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The Florajen Digestion Balance Patient Experience Study

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Abstract

Background: Antibiotics have long been associated with gastrointestinal (GI) side-effects, leading to antibiotic noncompliance, related morbidities and increased costs. Antibiotic-induced disruption of intestinal microbiota has created interest in prophylactic use of probiotics to prevent antibiotic-associated GI side-effects, with recent trials suggesting GI benefits with concomitant probiotic and antibiotic use. The aim of this study was to see if commercially available Florajen Digestion can help maintain GI health during antibiotic regimens in the community. **Methods:** This prescriber and pharmacist directed, open label, patient experience study took place between September 2018 and January 2019. Healthcare professionals (HCPs) and patients from 40 states participated. Florajen Digestion probiotic was given to patients free of charge through their prescriber or pharmacist when prescribed or dispensed antibiotics. Surveys were completed by HCPs and patients, who reported on antibiotics prescribed/taken, GI upset, compliance and product satisfaction. **Results:** A total of 839 HCPs and 404 patients completed the study. Although 63% of patients reported prior GI side-effects with antibiotic use, only 12% experienced GI upset with concomitant Florajen Digestion use. Approximately 93% of patients completed their antibiotic regimen, with 77% asserting that Florajen Digestion helped them complete their course of antibiotics and 88% extremely satisfied with the probiotic. Among HCPs, 94% believed reducing side-effects improved antibiotic compliance, with 88% stating that probiotics should be recommended concomitantly with oral antibiotics. **Conclusion:** The results reveal the GI benefits of concomitant use of Florajen Digestion probiotics with antibiotics and support recommendation of Florajen Digestion by HCPs when prescribing or dispensing antibiotics.

Keywords

Probiotics, Antibiotics, Antibiotic-Associated Diarrhea, *Clostridium difficile*

Infections, Diarrhea, Gastrointestinal Health, Prevention, Microbiota, Microbiome Dysbiosis

1. Introduction

Gastrointestinal (GI) upset is a frequent complication of broad-spectrum antibiotic use that can cause considerable patient distress and reduce treatment compliance. Of particular concern is antibiotic-associated diarrhea (AAD) that occurs in up to 39% or more of patients receiving antibiotics in the outpatient setting [1]. The defining symptom of AAD is the presence of 3 or more loose stools per day that develops within hours to 8 weeks following antibiotic exposure, with a median onset of 5 to 9 days [2] [3] [4] [5]. The presentation of AAD may be mild and self-limiting diarrhea to severe Clostridium difficile-associated diarrhea and pseudomembranous colitis [5] [6] [7]. Beside impacting patient adherence to antibiotic therapy, antibiotic-related GI side effects can greatly impact morbidity and increase health care costs [8].

The life-saving and transformative impact of antibiotics on medicine cannot be overstated, but their use carries potential risks. Of note is the deleterious impact of antibiotics on intestinal microbiota, a complex community of as many as 100 trillion diverse and interactive microbes that play a fundamental role in health and disease via its influence on metabolism, nutrition, and immune function [2] [9].

It is thought that antibiotics alter GI digestive functions in several ways. Direct toxic effects on the intestinal epithelial lining can produce irritation, increased inflammation, and disruption of nutrient absorption and motility patterns. Antibiotics also disturb the balance of intestinal microbiota leading to reduced abundance and diversity of gut bacteria. These changes impair the microbiota's capacity to resist invasion of pathogenic microorganisms [10] [11] [12] or prevent an overgrowth of endogenous, pathogenic bacteria, some of which may be drug resistant organisms [9]-[14]. Despite the eventual recovery of microbiota counts following antibiotic discontinuation, there can be long-lasting effects on the gut microbiome and patient disease susceptibility [2] [9] [14] [15] [16] [17].

Any type of antibiotic can cause GI distress and AAD. However, clindamycin, fluoroquinolones, and broad-spectrum penicillin and cephalosporins have been found to pose the greatest risk [16]. While it is known that a specific antibiotic can increase a patient's propensity to develop GI complications, so too is the patient's susceptibility. This susceptibility is increased by extremes in age, underlying co-morbidities, immunologic status, and recent hospitalization. Prolonged antibiotic use, oral administration, or taking more than one antibiotic creates further risk of AAD [16] [17] [18] [19].

