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AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEWS

The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association

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BACKGROUND & AIMS: The purpose of this review is to evaluate the risks associated with long-term use of proton pump inhibitors (PPIs), focusing on long-term use of PPIs for three common indications: gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and non-steroidal anti-inflammatory drug (NSAID) bleeding prophylaxis. **METHODS:** The recommendations outlined in this review are based on expert opinion and on relevant publications from PubMed, EMbase, and the Cochrane library (through July 2016). To identify relevant ongoing trials, we queried clinicaltrials.gov. To assess the quality of evidence, we used a modified approach based on the GRADE Working Group. The Clinical Practice Updates Committee of the American Gastroenterological Association has reviewed these recommendations. *Best Practice Advice 1*: Patients with GERD and acid-related complications (ie, erosive esophagitis or peptic stricture) should take a PPI for short-term healing, maintenance of healing, and long-term symptom control. *Best Practice Advice 2*: Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (eg, central obesity, large hiatal hernia). *Best Practice Advice 3*: Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI. *Best Practice Advice 4*: Asymptomatic patients with Barrett's esophagus should consider a long-term PPI. *Best Practice Advice 5*: Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs. *Best Practice Advice 6*: The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition. *Best Practice Advice 7*: Long-term PPI users should not routinely use probiotics to prevent infection. *Best Practice Advice 8*: Long-term PPI users should not routinely raise their intake of calcium, vitamin B12, or magnesium beyond the Recommended Dietary Allowance (RDA). *Best Practice Advice 9*: Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12. *Best Practice Advice 10*: Specific PPI formulations should not be selected based on potential risks.

Use of proton pump inhibitors (PPIs) in non-institutionalized adults in the United States doubled from 3.9% in 1999 to 7.8% in 2012.[1] During the same period the number of studies reporting on PPI-related adverse effects also doubled (Figure 1). Many PPIs are inappropriately prescribed, but this review focuses on PPIs prescribed long-term for three common conditions: gastroesophageal reflux disease (GERD),[2,3] Barrett's esophagus (BE),[4,5] and NSAID bleeding prophylaxis.[6,7] Our aim is to succinctly review the risks associated with long-term use of PPIs, and to help practitioners weigh the risks and benefits of PPIs when given for these indications.

What Are the Potential Risks Associated With Long-term Use of PPIs?

Our summary of the evidence for potential PPI-associated adverse effects is given in Table 1. Table 2 summarizes the absolute and relative risks of PPIs based on published data regarding relative risk and the background incidence of the relevant adverse effect. Throughout this review, we have assumed a class effect regarding PPIs because there is no high quality evidence that PPI formulations significantly differ in their potential adverse effects.

Kidney Disease

Case reports have linked PPIs to acute interstitial nephritis (AIN) and acute kidney injury (AKI) since 1992.[8] In 2016, two studies received widespread attention because they connected PPIs to an excess risk for chronic kidney disease (CKD) not explained solely by risk for AKI.[9,10] The first of these studies, by Lazarus et al, examined a cohort of 10,482 patients who were actively followed and a larger cohort of 249,751 patients whose data was retrieved retrospectively.[9] After adjusting for confounders, the authors found that PPIs were associated with a 50% increase in the risk for CKD in the smaller cohort and a 17% risk increase in the larger cohort. The second study, by Xie et al, compared 173,321 PPI users with 20,270 H2RA users in a VA dataset.[10] The authors included only patients who had a normal eGFR at baseline, and followed patients for up

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Best Practice Recommendations

Best Practice Advice 1: Patients with GERD and acid-related complications (i.e., erosive esophagitis or peptic stricture) should take a PPI for short-term healing and for long-term symptom control.

Rationale: PPIs are highly effective in healing esophagitis and for GERD symptom control, and this benefit is likely to outweigh PPI-related risks. There is no evidence for or against PPIs in asymptomatic patients with healed esophagitis or for PPIs beyond 12 months.

Best Practice Advice 2: Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (eg, central obesity, large hiatal hernia).

