Controversies Around Measuring Drug Toxicity: US Food and Drug Administration and Gastrointestinal Perspectives

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During Digestive Disease Week (DDW) 2019, the American Gastroenterological Association's Clinical Practice section and the Division of Gastroenterology and Inborn Errors Products of the Center for Drug Evaluation and Research, US Food and Drug Administration (FDA) co-sponsored a symposium on assessing and monitoring toxicity of medicines used in gastrointestinal (GI) disorders. This report is the third in a series of articles in this journal on core aspects of GI drug development. Its aim is to promote an interchange of ideas among pharmaceutical companies, clinicians, and regulators to advance the development and use of new therapies for GI disorders.

Overview of Drug and Biologic Safety Information

Dr Joyce Korvick of Division of Gastroenterology and Inborn Errors Products presented an overview of the evaluation of drug safety in the premarket and postmarket life cycle of drugs and biological products, discussed challenges for the assessment of safety, particularly the balance of benefits and risks, and discussed real-world evidence and real-world data, which have been the focus of the 21st Century Cures Act.[1] As a matter of general process, the FDA evaluates benefits and risks for the population, the provider for the patient, and the patient for himself or herself, specifically in the context of his/her own personal values. The Center for Drug Evaluation and Research considers the therapeutic context, the evidence, the uncertainties, the regulatory options, and tradeoffs between benefits and risks. Benefit and risk assessments are completed for products throughout their lifecycle, from development, through approval and into the postmarketing setting.[2]

Before marketing of a drug or biologic product, the evaluation of safety is based upon information submitted in the New Drug Application or Biologics License Application.[3] Safety data are collected from well-controlled clinical trials in specific patient populations to treat specific diseases. Although common adverse reactions are detected in the review of these data, rare or infrequent events may not be detected, given the limitations of the studies' sample size.

Postapproval pharmacovigilance assessment relies upon data from various sources, including observational studies, FDA Adverse Events Reporting System (FAERS),[4] the medical literature, and the FDA's Sentinel System for identifying and assessing drug safety signals in a distributed data network that contains curated electronic health data.[5] Clinical trials conducted after approval may provide additional safety data. Data from in vitro or animal studies may also suggest potential safety signals. The determination of whether there is a causal association between a product and an adverse event (AE) is based on the strength of evidence from the totality of data for the product under review.

Challenges evaluating the benefit of GI therapeutic products can include small efficacy margins, large placebo effects, and outcome measures that are evolving and often rely on patient-reported outcomes rather than objective disease measures. This is particularly challenging for pediatric study designs, because pediatric patient-reported outcomes may be very different to those in adults and quantification of disease severity may be difficult. Challenges in evaluating the benefit in chronic GI diseases include the complexities of chronic administration, such as treatment switching, the impact of the actual disease over time as opposed to the treatment itself, a low prevalence of certain conditions, small trials, and issues in study design. Challenges specific to evaluating the safety of proton pump inhibitors (PPIs) in observational and health records databases, as further discussed later, include variability in the methods by which over-the-counter use is recorded, lack of accurate dosing information, switching of health care settings or insurance providers, and protopathic bias.

The FDA has developed a framework for its real-world evidence program, and a website has been designed to capture current information around the development and use of real-world data and real-world evidence at the FDA.[6]

Safety of Serotonin Type 3 Antagonists and Serotonin Type 4 Agonists: Clinical Perspective

Dr Nimish Vakil presented a clinician's perspective regarding the history and toxicity of serotonergic agents for GI disorders leading to some recent changes in regulatory approval. A number of serotonin (5-HT) receptors are found

Abbreviations used in this paper: **AE, adverse event; CV, cardiovascular; DDW, Digestive Disease Week; FAERS, FDA Adverse Events Reporting System; FDA, US Food and Drug Administration; IBS-D, diarrhea-predominant irritable bowel syndrome; NRSI, nonrandomized study of an intervention; PPI, proton pump inhibitor; RCT, randomized controlled trial; 5-HT, serotonin.**

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in the GI tract, where 5-HT has an important role as a neurotransmitter. The principal agents that have established efficacy in GI disorders are 5-HT_3 antagonists and 5-HT_4 agonists. Although their efficacy has been demonstrated in randomized controlled trials (RCTs), there have been concerns related to toxicity.

