DATAMONITOR

Stakeholder Insight: Cancer Pain

Physician survey highlights inadequacies in education and treatment

Estimated to affect over 6 million individuals across the seven major markets in 2009, the population of patients suffering from cancer pain is expected to grow in the future as a result of the rising incidence of cancer and increasing life expectancy of cancer patients.

According to results from Datamonitor's physician survey, many cancer patients still receive inadequate pain management despite the availability of a wide range of analgesics and treatment guidelines. Increased education of cancer pain and its management among physicians and patients is key to improving treatment outcomes.

This study is based on a survey of 180 oncologists, palliative medicine specialists, pain specialists and anesthetists across the US, Japan, France, Germany, Italy, Spain, and UK.

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ABOUT DATAMONITOR HEALTHCARE

Datamonitor Healthcare provides a total business solution to the pharmaceutical and healthcare industries. Its services reflect its expertise in therapeutic, strategic and eHealth market analysis and competitive intelligence. For more details of Datamonitor Healthcare's syndicated and customized products and services, please refer to the Appendix or contact:

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About the Central Nervous System pharmaceutical analysis team

Datamonitor's therapeutic area studies comprise the following features:

- clinical opinion leader intelligence and best-in-class case studies, leading to actionable recommendations;
- R&D pipeline and unmet need analysis;
- analysis of current physician attitudes and perception;
- scenario-based volume and revenue forecasting;
- supporting presentations, Excel-based forecasts and key conclusions.

The CNS team is headed by Ben Greener. Since joining Datamonitor in 2001, Ben has authored and managed over a hundred large market analysis reports for the company in the field of CNS. In addition to Datamonitor reports, Ben has also written several healthcare market-focused articles for recognized trade publications and has hosted CNS seminars across the globe.

Ben Greener holds a BSc (Hons) degree in Biological Sciences from the University of Sheffield, where in his final year he specialized in areas of neuroscience. He can be contacted on +44 (0)20 7551 9027 and at bgreener@datamonitor.com.

CHAPTER 1 EXECUTIVE SUMMARY

Scope of the analysis

Datamonitor's *Stakeholder Insight: Cancer Pain* is based on a survey of 180 oncologists, palliative medicine specialists, pain care specialists and anesthetists, conducted in the seven major markets (the US, Japan, France, Germany, Italy, Spain and the UK), supplemented by in-depth interviews with seven key opinion leaders. The analysis within this report compares findings from the physician survey with recent epidemiological surveys, clinical developments, recommendations in current treatment guidelines and key opinion leader views. These analyses will help you to:

- understand differential treatment and unmet needs in key subtypes of cancer pain;
- target physicians more effectively, through an understanding of prescribing behavior and its influences;
- validate new product forecasting based on prevalence and treatment rates;
- benchmark brand awareness and perceptions surrounding product positioning in order to formulate competitive lifecycle management strategies.

Datamonitor insight into the cancer pain market

In the course of its research and analysis for *Stakeholder Insight: Cancer Pain*, Datamonitor identified the following key conclusions:

- ***The incidence of cancer pain is set to increase in the future*** — *Physicians estimate 65% of all cancer patients experience pain. On this basis, approximately 6.7 million cancer patients are affected by pain across the seven major markets (US, Japan, France, Germany, Italy, Spain and the UK) in 2009. The incidence of cancer is expected to rise in the future, driven by the elderly and minority populations. Datamonitor believes that the rising incidence of cancer will in turn lead to a global increase in the number of individuals suffering from cancer-related pain.*
- ***The pharmacological treatment rate for cancer pain is sub-optimal*** — *Although almost 100% of patients with severe cancer pain receive pharmacological treatment for their pain, Datamonitor's primary research indicates that the pharmacological treatment rates for cancer pain of mild*

and moderate intensities are relatively low. Furthermore, over a fifth of breakthrough cancer pain patients do not receive pharmacological treatment. Key barriers to the use of analgesics in the cancer pain population include: under-reporting of pain by cancer patients, inadequate pain assessment by physicians and concerns surrounding use of opioid analgesics.

- ***Physician education is required to improve cancer pain management*** *— Key opinion leaders cite inadequate pain assessment, resulting from lack of physician training as a key reason for the sub-optimal pharmacological treatment rate of cancer pain. Improved physician education currently represents the greatest unmet need in the treatment of all forms of cancer pain. Datamonitor believes pharmaceutical companies should seize the opportunity to play a pivotal role in the provision of education programs which inform physicians on methods of assessing pain, as well as the availability and appropriate use of analgesics for different subtypes of cancer pain.*

- ***Commercial opportunities exist for opioids with a more favorable side-effect profile*** *— Orally administered opioids form the mainstay of treatments for patients with severe cancer pain, including breakthrough pain. Morphine and oxycodone are the two most commonly prescribed opioids for the management of severe cancer pain. However, the side-effect profile of opioids is undesirable and can be dose-limiting. Therefore, opioid formulations which offer a superior side-effect profile to morphine and oxycodone is an area of significant opportunity to pharmaceutical companies.*

- ***There is demand for improved treatments for neuropathic cancer pain*** *— Datamonitor's survey results demonstrate that physicians across the seven major markets are least satisfied with available drug treatments for neuropathic cancer pain. Indeed, few studies have specifically examined the efficacy of drugs indicated for neuropathic pain in the cancer population. Pipeline neuropathic pain drugs which are able to demonstrate superior efficacy than available treatment options can therefore expect to receive a strong uptake.*

Please see the accompanying PowerPoint document for the in-depth Executive Presentation. For treatment trees based on primary research with 180 oncologists, palliative medicine specialists, pain care specialists and anesthetists, please refer to the accompanying Excel deliverable.

Contributing experts

The following key physician opinion leaders were interviewed by Datamonitor during the course of this report:

Dr. Paul Farquhar-Smith, Consultant in Anesthetics, Pain and Intensive Care at the Royal Marsden NHS Foundation Trust, London, UK.

Dr. Marilène Filbet, Director of the Palliative Care Unit at the University Hospital Lyon Sud, Lyon, France.

Prof. Jean-Pierre Marie, Head of the Hematology and Medical Oncology Department, Hotel-Dieu of Paris, France.

Dr Gary McCleane, Consultant in Pain Management at the Rampark Pain Center, Lurgan, Northern Ireland, United Kingdom. Dr McCleane has over 15 years experience in pain management and has authored over 70 scientific papers and book chapters related to pain management. In addition, he is the author and/or editor of four pain-related books.

Dr. Carla Ripamonti, Palliative Care Unit of Day Hospital and Out Patient Clinic. National Cancer Institute of Milan, Italy. Dr Ripamonit is Consultant of the Collaborative Center for Cancer Pain Relief of the World Health Organization; Member of the Steering Committee of the Research Network of the European Association for Palliative Care; Vice Director of 'School of training and updating in Palliative Medicine', National Cancer Institute of Milan; and Professor of Palliative Medicine at the School of Specialization in Oncology of the University of Milan.

US Professor of Anesthesiology – requested total anonymity.

Japanese Professor of Anesthesiology – requested total anonymity.

Related reports

Datamonitor (2009) *Forecast Insight: Neuropathic Pain – Brighter future for pipeline drugs while current brands downgraded,* December 2009, DMHC2567.

Datamonitor (2009) *Cephalon Inc.: PharmaVitae Profile*, December 2009, CSHC1481.

Datamonitor (2009) *Pipeline and Commercial Insight: Supportive Care in Oncology – Innovation and market growth opportunities in bone metastases and emerging supportive care opportunities*, November 2009, DMHC2557.

Datamonitor (2009) *Pfizer Inc.: PharmaVitae Profile*, July 2009, CSHC1454.

Datamonitor (2009) *Forecast Insight: Opioids – Saturation limits the commercial potential of individual brands*, March 2009, DMHC2483.

Datamonitor (2009) *Stakeholder Opinions: Back Pain – Gain competitive edge by targeting subpopulations,* March 2009, DMHC2485.

Datamonitor (2008) *Commercial Insight: Pain Market Overview – Non-traditional analgesics and opioid reformulations to sustain sector growth*, October 2008, DMHC2444.

Upcoming related reports

Datamonitor (2009) *Stakeholder Opinions: Anti NGF Therapies in Pain,* March 2009, DMHC2581.

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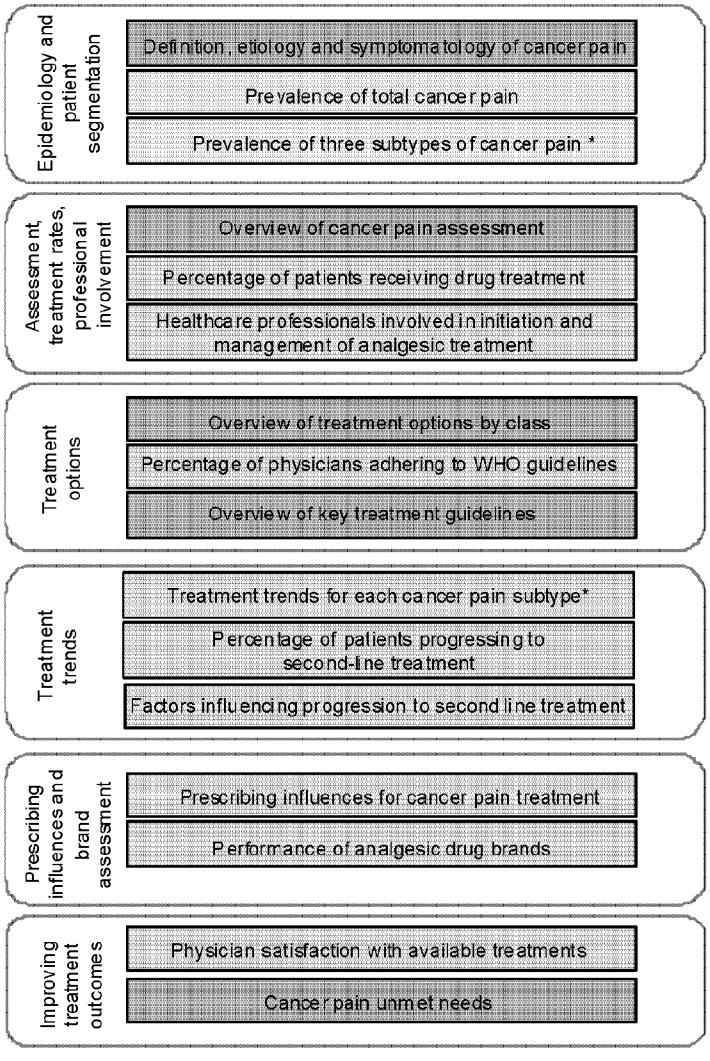
CHAPTER 2 INTRODUCTION AND SCOPE

This *Stakeholder Insight* report is based on a survey of 180 physicians (comprising oncologists, palliative medicine specialists, pain care specialists and anesthetists), conducted across the seven major pharmaceutical markets (the US, Japan, France, Germany, Italy, Spain and the UK). For a detailed breakdown of the physician sample, please refer to the section titled Physician sample breakdown in Appendix A. Analysis in this report is supported by in-depth interviews carried out with seven key international opinion leaders.

Coverage of the Stakeholder Insight Survey

Stakeholder Insight: Cancer Pain covers key issues in cancer pain. Figure 1 provides a diagrammatic overview of the specific issues in this report, and which sections are supported by the physician survey.

Figure 1: Diagrammatic overview of the coverage of the Stakeholder Insight: Cancer Pain survey, 2009



* Neuropathic, non-neuropathic and breakthrough cancer pain. Neuropathic and non-neuropathic cancer pain prevalence estimates are split by pain intensity.

WHO = World Health Organisation

= analysis of secondary sources

= analysis of *Stakeholder Insight 2009: Cancer Pain* survey

= analysis of secondary sources and survey results

= based upon key opinion leader (KOL) interviews

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536 DATAMONITOR

Epidemiology and patient segmentation

- Definition, etiology and symptomatology of cancer pain.
- Prevalence of total cancer pain (regardless of subtype and severity).
- Prevalence of three key subtypes of cancer pain: neuropathic cancer pain, non-neuropathic cancer pain and breakthrough cancer pain. Prevalence estimates for neuropathic and non-neuropathic cancer pain are further split by pain intensity (mild, moderate and severe).

Assessment, treatment rates and professional involvement

- Overview of cancer pain assessment.
- Percentage of patients with neuropathic, non-neuropathic and breakthrough cancer pain receiving pharmacological treatment.
- Healthcare professionals involved in initiation and management of analgesic treatment in cancer pain.

Treatment options

- Overview of treatment options by class.
- Percentage of physicians adhering to the three step "analgesic ladder" approach as published by the World Health Organization (WHO).
- Overview of key treatment guidelines.

Treatment trends

- Prescribing trends for neuropathic, non-neuropathic and breakthrough cancer pain.
- Percentage of patients with neuropathic, non-neuropathic and breakthrough cancer pain progressing to second-line analgesic treatment.
- Relative importance of nine factors when deciding to progress patients with each subtype of cancer pain to second-line therapy.

Key prescribing influences and brand assessment

- Physician rated drug and non-drug prescribing influences for cancer pain.
- Performance of three branded drugs in terms of factors such as efficacy, onset of action, lack of drug-drug interaction, duration of action, side-effect profile, flexible dosing frequency, cost, physician product familiarity, recommendation in treatment guidelines and convenience of administration.

Improving treatment outcomes

- Physicians' satisfaction with currently available therapies for neuropathic, non-neuropathic and breakthrough cancer pain.
- Major unmet needs in cancer pain based upon interviews with key opinion leaders.

Assumptions and caveats

The principal caveat concerning the analysis of the *Stakeholder Insight 2009: Cancer Pain* Survey is that it is based on the perception of 180 physicians. To help validate respondent answers, Datamonitor conducted interviews with seven key opinion leaders and carried out extensive literature reviews.

Two caveats relate to the epidemiology of cancer pain covered in CHAPTER 4.

- Datamonitor employed 5-year cancer prevalence estimates from Globocan (Globocan, 2009; http://www-dep.irac.fr) in order to size the cancer pain population across the seven major markets. As with the 1-year prevalence, 5-year prevalence estimates from Globocan only include cancer patients who are still alive on the day that the prevalent population is measured. Those that were diagnosed 5 years ago are more likely to have died than those diagnosed in the year before measurement. Assuming cancer pain patients are more likely to have had advanced stage of disease and shorter survival, this will bias population size estimates. Some of the patients who were diagnosed with cancer 5 years ago may have been cured. If this was a significant proportion, it would cause an overestimate of the diagnosed cancer population that are still alive. However, 5 years is the standard cut-off for diseased/cured in cancer epidemiology.

- Due to the dearth of published studies examining the prevalence of non-neuropathic cancer pain, Datamonitor has based its prevalence estimate for this category of cancer pain upon Grond *et al.'s* (2006) survey. Grond *et al.'s* 1996 study reported cancer pain to be neuropathic in origin in 34% of cases. On this basis, Datamonitor has assumed that the remaining 66% of patients with cancer pain experience non-neuropathic pain.

Two further caveats relate to the proportion of cancer pain patients receiving first-line treatment with each drug class and molecule, as presented in the treatment trees in CHAPTER 3 and discussed in the section titled 'Trends in first-line treatment' in CHAPTER 7:

- Physicians surveyed by Datamonitor were asked to select the first line drug (or drugs) that they most commonly prescribe to patients with each subtype of cancer pain. Physicians were also asked to specify the percentage of patients that they prescribe this regimen to. In clinical practice, physicians may prescribe several drug regiments that they regard as first-line pharmacological treatment.

- Datamonitor recognizes that bisphosphonates have well-established clinical effects on cancer pain caused by bone metastases. However, since the focus of Datamonitor's primary research survey was on the use of analgesic drugs, prescribing of bisphosphonates for the treatment of cancer pain is not examined in this report.

Future trends

The WHO warns that cancer numbers will grow over the coming years, with the estimated annual number of new cases expected to rise from 10 million in 2000 to 15 million by 2020 (World Health Organization, 2003; www.who.int). Cancer is therefore becoming an increasingly important factor in the global burden of disease, mainly due to steadily aging populations in both developed and developing countries. Datamonitor believes that the rising incidence of cancer will in turn lead to a global increase in the number of individuals suffering from cancer-related pain.

CHAPTER 3 COUNTRY TREATMENT TREES

Introduction to treatment trees

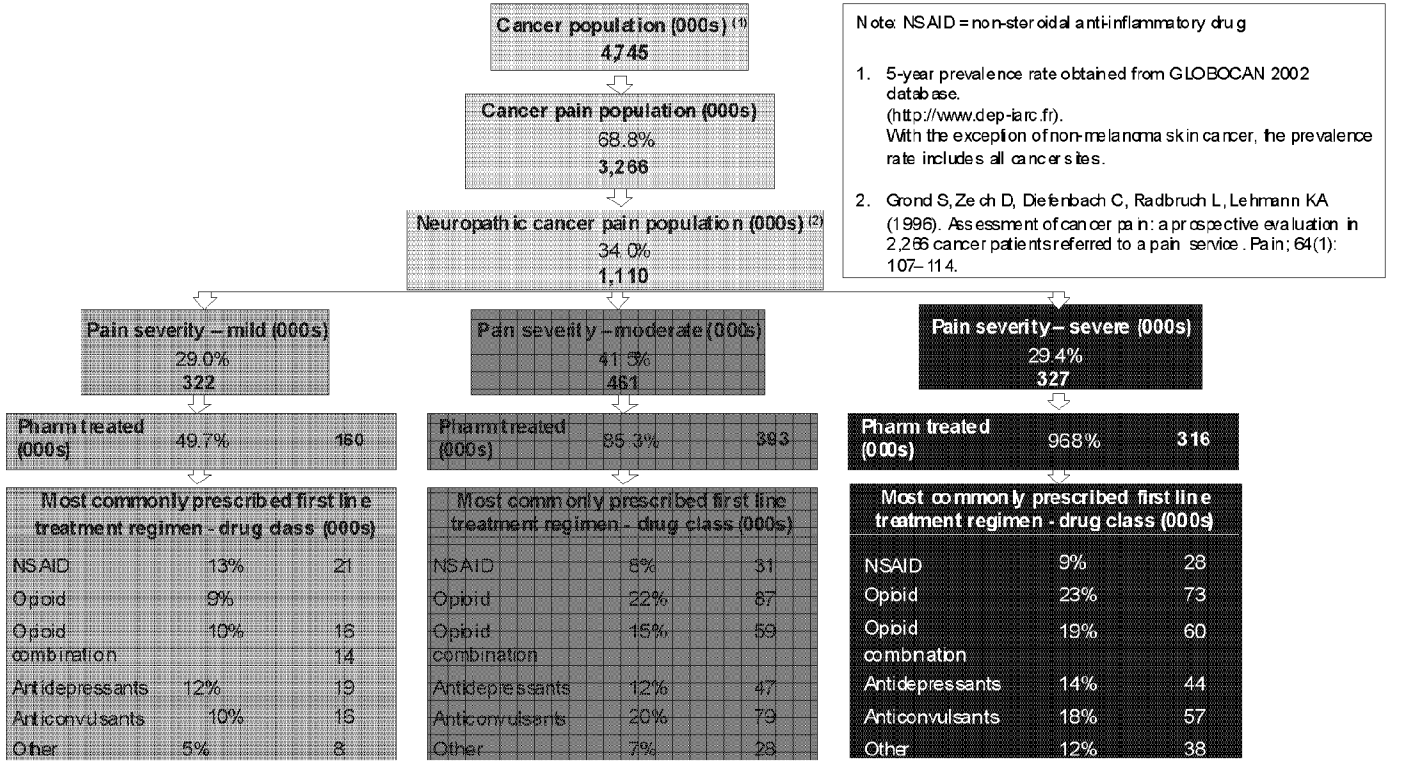
This chapter presents treatment tress for three key forms of cancer pain (neuropathic, non-neuropathic and breakthrough) for each of the seven major markets (the US, Japan, France, Germany, Italy, Spain and the UK). The treatment trees are based on primary research with 180 oncologists, palliative medicine specialists, pain care specialists and anesthetists.

The following information is presented:

- estimated prevalent cancer population in 2009;
- prevalent neuropathic, non-neuropathic and breakthrough cancer pain populations;
- percentage and number of patients with mild, moderate or severe disease;
- physician-estimated pharmacological treatment rates;
- preferred treatment classes.

US

Figure 2: US neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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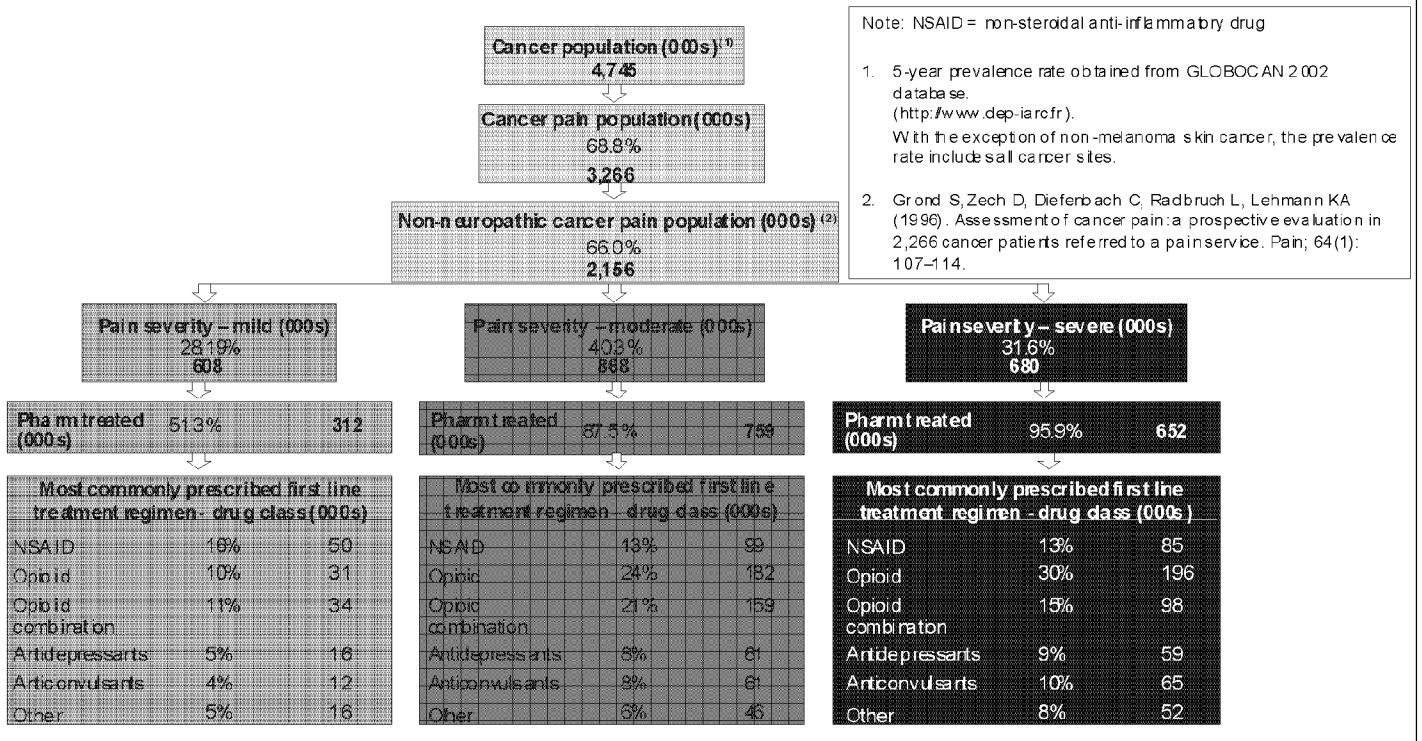
Figure 3: US non-neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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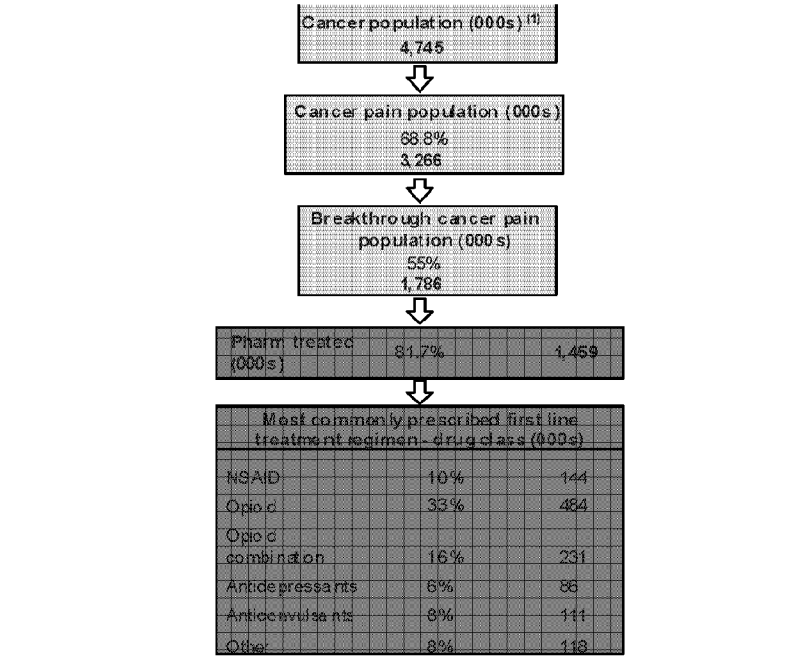
Figure 4: US breakthrough cancer pain population, split by drug-treated population and drug-class usage



Note: NSAID = non-steroidal anti-inflammatory drug

1. Five-year prevalence rate obtained from GLOBOCAN 2002 database. (http://www.dep-iarc.fr). With the exception of non-melanoma skin cancer, the prevalence rate includes all cancer sites.

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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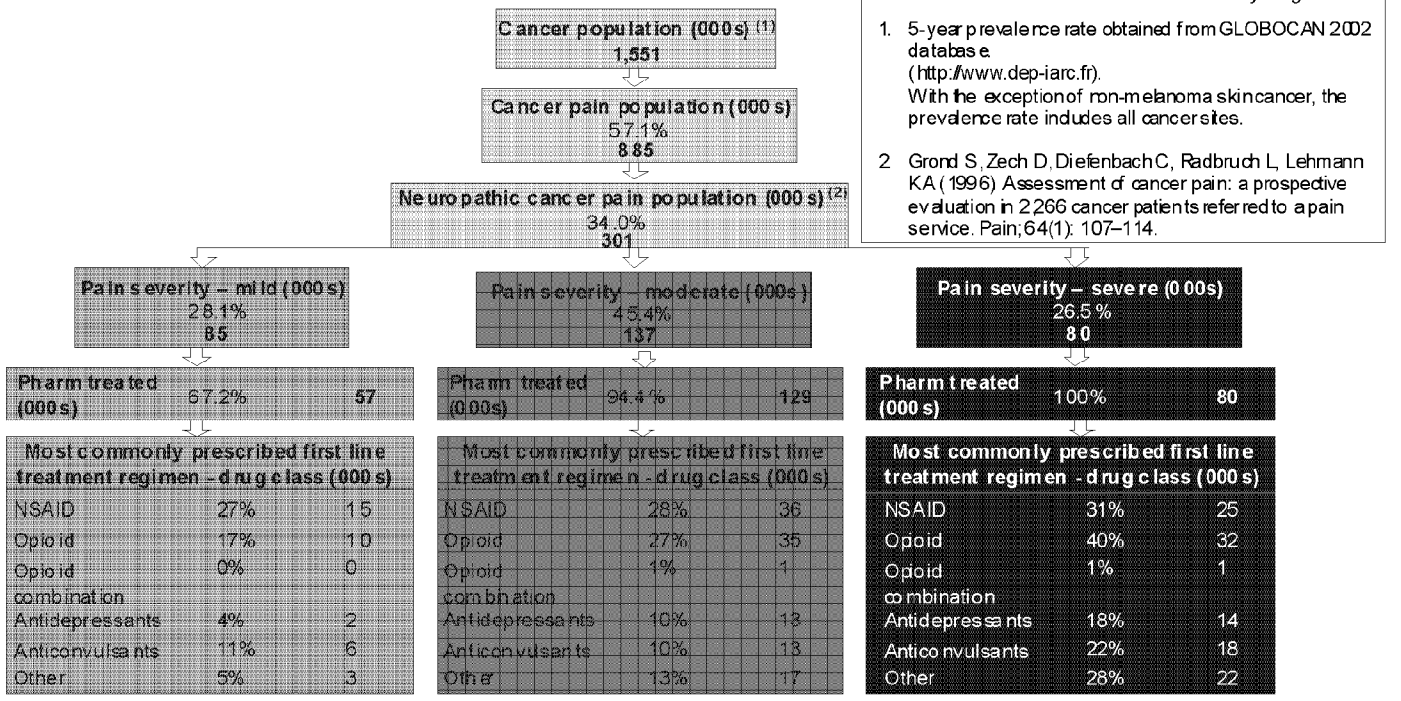
Japan

Figure 5: Japanese neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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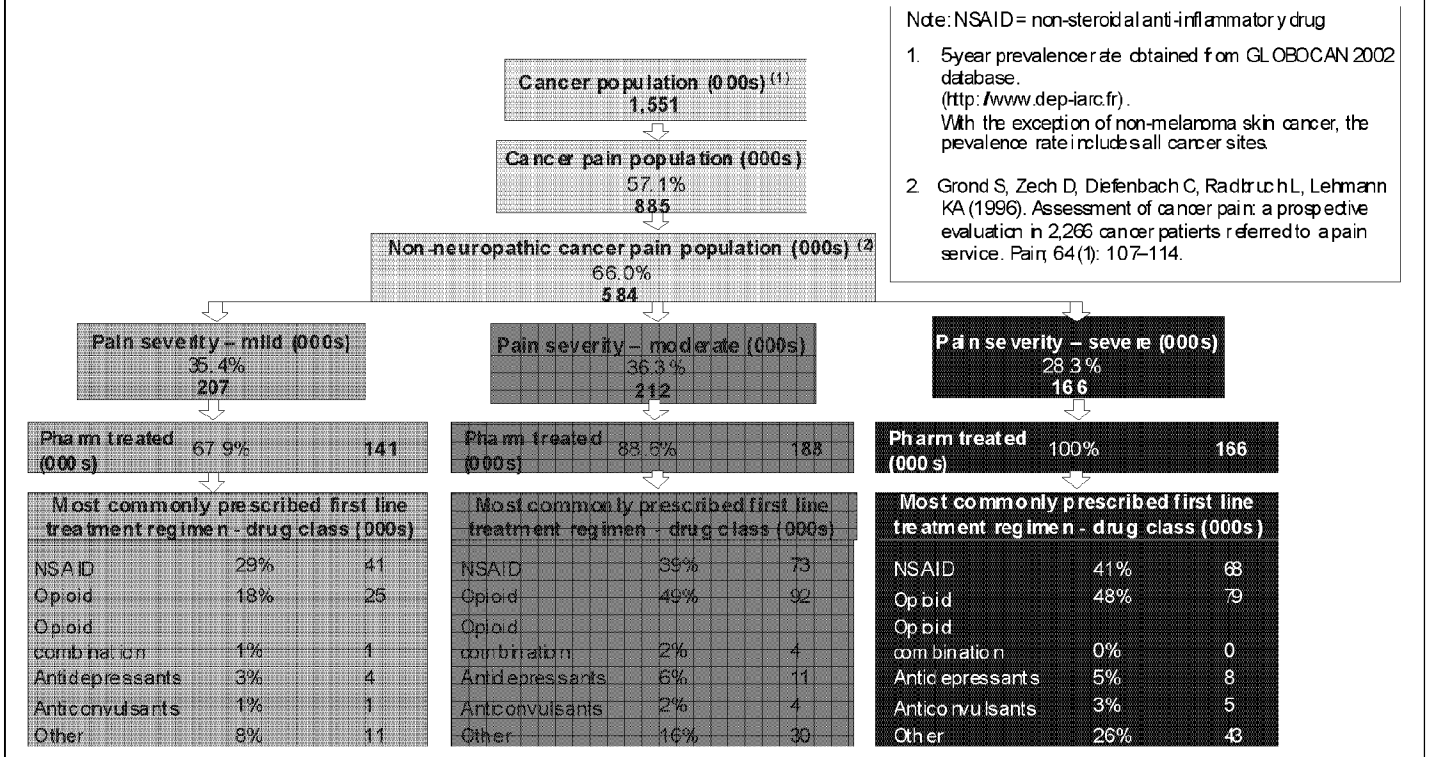
Figure 6: Japanese non-neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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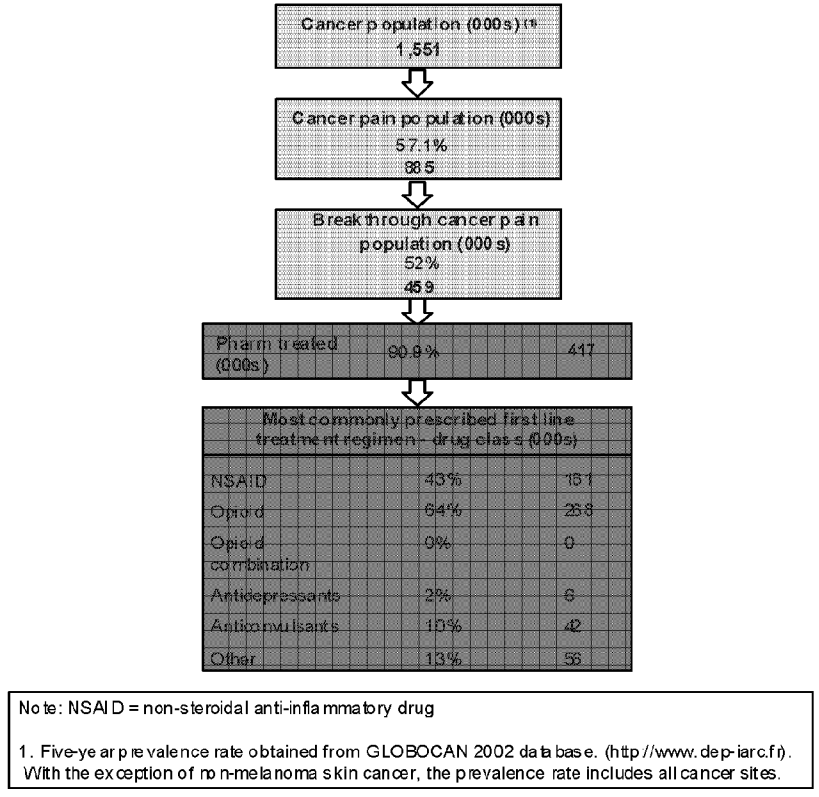
Figure 7: Japanese breakthrough cancer pain population, split by drug-treated population and drug-class usage



Note: NSAID = non-steroidal anti-inflammatory drug

1. Five-year prevalence rate obtained from GLOBOCAN 2002 database. (http://www.dep-iarc.fr). With the exception of non-melanoma skin cancer, the prevalence rate includes all cancer sites.

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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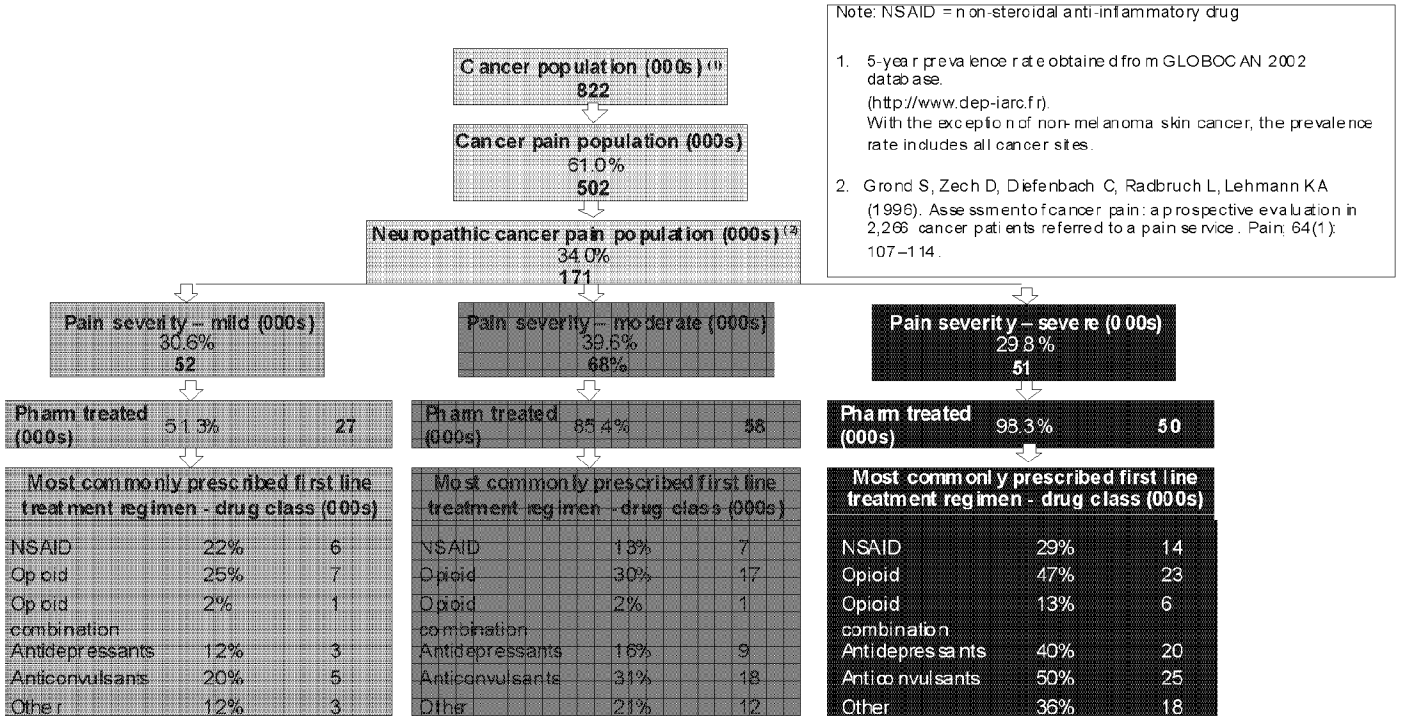
France

Figure 8: French neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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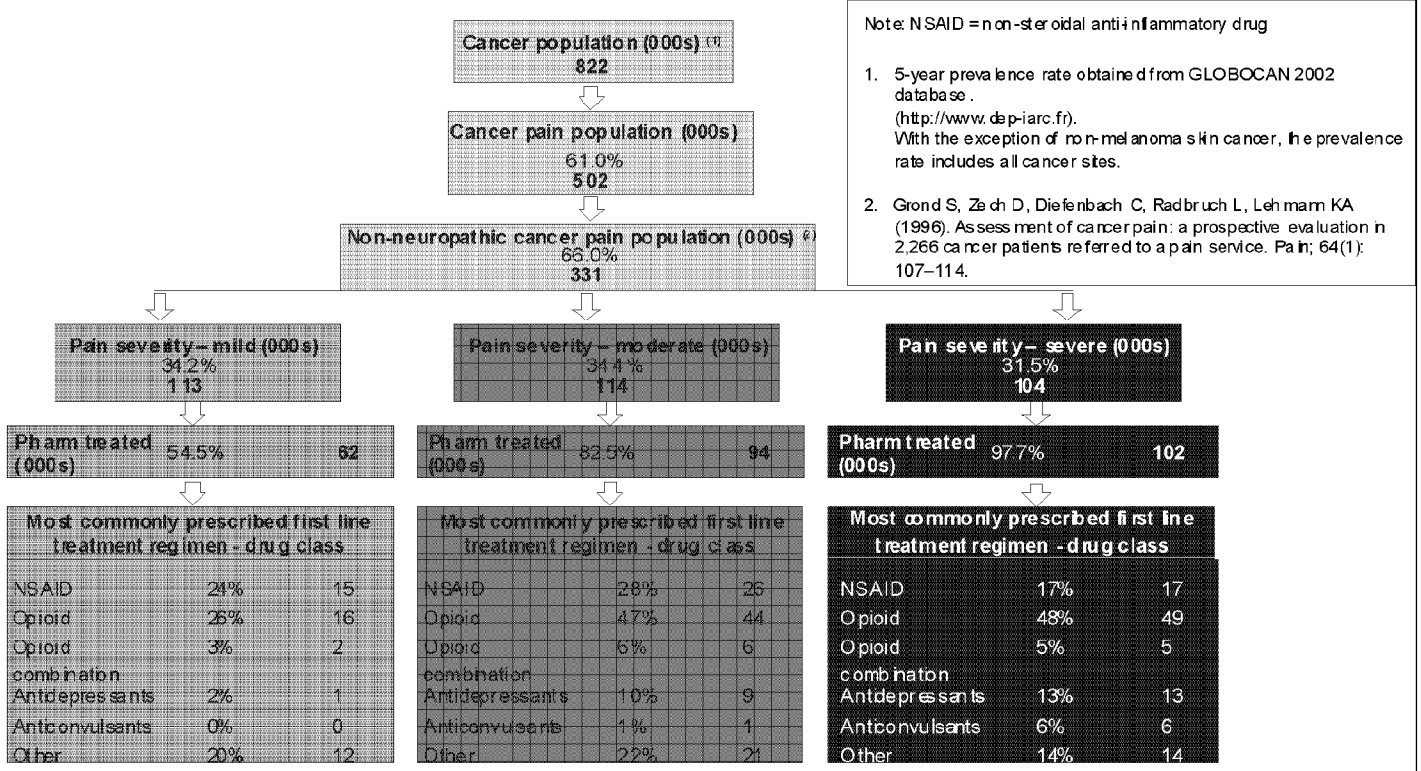
Figure 9: French non-neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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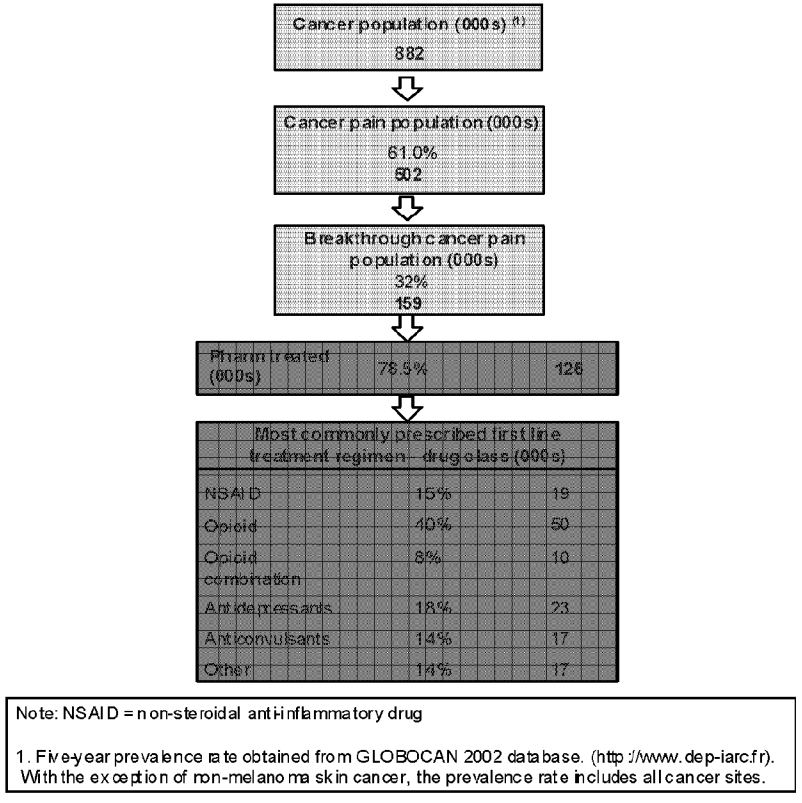
Figure 10: French breakthrough cancer pain population, split by drug-treated population and drug-class usage



Note: NSAID = non-steroidal anti-inflammatory drug

1. Five-year prevalence rate obtained from GLOBOCAN 2002 database. (http://www.dep-iarc.fr). With the exception of non-melanoma skin cancer, the prevalence rate includes all cancer sites.

