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CONSTIPATION:
A TECHNICAL OVERVIEW OF SYMPTOMS,DEFINITIONS, CURRENT MEASUREMENT TECHNIQUES AND THE REGULATORY LANDSCAPE

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Introduction

Almost everyone will suffer from constipation at some stage during their life, and while common, constipation is one of the most difficult gut symptoms to define as it means so many different things to different individuals, from patient to physician. Constipation is physically and psychologically troublesome for many sufferers, and can significantly interfere with daily life and overall well-being. In the general population, the incidence of constipation varies from 2 to 27%[-4], with women, individuals who are overweight and the elderly being affected more commonly[5-7]. Because life expectancy and obesity are increasing, the prevalence of constipation is increasing, with a knock-on effect on the quality of life and socioeconomic burden. The health care costs of constipation are significant, with an estimated $700 million spent annually on laxatives alone in the USA[8]. Constipation is a symptom based disorder, and it's definition in largely subjective. Constipation can present many various symptoms, such as the frequency, consistency, and effort required to expel stool. In the absence of symptoms such as bleeding, anaemia, fever, and weight loss, chronic persistent constipation is likely to be a functional disorder, which has no known cause. Most people report having at least three bowel movements per week, so that two or fewer is often thought of as abnormal.

However, many manage just fine with fewer, while others are uncomfortable within the normal range. Frequency alone, therefore, cannot be considered a sole indicator of constipation. The consistency or form of the stool, the effort required to expel it, how complete the individual fees the bowel movement is and the accompanying abdominal discomfort, bloating and distension are at least as important to consider as frequency. It is estimated that only approximately one third of constipated patients will seek medical attention but the majority will use over-the-counter medications or supplements, such as laxatives, probiotics, fibre or homeopathic remedies, to improve their symptoms. Food based products (such as probiotics, prebiotics, fibre) purported to have a beneficial effect on gastrointestinal health have become increasingly popular with consumers.

Opportunities for foods

Considering the prevalence of constipation, and demographic trends which predict further increases in incidence, there are clear opportunities for food companies to develop product strategies to alleviate constipation symptoms. In Europe any food products claiming to have a beneficial health effect must be approved by the European Food Safety Authority, which evaluates the scientific data presented and provides an opinion on whether there is sufficient scientific evidence to support the claim. As shown in table 1 there has been a very poor success rate, to date, with dossiers submitted to EFSA, with claims ranging from improving intestinal transit time, improving faecal bulk, improving bowel regularity, maintaining normal bowel function etc. The overwhelming reason for the negative opinions is the lack of convincing evidence of efficacy, in turn related to poorly designed clinical studies, or a complete absence of clinical evidence.

Table 1: Summary of EFSA Opinions on health claims related to constipation symptoms. Positive opinions are highlighted in green. All other opinions are negative.

Food product	Health Claim requested/granted	Comment	EFSA Ref
EFSA Article 13(5) – "new function" health claims			
"Transitech®" (hydroxyanthracene derivitaves from plant material, and microorganisms S cerevisiae and B longum)	Improvement of bowel function - reduced transit time, more frequent bowel movements, increased faecal bulk, softer stools	Claim wording approved by EFSA "Hydroxyanthracene derivatives improve bowel function". Dose should provide 10 mg hydroxyanthracene derivatives per day	EFSA Journal 2013; 11(10): 3412
"Transitech®" (hydroxyanthracene derivitaves from plant material, and microorganisms S cerevisiae and B longum)	Improves transit and durably regulates it	Combination is not sufficiently characterised	EFSA Journal 2012;10(9): 2887
Sugar beet fibre	Increasing faecal bulk	Claim wording approved by EFSA "Sugar beet fibre increases faecal bulk". To bear the claim a food should be at least "high in fibre" as per Reg (EC) No 1924/2006.	EFSA Journal 2011;9(12): 2468