The 5-HT_3 receptors are located on enteric neurons; 5-HT_3 antagonists exert their effects through a ligand-gated ion channel.[7] They increase transmitter release and intestinal secretion. The 5-HT_3 antagonists that are approved in the United States are alosetron and ondansetron. The 5-HT_3 antagonists are effective in diarrhea-predominant irritable bowel syndrome (IBS-D).[8] Alosetron was initially approved for the treatment of IBS-D in February 2000. By November 2000, there had been around 70 AE reports, including 49 cases of ischemic colitis and 21 of severe constipation, with 34 hospitalizations and 3 deaths. After consumer petitions, the drug was withdrawn in November 2000 after discussions with the manufacturer and patient groups. In November 2002, in response to patient and physician advocacy, the drug was reintroduced under a risk management plan that was converted to a risk evaluation and management program in 2010. Modifications to alosetron use included a lower starting dose and cautious dose adjustment.[9]

Ondansetron is primarily used for the treatment of nausea and vomiting. A single 32-mg intravenous preparation of ondansetron was withdrawn in 2012 after it was shown to prolong the QTc interval and cause malignant ventricular arrhythmias (torsade de pointes) in some patients.[10] Preliminary studies have suggested efficacy of lower doses of the oral form of ondansetron in IBS-D.[11]

The 5-HT_4 agonists that have been approved in the United States include cisapride, tegaserod, and prucalopride. Cisapride was approved in 1993 for nocturnal heartburn. Reports of serious cardiac rhythm disturbances began to appear and, in 1995, a black box warning was issued warning of interactions with some drugs. From 1996 to 1998, this was expanded to include more drugs and, in 2000, the drug was withdrawn. In vitro and animal experiments demonstrated that cisapride had an effect on the hERG channel in the heart predisposing to arrhythmias.

Tegaserod was initially approved in 2002 for women with IBS with predominant constipation. In 2004, the indication was expanded to chronic idiopathic constipation in men and women. In February 2007, the FDA was notified of an imbalance in cardiovascular (CV) events in tegaserod-treated patients compared with placebo, and the drug was withdrawn in March 2007. In 2018, a marketing application was submitted to the FDA to support the reintroduction of tegaserod to the US market. Review by the FDA and the Gastrointestinal Drugs Advisory Committee concluded that while a CV signal may exist for tegaserod, its overall strength was weak. The drug was re-introduced to the US market in 2019 with a statement that its use was contraindicated in patients with a history of transient ischemic attacks, stroke, angina, or myocardial infarction.[12] Prucalopride is more receptor-specific and seems to lack the side effects seen with other 5-HT_4 receptor antagonists.

The history of these drugs suggests that agents that target a specific receptor have more predictable effects. Limiting the use of agents to patients with severe symptoms and no predisposing risk factors is another method to mitigate risk. Re-engineering the chemical structure of the drug and developing new molecules with targeted effects are other strategies that have been effective.

FDA Surveillance of Postmarketing AE Reports and Drug Safety

Dr Lisa Harinstein of the Division of Pharmacovigilance of the US FDA discussed the use of postmarketing safety surveillance to identify or refine safety signals for drugs and therapeutic biologic products.[13] Postmarketing safety surveillance is critical because of differences in how and in whom the product is to be used in the real-world setting as compared with preapproval clinical trials. She focused on surveillance of the FAERS database to identify safety issues as it is specifically designed to support the FDA's postmarketing safety surveillance program for drugs and biologics.[14] FAERS contains AE reports, medication error reports, and product quality complaints resulting in AEs submitted to FDA. As of May 2019, FAERS contained approximately 18 million reports. The FAERS public dashboard is available for the general public to search for AE information.[15]

Safety evaluators in FDA's Office of Surveillance and Epidemiology are tasked with carefully reviewing and interpreting AE reports in the FAERS database to identify new safety information.[16] Importantly, the presence of a report in FAERS does not establish a causal relationship between the product and the AE, and reports may lack information for proper evaluation.[14] Further analysis of the FAERS database to identify a case series and evaluation of other data sources including, but not limited to, clinical trial data, medical literature, and public health databases, are undertaken so that conclusions regarding the signal (eg, continued monitoring, action required such as updating of labeling) can be made within the context of all available safety data.[16]

To highlight the clinical impact of postmarketing safety surveillance, 2 recent safety issues involving GI drugs were presented, namely, serious cardiac events associated with higher than recommended doses of loperamide and serious pancreatitis in patients without a gallbladder receiving eluxadoline. Both safety issues were identified from postmarketing reports received in the FAERS database[17,18] and resulted in issuance of Drug Safety Communications[19,20] and labeling updates.[21–23] In January 2018, the FDA communicated about efforts to work with manufacturers to restrict over-the-counter loperamide packaging because of continued receipt of AE reports.[24] Additionally, the FDA performed a 1-year reassessment of cases of pancreatitis with eluxadoline after the product was contraindicated in patients without a gallbladder. This showed that the number of cases of pancreatitis, including in patients without a gallbladder, declined, without an apparent decrease in overall eluxadoline use. Thus, the contraindication remained

appropriate upon re-assessment.[25] These 2 examples underscore the importance of continued surveillance of post-marketing safety issues to make informed decisions on risk.

