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Progress of constipation in patients who make chronic use of stimulant laxatives when a fiber supplement is introduced

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KEYWORDS

Chronic constipation, stimulant laxatives, fiber supplement

ABBREVIATIONS

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios [Spanish Agency of Medicines and Medical Devices]

ABSTRACT

Objective: To determine the progress of constipation in patients who make chronic use of stimulant laxatives when a fiber supplement is introduced in their diet.

Design: Epidemiological, multicenter and prospective cohort study with a 10-week follow-up. Site: the study was conducted in 16 community pharmacies. Participants: 106 chronically constipated patients, self-medicated with stimulant laxatives, in whose diet fiber is introduced and who are kept under observation to record what happens when laxative is gradually withdrawn. *Main medications:* Frequency of bowel movements and consistency of stool. The laxatives required and gastrointestinal symptoms are quantified.

Results: At base level, 94.2% of patients required laxatives, the average number of bowel movements/week was 4.2 (DE 2.4) and only 4.8% of patients had a normal consistency of stool (4 on the Bristol Stool Chart). From the first week of treatment with fiber, a significant reduction in the use of stimulant laxatives was reported (P<0.02). Of the patients who completed the study, less than half (41%) required a few doses of stimulant laxatives during the last week and 59% of patients managed to discontinue their use. 98.4% of patients evaluated the use of fiber as "sufficiently/very/extremely" easy.

Conclusions: In patients who suffer from constipation and make chronic use of stimulant laxatives, the gradual introduction of a fiber supplement maintains the patient's frequency of evacuations and normal consistency of stool, reducing the need for use of stimulant laxatives, whose use should be occasional as opposed to chronic.

INTRODUCTION

Constipation is a multifactor clinical picture that is diagnosed according to Rome IV criteria (1). It is a very frequent clinical situation that affects between 2% and 28% of the general population (2-5). In Spain, the prevalence is even higher and is estimated at 29.5% (6).

Constipation has many causes, one of which is the abuse of stimulant laxatives. These are classified in 3 groups:

1. Anthraquinone derivatives: derived from plants whose active ingredients are glycosides. The group includes sacred bark, senna, aloe, frangula bark and rhubarb. It is demonstrated that their chronic use can produce *Melanosis coli*, which disappears after a number of months following discontinuation of use.
2. Polyphenolic laxatives: they contain picosulfate and bisacodyl (7).
3. Ricin oil: its stimulant action comes from ricinoleic oil (8).

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The harmful effects caused by the continuous use of these agents on the myenteric plexus are controversial (9). In any case, a frequent or prolonged use is not recommended due to the risk of causing a water-electrolyte imbalance and because they can cause dependence or habituation (10-14). Its use should be limited to acute cases or as a rescue medication.

When the recommended dose and/or the time of administration of these laxatives are exceeded, the result is habituation of the intestinal nervous plexus to the stimulus, as the intestinal muscular tone and the nerve response are lost, producing a dilation of the intestine and ineffective peristalsis. This triggers a dependence to the laxative, and the need for an increasingly higher dose to prevent acute constipation. These symptoms last no longer than 1 to 3 weeks, but they cause much discomfort and worsening of the quality of life, which make it difficult to discontinue the medication. Therefore, abuse or misuse of this type of laxatives is a direct cause of chronic constipation (15,16).

Chronic constipation must be treated with laxatives that increase the intestinal bolus, like fiber or osmotic laxatives. This study was designed to find out if the patients who chronically use stimulant laxatives manage to quit the medication with the concomitant use of a fiber supplement (Casenfibra®).

MATERIAL AND METHODS

A 2.5-month, open label, multicenter, prospective cohort study in 16 community pharmacies of the Madrid and Barcelona Community. A total of 104 patients were examined (Figure 1).

The study was classified by the Spanish Agency of Medicines and Medical Devices (AEMPS) and approved by the Ethics Committee of the Gregorio Marañón Hospital in Madrid.

The study was coordinated by a pharmacist and a gastroenterologist.

