Adopting new enrollment criteria for pharmaceutical trials in constipation: look before leaping

William E. Whitehead and Giuseppe Chiarioni

Introduction

In this issue Dr Camilleri provides an important critique of the use of the Rome III criteria for functional constipation as inclusion criteria for clinical trials of new drugs or other therapies for chronic constipation. He points out that the Rome criteria for functional constipation require the presence of any two of six symptoms, some of which are suggestive of slow transit (e.g. less than three stools per week, hard or lumpy stools) and some of which are suggestive of evacuatory dysfunction (e.g. straining, sensation of anorectal blockage, and manual maneuvers to facilitate defecation). He reminds us that recent studies suggest that patients with evacuation disorders show a poor response to laxatives and suggests that, consequently, the use of inclusion/exclusion criteria that do not distinguish among subtypes of constipation may lead to an underestimation of the efficacy of new therapeutic agents with a mechanism of action similar to laxatives and to an overestimation of the sample sizes required to adequately power clinical trials. He ends by proposing alternative symptom criteria for clinical trials based on the presence of key symptoms of infrequent stools and hard or lumpy stool consistency, combined with the absence of excessive straining and manual maneuvers to facilitate defecation.

This is a valid concern: inclusion criteria based only on the Rome III criteria for functional constipation will inevitably result in the inclusion of a heterogeneous group of patients with constipation. However, one should be cautious about embracing new symptom criteria before evaluating their sensitivity and specificity for discriminating patients with disordered defecation from patients with other types of chronic constipation.

The comments below begin with an explanation of the rationale behind the Rome III symptom criteria for functional constipation, including comments on why the Rome criteria for functional constipation are different for children and adolescents compared with adults. Then we summarize published evidence suggesting that the new symptom criteria proposed by Dr Camilleri have only modest sensitivity and specificity and may require further testing to make sure they will achieve the objective of reducing the heterogeneity of study populations in clinical trials.

Rationale behind development of the Rome III criteria for functional constipation

There are at least four physiological mechanisms for the symptom of constipation: slow transit, when decreased peristaltic motility results in delayed transit throughout the colon; functional outlet obstruction (also called pelvic floor dyssynergia), when the pelvic floor muscles fail to relax or paradoxically contract during attempted defecation; obstructed defecation, when mechanical factors such as rectocele or rectal prolapse impair rectal evacuation; and 'normal transit' or idiopathic constipation, when there is neither evidence for delayed transit nor outlet delay but the patient nevertheless complains of constipation. There are no reliable community surveys of the prevalence of these four types of constipation because physiological tests are required to distinguish them. However, in the largest clinical series tested by transit studies and anorectal manometry [Nyam *et al.* 1997] slow transit constipation had a prevalence of 8%, pelvic floor dyssynergia had a prevalence of 27%, and the remaining 65% had normal tests (idiopathic

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constipation). The prevalence of obstructed defecation was not reported but was apparently small.

The committee of experts who developed the Rome criteria for functional constipation were mindful of the diversity of causes of chronic constipation. However, they were also aware that symptoms are an unreliable way of discriminating among these subtypes of constipation (see below). For this reason they elected to provide symptom criteria only for the purpose of identifying patients with clinically significant chronic constipation [Longstreth *et al.* 2006]. Their expectation was that additional physiological tests such as anorectal manometry, balloon evacuation, and whole gut transit would be required to discriminate the subtypes. This is exemplified by the criteria published by the Rome Foundation for disordered defecation [Wald *et al.* 2006], which require that a patient satisfy symptom criteria for functional constipation as well as exhibiting at least two of three physiological indicators of outlet dysfunction (incomplete evacuation of the rectum, failure to relax pelvic floor muscles when straining, and/or inadequate rectal propulsive forces). No comparable physiological criteria were specified for slow transit or idiopathic constipation, although these are incorporated into the recently published diagnostic algorithms for chronic constipation [Bharucha and Wald, 2010].

Symptoms fail to discriminate outlet dysfunction from other types of constipation

The paper by Rao and colleagues [Rao *et al.* 2004], which Dr Camilleri cites, suggests that symptoms of excessive straining and incomplete evacuation have good sensitivity for the diagnosis of outlet dysfunction (84% and 76% respectively), and that manual maneuvers to facilitate defecation may also be useful (endorsed by 54% of women and 25% of men with outlet dysfunction). However, this study does not address the specificity of symptom criteria for outlet dysfunction. Three studies [Grotz *et al.* 1994; Glia *et al.* 1999; Minguez *et al.* 2004] have reported that the proportion of patients with other types of constipation who endorse these symptoms is high. Table 1 shows the inability of symptoms to discriminate between subtypes of constipation in two large clinical series. In the first study [Grotz *et al.* 1994] patients were classified as normal transit (NTC), slow transit only (STC),

pelvic floor dyssynergia (PFD), or combined STC+PFD on the basis of a radiopaque marker transit study, balloon evacuation test, anorectal manometry, and defecography. In the second study [Glia *et al.* 1999] patients were classified into these categories based on a radiopaque marker transit study, defecography, anorectal manometry, and electromyography. None of these symptoms discriminated PFD from other types of constipation at statistically significant levels, although in the Grotz study, there was a trend for the symptom of feeling of anal blockage to discriminate the PFD group from other types of constipation. Having less than three stools per week discriminated STC from other types of constipation in the Glia study but not in the Grotz study.