Safety of PPIs: Clinical Perspective

Dr Paul Moayyedi presented the clinical perspective of balancing concerns of benefits and risks pertaining to PPIs. These drugs are very effective for erosive esophagitis with a number needed to treat of <2,[26] representing one of the most effective therapies that we have for any disease. There is also good or moderate quality evidence that PPIs are effective in gastroesophageal reflux disease, heartburn,[27] dyspepsia,[28] functional dyspepsia,[29] and in prevention of nonsteroidal anti-inflammatory disease-induced peptic ulcer.[30] The problem is that many of these issues are seen as trivial problems or "lifestyle" diseases. Against this background, there are now many papers reporting associations between PPI use and a myriad of diseases.[31] PPIs have been linked with pneumonia,[32] fracture,[33] *Clostridium difficile*-associated diarrhea,[34] CV disease,[35] chronic kidney disease,[36] dementia,[37] and even all-cause mortality.[38] However, many of these associations are based on observational studies of administrative databases; these consistently show that, on average, sicker patients are prescribed PPIs. Because sick patients are more likely to develop other illnesses, these associations may be due to residual confounding. Indeed, the estimates of effect move close to unity when adjusted for confounding factors. Studies usually report statistically significant results even with the adjusted analyses. However, because they are based on administrative databases that do not capture all known confounding factors and cannot address unknown confounding factors, there is a strong suspicion that the modest effect sizes they report would not be present if the analyses could adjust for all confounding factors.[39] These suspicions seem to be justified as a large RCT involving 17,598 participants randomized to PPI or placebo and followed for 3 years did not find any harms from PPI use apart from a modest increase in enteric infections such as *Salmonella* and *Campylobacter*.[40] For example, the odds ratio of experiencing a myocardial infarction in the PPI arm versus placebo was 0.94 (95% confidence interval, 0.79–1.12). The odds of developing a new cancer during follow-up was 0.99 (95% confidence interval, 0.87–1.13), and all-cause mortality had a hazard ratio of 1.03 (95% confidence interval, 0.92–.15). A randomized trial is the optimal design to answer questions of benefit or harm of a drug as it balances confounding factors between groups. Although it is still possible that PPIs may cause very modest harm over a duration of >3 years, this trial provides reasonably robust evidence that PPIs are at least not as harmful as observational studies suggest, and may not cause harm at all.

How do clinicians balance the robust evidence for benefit with more uncertain evidence regarding harm? A consistent finding in psychology is that patients place a more negative value for harm than they place a positive value for benefit.[41] Clinicians should reflect this asymmetry and, if risks and benefits are roughly equivalent, they should not prescribe the drug in most patients. Therefore, in situations where PPI is of uncertain benefit, such as for chronic cough, globus, chronic sore throat (thought to be related to gastroesophageal reflux disease, but with very little evidence[42]), these drugs should be avoided. Patients are often discharged from the hospital on a PPI for unclear indications. Again, the need for acid suppression should be reviewed and, where appropriate, the drug should be discontinued. Finally, there are situations where PPIs may be helpful such as prevention of peptic ulcer in those on NSAIDs or anticoagulation. However, the benefit is very modest in low-risk groups[43] and it is probably inappropriate to prescribe acid suppression for those. There are a few indications, such as Barrett's esophagus, where PPIs should be given long term every day; a randomized trial has suggested that high-dose PPI therapy may reduce all-cause mortality.[44] For most other indications, such as heartburn and dyspepsia, PPIs should be given in the lowest dose that controls symptoms, and for the shortest duration possible. Often these drugs can be discontinued in these patients in the long term when PPIs are used "on demand"[45] and attempts to stop the drugs completely are made every 6–12 months.[46]

FDA Assessment of Nonrandomized Studies of Drug Safety

Dr Joel Weissfeld of the Division of Epidemiology of the US FDA presented 2 examples to illustrate FDA's approaches to assessing evidence from nonrandomized studies of drug safety. A nonrandomized study of an intervention (NRSI) is a study in

Table 1. The 5 Nonrandomized (Matched Case-Control) Studies Identified by the FDA in August 2009 in the Evaluation of PPI Safety Risk

						Case Group	
Author, Year	Data Source	Location	Period	Fracture Location	Age (y)	N	Female (%)
Yang et al, 2006[33]	GPRD	UK	1987–2003	Hip	≥50	13,556	79.9
Vestergaard et al, 2006[49]	DNR	Denmark	2000	Any	Any	124,655	51.8
Kaye and Jick, 2008[50]	GPRD	UK	1995–2005	Hip	50–79	1098	71.6
Targownik et al, 2008[51]	PHRDR	Manitoba	1996–2004	Hip, spine, or wrist	≥50	1830	NR
Corley et al, 2010[53]	KPNC	Northern California	1995–2007	Hip	≥18	33,752	65.7

DNR, Danish National Registers; FDA, US Food and Drug Administration; GPRD, General Practice Research Database; KPNC, Kaiser Permanente, Northern California; NR, not reported; PHRDR, Population Health Research Data Repository; PPI, proton pump inhibitor.

