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A discrete-choice experiment of United Kingdom patients' willingness to risk adverse events for improved function and pain control in osteoarthritis

A.B. Hauber †*, N.K. Arden ‡, A.F. Mohamed †, F.R. Johnson †, P.M. Peloso §, D.J. Watson §, P. Mavros §, A. Gammaitoni ||, S.S. Sen §, S.D. Taylor §

† *Health Preference Assessment, RTI Health Solutions, USA*
‡ *Department of Musculoskeletal Epidemiology and Rheumatic Diseases, NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, USA*
§ *Merck Sharp & Dohme Corp., USA*
|| *VP of Scientific Affairs, Pain Group, Nuvo Research US, USA*

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SUMMARY

Objective: To assess patient preferences for treatment-related benefits and risks associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the management of osteoarthritis (OA).
Design: Using a chronic-illness panel in the United Kingdom, patients 45 years or older with a self-reported diagnosis of OA were eligible to participate in the study. Patient preferences were assessed using a discrete-choice experiment that compared hypothetical treatment profiles of benefits and risks consistent with NSAID use. Benefit outcomes (ambulatory pain, resting pain, stiffness, and difficulty doing daily activities) were presented on a 0-to-100 mm scale. Risk outcomes (bleeding ulcer, stroke, and myocardial infarction [MI]) were expressed as probabilities over a fixed time period. Each patient answered 10 choice tasks comparing different treatment profiles. Preference weights were estimated using a random-parameters logit model.
Results: Final sample included 294 patients. Patients ranked reductions in ambulatory pain and difficulty doing daily activities (both: 6.32; 95% confidence interval [CI]: 5.0–7.6) as the most important benefit outcomes, followed by reductions in resting pain (2.80; 95% CI: 1.8–3.8) and stiffness (2.65; 95% CI: 0.9–4.4). Incremental changes (3%) in the risk of MI or stroke were assessed as the most important risk outcomes (10.00; 95% CI: 8.2–11.8; and 8.90; 95% CI: 7.3–10.5, respectively).
Conclusion: Patients ranked ambulatory pain as a more important benefit than resting pain; likely due to its impact on ability to do daily activities. For a 25-mm reduction, patients were willing to accept four times the risk of MI in ambulatory pain vs resting pain.

Introduction

Osteoarthritis (OA) is the most common form of arthritis, characterized by pain, swelling, and a sensation of stiffness in the joints. It can occur in any synovial joint but most commonly affects the hips, knees, hands, and lumbar or cervical spine. The onset of symptomatic OA usually occurs in individuals over 50 years of age. OA affects approximately 8.5 million individuals in the United Kingdom (UK)[1].

There is currently no cure for OA, and treatment is palliative. Nonselective, nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol are the most commonly used treatments for the pain and inflammation of OA[2–5]. The most common side effects of NSAIDs and paracetamol are gastrointestinal (GI) in nature and include nausea, dyspepsia, and ulcers. A newer class of NSAIDs, selective cyclooxygenase-2 (COX-2) inhibitors, has been developed and is associated with a lower rate of GI side effects compared with older, more commonly used nonselective NSAIDs. Recently, nonselective NSAIDs and selective COX-2 inhibitors have been linked to risks of thrombotic cardiovascular events (myocardial infarctions [MIs] and strokes)[6–13]. Despite these risks, NSAIDs and selective COX-2 inhibitors are still widely prescribed for patients with OA[14,15].

In order to make an informed decision, patients must be advised of both the benefits and risks of medications. However, Katz *et al.*[16] found that disclosure of side effects of NSAIDs to patients is limited and that patients initiating a new prescription for an NSAID, who

* Address correspondence and reprint requests to: A.B. Hauber, Health Preference Assessment, RTI Health Solutions, 200 Park Offices Drive, PO Box 12194, Research Triangle Park, NC 27709-2194, USA. Tel: 1-919-597-5149; Fax: 1-919-541-7222.
E-mail address: abhauber@rti.org (A.B. Hauber).

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have the most to benefit from the therapy, are told the least. In addition, Kopec *et al.*[17] found that risk tolerance for OA medications varied widely among patients but that clinical, sociodemographic, and psychological characteristics did not explain this variation.

Regulatory authorities routinely appraise a drug's safety and efficacy as part of the approval process; however, these safety and efficacy tradeoffs are not made using directly comparable metrics, as no standard quantitative method currently exists for weighing the relative preference of treatment benefits and risks among relevant stakeholders. Patient-preference methods such as discrete-choice experiments have been used increasingly in recent years to quantify the relative importance of the benefits and risks of different drugs to patients and other stakeholders in the drug approval process[18–20]. The primary objective of this study was to quantify benefit-risk preferences for patients with OA with respect to medication outcomes associated with nonselective NSAIDs and selective COX-2 inhibitors. Specifically, our objective was to estimate OA patients' risk tolerance for serious adverse events including bleeding ulcer, MI, and stroke. It is intended that this information be used to inform evaluations of new and existing NSAID treatments.

