Original Article

Severe Multiple Drug Intolerance Syndrome in Fibromyalgia and Irritable Bowel Syndrome

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What is already known about this topic? Multiple drug intolerance syndrome (MDIS) describes patients with multiple nonimmunologically mediated adverse reactions to medications. MDIS, fibromyalgia, and irritable bowel syndrome (IBS) overlap in patient characteristics and interactions with health care.

What does this article add to our knowledge? Patients with fibromyalgia and IBS have significantly higher rates of severe MDIS. This was associated with polypharmacy in both groups. Patients with IBS more often reported gastrointestinal symptoms as adverse medication reactions.

How does this study impact current management guidelines? Fibromyalgia and IBS should be noted during the evaluation of drug allergy labels. These findings highlight the need for therapeutic options for patients with MDIS and delabeling strategies for patients with multiple comorbidities.

BACKGROUND: Multiple drug intolerance syndrome (MDIS) describes patients with multiple nonimmunologically mediated adverse reactions to medications. Patients with more than 10 medication intolerance labels are considered to have severe MDIS. There is overlap in the characteristics of patients with MDIS and fibromyalgia and irritable bowel syndrome (IBS). Severe MDIS can limit treatment options in this already complex patient group.

OBJECTIVE: This study assessed the prevalence of severe MDIS in patients with fibromyalgia and IBS and its associated risk factors.

METHODS: A retrospective chart review identified patients diagnosed with fibromyalgia or IBS who had been seen at a large academic center from August 2019 to July 2020. Exact birthdate- and sex-matched controls who had been seen within the same time frame were selected at random. Listed drug intolerance data and patient characteristics were then analyzed with logistic regression and χ^2 testing.

RESULTS: Patients with fibromyalgia and IBS were 12 and 3 times more likely to have severe MDIS compared with controls, respectively. Severe MDIS was associated with polypharmacy in both groups. Opiates were the most frequently reported drug intolerance across all participants. Although patients with IBS more often reported gastrointestinal symptoms as adverse reactions, individuals with fibromyalgia did not more frequently report pain or behavioral changes as adverse reactions.

CONCLUSIONS: There was an increased rate of severe MDIS in patients diagnosed with fibromyalgia and IBS. Additional studies are needed to better understand the morbidity of MDIS and how it can best be managed in patients with fibromyalgia and IBS. **(J Allergy Clin Immunol Pract 2024;■:■-■)**

Key words: *Fibromyalgia; Irritable bowel syndrome; Multiple drug intolerance; Medication; Drug allergy label; Delabel*

Multiple drug intolerance syndrome (MDIS) is defined as having nonimmunologic adverse reactions to 3 or more unrelated medications classes.[1,2] This can complicate treatment options for complex patients and strain physician-patient relationships. In the general population, MDIS is estimated to afflict 2% to 6% of individuals and has been related to increased health care utilization and lower quality of life.[1-3] An elevated risk of MDIS has been associated with increasing age, number of comorbid diseases, female sex, polypharmacy, anxiety, depression, and somatization symptoms.[1,2,4,5] Severe MDIS (S-MDIS) has been defined as having 10 or more unique drug allergy labels that span 4 or more medication categories.[1]

There are several similarities between patients with MDIS, fibromyalgia, and irritable bowel syndrome (IBS) including higher rates of anxiety, depression, and lower quality of life.[6-9] Like MDIS, fibromyalgia and IBS populations have been associated with polypharmacy[10,11] and increased health care utilization.[12-14] Both IBS and fibromyalgia are functional somatic disorders that cannot be explained by a structural pathology. Functional somatic disorders are thought to be driven by the

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Abbreviations used
CCI- Charlson Comorbidity Index
IBS- Irritable bowel syndrome
ICD-10- International Classification of Diseases, 10th Revision
MDIS- Multiple drug intolerance syndrome
NSAID- Nonsteroidal anti-inflammatory drug
OR- Odds ratio
S-MDIS- Severe multiple drug intolerance syndrome

central amplification of incoming stimuli to the point that a benign stimulus becomes noxious to patients.[15,16] As such, it seems possible that these patients may also have amplification of side effects and intolerances to medications.

Although there are often anecdotal associations between fibromyalgia, IBS, and MDIS, the prevalence of MDIS has not been well defined in these populations. To address this dearth in the literature, the present study sought to assess the relationship between fibromyalgia, IBS, and MDIS. We hypothesized that there would be a higher prevalence of MDIS in patients diagnosed with fibromyalgia or IBS. Furthermore, we hypothesized that the listed drug allergy labels in patients with fibromyalgia and IBS would be associated with the symptomatology of their underlying disorder.

METHODS

Sample selection

A chart review was performed evaluating the 756,741 patients seen at a tertiary care academic center from August 2019 to July 2020. Patients who carried a diagnosis of fibromyalgia and IBS were identified by International Classification of Diseases, 10th Revision (ICD-10) codes M79.7 and K58, respectively; diagnosis of anxiety and depression was based on ICD-10 codes F41 and F32-33, respectively. Patient controls were selected based on matching exact birthdates and sex. Information about demographics (ie, age, sex, race, ethnicity, and marital status), drug allergy labels, and comorbid conditions was extracted from the chart. This study was approved by the institutional review board at the University of Texas Southwestern Medical Center.

Study variables

Most drug allergy labels in electronic medical records are related to drug intolerances rather than hypersensitivity reactions; however, they are indicated in the "allergy" field of a patient's chart. Thus, the term "drug allergy label" will be used to indicate medications listed in this field. In the present study, polypharmacy was defined as having 15 or more medications listed as "active" in the patient's chart. Although the definition of polypharmacy varies,[17-19] this criterion was used based on the average number of medications across all groups. Frequent health care utilization was defined as having 10 or more visits within the last year including inpatient admission, emergency department, outpatient clinic, and virtual visits. The Charlson Comorbidity Index (CCI) predicts 10-year survival in patients based on underlying medical conditions[20] and was used to estimate comorbid disease burden. For use in analyses, the CCI was dichotomized such that $0 = \text{CCI} < 4$ and $1 = \text{CCI} \geq 4$. A score of 4 was selected as a clinically relevant cut point as it predicts a 53% 10-year survival.[20] This score was part of the extracted medical record data.