Table 2. Results, Adjusted ORs and 95% CIs from 5 Nonrandomized (Matched Case-Control) Studies Identified by the FDA in August 2009 to Evaluate PPI Safety Risk

Author, Year	Exposed Category	Reference Category	OR (95% CI)
Yang et al, 2006[33]	PPI >1 year	Nonuse	1.4 (1.3–1.6)
Vestergaard et al, 2006[49]	PPI in last year	Nonuse	1.2 (1.1–1.4)
Kaye and Jick, 2008[50]	≥1 PPI prescription	No PPI prescription	0.9 (0.7–1.1)
Targownik et al, 2008[51]	Continuous PPI ≥7 years	Nonuse (PPI or H_2RA)	1.9 (1.2–3.2)
Corley et al, 2010[53]	PPI ≥2-year	Nonuse (PPI or H_2RA)	1.3 (1.2–1.4)

CI, confidence interval; FDA, US Food and Drug Administration; H_2RA, histamine$_2$-receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor.

which the intervention is assigned during the course of usual treatment decisions rather than allocated by randomization.[47] Unlike RCTs, NRSIs might use a case-control or cohort study method to construct treatment groups for comparison.

The first example concerned an assessment completed in August 2009 to inform an FDA decision in 2010 about PPIs and bone fracture. In May 2010, the FDA notified the public about its intent to amend PPI labels by adding a Warning and Precaution for Bone Fracture.[48] The August 2009 assessment considered evidence from 5 NRSIs (Table 1). Each used the matched case-control method to measure associations between PPI and fractures of the hip, spine, or wrist. Table 2 displays the ORs to present a representative result from each NRSI. Along with other factors, results from these NRSIs contributed to the FDA's decision to label PPIs for Risk of Bone Fracture, as a Warning and Precaution.[48]

Assessing the totality of evidence then available,[33,49–54] the FDA publicly communicated the evidence for an association between fracture and high dose or long duration PPI therapy while expressing causal uncertainty by stating, "It is not clear if the use of proton pump inhibitors is the cause of the increased risk of fractures seen in some epidemiologic studies."[48]

The second example concerned an assessment completed in October 2018 to inform an FDA decision in December 2018 about the CV safety of prucalopride, approved by the FDA in December 2018 for chronic idiopathic constipation. The October 2018 assessment (available on Drugs@FDA[55]) concerned Study 802, an industry-sponsored NRSI entitled "A Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort."[56] Study 802 addressed CV safety with real-world data from 4 European health care databases. In each database separately, Study 802 used a common protocol to estimate prucalopride-associated risks for myocardial infarction, stroke, and CV death. Investigators combined results from these databases to evaluate the risk for major adverse CV events in chronically constipated adults who started treatment with prucalopride versus polyethylene glycol. Using a framework for judging the potential for bias in estimates produced by NRSIs,[47] the FDA assessed Study 802 to be at risk of bias, but after accounting for this, it determined that the study provided enough evidence to reasonably exclude a large CV risk, a determination communicated in the FDA-approved product label.[57]

Summary

The safety monitoring of drugs, including those for GI disorders, is complex and multifaceted. The FDA plays a critical role in the evaluation of drug safety before approval and after introduction into clinical practice. Clinicians likewise have an important role in reporting AEs that they encounter and in contributing, where appropriate, to postmarketing surveillance studies and reporting safety concerns via the FDA MedWatch system. This report details some of the activities and responsibilities of the FDA, and some clinical perspectives on PPIs and serotonergic agents. Concerns about PPI safety are highly prevalent and have led some patients to discontinue treatment, often without discussing it with their physicians.[58] A recent, large, 3-year, placebo-controlled RCT with pantoprazole[40] offers evidence that complements NRSIs of PPI safety. Recent FDA reviews of the safety and performance of serotonergic agents has led to the reapproval of alosetron for a specific subset of women with severe IBS-D, the approval and reintroduction of tegaserod for women >65 years of age with IBS with predominant constipation and no history of major CV events, and the approval of prucalopride for chronic idiopathic constipation.

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Conflicts of interest
The authors have made the following disclosures: Dr Howden is a consultant for Alfasigma, Ironwood, ISOThrive, Otsuka, Phathom, and RedHill Biopharma. Dr Vakil is a consultant for Ironwood, ISOThrive and Otsuka, and has received research support from Ironwood, Allergan and Impleo. Dr Harris is a consultant for RedHill Biopharma, Sienna Biopharmaceuticals, Applied Molecular Therapeutics, US WorldMeds, Thetis Pharmaceuticals, Invicro, Protagonist Therapeutics, and Aptevo Research and Development. Q4