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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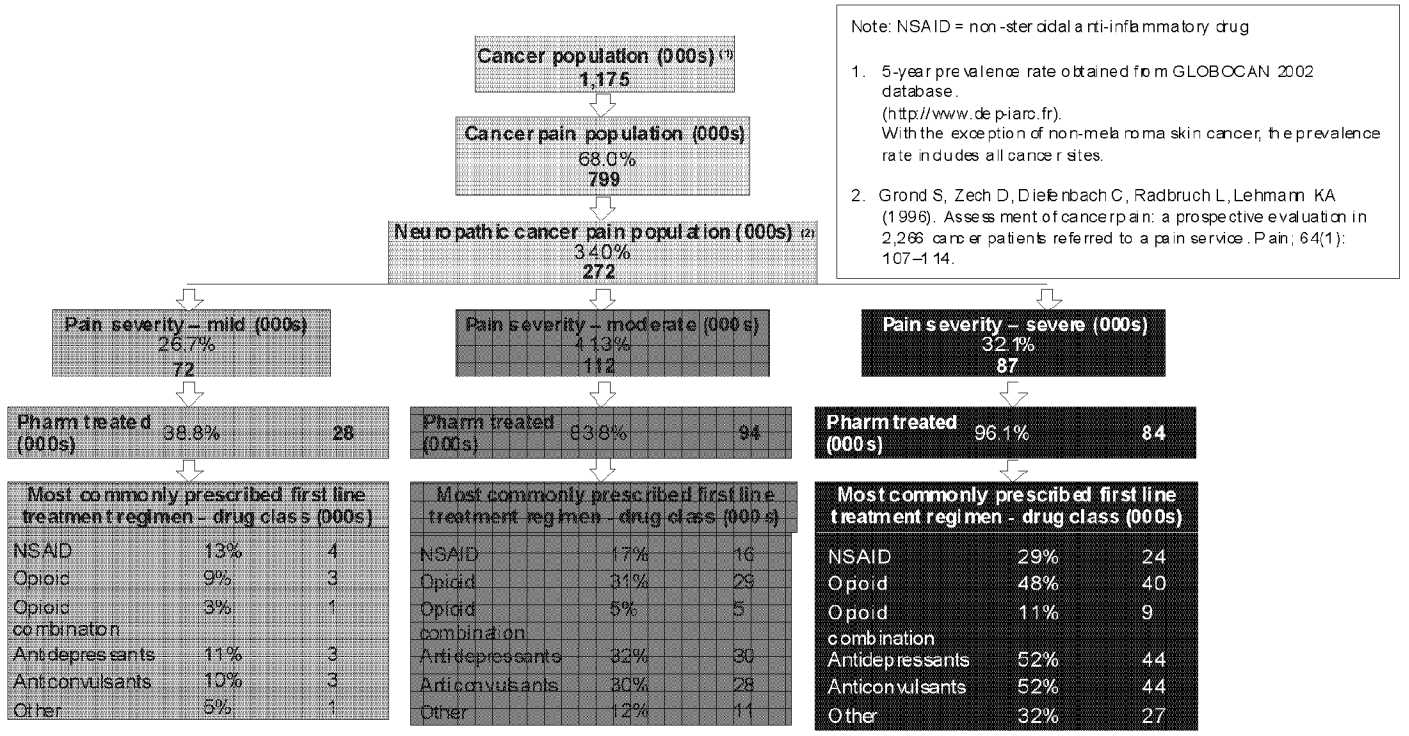
Germany

Figure 11: German neuropathic cancer pain population split by disease severity, drug-treated population and drug-class



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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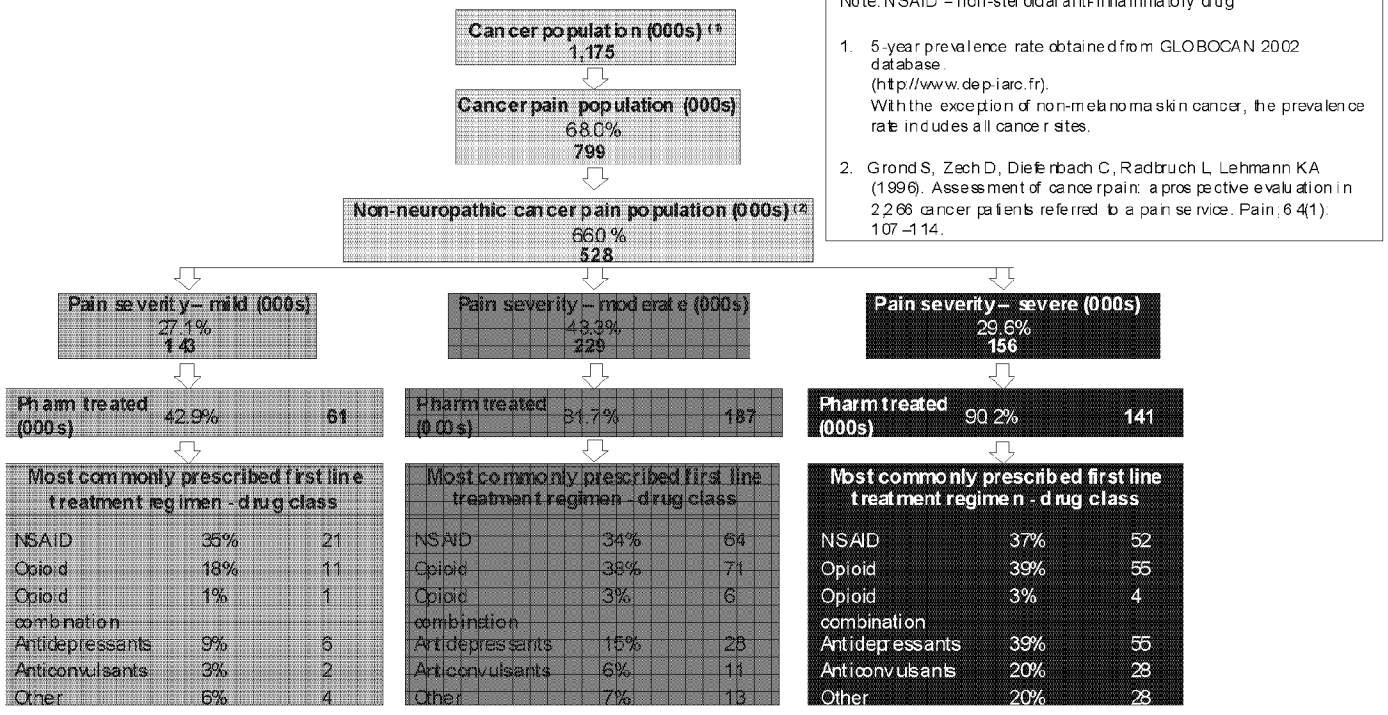
Figure 12: German non-neuropathic cancer pain population, split by disease severity, drug-treated population and drug-class usage



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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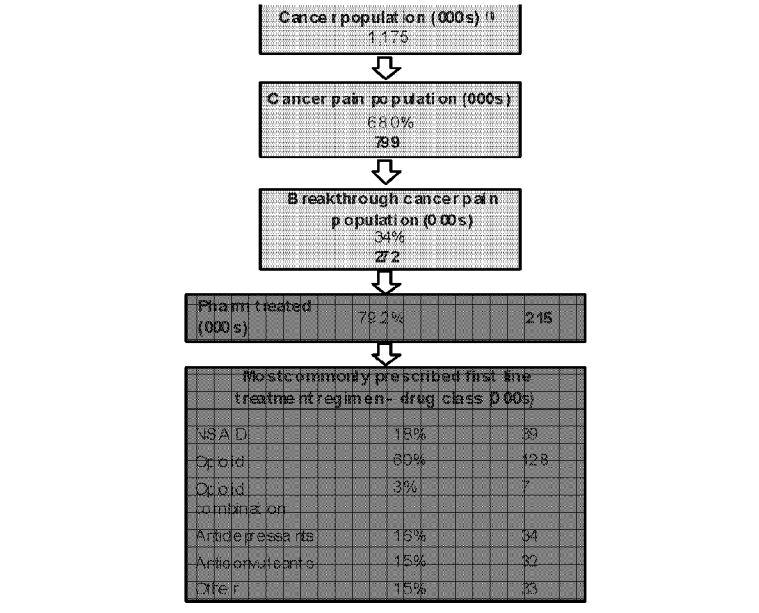
Figure 13: German breakthrough cancer pain population, split by disease severity, drug-treated population and drug-class usage



Note: NSAID = non-steroidal anti-inflammatory drug

1. Five-year prevalence rate obtained from GLOBOCAN 2002 database. (http://www.dep-iarc.fr). With the exception of non-melanoma skin cancer, the prevalence rate includes all cancer sites.

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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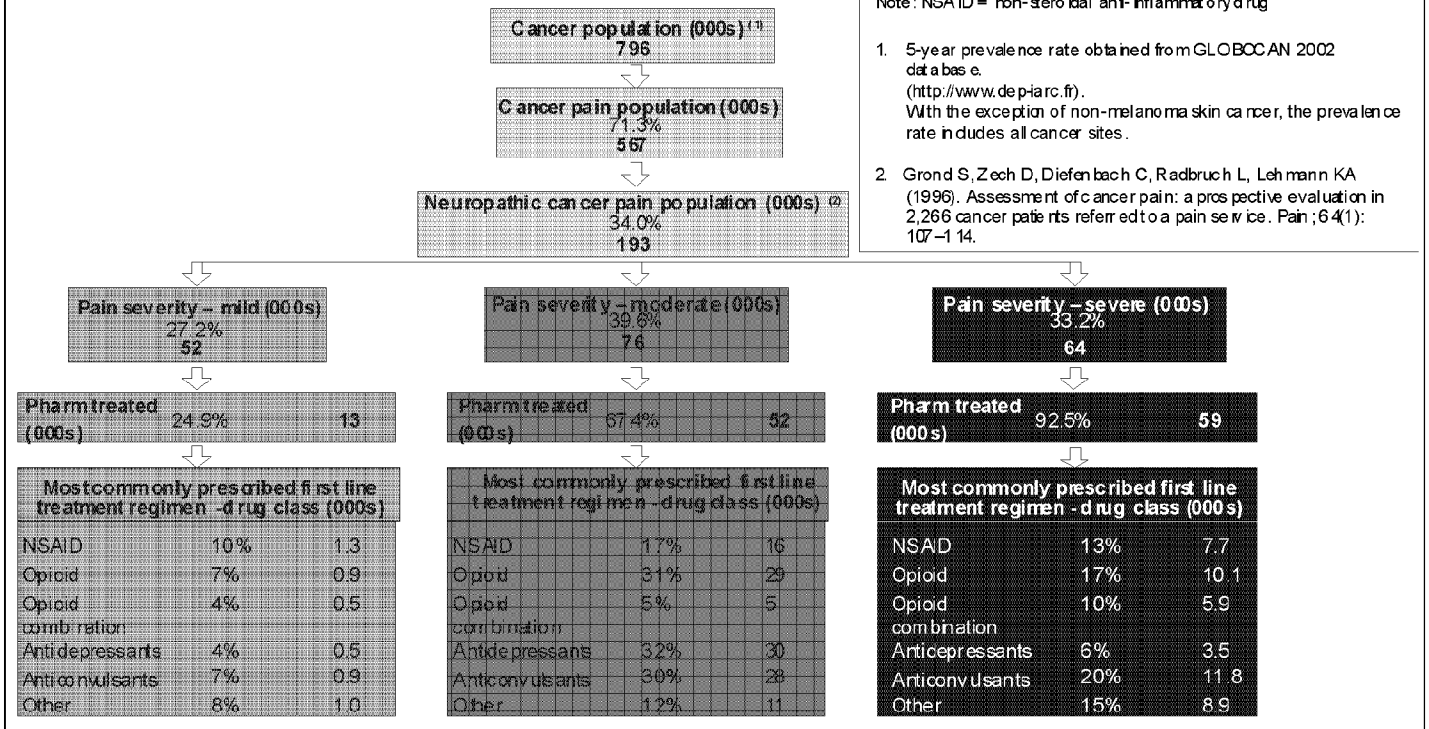
Italy

Figure 14: Italian neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class usage



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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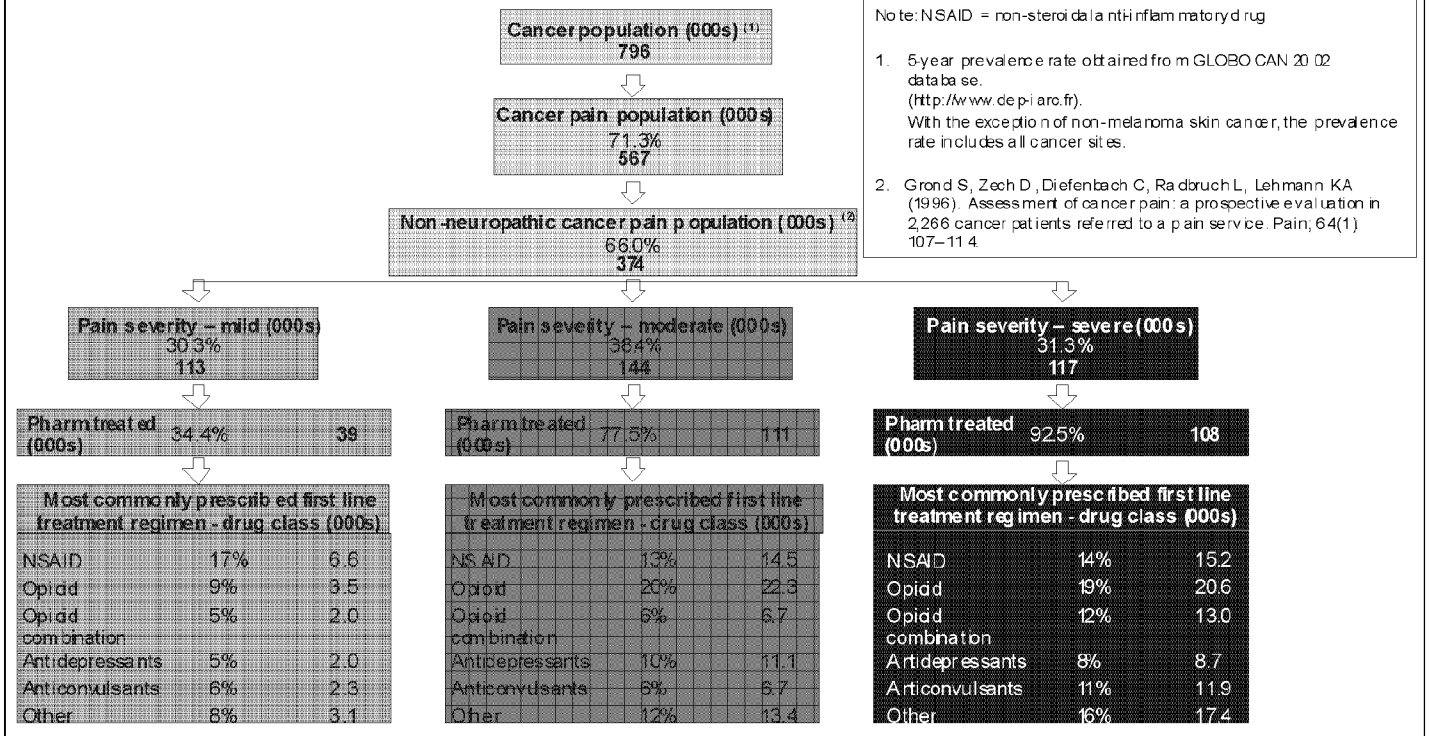
Figure 15: Italian non-neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class usage



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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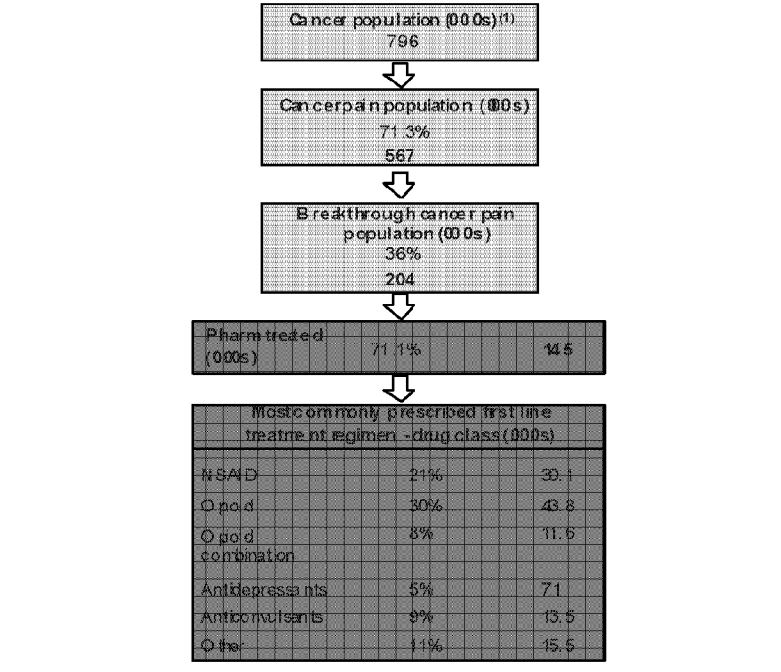
Figure 16: Italian breakthrough cancer pain population, split by drug-treated population and drug-class usage



Note : NSAID = non-steroidal anti-inflammatory drug

1. Five-year prevalence rate obtained from GLOBOCAN 2002 database. (http://www.dep-iarc.fr). With the exception of non-melanoma skin cancer, the prevalence rate includes all cancer sites.

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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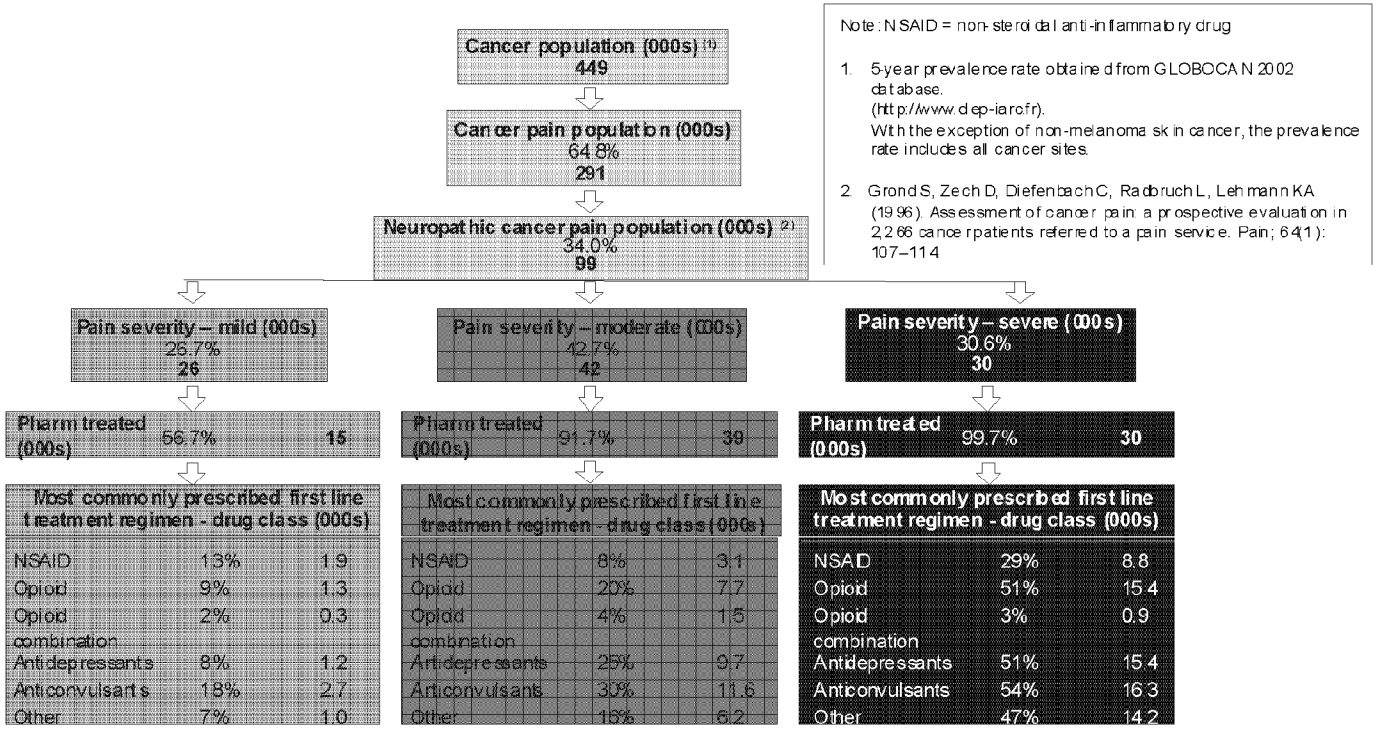
Spain

Figure 17: Spanish neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class usage



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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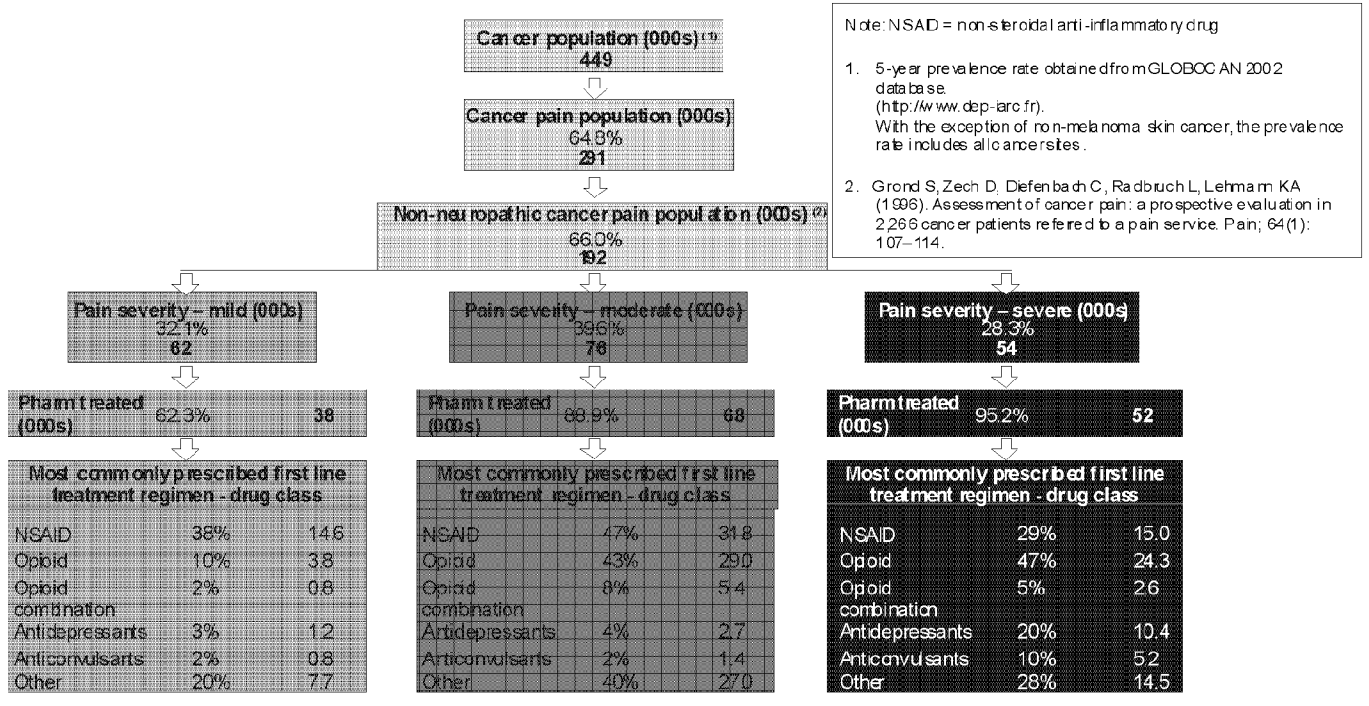
Figure 18: Spanish non-neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class usage



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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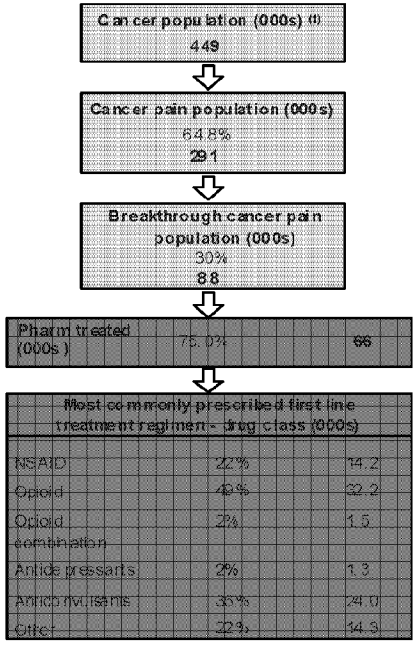
Figure 19: Spanish breakthrough cancer pain population, split by drug-treated population and drug-class usage



Note: NSAID = non-steroidal anti-inflammatory drug

1. Five-year prevalence rate obtained from GLOBOCAN 2002 database. (http://www.dep-iarc.fr). With the exception of non-melanoma skin cancer, the prevalence rate includes all cancer sites.

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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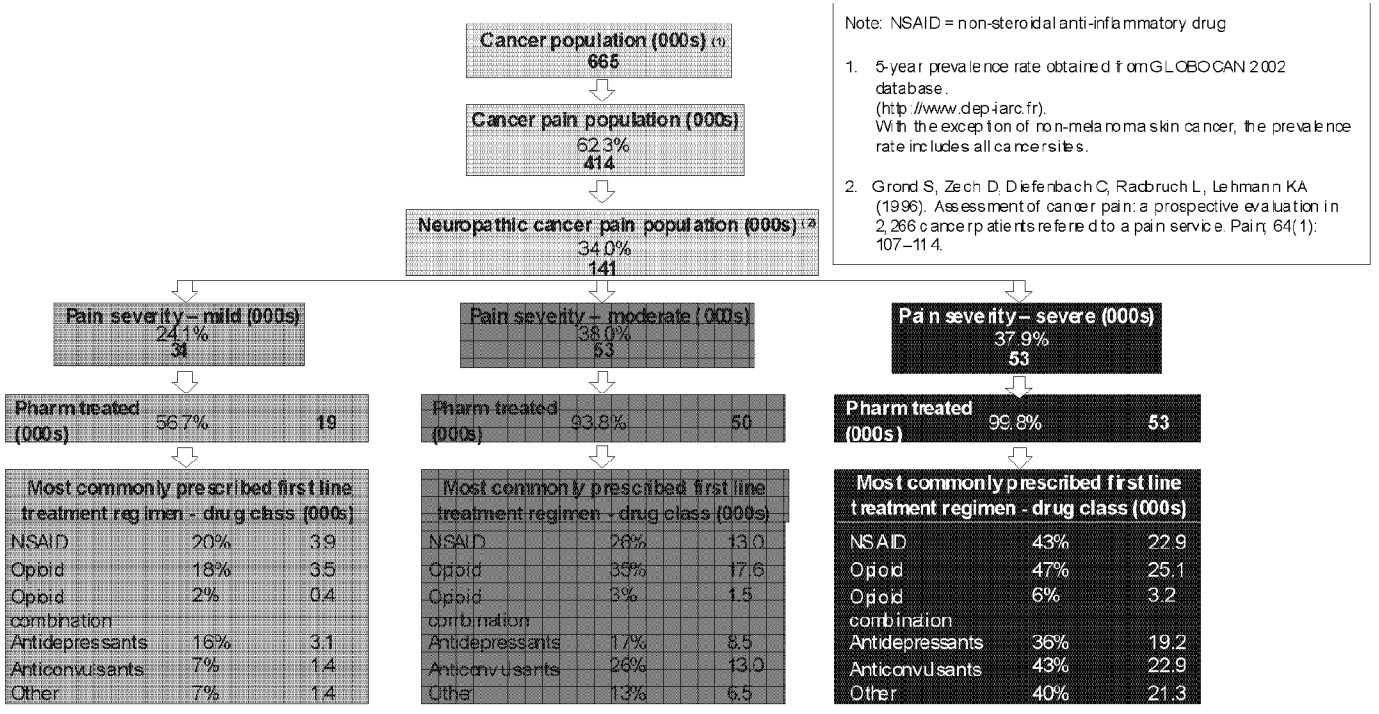
UK

Figure 20: UK neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class usage



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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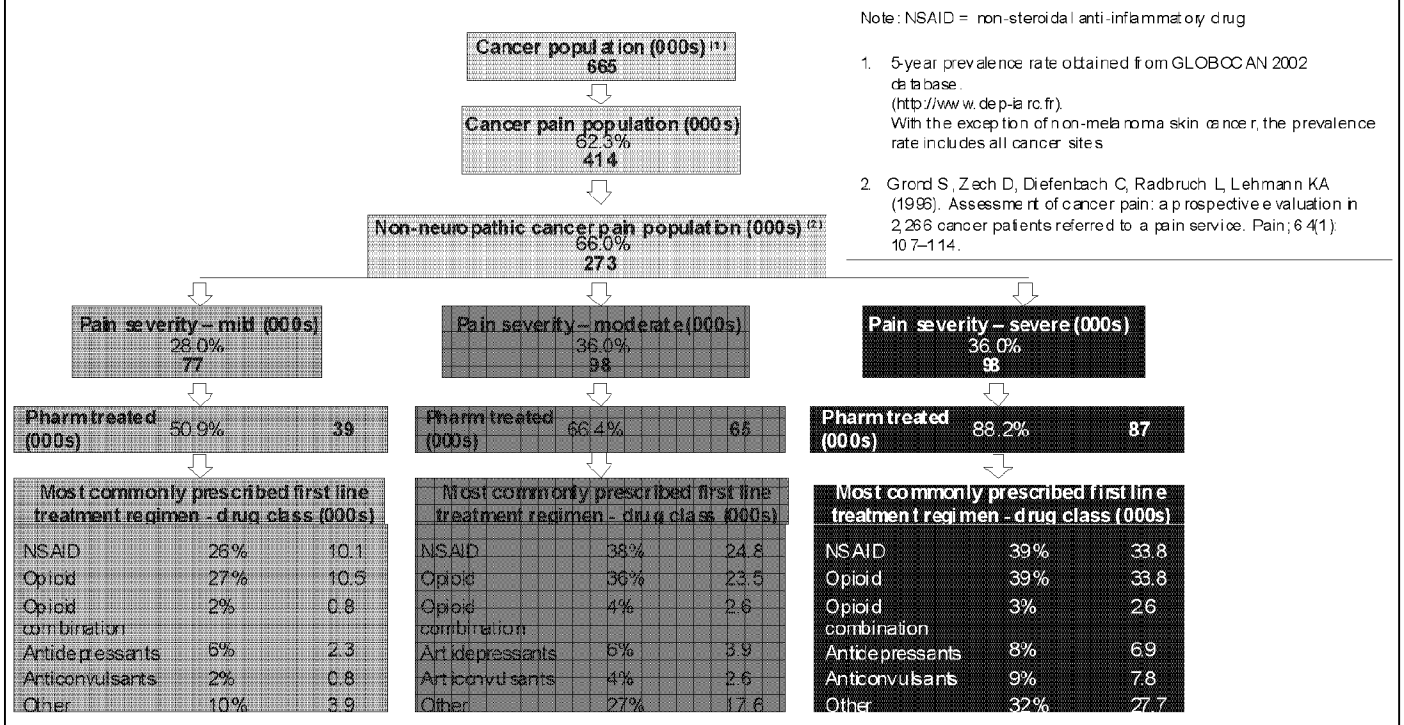
Figure 21: UK non-neuropathic cancer pain population, split by pain severity, drug-treated population and drug-class usage



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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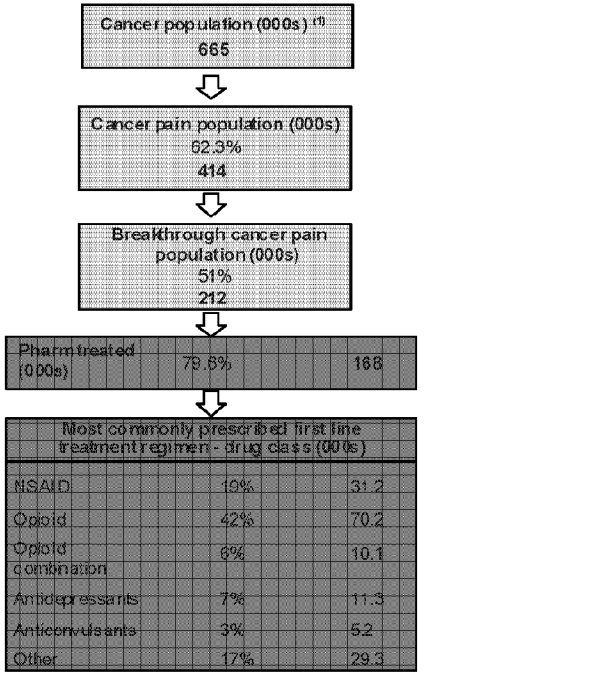
Figure 22: UK breakthrough cancer pain population, split by drug-treated population and drug-class usage



Note: NSAID = non-steroidal anti-inflammatory drug

1. Five-year prevalence rate obtained from GLOBOCAN 2002 database. (http://www.dep-iarc.fr). With the exception of non-melanoma skin cancer, the prevalence rate includes all cancer sites.

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536

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CHAPTER 4 EPIDEMIOLOGY AND PATIENT SEGMENTATION

- *Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain associated with cancer can result from the cancer itself or cancer-related treatments including radiotherapy, chemotherapy and surgery.*

- *Cancer pain may be described in terms of three broad categories: neuropathic pain, non-neuropathic pain and breakthrough pain. Neuropathic pain is initiated or caused by a primary lesion or dysfunction in the nervous system. Breakthrough pain refers to a transitory flare of pain that 'breaks through' chronic pain analgesia. However, patients may experience more than one type of cancer-related pain.*

- *Physicians taking part in Datamonitor's survey estimated that 65% of all cancer patients are affected by pain, a figure which lies mid-way between the prevalence rates of 34% and 88% cited in published epidemiological studies. On the basis of primary research, Datamonitor estimates pain to affect 6.7 million cancer patients across the seven major markets in 2009.*

- *Obtaining accurate prevalence estimates of neuropathic versus non-neuropathic pain is complicated by the fact that patients may experience more than one pain type at any given time. Based on prevalence data from a published large-scale survey, Datamonitor estimates neuropathic and non-neuropathic pain to affect almost 2.3 million and 4.4 million individuals, respectively, across the seven major markets in 2009.*

- *According to physicians taking part in Datamonitor's survey, 42% of all cancer pain patients experience breakthrough pain, a figure which is lower than that documented in published prevalence studies. On the basis of this primary research, Datamonitor estimates that almost 3.2 million patients with cancer pain suffer from breakthrough pain across the seven major markets in 2009.*

- *Published literature indicates that chronic pain syndromes related to cancer treatments are common in cancer survivors. With the number of cancer survivors expected to increase significantly over the next decade, this represents an important insight for manufacturers of analgesics.*

- *The incidence of cancer is expected to rise in the future, driven by the elderly and minority populations. Datamonitor believes that the rising incidence of cancer will in turn lead to a global increase in the number of individuals suffering from cancer-related pain.*

Disease definition

According to the International Association for the Study of Pain (IASP), pain is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (International Association for the Study of Pain, 2009).

The American Society of Anesthesiologists defines cancer pain as pain that is attributable to the cancer or its therapy (American Society of Anesthesiologists, 2009; www.asahp.org). For patients with cancer, the possibility of severe and uncontrolled pain is one of the most feared consequences of the disease (Portenoy & Lesage, 1999). In some cases of cancer, pain may be the first sign of malignancy.

As is the case for all forms of pain, cancer pain is highly subjective and unique to the patient experiencing it. An individual's perception of pain and appreciation of its meaning are complex phenomena that involve psychological and emotional processes, in addition to activation of nociceptive pathways. Each of these psychosocial and behavioral factors may affect the patient's perception of physical pain (McGrath, 1990). The subjective nature of pain is clearly conveyed in the following definition of pain by the pain expert Margo McCaffrey, MSN, RN, FAAN: "Pain is whatever the experiencing person says it is, and exists whenever he says it does." (Cancer Pain, 2002; www.cancer-pain.org).

For the purposes of this study, cancer pain is described in terms of the following three categories: neuropathic pain, non-neuropathic pain and breakthrough pain. However, many patients suffering from cancer experience more than one type of pain.

Neuropathic and non-neuropathic cancer pain

Neuropathic pain is "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (International Association of the Study of Pain, 2008; www.iasp-pain.org). Neuropathic pain is not associated with nociceptive stimulation, although the passage of nerve impulses that is ultimately perceived as pain by the brain is the same in both nociceptive and neuropathic pain. Neuropathic pain is sometimes characterized by the inability of opioids to produce analgesia.

Unlike neuropathic pain, non-neuropathic pain occurs in the setting of a normal, undamaged nervous system. Nociceptive pain is the most well-known type of non-neuropathic pain and is caused by acute tissue injury detected by nociceptors at the site of the injury. Nociceptors are free nerve endings located in skin, viscera, muscle,

fascia, blood vessels and joint capsules. They have various receptors on their surface that modulate their sensitivity, including gamma-amino butyric acid (GABA), opiate, bradykinin, histamine, serotonin and capsaicin receptors (Millan, 1998). Nociceptive pain is further divided into somatic or visceral pain (Medscape, 2009; http://cme.medscape.com). Somatic pain arises from bone, joint, muscle, skin or connective tissue, while visceral pain arises from visceral organs such as the gastrointestinal tract and pancreas (Cancer Pain Management in Children, 2009; www.childcancerpain.org).

Cancer pain is not easily classified as being exclusively nociceptive or neuropathic in nature. As such, many patients with cancer have a mixed pain syndrome; that is, a combination of both nociceptive and neuropathic pain.

Breakthrough pain

For the purposes of this report, breakthrough pain refers to an acute flare of pain that 'breaks through' the chronic pain analgesia. In the cancer population, the term breakthrough pain typically refers to a transitory flare of pain in the setting of chronic pain managed by opioid drugs (Portenoy & Hagen, 1990). Breakthrough pain usually occurs at the same site as the background pain (Portenoy & Hagen, 1990; Hwang *et al.,* 2003).

However, it is important to note that there is currently no unanimous definition of breakthrough pain in either malignant or non-malignant diseases (Svendsen *et al.,* 2005; William & Macleod, 2008). The lack of consensus definition is exemplified by an international survey of cancer pain characteristics conducted by the IASP's Task Force on Cancer Pain. The IASP's survey found large differences in the diagnosis and treatment of breakthrough pain, thereby suggesting that breakthrough pain is either defined or recognized differently in different countries (Caraceni *et al.,* 2004). Cancer pain specialists worldwide have supported this conclusion. For example, according to Dr Sebastiano Mercadante, professor of palliative medicine at the University of Palermo, Italy, the term 'breakthrough pain' is uniquely American-English and does not have a clear equivalent in other languages in Europe. Conversely, the term 'episodic' or 'transient' pain is used more commonly in French, German, Italian and Spanish (WHO Pain and Palliative Care Communications Program, 1999; http://whocancerpain.wisc.edu). To avoid confusion, some experts have advocated the use of broader terms like episodic pain in place of breakthrough pain, whereas others have listed the types of breakthrough pain depending on its predictability and precipitating factors. Types of breakthrough pain include idiopathic, incidental and end of dose (Hwang *et al.,* 2003).

Views expressed by interviewed key opinion leaders indicate that opinion remains divided on whether breakthrough pain is well defined:

> *"Yes it is true, the definition* [of breakthrough pain] *is not easy."*
>
> EU key opinion leader

> *"I believe that Portenoy has given a very good definition of breakthrough pain."*
>
> EU key opinion leader

> *"I think everybody understands it* [the term breakthrough pain]. *This might have been true in the 1980s, but now I do not believe it, because there are a lot of explanations at conferences and congresses about it* [breakthrough pain]."
>
> EU key opinion leader

Etiology

Cancer pain may be caused by both the disease and associated treatments

Pain associated with cancer can have multiple causes. Pain syndromes most commonly seen are those resulting from the cancer itself or cancer-related treatment. This is to be expected, as a substantial proportion of patients across the seven major markets (US, Japan, France, Germany, Italy, Spain and the UK) undergo one or more of the conventional types of cancer therapy. According to an international, cross-sectional survey of clinicians conducted by the IASP, a large majority of patients (92.5%) experience one of more pains caused directly by the cancer, whereas 20.8% of patients have one of more pains caused by cancer therapies (Caraceni & Portenoy, 1999). An interviewed key opinion concurs with the researchers:

> *"Probably 20%* [of pain cases], *I would say* [are caused by treatments]."
>
> EU key opinion leader

Nociceptive pain is typically caused by tumor growth, whereas neuropathic pain has a more complex and variable etiology and may be the result of the tumor itself or from treatment of the cancer. Indeed, in some cases, neuropathic pain may be totally

unrelated to the cancer and its treatments. Similarly, breakthrough cancer pain may result from the cancer or cancer treatment. Furthermore, breakthrough pain may be precipitated (also known as incident breakthrough pain) i.e. triggered by a specific activity, like coughing, moving, or going to the bathroom (Svendsen *et al.,* 2005), or it may be spontaneous.

Tumor growth often results in nociceptive pain

Pain caused by the cancer itself often results from the pressure of the tumor on one of the body's organs or on bones or nerves. Tumor secretion of inflammatory and prohyperalgesic mediators can also result in pain (International Association for Study of Pain, 2009; www.iasp-pain.org). Metastatic spread of cancer to bone is a particularly common cause of cancer pain (Banning *et al.,* 1991; Cherny, 2006). According to Cherny (2002), pain is directly related to the presence of primary or metastatic disease in approximately two thirds of patients with cancer. Typically, non-neuropathic (nociceptive) pain is caused by tumor growth, metastases to the bones, muscles or joints, or cancer that is causing a blockage in an organ such as the colon or digestive system (Cancer Pain, 2008; www.cancer-pain.org).

Chemotherapy, radiotherapy and surgery are key causes of treatment-related cancer pain

Diagnostic and therapeutic procedures which can give rise to cancer pain include: chemotherapy, radiotherapy, surgery, biopsies, blood draws, lumbar punctures and laser treatments. Chemotherapeutic agents such as vincristine, platinum, taxanes, thalidomide and bortezomib can cause pain in several ways. The most common side effects of chemotherapy that cause pain are mouth sores (stomatitis) and peripheral neuropathy (numb and sometimes painful sensations in the feet, legs, fingers, hands and arms). An interviewed key opinion leader confirms:

> *"I am a hematologist and one of the most frequent problems with which we are faced is oral pain due to mucositis after chemotherapy."*
>
> EU key opinion leader

Some patients also experience bone and joint pain from chemotherapy medications and from some medications used to offset the impact of the chemotherapy on blood counts and the risk of infection (Understanding cancer pain, 2002; www.cancer-pain.org).

Radiation treatment can also cause pain through affecting normal cells surrounding the cancerous tumor being treated. This can cause skin redness and irritation

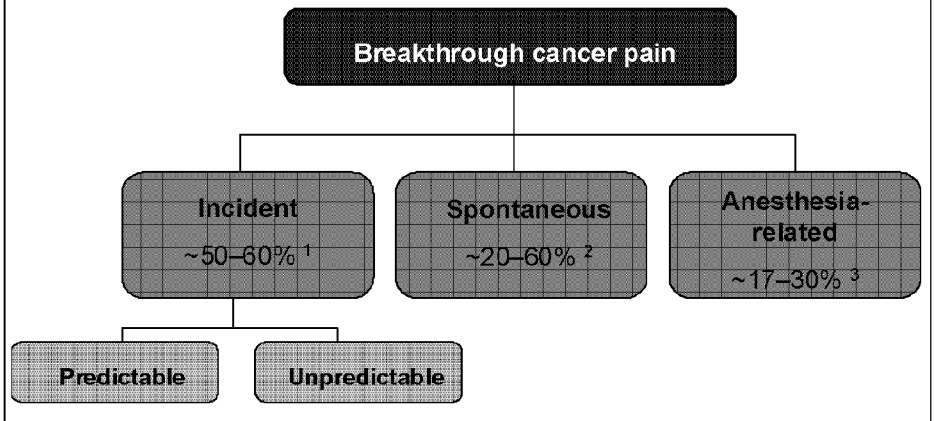
(Cancer Research, 2008; www.cancerhelp.org.uk) and also post-radiation pelvic pain syndrome (International Association for the Study of Pain, 2009; www.iasp-pain.org).

Surgical interventions (including biopsies) can also give rise to nerve damage and chronic post-operative pain. Furthermore, cancer patients who have undergone amputation of a limb due to sarcoma or osteosarcoma may experience painful sensations in the absent limb, a condition known as phantom pain.

