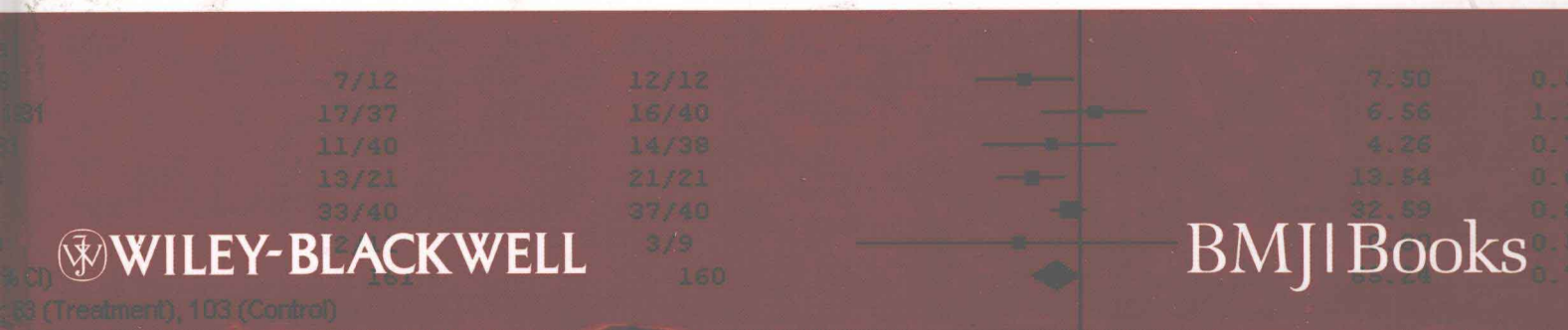
EVIDENCE-BASED GASTROENTEROLOGY & HEPATOLOGY

THIRD EDITION

Edited by
John W.D. McDonald
Andrew K. Burroughs
Brian G. Feagan
M. Brian Fennerty



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1 Introduction

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Over the past three decades the emergence of evidence-based medicine (EBM) has had a substantial impact on clinical practice. In the first half of the twentieth century, diagnostic tests or treatments, usually based on a strong scientific rationale and experimental work in animals, were routinely introduced into clinical care without good scientific proof of efficacy in people. Some of these interventions, such as gastric freezing for the treatment of ulcers and penicillamine therapy for primary biliary cirrhosis, were ultimately shown to be ineffective and harmful [1, 2]. There is little doubt that the widespread acceptance by physicians of unproved treatments has been detrimental to the well-being of many patients.

Fortunately, the need for a more critical approach to medical practice was recognized. In 1948 the first randomized controlled trial (RCT) in humans was carried out under the direction of the British Medical Research Council [3]. Epidemiologists and statisticians, notably Sir Richard Doll and Sir Bradford Hill, provided scientific leadership to the medical community, which responded with improvements in the quality of clinical research. The use of randomized allocation to control for confounding variables and to minimize bias was recognized as invaluable for conducting valid studies of treatments. The initiation of these landmark experiments defined a new era in clinical research; the RCT soon became the benchmark for the evaluation of medical and surgical interventions. Gastroenterologists played an important part in these early days. In 1955, Professor Sidney Truelove conducted the first randomized trial in the discipline of gastroenterology [4]. He and his colleagues proved that cortisone was more effective than a placebo for the treatment of ulcerative colitis. As noted in Chapter 12, this treatment has stood the test of time. The ascendancy of the RCT was accompanied by a call for greater scientific rigor in the usual practice of clinical medicine. Strong advocates of the application of epidemiological principles to patient care emerged and found a growing body of support among clinicians.