Rationale: Short-term PPIs are highly effective for uncomplicated GERD. Most patients with uncomplicated GERD respond to short-term PPIs and are subsequently able to reduce PPIs to less than daily dosing. Because patients who cannot reduce PPIs face lifelong therapy, we would consider testing for an acid-related disorder in this situation. However, there is no high-quality evidence on which to base this recommendation.

Best Practice Advice 3: Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI.

Rationale: PPIs have a clear symptomatic benefit and a possible benefit in slowing progression of Barrett's. There is likely to be a net benefit for long-term PPIs in these patients.

Best Practice Advice 4: Asymptomatic patients with Barrett's esophagus should consider a long-term PPI.

Rationale: The evidence that PPIs slow progression of Barrett's is low in quality but the evidence of PPI adverse effects is also low in quality. Because there is no high quality evidence on either side of this question, this is a weak recommendation and this decision should be individualized with patients.

Best Practice Advice 5: Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs.

Rationale: PPIs are highly effective in preventing ulcer-related bleeding in appropriately selected patients who take NSAIDs, and this benefit is likely to outweigh PPI-related risks.

Best Practice Advice 6: The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition.

Rationale: Long-term PPI users often receive PPIs at doses higher than necessary to manage their condition. Since PPI reduction is often successful, it is logical to periodically reevaluate PPI dosing so that the minimum necessary dose is prescribed.

Best Practice Advice 7: Long-term PPI users should not routinely use probiotics to prevent infection.

Rationale: There is no evidence for or against probiotics to prevent infections in long-term users of PPIs.

Best Practice Advice 8: Long-term PPI users should not routinely raise their intake of calcium, vitamin B12 or magnesium beyond the Recommended Dietary Allowance (RDA).

Rationale: There is no evidence for or against use of vitamins or supplements beyond the RDA in long-term users of PPIs. Many adults fall below the RDA in several vitamins or minerals and, in these adults, it is reasonable to raise intake to meet the RDA regardless of PPI use.

Best Practice Advice 9: Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12.

Rationale: There is no evidence for or against dedicated testing for patients taking long-term PPIs. Such screening (eg, for iron or vitamin B12 deficiency) can be offered but is of no proven benefit.

Best Practice Advice 10: Specific PPI formulations should not be selected based on potential risks.

Rationale: There is no convincing evidence to rank PPI formulations by risk.

to 5 years for incident CKD, defined as an eGFR of less than 60 ml/min/1.73 m^2. They found a 1.8% absolute annual excess risk for CKD associated with PPIs compared to H2RAs. Also, the PPI-CKD relationship persisted despite adjusting for AKI, implying that not all of the observed risk could be attributed to AIN. Although there was evidence that patients who used PPIs for longer durations had higher risks for CKD, patients who used PPIs for two years or more actually appeared to be protected against CKD. These studies are thought-provoking but are retrospective analyses with inherent limitations. One cannot be certain whether their observations are best explained by PPIs or by uncaptured baseline differences between PPI users and non-users (for example, in the degree of severity within important comorbidity categories such as diabetes).

Dementia

Build-up of amyloid-β (Aβ) protein predisposes to Alzheimer's disease. Microglial cells use V-type ATPases to degrade amyloid-β, and PPIs may block V-ATPases to increase isoforms of amyloid-β in mice.[11] Building on this, two recent clinical studies tested for an association between exposure to PPIs and dementia. Haenisch et al followed 3,327 non-institutionalized German adults aged 75 years or more with serial neuropsychiatric examinations. PPIs were associated with a 38% increased risk for dementia, with similar risk increases for Alzheimer's and non-Alzheimer's dementia.[12] Gomm et al extended these results by retrospectively querying an insurance database covering more than half of the German population over 75 years old.[13] They found a 44% higher risk for dementia in regular users of PPIs compared to non-users; when occasional users of PPIs were compared to non-users, there was a 16% higher risk. It is well established that patients who initiate PPIs have more comorbidities than those who do not, and this may be particularly true for older adults. In this study, adults selected for PPIs had strikingly higher baseline rates of depression, stroke, and polypharmacy. Although the study adjusted for these baseline characteristics, additional

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