Bridging the gap between payer and provider perspectives

THE AMERICAN JOURNAL OF MANAGED CARE®

April 2015
Volume 21
Special Issue 5

Evidence-Based Diabetes Management

MANAGING COMORBID CONDITIONS SPECIAL ISSUE

Provider Feature

Unraveling the Mysteries and Extensive Needs of Emergency Department "Superutilizers"

When 5% of Medicaid recipients account for 54% of spending, cost is just the beginning of the problem.

TONY HAGEN

After his heart attack in 2009, Troy Johnson, who suffers from type 2 diabetes mellitus (T2DM), came to frequent the hospitals in and around Camden, NJ. At 345 pounds, the 51-year-old maintenance worker had a history of not eating properly or exercising regularly; he later compounded his medical problems by stepping on a nail, which led to an infection that doctors were unable to bring under control.

Johnson had no health insurance. He took whatever medication he could afford sparingly to make it last, and he frequently ran out of bandages for his foot wound. The only way he could get any medical attention was to show up in the emergency department (ED), so he did. Records show that he visited often, about once every 3 months for up to 3 years.

A term has been coined for Johnson and patients like him: the "superutilizer."[1] Pioneering work by Jeffrey Brenner, MD, founder and CEO of the Camden Coalition of Healthcare Providers and a 2013 MacArthur Fellow,[2,3] found ways to identify patients like Johnson, and then to reduce the frequency of their ED visits. It requires addressing not only their chronic conditions but

(continued on page SP154)

Pharma Feature

Studies Are Showing SGLT2s Also Help Control Hypertension, Eliminate Some Side Effects

ANDREW SMITH

The market already abounded with type 2 diabetes mellitus (T2DM) treatments that produce comparable reductions in glycated hemoglobin (A1C) levels when the first sodium-glucose co-transporter 2 (SGLT2) inhibitor arrived.

Analysts predicted solid but unspectacular sales, both for canagliflozin (Invokana)[1] and the entire drug class,[2] on grounds that SGLT2 inhibitors reduced A1C about as much as everything else did, giving doctors no compelling reason to switch from standbys like sitagliptin (Januvia).

Subsequent research, however, indicates that SGLT2 inhibitors may perform somewhat better than expected. They have lowered A1C levels significantly more than rivals, helped patients lose more weight than other oral therapies and, perhaps most significantly, proved their ability to combat hypertension.

Initial monotherapy trials of the 3 SGLT2 inhibitors approved to date—canagliflozin, dapagliflozin (Farxiga), and empagliflozin (Jardiance)—reported average reductions in systolic blood pressure (BP) that range from 2.3 mm Hg to 5 mm Hg.[3,4] Recent studies conclude they may actually reduce BP by 7 mm Hg to 10 mm Hg.[5] Should such findings convince physicians to abandon old favorites for the newer drugs? Researchers who have studied them believe they may be right for certain

(continued on page SP156)

Coordinated Care

When Moving to Collaborative Care, a Challenge Is Figuring Out How to Pay for It

MARY K. CAFFREY

For several years now, the evidence has been consistent on how to best treat patients with both diabetes and behavioral health issues. Collaborative care models produce better health outcomes for patients, and can save money, too.[1,2]

The concept behind embedding behavioral health providers in the primary care practice is simple. Comorbidities such as depression or substance abuse are met head on, reducing the likelihood that patients with chronic conditions will skip expensive medications or refuse to see a specialist, resulting in emergency department (ED) visits, hospitalizations, and readmissions.

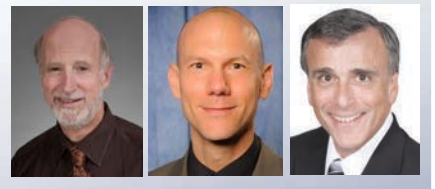
And yet, that simple idea can conflict with reality on many points. Sometimes, it's a primary care physician (PCP) who isn't ready to share control of a patient; more often, practices that want to pursue a collaborative care model struggle to make the finances work. For decades, insurers carved out behavioral health from the rest of medical care; while that is changing under the Affordable Care Act, long-term patterns of care delivery and payment are not easily abandoned. Collaborative care models require funding the salary of a care coordinator, or a diabetes educator, or both.

At professional meetings during 2014,[3,4] questions that followed presentations on collaborative care often focused on these practical concerns. With much of medicine still locked in a fee-for-service (FFS) payment model,

(continued on page SP158)

AJMC®

Panel Discussion: Mental Health and Comorbidities SP151



AJMC convenes a panel discussion on improving mental health delivery, including how collaborative care can benefit patients with comorbidities, including diabetes.

Also in this issue...

SP152 *A joint initiative by the American Medical Association and the CDC seeks to identify persons with prediabetes before it progresses to type 2 diabetes mellitus. Getting those estimated 86 million Americans to eat healthier and embrace lifestyle changes will save the US healthcare system millions, according to Ann Albright, PhD, RD, of the CDC's Office of Diabetes Translation.*

THE AMERICAN JOURNAL OF MANAGED CARE

PUBLISHING STAFF

Brian Haug
PRESIDENT

Drew Colon
ASSOCIATE PUBLISHER

Nicole Beagin
ASSOCIATE EDITORIAL DIRECTOR

Mary K. Caffrey
MANAGING EDITOR

Surabhi Dangi-Garimella, PhD
MANAGING EDITOR

David Allikas
QUALITY ASSURANCE EDITOR

Sara Stewart
DIRECTOR OF SALES

Gilbert Hernandez
NATIONAL ACCOUNTS ASSOCIATE

Gwendolyn Salas
DESIGN DIRECTOR

Jeff D. Prescott, PharmD, RPh
SENIOR VICE PRESIDENT, OPERATIONS AND CLINICAL AFFAIRS

CORPORATE

Mike Hennessy
CHAIRMAN AND CEO

Jack Lepping
VICE CHAIRMAN

Tighe Blazier
PRESIDENT

Neil Glasser, CPA/CFE
CHIEF FINANCIAL OFFICER

John Maglione
EXECUTIVE VICE PRESIDENT AND GENERAL MANAGER

Jeff Brown
VICE PRESIDENT, EXECUTIVE CREATIVE DIRECTOR

Teresa Fallon-Yandoli
EXECUTIVE ASSISTANT

Michael J. Hennessy Associates, Inc.

Office Center at Princeton Meadows, Bldg. 300
Plainsboro, NJ 08536 • (609) 716-7777

The American Journal of Managed Care ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 666 Plainsboro Rd, Bldg. 300, Plainsboro, NJ 08536.

A new option for type 2 diabetes therapy starts here

Trulicity™ is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use: Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. Has not been studied in patients with a history of pancreatitis; consider another antidiabetic therapy. Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Not a substitute for insulin. Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. Not for patients with pre-existing severe gastrointestinal disease. Has not been studied in combination with basal insulin.

Select Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies.

Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Counsel regarding the risk factors and symptoms of thyroid tumors.

Please see Important Safety Information including Boxed Warning about possible thyroid tumors including thyroid cancer and Brief Summary of Prescribing Information on following pages.

trulicity™

dulaglutide injection once weekly

0.75 mg/0.5 mL, 1.5 mg/0.5 mL

A new once-weekly GLP-1 RA therapy is now approved[1]

Trulicity™ offers proven A1C reduction and once-weekly dosing in the Trulicity pen.[1]

Trulicity is a new option for adult patients with type 2 diabetes who need more control than oral medications are providing.[1]

To learn more about Trulicity, visit www.trulicity.com or contact your Lilly Account Manager.

Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

In male and female rats, dulaglutide causes dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies.

Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Counsel regarding the risk factors and symptoms of thyroid tumors.

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

Risk of Thyroid C-cell Tumors: Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (eg, a mass in the neck, dysphasia, dyspnea, persistent hoarseness). Patients with elevated serum calcitonin (if measured) and patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation.

Pancreatitis: Has been reported in clinical trials. Observe patients for signs and symptoms including persistent severe abdominal pain. If pancreatitis is suspected discontinue Trulicity promptly. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapy.

Please see Important Safety Information continued on following page.

DG92365 09/2014 PRINTED IN USA

Important Safety Information, continued

Hypoglycemia: The risk of hypoglycemia is increased when Trulicity is used in combination with insulin secretagogues (eg, sulfonylureas) or insulin. Patients may require a lower dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia.

Hypersensitivity Reactions: Systemic reactions were observed in clinical trials in patients receiving Trulicity. Instruct patients who experience symptoms to discontinue Trulicity and promptly seek medical advice.

Renal Impairment: In patients treated with GLP-1 RAs there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. In patients with renal impairment, use caution when initiating or escalating doses of Trulicity and monitor renal function in patients experiencing severe adverse gastrointestinal reactions.

Severe Gastrointestinal Disease: Use of Trulicity may be associated with gastrointestinal adverse reactions, sometimes severe. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

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

The most common adverse reactions reported in ≥5% of Trulicity-treated patients in placebo-controlled trials (placebo, Trulicity 0.75 mg and 1.5 mg) were nausea (5.3%, 12.4%, 21.1%), diarrhea (6.7%, 8.9%, 12.6%), vomiting (2.3%, 6.0%, 12.7%), abdominal pain (4.9%, 6.5%, 9.4%), decreased appetite (1.6%, 4.9%, 8.6%), dyspepsia (2.3%, 4.1%, 5.8%), and fatigue (2.6%, 4.2%, 5.6%).

Gastric emptying is slowed by Trulicity, which may impact absorption of concomitantly administered oral medications. Use caution when oral medications are used with Trulicity. Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered with Trulicity. In clinical pharmacology studies, Trulicity did not affect the absorption of the tested, orally administered medications to a clinically relevant degree.

Pregnancy: There are no adequate and well-controlled studies of Trulicity in pregnant women. Use only if potential benefit outweighs potential risk to fetus.

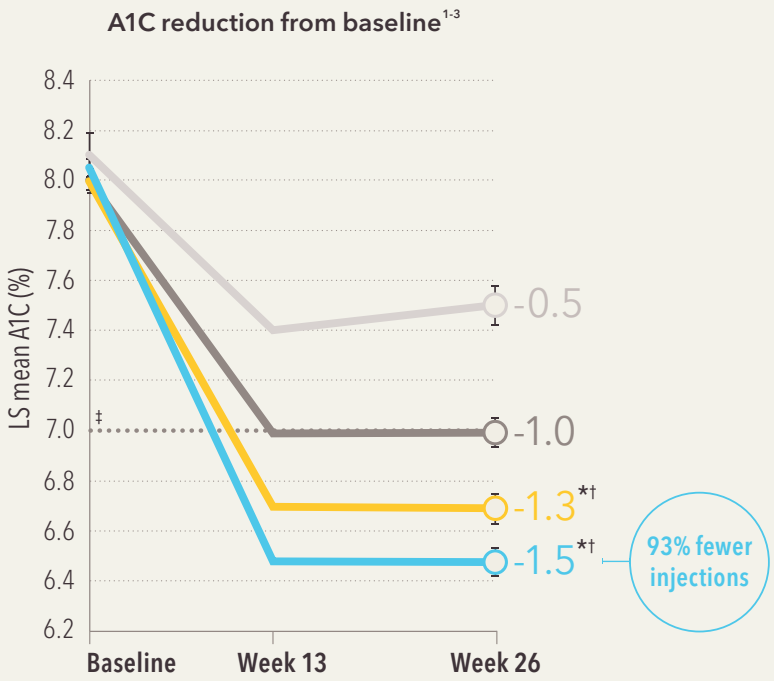
Nursing Mothers: It is not known whether Trulicity is excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue Trulicity taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of Trulicity have not been established and use is not recommended in patients less than 18 years of age.

Please see Brief Summary of Full Prescribing Information including Boxed Warning about possible thyroid tumors including thyroid cancer on following pages. Please see Instructions for Use included with the pen.

DG HCP ISI 18SEP2014

Once-weekly Trulicity showed significant A1C reduction[1]



- **Placebo** (n=141; Baseline A1C: 8.1%)
- **Byetta® (10 mcg BID)** (n=276; Baseline A1C: 8.1%) **Injections: ~730/year**
- **Trulicity™ (0.75 mg)** (n=280; Baseline A1C: 8.1%) **Injections: ~52/year**
- **Trulicity™ (1.5 mg)** (n=279; Baseline A1C: 8.1%) **Injections: ~52/year**

Data represent least-squares mean ± standard error.

* Multiplicity-adjusted 1-sided *P* value <.025 for superiority of Trulicity vs Byetta for A1C.

† Multiplicity-adjusted 1-sided *P* value <.001 for superiority of Trulicity vs placebo for A1C. Mixed model repeated measures analysis.
After 26 weeks, placebo-treated patients were switched in a blinded fashion to Trulicity 1.5 mg or Trulicity 0.75 mg.

‡ American Diabetes Association recommended target goal. Treatment should be individualized.[4]

- 52-week, randomized, placebo-controlled phase 3 study (open-label assignment to Byetta or blinded assignment to Trulicity or placebo) of adult patients with type 2 diabetes treated with maximally tolerated metformin (≥1500 mg/day) and Actos® (up to 45 mg/day)
- Primary objective was to demonstrate superiority of Trulicity 1.5 mg vs placebo on change in A1C from baseline at 26 weeks (-1.5% vs -0.5%, respectively; difference of -1.1%; 95% CI [-1.2, -0.9]; multiplicity-adjusted 1-sided *P* value <.001; analysis of covariance using last observation carried forward); primary objective met

References

1. Trulicity [Prescribing Information]. Indianapolis, IN: Lilly USA, LLC; 2014.
2. Data on file, Lilly USA, LLC. TRU20140910A.
3. Data on file, Lilly USA, LLC. TRU20140919C.
4. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(Suppl 1):S14-S80.

trulicity™

dulaglutide injection once weekly

0.75 mg/0.5 mL, 1.5 mg/0.5 mL

Trulicity™

(dulaglutide)

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

WARNING: RISK OF THYROID C-CELL TUMORS

- **In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies.**
- **Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Counsel regarding the risk factors and symptoms of thyroid tumors.**

INDICATIONS AND USAGE

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

Limitations of Use:
Not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise. Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. It is not a substitute for insulin. Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. Not recommended in patients with pre-existing severe gastrointestinal disease. The concurrent use of Trulicity and basal insulin has not been studied.

CONTRAINDICATIONS

Do not use in patients with a personal or family history of MTC or in patients with MEN 2. Do not use in patients with a prior serious hypersensitivity reaction to dulaglutide or to any of the product components.

WARNINGS AND PRECAUTIONS

Risk of Thyroid C-cell Tumors: In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. Glucagon-like peptide (GLP-1) receptor agonists have induced thyroid C-cell adenomas and carcinomas in mice and rats at clinically relevant exposures. It is unknown whether Trulicity will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of this signal could not be determined from the clinical or nonclinical studies. One case of MTC was reported in a patient treated with Trulicity. This patient had pretreatment calcitonin levels approximately 8 times the upper limit of normal (ULN). Trulicity is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the risk for MTC with the use of Trulicity and inform them of symptoms of thyroid tumors (eg, a mass in the neck, dysphagia, dyspnea, persistent hoarseness). The role of serum calcitonin monitoring or thyroid ultrasound monitoring for the purpose of early detection of MTC in patients treated with Trulicity is unknown. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin as a screening test for MTC and a high background incidence of thyroid disease. Very elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. Patients with thyroid nodules noted on physical examination or neck imaging should also be referred to an endocrinologist for further evaluation.

Pancreatitis: In Phase 2 and Phase 3 clinical studies, 12 (3.4 cases per 1000 patient years) pancreatitis-related adverse reactions were reported in patients exposed to Trulicity versus 3 in non-incretin comparators (2.7 cases per 1000 patient years). An analysis of adjudicated events revealed 5 cases of confirmed pancreatitis in patients exposed to Trulicity (1.4 cases per 1000 patient years) versus 1 case in non-incretin comparators (0.88 cases per 1000 patient years). After initiation of Trulicity, observe patients carefully for signs and symptoms of pancreatitis, including persistent severe abdominal pain. If pancreatitis is suspected, promptly discontinue Trulicity. If pancreatitis is confirmed, Trulicity should not be restarted. Trulicity has not been evaluated in patients with a prior history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: The risk of hypoglycemia is increased when Trulicity is used in combination with insulin secretagogues (eg, sulfonylureas) or insulin. Patients may require a lower dose of sulfonylurea or insulin to reduce the risk of hypoglycemia.

Hypersensitivity Reactions: Systemic hypersensitivity reactions were observed in patients receiving Trulicity in clinical trials. If a hypersensitivity reaction occurs, the patient should discontinue Trulicity and promptly seek medical advice.

Renal Impairment: In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Because these reactions may worsen renal failure, use caution when initiating or escalating doses of Trulicity in patients with renal impairment. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.

Severe Gastrointestinal Disease: Use of Trulicity may be associated with gastrointestinal adverse reactions, sometimes severe. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

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

ADVERSE REACTIONS

Clinical Studies 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.

Pool of Placebo-controlled Trials:

These data reflect exposure of 1670 patients to Trulicity and a mean duration of exposure to Trulicity of 23.8 weeks. Across the treatment arms, the mean age of patients was 56 years, 1% were 75 years or older and 53% were male. The population in these studies was 69% White, 7% Black or African American, 13% Asian; 30% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.0 years and had a mean HbA1c of 8.0%. At baseline, 2.5% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60mL/min/1.73 m^2) in 96.0% of the pooled study populations.

Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of Trulicity-Treated Patients: Placebo (N=568), Trulicity 0.75mg (N=836), Trulicity 1.5 mg (N=834) (listed as placebo, 0.75 mg, 1.5 mg) nausea (5.3%, 12.4%, 21.1%), diarrhea[a] (6.7%, 8.9%, 12.6%), vomiting[b] (2.3%, 6.0%, 12.7%), abdominal pain[c] (4.9%, 6.5%, 9.4%), decreased appetite (1.6%, 4.9%, 8.6%), dyspepsia (2.3%, 4.1%, 5.8%), fatigue[d] (2.6%, 4.2%, 5.6%). ([a] Includes diarrhea, fecal volume increased, frequent bowel movements. [b] Includes retching, vomiting, vomiting projectile. [c] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, gastrointestinal pain. [d] Includes fatigue, asthenia, malaise.) Note: Percentages reflect the number of patients that reported at least 1 treatment-emergent occurrence of the adverse reaction. Gastrointestinal Adverse Reactions: In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving Trulicity than placebo (placebo 21.3%, 0.75 mg 31.6%,1.5 mg 41.0%). More patients receiving Trulicity 0.75 mg (1.3%) and Trulicity 1.5 mg (3.5%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.2%). Investigators graded the severity of gastrointestinal adverse reactions occurring on 0.75 mg and 1.5 mg of Trulicity as "mild" in 58% and 48% of cases, respectively, "moderate" in 35% and 43% of cases, respectively, or "severe" in 7% and 11% of cases, respectively. In addition to the adverse reactions ≥5% listed above, the following adverse reactions were reported more frequently in Trulicity-treated patients than placebo (frequencies listed, respectively, as: placebo; 0.75 mg; 1.5 mg): constipation (0.7%; 3.9%; 3.7%), flatulence (1.4%; 1.4%; 3.4%), abdominal distension (0.7%; 2.9%; 2.3%), gastroesophageal reflux disease (0.5%; 1.7%; 2.0%), and eructation (0.2%; 0.6%; 1.6%).

Pool of Placebo- and Active-Controlled Trials:

The occurrence of adverse reactions was also evaluated in a larger pool of patients with type 2 diabetes participating in 6 placebo- and active-controlled trials evaluating the use of Trulicity as monotherapy and add-on therapy to oral medications or insulin. In this pool, a total of 3342 patients with type 2 diabetes were treated with Trulicity for a mean duration 52 weeks. The mean age of patients was 56 years, 2% were 75 years or older and 51% were male. The population in these studies was 71% White, 7% Black or African American, 11% Asian; 32% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.2 years and had a mean HbA1c of 7.6-8.5%. At baseline, 5.2% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60 ml/min/1.73 m^2) in 95.7% of the Trulicity population. In the pool of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed as ≥5% above.

