Dig Dis Sci (2017) 62:2999–3013
DOI 10.1007/s10620-017-4633-8

ORIGINAL ARTICLE

From Harmful Treatment to Secondary Gain: Adverse Event Reporting in Dyspepsia and Gastroparesis

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Received: 27 February 2017 / Accepted: 24 May 2017 / Published online: 2 June 2017

Abstract
Introduction Medical management of gastroparesis and functional dyspepsia remains difficult with several recent trials showing limited or no benefit. If treatment comes with only marginal improvements, concerns about adverse events become more relevant. We therefore examined the type and outcomes of side effects submitted to a public repository.
Methods We searched the Federal Adverse Event Reporting System for reports associated with the treatment of dyspepsia or gastroparesis. Demographic data, medications used and implicated, side effects, and outcomes were abstracted for the years 2004–2015.
Results Acid-suppressive agents and prokinetics were the most commonly listed medications with a stronger emphasis on prokinetics in gastroparesis. Submissions related to metoclopramide by far exceeded reports about other agents and mostly described tardive dyskinesia or other neurological concerns. They peaked around 2012, driven by submissions through legal workers. Most reports about metoclopramide described short-term use to prevent or treat nausea and vomiting. Concerns about acid-suppressive medications increased over time and spanned a wide spectrum of potential problems, including osteoporosis, worsening renal function, or cardiac events.
Conclusion Despite biasing factors, such as pending legal action, the voluntary repository of adverse events provides insight into current medical practice and its associated risk. Knowing about common and uncommon, but potentially serious risks may enable patients and providers to decide on effective and safe management strategies.

Keywords Metoclopramide · Tardive dyskinesia · Antiemetic · Proton pump inhibitor

Introduction

Medical management of gastroparesis and functional dyspepsia remains a challenge. Many patients with these disorders receive acid-suppressive medication as first step [1, 2]. Such an approach is becoming more controversial due to limited efficacy [3], the potential to mask and delay the correct diagnosis of other disorders [4], and increasing concerns about the safety of long-term use of these medications [5, 6]. Beyond such empiric therapy, recent studies failed to show consistent benefit of interventions ranging from prokinetics to antidepressants [7–13]. These reports about marginal or even missing benefit contrast with withdrawal of agents promoted for the treatment of functional diseases due to severe side effects [14–16]. The importance of drug safety is certainly well established and plays a key role in the approval through the Food and Drug Administration (FDA), which requires both demonstrated benefit and an acceptable safety profile. While the process is currently under review to incorporate various viewpoints, including patient perspectives [17], decisions generally follow a detailed review and discussion by expert panels. Recommendations are primarily based on data derived from randomized trials that are designed to define risk and benefit

Electronic supplementary material The online version of this article (doi:10.1007/s10620-017-4633-8) contains supplementary material, which is available to authorized users.

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and relate it to the established standard of care. Such trials capture side effects as identified by systematically monitored symptoms or test results. These large and costly trials are powered to detect relevant differences in benefit or risk and thus focus on events that are sufficiently common to allow a meaningful statistical analysis. The data obtained form the basis of evidence-based treatment and enable us to counsel patients about both the probability of improvement and the potential of common adverse events. However, rare problems may either be missed completely or misjudged in their relative importance.

Consistent with these theoretical considerations, post-marketing surveillance rather than trial data identified increases in risk of potentially fatal arrhythmias with cisapride and ischemic events for alosetron and tegaserod [15, 18]. The Federal Adverse Event Reporting System (FAERS) of the FDA functions as a data repository for possible side effects attributed to medical therapy. Drug manufacturers are required to submit information about adverse events related to their products. In addition, end users, physicians, pharmacists, legal professionals, and others can report suspected or proven side effects of medical treatments. Thus, FAERS functions as a potentially useful tool in the ongoing surveillance of approved medications. When examined over time, the data repository may allow us to see possible shifts in commonly used treatment approaches, even though the results, by definition, do not provide information about benefit and may be skewed by agent-specific differences in the likelihood of adverse effects.

Gastroparesis and functional dyspepsia are disorders of the upper gastrointestinal tract defined by similar symptoms plus the documented presence of delayed gastric emptying as the defining difference between the two disorders [19, 20]. Despite the obvious emphasis on emptying in differentiating the two disorders, symptom severity poorly correlates with measures of gastric emptying and treatment effects similarly do not show a correlation between symptomatic changes and treatment-induced changes in emptying [21]. In the USA, metoclopramide is the only FDA-approved medication that targets gastric motility and emptying. The link between this dopamine receptor antagonist and neurological side effects, especially tardive dyskinesia, has prompted ongoing discussions about its use [22, 23]. Nonetheless, prokinetics including metoclopramide continue to be among the agents considered in the management of these disorders [24–26]. The purpose of this investigation was to query FAERS for the period between 2004 and 2015, comparing demographic information provided, trends in medications use, and associated adverse events reported for the two disorders. The assumption was that the underlying illness, shifting options or preferences for medical treatments, and newly emerging information about possible medication side effects all influence reporting will all be reflected in this data repository.

Methods

Using the key words "dyspepsia," "diabetic gastroparesis," "gastroparesis," and "impaired gastric emptying" as listed treatment indications, we queried FAERS (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects.htm) for the period between January 2004 and December 2015. In the first iteration, we extracted case identification number, age, sex, weight, event date, reporting entity (predefined as consumer, physician, pharmacist, legal worker, or other), reporting country (not consistently available for 2004 and 2005), number and class of medications used with their dosage, presumed role in the reported event (predefined as coinciding, primary or secondary suspect; we collapsed primary and secondary suspect into the category "implicated"; if a report contained a primary and one or more secondary suspects, the latter agents were considered as potential, but only the primary suspect was categorized as implicated), nature of the adverse event, and listed outcomes (predefined as death, life threatening, hospitalization, disability, and other). In the description of results, only positively defined categories are given for reporting entity and outcomes, with "other" making up the difference to 100%. Causal attributions listed for the different combinations of medications and adverse events were abstracted based on the classification in FAERS and were not corrected based on known side effect profiles of the implicated agents, possible mechanistic links, or the reporting entity. As a second step, multiple listings of a single agent were eliminated as were duplicate reports based on their unique case identifier or identical drug combination, demographic data, and event date. If multiple problems were reported related to a single agent, we abstracted the adverse event and outcome creating a hierarchy based on severity and, as secondary criteria, on symptom category or system affected, and frequency of listings within a given report. Medications and adverse events were entered with free texting and—in the case of drugs—were based on trade names until 2015, when the generic classification was consistently added. We used broader categories to focus on a more a predefined set of drugs taken and problems encountered. Considering the focus of this study, we separately assessed reports on agents or classes targeting gastrointestinal disorders with a special emphasis on motility (cisapride, domperidone, metoclopramide, tegaserod, anticholinergic agents), antiemetics, and agents commonly prescribed in patients with functional gastrointestinal disorders (antidepressants, proton pump inhibitors). Other medications were coded as alpha$_2$-delta blockers, antibiotics, anticoagulants, anticonvulsives, antidiabetics, antihistamines,