Food product	Health Claim requested/granted	Comment	EFSA Ref
EFSA Article 13(5) – "new function" health claims			
Sugar beet fibre	Decreasing intestinal transit time	No conclusion can be drawn from 3 of 4 human intervention studies owing to methodological weaknesses, whereas 1 study showed no effect of the consumption of sugar beet fibre on decreasing orofaecal transit time	EFSA Journal 2011;9(12): 2467
Synbio (L rhamnosus IMC 501® and L paracasei IMC 502®	Maintaining and improving intestinal well-being	Only 1 human study evaluated outcomes related to the claimed effect and that the weaknesses of study limited its value for the scientific substantiation of the claimed effect	EFSA Journal 2010; 8(9): 1773
Bimuno® GOS	Reducing gastro-intestinal discomfort	Did not provide any studies from which data could be used for claimed effect of reducing gastro-intestinal discomfort	EFSA Journal 2014;12 (7): 3756
Combination of B longum LA 101, L helveticus LA 102, L lactis LA 103, S thermophilus LA 104	Reducing gastro-intestinal discomfort.	The only human study provided for the substantiation of the claim didn't find an effect of a combination of the bacterial strains on gastrointestinal discomfort	EFSA Journal 2014; 12 (5): 3659
Combination of B longum LA 101, L helveticus LA 102, L lactis LA 103, S thermophilus LA 104	Improvement of bowel function by increasing stool frequency	Human study provided for the substantiation of the claim did not find an increase in stool frequency	EFSA Journal 2013;11(6): 3256
Lactobacillus rhamnosus GG	Maintenance of normal defecation during antibiotic treatment	information submitted from 5 out of 7 human intervention studies is insufficient to allow a full scientific evaluation	EFSA Journal 2013; 11(6):3256

EFSA Article 14 – children's development and health			
Beta-palmitate	Softening of stools pursuant	Of 2 human intervention studies, 1 one suggested a stool-softening effect of beta-palmitate but the 2nd didn't, & 1 animal study did not support a stool-softening effect, and the mechanistic evidence by which beta-palmitate could contribute to the softening of stools is weak	EFSA Journal 2014; 12(2): 3578

Food product	Health Claim requested/granted	Comment	EFSA Ref
Article 13(1) – general function health claims			
Isomalto-oligosaccharides	Normal bowel function/ gastrointestinal function/colonic function	No human studies provided from which conclusions could be drawn for the claimed effect	EFSA Journal 2010; 8 (10):1801
Hibiscus sabdariffa L	Improvement of bowel motor function	No cause and effect established	EFSA Journal 2009; 7(9):1293
Bifidobacterium animalis subsp. lactis LMG P-21384	Changes in bowel function	No human intervention studies were provided from which conclusions could be drawn for the scientific substantiation of the claim	EFSA Journal 2012; 10 (8):2851
Group of bacterial species	Intestinal mobility, reducing GI discomfort associated with increased transit time, relief of abdominal discomfort and pain, reduce the daily number of bowel movements	Data provided were not sufficient to characterise the microorganisms	EFSA Journal 2012; 10 (8): 2854
Dried plums of 'prune' cultivars (Prunus domestica L)	maintenance of normal bowel function	to obtain the claimed effect, about 100 g of dried plums (prunes) should be consumed daily	EFSA Journal 2012;9(6): 2254
Partially hydrolysed guar gum (PHGG)	"bowel function", and "intestinal health and regularity"	only human intervention study provided from which conclusions could be drawn did not show any effect on stool frequency or consistency, and that PHGG induced an increase rather than a decrease in colonic transit time	EFSA Journal 2011; 9(6):2254
Sugar beet fibre	Changes in bowel function	No relevant human intervention data provided	EFSA Journal 2011; 9(4):2034
Galacto-oligosaccharides (GOS) Bifidobacterium longum BB536	Maintains a healthy normal digestive system	No references provided from which conclusions could be drawn for the scientific substantiation of the claimed effect	EFSA Journal 2011; 9(4):2060
Bifidobacterium longum BB536	Improvement of bowel regularity	The human intervention studies provided had weaknesses in the study designs and statistical analyses, and no conclusions could be drawn	EFSA Journal 2011; 9(4):2041
Lactobacillus paracasei B21060	Maintenance of a normal intestinal transit time	No human studies were provided that addressed endpoints related to intestinal transit time.	EFSA Journal 2010; 8(10):1817

