Published in final edited form as:
Am J Gastroenterol. 2009 April ; 104(4): 920–922. doi:10.1038/ajg.2009.20.

Is Adequate Relief Fatally Flawed or Adequate as an End Point in Irritable Bowel Syndrome?

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Abstract

There is controversy on the validity of binary end points used in irritable bowel syndrome (IBS) clinical trials. In a usual-care observational study, baseline severity influenced the response measured as satisfactory relief. This editorial reviews the observations from a non-pharmacological study to assess the effect of baseline severity on the performance of binary end points in large drug trials. The pivotal finding is that once the patients who reported adequate relief at baseline were excluded from the analysis, baseline severity no longer affected the proportion of patients reporting adequate relief of IBS with treatment. As large drug trials enriched the study cohorts for at least moderate severity after a no-treatment, run-in period, it seems likely that the precaution of excluding mild disease *de facto* resolved the hypothetical weakness of the adequate relief end point. Given the high responsiveness and longitudinal construct validity demonstrated with adequate relief end point, it should be accepted as a trial end point.

Patient-reported outcomes are generally preferred in assessing the effects of treatments as they reflect the observation on outcome of the patient rather than the caregiver (1). The selection of appropriate outcome measures may involve several steps, as detailed in the patient-reported outcomes guidance document (1): First, identifying the concepts and domains that are important to the intended patient population, and hypothesizing the expected relationships among concepts; second, development of outcome measures with appropriate format, instructions, scoring, administration, and refining it with experience; third, assessing the properties of the instrument for score reliability, validity and ability to detect change, administrative and respondent burden, and revising it with experience; and fourth, modification of the instrument to be relevant to the concepts measured, populations studied, research application, instrumentation, and method of administration.

Over the past 10 years, a variety of binary end points and end points based on Likert-type response or visual analog scales have been used to assess the efficacy of treatment in patients with irritable bowel syndrome (IBS). These included adequate relief, satisfactory relief, Subject Global Assessment of Relief (SGA), a modified version of the SGA, Global Improvement Scale, IBS Severity Scoring System (IBS-SSS), abdominal discomfort/pain score, and abdominal pain severity score. The descriptions of these end points, the nature of the responses (binary vs. scale vs. score), and medications are summarized elsewhere (2).

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DISCLOSURE

Dr Camilleri reports having served as a consultant to and having received research grants from pharmaceutical companies, but he received no support for authoring this editorial.

It is estimated that close to 20,000 patients have been evaluated in those studies over more than a decade. In general, academic clinicians with specific expertise in IBS in Europe and the United States (3, 4) have concluded that the binary and global end points showed evidence of responsiveness in the clinical trials. Adequate relief was earlier shown to be associated with improvement of multiple secondary end points (5) and to be associated with clinically and statistically significant benefit with several drugs in IBS trials, including alosetron, cilansetron, dextofisopam, and asimadoline. Similarly, some trials with tegaserod used satisfactory relief and showed significance as primary end points were concurrent with improvements in multiple secondary end points. As a clinician who had access to medications such as alosetron and tegaserod, which showed efficacy based on these end points, I observed that the reported trial efficacy was mirrored by effectiveness in clinical practice. Formal studies documented improved quality of life in patients who received medications that were associated with an increased proportion of adequate relief responders as compared with placebo in clinical trials. For example, this was demonstrated with alosetron treatment (6).

In a prior publication in this journal, Whitehead *et al*. (7) suggested that binary end points are suboptimal for detection of clinically meaningful effects of medications in IBS, and that they are biased toward patients with mild IBS as the proportion of patients showing response to usual care was greater among those with mild vs. moderate vs. severe IBS, when severity was based on the IBS-SSS score. This conclusion was therefore based on an observational study that assessed satisfactory (not “adequate”) relief in IBS patients in managed care (8). It is not clear whether the observations in a usual-care setting are generalizable to clinical trials that assess specific treatment interventions; in usual-care “studies” that are not placebo or comparator controlled, patients are taking multiple different treatment regimens. Patients participating in a clinical trial can differ from patients in a managed-care setting, whose symptoms are more likely to be mild and less likely to meet screening criteria to be included in a clinical trial. Despite the relatively small size (n = 350 patients) of the study by Whitehead *et al*. relative to the demonstrated responsiveness of binary end points in ~13,000 patients in clinical trials of at least three pharmaceutical products, the validity of the binary end points is questioned by regulatory agencies.

So, one might ask: “Is “adequate relief” fatally flawed or is it “adequate” for IBS treatment trials?” The Rome III recommendation (9) suggested that it was flawed and required further validation. Is it possible to enhance the validity of “adequate relief” as an end point?

The paper from Passos *et al*. (10) in this month’ s issue of the journal adds useful information to the ongoing debate on the validity of adequate relief as an end point in IBS trials. The most important strengths of the paper are: first, it has confirmed the observation of Whitehead *et al*. that baseline severity impacts the proportion of adequate relief responders in a non-pharmacological treatment trial. Second, once the patients who reported adequate relief at baseline (28% in the study of Passos *et al*.) were excluded from the analysis, baseline severity no longer affected the proportion of patients reporting adequate relief of IBS in response to a non-pharmacological treatment. The study suggests that a simple, eminently feasible precaution can be instituted to manage the confounding effect of baseline severity on treatment outcomes measured using adequate relief as end point. Thus, the authors propose that inclusion of a run-in period to ensure that patients are still sufficiently symptomatic at the start of the randomized treatment would restore the validity of adequate relief as an end point in IBS clinical trials. However, it must be noted that, in randomized, placebo-controlled studies with alosetron (11) or dextofisopam (4), adequate relief responses were not sensitive to baseline severity.

