Am. J. Trop. Med. Hyg., 82(2), 2010, pp. 301–305
doi:10.4269/ajtmh.2010.09-0538

Travel and Travelers' Diarrhea in Patients with Irritable Bowel Syndrome

Herbert L. DuPont,* Greg Galler, Francisco Garcia-Torres, Andrew W. DuPont, Anthony Greisinger, and Zhi-Dong Jiang

University of Texas School of Public Health, Houston, Texas; St. Luke's Episcopal Hospital, Houston, Texas; Baylor College of Medicine, Houston, Texas; Kelsey Research Foundation, Houston, Texas; Kelsey-Seybold Clinic, Houston, Texas; University of Texas Medical Branch, Galveston, Texas

Abstract. This study evaluated occurrence of travel and travelers' diarrhea in patients with irritable bowel syndrome (IBS). A survey was mailed to 591 patients of a clinical practice who had IBS. Based on survey responses, patients were categorized as having IBS, post-infectious IBS (PI-IBS), unclassified functional bowel disorder (UFBD), or post-infectious UFBD (PI-UFBD). Of 201 persons who returned questionnaires meeting inclusion criteria, 57.7%, 11.4%, 24.9%, and 6.0% had IBS, UFBD, PI-IBS, and PI-UFBD, respectively. Travel during six months before illness onset was more common in patients with PI-IBS or PI-UFBD than in persons with idiopathic IBS or UFBD ($P = 0.006$). Survey results demonstrated that 16.1% of post-infectious bowel disorder cases and 7.5% of overall IBS cases in a general medical population developed chronic disease within six months of an international trip. Symptoms of established functional bowel disorder in each clinical category were shown to worsen after travel-related acute diarrhea.

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal (GI) disorders in Western countries,[1] causing illness in approximately 10–15% of western populations.[2] Approximately 7–31% of IBS cases develop after a discrete bout of infectious diarrhea and are referred to as post-infectious IBS (PI-IBS) cases.[3] The symptoms of PI-IBS and IBS are similar, although slight differences in overall pathogenesis have been noted, including increased numbers of enteroendocrine cells, more days of pain, and more diarrheal features in patients with PI-IBS than in those with IBS.[4] The underlying cause for these differences remains unknown. However, alterations in inflammatory processes after initial GI infection have been implicated.[3,5]

Acute gastrointestinal infections leading to PI-IBS occur after exposure to enteropathogens, usually bacterial, and often develop during a period of travel, especially to non-industrialized areas such as Latin America, Africa, and southern Asia.[6] Until the recognition of PI-IBS, the main concern in management of travel-related infectious diarrhea (i.e., travelers' diarrhea) was alleviation of symptoms to prevent incapacitation during travel. The attention is now turning toward prevention of diarrhea and PI-IBS.[7] Prospective studies have found that PI-IBS will develop in approximately 7–14% of persons who experience diarrhea during a trip to a developing country.[8,9]

The present study was performed to 1) identify patients with IBS in whom their illness developed after an acute bout of diarrhea (considered as PI-IBS) in a general medical population with IBS, 2) clinically compare illness of patients with PI-IBS with that seen in patients with idiopathic IBS, and 3) determine the temporal relationship of travel with the development and acute diarrhea to the worsening of persistent intestinal disorders.

MATERIALS AND METHODS

Study setting. The study was conducted at Kelsey-Seybold Clinic (KSC), a large multispecialty medical organization in Houston, Texas, that provides care to an ethnically diverse population of approximately 350,000 patients at 18 clinic locations. The Center for Digestive Diseases at the Kelsey Research Foundation designed and conducted the study.

Survey design. Research staff developed a 26-question survey for the study using Rome II criteria to determine the presence of active IBS. In the questionnaire, persons were asked to provide demographic information, clinical attributes of their functional bowel disorder, travel habits before development of IBS, and the degree to which their IBS interfered with daily living activities and travel habits.

Study design. Eligibility status was determined by searching the KSC electronic database of patients. During January 2006–May 2008, 997 patients were diagnosed with IBS at least twice by medical staff at KSC. The first 591 of these patients were mailed an invitation letter describing the study, a copy of the questionnaire, and a postage-paid envelope. A research assistant called patients who did not return the questionnaire to invite them to answer questions about the study and to remind them to return the questionnaire. Patients were called up to six times before being classified as nonresponsive. The research staff reviewed completed questionnaires and entered the responses into a database on a weekly basis.