Study population

The first 6 patients who came to the pharmacy for any reason and signed the informed consent form after meeting all inclusion criteria and no exclusion criteria were recorded consecutively.

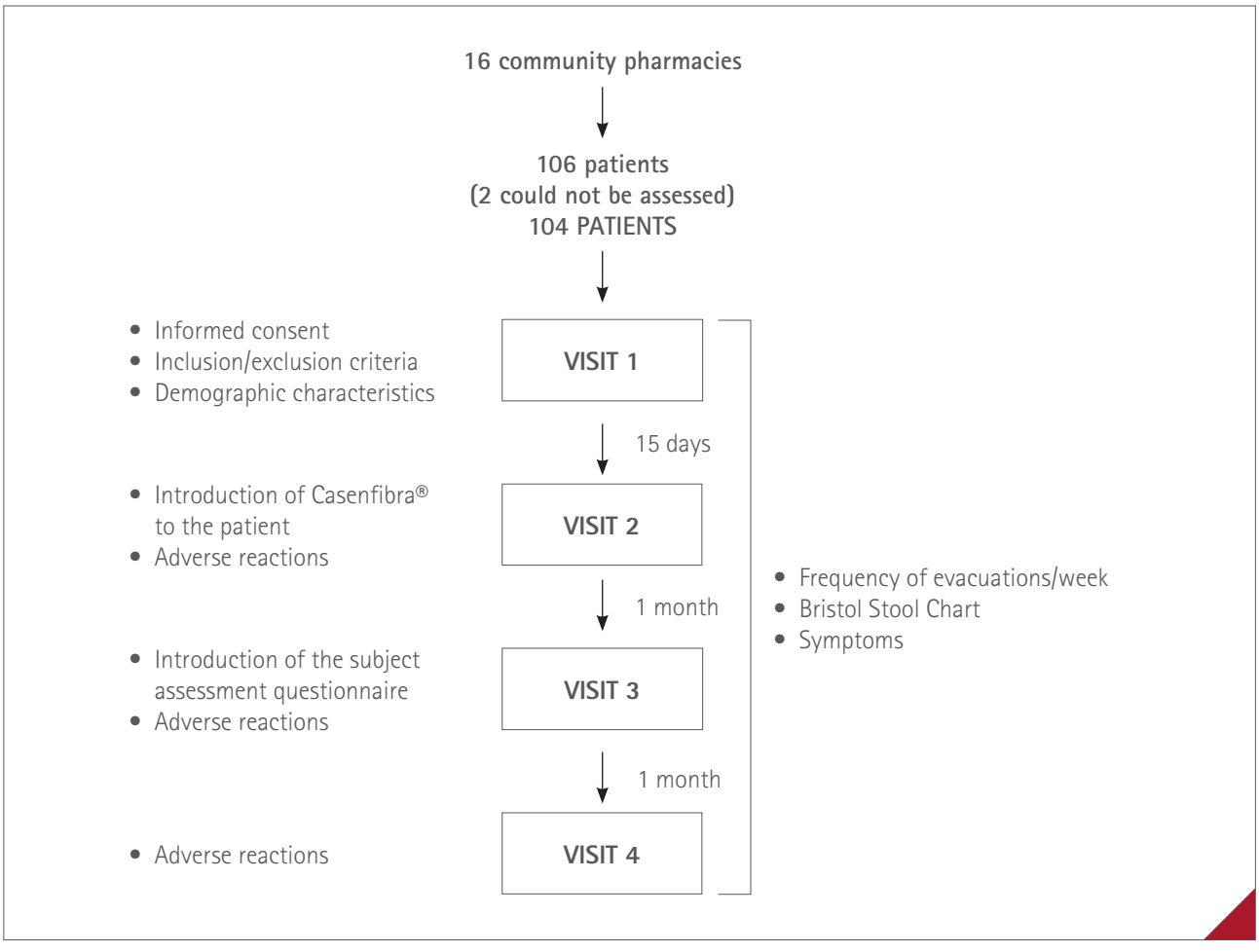

Figure 1 Overview of the study

The inclusion criteria were as follows: male and female patients aged between 18 and 75 who used stimulant laxatives (for at least 30 days, though not necessarily consecutively), and who were customers of the pharmacy (i.e. came in at least once a month in the 4 months prior to the start of the study for each patient).