As the number of randomized trials grew to the point of becoming unmanageable, it was recognized that there was a need to provide summaries of the evidence provided by these trials for the use of practitioners, who frequently lack both time and expertise to consult the primary research. Busy clinicians may consult local experts, with the tacit assumption that they will make recommendations based on evidence. Liberati and colleagues provided evidence that this approach led to inappropriate care for many women with breast cancer [5]. Subsequently, convincing evidence became available through the work of Antman *et al.* and of Mulrow that the conventional review article and the traditional textbook chapter are seldom comprehensive, and are frequently biased [6, 7]. More recently, Jefferson reinforced this conclusion on the basis of a survey concerning recommendations for vaccination for cholera, which appeared in editorials and review articles [8]. He pointed out that authors of editorials and reviews frequently resort to the "desk drawer" technique, pulling out evidence with which they are very familiar, but failing to assemble and review all of the evidence in a systematic way.

In the UK, Archie Cochrane, as early as 1979, made a compelling case that there was a need to prepare and maintain summaries of all randomized trials [9]. Cochrane's challenge to the medical community to use scientific methods to identify, evaluate and systematically summarize the world's medical literature pertaining to all health care interventions is now being met. From its inception in 1993, the electronic database prepared by the volunteer members of the Cochrane Collaboration and published as the *Cochrane Library* has grown exponentially [10]. Systematic reviews and especially Cochrane reviews are now widely used by clinicians in the daily practice of medicine, by researchers and by the public. Accordingly, data from systematic reviews published in the *Cochrane Library*

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are featured prominently in several chapters in *Evidence-based Gastroenterology and Hepatology*. Unfortunately, coverage in the *Cochrane Library* of topics in gastroenterology and hepatology is still far from complete.

Several other clinical epidemiologists played important roles in the evolution of evidence-based medicine. Beginning in the 1970s, David Sackett encouraged practicing physicians to become familiar with the basic principles of critical appraisal. Criteria developed by Sackett and others for the evaluation of clinical studies assessing therapy, causation, prognosis and other clinical topics were widely published [11, 12]. His text, *Clinical Epidemiology: a Basic Science for Clinical Medicine*, co-authored by colleagues Gordon Guyatt, Brian Haynes and Peter Tugwell, introduced many physicians to the concepts of EBM [13]. In the USA, Alvin Feinstein called attention to the need for increased rigor in the design and interpretation of observational studies and explored the scientific principles of diagnostic testing [14, 15]. Among gastroenterologists, Thomas Chalmers, a strong, early advocate for the RCT [16], was responsible for introducing gastroenterologists and others to the importance of randomized trials in gastroenterology and hepatology and to the concept of systematic reviews and meta-analysis as means of summarizing data from these studies [17, 18].

Despite the opposition of some, the popularity of EBM continues to grow [19]. Although the explanations for this phenomenon are complex, one factor is that many practitioners recognize that ethical patient care should be based on the best possible evidence. For this, and other reasons, the fundamental concept behind EBM – the use of the scientific method in the practice of clinical medicine – has been widely endorsed by medical opinion leaders, patients and governments.

What is evidence-based gastroenterology and hepatology?

Evidence-based gastroenterology and hepatology is the application of the most valid scientific information to the care of patients with gastrointestinal and hepatic diseases. Physicians who treat patients with digestive diseases must provide their patients with the most appropriate diagnostic tests, the most accurate prognosis and the most effective and safe therapy. To meet this high standard individual clinicians must have access to and be able to evaluate scientific evidence. Although many practitioners argue that this has always been the standard of care in clinical medicine, a great deal of evidence exists to the contrary. Wide variations in practice patterns among physicians have been documented for many treatments, despite the presence of good data from widely publicized RCTs and the promotion of practice guidelines by content experts. For example, Scholefield *et al.* carried out a survey of British surgeons who were questioned regarding the performance of screening colonoscopy for colon cancer [20]. Although this study was done in 1998 (after publication of the results of the RCTs described in Chapter 18 which demonstrated a benefit of this practice), many of these physicians failed to make appropriate recommendations for screening patients at risk. What is the explanation for this finding? One possibility is that many clinicians rely for information on their colleagues, on local experts, or on review articles or textbook chapters that are not based on the principles of EBM.

