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Quantifying Women's Stated Benefit–Risk Trade-Off Preferences for IBS Treatment Outcomes

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ABSTRACT

Background: The Food and Drug Administration, currently, is exploring quantitative benefit–risk methods to support regulatory decision-making. A scientifically valid method for assessing patients' benefit–risk trade-off preferences is needed to compare risks and benefits in a common metric.
Objectives: The study aims to quantify the maximum acceptable risk (MAR) of treatment-related adverse events (AEs) that women with diarrhea-predominant irritable bowel syndrome (IBS) are willing to accept in exchange for symptom relief.
Methods: Research design: A stated-choice survey was used to elicit trade-off preferences among constructed treatment profiles, each defined by symptom severity and treatment-related AEs. Symptom attributes included frequency of abdominal pain and discomfort, frequency of diarrhea, and frequency of urgency. AE attributes included frequency of mild-to-moderate constipation and the risk of four possible serious AEs. Subjects: A Web-enabled survey was administered to 589 female US residents at least 18 years of age with a self-reported diagnosis of diarrhea-predominant IBS.
Measures: Preference weights and MAR were estimated using mixed-logit methods.
Results: Subjects were willing to accept higher risks of serious AEs in return for treatments offering better symptom control. For an improvement from the lowest to the highest of four benefit levels, subjects were willing to tolerate a 2.65% increase in impacted-bowel risk, but only a 1.34% increase in perforated-bowel risk.
Conclusions: Variation in MARs across AE types is consistent with the relative seriousness of the AEs. Stated-preference methods offer a scientifically valid approach to quantifying benefit–risk trade-off preferences that can be used to inform regulatory decision-making.
Keywords: benefit–risk analysis, conjoint analysis, incremental net benefits, irritable bowel syndrome, maximum acceptable risk.

Introduction

Several recent and well-publicized events involving withdrawals of drugs from the US market have highlighted the problem of balancing benefits and risks [1]. In all these cases, interventions offering potentially significant therapeutic benefits were found to carry increased risks of serious and, possibly, life-threatening adverse events (AEs). Decisions to halt the development or marketing of such therapies clearly require balancing benefits and risks. Despite the importance of establishing consistent and principled criteria for determining when benefits outweigh risks, experts have provided surprisingly little guidance to help decision-makers evaluate such trade-offs.

A review of past examples of product withdrawals and risk-management decisions in different countries reported that decisions, often, are inconsistent and are based on very limited scientific evidence beyond the original clinical trial data relating to safety and efficacy [2]. In addition, the recent Institute of Medicine report, The Future of Drug Safety, a study requested by the US Food and Drug Administration (FDA) to address recognized shortcomings of the US drug-safety system, noted that "in both the preapproval and the postmarketing setting, the risk-benefit analysis that currently goes into regulatory decisions appears to be ad hoc, informal, and qualitative" [3]. The FDA Amendments Act of 2007 called on the agency to collaborate with public and private entities to improve the quality of benefit–risk analysis (H.R. 3580 [Public Law 110-85] §904).

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Regulatory agencies do not require quantifying or even formal consideration of the values of patients, physicians, or other stakeholders in risk evaluations. The values and risk tolerance of patients with a particular condition may be presented to advisory panels and policymakers either individually or through advocacy organizations; however, there is no transparent or consistent mechanism currently in place for quantifying systematically the values and risk tolerance of these ultimate stakeholders.

The case of alosetron illustrates the need for quantitative, preference-based, benefit–risk analysis. Alosetron was approved for marketing by the FDA in February 2000. The approved indication was for diarrhea-predominant irritable bowel syndrome (IBS) in women only. Although clinical trials demonstrated that alosetron provided relief of abdominal pain and discomfort, improvement in urgency, and decreased frequency of diarrhea [4], safety signals indicated the possibility of serious gastrointestinal AEs. The most serious risk of concern associated with alosetron was the possibility that women with IBS taking the drug would develop a perforated bowel requiring surgery. As a result, alosetron was withdrawn from the market 9 months after launch. In June 2002, in response to pressure from patient organizations and reanalysis of data, the FDA reapproved the drug for restricted use in a more targeted indication under a risk-management program.

Understanding the value that women with IBS place on treatment outcomes and their willingness to accept risks in return for treatment benefits can help inform future regulatory and risk-management decision-making. In this study, we employed well-established stated-choice (SC) methods (also known as choice-format conjoint analysis or discrete-choice experiments) to quantify the maximum acceptable risk (MAR) of treatment-related AEs that women with diarrhea-predominant IBS are willing to accept in exchange for symptom relief. In a related

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study published in this journal, these estimates were used to construct preference weights, which were used in an event-simulation model, to estimate the incremental net benefits of alosetron [5].

Methods

SC Methods

In an SC survey, a sample of patients, physicians, or caregivers are asked to choose between treatment options where attribute levels are varied across options and across choice tasks [6–8]. SC methods yield quantitative estimates of trade-offs subjects are willing to make among treatment attributes and yield estimates of relative preference weights. These weights can be used to populate models in lieu of conventional health-state utilities or to scale therapeutic improvements in terms of one of the attributes, such as money, risk, or time [9,10].