Patient inclusion. Patients were categorized as having IBS if they were being treated for IBS at the clinic at the time of the survey and if they experienced abdominal discomfort or pain for at least three months during the past year and reported at least two of the following three conditions relating to the discomfort or pain: 1) it is relieved with bowel movements; 2) it is associated with a change in stool frequency; or 3) it is associated with a change in stool form (either looser or harder than normal) (Rome II criteria for IBS). Patients treated at the clinic for IBS with discomfort or pain with only one of these three symptoms were classified as having unclassified functional bowel disorder (UFBD). Persons who did not display any of these conditions were categorized as not having persistent functional bowel disorder and were removed from further analysis. Post-infectious IBS and post-infectious UFBD (PI-UFBD) were identified in patients who indicated that onset of their IBS or UFBD occurred after an acute bout of diarrhea associated with one or more of the following symptoms: fever, vomiting, abdominal pain or cramps, dysentery, or fecal urgency. Patients in whom IBS or UFBD development was unrelated to a bout of diarrhea or gastroenteritis were considered to have idiopathic forms of IBS or UFBD. All patients were

*Address correspondence to Herbert L. DuPont, 6720 Bertner Avenue, MC 1-164, Houston, TX 77030. E-mail: dupont@sleh.com

asked to indicate if they experienced diarrhea, constipation, or alternating diarrhea and constipation at least 75% of the time. Each patient was then classified as having alternating (mixed), constipation-predominant, or diarrhea–predominant IBS.

Travel-related IBS gastrointestinal disease. We assessed the occurrence of travel-related symptoms in two ways. First, when a functional bowel disorder (e.g., UFBD, IBS) developed within six months of travel, patients were considered to have travel-related functional bowel disorder. This feature was designed to determine the maximum potential importance of travelers' diarrhea in the development of functional bowel disease. Second, we asked all subjects with pre-existent functional bowel symptoms, if at any time their chronic intestinal disease was made worse by a bout of travelers' diarrhea.

Statistical analysis. Between-group comparisons were examined by chi-square test. When a statistical difference ($P \leq 0.05$) was seen for the four groups, subgroups of interest were compared for differences.

RESULTS

A total of 221 of 591 persons (37%) returned a completed questionnaire. The median age, ethnicity, and frequency of underlying comorbidity (e.g., presence of diabetes and hypertension) were similar in patients who returned the questionnaire and those who did not, providing evidence that the sample studied was representative of the clinical IBS population. Of the 221 questionnaires returned, 201 (91%) met inclusion criteria. One hundred sixteen patients (57.7%) were classified with IBS, 50 (24.9%) with PI-IBS, 23 (11.4%) with UFBD, and 12 (6.0%) with PI-UFBD. The demographic and selected epidemiologic findings in the four clinical groups are shown in Table 1. Females predominated in all four groups, without intergroup differences. Racial distribution was similar across the four groups, reflecting the makeup of the clinic population. The frequency of advanced education and family income ≥ $40,000 per year was similar in the four groups. The percentage of patients who reported having at least one family member with a diagnosis of IBS was similar in the four groups and ranged from 21.7% to 36.4%. The mean duration of IBS at the time the questionnaire was completed was similar for idiopathic IBS (12.73 years) and PI-IBS (12.52 years), both of which had a longer duration than UFBD (9.85 years) or PI-UFBD (8.59 years; $P = 0.038$). In each of the four functional bowel groups, the distribution of predominant clinical symptoms was comparable, with approximately one-third of patients in each group showing alternating, constipation-predominant, or diarrhea-predominant patterns (Table 2).

In general, there was not a substantial difference in the incidence of intestinal complaints reported by patients with IBS and patients with PI-IBS, although patients with PI-UFBD reported a greater number of complaints compared with patients with idiopathic UFBD (Table 2). The mean number of bowel movements per day was significantly different between groups; patients with idiopathic IBS and patients with PI-IBS had more frequent bowel movements than patients with idiopathic UFBD or PI-UFBD ($P = 0.042$). Abnormally formed stools were more prevalent in patients with IBS (76.1%) and PI-IBS (73.5%) than in patients with UFBD (39.1%) and PI-UFBD (54.5%). The rate of fecal straining was comparable in all four groups ($P = 0.163$), but fecal urgency and a sense of incomplete bowel evacuation were more common in patients with idiopathic IBS, PI-IBS, and PI-UFBD than in patients with UFBD. Abdominal bloating occurred most commonly in patients with IBS or PI-IBS.