The best way to manage AAD is to prevent it. To do so, the gut microbiota makes a useful target. In recent years, probiotics have been increasingly utilized as preventive treatment for antibiotic-induced microbiota dysbiosis and asso-

ciated adverse GI effects. The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines "probiotics" as "supplemental live microorganisms" that, when administered in adequate amounts, may confer multiple health benefits based on data from numerous human studies and positive meta-analyses [20] [21] [22] [23] [24]. The ISAPP consensus panel has further identified ways probiotics may exert their activity on the human microbiome that likely varies depending on microbiota strains or species [21].

Many clinical trials have looked at the effectiveness of probiotics in preventing antibiotic-associated GI complications. Systemic review and meta-analyses suggest that the use of several species and strains of probiotics can have an overall positive effect in preventing AAD, by as much as 51% in some populations [6] [24] [25] [26] [27]. No study, however, has looked at overall patient satisfaction and compliance to antibiotic therapy when a probiotic is taken to reduce mild to moderate GI effects. The greatest benefit for AAD reduction has been found in patients under the age of 65 years and appears dependent upon probiotic strain, dose and duration [28]. At this time, microbial strains believed to be most effective in treating antibiotic-related GI side-effects include *Lactobacillus* GG, *Lactobacillus acidophilus* La-5, *Bifidobacterium lactis* B-12, *and Saccharomyces boulardii* (a nonpathogenic yeast) [29] [30] [31] [32].

The 2019 Cochrane report on prevention of AAD recommends the use of high dose probiotics (≥5 billion CFUs per day) [23] [27]. Concerns have been raised about the safety of widespread probiotic use. However, a 2014 Agency for Healthcare Research and Quality (AHRQ) assessment concluded that probiotic supplements were generally safe in both young and old for short term use, but that there was insufficient data on long-term safety of these products [24] [33] [34] [35].

The 2012 National Health Interview Survey (NHIS) identified probiotics as the third most commonly used dietary supplement in U.S. adults. Probiotic use quadrupled between 2007 and 2012 with approximately 4 million (1.6 percent) of U.S. adults now using them: a number expected to rise. [36] Because probiotics are "over-the-counter," patients often self-prescribe, potentially making ill-informed choices. Pharmacists and medical providers are in a unique position to help patients navigate the available products and inform them of their benefits, especially with regard to their use with antibiotic therapy. In a recent international survey, 79% of health care professionals (medical doctors, pharmacists, dentists and allied health professionals) reported advising their patients on probiotic use but nearly 58% felt the need for more information [37].

Currently, there are no firm, medical guidelines on how probiotics should be administered. Commercial literature on various probiotic supplements offer conflicting instructions on how to take probiotics in relation to meals. Tomkins et al examined the effects of food exposure on probiotic viability during their transit through the GI tract and found dosing 30 minutes before or during food consumption ensured greater probiotic microbial survival [38]. With regard to probiotic use with antibiotics, there remains lack of clarity. A general recom-

mendation is to take the probiotic within 2 days of starting antibiotic therapy and to continue the probiotic for a minimum of 2 - 3 weeks following antibiotic discontinuation. Because living microorganisms comprise these supplements, refrigerated probiotics are recommended to reduce or delay the death of these microbes [39] [40].

2. Objectives

This was a prescriber and pharmacist directed, open label patient experience study. The primary objective of this study was to determine whether Florajen Digestion, a commercial probiotic with 3 bacterial strains, could help maintain GI health during antibiotic regimens in a community setting. Other trial objectives were:

1) To understand patient experience and satisfaction with Florajen Digestion.

2) To understand why and which antibiotics would trigger health professionals to recommend Florajen Digestion.

3) To understand healthcare professional (HCP) and patient expectations of probiotic use.

3. Methods

The BALANCE study was conducted between September of 2018 and January 2019. Healthcare professionals (HCPs) and patients from 40 states participated in the study. Prescribers (physicians, nurse practitioners, physician assistants) known to write large numbers of antibiotic prescriptions were invited to participate in the study. Pharmacists were recruited from a list of independent pharmacies that purchase, or have purchased, Florajen in the past. Patients were provided a 30-count bottle of refrigerated Florajen Digestion probiotic, free of charge, through their prescriber or pharmacist when recommending or dispensing antibiotics. Florajen Digestion is a commercial probiotic supplement containing a total 15 billion live cultures of *Lactobacillus acidophilus* La-14, *Lactobacillus acidophilus* NCFM, *Bifidobacterium lactis* Bi-07, *Bifidobacterium lactis* HN019, *and Bifidobacterium longum* BL-05. Surveys were completed by HCPs and patients, who reported on antibiotics prescribed and taken, compliance, past and/or current antibiotic-related GI upset, and product satisfaction.