Survey Development

Treatment-related benefits and risks were identified from a review of the literature, consultations with medical experts involved in IBS clinical trials, and interviews with women with diarrhea-predominant IBS. In each treatment-choice question in the survey, symptom attributes included 1) frequency of abdominal pain and discomfort; 2) frequency of diarrhea; and 3) frequency of feelings of urgency. AE attributes included 1) frequency of mild-to-moderate constipation and 2) risks of four additional AEs—three of them serious. AE risks included probabilities of moderate colitis, impacted bowel, severe colitis, and perforated bowel (Table 1). Probabilities of experiencing each AE ranged from 0% to 1%. Pretests were conducted using in-person interviews with eight women between 29 years and 60 years of age with a self-reported diagnosis of diarrhea-predominant IBS.

Figure 1 provides an example of the SC question format. We employed a commonly used algorithm to construct a statistically efficient experimental design resulting in 48 treatment-choice pairs [11–15]. We implemented an extension of Zwerina et al.'s algorithm that searches for maximum D-efficiency, subject to no dominated pairs, minimal overlaps, and best level balance [13,15]. The design with the highest D-score achieved an acceptable level of statistical efficiency for our sample size, as indicated by confidence intervals on the parameter estimates. Kanninen shows that prior information on parameter values can be used to improve design efficiency [14]. We did not have any information with which to specify priors for the parameters other than natural ordering, which we used in the search algorithm to screen out dominated pairs.

To reduce cognitive and time burden, treatment-choice questions were blocked into six sets of eight questions, and each subject was randomly assigned to one of the six sets. The final survey instrument also included questions regarding each subject's personal characteristics (e.g., age and education) and experience with IBS and IBS treatments. The survey was approved by the Research Triangle Institute's Office of Research Protection and Ethics.

Survey Sample

The Web-enabled survey was programed by Ipsos Observer, an international survey-research firm [16], and administered to female members of the Ipsos Online Access Panel. All subjects were required to have had a physician diagnosis of diarrhea-predominant IBS (self-reported) and to be US residents, at least 18 years of age. Study subjects were entered into a drawing to win one of the five $100 cash prizes offered as an incentive for their participation.

Table 1 Irritable bowel syndrome (IBS) treatment attributes and levels

Treatment attribute	Levels
Frequency of abdominal pain and discomfort	No IBS pain and discomfort
	IBS pain and discomfort for 1 week a month
	IBS pain and discomfort for 2 weeks a month
	IBS pain and discomfort for 3 weeks a month
	IBS pain and discomfort for 4 weeks a month
Diarrhea frequency	No diarrhea
	Diarrhea 2 times a day
	Diarrhea 4 times a day
	Diarrhea more than 4 times a day
Urgency frequency	No urgency
	Urgency 2 days a week
	Urgency 5 days a week
	Urgency 7 days a week
Frequency of mild-to-moderate constipation	No constipation
	Constipation 1 week a month
	Constipation 2 weeks a month
	Constipation 3 weeks a month
	Constipation 4 weeks a month
Chance of serious adverse event	No chance of severe adverse event
	1 person out of 1000 (0.1%) will have moderate colitis requiring doctor's care
	5 people out of 1000 (0.5%) will have moderate colitis requiring doctor's care
	10 people out of 1000 (1%) will have moderate colitis requiring doctor's care
	1 person out of 1000 (0.1%) will have an impacted bowel requiring doctor's care
	5 people out of 1000 (0.5%) will have an impacted bowel requiring doctor's care
	10 people out of 1000 (1%) will have an impacted bowel requiring doctor's care
	1 person out of 1000 (0.1%) will have severe colitis requiring hospitalization
	5 people out of 1000 (0.5%) will have severe colitis requiring hospitalization
	10 people out of 1000 (1%) will have severe colitis requiring hospitalization
	1 person out of 1000 (0.1%) will have a perforated bowel requiring surgery
	5 people out of 1000 (0.5%) will have a perforated bowel requiring surgery
	10 people out of 1000 (1%) will have a perforated bowel requiring surgery

Statistical Analysis

We used multivariate, random-parameters panel-logit regression to estimate preference parameters for each attribute level [17]. Explanatory variables in the random-parameters logit model included all attribute levels listed in Table 1. All statistical analyses were conducted using GAUSS 7.0 (Aptech Systems, Inc., Black Diamond, WA) [18].

The parameter estimates from SC models are preference weights that indicate the relative strength of subjects' preference for each attribute level. Attribute levels were effects coded. The preference weight for the omitted category is the negative sum of the included-category parameters [19]. Thus, zero is the mean effect for each attribute, and positive and negative preference weights are interpreted relative to the mean effect of the attribute on treatment choice.

MAR Calculations

Estimated preference parameters were used to calculate the mean MAR for each serious AE—impacted bowel, severe colitis, and

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