The pharmacists were provided with a questionnaire designed by the coordinating gastroenterologist to help them give reliability to the answers related to the exclusion criteria: patients with irritable bowel syndrome, Crohn's disease, intestinal obstruction, fecal impaction or colon dilation or with severe constipation and significant slowing down of colon transit, who experienced heavy bleeding in the last 4 months and patients with cognitive deterioration.

The study participants were given a diary in which they recorded the consistency of their stool, intestinal symptoms and use of laxatives for 15 days. From that moment on and for the following 8 weeks, they were instructed to take a fiber supplement (Casenfibra®) at the highest dose of 3 sachets/day. They started with a dose of 1 sachet/day, increasing later one daily sachet [sic] for better tolerance. During this period, we continued to collect in the questionnaire the same information as at base level. Likewise, the patient recorded in the diary if he/she had taken the fiber supplement. If not, he/she provided the reason. If yes, the patient provided the number of sachets taken daily.

When the patients reported a score of 4 (or higher) on the Bristol Stool Chart for consistency (Figure 2), they had to gradually reduce the dose of stimulant laxatives until they managed to take just fiber.

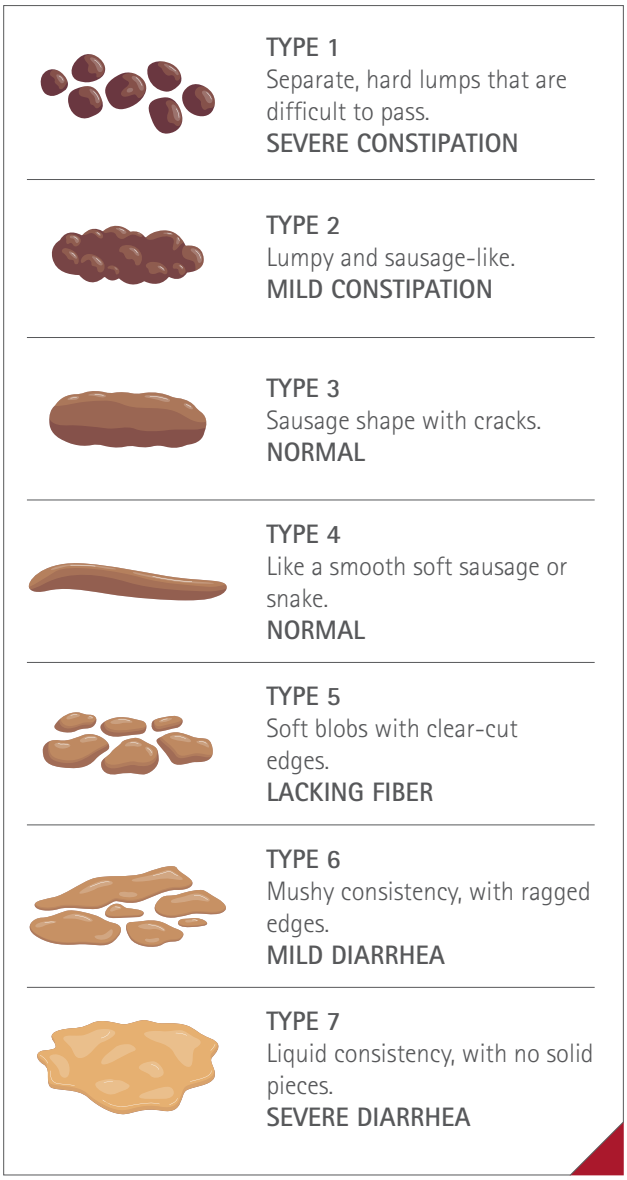

Figure 2 Bristol Stool Chart

Variables

The demographic (date of birth, gender, weight and height) and clinical data related to the patient's constipation and the use of stimulant laxatives, as the different pharmacological treatments used during the study were collected in a single visit.