Food product	Health Claim requested/granted	Comment	EFSA Ref
Article 13(1) – general function health claims			
Wheat bran fibre	Increase in faecal bulk and reduction in intestinal transit time	"Wheat bran fibre contributes to an increase in faecal bulk", "Wheat bran fibre contributes to a reduction in intestinal transit time" for at least 10 g per day	EFSA Journal 2010; 8 (10):1817
Methylsulphonylmethane (MSM)	Maintenance of normal bowel function	No references were provided from which conclusions could be drawn	EFSA Journal 2010; 8(10):1746
Prune juice	Maintenance of normal bowel function	Human intervention studies cited used interventions other than prune juice, and the other references provided only general background information and didn't provide data to substantiate the claimed effect	EFSA Journal 2010; 8 (10):1768
Lactulose	Reduction in intestinal transit time	"Lactulose contributes to a reduction in intestinal transit time" at least 10g of lactulose/d	EFSA Journal 2012; 8 (10): 1806
Polydextrose	Changes in bowel function and and reduction of gastro-intestinal discomfort	No references were provided from which conclusions could be drawn for the scientific substantiation of the claims.	EFSA Journal 2011;9(6): 2256
Resistant maltodextrin	Changes in bowel function	No references in an EU language that addressed the claimed effect were provided	EFSA Journal 2011;9(4): 2070
Acacia gum (gum Arabic)	Improved intestinal conditions (pH, SCFA production) and intestinal functions	1 study did not show an effect of acacia gum on stool frequency or wet and dry faecal weight, 1 study showing an effect of acacia gum on faecal weight, but not on stool frequency, was a small study in which the assessment of faecal weight and stool frequency was a secondary endpoint	EFSA Journal 2011;9(4): 2022
Fructooligosaccharides (FOS)	Changes in bowel function, reduction of gastro-intestinal discomfort	the only relevant human study showed no effect of FOS on bowel function. No references were provided from which conclusions could be drawn for the scientific substantiation of GI discomfort	EFSA Journal 2011;9(4): 2023
konjac mannan (glucomannan)	Normal bowel function	No studies were provided from which conclusions could be drawn for the substantiation of the claimed effect	EFSA Journal 2010; 8(10): 1798
"Wheat dextrin"	Maintenance of normal bowel function	Only 1 study reported an effect of wheat dextrin on stool weight in a small sample of subjects at a dose considerably higher than the doses proposed in the conditions of use, while the 2 other human studies provided did not show an effect on the outcomes which were related to the claimed effects	EFSA Journal 2010; 8 (10): 1761
Hydroxypropyl methylcellulose (HPMC)	Maintenance of normal bowel function	No references were provided from which conclusions could be drawn for the scientific substantiation of the claimed effect	EFSA Journal 2010; 8 (10): 1739

The EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) issued guidance on the scientific requirements for health claims related to gut and immune function (EFSA Journal 2011;9(4):1984), in which they state in section 3.1. on claims on bowel function that "Normal bowel habits vary considerably from person to person with regard to frequency of bowel movements, and bulk and consistency of stools. Constipation is associated with longer transit time, less frequent bowel movements, reduced faecal bulk and harder stools..." EFSA currently has an open consultation process ongoing (closing date for submissions is Sept 10th 2014) in order to revise this guidance on the scientific requirements for health claims related to gut and immune function.
Based on the EFSA guidance, and our experience in conducting clinical studies in the area of constipation, this whitepaper outlines various aspects that should be taken into consideration when designing and conducting clinical intervention studies.

Definition of constipation

Definition of constipation is very subjective and hence symptom-based diagnostic criteria (Rome criteria) have been developed by groups of experts. The "Rome process" is an international effort to create scientific data to help in the diagnosis and treatment of functional gastrointestinal disorders (FGIDs), such as irritable bowel syndrome (IBS), functional dyspepsia and functional constipation. The Rome criteria view functional constipation as: "...a group of functional disorders which present as persistent difficult, infrequent or seemingly incomplete defecation." The word functional implies that the cause is unknown (idiopathic). The consensus documents Rome I, II and III are considered the gold standard in diagnosing functional GI conditions. Table 2 summarises the Rome criteria for functional constipation.

Table 2: Definitions and symptoms of functional constipation. Adapted from the Rome Foundation website www.romecriteria.org

Symptom	Rome I (1994)	Rome II (1999)	Rome III (2006)
Duration	Two or more of the following for at least 3 months	At least 12 weeks, which need not be consecutive, in the preceding 12 months of two or more of the following	Two or more of the following for at least 3 months, with symptom(s) onset at least 6 months before diagnosis
Straining	>25% of the time	>25% of the time	During 25% of defecations
Hard/lumpy stools	>25% of the time	>25% of the time	At least 25% of defecations
Tenesmus	Sensation of incomplete evacuation >25% of the time	Sensation of anorectal obstruction/blockage in >25% of defecations	Sensation of incomplete evacuation in at least 25% of defecations
Manoeuvres to facilitate defecation	–	>25% of defecations (eg, digital evacuation, support of the pelvic floor)	In at least 25% of defecations (eg, digital evacuation, support of the pelvic floor)
No. of bowel movements	≤2 per week	<3 per week	<3 per week
Abdominal pain	Not required	–	–
Loose stools	Not present	Not present	Rarely present without use of laxatives