Two important points about EBM should be emphasized. First, use of the principles of EBM in the management of patients is complementary to traditional clinical skills and will never supersede the recognized virtues of careful observation, sound judgment and compassion for the patient. It is noteworthy that many good doctors have intuitively used the basic principles of EBM; hence the promotion of such well-known clinical aphorisms as "go where the money is" and "do the last test first". Knowledge of EBM enables physicians to understand why these basic rules of clinical medicine are valid through the use of a quantitative approach to decision making. This paradigm can in no way be considered detrimental to the doctor-patient relationship.

Second, although RCTs are the most valuable source of data for evaluating health care interventions, other kinds of evidence must frequently be used. In some instances, most obviously in studies of causation, it is neither possible nor ethical to conduct RCTs. Here, data from methodologically rigorous observational studies are extremely valuable. A dramatic example was the demonstration by several authors (quoted in Chapter 27) that the relative risk of hepatocellular carcinoma in chronic carriers of the hepatitis B virus is dramatically higher than in persons who are not infected. Although these data are observational, the strength of the association is such that it is exceedingly unlikely that a cause other than hepatitis B virus is responsible for the development of cancer in these people. Case-control studies are especially useful for studying rare diseases and for the initial development of scientific hypotheses regarding causation. The etiological role of non-steroidal anti-inflammatory drugs in the development of gastric ulcer was recognized using this methodology [21]. Finally, case series can provide compelling evidence for the adoption of a new therapy in the absence of data from RCTs, if the natural history of the disease is both well characterized and severe. An example is the identification of orthotopic liver transplantation as a dramatically effective intervention for patients with advanced liver disease.

Box 1.1 shows a generally agreed approach to ranking the strength of evidence that arises from various types of studies of health care interventions, and this system is used throughout the book. This ranking of evidence has

Box 1.1 Grading of recommendations and levels of' evidence used in *Evidence-based Gastroenterology and Hepatology*

Grade A
Level 1a
- Evidence from large randomized clinical trials (RCTs) or systematic reviews (including meta-analyses) of multiple randomized trials which collectively have at least as much data as one single well-defined trial.

Level 1b
- Evidence from at least one "All or none" high quality cohort study; in which *all* patients died/failed with conventional therapy and some survived/succeeded with the new therapy (e.g. chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation): or in which many died/failed with conventional therapy and *none* died/failed with the new therapy (e.g. penicillin for pneumococcal infections).

Level 1c
- Evidence from at least one moderate sized RCT or a meta-analysis of small trials which collectively only has a moderate number of patients.

Level 1d
- Evidence from at least one RCT.

Grade B
Level 2
- Evidence from at least one high quality study of non-randomized cohorts who did and did not receive the new therapy.

Level 3
- Evidence from at least one high quality case control study.

Level 4
- Evidence from at least one high quality case series.

Grade C
Level 5
- Opinions from experts without reference or access to any of the foregoing (for example, argument from physiology, bench research car first principles)

appeared in a number of publications; we have chosen to reproduce it from *Evidence-based Cardiology*, along with the system used by its editors, Yusuf *et al.*, for making recommendations on the basis of these levels of evidence [22]. As mentioned in Box 1.1, throughout this book recommendation grades appear as **A** or **A1a**.

Clinical decision making in gastroenterology and hepatology

Clinical decision making by gastroenterologists usually falls into one of the following categories:

- Deciding whether to apply a specific diagnostic test in arriving at an explanation of a patient's problem, or determining the status of the patient's disease.
- Offering a prognosis to a patient.
- Deciding among a number of interventions available for managing a patient's problem. In this category, the first question is "Does a given intervention do more good than harm?" The second is "Does it do more good than other effective interventions?" The third is "Is it more or less cost-effective than other interventions?"