To compare drug allergy labels and listed reactions, the control groups for both fibromyalgia and IBS were combined into a single group. A manual review of all items in the drug allergy history was completed to categorize medication classes and reactions. This involved reviewing 16,789 listed allergy labels and reaction entries to remove various nonmedication items and duplicates. Compound medications were broken into their parts and subsequently catalogued. Similarly, if multiple reactions were listed, each reaction was categorized such that a patient may have more than 1 reaction per medication. As described previously,[1] patients with 10 or more unique drug allergy labels were considered to have S-MDIS. These reactions were not verified through patient history or further chart review. These drug allergy labels can encompass both medication intolerances and true immunologically mediated hypersensitivity reactions. As patients categorized as having S-MDIS had 10 or more drug allergy labels, it would be extremely unlikely that these were truly immunologically mediated drug hypersensitivity reactions.[21]

Statistical analyses

Before conducting analyses, patients who identified as Native American, Pacific Islander, multiracial, and "other" were combined into 1 "other" race category. To determine differences between both the fibromyalgia and IBS cohorts and their respective control groups on categorical demographic and clinical outcomes, including reported drug allergy labels, a series of χ^2 analyses were performed. Where significantly different group proportions were found, a *post hoc* analysis was conducted using the z statistic for proportions; P values were Bonferroni corrected to maintain a family wise error rate of $\alpha_{FWE} = 0.05$. For continuous demographic and clinical outcomes, an independent samples t-test was conducted. To examine the effects of demographic (ie, age, sex, race, ethnicity, and marital status) and clinical (ie, fibromyalgia/IBS, anxiety diagnosis, depression diagnosis, polypharmacy, number of visits, and CCI) characteristics on the likelihood of having S-MDIS (yes/no), a binary logistic regression analysis was conducted separately in both the fibromyalgia and IBS cohorts. Additional sensitivity (binary logistic regression) analyses were conducted to determine whether those with both fibromyalgia and IBS had a higher rate of S-MDIS relative to their respective control group as well as to those with only fibromyalgia or only IBS. The clinical group was dummy coded with (a) the control group serving as the reference category and (b) those with only fibromyalgia/IBS as the reference category. Finally, to determine whether polypharmacy and/or CCI moderate the relationship between (1) fibromyalgia (vs comparisons) and S-MDIS and (2) IBS (vs comparisons) and S-MDIS, binary logistic regression analyses were repeated with the inclusion of fibromyalgia × CCI and fibromyalgia × polypharmacy interaction terms for the fibromyalgia cohort and IBS × CCI and IBS × polypharmacy interaction terms for the IBS cohort. All statistical analyses were performed using IBM SPSS Statistics for Windows (released 2020, version 27.0; IBM Corp, Armonk, NY). Results were deemed statistically significant at $P \leq .05$.

RESULTS

S-MDIS in fibromyalgia

A total of 1,479 patients with fibromyalgia were identified during the chart review, all of whom were included in the fibromyalgia cohort. Patients with fibromyalgia were 55 years old, on average, and primarily female (95.5%). They identified entirely as non-Hispanic, whereas approximately 10% of the control group identified as Hispanic ($\chi^2[1] = 131.21$, $P \leq .001$).

TABLE I. Characteristics of fibromyalgia cohort with control group comparisons

	Fibromyalgia (n = 1479)	Control (n = 1463)	Statistical comparisons		
Characteristic	**Mean ± SD**	**Mean ± SD**	***df***	***t***	***P***
Age	55.00 ± 14.56	55.09 ± 14.40	2940	0.17	.864
CCI	2.29 ± 2.39	1.50 ± 2.20	2924.52	−9.28	<.001
No. of drug allergy labels	3.30 ± 4.68	1.23 ± 1.95	1980.27	−15.74	<.001
No. of medications	16.14 ± 9.03	8.59 ± 6.84	2746.00	−25.57	<.001
No. of visits	6.18 ± 7.76	2.57 ± 4.18	2273.86	−15.70	<.001
No. on problems list	15.25 ± 12.93	7.55 ± 8.16	2265.82	−17.95	<.001
	n (%)	**n (%)**	***df***	χ^2	***P***
Sex					
Female	1397 (95.5)	1411 (95.4)	1	0.01	.930
Male	66 (4.5)	68 (4.6)			
Race*					
White	903 (80.1)	882 (74.8)	3	76.08	<.001
Black	165 (14.6)	211 (17.9)			
Asian	13 (1.2)	77 (6.5)			
Other	47 (2.0)	9 (0.8)			
Ethnicity*					
Non-Hispanic	993 (100.0)	1090 (87.7)	1	131.21	<.001
Hispanic	0 (0.0)	153 (12.3)			
Marital Status*					
Married	763 (60.5)	766 (60.4)	2	0.10	.950
Divorced/single	383 (30.3)	381 (30.0)			
Other	116 (9.2)	121 (9.5)			
Anxiety (yes)	332 (22.4)	112 (7.7)	1	125.59	<.001
Depression (yes)	385 (26.0)	105 (7.2)	1	188.34	<.001
IBS (yes)	69 (4.7)	0 (0.0)	1	69.89	<.001
Severe MDIS	105 (7.1)	10 (0.7)	1	80.60	<.001

CCI, Charlson Comorbidity Index; *df*, degrees of freedom; *IBS*, irritable bowel syndrome; *MDIS*, multiple drug intolerance syndrome; *SD*, standard deviation.
*Indicates 31.6%, 21.6%, and 18.4% missingness for race, ethnicity, and marital status, respectively. Fisher's exact test used when the expected cell count <5.

Most participants identified as White (80.1% vs 74.8%) in both the fibromyalgia and control groups, respectively, followed by Black (14.6% vs 17.9%) and Asian (1.2% vs 6.5%); although small, these differences were significant ($\chi^2[3] = 76.08$, $P < .001$). In comparison with the control group, the fibromyalgia group also had a significantly higher proportion of patients with anxiety (22.4% vs 7.7%; $\chi^2[1] = 125.59$, $P \leq .001$) and depression (26.0% vs 7.2%; $\chi^2[1] = 188.34$, $P \leq .001$), as well as IBS (4.7% vs 0%; $\chi^2[1] = 69.89$, $P \leq .001$).

