



DIABETES IS PRIMARY

TIMELY NEWS AND NOTES FOR PRIMARY CARE PROVIDERS
from the American Diabetes Association

FROM THE JOURNALS

Drugs Work When Patients Take Them

Information on whether patients with diabetes (or any other ailment) actually take the drugs prescribed to them is, we humbly suggest, rather important for guiding the longer-term care of patients. And yet, it seems that physicians may well be flying blind when it comes to deciding what drugs a patient should take and whether a patient actually ever takes them.

As a case in point, Tseng et al. (*Diabetes Care*, <http://doi.org/cdgs>) detail an analysis of millions of insurance claims for antihyperglycemia medications and suggest that as few as 8% of patients likely receive metformin as a first-line therapy for the American Diabetes Association/European Association for the Study of Diabetes–recommended 60 days before moving on to second-line therapies.

Perhaps more concerning is that reportedly a full 28% don't receive any metformin at all before commencing second-line therapies. As a result, the authors suggest that apparent treatment failures of metformin might actually be attributable to nonadherence to guidelines and consequently the use of (more expensive) second-line medications.

The authors concede that claims data have their limits in terms of monitoring drug usage overall (i.e., they cannot detect prescriptions for uninsured patients or those paid for out of pocket, particularly generic drugs).

However, the authors say that, based on these data, there is likely a pressing need for point-of-care providers to start monitoring prescribing patterns and that, on a population level, approaches are needed to improve adherence. The authors particularly highlight electronic health records (EHRs) as a readily available source of data to tackle the issue.

Author Kenneth Mandl provided *Diabetes Care* with some further analysis: "Even though pharmacy benefit managers have extensive real-time data about whether and when a patient has filled her prescriptions, this infor-

mation rarely influences a physician's practice. Clinicians don't know if their patients are being adherent to the medications they prescribe. We have shown that at least some of the time, flying blind likely confuses physicians into thinking that poor adherence represents a lack of medication efficacy. And this leads doctors to move on to the next, and often more expensive, option."

Is Technology the Answer to This?

A survey published in September 2017 by Medscape (<http://wb.md/2y1Wte3>) suggests there is still some way to go, particularly with patient adoption of EHR/patient-portal use—more than two-thirds of practices offering patient portals report that only a quarter of their patients actually log in.

But when physicians were asked about how they use their EHRs (besides documenting a patient visit), half reportedly used it to identify patients requiring a follow-up visit, and 42% used it "to identify patients who need additional treatments." Presumably, if that last figure is indeed reflective of EHR usage, leveraging these systems to improve drug adherence is going to take quite some work. That's not the worst of it; 12% of self-employed and 4% of employed physicians reportedly don't have an EHR at all.

About Skipping Breakfast

Skipping breakfast apparently does influence glycemic responses after lunch, according to Jakubowicz et al. (*Diabetes Care* <http://doi.org/cdgt>). As a result, they now suggest that consuming breakfast might well be an important strategy to control glycemia in the very short term in type 2 diabetes. And according to the authors, the effect seems to be related to the circadian clock.

The cross-over study randomly assigned both healthy individuals and those with type 2 diabetes to two test days, one with and one without breakfast. Then, with regular blood samples throughout the day, the researchers measured various circadian clock–related gene expression markers, plus blood glucose, insulin, glucagon-like peptide 1 (GLP-1), and a range of other blood markers.

They say that skipping breakfast did alter gene expression in both groups, but that the glucose excursion was

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much greater, and insulin and GLP-1 response much smaller, in the individuals with type 2 diabetes. Author Oren Froy told *Diabetes Care* that, "As breakfast skipping adversely affects clock- and clock-controlled gene expression and is correlated with increased postprandial glycemic response, consumption of breakfast should be an important strategy when targeting glycemic control in type 2 diabetes."

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ADA NEWS

Hurricane Relief and Natural Disaster Information

When Hurricanes Harvey, Irma, and Maria hit the southern United States and Caribbean islands in August and September, the American Diabetes Association (ADA) sprang to action to help support people facing the challenges of surviving a hurricane while living with diabetes.

The Diabetes Emergency Relief Coalition, a group of eight leading diabetes care and research organizations convened by ADA, continued to provide crucial diabetes supplies to regions affected by the hurricanes in the weeks that followed. Members of the coalition (ADA, JDRF, Insulin for Life USA, the Endocrine Society, the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, Research! America, and the T1D Exchange) worked with local volunteers

and organizations to identify and meet urgent needs. Thousands of pounds of free diabetes supplies, including insulin, syringes, pen needles, alcohol pads, blood glucose meters, glucose test strips, and lancets, were shipped to Texas and Florida and to Puerto Rico in advance of Hurricane Maria. The coalition also participated in efforts to engage private deliveries to Puerto Rico and the U.S. Virgin Islands, given extensive shipping and transportation problems in the region.

