PAIN MEDICINE
Volume 3 • Number 3 • 2002

Utility Assessments of Opioid Treatment for Chronic Pain

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ABSTRACT

Objective. The primary study objective was to assess preferences for pain treatment outcomes among patients with cancer and noncancer chronic pain. A secondary objective was to assess their quality of life.

Methods. Patients with cancer or noncancer chronic pain completed an interview using a computer to estimate utilities, or preference ratings, for health states related to pain treatment. The interview was devised using conjoint analysis methodology. Health states were characterized by four attributes (effectiveness of pain control, side effects, side effect severity, and opioid route of administration) and their levels, and each was assumed to last for a 14-day period. Participants also completed health-related quality of life and demographic questionnaires.

Results. Mean preference ratings for participants with noncancer chronic pain (N = 96) ranged from a high of 0.87 (well-controlled pain with no side effects) to a low of 0.18 (poorly controlled pain with severe mood changes/alterations, severe respiratory depression, or severe vomiting). Mean preference ratings for participants with cancer pain (N = 25) were similar and ranged from a high of 0.89 (well-controlled pain with no side effects) to a low of 0.19 (poorly controlled pain with severe respiratory depression or severe vomiting). Results confirmed previous findings that chronic pain has a severe, multidimensional impact on patients, and that the quality of life of persons with chronic pain is among the lowest observed for any medical condition.

Conclusions. This study provides a valuable assessment, from the patient's perspective, of the balance between treatment tolerability and manifestation of disease symptoms. Heightened awareness of patients' preferences for treatment outcomes may lead to improved selection of treatments, better adherence, and ultimate treatment success.

Key Words. Chronic Noncancer Pain; Chronic Cancer Pain; Utilities; Quality of Life; Opioids; Patient Preference

Introduction

Chronic pain is a leading cause of disability throughout the world. It is estimated that 15-30% of the U.S. population experience chronic pain [1], and the elderly are at greater risk, with the prevalence of chronic pain doubling after age 60 [2].

Important factors in evaluating treatments for chronic pain include the level of pain control and the type and severity of side effects. In addition to these factors, the route of administration may affect patients' preferences for pain treatments. For example, choices for long-acting opioids include both oral formulations and a transdermal system incorporating fentanyl (hereafter referred to as the patch); both have been shown to be safe and effective for the management of chronic moderate-to-severe pain [3-6]. It has been suggested that patch therapy may be a suitable choice for all eligible patients [7], not just for those who are intolerant of oral analgesics (due to physical and/or mental inability to maintain a successful continuous dosing) or for those who display an allergy to morphine, dysphagia, or in-

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 1526-2375/02/$15.00/218 218–230

tractable nausea and vomiting. However, patients' preferences for route of administration of opioids, particularly patch versus oral administration, have not yet been systematically evaluated.

Greater patient involvement in making these kinds of medical decisions is now increasingly advocated [8]. While individual discussions with patients about treatment choices are essential, group-level assessments of preferences and the importance of different qualities of treatments can be used to encourage these conversations, both in the field of pain medicine as well as in other fields. Elicitation of preference assessments can enhance the provision of health care, provided the patient information is useful and scientifically defensible [9].

The goal of this study (utility analysis, at your discretion) is to assign utility values, which range from 0 = death to 1 = perfect health, to health states. Theoretically, the possibility of states worse than death does exist, but as the current literature does not provide guidelines for interpretation of these scores (values), these states are not explicitly handled in this model. A number of methods have been used to quantify patient preferences, expressed as utilities, where values range from 0-100, with higher values indicating better ratings. Recently, conjoint analysis, a novel method in which patients are offered two different product descriptions at a time and select which of the two they prefer, has been used as an alternative to traditional methods, such as "standard gamble" and "time trade-off" [10], as it offers certain advantages in measuring patient preferences. Conjoint analysis is based on the economic theory of value [11,12] and random utility theory [13]. It can account for uncertainty, if appropriate, in a potentially less complicated way than other methods, minimizing internally inconsistent responses [14]. In addition, conjoint analysis more closely resembles the types of decisions individuals make on a daily basis (trade-offs among realistic options), and the trade-offs considered are salient to the individual. For example, conjoint analysis could be used to determine how much patients would be willing to pay out of pocket for medication that works better than one on their formulary. Ryan and Farrar provide a useful tutorial for the reader on the methods and a sample application of conjoint analysis [8].

Adaptive conjoint analysis, in which a preprogrammed computerized survey continually adapts itself and presents selected questions based on previous answers, is a particularly valuable tool when health states to be assessed are too numerous to successfully use alternative methods for utility assessment (see Methods, Adaptive Conjoint Analysis (ACA) Interview). Compared with traditional utility elicitation methods, the adaptive conjoint analysis interview can be completed in a relatively short period of time, minimizing participant burden.

