From: Russell Portenoy, MD <RPorteno@chpnet.org>
To: Napoli, Andrew; Nathanel Katz MD; Alicia Shillington
CC: Narayana, Arvind; Carla Frye
Sent: 8/12/2010 11:30:30 AM
Subject: RE: Burden of Illness Poster Draft for Review
Attachments: NarayanalASP NBTPS Poster081110.doc

I made some suggestions. If it were possible just to have the prevalence of BTP in cancer vs. non-cancer added to the interim results, it would be nice.

Great work.

Thank you.

Russ

From: Napoli, Andrew [mailto:anapoli@cephalon.com]
Sent: Wednesday, August 11, 2010 12:10 PM
To: Nathanel Katz MD; Russell Portenoy, MD; 'Alicia Shillington'
Cc: Narayana, Arvind; 'Carla Frye'
Subject: Burden of Illness Poster Draft for Review

Dear Authors,

As promised, please find the updated burden of illness study poster draft for review. Based on Arvind's direction, we have inserted the interim data (the additions are in red text). There are a couple placeholders for patient demographic and disposition data that should be available soon.

Because we have a relatively tight timeline to get this into layout, printed, and shipped to Canada, I'm hoping that you can review and provide comments this week. If it would expedite things to have a conference call, let me know and I will schedule it ASAP.

Regards,

Andy

From: Narayana, Arvind
Sent: Tuesday, August 10, 2010 4:31 PM
To: Nathanel Katz MD (nkatz@analgesicresearch.com); rporteno@chpnet.org
Cc: Napoli, Andrew; Alicia Shillington; Carla Frye; Larijani, Susan
Subject: interim results of the burden of illness study

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Dear Russ & Nat,

I hope everything is going well for both of you. The purpose of this e-mail is to share some interim results of the burden of illness study with you. In the next few days you

should be receiving the updated IASP poster for your review and approval. This updated poster incorporates your earlier comments as well as the interim data. Attachment one is a recent weekly report outlining overall disposition of patients including reasons for exclusion from the study. Attachment two is the interim results on prevalence, characteristics of breakthrough pain, functionality, and productivity. Please note that the overall number of patients between attachment one and attachment two are slightly different. I hope to update attachment two with a disposition table which matches the interim results. I have also requested some additional demographic information on race and geography to be included in the poster. Finally, for your background I have also attached the most recent versions of the protocol and survey instrument as attachments three and four.

I look forward to hearing your feedback on the poster. If after reviewing these interim results or the poster and would like to set up a teleconference for us to discuss, we would be happy to set that up quickly. Thanks. Have a nice rest of your day. Arvind

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The National Breakthrough Pain Survey (NBPTS): Design, Methodology, and Interim Results

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INTRODUCTION

- Breakthrough pain (BTP) is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain in patients receiving long-term opioid therapy (Portenoy and Hagen, 1990).
- A survey of community-dwelling patients with chronic cancer or non-cancer pain suggests that the prevalence of BTP is 30-50% (Portenoy et al, 2010a).
- Several surveys of cancer patients indicate that BTP is associated with more severe pain, less effective analgesic treatment, impaired function, mood disturbance and relatively poorer quality of life (Portenoy et al, 1999; Portenoy et al, 2010b; Portenoy and Hagen, 1990; Zeppetella et al, 2001; Zeppetella et al, 2010). More limited data in noncancer patients suggest~~s~~ similar associations (Portenoy et al, 2006; Portenoy et al, 2010b; Svendsen et al, 2005).
- There also are limited data indicating that the presence of cancer-related BTP may increase healthcare costs (Fortner et al, 2002).
- To further describe the ~~illuminate this~~ epidemiology and illness burden associated with BTP, ~~,~~ the National Breakthrough Pain Survey (NBTPS) has ~~been undertaken to~~ evaluated ~~evaluate~~ BTP in a population of commercially-insured patients identified from a large administrative claims database in the United States (U.S.).

