“First Do No Harm”: Adverse Events from Pharmaceutical Treatment of Gastroparesis and Dyspepsia

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Dyspepsia, a symptom that impacts at least 10% of Americans, can be troubling to disabling, impairing work and relationships [1]. Dyspepsia refers to a chronic or recurrent upper gastrointestinal symptom complex presumed to arise from the gastroduodenum rather than the esophagus; epigastric pain or discomfort, fullness after meals, or inability to finish a normal-sized meal (early satiety), and nausea with or without vomiting all are dyspeptic symptoms that can negatively impact the quality of life. If delayed gastric emptying accompanies these symptoms, a diagnostic label of gastroparesis is usually applied [2]. Many other underlying causes of dyspepsia need to be considered, from peptic ulceration including *Helicobacter pylori* infection to gastroesophageal reflux disease (GERD), biliary tract disease, and rarely esophagogastric cancers, but the most frequent explanation encountered in practice is functional dyspepsia [1].

Often misdiagnosed as GERD and treated with proton pump inhibitors (PPIs) with modest to no benefit [3], functional dyspepsia is common, with a prevalence of 5–11% [1]. Functional dyspepsia according to the Rome IV diagnostic criteria [4] comprises postprandial distress syndrome (bothersome postprandial fullness or early satiety severe enough to impact on regular activities for 3 or more days per week in the past 3 months) or the epigastric pain syndrome (bothersome epigastric pain or epigastric burning 1 or more days per week in the past 3 months),

although many patients complain of both syndromes [4]. Recent evidence has identified duodenal inflammation in functional dyspepsia, with a small but significant increase in eosinophils in the duodenal mucosa (and in some cases mast cells), most notably in subjects with early satiety and postprandial distress [5, 6].

Gastroparesis, a condition less common but more serious than functional dyspepsia, carries a significantly decreased 5-year survival rate of 67% compared to an age- and sex-adjusted control rate of 81% [7] and is estimated to affect 4 million Americans, of which up to 25% have diabetic neuropathy [8]. Gastroparesis is defined by upper gastrointestinal symptoms with evidence of delayed gastric emptying in the absence of mechanical gastric outlet obstruction [8]. Since one in four patients with functional dyspepsia has evidence of delayed gastric emptying consistent with mild-to-moderate gastroparesis [2], applying the correct label can be confusing. In functional dyspepsia, unlike gastroparesis, vomiting is not prevalent, and symptoms correlate poorly if at all with gastric emptying delay [1]; further, this disorder, unlike true gastroparesis, is not associated with any known increased mortality risk [9].

After appropriate diagnostic evaluation, functional dyspepsia may respond to simple management strategies including diet, lifestyle modifications, and stress reduction, but many patients experience ongoing symptoms that require escalation to drug therapy. Pharmacologic options include acid suppression, usually with a PPI, prokinetic agents including metoclopramide or domperidone, and, if these fail, an antidepressant with the best evidence of efficacy in the tricyclic antidepressant class [10]. Since these disorders likely have multiple underlying etiologies and are associated with depression, anxiety or somatization, therapy is complicated by the difficulties inherent in predicting likely responders to a specific therapy, and the

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modest therapeutic gain over placebo [1, 10]. Although gastroparesis is usually managed with dietary advice (small frequent low fat, low-fiber meals, and if needed splitting solids and liquids), prokinetic and anti-nausea drugs, and, if applicable, tight glycemic control, many cases are refractory to pharmacologic therapy. In the minority of cases, gastroparesis is severe enough for interventional implantable gastric electrical stimulation therapy, a therapy that reduces vomiting frequency [8].

The chronic nature of dyspepsia and gastroparesis combined with the potential risks of pharmaceutical management raises the question of whether attempts to treat patients are causing more harm than good. In this issue of *Digestive Diseases and Sciences*, Bielefeldt has taken a novel approach to quantifying iatrogenic complications in a retrospective adverse event database study of gastroparesis or dyspepsia [11]. This study extracted all reports of adverse events associated with treatment of dyspepsia or gastroparesis from the Federal Adverse Event Reporting System (FAERS) over an 11-year period [11], with the aim of describing the trends in medication use and associated adverse events. The authors identified 1245 and 21,243 reports listing gastroparesis or dyspepsia, respectively; the demographics of these reports mirrored published epidemiologic factors with a female predominance and mean age in the sixth decade [1, 8]. It is unclear whether FAERS reports associated with treatment of dyspepsia refer to the syndrome of functional dyspepsia or with isolated dyspepsia, a symptom commonly accompanying gastroesophageal reflux disease [1, 3]. This distinction remains important globally since treatment of functional dyspepsia can include the use of the few prokinetic agents available for functional dyspepsia, including, metoclopramide, a drug that is not generally recommended [12]. Reports in which gastroparesis was the treatment indication included concurrent hypoglycemic agents in 29% [11] consistent with the predicted prevalence of diabetes mellitus [8].