Surveys given to HCPs sought their reasons for providing Florajen Digestion to the patient. Among reasons listed from which to choose included belief in the product's efficacy, stability and culture potency, patient satisfaction, antibiotic compliance, and familiarity with the Florajen brand. Further information was elicited about the provider's overall belief in probiotic GI benefits, patients' past history of GI distress while taking antibiotics and which antibiotics would motivate a medical recommendation for probiotics.

Inclusion criteria required that patients were being treated with a first course of antibiotics with a regimen less than or equal to 10 days. Additionally, patients had to be appropriate for probiotic therapy, and not immunocompromised. Pa-

tient respondents reported on demographic data such as age, sex and ethnicity as well as past history of antibiotic-induced GI side effects.

Patients were instructed to begin taking Florajen Digestion at the start of their antibiotic regimen. The probiotic was to be taken daily 1 to 2 hours before or after their antibiotic and continued at least 2 - 3 weeks after antibiotic discontinuation or until all of the dispensed probiotic was gone. Patients were then asked to complete a survey seeking information about their history of antibiotic use and feedback about general GI health, new GI distress, compliance with the antibiotic and probiotic regimen, and overall satisfaction with Florajen Digestion. Every patient who returned the survey received a $5 Starbucks gift card. Healthcare professionals received no compensation.

4. Results

1) Prescriber and Pharmacist responses

A total of 831 surveys were completed by HCPs from 40 states. Pharmacists (#562) surpassed prescribers (#269) in responses, however, both prescribers and pharmacists were nearly equal in their prioritization of antibiotics that would induce them to recommend Florajen Digestion. Specifically, Penicillins (Amoxicillin, Augmentin, etc), clindamycin, ciprofloxacin and doxycycline ranked as the top 4 antibiotics of concern [Figure 1].

Perceived clinical efficacy was the leading reason for HCPs to recommend Florajen Digestion to patients, although pharmacists placed slightly more importance on compliance, patient satisfaction and stability compared to prescribers.

Over 90 percent of HCPs believed that antibiotic compliance increased when related side effects were reduced [Figure 2]. To that end, most of the participating HCPs felt strongly that probiotics should be recommended when antibiotics

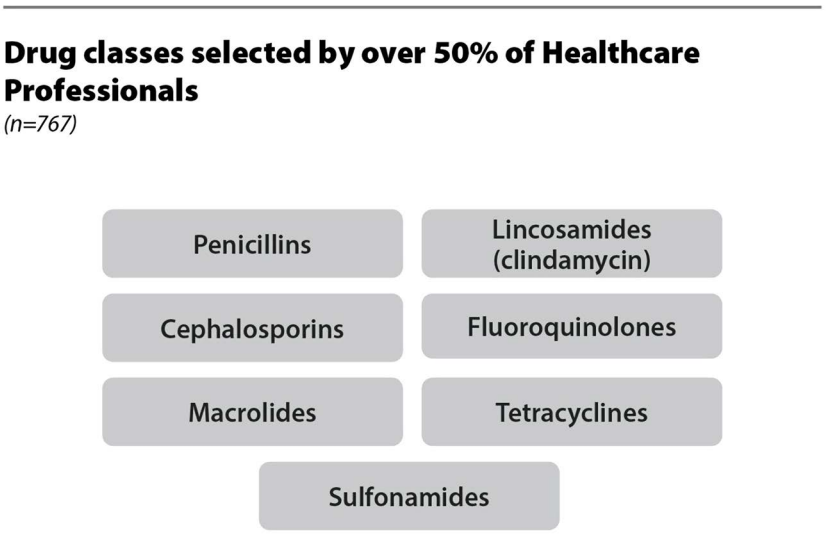

Figure 1. Antibiotic drug classes likely to generate a Florajen digestion recommendation by HCPs.