On average, those with fibromyalgia had approximately twice the number of listed medications than that for controls ($M_{\text{fibromyalgia}} = 16.14 \pm 9.03$, $M_{\text{control}} = 8.59 \pm 6.84$; $t[2746] = -25.57$, $P \leq .001$), as well as the number of diagnoses on the patient's "problem list" ($M_{\text{fibromyalgia}} = 15.25 \pm 12.93$, $M_{\text{control}} = 7.55 \pm 8.16$; $t[2266] = -17.95$, $P \leq .001$). The fibromyalgia group also had significantly more visits ($M_{\text{fibromyalgia}} = 6.18 \pm 7.76$, $M_{\text{control}} = 2.57 \pm 4.18$; $t[2274] = -15.70$, $P \leq .001$) and higher CCI values ($M_{\text{fibromyalgia}} = 2.29 \pm 2.39$, $M_{\text{control}} = 1.50 \pm 2.20$; $t[2925] = -9.28$, $P \leq .001$) compared with healthy controls, on average. In addition, the number of drug allergy labels was higher, on average, in the fibromyalgia group in comparison with that in the control group ($M_{\text{fibromyalgia}} = 3.30 \pm 4.68$, $M_{\text{control}} = 1.23 \pm 1.95$; $t[1980] = -15.74$, $P \leq .001$). Demographic and clinical characteristics for the fibromyalgia and control cohorts are provided in Table I.

Further, of the 1,479 patients with fibromyalgia, 7.1% met criteria for S-MDIS, in contrast to only 0.7% of control patients meeting these criteria. Those with ≥10 drug allergy labels ($n_{\text{fibromyalgia}} = 92$, $n_{\text{control}} = 10$) had an overall average of 15.28 ± 7.07 drug allergy labels ($M_{\text{fibromyalgia}} = 15.37 \pm 7.32$, $M_{\text{control}} = 14.50 \pm 4.25$; $t[100] = -0.368$, $P = .714$), spanning 8.04 ± 2.21 drug allergy classes, on average ($M_{\text{fibromyalgia}} = 7.99 \pm 2.23$, $M_{\text{control}} = 8.50 \pm 2.01$; $t[100] = 0.693$, $P = .490$) (Figure 1). After statistical analysis was completed, a singular patient with over 10 drug allergy labels in the fibromyalgia group was found to have only 3 medication allergy classes.

To assess the effect of demographic and clinical characteristics on S-MDIS, a binary logistic regression analysis was conducted in which S-MDIS (yes/no) was specified as the outcome. Results suggested significant effects of fibromyalgia (B = 2.50, $P < .001$; odds ratio [OR] = 12.14, 95% confidence interval [5.36-27.47]), polypharmacy (B = 1.08, $P < .001$; OR = 2.95 [1.56-5.59]), and CCI (B = 0.66, $P = .021$; OR = 1.93 [1.11-3.38]). That is, those with fibromyalgia have a much higher likelihood of experiencing S-MDIS than do their healthy control counterparts, which can be expected to increase as polypharmacy scores and CCI values increase, on average. Although nonsignificant, both increasing age and married status tended to be associated with S-MDIS. There was no significant association between anxiety, depression, or health care utilization and the likelihood of experiencing S-MDIS. Results from the binary

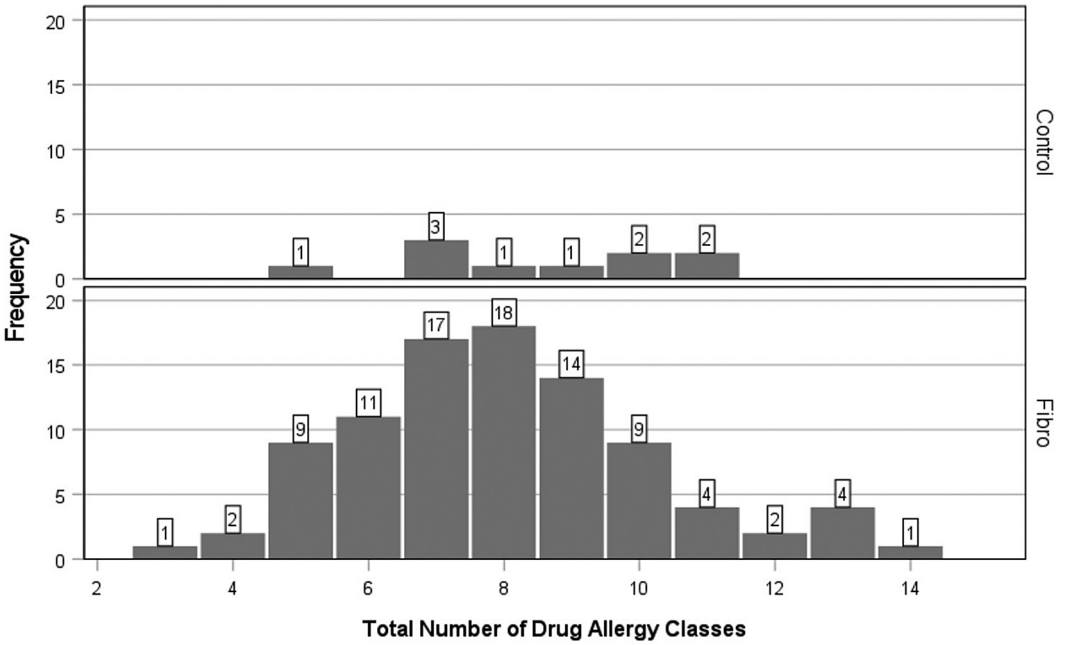

FIGURE 1. Frequency of the total number of drug allergy classes by clinical group in the fibromyalgia cohort. *Fibro*, Fibromyalgia.

logistic regression conducted in the fibromyalgia cohort are presented in Table II. Results from the binary logistic regression (sensitivity) analysis in which the rate of S-MDIS for those with both fibromyalgia and IBS was contrasted to both the control group and those with only fibromyalgia revealed a significantly higher rate of S-MDIS in those with both fibromyalgia and IBS relative to the control group (B = 2.52, $P < .001$; OR = 12.41 [5.49, 28.04]) but not relative to those with only fibromyalgia (B = 0.49, $P = .269$; OR = 1.63 [0.68, 3.91]).

