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Patient dissatisfaction with medical therapy for chronic constipation or irritable bowel syndrome with constipation: analysis of N-of-1 prospective trials in 81 patients

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Summary

Background: Patients with chronic constipation (CC) or with irritable bowel syndrome with constipation are often dissatisfied about their medical therapy, but their condition remains poorly defined.

Aims: To evaluate the patients' satisfaction rates and which factors predict favourable outcomes through the aggregate analysis of N-of-1 trials.

Methods: Eighty-one outpatients with CC or with irritable bowel syndrome with constipation underwent N-of-1 trials with at least a one-month cycle of effective treatment. Three primary endpoints (satisfaction with therapy, improvement after treatment and an extended satisfaction criterion including both endpoints) were adopted to define satisfaction with therapy. Dyssynergia, resting anal pressure, colonic transit time and somatisation were assessed. The Patient Assessment of Constipation-Symptoms (PAC-SYM) questionnaire and its Modified version (M-PAC-SYM) measured constipation severity. Straining at defecation, stool frequency and form were daily recorded. *K* statistics for agreement and logistic regression were used at statistical analysis.

Results: Satisfaction with therapy was not achieved by 43% of patients, who had a significantly lower Body Mass Index (BMI) and more severe constipation at baseline. Only the change in constipation severity according to M-PAC-SYM remained significantly associated with satisfaction with therapy (OR = 4.3; $P < 0.001$) at multivariate analysis.

Conclusions: Satisfaction with therapy is often an unmet need for patients with CC or with irritable bowel syndrome with constipation. Lower BMI and more severe constipation are associated with worse outcome. Changes in M-PAC-SYM reflect satisfaction with therapy. ClinicalTrials.gov no. NCT02813616.

Congress presentations: The abstract of this study was presented at DDW in San Diego (USA) and at the SINGEM National Congress of Pisa (Italy), where it was awarded the prize as the best oral communication.

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[*] See Appendix 1 for the members of the Italian Society of Neurogastroenterology, Motility (SINGEM) Study Group.

1 | INTRODUCTION

Chronic constipation (CC) is a common condition characterised by unsatisfactory defecation related to either infrequent or difficult passing of stool or both.[1] CC largely overlaps with irritable bowel syndrome with constipation (IBS-C), where abdominal pain is the patient's main complaint.[2] Internet surveys have shown that patients with CC are dissatisfied with their defecation in spite of effective treatment being taken[3,4] and often in spite of normal bowel frequency.[3,5]

Defining "satisfaction with therapy" or "adequate relief of symptoms" for patients with CC is extremely important in clinical practice for several reasons: new and more expensive medication can be initiated when the older/cheaper treatments have failed,[6] diagnostic algorithms suggest that functional diagnostic tests should be reserved to patients with inadequate response to laxatives,[7] and—last but not least—more invasive therapeutic approaches have to be used in patients refractory to adequate therapies.[8] Recently, a consensus of experts has set standardised criteria for assessing the failure of treatment to provide an adequate relief of symptoms in patients with CC[9]: inadequate bowel frequency, no improvement of stool consistency and straining on most occasions have been proposed to reflect treatment failure. Another approach to establish treatment failure has been to define a symptom severity scale with a threshold below which symptoms are considered as not improved. M-PAC-SYM is a modified 11-item score of the Patient Assessment of Constipation Symptoms (PAC-SYM) score, which has been used to define the symptoms severity of outpatients with CC and IBS-C enrolled in Italian referral centres: a >0.24 decrease was the minimal difference to define improvement after treatment.[5] Furthermore, a recent secondary analysis of four randomised controlled trials with prucalopride has defined a >0.64 decrease in the standard PAC-SYM score as the minimal difference to define improvement.[10]