Methods used to measure clinical outcom for constipation

As part of any clinical study to evaluate the effectiveness of an intervention, such as a food ingredient, a number of different methods can be used to assess the symptoms of constipation and establish if there is a change following the intervention. The outcomes that will often be measured in constipation studies include changes in the number of spontaneous bowel movements (SBMs; i.e. bowel movements occurring without the use of laxatives, suppositories or enemas), complete spontaneous bowel movements (CSBMs, spontaneous bowel movements that the individual feels are complete or that he or she feels satisfied with) change in stool consistency, reduction in the use of laxatives, improvement in the quality of life, reduction in gut transit time, increase in faecal bulk and changes in the composition of the gut microbiota. For pharmaceutical studies SBMs or CSBMs have been the most common primary endpoints in recent studies, with individual symptoms and some measure of quality of life as secondary endpoints.

Validated questionnaires: Several constipation-specific questionnaires have been developed to assess aspects such as symptoms and the subjects' quality of life. Two of the most used questionnaires are the Patient Assessment of Constipation Symptoms (PAC-SYM)15 and Patient Assessment of Constipation - Quality of Life questionnaire (PAC-QOL)16. The PAC-SYM questionnaire is a 12-item self-report instrument divided into abdominal, rectal and stool symptoms. The PAC-QoL is a 28 item questionnaire with four subscales (worries and concerns, physical discomfort, psychosocial discomfort, and satisfaction) and an overall scale, providing a comprehensive assessment of the burden of constipation on patients' everyday functioning and well-being. Both questionnaires have been validated and shown to be internally consistent, reproducible, valid and responsive to improvements over time.

Symptom diaries are generally used to monitor and record the date and time of each SBM, straining during defecation, incomplete evacuation, a feeling of blockage and if any manual manoeuvres are used to assist with defecation. In addition, diaries stool consistency using the Bristol Stool Scale, abdominal pain, and medication or laxative use during the run-in and intervention periods.

Gut transit: These measurements indicate how long it takes food to pass through the gastrointestinal tract, and the most typical measurement is whole gut or oral-faecal transit time. This is the time taken from mouth to anus and in a healthy individual will vary from 35-45hrs. There are a variety of methods used (for a review of some see Rao et al17).

Radio-opaque markers (ROM) and X-ray: A gelatin capsule containing 20-24 individual markers is ingested, and an X-ray of the abdominal area is taken after 5 days to ascertain how many pellets have been passed and the location of any remaining pellets. ROMs are not absorbed and recovery rates are in excess of 98%18, and this is the most common method of gut transit measurement. In the context of food studies, it may be preferable to count the ROMs in the stool samples rather than expose the volunteers to radiation, in which case the subject collects stool samples for 5 days and these are x-rayed. In order to reduce subjective interpretation by radiologists, usually 2 individual readers are used. Gut transit is considered normal if more than 80% of the ROMs have been passed in 5 days.

Coloured markers: A coloured marker, such as carmine or activated charcoal, is ingested and each stool sample collected after ingestion is examined for the appearance of the coloured marker.
Wireless motility capsule: The subject ingests a disposable wireless capsule, which sends data in real time to a wearable monitor that records pH, temperature and intraluminal pressure data for 5 days19. This method is standardised and validated, radiation-free but is less widely available and tends to be more costly.

Colonic scintigraphy: The subjects ingests a radioisotope marker (usually 99Technetium or 113Indium) in a capsule and images are captured with a gamma camera taken at 24, 48, and 72 hours for colonic transit.

Faecal bulk (or volume): This is a measure of the weight of faeces produced, and can be measured either as wet faecal weight or dry faecal weight. All stool samples are collected for a period (e.g. 5 days) and the weights are typically expressed as the average weight per day. Faecal bulk comprises of unfermented fibre, salts, water and bacterial mass, and increased faecal bulk increases the water-holding capacity of faeces leading to a softer stool. For dry weight, the total stool (or a representative sample such as 10 g) is oven or freeze dried until the weight remains constant, indicating that all water has been removed – this is a more standardised method as the weight is independent of stool consistency.

Gut microbiota: There is increasing scientific data to indicate that the bacterial community in the gut, which are predominantly present in the colon, may influence functional bowel disorders, through the metabolic activity of the luminal microbiota and the potential for the gut microbiota to influence gut function via interactions with the mucosal immune pathway and/or influencing epithelial permeability20-21. Hence, increasingly gut health related food intervention studies are exploring the composition of the GI microbiota pre- and post-intervention in order to establish if the food ingredient in question changes the microbiota, and if this has any impact on health measures. Our group has carried out recent clinical studies that explore the inter-relationship between diet, gut microbiota and health in the elderly22 and in professional athletes23, both ideal target groups for specifically designed food products.