A comprehensive approach would incorporate many different types of evidence (e.g. RCTs, non-RCTs, epidemiologic studies and experimental data), and examine the architecture of the information for consistency, coherence and clarity. Occasionally, the evidence does not completely fit into neat compartments. For example, there is strong (A1a) evidence through very large randomized trials that fecal occult blood testing on an annual or semi-annual basis modestly reduces mortality from colon cancer in a population at average risk for this disease. The evidence that direct examination of the colon at intervals of five to ten years results in even greater benefit has been derived only from case control studies (B3). Physicians, patients and policy advisers should have both levels of evidence available to make informed decisions.

Recommendation grades appear either within the text, for example **A** and **A1a** or within a table in the chapter.

The grading system clearly is only applicable to preventative or therapeutic interventions. It is not applicable to many other types of data such as descriptive, genetic or pathophysiologic.

Application of a diagnostic test

Example: A four-year-old child is experiencing diarrhea and has a positive family history of celiac disease. Should a serological test for antiendomysial antibody (EMA) be done?

Chapter 10 includes an extensive treatment of this topic with a summary of studies (see Table 10.1) that included various groups of patients with a greater or lesser probability of having celiac disease (ranging from patients with gastrointestinal symptoms to patients in whom celiac disease was suspected on clinical grounds). Several studies listed in Table 10.1 and the study of Cataldo *et al.* [23] are relevant to this patient.

When evaluating this test the reader may wish to adopt the approach of Kitching *et al.* for deciding on the clinical usefulness of a diagnostic test (Figure 1.1) [24].

The criteria listed in Figure 1.1 for validity of a diagnostic test were clearly met in Cataldo's study. In Chapter 10 Gregor and Say explore the utility of the test and point out that tests with high positive likelihood ratios (LR > 10) and

- **Are the study results valid?**

1 Was there an independent blind comparison (or unbiased comparison) with a reference ("gold") standard of diagnosis?
2 Was the diagnostic test evaluated in an appropriate spectrum of patients (like those seen in the reader's practice)?
3 Was the reference standard applied regardless of the diagnostic test result?

- **What are the results?**

Cataldo F, Ventura A, Lazzari R *et al.* Antiendomysium antibodies and celiac disease: solved and unsolved questions. An Italian multicentre study. *Acta Paediatr* 1995;**84**:1125–31.
A study of IgA endomysium antibodies (EMA) in 1485 children with gastrointestinal disease (688 with celiac disease confirmed by intestinal biopsy)

Results for antiendomysial antibody (EMA) test

	No. of patients with biopsy proven celiac disease		
	Present	Absent	Totals
EMA positive	645	20	665
	a	b	a+b
EMA negative	c	d	c+d
	43	777	810
	a+c	b+d	a+b+c+d
Totals	688	797	1485

Sensitivity = a/(a + c) = 645/688 = 0·94
Specificity = d/(b + d) = 777/797 = 0·97
Likelihood ratio (positive result) = sensitivity/(1–specificity) = 0·94/(1–0·97) = 31
Likelihood ratio (negative result) = (1–sensitivity)/specificity = (1–0·94)/0·97 = 0·06
Positive predictive value = a/(a + b) = 645/665 = 0·97
Negative predictive value = d/c + d = 777/810 = 0·96

Figure 1.1 Approaches to evaluating evidence about diagnosis.

low negative likelihood ratios (LR < 0.1) are generally considered to be clinically useful. The EMA test clearly falls into this category. The authors draws attention to the fact that the probability that a specific patient actually has celiac disease (based on a positive test), or does not have it (based on a negative test), also depends on the pretest odds of the patient having the disease (see Table 1.1).

If the child in question, whose pretest likelihood of celiac disease is estimated to be 8%, has a negative test it may be concluded that the child almost certainly does not have celiac disease; on the other hand, if the child has a positive test, the likelihood of him or her having celiac disease is still only 65%.

As Gregor and Alidina point out, the implications of misdiagnosis must be considered carefully. In the circumstance of a positive test in the child with non-specific symptoms the physician and the child's parents should consider whether it is now reasonable to proceed to intestinal biopsy to confirm the diagnosis, rather than recommending a gluten-free diet, presumably for life. If a search for other clinical or laboratory clues reveals that celiac disease is very likely to be the correct diagnosis, the pretest likelihood may

Table 1.1 The anti-endomysial antibody (EMA) test for celiac disease. Dependence of post-test likelihood of celiac disease on pretest likelihood, assuming positive LR = 31, negative LR = 0.06.