Beyond the standardised criteria to define satisfaction with therapy, it may be very helpful in both clinical practice and clinical trials to identify outcome-predicting factors. IBS diagnosis has been demonstrated to be a factor predicting more severe disease and poorer quality of life than CC.[2] Higher somatisation scores have shown to be associated with more severe IBS,[11] but were not related with the persistence of CC.[12] Among the physiological variables delayed colonic transit[13] and increased resting pressure of the anal sphincter[14,15] have been associated with more severe constipation, but this relationship remains controversial.[16-19]

N-of-1 trials are considered the most rigorous method of treatment effectiveness evaluation in a single patient as, in contrast with randomised controlled trials, they account for the huge heterogeneity among patients in clinical practice. N-of-1 trials can also be used to determine which prognostic factors match with improved patient care.[20] We have for the first time applied this methodology to evaluate patients with CC or IBS-C, who prospectively underwent standardised one-month cycle of effective[21,22] treatment for CC. Through the aggregate analysis of these N-of-1 trials, our study aimed to establish: (a) the frequency of patients achieving satisfaction with therapy, (b) factors predicting a favourable outcome.

2 | METHODS

2.1 | Patients

Between February 2016 and May 2018, 81 patients (74 females, mean age 48 ± 14 years, range 20-76; mean BMI 22.5 ± 3.0 range 17.1-30.1) fulfilling the Rome III criteria[23] for CC or IBS-C, were admitted to 11 Italian tertiary care outpatient clinics, completed at least the first-month-of-the-study cycle and thus were included in the analysis of the results. Ten other patients (10 females, mean age 50 ± 19 years, range 23-74 years; mean BMI 21.5 ± 2.9 range 16.4-26.4; CC = 7 IBS-C = 3) were enrolled, but did not attend the first follow-up visit and were excluded from the analysis.

All the examinations (*eg* blood biochemistry, endoscopic and radiological investigations to exclude secondary causes of constipation) were performed when indicated: full blood count, thyroid-stimulating hormone and calcium blood levels were normal in all the patients. All pregnant women and patients previously submitted to abdominal surgery, except for appendectomy, were excluded. All the patients gave their written informed consent to the study. The protocol was approved by the Ethics Committee of the coordinating centre on 2 February 2016 and registered in ClinicalTrials.gov (ref. no. NCT02813616).

2.2 | Baseline investigation

Questionnaires: At enrolment every patient completed a questionnaire to confirm their fulfilment of the Rome III criteria for CC or IBS-C.[23] Considering the overlap between the two groups, an additional question on the "presence of recurrent abdominal pain (at least 3 days a month in the last 3 months) that improves with defecation or with a change in the frequency and form of stools" was used to distinguish IBS-C from CC. Previous surgery for constipation, hysterectomy and childbirth in women were recorded.

Treatments taken for CC or IBS-C in the month before enrolment were recorded, including multiple treatments (diet and lifestyles, phyto-therapies, fibers and bulking agents), stimulant laxatives (bysacodil, senna), osmotic laxatives (macrogol), rectal options (enema, suppository) and prucalopride or linaclotide. A "satisfaction with therapy" score (on a 7-point Likert scale: 1 = extremely dissatisfied, 2 = very dissatisfied, 3 = dissatisfied, 4 = partially satisfied, 5 = satisfied, 6 = very satisfied, 7 = extremely satisfied) together with PAC-SYM[24] and its modified version (M-PAC-SYM)[5] (scoring from 0 = absent to 4 = very strong) were recorded. Somatisation,[25] quality of life,[26] digital rectal examination to test for dyssynergia,[27] colonic transit time[28] and anal resting pressure at anorectal manometry[14] were recorded with standardised techniques (see File S1).