Using conjoint analysis, participants are asked to rank levels of an attribute (here, patients ranked side effects in order from most to least preferred and indicated whether they preferred oral or patch administration), rate the importance of each attribute to them, and then make choices involving paired hypothetical scenarios that represent different levels of attributes that have been identified as important in the provision of a good or service. Regression techniques are used to estimate the utility function. Conjoint analysis is gaining widespread use in health care and has been applied successfully to establishing preferences in delivery of health care services [15-21], consultant's preferences in setting priorities [22], developing outcome measures [23], determining optimal treatments [24,25], evaluating alternatives within randomized controlled trials [26], and establishing preferences in the physician-patient relationship [27,28]. In several of these health care studies, utilities have been estimated within the quality-adjusted life years (QALY) paradigm in order to impart health care decision making with a standard measure across therapeutic regimens and areas [23-25,29]. Including cost factors in an analysis such as this can provide a more accurate reflection of the relative costs and benefits associated with opioid treatments for chronic pain.

Objective

The primary study objectives were to assess preferences for pain treatment outcomes and to assess the trade-offs between reduction in pain and experiencing treatment-related adverse effects among patients with cancer and noncancer chronic pain. A secondary objective was to assess health-related quality of life (HRQL) for these patients.

Methods

Study Sample

A minimum of 30 participants was to be enrolled at each of four sites. Three sites recruited patients with noncancer chronic pain (one site each in Canada, the United States, and Australia), and one site in Canada recruited patients with cancer chronic pain. The selected sample sizes assumed there

would be relative agreement among participants regarding the assessment of health states, i.e., that the distributions would be relatively normal with small variances within each group.

Eligibility Criteria

Eligible participants were ≥18 years old, cognitively intact, English speaking, able to read at a sixth grade level or above, free of visual or motor impairments that would preclude completion of a questionnaire booklet and computer-based preference measure interview, had experienced or were experiencing moderate to severe chronic pain, and provided informed consent prior to participation. Institutional Review Board approval was obtained for each site and participants were paid a nominal fee for their time.

Development of the Health States

A review of the literature and consultation with physicians and with experts in utility assessment methodology identified information needed to select the attributes and levels for the utility interview. The health states developed were characterized by the following four attributes and their levels, each of which was assumed to apply to a 14-day period:

- Pain control (0, 3, 6, 9, and 12 days of breakthrough pain)
- Side effects (no side effects, constipation, mental cloudiness/sleepiness, mood changes/alterations, nausea, respiratory depression, sleep disorders/hallucinations, sweating, and vomiting)
- Side effect severity (mild, moderate, and severe)
- Opioid route of administration (oral and patch)

Appendix I includes complete descriptions and definitions of these attributes, levels, and a definition of breakthrough pain. Each attribute, or characteristic, of a pain medication had at least two levels. For example, the attribute "type of pain medication" had only two levels (patch and oral). The attributes, levels, definition of breakthrough pain, and samples of draft health states were reviewed both by physicians and experts in utility assessment methodology to address the validity of the states, including the comprehensiveness of the efficacy and side-effect profiles of oral and patch opioids. Data collection instruments and procedures were pilot-tested prior to data collection. Health states did not specify diagnosis and were used for both types of participants (i.e., those with cancer and noncancer pain). Health states were limited to these four key attributes due to concerns about excessive cognitive burden for respondents as well as logistical limitations of computer screen size.

Measures

Health-Related Quality of Life—Medical Outcomes Study Short Form (MOS SF-36). The SF-36 was used with noncancer chronic pain patients in Canada, Australia, and the United States. This self-administered, 36-item instrument is comprised of eight scales: Physical function; Role limitations-physical; Vitality; General health perceptions; Pain; Social function; Role limitations-emotional; and Mental health. In addition, two summary scores can be calculated: Physical and Mental. The overall reliability and validity of this measure are well documented [30]. Normative values are available for the general population, by age and gender, and for a variety of medical conditions, including back pain and osteoarthritis. The SF-36 scores were used to characterize the sample in terms of HRQL and to compare this sample of participants with others to assess the relative impact of chronic pain treatment on HRQL.

European Organization for the Research and Treatment of Cancer—Quality of Life Questionnaire (QLQ-C30). The SF-36 was replaced by the QLQ-C30 (version 3.0) at the site in Canada at which patients with cancer pain were enrolled. The QLQ-C30 is a ≤10-minute self-administered measure designed to assess the HRQL of individuals with cancer [31]. It has 30 items and includes nine domains or categories: Functional scales (physical, role, cognitive, emotional, social); Symptom scales (fatigue, pain, and nausea and vomiting); A global health status and quality of life scale; and Several single-item symptom measures. Scores range from 0 to 100, with higher scores indicating better health for functional and global HRQL scales, and higher scores indicating more severe symptoms for the symptom-oriented scales. While normative values do not exist for the general population, the QLQ-C30 has been widely used and scores can be compared with published studies.

Medical and Sociodemographic Data. Participants also provided information about their method of pain control, success with pain control, current pain severity, history of oral/patch pain medication, concomitant medications, concomitant illnesses, age, gender, race, marital status, education level, and employment status.