Pretest likelihood of celiac disease	Post-test likelihood with a positive EMA test (%)	Post-test likelihood with a negative EMA test (%)
8% (non-specific symptoms, positive family history)	65	0.5
50% (more specific symptoms)	97	6
0.25% (population screen)	8	0.02

Data from Chapter 10.

be as high as 50%. This would raise the post-test likelihood to 97%. The physician and parents may be comfortable accepting the diagnosis and proceed to a trial of a gluten-free diet, rather than subjecting a young child to intestinal biopsy. This is an excellent example of how a skilled clinician must integrate the principles of evidence-based medicine with traditional clinical skills and judgment.

Offering a prognosis

Example: A 50-year-old woman with recently diagnosed celiac disease. has learned at a meeting of the local celiac society that patients with celiac disease have a substantial increase in the risk of developing a number of cancers and that this cancer risk is reduced by strict adherence to a gluten-free diet.

Chapter 10 describes the types of study which are relevant to determination of prognosis and discusses the strengths and weaknesses of case-control and cohort studies.

Gregor and Alidina point out that certain case-control studies which reported very high mortality and malignancy rates may have been subject to selection bias (inclusion of particularly ill or refractory patients) and measurement bias (patients with abdominal symptoms being more likely to undergo investigations such as small bowel biopsy which may lead to a diagnosis of celiac disease). They refer to a British study in which a cohort of patients with celiac disease was assembled and followed for ten years. This design attempts to minimize the biases that are inherent in the case-control studies. Table 1.2 shows that the risk of certain cancers is increased compared to the risk in the general population. Table 1.3 shows that strict adherence to a gluten-free diet significantly reduced this risk and may have eliminated the excess risk for several of the identified cancers.

Table 1.2 Cancer mortality in 210 patients with celiac disease at the end of 1985.

Site of cancer	ICD8	O	E	O/E	P
All sites	140–208	31	15.48	2.0	[b]
Mouth and pharynx	141–147	3	0.31	9.7	[a]
Esophagus	150	3	0.24	12.3	[a]
Non-Hodgkin's lymphoma	200, 202	9	0.21	42.7	[b]
Gastrointestinal tract	151–154	3	3.07	1.0	NS
Remainder		13	11.65	1.1	NS

[a] $p < 0.01$.
[b] $p < 0.001$.
O: observed numbers; E: expected numbers.
Source: Holmes GKT *et al. Gut* 1989; **30**: 333–338 [25].

On the basis of this evidence it is reasonable to advise the patient that her disease does carry with it an increased risk of certain relatively uncommon cancers and that adherence to a strict gluten-free diet appears to minimize this increased risk.

Recommendations concerning therapy

We have provided examples of how evidence concerning the use of diagnostic tests and prognosis can be analyzed and incorporated into clinical practice. Most chapters in this book deal more extensively with evidence concerning therapy and rely heavily on data from randomized trials and meta-analyses.

Example: Should a 28-year-old woman who has had an uncomplicated resection of the terminal ileum for Crohn's disease receive maintenance therapy with an S-aminosalicylate (ASA) product? Prior to the surgery she had had steroid-dependent disease and had failed treatment with both azathioprine and methotrexate.

A search of the literature for placebo-controlled randomized trials of 5-ASA for maintenance of remission in patients with a surgically induced remission of disease would reveal several trials. The largest published trial is that of McLeod and colleagues, who randomized 163 adult patients to receive either 3 g/day of 5-ASA or a placebo following surgery [26]. The primary outcome of interest was the recurrence of active Crohn's disease as defined by the recurrence of symptoms and the documentation of active disease either radiologically or endoscopically. At

Table 1.3 Cancer morbidity by diet group.