The main variables were the variation of the intestinal rhythm and of stool consistency. We quantified the weekly number of bowel movements, stool consistency according to the Bristol Stool Chart, and the use of laxatives (commercial name, frequency of use and doses) and gastrointestinal symptoms present: abdominal distension, pain and discomfort, bowel movements, if the evacuation strain was prolonged or excessive and the presence of any unsatisfactory evacuation.

We produced a patient questionnaire in which we asked the efficacy they observed (subjective efficacy), the ease of administration of the fiber, the acceptability, evaluation of texture, taste and degree of recommendation they would have for the product.

The items of the overall evaluation questionnaire were grouped in 3 categories: Nothing/almost nothing; little/some; enough/a lot/very much.

Statistical analysis

The analysis population included all patients with data, though not all had diary data.

The descriptive statistics of variables were performed by including central tendency and dispersion for the quantitative variables and absolute and relative frequencies for the qualitative variables.

With reference to the diary variables, the descriptive results for each week were examined (from Week 0 to Week 10). The missing data were never supplied starting from the available data.

Of the patients with complete data, we calculated the statistical significance (p-value) of each week of follow-up vs. Week 0. We used the McNemar test for binary variables, the Student's T-test for matching data in the quantitative data, and the Mantel-Haenszel test for the ordinal variables. No adjustments were made to control type I errors despite their large number.

The type of distribution of variables was studied and their adjustment to Gauss distribution was evaluated using the Kolmogorov-Smirnov test. If the data did not meet the assumption of normality, statistical, as opposed to parametric, methods were used in the analyses.

All statistical tests were conducted with a 5% level significance level. **(Figure 3)**

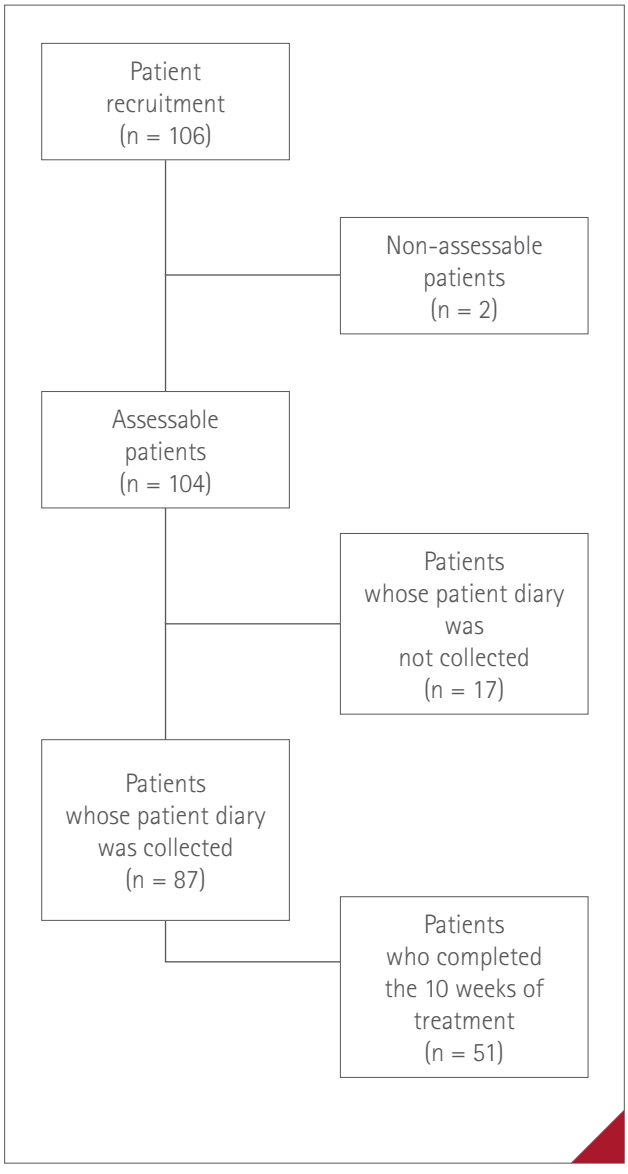

Figure 3 Study patients flowchart

RESULTS

Patient characteristics

106 patients were recruited, two of whom could not be assessed. The diary was collected from 87 out of the final 104 patients (84%). Of these, 51 patients completed the 10 weeks of treatment.