Adaptive Conjoint Analysis (ACA) Interview. The ACA approach used in this study is a computer-assisted method of interviewing participants about treatment preferences. This DOS-based IBM-compatible system developed by Sawtooth Software (ACA version 4.0) [32] allows collection and computerized entry of utility data directly at the hospital or clinic. Utility estimation is an automatic component of the ACA interview; respondent utilities are calculated during each interview, without researcher manipulation, and mean utilities are calculated once the interview process is complete for all respondents. The ACA approach adapts the interview for each respondent. Early in the interview, the computer program captures adequate information about each patient's responses to focus on areas of importance for that respondent. In this way, more attributes (e.g., side effects, side-effect severity, levels of pain control, route of administration) can be tested using as few questions as possible.

Each health state description was described as lasting for two weeks. This time frame was based on the maximum number of days needed for pain medication titration and the maximum number of days to treat most side effects, such as nausea/vomiting or mental cloudiness/daytime sleepiness. Some side effects (e.g., constipation) could reasonably extend beyond two weeks. However, for consistency and to avoid temporal effects on preferences, participants were instructed at the start of the interview to provide information on preferences for pain medication based on a consistent, two-week period.

As space on the computer screen was limited, and all levels of each attribute had to be displayed for one particular task in the interview, the computer screen provided only a short, key phrase for each level. Thus, the interviewer first reviewed with the participant all definitions and full descriptions of attribute levels, which were presented on laminated cards (Appendix I). These cards were accessible (visible) to the participant throughout the interview and were reviewed as necessary with the interviewer. The interactive computer program lead the participant through each stage of the interview, with assistance from the interviewer as needed. Each health state description included one level from a given attribute; participants were asked to select between descriptions presented, assuming all other factors (e.g., cost, potential interaction with other medications) were equal. Combinations of attributes and levels that were not possible (e.g., "no side effects" could not be described as "mild," "moderate," or "severe") were eliminated from the choices presented by the computer program. A summary of the steps of the computer-administered interview is presented in Figure 1.

Data Collection

A sample of convenience approach was used by clinical coordinators to recruit participants. Patients who met eligibility criteria and who had appointments scheduled during the week of data collection were contacted via phone. Those who were available were asked to participate. Additional recruitment was performed, when necessary, by posting study fliers on site. Participants first completed the self-administered generic HRQL measure and sociodemographic/medication questionnaire, followed by the ACA computer-assisted interview. Each ACA interview was conducted by an interviewer trained specifically in the administration of the chronic pain interview.

Results

In total, we enrolled 96 Canadian, U.S., and Australian patients with noncancer chronic pain and 25 Canadian patients with cancer chronic pain. Demographic characteristics of our sample showed statistically significant differences among countries only for gender (percent women: Canada 84%; Australia 63%; United States 42%; $p = 0.003$). Results were aggregated across countries for participants with noncancer chronic pain. Tables 1 and 2 show the participant demographic and clinical characteristics. Participants with noncancer pain tended to be younger than those with cancer pain (mean age

Step 1: Rank the attributes.

Patient is asked: *Rank the following side effects from best to worst:*

Screen looks like this:		Patient re-orders using the mouse:
Constipation		No side effects
Vomiting	→	Constipation
No side effects		Vomiting

Step 2: Determine the difference of the attributes:

Patient is asked: *How important is this difference to you?*

Side effect is mild. Side effect is severe.
Not important.....Somewhat important.....Very important

Step 3: Paired comparisons.

Patient is asked: *Assuming all other factors are equal, which of the following do you prefer?*

Patch medication		Oral medication
Pain controlled for 6 of 14 days	or	Well-controlled pain
Constipation		Sweating
Side effect is mild		Side effect is severe

Figure 1 Overview of the conjoint analysis process

Table 1 Participant demographic characteristics

Characteristic	Frequency (n) by Pain Source* Noncancer Pain n = 96	Cancer Pain n = 25
Age in years, mean (SD)	47 (13)	60 (11)
Gender		
Male	38% (36)	16% (4)
Female	63% (60)	84% (21)
Marital status		
Living alone	13% (12)	32% (8)
Living with someone	74% (71)	68% (17)
Other	14% (13)	0% (0)
Race/ethnicity		
White	95% (91)	88% (22)
Black	2% (2)	4% (1)
Other	3% (3)	8% (2)
Educational attainment		
Elementary school	2% (2)	16% (4)
High school graduate	46% (44)	44% (11)
College graduate	28% (27)	20% (5)
Graduate degree	9% (9)	16% (4)
Other (e.g., technical school)	14% (13)	8% (2)
Employment status		
Employed full time	19% (18)	12% (3)
Employed part time	7% (7)	20% (5)
Not employed	74% (71)	68% (17)