In all assessments of functional impairment associated with persistent abdominal symptoms, with the exception of avoidance of planned activities, both IBS groups (idiopathic IBS and PI-IBS) had higher scores, indicating greater impairment, than patients with idiopathic UFBD or PI-UFBD (Table 3). Patients with IBS or PI-IBS more often had trouble performing at work or school, missed work or school, were embarrassed, or had trouble sleeping because of their intestinal symptoms. Persons with PI-IBS or idiopathic IBS were also significantly more likely to stop leisure activities and cancel social plans. Patients with PI-IBS and PI-UFBD were more likely to avoid planned activities than those with idiopathic IBS or UFBD.

Sixteen of the 195 patients (8.2%) who responded to the survey question and had any of the four functional bowel disorders (i.e., IBS, PI-IBS, UFBD, or PI-UFBD) experienced onset of their chronic intestinal disease after an international trip and were considered to have travel-related functional bowel disorder. International travel during the six months before the onset of persistent intestinal symptoms was most common in patients with PI-IBS (7 of 50, 14.0%) and PI-UFBD (3 of 12, 25.0%) compared with patients with idiopathic IBS (5 of 111, 4.5%) or idiopathic UFBD (1 of 22, 4.5%) ($P = 0.006$). The regions or countries visited by the seven patients in whom PI-IBS developed after travel were the following: Middle East (n = 1); England and Vietnam (n = 1); Mexico (n = 3); and

TABLE 1
Demographic comparisons in persons with persistent functional bowel disorder*

Characteristic	IBS (n = 116)	UFBD (n = 23)	PI-IBS (n = 50)	PI-UFBD (n = 12)	*P*
Female, no. (%)	92† (81.4)	14† (63.6)	38 (76.0)	11 (91.7)	0.179
Race, no. (%)					
White	64† (56.1)	16 (69.6)	22 (44.0)	4 (33.3)	
Black	30† (26.3)	4 (17.4)	11 (22.0)	3 (25.0)	
Hispanic	13† (11.4)	0 (0)	13 (26.0)	3 (25.0)	
Asian	3† (2.6)	2 (8.7)	0 (0)	1 (8.3)	
Other	4† (3.5)	1 (4.3)	4 (8.0)	1 (8.3)	0.647
Education: college or graduate school, no. (%)	83† (72.2)	12† (54.5)	32† (65.3)	7† (58.3)	0.334
Family income ≥ $40,000/year, no. (%)	78† (72.9)	10† (52.6)	32† (65.3)	7† (58.3)	0.271
Family member with IBS, no. (%)	40† (34.8)	5† (21.7)	13† (26.0)	4† (36.4)	0.392
Mean ± SD duration of functional bowel disorder, years	12.73 ± 11.32	9.85 ± 13.40	12.52 ± 11.66	8.59 ± 10.69	0.037‡

* IBS = irritable bowel syndrome; UFBD = unclassified functional bowel disorder; PI-IBS = post-infectious irritable bowel syndrome; PI-UFBD = post-infectious unclassified functional bowel disorder.
† Number of patients responding to this category, which may differ from total number of patients.
‡ Subgroup comparisons: IBS vs. UFBD, $P = 0.041$; IBS vs. PI-IBS, $P = 0.1571$; PI-IBS vs. PI-UFBD, $P = 0.0357$.

TABLE 2
Clinical comparisons in persons with persistent functional bowel disorder*

Clinical characteristic	IBS (n = 113)	UFBD (n = 18)	PI-IBS (n = 49)	PI-UFBD (n = 12)	*P*
IBM symptom predominance					
Constipation, no. (%)	38 (33.6)	7 (38.9)	24 (49.0)	4 (33.3)	
Diarrhea, no. (%)	41 (36.3)	7 (38.9)	9 (18.4)	4 (33.3)	
Alternating, no. (%)	34 (30.1)	4 (22.2)	16 (32.7)	4 (33.3)	0.332
Mean number of bowel movements per day	2.36†	1.38†	2.42†	2.27†	0.042‡
Stools of abnormal form, no. (%)	83† (76.1)	9† (39.1)	36† (73.5)	6† (54.5)	0.036§
Fecal straining, no. (%)	62† (57.9)	10† (43.5)	34† (70.8)	6† (60.0)	0.163
Fecal urgency, no. (%)	78† (75.0)	5† (22.7)	34† (72.3)	10† (90.9)	< 0.0001¶
Incomplete bowel movements, no. (%)	91† (83.3)	11† (47.8)	40† (80.0)	8† (72.7)	0.002#
Bloating, no. (%)	94† (81.7)	13† (56.5)	43† (86.0)	8† (66.7)	0.018**