Breakthrough pain may occur spontaneously or be precipitated

As summarized in Figure 23, breakthrough pain in cancer may occur spontaneously or it may be precipitated by sudden movements (this is also known as incident breakthrough pain; Svendsen *et al.,* 2005).

Figure 23: Key etiologies of breakthrough pain



1) Portenoy & Hagen, 1990; Stromgren *et al.,* 2004.
2) Portenoy & Hagen, 1990; Petzke *et al.,* 1999; Stromgren *et al.,* 2004; Zeppetella *et al.,* 2000.
3) Zeppetella *et al.,* 2000; Portenoy & Hagen, 1990.

Source: Various (see above) DATAMONITOR

About 20–60% of breakthrough pain in cancer patients occurs spontaneously (Portenoy & Hagen, 1990; Petzke *et al.,* 1999; Stromgren *et al.,* 2004; Zeppetella *et al.,* 2000), and 50–60% is precipitated (Portenoy & Hagen, 1990; Stromgren *et al.,* 2004).

Approximately 17–30% of breakthrough pain in cancer patients is related to the analgesic regimen (Zeppetella *et al.,* 2000; Portenoy & Hagen, 1990). A decrease in the plasma concentration of, for example, an opioid at the end of a dosing interval

may give rise to increase of pain intensity, the so-called 'end-of-dose failure' (Svendsen *et al.,* 2005).

For some cancer patients, pain may arise from pre-existing health conditions

Some cancer patients may experience pain that is unrelated to the cancer or its treatment, such as diabetic neuropathic pain, osteoarthritis or pain after surgery for unrelated conditions. In approximately 10% of cancer patients who have pain, the pain is unrelated to the disease or treatment and is most often caused by muscles and connective tissue (Twycross, 1994). Such complications may be particularly relevant in the case of elderly patients who typically present with pre-existing health conditions.

Symptomatology

The symptoms of cancer pain vary from patient to patient. The amount of pain experienced is dependent on the type of cancer, the stage or extent of the disease, and the pain threshold (tolerance for pain) of the individual patient. Additionally, the symptoms of cancer pain depend on the pain classification (i.e. neuropathic, non-neuropathic or breakthrough pain). For example, neuropathic cancer pain is commonly associated with several distinct pain experiences. The first is abnormal or unfamiliar sensations called dysesthesia, which include shooting, lancing or burning pain. Another feature is the ability of otherwise normally non-painful stimuli to produce pain (allodynia), or when the pain messages from a normally painful event is exacerbated so that a much greater pain is felt (hyperpathia).

Breakthrough pain usually occurs at the same site as the background pain (Portenoy & Hagen, 1990; Hwang *et al.,* 2003). Common characteristics of breakthrough pain are that it has a very rapid onset (less than 3 minutes in 43% of patients) and often has a short duration (around 20 minutes in 44% of patients) (Wright, 2004). According to more recent results from a European survey of cancer patients' experiences of breakthrough pain, the median number of breakthrough cancer pain episodes per day is three. The European survey also reported each episode of breakthrough pain to have a mean duration of 60 minutes (40 minutes longer than that reported by Wright *et al.,* 2004), with 96% of the pain episodes described as moderate to severe (Davies *et al.,* 2009). Bone pain is often described as dull and aching, except when it is associated with muscle spasms, in which case the pain may be sharp and excruciating.

Cancer pain may be segmented according to duration (acute and chronic) and severity (mild, moderate or severe). Datamonitor has utilized these categories for the purposes of its survey.

Acute versus chronic

Acute pain has a sudden onset, is of short duration and usually manifests in ways that can be easily described and observed. For example, it may cause sweating or increased heart rate. Acute pain experienced by cancer patients is typically caused by tests, procedures or surgeries (Doyle *et al.,* 2005).

Pain is considered chronic when it lasts beyond the normal time expected for an injury to heal or an illness to resolve (Cancer Pain, 2002; www.cancer-pain.org). According to the American Cancer Society, many patients with chronic cancer pain (pain that lasts longer than 3 months) have two types of pain: persistent pain and breakthrough pain (American Cancer Society, 2008; www.cancer.org).

Pain severity

Pain varies in intensity and may be classified as mild, moderate and severe. For the purposes of this study, mild, moderate and severe cancer pains are assumed to be equivalent to 1–4, 5–6, and 7–10, respectively, on the Brief Pain Inventory (BPI). The BPI was developed by the Pain Research Group to provide information on the intensity of pain as well as the degree to which pain interferes with function. The measure asks patients to rate their pain at the time of responding to the questionnaire and also at its worst, least and average over the previous week (Fabry Registry, 2008; www.lsdregistry.net).

As with cancer pain as a whole, the incidence of mild, moderate and severe pain is often dependent on the type of cancer, disease stage and the pain tolerance of the individual patient. Interviewed key opinion leaders confirm that cancer pain severity varies according to tumor type, with hematological cancers giving rise to the least severe pain, and bone metastases frequently causing severe pain.

> *"For lymphoma and leukemia patients in palliative care, in the last stages of the disease, the pain due directly to the tumor is usually not very painful because it is not a big mass (except myeloma)."*
>
> EU key opinion leader

In addition, an interviewed key opinion leader reports that disease progression is associated with increased pain severity.

> *"In my experience, the patient may sometimes have severe pain during chemotherapy but in general, the progression of disease is a predictor of an increase in pain."*
>
> EU key opinion leader

According to the 2007 European Pain in Cancer Survey (EPIC), patients across 11 European countries and Israel (n = 3,066) reported a mean pain intensity level of 6.38 (on a scale of 0–10) (EPIC Survey. Final Results presentation, 2007; www.paineurope.com). Risk factors identified as determinants of more severe cancer pain in published surveys include belonging to a minority group (Hiraga *et al.,* 1991; Cleeland *et al.,* 1997), being female (Cleeland *et al.,* 1997), or being elderly (Cleeland *et al.,* 1997; Ferrell, 1996).

Prevalence of cancer pain

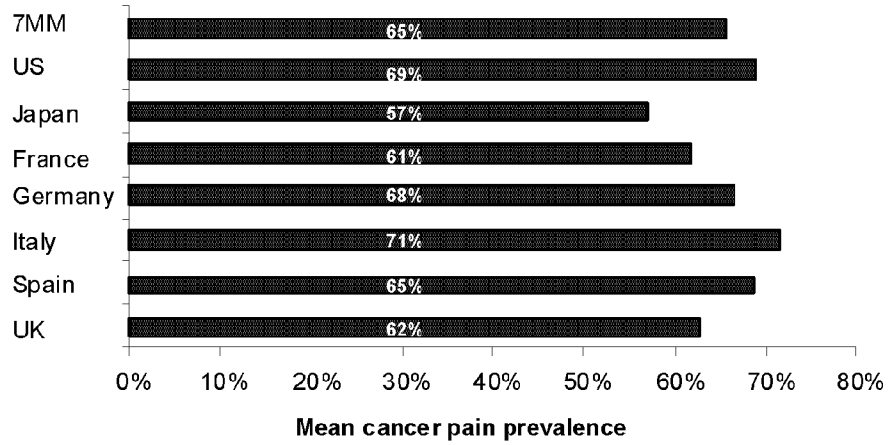
An estimated 6.7 million individuals suffer from cancer pain across the seven major markets in 2009

Physicians surveyed by Datamonitor were asked to estimate the prevalence of pain in their cancer patients (at all stages of the disease). Figure 24 summarizes the mean cancer pain prevalence rate reported by physicians across the seven major markets (US, Japan, France, Germany, Italy, Spain and the UK).

As can be seen in Figure 24, interviewed physicians across the seven major markets reported pain to affect a mean 65% of cancer patients (across all stages of the disease and tumor types). Therefore, the mean prevalence rate reported by interviewed physicians lies mid-way between the prevalence rates of 34% (Mercadante *et al.,* 2008) and 88% (European Pain in Cancer survey, 2007; www.paineurope.com) cited in published epidemiological studies identified by Datamonitor. For an overview of published epidemiological studies on cancer pain, please refer to Table 2.

The cancer pain prevalence rates reported by interviewed physicians vary between countries, from 57% in Japan to 71% in Italy. It is possible that this variation in prevalence is due to failure to recognize cancer pain and differences in the interviewed physician sample (types of cancer treated), rather than a major difference across the patient populations.

Figure 24: Cancer pain prevalence across the seven major markets, 2009



7MM = seven major markets (US, Japan, France, Germany, Italy, Spain and the UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, 2009 (S.4) (n=180)

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An EU-based key opinion leader reports a higher prevalence of cancer pain than that reported by physicians taking part in Datamonitor's survey.

> *"About 80% of* [the cancer] *patients that I see every day suffer from pain. This population is not patients with terminal cancer, but it is a population of patients on oncological therapies."*
>
> EU key opinion leader

The high prevalence of cancer pain is reiterated by a second key opinion leader:

> *"I think if you ask the* [cancer] *patients, it is really very rare that they do not have any pain."*
>
> EU key opinion leader

Table 1 summarizes the populations of cancer pain sufferers across the seven major markets, based on prevalence estimates provided by physicians surveyed for Datamonitor's study. Over 6.7 million individuals are estimated to be affected by cancer pain in 2009. However, due to Globocan's exclusion of prevalence data for non-melanoma skin cancer (Globocan, 2009; http://www-dep.irac.fr) it is likely that the prevalence of cancer pain is even higher than this estimation.

Table 1:	Prevalence of cancer pain across the seven major markets, 2009						
Country	**US**	**Japan**	**France**	**Germany**	**Italy**	**Spain**	**UK**
5-year cancer prevalence (000s) [1]	4,745	1,551	822	1,175	796	449	665
Mean cancer pain prevalence rate [2]	68.8%	57.1%	61.0%	68.0%	71.3%	64.8%	62.3%
Total cancer pain population (000s)	**3,266**	**885**	**502**	**800**	**567**	**291**	**414**

1. Globocan 2002 (http://www.-dep.iarc.fr) NB: Prevalence figures exclude non-melanoma skin cancer
2. Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, 2009, S.4 (n=180)

Source: Various (see above) DATAMONITOR

As can be seen in Table 1, the US contains the largest population of cancer pain patients, approaching 3.3 million. By comparison, Spain contains the smallest cancer pain population at 291,000.

Published epidemiological estimates of cancer pain prevalence vary widely

Numerous studies have documented the prevalence of pain among cancer patients. According to Portenoy & Lesage (1999), pain affects between 30% and 50% of cancer patients undergoing chronic treatment. Of 28 epidemiological surveys identified by Goudas *et al.* (2005), no single survey reported a cancer pain prevalence below 14%. By comparison, published studies identified by Datamonitor report cancer pain prevalence rates ranging from 34% (Mercadante *et al.,* 2008) to 88% (European Pain in Cancer survey, 2007; www.paineurope.com) (See Table 2).

It is therefore evident that published estimates of cancer pain prevalence are highly variable. According to the IASP, the wide variation of prevalence rates reported in studies is due to the following reasons:

- lack of standardization in definitions of pain and in the measures used to assess it;
- heterogeneity of nociceptive and neuropathic pain conditions;

- heterogeneity of cancer diagnoses and the variety of treatment settings in which epidemiological studies are conducted (International Association for the Study of pain, 2009; www.iasp-pain.org).

In addition, Datamonitor believes that the fluctuating nature of cancer pain intensity throughout the course of the disease and the fact that patients may experience more than one type of cancer-related pain represent further challenges to the gathering of accurate epidemiology data.

The majority of published prevalence studies on cancer pain have focused on adult patients. As such, the occurrence of cancer pain across the lifespan (particularly among children and the elderly) has received comparatively little attention from researchers. For this reason, McGuire (2004) proposes that longitudinal studies delineating specific issues in groups such as the elderly, children and vulnerable populations are essential to improving our understanding of the occurrence and effects of cancer pain.

Table 2 summarizes key studies that have investigated the prevalence of pain in cancer patients across the seven major markets.

Table 2: Epidemiology surveys of cancer pain

Country	Study population	Study methodology	Outcome	Author notes	Reference
US	1,308 outpatients with metastatic cancer	Patients from 54 treatment locations affiliated with the Eastern Cooperative Oncology Group rated the severity of their pain during the preceding week.	67% (871/1,308) of patients reported that they had pain or had taken analgesic drugs daily during the week preceding the study.	Many patients with cancer have considerable pain and receive inadequate analgesia.	Cleeland *et al.* (1994)
US	240 oncology inpatients and outpatients	Patients completed the Functional Assessment Cancer Therapy (FACT-G) Memorial Symptom Assessment Scale (MSAS), and the Brief Pain Inventory.	Pain was found to affect 59% of patients.	Routine, comprehensive symptom assessment may identify a significant fraction of patients who urgently require intensive symptom palliation.	Chang *et al.* (2000)
Japan	n/k	A 1987 nationwide survey of cancer pain and analgesic methods.	The incidence of pain in the terminal stage was in the range of 68–72%.	n/a	Hiraga *et al.* (1991)
Europe	5,084 patients suffering from a solid or blood-borne tumor of all stages (aged ≥18 years).	Survey covering 12 European countries. Respondents were recruited through a multi-modal approach.	56% experienced moderate to severe cancer pain several times a month or more.	n/a	EPIC* survey, 2007 (www.paineurope.com)
France	642 patients suffering from a solid or blood-borne tumor of all stages (aged ≥18 years).	Respondents were recruited through a multi-modal approach.	62% experienced moderate to severe cancer pain several times a month or more.	n/a	EPIC* survey, 2007 (www.paineurope.com)
France	605 patients with cancer.	Multicenter, representative cross-sectional survey of 20 treatment centers.	57% (340/601) of patients with cancer reported pain due to their disease.	The assessment and treatment of cancer pain in France remains inadequate.	Larue *et al.* (1995)
Germany	2,266	Prospective study of cancer patients.	30% presented with 1, 39% presented with 2 and 31% presented with 3 or more distinct pain	The variety of pain syndromes evaluated in the patients confirms the importance of	Grond *et al.* (1996)

Table 2: Epidemiology surveys of cancer pain

Country	Study population	Study methodology	Outcome	Author notes	Reference
			syndromes.	comprehensive pain assessment prior to treatment.	
Italy	457 patients suffering from a solid or blood-borne tumor of all stages.	Respondents were recruited through a multi-modal approach.	88% experienced moderate to severe cancer pain several times a month or more.	n/a	EPIC* survey, 2007 (www.paineurope.com)
Italy	258 patients who had been hospitalized for at least 24 hours.	Patients were interviewed by nine physicians using a brief structured questionnaire prepared ad hoc.	51.5% of patients experienced pain during the previous 24 hours caused by surgery (49.6%) or by the tumor mass itself (29.3%).	It is necessary to persevere with continuing educational and informative programs in order to reduce the frequency and severity of pain.	Ripamonti *et al.* (2000)
Italy	2,655	National cross-sectional survey to draw information on pain prevalence and intensity from patients admitted to oncologic centers.	901 patients (34%) reported pain.	The results of this survey indicate a need for continuing educational and informative programs in pain management for oncologists and more generally for any physician dealing with cancer patients.	Mercadante *et al.* (2008)
UK	400	Retrospective case not study of patients referred to three palliative care centers in London, UK. 95% (380/400) of patients referred had a cancer diagnosis.	Pain was found to affect 64% of patients.	Different patient subgroups may have different needs in terms of symptoms, which will be relevant for the planning and rationalization of palliative care services.	Potter *et al.* (2003)
UK	157	Survey conducted by CancerBACUP. Questionnaires were sent to patients requesting	More than two-thirds (70%) of the 157 patients with cancer taking part in	CancerBACUP concludes that many patients accept pain as an inevitable part	Mayor (2000)

Table 2: Epidemiology surveys of cancer pain

Country	Study population	Study methodology	Outcome	Author notes	Reference
		information from the charity's telephone helpline.	the survey reported that they had experienced pain as a result of their cancer. 77% experienced pain as a result of their treatment.	of cancer and do not seek sufficient help to relieve this pain.	
UK	617 patients suffering from a solid or blood-borne tumor of all stages (aged ≥18 years)	Respondents were recruited through a multi-modal approach.	65% experienced moderate to severe cancer pain several times a month or more.		EPIC* survey, 2007 (www.paineurope.com)
China	1,555	60 cancer patients from each province were randomly selected to participate.	61.6% (958/1,555) of patients had different types of cancer-related pain. The majority of pain (85.1%) was caused by advanced cancer.	n/a	Liu *et al.* (2001)

EPIC = European Pain in Cancer Survey
n/a = not applicable
n/k – not known
* The EPIC survey was conducted by an independent market research company under the auspices of the European Association of Palliative Care (EAPC) and with the help of a Steering Panel comprising of the European Oncology Nursing Society (EONS), the Lance Armstrong Foundation and OPEN Minds – a group of leading experts from across Europe specializing in research and the management of persistent pain and sponsored by a restricted educational grant from Mudipharma International Limited.

Source: Various (see above)

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Neuropathic versus non-neuropathic cancer pain

Distinguishing between neuropathic and non-neuropathic pain is often difficult

Neuropathic pain is poorly understood and as a result it is often difficult for physicians to distinguish between neuropathic and non-neuropathic (nociceptive) pain. Estimating the breakdown of neuropathic versus non-neuropathic pain is further complicated by the fact that patients may experience more than one pain type at any given time. For example, it has been estimated that almost one quarter of patients experience two or more pain types at any given time (Caraceni & Portenoy, 1999). Furthermore, a German-based study reported 30% of cancer patients to present with one, 39% with two and 31% with three or more distinct pain syndromes (Grond *et al.*, 1996). An interviewed key opinion leader concurs that pain syndromes are common among cancer patents.

> *"Normally,* [cancer] *patients suffer not only from neuropathic pain but other pains."*
>
> Japanese key opinion leader

Despite these difficulties, several studies have endeavored to analyze the breakdown of different pain syndromes in the cancer population. In a study by Andersen & Sjøgren (1998), it was reported that 51% of cancer patients experienced nociceptive pain. An international survey evaluating a total of 1,095 patients reported 39.7% of cancer pains to have neuropathic mechanisms (Caraceni & Portenoy, 1999). By comparison, according to Grond *et al.'s* (1996) study of 2,266 cancer patients, pain was classified as being neuropathic in origin in 34% of cases.

Interviewed key opinion leaders concur that approximately 30% of cases of cancer pain are neuropathic in nature.

> *"I believe that only a minority* [of cancer pain patients] *have real neuropathic pain. Sometimes there are mixed forms of neuropathic plus somatic pain, but the* [prevalence of] *pure neuropathic pain is no more than 30%."*
>
> EU key opinion leader

> *"It is difficult to say* [the proportion of all cancer pain cases that are neuropathic in nature], *but maybe 25% or 30%."*
>
> EU key opinion leader

"I would say it [the proportion of neuropathic cancer pain] *was 30%."*

EU key opinion leader

Neuropathic cancer pain affects almost 2.3 million individuals across the seven major markets

Table 3 summarizes the populations of cancer pain sufferers affected by neuropathic pain across the seven major markets. In order to determine the number of cancer pain patients affected by neuropathic pain, Datamonitor has applied the prevalence estimate of 34% reported in Grond *et al.'s* (1996) study to the prevalent cancer pain population calculated in Table 1 for each of the seven major markets. The study by Grond *et al.* was selected on the basis of its large sample size. As can be seen in Table 3, almost 2.3 million cancer pain patients across the seven major markets experience neuropathic pain.

Table 3: Prevalence of neuropathic cancer pain across the seven major markets, 2009

Country	US	Japan	France	Germany	Italy	Spain	UK
Total cancer pain population (000s) (1)	3,266	885	502	800	567	291	414
Neuropathic cancer pain prevalence (2)	34%	34%	34%	34%	34%	34%	34%
Neuropathic cancer pain population (000s)	**1,110**	**301**	**171**	**272**	**193**	**99**	**141**

1. Please refer to Table 1 for methodology behind Datamonitor's prevalence estimate for the total cancer pain population.
2. Grond *et al.* (1996).

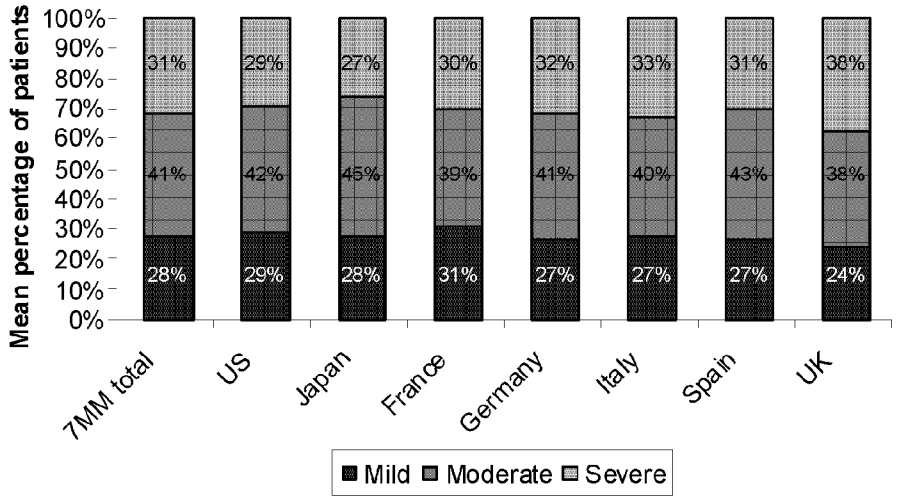
Source: Various (see above) DATAMONITOR

Mild, moderate and severe chronic neuropathic cancer pain

Interviewed physicians were asked to estimate the proportion of their cancer patients seen monthly who suffer from chronic neuropathic cancer pain of each severity (mild, moderate and severe).

Figure 25 presents the physician-estimated mean proportion of chronic neuropathic cancer pain patients affected by mild, moderate and severe pain across the seven major markets.

Figure 25: Proportion of patients affected by each severity of chronic neuropathic cancer pain across the seven major markets, 2009



7MM = seven major markets (US, Japan, France, Germany, Italy, Spain and the UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, 2009 (Q1.4)

DATAMONITOR

As can be seen in Figure 25, the proportion of chronic neuropathic cancer pain patients affected by each severity of pain is broadly comparable across the seven major markets. According to physicians interviewed by Datamonitor, moderate pain is the most predominant pain intensity experienced by patients, affecting a mean 41% of chronic neuropathic cancer pain patients across the seven major markets in 2009.

Table 4 summarizes the populations of chronic neuropathic cancer pain patients affected by each severity of pain (mild, moderate and severe) across the seven major markets in 2009. In order to determine the number of chronic neuropathic cancer pain patients affected by each pain severity, Datamonitor has applied the mean severity estimates from respondents to the prevalent chronic neuropathic cancer pain population in each of the seven major markets as calculated in Table 3.

Datamonitor estimates mild, moderate and severe pain to affect a total of 645,000, 950,000 and 692,000 neuropathic cancer pain patients, respectively, across the seven major markets in 2009. In view of the larger prevalent population affected by moderate neuropathic cancer pain, Datamonitor believes that pharmaceutical

companies manufacturing analgesics would be well served to target the population of cancer pain patients.

Table 4: Prevalence of each severity of chronic neuropathic cancer pain across the seven major markets, 2009

Country	US	Japan	France	Germany	Italy	Spain	UK
Neuropathic cancer pain population (000s) [1]	1,110	301	171	272	193	99	141
Mild pain prevalence [2]	29.0%	28.1%	30.6%	26.7%	27.2%	26.7%	24.1%
Mild chronic neuropathic cancer pain population (000s)	**322**	**85**	**52**	**73**	**52**	**26**	**34**
Moderate pain prevalence [2]	41.5%	45.4%	39.6%	41.3%	39.6%	42.7%	38.0%
Moderate chronic neuropathic cancer pain population (000s)	**461**	**137**	**67**	**112**	**76**	**42**	**53**
Severe pain prevalence [2]	29.4%	26.5%	29.8%	32.1%	33.2%	30.6%	37.9%
Severe chronic neuropathic cancer pain population (000s)	**327**	**80**	**51**	**87**	**64**	**30**	**53**

1. Please refer to Table 3 for methodology behind Datamonitor's prevalence estimate for neuropathic cancer pain.

2. Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, Q1.4 (n=180)

Source: Various (see above) DATAMONITOR

Non-neuropathic cancer pain affects an estimated 4.4 million patients across the seven major markets

Table 5 summarizes the populations of cancer patients estimated to be affected by non-neuropathic pain across the seven major markets.

Due to the dearth of published studies examining the prevalence of non-neuropathic cancer pain, Datamonitor's prevalence estimate for this category of cancer pain is based upon Grond *et al.'s* (2006) survey. Grond *et al.'s* (1996) study reported cancer pain to be neuropathic in origin in 34% of cases. On this basis, Datamonitor has assumed that 66% of patients with cancer pain experience non-neuropathic pain. In

order to determine the number of cancer pain patients affected by neuropathic pain, Datamonitor has applied the prevalence estimate of 66% to the prevalent cancer pain population calculated in Table 1 for each of the seven major markets. However, Datamonitor recognizes that a proportion of cancer patients may experience pain caused by both neuropathic and neuropathic mechanisms concurrently.

As presented in Table 5, Datamonitor estimates non-neuropathic pain to affect over 4.4 million cancer pain patients across the seven major markets.

Table 5: Prevalence of non-neuropathic cancer pain across the seven major markets, 2009

Country	US	Japan	France	Germany	Italy	Spain	UK
Total cancer pain population (000s) [1]	3,266	885	502	800	567	291	414
Non-neuropathic cancer pain prevalence [2]	66%	66%	66%	66%	66%	66%	66%
Non-neuropathic cancer pain population (000s)	**2,155**	**584**	**331**	**528**	**374**	**192**	**273**

1. Please refer to Table 1 for methodology behind Datamonitor's prevalence estimate for the total cancer pain population.
2. Datamonitor estimate. Based on Grond *et al.*'s (1996) large-scale survey which found cancer pain to be neuropathic in origin in 34% of cases, Datamonitor has assumed that the remaining 66% of cancer pain patients experience non-neuropathic pain.

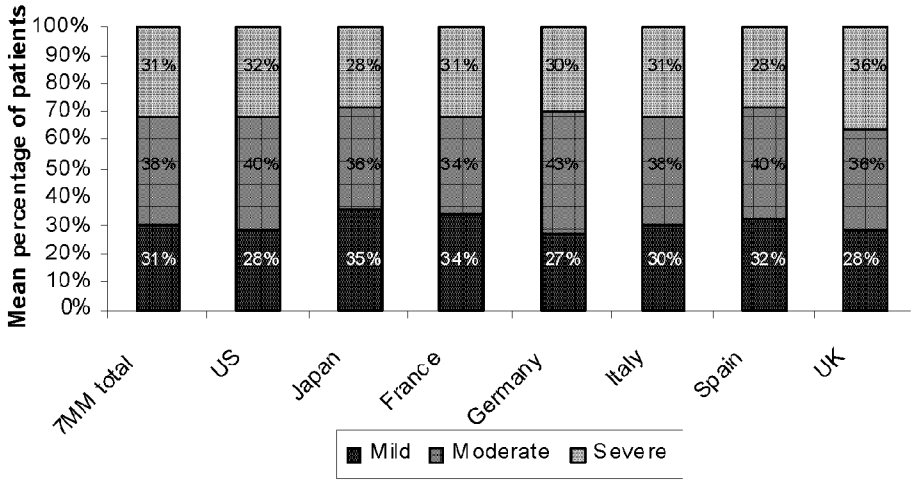
Source: Various (see above). DATAMONITOR

Mild, moderate and severe chronic non-neuropathic cancer pain

Interviewed physicians were asked to estimate the proportion of their cancer patients seen monthly who suffer from chronic non-neuropathic cancer pain of each severity (mild, moderate and severe).

Figure 26 presents the physician-estimated mean proportion of chronic non-neuropathic cancer pain patients affected by mild, moderate and severe pain across the seven major markets.

Figure 26: Proportion of patients affected by each severity of chronic non-neuropathic cancer pain, across the seven major markets, 2009



7MM = seven major markets (US, Japan, France, Germany, Italy, Spain and the UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, 2009 (Q1.5).

DATAMONITOR

As can be seen in Figure 25, physician-related prevalence rates of mild, moderate and severe chronic non-neuropathic pain are similar to those reported for neuropathic cancer pain in Figure 24. Similarly, the proportion of chronic non-neuropathic cancer pain patients affected by each severity of pain is broadly comparable across the seven major markets (US, Japan, France, Germany, Italy, Spain and the UK). According to physicians surveyed by Datamonitor, moderate pain is the most predominant pain intensity experienced by patients with non-neuropathic cancer pain, with this pain severity affecting a mean 38% of chronic non-neuropathic cancer pain patients across the seven major markets in 2009. Physicians in the UK estimate moderate and severe pain to affect equal proportions of chronic non-neuropathic cancer pain patients.

Table 6 summarizes the populations of chronic non-neuropathic cancer pain patients affected by each severity of pain (mild, moderate and severe) across the seven major markets in 2009. In order to determine the number of chronic non-neuropathic cancer pain patients affected by each pain severity, Datamonitor has applied the mean severity estimates from respondents to the prevalent chronic non-neuropathic cancer pain population in each of the seven major markets as calculated in Table 5.

Table 6:	Prevalence of each severity of chronic non-neuropathic cancer pain across the seven major markets, 2009						
Country	**US**	**Japan**	**France**	**Germany**	**Italy**	**Spain**	**UK**
Non-neuropathic cancer pain population (000s) [1]	2,155	584	331	528	374	192	273
Mild pain prevalence [2]	28.2%	35.4%	34.2%	27.1%	30.3%	32.1%	28.0%
Mild chronic non-neuropathic cancer pain population (000s)	**608**	**207**	**113**	**143**	**113**	**62**	**77**
Moderate pain prevalence [2]	40.3%	36.3%	34.4%	43.3%	38.4%	39.6%	36.0%
Moderate chronic non-neuropathic cancer pain population (000s)	**868**	**212**	**114**	**229**	**144**	**76**	**98**
Severe pain prevalence [2]	31.6%	28.3%	31.5%	29.6%	31.3%	28.3%	36.0%
Severe chronic non-neuropathic cancer pain population (000s)	**680**	**166**	**104**	**156**	**117**	**54**	**98**

1. Please refer to Table 5 for methodology behind Datamonitor's prevalence estimate for non-neuropathic cancer pain.

2. Datamonitor, *Stakeholder Insight 2009: Cancer Pain survey*, Q1.5 (n=180)

Source: Various (see above) DATAMONITOR

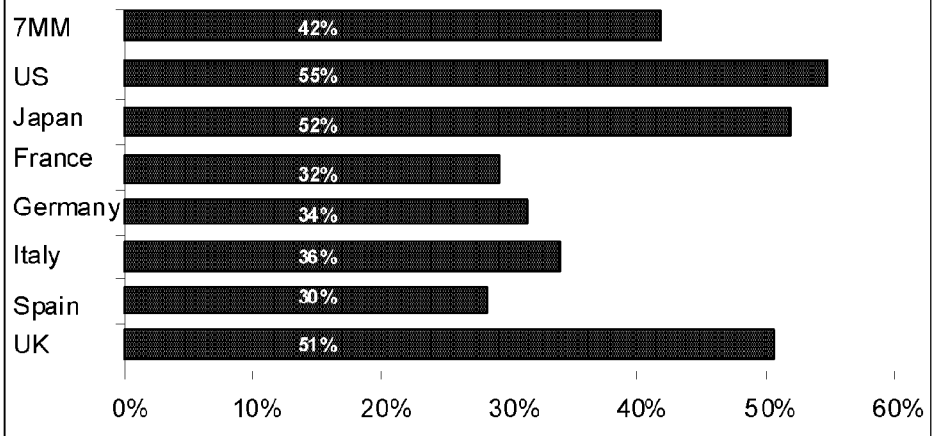
As seen in Table 6, Datamonitor estimates mild, moderate and severe pain to affect a total of 1.3 million, 1.7 million and 1.4 million non-neuropathic cancer pain patients, respectively, across the seven major markets in 2009.

Breakthrough cancer pain

Almost 3.2 million patients with cancer pain suffer from breakthrough pain across the seven major markets

Physicians surveyed by Datamonitor were asked to estimate the proportion of their cancer pain patients who experience breakthrough pain. Figure 27 summarizes the mean percentage of cancer pain patients who experience breakthrough pain, as reported by physicians across the seven major markets.

Figure 27: Proportion of cancer pain patients experiencing breakthrough pain across the seven major markets, 2009



7MM = seven major markets (US, Japan, France, Germany, Italy, Spain and the UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, 2009 (Q5.1) (n=180)

DATAMONITOR

As can be seen in Figure 27, prevalence rates of breakthrough pain reported by surveyed physicians range from 30% in Spain to 55% in the US (with an average of 42% across the seven major markets). Therefore, physicians surveyed report lower prevalence figures for breakthrough cancer pain than has been documented by published prevalence studies identified by Datamonitor. (For published prevalence studies for breakthrough cancer pain, please refer to Table 8).

The higher prevalence of breakthrough pain in the US and UK relative to the four major EU markets (France, Germany, Italy and Spain) is in keeping with the IASP's conclusion that breakthrough pain is either defined or recognized differently in different countries (Caraceni *et al.,* 2004) and supports Dr Sebastiano Mercadante's assertion that breakthrough pain is a uniquely American-English term. That said, the comparable prevalence rate of breakthrough cancer pain reported by physicians in Japan (51.9%) contradicts this viewpoint.

The relatively low prevalence figures reported by EU physicians may imply that physicians across the EU are not as familiar with the term 'breakthrough pain' as physicians in the US, UK and Japan. Surveyed physicians in Spain reported the lowest prevalence rate for breakthrough cancer pain, at 30% (Figure 27). According

to Gomez-Batiste *et al.* (2002), under-treatment of breakthrough pain in Spain is well documented and is thought to be the consequence of low detection rates.

Qualitative interviews sought to gauge key opinion leaders' views on the prevalence rates of breakthrough pain reported by respondents taking part in Datamonitor's survey. One key opinion leader believes the prevalence of breakthrough cancer pain to be higher than the average rate of 42% reported by surveyed physicians.

> *"It* [the prevalence of breakthrough cancer pain] *would be high. It would be 50 to 60%."*
>
> EU key opinion leader

However, another EU-based key opinion leader believes the prevalence of breakthrough pain to be lower than that reported by physicians surveyed by Datamonitor.

> *"I believe that real, pure breakthrough pain is* [present] *in 20–30% of patients, no more."*
>
> EU key opinion leader

Interviewed key opinion leaders also report that the prevalence of breakthrough cancer pain varies according to the stage of cancer and tumor type. For example, one key opinion leader reports a higher prevalence rate of breakthrough pain among advanced cancer patients.

> *"I mostly work in the last stage of palliative care and I think we have between 60% and 70% of the patients who experience breakthrough pain. It increases with the progression of the disease."*
>
> EU key opinion leader

Furthermore, one key opinion leader reports that for patients with hematological cancers, the prevalence of breakthrough pain is lower than that cited by physicians taking part in Datamonitor's survey.

> *"It* [breakthrough pain] *is not in a majority of patients. These* [breakthrough pain] *patients are probably no more than 15 or 20% of the patients* [with hematological cancers]."
>
> EU key opinion leader

Table 7 summarizes the populations of cancer pain patients suffering from breakthrough pain across the seven major markets, based on prevalence estimates provided by physicians surveyed by Datamonitor. Almost 3.2 million cancer pain patients across the seven major markets are estimated to be affected by breakthrough pain in 2009.

Table 7: Prevalence of breakthrough pain among cancer pain patients across the seven major markets, 2009

Country	US	Japan	France	Germany	Italy	Spain	UK
Total cancer pain population (000s) [1]	3,266	885	502	800	567	291	414
Mean % of cancer pain patients with BTP [2]	54.7%	51.9%	31.7%	34.0%	35.9%	30.3%	51.1%
Total breakthrough cancer pain population (000s)	**1,785**	**459**	**159**	**272**	**204**	**88**	**212**

BTP = breakthrough pain
1. Please refer to Table 1 for methodology behind Datamonitor's prevalence estimate for the total cancer pain population.
2. Datamonitor, *Stakeholder Insight 2009: Cancer Pain survey*, Q5.1 (n=180)

Source: Various (see above) DATAMONITOR

In comparison to the prevalence of total cancer pain, fewer studies have specifically investigated the prevalence of breakthrough pain in cancer patients. Accordingly, Caraceni *et al.* (2004) proposes that additional studies are needed to clarify the epidemiology of breakthrough pain in cancer patients and the range of pathophysiologies that underlie the condition.

The reported prevalence of breakthrough pain in studies of cancer patients varies according to differences in definition and setting (Svendsen *et al.,* 2005). However, the consensus appears to be that breakthrough pain is a common feature of cancer patients. Surveys also indicate that breakthrough pain is associated with a relatively more severe pain syndrome, high pain-related distress and impaired quality of life (Portenoy *et al.,* 1999; Zeppetella *et al.,* 2000; Hwang *et al.,* 2003).

Table 8 summarizes key studies that have investigated the prevalence of breakthrough pain in cancer patients across the seven major markets.

Table 8: Epidemiology surveys of breakthrough cancer pain

Country	Study population	Study methodology	Outcome	Author notes	Reference
International	1,095	An international group of investigators assembled by a task force of the International Association for the Study of Pain evaluated the prevalence and characteristics of BTP as part of a prospective, cross-sectional survey of cancer pain.	The prevalence of BTP was 64.8%.	Physicians from English-speaking countries were significantly more likely to report BTP than other physicians. These data confirm the high prevalence of BTP.	Caraceni *et al.* (2004)
11 European countries and Israel	573	Telephone survey conducted in 2006–07. Of the 5,084 adult patients randomly contacted, 573 were randomly selected for the second survey phase.	Of the patients prescribed analgesics, 63% experienced BTP.	Across Europe and Israel, treatment of cancer pain is suboptimal. Management guidelines should be revised to improve pain control in patients with cancer.	Breivik *et al.* (2009)
US	63	A prospective survey of patients with cancer pain. Data were collected during a 3-month period from consecutive patients who reported moderate pain more or less for 12 hours daily and stable opioid dosing for a minimum of 2 consecutive days.	64% (41/63) reported BTP. The pain was related to the tumor in 42 (82%), the effects of therapy in seven (14%), and neither in two (4%).	These data clarify the spectrum of BTP and indicate their importance in cancer pain management.	Portenoy & Hagen (1990)
US	178	Cross-sectional survey of inpatients with cancer.	Of the 162 patients who met the criteria for controlled background pain, 51.2% (84) patients experienced BTP during the previous day. The mean number of episodes was 6 (range 1–60).	The findings suggest the need for further studies of BTP and more effective therapeutic strategies.	Portenoy *et al.* (1999)
Germany	613	Survey of transitory pains (BTPs) on admission to a multidisciplinary pain clinic.	BTP was reported by 243 (39%) of 613 consecutive cancer pain patients.	Gender, age, site, and therapy were not related to the presence of BTP.	Petkze *et al.* (1999)

Table 8: Epidemiology surveys of breakthrough cancer pain

Country	Study population	Study methodology	Outcome	Author notes	Reference
Spain	397	Assessment of prevalence of BTP among oncology patients managed by palliative care teams in Catalonia, Spain and to characterize the frequency, intensity and treatment of breakthrough pain episodes.	BTP was reported by 163 (41%) of patients, with a total of 244 episodes (mean 1.5 episodes/patient/day).	Morphine was used to treat 52% BTP episodes, while 25% were untreated. These findings indicate that BTP remains under recognized and under-treated in Spain.	Gomez-Batiste *et al.* (2002)
UK	245	A prospective survey to determine the prevalence and characteristics of BTP in cancer patients admitted to a hospice.	Of the 245 patients, there were 404 pains (range one to five per patient); of these patients, 218 (89%) had BTP. BTP was classified as somatic (46%), visceral (30%), neuropathic (10%), or mixed etiology (16%). The average number of daily BTP episodes was four (range one to 14); 49% occurred suddenly. Most (59%) were unpredictable, and 72% lasted less than 30 minutes.	BTP is common among patients admitted to the hospice in the study. It is frequent, short, often unpredictable and not necessarily related to chronic pain, making treatment difficult.	Zeppetella *et al.* (2000)

BTP = breakthrough pain

Source: Various (see above)

DATAMONITOR

Trends in cancer pain prevalence

Pain prevalence typically increases with disease progression

Although pain may occur at any point during the cancer trajectory, cancer pain is typically more prevalent in the advanced stages of disease. For example, cancer-related pain has been estimated to affect 30–50% of patients under chronic treatment but more than 70% of patients with advanced disease (Portenoy & Lesage, 1999). Similarly, a population-based study in the Netherlands found the prevalence of moderate/severe pain to be 70–75% in patients for whom treatment was no longer feasible (van den Beuken-van Everdingen *et al.,* 2007). A recent Italian mortality follow-back survey reported 82.3% of patients to experience pain in the last 3 months of life, with 61.0% of those patients experiencing very distressing pain (Costantini *et al.,* 2009). Interviewed key opinion leaders discuss the prevalence of pain among advanced cancer patients:

> *"I work in palliative care and so mostly work with patients with advanced cancer. I would say between 80% and 90% of the patients* [experience cancer pain]."
>
> EU key opinion leader

> *"It* [cancer pain] *increases with progression of the disease because there are many more sites of dissemination of cancer, many organs and structures involved."*
>
> EU key opinion leader

Cancer pain is especially prevalent in patients with metastatic disease, particularly those with bone metastases (David & Walsh, 2004; Mercadante, 1997). Bone metastases are an adverse complication of many advanced cancers, most frequently those of the breast, prostate, lung, thyroid and kidney, as well as hematological malignancies such as multiple myeloma (Roodman, 2004). Almost 70% of patients with breast and prostate cancer are eventually affected by bone metastases (Coleman and Rubens, 1987). Bone metastases patients have described a deep, boring pain sensation that is not relieved by sleep or lying down (Coleman, 1997).

Treatment-related chronic pain is common in cancer survivors

Due to advances in strategies to detect cancer early and treat it effectively, the number of people surviving the disease is higher than several decades ago. Today, 75% of children and two out of three adults will survive cancer, whereas 50 years ago just one in four survived. Furthermore, in the US, the cancer-related death rate has dropped by 1.1% per year over 1993–2002 (Burton *et al.,* 2007).

Nevertheless, individuals in whom cancer has been effectively eradicated may experience unique, long-term healthcare issues related to their cancer treatment, including pain. Pain in cancer survivors is caused by residual tissue damage from the cancer and/or the cancer therapy. Neuropathies secondary to surgery, radiation therapy and chemotherapy are the most common treatment-induced chronic pain syndromes in cancer survivors (Levy *et al.,* 2008). This, in turn, poses new challenges in terms of patient care.

> *"It* [chronic pain among cancer survivors] *can happen after some kinds of chemotherapy or surgery or radiotherapy…This kind of pain is often neuropathic pain."*
>
> EU key opinion leader

Although less well studied than pain in cancer patients undergoing treatment, several studies have documented the prevalence of pain in survivors of cancer. A meta-analysis of 52 studies reported a pain prevalence of 33% among patients after curative treatment (van den Beuken-van Everdingen, 2007). Among 85 female breast cancer survivors, Gulluoglu *et al.* (2006) found that 39 (46%) reported chronic pain (defined as pain at treatment-related regions for a duration of at least 3 months after completion of treatment). Radiotherapy was found to be significantly related to chronic pain in the study population (p=0.049) (Gulluoglu *et al.,* 2006).

Surgery-related chronic pain syndromes are common in breast and lung cancer survivors; chronic pain is seen in 50% of mastectomy patients (Jung *et al.,* 2003). Similarly, a recent survey by Gärtner *et al.* (2009) found 47% of women to experience pain symptoms 2 to 3 years after breast cancer treatment. Factors associated with chronic pain included young age (18–39 years) and adjuvant radiotherapy, but not chemotherapy (Gärtner *et al.,* 2009). Current literature estimates the incidence of chronic post-thoracotomy pain (CPTP, defined as an aching or burning sensation that persists or recurs along the thoracotomy scar postoperatively) to be around 26–67% (Katz *et al.,* 1996; Pluijims *et al.,* 2006; Dajczman *et al.,* 1991; Kalso *et al.,* 1992).

While the prevalence figures reported in published studies are high, it is possible to speculate that survivors of cancer under-report their pain due to fatalism about the possibility of achieving pain control and fear that pain is indicative of recurrence of their cancer. The number of cancer survivors is expected to increase significantly over the next decade (Sun *et al.*, 2008).