Other Adverse Reactions:

Hypoglycemia: **Incidence (%) of Documented Symptomatic (≤70 mg/dL Glucose Threshold) and Severe Hypoglycemia in Placebo-Controlled Trials:** Add-on to Metformin at 26 weeks, Placebo (N=177), Trulicity 0.75 mg (N=302), Trulicity 1.5 mg (N=304), Documented symptomatic: Placebo: 1.1%, 0.75 mg: 2.6%, 1.5 mg: 5.6%; Severe: all 0. Add-on to Metformin + Pioglitazone at 26 weeks, Placebo (N=141), TRULICITY 0.75 mg (N=280), Trulicity 1.5 mg (N=279), Documented symptomatic: Placebo: 1.4%, 0.75 mg: 4.6%, 1.5 mg: 5.0%; Severe: all 0. Hypoglycemia was more frequent when Trulicity was used in combination with a sulfonylurea or insulin. Documented symptomatic hypoglycemia occurred in 39% and 40% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with a sulfonylurea. Severe hypoglycemia occurred in 0% and 0.7% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with a sulfonylurea. Documented symptomatic hypoglycemia occurred in 85% and 80% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with prandial insulin. Severe hypoglycemia occurred in 2.4% and 3.4% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with prandial insulin. Heart Rate Increase and Tachycardia Related Adverse Reactions: Trulicity 0.75 mg and 1.5 mg resulted in a mean increase in heart rate (HR) of 2-4 beats per minute (bpm). The long-term clinical effects of the increase in HR have not been established. Adverse reactions of sinus tachycardia were reported more frequently in patients exposed to Trulicity. Sinus tachycardia was reported in 3.0%, 2.8%, and 5.6% of patient treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Persistence of sinus tachycardia (reported at more than 2 visits) was reported in 0.2%, 0.4% and 1.6% of patients treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Episodes of sinus tachycardia, associated with a concomitant increase from baseline in heart rate of ≥15 beats per minute, were reported in 0.7%, 1.3% and 2.2% of patient treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Immunogenicity: Across four Phase 2 and five Phase 3 clinical studies, 64 (1.6%) TRULICITY-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in Trulicity (ie, dulaglutide). Of the 64 dulaglutide-treated patients that developed dulaglutide ADAs, 34 patients (0.9% of the overall population) had dulaglutide-neutralizing antibodies, and 36 patients (0.9% of the overall population) developed antibodies against native GLP-1. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to dulaglutide cannot be directly compared with the incidence of antibodies of other products. Hypersensitivity: Systemic hypersensitivity adverse reactions sometimes severe (eg, severe urticaria, systemic rash, facial edema, lip swelling) occurred in 0.5% of patients on Trulicity in the four Phase 2 and Phase 3 studies. Injection-site Reactions: In the placebo-controlled studies, injection-site reactions (eg, injection-site rash, erythema) were reported in 0.5% of Trulicity-treated patients and in 0.0% of placebo-treated patients. PR Interval Prolongation and Adverse Reactions of First Degree Atrioventricular (AV) Block: A mean increase from baseline in PR interval of 2-3 milliseconds was observed in Trulicity-treated patients in contrast to a mean decrease of 0.9 millisecond in placebo-treated patients. The adverse reaction of first degree AV block occurred more frequently in patients treated with Trulicity than placebo (0.9%, 1.7% and 2.3% for placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively). On electrocardiograms, a PR interval increase to at least 220 milliseconds was observed in 0.7%, 2.5% and 3.2% of patients treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Amylase and Lipase Increase: Patients exposed to Trulicity had mean increases from baseline in lipase and/or pancreatic amylase of 14% to 20%, while placebo-treated patients had mean increases of up to 3%.

DRUG INTERACTIONS

Trulicity slows gastric emptying and thus has the potential to reduce the rate of absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with Trulicity. Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered with Trulicity. In clinical pharmacology studies, Trulicity did not affect the absorption of the tested, orally administered medications to any clinically relevant degree.

USE IN SPECIFIC POPULATIONS

Pregnancy - Pregnancy Category C: There are no adequate and well-controlled studies of Trulicity in pregnant women. The risk of birth defects, loss, or other adverse outcomes is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes to maintain good metabolic control before conception and throughout pregnancy. Trulicity should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In rats and rabbits, dulaglutide administered during the major period of organogenesis produced fetal growth reductions and/or skeletal anomalies and ossification deficits in association with decreased maternal weight and food consumption attributed to the pharmacology of dulaglutide.

Nursing Mothers: It is not known whether Trulicity is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for clinical adverse reactions from Trulicity in nursing infants, a decision should be made whether to discontinue nursing or to discontinue Trulicity, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of Trulicity have not been established in pediatric patients. Trulicity is not recommended for use in pediatric patients younger than 18 years.

Geriatric Use: In the pool of placebo- and active-controlled trials, 620 (18.6%) Trulicity-treated patients were 65 years of age and over and 65 Trulicity-treated patients (1.9%) were 75 years of age and over. No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment: There is limited clinical experience in patients with mild, moderate, or severe hepatic impairment. Therefore, Trulicity should be used with caution in these patient populations. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no clinically relevant change in dulaglutide pharmacokinetics (PK) was observed.

Renal Impairment: In the four Phase 2 and five Phase 3 randomized clinical studies, at baseline, 50 (1.2%) Trulicity-treated patients had mild renal impairment (eGFR ≥60 but <90 mL/min/1.73 m^2), 171 (4.3%) Trulicity-treated patients had moderate renal impairment (eGFR ≥30 but <60 mL/min/1.73 m^2) and no Trulicity-treated patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). No overall differences in safety or effectiveness were observed relative to patients with normal renal function, though conclusions are limited due to small numbers. In a clinical pharmacology study in subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in dulaglutide PK was observed. There is limited clinical experience in patients with severe renal impairment or ESRD. Trulicity should be used with caution, and if these patients experience adverse gastrointestinal side effects, renal function should be closely monitored.

Gastroparesis: Dulaglutide slows gastric emptying. Trulicity has not been studied in patients with pre-existing gastroparesis.

OVERDOSAGE

Overdoses have been reported in clinical studies. Effects associated with these overdoses were primarily mild or moderate gastrointestinal events (eg, nausea, vomiting) and non-severe hypoglycemia. In the event of overdose, appropriate supportive care (including frequent plasma glucose monitoring) should be initiated according to the patient's clinical signs and symptoms.

PATIENT COUNSELING INFORMATION See FDA-approved Medication Guide

- Inform patients that Trulicity causes benign and malignant thyroid C-cell tumors in rats and that the human relevance of this finding is unknown. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, persistent hoarseness, dysphagia, or dyspnea) to their physician.
- Inform patients that persistent severe abdominal pain, that may radiate to the back and which may (or may not) be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue Trulicity promptly, and to contact their physician, if persistent severe abdominal pain occurs.
- The risk of hypoglycemia may be increased when Trulicity is used in combination with a medicine that can cause hypoglycemia, such as a sulfonylurea or insulin. Review and reinforce instructions for hypoglycemia management when initiating Trulicity therapy, particularly when concomitantly administered with a sulfonylurea or insulin.
- Patients treated with Trulicity should be advised of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients treated with Trulicity of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs.
- Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of GLP-1 receptor agonists. If symptoms of hypersensitivity reactions occur, patients must stop taking Trulicity and seek medical advice promptly.
- Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant.
- Prior to initiation of Trulicity, train patients on proper injection technique to ensure a full dose is delivered. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.
- Inform patients of the potential risks and benefits of Trulicity and of alternative modes of therapy. Inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and advise patients to seek medical advice promptly.
- Each weekly dose of Trulicity can be administered at any time of day, with or without food. The day of once weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days before. If a dose is missed and there are at least 3 days (72 hours) until the next scheduled dose, it should be administered as soon as possible. Thereafter, patients can resume their usual once weekly dosing schedule. If a dose is missed and the next regularly scheduled dose is due in 1 or 2 days, the patient should not administer the missed dose and instead resume Trulicity with the next regularly scheduled dose.
- Advise patients treated with Trulicity of the potential risk of gastrointestinal side effects.
- Instruct patients to read the Medication Guide and the Instructions for Use before starting Trulicity therapy and review them each time the prescription is refilled.
- Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.
- Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels towards the normal range. HbA1c is especially useful for evaluating long-term glycemic control.

Eli Lilly and Company, Indianapolis, IN 46285, USA

US License Number 1891

Additional information can be found at www.trulicity.com

DG HCP BS 18SEP2014

Trulicity™ (dulaglutide) HCP BS 18SEP2014

Examining the Effect of Comorbidities, and Reflecting on the Loss of a Pioneer

With this issue of *Evidence-Based Diabetes Management*, we examine how diabetes mellitus, especially type 2, rarely acts alone. Quite often this disease follows obesity, and patients also experience a myriad of other adverse health effects. The most common are hypertension and heart disease; among the less common diseases are gout, kidney disease, or macular edema. In recent years, physicians are understanding the connections between mental health conditions like depression and poor glycemic control. In some cases, the medication taken to address behavioral health conditions may contribute to obesity and bring on diabetes. Also, persons with mental health issues may be less likely to exercise or eat properly. Understanding how the constellation of symptoms interact with one another is essential to managing them, and coordinating care for patients who suffer multiple conditions is a key component of the Affordable Care Act (ACA). Pioneering physicians like Jeffrey Weber, MD, are understanding the common mental and physical threads that run through patients who frequently land in the emergency department—the "superutilizers" who account for so much of our Medicaid spending. On the pharmaceutical front, research in the past year has shown that a powerful new drug class, the SGLT2 inhibitors, may do more than transport glucose out of the system in a different way. As our cover story details, this class appears to offer benefits in helping patients control blood pressure, perhaps without some side effects and with some additional benefits.

Finally, we are sad to report that this issue covers what turned out to be our final discussion with a true pioneer. Wayne Katon, MD, of the University of Washington, realized 3 decades ago that those who suffer from untreated mental health problems are less likely to follow regimens for other ailments, in particular diabetes. At the same time, he saw that treatment for mental health outside of the primary care setting was often impractical. Dr Katon spent the rest of his career taking on both problems, developing models for primary care physicians and psychiatrists to work under one roof. His groundbreaking studies proved the approach improved glycemic control and feelings of well-being for patients, while saving money. In December, Dr. Katon told us that due to the ACA he was receiving more inquiries about his innovative care models than at any other time in his career. On March 1, 2015, Dr Katon died of lymphoma; we join with all who will miss his insights on the practical needs of patients.

As always, we appreciate your readership. Please look for updates on our live meetings and our conference coverage at www.ajmc.com.

Sincerely,

Brian Haug
President, *The American Journal of Managed Care*

EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in diabetes management.

What NCQA Recognition Means for Patients With Diabetes

Robert A. Gabbay, MD, PhD

ABOUT THE EDITOR

Joslin Diabetes Center

ROBERT A. GABBAY, MD, PhD

Robert A. Gabbay, MD, PhD, is chief medical officer and senior vice president of Joslin Diabetes Center. He serves as editor in chief of *Evidence-Based Diabetes Management*.

In January, just as the previous issue of *Evidence-Based Diabetes Management* was going to press, Joslin Diabetes Center received important news that I am proud to share: Joslin has earned the highest level of recognition from the National Committee for Quality Assurance (NCQA) as a Patient-Centered Specialty Practice (PCSP).

The PCSP designation is modeled on and complements NCQA's Patient-Centered Medical Home (PCMH) Recognition Program. Many of you in primary care are familiar with the Medical Home model; it uses the concept of teamwork to improve the patient experience, takes a population-based approach to manage those in the practice with risk stratification, proactive care and outreach for those in need, and has been shown to improve outcomes in a variety of different primary care settings. The PCSP recognition highlights the rest of the continuum of specialists ("Neighbors of the Medical Home") that are needed to provide outstanding diabetes care. It is clear for diabetes, as much as for any chronic disease, that optimal care requires a team-based approach: primary care providers, endocrinologists, ophthalmologists, nephrologists, diabetes educators, dietitians, and a broad coordinated neighborhood are needed to achieve optimal results. The "neighbors" of medical specialties are those that surround and inform the medical home and colleagues in primary care.

Being recognized for providing quality care is always good news, but this news truly sets us apart. "Three-level" recognition by the NCQA as a Patient-Centered Specialty Practice (PCSP) means that Joslin was cited for its responsiveness both to patients and to medical colleagues, for its cooperation with healthcare groups, and for its dedication to continuous improvement. NCQA's standards are well recognized, as the organization is celebrating its 25th year of working to improve healthcare quality by providing both standards of measurement and transparency for the benefit of providers and consumers.

For patients with diabetes, knowing that a healthcare provider is responsive to others is exceedingly important. Much of the challenge of living with diabetes involves dealing with "the system" and its many moving parts, which at times seem incapable of working together on one's behalf. That's why PCSP recognition is so special.

The thinking behind both models is simple: adapt the care to the patient, instead of expecting the patient to adapt to the care. In diabetes care, especially, we ask so much from our patients. Persons with type 1 diabetes mellitus (T1DM) typically check their blood sugar several times a day, and they have to take insulin. Those with type 2 diabetes mellitus (T2DM) may take a host of medications, including insulin. There are challenges to focusing on a healthy meal plan and exercise. We ask patients to follow up on referrals to eye or foot specialists and then they need to coordinate care across the many providers, often spread across different health systems.

ROBERT A. GABBAY, MD, PhD, center, and staff of the Joslin Diabetes Center celebrate the recent recognition from the National Committee for Quality Assurance.
Photo courtesy of Joslin Diabetes Center

Everyone at Joslin is proud to have met or exceeded national standards for:

- Communicating with primary care clinicians to exchange key information and establish coordinated care plans
- Providing timely access to care and clinical advice based on patient need
- Using a systematic approach to track referrals and coordinate care
- Measuring and improving performance over time.

The last measure is especially important, because we must constantly monitor our quality of care, not just to keep up current standards but also to seek new ways to improve delivery, either through better technology or through feedback we get from patients and families.

Notice how much of this designation involves the mechanics of how we provide care—coordination, tracking, referring. These are the components that make up the *patient experience*. As important as it is to have groundbreaking clinical research, to have the people who will one day find a cure for diabetes, it is essential that we do all we can to make care as seamless as possible for those who must live with this disease today.

Doing a better job of coordinating care, of making sure referrals are properly tracked, of making sure that patients receive follow-up care—all these things produce results such as better glycemic control, fewer complications, and fewer days in the hospital or the emergency department. And that's the ultimate goal of patient-centered care. **EBDM**

NEWS FROM JOSLIN

Joslin Researchers Use MRI to Visualize Pancreas Inflammation in Early T1DM

JOSLIN NEWS SERVICE

A pilot study led by researchers at Joslin Diabetes Center has revealed that it is possible to use magnetic resonance imaging (MRI) to "see" the inflammation in the pancreas that leads to type 1 diabetes mellitus (T1DM). The findings, published February 3, 2015, in the *Proceedings of the National Academy of Sciences*, could aid efforts to slow or halt the disease at an early stage, and could also guide insights into how diabetes progresses.

This clinical study tested the possibility of imaging inflammation in the pancreas of human volunteers using ferumoxytol, a coated iron nanoparticle approved by the FDA as an iron replacement therapy, and MRI. Ferumoxytol leaks out of blood vessels in areas of inflammation and is taken up by immune cells called macrophages, which congregate at sites of inflammation. Autoimmunity and inflammation directed against the pancreas and its insulin-producing beta cells underlie the development of T1DM. However, while tests for autoantibodies (antibodies against the pancreas) can reveal whether a patient's immune system has at some point attacked the pancreas, these antibodies are not always a good marker for predicting whether a given individual will develop full-blown diabetes.

"Many people have genetic variants that put them at risk for type 1 diabetes," explains study co-lead author Jason Gaglia, MD, MMSc, assistant investigator in the Section of Immunobiology at Joslin. "Some develop autoimmunity, but only a small number develop clinical disease."

In addition, the development of therapies that could potentially halt patients' progression from pancreatic inflammation to diabetes has been hampered by the long lead times needed in order to tell whether a given therapy has an effect. "If you want to study in people an immunomodulatory agent right now, for diabetes it takes years," Gaglia says. He explains that the end measurements for whether such therapies work relate directly to pancreatic function, changes in which may not become apparent for a long time. With imaging, he continues, "you could have an answer in a matter of months."

For the study, researchers recruited 11 patients with newly diagnosed T1DM and evidence of antibodies against the pancreas, a sign that their beta cells were under inflammatory attack. They also recruited 10 controls with no sign or family history of diabetes. To visualize inflammation across the whole pancreas, the researchers adapted MRI mapping algorithms originally developed for whole brain scanning. All other components of the experiment, including MRI equipment and ferumoxytol, are widely available. Gaglia notes that the ferumoxytol dose used in this imaging study is approximately one-fourth of the dose used therapeutically for iron replacement. "These are all off-the-shelf components," he says. "Other centers can do this now."

Ferumoxytol-MRI images of the patient group showed clear evidence of ferumoxytol accumulation in the pancreas, indicating ongoing inflammation. By comparison, images from the control group did not.

The researchers believe this imaging technique could have a range of applications in diabetes research and help build a better understanding of the natural history of T1DM. Already, Gaglia says, the ferumoxytol-MRI images revealed that in their patient group, "inflammation was not uniform across the entire pancreas. There was also a large amount of variation between individuals, which aligns with what you see clinically. That's never been shown in living humans before."

This imaging approach could, in the future, help better define which patients with autoimmunity will likely progress to diabetes and classify subgroups of patients who might benefit from different therapeutic strategies. It could also identify those patients with early signs of autoimmunity who might be good candidates for clinical research studies.

"Only about 5% of the first degree family members of a person with diabetes will develop occult disease," said Gaglia, who is firm that for the moment this imaging technique should only be used in the context of research. "It might make sense to scan people in that group to see who is likely to progress and who isn't. Those who are progressing may be the ones you would want to recruit for research on immunomodulatory therapies."

REFERENCE

Gaglia JL, Harisinghani M, Aganj I, et al. Noninvasive mapping of pancreatic inflammation in recent-onset type-1 diabetes patients [published online February 3, 2015]. *Proc Natl Acad Sci.* pii:201424993.

A Look at the Unhealthiness of Sitting, and a Call for More Research on Its Effects

Mary K. Caffrey

Sitting for long periods is associated with chronic disease and even early death. Yet researchers have little understanding of why this is true, even though the world is increasingly designed for sitting, according to a meta-analysis published January 20, 2015, in the *Annals of Internal Medicine*.[1]

Both the study and an accompanying editorial read like a call to arms for researchers in basic science and in the healthcare industry, as the data clearly show the cost implications of caring for an aging population who bear the lifetime effects of sitting at desks and watching TV. The meta-analysis received widespread attention, with headlines warning that a small dose of exercise was not enough to offset the effects of sitting all day.[2]

The authors, led by Aviroop Biswas, BSc, and Paul I Oh, MD, MSc, examined studies involving all-cause mortality, cardiovascular disease, diabetes, and cancer in adults by searching scientific databases for all studies published through August 2014.[1] Forty-seven studies met the criteria, and meta-analyses were performed on 41. Data pooled from the studies found that after adjusting for levels of physical activity, prolonged periods of sitting were positively correlated with:

- All-cause mortality (hazard ratio [HR] ,1.240; 95% CI, 1.09-1.41)
- Cardiovascular disease mortality (HR, 1.179; 95% CI, 1.106-1.257)
- Cardiovascular disease incidence (HR, 1.143; 95% CI, 1.002-1.729)
- Cancer mortality (HR, 1.173; 95% CI, 1.108-1.242)
- Cancer incidence (HR, 1.130; 95% CI, 1.053-1.213)
- Type 2 diabetes mellitus (T2DM) (HR 1.910; 95% CI, 1.642-2.222)

An accompanying editorial by Brigid M. Lynch, PhD, and Neville Owen, PhD, of the Baker IDI Heart and Diabetes Institute of Melbourne, Australia, found the implications of the study "far-reaching." "Sedentary behavior is ubiquitous," they wrote. "Society is engineered, physically and socially, to be sitting-centric."[3]

Connections among sedentary behavior, chronic disease, and their fallout in managed care have been researched previously. In 2012, *The American Journal of Managed Care* reported results from Quinn et al, which found overweight and obese men were less likely to undergo screenings for colorectal and prostate cancer, even though the men presented risk factors, such as sedentary lifestyles and diets that were low in fruits and vegetables.[4]

In their *Annals* editorial, Lynch and Owen draw connections between the meta-analysis findings and what they mean for governments that fund all or most of a nation's healthcare coverage, given how little is known about the science behind how sitting affects cardiovascular activity. (They note, for example, that the Australian government recommends at least 5 hours of moderate physical activity each week.)[3]

To address the lack of research in the field, they draw attention to the following areas of work:

- **Isotemporal substitution modeling.** This examines the effects of different associations when time spent doing 1 activity is altered by another activity while time is constant.
- **Objective activity monitoring.** At present, most activity is self-reported. Lynch and Owen recommend using devices to track activity more precisely, such as whether the per-

TV Watching Appears Worse Than Other Forms of Sitting

MARY K. CAFFREY

If sedentary behavior is less healthy than being active, are some sedentary behaviors unhealthier than others?