antihypertensives (subgroups: angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, beta blocker, calcium channel blocker, diuretic, other), antipsychotics, antivirals, benzodiazepines, bisphosphonates, cardiac medications, chemotherapeutic agents, dopaminergic agents, eye drops, growth factors, hypnotics, immunosuppressants, inhalers, lipid-lowering agents, medications targeting endocrine or metabolic processes (other than sex hormones), muscle relaxants, non-steroidal anti-inflammatory drugs, opioids, platelet aggregation inhibitors, sex hormones, steroids, stimulants, supplements (vitamins, minerals, enzymes, fiber), triptans, or "other." For adverse events, we used differentiating terms to describe gastrointestinal symptoms or diagnoses (abdominal bloating or distension, abdominal pain, anorexia and weight loss, diarrhea, dyspepsia, dysphagia, flatulence, gastroesophageal reflux, gastrointestinal bleeding, ischemic colitis, nausea and/or vomiting, pancreatitis, Clostridium difficile colitis, other inflammatory bowel diseases) and encoded other problems based on common symptoms (dizziness and gait problems, headaches, pain not related to the abdomen, hearing impairment or ear symptoms, visual or eye problems), affected systems or structures (cardiovascular problems with separate codes for myocardial infarction and stroke, cutaneous, musculoskeletal, neurological illnesses with a special category for tardive dyskinesia, oropharyngeal, psychiatric, pulmonary, renal, or urogenital problems or disorders), or relevant mechanisms or outcomes (accidents and falls, allergic or anaphylactic reactions, cardiac or respiratory arrest). The purpose of this strategy was to capture at least the 30 most common agents or problems associated with common and/or severe, potentially life-threatening side effects or fatal outcomes. Finally, we added contextual information by reviewing all reports listing tardive dyskinesia as adverse effect and reviewed all reports that included metoclopramide as the most commonly reported problem and agent, respectively. We abstracted age, sex, reporting entity, presumed role of the listed agent(s) and assessed all reports listing metoclopramide for indications of medication use. As described above, we excluded double reports based on case number and review of data.

We used Stata 14.0 (StataCorp, College Station, TX) for data extraction, descriptive and analytical statistics. All data are given as mean with standard error of the mean. Group comparisons were made using X^2 tests, Kruskal–Wallis rank tests, or Student's t test, as appropriate with $P < 0.05$ being considered statistically significant.

Results

During the years studied, FAERS received 1245 and 21,243 reports that listed as treatment indication gastroparesis or dyspepsia, respectively. Consistent with a general rise of submission to FAERS, concerns related to the treatment of these disorders also increased with a peak in 2011, largely driven by reports about adverse effects of metoclopramide. Throughout the entire period covered, adverse events attributed to treatments for dyspepsia or gastroparesis accounted for less than 1% of all reports, but grew at a faster rate for dyspepsia as the underlying problem compared to overall time trends in submissions (Fig. 1a).

Reports providing information about the sex of the affected individual showed a female predominance, with a significantly higher fraction of women in claims related to adverse events during the treatment of gastroparesis (Table 1). The age listed in submitted reports related to gastroparesis was significantly lower compared to dyspepsia and all reports received by the FDA, even though the mean consistently ranged within the lower to mid-fifties for both diagnoses (Table 1). Looking at information about the possible cause of gastroparesis, 237 (19.0%) reports listed diabetic gastroparesis as the treatment indication. Reviewing all medications included in these submissions, 69 (29.1%) of these case files included antidiabetic drugs or insulin, compared to 100 of the remaining 1008 (7.4%; $P < 0.01$) reports.

The relative distribution of key variables differed between the subgroups. Lawyers and other legal workers were the primary source for submissions for gastroparesis, with customers and/or their relatives accounting for most of the reports for dyspepsia or the entirety of information received by the FDA (Table 1). During the period studied, the fraction of reports submitted by physicians decreased with a rise in customer-initiated submissions; in parallel with the mentioned increase in reports in 2011 and 2012, there was transient peak in reports through legal workers (Fig. 1b, c). Focusing on the two cohorts with dyspepsia and gastroparesis, respectively, more than two-thirds of the submissions listed a single agent only (dyspepsia: 69.2% vs. gastroparesis: 78.0%; $P < 0.001$) with the mean number of distinct agents being 3.5 ± 7.8 and 1.6 ± 1.9 for gastroparesis and dyspepsia, respectively ($P < 0.001$). Considering the higher number of reports listing multiple medications, the cohorts differed in the relative fraction of agents considered to be concomitant rather causally involved in the described adverse events (Table 1). Included information about outcomes showed lower reported fatal events compared to all submissions to FAERS with rates being higher in gastroparesis than dyspepsia (Table 1). Conversely, disabilities were attributed to adverse drug effects in slightly more than 3% of all submissions, compared to more than 20% in gastroparesis and 15% in dyspepsia (Table 1).