2.3 | N-of-1 intervention schedule

On the first N-of-1 trial cycle, the patients were treated with a standardised one-month therapy with macrogol (17-34 mg per day). At each

N-of-1 trial cycle, those patients satisfied with therapy continued on the same therapy for one more month. On the contrary, the dissatisfied patients were invited to change therapy, those with a diagnosis of CC being directed according to European reccomendations[6] to 1-month therapy with prucalopride (2 mg/day), those with a diagnosis of IBS-C to 1-month therapy with linaclotide (290 μg/day), that is prescribed as first or second-line treatment in patients with IBS-C.[29] During the study period, the patients were allowed to take bisacodyl (max 2 tablets a day, 5 mg each) and rectal enemas (one weekly) or otilonium bromide (max 2 tablets a day, 40 mg each) as rescue therapies for constipation or abdominal pain, respectively. The trial stopped after 2 consecutive months in which patients were satisfied with treatment, after three cycles or when patients were lost to follow-up. The details on the sequences of treatment together with the deviations from the assigned treatment protocol are provided in File S2.

2.4 | Longitudinal evaluations

During each N-of-1 trial cycle, the patients kept a daily record of their bowel habits (stool frequency and consistency according to the Bristol stool chart score), abdominal pain (scored from 0 to 10) and any straining, incomplete evacuation and urgency. At each follow-up visit, the patients recorded their score for "satisfaction with therapy", "improvement after treatment" and "constipation severity" according to PAC-SYM.

2.5 | Endpoint definitions

2.5.1 | Based on Likert's scales

Endpoint 1. "Satisfaction with therapy" was evaluated with a 7-point Likert's scale as previously described.

Endpoint 2. "Improvement after treatment" was evaluated with a global rating-of-change scale (−7 to +7: −7 = extremely worsened, 0 = unchanged, +7 = extremely improved). "Improvement after treatment" was defined by an increase in the global rating-of-change scale of ≥2 points.

Endpoint 3. The "extended satisfaction criterion" occurred when endpoint 1 or 2 were achieved. This criterion was used because the results showed that in 24% of the treatment cycles, the patients improved after treatment, but remained unsatisfied. Accordingly, the extended satisfaction criterion was introduced in order to include all the positive effects (satisfaction or improvement) of treatment.

2.5.2 | Based on the patients' daily diaries or PAC-SYM questionnaires

1. "Normalisation of bowel frequency". Bowel frequency >3 bowel movements per week or increase in bowel movements/week >1.
2. "Normalisation of stool form". Bristol score ≥3 or change in Bristol score ≥0.3.
3. "Normalisation of strain". Straining reported on <50% of bowel movements.
4. Δ-PAC-SYM >0.64.
5. Δ-M-PAC-SYM >0.24.

2.6 | Statistical analysis

We computed the absolute and relative frequencies or means and standard deviations for discrete or continuous variables respectively. The level of agreement on the different endpoint definitions and the extended satisfaction criterion was evaluated with κ statistics. The secondary endpoints association with the extended satisfaction criterion was evaluated by logistic regression analysis. Any antecedents of the extended satisfaction criterion were evaluated with random-intercept multiple logistic regression. The number of patients planned for the study was 90. With 77 patients completing 155 trial cycles, the accrued sample size achieves 83% power of detecting a $f = 0.17$ effect size difference in treatment response likelihood for patients reporting each constipation-related symptom (absent-mild symptoms vs moderate-severe PAC-SYM items). This effect size difference approximately accounts for 3% of variance in the outcome of interest.

All the statistical analysis was conducted by software (SAS Institute Inc, SAS® rel. 9.4).

3 | RESULTS

The characteristics of the 81 patients (33 with IBS-C and 48 with CC) who completed at least one treatment cycle are reported in Table 1. At enrolment, 75 patients (93%) had already taken pharmacological treatment, 33 (41%) had an altered somatisation score; the physical and mental quality of life was impaired for 7 (9%) and 19 (23%) patients respectively. The colonic transit time was delayed in 12 (15%) patients. The anal resting pressure was increased in 13 (16%) patients; dyssynergia was found in 25 (31%) patients.