Method

Study sample

The target sample size in this study was 300 respondents. Minimum sample sizes in discrete-choice experiments depend on a number of criteria, including the question format, the complexity of the choice task, the desired precision of the results, and the need to conduct subgroup analyses[21]. Researchers commonly apply a rule of thumb such as that proposed by Orme[22]. Most discrete-choice experiments in health that include numbers of attributes and levels similar to those in this study use sample sizes between 100 and 300 respondents[23].

Respondents were recruited *via* e-mail invitation from Harris Interactive's (Rochester, New York, USA) online chronic-illness panel in the UK. Adults are recruited into the panel and agree to take surveys for which they receive points that can be redeemed for merchandise. After enrollment, panelists are screened for a number of diagnosed chronic illnesses, including OA. Even though the panel is representative of the general UK population, the panel members who were eligible and consented to participate in our survey may not be representative of the OA patient population in the UK.

Participating patients were required to have a self-reported physician's diagnosis of OA and to be a UK resident aged 45 years or older. Harris Interactive administered the 25-min online survey in August 2009. The survey did not require review by the National Research Ethics Committee (NRES) because this study was neither interventional nor observational and because respondents were not recruited through the National Health Service (NHS). The survey was approved by RTI International's Office of Research Protection and Ethics (Research Triangle Park, North Carolina, USA), and patients were required to provide online informed consent prior to participating in the survey.

Discrete-choice experiments

Discrete-choice experiments (also known as choice-format conjoint analysis) are used to quantify decision criteria for attributes of health and health care[23,24] and patient preferences in OA[25–27]. Discrete-choice experiments are a systematic method of eliciting tradeoffs to quantify the relative importance patients assign to various treatment attributes and outcomes. Discrete-choice experiments are based on the premise that medical interventions are composed of a set of attributes and that the ability of a particular intervention to satisfy the needs or wants of an individual is a function of these attributes[18,21,28]. In the experiment, respondents are presented with a series of questions in which they are asked to choose a preferred alternative from a set of hypothetical treatment profiles. These treatment profiles vary by levels of treatment attributes.

Survey instrument

We reviewed package inserts and clinical-trial literature and consulted with clinical experts to identify the most common benefit outcomes and most serious adverse events associated with nonselective NSAIDs and selective COX-2 inhibitors. We identified seven attributes—four benefits and three risks—to describe the OA medication-attribute profiles in this study (Table I). Each of the medication-related benefits (reductions in ambulatory pain, resting pain, stiffness, and difficulty doing daily activities) and risks (bleeding ulcer, stroke, and MI), were varied across four possible levels. The range of levels of each attribute was intended to meet three criteria: (1) the range of levels should span the clinically relevant range of outcomes that has been seen or might be expected to be seen in clinical trials or clinical practice, (2) differences in levels should encompass the range of improvements in efficacy outcomes or the range of increases in adverse-event outcomes that potentially could be seen in clinical trials or clinical practice, and (3) the range of levels should encompass the maximum range over which respondents are willing to accept tradeoffs among attributes.

The benefits were developed to correspond to three domains of the Western Ontario and McMaster (WOMAC) Index of OA (pain, stiffness and physical function) because these domains are commonly used as clinical-trial endpoints in OA studies[29]. Using clinician recommendations, we considered two independent pain attributes, resting pain and ambulatory pain, because these two

Table I
Beneficial and negative attributes and their different levels used in the survey instrument

Attribute labels	Abbreviated label	Levels*
Pain while moving around 1 h after taking the medicine	Ambulatory pain	None (0 mm) Mild (25 mm) Moderate (50 mm) Severe (75 mm)
Pain while sitting, lying down, or sleeping 1 h after taking the medicine	Resting pain	None (0 mm) Mild (25 mm) Moderate (50 mm) Severe (75 mm)
Stiffness 1 h after taking the medicine	Stiffness	None (0 mm) Mild (25 mm) Moderate (50 mm) Severe (75 mm)
Difficulty doing your daily activities 1 h after taking the medicine	Difficulty doing daily activities	None (0 mm) Mild (25 mm) Moderate (50 mm) Severe (75 mm)
Chance of a bleeding ulcer requiring an operation within the next year because of the medicine	Ulcer risk	None 10 out of 1,000 (1.0%) 50 out of 1,000 (5.0%)† 100 out of 1,000 (10.0%)†
Additional chance of a heart attack or stroke within the next 5 years because of the medicine‡	Heart-attack risk/ stroke risk	No chance 5 out of 1,000 (0.5%) 15 out of 1,000 (1.5%) 30 out of 1,000 (3.0%)

* On a 0-to-100 mm visual analog scale, unless stated otherwise.
† Not relevant for the average OA population.
‡ Heart-attack and stroke risks are both cardiovascular risks and could not be included at the same time because they are inherently correlated. In the discrete-choice survey, heart-attack risk was shown half the time, and stroke risk was shown the other half.