With more than 113 million prescriptions dispensed annually, proton pump inhibitors (PPIs) are one of the most frequently prescribed drug classes worldwide.1 Despite their widespread use, often in combination with other medications, the potential involvement of PPIs in drug interactions is not widely appreciated. Elsewhere in JAMA Network Open, Carollo and colleagues2 explored the extent to which 5 different information sources (Lexicomp, Micromedex, INTERCheck WEB, Epocrates, and drugs.com) provide consistent advice regarding drug interactions involving PPIs.

These 5 interaction checkers reported hundreds of interactions but exhibited poor agreement on the identification of specific interactions. For example, methadone was identified as having a severe interaction with omeprazole by 2 information sources, while the other 3 resources listed no such interaction. The authors also found poor agreement on the classification of the clinical importance of specific drug interactions. For instance, while all 5 interaction checkers identified a potential interaction between mycophenolate and pantoprazole, 1 categorized the interaction as mild, 3 framed it as moderate, and 1 deemed it severe.

Although these findings may seem disconcerting, they are typical of the drug interaction literature more generally. This reflects the low quality of evidence—principally case reports and volunteer studies—that accounts for most of what we know about drug interactions.

What should clinicians know about drug interactions involving PPIs? Here, we outline the ways in which PPIs can interact with other drugs, highlight clinically important examples, and offer strategies for their mitigation.

All drug interactions can be characterized as 1 of 2 types. Pharmacokinetic interactions result when one drug increases or decreases the concentration of another, by altering its absorption, metabolism, distribution, elimination, or some combination of these processes. In contrast, pharmacodynamic interactions involve no changes in drug concentration; instead, these interactions result from opposing, additive, or even synergistic drug effects at the receptor, tissue, or organ level. This framing allows us to consider PPI interactions by their general mechanisms.

Pharmacokinetic Interactions Involving PPIs

Impaired Drug Absorption

PPIs increase gastric pH, potentially hindering the absorption of drugs that require an acidic milieu to dissolve, because dissolution is necessary for absorption to occur. The interactions of primary concern in this regard involve tyrosine kinase inhibitors (eg, dasatinib, erlotinib), protease inhibitors (eg, atazanavir, indinavir), antifungals (eg, ketoconazole, itraconazole), and mycophenolate.3,4 For example, PPIs reduce the area under the concentration-time curve (AUC; a measure of total systemic drug exposure) of atazanavir by 90% and of indinavir and itraconazole by 60%.4,5 A higher gastric pH can also impede iron absorption by promoting the less well-absorbed ferric (Fe³⁺) redox state. The combined use of PPIs with oral iron preparations makes this one of the most common drug interactions involving PPIs.

Impaired Hepatic Metabolism

Most PPIs are primarily metabolized by cytochrome P450 (CYP) isoenzymes 2C19 and 3A4. Consequently, they have the potential to compete with other drugs metabolized by these same
enzymes. Inhibition of CYP2C19 is most likely with omeprazole, esomeprazole, and lansoprazole, and least likely with pantoprazole, while CYP3A4 inhibition is most likely with omeprazole.5 (Although rabeprazole mainly undergoes nonenzymatic metabolism, its thioether metabolite competitively inhibits both CYP2C19 and CYP3A4, meaning that rabeprazole can still perpetuate these interactions.)3,5 A potential consequence of PPI-mediated CYP inhibition is an increase in serum concentrations of drugs metabolized by CYP2C19 (eg, phenytoin, diazepam) and CYP3A4 (eg, carbamazepine, tacrolimus, and cyclosporine).3,4 Studies suggest that omeprazole increases the AUC of phenytoin by 10% and carbamazepine by 89%, while lansoprazole increases the AUC of tacrolimus by 50%.3 While CYP2C19 and CYP3A4 metabolize many different drugs, these agents warrant emphasis because each has a narrow therapeutic index. Inhibition of CYP2C19 can also hinder the metabolism of clopidogrel (a prodrug) to its active metabolite, potentially undermining its effectiveness. The clinical relevance of this interaction is disputed, but most studies suggesting a problem implicate omeprazole. Pantoprazole does not inhibit CYP2C19 and can be used instead. Finally, unlike absorption-mediated interactions with PPIs, competitive inhibition can be minimized by separating the administration of interacting drugs by several hours.

Regarding the inconsistently reported interaction between methadone and PPIs noted in the study by Carollo et al.,2 proposed mechanisms include increased absorption and decreased metabolism of methadone, but the supporting evidence is limited to rat and in vitro studies. In our view, a meaningful interaction between these drugs is exceedingly improbable.

Other mechanisms by which PPIs might increase drug concentrations have been proposed but are less well characterized. For example, PPIs may inhibit the renal tubular secretion of methotrexate. Given the drug's narrow therapeutic index, management options include close monitoring for signs of toxic effects, transient PPI discontinuation, or switching to a histamine-2 receptor antagonist.4

In theory, PPI concentrations could be influenced by the coadministration of drugs that inhibit or induce CYP2C19 or CYP3A4. However, such interactions are unlikely to be clinically relevant.

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**Pharmacodynamic Interactions Involving PPIs**

**Vitamin B₁₂ Deficiency**

Reduced gastric acidity impairs the release of dietary vitamin B₁₂ from food proteins. Long-term PPI use can cause vitamin B₁₂ deficiency, and this may be compounded by concomitant use of metformin, which impairs vitamin B₁₂ absorption in the distal ileum. Vitamin B₁₂ deficiency was found in a third of people coprescribed these medications.6

**Hypomagnesemia**

The intestinal absorption of magnesium is an active process mediated by transient receptor potential melastin (TRPM) 6 and 7 channels.7 PPI-related alterations in small intestinal pH inhibit TRPM6/7 activity, impairing magnesium absorption. While this rarely causes hypomagnesemia on its own, the concomitant use of drugs that cause renal magnesium wasting (principally loop and thiazide diuretics) is associated with an increased risk of hospitalization with hypomagnesemia.7

**Mitigating Drug Interactions Involving PPIs**

The easiest way to mitigate interactions involving PPIs is to minimize overuse of the drugs. When a PPI is indicated, 2 strategies can reduce the impact of CYP inhibition: (1) preferential use of pantoprazole, which has a lower propensity for CYP-mediated drug interactions, and (2) separating drug administration by several hours. The latter will generally ameliorate these interactions, which are competitive in nature. Vitamin B₁₂ deficiency or hypomagnesemia are easily remedied but should be recognized as potential adverse drug events warranting consideration of deprescribing.
opportunities. Finally, inquiring about nonprescription medications is essential given the over-the-counter availability of PPIs.

In the study by Carollo et al,2 the poor agreement among widely used drug interaction resources presents an important problem. Being overly inclusive regarding potential interactions risks inundating clinicians with alerts, diminishing their perceived importance or causing them to be ignored altogether (so-called alert fatigue).8 As noted by Carollo and colleagues,2 their results highlight the need for standardization in the methods used to evaluate and report drug interactions. In the meantime, we can take comfort in knowing that the number of clinically relevant drug interactions with PPIs is low, and only a few are likely to be consequential. However, considering the extremely high prevalence of PPI use, these interactions remain of potential relevance to large numbers of patients. The risk of harm can be meaningfully reduced with attention to a few key drug classes, mindful prescribing habits, and the regular involvement of a pharmacist.

ARTICLE INFORMATION
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