Commenting on the current state of analgesic treatment for cancer pain survivors, one key opinion leader believes that this population requires more attention and regular assessment:

> *"I believe that these kinds of patients* [survivors of cancer] *need to have more attention* [from physicians] *because patients are seen only when they are in a terminal stage or better stage. But the survivors* [of cancer] *do have pain. They need to be evaluated on a regular basis."*
>
> EU key opinion leader

> *"No, patients with long-term pain from cancer chemotherapy are not well treated. I think there needs to be recognition that cancer treatments can cause long-term disabling symptoms or problems. We need effective and simple treatments for that type of pain."*
>
> EU key opinion leader

In view of the growing population of cancer survivors, it is important that healthcare providers acknowledge the impact of chronic, persistent pain in the quality of cancer survivorship and implement effective treatments. Likewise, Datamonitor believes that this population must not be overlooked by companies developing and marketing treatments for cancer pain.

Projected increase in cancer rates will cause cancer pain population to grow

Cancer is becoming an increasingly important factor in the global burden of disease, mainly due to steadily aging populations in both developed and developing countries. Datamonitor believes that the rising incidence of cancer will in turn lead to a global increase in the number of individuals suffering from cancer-related pain. This view is shared by an interviewed key opinion leader:

> *"The prevalence* [of cancer pain] *will increase, because the number of cancer patients is still increasing and the cancer increasing the most in*

France is lung cancer. Lung cancer gives a lot of bone metastases, which is painful. We also have an ageing population."

EU key opinion leader

The WHO warns that cancer numbers will grow over the coming years, with the estimated annual number of new cases expected to rise from 10 million in 2000 to 15 million by 2020 (World Health Organization, 2003; www.who.int). With regards to the US, research indicates that the incidence of cancer is expected to rise sharply over the next two decades, driven mainly by the elderly and minority populations. According to recent research by Smith *et al.* (2009), between 2010 and 2030, cancer incidence in the US is projected to increase by approximately 45%, from 1.6 million in 2010 to 2.3 million in 2030. A 67% increase in cancer incidence is projected in adults aged over 65 years, versus an 11% increase among younger adults. The incidence of cancer in minorities over the same period is expected to rise by 99% compared to only a 31% increase in Caucasians. The study also indicates that a larger proportion of new cases will involve cancers that currently have low survival rates, including liver, stomach, pancreas and lung. Likewise, in the EU region, the aging population is expected to cause the total number of new cases of cancer to increase (Ferlay *et al.,* 2006), with new cases in England predicted to increase by 33%, from 224,000 in 2001 to 299,000 in 2020 (Möller *et al.,* 2007).

Impact of cancer pain

Cancer pain has a deleterious impact on quality of life

Cancer pain is a substantial burden for the cancer patient and has a profound impact on quality of life (Ferrell *et al.,* 1989; Strang, 1998; Nie *et al.,* 2000; Kuzeyli *et al.,* 2005). Physical/functional wellbeing, emotional wellbeing and social wellbeing are areas of life most commonly affected by cancer pain (Moinpour & Chapman, 1991; Padilla *et al.,* 1990). Studies have demonstrated an association between cancer pain and depression (Ciaramella & Poli, 2001; Rao & Cohen, 2004), with one large-scale European survey reporting 21% of cancer patients having been diagnosed with depression because of their pain (Breivik *et al.,* 2006). Associations between cancer pain and insomnia (Davidson *et al.,* 2002) and anxiety (Thielking *et al.,* 2003) have also been demonstrated.

Despite these adverse consequences, a 2007 European survey found that 50% of cancer patients did not believe that their healthcare professional took their quality of

life into consideration to a great extent (EPIC Survey. Final Results presentation, 2007; www.paineurope.com).

Ultimately, then, it is essential that pain is effectively diagnosed and treated in order to optimize quality of life for patients with cancer.

Breakthrough pain is a common cause of hospital admissions

Treatment-related pain may lead to interruptions in therapy, changes in the cancer regimen and, in some cases, cessation or potentially curative therapy (International Association for the Study of Pain, 2009; www.iasp-pain.org). In addition, breakthrough pain is a common cause of hospital admissions (Grant *et al.,* 1995; Fortner *et al.,* 2002) and accounts for 4.4–7.6% of readmissions (Grant *et al.,* 1995; Fortner *et al.,* 2003; Wang *et al.,* 2003). Patients with breakthrough pain have higher direct pain-related costs than patients without breakthrough pain—$1,080 compared to $750, respectively (Fortner *et al.,* 2003)—and are approximately 2.5 times more likely to seek care in an emergency department than patients with chronic pain but without breakthrough pain (Fortner *et al.,* 2002).

CHAPTER 5 ASSESSMENT, PHARMACOLOGICAL TREATMENT RATES AND PROFESSIONAL INVOLVEMENT

- *Assessing the etiology and severity of cancer pain is a major determinant of initial drug treatment and the key to the success of analgesic treatment. A variety of instruments have been developed to assess the intensity of cancer pain including numerical, verbal and visual rating scales.*

- *Interviewed key opinion leaders report that only specialists in pain medicine and supportive care routinely assess whether cancer pain is neuropathic or non-neuropathic in origin. Since oncologists play the greatest role in initiating and managing analgesic treatment in cancer pain patients, it is possible to speculate that neuropathic pain is not distinguished from non-neuropathic pain in the majority of cases. However, it is possible to determine whether cancer pain is neuropathic in origin through patients' treatment response to different drug classes (e.g. NSAIDs and anticonvulsants).*

- *According to results of Datamonitor's survey, severe cancer pain is relatively well treated, with estimated treatment rates for severe neuropathic and severe non-neuropathic cancer pain standing at 98% and 94%, respectively, across the seven major markets in 2009. By comparison, pharmacological treatment rates for cancer pain of mild and moderate intensities are relatively low. Improving pharmacological treatment rates represents a key unmet need in the treatment of cancer pain.*

- *Physicians taking part in Datamonitor's survey estimated that 80% of patients experiencing breakthrough cancer pain received pharmacological treatment for this form of pain. By comparison, results of a large-scale survey, completed in 2007 found reported that just 33% of patients experiencing breakthrough cancer pain to be taking additional analgesics for the pain.*

- *Through interviews with key opinion leaders, Datamonitor has identified three key barriers which may be hindering use of analgesics in the cancer pain population. These are: under-reporting of pain by cancer patients, inadequate pain assessment by physicians and concerns surrounding use of opioid analgesics.*

- *Oncologists are the healthcare professionals most likely to initiate and manage pharmacological treatment of cancer pain. According to Datamonitor's primary research, oncologists initiate and manage analgesic treatment in 45% and 44% of patients with cancer pain, respectively, across the seven major markets. It is therefore important for manufacturers of analgesic treatments for cancer pain to target oncologists in their marketing efforts.*

Assessment of cancer pain

Assessing the etiology and severity of cancer pain is a major determinant of initial drug treatment and the key to the success of treatment. Failure to assess pain severity and pain type accurately can lead to under-treatment. According to the National Cancer Institute, the following are essential to the initial assessment of cancer pain:

- detailed history;
- physical examination;
- psychosocial evaluation;
- diagnostic evaluation.

The National Cancer Institute also maintains that pain assessment should occur:

- at regular intervals after initiation of treatment;
- at each new report of pain;
- at a suitable interval after pharmacologic or non-pharmacologic intervention (e.g. 15 to 30 minutes after parenteral drug therapy and 1 hour after oral administration) (National Cancer Institute, 2009, www.cancer.gov).

Similarly, clinical recommendations from the European Society for Medical Oncology state that all patients should be evaluated for the presence of pain at every visit (Jost *et al.,* 2009; http://annonc.oxfordjournals.org). In addition, guidelines published by the National Comprehensive Cancer network (NCCN, *Adult cancer pain*, 2002; http://www.nccn.org) place emphasis upon continuous reviews of treatment to ensure pain has not increased and side effects are manageable.

The mainstay of pain assessment is the patient self-report. However, family members and caregivers are often used as proxies for patient reports, particularly in situations in which communication barriers exist (e.g. cognitive impairment or language difficulties). A US-based key opinion leader comments on the assessment of cancer pain:

> *"Cancer pain assessment is like any medical assessment, you focus on the history of the pain, including its onset, its duration, its location, its*

severity, precipitating factors, aggravating factors, mitigating factors, treatments that have been tried and side effects of those treatments."

US key opinion leader

Pain subtype

Assessment of cancer pain is complicated by the number of pain syndromes (nociceptive, neuropathic, or mixed) and the common assumption that, because a patient has both pain and cancer, the two are causally related. As discussed in CHAPTER 4, patients may have a variety of pains quite unconnected with the cancer or its associated treatment, especially if they are elderly and have a variety of co-existing conditions such as arthritis. As such, Zekry *et al.* (1999) propose that pre-existing conditions should be addressed in the initial assessment of cancer pain, along with pain severity, opioid history and side effects and previous opioid dosing. Careful analysis of the cause of each type of pain is essential if accurate diagnosis and precise treatment is to be achieved (Lovel and Hassan, 1999).

Key opinion leaders interviewed by Datamonitor discuss how neuropathic pain is distinguished from non-neuropathic pain when assessing a patient with cancer.

"First of all, I ask the patient what type of pain they have, and I follow up with a neurological examination, and a questionnaire on the type of pain, and a description of the pain from the patient is sought."

EU key opinion leader

"[I use] *the historical information that the patient gives* [in order to distinguish neuropathic from non-neuropathic pain] *and the descriptors they use. If they* [patients] *use words like burning, electrical tingling, numbness, then they are talking about neuropathic pain."*

US key opinion leader

In addition to the qualitative descriptors of pain cited by interviewed key opinion leaders, it is possible to determine whether cancer pain is neuropathic in origin through patients' treatment response to different drug classes. For example, if a patient does not experience pain relief with an NSAID yet does so with an anticonvulsant drug, it is likely that the pain is neuropathic in origin.

Despite the importance of distinguishing between neuropathic and non-neuropathic cancer pain, key opinion leaders report that only specialists in pain medicine and supportive cancer care routinely make this distinction when assessing cancer pain.

> *"It* [distinguishing between neuropathic and non-neuropathic cancer pain] *is not routine…it is routine for physicians that are involved in supportive cancer care but I believe we are the only ones, and it is routine for physicians involved in pain therapy. It is not routine for oncologists* [to distinguish between neuropathic and non-neuropathic pain], *because most of them send their patients to the palliative care unit or supportive cancer unit or pain therapy unit."*
>
> EU key opinion leader

> *"I would say it* [distinguishing between neuropathic and non-neuropathic] *is important in determining how any pain is treated, cancer or non cancer."*
>
> US key opinion leader

> *"Oncologists just consider the pain as pain, and maybe do not try to differentiate* [neuropathic from non-neuropathic] *but just address it with a broad brush style."*
>
> US key opinion leader

As discussed in the section of this chapter titled 'Professional involvement', Datamonitor's primary research indicates that oncologists are the healthcare professionals that initiate and manage analgesic treatment in the majority of cancer pain cases. Assuming that these healthcare professionals, who are responsible for treating the primary disease, also assess cancer pain, it is possible to speculate that neuropathic is not distinguished from non-neuropathic pain in the majority of cases.

Hjermstad *et al.* (2009) propose that international agreement on how to classify and assess cancer pain is needed in order to improve cancer pain management and research.

Pain severity

A variety of instruments have been developed to assess the intensity of cancer pain and aim to provide some numerical and semi-objective basis to what is essentially a

highly subjective experience. Pain severity scales can also help in titrating analgesics and in monitoring for increases in pain with progressive disease.

Scales commonly used to assess pain severity include:

- numerical rating scale (e.g., 0 to 10 with 0 being 'no pain' and 10 being 'pain as bad as you can imagine');
- verbal rating scales (e.g. "no pain," "mild pain", "moderate pain," severe pain");
- visual analogue scale (e.g. a 10cm line with anchors such as "no pain" on the left and "severe pain" on the right; the patient indicates the place on the line that best represents the intensity of pain);
- face pain rating scale (patients are asked to point to a face illustrating how much they hurt, ranging from faces depicting 'no pain' to 'very much pain').

These scales are recognized by several organizations including the National Comprehensive Cancer Network (NCCN, *Adult cancer pain*, 2002, http://www.nccn.org). In view of the ease of use of these scales, their popularity among physicians is unsurprising.

According to an interviewed key opinion leader, a visual analog scale is most commonly used to assess cancer pain in France.

> *"We use the EVA (Eschelle visuelle analogique), a very simple scale where it is 'no pain' to 'intolerable pain' on a scale that is one to ten and we ask the patient to set the level. All the nurses or students or medical doctors have this scale in their pocket."*
>
> EU key opinion leader

Although perhaps most commonly associated with pediatrics, several investigators have used the face pain scales with adults, especially the elderly, and have had successful results. Indeed, this indicates that they are highly effective for assessing pain in older adults (Flaherty, 2000). Simple worded questions and tools that can be easily understood are the most effective, as older adults frequently encounter numerous factors, including sensory deficits and cognitive impairments.

Besides assessment tools like numeric rating scales or visual analogue scales, tools now frequently used in the daily clinical setting include the Edmonton Symptom Assessment System, the Mini Mental State Examination, and the CAGE

questionnaire (Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers) (Yennurajalingam *et al.,* 2004).

Pharmacological treatment rates

Cancer pain is sub optimally treated across the seven major markets

Physicians surveyed by Datamonitor across the seven major markets (US, Japan, France, Germany, Italy, Spain and the UK) were asked to estimate the percentage of their cancer pain patients which were receiving pharmacological treatment for their pain. Results indicate that severe chronic neuropathic pain is the most well-treated cancer pain condition, with a mean 98% of patients receiving analgesic drug treatment. The drug-treatment rate of severe non-neuropathic cancer pain is slightly lower, standing at 94% across the seven major markets in 2009. Untreated severe pain can be debilitating and hugely detrimental to a patient's quality of life. Therefore, with 2% of severe chronic neuropathic cancer pain patients and 6% of severe non-neuropathic cancer pain patients not receiving pharmacological treatment, it is apparent that there is scope for improvement in treatment rates for severe cancer pain.

Results of Datamonitor's physician survey also indicate that despite the plethora of available drug treatments, pharmacological treatment rates for cancer pain of mild and moderate intensities are relatively low. For example, in relation to neuropathic cancer pain, surveyed physicians across the seven major markets in 2009 reported mean pharmacological treatment rates of 49% for mild pain and 87% for moderate pain. For non-neuropathic cancer pain, physicians reported drug treatments of 52% and 82% for mild and moderate pain intensities, respectively. As such, Datamonitor believes that available pharmacological treatment options are under-utilized by physicians treating cancer pain. An interviewed key opinion leader comments on the pharmacological treatment rates reported by physicians taking part in Datamonitor's survey:

> *"I am appalled that so few people receive* [drug] *treatment. I think that we clearly have to do a better job at all levels."*
>
> US key opinion leader

Compounding this finding, results from a large-scale European survey showed that one third of chronic cancer pain sufferers were not receiving treatment (Breivik *et al.,*

2006). Furthermore, the EPIC survey—a large scale survey involving more than 5,000 cancer patients across 12 different countries—reported that 23% of patients who experience moderate to severe cancer pain (rated as 5 or more) do not receive treatment for their pain (Pain in Europe, 2009; www.painineurope.com). According to Van den Beuken-van Everdingen *et al.* (2007), the prevalence of cancer pain and its under treatment has remained consistently high and largely unchanged for more than four decades. An interviewed key opinion leader believes that chronic cancer pain is not as well treated as the cancer itself.

> *"It is true that the chronic* [cancer] *pain* [population] *are probably not very well taken account of compared to the treatment of the cancer* [itself]. *I know that in many suburbs or in the countryside, patients have no access to specialized outpatient consultation for chronic pain and there is certainly not enough cover."*
>
> EU key opinion leader

In relation to breakthrough cancer pain, physicians surveyed by Datamonitor report a pharmacological treatment rate of almost 80% in 2009. It is therefore assumed that 20% of patients with breakthrough pain are either receiving no treatment at all for their breakthrough pain or are receiving non-drug treatment options. However, in view of the intense and often debilitating nature of breakthrough cancer pain, Datamonitor regards the pharmacological treatment rate of 80% to be sub-optimal.

Of the seven major markets examined in Datamonitor's survey, Italy recorded the lowest pharmacological treatment rate for breakthrough cancer pain (71%) as well as for each severity of neuropathic cancer pain (25%, 67% and 93% for mild, moderate and severe pain respectively), indicating that under-treatment is a particular problem in this country.

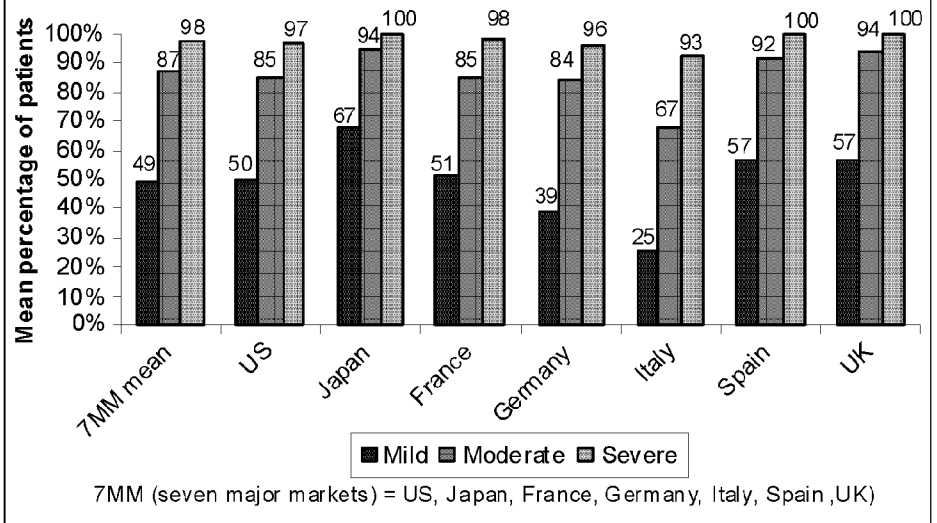
Under treatment of cancer pain can affect physical functioning, psychological well-being and social interactions and can therefore have a deleterious impact on the quality of life of cancer patients. Datamonitor therefore believes that improving the pharmacological treatment rate represents a key unmet need in the treatment of cancer pain.

Chronic neuropathic cancer pain

Datamonitor asked physicians to estimate the percentage of their patients with each severity of chronic neuropathic cancer pain that receive pharmacological treatment for their pain. As illustrated in Figure 28, physicians across the seven major markets estimated that in 2009, a mean of 49%, 87% and 98% patients with mild, moderate

and severe chronic neuropathic pain, respectively, received pharmacological treatment for their pain.

Figure 28: Percentage of patients with chronic neuropathic cancer pain receiving pharmacological treatment, across the seven major markets, 2009



7MM (seven major markets) = US, Japan, France, Germany, Italy, Spain ,UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q3.1 (n=78) Datamonitor

DATAMONITOR

As seen in Figure 28, the proportion of cancer patients receiving pharmacological treatment for cancer pain increases with the severity of pain experienced. However, across the seven major markets, Datamonitor's survey results also indicate that while the treatment rate of chronic neuropathic cancer pain increases substantially between mild and moderate pain intensities (increasing by a mean of 38%), the increase in treatment rate is less marked between moderate and severe pain intensities (with a mean increase of just 11%).

An interviewed key opinion leader speculates on the reasons for the physician-reported treatment rate for chronic neuropathic cancer pain.

> *"It may be a reflection of the inefficiency of diagnosis and the common side effects with commonly used treatment for neuropathic pain, so patients and the prescribers may decide that the patient is better to have*

the pain [and no drug treatment] *than to begin effective treatment with treatment related side effects."*

EU key opinion leader

In terms of country-specific differences in treatment rates, the percentage of patients receiving pharmacological treatment for mild, chronic neuropathic cancer pain ranged from 25% (Italy) to 67% (Japan). Meanwhile, for moderate chronic neuropathic pain, pharmacological treatment rates ranged from 67% (Italy) to 94% (Japan and the UK). Pharmacological treatment rates for severe, chronic neuropathic cancer pain ranged from 93% (Italy) to 100% (Japan, Spain and the UK). Therefore, according to Datamonitor's primary research, the pharmacological treatment rate for patients with chronic, neuropathic cancer pain of all severities is lowest in Italy. Conversely, Japanese and UK-based physicians surveyed by Datamonitor reported the highest pharmacological treatment rates for moderate and severe chronic neuropathic pain across each of the seven major markets.

Almost half a million patients with chronic neuropathic pain do not receive pharmacological treatment for their pain across the seven major markets

Datamonitor has used treatment rates provided by interviewed physicians (Figure 28) to estimate the number of patients with chronic neuropathic pain not receiving pharmacological treatment across the seven major markets. On this basis, Datamonitor estimates that 477,000 patients with chronic, neuropathic cancer pain across the seven major markets are not receiving pharmacological treatment for their pain. It is assumed that these patients are either receiving no analgesic treatment or are being treated with non-pharmacological treatment options.

Table 9 summarizes the estimated number of patients with mild, moderate and severe chronic neuropathic cancer pain not receiving pharmacological treatment for their pain.

Table 9:	Population of patients with each severity of chronic neuropathic cancer pain not receiving pharmacological treatment across the seven major markets, 2009						
Country	**US**	**Japan**	**France**	**Germany**	**Italy**	**Spain**	**UK**
Mild chronic neuropathic cancer pain population (000s) [1]	322	85	52	73	52	26	34
Percentage of mild patients not receiving pharmacological treatment (%) [2]	50	33	49	61	75	43	43
Population of mild chronic neuropathic cancer pain patients not receiving pharmacological therapy (000s)	161	28	25	45	39	11	15
Moderate chronic neuropathic cancer pain population (000s) [1]	461	137	67	112	76	42	53
Percentage of moderate patients not receiving pharmacological treatment (%)[2]	15	4	15	16	33	8	6
Population of moderate chronic neuropathic cancer pain patients not receiving pharmacological therapy (000s)	69	5	10	18	25	3	3
Severe chronic neuropathic cancer pain population (000s) [1]	327	80	51	87	64	30	53
Percentage of severe patients not receiving pharmacological treatment (%)[2]	3	0	2	4	7	0	0
Population of severe chronic neuropathic cancer pain patients not receiving pharmacological therapy (000s)	10	0	1	3	4	0	0
Total population of chronic neuropathic pain patients not receiving pharmacological treatment (000s)	**240**	**34**	**37**	**66**	**69**	**15**	**18**

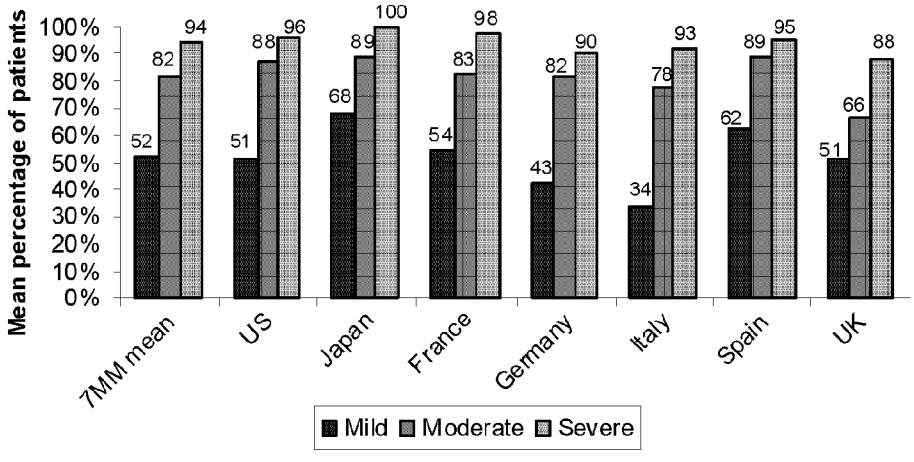
1. Please refer to Table 3 for methodology behind Datamonitor's prevalence estimate for neuropathic cancer pain. Please refer to Table 4 for methodology behind Datamonitor's prevalence estimate for each severity of neuropathic pain (mild, moderate and severe).
2. Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, Q3.1 (n=180). In order to determine the percentage of patients not receiving pharmacological treatment for their cancer pain, Datamonitor has subtracted the percentage of patients receiving pharmacological therapy from 100.

Source: Various (see above) DATAMONITOR

Chronic non-neuropathic cancer pain

Interviewed physicians were asked to estimate the percentage of their patients with each severity of chronic non-neuropathic cancer pain (mild, moderate and severe) receiving pharmacological treatment for their pain. As shown in Figure 29, physicians across the seven major markets estimated that in 2009, 52%, 82% and 94% of patients with mild, moderate and severe chronic non-neuropathic pain, respectively, received pharmacological treatment. Therefore, overall pharmacological treatment rates for moderate and severe chronic non-neuropathic cancer pain were reported to be slightly lower than those for chronic neuropathic cancer pain of the same severities.

Figure 29: Percentage of patients with chronic non-neuropathic cancer pain receiving pharmacological treatment across the seven major markets, 2009



7MM (seven major markets) = US, Japan, France, Germany, Italy, Spain ,UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q4.1 (n=94) Datamonitor

DATAMONITOR

As illustrated in Figure 29, interviewed physicians in each of the seven major markets report the pharmacological treatment rate of chronic non-neuropathic pain to increase with pain severity. However, as seen in the treatment of chronic neuropathic cancer pain (Figure 28), Datamonitor's survey results indicate that although the treatment of chronic non-neuropathic cancer pain increases substantially between mild and

moderate pain intensities (increasing by a mean of 30%), the increase in treatment rate is less marked between moderate and severe pain intensities (with a mean increase of only 12%). Spanish physicians taking part in Datamonitor's survey reported the smallest increase in use of pharmacological treatment between patients with moderate and severe chronic non-neuropathic cancer pain, standing at 6%.

The estimated proportion of patients receiving pharmacological treatment for mild, chronic non-neuropathic cancer pain across the seven major markets ranged from 34% (Italy) to 68% (Japan), while for moderate chronic non-neuropathic pain, pharmacological treatment rates ranged from 66% (UK) to 89% (Japan and Spain). Pharmacological treatment rates for severe, chronic non-neuropathic cancer pain ranged from 88% (UK) to 100% (Japan). Therefore, according to Datamonitor's primary research, the pharmacological treatment rate for patients with moderate and severe chronic, non-neuropathic cancer pain is lowest in the UK. It is possible to speculate that the low treatment rate of cancer pain in the UK may be a consequence of low detection rates, indicating that actions to improve the assessment and detection of cancer pain are of greatest need in the UK.

Almost one million patients with chronic non-neuropathic cancer pain do not receive pharmacological treatment for their pain across the seven major markets

Datamonitor has used treatment rates provided by interviewed physicians (Figure 29) to estimate the number of patients with chronic non-neuropathic pain not receiving pharmacological treatment across the seven major markets. On this basis, Datamonitor estimates that 962,000 patients with chronic, non-neuropathic cancer pain across the seven major markets are not receiving pharmacological treatment. It is assumed that these patients are either receiving no analgesic treatment or are being treated with non-pharmacological treatment options.

Table 10 summarizes the estimated number of patients with mild, moderate and severe chronic non-neuropathic cancer pain not receiving pharmacological treatment for their pain.

Table 10: Population of patients with each severity of chronic non-neuropathic cancer pain not receiving pharmacological treatment across the seven major markets, 2009

Country	US	Japan	France	Germany	Italy	Spain	UK
Mild chronic non-neuropathic cancer pain population (000s) (1)	608	207	113	143	113	62	77
Percentage of mild patients not receiving pharmacological treatment (%) (2)	49	32	46	57	66	38	49
Population of mild chronic neuropathic cancer pain patients not receiving pharmacological therapy (000s)	298	66	52	82	75	24	38
Moderate chronic neuropathic cancer pain population (000s) (1)	868	212	114	229	144	76	98
Percentage of moderate patients not receiving pharmacological treatment (%)(2)	12	11	17	18	22	11	34
Population of moderate chronic neuropathic cancer pain patients not receiving pharmacological therapy (000s)	104	23	19	41	32	8	33
Severe chronic neuropathic cancer pain population (000s) (1)	680	116	104	156	117	54	98
Percentage of severe patients not receiving pharmacological treatment (%)(2)	4	0	2	10	7	5	12
Population of severe chronic neuropathic cancer pain patients not receiving pharmacological therapy (000s)	27	0	2	16	8	3	12
Total population of chronic neuropathic pain patients not receiving pharmacological treatment (000s)	**429**	**90**	**73**	**138**	**114**	**35**	**83**

1. Please refer to Table 5 for methodology behind Datamonitor's prevalence estimate for non-neuropathic cancer pain. Please refer to Table 6 for methodology behind Datamonitor's prevalence estimate for each severity of non-neuropathic pain (mild, moderate and severe).
2. Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, 2009, Q4.1 (n=180). In order to determine the percentage of patients not receiving pharmacological treatment for their cancer pain, Datamonitor has subtracted the percentage of patients receiving pharmacological therapy from 100 (Figure 12).

Source: Various (see above) DATAMONITOR

Over a fifth of breakthrough cancer pain patients do not receive pharmacological treatment

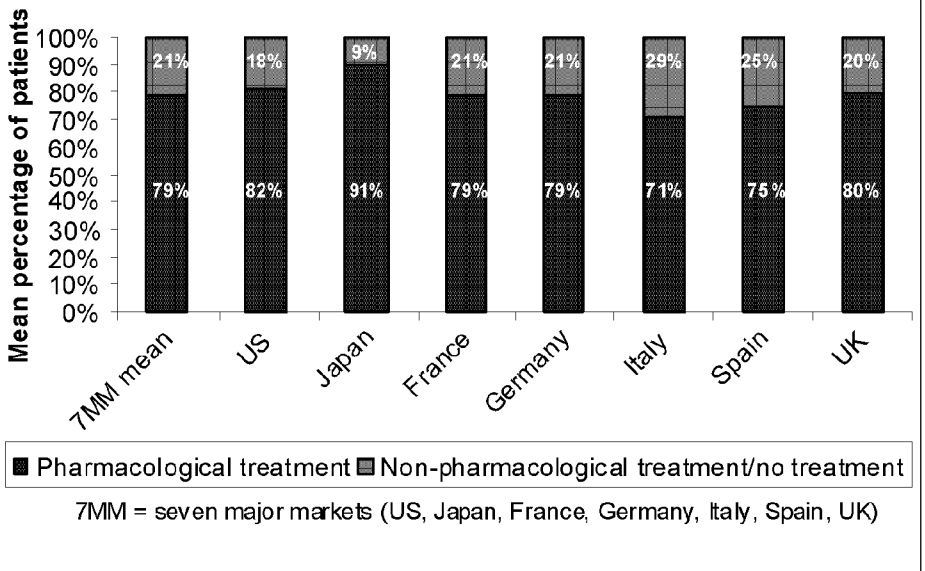
Datamonitor asked physicians across the seven major markets to estimate the percentage of their patients with breakthrough cancer pain receiving pharmacological treatment for their breakthrough pain. As shown in Figure 30, physicians across the seven major markets estimated that 79% of patients with breakthrough cancer pain receive pharmacological treatment for their pain. By comparison, results of the 2007 EPIC survey reported just 33% of patients experiencing breakthrough cancer pain to be taking additional analgesics for the pain (EPIC Survey. Final Results presentation, 2007; www.paineurope.com). Nevertheless, in view of the often debilitating nature of breakthrough cancer pain and the significant impact which it has on the daily lives of cancer patients, Datamonitor regards the pharmacological treatment rate of 79% to be relatively low. It is therefore necessary for the pharmacological treatment rate for breakthrough cancer pain to increase in order to improve the quality of life for cancer patients.

> *"There are a lot of patients who are not receiving the appropriate treatment* [for breakthrough pain]."
>
> EU key opinion leader

Figure 30 summarizes the proportion of cancer patients with breakthrough pain receiving pharmacological treatment, as reported by interviewed physicians across the seven major markets in 2009.

Physicians in Japan reported the highest pharmacological treatment rate for cancer patients with breakthrough pain, standing at 91% in 2009. By comparison, Italian physicians reported the lowest treatment rate for breakthrough cancer pain patients at 71%. As such, 29% of patients with breakthrough cancer pain in Italy are being treated with non-pharmacological treatments or are not receiving any treatment. The low treatment rate reported by Italian physicians relative to the six remaining markets (the US, Japan, France, Germany, Spain and the UK) is in keeping with those reported for chronic neuropathic and chronic non-neuropathic cancer pain, indicating that measures to improve the treatment rate of cancer pain are of greatest need in Italy.

Figure 30: Percentage of patients with breakthrough cancer pain receiving pharmacological treatment across the seven major markets, 2009



7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q5.2 (n=179) Datamonitor

DATAMONITOR

Approximately 577,000 patients with breakthrough pain do not receive pharmacological treatment for their pain across the seven major markets

Datamonitor has used treatment rates provided by interviewed physicians (Figure 30) to estimate the number of patients with chronic non-neuropathic pain not receiving pharmacological treatment across the seven major markets. On this basis, Datamonitor estimates that 577,000 patients with breakthrough cancer pain across the seven major markets are not receiving pharmacological treatment. It is assumed that these patients are either receiving no analgesic treatment or are being treated with non-pharmacological treatment options.

Table 11 summarizes the estimated number of patients with mild, moderate and severe chronic non-neuropathic cancer pain not receiving pharmacological treatment for their pain.

Table 11:	Population of patients with breakthrough pain not receiving pharmacological treatment across the seven major markets, 2009						
Country	**US**	**Japan**	**France**	**Germany**	**Italy**	**Spain**	**UK**
Breakthrough cancer pain population (000s) [1]	1,785	459	159	272	204	88	212
Percentage of breakthrough cancer pain patients not receiving pharmacological treatment (%) [2]	18	9	21	21	29	25	20
Population of breakthrough cancer pain patients not receiving pharmacological therapy (000s)	**321**	**41**	**33**	**57**	**59**	**22**	**42**

BTP = breakthrough pain
1. Please refer to Table 8 for methodology behind Datamonitor's prevalence estimate for breakthrough cancer pain.
2. Datamonitor, *Stakeholder Insight: Cancer Pain* survey, 2009, Q5.2 (n=179). In order to determine the percentage of patients not receiving pharmacological treatment for their cancer pain, Datamonitor has subtracted the percentage of patients receiving pharmacological therapy from 100 (Figure 13).

Source: Various (see above) DATAMONITOR

Potential reasons for under-use of pharmacological treatments

Datamonitor's primary research indicates that pharmacological treatments which are able to relieve pain are currently under-used in patients with cancer pain, even among those patients who experience breakthrough pain. Through interviews with key opinion leaders, Datamonitor has identified several barriers which may be hindering use of analgesics in the cancer pain population. These barriers may relate to the patients themselves, healthcare professionals, or concerns surrounding the risk of tolerance and addiction associated with analgesics.

Under-reporting of pain by patients

Under-reporting of pain represents a key barrier to adequate pain relief among cancer patients. Patients may not report their cancer pain until asked by a physician or may delay telling anyone about it. For example, pre-intervention findings from a prospective, longitudinal clinical trial have shown that chemotherapy patients were reluctant to communicate their pain with healthcare professionals (Sun *et al.,* 2007).

There are several reasons why cancer patients may be hesitant to report the presence of cancer pain (Ward *et al.,* 2001; Ward *et al.,* 2000; Pargeon & Hailey, 1999; Ward *et al.,* 1993; Potter *et al.,* 2003), including the following:

- patients may regard pain as a normal and inevitable consequence of cancer.
- conversely, patients may fear that pain is indicative of advancing disease.
- fatalism about the possibility of achieving pain control.
- patients may feel that 'good' patients do not bother the physician by complaints of pain.
- patients may think that the treatment of cancer takes precedence and fear that reporting pain will distract physicians from treating the primary disease.
- patients may think they should only take analgesics if they have severe pain, thereby failing to report (and receive treatment for) mild to moderate cancer pain.
- fears of side effects of analgesics as well as drug tolerance and addiction.
- patients may think that taking analgesics means they have stopped fighting the cancer.

Key opinion leaders reiterate these patient-related reasons for under-reporting of pain:

> *"I think the patient themselves do not want to distract the oncologists from the disease. If they* [patients] *talk too much about the pain, they are afraid that the physician might change the treatment to something not as effective."*
>
> EU key opinion leader

> *"Because they* [patients] *are focused on the disease itself (cancer) and for them the pain is normal, they do not complain as much concerning the pain that they are experiencing."*
>
> EU key opinion leader

> *"There is perhaps a reluctance to report pain on behalf of the patient because they want their oncologist focused on treating the cancer, and perhaps patients might think pain is part of having cancer There are also*

fears that patients may have regarding the meaning of the pain, i.e. the worse the pain is, the more severe and deadly the cancer might be."

US key opinion leader

"Some patients may feel that if they say they have pain then they are admitting that their disease is progressing and they would prefer to say nothing and to act like it does not exist. For example, if you have a tooth pain, you do not go to the dentist very quickly…you hope that tomorrow it will be over. They [patients] *put their heads under the sand and they do not focus on the truth."*

EU key opinion leader

In July 2009, the National Pain Care Policy Act (HR 756/S660) passed the full House of Representatives and has since been introduced in the US Senate, where it has been accepted for inclusion as an amendment to healthcare reform legislation before the Health, Education, Labor and Pensions Committee. A key provision of the act is to develop and implement a national pain-management public outreach and awareness campaign (Brawley *et al.*, 2009). It is therefore hoped that successful implementation of this campaign will lead to an increase in the number of cancer patients experiencing pain to request treatment from their physician in the US. In a related vein, Datamonitor believes that pharmaceutical companies would benefit from working with patient advocacy groups in order to raise awareness among cancer patients and their families about the necessity of seeking pain management and communicate that effective analgesics are available for cancer pain. In doing so, it is important to convey to patients that it is part of the healthcare provider's role to provide pain relief and that, in most instances, pain relief can be achieved. This view is also expressed by an interviewed key opinion leader.

"I think we can extend education to patients. These people should be empowered to seek care from either generalists or specialist physicians to address that pain as a problem in its own right rather than just as a symptom of another problem."

US key opinion leader

Inadequate pain assessment by physicians

Pain experienced by cancer patients may go untreated due to physicians failing to address the issue of pain unless it is raised by the patient. Significant pain assessment and management deficiencies are consistently reported in the clinical

settings where cancer patients are seen (Fine *et al.,* 2004). According to the EPIC survey—the largest study to date into the prevalence, treatment and impact of cancer pain—almost a quarter (23%) of cancer patients report that their health care professional never or rarely asks them about their pain. Results of the EPIC survey also report that only 33% of cancer patients recall having had their pain assessed using a pain scale. The same proportion (33%) of patients interviewed also believed that their doctor does not have enough time to discuss their pain (EPIC Survey, Final Results presentation, 2007; www.paineurope.com), a view also expressed by an interviewed key opinion leader.

> *"The oncologists do not have time. They are very busy with patients and sometimes there are 40 patients to see in one afternoon. They are more focused on the disease and chemotherapy."*
>
> EU key opinion leader

Studies report that physicians themselves indicate pain assessment to be inadequate in cancer patients. For example, Von Roenn *et al.*'s (1993) survey of the attitudes of 897 physicians in the Eastern Cooperative Oncology Group found that 86% of physicians thought that most cancer patients did not receive enough pain medication and 76% felt that poor pain evaluation was the main barrier to effective pain management.

Interviewed key opinion leaders cite lack of pain education in medical training as the reason behind inadequate pain assessment in cancer patients:

> *"I think that all pain is under treated due to inadequate assessment, and that stems back to the lack of adequate education in the undergraduate medical years, and then that unfortunately persists on into postgraduate, residency training and then that persists even into ongoing practice."*
>
> US key opinion leader

> *"The physicians do not do an adequate job of assessing pain and that is due to lack of education and training, and also lack of time. Oncology physicians are obviously focused upon the cancer and treating it, so some of the pain and the other collateral issues may not get the attention that should be paid to them. Sometimes physicians do not assess, they relegate that job to physician extenders like nurse practitioners or physician assistants."*
>
> US key opinion leader

However, one key opinion leader believes that whether or not a patient is hospitalized is a key factor determining whether cancer pain is adequately assessed:

> *"I will separate the hospitalized* [cancer] *patients* [from non-hospitalized cancer patients]. *In hematology when we are giving any chemotherapy, the patient is hospitalized for a long time (minimum of one month), so in these patients I think that the pain is quite well recognized and treated, because the nurses are experienced in asking the patients. The problem is completely different for outpatients who come in just for chemotherapy. Among these* [non-hospitalized] *cases I think it is true that it* [cancer pain] *is underestimated.*
>
> EU key opinion leader

Furthermore, a retrospective review indicates that even when pain intensity assessments are conducted in palliative care settings, it is possible that there are inconsistencies in the way assessments are performed (Bruera *et al.,* 2005). Bruera and co-workers (2005) conducted a retrospective review of charts of patients who had received palliative care consultation and found that the agreement of pain intensity between the palliative care consultant, registered nurse and clinical nurse assistant was poor. The authors concluded that better education on how to perform standard pain intensity assessments is needed.

In a related vein, an interviewed key opinion leader believes that oncologists and nurses assess cancer pain less frequently than physicians specializing in pain and palliative medicine.

> *"I am afraid it is always the* [pain and palliative care] *specialists who are more worried about pain than others. If you look at what the nurses or physicians are doing day to day, it is not focused on pain and they do not practice regular assessments or systematic assessments. It is very strange, because they should do that because it is law, but they do not. Oncologists or nurses - they take arterial pressure, temperature and blood samples, but they forget the pain."*
>
> EU key opinion leader

Seemingly in recognition of the fact that poor pain assessment may be the result of inadequate knowledge on the part of physicians, a key provision of the National Pain Care Policy Act (HR 756/S660) in the US is to create an education and training grant program to improve health professionals' understanding and ability to assess and appropriately treat pain (Brawley *et al.,* 2009). Datamonitor believes that the

assessment and treatment of cancer pain in the six major non-US pharmaceutical markets (Japan, France, Germany, Italy, Spain and the UK) would benefit similar educational programs. As such, pharmaceutical companies could take advantage of this opportunity to play a pivotal role in promoting effective pain assessment.

Patient and physician concerns surrounding use of opioids

Both key opinion leaders interviewed by Datamonitor and published studies report that prevailing attitudes about pharmacological treatment options represents a key barrier to adequate treatment of cancer pain. Cancer patients (and their families) may harbor unfounded concerns about the risk of tolerance and dependence associated with opioids. Additionally, worries about unmanageable side effects can result in poor adherence to a prescribed analgesic regimen (Miaskowski *et al.*, 2001). In a study carried out by Radbruck *et al.* (2002), patients' and caregivers' fear of addiction to and concern about side effects of morphine were found to be among the major barriers to adequate pain relief in cancer patients in Germany. In addition, an internet survey by Simone *et al.* (2008) found 'fear of addiction' to be a reason for not taking analgesics for 79% of radiation oncology patients. Higher levels of concern about analgesic treatments have been found among those patients who are older, less educated and have low incomes (Ward *et al.*, 1993).

As a result of fears of tolerance, addiction and side effects associated with opioid use, cancer patients may either fail to report their pain to their physician, thereby remaining untreated, or may be reluctant to take pain medication that is prescribed. Key opinion leaders interviewed by Datamonitor support this view:

> *"I believe that sometimes the patients and their families fear the use of opioids, and so they prefer to say that their pain intensity is mild rather than moderate or severe, because they do not want to receive large amounts of opioids. I am sure that for example in the home care programs, in the outpatient setting, most of the drugs that we prescribe are not used."*
>
> EU key opinion leader

> *"The patient and their family are sometimes very afraid about opioids."*
>
> EU key opinion leader

> *"I think there is still an opioid phobia now. Just last week one patient said to me 'this is morphine and I do not want to increase the dose because I could get addicted' and it was very difficult. They* [patients] *are afraid of*

the drugs. The media also often mentions addiction and that does not help."

EU key opinion leader

It is possible that confusion in the terminology associated with addiction and physical dependence may contribute to patients' concerns about opioid use. Although important in considering opioid regimen in patients with non-malignant chronic pain (Nedeljkovic *et al.,* 2002), research has demonstrated that neither physical dependency nor addiction are significant problems in the management of cancer patients (Portenoy 1996).