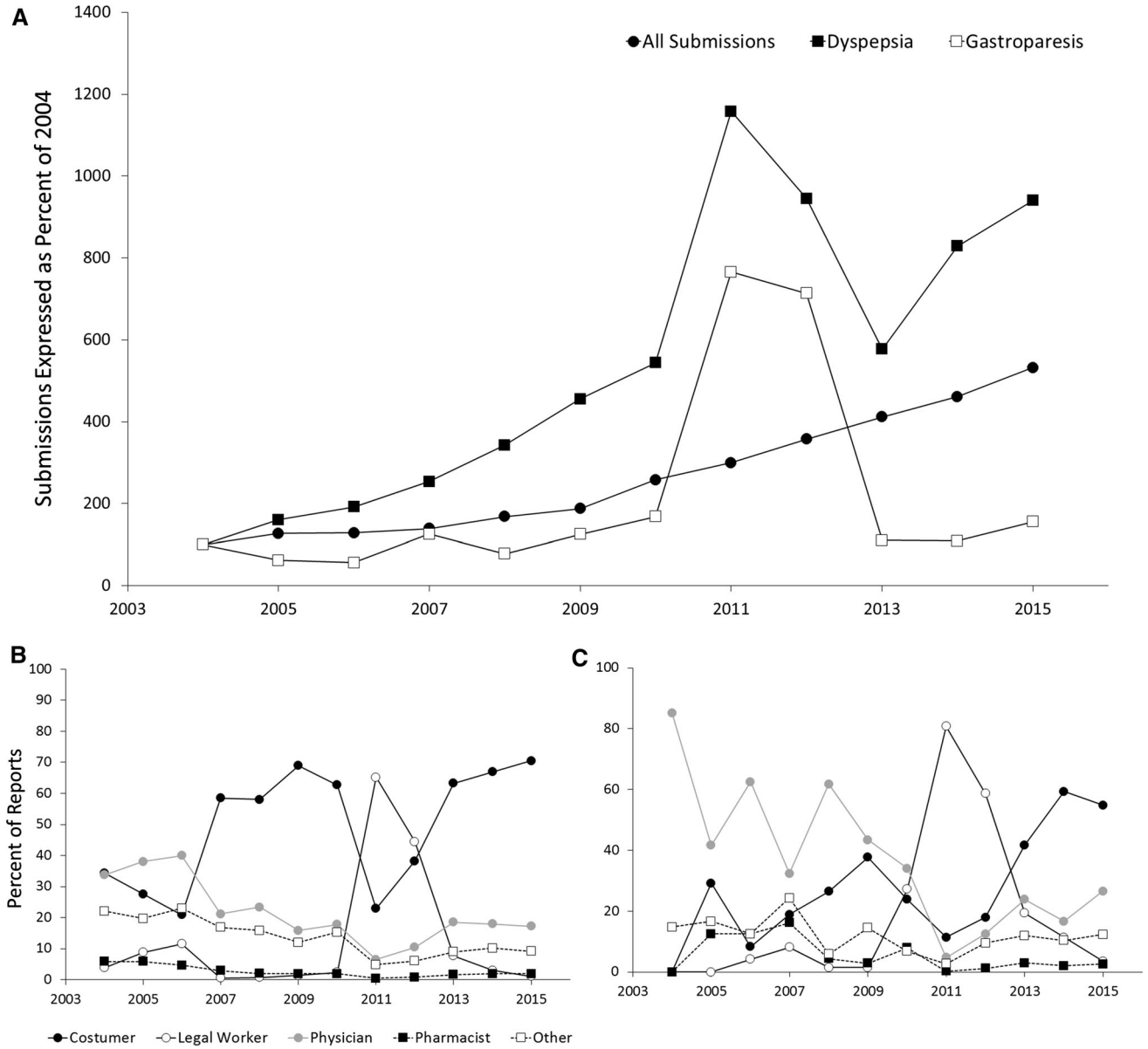

Fig. 1 Time trends in submissions to FAERS. **a** Changes in the number of case reports are expressed as percentage of 2004 results and plotted for the period studies. The number of all submissions (*black circles*) functions as reference, with dyspepsia (*black squares*) and gastroparesis (*white boxes*) being displayed separately. The relative fractions of reporting entities are shown for the period studied using the predefined groups of consumers (*black circles*), legal workers (*white circles*), physicians (*gray circles*), pharmacists (*black box*), and other (*white box*). **b** represents data for dyspepsia, **c** results for gastroparesis

Medications Implicated

Reports on adverse events related to treatment of dyspepsia listed acid-suppressive drugs and antacids followed by metoclopramide within the top five substances used and implicated (Fig. 2a). Proton pump inhibitors accounted for 61.1% of the acid-suppressive medications suspected to have caused an adverse effect. As shown in Fig. 2b, only submissions about potential effects of metoclopramide showed a distinct peak from a baseline of about 20 reports annually to more than 2700 in 2011, before dropping back down into the prior range by 2013. These significant changes in submissions indirectly affected the relative weight of reports on other agents, which remained stable or continued to increase consistent with the gradual increase in overall reporting of adverse events to the FDA (data not shown). The relative weight of different drugs shifted slightly when we moved the focus from all medications listed to agents considered the likely cause of an adverse event (Fig. 2a; Supplementary Table 1).

Adverse events related to treatment of gastroparesis also listed metoclopramide and acid-suppressive medications

Table 1 Comparison of basic demographic information, reporting entity, suspected role in the adverse event, and outcome for submissions entered into FAERS between 2004 and 2015

	All reports	Dyspepsia	Gastroparesis	*P* value
Reports entered	8,281,291	33,271	4472	
Women (%)	62.28	64.16	73.82	<0.001
Age (years)	54.19 ± 19.19	57.82 ± 17.50	52.49 ± 17.29	<0.001
Reporter (%)				<0.001
Customer	44.76	50.6	27.2	
Legal worker	3.12	23.4	39.2	
Physician	27.22	15.08	22.0	
Pharmacist	4.24	1.5	3.1	
Other	20.66	9.4	8.6	
Role code (%)				<0.001
Primary suspect	61.79	31.63	16.15	
Secondary suspect	13.75	13.46	5.48	
Concomitant	24.23	54.58	78.35	
Other	0.23	0.32	0.02	
Outcome (%)				<0.001
Death	13.90	3.80	8.4	
Life threatening	2.7	2.48	3.2	
Disability	3.16	15.09	22.5	
Hospitalization	33.57	28.55	20.0	
Other	46.66	50.0	46.0	

among the top five agents used, with metoclopramide-related submissions showing the previously mentioned peak in 2011 (Fig. 2). However, prokinetics were more not only more commonly used, but also more often implicated as causes for the observed adverse events, with metoclopramide, cisapride, tegaserod, and domperidone accounting for nearly 71% of all reports (Fig. 3a; Supplementary Table 2). This number likely underestimates the role of agents targeting gastric motility as erythromycin accounted for 46 of 161 cases with antibiotics listed as part of gastroparesis therapy, which is significantly higher than the seven instances in 576 patients with dyspepsia ($P < 0.001$) receiving antibiotics based on the submitted list. Proton pump inhibitors (PPI) accounted for 82.0% of the acid-suppressive medications ($P < 0.001$ compared with reports related to dyspepsia treatment) implicated in side effects. Only tegaserod also had a distinct peak as reports surfaced soon after its approval and rapidly fell after the agent was withdrawn from the market. The relative contribution of different drugs changed as we focused on agents with likely causal role rather than all and often only coincidentally taken medications. Prokinetics accounted for 16.3% of all drugs listed, but were considered the likely culprit in 70.8% of all submissions (Supplementary Table 2).

Considering the role of metoclopramide in the overall case burden and reported impact of adverse events, all cases within the FAERS data repository listing metoclopramide were separately analyzed. Data reflected the significant increase in submissions during the period from 2011 to 2013, with a shift in indications to dyspepsia (Supplementary Tables 3, 4). Before and after this peak, physicians submitted most reports related to the agent. While many submissions did not clarify the indication for therapy, symptomatic therapy for prevention or treatment of nausea was the reason given most frequently prior to and after the sudden and transient change in submissions around 2012.

As some data suggest an increased use of symptomatic therapy after the withdrawal of cisapride and tegaserod and after the FDA warnings related to metoclopramide use [23, 27], we specifically examined claims listing various antiemetics. These agents accounted for 2.5 and 0.7% of all agents listed with gastroparesis and dyspepsia as reported indications and dropped to 1.2% and <0.1% of the implicated agents, respectively ($P < 0.01$). The small number of reports did not allow an analysis of time trends or the relative contribution of different drug classes.

Adverse Events

Tardive dyskinesia and other neurologic events other than cerebrovascular accidents clearly accounted for the highest number of submissions with 22.0% of the reports with dyspepsia as primary indication. The fraction increased to 29.6% if we focused on reports that identified the presumed culprit (Fig. 4a). The next most common problems were