Results from the binary logistic regression analysis in which a fibromyalgia × CCI interaction term was included revealed significant effects for polypharmacy (B = 1.10, $P < .001$; OR = 3.00 [1.59, 5.69]), marital status (B = 0.57, $P = .041$; OR = 1.76 [1.02, 3.04]), and fibromyalgia (B = 2.61, $P < .001$; OR = 13.64 [4.49, 41.46]). The fibromyalgia × CCI interaction effect, however, was nonsignificant. Finally, results from the binary logistic regression analysis in which a fibromyalgia × polypharmacy interaction term was included similarly revealed significant effects for fibromyalgia (B = 4.64, $P < .001$; OR = 102.99 [11.10, 955.97]) and polypharmacy (B = 0.19, $P < .001$; OR = 1.21 [1.11, 1.32]). The main effect for age was also found to be significant (B = 0.02, $P = .032$; OR = 1.02 [1.00, 1.04]); however, CCI was nonsignificant. Lastly, the fibromyalgia × polypharmacy interaction term was significant (B = −0.14, $P = .002$; OR = 0.87 [0.79, 0.95]), indicating that the magnitude of the relationship between fibromyalgia and S-MDIS decreases on average, as one's polypharmacy value increases.

TABLE II. Binary logistic regression with S-MDIS as an outcome (fibromyalgia cohort)

Variable	B	*P*	Odds ratio (95% CI)
Fibromyalgia	**2.50**	**<.001**	**12.14 (5.36-27.47)**
Anxiety	0.36	.229	1.43 (0.80-2.58)
Depression	−0.03	.915	0.97 (0.53-1.77)
Polypharmacy*	**1.08**	**<.001**	**2.95 (1.56-5.59)**
Health care utilization	0.55	.066	1.73 (0.97-3.08)
CCI	**0.66**	**.021**	**1.93 (1.11-3.38)**
IBS	0.41	.357	1.51 (0.63-3.61)
Age	0.02	.062	1.02 (1.00-1.04)
Sex (female)	0.52	.495	1.68 (0.38-7.45)
Race (Black)†	−0.35	.330	0.70 (0.35-1.43)
Race (Asian)†	−0.09	.905	0.91 (0.20-4.20)
Ethnicity (Hispanic)	0.65	.547	1.92 (0.23-16.07)
Marital status (married)	0.54	.051	1.72 (1.00-2.95)

CCI, Charlson Comorbidity Index; *CI*, Confidence interval; *IBS*, irritable bowel syndrome; *S-MDIS*, severe multiple drug intolerance syndrome.
Values with $P < .05$ are bolded.
*Polypharmacy was defined as 15+ listed medications; increased health care use was defined as 10+ health care visits.
†Reference category for race is "White."

S-MDIS in irritable bowel syndrome

Evaluation of the electronic health record identified 1,195 patients with IBS—all of whom comprised the IBS cohort. The IBS cohort did not include anyone who identified as Hispanic, whereas 11.6% of those in the control group identified as Hispanic ($\chi^2[1] = 121.57$, $P \leq .001$). Significant differences between the groups on race were similarly noted, with the IBS group having more patients who identified as White (82.5% vs 79.1%). The control group had a higher proportion of patients who identified as Black (14.6% vs 11.1%) and Asian (5.9% vs 2.9%) ($\chi^2[3] = 39.13$, $P \leq .001$). There was a significantly larger proportion of IBS patients with depression (25.4% vs 8.3%; $\chi^2[1] = 121.73$, $P \leq .001$), anxiety (31.1% vs 7.5%; $\chi^2[1] = 211.09$, $P \leq .001$), and fibromyalgia (5.8% vs 0%; $\chi^2[1] = 69.35$, $P \leq .001$) in comparison with healthy controls.

On average, patients with IBS had almost triple the number of health care visits in the preceding year ($M_{IBS} = 8.22 \pm 9.40$,

TABLE III. Characteristics of IBS cohort with control group comparisons

	IBS (n = 1195)	Control (n = 1166)	Statistical comparisons		
Characteristic	**Mean ± SD**	**Mean ± SD**	***df***	***t***	***P***
Age	56.18 ± 18.04	55.81 ± 18.04	2359	−0.50	.617
CCI	2.49 ± 2.86	1.69 ± 2.34	2290.11	−7.46	<.001
No. of drug allergy labels	2.77 ± 3.67	1.32 ± 2.69	2191.30	−11.00	<.001
No. of medications	13.41 ± 8.28	8.49 ± 6.72	2273.93	−15.83	<.001
No. of visits	8.22 ± 9.40	2.54 ± 4.06	1632.45	−-19.13	<.001
No. on problems list	15.91 ± 13.53	7.54 ± 8.12	1869.72	−17.22	<.001
	n (%)	**n (%)**	***df***	χ^2	***P***
Sex					
Female	950 (79.6)	931 (79.8)	1	0.03	.878
Male	244 (20.4)	235 (20.2)			
Race*					
White	884 (82.5)	742 (79.1)	3	39.13	<.001
Black	119 (11.1)	137 (14.6)			
Asian	31 (2.9)	55 (5.9)			
Other	38 (3.5)	4 (0.4)			
Ethnicity*					
Non-Hispanic	991 (100.0)	888 (88.4)	1	121.57	<.001
Hispanic	0 (0.0)	116 (11.6)			
Marital status*					
Married	650 (57.6)	571 (55.9)	2	1.30	.523
Divorced/single	374 (33.1)	342 (33.5)			
Other	105 (9.3)	109 (10.7)			
Anxiety (yes)	372 (31.1)	87 (7.5)	1	211.09	<.001
Depression (yes)	303 (25.4)	97 (8.3)	1	121.73	<.001
Fibromyalgia (yes)	69 (5.8)	0 (0.0)	1	69.35	<.001
Severe MDIS	13 (1.1)	66 (5.5)	1	38.15	<.001

CI, Confidence interval; *df*, degrees of freedom; *CCI*, Charlson Comorbidity Index; *IBS*, irritable bowel syndrome; *MDIS*, multiple drug intolerance syndrome.
*Indicates 14.9%, 15.5%, and 8.9% missingness for race, ethnicity, and marital status, respectively. Fisher's exact test used when expected cell count <5.

$M_{control} = 2.54 \pm 4.06$; $t[1632] = -19.13$, $P \leq .001$) and more than double the number of listed diagnoses on the "problem list" ($M_{IBS} = 15.91 \pm 13.53$, $M_{control} = 7.54 \pm 8.12$; $t[1870] = -17.22$, $P \leq .001$) as compared with the control group. The IBS group had a significantly higher number of drug allergy labels in comparison with healthy controls ($M_{IBS} = 2.77 \pm 3.67$, $M_{control} = 1.32 \pm 2.69$; $t[2191] = -11.00$, $P \leq .001$). Similarly, CCI values ($M_{IBS} = 2.49 \pm 2.86$, $M_{control} = 1.69 \pm 2.34$; $t[2290.11] = -7.46$, $P \leq .001$) and the number of active medications ($M_{IBS} = 13.41 \pm 8.28$; $M_{control} = 8.49 \pm 6.72$; $t[2273.93] = -15.83$, $P \leq .001$) were also higher in the IBS cohort when compared with the control group, on average. Demographic and clinical characteristics for the IBS and control groups are provided in Table III.