In addition to concerns surrounding the side effects and risk of tolerance and dependence associated with opioids, research indicates that patient perceptions about the role of opioids in the treatment of cancer pain may also represent an important reason for under-use of pharmacological treatments. A qualitative, in-depth interview study found that patients with cancer interpreted the offer of morphine for pain relief as a signal that their health professional thought that they were dying because opioids were interventions used only as a 'last resort' (Reid *et al.,* 2008). Participants in the study rejected morphine and other opioids as analgesics because they were not ready to die, despite the pain experienced as a consequence. The authors of the study concluded that the idea among cancer patients that opioids represent a comfort measure for the dying and not legitimate analgesics may represent a greater barrier to their uptake than concerns about tolerance or addiction (Reid *et al.,* 2008).

Therefore, Datamonitor believes that increased patient education regarding analgesic treatment options is critical to improving outcomes for patients with cancer pain, a view shared by an interviewed key opinion leader:

"The [cancer pain patient] *population has to be informed regarding the correct use of drugs."*

EU key opinion leader

Concerns about the risks associated with opioid use are present not only among the patient population but also extend to healthcare professionals. Healthcare providers may be overly concerned about opiate toxicities (Grossman, 2004) and the regulation of controlled substances, and may fear patients becoming addicted or tolerant to analgesics. In this vein, fear of potential liability and censure by regulatory agencies for prescribing opioids among physicians in general practice may play another role in

the under-treatment of cancer pain (McCarberg & Barkin, 2001; NCCN, 2005). A key opinion leader concurs that physicians are fearful of prescribing opioids:

> *"Certainly there are fears among patients and their families but also fears among physicians about the possibility of addiction to opioid pain medications. There are fears among physicians of some of the law enforcement and regulatory issues that are attached to prescribing controlled substances and a lot of these fears are not based in reality, but primarily based in perception."*
>
> US key opinion leader

> *"People being wary* [of opioids] *to the point of not prescribing opioid drugs. To exclude use of them for those reasons is probably not right."*
>
> EU key opinion leader

Another key opinion leader reports that concerns surrounding prescribing of opioids are prevalent among general practitioners.

> *"Obviously the General Practitioners are really afraid concerning the use of morphine."*
>
> EU key opinion leader

It is therefore evident that in order to improve treatment rates among patients with cancer pain, improved physician training in cancer pain management is required, a view shared by an interviewed key opinion leader:

> *"My opinion is that it is absolutely necessary to do educational programs for physicians, because physicians that are not specialists in pain therapy and palliative care (i.e. the oncologists, the physicians working in internal medicine, the geriatricians), all these specialists need to have an improvement in their knowledge regarding the use of opioids or analgesics in neuropathic and non-neuropathic pain."*
>
> EU key opinion leader

Professional involvement

Cancer patients often present with a variety of symptoms, of which pain is only one. Thus, it may be necessary to treat cancer patients using a variety of different

strategies. Accordingly, throughout the course of treatment, a cancer patient will encounter many different healthcare professionals in a variety of settings. A multidisciplinary team (MDT) is a group of healthcare professionals who work together to review all relevant treatment options and develop an individual treatment plan for each cancer patient. This collaborative approach enables the team to make the most appropriate treatment and supportive care decisions for a patient while taking into account their individual preferences and circumstances.

The multidisciplinary team comprises healthcare professionals from a number of disciplines and may include oncologists, nurses, radiologists, surgeons, anesthetists, physiotherapists, occupational therapists, neurologists and hematologists. According to Simpson (2000), a multi-disciplinary approach by a coordinated team is needed so that pain management can be tailored to individual requirements and the need for crisis interventions can be reduced.

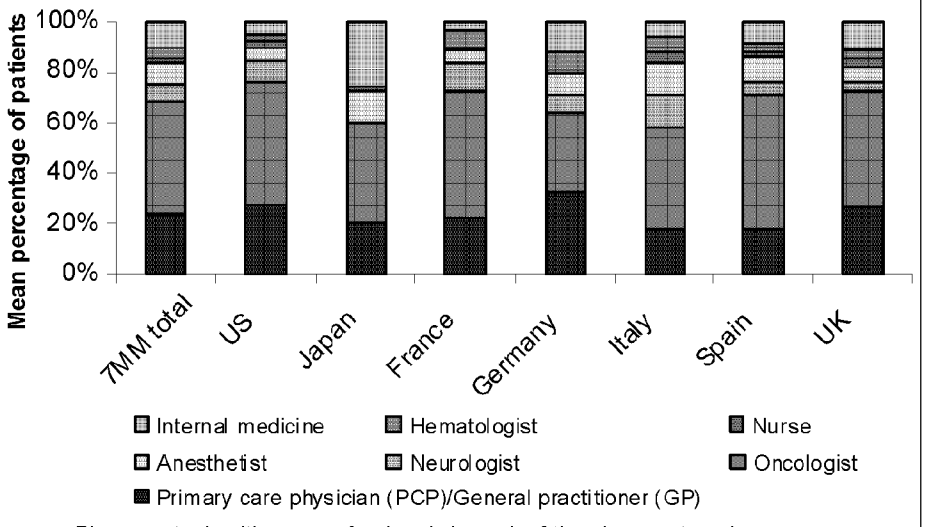
In recognition of the wide range of healthcare professionals who may be involved in the multidisciplinary team, Datamonitor's primary research survey sought to elucidate the healthcare professionals involved in the initiation and management of analgesic treatment in the cancer pain population. The findings of Datamonitor's survey indicate that across the seven major markets, oncologists initiate and manage analgesic treatment in the majority of cancer pain patients. Second to oncologists, primary care physicians (PCPs) also play a key role in the initiation and management of cancer pain. It is therefore important for pharmaceutical companies marketing analgesic treatments for cancer pain to target oncologists and PCPs. According to Datamonitor's primary research, non-specialists in palliative medicine or pain medicine are responsible for the initiation and management of analgesic treatment in the majority of patients with cancer pain.

Oncologists initiate analgesic treatment in the majority of cancer pain patients

Interviewed physicians across the seven major markets were asked to estimate the percentage of their cancer patients whose pain treatment is initiated by a range of healthcare professionals. Respondents were asked to consider all of their cancer pain patients, regardless of disease stage or pain severity.

Figure 31 presents the proportion of cancer pain patients whose analgesic treatment is initiated by each healthcare professional across the seven major markets in 2009.

Figure 31: Percentage of cancer pain patients whose analgesic treatment is initiated by each healthcare professional, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q2.1 (n=180) Datamonitor

DATAMONITOR

As can be seen in Figure 31, oncologists play the greatest role in initiating analgesic treatment for cancer pain. According to Datamonitor's survey, analgesic treatment is initiated by oncologists in an average of 45% of cancer pain patients across the seven major markets. Given that oncologists are the healthcare professionals responsible for treating the primary disease, cancer, it is unsurprising that oncologists also play the greatest role in initiating analgesia for pain caused by the cancer or its associated treatments (e.g. radiotherapy and chemotherapy), a point reiterated by an interviewed key opinion leader:

> *"That* [the predominance of oncologists] *is easy to answer because they* [oncologists] *are patients' attending doctors."*
>
> Japanese key opinion leader

The exception is to this trend is Germany, where PCPs play a marginally greater role than oncologists, initiating analgesia in, on average, 33% of cancer pain cases, compared to the 32% of cases in which treatment is initiated by oncologists.

Datamonitor's survey also indicates that PCPs play a key role in initiating pharmacological treatment for cancer pain. Across the seven major markets, PCPs initiate analgesic treatment in a mean 24% of cancer pain patients. In Japan, while oncologists initiate analgesic treatment in 39% of cancer pain patients, physicians specializing in internal medicine initiate analgesic treatment in an average 26% of patients. However, a Japanese key opinion leader interviewed by Datamonitor disagreed with the findings of Datamonitor's survey, reporting that 50% of cases of pain in cancer patients are managed by oncologists.

> *"I think this number* [of oncologists] *should be higher. Oncologists are the one who treat the patients, so I think 50% of the patients* [with pain] *are managed by their oncologists. Anesthesiologists and doctors who specialize in palliative care are also involved. That is about it."*
>
> Japanese key opinion leader

The same key opinion leader also reports that a multidisciplinary team rarely manages cancer in Japan.

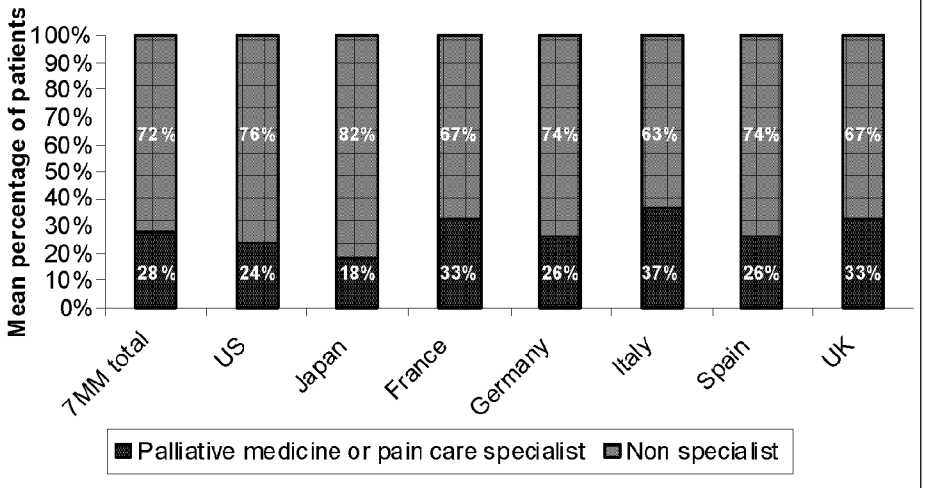
> *"That* [the involvement of a multidisciplinary team managing cancer] *is a very rare case in Japan"*
>
> Japanese key opinion leader

Analgesic treatment is predominantly initiated by non-specialists in palliative care or pain medicine

Healthcare professionals listed in Figure 31 may possess specialist expertise in palliative care or pain medicine. For example, once qualified, nurses may undertake specific training in palliative care or pain management.

Datamonitor's survey analyzed the proportion or healthcare professionals initiating analgesic treatment in cancer pain patients who were specialists in palliative medicine or pain management. Figure 32 presents the mean number of cancer pain patients across the seven major markets whose analgesia is initiated by specialists in palliative medicine/pain management specialists versus non-specialist physicians.

Figure 32: Percentage of cancer pain patients whose analgesic treatment is initiated by specialists in palliative medicine or pain medicine versus non-specialists, 2009



7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q2.1 (n=180) Datamonitor

DATAMONITOR

As seen in Figure 32, across the seven major markets, non-specialists in palliative medicine or pain care initiate analgesic treatment in the majority of cancer pain patients (72%). This finding is closely in line with results of the 2007 European EPIC survey in which 73% of patients reported never having been referred to a pain management specialist or a pain clinic about their cancer pain (EPIC Survey. Final Results presentation, 2007; www.paineurope.com).

Cancer pain treatment is largely managed by oncologists

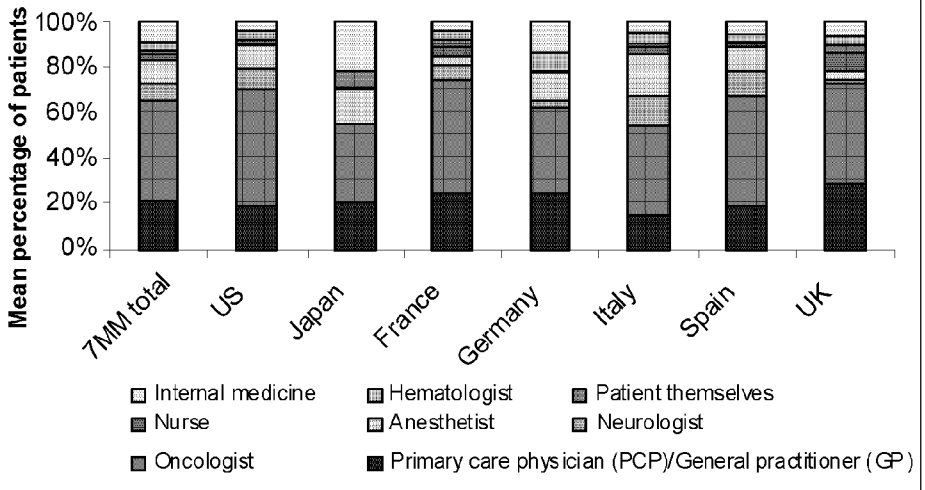
Analgesic treatment in cancer patients may not necessarily be managed by the same healthcare professional who initiates treatment. Furthermore, once analgesic treatment has been initiated, a proportion of patients may control their pain themselves through the use of patient-controlled analgesia (PCA). In a hospital setting, PCA involves an electronically controlled infusion pump that delivers a prescribed amount of intravenous analgesic to the patient when he or she activates a button. In some cases, the pump is set to deliver a small, constant flow of pain medication (Web MD, Pain Management: Patient-Controlled Analgesia, 2009; www.webmd.com). The primary advantage of PCA is the shortened interval between

patient-defined need to the time of actual analgesic administration, allowing for immediate relief of breakthrough cancer pain. However, some patients may be unwilling to use the PCA or be unable to do so due to physical disability or cognitive impairment.

Datamonitor's primary research survey sought to determine those healthcare professionals who are involved in the management of analgesic treatment in the cancer pain population. The survey also sought to determine the proportion of cancer pain patients using PCA. Interviewed physicians across the seven major markets were asked to estimate the percentage of their cancer patients whose pain treatment is managed by a range of healthcare professionals and the patient themselves. Respondents were asked to consider all of their cancer pain patients, regardless of disease stage or pain severity.

Figure 33 presents the proportion of cancer pain patients whose analgesic treatment is managed by each healthcare professional (and the patient themselves) across the seven major markets in 2009.

Figure 33: Percentage of cancer pain patients whose analgesic treatment is initiated by each healthcare professional, 2009



Please note: healthcare professionals in each of the above categories may specialize in palliative care/pain medicine

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q2.1 (n=180) Datamonitor

DATAMONITOR

In keeping with the trend observed relating to the initiation of cancer pain treatment, Datamonitor's primary research indicates that oncologists are the healthcare professionals responsible for managing cancer pain treatment in the majority of cases. Across the seven major markets, analgesic treatment is managed by oncologists in an average of 44.2% of cancer pain patients. This figure is closely in line with results of the 2007 EPIC survey which showed medical oncologists to be responsible for managing cancer pain in 42% of the 573 patients contacted (EPIC Survey. Final Results presentation, 2007; www.paineurope.com). According to Datamonitor's survey, the proportion of cancer pain patients whose pain is managed by oncologists is highest in the US (52%) and lowest in Germany (38%). According to a key opinion leader interviewed by Datamonitor, improvements in available treatments for cancer pain have resulted in fewer patients being referred to pain care specialists. As a result, oncologists now play a greater role in the management of cancer pain than was the case historically.

> *"In the past, patients with cancer-related pain would have been referred* [to pain care specialists] *because treatment was ineffective and pain physicians had a greater ability to perform interventional techniques. Nowadays, with some improvement in available treatments, the need for interventional treatment like that has decreased and the oncologists have been able to manage the patients as effectively as a trained pain physician."*
>
> EU key opinion leader

Since oncologists are the healthcare professionals most likely to initiate and manage analgesic treatment in cancer patients, Datamonitor recommends that companies marketing analgesics for cancer pain should direct their physician detailing efforts towards oncologists.

As can be seen in Figure 33, PCPs are second only to oncologists in the management of cancer pain. According to Datamonitor's survey, PCPs manage pain in an average of 21% of cancer patients across the seven major markets. Once again, this figure is in line with that of the EPIC survey which reports general/family practitioners to be responsible for managing cancer pain in 19% of the 573 patients contacted (EPIC Survey. Final Results presentation, 2007; www.paineurope.com). Although the percentage of cancer pain patients treated by PCPs is lowest in Italy (14%), an interviewed key opinion leader reports that PCPs in Italy are increasingly managing cancer pain.

> *"Until 1 or 2 years ago, no general practitioner was interested in treating cancer pain. The primary care physicians are starting just now to consider*

> *patients with pain, because they receive money from the healthcare system for every patient with pain, or every patient with terminal cancer. Most of them* [PCPs] *prescribe the same drugs that are prescribed by the oncologists or the pain therapy physicians. When the patient is discharged from the hospital they continue the prescription of the hospital physician. Only a small number of general practitioners in Italy are really able to prescribe a good analgesic therapy, a personalized analgesic therapy."*
>
> EU key opinion leader

A notable exception to the trend for PCPs to be the second most frequently mentioned healthcare professional managing cancer pain is in Japan, where physicians specializing in internal medicine manage analgesic treatment in an average of 22% of cancer pain patients, compared to PCPs who manage cancer pain in around 20% of patients.

Although oncologists and PCPs are responsible for managing cancer pain in the majority of patients, an interviewed key opinion leader believes that these healthcare professionals employ treatments that are outdated, compared to the treatments administered by pain specialists.

> *"Treatment of cancer pain now is largely provided by oncologists and primary care physicians with treatments that pain physicians would have used and have moved on from 10 or 15 years ago, so it is old fashioned. Maybe one example of that would be oncologists and palliative care physicians using ketamine in cancer pain treatment, which is a drug that we stopped using in anesthetic practice 10 years ago."*

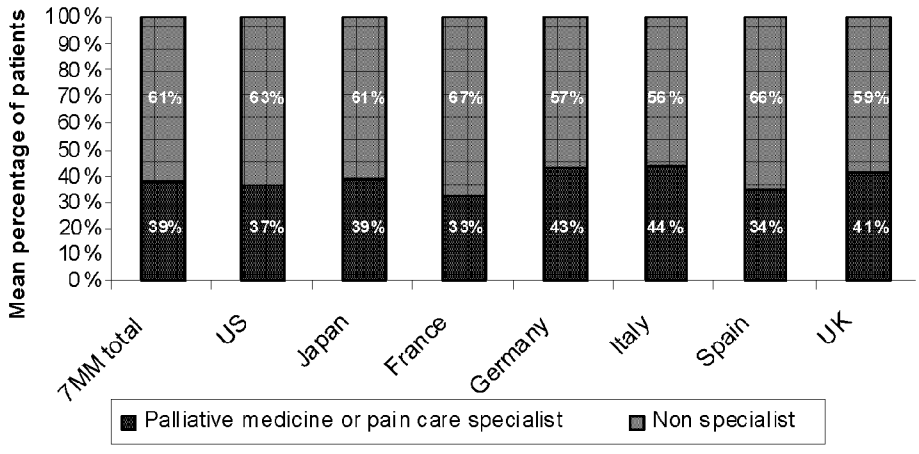
With regards to PCA, Datamonitor's primary research indicates that a mean 2.3% of patients manage their pain using this method across the seven major markets. Use of PCA is greatest in Japan, accounting for 6.3% of patients with all types of cancer pain. Conversely, the US records the lowest use of PCA, with just 0.3% of cancer patients managing their pain in 2009. An interviewed key opinion leader comments on the low use of PCA among the cancer pain population.

> *"It* [the number of patients using patient controlled analgesia] *would be a very small proportion; it would be way less than 5%. I think it* [PCA] *is more invasive and constraining for the patient to use it and there are cost implications with it as well."*
>
> EU key opinion leader

Non-specialists in palliative care or pain medicine typically manage analgesic treatment

Datamonitor's survey analyzed the proportion or healthcare professionals managing analgesic treatment in cancer pain patients who were specialists in palliative medicine or pain management. Figure 34 presents the mean number of cancer pain patients across the seven major markets whose analgesia is managed by specialists in palliative medicine/pain management specialists versus non-specialist physicians.

Figure 34: Percentage of cancer pain patients whose analgesic treatment is managed by specialists in palliative medicine or pain medicine versus non-specialists, 2009



7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q2.1(e) (n=180) Datamonitor

DATAMONITOR

As was the case for initiation of analgesic treatment (Figure 32), Datamonitor's primary research found that non-specialists in palliative medicine or pain care manage analgesic treatment in the majority of cancer pain patients (72%). However, it is worth noting that a greater proportion of specialist physicians manage (39%) (Figure 34) than initiate cancer pain analgesia (28%) (Figure 32).

CHAPTER 6 TREATMENT OPTIONS AND CLINICAL GUIDELINES

- *The key objectives of cancer pain management are to decrease pain and improve patient quality of life. Although effective pain management may include pharmacologic and non-pharmacologic measures, oral analgesic drugs form the mainstay of cancer pain treatment.*

- *There are a vast range of drugs on the market currently prescribed for the treatment of cancer pain. Key drug classes include non-steroidal anti-inflammatory drugs (NSAIDs) and opioids (both weak and strong). In addition, antidepressants and anticonvulsants are widely recognized as adjuvant treatments for difficult to treat pain syndromes associated with cancer, such as neuropathic pain.*

- *The three-step 'analgesic ladder' for the treatment of cancer pain, published by the World Health Organization (WHO), outlines the titration of non-opioid, opioid and adjuvant analgesics, alone or in combination, to meet the needs of the individual patient. The principles of this approach have formed the backbone of subsequently published clinical guidelines.*

- *Datamonitor's Stakeholder Insight 2009: Cancer Pain survey revealed that across the seven major markets, an average 80% of physicians adhere to guidelines issued by the WHO when treating patients for cancer pain. The proportion of US physicians following the guidelines of the WHO is substantially lower than in the other major markets, standing at 50% in 2009.*

- *The low adherence rate to WHO guidelines among US physicians may be attributable to lack of awareness as a result of inadequate undergraduate training in palliative care. Furthermore, perceived deficiencies in the guideline may prompt physicians to use alternative published guidelines for the management of cancer pain. Guidelines for the management of cancer pain have been published by several organizations in the US, including the American Pain Society, National Comprehensive Cancer Network (NCCN) and the Agency for Health Care Research and Quality (AHRQ).*

Treatment options

The basic principles of pain management are to decrease pain and improve quality of life, to do no further harm, to allow patients and carers choices, and to use resources as effectively as possible (Simpson, 2000). In relation to chronic cancer pain, a key goal of treatment is not simply pain relief, but also pain prevention (Jacox *et al.,* 1992; Cherny & Portenoy, 1994; Levy 1994; Twycross, 1994).

Although effective pain management may include pharmacologic and non-pharmacologic measures (Menefee & Monti, 2005; Pharo & Zhou, 2005), oral analgesic drugs remain the mainstay of cancer pain management.

Pharmacological treatment options

These is a vast range of drugs on the market currently used in the treatment of cancer pain, of which oral analgesics incorporating non-opioids, weak opioids and strong opioids are the mainstay. However, the variety of co-morbidities and types of pain experienced (including nociceptive, neuropathic and breakthrough pain) means that specific pharmacological treatments are not always suitable or totally effective in controlling an individual's pain. Thus, treatment of cancer pain often necessitates the addition of other drugs not primarily indicated for pain (adjuvants). Adjuvant drugs are valuable during all phases of pain management to enhance analgesic efficacy, treat concurrent symptoms, and provide independent analgesia for specific types of pain (National Cancer Institute, 2009; www.cancer.gov). Antidepressants and anticonvulsants are widely recognized as adjuvant treatments for difficult pain syndromes associated with cancer such as neuropathic and bone pain.

The key drug classes prescribed for the treatment of cancer pain are discussed in the following paragraphs.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) possess both analgesic and anti-inflammatory properties. In general, all NSAIDs exhibit a similar mechanism of action: the inhibition of cyclo-oxygenase (COX) activity, an enzyme required for the synthesis of prostaglandins—a hormone-like substance produced by the body that causes inflammation and pain. NSAIDs work by decreasing prostaglandin-induced pain and inflammation. However, because of differences in their mode of action, NSAIDs can be further divided into two key groups:

- traditional NSAIDs;
- cyclooxygenase (COX)-2 inhibitors.

Conventional NSAIDs (e.g. aspirin and ibuprofen) inhibit both COX-1 and COX-2 enzymes. COX-2 inhibitors, however, exhibit a greater selective inhibition of COX-2 than COX-1. COX-2 inhibitors were developed specifically to offer a new measure of safety in respect to the prevention of the gastrointestinal side effects that are common to COX-1 inhibitors. Indeed, as demonstrated by a systematic review of randomized controlled trials (Roelofs *et al.,* 2008), COX-2 inhibitors do possess a lower risk of gastrointestinal side effects when compared with the traditional NSAIDs. However, between 2004 and 2005, two of the marketed COX-2 inhibitors, Vioxx (rofecoxib; Merck & Co) and Bextra (valdecoxib; Pfizer) were withdrawn from the market due to an increased risk of adverse cardiovascular events in patients taking these medications. Celebrex (celecoxib; Pfizer) is still available for use, but should be used at the lowest possible dose (not to exceed 200mg twice daily) and with extreme caution in patients with existing cardiovascular disease (Celebrex prescribing information, 2009; http://pfizer.com).

The role of NSAIDs in the treatment of mild cancer pain has been well established either alone or in association with opioids (Mercadante, 2001). Indeed, the first step of the World Health Organization's three step analgesic ladder recommends the use of a non-opioid analgesic such as acetaminophen or a NSAID (WHO, Cancer Pain Relief, 1996; http://whqlibdoc.who.int). Due to the anti-inflammatory properties of NSAIDs, drugs belonging to this class are particularly beneficial in pain due to bone cancer or metastasis (International Association for the Study of Pain, 2009; www.iasp-pain.org).

As there is no clearly superior NSAID (McNicol *et al.,* 2004), the choice of NSAID should be based on the drug's toxicity profile. Among the older NSAIDs, ibuprofen seems to have the best combination of efficacy and tolerable side effects (Mercadante, 2001).

Opioids

Opioid receptors are located throughout the central nervous system (CNS), particularly at the point where nociceptors terminate at the spinal cord and on the pain neurons leading from the spinal cord to the brain. Opioid analgesics activate opioid receptors, particularly mu receptors, within the spinal cord dorsal horn and CNS, causing a decrease in neural activity.

Opioids are classified as agonists, mixed agonist-antagonists, or partial agonists by their activity at opioid receptors. Narcotic agonists achieve their analgesia through

their interaction with opiate receptors in the CNS, primarily the mu and kappa opioid receptors. There is some evidence to suggest that these agents also act at the delta opioid receptors. The mu receptor has been identified in the neural tissue of areas that are part of the body's descending pathway. Indeed, the analgesic potency of opioid agonists correlates directly with their affinity for the mu receptor (Opioid Receptors, 2008; www.opioids.com). Key side effects associated with opioid medications include: constipation, nausea and vomiting, sleepiness, cognitive impairment and respiratory depression. Furthermore, long-term use of opioids may lead to tolerance and physical dependence. Tolerance may be dealt with by increasing the dose, by changing the opioid (cross-tolerance is not complete), by changing the route or by adding other drugs (International Association for the Study of Pain, 2009; ww.iasp-pain.org).

For mild to moderate cancer pain, the second step of the World Health Organization's (WHO) analgesic ladder recommends the use of a weak opioid in combination with a non-opioid with or without an adjuvant. The third step of the ladder recommends use of a stronger opioid in combination with a non-opioid, with or without an adjuvant (World Health Organization, 1996; http://whqlibdoc.who.int). Weak opioids include codeine and tramadol, whereas strong opioids include morphine, diamorphine, fentanyl, buprenorphine, oxycodone and methadone.

Long-acting opioids (controlled release or slow release) are used for stable or baseline pain. They are usually administered twice daily by mouth. Conversely, fast and short-acting opioids are used for breakthrough or incident pain when needed (via oral, transmucosal or inhaled routes of administration) (International Association for the Study of Pain, 2008; www.iasp-pain.org).

Oral administration of opioids is preferred as it is effective, simple and less expensive than parenteral administration. Transdermal, subcutaneous or intravenous routes are necessary when patients are unable to take the opioid orally, for example due to vomiting or inability to swallow.

Opioid fixed-dose combinations

Combination analgesics combine two analgesics with different modes of action in a single tablet or capsule. A variety of combination analgesics are available. The most popular combinations consist of paracetamol (known as acetaminophen in the US) with weak opioids such as codeine, dihydrocodeine or dextropropoxyphene. Other examples of opioid fixed-dose combinations include the following:

- oxycodone and acetaminophen;

- oxycodone and aspirin;
- oxycodone and ibuprofen;
- hydrocodone and acetaminophen
- hydrocodone and ibuprofen.

Antidepressants

Antidepressant drugs—encompassing both tricyclics and serotonin and norepinephrine reuptake inhibitors (SNRIs)—are prescribed as adjuvant treatments for patients with cancer pain. Antidepressants are though to exert an analgesic effect by increasing levels of epinephrine and serotonin at nerve endings and thereby strengthening the system that inhibits pain transmission down the spine (Covington, 2001). Cancer patients with neuropathic pain characterized by continuous dysesthesias are generally believed to be the most likely to benefit from antidepressant management (National Cancer Institute, 2009; www.cancer.gov).

Tricyclic antidepressants have been shown to be effective for the treatment of neuropathic pain syndromes (Magni *et al.,* 1987; Parnerai *et al.,* 1991) and are generally considered first-line therapy for many neuropathic pain syndromes (Portenoy & Frager, 1999; Guay, 2001). However, a randomized, placebo-controlled study of amitriptyline for neuropathic pain in cancer patients found only slight analgesic benefit with slightly worse adverse effects (Mercadante *et al.,* 2002).

A key advantage of prescribing antidepressants for neuropathic pain is their ability to ameliorate co-morbid depression. According to the International Association for the Study of Pain, if a patient experiences both neuropathic pain and depression, a drug should be selected that can relieve both (e.g. dual-action antidepressants that inhibit both norepinephrine and serotonin) (International Association for the Study of Pain, 2009; www.iasp-pain.org).

Common side effects of antidepressants include constipation, dry mouth, blurred vision, cognitive changes, tachycardia and urinary retention (National Cancer Institute, 2009, www.cancer.gov).

Anticonvulsants

Like antidepressants, anticonvulsant drugs are prescribed as adjuvant treatments in the management of cancer pain. Anticonvulsants have an established role in the treatment of neuropathic pain, with Lyrica (pregabalin; Pfizer), Neurontin (gabapentin;

Pfizer) and Tegretol (carbamazepine; Novartis) each indicated for neuropathic pain conditions. However, to date, no anticonvulsant drug possesses a specific indication for neuropathic cancer pain. According to Bruera & Ripamonti (1993), anticonvulsants such as gabapentin, carbamazepine and phenytoin are most frequently used for the management of neuropathic pain characterized by lancinating sensations.

Although clinical experience with carbamazepine in the treatment of neuropathic pain is extensive, use of the drug is limited in the cancer population due to concerns that it causes bone marrow suppression, in particular leucopenia (National Cancer Institute, 2009; www.cancer.gov). Several published studies report gabapentin to be an efficacious treatment in the management of neuropathic pain associated with cancer and its treatment (Caraceni *et al.,* 2001; Chandler & Williams, 2000; Caraceni *et al.,* 1999; Oneschuk & al-Shari, 2003; Caraceni *et al.,* 2004; Ross *et al.,* 2005). A randomized open-label trial of gabapentin combined with an opioid (n=38) versus an opioid alone (n=37) for the management of neuropathic cancer pain suggests that the combination group achieved superior relief than those receiving opioid monotherapy (Keskinbora *et al.,* 2007).

Side effects of anticonvulsant drugs vary widely, but include fatigue, nausea and vomiting. In addition, anticonvulsants often lead to cognitive and behavioral side effects including impaired attention, mood depression, anxiety and irritability (Nadkarni & Devinsky, 2005).

Other pharmaceutical treatment options

In addition to NSAIDS, opioids, antidepressants and anticonvulsants, several additional pharmacological treatments are also prescribed for the management of cancer pain. These are described below.

Corticosteroids

Corticosteroids are potent anti-inflammatory agents that are widely used to treat inflammatory conditions. Drugs belonging to this class are prescribed as adjuvant analgesics for cancer pain of bone, visceral and neuropathic origin (National Cancer Institute, 2009; www.cancer.gov). They can be useful in pain due to edema (e.g. in the brain, spinal cord or liver) and can also alleviate nausea and increase mood and appetite (International Association for the Study of Pain, 2009; www.iasp-pain.org).

Although corticosteroids are widely accepted in the treatment of cancer pain (mostly via the oral route) available data remain inadequate for definitive conclusions

regarding efficacy and dosing guidelines (Lussier *et al.,* 2004; Guay, 2001; Wooldridge *et al.,* 2001).

Adverse effects of corticosteroids include neuropsychiatric syndromes, gastrointestinal disturbances, proximal myopathy, hyperglycemia, aseptic necrosis, capillary fragility and immunosuppression. The risk of adverse effects increases with the duration of use and, as such, use is frequently restricted to patients with a limited life expectancy (National Cancer Institute, 2009; www.cancer.gov).

Ketamine

Ketamine is an NMDA (N-methyl-D-aspartate) receptor antagonist that has been used in subcutaneous or intravenous infusions to alleviate opioid-induced hyperalgesia and tolerance. Agents that block the activity of NMDA receptors are helpful in treating poorly responsive pain syndromes, especially neuropathic pain, and the addition of ketamine to opioid therapy has been shown to be beneficial in chronic pain (Mercadante and Portenoy 2001). Although ketamine can be administered by mouth, its oral bioavailability is low and variable (International Association for the Study of Pain, 2009; www.iasp-pain.org).

Bisphosphonates

Bisphosphonates are derived from naturally occurring pyrophosphate and were discovered over 3 decades ago during investigations into the absence of calcification in soft tissue. Although these antiresorptive agents are used both in the prevention and treatment of osteoporosis, they also play a role in the management of bone pain as well as the prevention of skeletal complications in patients with metastatic bone cancer (Guay, 2001; Ripamonti & Fulfaro, 2000; McDonnell *et al.,* 2001; Rodrigues *et al.,* 2004). Please note that use of bisphosphonate drugs was not examined in Datamonitor's physician survey.

Treatment guidelines

Treatment guidelines shape how a physician chooses to treat a disease, and are therefore important to understanding prescribing trends. Several guidelines are available for the treatment of cancer pain, including those published by the following organizations:

- World Health Organization;
- American Pain Society;

- National Comprehensive Cancer Network;
- European Society for Medical Oncology;
- Scottish Intercollegiate Guidelines Network;
- Japanese Society for Palliative Medicine;
- Agency for Healthcare Research and Quality.

Datamonitor's primary research demonstrates that the treatment guidelines established by the World Health Organization (WHO) are widely accepted and adhered to by the majority of physicians treating cancer pain in the seven major markets (the US, Japan, France, Germany, Italy, Spain and the UK).

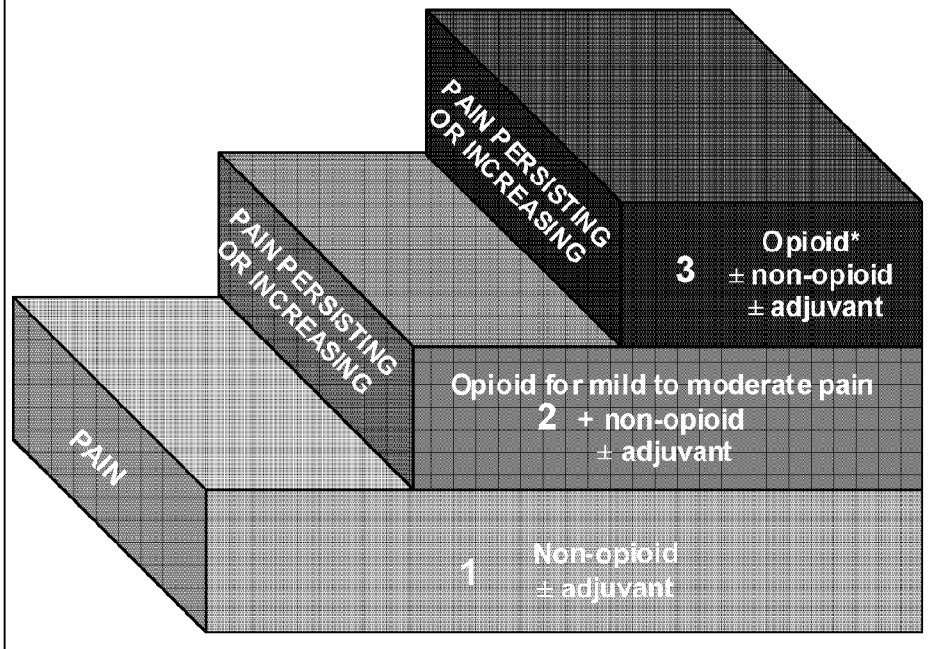
The World Health Organization's three-step 'analgesic ladder'

In 1986, the WHO published analgesic guidelines for the treatment of cancer pain based on a three-step 'treatment ladder' and practical recommendations (WHO, Cancer Pain Relief, 1996; http://whqlibdoc.who.int). The guidelines aim to achieve a pain-free state with minimal side effects, based on the principles of: (1) by mouth; (2) by the clock; (3) by the ladder; (4) for the individual; and (5) attention to detail

The WHO's analgesic ladder outlines the titration of non-opioid, opioid and adjuvant analgesics, alone or in combination, to meet the needs of the individual patient. The first step recommends the use of a non-opioid analgesic, the second a weak opioid for mild to moderate pain and the third step a stronger opioid for moderate to severe pain. Importantly, only one drug from each of the groups should be used at the same time (WHO, Cancer Pain Relief, 1996; http://whqlibdoc.who.int).

The sequential use of drugs for the treatment of cancer pain, as recommended by the 'three-step analgesic ladder' of the WHO, is illustrated in Figure 35.

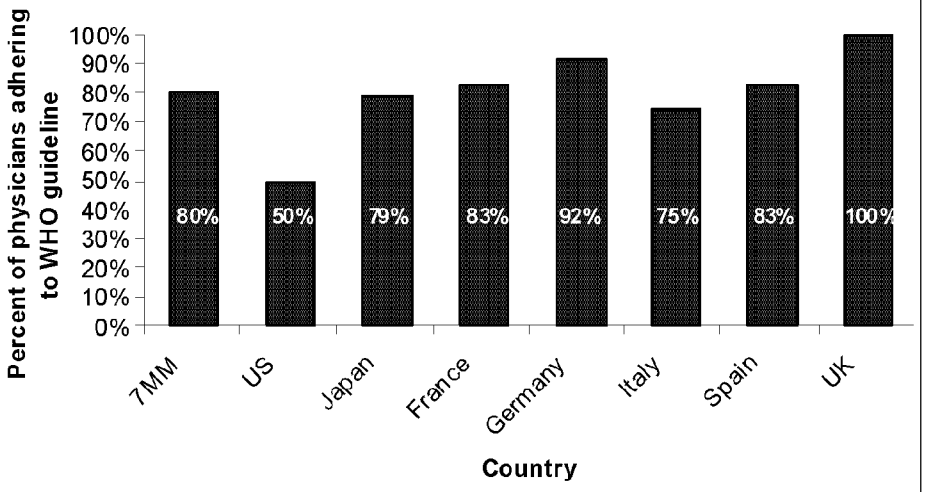
Figure 35: World Health Organization's three-step analgesic ladder



Source: World Health Organization, 1996, http://whqlibdoc.who.int DATAMONITOR

Physicians in each of the seven major markets were asked to report whether they adhered to the WHO's three-step 'analgesic ladder' approach when treating patients with cancer pain. Figure 36 presents the mean percentage of physicians who adhere to the guidelines of the WHO in each of the seven major markets.

Figure 36: Percentage of physicians adhering to World Health Organization guideline, by country, 2009



WHO = World Health Organization

7MM = US, Japan, France, Germany, Italy, Spain and the UK

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q6.1 (n=180)

DATAMONITOR

Although the three-step analgesic ladder was originally published in 1986, results of Datamonitor's primary research (Figure 36) demonstrate that the WHO method of treating cancer pain continues to play a key role across the seven major markets. An average of 80% of physicians across the seven major markets adhere to the guidelines issued by the WHO when treating patients for cancer pain, with adherence rates ranging from 50% (US) to 100% (UK).

Only 50% of US physicians adhere to WHO cancer pain guidelines

According to Datamonitor's primary research, the proportion of US physicians following the guidelines of the WHO is substantially lower than in the other major markets, standing at 50% in 2009. The low adherence rate to WHO guidelines among US physicians may be attributable to lack of awareness as a result of inadequate undergraduate training in palliative care. It may also be linked to perceived

deficiencies in the guideline, prompting physicians to use alternative published guidelines for the management of cancer pain.

Inadequate palliative care training may have led to limited awareness of WHO analgesic ladder

Firstly, it is possible to speculate that not all US-based physicians may be aware of the WHO guidelines. Inadequate undergraduate training in all aspects of palliative care has been well documented (Billings & Block, 1997). For example, a study of 81 physician trainees found that few were familiar with the stepwise progression of analgesic selection outlined in the WHO guidelines (Mortimer & Bartlett, 1997). Furthermore, according to a telephone survey of associate deans for medical education, 67% reported that insufficient time is currently given to palliative care in the undergraduate medical curriculum in the US (Sullivan *et al.,* 2004).

Perceived deficiencies of WHO guidelines may prompt use of alternative guidelines in the US

A second potential reason for the low adherence rate to the WHO guidelines among US physicians is the perceived deficiencies of the guidelines. A key problem identified with the use of the ladder is the treatment of bone pain, where some physicians believe that the second step is useless and progress should be rapidly made to the third step, as the patients' condition dictates (Miguel, 2000). Some experts also find the analgesic ladder too simplistic as it does not address 'total pain' (Breivik, 2002). A US-based interviewed key opinion leader reports that treatment approaches employed in specialist pain centers are more complex than the approach advocated by the WHO.

> *"In our practice (we are a subspecialist group), that* [the WHO analgesic ladder] *is very elementary and I guess we use it conceptually as a foundational background but our approaches tend to be much more complex than just the simple three-step ladder."*
>
> US key opinion leader

However, the most important deficiency in the ladder is that it does not address treatment of those patients who have failed to achieve adequate pain relief or have developed undesirable side effects with oral or transdermal drugs. The change of route of administration or the use of alternative opioids is an option but some physicians recommend the addition of a fourth 'interventional' step to the ladder (Miguel, 2000). The fourth step would include the use of nerve blocks, spinal administration of local anesthetics, opioids, alpha-2-agonists, spinal cord stimulation

and surgical interventions. These interventional options can be used as sole agents or as useful adjuncts to supplement analgesia provided by opioids, thus decreasing opioid dose requirements and side effects (Miguel, 2000).

More recent guidelines for cancer pain treatment, such as those of the National Comprehensive Cancer Network (NCCN) (Benedetti *et al.,* 2000), may provide a more complete set of guidelines than the WHO. The NCCN guidelines cover initial assessment of pain, treatment of the pain, reassessment and subsequent strategies including reviewing opioid titration, cause of the pain, non-medical therapies and psychological support. Emphasis is placed upon continuous reviews of treatment to ensure pain has not increased and side effects are manageable. Further to the guidelines of the NCCN, guidelines for the management of cancer pain have been published by several organizations in the US including the American Pain Society APS, 2006; www.ampainsoc.org), and the Agency for Health Care Research and Quality (AHRQ).

In view of the deficiencies of the WHO three-step analgesic ladder reported by some commentators, it is possible that US physicians are electing to use alternative cancer pain guidelines available in the US, such as those published by the NCCN, APS and AHRQ, thereby accounting for the relatively low rate of adherence to the WHO approach in the US. An interviewed key opinion leader concurs that the cancer pain guidelines of the WHO are outdated.

> *"The opinion in the cancer pain field that the WHO ladder is probably a little bit antiquated and should be thought about being changed, although nobody has got anything to replace it with just yet. There is merit in a simply system but it perhaps needs to catch up with the changes and developments that have happened over the last 20 years in cancer pain management."*
>
> EU key opinion leader

Adherence to WHO guidelines is highest among UK-based physicians

Compared to the US, EU-based physicians report greater adherence to WHO cancer pain guidelines. According to Datamonitor's primary research, a mean 86% of physicians across the 5EU (France, Germany, Italy, Spain and the UK) adhere to the guidelines published by the WHO when treating patients for cancer pain. A likely reason for this is the fact that clinical recommendations of the European Society for Medical Oncology are based upon the WHO's three-step analgesic ladder (Jost & Roila, 2008).

Significantly, 100% of UK-based physicians surveyed by Datamonitor report the highest level of adherence to the WHO three-step analgesic ladder in 2009. Datamonitor believes that this high adherence rate reflects the absence of guidelines published by the National Institute of Health and Clinical Excellence (NICE) in the UK.