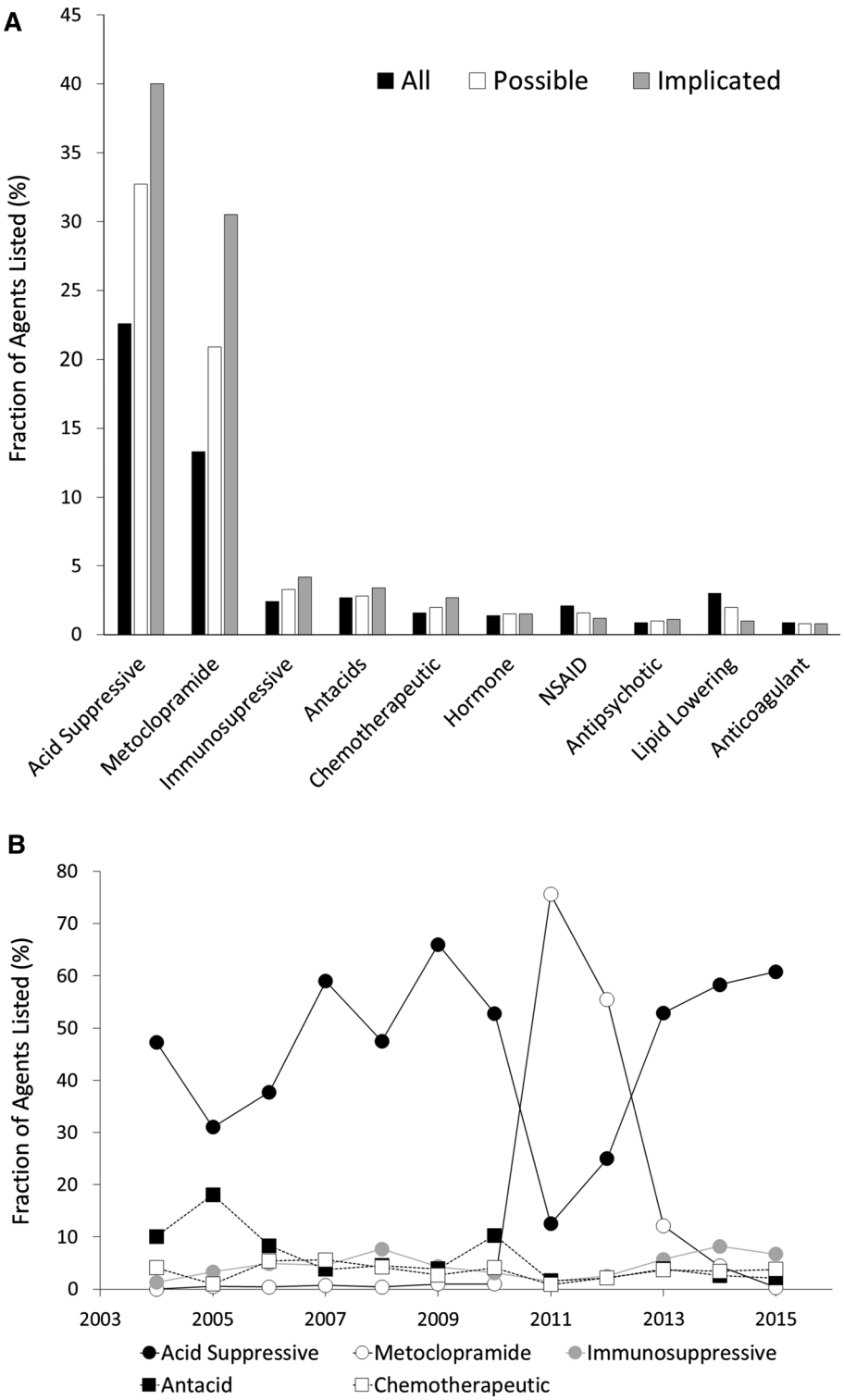

Fig. 2 Medications associated with adverse events during treatment for dyspepsia. All data are shown as percentages of reports. **a**—The *bar graph* depicts the 10 most commonly listed medications/classes. *Black bars* show results if all medications are included, *white bars* focus on agents considered as possible culprits, and *gray bars* only represent medications implicated as cause of the reported problem. **b**—Trends are displayed for reports on the five most commonly implicated agents (*black circles* acid-suppressive medications; *white circles* metoclopramide; *gray circles* immunosuppressive agents; *black squares* antacids; *white squares* chemotherapeutic agents). *NSAID* non-steroidal anti-inflammatory drugs

listed as adverse events, but do not truly fit the definition of a side effect as they either described a lack of benefit or an inappropriate medication choice, dosing, or concerns related to the production process or product rather than its effects. In this context, use for an unapproved indication accounted for 17.1% of the claims and 27.8% reported inappropriate treatment durations with 45.8% of these concerns being connected to metoclopramide. Pain, cutaneous side effects, nausea or vomiting, dyspeptic symptoms, and anxiety or depression accounted for 2–4% of the

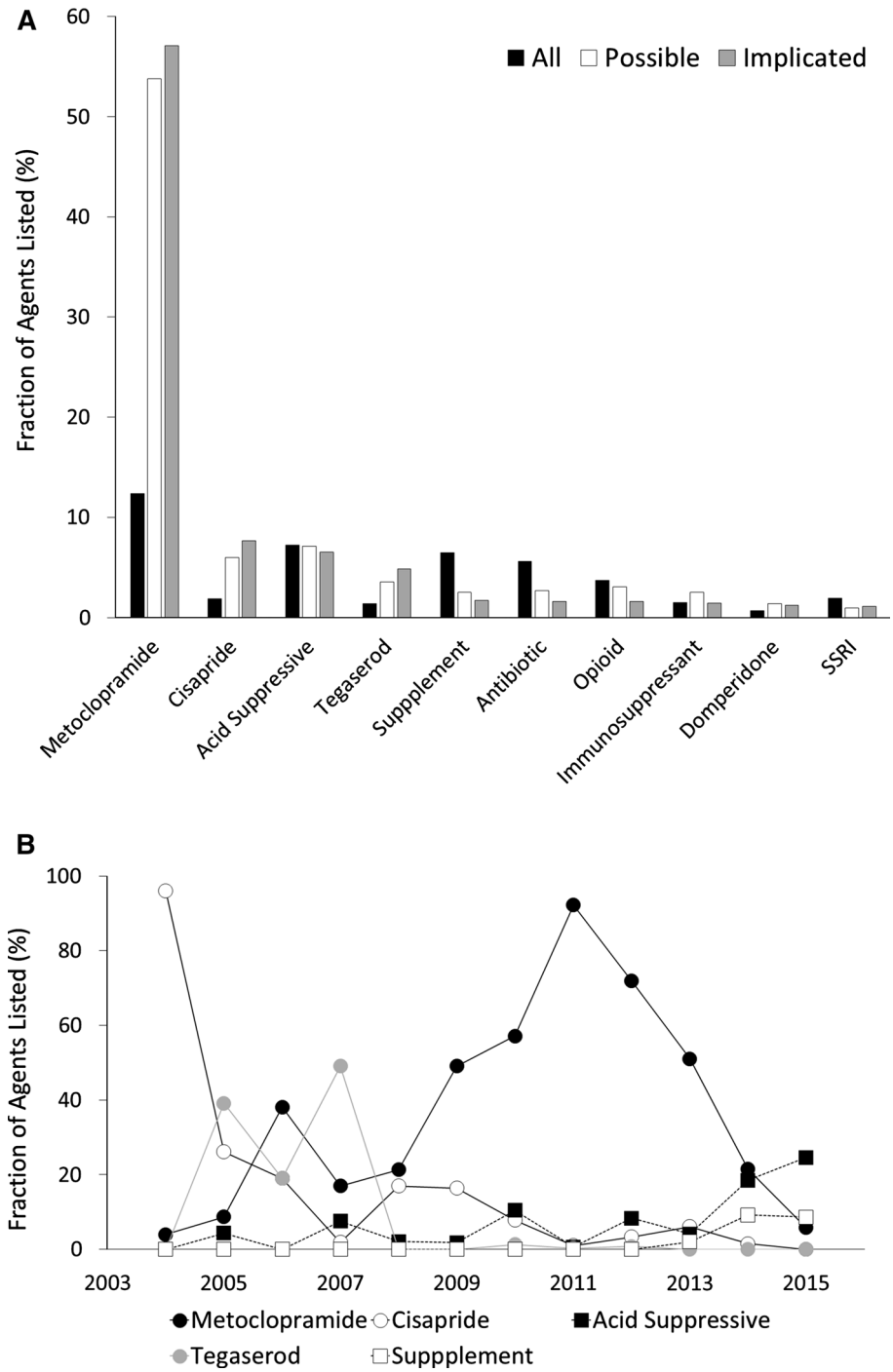

Fig. 3 Medications associated with adverse events during treatment for gastroparesis. All data are shown as percentages of reports. **a**—The *bar graph* depicts the 10 most commonly listed medications/classes. *Black bars* show results if all medications are included, *white bars* focus on agents considered possible culprits, and *gray bars* only represent medications implicated as cause of the reported problem. **b**—Trends are displayed for reports on the five most commonly implicated agents (*black circles* metoclopramide; *white circles* cisapride; *gray circles* acid-suppressive medications; *black squares* tegaserod; *white squares* supplements). *SSRI* selective serotonin reuptake inhibitor