Notably, the proportion of S-MDIS was 5 times higher in the IBS group than in the control group (5.5% vs 1.1%). Those with ≥10 drug allergy labels ($n_{IBS} = 58$, $n_{control} = 13$) had an overall average of 14.38 ± 6.59 drug allergy labels ($M_{IBS} = 13.47 \pm 5.01$, $M_{control} = 18.46 \pm 10.58$; $t[13.23] = 1.661$, $P = .120$), spanning 8.00 ± 2.25 drug allergy classes, on average ($M_{IBS} = 7.69 \pm 1.89$, $M_{control} = 9.38 \pm 3.15$; $t[14.00] = 1.866$, $P = .083$) (Figure 2). On review, the individual with only 3 drug classes noted in Figure 2 had several "other medication" allergy labels listed for a total of 5 separate medication classes. Results from a binary logistic regression, in which S-MDIS (yes/no) was specified as the outcome but with the main effect of IBS (yes/no) in the model, suggested significant effects of IBS (B = 1.17, $P = .002$; OR = 3.23 [1.52-6.88]), polypharmacy (B = 0.63, $P = .040$; OR= 1.88 [1.03-4.12]), increased health care utilization (B = 0.79, $P = .012$; OR = 2.21 [1.19-4.11]), age (B = 0.03, $P = .017$; OR = 1.03 [1.00-1.05]), female sex (B = 1.39, $P = .009$; OR = 4.00 [1.41-11.40]), and "married" marital status (B = 1.02, $P = .002$; OR = 2.77 [1.44-5.34]). There was no significant association with anxiety, depression, or CCI scores. Results from the binary logistic regression conducted in the IBS cohort are presented in Table IV. Results from the binary logistic regression (sensitivity) analysis in which the rate of S-MDIS for those with both IBS and fibromyalgia was contrasted to both the control group and those with IBS only revealed a significantly higher rate of S-MDIS relative to the control group (B = 1.19, $P = .040$; OR = 3.28 [1.05, 10.20]) but not relative to those with only IBS (B = 0.55, $P = .243$; OR = 1.73 [0.69, 4.32]).

Results from the binary logistic regression analysis in which an IBS × CCI interaction term was included revealed significant effects for the number of visits (B = 0.68, $P = .029$; OR = 1.98 [1.07, 3.65]), marital status (B = 1.05, $P = .002$; OR = 2.86 [1.48, 5.55]), female sex (B = 1.46, $P = .006$; OR = 4.30 [1.51, 12.28]), and IBS (B = 1.42, $P = .006$; OR = 4.15 [1.50, 11.46]). The IBS × CCI interaction effect, however, was nonsignificant. Results from the regression analysis in which an IBS × polypharmacy interaction effect was included were similar. Significant effects included that for age (B = 0.02,

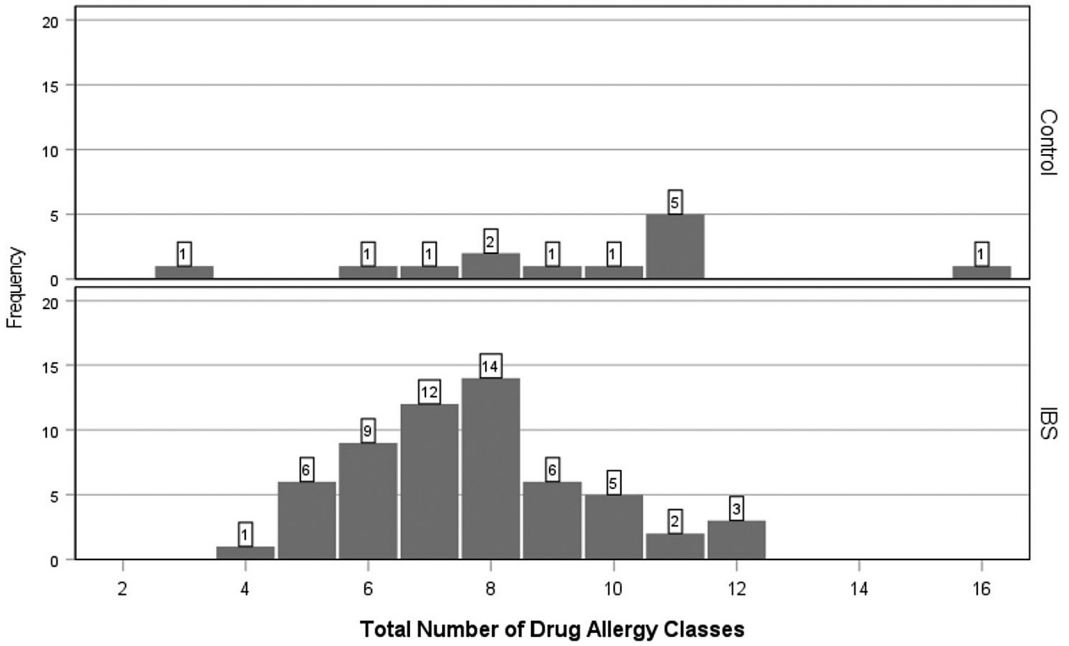

FIGURE 2. Frequency of the total number of drug allergy classes by clinical group in the IBS cohort. *IBS*, Irritable bowel syndrome

P = .028; OR = 1.02 [1.00, 1.05]), polypharmacy (B = 0.11, P = .005; OR = 1.11 [1.03, 1.20]), marital status (B = 1.15, P = .001; OR 3.14 [1.58, 6.23]), and female sex (B = 1.50, P = .008; OR = 4.46 [1.49, 13.37]). The IBS × polypharmacy interaction effect was nonsignificant.