The ADA Call Center, **1-800-DIABETES**, responded to hundreds of calls for help, and staff, volunteers, and coalition partners reached out to program participants, camp families, and donors to ensure that affected communities had access to the supplies and resources they needed. A hotline, 1-314-INSULIN, was also set up for health care providers from affected areas who were in need of diabetes supplies. In addition, the ADA website (diabetes.org) posted and regularly updated lists of resources and information specific to affected areas, as well as links for people wishing to donate diabetes supplies or money to the relief effort.

Help your patients with diabetes prepare for future natural disasters by checking out the following links on the ADA website:

- Diabetes tips for first responders (<http://bit.ly/2ymeY9e>)
- Information on how to care for yourself or a loved one with diabetes during an emergency situation (<http://bit.ly/2yBm5eZ>)
- The rights of people with diabetes in emergency shelters (<http://bit.ly/2xAiTBP>)

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Good to Know: Drug Target Hunting

While there have been many recent publications on antidiabetes drugs, the hunt for new targets continues at a rapid pace.

A meta-analysis of genome-wide association data by Scott et al. (*Diabetes*, <http://doi.org/gbvxtg>) involving many thousands of individuals has identified a series of new genetic signals they say potentially expands the number of therapeutic targets for type 2 diabetes. In particular, they say that, as well as confirming many previous genetic associations with type 2 diabetes, they have now reportedly “refined” the location of causal DNA variants at 13 novel and 69 established genetic loci/signals. Author Mark McCarthy told *Diabetes*: “We already see a strong overlap between the genetic signals we find and the drugs already used to treat diabetes. This gives us confidence that new genetic signals are likely signposts to ways of treating or preventing the disease.”

Meanwhile another genome-wide association study by Zhao et al. (*Nature Genetics*, <http://doi.org/gbt4cb>), again involving many thousands of individuals, has identified a whole series of genetic signals linked to type 2 diabetes and, in some cases, also coronary heart disease. As a result, they say the findings likely indicate that there are biological pathways that are shared between

the diseases and that would point toward there being potential targets for therapy that target both diseases at the same time. Author Benjamin Voight said in an institutional press release (<http://bit.ly/2xuLp60>), “I’m hopeful that with the advanced genomic engineering techniques now available, we’ll be able to quickly convert our human genetics observations into concrete details regarding the molecular mechanisms involved in both heart disease and diabetes.”

Translating apparent genetic associations with diseases into drug targets can be an intricate task, although it can be done. Mercader et al., (*Diabetes*, <http://doi.org/cdgv>) detail one such effort, first identifying that a variant in the gene that encodes insulin-like growth factor 2 is likely associated with a reduction in type 2 diabetes risk of ~20%. With a series of follow-up experiments, they then detail how the likely mechanisms affect risk of the disease. On that basis, they say reducing the expression of isoform 2 of the gene in certain tissues could potentially be achieved pharmacologically.

Author Jose Florez told *Diabetes*: “Finding a genetic association is only the first step toward elucidating molecular mechanism and direction of effect, both of which we have pursued here to begin translating genetics into therapeutics.”

MARKETPLACE

PROGRESSION OF AND FDA APPROVAL FOR ARTIFICIAL PANCREAS TECHNOLOGY

Tandem Diabetes Care, Inc., has announced (<http://bit.ly/2wieL79>) that it has received approval from the U.S. Food and Drug Administration (FDA; <http://bit.ly/2xEEM37>) for a tie-up between its t:slim X2™ insulin infusion pump and Dexcom’s G5 mobile continuous glucose monitoring (CGM) system. The combination is now reportedly approved for use by children ≥6 years of age, a drop from an age limit of 12 years on previous models. The system also received approval to let users make treatment decisions without first needing to use a fingerprick test to determine blood glucose (although fingerpricks are still needed for calibration). Users can reportedly view the CGM data on the pump’s screen, as well as in a smartphone app (which we imagine will be a huge win for patients and also parents of children with type 1 diabetes).