problems reported (Fig. 4a; Supplementary Table 5). Results were similar for gastroparesis as listed indication with tardive dyskinesia and neurologic side effects accounting for 41.5% of adverse effects for all agents, and 53.1% of the reports for medications considered to be the cause of an observed side effect (Fig. 5a; Supplementary Table 6). Other concerns were responsible for less than 5% of the reports and included EKG changes and arrhythmias, other cardiac side effects, emotional and psychiatric problems, and issues that again may not be considered a true side effect, namely the lack of perceived benefit or inappropriate dosing and product defects.

Looking at the reported adverse events over time, we see distinct peaks for tardive dyskinesia and neurologic problems, which parallel the rate of submissions about metoclopramide (Figs. 4b, 5b). Before and after the period between 2009 and 2013, submissions related to tardive dyskinesia remained at a low level, while 5–6% of the

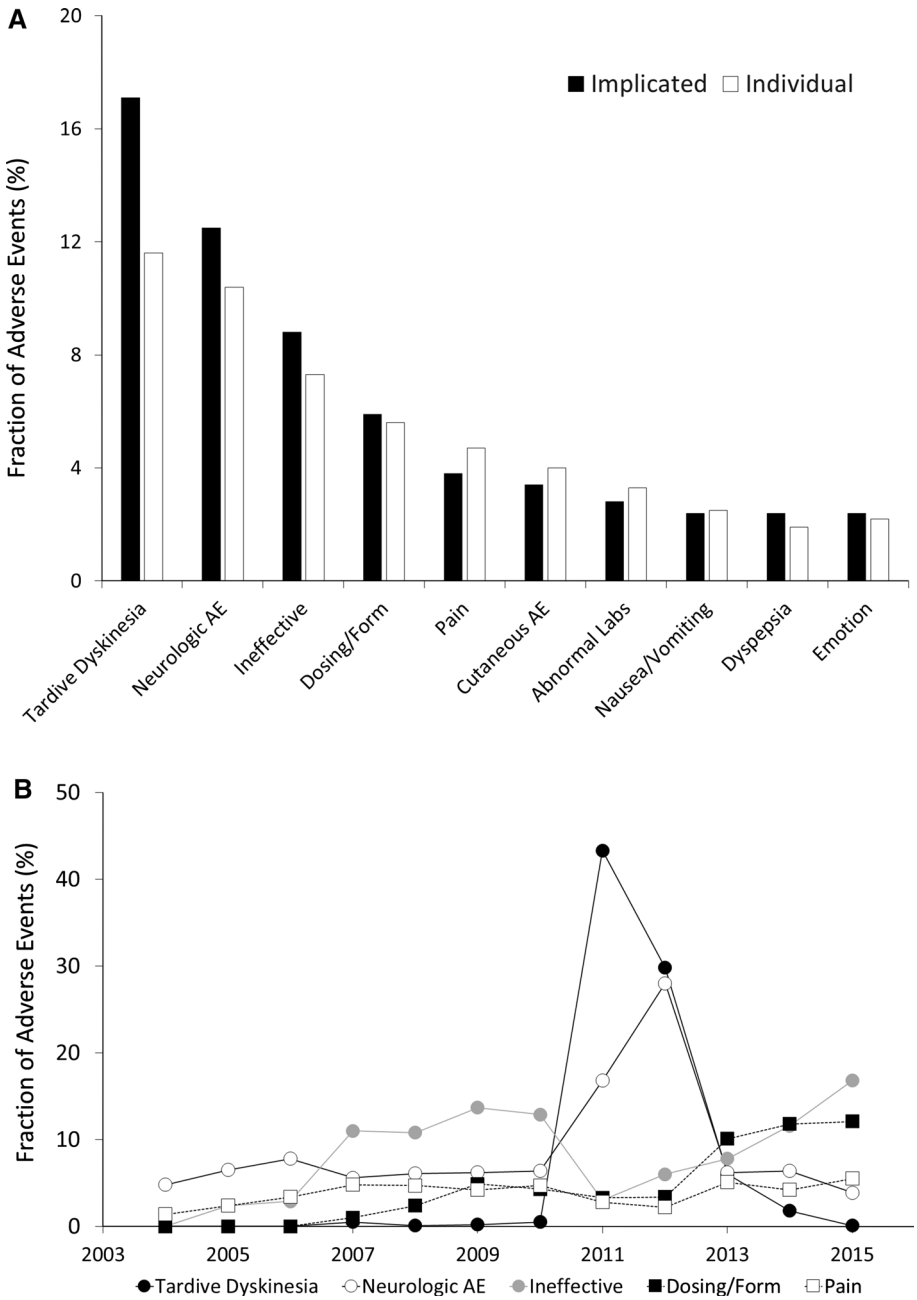

Fig. 4 Reported adverse events linked to the medical treatment of dyspepsia. **a**—*White bars* represent all reported problems; *black bars* show only events linked to agents implicated as underlying cause. **b**—Time trends of the five most commonly reported problems are plotted for the period of the study (*black circles* tardive dyskinesia; *white circles* other neurological adverse events except for stroke; *gray circles* ineffective treatment; *black squares* concerns about dosing or form/properties of the product; *white squares* pain other than abdominal pain or headache). All results are shown as percentages. *AE* adverse events

reports focused on other neurologic problems attributed to drug therapy of dyspepsia or gastroparesis. Distinct peaks were not evident with any of the other reports about adverse events.

