PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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PPI Therapy and Gastric Cancer

Long-term use of proton pump inhibitors was associated with a >2-fold increase in risk of gastric cancer in patients with prior *H. pylori* eradication. The risk was increased with higher frequency and longer duration of PPI use.

Background: *H. pylori* eradication reduces risk of gastric cancer by at least one-third, but there are few data on other modifiable risk factors. PPIs are associated with an increase in risk, but it has not been known whether this risk could be eliminated by clearance of *H. pylori*.

Methods: Data were analyzed for all patients in Hong Kong who received clarithromycin-based triple therapy, the first-line treatment for *H. pylori* infection in 2003–2012, the study period. Patients who received a diagnosis of gastric cancer within 1 year after triple therapy were excluded from the analysis, as were those with failed *H. pylori* eradication. The primary outcome was the development of gastric adenocarcinoma, and the primary exposure of interest was prescription of PPIs after receiving successful *H. pylori* eradication therapy. The study included 2 comparison groups of patients with successful triple therapy: those who received no PPIs and those who received histamine-2 receptor antagonists (H2RAs).

Results: The study cohort comprised >63,000 patients who received successful *H. pylori* eradication therapy. The mean age was 55 years, 47% of study patients were men, and the median follow-up time was 7.6 years. Nearly 3300 patients (5% of the cohort) were PPI users, with a median duration of use of almost 3 years; nearly 22,000 patients (35%) were H2RA users. Gastric cancer developed in 153 patients (0.24%) during follow-up. Patients who used a PPI ≥1 time per week had a >2-fold higher incidence of gastric cancer than those with less frequent use (hazard ratio,* 2.44 after propensity score adjustment;* p=0.002). The propensity score-adjusted absolute risk increase with PPI use was 4.29 excess gastric cancer cases per 10,000 person-years. A gradient in risk was observed with frequency of PPI use (less than once a week, weekly, and daily) and with duration of use (≥1 year, ≥2 years, or ≥3 years). Risk of gastric cancer was not associated with use of H2RAs.

Discussion: PPIs may increase gastric cancer risk by acid suppression, which could worsen atrophic gastritis, and by stimulating gastrin, a growth factor. Long-term PPIs should be prescribed cautiously after successful clearance of *H. pylori*.

Cheung K, et al: Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study. *Gut* 2017; doi 10.1136/gutjnl-2017–314605. From the University of Hong Kong; and other institutions. **Source of funding not stated. One study author disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

***See Reference Guide.**

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Prenatal Safety of Methylphenidate

According to the results of a study conducted by the International Pregnancy Safety Study Consortium, methylphenidate exposure during pregnancy is associated with a small increase in risk of congenital cardiac malformations, while amphetamine exposure is not.[1]

Methods: The study was conducted in 2 populations in tandem. The primary analysis included pregnant women enrolled in Medicaid during 2000–2013. Results of this analysis were validated in a cohort of all women enrolled in the national health registries of 5 Scandinavian countries during a similar time span. A pregnancy was considered exposed if a woman filled a prescription for a stimulant—methylphenidate or amphetamine/dextroamphetamine—during the first 90 days of pregnancy, the period of embryogenesis. Pregnancy was considered unexposed if no ADHD medication prescription was filled in the 3 months before conception to the end of the first trimester. Pregnancies were excluded from the analysis if there was a fetal chromosomal abnormality or exposure to a known teratogen. Outcomes were analyzed separately for all malformations and for cardiovascular malformations. The analyses were adjusted for a broad range of known or possible risk factors, and sensitivity analyses were carried out using a propensity score* based on 200 potential confounding factors. The primary U.S. methylphenidate analysis was repeated in the Nordic cohort, but the amphetamine analysis was not because there were too few exposed pregnancies.

Results: Of >1.8 million U.S. pregnancies ending in a live birth, only about 2000 (0.11%) were exposed to methylphenidate and about 5500 (0.31%) to amphetamine. In the U.S. cohort, the fully adjusted model found no association for either category of malformation with amphetamine exposure. In contrast, for methylphenidate-exposed pregnancies, the fully adjusted relative risks* were 1.11 for any malformation and 1.28 for cardiac malformations. Propensity score adjustment had a negligible effect on these results. When specific cardiac malformations were examined, methylphenidate was associated with increased occurrence of conotruncal defects (relative risk, 3.44), but this finding was based on a small number of cases. The observations were generally confirmed in the Nordic cohort. In pooled data from the 2 cohorts, the relative risks for any malformation and a cardiac malformation with methylphenidate were 1.07 and 1.28, respectively.