Site of cancer	Diet group[a]	No.	O	E	O/E	P
All sites	1	108	14	9.06	1.5	
	2	102	17	6.42	2.6	[c]
Mouth, pharynx,	1	108	1	0.33	3.0	
esophagus	2	102	5	0.22	22.7	[c]
Non-Hodgkin's	1	108	2	0.12	16.7	[b]
lymphoma	2	102	7	0.09	77.8	[c]
Remainder	1	108	11	8.61	1.3	
	2	102	5	6.11	0.8	

[a] Diet group 1, strict adherence to gluten-free diet; group 2, reduced gluten diet or normal diet. Source: Holmes G KT *et al. Gut* 1989; **30**: 333–338 [25].
[b] $p < 0–01$.
[c] $p < 0.001$.

- **Are the results valid?**

1 Was the assignment of patients to treatment really randomized (and the randomization code concealed)?
2 Were all patients who entered the study accounted for at its conclusion?
3 Were the clinical outcomes measured blindly?

- **Is the therapeutic effect important?**

1 Were both statistical and clinical significance considered?
2 Were all clinically important outcomes reported?

- **What are the results?**

McLeod RS, Wolff BG, Steinhart AH *et al.* Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. *Gastroenterology* 1995;**109**:404–13.

Randomized controlled trial in which 163 patients with Crohn's disease who had all visible disease resected were randomized to receive mesalamine (Pentasa) 3 g daily or a placebo for a median period of 34 months. Primary outcome was recurrent Crohn's disease defined by recurrence of symptoms and radiographic or endoscopic documentation of recurrence.

	Recurrent Crohn's disease		Risk (%)	ARR (%)	RRR (%)
	Yes	No			
5-ASA	27	60	31	10	24
Placebo	31	45	41	–	–

ARR, absolute risk reduction; RRR, relative risk reduction.

- **Are the results relevant to my patient?**

1 Were the study patients recognizably similar to my own?
2 Is the therapeutic maneuver feasible in my practice?

Figure 1.2 Elements of a valid and useful randomized trial.

the end of the follow-up period (maximum duration 72 months, median duration 34 months), 31% of patients who received active treatment remained in remission compared with 41% of those who received a placebo ($p = 0.031$); 5-ASA was well tolerated. A low proportion of patients developed adverse reactions in the control and active treatment groups. One patient treated with 5-ASA developed pancreatitis that was attributed to the study drug. The results of this study can be evaluated using the guidelines described in Figure 1.2, which is modeled after the approach of Kitching *et al.* [24].

Are the results of this study valid?

A review of the methods section of the article confirms that an appropriate method of randomization was employed (computer-generated in permutated blocks), which insured concealment of the randomization code [26]. Furthermore, inspection of the baseline characteristics of the treatment and control groups shows that they are well balanced with respect to such confounding variables as the time from surgery to randomization. This information further supports the legitimacy of the randomization process. Assessment of the method of randomization is important, because non-randomized designs are especially vulnerable to the effects of bias. Studies which employ "quasi-randomization" schemes such as allocation to treatment according to the day of the week or alphabetically by the patient's surname have been shown to consistently overestimate the treatment effect identified by RCTs that employ a valid randomization scheme [27, 28]. However, it may be noted that 87 patients were randomized to 5-ASA, compared with only 76 patients in the control group. This observation raises the concern that the analysis might not have been done according to the "intent to treat" principle which specifies that patients are analyzed in the group to which they were originally assigned, irrespective of the treatment that was ultimately received. The use of this strategy reduces the possibility of bias, which might occur if investigators selectively withdrew from the analysis patients who had done poorly or experienced toxicity. For this reason, the intent to treat principle yields a conservative estimate of the true benefit of the treatment. However,

detailed review shows that in this study the discrepancy in patient numbers occurred because five patients who were randomized to the active treatment group withdrew consent prior to receiving the study medication and were not included. Thus, it appears that the analysis was based on the intent to treat principle.

