Impaired Gastric Emptying in Primary Sjögren's Syndrome

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ABSTRACT. ***Objective.*** To investigate the prevalence of impaired gastric emptying (IGE) and its relation to autonomic nervous dysfunction (AD), functional bowel syndrome, and inflammatory and serological variables in patients with primary Sjögren's syndrome (pSS).

Methods. Twenty-eight patients with pSS according to the American-European Consensus Criteria were included in the study. Gastric emptying was evaluated by the octanoate breath test from which half-time (t_{half}) and lag-time (t_{lag}) were determined and compared with the results from 50 healthy controls. Autonomic nervous function was evaluated by 5 objective autonomic reflex tests (ART) and by the Autonomic Symptom Profile (ASP) questionnaire evaluating AD symptoms. These results were compared with previously investigated healthy ART controls and population-based ASP controls. Patients were also assessed regarding symptoms of functional bowel syndrome.

Results. The t_{half} and the t_{lag} were significantly prolonged in patients compared to controls. Forty-three percent of patients with pSS presented signs of IGE and 29% fulfilled the criteria for gastroparesis. Significant correlations were found between t_{lag} and increased levels of IgG ($p = 0.02$) and erythrocyte sedimentation rate (ESR; $p = 0.01$). In addition, rheumatoid factor (RF) seropositives showed objective signs of IGE to a greater extent than RF seronegatives. No associations between IGE, ART variables, ASP variables, or gastrointestinal symptoms were found.

Conclusion. IGE was common in pSS. Associations with inflammatory and serological features of pSS could imply immunological mechanisms behind the IGE. Objective signs of IGE were not associated with objective signs or subjective symptoms of AD or functional bowel syndrome. (First Release September 1 2010; J Rheumatol 2010;37:2313–18; doi:10.3899/jrheum.100280)

Key Indexing Terms:
SJÖGREN'S SYNDROME GASTROPARESIS AUTONOMIC NERVOUS SYSTEM DISEASES

Primary Sjögren's syndrome (pSS) is an autoimmune disease mainly affecting exocrine glands, leading to decreased secretion and mucosal dryness. Nevertheless, pSS has also been shown to affect multiple nonexocrine organs such as the nervous system and the gastrointestinal (GI) tract. Studies have found signs of autonomic nervous dysfunction (AD) in pSS[1,2], reminiscent of what has also been reported in other autoimmune diseases such as inflammatory bowel disease[3,4,5,6], rheumatoid arthritis[7], systemic sclerosis (SSc)[8], and systemic lupus erythematosus[9]. Various GI symptoms such as dysphagia, symptoms of gastroparesis, and irritable bowel syndrome (IBS) have been reported to be more common in patients with pSS than in the general population[10,11,12]. Gastroparesis is commonly found in patients with diabetes mellitus[13] and has also been described in patients with hypothyroidism[14]. However, only 1 study has reported objective signs of impaired gastric emptying (IGE) in patients with pSS[15]. Symptoms of IGE and other GI symptoms are frequently encountered in patients with pSS[10,11,12]; our objective was to assess the prevalence of IGE in pSS, using the octanoate breath test, and to study the association of IGE with objective signs and symptoms of AD, symptoms of IBS, and functional dyspepsia (FD), as well as with inflammatory and serological features of pSS. To correlate these associations, all tests were performed in a narrow time range; most were performed the same day and at most within 4 weeks.

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MATERIALS AND METHODS

Study population. Twenty-eight patients with pSS (26 women, median age 62 yrs, range 29–65 yrs) according to the American-European Consensus Criteria[16], from the outpatient clinic at the Department of Rheumatology at Skåne University Hospital, Malmö, Sweden, were included in the study. They were prospectively followed with regard to signs and symptoms of AD[10].

Controls. The octanoate breath test controls consisted of 50 healthy controls recruited among laboratory staff, their relatives, and friends (25 women, median age 43 yrs, range 25–59 yrs). The control group for the deep-breathing test and orthostatic heart rate test consisted of 56 healthy

individuals (22 women, median age 40 yrs, range 16–59 yrs), all of whom had passed a health examination without signs of cardiovascular disease, respiratory disorders, or diabetes mellitus[17]. The controls for the orthostatic blood pressure reaction test consisted of 238 healthy nondiabetic individuals (106 women, median age 60 yrs, range 16–96 yrs)[18]. The finger skin blood flow test controls were 80 healthy subjects (37 women, median age 43 yrs, range 19–81 yrs), all nonsmokers with no history of vascular disease, and were not taking any medication[19].