Discussion: Methylphenidate was associated with a 28% increased risk of cardiac malformations; this increase corresponds to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy. ADHD medication use is increasing in women of childbearing age, in whom a substantial portion of pregnancies are unplanned, as well as in pregnant women.[2] Although the absolute risk with methylphenidate is small, it should be considered for women who are or could become pregnant.

[1]Huybrechts K, et al: Association between methylphenidate and amphetamine use in pregnancy and risk of congenital malformations: a cohort study from the International Pregnancy Safety Study Consortium. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3644. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

[2]Cooper W: Shedding light on the risks of methylphenidate and amphetamine in pregnancy [editorial]. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3882. From Vanderbilt University School of Medicine, Nashville, TN. T**he author declared no competing interests.**

Common Drug Trade Names: amphetamine/dextroamphetamine—*Adderall, Dexedrine*; methylphenidate—*Concerta, Ritalin*

***See Reference Guide.**

Semaglutide Approval

The once-weekly injectable glucagon-like peptide (GLP-1) receptor agonist semaglutide (*Ozempic*) has received FDA approval as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The drug will be available in pre-filled pens at dosages of 0.5 mg and 1 mg.

In clinical trials, semaglutide produced clinically meaningful and statistically significant reductions in HbA_{1c} compared with placebo, sitagliptin, and exenatide extended-release, as well as reductions in body weight. Common adverse effects of semaglutide include nausea, vomiting, diarrhea, abdominal pain, and constipation. Serious adverse effects could include medullary thyroid carcinoma (MTC), pancreatitis, hypoglycemia,

and kidney failure. The agent should not be used in patients who have a personal or family history of MTC or those who have multiple endocrine neoplasia syndrome type 2. Semaglutide is not recommended as first-line treatment for diabetes—it is not a substitute for insulin—and it is not known whether it can be used by patients with a history of pancreatitis.

Novo Nordisk receives FDA approval of Ozempic® (semaglutide) injection for the treatment of adults with type 2 diabetes [press release]. Bagsvaerd, Denmark; Novo Nordisk: December 5, 2017. Available at http://press.novonordisk-us.com.

Common Drug Trade Names*: exenatide, extended-release—*Bydureon*; semaglutide—*Ozempic*; sitagliptin—*Januvia

Type 1 Diabetes Standards of Care

The 2017 annual update of the American Diabetes Association's Standards of Medical Care for type 1 diabetes includes recommendations about monitoring glycemia, HbA_{1c} targets, non-insulin and investigational medications, and treatment of hypoglycemia.

Monitoring Recommendations. Patients receiving intensive insulin regimens—i.e., multiple daily injections or continuous subcutaneous insulin infusion—should self-monitor blood glucose before meals and snacks; at bedtime; occasionally after meals when they suspect low blood glucose; after treating low glucose until they are normoglycemic; and before exercise and critical tasks such as driving. This could be as often as ≥6–10 times daily.

Continuous glucose monitoring, combined with intensive insulin regimens, can further lower HbA_{1c} levels in selected adults (aged ≥25 years) and may particularly benefit those with hypoglycemia unawareness or frequent hypoglycemic episodes. Because of variable adherence, continuous glucose monitoring requires an assessment of individual readiness and ongoing education and support.

HbA_{1c} should be tested semi-annually in patients who are meeting treatment goals and have stable glycemic control and quarterly in those whose regimens have changed and others. Point-of-care A_{1c} testing allows more timely treatment changes.

Treatment. Avoiding hypoglycemia should always take precedence over achieving A_{1c} targets. A reasonable HbA_{1c} target for most is <7%, and a more stringent goal can be considered in selected patients, such as those with recent-onset diabetes or no cardiovascular disease, as long as this can be achieved without hypoglycemia or other adverse effects. Less stringent goals, such as <8%, may be considered in patients with limited life expectancy, extensive complications/comorbidity, or a history of severe hypoglycemia.

Most patients with type 1 diabetes should receive both prandial and basal insulin; rapid-acting insulin analogues are preferred to reduce hypoglycemia risk. However, patient education about matching prandial insulin dosing to carbohydrate intake, premeal glucose levels, and anticipated exercise should be considered.