Comparing the IBS-C vs CC group (Table 1), the previous treatments with stimulant laxatives, rectal options and osmotic laxatives were more frequent in patients with CC than in IBS-C. The anorectal resting pressure recorded with manometry was greater in CC than in IBS-C. The IBS-C patients tended to be less satisfied of their previous treatments, to have more severe constipation, higher somatisation scores and poorer quality of life compared to the patients with CC. The outcome was not significantly different according to the different diagnosis.

3.1 | Per-patient analysis

Four patients were excluded from the analysis because they did not answer on the treatment satisfaction items in the one cycle month.

TABLE 1 Baseline characteristics of the patients

	All patients	IBS-C	CC	*P*
N	81	33	48	
Age (y)	48 ± 14	47 ± 15	48 ± 14	0.77
Women, N (%)	74 (91)	30 (91)	44 (92)	0.58
BMI	22.5 ± 3.0	23.2 ± 3.3	22 ± 2.8	0.06
Tertiary education, N (%)	26 (32)	9 (27)	17 (35)	0.84
Childbirth N (%)	41 (51)	17 (21)	24 (30)	1
Hysterectomy N (%)	9 (11)	3 (4)	6 (7)	0.73
Surgery for constipation N (%)	3 (4)	2 (2)	1 (1)	0.56
Previous treatments, N (%)				
Multiple treatments	47 (58)	23 (70)	23 (50)	<0.01
Stimulant laxatives	7 (9)	0	7 (15)	
Osmotic laxatives	8 (10)	2 (6)	6 (12)	
Rectal options	7 (9)	0	7 (15)	
Prucalopride or linaclotide	6 (7)	3 (9)	3 (6)	
No treatments	6 (7)	4 (12)	2 (4)	
Satisfaction (1–7)	2.5 ± 1.3	2.53 ± 1.3	2.56 ± 1.3	0.08
PAC-SYM	1.9 ± 0.7	2 ± 0.6	1.8 ± 0.74	0.15
M-PAC-SYM	2.0 ± 0.7	2.2 ± 0.6	1.86 ± 0.71	0.10
Somatisation	61.1 ± 10.7	63.9 ± 9.8	59.5 ± 10.7	0.11
Quality of life				
SF36 F	42.8 ± 9.4	41.2 ± 9.5	45.2 ± 9.1	0.15
SF36 M	36 ± 10.7	39.2 ± 10.3	40.5 ± 9.9	0.56
Rectal examination[a]				
Anal resting pressure, N (%)				
Decreased	10 (13)	5	5	0.68
Normal	53 (70)	21	32	
Increased	13 (17)	6	7	
Anal squeeze pressure				
Decreased	8 (11)	4	4	0.64
Normal	10 (13)	5	5	
Increased	58 (76)	23	35	
Dyssynergia	25 (33)	14	11	0.19
Colonic transit (h)	52.3 ± 19.9	53.1 ± 18.4	53.5 ± 20.7	0.57
Resting anal pressure (mm Hg)	67.6 ± 21.7	61.4 ± 16.9	71.2 ± 22.8	0.03

Note: Data are N = number or mean ± SD.

[a]Not reported in five patients.

The remaining 77 patients underwent 155 N-of-1 trial month cycles, (19 patients-one cycle, 38-two cycles and 20-three cycles; 110 with macrogol, 17 with prucalopride and 28 with linaclotide; two patients with CC received prucalopride and five patients with IBS-C received linaclotide as first-line treatment instead of macrogol (See details in File S2). Rescue therapy for constipation (bisacodyl or rectal enema) occurring more than once a week, was administered to 34%, 16% and 45% of patients during the first, second and third trial month respectively.

Table 2 shows the characteristics of the patients who achieved or not the endpoint 1 in at least one treatment cycle. Those patients who did not achieve the endpoint had significantly lower BMI and more severe constipation at baseline.