Narcotics are the most frequent drug allergy label in fibromyalgia and IBS

Narcotics were the most reported drug allergy label in patients with fibromyalgia and IBS, as well as their matched controls ($\%_{control}$ = 18.0, $\%_{fibromyalgia}$ = 16.8, and $\%_{IBS}$ = 16.7). Narcotics superseded a penicillin allergy label that has been reported as the most common medication allergy in the United States.[22,23] As seen in Figure 3, penicillin, sulfonamides, and nonsteroidal anti-inflammatory drugs (NSAIDs) were the most frequently reported medication allergies after narcotics. Results from a χ^2 analysis found a significant difference in reported drug allergy labels among the IBS, fibromyalgia, and control groups ($\chi^2[72] = 313.75$, $P < .001$). Following this, a *post hoc* analysis was conducted using Bonferroni corrections for multiple comparisons, such that statistical significance was evaluated at $P <$ .001. Although penicillin allergy was the second most frequently reported allergy label across all 3 groups, it was more frequently reported in the control group ($\%_{control}$ = 12.55, $\%_{fibromyalgia}$ = 7.98, and $\%_{IBS}$ = 9.20). Patients with fibromyalgia were more likely to report an adverse reaction to sulfonamides compared with controls ($\%_{control}$ = 10.29, $\%_{fibromyalgia}$ = 7.91, and $\%_{IBS}$ = 9.23) and more likely to report an NSAID allergy than patients with IBS ($\%_{control}$ = 6.41, $\%_{fibromyalgia}$ = 7.42, and $\%_{IBS}$ = 5.49). Both IBS and fibromyalgia groups were more likely to report an allergy to antidepressants and antipsychotics than controls ($\%_{control}$ = 2.57, $\%_{fibromyalgia}$ = 5.52, and $\%_{IBS}$ = 4.34). Medications for gastrointestinal symptom management were more often reported by the IBS group than controls ($\%_{control}$ = 1.74, $\%_{fibromyalgia}$ = 2.41, and $\%_{IBS}$ = 3.15). This can be seen in further detail in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org).

TABLE IV. Results from binary logistic regression with S-MDIS as an outcome (IBS cohort)

Variable	B	*P*	Odds ratio (95% CI)
IBS	**1.17**	**.002**	**3.23 (1.52-6.88)**
Anxiety	0.32	.321	1.38 (0.73-2.60)
Depression	0.41	.210	1.51 (0.79-2.87)
Polypharmacy*	**0.63**	**.040**	**1.88 (1.03-3.43)**
Health care utilization	**0.79**	**.012**	**2.21 (1.19-4.11)**
CCI	0.10	.738	1.11 (0.60-2.05)
Fibromyalgia	0.67	.136	1.96 (0.81-4.73)
Age	**0.03**	**.017**	**1.03 (1.00-1.05)**
Sex (female)	**1.39**	**.009**	**4.00 (1.41-11.40)**
Race (Black)†	−0.26	.574	0.77 (0.31-1.92)
Race (Asian)†	−0.91	.381	0.40 (0.05-3.07)
Ethnicity (Hispanic)	−16.47	.997	0.00 (−)
Marital status (married)	**1.02**	**.002**	**2.77 (1.44-5.34)**

Values with $P < 0.05$ are bolded.
CCI, Charlson Comorbidity Index; *CI*, confidence interval; *IBS*, irritable bowel syndrome; *S-MDIS*, severe multiple drug intolerance syndrome.
*Polypharmacy was defined as 15+ listed medications; increased health care use was defined as 10+ health care visits.
†Reference category for race is "White."

Rash and hives were the most frequently reported reactions attributed to drug allergy labels among all 3 cohorts, followed by gastrointestinal symptoms and itching. As seen in Figure 4, these 3 symptoms encompassed approximately 60% of all reported reactions. Results from a χ^2 analysis found a statistically significant difference in reported reaction characteristics between the IBS, fibromyalgia, and control groups