Adverse events related to the treatment of dyspepsia in the FAERS database were most commonly associated with acid suppression followed by those associated with metoclopramide, whereas this order was reversed for events related to the treatment of gastroparesis [11]. Most reports were lodged by the customer in dyspepsia cases (51%), but in gastroparesis, legal workers were the most common reporter in 39% of cases, skewed by a 4000% transient increase in reporting of tardive dyskinesia due to metoclopramide in 2011 of which 98% originated from legal sources in relation to a class action [11]. This represents a reporting bias with potential financial incentives. Other data suggest tardive dyskinesia from metoclopramide has an estimated incidence of <0.1% among those prescribed the drug, with a dose-related risk [13].

Tardive dyskinesia is an important and significant adverse effect of metoclopramide use. Although over-represented and skewed in the FAERS data, the results should prompt clinicians to be mindful of the risks and adhere to the FDA-recommended therapy duration of up to 12 weeks. Clinicians outside of the USA need to interpret this in the context of the availability of other prokinetic agents with less central dopamine antagonism such as domperidone. More generally, patients with gastroparesis or dyspepsia should be regularly reassessed and considered for a “drug holiday.” It is important when prescribing metoclopramide to always warn the patient of the potential risk of tardive dyskinesia, as stopping the drug does not reverse the disease in half of affected cases, and to use the lowest effective dose for no longer than 12 weeks [13].

There is a growing concern about the use of PPIs, especially in younger patients, with anecdotally many patients now asking their physician to cease the treatment following media reports of potentially serious adverse effects. Acid-suppressing medications in the Bielefeldt study were implicated in 10% of 1944 reports of neurological side effects, 24% of 211 reports of myocardial infarction and stroke, 84% of 257 reports of osteoporosis and 50% of 135 reports of renal failure [11]. Reports of adverse effects due to PPIs do not support a true causal relationship. Although a critical review of the relevant literature does demonstrate associations between PPIs and serious skeletal, renal, gastrointestinal, and neurological events, these findings are based on epidemiological evidence. In Table 1, a summary of the criteria proposed by Bradford Hill for assessing causality and the association between PPIs and adverse events are presented; much of the data are weak and potentially subject to major bias including confounding [14–19]. Notably, no reports of hypomagnesemia due to acid-suppressing medications were described by Bielefeldt, despite this being a recognized adverse effect of PPI, probably due to its extreme rarity [20].

Histamine 2 receptor antagonists (H₂RAs), a small portion of claims implicating acid suppression, were mostly associated with concerns of limited or absent efficacy, or a false-positive drug screen. A meta-analysis based on older studies suggested that H₂RA therapy is efficacious in functional dyspepsia [21], of interest as more recently duodenal eosinophilia and increased mast cells (that may release histamine) [5, 6] or duodenal changes in the microbiome that might release excess histamine [22] suggest that antagonizing histamine might do more good than just reduce gastric acid secretion [1]. Histamine antagonism may thus be an alternative therapy in functional dyspepsia with equal efficacy and lower risk of adverse events than with other drugs.

Table 1 Reported complications of proton pump inhibitor (PPI) use and assessment of the strength of evidence using the Bradford Hill criteria and summary of Oxford Centre for Evidence-Based Medicine (OCEBM) level of evidence [25]