The rate of achievement of the endpoint 1 after first treatment cycle (33%) in the 18 patients who had previously received osmotic laxatives alone or in combination before enrolment was not significantly different ($P = 0.43$) from the rate in patient previously receiving other treatments or none (24%). The frequency of rescue therapy

TABLE 2 Baseline characteristics of patients who achieved or not the endpoint 1 (Satisfaction with therapy score > 4) in at least one treatment cycle

	Satisfaction with therapy		
	No	Yes	*P*
N (%)	33 (43)	44 (57)	
Age (y)	44 ± 14	50 ± 14	0.06
Women, N (%)	32 (97)	38 (86)	0.14
BMI	21.5 ± 2.6	23.1 ± 3.1	0.01
CC, N (%)	23 (70)	25 (57)	0.59
IBS-C, N (%)	10 (30)	19 (43)	
Satisfaction (1–7)	2.4 ± 1.1	2.8 ± 1.4	0.39
PAC-SYM	2.1 ± 0.49	1.7 ± 0.81	0.02
M-PAC-SYM	1.93 ± 0.47	1.56 ± 0.78	0.03
Somatisation	62.3 ± 11.7	60.6 ± 9.9	0.36
Quality of life			
SF36 F	42.1 ± 8.3	44.5 ± 10	0.32
SF36 M	37.3 ± 10	41.2 ± 9.9	0.30
Rectal examination[a]			
Anal resting pressure, N (%)			
Decreased	3 (9)	7 (16)	0.75
Normal	23 (70)	30 (68)	
Increased	6 (18)	7 (16)	
Anal squeeze pressure, N (%)			
Decreased	5 (15)	3 (7)	0.47
Normal	3 (9)	7 (16)	
Increased	24 (73)	34 (77)	
Dyssynergia	8 (24)	17 (39)	0.21
Colonic transit (h)	55.5 ± 20.10	51.5 ± 19.30	0.2
Resting anal pressure (mm Hg)	69.1 ± 16.8	67.4 ± 23.8	0.35

Note: Data are N = number or mean ± SD.
[a]Not reported in one patient.

was not significantly different (*P* = 0.38) in patients who achieved (60%) or not (59%) the endpoint 1.

Improvement after treatment (endpoint 2) was achieved by 60 patients (78%) in at least one treatment cycle. More patients with IBS-C than CC reached endpoint 2 (93% vs 75%, *P* = 0.048); no further statistically significant differences were found regarding the baseline characteristics between the groups. All the patients reaching endpoint 2 were also satisfied with endpoint 1 at least once.

3.2 | Per-treatment-cycle analysis

At multivariate logistic regression analysis only "no response to treatment" (*ie* change in M-PAC-SYM ≤0.24) remained significantly associated with "no satisfaction with therapy" as based on the extended satisfaction criterion (OR = 4.3; CI 1.9–9.9; *P* < 0.001).

At stepwise logistic regression (*C* statistics = 0.73), the patients with higher symptom severity at baseline had lower probability to reach the extended satisfaction criterion; however, this relationship was modulated by somatisation as the patients with higher somatisation scores had a better probability of treatment response (logistic regression equation parameters: intercept: 15.7, *P* < 0.01; M-PAC-SYM: −8.8, *P* < 0.01; M-PAC-SYM*SOM: 0.13, *P* = 0.01; SOM: −0.20, *P* = 0.04).

Table 3 provides the sensitivity, specificity and κ agreement statistics of the association between improvement in constipation severity, normalisation of stool frequency, stool form and straining and the extended satisfaction criterion. Both the normalisation of stool frequency and that of stool form were the endpoints least frequently associated with the extended satisfaction criterion (κ = 0.03 and κ = 0.05, respectively) as such endpoints were met in about all the treatment cycles even when the extended satisfaction criterion was not met (*ie* stool frequency and form normalised but the patients did not feel satisfied or improved). Slightly better agreement was observed for the other endpoints, with M-PAC-SYM having the highest κ statistics (0.24).