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OBJECTIVES

Primary Objectives

- Evaluate the burden of BTP in a commercially-insured U.S. population of opioid-treated cancer and noncancer patients with controlled, persistent pain, including:
  - Patient-reported pain severity or functional impairment in the previous 24 hours and 7 days
  - Quality of life in the previous 4 weeks
  - Lost workdays or presenteeism in the last 28 days and 365 days
  - Days out of role (e.g., work or school absence, inability to perform normal daily activities) in the last 28 and 365 days
  - Healthcare consumption in the previous 12 months from the date of survey

Secondary Objectives

- Evaluate the prevalence of BTP in a representative, commercially-insured U.S. population with controlled persistent pain who are taking daily opioid therapy
- Characterize the ~~etiology of pain, symptoms and severity,~~ demography, disease and comorbidities, and medication treatment patterns in this population
- Describe the phenomenology and etiology of BTP in this population

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METHODS

Data Source

- Survey participants are commercially-insured health plan members identified from the insurer's administrative claims database who, u~~.~~
- ~~U~~pon enrollment into a plan, ~~members~~ agree~~d~~ to participat~~e ion~~ in plan~~-~~ authorized surveys
-
- Sampling pool was first ~~Of the approximately 33 million patients who are members,~~ limited to the 6.4 million who are currently active in the health plans, are ≥18 years of age, and have been continuously enrolled for ≥12 months, and then further reduced by eligibility criteria to approximately 50,000 health plan members
  - The sampling frame for these eligible members was stratified based on census region to be representative of the commercially-insured U.S. population.

NOTE: SOME MENTION OF HOW THE SAMPLE POOL WAS REDUCED TO 50,000 WOULD BE GOOD, E.G., ELIGIBILITY REVIEW

Survey Design

- Institutional review board approval was received for the protocol and the survey instruments.
- Based on a review of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes and pharmacy prescription claims,

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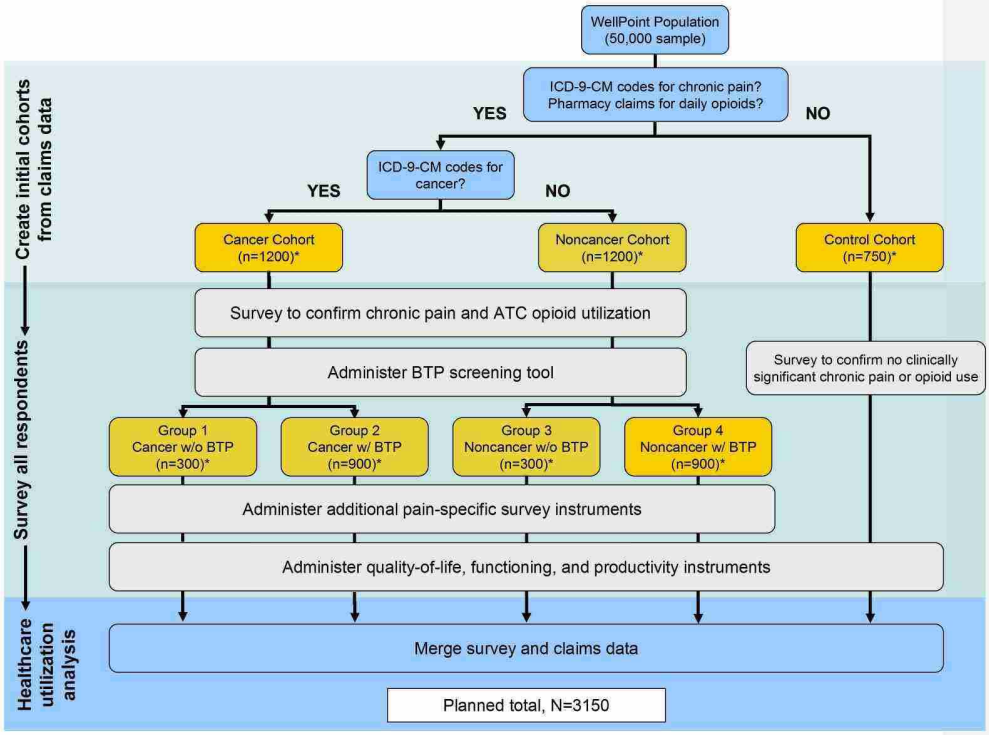
eligible patients were divided into a control cohort and 2 pain cohorts, which were subdivided into 4 groups (**Figure 1**).