American Pain Society

The American Pain Society's (APS') 'Guidelines for the management of cancer pain in adults and children' was published in 2005 (Miaskowski *et al.,* 2005). Analgesic medications recommended in the APS guidelines for cancer patients include hydrocodone and acetaminophen and oxycodone with acetaminophen. For the treatment of breakthrough cancer pain, the APS recommends administering a long-acting opioid on an around-the-clock basis, along with an immediate-release opioid to be used on an as-needed basis. The guidelines state that meperidine should not be used in the management of chronic cancer pain.

European Society for Medical Oncology

Clinical recommendations published by the European Society for Medical Oncology (ESMO) address the basic management of cancer pain using the step-wise escalation approach of the WHO (Jost, Roila; ESMO Guidelines Working Group; 2009). ESMO advises that all patients should receive around the clock dosing with provision of a 'breakthrough dose' to manage transient exacerbations of pain. For the treatment of neuropathic pain, non-opioid and opioid analgesics may be combined with antidepressive or neuroleptic psychoactive drugs or anti-epileptic drugs. Opioid doses should be titrated to take effect as rapidly as possible. The recommendations report that in the case of refractory pain at the end of life, sedation may be the only therapeutic option capable of providing adequate pain relief.

Scottish Intercollegiate Guidelines Network

In the absence of guidelines from NICE, guidelines published by the Scottish Intercollegiate Guidelines Network (SIGN) represent the key UK guidelines for the treatment of cancer pain in adults (SIGN, 2008; www.sign.ac.uk). The guidelines, published in November 2008, state that the principles outlines in the WHO's cancer pain relief program should be followed when treating pain in patients with cancer. All patients with moderate to severe cancer pain, regardless of etiology, should receive a trial dose of opioid analgesia.

In terms of step one of the WHO analgesic ladder, the SIGN advises that patients at all stages of the WHO analgesic ladder should be prescribed paracetamol and/or a non-steroidal anti-inflammatory drug unless contraindicated. Patients with neuropathic pain should be prescribed either a tricyclic antidepressant (e.g. amitriptyline or imipramine) or anticonvulsant (e.g. gabapentin, carbamazepine or phyenytoin) with careful monitoring of side effects. The SIGN does not recommend Cannabinoids for the treatment of cancer pain. At step two of the analgesic ladder, the network states that for the treatment of mild to moderate cancer pain, weak opioids such as codeine should be prescribed in combination with a non-opioid analgesic. Oral morphine is recommended as first-line treatment for severe cancer pain (step three of the analgesic ladder). Diamorphine is recommended as first-line subcutaneous therapy to treat severe cancer pain. The oral route should be used for administration of opioids, if practical and feasible. The SIGN advises that when using oral morphine for breakthrough pain, the dose should be one sixth of the around the clock morphine dose and should be increased appropriately whenever the around the clock dose is increased (SIGN, 2009; www.sign.ac.uk).

Japanese Society for Palliative Medicine

The Japanese Society for Palliative Medicine established guidelines for the clinical practice of cancer pain management supported by evidence-based medicine in 1999. As summarized by an interviewed key opinion leader, these guidelines are grounded in the principles of the WHO's three-step analgesic ladder.

> *"Based on WHO, the Japanese society of palliative medicine has created guideline for specifically for Japanese people. However, this is pretty much the same as WHO's guideline. I believe these two are the major ones in Japan."*
>
> Japanese key opinion leader

> *"WHO style is widely used in Japan. So this is the very base of our practice."*
>
> Japanese key opinion leader

CHAPTER 7 TREATMENT TRENDS

- *According to results of Datamonitor's primary research survey, the proportion of patients with chronic neuropathic and non-neuropathic cancer pain receiving the most commonly prescribed first-line drug treatment increases with pain severity (mild, moderate and severe). As such, physicians select from the fewest first-line drug regimens when treating patients with severe cancer pain.*

- *In line with recommendations provided by the World Health Organization, Datamonitor's primary research survey found that NSAIDs feature heavily the first-line drug regimen for mild cancer pain (both neuropathic and non-neuropathic).*

- *A sizeable proportion of patients with mild chronic neuropathic cancer pain and mild chronic non-neuropathic cancer pain receive an opioid as part of the most commonly prescribed first-line drug regimen for this subtype of cancer pain. It is possible that physicians may prescribe opioids for mild cancer pain in anticipation of the pain increasing in intensity.*

- *Opioids represent the predominant drug class contained within the most commonly prescribed first-line drug regimen for moderate and severe non-neuropathic cancer pain. Across the seven major markets, fentanyl and oxycodone are the most commonly prescribed first-line opioids for the management of moderate non-neuropathic cancer pain. By comparison, morphine represents the most commonly prescribed first-line opioid for the management of severe non-neuropathic cancer pain across the seven major markets.*

- *The proportion of chronic cancer pain patients progressing from first to second-line therapy steadily increases with pain intensity. Across the seven major markets, 46% of patients with severe, chronic neuropathic cancer pain and to 44% of patients with severe, chronic, non-neuropathic cancer pain progress to second-line analgesic treatment. Therefore, patients with severe cancer pain represent a target patient group to companies marketing analgesics.*

- *Almost one third (32%) of patients with breakthrough cancer pain across the seven major markets fail on first-line analgesic treatment and progress to second-line treatment. This suggests that breakthrough cancer pain is well-managed by first-line treatments for around 68% of patients. Other than failure to achieve pain relief, slower than required onset of action is the most important factor considered by physicians when progressing patients with breakthrough cancer pain to second line therapy.*

Trends in first-line treatment

Physicians surveyed by Datamonitor were asked to select the first-line drug regimen that they would most commonly prescribe to cancer patients with each subtype of cancer pain: neuropathic, non-neuropathic (split by severity) and breakthrough pain. Physicians were also asked to estimate the proportion of patients that they would prescribe their most commonly prescribed drug regimen to.

The proportion of patients receiving the most commonly prescribed first-line drug therapy increases with pain severity

Physicians treating cancer pain have a broad array of pharmacological treatment options from which to select, including NSAIDs, opioids (weak and strong), antidepressants, anticonvulsants and corticosteroids. The availability of a broad range of drugs means that, depending on the needs of an individual patient, physicians may select a first-line drug regimen from several drug regimens which are regarded as first-line treatment.

Datamonitor's *Stakeholder Insight 2009: Cancer Pain* survey sought to determine the proportion of patients with each subtype of cancer pain receiving the most commonly prescribed first-line drug regimen in each country. According to data gathered from 180 physicians across the seven major markets, the proportion of patients with chronic neuropathic and non-neuropathic cancer pain receiving the most commonly prescribed first-line drug treatment increases with pain severity (mild, moderate and severe). As such, physicians select from fewer first-line drug regimens when treating patients with severe cancer pain, compared to patients with mild and moderate cancer pain severities.

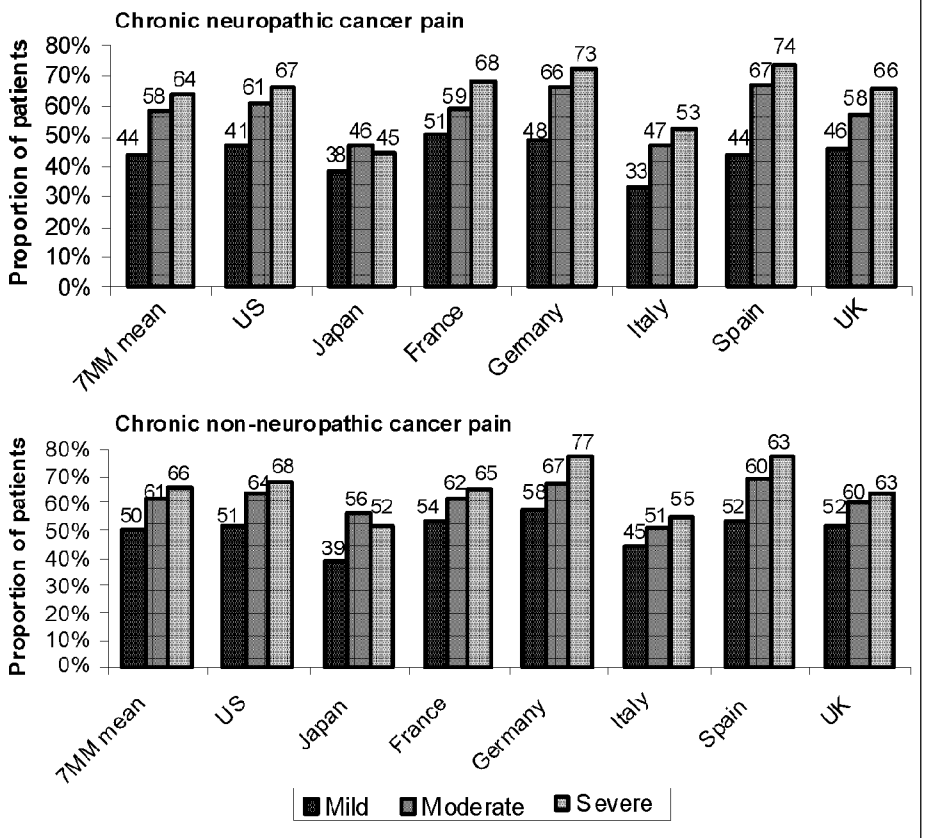
Chronic neuropathic and non-neuropathic cancer pain

Figure 37 presents the proportion of patients with each severity of chronic neuropathic and non-neuropathic cancer pain (mild, moderate and severe) receiving the most commonly prescribed first-line drug regimen for their pain across the seven major markets.

As seen in Figure 37, the mean proportion of patients receiving the most commonly prescribed first-line drug regimen for both chronic neuropathic and non-neuropathic cancer pain increases with pain severity (mild, moderate, severe). (However, a notable exception to this trend is Japan, where a smaller proportion of patients with

severe than moderate neuropathic and non-neuropathic cancer pain receive the most commonly prescribed first-line drug regimen).

Figure 37: Proportion of patients receiving the most commonly prescribed first-line drug regimen for chronic neuropathic and non-neuropathic cancer pain, by severity, across the seven major markets, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q3.2 (n=175), Q3.3 (n= 178), Q3.4 (n = 177), Q4.2 (n=179), Q4.3 (n= 179), Q4.4 (n = 177).

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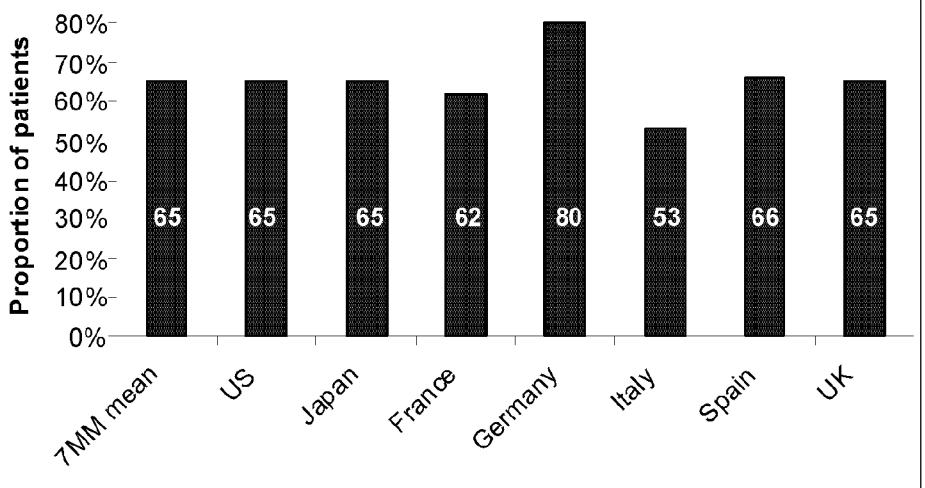
The finding that across the six major pharmaceutical markets (US, France, Germany, Italy, Spain and the UK), the proportion of patients receiving the most commonly prescribed first-line drug regimen increases with pain severity indicates that physicians employ a larger number of first-line drug regimens when treating mild cancer pain patients compared to severe cancer pain patients. As such, it appears

that physicians' confidence in selecting the appropriate first-line drug regimen increases in line with the severity of cancer pain.

Breakthrough cancer pain

Figure 38 presents the proportion of patients with breakthrough cancer pain receiving the most commonly prescribed first-line drug regimen across each of the seven major markets.

Figure 38: Proportion of patients receiving the most commonly prescribed first-line drug regimen for breakthrough cancer pain across the seven major markets, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q5.3 (n=179).

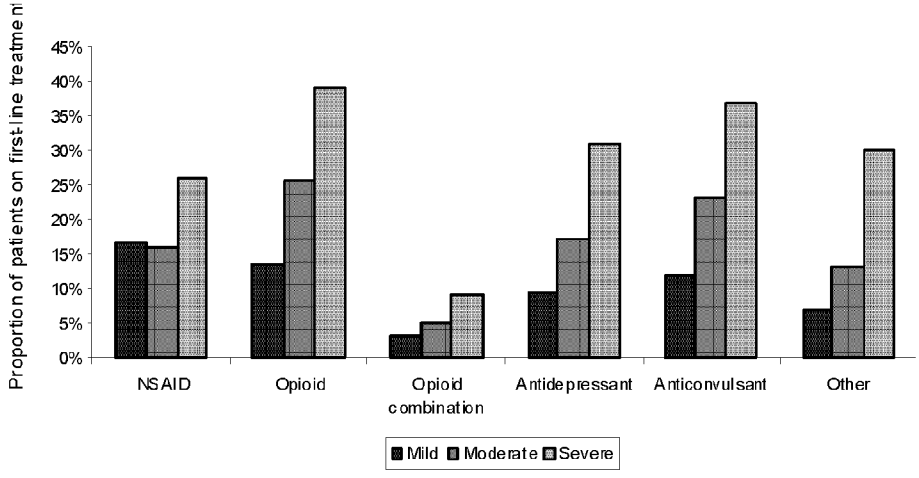
DATAMONITOR

According to results of Datamonitor's primary research survey, an average 65% of patients with breakthrough cancer pain receive the most commonly prescribed first-line regimen for this subtype of pain across the seven major markets. Therefore, 35% of patients with breakthrough cancer pain receive treatments with first-line drug regimens, which are not regarded as the most commonly prescribed. As seen in Figure 38, 80% of patients in Germany receive the most commonly prescribed first-line regimen for breakthrough pain. This indicates that physicians in Germany select from a smaller range of first-line treatment regimens than physicians in the remaining six major pharmaceutical markets when treating patients with breakthrough cancer pain.

Chronic neuropathic cancer pain

Figure 39 illustrates the proportion of patients receiving the most commonly prescribed first line treatment regimen split by class. The total percentage of patients receiving these classes as first line treatment will be larger to take into consideration other potential treatment regimens used. Please note that these other regimens were not examined in the survey.

Figure 39: Proportion of patients with chronic neuropathic cancer pain receiving each drug class as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



NSAIDS = non-steroidal anti-inflammatory drugs

Others include: corticosteroids, antispasmodics, cannabinoids, topical local anesthetics, ketamine, capsaicin and lidocaine

Seven major markets = US, Japan, France, Germany, Italy, Spain and the UK

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q3.2 (n=175), Q3.3 (n= 178), Q3.4 (n = 177). DATAMONITOR

Datamonitor's primary research identified the following key trends in relation to the most commonly prescribed first-line drug regimen for chronic, neuropathic cancer pain:

- NSAIDs represent the predominant drug class contained within the most commonly prescribed first-line drug regimen for patients with mild, chronic neuropathic cancer pain;

- A sizeable proportion of patients with mild, chronic neuropathic cancer pain receive an opioid as part of the most commonly prescribed first-line drug regimen for this subtype of cancer pain. It is possible that physicians may prescribe opioids for mild neuropathic cancer pain in anticipation of the pain increasing in intensity;
- Opioids represent the predominant drug class contained within the most commonly prescribed first-line regimen for moderate and severe chronic neuropathic cancer pain. Opioid combinations rarely constitute part of the most commonly prescribed first-line drug regimen for chronic, neuropathic cancer pain;
- For the treatment of moderate and severe chronic neuropathic cancer pain, corticosteroids are the most frequently prescribed drugs within the drug classes categorized as 'other'.

Although NSAIDs are frequently contained within the most commonly prescribed first-line drug regiment for patients with mild, chronic neuropathic cancer pain, published research indicates that NSAIDS possess limited utility in the management of neuropathic pain (Max *et al.* 1998). Additionally, a key opinion leader states that due to the risk of adverse events, NSAIDs are not used to treat pain in patients with hematological cancers.

> *"We do not use anti-inflammatory drugs, because as hematologists we know that we have affects like thrombocytopenia, neutropenia so usually we do not use it."*
>
> EU key opinion leader

One EU-based key opinion leader reports opioids to be the most commonly prescribed drugs for the management of neuropathic cancer pain, although believes their use to be an outdated prescribing practice.

> *"It* [first-line treatment for severe, chronic neuropathic cancer pain] *would be an opioid and in almost all cases that is actually a rather poor reflection on our treatment of these patients that we would utilize out dated treatments such as those."*
>
> EU key opinion leader

Neuropathic pain often co-exists with non-neuropathic pain. Therefore, the more dominant use of opioid drugs over traditional treatments for neuropathic pain (i.e. antidepressants and anticonvulsants) as part of the most commonly prescribed first-

line drug regimen may reflect the fact that a proportion of the patients treated by surveyed physicians experience mixed pain syndromes. In keeping with this view, an interviewed key opinion leader believes that only a minority of cancer patients present with exclusively neuropathic pain.

> *"I believe that only a minority* [of cancer pain patients] *have real neuropathic pain. Sometimes there are mixed forms of neuropathic plus somatic pain, but the* [prevalence of] *pure neuropathic pain is no more than 30%."*
>
> EU key opinion leader

According to several key opinion leaders, antidepressants and anticonvulsants are prescribed in conjunction with opioids.

> *"For moderate neuropathic pain usually we use gabapentin and sometimes, if it is not enough we add clonazepam. It is a combination of gabapentin and clonazepam."*
>
> EU key opinion leader

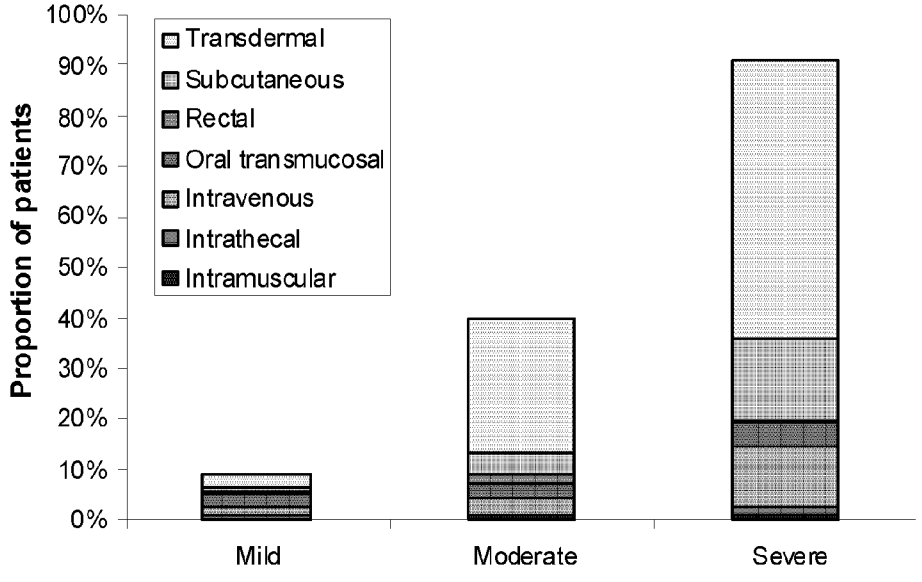
> *"For moderate* [neuropathic cancer] *pain we might also simultaneously start duloxetine, Cymbalta. There are some physicians that might at that point go to an opioid in addition, not as a single agent, but as part of a combination."*
>
> US key opinion leader

> *"I think there may be a tendency to add in an anticonvulsant such as pregabalin or some opioid for moderate neuropathic cancer pain."*
>
> EU key opinion leader

Figure 40 illustrates the proportion of patients receiving the most commonly prescribed first line treatment regimen split by formulation.

As seen in Figure 40, the proportion of patients receiving transdermal, subcutaneous and intravenous opioid formulations as part of the most commonly prescribed first-line drug regimen increases in accordance with severity of chronic neuropathic cancer pain experienced.

Figure 40: Proportion of patients with chronic neuropathic cancer pain receiving each opioid formulation (excluding oral ingested) as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



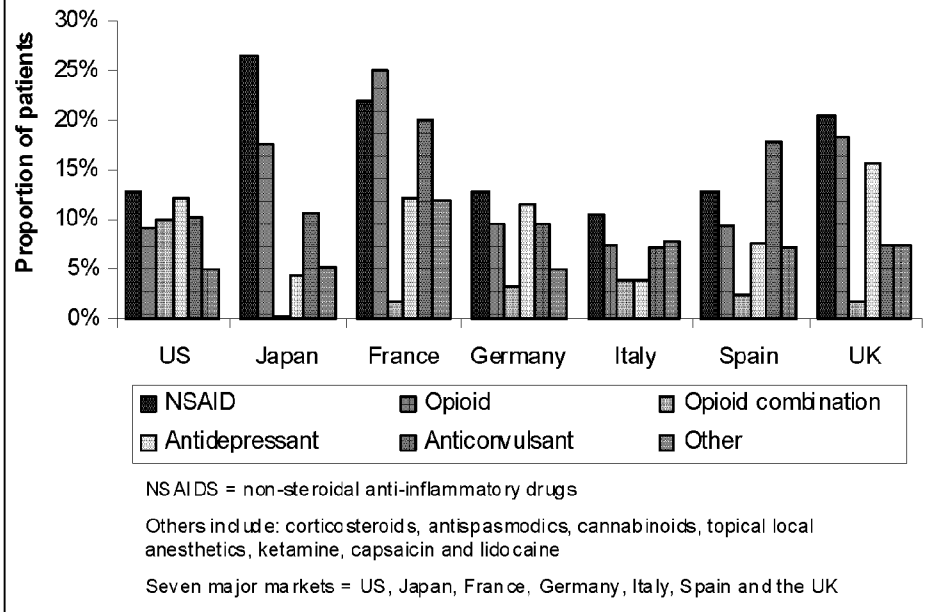
Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q3.2 (n=175), Q3.3 (n= 176), Q3.4 (n = 177).

DATAMONITOR

Mild

Figure 41 illustrates the proportion of patients with mild, chronic neuropathic cancer pain receiving the most commonly prescribed first line treatment regimen split by class across each of the seven major markets. The total percentage of patients receiving these classes as first line treatment will be larger to take into consideration other potential treatment regimens used. Please note that these other regimens were not examined in the survey.

Figure 41: Proportion of patients with mild chronic neuropathic cancer pain receiving each drug class as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



NSAIDS = non-steroidal anti-inflammatory drugs

Others include: corticosteroids, antispasmodics, cannabinoids, topical local anesthetics, ketamine, capsaicin and lidocaine

Seven major markets = US, Japan, France, Germany, Italy, Spain and the UK

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q3.2 (n=175)

DATAMONITOR

Datamonitor's primary research identified the following key trends in relation to the most commonly prescribed first-line drug regimen for mild chronic, neuropathic cancer pain:

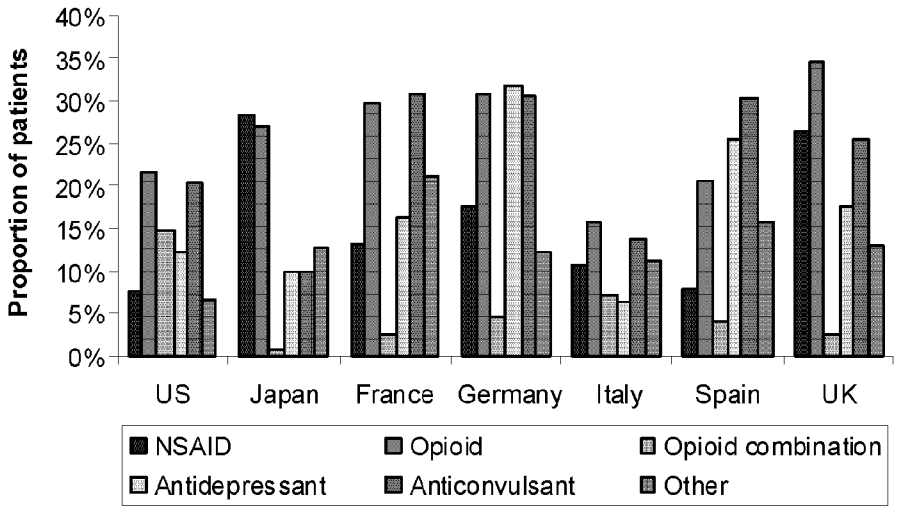
- Prescribing of NSAIDs as part of the most commonly prescribed first-line drug regimen for mild chronic neuropathic cancer pain is highest in Japan;
- Use of opioid combinations as part of the most commonly prescribed first-line drug regimen for mild, chronic neuropathic cancer pain are most popular in the US market.

Moderate

Figure 42 illustrates the proportion of patients with moderate, chronic neuropathic cancer pain receiving the most commonly prescribed first line treatment regimen split

by class across each of the seven major markets. The total percentage of patients receiving these classes as first line treatment will be larger to take into consideration other potential treatment regimens used. Please note that these other regimens were not examined in the survey.

Figure 42: Proportion of patients with moderate chronic neuropathic cancer pain receiving each drug class as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



NSAIDS = non-steroidal anti-inflammatory drugs

Others include: corticosteroids, antispasmodics, cannabinoids, topical local anesthetics, ketamine, capsaicin and lidocaine

Seven major markets = US, Japan, France, Germany, Italy, Spain and the UK

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q3.3 (n=178)

DATAMONITOR

Datamonitor's primary research identified the following key trends in relation to the most commonly prescribed first-line drug regimen for moderate chronic, neuropathic cancer pain:

- Opioids represent the predominant drug class contained within the most commonly prescribed first-line drug regimen for patients with moderate, chronic neuropathic cancer pain in the UK;

- Use of opioid combinations as part of the most commonly prescribed first-line drug regimen for moderate, chronic neuropathic cancer pain are most popular in the US market;
- Use of anticonvulsants as part of the most commonly prescribed first-line drug regimen for moderate neuropathic cancer pain is greatest in France, Germany and Spain;

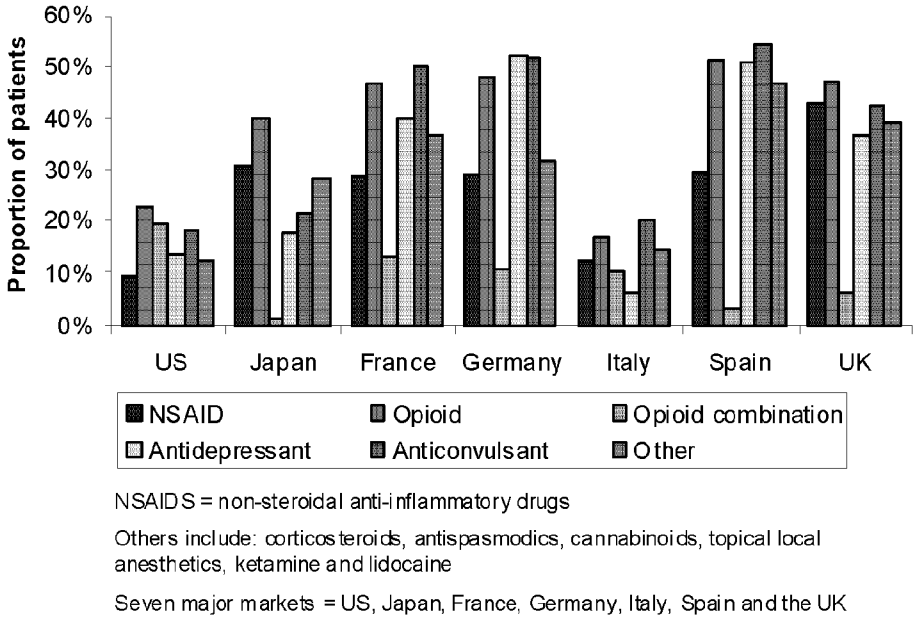
Severe

Figure 43 illustrates the proportion of patients with severe, chronic neuropathic cancer pain receiving the most commonly prescribed first line treatment regimen split by class across each of the seven major markets. The total percentage of patients receiving these classes as first line treatment will be larger to take into consideration other potential treatment regimens used. Please note that these other regimens were not examined in the survey.

Datamonitor's primary research identified the following key trends in relation to the most commonly prescribed first-line drug regimen for severe chronic, neuropathic cancer pain:

- Use of opioid combinations as part of the most commonly prescribed first-line drug regimen for severe, chronic neuropathic cancer pain are most popular in the US market;
- Anticonvulsants are more commonly prescribed than opioids as part of the most commonly prescribed first-line drug regimen for patients with severe chronic neuropathic cancer pain in France, Germany and Spain.

Figure 43: Proportion of patients with severe chronic neuropathic cancer pain receiving each drug class as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



NSAIDS = non-steroidal anti-inflammatory drugs

Others include: corticosteroids, antispasmodics, cannabinoids, topical local anesthetics, ketamine and lidocaine

Seven major markets = US, Japan, France, Germany, Italy, Spain and the UK

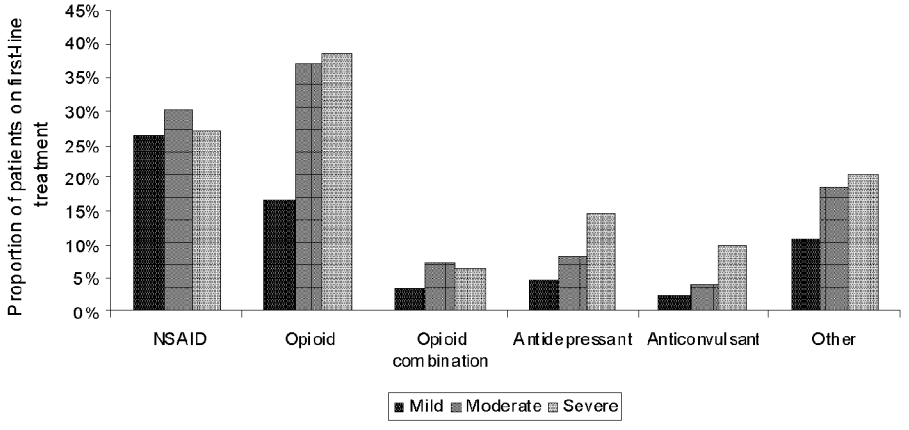
Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q3.4 (n=177)

DATAMONITOR

Chronic non-neuropathic cancer pain

Figure 44 illustrates the proportion of patients receiving the most commonly prescribed first line treatment regimen for chronic non-neuropathic cancer pain, split by class. The total percentage of patients receiving these classes as first line treatment will be larger to take into consideration other potential treatment regimens used. Please note that these other regimens were not examined in the survey.

Figure 44: Proportion of patients with chronic non-neuropathic cancer pain receiving each drug class as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



NSAIDS = non-steroidal anti-inflammatory drugs

Others include: corticosteroids, cannabinoids, antispasmodics, topical local anesthetics, ketamine, capsaicin and lidocaine

Seven major markets = US, Japan, France, Germany, Italy, Spain and the UK

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q4.2 (n=179), Q4.3 (n= 179), Q4.4 (n = 177).

DATAMONITOR

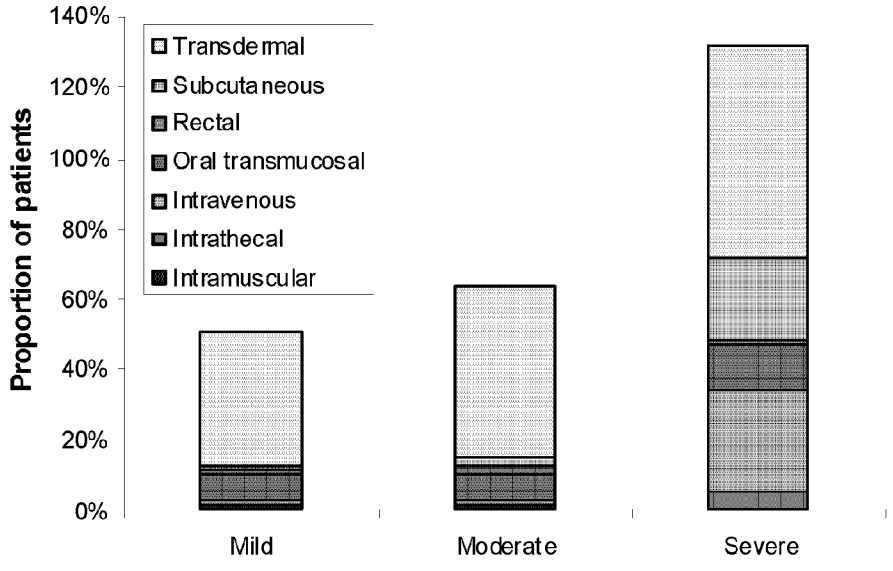
Datamonitor's primary research identified the following key trends in relation to the most commonly prescribed first-line drug regimen for chronic, non-neuropathic cancer pain:

- NSAIDs represent the predominant drug class contained within the most commonly prescribed first-line drug regimen for patients with mild, chronic non-neuropathic cancer pain;
- A notable proportion of patients receive an opioid as part of the most commonly prescribed first-line treatment regimen for mild, non-neuropathic cancer pain;
- Opioids represent the predominant drug class contained within the most commonly prescribed first-line drug regimen for moderate and severe non-neuropathic cancer pain;

- Considerably fewer patients with non-neuropathic than neuropathic cancer pain receive anticonvulsants and antidepressants as part of the most commonly prescribed first-line drug regimen across the seven major markets. This is unsurprising given that drugs belonging to these classes are indicated for neuropathic pain;
- Within the drug classes categorized as 'other', corticosteroids are the most commonly prescribed drugs forming part of the first-line drug regimen for patients with moderate and severe non-neuropathic cancer pain.

Figure 45 illustrates the proportion of patients receiving the most commonly prescribed first line treatment regimen split by formulation.

Figure 45: Proportion of patients with chronic non-neuropathic cancer pain receiving each opioid formulation (excluding oral ingested) as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q4.2 (n=179), Q4.3 (n= 179), Q4.4 (n = 177). DATAMONITOR

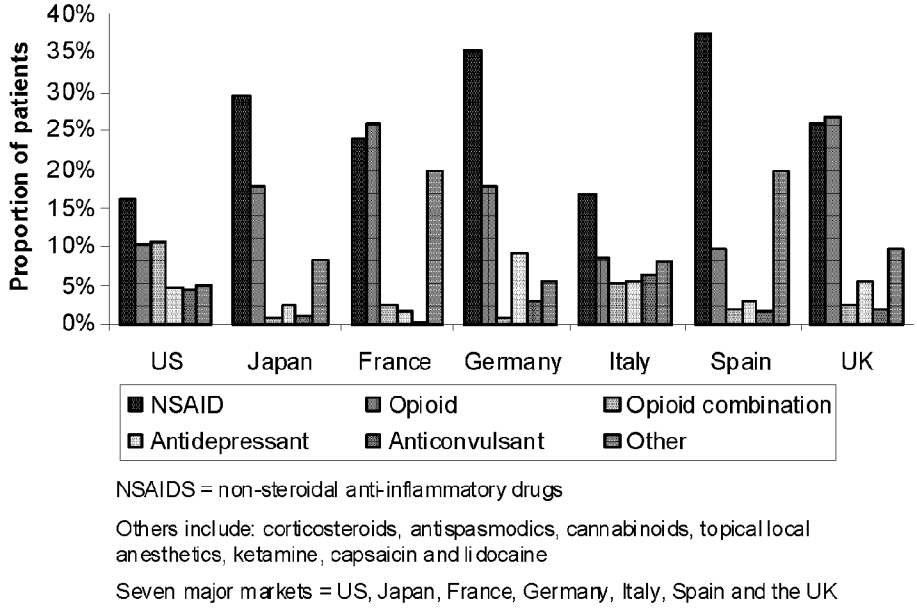
As seen in Figure 45, the proportion of patients receiving subcutaneous and intravenous opioid formulations as part of the most commonly prescribed first-line

drug regimen increases markedly between moderate and severe non-neuropathic cancer pain severities across the seven major markets.

Mild

Figure 46 illustrates the proportion of patients with mild, chronic non-neuropathic cancer pain receiving the most commonly prescribed first line treatment regimen split by class across each of the seven major markets. The total percentage of patients receiving these classes as first line treatment will be larger to take into consideration other potential treatment regimens used. Please note that these other regimens were not examined in the survey.

Figure 46: Proportion of patients with mild chronic non-neuropathic cancer pain receiving each drug class as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



NSAIDS = non-steroidal anti-inflammatory drugs

Others include: corticosteroids, antispasmodics, cannabinoids, topical local anesthetics, ketamine, capsaicin and lidocaine

Seven major markets = US, Japan, France, Germany, Italy, Spain and the UK

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q4.2 (n=179). DATAMONITOR

Datamonitor's primary research identified the following key trends in relation to the most commonly prescribed first-line drug regimen for mild chronic, non-neuropathic cancer pain:

- Use of opioid combinations as part of the most commonly prescribed first-line drug regimen for mild, chronic non-neuropathic cancer pain are most popular in the US market.

According to an interviewed Japanese key opinion leader, NSAIDs are commonly prescribed for the treatment of mild non-neuropathic cancer pain in Japan. This opinion concurs with the findings of Datamonitor's primary research.

> *"All in all, it* [treatment for mild non-neuropathic pain] *is NSAIDs."*
>
> Japanese key opinion leader

Moderate and severe

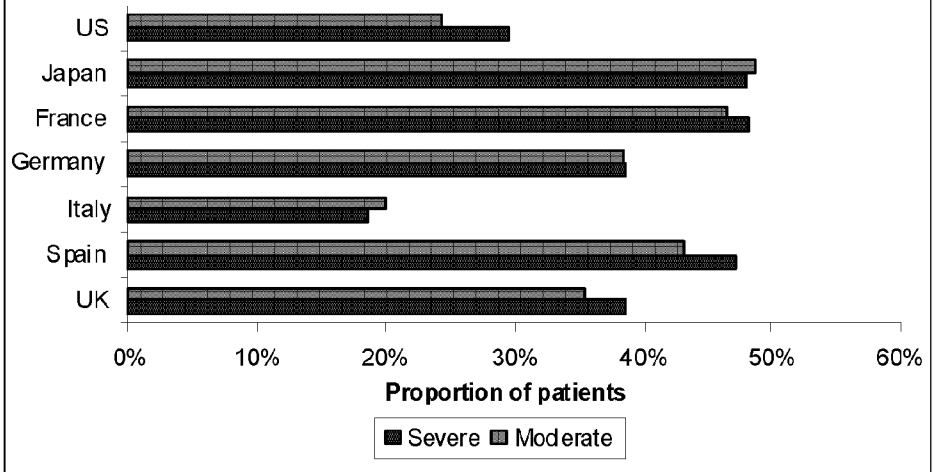
Figure 47 illustrates the proportion of patients with moderate and severe, chronic non-neuropathic cancer pain receiving opioid drugs as part of the most commonly prescribed first line treatment regimen across each of the seven major markets. The total percentage of patients receiving this class as first line treatment will be larger to take into consideration other potential treatment regimens used. Please note that these other regimens were not examined in the survey.

As seen in Figure 47, the proportion of moderate non-neuropathic cancer pain patients receiving an opioid as part of the most commonly prescribed first-line regimen is highest in Japan, followed by France. Oxycodone represents the most commonly prescribed opioid for moderate, non-neuropathic cancer pain in Japan, a finding supported by an interviewed key opinion leader:

> *"When the pain increased to the level of moderate, I prescribe codeine, but in Japan as a whole, oxycodone is used half of the time."*
>
> Japanese key opinion leader

The proportion of patients with severe non-neuropathic cancer pain receiving an opioid as part of the most commonly prescribed first-line regimen is highest in Japan and France. In Japan, oxycodone represents the most commonly prescribed opioid for severe non-neuropathic cancer pain, whereas the most commonly prescribed opioid drug for this indication in France is morphine.

Figure 47: Proportion of patients with moderate and severe chronic non-neuropathic cancer pain receiving opioids as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q4.3 (n=179), Q4.4 (n = 177).

DATAMONITOR

Breakthrough cancer pain

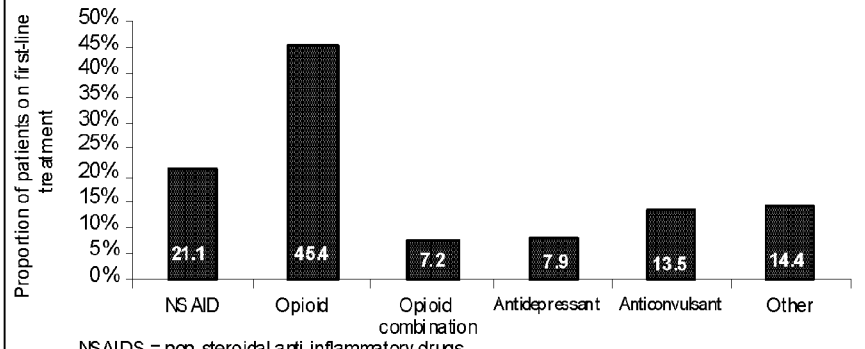
Figure 48 illustrates the proportion of patients receiving the most commonly prescribed first-line treatment regimen for breakthrough cancer pain, split by class. The total percentage of patients receiving these classes as first line treatment will be larger to take into consideration other potential treatment regimens used. Please note that these other regimens were not examined in the survey.

Datamonitor's primary research identified the following key trends in relation to the most commonly prescribed first-line drug regimen for breakthrough cancer pain:

- Of each of the key drug classes, opioids play the greatest role in the most commonly prescribed first-line regimen for patients with breakthrough cancer pain across the seven major markets in 2009;
- Morphine is the most commonly prescribed opioid for breakthrough cancer pain across the seven major markets, followed by fentanyl.

Datamonitor believes that any new product entering this niche market would have to demonstrate a faster onset of action and provide greater analgesia than morphine.

Figure 48: Proportion of patients with breakthrough cancer pain receiving each drug class as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



NSAIDS = non-steroidal anti-inflammatory drugs

Others include: corticosteroids, antispasmodics, cannabinoids, topical local anesthetics, ketamine, capsaicin and lidocaine

Seven major markets = US, Japan, France, Germany, Italy, Spain and the UK

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q5.3 (n=179). DATAMONITOR

In keeping with the treatment trends identified by Datamonitor's primary research, a key opinion leader comments that standard release opioid drugs such as morphine are regarded as first-line treatment for breakthrough cancer pain, while rapidly acting opioids (including Cephalon's fentanyl drugs; Actiq and Fentora) are viewed as second-line treatment options.

> *"The standard regular release opioids, morphine, oxycodone, hydromorphone, oxymorphone* [are the first-line treatments for breakthrough cancer pain]. *Then, in some situations if the patients have failed trials on those then we might consider rapid onset fentanyl products such as Actiq or Fentora as a second-line breakthrough pain medication. Most people will respond to the standard opioids and then we may utilize the rapid onset drugs as a second line breakthrough medication."*
>
> US key opinion leader

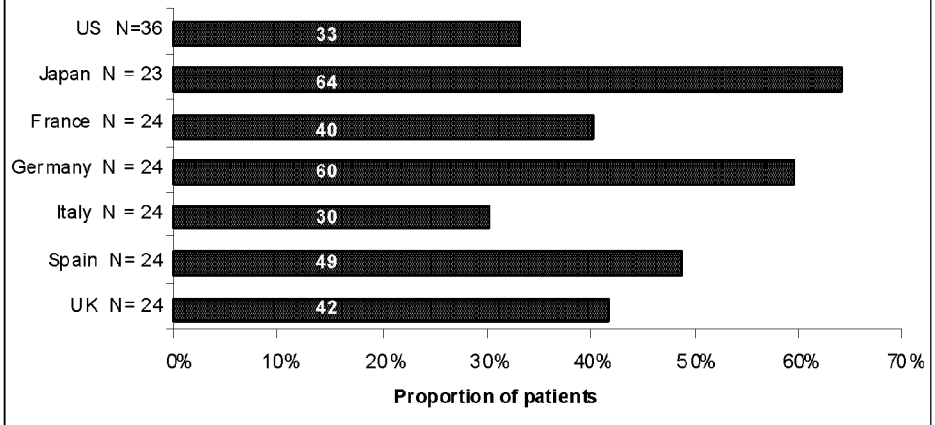
In terms of prescribing of opioids in the US market, the less frequent use of fentanyl relative to morphine may be attributable to restrictions imposed by insurance companies. An interviewed key opinion leader comments:

> *"Yes* [both Actiq and Fentora are reimbursed in the US] *but there is a lot of variability, and we get denials from insurance companies not infrequently for one or the other or both of those drugs."*
>
> US key opinion leader

Datamonitor believes that such restrictions represent a key threat to US sales of recently launched and developmental opioid drugs indicated for breakthrough cancer pain.