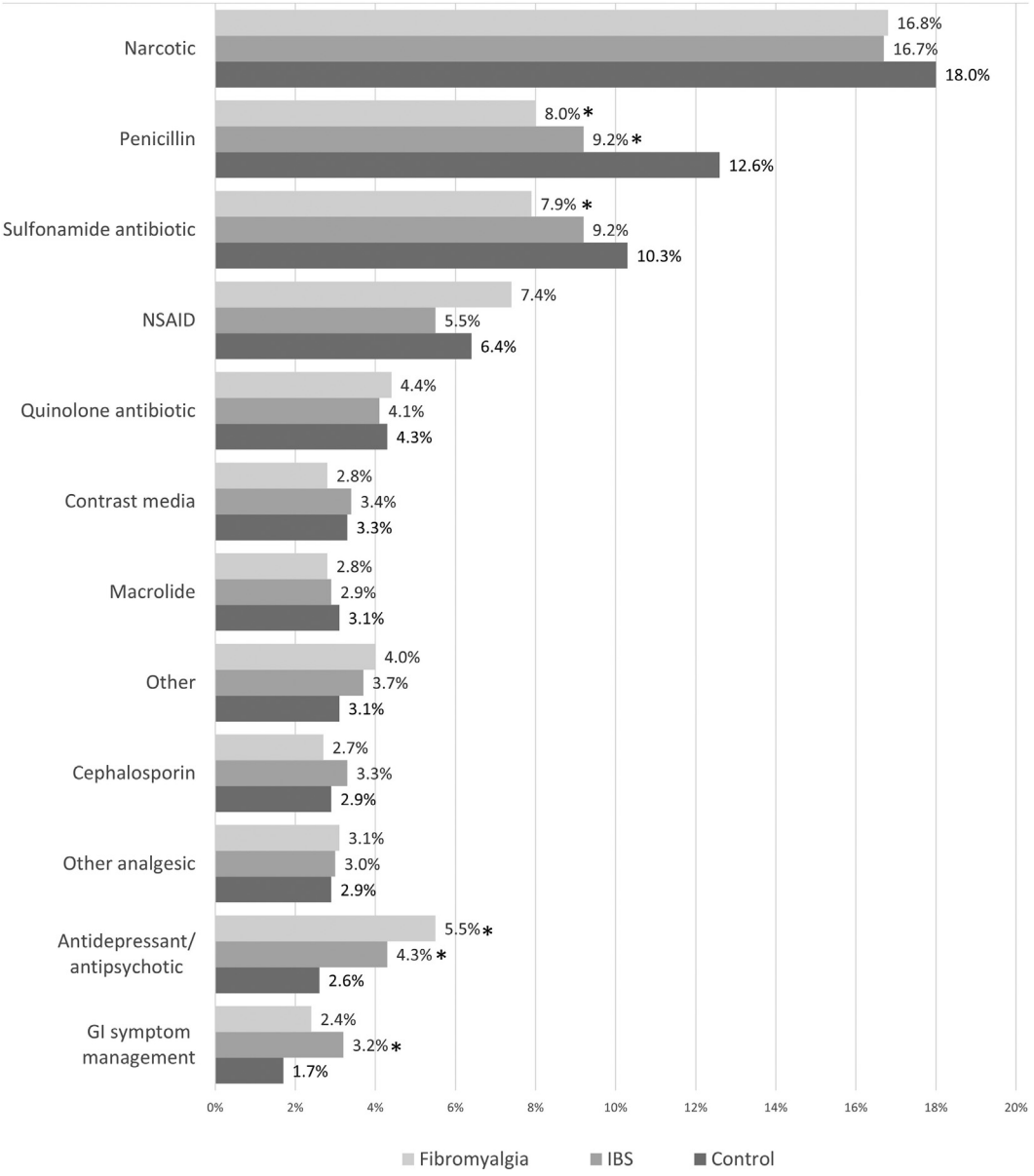

FIGURE 3. Drug allergy labels in patients with fibromyalgia and IBS, and controls. Percentages were calculated by comparing the number of patients with the reported symptoms by the total number of subjects in that cohort. *Indicates a statistically significant difference from the control group at a level of $P < .05$. †Indicates a statistically significant difference between cohort groups at a level of $P < .05$. *GI*, Gastrointestinal; *IBS*, irritable bowel syndrome; *NSAID*, nonsteroidal anti-inflammatory drug.

($\chi^2[20] = 117.43$, $P < .001$). Following this, a *post hoc* analysis was conducted using Bonferroni corrections for multiple comparisons, such that statistical significance was evaluated at $P < .001$. Healthy controls more often reported rash and hives than either cohort group ($\%_{control} = 35.24$, $\%_{fibromyalgia} = 28.21$, and $\%_{IBS} = 28.40$). Patients with IBS more often reported gastrointestinal symptoms as an adverse reaction ($\%_{control} = 18.60$, $\%_{fibromyalgia} = 20.72$, and $\%_{IBS} = 21.97$) when compared with the control group. The IBS cohort also reported cough and shortness of breath with less frequency than controls ($\%_{control} = 5.03$, $\%_{fibromyalgia} = 4.58$, and $\%_{IBS} = 3.57$). Patients with fibromyalgia did not report behavioral changes ($\%_{control} = 3.97$, $\%_{fibromyalgia} = 4.92$, and $\%_{IBS} = 5.09$) or muscle/joint pains ($\%_{control} = 2.71$, $\%_{fibromyalgia} = 3.56$, and $\%_{IBS} = 2.72$) at a higher frequency than controls or patients with IBS. Patients with fibromyalgia less often reported swelling and angioedema than patients with IBS or controls ($\%_{control} = 7.71$, $\%_{fibromyalgia} = 5.47$, and $\%_{IBS} = 7.61$) and more often reported itching than patients with IBS ($\%_{control} = 10.62$, $\%_{fibromyalgia} = 11.29$, and $\%_{IBS} = 9.20$). As compared with controls, the fibromyalgia cohort reported headache more frequently ($\%_{control} = 2.26$, $\%_{fibromyalgia} = 3.50$, and $\%_{IBS} = 3.18$). Both IBS and fibromyalgia groups more often reported "other" free text reactions that were difficult to categorize.

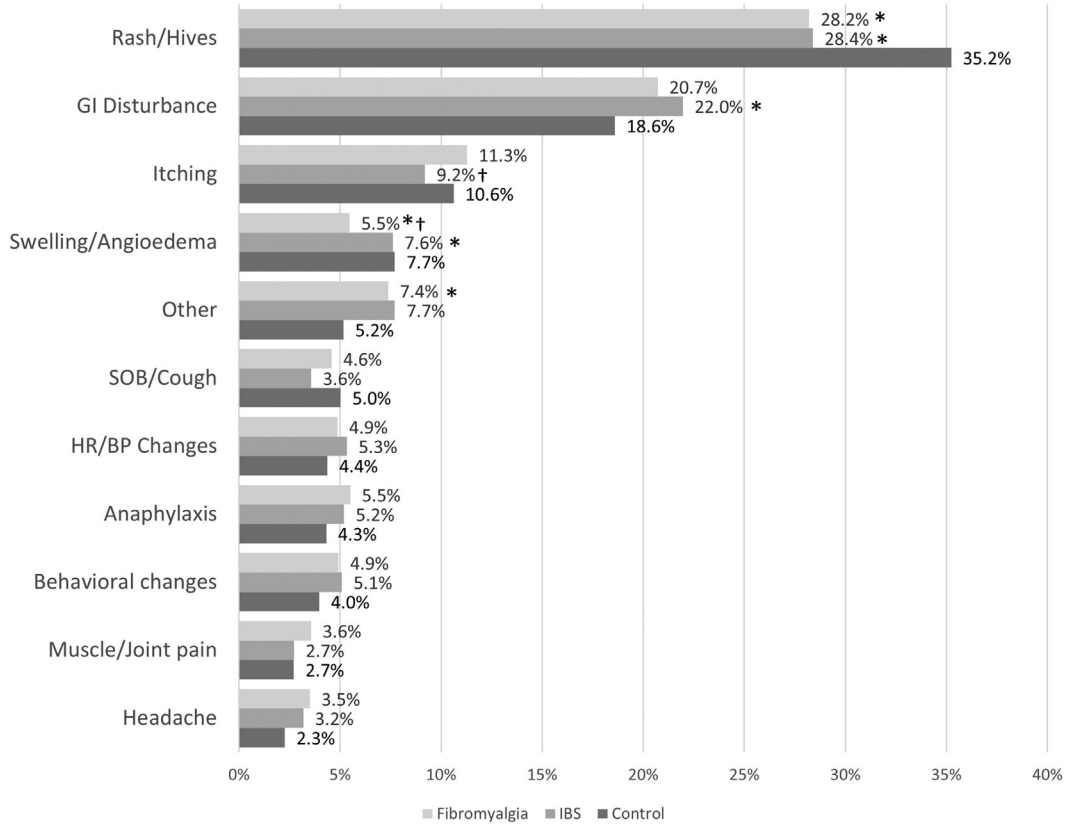

FIGURE 4. Reaction characteristics in drug allergy labels of fibromyalgia, IBS, and controls. Percentages were calculated by comparing the number of patients with the reported symptoms by the total number of subjects in that cohort. *Indicates a statistically significant difference from the control group at a level of $P < .05$. †Indicates a statistically significant difference between cohort groups at a level of $P < .05$. *BP,* Blood pressure; *GI*: gastrointestinal; *HR*, heart rate; *IBS*, irritable bowel syndrome; *SOB*, shortness of breath.