Minguez and colleagues [Minguez *et al.* 2004] compared 24 patients with PFD with 106 patients with chronic constipation who did not have dyssynergia when tested by anorectal manometry and defecography. On a 30-day symptom diary, 92% of the dyssynergia group reporting straining on more than 25% of defecations but so did 85% of constipated controls (difference not significant). By questionnaire, 63% of the dyssynergia group reported a sensation of anorectal obstruction compared with 39% of controls with constipation ($p < 0.05$). There was no difference in reported use of manual maneuvers to facilitate defecation (frequency not reported), and no differences in the proportion with fewer than three stools per week or the proportion with frequent hard stools. This is consistent with our own experience [Chiarioni *et al.* 2005]: we enrolled 52 patients with fewer than three bowel movements per week plus delayed whole gut transit (greater than 20% retention of radiopaque markers at 5 days), but 34 of them (65%) were found to have PFD when tested with anorectal manometry and a balloon evacuation test, and these patients showed a good clinical response to biofeedback training.

Differences between adult and pediatric criteria for functional constipation

Dr Camilleri is also critical of the fact that the pediatric Rome criteria for functional constipation [Di Lorenzo *et al.* 2006] differ from the adult criteria and do not include symptoms of outlet dysfunction. The pediatric criteria are intentionally different from the adult criteria in that they depend on behavioral observations by

Table 1. Inability of symptoms to discriminate subtypes of constipation.

Symptom	[Grotz <i>et al.</i> 1994]				[Glia <i>et al.</i> 1999]			
	NTC [%]	STC [%]	PFD [%]	STC + PFD [%]	NTC [%]	STC [%]	PFD [%]	STC + PFD [%]
Excessive straining	60	64	73	75	74	71	72	77
Feeling of incomplete emptying	60	77	70	79	77	61	97	63
Anal blockage	27	29	47	42	—	—	—	—
Digital maneuvers	32	7	41	33	32	7	41	33
<3 stools/week	38	54	40	67	40	82*	53	85
Hard stools	72	69	70	71	47	46	34	48

NTC, normal transit constipation; STC, slow transit constipation; PFD, pelvic floor dyssynergia; STC + PFD, combined slow transit and dyssynergia. * $p < 0.05$.

parents rather than on symptoms reported by children because children are presumed to be less reliable reporters of their symptoms. However, it is not correct that the pediatricians who developed the Rome criteria believed outlet dysfunction to be irrelevant to constipation in children; rather intentional stool withholding (which is indistinguishable from pelvic floor dyssynergia) is considered to be the most common etiology for constipation and encopresis in children [Di Lorenzo *et al.* 2006; Loening-Baucke, 2004] and is represented in the behavioral signs used to diagnose pediatric functional constipation.

What can be done to improve inclusion criteria for clinical trials?

We are in agreement with Dr Camilleri that there is a need to develop more sensitive and specific inclusion criteria for clinical trials of new treatments for chronic constipation. However, we recommend that new symptom criteria such as those proposed by Dr Camilleri be tested for sensitivity and specificity to make sure they are able to improve on existing criteria before they are adopted. On the basis of published studies comparing these and similar symptom criteria against physiological assessments, we are not optimistic that these symptom criteria will achieve the intended purpose. Moreover, there is a cost to changing inclusion criteria prematurely, which is that older studies become difficult to compare to new ones.

In practice, the Rome criteria for functional constipation are rarely applied 'out of the box' as inclusion criteria; rather most investigators modify the criteria by requiring a higher baseline

threshold for the symptoms they expect to be most responsive to their intervention.

Another approach to improving inclusion/exclusion criteria is by incorporating a digital rectal examination or balloon evacuation test into the screening protocol. There is emerging evidence that digital rectal examination has reasonable sensitivity (75%) and specificity (87%) for identifying pelvic floor dyssynergia [Tantiphlachiva *et al.* 2010], and the balloon evacuation test, which can be accomplished with a Foley catheter in any clinical setting in 10 minutes, has repeatedly been shown to discriminate pelvic floor dyssynergia from other types of constipation with a high degree of specificity [Chiarioni *et al.* 2005; Minguez *et al.* 2004].

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Conflict of interest statement

None declared.

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