Octanoate breath test. A standardized omelette was ingested after an overnight fast from 10 PM. The subjects were allowed to drink water until 1 hour before the test. During the test the subjects were in a seated position. The omelette contained 1 normal-size egg, 30 ml flour, 30 ml of 40% fat cream, salt, dill, and 100 μl octanoic acid (Euriso-top, Saint-Aubin, France). The yolk was separated from the white and the octanoic acid was injected into the yolk. The yolk was then baked separately in a microwave oven for 30 s. The egg white, flour, cream, salt, and dill were then added and the omelette was baked for another 2 min in the microwave oven. End-tidal breath samples were obtained before the meal and subsequently every 15 min for the next 4 hours. The test tubes used for breath samples were Labco Exetainer® 12 ml (Labco Limited, High Wycombe, Buckinghamshire, UK). The tubes were then sent to the Department of Clinical Chemistry, Linköping University Hospital, for analysis. The half-time (t_{half}) and lag-time (t_{lag}) for gastric emptying were calculated as described in detail by Ghoos, *et al*[20], whose method was used for the test after slight modifications in accord with instructions from the laboratory where the analysis was conducted. The t_{half} is defined as the time from ingestion of a bolus until 50% of the bolus has been cleared from the stomach. The t_{lag} is the time from ingestion until the bolus is beginning to be cleared from the stomach. Because the t_{half} and t_{lag} were affected by age and sex, these variables were standardized accordingly and expressed as z-scores. Impaired gastric emptying (IGE) was defined as a z-score for t_{half} and/or $t_{lag} \geq 2$ and gastroparesis as a z-score for $t_{half} \geq 2$.

Laboratory tests. Blood samples were taken to assess signs of disease activity in pSS and included analyses of erythrocyte sedimentation rate (ESR), immunoglobulin G (IgG), and complements (C3 and C4). In addition, patients with pSS were tested for presence of rheumatoid factor (RF), antinuclear antibodies (ANA), anti-SSA antibodies, and anti-SSB antibodies. Thyroid-stimulating hormone (TSH), vitamin B12, and p-glucose were also assessed to rule out thyroid disease, B12 deficiency, and diabetes mellitus, respectively. All blood analyses were performed as routine analyses at the Departments of Clinical Chemistry and Immunology, Skåne University Hospital, Malmö and Lund.

Autonomic nerve function tests. The deep-breathing test was done after supine rest for 15 min. The heart rate was monitored by electrocardiogram (ECG) for 4 min and, once constant, 6 maximal expirations and inspirations were performed during a 1-min period. An expiration/inspiration (E/I) ratio was calculated as the mean of the longest R-R intervals during the expirations divided by the mean of the shortest R-R intervals during inspirations[21]. The E/I ratio mainly reflects parasympathetic nervous function[21,22].

For the orthostatic heart rate and blood pressure test, the subject was strapped on a tilt table, kept supine for 10 min, and then within 2 s tilted to an erect position, in which the subject remained for 8 min. ECG was used to monitor heart rate from 1 min before tilt. Systolic and diastolic blood pressures were measured before and every minute after tilt. A mean of the R-R intervals before tilt (A) and the shortest R-R interval after tilt (B) were determined from which an acceleration index, defined as $(A - B)/(A \times 100)$, was calculated[23,24]. The systolic and the diastolic blood pressures before tilt (SBP_{rest} and DBP_{rest}) as well as the lowest systolic and diastolic blood pressures during the first 8 min after tilt (lSBP and lDBP) were determined. Orthostatic SBP and DBP ratios were then calculated:

$$\text{lSBP ratio} = \text{lSBP}/\text{lSBP}_{rest} \text{ and lDBP ratio} = \text{lDBP}/\text{DBP}_{rest}$$