Several studies published in the past year have identified excessive television watching as singularly unhealthy compared with long hours in front of a computer or at the wheel of vehicle. However, that may have mostly to do with what people aren't doing when they're watching TV.

A study published in June 2014 in the *Journal of the American Heart Association* found that "Television viewing was directly associated with all-cause mortality," while computer use and time spent driving were not.[1] The study examined a cohort of 13,284 Spanish university graduates with a mean age of 37 years who were followed for an average of 8.2 years.

Regression models were used to examine the association between different sedentary behaviors and total mortality. According to the authors, when television was analyzed as a separate variable, the all-cause mortality incidence rate ratios (IRRs) for each additional 2 hours per day were 1.40 (95% CI, 1.06-1.84). By comparison, the IRRs were 0.96 (95% CI, 0.79- 1.18) for an additional 2 hours a day of computer use and 1.14 (95% CI, 0.90-1.44) for an additional 2 hours of driving, after adjusting for age, sex, smoking status, total energy intake, body mass index (BMI), physical activity, and whether the participants followed a Mediterranean diet.[1] The authors were surprised by the results, but noted that they were consistent with studies conducted elsewhere, including those in the United States.

A study published in the *British Journal of Cancer* in January 2015 found that prolonged television watching was not only associated with diabetes and obesity, but might also be involved with a higher incidence of colorectal cancer.[2] An analysis of 31,065 men evaluated the effects of sitting while watching TV—and how time spent sitting affected other leisure activities—on the risk of colorectal cancer.

The study divided the cohort into risk groups based on number of TV hours watched per week: up to 6 hours, 7 to 13 hours, 14 to 20 hours, and 21 hours or more. Prolonged sitting while watching TV was significantly associated with increased risk of colorectal cancer, and adjusting for physical activity or BMI did not change the estimates. The men in the 2 groups that watched the most TV per week had the highest risks of colorectal cancer. With 1.0 as the reference for those watching up to 6 hours per week, the risk ratio (RR) for those watching 7 to 13 hours was 1.09; 14 to 20, 1.16; and 20 or more, 1.10 (however, this last set included a subset of patients with significantly higher risk of developing an adenoma).[2]

What is it about TV watching, compared with other sedentary behaviors, that is potentially so damaging to one's health? Researchers who published a study in the July 2014 issue of *JAMA Internal Medicine* tried to answer that question while investigating a group of women with gestational diabetes mellitus (GDM) who were at high risk of developing type 2 diabetes mellitus (T2DM).[3]

A cohort of 4554 women from the Nurses' Health Study II were followed as part of the Diabetes & Women's Health Study. Physical activity and television watching were assessed in 1991, 1997, 2001, and 2005. Compared with women who maintained the same level of physical activity, the women with GDM who increased their exercise by the equivalent of 150 minutes of moderate activity per week had a 47% lower risk of developing T2DM, and this association remained significant after adjusting for BMI.[3]

Conversely, as with the British study, the risk ratios (RRs) for T2DM associated with watching television increased along with the number of hours watched per week. With 1.0 as the RR reference for those watching 0 to 5 hours per week, the RR rose to 1.28 for 6 to 10 hours per week, 1.41 for 11 to 20 hours, and 1.77 for 20 hours or more.[3]

The researchers found that "Time spent watching TV was associated with an increased risk of T2DM. Other sedentary behaviors, such as sitting at work or away from home or driving, and other (types of) sitting at home, were unrelated to T2DM risk."[3]

In their paper, the team posited both biological and social explanations for the phenomenon. Physical activity, they wrote, leads to increased insulin-stimulated glucose uptake into active skeletal muscle, which accounts for 80% of disposal. Physical activity may also affect body fat distribution and the loss of visceral fat, which is associated with insulin resistance. Moving, quite simply, prevents weight gain, which is a predictor of T2DM.

It's not that TV watching causes T2DM per se, but that too much TV watching occupies too many hours that the viewer could spend being more physically active; thus, the authors explain, TV watching is correlated with an overall unhealthy lifestyle. "TV watching acts as a sedentary replacement for physical activity, leading to a reduction in energy expenditure," they write. "TV watching is associated with 'mindless' eating. Finally, while watching TV, women may be influenced by commercial food advertisements."[3] **EBDM**

References

1. Basterra-Gotari FJ, Bes-Rastrollo M, Gea A, Nunez-Cordoba JM, Toledo E, Martinez-Gonzales MA. Television viewing, computer use, time driving and all-cause mortality: the SUN cohort. *J Am Heart Assoc.* 2014;3(3):e000864.

2. Cao Y, Keum NN, Chan AT, Fuchs CS, Wu K, Giovannucci EL. Television watching and risk of colorectal adenoma [published online January 15, 2015]. *Br J Cancer*. doi:10.1038/bjc.2014.655.

3. Bao W, Tobias DK, Bowers K, et al. Physical activity and sedentary behaviors associated with risk of progression from gestational diabetes mellitus to type 2 diabetes mellitus. *JAMA Intern Med.* 2014;174(7):1047-1055.

son was walking up an incline or suddenly accelerating, to reduce errors and to provide a more complete picture of activity.

- **Studies of population subgroups.** Authors of the editorial note that limited information about subgroups is available, even though it is unlikely that risk levels are the same across the population.[3]

ARE STANDING DESKS A SOLUTION?

The adverse effects of too much sitting have gained attention in recent years. Manufacturers have promoted different models of "standing desks," which give office workers the ability to stay in an upright position, with potential health benefits. Now, the effects of the desks are being measured, and an early review of studies appeared in January 2015 in *Preventive Medicine*.[5]

MacEwen et al compared the effects of different models. Treadmill desks produced the greatest physiological outcomes, including improved postprandial glucose, high-density lipoprotein cholesterol, and anthropometrics, while standing desks were associated with few physiological changes. Both styles showed mixed results for improving psychological well-being and had little impact on work performance, the authors found.[5] **EBDM**

References

1. Biswas A, Oh, PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med*. 2015;162(2):123-132.

2. Doyle K. Gym time won't cancel out too much sitting. Reuters website. http://newsdaily.com/2015/01/gym-time-wont-cancel-out-too-much-sitting/. Published January 20, 2015. Accessed February 4, 2015.

3. Lynch BM, Owen N. Too much sitting and chronic disease risk: steps to move the science forward. *Ann Intern Med*. 2015;162(2):146-147.

4. Quinn VP, Jacobsen SJ, Slezak JM, et al. Preventive care and health behaviors among overweight/obese men in HMOs. *Am J Manag Care*. 2012;18(1):25-32.

5. MacEwen BT, MacDonald DJ, Burr JF. A systematic review of standing and treadmill desks in the workplace. *Prev Med*. 2015;70C:50-58.

Study Finds Older Adults With T2DM, Comorbidities Aren't Getting Enough Treatment Time

Tony Hagen

The CMS policy change that will pay primary care doctors to coordinate care, taking more time with patients who have multiple chronic conditions, is probably long overdue, if a 2014 study of older adults is any sign. (See **cover story**). Researchers conducted a series of small-group interviews involving 32 older patients, all of whom suffered from type 2 diabetes mellitus (T2DM) and other comorbidities. The older adults expressed great frustration over not having enough time to consult with doctors, and said they needed more individualized treatment plans than they are getting, according to results published in *Clinical Diabetes*, a journal of the American Diabetes Association.[1]

The study also concluded that both doctors and older patients need tools and training, so that patients' needs can be better interpreted and addressed. Based on the results, this may be true even if patients are achieving relatively good glycemic control—patients who by some standards were receiving quality care nonetheless told researchers they often felt overwhelmed.

The research team encouraged greater consideration of older adults' preferences for care, in part because the Affordable Care Act (ACA) calls for shared decision making in healthcare. But the ACA also presents some inherent conflicts: while in some aspects it calls for personalized approaches to care, it is also moving toward a "value-based" reimbursement approach that rewards accountable care organizations, or ACOs, for population health management. Diabetes measures are a key component of ACO Medicare reimbursement.

In the January issue of *Evidence-Based Diabetes Management*, Patrick J. O'Connor, MD, MA, MPH, a senior clinical investigator for HealthPartners, discussed how the importance of meeting targets impacts both doctors and patients. He said that physicians and researchers alike must start to pay attention to the concept of "minimally disruptive medicine." Patients get frustrated when doctors pile on too many pills to help patients meet targets when they are already very close to goal, if it means living with too many side effects or high out-of-pocket costs.[2] And, there has long been a recognition that Medicare reimbursements do not reward physicians for taking time to tailor treatment plans to individual patients. So starting this year, CMS has moved to reward primary care physicians with payments of $40 per month per patient to coordinate care for patients with more than 1 chronic condition. Collecting this fee will require the patient's involvement, consent, and a personal care plan.[3]

The focus group study, which took place in central Pennsylvania, involved patients aged 60 to 88 years (average age, 75.3 years). Most study participants were overweight, with an average body mass index of 32.5. Participants were 44% male and 100% non-Hispanic white; 52% had a college degree or higher level of education, 60% were married, and 84% were retired.

The study recruited patients who had been diagnosed with T2DM for at least 1 year, and who suffered from at least 1 other comorbidity. On average, patients had lived with T2DM for 15 years, and 87.5% were taking at least 1 oral hypoglycemic medication. Nearly half (46%) had been prescribed injectable insulin, although as a group they enjoyed good glycemic control, with their mean glycated hemoglobin (A1C) at 7.0 (range 5.6-8.2). Importantly, the authors cited 2 recent qualitative studies involving providers that "spoke of conflicts between balancing patients' preferences with their own decisions for care and weighing the risks and benefits of adhering to treatment guidelines."[1] These studies called for more "patient-centered" approaches to care.[4,5]

STUDY TESTIMONIALS

> "Patients described feeling frustrated and overwhelmed with the multiple lifestyle, self-care, and medical demand required to manage their diabetes and comorbidities."

> "Strategies that facilitate a mutual understanding of treatment preferences may help providers and older adults with T2DM manage multiple health conditions more effectively and with greater peace of mind."

> "I used to walk all the time, and now I can't with the spinal stenosis and the arthritis. I don't know what to do about it. They just don't want to understand that I can't exercise."

> "I think doctors discriminate against older people in that respect. They say that you're OK, and you're not."

Eight 60-minute focus group sessions took place, with between 2 and 6 participants in each group. The participants' chief complaints about their doctors were lack of empathy and understanding, unwillingness to hear patients talk about their health concerns, insensitivity and age discrimination, and an unwillingness to treat older patients with T2DM.

"Strategies that facilitate a mutual understanding of treatment preferences may help providers and older adults with T2DM manage multiple health conditions more effectively and with greater peace of mind," the authors wrote.

The 6 most commonly reported conditions participants had, in addition to T2DM, were hypertension, arthritis, retinopathy, hypercholesterolemia, coronary artery disease, and neuropathy.

The study's goal was to determine what perceived challenges the patients felt served as barriers to the kind of care they expected from their doctors. Among the conclusions was that financial savings could be achieved by addressing some of these challenges.

The report indicated that these patients "described feeling frustrated and overwhelmed with the multiple lifestyle, self-care and medical demands required to manage their diabetes and other chronic comorbidities." However, the arrival of diabetes-specific complications tended to motivate older patients to better self-manage their health, the study said.

A frequent complaint (by 18 of 32 participants) was that healthcare providers were hesitant to treat them after finding out they had T2DM. "If I have a cut on my finger, they don't want to take care of it because I'm diabetic," an unnamed patient was quoted as saying. "They told me there was surgery for spinal stenosis, but they won't do the surgery because I'm diabetic," the patient said, adding, "I

think they're worried about complications and malpractice. But they aren't looking out for my best interests."

Others told the authors they believed that age discrimination was a factor in their treatment, with 1 woman stating that doctors were sometimes not as aggressive in treating someone her age because she was "closer to death" than younger patients.

Another woman said doctors tend to offer meaningless reassurance to older patients, even though genuine acknowledgment of the patient's condition would be more helpful. "I think doctors discriminate against older people in that respect. They say that you're OK, and you're not," she said.

More time reviewing individual preferences for care would be appreciated, the study participants said. In addition, some told the research team that doctors are not tailoring care to address the specific medical histories of older patients. For example, 1 patient expressed frustration with a doctor's orders to exercise more. "I used to walk all the time, and now I can't with the spinal stenosis and arthritis. I don't know what to do about it. They just don't want to understand that I can't exercise," the patient said.

Study authors concluded that older adults need individualized treatment plans and more "in-depth" communication with their healthcare providers.

"Discussing perceived challenges to diabetes and comorbidity management may provide a systematic way to include older adults in the evaluation and treatment process, thereby enhancing the therapeutic alliance and lowering the economic burden of T2DM care," the authors wrote.

Participants in the study stated that doctors were not fully aware of the difficulties of living with T2DM and managing other chronic ailments. The *Clinical Diabetes* researchers cited studies that appeared in 2011 and 2012 in which care providers acknowledged the difficulty of managing comorbidities, and the need for individualized medicine.[4,5] These studies cited the challenge of balancing a patient's desire for more involvement in the treatment process with the provider's own judgment about the best course of treatment and the need to avoid risk.

The researchers who interviewed the older patients acknowledged that care providers were not similarly interviewed as part of their study and recommended that future research "involve the collection of mixed-method data from physician-patient pairs to assess communication and shared decision making regarding T2DM and comorbidity management." **EBDM**

References

1. Beverly EA, Wray LA, Chiu CJ, LaCoe CL. Older adults' perceived challenges with health care providers treating their type 2 diabetes and comorbid conditions. *Clin Diabetes.* 2014;32(1)12-17.

2. Caffrey MK. A look beyond findings on telephone intervention reveals why having data matters. *Am J Manag Care*. 2015;21(SP2):SP45.

3. Caffrey MK. How will managed care implement the new $40 CMS coordination fee? *AJMC* website. http://www.ajmc.com/focus-of-the-week/1114/How-Will-Managed-Care-Implement-the-New-40-CMS-Coordination-Fee. Published November 14, 2014. Accessed February 5, 2015.

4. Luijks HD, Loeffen MJ, Lagro-Janssen AL, van Weel C, Lucassen PL, Schermer TR. GPs considerations in multimorbidity management: a qualitative study. *Br J Gen Pract*. 2012; 62:e503-e510.

5. Fried TR, Tinetti ME, Iannone L. Primary care clinicians' experiences with treatment decision making for older persons with multiple conditions. *Arch Intern Med*. 2011;171:75-80.

Implementing JNC 8 Guidelines Is Generally Cost-Effective, According to *NEJM* Findings

Mary K. Caffrey

A year ago, the 2014 recommendations of the Eighth Joint National Committee (JNC 8) received plenty of attention, as they called for 3 key changes from the 2003 guidelines[1,2]:

- For adults less than 60 years of age, without diabetes or chronic kidney disease (CKD), the diastolic blood pressure treatment goal should be <90 mm Hg.
- For adults 60 years or older, without diabetes or CKD, the systolic blood pressure goal should be <150 mm Hg and the diastolic goal should be <90 mm Hg.
- For all adults with diabetes or CKD, the systolic blood pressure goal should be <140 mm Hg and the diastolic goal should be <90 mm Hg.

Data reported in the *Journal of the American Medical Association* suggested that these relaxed guidelines would mean that 1% of adults aged 18 to 59 years and 8% of adults 60 years and older would no longer be eligible for blood pressure therapy. However, that would still leave 28 million adults in the United States with uncontrolled blood pressure.[3]

Should all these potential patients be treated? Specifically, is treating these individuals worth the cost? That second question was addressed in a January 2015 article in the *New England Journal of Medicine*, "Cost-effectiveness of hypertension therapy according to 2014 guidelines."[2]

In the article, authors led by Andrew E. Moran, MD, MPH, write that their purpose is to address a challenge posed by the American College of Cardiology and the American Heart Association, which called for the inclusion of cost-effectiveness analyses and recommendations in practice guidelines. The authors used the Cardiovascular Disease Policy Model to calculate the cost of hypertension monitoring and treatment, the costs averted with treating cardiovascular disease (CVD), and quality-adjusted life-years (QALYs) for adults between the ages of 35 and 74 years for a 10-year period through 2024.

Cost-effectiveness was assessed based on age and hypertension level, and whether the patient had comorbidities of CKD or diabetes. Cost-effectiveness was defined as $50,000 per QALY.

The argument for cost-effectiveness has become important in the care of patients with diabetes and other comorbidities, as patients typically take multiple medications, each with its own cost—both to the payer and to the patient in the form of a co-pay—as well as some side effects. Finding the right balance of cost, achievement such targets as blood pressure and glycated hemoglobin, side effects, and overall health can vary from patient to patient, despite the movement toward quality measures based on population health.[4]

In that context, the *NEJM* article reports several important findings:

- Full implementation of the JNC 8 guidelines for hypertension would result in approximately 56,000 fewer cardiovascular events and 13,000 fewer deaths.[2]
- Projections show that treating patients with existing CVD or stage 2 hypertension would save lives and produce cost savings for men between the ages 35 and 74 years, and for women between the ages of 45 and 74 years. Treating men or women with hypertension but without CVD would remain a *cost-saving* even if strategies to increase medication adherence *doubled* treatment costs.
- Treatment of stage 1 hypertension was *cost-effective* for all men and for women between the ages of 45 and 74 years; however, treating women with stage 1 hypertension without CVD had intermediate or low cost-effectiveness.

The authors write that more frequent office visits, home blood pressure monitoring, pharmacist involvement, or interventions to ensure medication adherence all add value, "even if they require an additional annual investment of up to $1230 per patient in men with CVD, $600 in men with stage 2 hypertension without CVD, and $650 in women with CVD."[2]

Of note, the authors project that achieving the modified treatment goals of 150/90 mm Hg for patients between 60 and 74 years of age would be cost-effective even if a higher rate of medication side effects were assumed. However, they offer the caveat that these older patients have varying degrees of functionality, and patient-by-patient decisions must be made for this reason. "Better predictors of adverse effects of medications are needed to guide the decision to withhold or withdraw treatment from individual patients in this group," they write.[2]

The authors note their study does not consider the synergistic effects of modifying diet or exercise, or the relative merits of different classes of hypertensive medication. **EBDM**

References

1. Page MR. The JNC 8 hypertension guidelines: an in-depth guide. *Am J Manag Care*. 2014;20(SP1)SP5-SP6.

2. Moran AE, Odden MC, Thanataveerat A, et al. Cost-effectiveness of hypertension therapy according to 2014 guidelines. *N Engl J Med*. 2015;372:447-455.

3. Navar-Boggan AM, Pencina MJ, Williams K, Sniderman AD, Peterson ED. Proportion of US adults potentially affected by the 2014 hypertension guidelines. *JAMA*. 2014;311:1424-1429.

4. Caffrey MK. A look beyond findings on telephone intervention reveals why having data matters. *Am J Manag Care*. 2015;21(SP2):SP45.

Weighing the Options With Bariatric Surgery: Long-Term Results Compare Risks, Health Outcomes

Surabhi Dangi-Garimella, PhD

Obesity has grown from a health concern to an epidemic, not just in the United States, but globally. Genetic, dietary, and environmental factors all play a role in the weight gain of obese individuals who suffer from numerous comorbidities, including type 2 diabetes mellitus (T2DM), cardiovascular disease, asthma, osteoarthritis, and cancer.[1] The disease burden associated with these comorbidities translates into increasing expenditures that are a tremendous strain on the healthcare system.