Figure 1. Survey Design



ATC=around-the-clock; BTP=breakthrough pain.

*Planned sample size.

- Identified patients were contacted by telephone, according to a standard protocol, to obtain verbal consent for participation. They were then screened to confirm the presence of chronic pain and daily opioid use. Patients without clinically significant chronic pain were assigned to the control cohort.

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- Patients with clinically significant chronic pain on daily opioid therapy were divided into cancer and noncancer cohorts based on the presence or absence of a cancer diagnosis (ICD-9-CM code or Current Procedural Terminology [CPT] code indicating receipt of chemotherapy or radiation).
- All pain patients were ~~then~~ administered a screening tool to determine the presence of controlled persistent pain, with or without BTP. The cancer cohort was further subdivided into groups 1 and 2, and the noncancer cohort was divided into groups 3 and 4, according to the absence or presence of BTP, respectively.
- Surveys assessing quality of life, functionality, and productivity were administered to all patients. Additional pain-specific surveys were administered to patients as appropriate to assess pain symptom severity and burden of illness.
- Claims data and survey data were then merged to complete the utilization and cost analysis.

Patient Selection

All Patients

- Inclusion criteria
  - ≥18 years of age at the time of the survey
  - Able to provide informed consent
  - Fluent in English

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- Current member with a minimum of 12 months of continuous enrollment in an affiliated health plan before the survey date

Control Cohort

- Exclusion criteria
  - A medical claim or an ICD-9-CM code associated with chronic pain within the last 12 months or verification of a clinically significant chronic pain condition via telephone interview
  - An opioid prescription claim within the past 3 months or determination of the use of opioids for a chronic pain condition during the telephone interview

Cancer and Noncancer Pain Cohorts

- Inclusion criteria
  - ≥2 medical claims with an ICD-9-CM code associated with chronic pain separated by ≥3 months
  - ≥3 opioid prescription claims within 3 months using the Medication Refill Adherence (MRA) measure of ≥90% to assess daily use
  - Responses on screening interview that meet criteria for "controlled baseline pain"
- Exclusion criteria
  - An ICD-9-CM diagnostic code (medical claims) or Healthcare Common Procedure Coding System (HCPC) code (ambulatory services) for drug

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abuse or dependence concurrent with a pharmacy claim for methadone

- Pain determined through the interview to be acute, intermittent, or inadequately controlled persistent pain (i.e., background pain)

Assessments

~~*Primary*~~

- ~~Difference between patients with BTP (groups 2 and 4) and patients in the control cohort in the following outcome measures of the burden on health:~~
  - ~~Health-related quality of life, as measured by the 12-Item Short Form version 2 (SF-12) Health Survey~~
  - ~~Productivity – days out of role (e.g., work or school absence, inability to perform normal daily activities) and presenteeism, as measured by the Sheehan Disability Scale (SDS) and the World Health Organization Health and Work Performance Questionnaire (HPQ) Short Form~~
  - ~~Use of healthcare in the 12 months before the survey date~~

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~~*Secondary*~~

- ~~Difference between patients with BTP (groups 2 and 4) and patients without BTP (groups 1 and 3) in:~~
  - ~~Patient-reported pain severity and impact, as measured by the Brief Pain Inventory (BPI)~~
  - ~~Health-related quality of life, as measured by the SF-12~~

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~~–Productivity, including presenteeism, as measured by the SDS and HPQ~~

~~–Use of healthcare in the 12 months before the survey date~~

~~•Prevalence of BTP in opioid-treated patients with controlled persistent pain~~

~~•Description of the etiology of pain, symptoms and severity, demography, and comorbidity~~

~~•Treatment patterns (e.g., pharmacy claims for opioids and strengths administered) in the patient groups with BTP (groups 2 and 4)~~

Survey Instruments

- Demographic information was recorded for all patients, and patients in groups 1 to 4 were administered an introductory screening questionnaire to confirm the presence of controlled persistent pain and the presence or absence of BTP.
- An overview of instruments administered to patients to assess pain symptom severity and burden of illness is presented in **Table 1**.

