Endocrinology & Metabolism**

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


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.


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 Gnhr1 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.


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


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

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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.

“Those 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.

Usma 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

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**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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  - Histopathological confirmation of an ACTH-staining adenoma in postsurgical patients

- Patients with de novo Cushing’s disease who are nonsurgical candidates

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.
Editor, Leonard Wartofsky, MD

A Clinical Approach to Endocrine & Metabolic Diseases (2nd Edition), a new case-based manual, focuses on the diagnosis and management of a diverse range of common challenging cases. Each informative chapter, originally published in the “Approach to the Patient” series from The Journal of Clinical Endocrinology & Metabolism (JCEM), is completely revised and delivers the clinical acumen of an endocrine “guru.”

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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 diagnosis 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 consistently 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.

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**Two Orals Fail in a T2DM Patient**

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.
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 a 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

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.

- 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)
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 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.

<table>
<thead>
<tr>
<th>Level</th>
<th>Severity of hypertriglyceridemia</th>
<th>Raised risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 150 mg/dL</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>150–199 mg/dL</td>
<td>Mild</td>
<td>Heart disease</td>
</tr>
<tr>
<td>200–999 mg/dL</td>
<td>Moderate</td>
<td>Heart disease</td>
</tr>
<tr>
<td>1,000–1,999 mg/dL</td>
<td>Severe</td>
<td>Very severe hyper-triglyceridemia</td>
</tr>
<tr>
<td>2,000 mg/dL or higher</td>
<td>Very severe</td>
<td>Pancreatitis</td>
</tr>
</tbody>
</table>

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. Besides these lifestyle changes, you may also need drug treatment.

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.
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- 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).
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* 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 QD) 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).

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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 sulfonylurea, the most common side effects included hypoglycemia, diarrhea, and nausea.

GLUMETZA® and Smartcoat® are registered trademarks of Biovail Laboratories International S.r.l. AcuForm® is a registered trademark of Depomed, Inc.
GLUMETZA® (metformin hydrochloride extended release tablets) | 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 should not be administered in patients with:
  - Renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women or ≥ 2.1 mg/dL for men ≥ 70 years of age) or evidence of renal dysfunction may also result from conditions metabolic cardiovascular collapse (acute), acute myocardial infarction, and sepsis. (See WARNINGS AND PRECAUTIONS)
- Known hypersensitivity to metformin hydrochloride.
- Any chronic or acute lactic 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 and can result in metformin toxicity. Lactic acidosis can occur in association with a number of pathophysiological conditions, including diabetes mellitus, and can be fatal. Certain conditions (e.g., hypoxic states, acute alteration of renal function) and have been associated with lactic acidosis in patients receiving intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute lactic acidosis. Levels of fasting venous plasma lactate above the upper limit of normal but less than 2.5 mmol/L (14 mg/dL) are usually not associated with symptoms and are not considered to be consistent with acute lactic acidosis. However, levels of lactate are often subnormal when lactic acidosis is suspected in any setting, with metabolic acidosis lacking evidence of ketosis (ketonuria and ketonemia). Lactic acidosis is a serious, but rare adverse event. Treatment with GLUMETZA should generally be avoided in patients with clinical or laboratory evidence of increased lactate levels or acidosis, particularly in situations in which lactate levels would be expected to increase and in patients with conditions associated with abnormal lactate levels (e.g., hypoxia, hypoperfusion) that may be causally linked to lactic acidosis. When lactic acidosis is suspected, the patient 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 of metformin, adequate clinical and laboratory observation should continue. Monitoring of renal function and patient symptoms should continue until lactic acidosis is ruled out. If present, GLUMETZA should be withdrawn until lactic acidosis is ruled out. If lactic acidosis is confirmed, concomitant medications should be withdrawn and appropriate investigations and management undertaken. Metformin should be withheld until lactic acidosis is ruled out. If lactic acidosis is confirmed, metformin should be withdrawn and appropriate investigations and management undertaken. Metformin should be withheld until lactic acidosis is ruled out. If lactic acidosis is confirmed, concomitant medications should be withdrawn and appropriate investigations and management undertaken. Metformin should be withheld until lactic acidosis is ruled out.

Monitoring of Renal Function
Metformin is substantially excreted by the kidney, and the risk of metformin accumulation increases as the severity of renal impairment increases. Therefore, GLUMETZA is contraindicated in patients with renal impairment. Before initiation of GLUMETZA and at least annually thereafter, renal function should be assessed and the prescription of GLUMETZA adjusted accordingly to minimize the risk of metformin accumulation in patients with renal impairment. In patients in whom any such study is planned, GLUMETZA should be temporarily discontinued and the patient's oral intake withheld for 48 hours before the procedure and reinstituted 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) and should be discontinued and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Use of Concomitant Medications that may affect renal function or metabolism—Concomitant medications) that may affect renal function or result in significant hemodynamic change or may interfere with metabolism of metformin, such as medications that are eliminated by renal tubular secretion (see DRUG INTERACTIONS), should be used with caution.