The average age was 52.6 (±13.4) years old, with female as the prevailing gender (90.4%) and an average BMI 25.5 (±4.9) kg/m2.

87.5% of patients stated they consumed a sufficient amount of fiber-rich foods (vegetables, fruit. legumes and whole wheat foods).

On the base level, the progress time of chronic constipation was equal to or higher than 3 years in 76% of patients. The average number of weekly evacuations was 4.2 (±SD 2.4) and only 4.8% of patients had normal stool consistency. The most common intestinal symptoms were: unsatisfactory evacuations, prolonged or excessive evacuation strain, discomfort and abdominal distension, bowel movements and abdominal pain.

45.2% of patients declared they suffered from constipation despite receiving treatment and 94.2% had used at least one laxative in the past week for an average period of 4.1 (SD 2.5) days. The most commonly used laxatives were Dulcolax® (bisacodyl), Fave De Fuca® (*Rhamnus frangula L, Rhamnus purshianus D.C* and *Fucus vesiculosus L., alga)* and glycerin suppositories or microenemas.

Concomitant treatments were also assessed, as some could actually cause constipation *per se*. The most commonly used treatments were tramadol (6.9%), omeprazole (5.7%), atorvastatin, enalapril and simvastatin (4.6% each).

100% of patients took the fiber supplement during the entire study, with the exception of Week 4 (1 patient), Week 6 (1 patient), Week 8 (3 patients), 9 (2 patients) and 10 (2 patients). The reason for not taking the fiber supplement was the onset of discomfort symptoms, like gas and acid, forgetting or travelling away from home with no access to it.

The results show that the change vs. the baseline started to be statistically significant ($p<0.05$), both in the use and in the number of days that stimulant laxatives were used, starting from Week two, which coincided with the start of fiber intake. Table 1 shows the weekly use of stimulant laxatives. Table 2 shows data related to only the 51 patients who completed the 10 weeks of treatment and the number of days that these 51 patients used stimulant laxatives.

Table 1 Use of stimulant laxatives per week

Week →	1	2	3	4	5	6	7	8	9	10
Has used stimulant laxatives										
N	78	62	73	66	62	58	62	57	58	51
No	10 (12.8%)	8 (12.9%)	23 (31.5%)	28 (42.4%)	31 (50.0%)	30 (51.7%)	35 (56.5%)	32 (56.1%)	33 (56.9%)	30 (58.8%)
Yes	68 (87.2%)	54 (87.1%)	50 (68.5%)	38 (57.6%)	31 (50.0%)	28 (48.3%)	27 (43.5%)	25 (43.9%)	25 (43.1%)	21 (41.2%)
Number of days he/she has used stimulant laxatives										
N	78	62	73	66	62	58	62	57	58	51
Average (SD)	3.9 (2.7)	3.6 (2.7)	2.9 (2.7)	2.4 (2.8)	2.2 (2.8)	1.5 (2.2)	1.9 (2.8)	2.0 (2.7)	1.7 (2.6)	1.7 (2.7)
95% CI	(3.3 ; 4.5)	(2.9 ; 4.2)	(2.3 ; 3.5)	(1.7 ; 3.1)	(1.5 ; 3.0)	(1.0 ; 2.1)	(1.2 ; 2.6)	(1.3 ; 2.7)	(1.0 ; 2.4)	(0.9 ; 2.4)
Median (min./max.)	3.5 (0.0 ; 7.0)	3.0 (0.0 ; 7.0)	2.0 (0.0 ; 7.0)	1.0 (0.0 ; 7.0)	0.5 (0.0 ; 7.0)	0.0 (0.0 ; 7.0)	0.0 (0.0 ; 7.0)	0.0 (0.0 ; 7.0)	0.0 (0.0 ; 7.0)	0.0 (0.0 ; 7.0)
P25 ; P75	(1.0 ; 7.0)	(1.0 ; 7.0)	(0.0 ; 6.0)	(0.0 ; 5.0)	(0.0 ; 5.0)	(0.0 ; 3.0)	(0.0 ; 4.0)	(0.0 ; 4.0)	(0.0 ; 2.0)	(0.0 ; 2.0)