For the finger skin blood flow test, the subject was seated in a semirecumbent position with the left hand on an aluminum holder, situated at heart level and with the middle finger placed in a groove of the holder. The temperature of the aluminum holder was kept stable at 40°C by a Peltier element. The finger skin blood flow was monitored using a laser Doppler imaging device, scanning an area of 2 × 2 cm of the distal phalanx of the third finger. The blood flow was then subsequently monitored every minute for 6 min during the heating procedure (h). The subject then immersed the contralateral hand and forearm into a water bath, kept at a stable temperature of 15°C, and kept it immersed for 3 min. A scan was performed every 30 s during immersion and afterward for another 3 min. Hence the finger skin blood flow of the left hand was monitored during the contralateral cooling procedure (c). By dividing the lowest finger skin blood flow value during the first minute of contralateral cooling (LDIc) by the mean of the last 2 measurements of finger skin blood flow at rest, before the cooling procedure (LDIh), a vasoconstriction (VAC) index could be calculated (VAC index = LDIc/LDIh). This has been shown to be a sensitive test for sympathetic nervous function in the skin[19].

Because autonomic nervous function deteriorates with advancing age, the autonomic nervous function variables were age-corrected and expressed as z-scores by comparison with the 3 control groups. The z-scores were then compared to detect differences between patients with pSS and controls. Because sex does not seem to significantly affect autonomic variables measured in these tests[17,19], data were not matched for sex.

All tests were performed under standardized conditions and stable temperature and subjects were not allowed to eat or drink coffee or smoke prior to testing.

Questionnaire. The self-completed Autonomic Symptom Profile (ASP), assessing AD symptoms, was filled in during the octanoate breath test. The ASP evaluates presence and severity of AD symptoms in various AD domains. Its English original version has been validated in patients with AD of various etiologies[25] for subsequent use in patients with diabetes mellitus[26] as well as pSS[27]. It has also been translated into Swedish and validated in patients with diabetes mellitus[28] and used in patients with pSS[10]. Further, the patients were assessed by a gastroenterologist for the presence of symptoms of IBS and FD, according to the Rome III criteria[29]. The assessment was based on the answers from the ASP.

Statistical analyses. Because the t_{half} and t_{lag} were affected by age and sex, these variables were standardized using a linear regression model into which age and sex were added as covariates and the variables were expressed as z-scores. Z-scores ≥ 2 were considered pathological. Because of a skewed distribution of several variables, the Mann-Whitney U test and Fisher's exact test were used for comparisons between groups and Spearman's rank correlation test for correlations. Results are presented as median [interquartile range (IQR) limits] if not stated otherwise. P values < 0.05 were considered statistically significant.

The study was approved by the ethics committee at Lund University (LU563-2008). All participants gave written informed consent according to the Declaration of Helsinki.

RESULTS

Patient characteristics. None of the 28 patients examined had previously undergone any GI surgery. Six of the patients were taking medication known to affect autonomic nervous function (ß-blockers, n = 1, angiotensin-converting enzyme inhibitors 1, angiotensin II receptor blockers 1, calcium channel blockers 1, pilocarpine 2, diuretics 1), all of which were discontinued 24 hours prior to autonomic nervous function testing and the octanoate breath test. In addition, 2 patients were currently treated with selective serotonin reuptake inhibitors (SSRI), 1 patient with a combination of mirtazapin and pregabalin, 1 patient with prednisolone 5 mg/day, and 3 patients with hydroxychloroquine, none of which were discontinued. Twenty-one percent of the

patients were current smokers. Patients were asked to refrain from smoking 24 hours prior to testing. All patients were nondiabetic and euthyroid. Further patient characteristics are presented in Table 1.

Octanoate breath test and clinical and laboratory associations. In patients with pSS, the age-standardized and sex-standardized t_{half} and t_{lag} were significantly prolonged in comparison to controls. Twenty-nine percent and 43% of patients with pSS had a pathologically prolonged t_{half} and t_{lag}, respectively, in comparison to controls (Table 2), and hence 29% and 43% presented signs of gastroparesis and IGE, respectively. If patients taking SSRI and pregabalin were excluded (medications that were not withheld and which could possibly interfere with gastric motility), the t_{half} and t_{lag} were still significantly prolonged in patients with pSS in comparison to controls ($p = 0.02$ and $p = 0.00$, respectively). Excluding patients taking medication withheld as well as those taking SSRI and pregabalin, the significant increase in t_{lag} remained ($p = 0.02$), while the increase in t_{half} became nonsignificant ($p = 0.14$). Excluding current smokers did not change the significant increase in t_{half} and t_{lag} ($p = 0.02$ and $p = 0.01$, respectively). Although 82% of patients reported various nonexocrine symptoms (Table 1), the presence of these was not associated with signs of IGE (data not shown).