Determinant of causality criteria	Postulated adverse effect				
	Dementia [14]	Osteoporosis and fracture [19]	Kidney disease [16]	Gastrointestinal [18] and prulmonary [15] infection	Hypomagnesemia [17]
Strength of association	Adjusted hazard ratio 1.44 (1.36–1.52) $P < 0.001$	Meta-analysis of 244,109 fracture cases, moderate increase in hip fracture risk RR = 1.26, 95% CI 1.16–1.36. Spine fracture RR = 1.58, 95% CI 1.38–1.82. Significant heterogeneity	Meta-analysis of 2.6 million patients, increased risk of AKI RR = 1.44, 95% CI 1.08–1.91, CKD RR = 1.36 (95% CI 1.07–1.72), AIN RR = 1.42 (95% CI 1.28–1.58)	Pneumonia meta-analysis of 6,351,656 patients in 26 studies. Pooled RR = 1.49 (95% CI 1.16–1.92) C difficile meta-analysis of 47 studies. Pooled OR 1.65 (95% CI 1.47–1.85)	Meta-analysis of 115,455 patients from 9 retrospective studies. Pooled OR = 1.78 (95% CI 1.07–2.92) Subject of less than 1% of FDA reports of PPI-associated adverse events
Consistency	Not reproduced in large human studies	18 international studies included. All cohort or case–control	9 international studies, high degree of heterogeneity	International studies, high degree of heterogeneity. High likelihood of publication bias for C. difficile infections	9 international studies, high degree of heterogeneity
Specificity	Low, evidence from retrospective prescribing database	Low, cohort and case–control data with high chance of confounding. Ascertainment of exposure especially limited	Low, cohort and case–control data with high chance of confounding. Ascertainment of exposure especially limited	Low, cohort and case–control data with high chance of confounding. Ascertainment of exposure especially limited	Removal of PPI leads to resolution in case studies
Temporality	Time interval of 6 years or less may be too short for clinical disease to occur	Heterogeneity in studies	Follow-up time not reported in many studies, ranges from 120 days to 14 years	Highest risk for CAP reported in first 30 days after initiation of therapy	All cases preceded by PPI use, short time from exposure to clinically apparent disease
Biological gradient	Not reported	No difference between short term (<1 year) or long term (>1 year) use	Some evidence of CKD and AIN being dose dependent	Not clear	Not clear based on available evidence
Plausibility	Possible vitamin B12 deficiency link and murine model of PPI induced beta-amyloid accumulation	Calcium absorption is pH dependent	AIN is thought to be idiosyncratic and dose dependent. The development of CKD is hypothesized to be due to impaired endothelial dysfunction and subclinical AIN	Acid suppression leading to bacterial overgrowth and increased risk of bacterial aspiration. Gastric acid suppresses C. difficile vegetations but not spores	Idiosyncratic PPI or pH-dependent inactivation of active magnesium absorption channel TRPM6/7 is proposed mechanism
Coherence	Molecular-based studies not yet available	PPI use does not appear to affect BMD in a dose-dependent way [24]		Weak and very low-quality evidence	Consistently demonstrated in case series and active magnesium transport channel implicated
Experiment	Retrospective cohort studies	Cohort studies and case–control studies	Cohort studies and case–control studies	Cohort studies and case–control studies	Cohort studies and case–control studies and active magnesium transport channel implicated

Table 1 continued

Determinant of causality criteria	Postulated adverse effect				
	Dementia [14]	Osteoporosis and fracture [19]	Kidney disease [16]	Gastrointestinal [18] and prulmonary [15] infection	Hypomagnesemia [17]
OCEBM level of evidence or GRADE quality of evidence	Level 4	Level 3	Level 3 GRADE = low for AKI and CKD. Insufficient quality for AIN	Level 3–4 GRADE = Very low for <i>C. difficile</i> infection	Level 3

RR relative risk, CI confidence interval, OR odds ratio, CAP community-acquired pneumonia, CKD chronic kidney disease, AIN acute interstitial nephritis, GRADE grading of recommendations assessment, development, and evaluation

In the study by Bielefeldt, there were no FAERS reports of an adverse event associated with tricyclic antidepressants or with mirtazapine as treatments for dyspepsia. There are data to support the efficacy of low doses of tricyclic antidepressants and possibly mirtazapine in functional dyspepsia but not gastroparesis, especially in the epigastric pain syndrome subtype [10, 23]. The lack of FAERS reports may reflect the tolerability of low-dose treatment or a hesitancy among prescribers to use these therapies.

A total of 8% of submissions reported lack of treatment benefit as an undesired outcome, but as Bielefeldt rightly observes, this is not a true adverse effect, although it reflects the challenging and refractory nature of these disorders and is likely an underestimate [11].

When managing dyspepsia and gastroparesis, Bielefeldt demonstrates that common medications used for these often refractory and difficult-to-manage disorders carry a risk of adverse effects although the absolute risk cannot be estimated using these data. Regardless, the findings should prompt a return to first principles of management starting with an explanation to the patient and a trial of simple lifestyle modifications with establishment of realistic management goals. Where pharmacologic treatment is necessary, medications should be reviewed and “drug holidays” considered. If therapy is ineffective or adverse events become apparent, switching within or between classes of drugs is a reasonable clinical strategy.

Key Messages

- Gastroparesis and functional dyspepsia can impair quality of life; of the limited treatment options available, patients are often prescribed prokinetic agents or acid-inhibiting medications.
- In a review of the US Food and Drug Administration (FDA) reported adverse events, prokinetic agents were

implicated in 57% of adverse events related to the treatment of gastroparesis and in 40% of adverse events related to the treatment of dyspepsia.

- Tardive dyskinesia, the most commonly reported adverse event, was likely due to a reporting bias associated with legal claims from 2009 to 2013.
- Although proton pump inhibitors were the second most common drug implicated in several adverse event reports including myocardial infarction, stroke, osteoporosis, renal failure, and ineffective treatment, the causality of these associations is limited—nil.
- Clinicians should consider the potential risks of medications and the limited evidence for clinically significant benefit when managing patients with gastroparesis or dyspepsia.

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