Table 2 Use of stimulant laxatives per week (patients who complete the 10 weeks) and number of days the patient has used laxatives

Week →	0	1	2	3	4	5	6	7	8	9	10
N	51	51	51	51	51	51	51	51	51	51	51
Has used laxatives											
Yes	49 (96.1%)	43 (84.3%)	41 (80.4%)	33 (64.7%)	29 (56.9%)	25 (49.0%)	22 (43.1%)	20 (39.2%)	21 (41.2%)	20 (39.2%)	21 (41.2%)
P-value	-	0.0920	0.0279	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Number of days he/she has used laxatives											
Average (SD)	4.0 (2.4)	3.5 (2.6)	2.8 (2.6)	2.5 (2.6)	2.1 (2.7)	2.1 (2.8)	1.4 (2.3)	1.7 (2.7)	1.8 (2.6)	1.6 (2.5)	1.7 (2.7)
95% CI	(3.3 ; 4.7)	(2.7 ; 4.2)	(2.1 ; 3.5)	(1.7 ; 3.2)	(1.3 ; 2.9)	(1.3 ; 2.9)	(0.8 ; 2.0)	(0.9 ; 2.5)	(1.0 ; 2.5)	(0.9 ; 2.3)	(0.9 ; 2.4)
P25 ; P75	(2.0 ; 7.0)	(1.0 ; 7.0)	(1.0 ; 5.0)	(0.0 ; 4.0)	(0.0 ; 4.0)	(0.0 ; 5.0)	(0.0 ; 2.0)	(0.0 ; 4.0)	(0.0 ; 4.0)	(0.0 ; 200)	(0.0 ; 2.0)
P-value	–	0.3001	0.0263	0.0032	0.0002	0.0002	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

The p value is expressed vs. the base level.