Correlating t_{half} and t_{lag} with inflammatory measurements (ESR, IgG, C3 and C4), t_{lag} was found to correlate significantly with both ESR ($r_s = 0.51$; $p = 0.01$) and IgG ($r_s = 0.43$; $p = 0.02$). In accordance, the ESR and IgG were found to be significantly increased in patients with abnormal t_{lag} in comparison with patients with normal t_{lag} [median IQR 24 (17–34) vs 9 (7–16), $p = 0.03$; and 19.6 (14.1–30.8) vs 15.2 (10.9–18.8), $p = 0.03$, respectively].

Moreover, comparing RF-seropositive with RF-seronegative patients, the former were found to have significantly prolonged t_{half} and t_{lag}. In addition, ANA-seropositive patients showed a nonsignificant tendency toward a prolonged t_{half} and t_{lag} in comparison to ANA-seronegative patients (Table 3).

Octanoate breath test and autonomic nervous function. Patients with pSS were found to have a significantly decreased E/I ratio as well as significantly decreased ratios of lSBP and lDBP in comparison to controls, indicating both parasympathetic and sympathetic dysfunction. Further, patients reported significantly more AD symptoms in comparison to controls, mirrored by significantly increased ASP domain scores as well as an increased ASP total score (Table 4).

However, correlating t_{half} and t_{lag} to the ART and ASP variables, only the lDBP ratio was found to be significantly correlated with t_{lag} ($r_s = –0.47$; $p = 0.01$). Of note, symptoms of gastroparesis were not significantly associated with the t_{half} or t_{lag} (data not shown).

Octanoate breath test and functional bowel symptoms. Thirteen patients (46%) were found to have IBS and 25 (89%) patients to have FD according to the Rome III criteria[29]. However, no significant associations between presence of symptoms of IBS or FD and signs of IGE were found (data not shown).

Table 1. Characteristics of the 28 patients with primary Sjögren's syndrome participating in the study. Results are presented as median (IQR) or percentage with abnormal findings.

Characteristic	
Age, yrs	62 (44, 63)
Men/women	2/26
Disease duration, yrs	16 (12, 26)
IgG, g/l	16.7 (11.5, 20.7)
C3, g/l	1.08 (0.87, 1.28)
C4, g/l	0.20 (0.15, 0.24)
Anti-SSA antibody seropositives	82
Anti-SSB antibody seropositives	50
ANA seropositives	89
RF seropositives	71
Lip biopsy positive/negative/not performed	68/11/21
Nonexocrine symptoms/signs of the following	82
Raynaud's phenomena	32
Arthralgia in joints of hands	71
Arthritis in joints of hands	25
Peripheral neuropathy	11
Vasculitis-purpura	4
Renal disease	0
Liver disease	0
Interstitial lung disease	0
Myositis	0
Smokers	21

IQR: interquartile range; ANA: antinuclear antibodies; RF: rheumatoid factor.

DISCUSSION

In this study we found that 43% of patients with pSS showed signs of IGE, while 29% fulfilled the criteria for gastroparesis. Interestingly, inflammatory variables and certain serological features of pSS were associated with signs of IGE. In addition, patients showed both objective signs and subjective symptoms of parasympathetic and sympathetic dysfunction. However, we found no association between IGE and objective and subjective AD, other nonexocrine symptoms, or GI symptoms.

Gastric emptying has been studied by Kovacs, *et al*[15], who found a pathological t_{half} in 70% of patients with pSS, using ventricular scintigraphy. That number is significantly higher than has been reported in patients with diabetes mellitus, where a prevalence of gastroparesis between 30% and 50% has been reported[30]. Although the prevalence of gastroparesis was higher in the study by Kovacs, *et al* (70% vs 29% in our study), which could be explained by differences in patient selection, control materials as well as methodological reasons, their findings were in accord with ours, as was their finding that pathological gastric emptying was not associated with signs of neuropathy.

