Overly conservative FDA label likely prevents use of metformin in many type 2 diabetics

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Many patients with type 2 diabetes in the United States may be discouraged from taking metformin—a proven, oral diabetes medicine—because the U.S. Food and Drug Administration inappropriately labels the drug unsafe for some patients also suffering from kidney problems, researchers from Penn Medicine and Weill Cornel Medical College report this week in a research letter published in *JAMA Internal Medicine*.

Amending the overly conservative FDA label—which differs from professional society recommendations—could extend the drug's use in nearly 1 million more diabetic patients with renal impairment, say the study's authors, Sean Hennessy, PharmD, PhD, associate professor of epidemiology in Penn's Center for Clinical Epidemiology and Biostatistics, and James H. Flory, MD, MSCE, of the division of

Endocrinology at Weill Cornell Medical College.

Certain patients with type 2 diabetes and renal impairment are discouraged from taking metformin to treat their diabetes because of the fear of lactic acidosis, which is too much acid in body that can case acute kidney injury, sepsis, liver failure and heart failure. To determine which patients can handle the drug, the FDA recommends measuring their serum creatinine levels to see if their kidneys are working properly—higher levels of creatinine are associated with poorer function. If it exceeds 1.4 mg/dL in women or 1.5 mg/dL in men, the FDA recommends against metformin.

But professional societies, such as the American Diabetes Association, say that's not the best measure of renal function, and that the FDA number is too conservative. They recommend taking the estimated glomerular filtration rates (eGFRs), a more modern tool that describes the flow rate of filtered fluid through the kidney. If a patient is above 30 mL/min (which equates to a serum creatinine level of roughly 2 mg/dL), the drug is safe to use. In other words, their kidneys are functioning properly enough to take metformin.

Metformin is the first-line drug that helps control blood sugar levels and is the only drug shown to improve cardiovascular outcomes. There are over 25 million people with type 2 diabetes today in the U.S., nearly 10 million of whom are taking the drug.

For the study, the authors sought to determine if there was gap in care because of the inconsistency between the professional recommendations and the FDA label. They examined data from 2007 to 2012 of patients taking only oral medication from the National Health and Nutrition Survey to assess how much metformin nonuse may be attributable to concern about safety. Serum levels and eGFR were examined as predictors of metformin use.

For patients with eGFRs between 30 and 60 mL/min, at which metformin use is contraindicated by the FDA but supported by professional guidelines, the metformin rates were between 48 and 57 percent. If the FDA relaxed their recommendation, the number of these patients taking metformin might increase by an additional 560,000, the authors report. For patients with GFRs greater than 60 to 90 mL/min, at which renal function is mildly impaired but the serum level is below the FDA cutoff, the rate was 80.6 percent. That could represent 425,000 additional patients on the drug if the FDA amended the label. Such numbers highlight missed opportunities for type 2 diabetic patients, the authors say.

"The FDA is overdue to revisit the contraindication to metformin use in patients with mild to moderate renal insufficiency," said Hennessy, "which is worsening the care of almost 1 million patients with type 2 diabetes in the U.S."

FDA citizen petitions were filed in 2012 and 2013, requesting that the metformin be relaxed and reframed in terms of the GFR measure, but no amendments have been made.

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