* IBS = irritable bowel syndrome; UFBD = unclassified functional bowel disorder; PI-IBS = pos-tinfectious irritable bowel syndrome; PI-UFBD = post-infectious unclassified functional bowel disorder.
† Number of patients responding to this category, which may differ from total number of patients.
‡ Subgroup comparisons: IBS vs. UFBD, $P = 0.0378$; PI-IBS vs. PI-UFBD, $P = 0.7021$.
§ Subgroup comparisons: IBS vs. UFBD, $P < 0.0001$; PI-IBS vs. PI-UFBD, $P = 0.0050$.
¶ Subgroup comparisons: IBS vs. UFBD, $P < 0.0001$; PI-IBS vs. PI-UFBD, $P = 0.0012$.
# Subgroup comparisons: IBS vs. UFBD, $P < 0.0001$; PI-IBS vs. PI-UFBD, $P = 0.243$.
** Subgroup comparisons: IBS vs. UFBD, $P < 0.0008$; PI-IBS vs. PI-UFBD, $P = 0.1452$.

Greece (n = 2). Patients in whom PI-UFBD developed had visited Peru (n = 1); France (n = 1); and an unspecified destination (n = 1) before disease onset. The five patients with idiopathic IBS in whom chronic intestinal illness developed after an international trip had visited Mexico (n = 2); Honduras (n = 1); Puerto Rico (n = 1); and Saudi Arabia, Japan, Thailand, and Costa Rico (n = 1). The one patient in whom UFBD developed after traveling had visited Mexico, Europe, and Japan.

Acute diarrhea associated with travel appeared to worsen underlying functional bowel disorder in 5 (10.4%) of 48, 1 (8.3%) of 12, 8 (7.5%) of 107, and 1 (5.0%) of 20 patients with PI-IBS, PI-UFBD, idiopathic IBS, and idiopathic UFBD, respectively. Patients with PI-IBS who reported worsening of symptoms after an episode of TD had traveled to the Venezuela (n = 1); Mexico (n = 3); and England, other European countries, Vietnam, and Hong Kong (n = 1). However, the patient with PI-UFBD who experienced symptom worsening had traveled only within the United States. Patients with idiopathic IBS who experienced worsening of symptoms had recently traveled to the Middle East and Yugoslavia (n = 1); Germany (n = 1); Dominican Republic (n = 1); the United States and Mexico (n = 1); and within the United States (n = 4). The one patient with idiopathic UFBD who reported worsening of symptoms had traveled within the United States.

DISCUSSION

Currently, it is not known how travel and acute diarrhea contribute to the development or worsening of post-infectious forms of IBS, but understanding the pathogenesis of PI-IBS may allow identification of risk factors that enable development of strategies for the prevention or alleviation of the disease. In the present study, patients with IBS were categorized as having either UFBD or IBS and subclassified as having idiopathic or post-infectious illness based on the historical presence or absence of antecedent diarrhea or gastroenteritis. We considered PI-IBS or PI-UFBD to be the diagnosis when their chronic GI disorder began immediately after a discrete bout of diarrheal disease. Gastrointestinal symptoms and the degree to which symptoms interfered with patients' daily lives were examined, as well as any travel that may have occurred within six months before symptom onset. All of the subjects enrolled had a clinic diagnosis of IBS, making it likely that they had variants of IBS, although the study required that Rome II criteria be met for the diagnosis at the time the questionnaire was completed.

Post-infectious IBS is generally thought to be a subset of idiopathic IBS because of the similarity of their overall symptoms, but it has been suggested that patients with PI-IBS may have a better prognosis than patients with idiopathic forms of the disorder. However, there is little evidence to support this concept.[5] Follow-up studies have shown that most persons with PI-IBS will still have the disorder after five[10] to six years.[4] In the present study, idiopathic IBS and PI-IBS showed similar durations of illness with means of 12.7 years and 12.5 years, respectively. The frequency of intestinal complaints, including stools of abnormal form, fecal urgency, common experience of incomplete bowel movements, bloating, and functional impairments, was compa-