Although the system is not a fully automated insulin delivery device yet, the update pathway promised from the manufacturers seems to suggest it will be possible to upgrade once research is complete and approvals are granted. A pivotal trial (<http://bit.ly/2hs0vVS>) is ongoing with the system, which crucially includes the company’s “predictive low glucose suspend” feature that is designed to predict hypoglycemia and take automated action to prevent it. The trial has a primary completion date of November 2017. Pending trial success and FDA approval, Tandem said in statements that it aims to launch new version(s) of the system in mid-2018.



TREATMENTS + THERAPIES



Artificial Pancreas System Offers Improved Glycemic Control During Winter Sports

One challenge facing artificial pancreas (AP) technology (and its users) is intensive exercise, because of the potential for dangerous hypo- and hyperglycemia episodes.

According to Breton et al. (*Diabetes Care*, <http://doi.org/cdgx>), available data on the performance of AP technology during exercise are limited, primarily because the systems have been too big. However, that is not the case now, and they detail the performance of one particular system on the ski slopes.

They report a trial of a closed-loop control (CLC) system during a prolonged skiing camp attended by teenaged type 1 diabetes patients. They reveal that improved glycemic control and reduced exposure to hypoglycemia is possible even during prolonged exercise, at high altitude, and during exposure to cold temperatures.

According to the authors, the randomized trial involved 32 adolescents with type 1 diabetes who attended a 5-day skiing camp at two sites in Virginia and Colorado. They compared the performance of the CLC system against an open-loop, physician-monitored system (the control).

They report that, after the daily sessions of skiing/snowboarding and evening activities, the CLC system managed to maintain overall blood glucose levels between 70 and 180 mg/dL about 71% of the time. In comparison, the control system only managed to be in range about 65% of the time. Throughout the day, the percentage time in range varied, but the maximum effect was seen late at night. There were no adverse events associated with the interventions (there were a few broken bones; it is skiing, after all), and reportedly, feedback from participants was overwhelmingly positive.

They conclude: “CLC in adolescents with type 1 diabetes improved glycemic control and reduced exposure to hypoglycemia during prolonged intensive winter sport activities, despite the added challenges of cold and altitude.”

FOURIER Trial: Evolocumab Has Heart Benefits and Does Not Increase Diabetes Risks

According to a prespecified analysis of the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial, evolocumab does not increase risk of diabetes or worsen existing diabetes in patients with atherosclerotic cardiovascular disease.

Sabatine et al., writing in *The Lancet Diabetes and Endocrinology* (<http://doi.org/cdgz>), report that the PCSK9 inhibitor reduced a composite measure of various cardiovascular outcomes by 17% in patients with diabetes and 13% in patients without diabetes. Importantly, risk of developing diabetes was not increased while on the drug and likewise did not worsen diabetes when present.

Both the authors and a separate editorial (<http://doi.org/cdg2>) suggest that the results might influence prescribing decisions and that the drug is likely safe and effective in the population studied. However, the editorial highlights that costs and access to the drug might preclude its widespread use in a number of countries.

IRIS Trial: Secondary Analysis Suggests That Diabetes Drug Pioglitazone Might Benefit High-Risk Stroke Patients

A secondary analysis of the IRIS (Insulin Resistance Intervention After Stroke) trial suggests that stroke patients with insulin resistance but not diabetes at high 5-year risk for having another stroke or myocardial infarction might benefit from the diabetes drug pioglitazone.

According to the analysis by Kernan et al. in *JAMA Neurology* (<http://doi.org/cfqg>), the absolute risk difference of 4.9% between high- and low-risk patients suggests that high-risk patients may derive benefit from the drug. However, the authors caution that this comes with an increased risk of bone fractures. As a result, they suggest that their results might help clinicians talk with patients about the likely benefits and harms of the therapy.



CONFERENCE SPOTLIGHT

News and Notes From the EASD Annual Scientific Meeting

The European Association for the Study of Diabetes (EASD) held its annual conference in Lisbon, Portugal, in September, with many major trials reporting their outcomes. Following are some of the reported findings with a focus on implications for primary care. (Note, however, that many conference presentations have not yet been through full peer-review or published in the scientific literature. We encourage readers to carefully evaluate study outcomes before implementing in any clinical environment.)

J-DOIT3: A Randomized, Controlled Trial of Intensive Therapy in Type 2 Diabetes

Focusing on intensive therapy in type 2 diabetes, the approach taken in J-DOIT3 (the Japan Diabetes Optimal Integrated Treatment Study for 3 Major Risk Factors of Cardiovascular Diseases) reportedly reduced by 24% (after adjusting for baseline risk factors) a composite of micro- and macrovascular complications, including myocardial infarction, stroke, and all-cause mortality versus standard care. The intervention reportedly involved aggressive targets for controlling blood pressure, lipids, and glucose levels. Senior author Takashi Kadowaki said in a statement (<http://bit.ly/2wOe74G>) at the conference: "The results of J-DOIT3 suggest that a multifactorial intervention with stricter targets than those recommended by current guidelines has benefit for the suppression of stroke and nephropathy in patients with type 2 diabetes." A follow-up observational study is reportedly ongoing to further evaluate outcomes.