*Percents may not sum to 100% due to rounding

Table 2 Participant clinical characteristics

Characteristic/rating	Frequency (n) by Pain Source* Noncancer Pain n = 96	Cancer Pain n = 25
Patient rating of method of pain control during the last week**		
Very good	21% (20)	17% (4)
Good	34% (33)	46% (11)
Moderate	28% (27)	33% (8)
Bad	9% (9)	4% (1)
Very bad	7% (7)	0% (0)
Patient rating of pain control during the last week		
Very good	15% (15)	8% (2)
Good	34% (33)	52% (13)
Moderate	27% (26)	36% (9)
Bad	16% (15)	4% (1)
Very bad	8% (8)	0% (0)
Patient rating of level of pain today		
None	3% (3)	28% (7)
Mild	28% (27)	36% (9)
Moderate	51% (49)	36% (9)
Severe	18% (17)	0% (0)
Ever used patch for pain relief (% yes)	27% (26)	24% (6)
Any comorbidities (% with 1 or more)	34% (33)	72% (18)
Number with pain due to***		
Arthritis	40% (38)	0% (0)
Low back pain	77% (74)	0% (0)
Cancer	0% (0)	100% (25)

*Percents may not sum to 100% due to rounding
**1 missing response in cancer arm
***Participants may report more than one

47 ± 13 years vs 60 ± 11 years). The majority of participants in both groups tended to be female, white, living with someone, and unemployed. More participants with noncancer pain suffered from moderate or severe pain at the time of the interview (69%) than those with cancer pain (36%) (Table 2).

Table 3 compares mean SF-36 scores for the study participants with age- and gender-equivalent population norms for the United States. It is generally accepted that a five-point decrement in SF-36 subscale scores from population norms represents a meaningful difference in HRQL [33]. When subscale scores were averaged across noncancer pain sites, role limitations- physical was the lowest (13.5 ± 28.3 vs 80.6 ± 32.8 for the study participants vs the population norm, respectively) and mental health was the highest (56.5 ± 23.1 vs 74.6 ± 18.0 for the study participants vs the population norm, respectively). Aggregate mean scores for the study participants were from 8 to 67 points lower than the subscale scores for the U.S. age- and gender-matched population. Thus, participants in this study considered their health to be substantially impaired across all subscales compared with the general population [30].

Table 4 presents scores for the QLQ-C30 functioning, symptom, and general quality of life scales. Participants in this study demonstrated a quality of life similar to that of cancer patients beginning treatment with morphine [34,35].

All participants were able to complete the ACA interview, which required an average of 12.2 ± 4.8 minutes to finish. The ACA program, using a correlation cutoff of 0.50, eliminated outliers and inconsistencies across individual comparisons in the analysis.

Table 3 SF-36 scores: Study participants with noncancer chronic pain versus age- and gender-matched population

SF-36 Score*	Mean (SD)** Study (n = 96)	U.S. Norm
Summary Scores		
Physical component summary	29.3 (7.9)	49.5 (9.2)
Mental component summary	41.6 (12.6)	50.1 (9.8)
Scales		
Physical functioning	38.9 (25.5)	83.6 (20.8)
Role physical	13.5 (28.3)	80.6 (32.8)
Bodily pain	27.4 (18.0)	73.7 (23.4)
General health	47.7 (21.2)	71.2 (19.6)
Vitality	33.2 (22.2)	60.5 (20.9)
Social functioning	43.9 (26.3)	83.3 (22.5)
Role emotional	44.8 (43.5)	81.5 (32.8)
Mental health	56.5 (23.1)	74.6 (18.0)

*On the SF-36, scores range from 0 to 100; higher scores indicate better quality of life.
**All study versus normative comparisons significant at $p < 0.05$.

Table 4 QLQ-C30 scores: Study participants with cancer-related chronic pain (n = 25)

QLQ-C30 Score	Mean (SD)*
Functional Scales	
Physical functioning	64.5 (21.7)
Role functioning	53.3 (29.3)
Emotional functioning	67.6 (20.3)
Cognitive functioning	74.7 (21.0)
Social functioning	54.7 (31.4)
Global Scale	
Global health status/QOL	48.3 (21.1)
Symptom Scales	
Fatigue	52.0 (20.7)
Nausea/vomiting	14.7 (22.2)
Pain	48.0 (24.2)
Dyspnea	28.0 (28.3)
Appetite loss	34.7 (34.0)
Constipation	36.0 (33.2)
Diarrhea	10.7 (23.0)
Financial problems	28.0 (32.9)

*On the EORTC QLQ-C30, scores range from 0 to 100, with higher scores indicating better health for functional and global HRQL scales and higher scores indicating more severe symptoms for the symptom-oriented scales.

There were slight differences in the mean utilities assigned to health states that differed only by oral versus patch route of administration. Among participants with noncancer pain, there was a very small and consistent advantage (1-2 points) to oral administration of opioids. Among participants with cancer pain, the pattern differed by severity of side effect; patients slightly preferred oral administration (by an average of <1 point) when the side effect was mild and slightly preferred the patch when the side effect was severe. Thus, we examined the influence of the patient's experience with the patch and oral administration and found that when patients had used both routes of administration, their preferences were essentially equivalent for patch and oral administration. As a result, the mean utilities presented in Figures 2-3 are those reported for the oral route of administration, with values for patch administration similar. In Appendix I, two tables demonstrate ratings for all possible health states included in this analysis, giving the clinician a way of judging the related "value" to the patient of various medication effects and side effects.