TABLE 3
Disruption of daily living activities*

Functional considerations†	IBS (n = 116)	UFBD (n = 23)	PI-IBS (n = 50)	PI-UFBD (n = 12)	*P*
Trouble performing at work or school, mean ± SD	3.06 ± 1.65‡	2.83 ± 2.04	3.36 ± 1.87	2.67 ± 2.31	0.512
Missed work or school, mean ± SD	2.13 ± 1.86‡	1.41 ± 1.94‡	2.08 ± 1.99	2.00 ± 2.26	0.815
Stopped leisure activities, mean ± SD	2.35 ± 1.69‡	2.00 ± 2.16‡	3.02 ± 1.77‡	1.67 ± 2.02	0.017§
Embarrassed, mean ± SD	3.16 ± 2.18‡	2.30 ± 2.38	3.44 ± 2.52	2.25 ± 2.70	0.147
Trouble sleeping, mean ± SD	2.27 ± 1.82‡	1.74 ± 1.96	2.66 ± 2.03	1.92 ± 2.07	0.236
Canceled social plans, mean ± SD	2.29 ± 1.85‡	1.83 ± 2.17	3.02 ± 2.08	1.92 ± 2.15	0.049¶
Avoided planned activities, mean ± SD	1.83 ± 1.93‡	1.26 ± 1.83	2.72 ± 2.47	2.17 ± 2.59	0.027#

* IBS = irritable bowel syndrome; UFBD = unclassified functional bowel disorder; PI-IBS = post-infectious irritable bowel syndrome; PI-UFBD = post-infectious unclassified functional bowel disorder.
† Responses used a visual analog scale ranging from 0 (never) to 6 (always).
‡ Number of patients responding to this category, which may differ from total number of patients.
§ Subgroup comparisons: IBS vs. PI-IBS, $P = 0.0612$; IBS vs. UFBD, $P = 0.7864$; PI-IBS vs. PI-UFBD, $P = 0.0205$.
¶ Subgroup comparisons: IBS vs. UFBD, $P < 0.0741$; IBS vs. PI-IBS, $P = 0.9430$; PI-IBS vs. PI-UFBD, $P = 0.0502$.
# Subgroup comparisons: IBS vs. UFBD, $P < 0.9534$; IBS vs. PI-IBS, $P = 0.0303$; PI-IBS vs. PI-UFBD, $P = 0.6734$.

rable for the two forms, casting doubt on a more benign course for post-infectious forms of IBS. It should also be noted that in the present study, a higher percentage of persons with PI-UFBD experienced abnormally formed stools, fecal straining and urgency, incomplete bowel movements, and bloating compared with patients with UFBD. This difference in symptoms between the idiopathic and post-infectious forms of UFBD may indicate the diversity of the two UFBD groups or suggest a difference in underlying pathophysiology between the two groups. The fact that such group-related differences were not seen between the PI-IBS and idiopathic IBS groups suggests a similarity in pathophysiology that is not shared by persons with UFBD.

Several studies have evaluated the effect of IBS on health-related quality of life (HRQOL) and found a reduction compared with healthy controls.[11,12] To date, no study examining HRQOL in patients with PI-IBS is available. However, because of the similar occurrence of symptoms in patients with IBS and those with PI-IBS, it seems likely that HRQOL in patients with PI-IBS would also decrease. In the present work, a significantly larger percentage of patients with PI-IBS stopped leisure activities than patients with PI-UFBD ($P = 0.02$), suggesting that symptoms of PI-IBS may be more disruptive than those of PI-UFBD. Patients with IBS and those with PI-IBS avoided planned activity because of symptoms, which indicates that both etiologies of IBS may affect overall patient well-being.

Acute infectious diarrhea associated with travel (i.e., travelers' diarrhea) has been identified as an important risk factor for the development of initial-onset IBS.[6] A study among U.S. students in Mexico for summer study abroad showed that 10% of persons who experienced a bout of travelers' diarrhea progressed to having IBS within six months of travel.[8] In another study, primarily among international visitors to Asia, a similar percentage of new-onset traveler's diarrhea–associated IBS cases was identified.[9] To examine a possible relationship between travel and IBS development in the present study, all patients were asked if they had traveled to a foreign country in the six months before onset of their IBS symptoms. We did not determine that a bout of diarrhea during travel was the initial PI-IBS-defining illness in the post-infectious groups. Sixteen persons in the study had taken a trip to a foreign country in the six months before onset of their IBS symptoms and were considered to have travel-related functional bowel disorder.

