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Improving Safety of Diabetes Mellitus Management

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Older adults experience adverse drug events (ADEs) far more often than younger persons. The reasons for this include age-related decline in kidney and liver function, comorbidities, and the use of multiple medications. Oral glucose-lowering agents and insulin are implicated in one-quarter of emergency hospitalizations for ADEs among older US adults.[1] Nearly all of these diabetes mellitus (DM)-related drug events are for hypoglycemia. Among oral agents, sulfonylureas lead to most hospital visits for hypoglycemia.

Although rates of DM complications have improved over the past 2 decades in the United States,[2] serious hypoglycemic events are on the rise.[3] Among older adults, especially those with longer duration of DM, severe hypoglycemic events are more common than many of the complications that glucose-lowering treatment is intended to prevent.[4] Despite these trends, current performance metrics and surveillance systems do not measure or evaluate severe hypoglycemia occurring during DM treatment.

It is time to improve the safety of DM management. The Department of Health and Human Services recently drafted a National Action Plan for Adverse Drug Event Prevention focused on glucose-lowering agents as 1 of 3 classes of medications (the others include anticoagulants and opioids).[5] The draft plan proposes 4 strategies for reducing ADEs: surveillance, prevention, incentives and oversight, and research.

As a first step in improving safety, clinicians and patients need to better understand which medications, and in which types of patients, pose the highest risk for hypoglycemia. Based on data from randomized clinical trials, insulin and sulfonylureas are well known to increase this risk. However, limited data exist on the magnitude of this risk among older adults, especially when glucose-lowering agents are used in combination or together with commonly prescribed therapies, such as antibiotics, β-blockers, or opioids. This is because trials often exclude older, frail adults with complex health problems or those with acute exacerbations of underlying comorbidities that require concomitant treatments.

In this issue of *JAMA Internal Medicine*, Parekh et al[6] bring us a step closer to a better understanding of severe hypoglycemia risk among older adults. The researchers examined

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interactions between commonly prescribed antibiotics and sulfonylureas and the risk for serious hypoglycemia. Using Texas Medicare claims data for older patients using glipizide or glyburide, the investigators calculated rates of emergency department or hospital admissions for hypoglycemia within 14 days of prescription fill for 1 of 16 antibiotics; 7 of these antibiotics were previously implicated in causing hypoglycemia, while 9 had no clear mechanism or evidence linking them to these ADEs. After adjustment for demographic characteristics, comorbidities, prior health care utilization, and hypoglycemia, and the indication for the antibiotic, they found that clarithromycin, levofloxacin, sulfamethoxazole/trimethoprim, metronidazole, and ciprofloxacin were significantly associated with increased odds of severe hypoglycemia. The numbers needed to harm were 71 for clarithromycin and 334 for ciprofloxacin, with numbers needed to harm ranging from 131 to 187 for the other antibiotics.

Concomitant use of these antibiotics with sulfonylureas was very common. Among patients using glipizide or glyburide, 28% had overlapping prescriptions for 1 of the 5 interacting antibiotics. As a result, 13% of all hypoglycemic events among patients taking sulfonylureas occurred in the context of using 1 of the interacting antibiotics.

When Parekh et al[6] examined ADEs, they hypothesized that several specific antimicrobial agents would result in clinically significant interactions. On the one hand, such deductive inquiries, grounded in the understanding of drug mechanisms, physiology, or prior information about possible harms, may be less likely to lead to spurious associations. On the other hand, many drug-drug interactions are not easy to predict. Since polypharmacy has become ubiquitous, better surveillance for drug-drug interactions is needed—both for interactions that may be suspected a priori, but also for those that are unexpected. Applying inductive reasoning and pattern recognition to “big data” with the use of advanced analytical techniques may aid in the detection of these interactions.[7]

One limitation of the study is that acute illness requiring an antibiotic may have largely contributed to severe hypoglycemia. For example, a urinary tract infection in an older woman may have resulted in a prescription for levofloxacin. The patient may have experienced mild fever and anorexia, leading to a skipped meal, which, in turn, precipitated a hypoglycemic reaction. However, the use of other antibiotics as a control group in the study mitigates this concern to some extent. Confirmation of these findings using other data sets would further increase the confidence in these associations. Although randomized clinical trials to corroborate the study’s results would not be feasible, the findings suggest that collection of data on concomitant medication use, including short-term prescriptions for acute conditions, may be useful to assess the safety of therapies during ongoing trials.

The findings by Parekh et al[6] underscore that the risk of hypoglycemia associated with glucose-lowering medications may be modified by ongoing chronic and short-term therapies, which may potentially interact with DM agents. In turn, the magnitude of the risk of hypoglycemia may substantially alter the expected health gains associated with glycemic control for individual patients.[8]

To enhance safe prescribing, clinicians and patients need to carefully consider the expected benefits and harms of glucose-lowering agents, in the context of each patient's values and preferences. Serious hypoglycemia substantially lowers health-related quality of life for many patients and, therefore, shifts the balance of benefits and harms. An older patient with a hemoglobin A_{1c} level of less than 9% of total hemoglobin (0.09 proportion of total hemoglobin) and at high risk for hypoglycemia, for whom this complication results in a small loss in quality of life, may experience net harm from treatment with glucose-lowering agents other than metformin.[8] In such a patient, the decision to avoid an offending antibiotic may lower the risk of hypoglycemia; in addition, the decision to use glucose-lowering treatments that are viewed as burdensome to the patient (because they lead to hypoglycemic reactions or other side effects) warrants reconsideration.

But better understanding of hypoglycemia risk, even with the knowledge about drug-drug interactions and higher-quality decision making in practice, may not be enough to ensure safety. As noted in the National Action Plan,[5] surveillance, oversight, and incentives are also needed to reduce ADEs. Without active surveillance, it is difficult to develop and target risk reduction strategies to patients, clinicians, and health systems that need them the most. Future quality measures that assess ADEs can help incentivize and inform implementation of strategies to reduce hypoglycemia. In turn, appropriate medication management that minimizes the risk of harm in this population is likely to improve health outcomes and lower costs of care.

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