A retrospective analysis, published in 2012 in the *Journal of Occupational and Environmental Medicine*, evaluated the incremental cost of smoking and obesity among employees and their dependents at the Mayo Clinic over a 7-year period.[2] The study reported that both smoking and obesity resulted in excessive healthcare costs among the more than 30,000 individuals included in the study—smokers were responsible for an average of $1275 higher annual healthcare costs than non-smokers, while obese individuals cost an average of $1850 more than normal-weight individuals. Morbidly obese individuals, the study found, had substantially greater expenses: up to $5500 per year.[2,3]

Bariatric surgical procedures remain a proven method for weight loss among obese individuals who may have given up on the diet, exercise, and medication route. While Roux-en-Y gastric bypass (gastric bypass) and sleeve gastrectomy are both quite commonly performed in the United States,[4] biliopancreatic bypass with a duodenal switch (duodenal switch) is performed in patients with a body mass index (BMI) greater than 50. However, a recent study published in *JAMA Surgery* found that the surgical procedure, performed laproscopically, resulted in higher rates of surgical, nutritional, and gastrointestinal adverse effects, even though the procedure produced more weight loss on average than gastric bypass.[5]

WEIGHT LOSS, BUT AT WHAT COST?

Studies have shown that as the prevalence of obesity has increased, surgical weight loss procedures have gained popularity, owing to expanded insurance coverage as well as improved perioperative safety.[6] However, there is a reason why some procedures are more commonly performed than others, the authors of the *JAMA Surgery* study discovered.

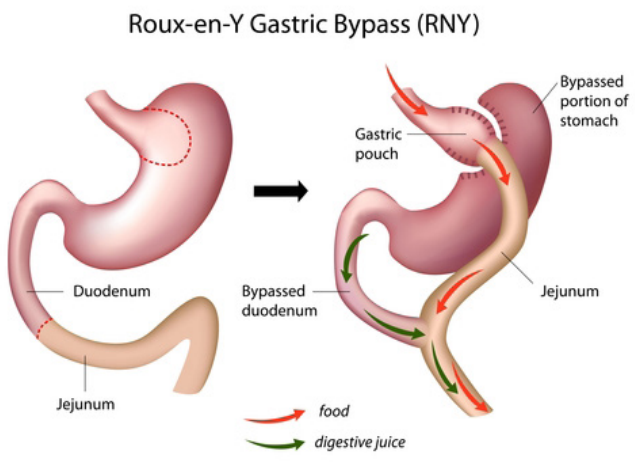
In the study, which was a randomized open-label trial conducted at Oslo University Hospital in Norway, 60 patients aged between 20 and 50 years were recruited between early 2006 and late 2007. Fifty-five of these patients, with a BMI between 50 and 60, were monitored for a 5-year period following the surgical procedure: either gastric bypass or duodenal switch. A shorter 2-year patient follow-up from this trial resulted in a series of publications that identified increased complications with duodenal switch, including gastrointestinal side effects and anal leakage of stool,[7] malnutrition,[8] and deficiencies in vitamins A, B_1, and D.[9] However, weight loss and reduction in total and low-density lipoprotein (LDL) cholesterol were significantly greater following duodenal switch than following gastric bypass.[8]

The 5-year follow-up, presented in the latest paper, evaluated the patients' vitamin and nutritional status, gastrointestinal side effects, health-related quality of life (through a questionnaire), and other adverse events or complaints that they had. This longer-term study found that gastric bypass resulted in an average reduction in BMI of 13.6 (95% CI, 11.0-16.1) while duodenal switch resulted in an average reduction of 22.1 (95% CI, 19.5-24.7), which reiterated previously published results. Total body weight loss was 26.4% (95% CI, 21.7-31.1) after gastric bypass and 40.3% (95% CI, 35.7-44.9) after duodenal switch. The researchers did not observe a significant difference in remission rates for T2DM and metabolic syndrome between the 2 patient cohorts. However, systolic blood pressure was much lower in both cohorts, while diastolic blood pressure was significantly reduced only after gastric bypass. Effects on cardiometabolic risk factors such as total cholesterol and LDL cholesterol were sustained at 5 years following the duodenal switch surgery. However, patients undergoing duodenal switch expressed lower serum concentrations of vitamin A, 25-hydroxyvitamin D, and ionized calcium, and an increase in higher parathyroid hormone levels, compared with those in the gastric bypass cohort.[5]

> *"Bariatric surgery remains a proven method for weight loss among obese individuals who may have given up on the diet, exercise, and medication routine. Studies have shown that as obesity has increased, surgical weight loss procedures have gained popularity."*

Gastrointestinal adverse effects were much more severe following duodenal switch: while both groups reported increased abdominal pain and indigestion during follow-up, patients with duodenal switch had significantly more diarrhea (though not statistically significant; $P = .07$) and increased gastroesophageal reflux ($P = .002$) compared with the gastric bypass patients. Further, social limitations due to altered bowel function were reported by 63% of duodenal switch patients and 25.9% of gastric bypass patients.[5]

While hospitalization for any reason was reported by 29% of gastric bypass patients and 58.6% of duodenal switch patients during the first 5 years after surgery, 44.8% of duodenal switch patients had to undergo additional procedures related to the initial surgery versus 9.7% of gastric bypass patients.[5]



Overall, "Duodenal switch was associated with more surgical, nutritional, and gastrointestinal adverse effects compared with gastric bypass," the authors concluded.

In an accompanying commentary in the same issue of *JAMA Surgery*, 2 surgeons from the University of Michigan stress that the high rates of complications presented by the authors would restrict the employment of duodenal switch as a first-line weight loss procedure. They recommend that patients should receive ample warning about risks associated with this surgery, and that the procedure should be reserved for compliant patients who are good with follow-up, to avoid the risk of fatal post operative complications.[10] **EBDM**

References

1. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of comorbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*. 2009;9:88-107.

2. Moriarty JP, Branda ME, Olsen KD, et al. The effects of incremental costs of smoking and obesity on health care costs among adults: a 7-year longitudinal study. *J Occup Environ Med*. 2012;54(3):286-291.

3. Obesity adds more to health care costs than smoking, study suggests. *ScienceDaily* website. http://www.sciencedaily.com/releases/2012/04/120403124252.htm. Published April 3, 2012. Accessed February 19, 2015.

4. Buchwald H, Oien DM. Metabolic/bariatric surgery Worldwide 2008. *Obes Surg*. 2009;19:1605-1611.

5. Risstad H, Søvik TT, Engström M, et al. Five-year outcomes after laparoscopic gastric bypass and laparoscopic duodenal switch in patients with body mass index of 50 to 60: a randomized clinical trial [published online February 4, 2015]. *JAMA Surg*. doi:10.1001/jamasurg.2014.3579.

6. Reames BN, Finks JF, Bacal D, Carlin AM, Dimick JB. Changes in bariatric surgery procedure use in Michigan, 2006-2013. *JAMA*. 2014;312(9):959-961.

7. Søvik TT, Karlsson J, Aasheim ET, et al. Gastrointestinal function and eating behavior after gastric bypass and duodenal switch. *Surg Obes Relat Dis*. 2013;9(5):641-647.

8. Søvik TT, Aasheim ET, Taha O, et al. Weight loss, cardiovascular risk factors, and quality of life after gastric bypass and duodenal switch: a randomized trial. *Ann Intern Med*. 2011;155(5):281-291.

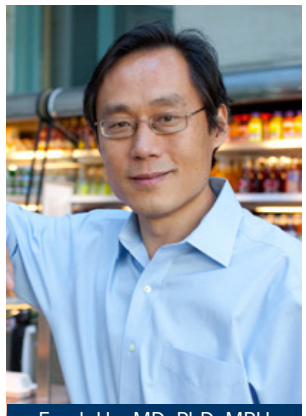
9. Aasheim ET, Björkman S, Søvik TT, et al. Vitamin status after bariatric surgery: a randomized study of gastric bypass and duodenal switch. *Am J Clin Nutr*. 2009;90(1):15-22.

10. Varban OA, Dimick, JB. Weighing the risks and benefits of bariatric surgery: choose your own adventure [published online February 4, 2015]. *JAMA Surg*. doi:10.1001/jamasurg.

Dietary Panel Releases Report, Cholesterol Removed From List of Nutrients to Avoid

Mary K. Caffrey

Dietary cholesterol may no longer be verboten for most Americans, if the US secretaries of Agriculture and Health and Human Services (HHS) accept a recommendation from the 2015 Dietary Guidelines Advisory Committee (DGAC).[1] The recommendation came after panel members spent more than a year reviewing the latest evidence on how what we eat—and where we eat—affects our overall health.


Frank Hu, MD, PhD, MPH

DGAC called for cholesterol to be removed from the list of "nutrients of concern for overconsumption" in a wide-ranging report issued February 19, 2015.[1] Ironically, the report came out just as the British journal *The Lancet* released a 6-part call to action for governments worldwide to take proactive steps against rising rates of obesity (see **SP148**). The change in the cholesterol recommendation was first reported by *The Washington Post*.[2]

The cholesterol change is based on a 2013 review by the American Heart Association and the American College of Cardiology[3]; the dietary panel said current evidence "shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol."[1]

The new recommendation has drawn mixed reviews; some say there is no reason for healthy adults to avoid naturally occurring cholesterol in foods like eggs or seafood. Others worry that Americans will take the change as a license to continue to add saturated fats to their diets, which, as the DGAC notes elsewhere, is a significant problem. And the change may not apply to persons with diabetes, which could create challenges for patients and those who treat them.[2]

The beef industry is expected to resist some findings, such as: "Moderate evidence indicates that healthy dietary patterns higher in vegetables, fruits, and whole grains and lower in red and processed meats, high-fat dairy products, refined grains, and sweets/sugar-sweetened beverages reduce the risk of developing type 2 diabetes."[1] The beverage industry is expected to respond to findings about added sugar, which include: "Strong and consistent evidence shows that intake of added sugars from food and/or sugar-sweetened beverages are associated with excess body weight in children and adults." The panel called for added sugar intake to be less than 10% of total calories.[1]

The day the report was released, the Physicians' Committee for Responsible Medicine filed a petition with the US Department of Agriculture for cholesterol to remain a "nutrient of concern" while praising the report for highlighting the benefits of plant-based diets. In a press release, the Physicians Committee said: "The major findings regarding sustainable diets were that a diet higher in plant-based foods, such as vegetables, fruits, whole grains, legumes, nuts, and seeds, and lower in calories and animal based foods is more health promoting and is associated with less environmental impact than is the current US diet."[4]

The report concludes the work of the advisory committee, which is convened every 5 years by law to advise the 2 secretaries, who get the last word on the 2015 *Dietary Guidelines for Americans*. The guidelines are the nation's official nutrition policy and affect everything from military meals to nutrition programs for poor mothers and children to school lunches. The 2010 guidelines informed the law that overhauled the National School Lunch Program, triggering a backlash from school cafeteria officials and students.[5,6]

The secretaries can change the recommendations, but historically, the DGAC's outline is left intact. (The report is subject to a 45-day comment period and a public hearing.)[7] A discussion of national nutrition policy and the 2015 guidelines featuring Frank Hu, MD, MPH, a DGAC member from the Harvard School of Public Health, took place April 17, 2015, at Patient-Centered Diabetes Care, in Boston. The meeting was hosted by *The American Journal of Managed Care* and Joslin Diabetes Center. (Look for the upcoming special issue of *Evidence-Based Diabetes Management* on the conference.)

While the cholesterol change will capture the public's attention, the 2015 report contains plenty of sobering news for public health officials. Starting in the late childhood years, Americans fall far short of recommended levels of fruit and vegetable consumption, and this pattern continues into early adulthood. As adults age, there is some recovery of vegetable consumption, and those aged 51 to 70 years report the highest vegetable intake. However, most Americans continue to consume less-than-recommended levels of dark green or other colored vegetables.

The report notes that (white) potatoes are "the most commonly consumed single vegetable," and account for 25 percent of all vegetable consumption. While the DGAC cites potatoes as "a good source of both potassium and fiber," the report also breaks down the methods of preparation, some of which are less than healthy: 31% being boiled (including mashed and in dishes such as potato salad, soups, and stews), 22% as chips, sticks, or puffs, 19% as french fries, 17% as baked, and 12% as home fries or hash browns.

As promised, the DGAC's scientific report bursts with information about changing patterns of American food consumption, and the implications for what Americans consume and overall health.[1,9] In fact, parts of the report lend credence to some of the complaints about the difficulty implemeting the school lunch program.

The report finds that "Action is needed across all sectors of food production, distribution, and consumption at individual behavioral and population levels….Individuals, families, schools, worksites, healthcare and public health settings, restaurants, and other food establishments must work together" to implement the following recommendations:

- Americans must increase their intake of underconsumed food groups—such as fruits and vegetables—and nutrient-dense foods, "while maintaining energy balance, and without increasing saturated fat, sodium, and added sugars." In other words, Americans must eat more vegetables without layering on added butter, cheese or salt.
- Adding more low-fat/fat-free fluid milk and yogurt to diets while decreasing cheese would result in higher intakes of magnesium, potassium, vitamin A, and vitamin D while reducing the intake of sodium and saturated fat.
- Replacing soft drinks and other sugar-sweetened beverages (including sports drinks) with non-fat fluid milk would substantially reduce added sugars and empty calories and increase the intake of shortfall nutrients, including calcium, vitamin D, and magnesium.[1]

Beyond the cholesterol recommendation, the DGAC's report listed several "nutrients of concern for underconsumption," which were vitamin D, calcium, potassium, fiber, and, for pregnant women especially, iron. Nutrients of concern for overconsumption were sodium and saturated fat. The panel also said that Americans "underconsume" vitamin A, vitamin E, folate, vitamin C, and magnesium.

The DGAC's recommendations on dairy are also likely to draw criticism. As reported in *Evidence-Based Diabetes Management*, a parade of witnesses testified at the panel's public hearing that there are ways to get calcium into diets without relying on dairy, and that dairy is harmful to some populations. The Harvard School of Public Health even released its own version of the "MyPlate" diagram with less focus on dairy.[9] **EBDM**

References

1. Scientific report of the 2015 Dietary Guidelines Advisory Committee. US Office of Disease Prevention and Health Promotion website. http://www.health.gov/dietaryguidelines/2015-scientific-report/. Published and accessed February 18, 2015.

2. Whoriskey P. The U.S. government is poised to withdraw longstanding warnings about cholesterol. *The Washington Post* website. http://www.washingtonpost.com/blogs/wonkblog/wp/2015/02/10/feds-poised-to-withdraw-long-standing-warnings-about-dietary-cholesterol/. Published February 10, 2015. Accessed February 11, 2015.

3. Gupta A, Smith DA. The 2013 American College of Cardiology/American Heart Association guidelines on treating blood cholesterol assessing cardiovascular risk: a busy practitioner's guide. *Endocrinol Metab Clin North Am.* 2014;43(4):869-892.

4. Dietary Guidelines Advisory Committee shows plant-based diets beat animal products for health promotion, disease prevention, sustainability [press release]. Washington, DC: Physicians' Committee for Responsible Medicine; February 19, 2015. http://www.pcrm.org/media/news/dietary-guidelines-plant-based-promotion/.

5. Caffrey MK. Dietary guidelines panel to take input from public. *Am J Manag Care*. 2014; 20 (SP1):SP3.

6. Caffrey MK. School lunch changes for 2015 may be just the start of rollback. *Am J Manag Care.* 2015;21(SP2)SP51-SP52.

7. 2015 Dietary Guidelines Advisory Committee submits report [press release]. Washington, DC: HHS website; February 19, 2015. http://www.hhs.gov/news/press/2015pres/02/20150219b.html.

8. *AJMC,* Joslin Diabetes Center join forces to host Patient-Centered Diabetes Care in Boston [press release]. Plainsboro, NJ: PRWeb; January 16, 2015. http://www.prweb.com/releases/2015/01/prweb12449739.htm.

9. Caffrey MK. Dietary patterns, and effect on population health, get attention from panel. *Am J Manag Care*. 2014;20(SP4):SP111-SP112.

Higher-Dose Liraglutide Creates New Options to Fight Obesity, but Payment Remains a Challenge

Andrew Smith

Obesity specialists hailed the December 23, 2014,[1] approval of high-dose liraglutide for weight management as a valuable addition to their meager arsenal. Not only is it just the fifth prescription drug cleared for long-term use in that capacity,[2] it also has a completely different mechanism of action from any of the others, so it may help patients who get little benefit from other therapies.

Carol Apovian, MD

Dosing and usage are perfectly straightforward in obese patients who are otherwise healthy. There is only 1 approved dose—3-mg daily injections—and there is only 1 approved usage—monotherapy. The only real decision is with the sequence of treatment—whether before or after other approved medications.

In obese patients who also suffer from type 2 diabetes mellitus (T2DM), however, the options multiply. Physicians can prescribe liraglutide at the 1.2- or 1.8-mg/d dosages previously approved for control of glycated hemoglobin (A1C), or at the new 3-mg/d dosage, and they can use combine liraglutide at any of those dosages with dozens of other medications.

Trials have yet to definitively establish the best strategy for mixing these endless options to maximize weight loss and keep A1C levels in check. There may not even be a "best" strategy beyond experimenting to see what works for each patient. There are, however, considerations that may help physicians experiment intelligently. "Regulators, researchers, and physicians are all beginning to take obesity more seriously, but there is still a tendency to look at it as a secondary problem compared to the 'serious' conditions that are often associated with it," said Louis J. Aronne, MD, the Sanford I. Weill Professor of Metabolic Research at Weill-Cornell Medical College and director of the school's Comprehensive Weight Control Center, in an interview with *Evidence-Based Diabetes Management*.

"We need to take obesity as seriously as any other condition and treat it as aggressively, because the more we learn about obesity, the more we realize how much it contributes to so many other problems. We are going to look back in 10 or 20 years and just kick ourselves for delaying medication until BMI 35 or more instead of attacking it with all we had at BMI 27," he said, referring to thresholds for body mass index (BMI) at which different treatments, including surgery, may be indicated.

There is, unfortunately, an obstacle that prevents physicians today from heeding Aronne's advice and using anti-obesity medications early and often: insurance coverage. Medicare never pays for them. Medicaid rarely pays for them. Private insurance programs sometimes pay for them, but only sometimes.[3] Most patients, moreover, cannot or will not purchase their own medications, because all the anti-obesity drugs approved for long-term use are only available in expensive branded versions. The 3-mg strength of liraglutide, for example, is expected to sell for about $900 a month.[4]

Prices like that, combined with lingering memories about the dangers of older diet drugs, have made long-term anti-obesity medications a niche product in a nation with nearly 80 million obese people. Indeed, a pair of medications approved with much fanfare in 2012, phentermine-topiramate (Qsymia) and lorcaserin (Belviq), each struggled to produce first-year sales of $30 million.[5] Physicians and researchers who specialize in obesity have been lobbying payers to change their practices, pointing not only to the American Medical Association's 2013 decision to recognize obesity as a disease[6] but also to estimates that obesity-related problems produce $190 billion in healthcare costs per year.[7]

Widespread payer coverage may well be a precondition for widespread use of anti-obesity medications, particularly if the key to real efficacy turns out to be using therapies in combination, a strategy that has proved the most effective way to manage everything from hypertension to cancer. As things stand, however, the 3-mg dose of liraglutide is an option that physicians can use only on the minority of patients who either have insurance that will pay or overstuffed wallets.

Obese diabetic patients who fall into one of those 2 categories are likely to lose considerable amounts of weight with the 3-mg liraglutide dose, which Novo Nordisk markets as Saxenda to separate it from the lower-dose options that treat diabetes under the Victoza brand. A phase 3a trial of the 3-mg version found that diabetic patients who began with an average BMI of 37 typically lost 5.9% of body weight after 56 weeks of use.[8] Notably, those results were for patients who were new to liraglutide. The typical weight reduction in patients who move to the 3-mg dose after years of using the formula at lower doses is uncertain. Such patients were excluded from the trial.