These results can be seen in detail in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This study evaluated the prevalence of S-MDIS in those with fibromyalgia and IBS. Patients with fibromyalgia and IBS were found to be approximately 12 and 3 times more likely to have S-MDIS, respectively, than age- and sex-matched control patients without these disorders. Consistent with previous evaluations of MDIS,[1,3] polypharmacy was associated with increased risk of MDIS in both groups. It may be that the heightened exposure to medications in both fibromyalgia and IBS increases the likelihood of having an adverse reaction, similar to the positive effect of age on S-MDIS found in the IBS cohort. Alternatively, it is also possible that a patient's numerous medication intolerances require physicians to work around these limitations by prescribing multiple, less effective medications.

Despite the clinical overlap of fibromyalgia and IBS, these patient groups had distinct variables associated with S-MDIS. An elevated CCI value has previously been associated with S-MDIS.[2] However, in the present study, a significant effect of CCI on S-MDIS was found only in the fibromyalgia group. It is unclear if this represents a subgroup of particularly complex patients or if S-MDIS plays a role in the increased burden of comorbid disease. Although both fibromyalgia and IBS are known to coexist with other organic diseases, IBS has not been associated with increased mortality.[6,24] In this analysis, elevated CCI was not a statistically significant factor in the IBS group. Further evaluation is needed to understand this discrepancy and its clinical relevance.

It is well documented that there are higher rates of anxiety and depression in patients with fibromyalgia[16,25-28] and IBS[6,7,29] as compared with healthy controls. The findings in the present study are consistent with these prior findings, albeit at the lower range of documented prevalence rates in the fibromyalgia cohort. Further, the prevalence of anxiety and depression in the control group was consistent with that for the general population.[30,31] Although anxiety and depression had a significant association with S-MDIS in both cohorts during the initial χ^2 analyses, this relationship was not present after accounting for additional demographic and clinical factors in the logistic regression analyses. This is contrary to previous studies[1,2,4] but suggests that fibromyalgia and IBS may pose as confounding variables in the evaluation of patients with MDIS.

The majority of patients in the present fibromyalgia cohort were female (95%), which is slightly higher than population estimates,[26] but consistent with other studies focusing on fibromyalgia diagnosed at academic medical centers.[32,33] This may reflect the use of outdated diagnostic criteria that favored the diagnosis in females.[34] Similarly, there was a large percentage of female patients with IBS, consistent with previously

described sex ratios.[35] MDIS has been associated with White race[2] and female sex.[1-3] Despite the variability in race and ethnicity between the cohort and control groups, limited US data suggest equal prevalence of fibromyalgia and IBS across ethnic groups and lower prevalence among Asian populations.[26,36,37] This may reflect the unreported demographic data in the sampled population of this study. MDIS was previously found to be associated with a marital status other than married.[2,4] In the present IBS cohort, marriage was associated with an increased risk of S-MDIS, although this relationship was nonsignificant in the fibromyalgia cohort. Although marriage can, in theory, provide social support, it may also be a source of stress for these patients. These findings, while discrepant from previous studies, may reflect regional variability in marriage rates or associated social expectations.

The high prevalence of a narcotic allergy label was an unexpected finding. This may reflect increased use of narcotics in the US population. Compared with other countries, US patients report higher rates of pain, and providers prescribe opioids more frequently.[38] However, patient perception of opioids, including fear of addiction,[39] may heighten sensitivity to the expected side effects of these medications. Narcotics are often associated with many intolerances and pseudoallergic reactions, and true IgE-mediated hypersensitivity is rare.[40] The rarity of true immunologically mediated hypersensitivity to opioids is not lost on providers. A review found that narcotic allergy alerts were the most commonly overridden drug allergy alerts in a Boston-based medical system.[41]

Antidepressants and antipsychotics were the fifth most reported drug allergy label for both IBS and fibromyalgia cohorts compared with the tenth most reported in healthy controls. This may represent an increased exposure to these medications as therapies for underlying IBS, fibromyalgia, or comorbid anxiety and depression. Adverse reactions to antidepressants and antipsychotics can range from intolerance symptoms, biochemical phenomenon, and, less commonly, hypersensitivity reactions.[42,43] Rates of adverse reactions tend to increase with polypharmacy.[44] However, for these patients, adjusting treatment regimens to minimize adverse reactions may prove to be challenging. Recent exploration into the genetics of hepatic enzymes may offer new verifiable metrics to personalize the pharmacologic management of psychiatric disorders.[45]

Considering the multiple somatic symptoms associated with IBS and fibromyalgia, we hypothesized that the leading adverse reactions would be consistent with the typical symptoms of the underlying syndrome. This was true in the IBS cohort in which there was a significantly higher rate of reported gastrointestinal symptoms as adverse reactions. However, the fibromyalgia cohort did not more frequently report muscle/joint pain or behavioral changes. Rather, patients with fibromyalgia more often reported itching. Notably, both IBS and fibromyalgia cohorts more often reported "other" atypical symptoms as an adverse reaction. This may represent the subjective nature of the symptoms of both disorders.

There are several limitations to this study. All data were extracted from the electronic health record by a chart review and were limited by the use of diagnostic codes. Furthermore, it was outside of the scope of this study to verify the diagnosis of fibromyalgia and IBS with the most updated guidelines. In addition, the study design precluded the investigators' ability to distinguish true immunologically mediated hypersensitivity drug reactions from medication intolerances. The subjective nature of medication intolerances in general poses a barrier to confirming these reactions through a chart review alone. As this study was completed at an academic medical center, it may reflect a more complex patient population with possibly more severe comorbid illnesses than those seen in the community setting. In addition, part of these data were collected during the COVID-19 pandemic, the impact of which is unclear.

Further evaluation is needed to understand which patients with fibromyalgia or IBS are at risk of developing MDIS and whether this can be prevented, possibly by reducing polypharmacy. Currently, there is no definitive management for patients with MDIS. However, targeted delabeling strategies may be helpful for such patients. Future longitudinal studies can help understand if the treatment of underlying fibromyalgia or IBS, if present, can reduce the burden of MDIS.

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