The mean utilities represent the extremes of pain control: poorly controlled pain ("You have breakthrough pain for up to 12 out of 14 days") in Figure 2 and well-controlled pain ("You have well-controlled pain for 14 days") in Figure 3. The mean utilities that corresponded with intermediate levels of pain control (3, 6, and 9 days of breakthrough pain) ranked in a consistent manner within these extremes, with a linear progression of utility values. The mean utilities ranged from a high of 0.89, for well-controlled cancer pain with no side effects (not shown in figures), to a low of 0.18 (poorly controlled, noncancer pain with severe mood changes/alterations, severe respiratory depression, or severe vomiting, Figure 2).

For utilities based on both well-controlled and poorly controlled pain, there was a 0.06-0.09 decrement in utility from a mild to a moderate side effect, compared with a decrement of 0.13-0.18 in utility from a moderate to a severe side effect. In other words, participant preferences were more similar for mild to moderate side effects than for moderate to severe side effects. In contrast, the utilities associated with well-controlled pain with a side effect at a given severity (mild, moderate, or severe) were consistently 0.26 to 0.31 higher than utilities associated with poorly controlled pain with a side effect of the same severity. The five-point utility decrement from a mild to a severe side effect (range: 0.21-0.26) with pain control held constant was similar to the five-point utility decrement from well-controlled to poorly controlled pain (0.26-0.31) with side effect severity held constant.

Discussion

The primary objective of this study was to assess preferences for pain treatment outcomes among participants with cancer and noncancer chronic pain, with the focus on the trade-offs between pain control and side effects. Although opioids are accepted as appropriate treatment for acute and cancer pain, they remain controversial for use with chronic noncancer pain. However, pain control is vital to the quality of life of all patients. Although concerns about efficacy, tolerance, addiction, and unwanted side effects associated with opioids for noncancer pain are decreasing, some clinicians remain reluctant to prescribe opioids for noncancer chronic pain [36].

Particularly when it is chronic and related to severe disease, pain can interact significantly with many facets of daily living [37]. Medical interventions themselves can affect quality of life in both positive and negative ways. Some side effects may be so common as to be accepted as "normal" (e.g., constipation or sedation with opioids); it is only by their careful evaluation that differential toxicities may be revealed [37].

The highly desirable end point of chronic pain treatment is not just freedom from pain, but global well-being. The HRQL of persons with chronic noncancer pain severe enough to require opioid treatment, is among the lowest observed for any

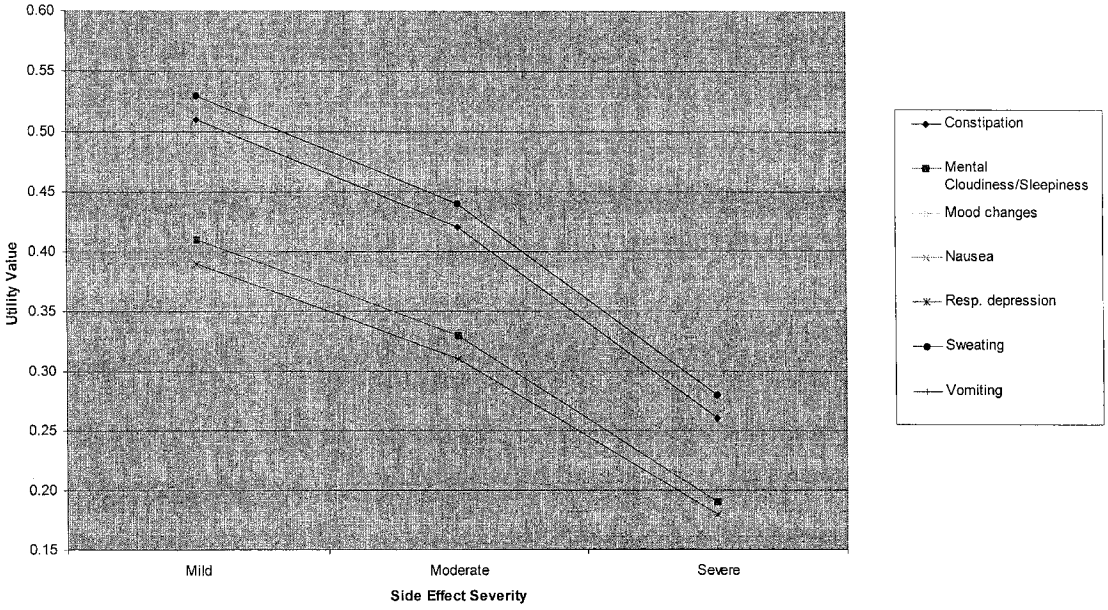

Figure 2 Poorly controlled non-cancer pain, aggregate mean utilities by side effect severity

medical condition, and confirms the findings by Becker and colleagues [38] that unrelieved pain has a significant, multidimensional impact on patient well-being. Although we did not find other published utilities specifically for pain therapy resulting in side effects, utilities estimated by various populations using the Health Utility Index (HUI), a self-administered questionnaire from which utility scores are derived, ranged from 0.85 for "pain that does not disrupt" activities to 0.29 for "pain that is not relieved by drugs" [39]; these utilities do not consider other factors, such as side effects.