The authors acknowledge weaknesses of their current paper: lack of drug treatment, focus on acupuncture and practitioner–patient relationship as treatment, small number of patients with mild symptoms, short duration of the study (3 weeks), and potential confounding due to concomitant pharmacological treatments including antidepressants. Nevertheless, the main recommendation to exclude baseline responders from randomization is consistent with the observations in the large drug-treatment trials (e.g., with alosetron), and justifies the validity of the outcomes previously reported in those trials based on adequate relief end points. Thus, patients included in several trials (e.g., with alosetron) were required to have minimum levels of pain and alteration in stool consistency to be eligible for randomization. Typically, severity of pain and discomfort were assessed daily on a 5-point scale (0, none; 1, mild; 2, moderate; 3, intense; and 4, severe) and average daily baseline pain and discomfort scores during the 2-week screening period were required to be between 1.0 and 3.3 (inclusive) for patients to enter the treatment phase. Similarly, stool consistency data were monitored daily and scored as follows: 0, no stool; 1, very hard; 2, hard; 3, formed; 4, loose; and 5, watery. During the screening period, average daily stool consistency scores of 2.5 or higher were required to exclude patients with hard stools and enroll patients whose predominant bowel abnormality was diarrhea. It is likely, therefore, that the large alosetron trials and the performance of the binary end point were not compromised by a greater response in those with mild symptoms as the latter were excluded from the trials (12–20).

As earlier trials that used binary end points did not classify patients according to the IBS-SSS, one cannot be sure that the severity scales actually match; however, patients with average daily pain scores >1 on the 0–4 scale for over 14 days, detailed above, are not likely to categorize their pain as mild or rate their pain with a score <75 on the IBS-SSS. It is important to note that the IBS-SSS instrument used by Whitehead *et al*. (7) to evaluate severity, and specifically recommended by Rome III (9), is itself the subject of controversy (4) and questionable validity. This is discussed in detail elsewhere (4). In summary, whereas IBS-SS has reasonable discriminant validity and responsiveness, current data on internal consistency, test–retest reliability, content and construct validity were all suboptimal and deemed to require further validation, and there are still no full publications that have tested the performance of this instrument in randomized controlled drug trials (4).

Three other preliminary reports or papers have assessed the influence of baseline severity on the performance of the adequate relief end point (12, 21, 22). Ameen *et al*. (12) studied the effect of alosetron and placebo in >1,200 IBS patients in an alosetron treatment database and detected no statistically significant effect of baseline severity. Leventer *et al*. (21) evaluated dextofisopam in 140 IBS patients in a prospective placebo-controlled study; there was no statistically significant effect of baseline severity (4). Lackner *et al*. (22) evaluated cognitive behavioral therapy in 75 IBS patients and identified ~70% adequate relief response in patients with moderate to severe IBS. This proportion of responders would not be expected using binary end points in the more severe IBS according to the data of Whitehead *et al*. (7).

Thus, the paper of Passos *et al*. is informative, and if the suggestion to exclude baseline responders before randomization is confirmed in prospective clinical trials involving drugs, it would provide a practical solution to enhance performance of adequate relief as an end point. Similarly, it would be important to apply the same type of analysis to other end points including the IBS-SSS, or a 50% improvement in primary symptom end points such as abdominal pain. Ultimately, it is reassuring to note that the data with ~13,000 patients included in the placebo-controlled trials with alosetron, tegaserod, and cilansetron were not fatally flawed because of a compromised end point, and that the exclusion of patients with insufficient baseline severity or symptom resolution during the run-in actually protected patients from exposure to medications that may have adverse effects. “Fortune favors the prepared mind”: the precaution taken may have also enhanced the performance of the end

point of adequate relief as patients with mild disease were essentially excluded in several of the drug trials that documented their clinical benefit. However, it is well known that only about 25–30% of IBS patients are consulters, and this is the population receiving treatment from physicians. It is likely that clinic populations reflect moderate to severe vs. mild symptoms, and that patients with moderate to severe disease are seeking treatment.

There are presently significant regulatory hurdles and delays in the development of medications for IBS, and we have observed the “flight” of major pharmaceutical companies from this therapeutic field (2). Patients have been the unfortunate victims. For the record, the current editors of this journal and the delegates assembled at a “conciliation meeting” in preparation of Rome III reports can attest to my personal opposition to the acceptance of the original paper (7) and the recommendations of Rome III (9), respectively.

The Rome Foundation is attempting to reconcile, under the chairmanship of this editorialist, the current impasse among academics and trialists. Patients, regulators, and stakeholders can be reassured that adequate relief and other end points (e.g., 50% improvement in severity) will be appraised on the basis of a thorough analysis of data from >10,000 patients who received five different pharmacological agents (BM Spiegel and R Bolus, personal communication). The analysis plan includes special attention to performance of end points relative to baseline severity, longitudinal construct validity, the impact of covariates, and defining minimum clinically important differences with the different end points. Until those data become available, Passos *et al*. (10) add credence to the validity of adequate relief as an end point, which is not fundamentally flawed and is at least good enough for IBS treatment trials. In the interest of our patients and their unmet clinical needs, the goal of the FDA, clinical gastroenterologists, and the pharmaceutical companies should be to bring safe and effective medications to patients. Given the high level of responsiveness and longitudinal construct validity demonstrated with binary end points and specifically “adequate relief,” it is time to move away from the theoretical questions about psychometric validation and from internecine squabbling between regulators and academicians. Our patients with IBS deserve better.

Acknowledgments

Dr Camilleri is supported by Grants RO1 DK-54681 and K24 DK-02638 from National Institutes of Health. He thanks Cindy Stanislav for secretarial support.

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