Figure 49 illustrates the proportion of patients with breakthrough cancer pain receiving opioids as part of the most commonly prescribed first line treatment regimen for this indication, across each of the seven major markets. The total percentage of patients receiving these classes as first line treatment will be larger to take into consideration other potential treatment regimens used. Please note that these other regimens were not examined in the survey.

Figure 49: Proportion of patients with breakthrough cancer pain receiving opioids as part of most commonly prescribed first-line drug regimen, across the seven major markets, 2009



Seven major markets = US, Japan, France, Germany, Italy, Spain and the UK

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q5.3 (n=179).

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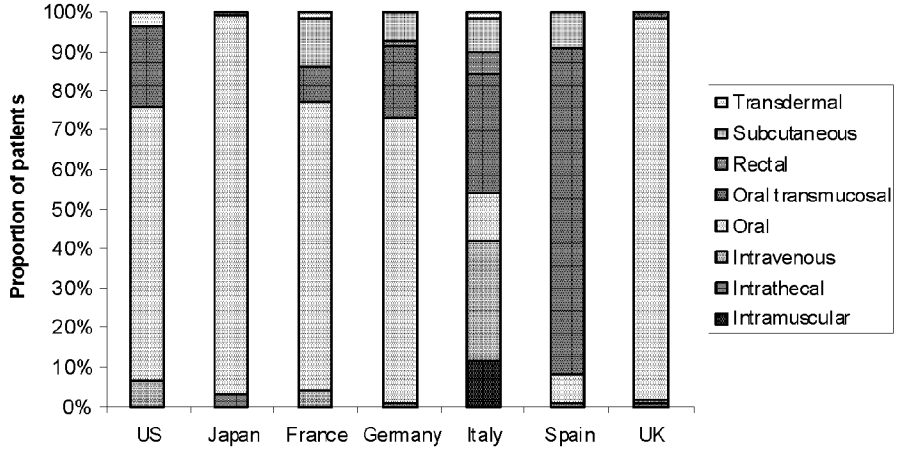
According to results of Datamonitor's *Stakeholder Insight 2009: Cancer pain* survey, prescribing of opioid drugs as part of the most commonly prescribed first-line drug regimen for breakthrough cancer pain is highest in Japan. Therefore, on the basis of Datamonitor's survey, Japan appears to represent an attractive target market for companies developing opioid formulations for breakthrough cancer pain.

In comparison to Japan, the proportion of patients with breakthrough cancer pain receiving opioids as part of the most commonly prescribed first-line regimen was considerably lower in Italy and the US.

Results of Datamonitor's primary research survey also reveal differences in the specific opioids that are most frequently prescribed. For example, in the US, France, Germany and UK, morphine represents the most commonly prescribed opioid for the first-line treatment of breakthrough cancer pain. However, fentanyl is the most commonly prescribed opioid for breakthrough cancer pain in Italy and Spain, while oxycodone is the most commonly prescribed opioid for this indication in Japan.

Figure 50 presents the proportion of patients with breakthrough cancer pain receiving the most commonly prescribed first line opioid split by formulation.

Figure 50: Proportion of patients with breakthrough cancer pain receiving each opioid formulation as part of the most commonly prescribed first-line treatment regimen across the seven major markets, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, DMHC2536, Q5.3 (n=179).

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As can be seen in Figure 50, oral formulations dominate the most commonly prescribed first-line opioids for breakthrough cancer pain in the US, Japan, France, Germany and the UK. By comparison, oral transmucosal and intravenous formulations are equally prescribed as part of the most commonly prescribed first-line treatment regimen for breakthrough cancer pain in Italy. Furthermore, according to the results of Datamonitor's primary research survey, oral transmucosal opioids (specifically fentanyl) are by far the popular most popular formulation forming part of the most commonly prescribed first line treatment for breakthrough cancer pain in Spain.

Progression to second-line analgesia

Second-line therapy is defined as the second choice of therapy when the first choice has not achieved the desired response or exhibits undesirable characteristics in a given patient. This may involve switching one or all of the regimen's constituent drugs or adding new products to the first-line regimen. Patients may be switched from one drug to another within a single drug class in order to achieve optimum pain relief with minimum toxicity. Alternatively, patients may be switched to an analgesic of a different drug class, in accordance with the WHO's three-step analgesic ladder.

Physicians surveyed by Datamonitor were asked to estimate the proportion of their patients suffering from each key subtype of cancer pain (chronic neuropathic, chronic non-neuropathic and breakthrough) of each severity (mild, moderate and severe) that progress to second-line analgesic treatment. Survey results indicate that across the seven major markets, comparable proportions of patients with neuropathic and non-neuropathic cancer pain progress to second-line treatment. Furthermore, the proportion of patients progressing to second-line therapy increases with pain severity. In terms of breakthrough cancer pain, almost one third of patients across the seven major markets progress to second-line analgesic treatment, indicating that for two thirds of patients, first-line treatment provides insufficient pain relief for breakthrough cancer pain.

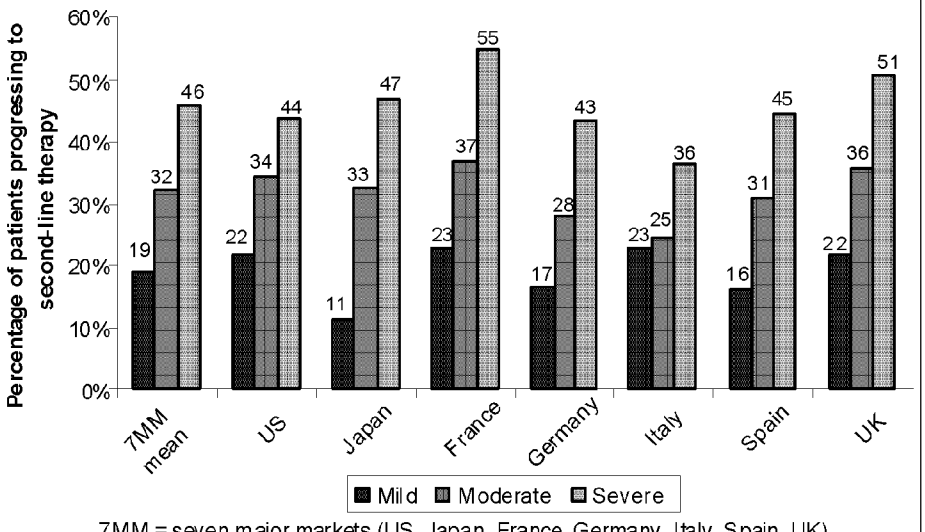
There are several reasons why a physician may decide to progress a cancer patient to second-line analgesic treatment, including: failure to achieve analgesic relief, slower than required onset of action, shorter duration of action than required, lack of flexible dosing frequency, development of tolerance or addiction to the drug, side effects, serious adverse events and patient non-adherence. Datamonitor's primary research survey found that beyond failure to achieve pain control, onset of action and gastrointestinal side effects are key factors considered by physicians when progressing patients with chronic neuropathic and non-neuropathic cancer pain to second-line therapy. In relation to breakthrough cancer pain, slower than required

onset of action is the second most important factor after failure to achieve pain relief when progressing patients to second-line treatment.

Chronic neuropathic cancer pain

Figure 51 summarizes the proportion of first-line chronic neuropathic cancer pain patients (at each pain severity) that progress to second-line analgesic treatment across the seven major markets.

Figure 51: Percentage of patients with chronic, neuropathic cancer pain progressing to second-line analgesic treatment across the seven major markets, 2009



7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q3.6 (n=180) Datamonitor

DATAMONITOR

Progression to second-line treatment among patients with chronic neuropathic cancer pain is highest in France

As illustrated in Figure 51, the proportion of chronic neuropathic cancer pain patients progressing to second-line therapy increases steadily with pain intensity. Across the seven major markets, 19% of patients with mild chronic neuropathic cancer pain progress to second line analgesic treatment, compared to 32% of patients experiencing moderate chronic neuropathic cancer pain and 46% of patients

experiencing severe, chronic neuropathic cancer pain. Therefore, to companies marketing analgesics for cancer pain, patients with severe cancer pain represent a target patient group, as these patients are most likely to progress to alternative or adjuvant pharmaceutical treatment options.

However, an interviewed key opinion leader believes that a considerably higher proportion of patients with chronic neuropathic cancer pain progress to second line analgesic treatment than reported by the results of Datamonitor's survey:

> *"Well I would have thought that* [the proportion of patients with neuropathic cancer pain that fail on first-line therapy] *could have been high, maybe 80 to 90%."*
>
> US key opinion leader

The proportion of chronic neuropathic cancer pain patients progressing to second-line treatment varies between countries. As seen in Figure 51, the proportion of patients with mild, chronic neuropathic cancer pain progressing to second-line analgesic treatment ranges from 11% (Japan) to 23% (France and Italy). Progression to second-line therapy among patients with moderate and severe chronic neuropathic cancer pain, meanwhile, is highest in France. According to French physicians surveyed by Datamonitor, 37% of patients with moderate chronic neuropathic cancer pain and 55% of patients with severe chronic neuropathic cancer pain progressed to second-line analgesic treatment in 2009. By comparison, progression to second-line analgesic treatment among patients with moderate and severe chronic neuropathic cancer pain was lowest in Italy.

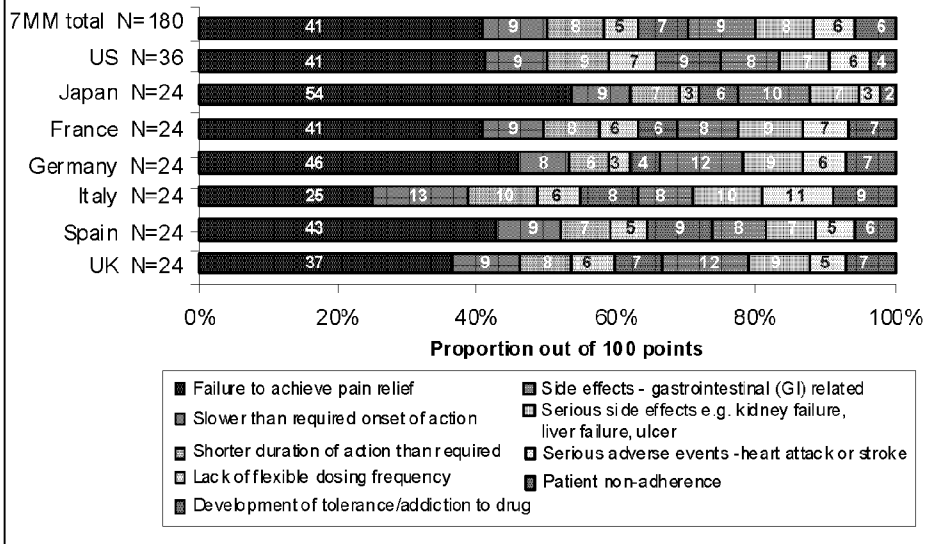
Inter-country variation in the proportion of patients progressing to second-line treatment may result from differences in frequency of pain assessment. In addition, variation may reflect differences in the time which patients in each country spend on first-line treatment before it is deemed either ineffective or insufficient as a monotherapy. On this basis, it is possible to speculate that the higher proportion of patients with moderate and severe chronic neuropathic cancer pain in France progressing to second-line analgesia may reflect a greater frequency of assessment and shorter time spent on first-line analgesia than in the remaining six major markets.

Other than failure to achieve pain relief, onset of action and gastrointestinal side effects are key factors considered by physicians

Through distributing 100 points across nine pre-defined factors, interviewed physicians were asked to indicate the relative importance of each factor when deciding to progress patients with chronic neuropathic cancer pain to second-line

therapy. Figure 52 illustrates the perceived importance of each of the nine factors across the seven major markets.

Figure 52: Importance of nine key factors when progressing chronic neuropathic cancer pain patients to second-line treatment, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q3.5 (n=180) Datamonitor

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Unsurprisingly, failure to achieve pain relief is by far the most important factor which physicians take into consideration when progressing patients with chronic neuropathic cancer pain from first to second-line analgesic treatment (Figure 52). This trend is consistent across each of the seven major markets, with all physicians reporting that failure to achieve pain relief is the most important factor. However, the importance of this factor also varied across the seven major markets, with physicians in Japan allocating the highest number of points (54/100) to 'failure to achieve pain relief'. By comparison, surveyed physicians in Italy allocated just 25/100 points to this factor.

Beyond failure to achieve pain relief, the next most important factors considered by physicians when progressing patients with chronic neuropathic cancer pain to second-line analgesic treatment were 'slower than required onset of action' and 'gastrointestinal related side effects', which each achieved a mean 9/100 points across the seven major markets. The factor 'onset of action' achieved the highest importance rating in Italy (13/100 points) and achieved comparable importance ratings across each of the remaining six major pharmaceutical markets. The onset of

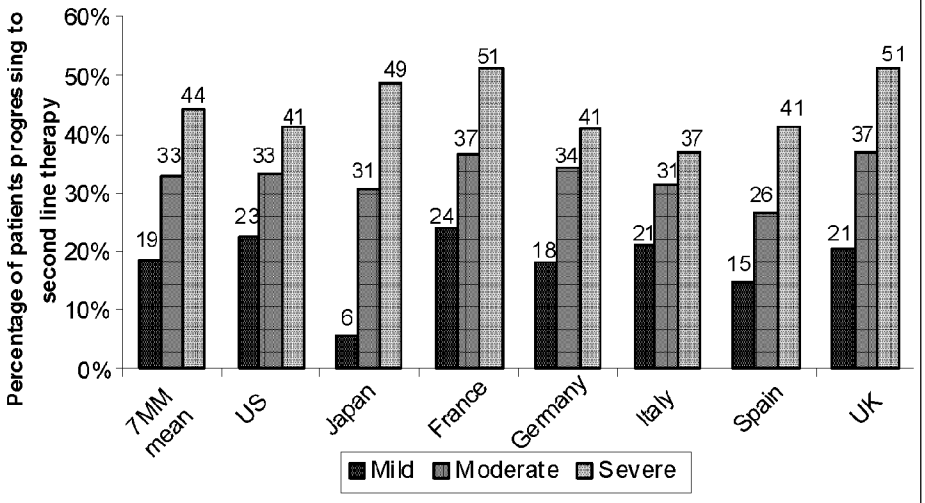
action of drugs currently approved for the treatment of neuropathic cancer pain varies from 8 weeks for Neurontin (gabapentin; Pfizer) to 1 week for Lyrica (pregabalin; Pfizer). Therefore, pipeline drugs which are able to demonstrate a superior onset of action to Lyrica while possessing comparable efficacy are likely to achieve a strong uptake in the neuropathic cancer pain population.

The importance of gastrointestinal related side effects when progressing patients with chronic neuropathic cancer pain from first to second-line therapy ranged from 8/100 points (in the US, France, Italy and Spain) to 12/100 points (Germany and the UK).

Chronic non-neuropathic cancer pain

Figure 53 summarizes the proportion of first-line chronic non-neuropathic cancer pain patients (at each pain severity) that progress to second-line analgesic treatment across the seven major markets.

Figure 53: Percentage of patients with chronic non-neuropathic cancer pain progressing to second-line analgesic treatment across the seven major markets, 2009



7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain*, survey DMHC2536, Q4.7 (n=180) Datamonitor

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Comparable proportions of patients with chronic non-neuropathic and neuropathic cancer pain progress to second-line analgesic treatment

As was the case for the treatment of chronic neuropathic cancer pain (Figure 51), Datamonitor's primary research survey indicates that the proportion of chronic non-neuropathic cancer pain patients progressing to second-line therapy increases with pain intensity. Across the seven major markets, 19% of patients with mild chronic non-neuropathic cancer pain progress to second-line analgesic treatment, compared to 33% of patients experiencing moderate chronic non-neuropathic cancer pain and 44% of patients experiencing severe, chronic non-neuropathic cancer pain. As such, comparable proportions of patients with chronic neuropathic and non-neuropathic cancer pain (of each severity) progress to second-line analgesic treatment. Therefore, to companies marketing analgesics for cancer pain, patients with severe cancer pain represent a target patient group as they are most likely to progress to alternative or adjuvant pharmaceutical treatment options.

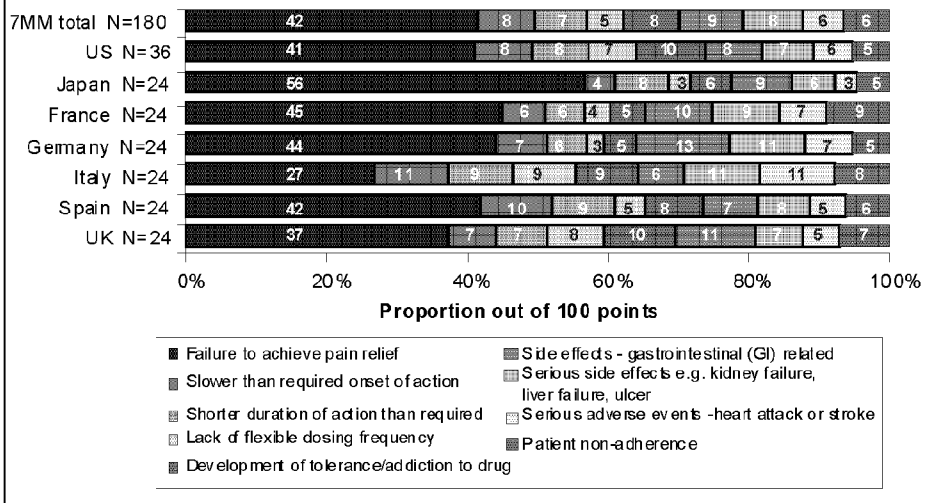
As seen in Figure 53, physicians in France reported the highest progression rate for patients with mild, chronic non-neuropathic cancer pain, standing at 24%. By comparison, in Japan, just 6% of patients with mild chronic, non-neuropathic cancer pain progress to second-line treatment, indicating that this form of cancer pain is well managed by first-line treatment for 94% of patients.

Progression to second-line therapy among patients with moderate and severe chronic non-neuropathic cancer pain is highest in France and the UK. In these two markets, a mean 37% of patients with moderate chronic, non-neuropathic cancer pain and a mean 51% of patients with severe, chronic, non-neuropathic cancer pain progress to second-line therapy. It is possible to speculate that the higher proportion of patients with moderate and severe chronic non-neuropathic cancer pain in France and the UK progressing to second-line analgesia may reflect a greater frequency of assessment and shorter time spent on first-line analgesia than in the remaining five major markets.

Aside from failure to achieve pain relief, gastrointestinal side effects are a key factor considered by physicians

Through distributing 100 points across nine pre-defined factors, interviewed physicians were asked to indicate the relative importance of each factor when deciding to progress patients with chronic non-neuropathic cancer pain to second-line therapy. Figure 54 illustrates the perceived importance of each of the nine factors across the seven major markets.

Figure 54: Importance of nine key factors when progressing chronic non-neuropathic cancer pain patients to second-line treatment, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q4.6 (n=180) Datamonitor

DATAMONITOR

As seen in Figure 54, akin to the treatment of chronic neuropathic cancer pain, physicians surveyed by Datamonitor report failure to achieve onset of action as the most important factor considered when progressing patients with chronic non-neuropathic cancer pain to second-line analgesic treatment. This trend is consistent across each of the seven major markets, with physicians attributing a mean 42/100 points to this factor in 2009. Physicians in Japan attributed the greatest importance (56/100 points) to failure to achieve pain relief, while physicians in Italy attributed the fewest points (27/100) to this factor.

Although garnering considerably fewer points than the factor 'failure to achieve pain relief', surveyed physicians reported gastrointestinal related side effects as the second most important factor considered when progressing chronic non-neuropathic cancer pain patients to second-line analgesic treatment. Results indicate that gastrointestinal side effects are a particularly important consideration for physicians in Germany, where this attribute garnered 13/100 points.

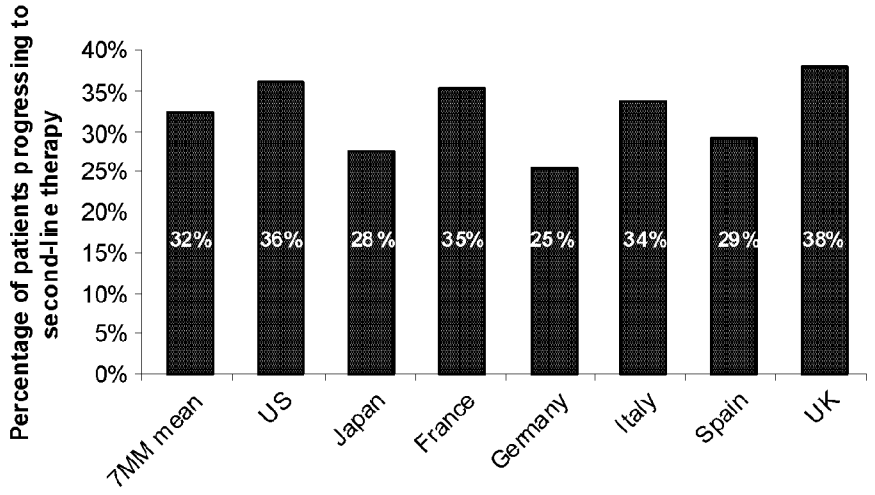
Breakthrough pain

Almost one third of breakthrough cancer pain patients progress to second-line treatment

Physicians interviewed by Datamonitor across the seven major markets were asked to estimate the percentage of their patients with breakthrough cancer pain that fail on first-line analgesic treatment and progress to second-line treatment.

Figure 55 summarizes the proportion of first-line breakthrough cancer pain patients that progress to second-line analgesic treatment.

Figure 55: Percentage of patients with breakthrough cancer pain progressing to second-line analgesic treatment across the seven major markets, 2009



7MM = seven major markets (US, Japan, France, Germany, Italy, Spain, UK)

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q5.6 (n=180)

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According to Datamonitor's primary research, almost one third (32%) of patients with breakthrough cancer pain fail on first-line analgesic treatment and progress to second-line treatment. This suggests that breakthrough cancer pain is well-managed by first-line treatments for around 68% of patients. When asked what proportion of

patients with breakthrough cancer pain fail on first-line treatment, interviewed key opinion leaders cite figures close to the 32% demonstrated by Datamonitor's survey.

> *"I would say that probably 25–30%, somewhere in there* [fail on first-line treatment]."
>
> EU key opinion leader

> *"It* [the proportion of patients with breakthrough cancer pain progressing to second –line analgesic treatment] *would be 20 to 30%."*
>
> EU key opinion leader

Rates of progression to second-line treatment among breakthrough cancer pain patients ranged from 25% (Germany) to 38% (UK). A similar proportion of breakthrough cancer pain patients in the US, France and Italy receive second-line therapy (34–36%).

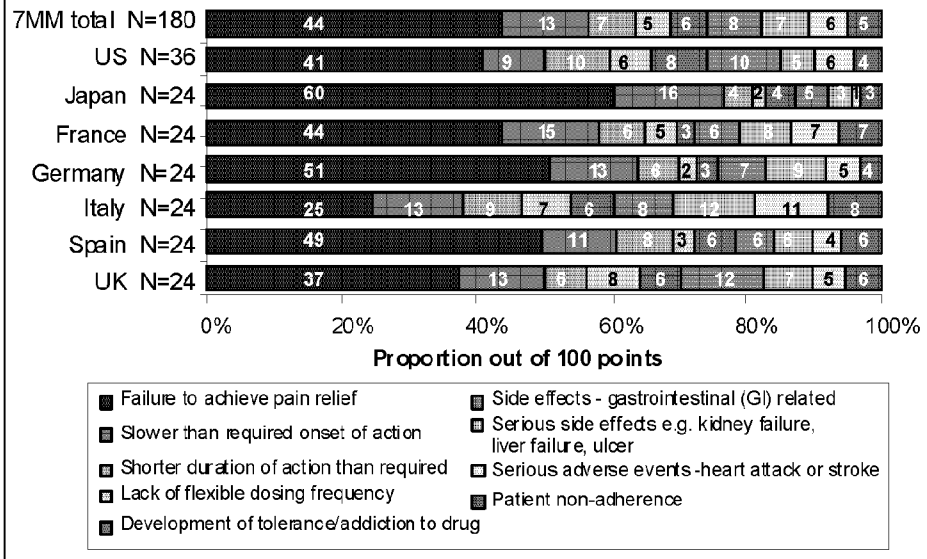
Cost and lack of flexible dosing frequency are of least importance when physicians progress breakthrough cancer pain patients to second-line therapy

Through distributing 100 points across nine predefined attributes, interviewed physicians were asked to indicate the relative importance of each attribute when deciding to progress patients with breakthrough cancer pain to second-line therapy. This is illustrated in Figure 56.

After 'failure to achieve pain relief', the most important factor considered by physicians when progressing patients with breakthrough cancer pain to second-line treatment is 'slower than required onset of action' (Figure 56). This is unsurprising, given that breakthrough cancer pain is characterized by a rapid onset and therefore necessitates treatment with a fast-acting analgesic.

Datamonitor's primary research also found that physicians, when deciding to progress patients with breakthrough cancer pain to second-line treatment, regard the cost of pain medications and the risk of serious side effects as being of least importance. Datamonitor believes that this reflects the severity of cancer pain and its hugely detrimental impact on patients' quality of life.

Figure 56: Importance of nine key factors when progressing breakthrough cancer pain patients to second-line treatment, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q5.5 (n=180)

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CHAPTER 8 PRESCRIBING INFLUENCES AND BRAND ASSESSMENT

- *According to the 180 physicians surveyed for Stakeholder Insight 2009: Cancer pain, published guidelines are the most dominant non-drug influence on physicians' prescribing decisions for cancer pain patients across the seven major markets. Therefore, drugs recommended in treatment guidelines are likely to benefit from the greatest uptake in the treatment of cancer pain.*

- *Published journal articles represent the second most important non-drug influence on physicians' prescribing decisions. As such, manufacturers of analgesics intending to target the cancer pain population would benefit from publishing positive clinical trial results in peer-reviewed journals that are read by oncologists, since these healthcare professionals initiate and manage analgesic treatment in the majority of patients with cancer pain.*

- *Beyond overall efficacy (demonstrable by reduction in pain), the two most important factors a physician will consider when prescribing a drug for neuropathic cancer pain are onset of action and duration of action.*

- *The most important drug attribute (beyond overall efficacy) influencing physicians' prescribing decisions for breakthrough cancer pain is onset of action. Cost issues exert the least influence on prescribing decisions for this subtype of cancer pain.*

- *Seventy-five per cent of US physicians surveyed by Datamonitor were able to rate Lyrica, a figure which Datamonitor regards as relatively low in view of the fact that the drug has been available in the US since 2005. The implication is that when treating cancer pain, oncologists are more familiar with traditional analgesics (such as non-steroidal anti-inflammatory drugs and opioids). Out of 10 attributes rated by physicians, Pfizer's neuropathic pain drug— Lyrica (pregabalin)—scored relatively highly on duration of action.*

- *Of Cephalon's two breakthrough cancer pain products—Actiq and Fentora—surveyed physicians were most familiar with Actiq. Contrary to clinical trial data indicating that Fentora possesses a more rapid onset of action than Actiq, physicians regard the drugs' onset of action as comparable.*

- *Datamonitor's primary research indicates that although Actiq and Fentora are both administered orally, physicians regard Fentora's effervescent buccal formulation as preferable to Actiq's transmucosal lozenge formulation in the treatment of breakthrough cancer pain. Fentora's superior rating in terms of route of administration may reflect the drug's more discreet formulation compared to the Actiq lollipop.*

This chapter discusses factors influencing physicians' prescribing decisions in the treatment of cancer pain. Non-drug and drug factors influencing prescribing decisions are ranked in terms of their relative importance, and branded drugs are evaluated according to their performance across several clinical attributes, based on the results of the Datamonitor survey of 180 oncologists, palliative care specialists, pain care specialists and anesthetists.

This will be followed by an assessment of physicians' perceptions of three branded drugs prescribed for the treatment of cancer pain: Pfizer's Lyrica (pregabalin), Cephalon's Actiq (oral transmucosal fentanyl) and Fentora (fentanyl buccal tablet).

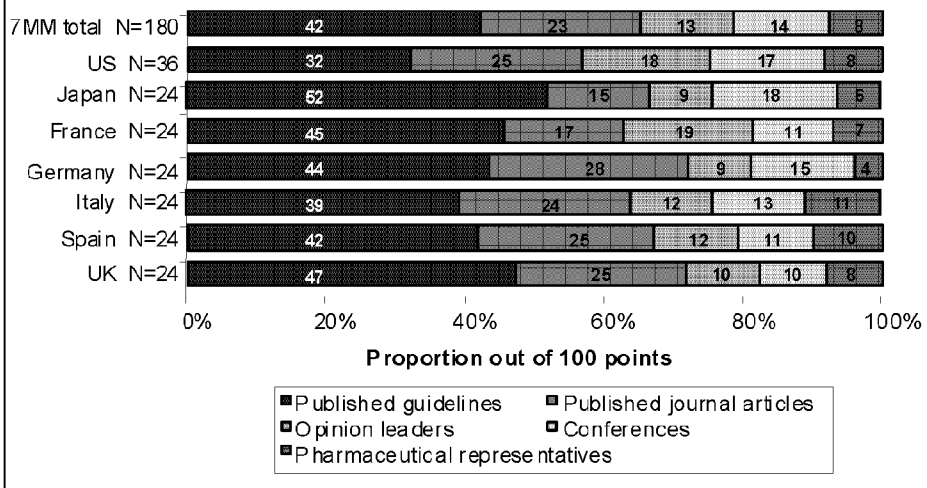
Factors influencing physician decision making

Physician prescription choice in the treatment of cancer pain is driven by both non-drug and drug factors. Non-drug factors which may influence prescribing decisions include published guidelines, published journal articles, the views of key opinion leaders, information conveyed at conferences and information communicated by pharmaceutical companies via representatives. Drug factors influencing physicians' prescribing decisions relate to the clinical attributes of available drug treatments and include: efficacy in reducing pain, onset of action, lack of drug-drug interaction, duration of action, overall side-effect profile, flexible dosing frequency, cost issues, and physician product familiarity, whether the drug is recommended in treatment guidelines and finally route of administration.

Non-drug factors

In order to determine the importance of non-drug factors, physicians were asked to distribute 100 points across five factors in terms of how they would influence the choice of analgesic treatment for patients with cancer pain (regardless of pain subtype or severity). The more points allocated to a factor, the greater is its influence. The relative weightings reported by physicians are shown in Figure 57.

Figure 57: Relative weighting given to each non-drug prescribing influence for cancer pain treatment across the seven major markets, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q6.2

DATAMONITOR

Published guidelines represent the greatest non-drug influence on prescribing decisions

According to the 180 physicians surveyed by Datamonitor, published guidelines are the most dominant non-drug influence on prescribing decisions for cancer pain patients across the seven major markets, with an average weighting of 42 across the seven major markets (the US, Japan, France, Germany, Italy, Spain and the UK). This trend is also consistent across the US, Japan and 5EU (France, Germany, Italy, Spain and the UK), with all physicians reporting that published guidelines are the most influential non-drug factor in their prescribing decisions for cancer pain. In view of the influential status of treatment guidelines on physicians' prescribing decisions, drugs recommended in treatment guidelines are likely to benefit from the greatest uptake in the treatment of cancer pain.

Interviewed physicians indicated that, secondary to treatment guidelines, information contained in published journal articles was also a key factor influencing their prescribing decisions for cancer pain. Across the seven major markets, published journal articles accrued an average weighting of 23%. Therefore, Datamonitor recommends that manufacturers of analgesics intending to target the cancer pain population should endeavor to publicize positive clinical trial results though publication in respected, peer-reviewed journals. However, as implied by an

interviewed key opinion leader, it is important for such articles to be published in journals that are read by oncologists.

> *"There are hundreds and hundreds of journals, yet most physicians read only a small number of journals, so if I published in a pain journal an oncologist or general practitioner would never see that. A lot of the useful treatments are hidden in the literature even though they are evidence based."*
>
> EU key opinion leader

Although journal articles were reported to be the second most important prescribing influence in the six major pharmaceutical markets (US, Japan, Germany, Italy, Spain and the UK) key opinion leaders were cited as the second most important prescribing influence for physicians in France.

In addition to published guidelines and journal articles, physicians indicated that they use other sources of information to guide them in making prescribing decisions, although these factors play a lesser role. Across the seven major markets, opinion leaders, conferences and pharmaceutical representatives achieved average weightings of 13, 14 and 8, respectively. The results therefore suggest that pharmaceutical companies have an opportunity to substantially increase their influence on physicians treating cancer pain, for example through continuing education of physicians through sponsorship of seminars and in conferences in the area of cancer pain management.

Drug factors

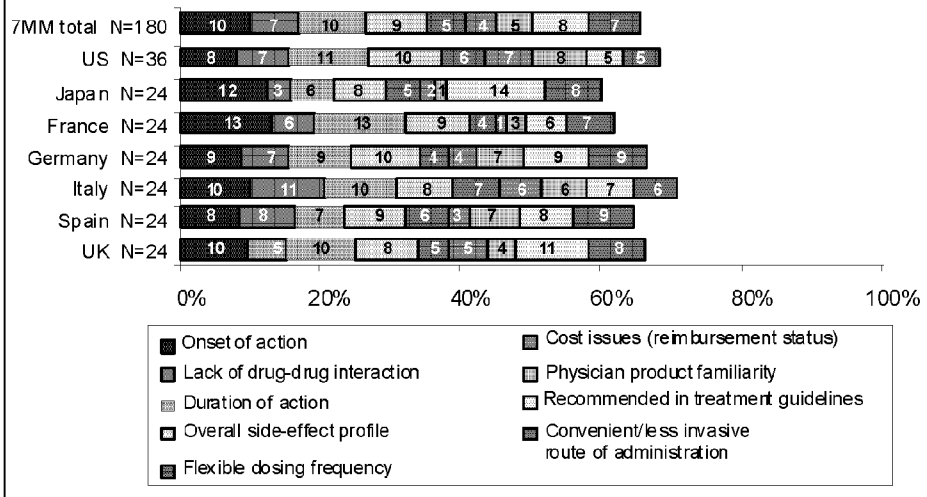
In order to determine the role of drug-specific factors in influencing physicians' prescribing decisions in cancer pain, interviewed physicians were asked to distribute 100 points across a predefined list of 10 clinical attributes to indicate their relative importance, allocating more points to the more important drug attributes. If an attribute was of no importance, physicians were allowed to allocate zero points.

In view of the different treatment strategies employed for neuropathic cancer pain and breakthrough cancer pain, physicians were asked to consider these cancer pain subtypes separately when rating the influence of clinical attributes on their prescribing behavior.

Neuropathic cancer pain

Figure 58 illustrates the comparative importance of 10 drug attributes in influencing physicians' prescribing decisions for neuropathic cancer pain patients.

Figure 58: Comparative importance of drug attributes influencing physicians' prescribing decisions for neuropathic cancer pain, across the seven major market, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q6.3

DATAMONITOR

Onset of action and duration of action are key prescribing influences in the treatment of neuropathic cancer pain

According to the 180 physicians interviewed by Datamonitor across the seven major markets, overall efficacy (demonstrable by reduction in pain) is the most dominant clinical attribute driving physicians' prescribing decisions for patients with neuropathic cancer pain. Across the seven major markets, the attribute 'overall efficacy' achieved an average weighting of 33. As could be expected, this trend is consistent across the US, Japan and 5EU—all physicians think that prescribing an effective analgesic drug is of utmost importance in neuropathic cancer pain.

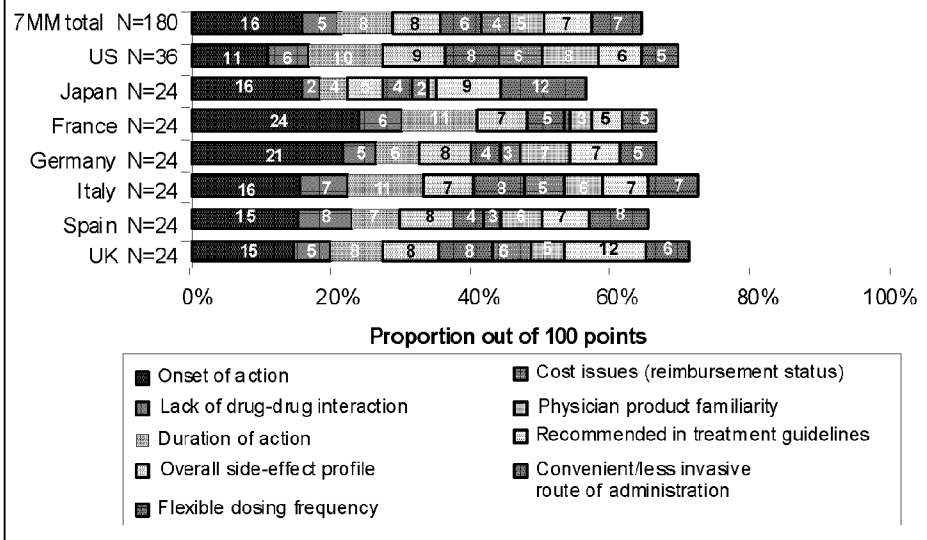
Beyond overall efficacy, onset of action and duration of action were rated by physicians as important prescribing influences in neuropathic cancer pain. These attributes each garnered a mean 10/100 points across the seven major markets. By comparison, cost issues (reimbursement status) represent the least important

prescribing influence in the treatment of this form of cancer pain across the seven major markets.

Breakthrough cancer pain

Excluding overall efficacy, Figure 59 illustrates the comparative importance of nine key attributes in influencing physicians' prescribing decisions for breakthrough cancer pain patients.

Figure 59: Comparative importance of drug attributes influencing physicians' prescribing decisions for breakthrough cancer pain, across the seven major market, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q6.3

DATAMONITOR

As seen in Figure 59, beyond overall efficacy, surveyed physicians regard onset of action to be the most important drug attribute influencing their prescribing decisions for patients with breakthrough cancer pain. This achieved a mean rating of 16/100 points across the seven major markets. By comparison, cost issues and a physician's familiarity with a product indicated for breakthrough cancer pain were viewed by surveyed physicians as the least important factors influencing their prescribing decisions, a clear indication of the severity of breakthrough pain. Key opinion leaders

interviewed by Datamonitor also report that cost is of little influence when deciding which drug to prescribe to patients with breakthrough cancer pain.

> *"No, cost is not an issue. If one needs to use an exceptional drug in certain circumstances then you should."*
>
> EU key opinion leader

> *"Let me emphasize that if the patients respond to the fentanyl products better than they respond to the others then we certainly may, despite the differences in cost, utilize those as the primary breakthrough medications."*
>
> US key opinion leader

Physician perception of key brands

In order to gain an understanding of how prescribers perceive three key drugs prescribed for cancer pain, interviewed physicians were asked to rate the performance, or predicted performance of each product on a scale of 1 to 100, where the higher the score the better the drug performed. Drugs were rated on the following attributes:

- overall efficacy demonstrable by reduction in pain (high efficacy = high score);
- onset of action (rapid onset = high score);
- lack of drug-drug interaction (low drug-drug interaction = high score);
- duration of action (long duration of action = high score);
- overall side-effect profile (favorable side-effect profile = high score);
- flexible dosing frequency e.g. dose quantity (flexibility in dose quantity = high score);
- cost (e.g. reimbursement (full reimbursement = high score);
- physician product familiarity (familiar with brand or company = high score);
- recommended in treatment guidelines (recommended as first line = high score);

- convenient/less invasive route of administration (convenient/less invasive route = high score).

Table 12 summarizes the drugs rated by respondents interviewed for this report.

Table 12: Summary of key branded analgesics prescribed for cancer pain in the seven major markets, 2009

Brand	Molecule	Drug class	Marketing company	Country availability
Lyrica	Pregabalin	GABA alpha-2-delta subunit agonist	Pfizer	US, France, Germany, Italy, Spain, UK
Actiq	Oral transmucosal fentanyl citrate	Mu-opioid receptor agonist	Cephalon	US, France, Germany, Italy, Spain, UK
Fentora	Fentanyl buccal tablet	Mu-opioid receptor agonist	Cephalon	US, France, Germany, Italy, Spain, UK

GABA = gamma-aminobutyric acid
Seven major markets = US, Japan, France, Germany, Italy, Spain, UK.
5EU = France, Germany, Italy, Spain and the UK

Source: Datamonitor DATAMONITOR

It is important to note that although Lyrica, Actiq and Fentora are each marketed in the US and EU, these products are not yet available in Japan. Therefore, physicians in Japan were asked to estimate the performance of the drugs based on data available and scores reflect the perception of the brand more than actual data. Table 13 shows the number and percentage of the physicians who were able to rate each drug under each consideration.

Table 13: Number and percentage of physicians who were able to rate each analgesic drug, 2009

Brand (generic)	Number of physicians able to rate each drug	Proportion of total physicians questioned
Lyrica (pregabalin)	142	79%
Actiq (oral transmucosal fentanyl citrate)	150	83%
Fentora (fentanyl buccal tablet)	118	66%

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q6.4, a-c DATAMONITOR

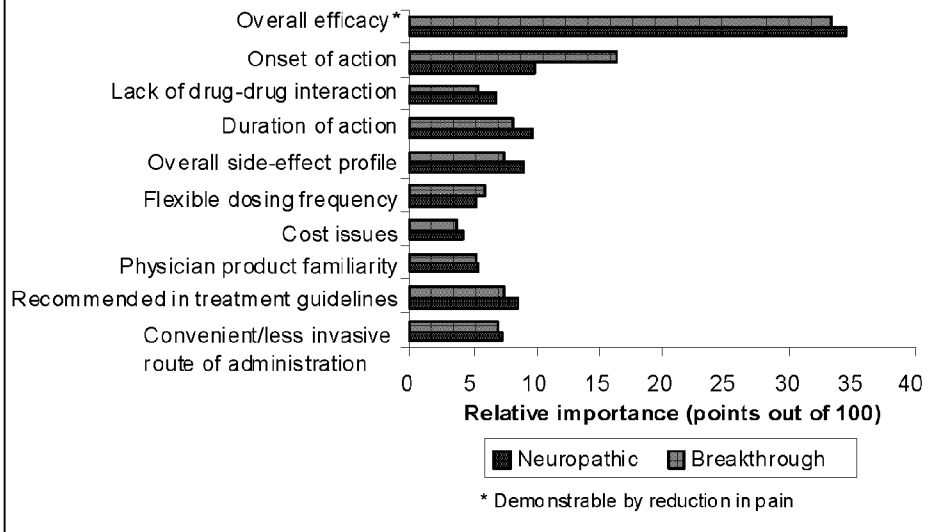
Surveyed physicians cited Actiq (fentanyl citrate; Cephalon) as the most well known brand: 150 (83%) were able to rate the drug, compared to 142 (79%) for Lyrica (pregabalin; Pfizer). Meanwhile, Fentora (fentanyl citrate; Cephalon) was the least well known of the three brands, with only 118 (66%) able to rate the drug.

Total scores per drug

Prior to rating the performance of each drug, physicians were asked to rate the relative importance of 10 clinical drug attributes when prescribing drug therapy for cancer pain, through distributing 100 points among each attribute. Physicians were asked to rate the importance of each drug attribute in relation to neuropathic and breakthrough pain separately.

Figure 60 illustrates the relative importance of 10 drug attributes in influencing physicians' prescribing decisions for neuropathic and breakthrough cancer pain.