Of course, now that liraglutide is approved at the 3-mg dose, physicians can experiment for themselves and see what effect the move up from lower doses tends to have on patient weight and blood sugar. That said, physicians who want to maximize weight loss while keeping diabetes in check have many options to try. Strategies endorsed by the Endocrine Society and the American Association of Clinical Endocrinologists (AACE) would be to stick with the 1.8-mg dose of liraglutide as a treatment for A1C, perhaps in combination with another treatment class that promotes weight loss, and then to add a different anti-obesity medication on top of that. This regimen would effectively create a combination anti-obesity treatment. [9,10]

Studies show that the individual components of such a strategy can each significantly impact patient weight. A trial that compared the sodium-glucose cotransporters type 2 inhibitor canagliflozin (Invokana) with sitagliptin (Januvia), for example, found that patients who added the former into combination therapy with metformin and sulfonylurea lost an average of 2.5 kg (5.5 lb), while those who added the latter into the same therapy gained a small amount.[11]

A trial that compared combining either liraglutide or sitagliptin with metformin found that patients who added the 1.8-mg dose of liraglutide lost an average of 3.68 kg (8.11 lb) in the next year while those who added sitagliptin lost an average of 1.16 kg (2.55 lb).[12] The trial of 3-mg liraglutide, moreover, found that diabetic patients who used the 1.8-mg dose lost an average of 4.6% of their body weight in 56 weeks.[8] And

FIGURE. Two Indications for Liraglutide

Marketed as Victoza

Approved by FDA on January 25, 2010

Dose 1.2 mg or 1.0 mg daily

Indicated for type 2 diabetes mellitus in some patients

Marketed as Saxenda

Approved by FDA on December 23, 2014

Dose 3 mg daily

Indicated for obesity

SOURCE: Novo Nordisk, FDA

THE AMERICAN JOURNAL OF MANAGED CARE 20

trials of other anti-obesity medications approved for long-term use found that the average patient typically loses more than 5% of body weight.[13]

The question, of course, is whether combining such treatments will produce the sum of their individual effects, produce somewhat less (because of duplication or interaction), or produce somewhat more (because of synergy).

Trials have yet to provide definitive answers about any of the countless possible combinations, but the general success of combination therapy against cancer, diabetes, and hypertension gives obesity researchers good reason to hope that benefits will prove additive or even synergistic for regimens that combine medications from unique classes.

If the effects of different medication types tend to add up or enhance one another, the potential benefits are clearly significant. A 250-lb patient who received the average benefits listed above from each of those 3 treatments would lose significantly more than 10% of his or her original body weight, which would constitute a major benefit.

"A 10% reduction in body weight greatly improves nearly every aspect of an obese patient's life, even if it leaves the patient in the obese category. That degree of weight loss will increase energy and decrease cholesterol, blood pressure, and blood sugar. It will help patients move better and sleep better and be more productive. It's a huge deal," said Caroline Apovian, MD, professor at the Boston University School of Medicine and director of the Nutrition and Weight Management Center at Boston Medical Center, in an interview.

Apovian believes that physicians should try to maximize weight loss among overweight patient with diabetes, and that the best strategy for doing so involves combinations of anti-obesity drugs and weight-reducing diabetes medications. Indeed, she is the lead author of new Endocrine Society guidelines that explicitly recommend the combination strategy (and the avoidance, wherever possible, of diabetes medications that promote weight gain).[9] Guidelines from AACE likewise suggest a combination of medications that reduce weight.[10]

"Ideally, you want to get aggressive about weight management before patients develop diabetes. The Diabetes Prevention Program found that a 7% reduction in body weight reduced diabetes risk by 58%," said Apovian. "But even in people who already have diabetes, a loss of just 5% of body weight is significant. The Framingham Study showed that it can reduce the risk of cardiovascular disease by 20% and reduce the need for medications that treat hypertension, diabetes, and lipids."

Medications tend to have a much more variable impact on patient weight than they have on A1C levels, which makes it hard to predict how much patients will lose on individual medications. In the trial of liraglutide 3 mg, for example, the trial in which the average weight loss was 5.9% of body weight, 22% of all patients lost more than 10% of their original body weight, but 50% lost less than 5%.[14] Results from the trials of diabetes medications tend to reveal a similar pattern. A modest average loss arises from a combination of substantial weight loss in some patients and virtually no weight loss in others. Finding a program that produces substantial declines for any particular patient often requires a fair amount of experimentation. It can also depend greatly upon patient behavior.

Some medications can certainly produce significant weight loss without any help from improved diet or increased exercise. Reductions reported in trials that test medications against conditions other than obesity demonstrate this clearly, because patients in such trials often lose significant amounts of weight despite receiving no instructions regarding diet or exercise. Still, patients often lose far more weight if they eat better and exercise more when they start taking a weight-reducing drug. While it's true that the simple act of eating better and exercising more does produce weight loss by itself, patients who start such efforts when they begin taking a weight-reducing medication often see far more additional benefit than their lifestyle changes would predict. Some weight-reducing medications, moreover, may only work in combination with diet and exercise, either because such activities trigger their effect or because their effect is making it easier to patients to stick with lifestyle changes.

"We know that initial weight loss is predictive of long-term success and that *more* weight loss produces *more* health benefits, so we try to maximize the weight lost on each serious attempt," said Donna H. Ryan, MD, an obesity drug researcher who is a professor emerita at Pennington Biomedical Research Center in Baton Rouge, Louisiana, told *EBDM*. "To do this, we use multiple approaches together. When patients are motivated to undertake the behaviors necessary to produce weight loss, we negotiate the most intensity in diet and exercise that patients can achieve, and we add in medications to amplify the weight loss response. After about 6 months, when weight loss plateaus, we pivot to a maintenance strategy, and continuing meds is an important part of that strategy. We believe that one of the most important aspects of these medications is that, as long as they are continued, weight loss is sustained. If we stop them, weight regain begins." **EBDM**

"We know that initial weight loss is predictive of long-term success and that more weight loss produces more health benefits, so we try to maximize the weight lost on each serious attempt."

—DONNA H. RYAN, MD, PENNINGTON BIOMEDICAL RESEARCH CENTER, BATON ROUGE, LOUISIANA

References

1. FDA approves weight management drug Saxenda [press release]. Silver Spring, MD: FDA Newsroom; December 23, 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427913.htm

2. Common weight-loss drugs. Mayo Clinic website. http://www.mayoclinic.org/healthy-living/weight-loss/in-depth/weight-loss-drugs/art-20044832?pg=2. Published October 14, 2014. Accessed February 17, 2015.

3. Andrews M. Many insurers do not cover drugs approved to help people lose weight. Kaiser Health News website. http://kaiserhealthnews.org/news/many-insurers-do-not-cover-drugs-approved-to-help-people-lose-weight/. Published January 6, 2015. Accessed February 17, 2015.

4. Novo Nordisk to promote drug to treat obesity in the United States. Reuters website. http://www.reuters.com/article/2014/12/29/novo-nordisk-obesity-fda-idUSL6N0UD0MB20141229. Published December 29, 2014. Accessed February 17, 2015.

5. Williams S. Have anti-obesity drug prospects finally gone belly up? the Motley Fool website. http://www.fool.com/investing/general/2014/03/04/have-anti-obesity-drug-prospects-finally-gone-bell.aspx. Published March 4, 2014. Accessed February 17, 2015.

6. Pollack A. AMA recognizes obesity as a disease. *The New York Times* website. http://www.nytimes.com/2013/06/19/business/ama-recognizes-obesity-as-a-disease.html. Published June 18, 2013. Accessed February 17, 2015.

7. Cawley J, Meyerhoefer C. The medical care costs of obesity: an instrumental variables approach. *J Health Econ*. 2012;31(1):219-230.

8. Phase 3a liraglutide 3 mg trial demonstrated significant weight loss and improved cardiovascular risk factors in adults with obesity and type 2 diabetes compared with placebo [press release]. Chicago, IL and Bagsværd, Denmark: Novo Nordisk Corporate Communications; June 21, 2014. http://novonordisk.com/include/asp/exe_news_attachment.asp?sAttachmentGUID=D869D535-6BD9-432A-84FF-DE4A6E5AFE8E.

9. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society Clinical Practice Guideline [published online January 15, 2015]. *J Clin Endocrin Metab*. doi:http://dx.doi.org/10.1210/jc.2014-3415.

10. Gonzalez-Campoy JM, St Jeor ST, Castorino K, et al. Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society. *Endocr Pract.* 2013;(suppl 3):1-82.

11. Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sylfonylurea. *Diabetes Care*. 2013;36(9):2508-2515.

12. Pratley R, Nauck M, Bailey T, et al. One year of liraglutide treatment offers sustained and more effective glycemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomized, parallel-group, open-label trial. *Int J Clin Pract.* 2011;65(4):397-407.

13. Colman E. Food and Drug Administration's obesity drug guidance document: a short history. *Circulation*. 2012;125:2156-2164.

14. Company announcement: people with type 2 diabetes achieve 6% weight loss with liraglutide 3 mg in phase 3a obesity trial [press release]. Bagsværd, Denmark: Novo Nordisk Corporate Communications; March 18, 2013. http://www.novonordisk.com/include/asp/exe_news_attachment.asp?sAttachmentGUID=872441e7-92cb-4a08-9bd7-ef262e9c797b.

Obesity Among Children and Teens Demands Stronger Response, *Lancet* Authors Find

Mary K. Caffrey

Rising rates of childhood and adolescent obesity worldwide demand a stronger, multifaceted response that specifically targets advertising to children, according to authors of an article in the journal *The Lancet*.[1]

The article, "Child and adolescent obesity: part of a bigger picture," with Tim Lobstein, PhD, of the World Obesity Foundation as the lead author, was included in a 6-part special section on the topic that appeared February 18, 2015. In a news release announcing the series, *Lancet* editors criticized the "unacceptably slow" progress in combatting obesity, with only 1 in 4 countries having implemented a policy on healthy eating as of 2010.[2]

While Lobstein and his coauthors mentioned several nations where obesity rates are climbing, they took special aim at the rise of obesity in the United States. Authors wrote that the average child's weight has risen by more than 5 kg (about 11 lb) in the past 30 years, and one-third of children are overweight or obese.

Promotion of energy-rich and nutrient-poor products, they write, encourages rapid weight gain in early childhood and exacerbates multiple risk factors for chronic disease. The authors devoted a major section of the article to documenting the connection between rising body mass index (BMI) and stunted height, and showed how this is occurring around the globe.

The authors called on public health officials worldwide to take aim at marketing campaigns that pitch unhealthy foods to children. They called for a campaign similar to one 2 generations ago that counteracted the marketing of breast milk substitutes by promoting breastfeeding, which has seen widespread success. The authors did not mince words about how proactive governments should be: "To meet this challenge, the governance of food supply and food markets should be improved and commercial activities subordinated to protect and promote children's health."

Among the authors' findings:

- A search of the PubMed database found that the number of papers on childhood obesity prevention rose from about 20 per year in the 1980s, to about 60 per year in the 1990s, to more than 1000 in 2013.
- Policy makers are often concerned about whether interventions into childhood obesity prevention are cost-effective, yet few have been tried outside of school settings. The authors analyzed cost-effectiveness of interventions across different countries and found only 1 that involved limits on television advertising aimed at children.
- In addition to known health effects, such as rising rates of diabetes in the United States, children who are overweight or obese experience serious social and emotional challenges. The authors write that on tests of quality of life, these children have significantly lower mean scores; they also face social discrimination and have higher rates of poor self-esteem and depression, lower academic achievement, and lower economic productivity.

The authors assert that this last finding, in particular, promotes the economic value of intervention, since it appears that children who grow up overweight or obese are set up for poorer job prospects.

Despite the rise in BMI, the authors believe messages to children and parents should not put too much emphasis on limiting food. Rather, they said, public health education must focus on the *quality* of foods children consume; nutrient-rich foods should be encouraged instead of high-energy ones. "Messages that promote the avoidance of excess weight might give the impression that children should be restricted in what they eat, rather than encouraged to eat healthy," the authors write.

The authors took aim at the promotion of soft drinks, which have been the subject of campaigns in the United States to tax or limit portion size, with mixed results.[3] And, as regulators did decades ago when they halted cigarette promotions aimed at children, the authors pointed out the dangers of failing to limit food marketing aimed at the young.

"The food industry has a special interest in targeting children," the authors wrote. "Not only can the companies influence children's immediate dietary preferences, but they also benefit from building taste preferences and brand loyalty early in life, which can last into adulthood."

The authors recommended a variety of steps by governments, including financial incentives or penalties, nutrient requirements, regulatory oversight of marketing, and public sector purchasing power. That last item was attempted, with considerable pushback, in the 2010 law that overhauled requirements for the National School Lunch Program in the United States.[4] **EBDM**

References

1. Lobstein T, Jackson-Leach R, Moodie ML, et al. Child and adolescent obesity: part of a bigger picture [published online February 18, 2015]. *Lancet*. doi:http://dx.doi.org/10.1016/S0140-6736(14)61746-3.

2. *The Lancet*: obesity series exposes "unacceptably slow" progress in tackling soaring global obesity rates over last decade [press release]. London: The *Lancet* Journals; February 17, 2015. Distributed via e-mail.

3. Caffrey MK. After the Republican wave, what will election 2014 mean for ACA Medicaid managed care? *American Journal of Managed Care* website. http://www.ajmc.com/focus-of-the-week/1114/After-the-Republican-Wave-What-Will-Election-2014-Mean-for-ACA-Medicaid-Managed-Care. Published November 5, 2014. Accessed February 19, 2015.

4. Caffrey MK. School lunch changes for 2015 may be just the start of rollback. *Am J Manag Care*. 2015; 21(SP2)SP51-SP52.

FDA Approves Toujeo, Basal Insulin Seen as Successor to Lantus

Mary K. Caffrey

The FDA on February 25, 2015, approved the basal insulin Toujeo, which Sanofi sees as a successor to Lantus to treat patients with type 1 (T1DM) and type 2 diabetes mellitus (T2DM). Toujeo, insulin glargine [rDNA origin], is administered in a 300 U/mL dose once a day in a disposable, prefilled pen.[1]

The approval in the United States was viewed as a mixed blessing for Sanofi, as analysts noted that FDA did not permit a label that highlighted Toujeo's lower rate of hypoglycemia than Lantus in clinical trials.[2] By contrast, the European Medicines Agency touted this benefit in granting its approval 2 days later.[3]

In its press release for the American market, Sanofi stated only, "All studies of the EDITION program successfully met the primary study endpoints by demonstrating similar blood sugar control with Toujeo as compared to Lantus."[1] The older insulin, which had its patent expire in February, has been a mainstay for Sanofi for more than a decade. Other options have entered the market, notably Afrezza, the inhaled insulin that took 3 attempts to win FDA approval.[4] (Sanofi paid $225 million to Afrezza maker MannKind at the end of 2014 for a licensing agreement for commercial, regulatory, and development activities for the drug.)[5]

Common adverse events reported for Toujeo (excluding hypoglycemia) included nasopharyngitis (12.8% in T1DM patients and 7.1% in T2DM patients) and upper respiratory tract infection (9.5% in T1DM patients and 5.7% in T2DM patients).[1]

FDA approval was based on results from the EDITION trial program, which was comprised of a series of international phase 3 studies that evaluated the efficacy and safety of Toujeo in more than 3500 adults, including both T1DM and T2DM patients. The trial compared a once-daily dose of Toujeo with the once-daily dose of Lantus, an injection that is only 100 U/mL of insulin glargine, a factor that FDA later noted.[2] Patients were followed in the open-label, randomized, active-control, parallel, treat-to-target studies of up to 26 weeks, with 6 months' safety extension.[1]

The market for insulin is potentially huge. The International Diabetes Federation estimates that more than 370 million people worldwide have diabetes, with nearly 95% suffering from T2DM, which is linked with numerous other comorbidities including obesity.[2] **EBDM**

References

1. Sanofi receives FDA approval of once-daily basal insulin Toujeo [press release]. Paris, France: PRNewsire; February 25, 2015. http://www.news.sanofi.us/2015-02-25-Sanofi-Receives-FDA-Approval-of-Once-Daily-Basal-Insulin-Toujeo.

2. Berkrot B. Sanofi's diabetes drug Toujeo gets US approval, label disappoints. Reuters website. http://www.reuters.com/article/2015/02/26/us-sanofi-sa-diabetes-toujeo-idUSKBN0LU13I20150226. Published February 26, 2015. Accessed February 27, 2015.

3. Hirschler B. Sanofi diabetes drug Toujeo wins EU green light, pricing in focus. Reuters website. http://uk.reuters.com/article/2015/02/27/us-sanofi-sa-diabetes-europe-idUKKBN0L-V1AQ20150227. Published and accessed February 27, 2015.

4. Kam K. Afrezza's initial sales create buying opportunity. Forbes website. http://www.forbes.com/sites/kenkam/2015/02/27/afrezzas-initial-sales-create-buying-opportunity/. Published and accessed February 27, 2015.

5. Forster C. Analysts weight in on MannKind following Q4 results. Seeking Alpha. http://seekingalpha.com/article/2961216-analysts-weigh-in-on-mannkind-following-q4-results?app=1&auth_param=r9ntj:1af3gt5:30510d62341274229ced294c8921bb9e&uprof=53&dr=1. Published and accessed February 28, 2015.

Glyxambi Approved, Combo Provides Actions of SGLT2, DPP-4 Inhibitors for Patients With T2DM

Mary K. Caffrey

On February 2, 2015, the FDA approved Glyxambi, an oral therapy combining empagliflozin and linagliptin, giving patients with type 2 diabetes mellitus (T2DM) a new option that combines the actions of both sodium glucose co-transporter-2 (SGLT2) and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Glyxambi combines 10 mg or 25 mg of empagliflozin, an SGLT2 inhibitor, and 5 mg of linagliptin, a DPP-4 inhibitor. It is a tablet, to be given once a day in the morning, according to an announcement from Eli Lilly and Boehringer Ingelheim Pharmaceuticals Inc, makers of the 2 therapies. The new combination therapy is not for persons with type 1 diabetes mellitus and is intended to be a an add-on to metformin, as part of a treatment plan that includes a healthy diet and exercise.

Persons with T2DM will be able to enjoy the advantages of 2 distinct mechanisms of action while only having to take 1 tablet. SGLT2 inhibitors transport glucose out of the system through the urine by blocking reabsorption through the kidneys. DPP-4 inhibitors increase hormones to encourage the pancreas to produce more insulin, and by stimulating the liver to produce less glucose. While not approved for weight loss, the majority of patients who take these therapies have lost weight.

The FDA based its approval on results from a phase 3 clinical trial which found that adults taking Glyxambi as an add-on to metformin showed statistically significant reductions in glycated hemoglobin (A1C) at 24 weeks compared with adults taking empagliflozin and linagliptin alone. Starting from a baseline A1C of 8%, adults in the trial achieved a mean A1C of 6.9% and 6.7% with Glyxambi, at the doses of 10 mg/5 mg and 25 mg/5 mg, respectively. This compared with A1Cs of 7.3% and 7.4% for empagliflozin alone at 10 mg and 25 mg, respectively, and 7.3% for linagliptin alone at 5 mg.

Common adverse events (AEs) are urinary tract infections (UTIs), although no patient discontinued use due to UTIs. Other AEs are nasopharyngitis and upper respiratory tract infections. Glyxambi should not be taken by patients with severe renal impairment, end-stage renal disease, or dialysis. **EBDM**

Reference

FDA approves first-in-class Glyxambi empagliflozin/linagliptin tablets for adults with type 2 diabetes [press release]. Ridgefield, CT, and Indianpolis, IN: PRNewswire; February 2, 2015. http://www.prnewswire.com/news-releases/us-fda-approves-first-in-class-glyxambi-empagliflozinlinagliptin-tablets-for-adults-with-type-2-diabetes-300028931.html.

FIRST-OF-ITS-KIND OBESITY DEVICE TARGETS NERVE PATHWAY

The FDA on January 14, 2015, approved a new type of weight loss device, one that seeks to take aim at the nerve pathway between the brain and the stomach that controls feelings of hunger and fullness.

Created by EnteroMedics, the Maestro Rechargeable System is the first device for treatment of obesity to gain approval since 2007. It is intended for use by patients 18 years and older who have been unable to lose weight through traditional programs. Patients must also have a body mass index (BMI) of 35 to 45 and at least 1 other obesity-related comorbidity, such as type 2 diabetes mellitus (T2DM).