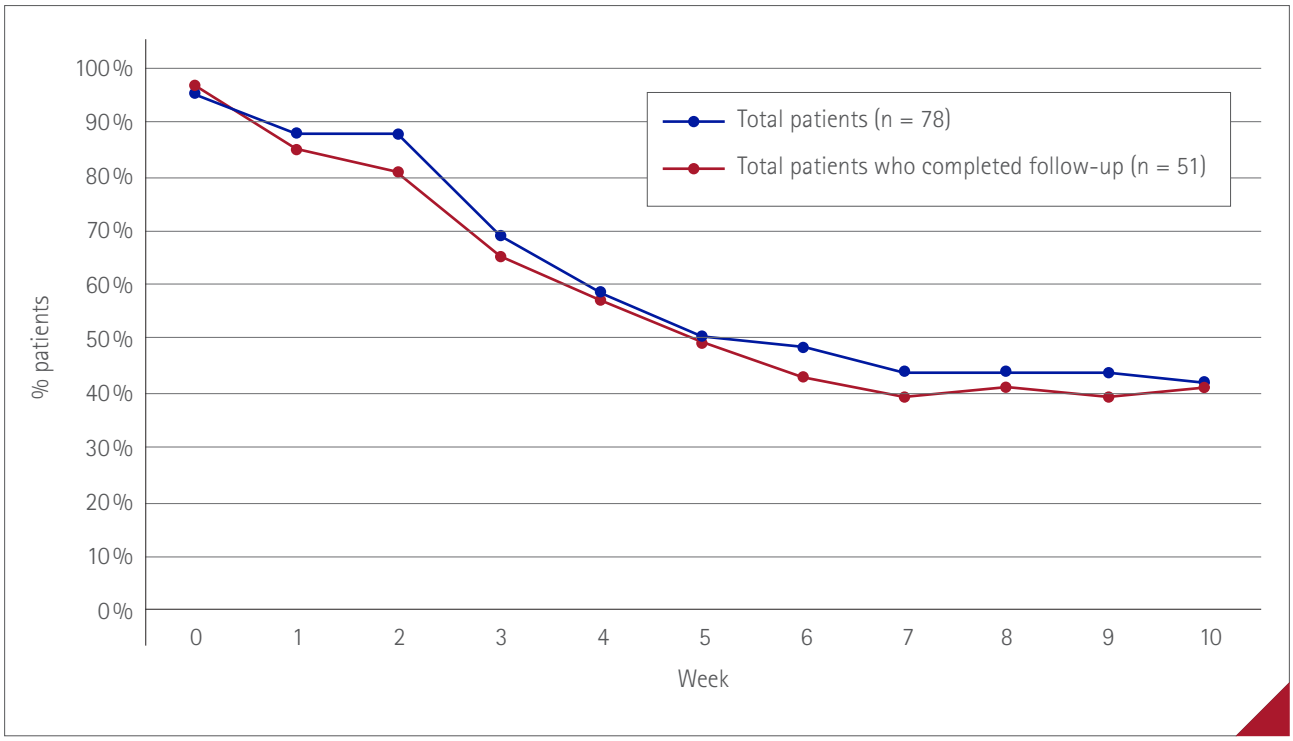

Figure 4 Use of stimulant laxatives per week (% of patients)

With reference to the frequency of bowel movements, it was observed that it was sufficiently homogenous (5.8 [±2.2] base level vs. 6.3 [±1.9] Week 10). Similarly, the average stool consistency did not change significantly: 3.7 (±1.1) baseline Week at 4.1 (±1.5) in Week 10 **(Figure 4)**.

As for gastrointestinal symptoms, they were reportedly reduced on Week 10 vs. the baseline **(Table 3)**.

Acceptability

The results of the questions in the patient questionnaires were grouped in various categories (nothing/almost nothing/little/some/enough/a lot/very much), as follows:

By grouping the categories of sufficient/much/very much in the concept "ease of use" this resulted in a 98.4%. The level of acceptability of the product was 85.5% (it was taken well, without rejection) and the lack of intestinal discomfort (extensive abdominal distension, fullness, etc.) was rated as 50% in these three joint categories.

The fiber texture and taste were considered good by 93.5% and 80.6%, respectively and 61.9% indicated that they would recommend the product.

Adverse events

60.9% of patients reported no adverse events. Conversely, 9.2% stopped taking the fiber supplement due to related discomfort: flatulence (8%), abdominal pain (2.3%) and aerophagia (1.1%).

There was only one patient with a product related severe adverse event who in the end stopped taking the medication.

Table 3 Symptoms during evacuation in Week 1 of treatment vs. Week 10

Symptoms	Week 1 of treatment (n=80)	Week 10 of treatment (n=58)
Abdominal distension	15 (18.8 %)	10 (17.2 %)
Bowel movements	36 (45.0 %)	22 (37.9 %)
Abdominal pain	32 (40.0 %)	12 (20.7 %)
Excessive prolonged strain	38 (47.5 %)	15 (25.9 %)
Abdominal discomfort	29 (36.3 %)	8 (13.8 %)
Unsatisfactory evacuation	45 (56.3 %)	13 (22.4 %)
Other	14 (17.5 %)	4 (6.9 %)

The patient reported uncontrolled arterial hypertension likely caused by Casenfibra®. In this case, the fiber could interfere with the oral absorption of the hypertensive drug due to local interaction at the intestinal level.