The association was strongest for patients with PI-IBS and PI-UFBD. In these groups, 10 of 62 individuals (16.1%) had taken an international trip during the six months before onset of their chronic intestinal disorder. In patients with idiopathic forms of persistent bowel disorder, 6 of 133 persons (4.5%) traveled internationally six months before onset of their intestinal disease, suggesting that these persons may actually have PI-IBS. These results provide evidence that 16.1% of all post-infectious functional bowel disorders and 7.5% of overall IBS cases in a general medical population with IBS had onset of their functional bowel disease within six months of an international trip. Furthermore, acute diarrhea associated with travel worsened underlying functional bowel disorder symptoms in some patients within each functional bowel disorder classification (i.e., IBS, PI-IBS, UFBD, PI-UFBD), suggesting that acute travel-related diarrhea may worsen gastrointestinal symptoms. Although enteric infection appears to be important in the pathogenesis of PI-IBS, enteric infection may play an undefined role in development idiopathic forms of disease. Enteric infections occur commonly in the United States, and illness may have developed in a proportion of persons with idiopathic IBS after gastroenteritis or enteric infection in their own city without travel.

Caveats of this study include its retrospective nature, the return rate of the questionnaire, and the use of a novel survey. The duration between patients' initial IBS diagnosis and contact for study participation ranged from one to two years. The length of this time interval may have produced recall bias, especially for response to questions relating to the onset and correlation of specific symptoms. The survey used in the current study had not been previously validated in this patient population. However, a validated PI-IBS HRQOL questionnaire was not available. Because of this, a novel survey that followed the general design of a previously validated IBS quality of life questionnaire[13] was developed for this study.

The current study examined the impact of travel and acute diarrhea on the development and worsening of PI-IBS. The study established that PI-IBS and IBS have similar clinical attributes and that post-infectious forms of GI infections may be more likely to occur in persons who travel. Furthermore, the study provides data indicating that after patients acquire PI-IBS, subsequent bouts of acute diarrhea often worsen their underlying symptoms. Although the study indicated associations between travel and the development and travelers' diarrhea with the worsening of IBS-like symptoms, the study was not designed to determine a cause and effect between travelers' diarrhea and the development of functional bowel disease, which would not be possible with a survey-based study. We are currently conducting studies to compare pathophysiologic and genetic differences between post-infectious and idiopathic forms of IBS and to examine the role of organism-specific enteric infections in the development of new-onset functional bowel disorder.

Received September 10, 2009. Accepted for publication November 3, 2009.

Acknowledgments: We thank Jessica Cantu, Pingal Desai, Heidi Hodgson, Lilia Martinez, Kimberly Stanley, Saraj Sunder, and Lynn Trenta for helping to collect data for this study. This study was presented at Digestive Disease Week, Chicago, IL, June 1, 2009.

Financial support: This study was supported by discretionary funds from the Kelsey Research Foundation; the University of Texas School of Public Health; and in part by the Public Health Service (grant DK 56338), which supported the Texas Gulf Coast Digestive Diseases Center. Herbert L. DuPont has received research support from Salix Pharmaceuticals, Inc., McNeil Consumer Healthcare, IOMAI Corporation, Intercell Corporation, and Optimer Pharmaceuticals, Inc. Zhi-Dong Jiang has received research support from Salix Pharmaceuticals, Inc., McNeil Consumer Healthcare, IOMAI Corporation, and Optimer Pharmaceuticals, Inc. Andrew DuPont has received research support from Salix Pharmaceuticals, Inc. Editorial assistance was provided under the direction of the authors by MedThink Communications with support from Salix Pharmaceuticals, Inc.

Authors' addresses: Herbert L. DuPont, Houston, TX, E-mail: dupont@sleh.com. Greg Galler, St. Luke's Episcopal Hospital, Houston, TX, E-mail: greg.galler@kelsey-seybold.com, Francisco Garcia-Torres, Kelsey-Seybold Clinic, Houston, TX, E-mail: fjgarcia-torres@kelsey-seybold.com, Andrew W. DuPont, University of Texas Medical Branch, Galveston, TX, E-mail: awdupont@utmb.edu. Anthony Greisinger, Kelsey Research Foundation, Houston, TX, E-mail: ajgreisinger@kelsey-seybold.com. Zhi-Dong Jiang, Houston, TX, E-mail: zhi-dong.jiang@uth.tmc.edu.

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