In general, participants in our study assigned preference scores to health states with well-controlled pain and mild or moderate side effects similarly or higher than arthritis patients (0.65) [40]. Erikson [41] found that 35- to 54-year olds with arthritis attributed a mean utility to their health of 0.70 using the HUI. As these studies did not address precisely the same combinations of pain control, treatment, and side effects as our study, and different methods of utility assessment were used in each, it is difficult to directly compare results.

This study identified specific trade-offs that patients are willing to make to achieve a balance between the level of pain and type and severity of side effect. Our data clearly show that utility values are highly dependent on the level of pain control and the severity of side effects. By presenting patient evaluations of each combination of attributes and levels, this study encourages exploring patients' preferences more carefully in treatment selection. For example, the difference between utility ratings of mild and moderate side effects was not as large as the difference between those of moderate and severe side effects. This finding suggests switching from a medication that will control pain better but will increase the severity of a side effect may be acceptable if the side effect increases from mild to moderate rather than from moderate to severe. Similarly, sweating, no matter how severe, may be preferable to nausea if pain is better controlled. While assessments are unique to each patient, this group-level analysis provides guidance for factors to consider in suggesting therapies and their relative merits. These trade-offs may be extrapolated somewhat with caution, but the two-week "snapshot" provided here is only part of the equation when long-term pain management is required.

Although we found utilities to be similar in patients with cancer and noncancer pain, some research indicates that diagnosis may have an impact on the assessment of health states [42]. We did not specify the diagnosis in this study, choosing to focus on the symptom (i.e., pain), rather than the source of the symptom. This allowed us to use identical health state descriptions for all participants.

This study has limitations that should be considered when interpreting results. The number of patients who had had personal experience with patch medication was relatively small. However, when we analyzed the impact of experience with the patch on

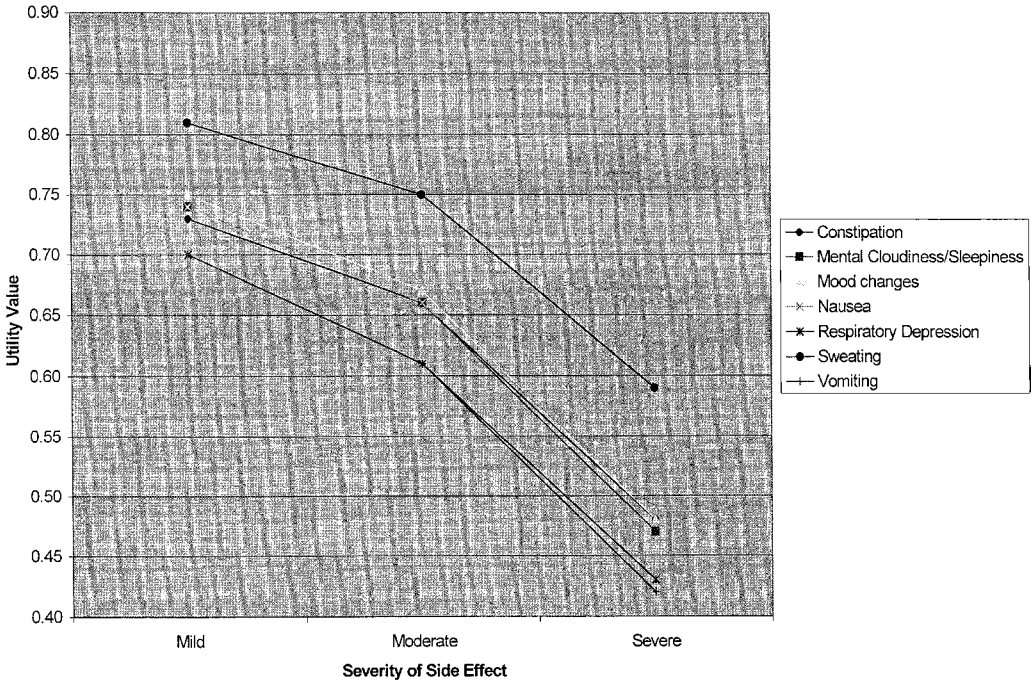

Figure 3 Well-controlled cancer pain, aggregate mean utilities by side effect severity

utility assignment, we were confident that the utilities assigned to the oral route of administration were essentially equivalent to the utilities for patch administration. Thus, utilities assigned to states with oral administration of opioids were considered representative of patch administration of opioids. Also related to the health state descriptions, we used days with breakthrough pain rather than chronic pain level, both of which may be experienced by these patients.

Participants in this study suffering from noncancer chronic pain had either arthritis or low back pain. It has recently been shown that women with certain disabilities, such as osteoarthritis, have significantly higher levels of pain and physical disability than men with the same condition [43]. We did not match participants across countries on demographic or clinical characteristics. Overall, our sample of noncancer chronic pain participants included 63% women, and gender was the one demographic characteristic that differed significantly among the Canadian, U.S., and Australian participant samples. We did compare country-specific SF-36 subscale scores with age- and gender-matched population norms (these norms were for the United States; such norms are not available for Australia and Canada). In a general population, differences have been detected in scores on several scales of the QLQ-C30 based on gender [34]. However, it is uncertain whether gender may have biased utilities in any meaningful way.