BMI, a measurement of body fat based on an individual's weight and height, is the most frequently used evaluation of whether a patient's weight is normal, overweight, or obese, but it is sometimes criticized as not the best measure in all circumstances. However, by this measure, more than one-third of adults in the United States are now obese, a fact that has caused alarm among public health officials, as it has been linked to rising rates of T2DM and other ailments, including certain types of cancer. The rise in obesity was cited by the FDA in granting the approval.

The Maestro Rechargeable System was approved even though the specific mechanism of how it blocks nerve activity is not fully understood. It features a rechargeable electrical pulse generator, wire leads, and electrodes implanted

surgically into the abdomen. It sends intermittent electrical pulses to the trunks in the abdominal vagus nerve, which is involved in regulating the emptying of the stomach and in signaling to the brain that the stomach feels empty or full. External controllers enable the patient to charge the device and healthcare professionals to adjust its settings in order to provide optimal therapy with minimal side effects.

The device was evaluated in a clinical trial with 233 patients with a BMI of 35 or greater. Weight loss and adverse events in 157 patients who received the active Maestro device (the experimental group) were compared with 76 patients in the control group who received a Maestro electrical pulse generator that was not activated. The study found that after 12 months, the experimental group lost 8.5% more of its excess weight than the control group. About half (52.5%) of the patients in the experimental group lost at least 20% of their excess weight, and 38.3% of patients in the experimental group lost at least 25% of their excess weight.

The study did not reach its primary end point, which was that the experimental group lost 10% more excess weight than the control group, but the FDA considered the clinical study and recommendations of an advisory panel as well as a survey of patients who said they would accept the risks of the device. The approval requires a 5-year follow-up study of at least 100 patients.

Serious adverse events included nausea, pain at the neuroregulator site, and vomiting, as well as surgical complications. Other adverse events included pain, heartburn, problems swallowing, belching, mild nausea, and chest pain. **EBDM**

Reference

FDA approves first-of-kind device to treat obesity [press release]. Silver Spring, MD: FDA Newsroom; January 14, 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430223.htm.

RANIBIZUMAB APPROVED TO TREAT DIABETIC RETINOPATHY IN PATIENTS WITH DME

On February 6, 2015, the FDA expanded the approved indications of ranibizumab to include treatment for diabetic retinopathy (DR) in patients with diabetic macular edema (DME). The drug, administered by a physician as a 0.3-mg injection once a month, is marketed as Lucentis by Genentech.

Diabetic retinopathy is the most common diabetic eye disease and is a leading cause of blindness in adults in the United States. According to the CDC, both type 1 and type 2 diabetes mellitus affect more than 29 million people in the United States; the disease is the leading cause of new blindness among persons aged 20 to 74 years.

Diabetic retinopathy becomes more common as persons with the disease age. "Diabetes is a serious public health crisis, affecting more patients every year," said Edward Cox, MD, MPH, director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research. "(This) approval gives patients with diabetic retinopathy and diabetic macular edema the first significant therapy to treat this vision-impairing complication."

FDA's approval for the ranibizumab indication came after 2 clinical studies involving 759 participants who were followed for 3 years. In the studies, participants being treated with the therapy showed significant improvement in the severity of their DR at 2 years compared with patients who did not receive an injection.

The most common side effects include bleeding of the conjunctiva, the tissue that lines the inside of the eyelids and covers the white part of the eye; eye pain; floaters; and increased pressure inside the eye (intraocular pressure). Serious side effects include infection within the eyeball (endophthalmitis) and retinal detachments.

The FDA granted ranibizumab for DR with DME breakthrough therapy designation; this occurs at the request of the sponsor if preliminary clinical evidence indicates the drug may demonstrate a substantial improvement over available therapies for patients with serious or life-threatening conditions. The FDA also reviewed the new use under the agency's priority review program, which provides for an expedited review of drugs that demonstrate the potential to be a significant improvement in safety or effectiveness in the treatment of a serious condition. Ranibizumab had been approved previously to treat DME and macular edema secondary to retinal vein occlusions. **EBDM**

Reference

FDA approves Lucentis to treat diabetic retinopathy in patients with diabetic macular edema [press release]. Silver Spring, MD: FDA Newsroom; February 6, 2015. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm433392.htm.

FDA Approves Aflibercept for Diabetic Retinopathy in Patients With Diabetic Macular Edema

Mary K. Caffrey

Aflibercept, to be marketed as Eylea, received approval March 25, 2015, from FDA for treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DMA).[1]

Aflibercept is an injectable treatment for DR, which the FDA cites as the most common diabetic eye disease and a leading cause of blindness among adults ages 20 to 74 years in the United States.[1] The risk of DR has increased as incidence of type 2 diabetes mellitus (T2DM) has gone up in recent decades. The number of Americans with type 1 diabetes and T2DM is about 29 million.[2]

With the approval of aflibercept, patients with DR have multiple treatment options, said Edward Cox, MD, MPH, director of the FDA's Office of Antimicrobial Products at the Center for Drug Evaluation and Research.

Doctors administer aflibercept by injection in the eye once a month for 5 months. Then, patients receive the injections once every 2 months. Treatment is given alongside appropriate efforts to control blood sugar, blood pressure, and cholesterol.

The FDA approval comes after safety and efficacy were demonstrated in trials involving 679 patients in 2 studies. Participants were randomly assigned to receive aflibercept injections or macular laser photocoagulation, a laser-based treatment used to burn small areas of the retina. At week 100, those being treated with the study therapy showed significant improvement in the severity of their DR, compared with patients who did not receive injections.

Common adverse events (AEs) associated with aflibercept included bleeding of the conjunctiva, eye pain, cataracts, floaters, increased eye pressure, and separation of the interior jelly of the eye from the retina. Serious AEs included eye infections and retinal detachments.

FDA approval follows prior designation of aflibercept as a breakthrough therapy. **EBDM**

References

1. FDA approves new treatment for diabetic retinopathy for patients with diabetic macular edema [press release]. Silver Spring, MD: FDA Newsroom; March 25, 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm439838.htm

2. American Diabetes Association. Economic costs of diabetes in the United States. *Diabetes Care*. 2013;36:1033-1046.

Panel Discusses ACA's Effect on Mental Health Delivery, Care for Those With Comorbidities

Mary K. Caffrey

Care for those with mental illness has come a long way recently, with the Affordable Care Act (ACA) ensuring that services are covered and a federal parity law requiring that coverage limits for mental health be no less generous than medical benefits. Those who work with the mentally ill or advocate on their behalf know that better laws are just the beginning of improving care, according to a panel of experts convened recently by *The American Journal of Managed Care*.

The panel discussion, moderated by **Surabhi Dangi-Garimella, PhD,** managing editor of *AJMC*'s Evidence-Based series, included **Stuart L. Lustig, MD, MPH,** lead medical director, child & adolescent care, Cigna Behavioral Health; **Paul Gionfriddo,** president and CEO, Mental Health America; and **Wayne J. Katon, MD,** director of the Division of Health Services and Epidemiology and professor and vice chair of the Department of Psychiatry and Behavioral Sciences, University of Washington Medical School.

ACA implementation will be only a first step toward treating mental illness with the same urgency as other chronic conditions, although the healthcare world is awakening to the fact that delaying mental health care only increases costs elsewhere, with most of the economic impact of mental illness occurring "on the medical side," as Katon explained. The panel discussed the connections between mental illness and chronic conditions such as diabetes and hypertension, which Katon and his colleagues have researched for decades. Thanks in part to the ACA, Katon said, their pioneering approach to collaborative care, known as TEAMcare, has drawn more interest in the past 5 years than in previous 25 that Katon and his colleagues have been researching these approaches.

"I think we have to move away from the idea that we're going to train enough psychiatrists or child psychiatrists to treat all people with mental illnesses," Katon said. "We do need team-based approaches."

EARLY IDENTIFICATION OF PROBLEMS

Better and earlier identification of persons with mental health problems is essential, starting with teenagers who are still in school, said Gionfriddo. This way, treatment can start before the illness becomes hard to treat and other comorbidities set in. "It's critically important that we move people's thinking upstream," he said. Mental illnesses are "the only chronic conditions that as a matter of public policy, we wait until Stage 4 to treat, and then often only through incarceration."

"Half of mental illness manifests itself by the age of 14, which makes this very much a disease of childhood," Gionfriddo said.

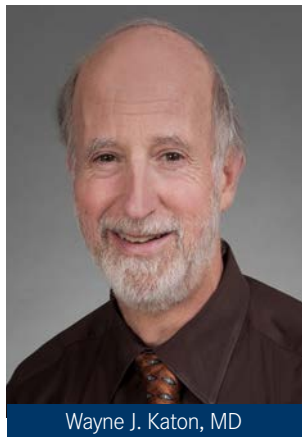

Paul Gionfriddo

Mental Health America's experience with online screening has been that many who screen positively for early stages of mental health disorders have never been diagnosed with a problem; the group encourages participants to use the results to open a dialogue with their local provider. The trouble is, Gionfriddo said, the parity law cannot fix disparities in the availability of mental health providers, especially in the South.

Katon and Lustig discussed the difficulties of access to care despite changes in laws to require insurance coverage. Most care for anxiety or depression starts with the primary care physician (PCP), Katon said, and referral rates for getting patients to see mental health providers are abysmal. Even when patients do seek a specialist, they average about 2 visits, which is not enough for adequate treatment.

MENTAL HEALTH AND COMORBIDITIES

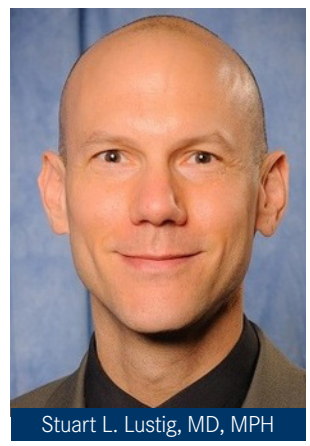
Depression and anxiety are risk factors for developing diabetes or hypertension, Katon explained; at the same time, suffering a chronic condition or a heart attack puts one at risk for depression. "There is a bidirectionality," he said.


Wayne J. Katon, MD

What's challenging is that the more complex the disease—and diabetes is very complex—the more difficult it can be for a patient who also has a mental health condition to maintain good adherence with medications. This is why, Katon said, that so much of the cost of mental illness actually comes from treating medical conditions. Patients with mental illness die younger than their counterparts, and while suicide and accident rates are higher, the more typical outcome is an early death from a poorly treated disease.

He offered the example of a person with depression who is newly diagnosed with type 2 diabetes mellitus (T2DM). "On the date of your diagnosis, you start 4 disease-controlling medications," he said adding that it doesn't help that some atypical antipsychotics can actually trigger the onset of T2DM by contributing to obesity.

Giofriddo emphasized that the relationship between mental health and comorbidities further points to the need to address conditions "upstream," before diseases worsen and become harder and more expensive to treat. "By waiting until later for anything, it complicates everything," he said. Lustig noted that payers and accountable care organizations are starting to realize the need for what he called "intensive case management," to make sure that doctors are talking to one another, that patients have proper transportation between appointments, and that there is a central point of contact and access to medication.


Stuart L. Lustig, MD, MPH

"It's resource-intensive," Lustig said, "But it's less resource-intensive than having patients get sicker and sicker."

Katon's TEAMcare approach goes beyond the coordination of services. The collaborative care model places the mental health professional alongside PCPs or in a consulting capacity to help the primary practice manage multiple patients and to ensure better diagnoses. Collaborative care improves patient education, allows for more frequent updates of medications, and ensures the ability to provide evidence-based psychotherapy in the primary care clinic.

"We have to think through what we will do with these people with comorbid illnesses," he said. Too often, opportunities are lost to provide better care that would lead to better outcomes—and save money.

EDITOR'S NOTE AJMC

When this panel discussion took place in December 2014, we planned to include this story in our special issue on managing comorbid conditions. As Evidence-Based Diabetes Management *went to press in March, we learned that Dr Wayne Katon had died from lymphoma after working for decades to promote collaborative care for patients with mental health issues and other conditions, including diabetes. Please see our President's message, on page SP139, in which he reflects on Dr Katon's contributions.*

IMPROVING ADHERENCE

Lustig said better community support and prevention services will help get patients who need help into the system; he agreed with the need to get patients with serious illnesses into the pipeline of care earlier. He and Katon also discussed the need for better education and close follow-up to get patients on the right medication at the right dose to improve adherence; the initial brief visit in which PCPs make a diagnosis, prescribe an antidepressant, and instruct the patient return in 4 to 6 weeks is often a recipe for failure, asserted Katon.

"Any time any clinician picks up a prescription pad, they are making a number of very specific assumptions about that patient that may or may not be accurate," Lustig said. Can the patient afford the medication? Is there access to follow-up care? Is the patient comfortable being on a psychotropic drug? Are there concerns about side effects? Psychotherapy and other treatments aside from drugs are time intensive, and that can interfere with adherence, Lustig added.

All 3 experts, however, were optimistic that the landscape for mental health care is improving despite the challenges. Just getting behavioral health included among the ACA's essential health benefits is a huge step forward, they agreed. **EBDM**

AMA, CDC Launch Diabetes STAT to Prevent More Cases of Type 2

Mary K. Caffrey

The president of the American Medical Association (AMA) and the director of CDC's Division of Diabetes Translation recently launched an initiative to screen for prediabetes and promote interventions to stop its progression, with the goal of halting more cases of type 2 diabetes mellitus (T2DM). The disease threatens 1 of 3 Americans.[1,2]


Robert M. Wah, MD

Diabetes STAT—which stands for Screen, Test, Act Today—was announced March 12, 2015.[2] It expands upon current efforts by the AMA, CDC, and partners like the YMCA to reach those with prediabetes. In a briefing with healthcare press, including *Evidence-Based Diabetes Management,* AMA President Robert M. Wah, MD, and CDC's Ann Albright, PhD, RD, outlined the effort to engage physicians, employers, commercial insurers, CMS, and even the food industry in the cause.

Wah and Albright described the effort as improving "linkages" among all those who play a role in preventing T2DM. Albright was adamant that this could not be a short-term, government-run fix with grant-based resources. "The time to act is now," she said. "We need a national, concerted effort to prevent additional cases of type 2 diabetes, and we need it now."

The roots of this launch have been in place for some time. In 2012, CDC launched the National Diabetes Prevention Program, and Albright said it demonstrated success with 70% of participants who were over 60 years of age.

They defined persons with prediabetes as having glycated hemoglobin (A1C) levels between 5.7 and 6.4 or fasting glucose between 100 mg/dL and 125 mg/dL. An estimated 86 million Americans have prediabetes but 90% of them don't know it, a fact that makes it hard for physicians and public health officials to keep the population with T2DM from rising.[1,2]

The impact of diabetes is mounting. A study by the American Diabetes Association showed that the disease cost the United States $245 billion in 2012 in medical spending and lost productivity, and that number had grown by $71 million since 2007.[1] "Our healthcare system simply cannot sustain the continued increases in the number of people developing diabetes," Albright said. "Screening, testing, and referring people at risk for type 2 diabetes to evidence-based lifestyle change programs are critical to preventing or delaying new cases."

Wah and Albright agreed that when persons with prediabetes are made aware of their diagnosis, especially by a physician, they typically do make lifestyle changes or take medication to get indicators like blood glucose under control. The outreach efforts to identify those at risk, therefore, are essential.


Ann Albright, PhD, RD

Diabetes STAT calls for multiple stakeholders to invest resources in reaching those with prediabetes and halting the disease, first by identifying those at risk and then by putting them through prevention programs that will help patients modify their eating patterns and increase exercise for the long haul. A key component before this rollout, Albright said, has been working with commercial insurers, CMS, and major employers to convince them that paying for diabetes prevention programs is just as cost-effective as paying for medication—and perhaps more so. "You can outeat any medication," she said. "It is imperative that we have a foundation of lifestyle change."

Health plans and accountable care organizations (ACOs) will have incentives in the next few years to embrace diabetes prevention and control, under both the Affordable Care Act and recent announcements by CMS that value-based reimbursement is on the way. The agency that is the nation's largest payer will require that 30% of Medicare payments be value-based by 2016 and 50% be value-based by 2018.[3] Already, diabetes-related measures are among the population health ratings that ACOs must track in determining Medicare reimbursement under the Medicare Shared Savings Program.[4]

The roots of this launch have been in place for some time. In 2012, CDC launched the National Diabetes Prevention Program, and Albright said it had demonstrated success with 70% of participants who were over 60 years of age. [5] Now, she said, it's time to reach many more people on a much bigger scale. Pilot projects in 4 states have given public health officials insights into the best way to connect the clinical care setting to the community centers that will deliver education programs necessary to get people to permanently change what they eat and surround themselves with the support systems to stick with behavioral change once they complete a program.

Wah said the AMA's role involves reaching physicians at every level to help them screen patients and then refer them to community centers, their local YMCA, or other places where they can gain access to the National Diabetes Prevention Program. A special website for physicians has been created as part of the initiative.[6]

"Long term, we are confident that this important and necessary work will improve health outcomes and reduce the staggering burden associated with the public health epidemic of type 2 diabetes," he said. **EBDM**

References

1. American Diabetes Association. Economic costs of diabetes in the United States. *Diabetes Care*. 2013;36:1033-1046.

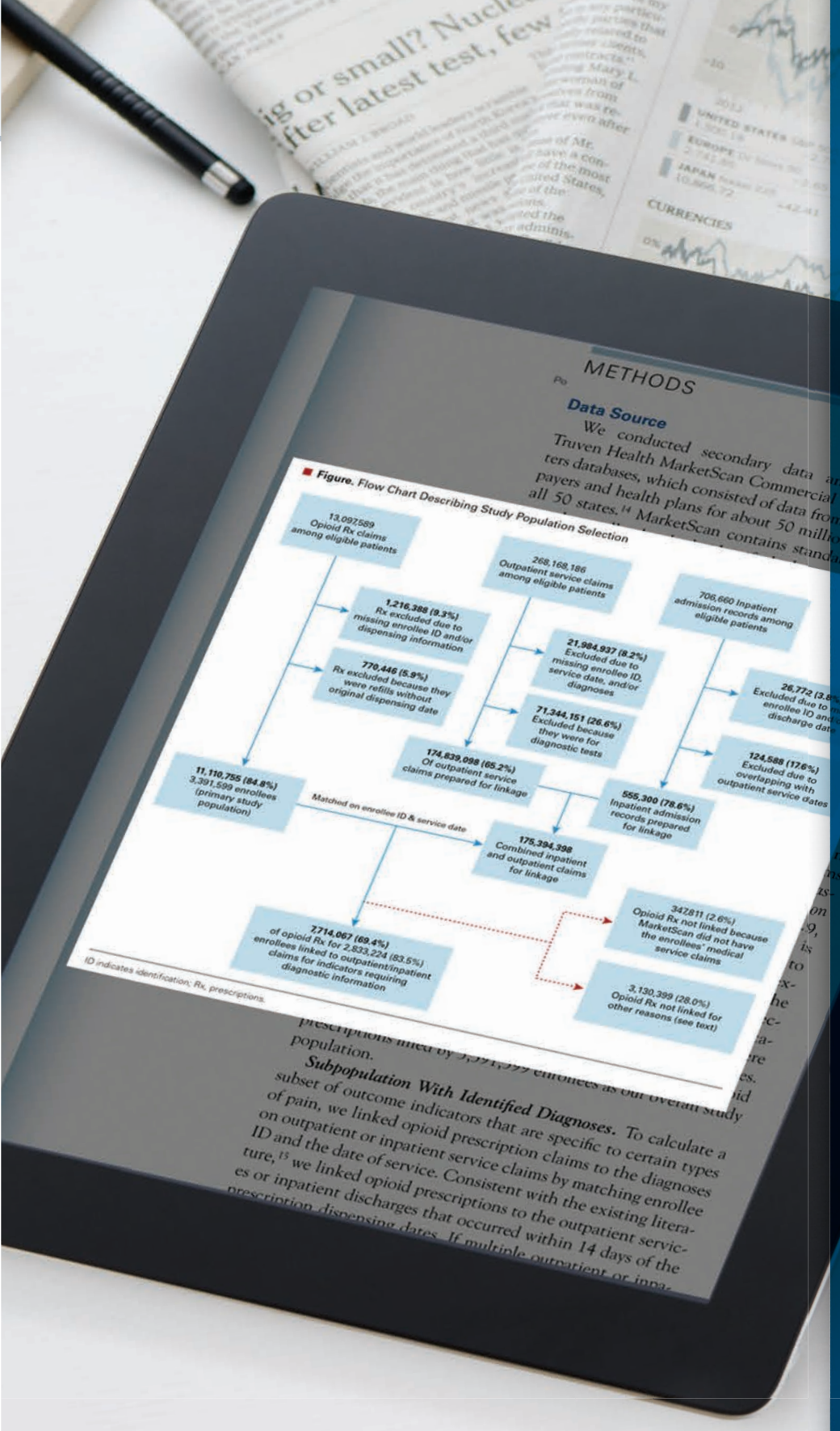
2. New AMA, CDC initiative aims to "Prevent Diabetes STAT" [press release]. Atlanta, GA: CDC Newsroom; March 12, 2015. http://www.cdc.gov/media/releases/2015/p0311-diabetes-stat.html.