Table 2. Results of octanoate breath test in 28 patients with primary Sjögren's syndrome (pSS) and 50 controls. Results are presented as z-scores [median (IQR)] adjusted for age and sex as well as percentage with pathological increased time defined as z-score ≥ 2.

Gastric Emptying Variable	Patients with pSS	Controls	p
Half-time (t_{half})	1.18 (–0.71, 2.06)	–0.06 (–0.72, 0.74)	0.03*
Half-time (t_{half}) pathological, %	29	2	0.0009**
Lag-time (t_{lag})	1.40 (–0.14, 3.11)	–0.03 (–0.57, 0.66)	0.0008**
Lag-time (t_{lag}) pathological, %	43	4	0.00004**

p values were calculated using the Mann-Whitney U test and Fisher's exact test, respectively; * $p < 0.05$, ** $p < 0.001$.

Table 3. Association between serological markers and gastric emptying variables in 28 patients with primary Sjögren's syndrome. Results are presented as z-scores [median (IQR)].

Marker	Half time (t_{half}) Seronegative	Half time (t_{half}) Seropositive	p	Lag time (t_{lag}) Seronegative	Lag time (t_{lag}) Seropositive	p
RF	–0.75 (–1.24, 0.25)	1.61 (0.09, 2.86)	0.02*	–0.44 (–0.91, 1.05)	2.39 (1.18, 4.22)	0.02*
ANA	–0.99 (–1.56, 0.40)	1.22 (–0.37, 2.40)	0.06	–0.80 (–0.95, –0.02)	1.81 (–0.01, 3.42)	0.06
Anti-SSA	1.65 (–1.36, 2.72)	1.13 (–0.51, 2.07)	0.93	1.81 (–0.96, 3.11)	1.40 (–0.11, 3.24)	0.70
Anti-SSB	0.03 (–1.03, 1.86)	1.40 (–0.04, 2.78)	0.34	0.67 (–0.78, 2.78)	2.38 (0.83, 4.80)	0.23

p values calculated using the Mann-Whitney U test; * $p < 0.05$. RF: rheumatoid factor; ANA: antinuclear antibodies.

Table 4. Results of objective autonomic nervous function tests (ART) and the Autonomic Symptom Profile (ASP) questionnaire in patients with primary Sjögren's syndrome (pSS). Results are presented as median (IQR). All variables presented as z-score except the gastroparesis and reflex syncope domains, which were presented as raw scores.

Variable	Patients with pSS	Controls	p
ART			
E/I ratio	–0.82 (–1.47, 0.20)	–0.25 (–0.62, 0.60)	0.01**
AI	–0.17 (–0.90, 0.51)	0.03 (–0.67, 0.65)	0.57
VAC index	0.31 (–0.43, 1.60)	0.09 (–0.67, 0.62)	0.07
lSBP ratio	–0.64 (–1.26, 0.27)	0.00 (–0.61, 0.70)	0.00**
lDBP ratio	–1.66 (–2.80, –0.29)	0.00 (–0.47, 0.54)	0.00 ***
ASP			
Orthostatic intolerance	1.35 (–0.31, 2.45)	–0.39 (–0.78, 0.79)	0.00***
Urinary dysfunction	0.12 (–0.55, 1.98)	–0.51 (–0.71, 0.32)	0.02*
Gastroparesis	0.00 (0.00, 1.50)	0.00 (0.00, 0.00)	0.00***
Autonomic diarrhea	0.66 (–0.53, 2.10)	–0.42 (–0.60, 0.68)	0.02*
Constipation	1.00 (–0.56, 2.60)	–0.30 (–0.52, –0.18)	0.07
Secretomotor dysfunction	3.36 (2.13, 4.41)	–0.45 (–0.72, 0.52)	0.00***
Pupillomotor dysfunction	1.84 (0.87, 3.00)	–0.42 (–0.71, 0.55)	0.00***
Vasomotor dysfunction	0.89 (–0.45, 2.78)	–0.33 (–0.49, –0.20)	0.00**
Reflex syncope	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.61
Sleep disorder	0.39 (–0.11, 1.80)	–0.05 (–0.79, 0.35)	0.00***
Total score	2.35 (0.72, 3.30)	–0.21 (–0.82, 0.72)	0.00***

p values calculated using the Mann-Whitney U test; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. IQR: interquartile range; E/I: expiration/inspiration; AI: acceleration index; VAC: vasoconstriction; lSBP: lowest systolic blood pressure; lDBP: lowest diastolic BP; ART: autonomic reflex test; ASP: Autonomic Symptom Profile.