Food Diaries: In addition to measuring the outcomes above, in any intervention study pertaining to gastrointestinal health, it is also important to have a good understanding of the habitual food consumption of the participant in order to understand the food groups and nutrients being consumed (e.g. in a fibre intervention study how much other fibre is consumed), and to ensure eating habits do not change over the course of the intervention period.

24 hour food recall diary is a retrospective method where an individual is interviewed about their food and beverage consumption during a defined period of time, typically the previous day or the preceding 24 hours. Recall of intake over a longer time period is problematic due to the limitations of memory. Several national surveys use the 24-hour recall method because of its high response rate and its ability to obtain detailed information.

A Weighed food diary which the volunteer completes at home listing all the foods and beverages consumed, and weights thereof, as well as cooking methods and brands of the food. A diary is provided to the subjects and either a 7 day diary, or a 3 day (with 2 days being weekdays and one day being a weekend day diary) is used. The subject is instructed by a nurse or nutritionist on how to fill out the diary and a balance is also provided.

Food frequency questionnaires (FFQ) are designed to assess habitual diet by asking about the frequency with which food items or specific food groups are consumed over a reference period (e.g. 6 months or a year). Some FFQs, known as semi-quantitative, can provide nutrient quantification and therefore also include portion size estimates. Some well-known FFQs are the Harvard or Willett questionnaire24, the Block questionnaire25 and the EPIC (European Investigation of Cancer) FFQ26, which is based on the Willet.

For each of the methods above data on intake of specific foods, food components or nutrients can be calculated using nutrient analysis programmes based on appropriate food composition tables, such as CAFÉ (Compositional Analyses from Frequency Estimates) or FETA (FFQ EPIC Tool for Analysis)27.

Conclusions

In summary, there is a significant opportunity for the development of food products to benefit patients who suffer from functional or occasional constipation. But in order to demonstrate a beneficial physiological effect it is essential that well designed and statistically powered clinical studies are carried out, with suitable endpoints (both in terms of symptoms and objective measures of gut physiology) to demonstrate a clinical benefit.

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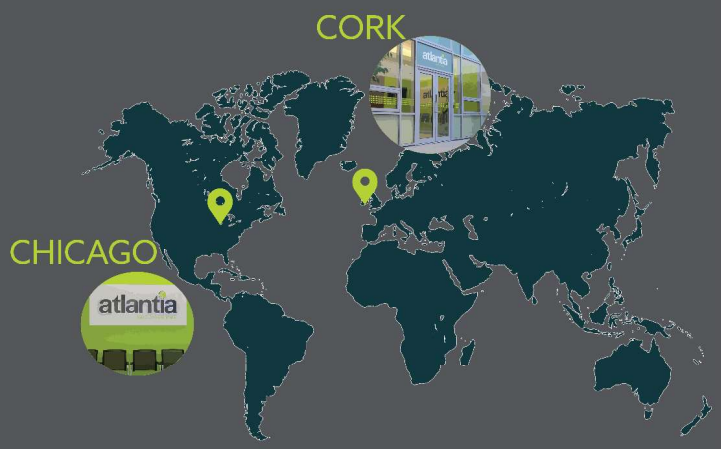
OUR CLINICAL EXPERTISE

DIGESTIVE HEALTH AND CONSTIPATION

Atlantia Food Clinical Trials has a particular strength in providing human dietary intervention studies in the area of digestive health, in accordance with EFSA guidelines on scientific requirements for health claims related to gut and immune function (EFSA Journal 2011; 9(4):1984). We have extensive expertise in looking at digestive health in a variety of populations such as healthy, including infants and elderly, and in patient groups (e.g. Irritable Bowel Syndrome). We also have experience in trials with different test products, from probiotics to protein, and fruit extracts to marine extracts. We work with our clients to design a study most suitable for their products in accordance with EFSA guidelines, analysing peer-reviewed publications, agreeing the most suitable end-points and statistically powering studies to ensure that studies will meet requirements. We have a large database of healthy, IBS and GI patient populations to support volunteer recruitment.

- We provide end to end solutions for the entire clinical study process
- ICH GCP Standard trials
- Reguratory environment expertise, including EFSA and FDA
- One company, with multi-centre capability



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