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Table 1. Overview of Survey Instruments

	Instrument	Assessments	Populations Studied	References Supporting Validity
Quality-of-life, functioning, and productivity survey instruments*	World Health Organization Health and Work Performance Questionnaire (HPQ)–Short Form	Workplace presenteeism and absenteeism	Workers in various occupations at large corporations	Kessler RC, et al. *J Occup Environ Med*. 2003;45:156-174 Kessler RC, et al. *J Occup Environ Med*. 2004;46(Suppl 6):S23-S37
	The 12-Item Short-Form (SF-12) Health Survey	Functional health and well-being	Respondents in U.S. large-population health surveys	Ware JE, et al. *Med Care*. 1996;34:220-233
	Sheehan Disability Scale (SDS)	Functional disability—impact on productivity (days out of role)	Respondents in U.S. large-population health surveys, including patients with various types of neuropathic pain	Arnold L, et al. *Prim Care Companion J Clin Psychiatry*. 2009;11:237-244 Galvez R, et al. *Eur J Pain*. 2007;11:244-255 Perez C, et al. *Cephalagia*. 2009;29:781-790 Sheehan DV, et al. *Int Clin Psychopharma-col*. 1996;11(Suppl 3):89-95
	Patient Health Questionnaire–2 (PHQ-2)	Screening for depression	Patients in primary care and obstetrics-gynecology clinics	Kroenke K, et al. *Med Care*. 2003;41:1284-1292
	Generalized Anxiety Disorder–7 Screener (GAD-7)	Screening for anxiety disorders	Primary care patients and the general population	Löwe B, et al. *Med Care*. 2008;46:266-274
Pain-specific survey instruments	Brief Pain Inventory (BPI)–Short Form	Severity and location of pain and impact of pain on daily functioning	Patients with pain from diseases or conditions such as cancer, osteoarthritis, low back pain, and postoperative pain	Cleeland CS, et al. *Ann Acad Med Singapore*. 1994;23:129-138 Cleeland CS. *Clin Cancer Res*. 2006;12(20 Suppl): 6236s-6242s Keller S, et al. *Clin J Pain*. 2004;20:309-318
	Breakthrough Pain Questionnaire (BPQ)	Severity, quality, and characteristics of baseline pain and breakthrough pain	Patients with chronic pain associated with cancer and other conditions	Portenoy R, et al. *J Pain*. 2006;7:583-591 Portenoy R, et al. *Pain*. 1999;81:129-134

*Administered to all patients.

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Use of Healthcare

- Direct (medical and prescription drug) use and costs per patient were determined for the 12 months before the survey date.
  - Medical costs were calculated based on claims for inpatient services (e.g., hospitalization, rehabilitation, residential or psychiatric facility), outpatient visits and procedures, physician services, emergency department visits, and other ancillary services (e.g., physical therapy, laboratory services).
  - Prescription drug costs were determined using the total pharmacy claims per patient-year.