The associations between delayed gastric emptying and certain inflammatory and serological variables are interesting and lend support to the hypothesis that immunologic mechanisms play a role in GI dysfunction in pSS, although this has to be investigated further in future larger-scale studies. Such an association between autoimmunity and GI dysfunction has been suggested previously, as inflammatory bowel disease and severe dysmotility have been reported to be coexisting illnesses in some patients[31]. Patients with severe dysmotility have also been shown to have autoantibodies against neuronal structures[32]. Further, patients with other rheumatologic illnesses such as SSc frequently devel-

op GI complications that correlate to the degree of inflammation[33].

Although gastroparesis, at least in diabetes mellitus, is thought to be related to AD[13,34], and we found both objective signs and subjective symptoms of AD in our material, signs of AD and impaired gastric emptying were found to be poorly associated. Autonomic dysfunction related to pSS has been attributed to various immunological mechanisms such as anti-muscarinic-3 receptor (M3R) antibodies[35,36,37], cytokines interfering with nervous signaling[38,39,40], and inflammation of autonomic nerves, nerve vessels and ganglia[41,42]. Because the M3R has a role in regulating GI motility[43], the anti-M3R antibodies also may be important in delayed gastric emptying, as suggested by Kovacs, *et al*[15] in patients with pSS and by Goldblatt, *et al*[44] in patients with SSc. However, the effects of these antibodies may not be detected by the cardiovascular autonomic reflex tests used in our study. The lack of association between signs of AD and objective signs of IGE could be due to differences in mechanisms behind cardiovascular AD and IGE, or the small sample size. End-organ failure, the effects of which it is difficult to distinguish from the effects of AD, may also obscure associations between AD signs and IGE. In the case of diabetes mellitus, similar difficulties correlating signs of objective autonomic dysfunction and autonomic dysfunction symptoms have been encountered. This difficulty further underlines that the autonomic tests currently used mainly reflect cardiovascular function or imply other underlying mechanisms, as suggested[30,45].

The lack of associations between gastroparesis symptoms and objective signs of IGE is in accord with our previous studies in diabetes mellitus[46]. This diagnostic challenge is well known and is currently under intensive evaluation[47,48]. Relative lack of variability of the gastroparesis domain score in ASP in patients with pSS, and the fact that these scores also might reveal functional bowel symptoms, may further explain this discrepancy. In our material there was no evidence that symptoms of IBS and FD were expressions of gastric dysmotility. Instead, these might be coexisting illnesses with different etiologies.

Because diabetes mellitus is known to be associated with gastroparesis, patients were evaluated for coexisting diabetes mellitus and all patients were found to have normal fasting glucose levels. When evaluating the patients for thyroid illness, known to frequently occur in the setting of pSS[49] and to cause various GI symptoms, 3 patients were found to be treated with levothyroxine for hypothyroidism. However, at the time of the study all patients were euthyroid and had normal levels of thyroid hormone. Atrophic gastritis, described as more common in pSS compared to the general population, could hypothetically also have influenced the results, prolonging gastric emptying[50]. However, normal B12 levels in all patients and thyroid illness in only 3 subjects suggest other reasons behind IGE in our study.

The strengths of our study were the use of the American-European Consensus Criteria and the comprehensive evaluation of AD and GI symptoms, the standardization of the octanoate breath test variables with regard to age and sex, as well as the use of a clinically feasible method of evaluating gastric emptying without radiation exposure. Another strength was the standardization of conditions of the tests, thus minimizing the role of concurrent medication, tobacco use, etc. The limitations were the relatively small size of the study, that the autonomic nervous function tests primarily evaluated cardiovascular AD, and that no analysis of anti-M3R could be performed.

Forty-three percent of patients with pSS were found to have objective signs of IGE, which was associated with increased levels of ESR and IgG, and was more common in RF-seropositive patients. Impaired gastric emptying was, however, poorly associated with both objective and subjective AD variables and gastrointestinal symptoms.

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