DISCUSSION

Although it may seem like a contradiction, the misuse of some laxatives can cause chronic constipation. This fact is more frequently associated with patients who self-medicate and those who have eating disorders.

Stimulant laxatives are the most commonly used and those that are mostly abused, including both those obtained with a medical prescription or pharmaceutical recommendation and those used as self-medication. The main reasons for this abuse are the absence of a prescription requirement, the wide knowledge by part of the general population due to advertising and its low cost. It must be added that they are considered harmless and they are not (17).

Despite their frequent use, few randomized and placebo-controlled studies have been conducted to determine their efficacy and safety during one month of treatment. These studies show a significant increase in evacuation frequency and improvement of stool consistency in favor of bisacondyl and sodium picosulfate vs. placebo. Hence, we cannot emphasize enough that there was a significantly high response to placebo (46 to 54%). Adverse events were generally mild but more common, up to 72% (7).

The adverse events and toxicity of stimulant laxatives usually include constipation (18) and cathartic colon (19-20).

There is still no recommended method of withdrawal from laxatives for people who present with habituation or dependence. However, it is important that withdrawal keeps a normal intestinal function (21).

Changes in lifestyle should be the first steps in the treatment of chronic constipation (22). This work evaluates the suitability of a fermentable and soluble fiber supplement that complements the diet, not a pharmacological one. It is the first work to date that evaluates this change of treatment.

The study used habitual parameters to measure the patient's constipation in primary care consultations. From the first week of treatment, a reduction in the use of stimulant laxatives and of the number of days when they were necessary was observed (P<0.02).

As no study similar to ours has been published to this date, we cannot make a comparison in terms of efficacy. However, a randomized, double-blind, placebo-controlled study showed that Orafti® (inulin), the same substance contained in Casenfibra®, is effective in healthy people with chronic constipation to significantly improve intestinal function (23). When Orafti® was introduced in the diet, an increase in evacuation frequency vs. placebo was observed (4.0 [2.5–4.5] vs. 3.0 [2.5–4.0] evacuations/week, p=0.038).

A review of the studies that compared fiber supplementation with placebo or other alternatives in adult patients with chronic constipation and irritable bowel syndrome (IBS) showed that supplementing with fiber is beneficial in cases of mild and moderate chronic constipation (Evidence Level II, Grade B) (24). Finally, the review by Okawa et al., highlights the efficacy of *psyllium* in the treatment of symptoms of IBS and functional constipation with an increase in the number of complete evacuations and an improvement of the score in the Bristol Stool Chart (25).

In our study, 94.2% of patients at the base level had used at least one laxative during the last week. Of the 51 patients who completed the 10 weeks of treatment, less than half the patients (41%) required a few doses of stimulant laxatives during the last week of study. There was a significant improvement in the reduction of laxatives used at the end of the study and 59% of patients managed to stop taking them.

Our results provide information unknown to this day on the potential use of this fiber as additional treatment of constipation in patients who make chronic use of stimulant laxatives.

In this study, we selected a fiber based on a mixture of soluble fibers (fructooligosaccharides and digestion resistant maltodextrin), but with a distinct degree of fermentability. The fiber selected has organoleptic advantages. It produces a non-viscous solution, is water soluble, colorless, odorless and tasteless, which makes it very easy to take and this was reflected in the acceptability results.

The advantage of this root fiber is that it does not cause habituation, it can be ingested by all kinds of patients, and its most common side effect is gastrointestinal discomfort that usually disappear (26). Additionally, the fiber has a prebiotic effect thanks to its colon fermentation (22).

The key strength of the study is its novelty with reference to its scope: The community pharmacy with a prospective follow-up. The weaknesses are those common to any type of observational study: not having a control group, we cannot subtract the possible placebo effect, but it is sure that each subject has been the control of him/herself, which allows us to compare data.

CONCLUSION

The high frequency of constipation suggests that this fiber could be a valid alternative for those patients who have chronic treatment with stimulant laxatives, in order to eliminate the dependence and associated constipation due to their misuse.

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