4 | DISCUSSION

Our results show that a considerable number of patients with CC or IBS-C treated with effective therapies are not satisfied with their defecation: 43% did not achieve an adequate relief of symptoms in line with the percentages of incompletely satisfied patients (47%) or very dissatisfied patients (28%) previously reported by Internet surveys.[3,4] These results indicate that whichever the type of patients' enrolment (Internet survey or tertiary care outpatient clinics) satisfaction with therapy often remains an unmet need in constipated patients.

It is quite possible that the percentage of dissatisfied patients in our study might have been reduced applying other therapeutic approaches such as combination of effective treatments, bio-feedback and neuro-modulators or prescribing the new treatments (prucalopride for CC and linaclotide for IBS-C) as first-line treatments before macrogol. However it should be noted that, despite the fact that almost all our patients achieved the normalisation of stool frequency and form, a considerable proportion of them remained dissatisfied, this indicating that whichever therapeutic approach might have been applied, its efficacy should have been directed toward something different than the mere normalisation of stool frequency and form.

We have investigated both clinical and physiological characteristics of patients possibly associated with outcome. Not unexpectedly, the patients with more severe constipation were more likely to have a less favourable outcome. More unexpectedly, a low BMI was also associated with a less favourable outcome. Previous epidemiological studies established an association between high BMI and diarrhoea,[30,31] but only in one recent Japanese study low BMI and intra-abdominal fat were reported to be associated with an increased risk of constipation and hard stools.[32] Moreover, in a recent study comparing individuals with a normal or prolonged balloon expulsion test, the latter group presented a significantly lower BMI.[33] It remains to be investigated

TABLE 3 Sensitivity, specificity and κ of agreement statistics on the association between improvement in constipation severity, normalisation of stool frequency, stool form and straining and the extended satisfaction criterion

	Extended satisfaction criterion				Statistics
	Sensitivity	Specificity	No	Yes	κ
PAC-SYM change	50 (40-60)	73 (57-85)			0.18
≤0.64			30	54	
>0.64			11	54	
M-PAC-SYM change	79 (70-87)	44 (29-70)			0.24
≤0.24			19	22	
>0.24			24	84	
Normalisation of bowel frequency	91 (84-96)	11 (3-25)			0.03
No			4	9	
Yes			33	97	
Normalisation of stool form	95 (89-98)	8 (2-22)			0.05
No			3	5	
Yes			34	100	
Normalization of straining	80 (71-87)	39 (24-55)			0.19
No			16	22	
Yes			25	87	

whether that association is related to differences in behavioural or dietary habits, hormone and neuro-transmitter release, colonic microbiome and colorectal or more widespread altered motor function impairing the maintenance of a normal body weight.

About one-fourth of patients did not achieve satisfaction with therapy despite the fact that they reported a significant improvement after treatment. Accordingly, we adopted an extended satisfaction criterion including both endpoints to encompass all the favourable effects of treatment. Using such an extended criterion we have analysed which features may reflect a favourable outcome in a series of standardised N-of-1 treatment cycles. Normalisation of stool frequency and normalisation of stool form were the least associated with the extended satisfaction criterion as almost all the patients normalised stool frequency and form, even when they were not satisfied or improved. In other words, the normalisation of both bowel frequency and/or stool form was sensitive but not specific to reflect an adequate relief of symptoms and represented a necessary but not sufficient condition for perceived efficacy. These results are in line with previous studies showing that unsatisfactory defecation is indeed less frequent when stool form is normal, but it may be present in patients reporting normal stool form and frequency.[5,19,34,35] In comparison with the normalisation of stool frequency and stool form, the normalisation of straining was less sensitive but more specific. Taken together, these results show that no single clinical parameter per se is able to capture patients' variability as regards treatment satisfaction and that such satisfaction appears to have a heterogeneous multi-dimensional construct not yet fully mapped into the current metrics. How much concomitant side effects,[9] different expectations about medications[36] and bio-psycho-social factors[37] also concur to patients' dissatisfaction were not formally addressed in the present study, but they too should be considered. In line with the multi-dimensional construct of patients' satisfaction, better agreement was observed with endpoint definitions based on a more comprehensive measurement of severity, such as the PAC-SYM questionnaires, with M-PAC-SYM having the highest κ statistics (0.24) and a significant association to satisfaction with therapy at multivariate logistic regression analysis.