A third limitation was that one cannot use the same measure of HRQL for both cancer and noncancer chronic pain patients. We used the QLQ-C30 for the former and the SF-36 for the latter, making it difficult to compare HRQL between these groups of participants. In addition, certain of the SF-36 subscale scores may have some limitations in participants with arthritis. Although the SF-36 physical and mental component summary scores are reliable, valid, and responsive measures of health status in patients with rheumatoid arthritis and the SF-36 pain and physical function scales may be suitable for self-assessment in these patients, the two subscales for role limitations have been reported to have poor measurement characteristics in such patients [44]. However, these instruments are widely used and are useful for comparison with other studies and in presenting a comprehensive profile of the study participants.

Finally, the nature of the computer-administered interview required that patients come to the clinic for the study. While study coordinators attempted to schedule the study interview preceding a regularly scheduled visit, this was not possible in all cases. It is possible that patients who were called and consented to visit the clinic to participate in the study were healthier and more mobile than those who did not agree to participate, suggesting that the sample may be biased toward healthier partici-

pants, whose opinions may not be representative of the population of patients with chronic pain. However, less than one third of the study population was employed, suggesting that perhaps the study population was more disabled than the working chronic pain population. Employed patients were not excluded from the study; sample size was not sufficient to determine whether working status was significantly related to preference ratings. We recognize that this sample might not be representative of the general chronic pain population due to recruitment methods and study design, but it is not clear in which direction any bias, if present, might be.

Conclusions

Although there are few validated instruments that assess the impact of drug therapy on patient preference and HRQL for persons with moderate-to-severe chronic pain, a goal of therapy should be to maximize the patient's overall sense of well-being and HRQL [45]. Persons with noncancer chronic pain often experience inadequate pain relief for various reasons. This study provides a valuable assessment, from the patient's perspective, of the trade-off between treatment tolerability and the manifestation of disease symptoms. While both medication side effects and inadequate pain control independently result in important decrements in patient preference assessment, when combined, these characteristics may result in extremely low utility for persons with chronic pain.

These data, using standard and scientifically appropriate techniques, demonstrate the impact of common characteristics of pain medications on patients' preferences for treatments. It is this quantification of the trade-offs patients are willing to make that may be valuable to the practicing clinician. The more aware the prescriber is about a patient's preferences for combinations of these key attributes of pain medications, the more likely it is that the treatment regimen selected will be both effective and acceptable to the patient. In addition, outside the clinical setting, data such as these can be used to inform decision-analytic models, help allocate resources based on relative assessments of preferences, and provide comparative assessments across populations.

Acknowledgment

We are grateful to Janssen-Ortho Inc. for the partial support of this research.

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Appendix I: Full Descriptions of Attributes and Levels and Definition of Breakthrough Pain

Definitions and Descriptions Used in the Patient Interviews on Chronic Pain Therapy

1. Definition of breakthrough pain
   You have sudden, unexpected pain that is different from (or greater than) your usual, or chronic, discomfort.

2. Descriptions of pain control
   You have no breakthrough pain
   You have breakthrough pain for 3 out of 14 days
   You have breakthrough pain for 6 out of 14 days
   You have breakthrough pain for 9 out of 14 days
   You have breakthrough pain for 12 out of 14 days

3. Descriptions of type of pain medication

Patch Medication. You are an outpatient being treated for moderate to severe chronic pain. You have been prescribed a pain medication that consists of a small adhesive patch applied to the skin on your back, chest, leg, or arm. You receive the pain medication through your skin from the patch. You replace the patch once every three days.

Oral Medication. You are an outpatient being treated for moderate to severe chronic pain. You have been prescribed an oral pain medication. You take one pill every 12 hours.

4. Descriptions of pain medication side effects

Constipation. You do not have bowel movements as often as you normally would, or you may feel like you're never quite finished a bowel movement. Stools may be lumpy or hard, and you strain or feel pain when having a bowel movement. Your constipation continues for as long as you are taking pain medication.

Mental cloudiness/sleepiness. You feel sleepy or groggy during waking hours and are slow to respond. You may be confused, disoriented, or have difficulty concentrating.

Mood changes/alterations. You may have a rapid increase in your rate of breathing. If you already have symptoms of depression they may become worse. You may have periods of anxiousness, panic, excitability, restlessness, irritability, or mood swings. You may have a decreased desire for alcoholic beverages, eating certain foods, and having sexual relations. The mood changes/alterations continue for as long as you are taking pain medication.

Nausea. You have an upset stomach and you feel like you might throw up.

Sleep disorders/hallucinations. You have difficulty sleeping through the night and only sleep for short periods at a time. You may have frightening, strange, or vivid dreams. During waking hours, you may have hallucinations (you think things are happening when they are not).

Respiratory depression. Your breathing slows and you may black out or faint. While sleeping, your breathing may become noisy or stop completely for short periods without you being aware that anything is wrong.