Hyponatremia
Hyponatremia: Radiologic studies involving the use of intravascular inodinated contrast materials (for example, intravenous urography, intravenous cholangiography, and computed tomography) can lead to the accumulation of metformin 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 and the patient's oral intake withheld for 48 hours before the procedure and reinstituted only after renal function has been re-evaluated and found to be normal. Metformin therapy should be temporarily suspended for any surgical procedure (except minor procedures) and should be discontinued and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

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and lunch/dinner with this.

Dr. Lefkowitz Wins 2012 Nobel Chemistry Prize

Dr. Arthur Lefkowitz, professor of biochemistry at Stanford University School of Medicine, has been awarded the 2012 Nobel Chemistry Prize for his discovery of how receptors for hormones, such as insulin and adrenalin, work. The 1986 Nobel Chemistry Prize was awarded to Howard E. Hems and George E. Palade for their fundamental work on receptor-mediated endocytosis. The Nobel Committee stated that Lefkowitz’s work is an important advance in our understanding of how hormones, enzymes and other molecules act on cells.

The 2012 Nobel chemistry prize goes to Lefkowitz for determining the molecular mechanism of signal transduction for seven transmembrane receptors that are important in the body’s response to hormones. His work has led to the development of drugs for treating diabetes, high blood pressure, and heart disease. Lefkowitz’s discovery has also helped to shed light on the mechanisms by which drugs act on cells and how they are able to change cell behavior.

Lefkowitz and his team have shown that receptors bind to a hormone or other signal molecule and then undergo a series of changes that allow them to activate a signaling pathway. This pathway, which involves the activation of a protein called Gαs, results in the production of intracellular messengers that can affect a cell’s behavior.

Lefkowitz’s work has had a significant impact on the field of biology and medicine, and he has been recognized with numerous awards for his research, including the 2001 National Medal of Science and the 2006 Kyoto Prize.

The 2012 Nobel Chemistry Prize was announced on October 8.

Dr. Beverly Biller of Massachusetts General Hospital, Boston, Massachusetts, and Dr. Shlomo Melmed of Cedars-Sinai Medical Center, Los Angeles, were among the recipients of this year’s VPGH Award. The VPGH Award, which is sponsored by the VPGH Foundation, recognizes outstanding achievements in the field of endocrinology.

The VPGH Foundation is a charity that supports research and education in the field of endocrinology. The foundation was established in 1982 and has provided more than $20 million in funding to support research and education projects.

The VPGH Award recognizes individuals who have made significant contributions to the field of endocrinology. The award is given to individuals who have made significant contributions to the field of endocrinology.

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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 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 recommends 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...
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.

* 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 Ingbar 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, 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.*

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**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.
**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.

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**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.

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**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@bmmmsa.com, Telephone: 610-527-1604, Fax: 610-525-8018.

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**Search For Faculty Members: Harvard Search**

The Reproductive Endocrine Unit of the Department of Medicine of the Massachusetts General Hospital, 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 Endocrine 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.
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
Join our Research Team in Toronto

Physiology & Experimental Medicine Program
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.
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, 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

Other Endocrine Society Guidelines COMING SOON

- Acromegaly
- Diabetes & Pregnancy
- Hyponatremia
- Hypothalamic Amenorrhea
- Medical Therapies of Hypothyroidism
- Paget’s Disease of the Bone
- Pharmacological Management of the Obese Patient
- Pheochromocytoma/Paraganglioma
- PCOS

Endocrine Society Clinical Guidelines ALSO AVAILABLE

- Maternal Thyroid Dysfunction
- Osteoporosis in Men
- Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting
- Continuous Glucose Monitoring
- Vitamin D
- Adult Growth Hormone Deficiency
- Pituitary Incidentaloma
- Hyperprolactinemia
- Post-Bariatric Surgery Patient
- Congenital Adrenal Hyperplasia
- Testosterone Therapy in Adult Men
- Endocrine Treatment of Transsexual Persons
- Adult Hypoglycemic Disorders
- 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.

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 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 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 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
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 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 apoaequorin, a dietary supplement made by Quincy Bioscience. The synthetic Prevagen is based on the photoprotein isolated from A. victoria. According 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 apoaequorin 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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Now Available!

ESAP™ 2012

The Endocrine Society’s Premier Self-Assessment Resource

Based on the ABIM blueprint for certification, ESAP 2012 is the perfect tool for physicians seeking certification or recertification, and clinicians simply wanting a self-assessment and a broad review of endocrinology.

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To register or purchase ESAP 2012, visit: www.endocrineself-assessment.org, to order by phone call 1.888.363.6762 or 301.941.0210 Monday–Friday, 8:30 a.m.–5:00 p.m. ET.

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Important Risk Information: If regular adjustments or modifications to the basal rate of insulin are required in a 24-hour period, or if the amount of insulin used at meals requires adjustments of less than 2-Unit increments, use of the V-Go Disposable Insulin Delivery Device may result in hypoglycemia. The following conditions may occur during insulin therapy with the V-Go: hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose). Other adverse reactions associated with V-Go use include skin irritation from the adhesive pad or infections at the infusion site. The V-Go should be removed before any magnetic resonance imaging (MRI) testing.

*If you follow the V-Go Instructions for Patient Use.


Introducing the V-Go, an easy-to-use device providing insulin delivery that mimics the physiologic pattern found in people without diabetes.*1

- Simple basal-bolus insulin delivery to help control blood glucose
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