In line with a previous study the severity of constipation tended to be greater in patients with IBS-C than in patients with CC.[2] This difference might be partly related to the multiplicity of somatic symptoms reflected by the higher somatisation scores in IBS-C patients. On the other hand, high somatisation scores seemed to modulate the negative effect that more severe constipation had on the outcome. The latter result should be verified in studies with a different experimental design as it may reflect the selection of patients with high somatisation scores, who perhaps were more interested to be followed up over a longer period of time according to the N-of-1 study design.

Several physiological variables including delayed colonic transit[13] and increased resting pressure of the anal sphincter[14,15] have been suggested to characterise more severe forms of constipation. In our study, these physiological alterations were not significantly associated with a worse outcome, in line with previous observations[16-19] advising clinicians for caution against over-interpreting physiological tests. On the other hand, it should be acknowledged that the number of patients was too limited to detect small differences and that the reproducibility of the tests might have been influenced by the multi-centre design of the study.

Also the presence of dyssynergia was not significantly associated with the outcome. Dyssynergia was not assessed in our study by balloon expulsion test, anorectal manometry or defecography, but only by digital rectal examination that has been shown to have a 91% positive

predictive value in the diagnosis of the condition.[27] Interestingly the frequency of dyssynergia that ranges from 15% to 53% according to the diagnostic technique,[38] was very similar in our series to the frequency reported with different techniques in a single referral centre.[39]

Although N-of-1 trials are typically used to evaluate the effectiveness of therapy in an individual patient, they can also be applied to determine which prognostic factors match with improved patient care.[20] The design of our study did not aim to achieve a balanced evaluation among different treatments. The choice of macrogol instead of linaclotide as the initial therapy in patients with IBS-C might be questioned, considering the non significant impact of macrogol in comparison to placebo on abdominal pain symptoms in IBS-C.[40] The differences in previous treatments according to the diagnosis might also have affected the expectations toward the prescribed old and new treatments in the different groups. The concomitant use of rescue therapies might also have influenced the achievement of satisfaction. On the other hand, the combination of individualised outcome data allowed us to analyse the effects of several potential prognostic factors in a considerable number of treatment cycles. It should be recognised that these effects should have emerged in a quite heterogeneous population that however resembles the heterogeneity of patients in clinical practice. In addition, how far our results can be extended to the general population or to other research settings should be established in further studies.

In conclusion, satisfaction with therapy in patients with IBS-C or with CC has a multi-dimensional construct where several other factors than the normalisation of stool frequency and form play a substantial role. Satisfaction with therapy is not fully mapped by a single scale, test or questionnaire: this leads to caution in any clinical decisions affected by such uncertainty. Low BMI should be considered among the factors influencing the outcome in constipated patients. The aggregate analysis of N-of-1 trials provides interesting clues on the role that clinical and physiological variables have on satisfaction with therapy for constipation in clinical practice.

ETHICS

Approval was obtained from all the Ethics committees of the participating centres, including the coordinating centre on 2 February 2016 (protocol no. 74-2016). Informed consent was obtained from all the patients. The protocol was registered on ClinicalTrials.gov (ref. no. NCT02813616).

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AUTHORSHIP

Guarantor of the article: Guido Basilisco.

Author contributions: Guido Basilisco, Elena Arsiè and Marina Coletta planned the study, collected and interpreted the data and drafted the manuscript. Giovanni Barbara collected and interpreted the data and participated in the draft of the protocol and the manuscript. Ambra Lovati was the study coordinator. All the authors collected the data and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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APPENDIX 1.

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