Tardive Dyskinesia

A total of 2717 separate submissions listed tardive dyskinesia as the main adverse effect of medical therapy. All but 42 of the submissions (98.3%) originated in legal offices with 99.9% invoking metoclopramide as the presumed cause. In 29 cases, case reports included other medications that have been linked to tardive dyskinesia, but were considered concomitant. Considering the high number of reported tardive dyskinesia, we separately examined all submissions to FAERS listing this adverse effect. During the period examined, a total of 23,433 case files described tardive dyskinesia as a side effect. Dyspepsia and gastroparesis accounted for 2776 (11.8%) of these cases, with essentially all of them being attributed to metoclopramide (see above). There was a distinct peak in submissions around 2011, largely driven by claims related to metoclopramide (Fig. 6a, b). While dyspepsia was the most commonly used indication specified in the claims (14.1%), the

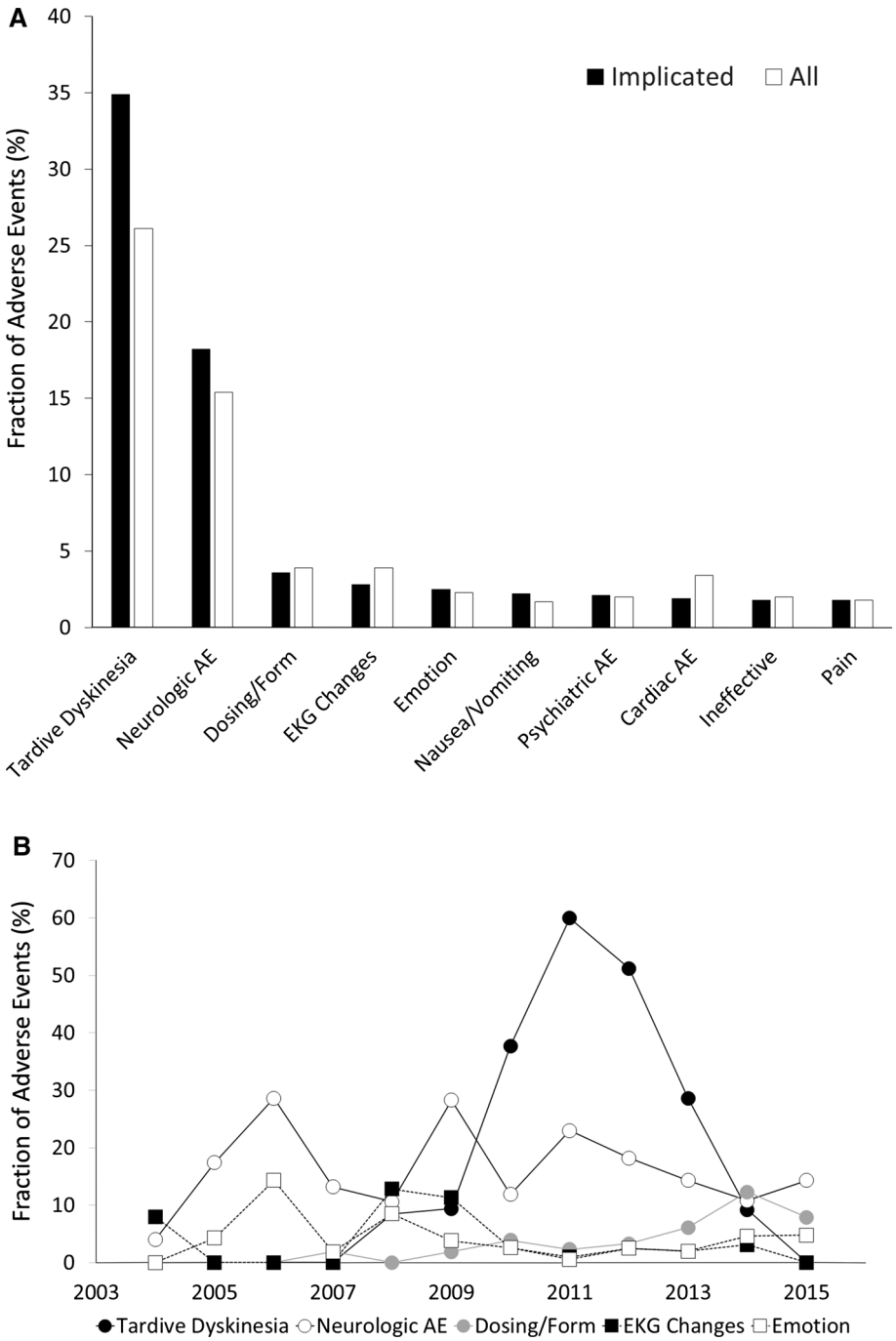

Fig. 5 Reported adverse events linked to the medical treatment of gastroparesis. **a**—*White bars* represent all reported problems; *black bars* show only events linked to the agents implicated as the underlying cause. **b**—Time trends of the five most commonly reported problems are plotted for the period of the study (*black circles* tardive dyskinesia; *white circles* other neurological adverse events except for stroke; *gray circles* concerns about dosing or form/properties of the product; *black squares* arrhythmia and related EKG changes; *white squares* emotional side effects). All results are shown as percentages. *AE* adverse events

majority (67.6%) of submissions labeled the treatment indication as "unknown" or provided no information about the condition treated.

Neurologic Side Effects

A total of 1944 reports (8.5% related to gastroparesis) attributed neurologic problems other than tardive dyskinesia or strokes to medical therapy. Patient characteristics reported included a female predominance of 68.6% and an age of 56.7 ± 19.0 years. Nearly three-quarters (72.3%) of the submissions came from legal workers, followed by patients and their families (16.1%) and physicians (5.3%). Metoclopramide accounted for 71.1% of the presumably responsible drugs. Acid-suppressive medications were considered as possible causes of neurologic side effects in 10.2%, followed by $\alpha 2\delta$-targeting agents in 1.1% with all other medications accounting for less than 1% of the submissions.

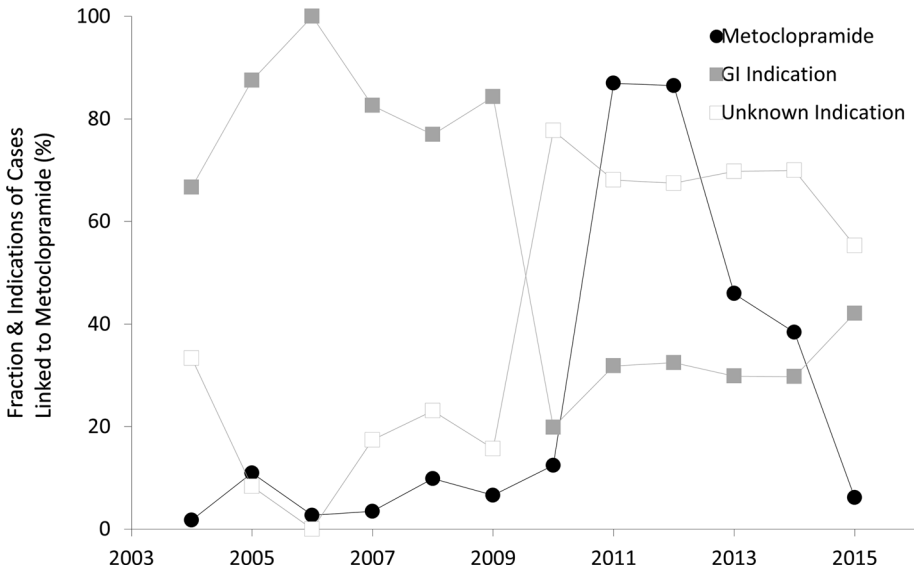

Fig. 6 Relative fraction of case reports of tardive dyskinesia related to metoclopramide (*black squares*). Submissions were separated based on the underlying indication as related to treatment of gastrointestinal disorders or symptoms (*gray squares*) and unknown causes (*white squares*)

Myocardial Infarction and Stroke

Acute myocardial infarctions or cerebrovascular accidents were described in 211 (55.6% myocardial infarctions) reports on treatment side effects with 7.6% being linked to gastroparesis. The mean age given in submissions was 61.2 ± 14.3 years; the gender distribution was equally split with 49% women. Acid-suppressive medications (23.7%) and non-steroidal anti-inflammatory drugs (NSAID; 17.1%) accounted for about 40% of all reports. While submissions for such acute ischemic events did not show a distinct peak during the time period investigated, all but two reports about NSAID effects were received by the FDA before 2007 and all focused on cyclooxygenase-2-specific agents.