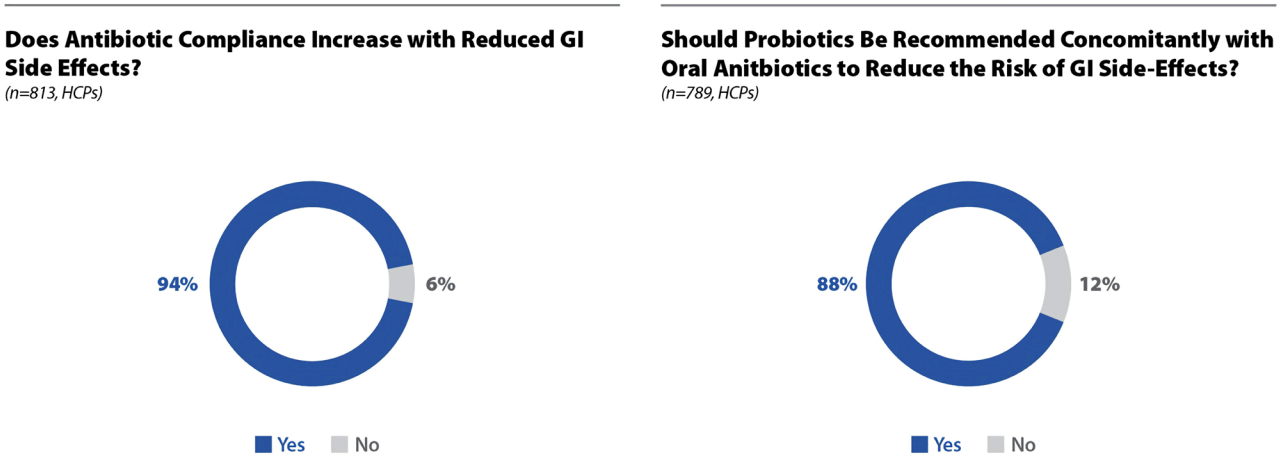

Figure 2. HCPs believe that antibiotic compliance increases with reduced GI side-effects and that Probiotics given concomitantly can reduce GI side-effects.

were prescribed to prevent or minimize GI side effects. A small percentage (<15%) of HCPs reported that they would only recommend probiotics if patients expressed a desire for them [Figure 2]. Despite HCP-stated acceptance of probiotic GI benefits when taking oral antibiotics, nearly two-thirds of HCPs testified that they did not know if the patient had previously experienced prior antibiotic-related side effects [Figure 3].

2) Patient Responses and Demographics

A total of 404 surveys were completed by patients who received Florajen Digestion from an HCP. The majority of patient respondents were Caucasian, female and represented a wide range in age [Table 1]. Interestingly, nearly half of pharmacist-initiated patient surveys came from patients over 60 years of age, whereas those under 60 years comprised nearly 70% of prescriber-initiated patient surveys.

A surprising majority of patients (59% to 69%) reported a past history of antibiotic-related GI side-effects, a higher incidence than reported in the literature [Table 1]. In this study, only 12% of patients reported GI side effects, which occurred in patients with and without a history of antibiotic GI upset [Figure 4]. No single antibiotic was identified as a primary perpetrator of GI upset.

Most compelling was that an average of 93% of patients completed their antibiotic regimen, with 77% claiming Florajen Digestion had helped them do so [Figure 4].

Forty one percent (41%) of patient respondents in this study revealed they had tried other probiotics with past antibiotic therapy; Culturelle and acidophilus were the most commonly cited. None reported prior Florajen Digestion use, however 76% of patients who tried other probiotics for antibiotic-associated GI side-effects, preferred Florajen Digestion [Figure 5]. It is not known if their probiotic choices were HCP-recommended.

Although a wide variety of antibiotics were prescribed to participating patients, Amoxicillin and Augment topped the list with nearly 30% of patient respondents

Table 1. Patient demographics.