Analysis Plan

Primary

- Patients with BTP (groups 2 and 4) were compared to patients in the control cohort in the following outcome measures of the burden on health:
  - Health-related quality of life, as measured by the 12-Item Short Form version 2 (SF-12) Health Survey
  - Productivity – days out of role (e.g., work or school absence, inability to perform normal daily activities) and presenteeism, as measured by the Sheehan Disability Scale (SDS) and the World Health Organization Health and Work Performance Questionnaire (HPQ) Short Form
  - Use of healthcare in the 12 months before the survey date

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Secondary

- Patients with BTP (groups 2 and 4) were compared to patients without BTP (groups 1 and 3) in:
  - Patient-reported pain severity and impact, as measured by the Brief Pain Inventory (BPI)
  - Health-related quality of life, as measured by the SF-12
  - Productivity, including presenteeism, as measured by the SDS and HPQ
  - Use of healthcare in the 12 months before the survey date
- Demography, prevalence of BTP, pain phenomenology, disease-related factors, and treatment patterns (e.g., pharmacy claims for opioids and strengths administered) were described

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INTERIM RESULTS

Survey Population

- As of July 30, 2010, a total of X number of patients were screened and 905 patients completed the survey.
  - X patients were in the cancer cohort and X patients were in the noncancer cohort. For this interim analysis the cancer and noncancer cohorts were combined.
  - Of note, X (X%) were ineligible because of uncontrolled persistent pain.

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Table 2. Interim Patient Demographics

Variable	No BTP (n =110)	BTP n=428)	Control (n=367)
Age, years			
Mean (SD)	52.5 (11.3)	49.5 (9.5)*	48.3 (18.0)
Sex, n (%)			
Male	41 (37)	170 (40)	177 (48)
Female	69 (63)	258 (60)	190 (52)
Race			
White			
Black			
Asian			
Other			
Geography			
Northeast			
South			
Midwest			
West			

* Data missing from 1 patient.

- Of the 538 patients with controlled persistent pain, 428 (79.6%) reported experiencing BTP.

Table 3. Interim Responses to the Breakthrough Pain Questionnaire (BPQ)*

Variable	Response
Number of BTP flares per day, median (mean)	2.0 (3.45)
Duration until peak pain, median (mean) minutes	10.0 (38.6)†
Duration from flare start to end, median (mean) minutes	90.0 (370.8)
Ability to often, almost always, or always predict BTP flares, n (%)	128 (30)

*Only patients with controlled persistent pain and BTP (n=428) responded to the full survey.
†n=321.

- Responses to quality of life, functioning, and productivity instruments show statistically significant differences between groups.

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Table 4. Interim Responses to Quality-of-life, Functioning, and Productivity Survey Instruments

Variable	No BTP (n =110)	BTP (n=428)	Control (n=367)
SDS Total, mean (SD)	3.8 (3.0)*	5.2 (3.0)*†	0.5 (1.2)
Days out of role (past 30 days)	4.6 (7.0)*	9.2 (10.4)*†	0.2 (0.8)
Days out of role (past 365 days)	61.8 (101.8)*	114.5 (136.7)*†	2.5 (5.6)
Unproductive days (past 30 days)	6.2 (9.4)*	10.1 (10.5)*†	0.5 (2.1)
Unproductive days (past 365 days)	66.3 (114.9)*	107.7 (129.6)*†	3.7 (20.5)
BPI total interference 24 hour, mean (SD)	25.0 (14.9)*	34.9 (16.0)*†	5.0 (9.2)
SF-12 Physical, mean (SD)	34.3 (10.0)*	29.2 (9.1)*†	53.4 (6.8)
SF-12 Mental, mean (SD)	48.8 (11.1)*	47.2 (11.5)*	54.7 (6.0)

*P<0.05 vs Control
†P<0.05 vs Chronic Pain

DISCUSSION

- This unique methodology illustrates the potential of an approach linking case definition from a large dataset to patient interviews in order to provide a broad evaluation of the burden of illness associated with BTP.
- Based on interim results, BTP was highly prevalent (79.6%) in this commercially-insured U.S. population of opioid-treated cancer and noncancer patients with controlled, persistent pain.
    - Patients with BTP reported substantial reductions of quality-of-life, functioning, and productivity compared with patients with controlled, persistent pain and no BTP, as well as compared with the control cohort.
- The complete results will provide the largest dataset of its kind available to date and will greatly improve understanding of the epidemiology and impact

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of BTP on community-dwelling cancer and noncancer populations with opioid-treated chronic pain syndromes.

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