3. Better, smarter, healthier: in historic announcement, HHS sets clear goals and timeline for shifting Medicare reimbursements from volume to value [press release]. Washington, DC: HHS; January 26, 2015. http://www.hhs.gov/news/press/2015pres/01/20150126a.html.

4. Caffrey MK. Among ACO Pioneers, data reveal diabetes performance paradox. *Am J Manag Care*. 2014; 20(SP18)SPxx.

5. YMCA diabetes prevention program. YMCA website. http://www.ymca.net/diabetes-prevention/. Accessed March 31, 2015.

6. Prevent Diabetes STAT Toolkit. American Medical Association website. http://www.ama-assn.org/sub/prevent-diabetes-stat/toolkit.html. Lauched March 12, 2015. Accessed March 31, 2015.



A One-Stop App for *Managed Care Professionals*

All our print and digital content in one place!

Access exclusive, original content from the industry's most trusted and most referenced managed care publication, *The American Journal of Managed Care* (*AJMC*). Whether on the road or in the home, managed care news and media are now at your fingertips—whenever you want it!

By downloading the *AJMC* app, you will gain access to exclusive content not seen anywhere else on the Web or in print. In addition to our peer-reviewed research, the app includes:

- In-depth author commentaries
- AJMCTV Peer Exchange videos
- CME resources
- Monthly "Payer Perspectives" Column
- And so much more

AJMC

Tablet Edition

Download to your tablet today!

Available on the App Store

ANDROID APP ON Google play

THE AMERICAN JOURNAL OF MANAGED CARE®

AJMC.com

Unraveling the Mysteries and Extensive Needs of Emergency Department "Superutilizers"
(CONTINUED FROM COVER)

JEFFREY BRENNER, MD

Founder and CEO
Camden Coalition of Healthcare Providers
Camden, New Jersey

COREY WALLER, MD

Director, Center for Integrative Services
Spectrum Health Medical Group
Michigan

DOUGLAS EGBY, MD

Vice President of Medical Services
Southcentral, Alaska

DEEPA BORDE, MD

Medical Director
UF Health Shands Care One
Gainesville, Florida

JACQUI PINKEY, MSW

Clinical social worker
UF Health Shands Care One
Gainesville, Florida

also their inability to self-manage their health needs. For patients like Johnson, diabetes is a frequent conspirator in the struggle, but it's not the only one.

Several years ago, Brenner's work with superutilizers caught the attention of CMS, because these patients account for an oversized share of Medicaid spending. A July 2013 informational bulletin from Cindy Mann, director of CMS' Center for Medicaid and Children's Health Insurance Program Services, cites the uneven spending distribution: statistics at that time showed 5% of beneficiaries accounted for 54% of spending, with the top 1% of the beneficiaries accounting for 25% of the spending. Among this 1%, 83% have at least 3 chronic conditions, and 60% have 5 or more such conditions.[1]

And yet, this utilization is not surprising. As Mann wrote, superutilizers are those with "complex, unaddressed health issues and a history of frequent encounters with healthcare providers."[1] Their healthcare is highly uncoordinated and rarely occurs in the appropriate setting.

Connecting these patients with primary care doctors, and getting them to seek preventive services—which will address their problems more effectively and at a lower cost—is a major objective of the Affordable Care Act (ACA). In that same 2013 memo, Mann noted that the Center for Medicare and Medicaid Innovation had awarded Cooper University Hospital in Camden $2.8 million "to expand the Camden Coalition superutilizer program to serve over 1200 patients, with an estimated 3-year savings of $6.2 million."[1]

For all his encounters with the healthcare system, Johnson's story got worse before it got better. He lost more than 70 pounds, but his foot eventually had to be amputated. Along the way he developed eye and bladder problems, and his ability to care for himself diminished. "I got in a stupor," Johnson says. "I didn't have a job, I was just sitting. Everything was coming down on me–God was picking on me."

These "frequent fliers," as they are also known, come in all shapes and sizes. As the CMS statistics show, they frequently suffer from multiple chronic conditions, which can include substance abuse or mental health problems. Many have compounding social obstacles such as inadequate housing or lack of transportation. Many do not have health insurance, and even those who have obtained it for the first time under the ACA may be unaccustomed to seeking care outside of the ED setting; many must be taught how to use insurance and find a primary care physician.

THE EMERGENCY DEPARTMENT AS HAVEN

Some, in fact, seek out the ED; to them, it is like an oasis of warmth and attention. Doctors and nurses come to know them over time, and stable personal relationships develop, in contrast to the turmoil they may endure on the streets or at home, says Corey Waller, MD, director of the Spectrum Health Medical Group Center for Integrative Medicine in Michigan. The center uses a health team approach to address the needs of superutilizers in the hospital network.

"What happens is, you get patients who show up to the ED and they get food and something warm to drink, and an extra blanket and get treated almost like family; despite the ongoing trauma that the medical system levies on them with feelings of guilt and blame and unnecessary testing, it still is the only place that's safe for them," Waller said.

Spectrum Health's system of 11 hospitals in Michigan's Grand Rapids area have a 70% market share and until recently saw 1000 superutilizers visiting EDs 10 times or more each year, with each patient costing the system $55,000 on average, for a total of $55 million a year. With the creation of the Center for Integrative Medicine, efforts were made to work more closely with these high-cost patients, and their numbers dropped by half.

"For some of our patients, we identify their issues, we stabilize them and get them into primary care; other ones have so many levels of complication that nobody feels comfortable with them, and so they stay within our clinic walls, and we see them as chronic patients," he said.

PATIENTS WITH COMPLEX, DIFFICULT NEEDS

According to Brenner, addressing these patients successfully is as much a matter of finding them appropriate medical care as it is about reeducating them and attending to their complex psychological needs. The Camden Coalition of Healthcare Providers brings an array of medical resources and practical expertise to bear on the problem in this poverty-stricken New Jersey city. The coalition successfully worked with Johnson, the T2DM foot patient, to help him overcome transportation problems and map out a program of medical care that would keep him out of the ED.

The coalition remains active with a patient for 90 to 120 days, teaching the patient how to function more independently. "The vast majority of people never go to the hospital except to be born and maybe once or twice in their lives," says Brenner. "Then there's the 1% of the population that consumes almost 30% of the costs, because they go back to the hospital a lot. They're very heterogeneous. If I said to you that all high utilizers are homeless, that would be wrong. If I said that all homeless are high utilizers, I'd be wrong. If I said that all high utilizers are diabetic, I'd be wrong. It's the combination of all of these things."

Indeed, a 2013 superutilizer summit co-sponsored by the Center for Health Care Strategies, a national nonprofit, identified diabetes, mental health, substance abuse, and cardiovascular problems as among the most frequent issues among recurring ED users. Addressing those factors can be a handful for doctors or other healthcare providers, but for superutilizers acting on their own it's almost impossible.[4]

"Let's imagine you were just diabetic. That's going to have a big impact on your life," Brenner said. "But if I add hypertension and cholesterol, now you're taking 7 pills a day, along with doctor visits. Let me throw in glaucoma, and now I'll throw in doctor visits every month. Now let's throw on top of that your hip's bothering you, you can't get around very well, and you're using a cane, and let's throw on top of that lack of family support and maybe you're living on Social Security. Well, the whole thing is toppling over."

EARLY LIFE TRAUMA A COMMON LINK

Brenner, Waller, and others working with high utilizers say that while T2DM and comorbidities certainly complicate the process of getting this population into effective treatment corridors, which would improve their lives while lowering the cost of care, the root of their problems are myriad traumas that many of these patients suffered in early life. Such problems contribute to both ineffective self-care and to self-destructive behavior, both of which must be addressed, providers say, before anything else can be fixed.

"The thing we have found all over the country is that the really extreme, often intractable, patients often have very high levels of early life trauma—the death of a parent, physical abuse, sexual abuse, one parent hitting another," Brenner shared. "It's had a very foundational impact on them. They don't form trusting relationships very easily. Their reaction to stress is often quite different. They're very disproportionally represented among frequently hospitalized patients."

Waller says 90% or more of the superutilizers in his system admit to early life

trauma, which he calls "pretty disturbing."

"Trauma leads to predictable behaviors—chronic anxiety, desire to escape, impulse control issues—somebody who needs an answer right now," Waller said. "We find that the only one that is consistently there for them is the healthcare system, not their neighbors, not their church, not their family, not their significant other, not their kids. When we asked them 'Where do you go if you need help with anything'? it's the hospital, because they know that it's there, and they know that people will be nice, and they know that they're not going to be at risk."

As a result, much of the work done by specialists at the programs run by Brenner and Waller is designed to address the psychological barriers to changing lifestyles and following treatment plans.

OTHER TYPES OF HIGH UTILIZERS

There are other classes of the superutilizer. In Alaska, Medicaid Division of Health Care Services director Margaret Brodie encounters young mothers who bring their children to the ED because they overreact to medical problems or don't have other alternatives, while other children turn up repeatedly after suffering from abuse.

There are "pre-superutilizers" who come in the form of unborn babies whose mothers have substance abuse disorders, says Waller. Right out of the womb, these babies end up in neonatal intensive care units at a cost of more than $5000 a day. At Spectrum Health, treatment of this group starts during pregnancy with behavioral therapy for the mother and identification of social barriers to successful behavior.

In the University of Florida health system in Gainesville, hospital administrators found that patients were flocking to the ED from surrounding counties because effective charity care was unavailable. The 2 clinics in town accepted only in-county residents and limited the number of cases each month. The solution, health workers said, was to establish a clinic alongside the ED that would address this supplementary need for care as well as the high utilizer population.

"People come to our area from other areas because they cannot get help," says Jacqui Pinkney, MSW, a clinical social worker at the UF Health Shands Care One Clinic in Gainesville. "We see that a lot because there are a lot of small counties that are between us and Tampa. I've had patients say that 'I moved to this area because I couldn't get help for this problem.'"

Winning trust from high utilizers so that they are willing to work with providers is key to the process, as many patients are distrustful and uncooperative.

Participation in the Care One Clinic is voluntary, says Deepa Borde, MD, medical director. "We have found that trying to enroll patients in our clinic when they are not ready and not interested ends up wasting resources, and so we do our best to be present and available and to continue to speak with these patients and try to gain their trust."

This can be a frustrating process, because when things don't work out, clinic staff end up learning that resources would have been better spent on a more willing patient.

"You keep scheduling these patients, but they don't show up," Borde said. "And then you can make calls in an emergency setting and you make another appointment, and they don't show up again, and they keep not showing and they're in your database and you're not impacting them. I guess it's a real life look at what can happen when you're trying to help frequent visitors. But at the same time, why aren't we saving this time by putting another patient in that slot?"

Much success has been achieved by going to the patient's bedside upon hospital admission and introducing the Care One program to the patient to directly address their patient's questions and concerns. Patients respond to this approach with greater interest, Borde said.

From November 2012 to January 2014, UF Health Shands achieved a 30% reduction in ED visits among patients who entered Care One. Hospitalizations among those patients were reduced by 25%. High utilizers were identified as having visited the ED more than 4 times in the 6 months prior to visiting Care One. The gains were recorded in the 6 months following first contact with Care One.

BUILDING RELATIONSHIPS; PUTTING PATIENTS FIRST

The Alaskan Medicaid office instituted a statewide program in December 2014 to reduce the superutilizer drain on ED resources. Brodie said the health solutions company MedExpert was given the contract to bring about a mixture of case management and "soft" relationship work to effect change. In 2013, 3% of Alaska Medicaid users accounted for 22% of all ED Medicaid expenses, Brodie said.

In particular, problems were noted in the Mountain View neighborhood of Anchorage, where a large proportion of residents earn low wages, and lacking transportation, stop at the only health facility on the local bus route: Alaska Regional Hospital. Among Medicaid frequent flyers, "Almost half of them came from the Mountain View area," visiting the ED 5 or more times in an 18-month period, Brodie said.

This program is also completely voluntary, as at UF Health, Brodie said in mid-January. "And so far it's working out pretty well. They've gotten well over 500 volunteers and it hasn't been 3 weeks yet. And recipents report things like, "'Boy, somebody finally cares about me!'"

> *"For some of our patients, we stabilize them and get them into primary care; other ones have so many levels of complication that nobody feels comfortable with them, and so they stay within our clinic walls, and we see them as chronic patients."*
>
> — COREY WALLER, MD

The program is something of a sea change for the general Alaskan population, Brodie said, but in part of Alaska the soft approach has been successfully used via the native-run Southcentral Foundation Nuka System of Care. Since the late 1990s Nuka has sought to improve outcomes among high utilizers and others by offering a sense of ownership and personalized attention, according to Douglas Eby, MD, vice president of medical services for Southcentral.

"We believe the customer-owner (patient) is in control of their own journey and we are there to help support it by cheerleading and helping them become more and more self-care capable and family care capable over time," he said. "What can we connect to that already exists inside of them that will help them make healthier choices and decisions?" The Nuka system operates on the philosophy that the medical system has in some sense failed its neediest patients by placing resources beyond their grasp or by treating them with mechanical indifference, Eby said, echoing a sentiment also expressed by Brenner of Camden.

"We have really damaged adults standing in front of us who were victims of physical and sexual abuse as kids, who are visiting the hospital over and over, and we're badgering them to take more personal responsibility. I mean, something seems really off about that," Brenner said.

A core element of the Nuka plan, which has been widely replicated by CareOregon and has attracted worldwide interest, is a team approach that begins with a case manager being assigned to a patient, draws in a team of health workers matched to the patient's needs, and leads to the development of a "wellness plan" for each patient's improvement, according to clinical social worker Melissa Merrick, director of Brief Intervention Services with Southcentral.

This can produce rapid or slow results or none at all, depending on the patient, she said.

One frequent ED user tended to demand services he didn't need and would fail to show up for appointments. He also tended to switch providers frequently, as patients are allowed to do in the Nuka system. This sent healthcare workers back to the starting point again and again.

"This individual would become fairly defensive and argumentative and was fairly challenging to work with. We put a limit on the providers he could move to. It kind of forced him to start addressing some of the issues. He still can be argumentative and be difficult to have conversations with, but he's actually engaging in services," Merrick said. Now, he's off pain medication and is exercising more and is less argumentative, she said. But the process took years.

A more successful case was a 74-year-old female cancer patient who also suffered from alcoholism and obesity. She "really embraced the services," Merrick said. "We developed a plan for her to attend a cancer support group monthly and meet with a dietician twice a month. She lost 50 pounds and no longer drinks." She's also developing stronger, more effective relationships with her adult children, whom she is now holding accountable for their actions. "She's very much a poster child for utilizing the system and all of the resources that are available to her," Merrick said. **EBDM**

References

1. Mann C. Targeting Medicaid superutilizers to decrease costs and improve quality. CMS Informational Bulletin. CMS website. http://www.medicaid.gov/federal-policy-guidance/downloads/CIB-07-24-2013.pdf. Published July 24, 2013. Accessed February 5, 2015.

2. How hot-spotting cut healthcare costs by 50%. Robert Wood Johnson Foundation website. http://www.rwjf.org/en/about-rwjf/newsroom/features-and-articles/Brenner11.html. Accessed February 5, 2015.

3. MacArthur Fellows Class of 2013, Jeffrey Brenner. MacArthur Foundation website. http://www.macfound.org/fellows/886/. Updated January 12, 2015. Accessed February 5, 2015.

4. Hasselman D. Superutilizer summit: common themes from innovative complex care management programs. Robert Wood Johnson Foundation website. http://www.rwjf.org/content/dam/farm/reports/reports/2013/rwjf407990. Published October 2013. Accessed February 5, 2015.

Studies Are Showing SGLT2s Also Help Control Hypertension, Eliminate Some Side Effects
(CONTINUED FROM COVER)

TABLE. Comparison of Approved SGLT2 Inhibitors

Canagliflozin[a]			Dapagliflozin[b]			Empagliflozin[c]		
Dose	A1C (%)	SBP (mm Hg)	Dose	A1C (%)	SBP (mm Hg)	Dose	A1C (%)	SBP (mm Hg)
100 mg	−0.77	−3.3	2.5 mg	−0.58	−4.6	10 mg	−0.62	−3.44
300 mg	−1.03	−5.0	5 mg	−0.77	−2.3	25 mg	−0.65	−4.16
			10 mg	−0.89	−3.6			

A1C indicates glycated hemoglobin; SBP, systolic blood pressure, SGLT2, sodium-glucose cotransporter-2.

[a]Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15(4):372-382.
[b]Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: an randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care*. 2010;33(10):2217-2224.
[c]Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension [published online September 30, 2014]. *Diabetes Care*.

patient groups. "The trial results suggest that SGLT2 inhibitors could be slightly better than other options for most patients with type 2 diabetes and quite a bit better for some patients who receive multiple medications for each condition," said Michael A. Weber, MD, a professor of medicine at the SUNY Downstate College of Medicine, in an interview with *Evidence-Based Diabetes Management*.

"When you start using an SGLT2 inhibitor to control diabetes in such patients, you can often eliminate the diuretic component of their blood pressure regimen," said Weber, who is also his school's assistant dean for research. "SGLT2 inhibitors produce similar diuretic effects—and work as well in combination with calcium channel blockers, ACE inhibitors, and others—but they seem to spare patients the risk of hypokalemia and uric acid buildup associated with traditional diuretics."

The substitution of an SGLT2 inhibitor for a diuretic eliminates a major safety risk for gout-prone patients, but Weber believes that physicians should at least consider the swap in all patients who receive a diuretic as part of combination therapy for hypertension. Such a recommendation has broad implications for SGLT2 inhibitor usage. More than 70% of all diabetics also suffer from high BP,[6] and many of them take the diuretics that the American Heart Association and American College of Cardiology recommend as the cornerstone of blood pressure treatment.[7]

The obvious link between T2DM and hypertension is obesity. A body mass index above 30 greatly increases the risk of developing either condition, or both. There are additional shared risk factors, including poor diet, insufficient exercise and others, but all of them combined are insufficient to explain why so many people have both conditions.

If they were fundamentally independent ailments that happened to share a number of risk factors, a person with a 60% risk of developing hypertension and a 60% risk of T2DM would have a 36% of developing both. In reality, the odds would be significantly higher, which suggests a deeper tie that has yet to be discovered.

Genetic predisposition provides the obvious explanation—and may ultimately prove to be the correct explanation—but research to date argues otherwise. There's relatively little overlap between the genes that are currently known to increase the risk of T2DM and those that are known to increase the risk of hypertension, according to George L. Bakris, MD, professor of medicine at the University of Chicago and the director of the ASH Comprehensive Hypertension Center.

Ongoing investigation of SGLT2 inhibitors, if it can fully explain the effect such medications have on BP, may help to explain the mystery. Researchers initially believed the diuretic effect of the drugs, combined with their tendency to promote weight loss, deserved the credit, but trial results eventually contradicted this hypothesis.