Patient Demographics and Clinical History							
Ethnicity n = 373		**Age** n = 354		**Gender** n = 393		**Percentage of patients reporting a history of antibiotic -associated GI side-effects** n = 384	
Caucasian	74%	<30	20%	Female	70%	Yes	63%
African-American/Black	7%	30 - 45	18%	Male	30%	No	28%
Hispanic	5%	46 - 60	22%			Don't Know	9%
Asian	10%	61 - 75	23%				
Middle Eastern	2%	75+	17%				
Other	2%						

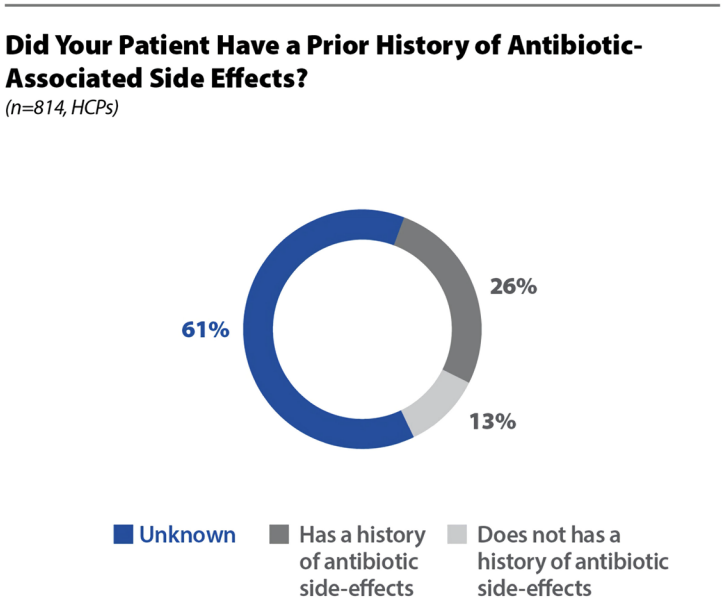

Figure 3. Percent of HCPs reporting they did not know if patients had prior history of antibiotic-associated side-effects.

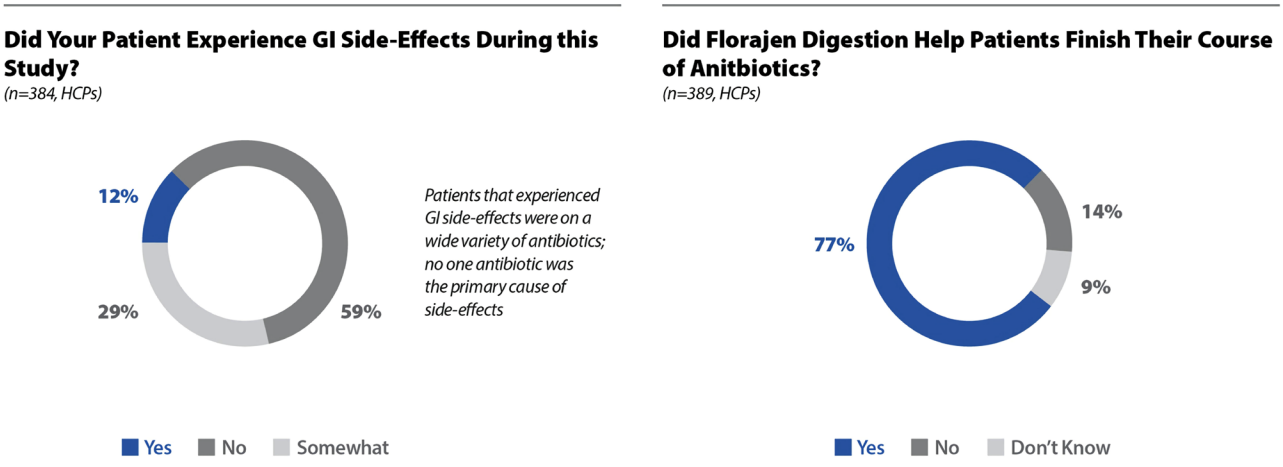

Figure 4. Percent of patients experiencing GI side-effects during this study and HCP perspective on whether Florajen digestion helped patients finish their course of antibiotics.