TOSCA.IT: Pioglitazone in Head-to-Head Trial With Sulfonylurea Is No Better for Heart Outcomes

In the pragmatic, randomized TOSCA.IT (Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention Trial), pioglitazone as an add-on to metformin was apparently similar to sulfonylurea (mostly glimepiride and gliclazide) as a metformin add-on for a primary composite outcome of all-cause mortality and various nonfatal heart outcomes in type 2 diabetes. In a simultaneously published article in *The Lancet Diabetes and Endocrinology* (<http://doi.org/cdg5>), authors Vaccaro et al. wrote: "Both of these widely available and affordable treatments are suitable options with respect to efficacy and adverse events, although pioglitazone was associated with fewer hypoglycemia events."

ACE: Acarbose Delays Diabetes Onset but Fails to Reduce Cardiovascular Events

Acarbose, an α -glucosidase inhibitor that was tipped as an antidiabetes drug targeting postprandial hyperglycemia, has failed to improve composite cardiovascular outcomes in patients with coronary heart disease and impaired glucose tolerance in the ACE (Acarbose Cardiovascular Evaluation) trial. However, it can apparently reduce progression to type 2 diabetes, according to Holman et al., who presented their results at the EASD meeting and simultaneously published them in *The Lancet Diabetes and Endocrinology* (<http://doi.org/cdg6>). They wrote: "On the basis of the data from this trial and the NAVIGATOR study, it seems that, despite the strong epidemiological data linking postprandial

hyperglycemia to increased cardiovascular risk, directly targeting postprandial hyperglycemia does not directly reduce the risk of cardiovascular events in populations at high risk of cardiovascular events and with impaired glucose tolerance.”

EXSCEL: Extended-Release Exenatide Falls Short of Showing Any Extra Benefits, But Does Demonstrate Safety

Extended-release exenatide is reportedly safe in terms of a composite measure of cardiovascular outcomes in type 2 diabetes, but at the same time did not help prevent extra events in comparison to control, according to Holman et al., who presented the results of EXSCEL (Exenatide Study of Cardiovascular Event Lowering) at the conference and in an article published simultaneously in the *New England Journal of Medicine* (<http://doi.org/cdg7>). The authors concluded: “Among patients with type 2 diabetes with or without previous cardiovascular disease, the incidence of major adverse cardiovascular events did not differ significantly between patients who received exenatide and those who received placebo.”

Nutrition: Sodium Intake and Sugar Substitutes in the Spotlight for Type 2 Diabetes Risk

In separate studies reported at the conference, elevated salt intake has been tied to increased risk of type 2 diabetes (<http://bit.ly/2ynXhWK>), while sugar substitutes that are often used in diet beverages might play havoc with glycemic

control (<http://bit.ly/2ftqwDD>), which raises the possibility that habitual consumption could increase type 2 diabetes risk. We underline that, in both cases, more studies are likely needed to definitively tie the two to diabetes risk. Nevertheless, these studies highlight that nutrition still plays a major part in managing risk and outcomes in diabetes.

Obese Wives Increase Risk of Diabetes in Husbands

Although individual risk factors for type 2 diabetes are well established, it seems social relationships might also play a role. According to Hulman et al. (<http://bit.ly/2xEuSie>), men might have additional risk for type 2 diabetes when the BMI of their wife increases. The relationship was apparently linear and significant and carried an incident rate ratio of 1.21 (95% CI 1.11–1.33)—in other words, an increased risk of 21%. The reverse relationship, the effect on women’s risk of diabetes due to obesity in their husband, was nonsignificant. The authors suggest that these findings likely reflect traditional gender roles at the time the data were collected and specifically that “wives might be more likely to be responsible for diet.” According to lead author Adam Hulman, who presented the study, the presence of obesity in female patients might be a signal to also pay attention to their spouse’s diabetes risk. The presentation slides and audio of the session are available via the EASD website (<http://bit.ly/2fsvBwc>).

To learn more about ADA’s continuing education opportunities, including Diabetes Is Primary events in your community, please visit <http://professional.diabetes.org/ce>.