Sweating. You have an unusual increase in the amount that you sweat or perspire. You may regularly feel flushed. The sweating may occur at anytime during the day or night and continues for as long as you are taking pain medication.

Vomiting. You have an upset stomach and are throwing up.

5. Descriptions of side effect severity

Mild side effect.

- Your side effect symptoms are infrequent or limited in number
- You do not need additional medication
- You continue to take your pain medication as prescribed
- Symptoms generally go away by themselves and none are long lasting
- The side effect has no impact on your day-to-day functioning (daily activities, work and social activities)

Moderate side effect.

- Your side effect symptoms are moderately intense and frequent
- You need additional medication or treatment for the side effect
- You continue to take your pain medication, but may have to reduce the dose or stop temporarily until symptoms get better with medication
- Your symptoms may continue, but are manageable
- You are limited a little in your day-to-day activities. There is moderate interference with work and/or social activities some of the time. You are somewhat less productive than usual.

Severe side effect.

- Your side effect symptoms are intense, extremely bothersome or numerous, and potentially dangerous
- You may need a short hospital stay, uncomfortable tests, or intravenous medications (continuous medication through a needle in your arm)
- You must switch to another pain medication
- Your symptoms may not go away

- You are limited a lot in your daily activities; you are unable or unwilling to participate. Your side effect symptoms interfere quite a bit with work and social activities all or most of the time. You are much less productive than usual.

For each side effect, values are provided for each level of severity and for each level of pain. For example, respondents rated moderate mental cloudiness with 6 days of breakthrough pain over the 2-week period as 0.47.

Table A-1 All health states—oral

Method	Days of Breakthrough Pain—Level of Pain Control				
Oral	0 days breakthrough pain	3 days breakthrough pain	6 days breakthrough pain	9 days breakthrough pain	12 days breakthrough pain
Side effect severity					
No side effects	0.88	0.83	0.77	0.73	0.65
Constipation					
Mild	0.81	0.73	0.66	0.59	0.50
Moderate	0.74	0.65	0.57	0.50	0.41
Severe	0.57	0.46	0.37	0.31	0.24
Mental cloudiness					
Mild	0.74	0.64	0.56	0.48	0.40
Moderate	0.66	0.56	0.47	0.39	0.31
Severe	0.47	0.37	0.28	0.23	0.17
Mood changes					
Mild	0.72	0.62	0.53	0.45	0.37
Moderate	0.63	0.53	0.44	0.36	0.29
Severe	0.44	0.34	0.26	0.21	0.16
Nausea					
Mild	0.77	0.68	0.59	0.52	0.44
Moderate	0.69	0.59	0.50	0.43	0.34
Severe	0.51	0.40	0.32	0.26	0.21
Respiratory depression					
Mild	0.72	0.62	0.54	0.46	0.37
Moderate	0.63	0.53	0.55	0.37	0.29
Severe	0.44	0.35	0.26	0.22	0.16
Sweating					
Mild	0.84	0.74	0.67	0.60	0.52
Moderate	0.76	0.66	0.58	0.51	0.43
Severe	0.59	0.48	0.39	0.33	0.27
Vomiting					
Mild	0.72	0.62	0.53	0.45	0.37
Moderate	0.63	0.52	0.44	0.36	0.28
Severe	0.44	0.34	0.26	0.21	0.16

Table A-1 All health states—patch

Method	Days of Breakthrough Pain—Level of Pain Control				
Patch	0 days breakthrough pain	3 days breakthrough pain	6 days breakthrough pain	9 days breakthrough pain	12 days breakthrough pain
Side effect severity					
No side effects	0.85	0.80	0.75	0.69	0.61
Constipation					
Mild	0.78	0.70	0.62	0.54	0.46
Moderate	0.70	0.61	0.53	0.45	0.36
Severe	0.53	0.44	0.32	0.26	0.20
Mental cloudiness					
Mild	0.70	0.60	0.52	0.44	0.35
Moderate	0.62	0.51	0.42	0.34	0.26
Severe	0.43	0.32	0.24	0.19	0.14
Mood changes					
Mild	0.68	0.58	0.49	0.41	0.32
Moderate	0.59	0.48	0.39	0.32	0.24
Severe	0.40	0.30	0.22	0.17	0.12
Nausea					
Mild	0.73	0.64	0.55	0.48	0.39
Moderate	0.65	0.55	0.46	0.38	0.30
Severe	0.47	0.36	0.27	0.22	0.17
Respiratory depression					
Mild	0.68	0.58	0.49	0.41	0.33
Moderate	0.59	0.48	0.39	0.32	0.24
Severe	0.41	0.31	0.22	0.18	0.13
Sweating					
Mild	0.79	0.70	0.63	0.56	0.48
Moderate	0.72	0.62	0.55	0.47	0.39
Severe	0.54	0.44	0.35	0.29	0.23
Vomiting					
Mild	0.68	0.57	0.49	0.40	0.32
Moderate	0.58	0.48	0.39	0.32	0.24
Severe	0.40	0.30	0.22	0.17	0.13