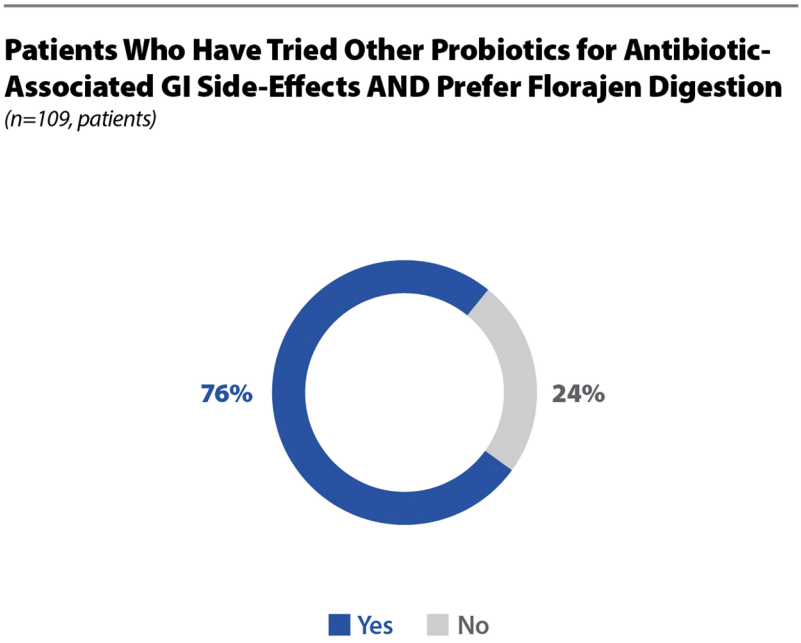

Figure 5. Percent of patients who have tried other probiotics and prefer Florajen digestion.

reporting that they were prescribed these two drugs. The duration of antibiotic and probiotic use ranged from 3 to 10 days with an average of 7 treatment days [Figure 6].

Overall satisfaction with Florajen Digestion was high at 88% [Figure 7].

5. Discussion

Gastrointestinal distress, including AAD, has emerged as a common complication of antibiotic use which can limit compliance to treatment regimen. Adverse GI side effects are believed to be related to antibiotic-induced disruption of existing intestinal microbiota and changes to intestinal epithelial integrity. Many outpatient and inpatient clinical trials have assessed prophylactic probiotic use with antibiotics to prevent, or minimize, GI side effects. The evidence suggests a moderate protective effect of probiotics in preventing AAD. Despite these findings, there remains a hesitancy among community-based HCPs to recommend probiotic use with antibiotics. This is not surprising, as many clinical trials have been small with researchers using varied, proprietary bacterial strains in their probiotic cocktails. Should HCPs choose to recommend the use of probiotics, they are only available to the public as over-the-counter supplements. To date, there is insufficient research to determine the efficacy of these commercial probiotic supplements in preventing antibiotic-related GI distress.

From the results of this study, it appears that a large majority of HCPs (94%) believe that reducing GI side-effects can increase antibiotic compliance, with most supporting prophylactic probiotic use with oral antibiotics. Despite agreeing that GI distress can negatively impact antibiotic compliance, a majority of

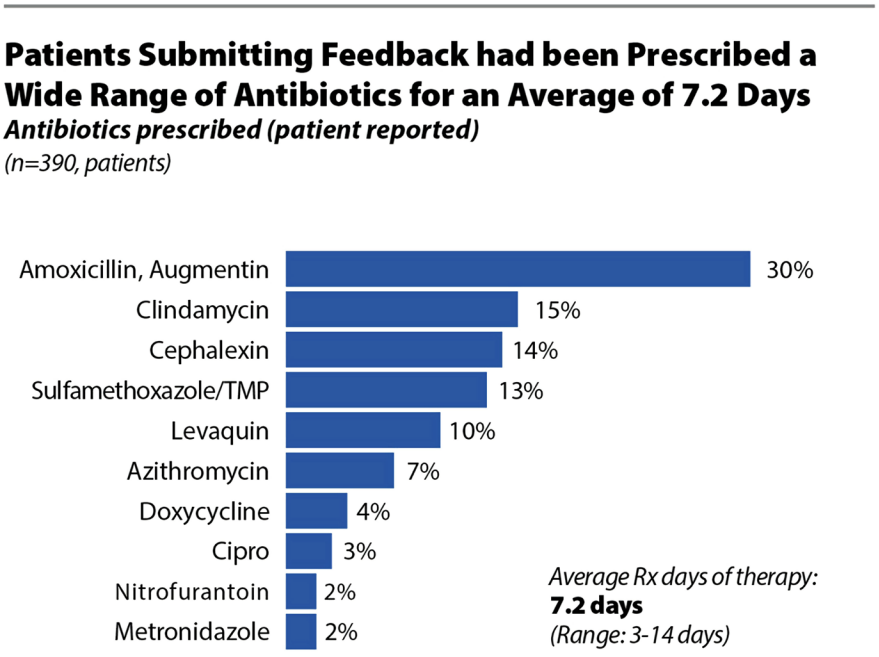

Figure 6. Antibiotics prescribed to patient respondents (patient reported).