Rapid-acting inhaled insulin, taken before meals, was shown to be noninferior to aspart insulin with respect to HbA_{1c} lowering, with less risk of hypoglycemia; but the availability of inhaled insulin cartridges in a limited number of doses limits patients' ability to fine-tune dosing.

Many other pharmacologic agents are being used or tested in type 1 diabetes: pramlintide, an injectable amylin analogue that delays gastric emptying and enhances satiety; metformin, which reduced insulin requirements and led to modest weight loss and lipid lowering in a clinical trial; liraglutide, which improved HbA_{1c} and led to weight loss, but at a cost of increased hypoglycemia risk; and sodium-glucose cotransporter-2 inhibitors that block glucose reabsorption in the kidney.

Glucagon should be prescribed for all patients at risk of clinically significant hypoglycemia and should be available to persons in close contact with the patient. Family members, school personnel, correctional institution staff, and/or coworkers should be instructed how to use glucagon kits.

Chamberlain J, et al: Treatment of type 1 diabetes: synopsis of the 2017 American Diabetes Association standards of medical care in diabetes. *Annals of Internal Medicine* 2017; doi 10.7326/M17–1259. From St. Mark's Hospital, Salt Lake City, UT; and other institutions. **Funded by the American Diabetes Association. Five of 7 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: glucagon—*GlucaGen*; liraglutide—*Victoza, Saxenda*; metformin—*Glucophage*; pramlintide—*Symlin

Genotype-Guided Warfarin Dosing

In a randomized trial of patients undergoing elective hip or knee arthroplasty, genotype-guided warfarin dosing was associated with fewer adverse outcomes than clinically guided warfarin dosing.[1] However, the risk reduction was driven largely by a lower incidence of international normalized ratio (INR) values ≥4, while rates of symptomatic adverse events did not differ significantly between treatments.

Methods: The Genetics Informatics Trial of Warfarin to Prevent Deep Vein Thrombosis trial was conducted at 6 U.S. medical centers in 1650 patients, aged ≥65 years, undergoing elective hip or knee arthroplasty. All patients were genotyped for polymorphisms in genes that influence warfarin sensitivity (VKORC1), S-warfarin metabolism (CYP2C9), or vitamin K metabolism (CYP4F2). Patients were then randomly assigned to genotype- or clinically guided warfarin dosing during the first 11 days of therapy. Dosing was guided by a web-based application that incor-porated clinical data for all patients and, in addition, data on gene polymorphisms for the genotype-guided group. The primary study outcome was a composite of major bleeding within 30 days, INR ≥4 within 30 days, death within 30 days, or venous thromboembolism within 60 days.

Results: In the genotype-guided group, 11% of patients experienced ≥1 composite endpoint, compared with 15% of the clinically guided group (p=0.02). None of the other individual outcomes within the composite differed significantly in incidence between the groups. No study patient died. For INR values ≥4, the difference in risk between the groups significantly favored genotype-guided dosing (p=0.04). Genotype dosing also significantly improved patients' percentage of time with INR in the therapeutic range: 55% versus 51% for clinically guided dosing (p=0.004). Genotyping especially benefited a pre-specified high-risk group.

Discussion: Previous studies of genotype-guided warfarin dosing, conducted mainly in patients with atrial fibrillation, have had mixed results. The present study was larger, used genotype-guided dosing for a longer period, and was based on more genes, allowing analysis of clinical outcomes rather than the surrogate outcome of percentage of time in the therapeutic range. However, the vast majority of patients (91%) were white, which limits the generalizability of the results because the gene variants are relatively uncommon in persons of African ancestry. The study results have no clear clinical implications, and although genotype-guided dosing might have some clinical utility, it is likely simpler and less expensive to implement wider use of clinical dosing algorithms.[2]

[1]Gage B, et al: Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: the GIFT randomized clinical trial. *JAMA* 2017;318 (September 16):1115–1124. From the University in St. Louis, MO; and other institutions. **Funded by National Heart, Lung, and Blood Institute; and other sources. Two of 26 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Emery J: Pharmacogenomic testing and warfarin: what evidence has GIFT Provided? [editorial]. *JAMA* 2017:318 (September 16):1110–1112. From the University of Melbourne, Australia. **The author declared no relevant financial relationships with commercial sources.**

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Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.