Osteoporosis

Complaints about osteoporosis and related fractures were listed as primary concerns in 257 submissions with 84.1% being attributed to PPI. Reports showed a distinct female predominance with 74.8% and an age of 57.5 ± 14.1 years. Most reports (66.9%) were received in 2013 and 2014. Corticosteroid use was considered as the likely cause of osteoporosis in one case, but was listed as concomitant therapy in additional 17 reports, which attributed the problem to PPI.

Renal Failure

Impairment of kidney function was the primary concern in 135 reports with 50.4% being attributed to the use of acid-suppressive medication. Chemotherapeutic agents (8.9%), antacids (7.4%), and NSAID (5.9%) were relatively commonly considered as likely culprits. Reports described a nearly balanced gender distribution with 46.6% women and an age of 62.6 ± 15.2 years. There was no apparent peak in submissions during the period examined.

False-Positive Drug Screen

Among the reports about abnormal laboratory tests, false-positive drug screens for methamphetamines were the most common concern with 35.1% (144 reports). The group was male-predominant (74.1%) and younger than the rest of the cohort with 36.2 ± 10.4 years. Acid-suppressive medication was thought to be responsible in 99.3% with all but three reports focusing on H2RA.

Ineffective Treatment

While not truly an adverse effect, the lack of treatment benefit treatment was reported as undesired outcome in 1233 (8.1%) submission. The demographic data were comparable to those for the entire cohort with a female predominance (58.7%) and a mean age of 56.0 ± 18.6 years. Acid-suppressive medications (88%) and antacids (1.9%) were the most common agents mentioned, followed by immunosuppressive drugs (1.7%), antidiarrheals (1.1%), and antihistamines (0.7%). While PPI accounted for most of the claims about problems with acid-suppressive agents submitted to FAERS, they were mentioned in 35.2% of the concerns about ineffective treatment in this class. Submissions increased in parallel with the overall increase in reports received by the FDA without a distinct peak.

Discussion

This analysis of largely voluntarily submitted adverse treatment effects reported in relation to medical therapy of two similar functional illnesses provides interesting insights into the potential power and the limitations of such data. First, the two most commonly listed drug classes, acid-suppressive and prokinetic medications, indeed play important roles in the accepted treatments for functional dyspepsia and gastroparesis [28, 29]. Thus, the pattern of drug use reported to FAERS may mirror clinical practice, even though results are obviously viewed through a lens focusing on negative effects rather than benefit. Second, submissions describe a cohort of patients with a basic demographic profile that is consistent with results published in epidemiological studies and large case series about functional dyspepsia or gastroparesis [27, 30–33]. This finding does not validate our results, but at least argues against significant data skewing due to focus-specific subgroups. Third, the relative role of agents listed differed between the two predefined cohorts, reflecting differences in the conceptual models of the underlying pathophysiology and appropriate treatment strategies of these two functional disorders of the stomach [19, 34]. Fourth, reports listed more medications in the cohort with gastroparesis with higher rates of agents used in the management of diabetes mellitus, hypertension, hyperlipidemia, or cardiac diseases, which may be interpreted as surrogate markers of differences in comorbidities that are more commonly seen in gastroparesis. Lastly, the approved indications for metoclopramide are diabetic gastroparesis and refractory gastroesophageal reflux disease, with the approval placing an emphasis on limiting therapy duration [35]. Our results demonstrate that even after the FDA issued a black-box warning about the potential risks of metoclopramide, most case reports listed diseases or problems other than the approved indications for the use of the agent.

While these points support the potential relevance of findings for patients and providers who deal with these disorders and their management, we also see evidence of data skewing. Reports on tardive dyskinesia or neurologic side effects of metoclopramide best exemplify the biasing of data. There was a transient rise by about 4000% in submissions about metoclopramide, largely driven by legal workers describing cases of tardive dyskinesia with often missing demographic and other details. It is thus impossible to definitively assess whether and how many of these reports may be duplicates. This important caveat raises questions about the true burden of this serious side effect. If we look at the findings before and after the likely distorted period of reports related to a pending legal action (see below), we see metoclopramide being consistently implicated in cases of tardive dyskinesia and accounting for 5–10% of the annual submissions reporting this complication. Going beyond tardive dyskinesia, we need to see these findings in the context of published trial data demonstrating a high incidence of other adverse effects in patients receiving metoclopramide [36, 37].

The above described dramatic, but transient changes in submission volume and patterns were limited to metoclopramide and likely driven by a class-action lawsuit that was eventually settled [38]. Thus, the hope for secondary gain may have influenced submissions. Other findings indicate that the largely voluntary post-marketing surveillance may reveal potentially important information about rare, but possibly relevant side effects. In this context, it is important to note reports about impaired renal function and interstitial nephritis, which surfaced throughout the entire period examined and were attributed to proton pump inhibitors in about half of the cases. A possible link between these agents and decreasing renal function surfaced as a concern in 2012 and was subsequently confirmed by several large case–control and prospective studies [39–43]. Reports about unusual or rare side effects may not only enter the public domain and give rise to concerns, but are also affected by emerging or ongoing discussions or controversies. This complex and likely reciprocal relationship is best exemplified by the many submissions that attribute osteoporosis and its complications to PPI, which had been reported in several large case–control series about 10 years ago [44–46]. Another variation of the complex relationship between events and reported adverse effects of drugs is the occurrence of false-positive tests for methamphetamines in patients taking H2RA. A higher likelihood of false-positive tests had first been published more than 25 years ago [47]. Interestingly, reports to FAERS described a younger and male-predominant group, which differs from the entire cohort, thereby raising the question whether claims were submitted to lend more credence to a claim explaining a test result with potential legal consequences. Alternatively, the differences in demographics could also represent a consequence of profiling law enforcement or others administering drug tests and primarily targeting younger males. The limited information available does not allow us to differentiate between these potential explanations.

Lack of efficacy was one of the more commonly reported adverse events, mostly involving acid-suppressive medications for dyspepsia. Histamine$_2$ receptor antagonists were less often listed in case reports overall, but accounted for more concerns about limited or lacking benefit when compared to PPI. While we cannot infer that lower rates of reports about ineffective treatment necessarily correlate with higher chances of treatment success, meta-analyses

indeed concluded that PPI are superior to placebo interventions in functional dyspepsia [48], while results for H2RA are ambiguous [49]. As is true for providers, patient views about of potential treatment outcomes are influenced by many factors that may create tensions between hope and fact-based expectations, with the former being quite prevalent in severe, potentially incurable diseases, such as cancers [50, 51]. Treatment failure may thus be more than maintaining the status quo and could trigger feelings of hopelessness, which may give rise to the perception of an adverse effect.