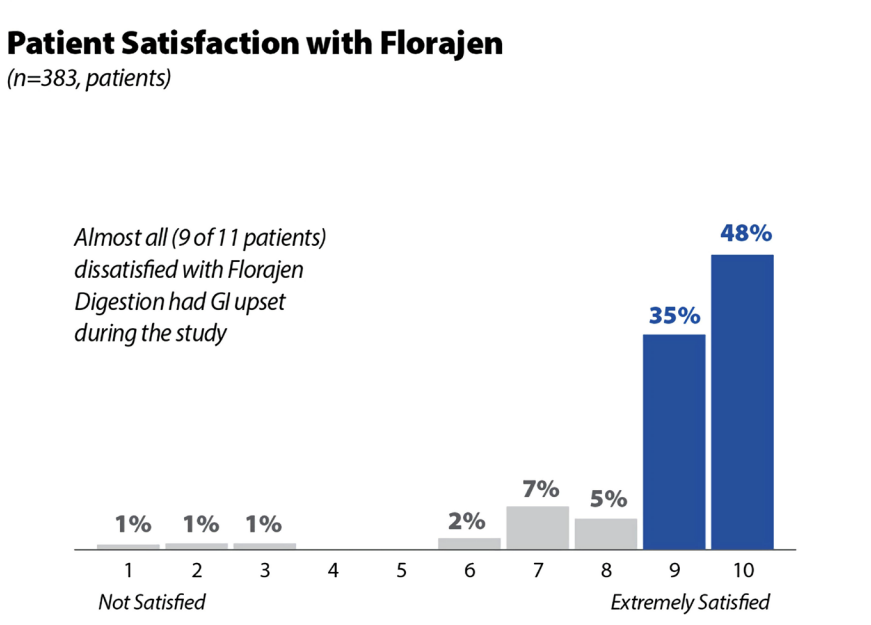

Figure 7. Percent of patients by level of satisfaction with Florajen digestion.

HCPs did not know if their patient had a history of antibiotic complications prior to prescribing the current antibiotic. This finding is concerning as it limits early identification of patients with higher risk for AAD and other GI upset.

While the literature often cites the incidence of antibiotic-related GI side-effects as high as 49%, the reported incidence of past antibiotic-associated GI distress in this study was considerably higher (63%) possibly indicating underreporting of these adverse effects or the increased participation of patients who had expe-

rienced antibiotic associated GI upset in the past. Despite the high prior occurrence of GI sequela, only 12% of participating patients in the BALANCE study reported GI side-effects. This may explain the very high compliance to both antibiotic and probiotic therapy (>91%) in this study, with most patients claiming Florajen Digestion helped them finish their course of antibiotics. Patients who did not fully comply with, or complete, their antibiotic treatment plan, identified GI-upset as the cause.

Perhaps mirroring the public at large, a majority of BALANCE study patients reported past use of probiotics for antibiotic-associated GI side-effects, although none testified to prior use of a Florajen product. A large majority of the patients surveyed, including those with a history of past probiotic use with antibiotics, reported "extreme satisfaction" with Florajen Digestion and 89% declared their intent to use this probiotic product with antibiotics in the future.

This was the first open label, patient experience study examining the concomitant use of a commercial probiotic supplement with antibiotic therapy in an outpatient setting. The strength of this study was the large number of HCPs and patients who chose to participate within the short trial time frame, providing good insight into HCP probiotic prescribing patterns as well as overall compliance with antibiotic and probiotic regimens. However, the study was limited by the subjective nature of the patients' responses as well as lack of ascertaining the exact nature of antibiotic-associated GI side-effects experienced by patients.

6. Conclusion

The Florajen Digestion BALANCE study provided feedback from hundreds of health care prescribers, pharmacists and patients to help gain insight about the GI health benefits of concomitant use of Florajen Digestion, a commercial probiotic supplement, with antibiotics. Results from this study support the recommendation of Florajen Digestion by HCPs when prescribing or dispensing antibiotics to help prevent GI side effects.

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Conflicts of Interest

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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