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Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Antipsychotic Drugs in Youth With Type 1 Diabetes May Affect Glycemic Control: A Population-Based Study

Antipsychotic drug intake in youth with type 1 diabetes appears to be associated with a variety of acute metabolic complications including worse glycemic control, according to a report in this issue of *Diabetes Care* (**p. 1051**). The population-based study, reported by Galler et al., is based on data from the German/Austrian Diabetes Survey (DPV) and involved just over 60,000 youths with type 1 diabetes. Overall, 291 patients were identified as having received some sort of antipsychotic drug over the duration of the survey (1995–2013). The study suggests that youths with type 1 diabetes taking antipsychotic medication typically had increased BMI and dyslipidemia plus increased frequencies of severe hypoglycemia, diabetic ketoacidosis, and hospital admissions. This was in comparison with youths with type 1 diabetes who did not receive antipsychotic drugs. Perhaps the most intriguing finding was that glycemic control (according to HbA_{1c} levels) was worse only in subjects treated with atypical or second-generation antipsychotic drugs. The authors indicate that these types of antipsychotic drugs typically target β-cells in the pancreas where insulin is produced, and this likely leads to insulin resistance and poorer glycemic control. In contrast, rates of severe hypoglycemia were only raised in patients receiving typical or first-generation antipsychotic drugs and not in patients receiving atypical antipsychotic drugs. The authors' conclusions are stark: "This analysis of a real-life survey demonstrated that subjects taking antipsychotic medication had worse glycemic control and a higher rate of acute complications compared with those not taking antipsychotic medication.... Health care teams caring for youth with type 1 diabetes on antipsychotic medication need to know about these findings." The outcome of this study is clear: the use of antipsychotic medication in type 1 diabetes in youth carries a risk of complications that should be carefully managed at the patient and clinical level.

Galler et al. Comparison of glycemic and metabolic control in youth with type 1 diabetes with and without antipsychotic medication: analysis from the nationwide German/Austrian Diabetes Survey (DPV). Diabetes Care 2015;38:1051–1057

Increased Risk of Acute Pancreatitis Is Likely Not Associated With Incretin-Based Therapy

In a nationwide population-based case-control study, in Denmark, an association between incretin-based drugs (GLP-1 receptor agonists and DPP-4 inhibitors) and an increased risk of acute pancreatitis appears not to exist, according to a report by Thomsen et al. (**p. 1089**). The hypothesis behind the study was that acute pancreatitis risk would increase with all antihyperglycemic therapies (and that included incretin-based therapies) on the basis that underlying diabetes and associated risk factors would be important. A series of studies have previously produced mixed results regarding the associations between incretin-based drug use and risk of acute pancreatitis, despite widespread use of the drugs. Such is the case that both the U.S. Food and Drug Administration and the European Medicines Agency have called for large high-quality studies to be performed to resolve the issue. This study goes some way toward fulfilling this call. It looked at the case records of patients who experienced first time hospitalization with acute pancreatitis between 2005 and 2012. In total, 89 patients with pancreatitis and 684 control subjects were identified as ever using incretins in the cohort. There was no difference, based on crude or adjusted odds ratios, between incretin and non–incretin-based antihyperglycemic therapy users in terms of risk of acute pancreatitis. Commenting on the research, Dr. Thomsen said: "Our findings add to the accumulating evidence from several large observational studies and a few randomized studies that there is no substantial increase in the risk of acute pancreatitis with incretin-based drugs. Pooled results from several ongoing incretin cardiovascular safety trials will provide further crucial knowledge on pancreatitis and pancreatic cancer risk in the future. In the meantime, large and carefully designed observational studies based on multinational existing databases could provide further safety evidence in this area." Any elevated risk of acute pancreatitis would be a major public health concern. While the use of incretins appears not to be associated with such an increase, underlying diabetes and related risk factors do appear to be linked to the risk of pancreatitis.

Thomsen et al. Incretin-based therapy and risk of acute pancreatitis: a nationwide population-based case-control study. Diabetes Care 2015;38:1089–1098

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Hemoglobin Glycation Index and Differential Risks and Benefits of Intensive Treatment of Diabetes

HbA_{1c} is a measure used widely in diabetes management to assess average plasma glucose concentrations over extended periods of time. Therefore, the suggestion that the measure may not accurately reflect actual plasma glucose levels in some patients and may have led to the increased harms observed in the ACCORD trial is likely to be of interest not least from a clinical perspective. The study by Hempe et al., which appears in this issue of *Diabetes Care* (**p. 1067**), examines whether a hemoglobin glycation index (HGI) (the difference between observed HbA_{1c} and predicted HbA_{1c}) can identify subpopulations of patients associated with harms or benefits from the so-called intensive (HbA_{1c} target of less than 6%) and standard (HbA_{1c} target of 7.0% to 7.9%) treatments that were used in the original study. The authors reasoned that "intensive treatment to a one-size-fits-all HbA_{1c} target of less than 6% (42 mmol/mol) may have inadvertently and disproportionately produced adverse outcomes in a subgroup…with diabetes with lower blood glucose levels than their HbA_{1c} would predict." The results are clear: intensive treatment was associated with improved outcomes (e.g., fewer cardiovascular events) in the low and moderate HGI subgroups but not in the high HGI subgroup. Moreover, the high HGI subgroup was associated with higher total mortality and a greater risk of hypoglycemia—which goes some way to explaining the outcome of the ACCORD trial. Commenting on the research, Dr. Hempe said: "Our report emphasizes the fact that HbA_{1c} does not reflect blood glucose concentration in the same way in everyone and that failure to recognize this can lead to suboptimal patient care. We are hopeful that publication of this ancillary study of the ACCORD trial will generate more research into the underlying mechanisms that cause person-to-person and racial differences in HbA_{1c}. Better understanding of these mechanisms could lead to new treatment algorithms to individualize patient care and will help usher in the evolving era of personalized medicine."

Hempe et al. The hemoglobin glycation index identifies subpopulations with harms or benefits from intensive treatment in the ACCORD trial. Diabetes Care 2015;38:1067–1074

Pharmacotherapy and Weight Management in Type 2 Diabetes: A Review

Weight loss in type 2 diabetes is often recommended but can be challenging for individuals to achieve via lifestyle interventions alone. Pharmacological interventions are available or emerging and, according to Van Gaal and Scheen in a review published in this issue of *Diabetes Care* (**p. 1161**), should be considered to help patients to achieve a healthier lifestyle. The main thrust of the review is that if pharmacological interventions are considered for a patient, any intervention should contribute to weight reductions and management of blood glucose levels. This is not something that currently available antidiabetes therapies actually achieve in terms of weight loss. In fact, some can actually contribute to weight gain. Examples include insulin, sulfonylureas, and thiazolidinediones. The only antidiabetes drug available that is weight neutral is metformin, according to the authors. The most promising approaches that are antidiabetic and have weight-loss potential include GLP-1 receptor agonists, SGLT2 inhibitors, and pramlintide. Antiobesity therapies that also help to manage blood glucose include orlistat, lorcaserin, phentermine plus topiramate, and a number of others. The potential of combination therapies is also considered. The authors point out that recent safety concerns over some antidiabetes drugs have led to market withdrawals, which means that there is an urgent need for new approaches. Future prospects that are being tested (pre)clinically are also considered. The review highlights that the pipeline for pharma-based therapies toward diabetes, weight management, and obesity is varied and healthy and suggests that the future for this approach holds great promise.

Van Gaal and Scheen. Weight management in type 2 diabetes: current and emerging approaches to treatment. Diabetes Care 2015;38:1161–1172

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