Case reports can include more than one medication used and more than a single indication or adverse effect per drug and patient. It is thus theoretically possible to determine the relative frequency of overlapping problems, such as gastroesophageal reflux and dyspepsia. Similarly, data may allow the identification of drug–drug interaction as a prior investigation on domperidone demonstrated [52]. FAERS data have also been used successfully to address concerns about specific side effects related to a given agent through disproportionality analyses [53, 54]. We chose a different approach that identified cases based on their listed treatment indication, which resulted in interesting findings, but does not enable us to compare results with similar studies in other disorders. Many submissions also did not list other agents, even though published data indicate that most patients receive a more complex treatment with acid-suppressive medications, antiemetics, and prokinetics being among the most commonly prescribed agents [27, 30, 55]. While the relative frequency of submissions to FAERS reflects this pattern for prokinetics, PPI, and H2RA, the paucity of case reports including antiemetics stands in striking contrast to the previously mentioned treatment of these disorders. When considered as a group, serotonin$_3$ receptor antagonists, phenothiazines, meclizine, dronabinol, and aprepitant accounted for less than 1% of submissions in dyspepsia and less than 2.5% in gastroparesis. We should not devise treatment strategies based primarily on widespread use of agents in clinical practice and the absence of negative news in a voluntary reporting system. However, concerns about metoclopramide, the only approved prokinetic in the USA, may be even more relevant as recent results showed only marginal benefits limited to women in a large trial targeting diabetic gastroparesis [56]. While the approach tested a different application form of metoclopramide, prior investigations had established equivalent effects when comparing the nasal spray with the conventional oral administration of tablets [57]. Finally, it is unclear whether the previously documented benefit of metoclopramide [58, 59] is truly due to its prokinetic effects or a consequence of its antiemetic properties, as emerging data question the impact of gastric emptying on treatment outcomes in gastroparesis [21]. Nausea and vomiting do not only affect many patients with gastroparesis and functional dyspepsia, they also significantly impair their quality of life [30, 55, 60, 61]. The current practice patterns apparently address this problem, but are largely based on effective treatments of acute symptoms, such as postoperative or chemotherapy-induced nausea and vomiting, as only few studies with small sample sizes suggest a possible benefit of granisetron in gastroparesis [62] and ondansetron in functional dyspepsia [63, 64]. Beyond the conceptual difference between acute, often drug-induced symptoms and the typically chronic problems of gastroparesis and functional dyspepsia, the mechanisms underlying the development of nausea and vomiting, and thus the response to similar treatments may differ and should prompt systematic studies in these disorders.

When we extracted data based on the agent used (i.e., metoclopramide), the most common indication for metoclopramide used its antiemetic rather than prokinetic effect, as malignancies, chemotherapy, periprocedural or perioperative treatment, and migraine management typically accounted for at least one-third of the reports. There was no obvious time trend despite the black-box warning the FDA mandated in 2009. The stable pattern may in part be due to the link between risk of tardive dyskinesia and chronic rather than acute treatment that accounted for most of these cases. Nonetheless, it is important to note in this context that metoclopramide is not included in guidelines for supportive therapy of highly emetogenic chemotherapy [65]. Trials comparing metoclopramide with other antiemetics, primarily various 5HT$_3$ receptor antagonists, demonstrated inferiority of metoclopramide in chemotherapy-induced vomiting [66] and nausea and vomiting for other reasons [67], including postoperative problems [68]. Similarly, ondansetron was comparable or better and clearly safer in the management of hyperemesis gravidarum [37, 69]. Refractory gastroesophageal reflux disease is the second of the two FDA-approved indications for metoclopramide. Except for the period between 2011 and 2013, reflux was more frequently listed as treatment indication than gastroparesis or dyspepsia. Again, supportive evidence is limited and largely based on studies prior to the more widespread and more effective use of PPI therapy. While metoclopramide improved symptoms of reflux, it did not change healing compared to placebo [70]. A small study demonstrated that a combination of cimetidine and metoclopramide was superior to the H2RA alone, but came with a high likelihood of side effects [71]. In infants with reflux symptoms, metoclopramide had either no effect or showed lower but still abnormal acid exposure [72, 73]. Consistent with these results, ranitidine, but not metoclopramide decreased acid exposure time in adults [74, 75]. Subsequent studies clearly established that

PPI therapy is superior and safer than the combination of metoclopramide and H2RA [76, 77]. With the strong recommendation to limit the duration of metoclopramide treatment and with the likely use of proton pump inhibitors, practitioners should reexamine whether there is truly any role for the agent in managing gastroesophageal reflux.

This study focused on adverse events, the key variable entered into FAERS. Assessing the utility of a drug or other forms of medical intervention requires an understanding of risks and benefits. Appropriately powered prospective trials provide the best source for such assessments. While we placed the data extracted from FAERS into a broader context and included discussions about the known main effects, the information about benefit reflects results from published studies rather than the case reports we analyzed. Data submitted to FAERS supplement results obtained in these prospective studies, as may reveal rare, but relevant problems. As previously mentioned, data within the FAERS repository are not systematically acquired, but depend largely on voluntary submissions. They can therefore not represent reliable information about the true incidence of different side effects, as such voluntary reports will likely underestimate the number of similar adverse events and as the denominator, meaning the number of treated persons, remains unknown. The unusual time trends seen in the case of metoclopramide highlight the potential skewing of data. This example demonstrates other weaknesses of this approach. As many reports included limited details, repeat submissions may not be easily recognized as such, leading to inflated numbers. Such an interpretation is difficult to separate from increased awareness due to publications or even marketing campaigns by law firms, which could lead to an increase in voluntary, perhaps often also delayed submissions. Many, in this specific example even most of the reports, were submitted by patients or legal workers, raising questions about the validity of claims or diagnoses. Patient or provider expectations may not only have played a role when such expectations were not met, such as shown with many submissions claiming lack of benefit, but may also decrease the likelihood of reporting effects that are known and thus anticipated, such as tremor with metoclopramide. Beyond such external motives, psychological mechanisms, such as somatization and catastrophizing, contribute to the manifestation of functional illnesses and may also affect the perception and reporting of adverse events. Many case reports focused on the presumed causative agent and its side effect only. We may thus underestimate the role of drug–drug interactions or preexisting conditions that contributed to these events and their outcomes. Considering an approach that used treatment indication rather than drug type as case identifier, we did not attempt a disproportionality analysis, which could lend more credence to the potential role of implicated medications in the reported events. Lastly, dyspepsia was not only one of the two indications we used to select cases, it was also listed as adverse event in some of the reported cases. It is impossible to determine whether the repeat listing refers to newly emerging, yet somewhat different dyspeptic symptoms, persistent problems due to ineffective treatment, or whether we are dealing with incorrect data entry.

Despite these shortcomings, the findings provide information about side effects related to commonly used therapies in these two functional disorders of the stomach. When viewed in the context of other studies, they should prompt us to reexamine our approach to supportive therapies that prevent or treat nausea and vomiting. The same is even more true for refractory gastroesophageal reflux disease. Studies reporting benefit of metoclopramide typically relied on suboptimal therapies and did not show equivalence or even superiority to the current standard of care, PPI therapy. Beyond the concerns related to metoclopramide, the results also raise questions about acid-suppressive medications, which are very commonly used and widely available as over-the-counter agents. While they are generally considered to be safe, our data are consistent with reports about a potentially increased risk of cardiovascular and renal diseases. The apparently often limited utility should motivate us to individualize and, if possible, discontinue their use.

Compliance with ethical standards

Conflict of interest Klaus Bielefeldt does not have any conflict of interest to declare.

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