Approximately 10% of patients in both treatment groups had incomplete follow-up. Methodologically rigorous studies have a very low proportion of patients for whom data are missing. This issue is important, since patients who are lost to follow-up usually have a different prognosis from those for whom complete information is available. If there is incomplete follow-up data for a substantial proportion of patients then the results are uninterpretable [29].

Turning to an assessment of the outcomes in this study, both the patients and investigators were unaware of the treatment allocation. Blinding is used to reduce bias in the interpretation of outcomes. This is especially important when a subjective outcome is evaluated [30]. In this study, objective demonstration of recurrent disease (endoscopy and/or radiology) was required in addition to the more subjective measure of the introduction of treatment for recurrent symptoms. Thus, the reader can be satisfied that the primary outcome measure was both clinically meaningful and objectively assessed.

Finally, the data analysis and results should be examined. A great deal of useful information can be obtained by reviewing the assumptions that were used in the sample size calculation. In this study, which analyzes a difference in proportions, the investigators had to define four variables: the alpha (type 1) error rate, the beta (type 2) error rate, the expected proportion of patients who would be expected to relapse in the placebo group, and the minimum difference in the rate of relapse which the investigator wished to detect. In this publication these parameters are easily identified. The rate of symptomatic recurrence was estimated to be 12.5% per year and it was anticipated that treatment with 5-ASA would reduce this rate by 50% to an absolute value of 6.25% per year. In contrast to the expected 50% relative risk reduction which was anticipated, the three-year actuarial risk of recurrence was 26% in the treatment group compared to 45% in the group that received 5-ASA ($p = 0.039$). Therefore, the relative risk reduction ((45–26%)/45% = 42%) is slightly lower than the figure which the investigators considered to be clinically meaningful. Furthermore, the probability of a type 1 error is described as a one-tailed value of $p = 0.05$. This implies that one-tailed statistical testing was used to derive the p value of 0.039. The use of one-sided statistical testing raises legitimate concerns regarding the statistical inferences made in the study [31]. It is inappropriate to hypothesize that 5-ASA therapy could only be beneficial, given that the drug can cause diarrhea and colitis [32]. For these reasons, uncertainty exists regarding both the clinical and statistical interpretation of these data.

Are the results of this valid study important?

To assess the importance of this result it is necessary to quantify the magnitude of the treatment effect. How the evidence is presented may influence both physicians and patients in making choices. The most basic means of expressing the magnitude of a treatment of fact is the absolute risk reduction (ARR), which is defined as the proportion of patients in the experimental group with a treatment success minus the proportion of patients with this outcome in the control group. In this instance the annual rate of relapse in the placebo-treated patients was 15% (success rate of 85%) compared with 8.7% (success rate of 91.3%) in those who received the active treatment. This yields an ARR of 6.3%. The number needed to treat (NNT), the number of patients with Crohn's disease who would have to be treated with 3 g/day of 5-ASA to maintain remission over a year, can be calculated as the reciprocal of this number, and is 16. Alternative ways of describing effectiveness include calculating the observed relative risk reduction (RRR = 63/15) of 42%, or even stating that about 90% of patients respond to maintenance therapy, ignoring the substantial placebo effect which is evident. The evidence presented as the ARR or NNT, rather than the numbers which show the treatment in a more favorable light, may still lead the physician to recommend this form of treatment and cause the patient to choose to accept this strategy over no intervention. However, the expectations of the physician and patients are likely to be more realistic than they may be if the physician accepts and promotes in an uncritical way the information that 90% of patients who receive 5-ASA maintenance therapy will remain in remission over one year [33].

Are these results applicable to my patient?

Following an assessment of the validity of the evidence using the criteria described in the preceding paragraphs, it is necessary to decide whether the conclusions of the study are relevant and important to the individual patient. An initial step is to evaluate the demographic characteristics of the patients in the RCT and compare them to those of the patient in question. If the patient for whom maintenance therapy is being considered is similar to the patients who were evaluated in the trial, it is reasonable to assume that she will experience the same benefit of therapy and is at no greater risk for the development of adverse drug

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