All medications in the class reduce A1C levels by reducing the amount of glucose that enters the blood via SGLT2 in the proximal renal tubules. This, in turn, increases the amount of glucose excreted via urine, increases the total amount of urine that users excrete and creates the diuretic effect.[8]

Trials revealed, however, that certain kinds of renal impairment can prevent this entire chain of events, including the increase in urine volume and the diuresis. If diuresis produced the blood pressure reductions (even in part) then people with such kidney problems would miss out on some or all of the BP benefit. In reality, such people see their BP decline about as much as other patients who take SGLT2 inhibitors.[9]

Researchers still believe diuresis produces some of the effect in many patients. They acknowledge, however, that many questions remain unanswered. "The precise mechanism of the blood pressure drop remains incompletely elucidated," wrote the authors of a recent paper on SGLT2 inhibitors and BP in the *Journal of the American Society on Hypertension*. "Based on current data, the blood pressure reduction is partially due to a combination of diuresis, nephron remodeling, reduction in arterial stiffness, and weight loss."[10]

History suggests that the mystery may endure. Thiazides have been around since the 1950s and studies have yet to explain exactly why they lower blood pressure as much as they do.[11] History also suggests that mysterious mechanisms are no barrier to usage. Thiazides have ranked among the world's most common and most useful medications for decades.

SGLT2 inhibitor sales have already topped some initial projections. Canagliflozin alone generated about $200 million in fourth quarter revenue of 2014, and many now expect usage to keep growing.[12]

A significant majority of hypertensive diabetics consistently fails to keep BP below target levels,[13] and a significant minority of all people with T2DM fails to keep A1C levels within target levels.[14] In cases where the problem reflects the inadequacy of treatment regimens (rather than poor patient compliance), guidelines advise physicians to change those regimens or expand them by adding a new class of drug. There are, of course, many drug classes to choose from, but SGLT2 inhibitors have a number of unique strengths beyond BP regulation.

"They have a truly novel mechanism of action, so when you add them to a regimen, you really get added benefit rather than partial duplication. They also tend to be very well tolerated on their own and in combination with other medications," Bakris said in an interview.

Bakris noted that SGLT2 inhibitors can produce urinary tract infections in some patients, especially uncircumcised men and women with a history of the problem, but argued that reports have exaggerated this side effect; he said this has distracted attention from more important therapeutic issues and should not stop patients from trying the class.

"SGLT2 inhibitors, as a class, tend to push everything in the right direction, not just A1C and blood pressure, but also diet and weight," Bakris said. "People who use these drugs tend to start eating better because they quickly realize that high-carb foods make them pee far, far more frequently than low-carb foods. People who use these drugs also tend to lose more weight than people who use other oral medications. That extra weight loss probably comes from the improved diet, but whatever the explanation, it's something that many physicians should pay more attention to. Patients who switch from treatments that promote weight gain, which are still common, to those that promote weight loss can drop 10 pounds of fat. Even if nothing else changes, that's a big improvement."

Of course, such a substitution in a pa-

THE AMERICAN JOURNAL OF MANAGED CARE

tient's diabetes regimen would probably produce other changes. The patient's BP would be likely to fall, and, according to at least 1 large study, A1C levels might also drop. The trial compared canagliflozin to sitagliptin for A1C control and found that the addition of the former drug to a regimen of metformin and sulfonylurea produced an average reduction of 1.03 percentage points after 52 weeks while the addition of the latter produced an average reduction of 0.66 percentage points. Patients who took canagliflozin, moreover, lost an average of 2.5 kg (5.5 lb) and saw their systolic blood pressure fell by 5 mm Hg. Patients who took sitagliptin generally gained a small amount of weight and saw no change in BP.[15]

If such results inspire physicians to substitute an SGLT2 inhibitor for sitagliptin, it will be good news for companies that make the latter class of drug. Sitagliptin sales (alone and in a formulation that combines it with metformin) approached $6 billion in 2013.[16]

If physicians prefer to add an SGLT2 inhibitor to sitagliptin, trials support that idea. The addition of dapagliflozin to sitagliptin, with or without metformin as a third treatment, reduced A1C levels by an average of 0.5 percentage points, based on a 24-week multicenter phase 3 study involving 432 patients who were randomized to receive dapagliflozin 10 mg/day or placebo added to sitagliptin (100 mg/day), with or without metformin. The results were published in March 2014 in *Diabetes Care*.[17]

Trials have yet to compare any SGLT2 inhibitor against metformin, used with or without a separate drug for hypertension, as an initial treatment for patients with mild elevations in both A1C and BP. There is, however, a theoretical case to be made for the idea.

Monotherapy trials of the 3 SGLT2 inhibitors report average reductions in A1C levels that range from 0.74 percentage points to 1.03 percentage points,[18-20] along with the average reductions in systolic blood pressure that range from 2.3 mm Hg to 5 mm Hg. While metformin and stand-alone BP medications can produce significantly greater effects, their relative strength may not help those who don't need it to reach targets.

SGLT2 inhibitors, moreover, are often (but not always) better tolerated than metformin, let alone a combination of metformin and a second medication. Their most common side effect is the weight loss, typically in the range of 2 kg to 3 kg,[21] which is rare for metformin users.

The best reasons for sticking with metformin, beyond the possible benefits of pushing A1C levels further below the 7% threshold, stem from its age. Metformin (like many blood pressure medications) sells in generic form for less than one-tenth the $350 monthly price of branded SGLT2 inhibitors that still enjoy years of patent protection. The older drug also has enough of a track record to assure physicians and patients about its long-term safety. For SGLT2 inhibitors, however, there are some unanswered questions.

> *"SGLT2 inhibitors, as a class, tend to push everything in the right direction, not just A1C and blood pressure, but also diet and weight."*
>
> GEORGE L. BAKRIS, MD

Concerns that dapagliflozin might trigger breast and bladder cancer led the FDA to delay that drug's approval until follow-up data arrived.[22] Concerns that canagliflozin might trigger cardiovascular events and other health problems led 5 of the 15 members on an FDA review panel to recommend against its approval.[23]

The agency has ordered drug makers to conduct multiple postmarketing studies for all 3 SGLT2 inhibitors. Johnson & Johnson, for example, must complete 5 separate studies of canagliflozin[24]:

- a cardiovascular outcomes trial
- an enhanced pharmacovigilance program that monitors malignancies, serious cases of pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes
- a bone safety study
- a pediatric pharmacokinetic and pharmacodynamic study
- a pediatric safety and efficacy study

Weber and Bakris both believe that lingering concerns about safety have slowed the adoption of SGLT2 inhibitors, and they both believe those concerns are probably misplaced. Follow-up research has addressed the questions raised by some earlier trials, they say, leaving no more reason to worry about the long-term safety of SGLT2 inhibitors than that of any other new drugs that doctors eagerly embrace.

Those same trials, meanwhile, have clearly demonstrated that SGLT2 inhibitors produce unique benefits and may thus prove to be considerably more useful than many originally expected. **EBDM**

References

1. Clarke T. US FDA approves Johnson & Johnson diabetes drug, canagliflozin. Reuters website. http://www.reuters.com/article/2013/03/29/johnsonjohnson-diabetes-idUSL3N-0CL1FV20130329. Published March 29, 2013. Accessed February 17, 2015.

2. Market brief: The market for type 2 diabetes therapeutics; key findings from a recent analysis of global drug development efforts. Drug Development and Delivery website. http://drug-dev.com/Main/Back-Issues/MARKET-BRIEF-The-Market-for-Type-2-Diabetes-Therap-641.aspx. Published November 19, 2013. Accessed February 17, 2015.

3. Simon JL, Timaeus S, Misita C. SGLT2 inhibitors: a new treatment option for type 2 diabetes. *Pharmacy Times.* http://www.pharmacytimes.com/publications/health-system-edition/2014/September2014/SGLT2-Inhibitors-A-New-Treatment-Option-for-Type-2-Diabetes. Published September 17, 2014. Accessed February 17, 2015.

4. Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension [published online September 30, 2014]. *Diabetes Care*. doi:10.2337/dc14-1096.

5. Oliva RV, Bakris GL. Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. *J Am Soc Hypertens.* 2014;8(5):330-339.

6. Klein R, Klein BEK, Lee KE, Cruickshanks KJ, Moss SE. The incidence of hypertension in insulin-dependent diabetes. *Arch Intern Med.* 1996;156(6):622-627.

7. Go AS, Bauman MA, Coleman King SM, et al. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology and the Centers for Disease Control and Prevention. *Hypertension.* 2014; 63:878-885.

8. Jabbour SA. SGLT2 inhibitors to control glycemia in type 2 diabetes mellitus: a new approach to an old problem. *Postgrad Med*. 2014; 126(1):111-117.

9. Kohan DE, Fiorett P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney International* 2014; 85:962-971.

10. Maliha G, Townsend RR. SLGT2 inhibitors: their potential reduction in blood pressure. *J Am Soc Hypertens.* 2015; 9(1):48-53.

11. Hughes AD. How do thiazide and thiazide-like diuretics lower blood pressure? *J Renin Angiotensin Aldosterone Syst.* 2004;5(4):155-160.

12. Williams S. 5 things Johnson & Johnson's management wants you to know. Motley Fool website. http://www.fool.com/investing/general/2015/01/26/5-things-johnson-johnsons-management-wants-you-to.aspx. Published January 26, 2015. Accessed February 17, 2015.

13. El-Shafie K, Rizvi S. Control of hypertension among type 2 diabetes. *Oman Med J.* 2010; 25(1):32-36.

14. Harris MI, Eastman RC, Cowie CC, et al. Racial and ethnic differences in glycemic control of adults with type 2 diabetes. *Diabetes Care*. 1999;22(3):403-408.

15. Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea. *Diabetes Care*. 2013;36(9):2508-2515.

16. Merck announces 4th quarter and full year 2013 results [press release]. Whitehouse Station, NJ: Business Wire; February 5, 2014. http://www.businesswire.com/news/home/20140205005626/en/Merck-Announces-Fourth-Quarter-Full-Year-2013-Financial-Results#.VOO5J_nF-Sp.

17. Jabbour SA, Hardy E, Sugg J, Parikh S. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care.* 2014;37(3):740-750.

18. Invokana website. Invokana monotherapy provided statistically significant reductions in A1C vs placebo at 26 weeks. http://www.invokanahcp.com/clinical-research-results/monotherapy-vs-placebo/A1C-reductions. Accessed February 17, 2015.

19. Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol*. 2013;1(3):208-219.

20. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care*. 2010;33(10):2217-2224.

21. Bailey CJ, Day C. SGLT2 inhibitors: glucuretic treatment for type 2 diabetes. Medscape website. http://www.medscape.com/viewarticle/726748_1. Accessed February 18, 2015.

22. Edney A. Bristol-AstraZeneca drug wins US FDA approval. *Bloomberg News* website. http://www.bloomberg.com/news/articles/2014-01-08/bristol-astrazeneca-diabetes-drug-wins-u-s-fda-approval. Published January 8, 2014. Accessed February 17, 2015.

23. Tucker ME. Most FDA advisers support diabetes drug canagliflozin, despite CV concerns. Medscape website. http://www.medscape.com/viewarticle/791413. Published January 11, 2013. Accessed February 17, 2015.

24. FDA approves Invokana to treat type 2 diabetes [press release]. Silver Spring, MD: FDA Newsroom; March 23, 2013. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345848.htm.

When Moving to Collaborative Care, a Challenge Is Figuring Out How to Pay for It
(CONTINUED FROM COVER)

how could practices, health systems, and accountable care organizations make the leap to value-based care while remaining on solid financial footing?

Howard C. Springer, administrative director of strategy for accountable care services for Swedish Medical Center in the Seattle, Washington, area, told *EBDM* it's not easy, but it can be done. And it's important that physicians accept a future with value-based payment models, which will let them gradually move away from FFS billing and thinking. "For those that are putting their head in the sand and saying, 'This too shall pass,' all indications are that we're going this way, and early adaptors will be better off," he said.

Springer, who joined Swedish in November 2013, is shepherding its healthcare delivery to value-based models, a task that requires a deep understanding of the twin movements under way: the revolution in how care is delivered, and the one in how we pay for it, the latter being not quite as far along. The challenge for Springer and healthcare executives like him is that the desire to deliver care more effectively can get ahead of the payment models themselves. Figuring out how to navigate this transition financially—while investing in electronic health records (EHRs), information and data analysis technology, and training—requires quite a balancing act, one for which there is no road map. Making the balance sheets work requires obtaining grants and other funding from other sources to finance investments in technology and sophisticated measurement tools, so that as FFS is phased out, Swedish will be ready for its replacement. And the "future" isn't far off. CMS has announced new targets for Medicare value-based reimbursements: 30% by 2016, and 50% by 2018.[5]

Among Springer's strategies is to bring comprehensive behavioral health services to the primary care setting, using the type of models pioneered by researchers at the University of Washington, whose 2010 paper in the *New England Journal of Medicine* reported that patients who received collaborative care for 12 months showed a 58% improvement in glycated hemoglobin (A1C) levels relative to the control group, as well as better results for low-density lipoprotein (LDL) cholesterol, blood pressure, and depression screenings.[1] The cost for the collaborative care group was lower, too: an average of $594 per patient for the year.[1]

GETTING BUY-IN FROM PRIMARY CARE DOCTORS

As Springer works to integrate behavioral health services into primary care, he encourages those PCPs who aren't ready to share control of a patient to see how the relationship benefits them. Is there a generational aspect to resistance? Yes and no, Springer said: while there are some older providers who have embraced collaborative care and some younger ones who resist it, current family medicine residencies tend to emphasize a more team-based approach.

"There's always going to be a contingent of primary care providers who are not team players," he said. "Then there's the other type of provider who is more socially engaged, more team oriented, who realizes, 'I like doing certain things, but I can't be all things to all people.'"

Research identifies that 80% of patients with behavioral health conditions present in the primary care or medical setting.[6,7] However, 60% to 70% of these receive no treatment for behavioral health conditions.[8,9] PCPs who refer the patient to the behavioral health provider "lose contact" with the referral, because most behavioral health is farmed out to outside provider groups that essentially limit access to services and do not communicate with the PCP. But in a team approach, that's not what happens—the care is all under 1 roof, so the patient is more likely to have a mental health or substance abuse issue addressed. And these, Springer said, are the patients who cost the healthcare system at least 2.5 to 3.2 times more than patients with a chronic medical condition.[10]. "This is the low-hanging fruit."

The PCP can try to handle a mental health case alone, or can turn it over for a behavioral health intervention of 1 to 4 visits. Addressing behavioral health issues within the primary care delivery team removes barriers that prevent patients from maintaining their LDL cholesterol or A1C levels, Springer said. The behavioral health interventions and care coordination have been shown to deal effectively with real-world issues, which Springer identified as "not being able to get medication, family stress, poor coping strategies—some of the nuts and bolts of survival in the community." Removing these barriers to failure, he said, can make or break a person's ability to stay on a health and medication regimen.

THE ARRIVAL OF THE CARE COORDINATION FEE

On October 31, 2014, CMS announced a fundamental shift toward value-based care: for the first time, it would pay PCPs to coordinate care for Medicare patients with multiple chronic conditions, even if the patient did not see the doctor that month. Starting in January 2015, physicians or "staff incident to" physicians can earn a "chronic care management" (CCM) fee of $42.60 per eligible patient per month under certain conditions[11]:

- The PCP must perform (and bill separately for) an initial preventive physical, followed by an annual wellness exam.
- Each eligible patient must have a written care plan, with 20 minutes spent each month on care coordination for that patient by a licensed care team member.
- The patient must have 24/7 access for urgent care needs, including telephone consultation, and the team is responsible for hospital post discharge and ED follow-up.
- The PCP must maintain all EHR activity.
- Most critically, the physician must get the patient's written consent to act as care coordinator, because the service is subject to a Medicare deductible. It is acknowledged that some patients who most need coordination may refuse to do this.[11]

Springer said this is an opportunity for some practices to collect a little over $40 per month per patient for services, which many were doing already without receiving reimbursement. This monthly payment aligns reimbursement with value-based care delivery. "It promotes overall care," he said. Once the PCP's scope of accountability increases—and a new revenue stream is added—the potential exists for practices to overhaul the way they deliver care. No longer will the entire financial enterprise depend on physicians seeing patients in 15-minute increments. More work can be shared by other licensed professionals, diabetes educators, or care coordinators. For example, say a practice has 2500 patients with 60% eligible for Medicare. Even if only 60% of these are eligible for the CCM fee, this will yield $460,000 a year for the practice. This reimbursement is not dependent on having a risk contract, which typically has 2 thresholds—reduced medical expense and quality improvement—and an 18-month payback period.

"Another example of real reimbursement with quick payback to Swedish Health delivery system is taking risk for employee health expenses. Taking this model and providing access to employees increases their access to complex care teams, improves care delivery, reduces total cost of care, and increases satisfaction. We call this the Quadruple Aim rather than the Triple Aim."

"Now they can invest in infrastructure for those patients who are at risk," Springer said. The practice will still collect some revenue in FFS for a time, but the CCM fee and certain risk arrangements will allow for the investments that will be needed to make the transition to value-based case.

But what the doctor does is part of the equation, Springer said. The shift will also require a commitment to patient engagement. When asked how practical it will be to ask seniors to make a co-payment for services they may think their doctor should provide anyway without a co-payment, Springer said that's the point: patients need to be involved, to have a "quasi-agreement" with their doctor and team and get their buy-in to manage multiple chronic conditions. "Without patient engagement you really can't change behavior." **EBDM**

References

1. Katon WJ, Lin EHB, Von Korff M, et al. Collaborative care for patients with depression and chronic illness. *N Engl J Med.* 2010;363:2611-2620.

2. Katon WJ, Russo J, Lin EHB, et al. Cost-effectiveness of a multicondition collaborative care intervention: a randomized controlled trial. *Arch Gen Psychiatry*. 2012;69(5):506-514.

3. Caffrey MK. Integrated care no longer an afterthought at APA. *The American Journal of Managed Care* website. http://www.ajmc.com/conferences/APA2014/Integrated-Care-No-Longer-an-Afterthought-at-APA. Published May 4, 2014. Accessed June 24, 2014.

4. Caffrey MK. Behavioral health session tackles diabetic burnout, mental health delivery: conference. *The American Journal of Managed Care* website. http://www.ajmc.com/conferences/ada-2014/Behavioral-Health-Session-Tackles-Diabetic-Burnout-Mental-Health-Delivery-. Published June 15, 2014. Accessed June 24, 2014.

5. Better, smarter, healthier: in historic announcement, HHS sets clear goals and timeline for shifting Medicare reimbursements from volume to value [press release]. Washington, DC: HHS; January 26, 2015. http://www.hhs.gov/news/press/2015pres/01/20150126a.html.

6. Reilly S, Planner C, Hann M, Reeves D, Nazareth I, Lester H. The role of primary care in service provision for people with severe mental illness in the United Kingdom. *PLoS One*. 2012;7(5):e36468.

7. Wang PS, Demler O, Olfson M, Pincus HA, Wells KB, Kessler RC. Changing profiles of services sectors used for mental healthcare in the United States. *Am J Psychiatry*. 2006;163(7):1187-1198.

8. Kessler RC, Demler O, Frank RG, et al. Prevalence and treatment of mental disorders, 1990 to 2003. *N Engl J Med*. 2005;352(24):2515-2523.

9. Wang PS, Gruber MJ, Powers RE, et al. Mental health service use among Hurricane Katrina survivors in the eight months after the disaster. *Psychiatr Serv*. 2007;58(11):1403-1411.

10. Simon GE, VonKorff M, Barlow W. Healthcare costs of primary care patients with recognized depression. *Arch Gen Psychiatry*. 1995;52:850-856.

11. Policy and payment changes to Medicare physician fee schedule for 2015 [press release]. Washington, DC: CMS; October 31, 2014. http://www.cms.gov/newsroom/mediareleasedatabase/fact-sheets/2014-Fact-sheets-items/2014-10-31-7.html.

Invokana®
canagliflozin tablets

More than 3 million prescriptions to date[1]*

2 Years
real-world experience
and counting†

Invokana® CarePath™

Find out about support for your members at INVOKANACarePath.com

Preferred for >75% of commercial and Medicare Part D lives[1]

Learn more about INVOKANA® at INVOKANAhcp.com

*Data on file. Based on TRx data sourced from IMS NPA and NSP databases, weekly data through 3/2/15.
†Approval from the Food and Drug Administration (FDA) was granted in March 2013.
Reference: 1. Data on file. Janssen Pharmaceuticals, Inc., Titusville, NJ.

Janssen Pharmaceuticals, Inc.

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

 February 2015 028004-150116

NOW AVAILABLE

Glyxambi®

(EMPAGLIFLOZIN/LINAGLIPTIN) TABLETS

10/5mg • 25/5mg

www.glyxambi.com

Boehringer Ingelheim

Lilly