Figure 60: Scoring of drug attributes influencing physicians' prescribing decisions for neuropathic and breakthrough cancer pain, across the seven major market, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q6.3 (n = 180)

DATAMONITOR

As seen in Figure 60, the greatest influence on physicians' prescribing behavior for both neuropathic and breakthrough pain across the seven major markets (US,

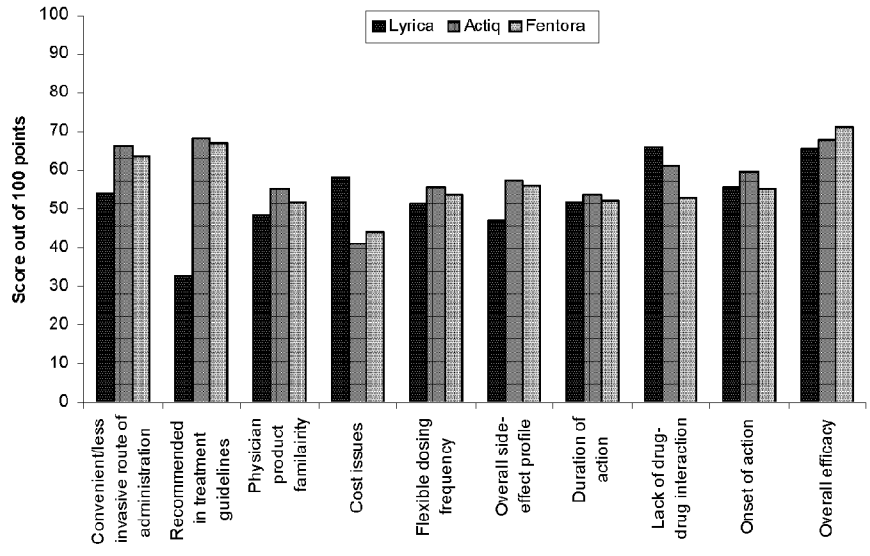
Japan, France, Germany, Italy, Spain and the UK), is overall efficacy (demonstrable by reduction in pain). However, physicians rated this attribute as slightly more influential in prescribing decisions for neuropathic cancer pain (35/100 points) than breakthrough cancer pain (33/100 points).

Unsurprisingly, given the characteristically rapid onset of breakthrough pain, the drug attribute 'onset of action' is of greater importance to physicians when prescribing analgesics for breakthrough cancer pain (16/100 points) compared to neuropathic cancer pain (10/100). In terms of overall side-effect profile, this attribute is of greater influence to physicians when prescribing drugs for neuropathic cancer pain (9/100 points) than breakthrough cancer pain (8/100 points).

In addition to rating the importance of each drug attribute on prescribing behavior, physicians were asked to rate the performance, or predicted performance of each of the three branded therapies (Lyrica, Actiq and Fentora) on a scale of 1 to 100, where 1 = low performance and 100 = high performance. Lyrica was rated in relation to treatment for neuropathic cancer pain whereas Actiq and Fentora were rated in relation to their use in the treatment of breakthrough cancer pain.

Figure 61 presents the mean physician-rated performance ratings for Lyrica, Actiq and Fentora across each drug attribute in the seven major markets. Ratings in Figure 61are weighted according to the relative importance of each attribute as summarized in Figure 60.

Figure 61: Weighted Lyrica, Actiq and Fentora performance scores across the seven major markets, 2009



Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q6.3 (n = 180), Q6.4 (n = 180)

DATAMONITOR

Overall score

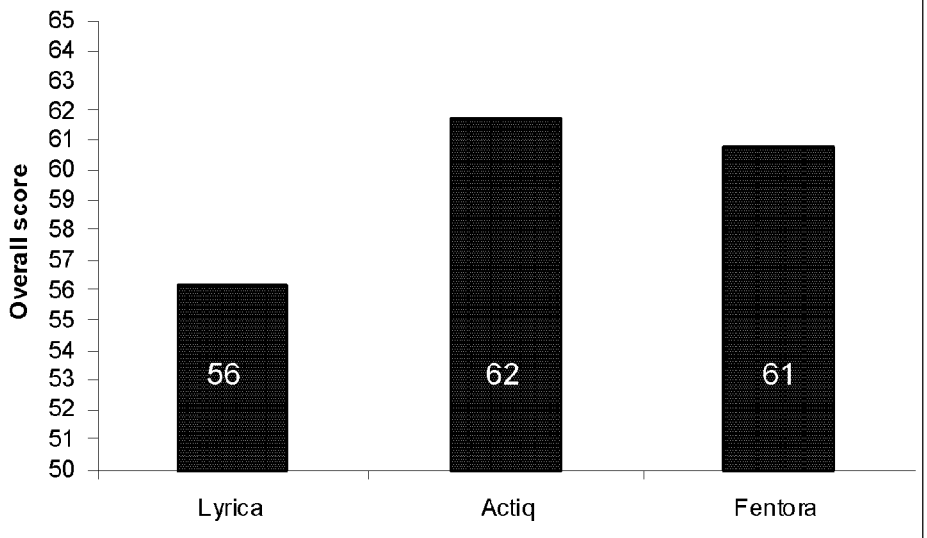
In order to calculate an overall score, it is important that the criteria are weighted in order of importance (see Figure 60). Datamonitor used the following calculation:

Overall score for Drug X = SUM (criteria weighting x [Drug X score / 100])

The neuropathic pain criteria weightings from Figure 60 are used to calculate the overall score of Lyrica. For Actiq and Fentora, the breakthrough pain criteria weightings from Figure 60 were applied.

Figure 62 illustrates how Lyrica, Actiq and Fentora drugs perform based on all criteria.

Figure 62: Overall perceived performance of Lyrica, Actiq and Fentora across the seven major markets



Seven major markets: US, Japan, France, Germany, Italy, Spain and the UK

Source: Datamonitor, *Stakeholder Insight 2009: Cancer Pain* survey, DMHC2536, Q6.3 (n = 180), Q6.4 (n = 180)

DATAMONITOR

Lyrica (pregabalin; Pfizer)

Lyrica (pregabalin) is a GABA alpha-2-delta subunit agonist, developed and launched by Pfizer (formerly Warner-Lambert). The drug was launched in the US in September 2005 for three indications:

- neuropathic pain associated with diabetic peripheral neuropathy;
- post-herpetic neuralgia;
- adjunctive treatment of partial onset seizures in adults with epilepsy (Pfizer press release, 2005; www.pfizer.com).

Later, in June 2007, Lyrica also received US Food and Drug Administration (FDA) approval for the management of fibromyalgia, a chronic, widespread pain condition (Pfizer press release, 2007; www.pfizer.com). In the EU, Lyrica is approved for the treatment of peripheral neuropathic pain, adjunctive therapy for partial onset seizures

in adults (Pfizer press release, 2004; www.pfizer.com), generalized anxiety disorder in adults and central neuropathic pain (Pfizer press release, 2006; www.pfizer.be). Lyrica has not yet been launched in Japan, although as of April 2009 Pfizer had filed a New Drug Application (NDA) for the treatment of neuropathic pain in this market (MedTRACK, November 2009, Copyright Datamonitor).

Lyrica is available in oral capsules (25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg and 300mg) (Lyrica prescribing information, 2009; www.pfizer.com) and is classified as a Schedule V controlled substance, a factor which increases the complexity of its prescribing. The drug's main product patents are not scheduled to expire until 2018 (Dolphin, November 2009, Copyright Thomson Scientific).

Although Lyrica has not been systematically examined in patients with cancer pain and is not approved in this indication, its established analgesic effects in neuropathic pain have led physicians to prescribe it off-label for cancer pain that is neuropathic in origin. An interviewed key opinion leader reports that current understanding of Lyrica's efficacy in neuropathic cancer pain is based upon clinical trial data from neuropathic non-cancer pain populations:

> *"It* [knowledge of Lyrica's efficacy in cancer pain] *is based on non-cancer neuropathic pain predominantly but that is always the case and many of the things we use have to be extrapolated from non-cancer neuropathic pain."*
>
> EU key opinion leader

Despite the dearth of published data for Lyrica as a treatment for neuropathic cancer pain, Lyrica's predecessor—Neurontin (gabapentin; Pfizer)—has demonstrated encouraging data among cancer patients suffering from intractable neuropathic pain (Caraceni *et al.,* 1999). Additionally, a pilot study sought to investigate the efficacy and safety of gabapentin monotherapy on the management of chemotherapy-induced neuropathic pain. Results found that gabapentin led to a complete response in 25.3% of patients (19/75), partial response in 44% (33/75), minor response in 25.3% (19/75), and no response in 5.3% (4/75). The authors concluded that gabapentin monotherapy was well tolerated and useful for the management of chemotherapy-induced neuropathic pain (Tsavaris *et al.,* 2008). One interviewed key opinion leader speculates that Lyrica may be superior to gabapentin in treating neuropathic cancer pain on account on its quicker titration.

> *"There are some thoughts that it* [Lyrica] *may be more advantageous than gabapentin* [for the treatment of neuropathic cancer pain], *not because of its efficacy or its side-effect profile but because it is dose twice daily and*

the titration is quicker than with gabapentin. Although it is often voiced that it [Lyrica] *is more effective* [than pregabalin], *this is not actually borne out by the data."*

EU key opinion leader

"I have seen more efficacy with gabapentin than pregabalin."

EU key opinion leader

However, one key opinion leader reports that Lyrica is recognized as a first-line treatment option for neuropathic cancer pain:

"It [Lyrica] *is recognized as being first line* [for neuropathic cancer pain]."

EU key opinion leader

Pfizer is currently conducting a Phase IV trial which aims to assess the analgesic efficacy of flexibly dosed Lyrica in the adjunctive treatment of cancer-induced bone pain. The estimated patient enrollment of the study is 310 and it is expected that the study will be completed in October 2010 (National Institutes of Health, 2009, NCT00381095; http://clinicaltrials.gov).

Physicians rated Lyrica relatively highly in terms of duration of action

Of the surveyed physicians, 75% (27/36) were able to rate Lyrica, a figure which Datamonitor regards as relatively low in view of the fact that the drug has been available in the US since 2005. The implication is that oncologists—who, according to Datamonitor's primary research, initiate and manage analgesia in the majority of cancer pain patients—are more familiar with traditional analgesics (such as non-steroidal anti-inflammatory drugs and opioids) than anticonvulsants when treating pain. (For further information on the healthcare professionals involved in cancer pain management, please refer to the section titled Professional involvement in CHAPTER 5). Physician awareness of Lyrica was highest in the 5EU, where 91% (109/120) of physicians were able to rate the drug. Awareness of Lyrica was lowest in Japan, with just 25% (6/24) of surveyed physicians able to rate the drug in this market. This low awareness was unsurprising, given that Lyrica is not yet available in Japan.

Lyrica's highest attribute rating was for overall efficacy (demonstrable by reduction in pain). However, Lyrica's rating on this attribute was surpassed by equivalent ratings for the two breakthrough cancer pain drugs; Actiq and Fentora. This positioning in relation to Actiq and Fentora is expected, since both these drugs are indicated for

breakthrough pain which requires rapid analgesic relief. Key opinion leaders interviewed by Datamonitor comment on Lyrica's efficacy in treating neuropathic cancer pain:

> *"It* [Lyrica] *is very good* [for neuropathic cancer pain]. *We prescribe a lot of pregabalin in our practice, and that is because it appears to be effective and it is well tolerated by most people and it is easy to titrate and it is desirable because if it is going to be helpful it will reveal its benefit within a couple of weeks."*
>
> EU key opinion leader

> *"Well for neuropathic* [cancer] *pain it* [Lyrica] *is likely to work in about one in four patients."*
>
> EU key opinion leader

> *"There is very mixed reaction* [among patients to Lyrica]. *Some people* [cancer pain patients] *get the most marvelous relief with it and think it is wonderful, but many other patients feel woozy and drowsy on it and they can put on weight, which maybe is not a problem with cancer pain management, but there are quite a few patients who do not like the way they feel when they are on it. It* [Lyrica] *is also an old drug."*
>
> EU key opinion leader

> *"I do not really believe that it* [Lyrica] *works very well. It takes a very long time to increase the dose to a good level and it does not work that well for the burning* [sensation associated with neuropathic pain]. *My opinion is that the improvement* [in pain relief] *is just 30%."*
>
> EU key opinion leader

Beyond overall efficacy, physicians rated Lyrica relatively highly on duration of action. As seen in Figure 60, duration of action is the most important attribute influencing physicians' prescribing decisions for neuropathic cancer pain. Lyrica is administered orally and is available in seven different dosage strengths. According to an interviewed key opinion leader, Lyrica is regarded as a first-line treatment for neuropathic cancer pain.

> *"Lyrica, tends to be a first line* [treatment for neuropathic cancer pain] *for a couple of reasons. Firstly we find it can be effective and secondly, it works quickly."*

US key opinion leader

However, the same key opinion leader reports that insurance companies hamper the use of Lyrica in neuropathic pain, permitting the drug's use only after a patient has failed to achieve satisfactory pain relief using Neurontin (gabapentin; Pfizer).

> *"We* [physicians] *get pushed back from the insurance carriers regarding use of pregabalin unless the patient has failed a trial of gabapentin, and that really makes no sense for several reasons. Number one, it may take several weeks to titrate a dosage of gabapentin that can be useful, on the other hand you have pregabalin which is going to show benefit within the first week or perhaps two, and so you can see results quicker with pregabalin than you can with gabapentin, and this makes it an obvious first choice. So from a humanitarian and ethical standpoint, it makes sense to start with pregabalin because of the quicker results."*

US key opinion leader

In relation to other drugs prescribed for the treatment of neuropathic cancer pain, an interviewed key opinion leader reports Lyrica's onset of action to be superior to that of tricyclic antidepressants and gabapentin:

> *"It* [the onset of action of Lyrica in neuropathic cancer pain] *is variable but it seems to be quicker than for the tricyclics or for gabapentin. For tricyclics, I would usually say to a patient it will take up to about a week, for the gabapentin I usually say up to about 4 to 5 days and pregabalin is probably a bit quicker than that, taking between 2 and 4 days to work."*

EU key opinion leader

Actiq (oral transmucosal fentanyl; Cephalon)

Actiq was developed by Abbott Laboratories and is now marketed by Cephalon. Actiq is an oral transmucosal formulation in the form of a lollipop stick of the opioid analgesic fentanyl, utilizing technology designed by Anesta. The product is indicated for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to opioid therapy for their underlying, persistent cancer pain. Actiq was approved by the FDA in November 1998 and was launched in the US in March 1999 (MedTRACK, November 2009, Copyright Datamonitor). A sugar-free formulation of Actiq was later approved in the US in September 2005. Actiq was launched in the UK in January 2001 by Elan, and the Mutual Recognition Procedure (MRP) was completed in June 2001, with numerous other European launches

following. Although Actiq was to be launched in Europe through Elan, by October 2002 Elan had divested all its rights back to Cephalon, and at that stage required all rights in Austria, Belgium, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Switzerland, the UK, the Philippines and Taiwan. Cephalon was to market the drug directly in the US, Germany and France.

Cephalon's Japanese marketing partner—Mitsubishi Tanabe Pharma—filed an NDA for Actiq in Japan in August 2008 (Mitsubishi Tanabe Pharma, State of New Product Development, 2009; www.mt-pharma.co.jp). On this basis, Datamonitor expects Cephalon's Japanese marketing partner to launch Actiq in Japan in 2010 (Datamonitor, *Forecast Insight: Opioids*, March 2009, DMHC2483).

Actiq came off patent in 2006, unleashing a flood of generics starting with Watson and Barr Pharmaceuticals, which introduced generic Fentanyl oral transmucosal formulation to the market in Q3 2006. Actiq garnered sales of $377m across the six major pharmaceutical markets (the US, France, Germany, Italy, Spain and the UK) in 2008 (MIDAS sales data, IMS Health, September 2008.

Actiq is available as an oral, transmucosal lozenge in six dosage strengths: 200mcg, 400mcg, 600mcg, 800mcg, 1,200mcg and 1,600mcg (Actiq package insert, 2009; www.actiq.com). The product is a Schedule II controlled substance, with an abuse liability similar to other opioids. For further information on Actiq, please refer to Datamonitor's report *Forecast Insight 2008: Opioids (DMHC2483).*

Actiq is the more widely recognized of Cephalon's two fentanyl products

Actiq is one of two fentanyl-based products marketed by Cephalon which physicians surveyed by Datamonitor were asked to rate the performance of. A total of 83% (150/180) of physicians across the seven major markets were able to rate Actiq's performance, compared to 66% (118/180) for Fentora. Similarly, as illustrated in Figure 61, Actiq also marginally outperformed Fentora in terms of the attribute 'physician product familiarity'. Therefore, results from Datamonitor's survey demonstrate that, of Cephalon's two fentanyl products, Actiq is the drug with which physicians are most familiar. Datamonitor believes that this reflects the fact that Actiq was the first drug to receive regulatory approval for the treatment of breakthrough cancer pain and is the more established of the two products in the market; Actiq launched in the US in 1999, with launch of Fentora taking place seven and a half years later. However, an interviewed key opinion leader indicates that Actiq's high level of recognition among physicians may suffer as a result of lack of promotion and the competition posed by new fentanyl products entering the market. For example, Meda's Onsolis (fentanyl buccal soluble film)—a thin soluble disc that attaches to the

inside of the cheek and is indicated for the treatment of breakthrough cancer pain—launched in the US in October 2009.

> *"It* [Actiq] *has got a bit of a problem now that it is not being actively promoted by the company anymore because there is a whole wealth of new designed or fentanyl designed delivery systems for breakthrough pain. There are lots of other fast acting fentanyl preparations entering the market at the moment."*
>
> EU key opinion leader

Physician awareness of Actiq was highest in the 5EU (France, Germany, Italy, Spain and the UK), where around 93% (113/120) of physicians were able to rate the drug. Product familiarity was particularly high in France and Italy where 100% of physicians surveyed were able to rate Actiq's performance. Although Actiq is not yet available in Japan, almost half (46%) of Japanese physicians surveyed by Datamonitor were familiar with the brand and able to rate its performance based on available data.

Contrary to clinical trial data, physicians rated Actiq's onset of action on a par with Fentora

Of the 10 attributes rated by surveyed physicians, Actiq achieved the greatest weighted score for overall efficacy, thereby outperforming Fentora's score on this attribute. Beyond overall efficacy, onset of action represented Actiq's second highest score. That Actiq should score relatively highly for this attribute is unsurprising in view of the drug's indication for breakthrough cancer pain, a condition that requires treatment with a rapid acting analgesic. However, surveyed physicians rated Actiq's performance in terms of onset of action to be on a par with that of its follow-on product, Fentora. An interviewed key opinion leader echoes the view expressed by surveyed physicians:

> *"It* [Fentora] *seems it is as quick as Actiq."*
>
> EU key opinion leader

The similar physician ratings for Actiq and Fentora in terms of onset of action stands at odds with recently published clinical trial data for the two products. According to Actiq's pivotal clinical trial data, approximately 50% of the reduction in pain intensity occurs within 15 minutes (Farrar *et al.,* 1998).

Despite the labels of both Fentora and Actiq stating that onset of action occurs 15 minutes after the initiation of treatment, buccal absorption is faster than transmucosal

absorption. According to Fentora's package insert, the rate of drug exposure is around 30% higher than that of Actiq (Fentora package insert, 2007; www.fentora.com). Furthermore, clinical trial data indicate that Fentora possesses a more rapid onset of action than Actiq. The Phase III clinical trial of Fentora in 103 non-cancer patients with breakthrough neuropathic pain found reductions in pain intensity and pain relief were significantly greater with Fentora than placebo at 10 minutes ($p<0.05$, $p=0.0005$, respectively) and were maintained throughout the 120-minute evaluation period ($p<0.0001$ for both PI and PR) (Cephalon press release, 2007; www.cephalon.com).

Nevertheless, one interviewed key opinion leader perceives Actiq to possess the more rapid onset of action:

> *"It* [the onset of action of Actiq] *is 5 to 10 minutes."*
>
> EU key opinion leader

Although surveyed physicians rate Actiq and Fentora similarly in terms of onset of action, key opinion leaders interviewed by Datamonitor comment that Actiq is not a popular treatment option among patients and that titration of the drug can be problematic.

> *"My population of* [cancer] *patients do not like this drug* [Actiq] *very much…probably because we do not know exactly the doses and probably because sometimes they have adverse effects. So it* [Actiq] *is not a good choice for me."*
>
> EU key opinion leader

> *"It* [Actiq] *is efficacious in less than half of the patients in whom I prescribe it. We are not able to use this drug in the best way because nobody knows the real rescue dose amount in respect to other drugs, or with respect to the chronic therapy."*
>
> EU key opinion leader

> *"Well it* [Actiq] *works well, but the problem is that it is difficult for the patient to do it and the titration is also not that easy."*
>
> EU key opinion leader

Fentora (fentanyl buccal tablet; Cephalon)

Cephalon's Fentora is an oral buccal tablet formulation of the opioid analgesic fentanyl and is indicated for the management of breakthrough pain in patients with cancer who are already receiving and are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain (Fentora package insert, 2007; www.fentora.com). Based on the same opioid molecule as Actiq, Fentora represents Cephalon's lifecycle management strategy aimed at minimizing losses to generic Actiq (which entered the market in 2006), thereby maintaining revenues from the short-acting opioids market. Fentora is a Schedule II controlled substance, with an abuse liability similar to other opioids.

Fentora was initially approved for breakthrough cancer pain in the US in September 2006 (Cephalon press release, 2006; www.cephalon.com). Cephalon launched the product in the US in October 2006 (MedTRACK, November 2009, Copyright Datamonitor). In April 2008, the European Commission granted marketing authorization for Fentora, allowing Cephalon to market the drug in the 27 member states of the European Union as well as Iceland and Norway (Cephalon press release, 2008; www.cephalon.com). The product launched in Europe in January 2009 under the brand name Effentora (Cephalon annual report 2008, February 23 2009; www.investors.cephalon.com). According to the National Institutes of Health, Fentora completed a Phase III clinical trial in breakthrough cancer pain in Japan in September 2009. Kyowa Hakko Kirin sponsored the study (National Institutes of Health, 2009, NCT00683995; http://clinicaltrials.gov).

Fentora is available as effervescent buccal tablets in six dosage strengths (100mcg, 200mcg, 300mcg, 400mcg, 600mcg and 800mcg). According to the patient and caregiver prescribing information on the product website, once Fentora is taken out of the blister pack, the patient must immediately place the tablet in the mouth above a rear molar tooth between the upper cheek and gum (Fentora package insert, 2007; www.fentora.com). It is to be left there where it will dissolve over 14 to 25 minutes. Patients are advised not to bite, chew or suck the tablets and that if they accidently swallow the medicine before it can cross the lining of the mouth then they may experience less pain relief.

In September 2007, Cephalon (in collaboration with the FDA) reinforced important prescribing and dosing information for Fentora in response to reports of serious adverse events, including some deaths in patients who were not appropriate candidates for Fentora. The drug's reinforced label restrictions are outlined below:

- Fentora is indicated only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.
- Fentora must only be prescribed to patients who are routinely taking around-the-clock opioids. Fentora should not be prescribed to patients for acute pain, postoperative pain, headache/migraine pain or sports injuries.
- Only one tablet per episode should be taken once a dose is established and patients must wait at least four hours before taking another dose of Fentora.
- Fentora is not bioequivalent to or a generic version of Actiq, and therefore Fentora should not be substituted for Actiq or any other fentanyl-containing pain medication (Cephalon press release, 2007; www.cephalon.com).

For further information on Fentora, please refer to Datamonitor's report *Forecast Insight 2008: Opioids (DMHC2483).*

Fentora's ratings for convenience of administration marginally outperform Actiq

Of the three analgesic products rated by surveyed physicians, Fentora was the least well-recognized, with 66% (118/180) of physicians across the seven major markets able to rate the drug, compared to 79% (142/180) for Lyrica and 83% (150/180) for Actiq. Datamonitor believes that this reflects the fact that Fentora is not as well established in the market as Actiq and Lyrica. (Fentora initially launched in October 2006, while Actiq launched in March 1999 and Lyrica launched in September 2005).

According to the results of Datamonitor's survey, physician familiarity with Fentora is highest in the EU, where an average of 71% of physicians (118/120) across this region were able to rate the product. Therefore, given that Fentora launched in the EU only relatively recently, the drug is already well recognized by physicians. Italian physicians are most familiar with Fentora, with 100% of surveyed physicians in this country able to rate the drug. It is reasonable to speculate that this indicates that Cephalon's physicians detailing efforts have been particularly effective in this market. In comparison to the EU, only 58% (21/36) of US physicians were able to rate the performance of Fentora. In Japan, 50% (12/24) of surveyed physicians were able to rate Fentora's performance, despite the fact that the drug has not yet launched in this market. As such, of the three products included in Datamonitor's survey, Fentora is the product most familiar to physicians in Japan.

Fentora's convenient route of administration was rated highly by surveyed physicians, garnering a mean of 72/100 across the seven major markets. An interviewed key opinion leader comments on Fentora's strengths as a treatment for breakthrough cancer pain. As such, Fentora's score compares favorably to Actiq's and Lyrica's mean scores of 68/100. Unlike Actiq, which is a lollipop formulation that must be held in the mouth for a period of 15 minutes, Fentora is a tablet that is placed between the upper cheek and gum.

> *"Fentora gets onboard quickly, is fairly easy to use and well tolerated so this agent is very useful in our practice."*
>
> US key opinion leader

Datamonitor's primary research therefore indicates that although Actiq and Fentora are both administered orally, physicians regard Fentora's effervescent buccal formulation as preferable to Actiq's transmucosal lozenge formulation in the treatment of breakthrough cancer pain. Fentora's superior rating in terms of route of administration may reflect the drug's more discreet formulation compared to the Actiq lollipop. A pill is easier to carry and more easily utilized by patients who may have co-ordination difficulties. Moreover, some patients may have difficulty moving the Actiq lozenge around the mouth—a process necessary to increase the rate or absorption—as it can be painful and may exacerbate bleeding in the mouth cavity. As such, the dissolvable nature of Fentora is an advantage over Actiq. Interviewed key opinion leaders discuss the delivery systems of Actiq and Fentora:

> *"The problem with Actiq is that very often the patients do not dissolve all the stick and there is a lot of fentanyl on the stick still."*
>
> EU key opinion leader

> *"I guess because it* [Fentora] *does not have the lollipop stick that Actiq does, it is less conspicuous and maybe easier for patients to use."*
>
> US key opinion leader

CHAPTER 9 IMPROVING TREATMENT OUTCOMES AND UNMET NEEDS

- *According to results of Datamonitor's primary research survey, physicians across the seven major markets believe that there remains room for improvement in the effectiveness of currently available prescription pain medicines in the treatment of cancer pain. This view is supported by published studies which report that a sizable proportion of patients with cancer pain fail to obtain satisfactory pain relief.*

- *In particular, survey results demonstrate that physicians across the seven major markets are least satisfied with available drug treatments for neuropathic cancer pain. It is therefore apparent that physicians face greater challenges in achieving satisfactory analgesic relief for patients with neuropathic cancer pain compared to neuropathic and breakthrough cancer pain.*

- *Interviewed key opinion leaders (KOLs) were unanimous in the view that improved physician education currently represents the greatest unmet need in the treatment of all forms of cancer pain. This represents a key opportunity for manufacturers to provide education programs which inform physicians on methods of assessing pain, as well as the availability and appropriate use of analgesics for different subtypes of cancer pain.*

- *Interviewed key opinion leaders believe that improved efficacy of pharmacological treatments currently represents the greatest unmet need in the treatment of neuropathic cancer pain. However, improved understanding of the pathophysiological mechanisms of neuropathic pain in cancer patients is needed in order to identify new techniques and therapies.*

- *Key adverse effects associated with opioid use include sedation, sedation, respiratory depression and constipation. Since opioids are prescribed for both neuropathic and non-neuropathic cancer pain (particularly among patients with severe pain), as well as breakthrough cancer pain, reduced opioid-related adverse events represents a principal unmet need in the management of cancer pain.*

- *Secondary to reduced opioid-adverse events, the second greatest unmet need in the management of breakthrough cancer pain is for an analgesic that acts rapidly, predictably and just for the duration of a breakthrough pain episode. The ideal treatment of breakthrough pain would match its onset and duration and would therefore typically have a rapid onset (within minutes) and a short duration of action (about 30 minutes in most cases).*

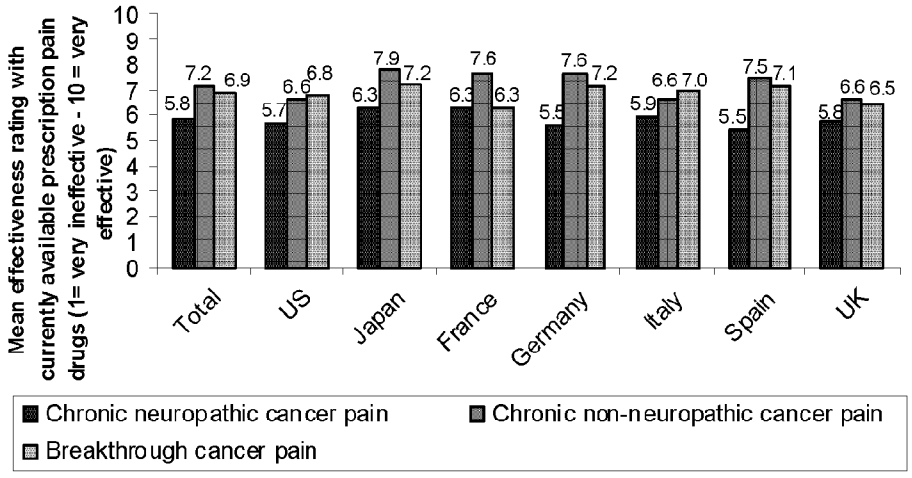
Effectiveness of available prescription pain medicines

Physicians interviewed by Datamonitor across the seven major markets (the US, Japan, France, Germany, Italy, Spain and the UK) were asked to rate the effectiveness of currently available prescription pain medicines in treating three key subtypes of cancer pain: chronic neuropathic cancer pain, chronic non-neuropathic cancer pain and breakthrough pain. Physicians surveyed by Datamonitor indicate that there remains room for improvement in available treatments for cancer pain. In particular, physicians across the seven major markets report the least satisfaction with available treatments for neuropathic cancer pain.

Surveyed physicians believe that there is room for improvement in the effectiveness of available mediations for cancer pain

Figure 63 shows physicians' effectiveness ratings of currently available prescription pain medicines in the treatment of three key subtypes of cancer pain: chronic neuropathic cancer pain, chronic non-neuropathic cancer pain and breakthrough pain.

Figure 63: Physicians' effectiveness rating of available prescription pain medicines in controlling three subtypes of cancer pain across the seven major markets, 2009



Source: Datamonitor, Stakeholder Insight 2009: Cancer Pain, DMHC2536, Q7.1

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As seen in Figure 63, physicians' effectiveness ratings for currently available pain medications for cancer pain are largely similar across each of the seven major markets. It is important to note that available prescription pain medications for neuropathic, non-neuropathic and breakthrough pain do not score above 8/10 across the seven major markets. Therefore, physicians believe that there remains room for improvement in drug treatments for cancer pain.

Several studies have sought to determine the treatment outcomes of cancer patients receiving treatment for pain. According to Zech *et al.* (1995), between 70 and 90% of all cancer pain can be controlled with oral medication. Adequate pain relief can be achieved in more than 75% of patients who receive optimal analgesic management using simple techniques such as opioids, non-opioid analgesics, and adjuvant medications, as suggested by the World Health Organization's analgesic ladder [World Health Organization, 1990; World Health Organization, 1996). According to research published in 2003 by the Ministry of Health, Labour and Welfare, only around 40% of cancer patients in Japan are free of pain, despite the steady rise in use of narcotic medicines since 1989 (Shionogi & Co. Ltd Annual Report 2008, www.shionogi.co.jp). These figures from Zech *et al.* (1995), the World Health Organization and the Japanese Ministry of Health, Labour and Welfare indicate that a sizable proportion of patients with cancer fail to obtain satisfactory pain relief and are consequently likely to require other pain management strategies, such as alternative routes of administration, nerve blocks or other invasive procedures (IASP, Pain Clinical Updates, 2005, www.iasp-pain.org).

A prospective study by Mishra *et al.* (2008) examined the 6-month outcomes of 818 neuropathic cancer pain patients managed according to the WHO analgesic ladder. At the end of 6 months, 53.2% patients had no pain and 41.9% of patients had mild pain as compared to 0% and 10.2% of patients at the first visit. However, 4.9% of patients had moderate pain even after the treatment.

Physicians are least satisfied with current treatments for neuropathic cancer pain

Results of Datamonitor's physician survey (Figure 63) demonstrate that physicians across the seven major markets are least satisfied with available treatments for neuropathic cancer pain, indicating that physicians face greater challenges in achieving satisfactory analgesic relief for cancer patients with this form of cancer pain. Available pharmacological treatments for neuropathic cancer pain achieved a mean effectiveness rating of almost 6/10 across the seven major markets. It is therefore apparent that physicians face greater challenges in achieving satisfactory analgesic relief for patients with neuropathic cancer pain compared to non-

neuropathic and breakthrough cancer pain. This key finding is supported by qualitative interviews with key opinion leaders:

> *"In my opinion, the neuropathic* [cancer] *pain has less efficient treatment."*
>
> EU key opinion leader

> *"The commonly used ones* [analgesics] *are relatively poor at improving quality of life* [in patients with neuropathic cancer pain]."
>
> EU key opinion leader

> *"It* [treatment for chronic non-neuropathic cancer pain] *is probably more efficient and I would say the majority of patients who correctly use morphine are able to control the pain, in around 70% of cases."*
>
> EU key opinion leader

Results of Datamonitor's survey also indicate that surveyed physicians believe that currently available prescription medicines are most effective in treating non-neuropathic cancer pain. The mean effectiveness rating for available treatments for breakthrough cancer pain was reported to be almost 7/10 across the seven major markets, thereby lying indicating that treatments for breakthrough pain are more effective than those for neuropathic cancer pain but are inferior to those available for the treatment of non-neuropathic cancer pain. An interviewed key opinion leader comments on the effectiveness of prescription medicines for breakthrough cancer pain.

> *"Treatment for breakthrough pain is relatively effective, but the payoff is side effects and one could argue that they should not need breakthrough medication in the first place, if the treatment was effective."*
>
> EU key opinion leader

Unmet needs

Seven key opinion leaders interviewed by Datamonitor were asked to discuss their views on what currently represents the greatest unmet needs in the treatment of cancer pain. In view of the different clinical attributes required by drugs indicated for each key subtype of cancer pain (neuropathic, non-neuropathic and breakthrough pain), unmet needs for these pain conditions are discussed separately. Interviewed key opinion leaders were unanimous in the view that improved physician education

currently represents the single greatest unmet need across each subtype of cancer pain.

Non-clinical unmet needs

Physician education represents the most pressing unmet need in the management of cancer pain

As discussed in CHAPTER 5, results from Datamonitor's primary research survey indicate that available pharmacological treatments for cancer pain are underutilized, particularly among cancer patients with mild to moderate pain as well as breakthrough pain. Inadequate pain assessment by physicians is one potential reason for the under-utilization of drug treatments. Indeed, key opinion leaders believe that inadequate pain assessment is the result of insufficient training in pain management in undergraduate medical training. (For further information on pharmacological treatment rates for cancer pain across the seven major markets and key reasons for under-use of drug therapies, please refer to CHAPTER 5).

In keeping with these findings, key opinion leaders interviewed by Datamonitor unanimously agreed that physician education currently represents the greatest unmet need in the management of cancer pain. As summarized in the following quotes, physicians believe that the need for physician education spans each key subtype of cancer pain—breakthrough pain, neuropathic and non-neuropathic—and is required throughout undergraduate and postgraduate medical training.

> *"My opinion is that it is absolutely necessary to do educational programs for physicians, because physicians that are not specialists in pain therapy and palliative care (i.e. the oncologists, the physicians working in internal medicine, the geriatricians)...all these specialists need to have an improvement in their knowledge regarding the use of opioids or analgesics in neuropathic and non-neuropathic pain."*
>
> EU key opinion leader

> *"We have to have a multi-pronged approach to improve pain education starting at the undergraduate level through postgraduate training and then into their professional careers."*
>
> US key opinion leader

"Education at all levels in healthcare professions [is needed]. *Pain education has to be included in the undergraduate medical curriculum and has to continue to be part of an ongoing training after medical school and then physicians that are in practice should stay up to date with advances in pain care. They also should have a network of consultants that they can refer to for help when they have pain issues that are beyond their level of knowledge and skill and expertise."*

US key opinion leader

"The first thing to do is not to have new drugs. We just need better education of the doctors and of the patients, because now in this day and age we can't only treat cancer and forget pain. The first need is to have a better training for young medical doctors and to have post education training to explain the role of and good use of morphine, because we have got good drugs for the majority of non breakthrough pain and non neuropathic pain, but they are not used appropriately."

EU key opinion leader

"I think the oncologists are not the ones who are asking the patients about breakthrough pain. They do not know that and they have not had the training to understand what breakthrough pain is. They know the background pain, but not the breakthrough pain. If you do not ask the patient, you do not know that they have had breakthrough pain."

EU key opinion leader

"I think in practice they [physicians] *do not know about neuropathic and non-neuropathic pain. It is a lack of training… they can probably use the three steps of the WHO* [World Health Organization]*, but neuropathic pain is more a specialist thing."*

EU key opinion leader

When asked about the existence of current initiatives that have the potential to improve physician education and ameliorate the under-utilization of drug treatments in the management of cancer pain, a US-based key opinion leader cites the recently published MayDay Pain Report (A Call to Revolutionize Chronic Pain Care in America, 2009; www.maydaypainreport.org):

"There are institutional steps being taken by individual institutions and then there are some broader initiatives that are in progress and you may

be aware of the MAYDAY Pain Report that was released [at the beginning of November 2009]."

US key opinion leader

The report, titled 'A Call to Revolutionize Chronic Pain Care in America: An Opportunity in Health Care Reform', was published on November 4, 2009 by the Mayday Fund Special Committee on Pain and the Practice of Medicine. A central tenet of the report is that all stakeholders—state medical boards, deans of medical and other health professional schools, directors of residency training programs in specialties and subspecialties that provide primary care, professional societies and all others—should make sure that every trainee and health practitioner in the health profession has the skills to assess and treat pain effectively, including chronic pain. The report also states that licensing examinations should include assessment of clinical knowledge related to appropriate pain care. A second important recommendation states that the Health Resources and Services Administration should expand funding for pain training programs that address competencies in pain assessment and management aimed at pediatric and adult primary care physicians, as well as other health professionals who manage pain such as nurses, pharmacists, psychologists, physical therapists and other providers (A Call to Revolutionize Chronic Pain Care in America, 2009; www.maydaypainreport.org). Datamonitor believes that the implementation of these recommendations bodes well for the future training of physicians responsible for the management of cancer pain in the US.

The prevailing consensus among key opinion leaders that physician education remains the greatest unmet need in the treatment of cancer pain represents a key opportunity to pharmaceutical companies marketing analgesics. Industry-sponsored education programs which inform physicians on methods of assessing pain, as well as the availability and appropriate use of analgesics for different subtypes of cancer pain, have the potential to increase the pharmaceutical treatment rate in the cancer pain population. As discussed in CHAPTER 5, oncologists and primary care physicians are the key healthcare professionals responsible for initiating and managing analgesic treatment in patients with cancer pain. Therefore, pharmaceutical companies sponsoring such education programs would be best served to ensure that oncologists and primary care physicians are the target audience.

An EU-based key opinion leader comments on the utility of previous training sessions provided by pharmaceutical companies 10 years ago:

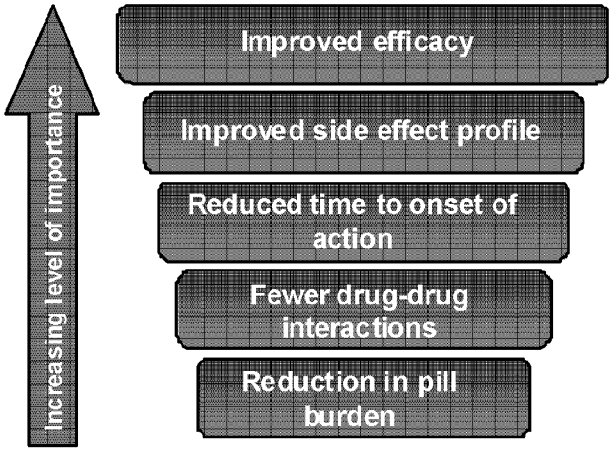
"I remember when we started with slow release opioid in the 1990s. The people who were presenting the drug at the hospital ran a lot of training sessions and it was very good, I think."

EU key opinion leader

Clinical unmet needs: neuropathic cancer pain

Figure 64 illustrates the key unmet needs in relation to neuropathic cancer pain.

Figure 64: Key unmet needs in the treatment of neuropathic cancer pain, 2009



Source: Datamonitor

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Improved efficacy

Although few studies of neuropathic pain have been conducted in patients with cancer, a variety of pharmacologic therapies are prescribed for this patient group. Outlined below are the results of several studies investigating the efficacy of available treatments for the treatment of neuropathic cancer pain:

- **Gabapentin** – among patients with chemotherapy-induced neuropathic pain, gabapentin led to a complete analgesic response in 25.3% of patients (19/75), partial response in 44% (33/75), minor response in 25% (19/75) and no response in 5% (4/75) (Tsavaris *et al.,* 2008).

- **Tramadol** – a small-scale study (n = 36) involving patients with neuropathic cancer pain reported a reduction in mean pain intensity of 57% (from 6.8 at baseline to 2.9 at day 45 on the 10-point scale) in the tramadol group

compared with 39% in the placebo group (from 7 to 4.3) (Arbaiza & Vidal, 2007);

- **Amitriptyline** – a randomized, placebo-controlled, double-blind, cross-over study involving patients with neuropathic cancer pain (n = 16) reported the analgesic effects of amitriptyline to be slight and associated with adverse effects. The authors concluded that the extensive use of the drug for cancer pain should be questioned (Mercadante *et al.,* 2002);

- **Nortriptyline** – A Phase III evaluation of nortiptyline for alleviation of symptoms of cis-platinum peripheral neuropathy concluded that nortriptyline provides modest improvement at best over placebo in terms of chemotherapy-related neuropathy (n = 51) (Hammack *et al.,* 2002).

- **Venlafaxine** – a 10 week, randomized, double-blind, crossover comparison of venlafaxine and placebo in patients with neuropathic cancer pain reported that average daily pain intensity was not significantly reduced by venlafaxine compared with placebo. However, the average pain relief and maximum pain intensity were significantly lower with venlafaxine compared with placebo (Tasmuth *et al.,* 2002).

As can be seen in the summaries studies, published studies demonstrate that available drug treatments provide insufficient analgesic relief to patients with neuropathic cancer pain.

Furthermore, physicians surveyed by Datamonitor report the least satisfaction with available treatments for neuropathic cancer pain, relative to non-neuropathic and breakthrough cancer pain. (For further information on physicians views on the effectiveness of current treatments, please refer to the section title 'Effectiveness of available prescription pain medicines'). Key opinion leaders interviewed by Datamonitor expressed the same view as surveyed physicians.

> *"The reality is, any drug we use, it is not effective for neuropathic pain."*
>
> Japanese key opinion leader

> *"It is probably 30% of patients* [with chronic neuropathic cancer pain*] that are quite well treated, but the majority* [of patients] *have no real improvement."*
>
> EU key opinion leader

It is therefore apparent that despite a spectrum of drugs available with different modes of action, neuropathic pain is a complex pain problem that is often refractory to treatment. As such, many patients with neuropathic cancer pain remain inadequately treated. For this reason, drugs with improved efficacy represent the greatest clinical unmet need in the treatment of neuropathic cancer pain. However, the underlying mechanisms of neuropathic cancer pain are poorly understood (Paice, 2003). Consequently, Datamonitor believes that improved understanding of the pathophysiological mechanisms of neuropathic pain in cancer patients is needed in order to identify new techniques and therapies that will relieve neuropathic pain among cancer patients.

Improved side-effect profile

According to studies involving non-cancer neuropathic pain patients, traditional anticonvulsants, tricyclic antidepressants and opioids have an improved efficacy over newer generation anticonvulsants or the serotonin-norepinephrine reuptake inhibitor (SNRI) Cymbalta (duloxetine, Eli Lilly) for relieving neuropathic pain (Goldstein *et al.,* 2003; Finnerup *et al.,* 2005; Beydoun & Kutluay 2002; Carrazana and Mikoshiba, 2003). However, these drugs are hindered by their poor side-effect profiles, hence restricting their use. For example, potential adverse effects of older anticonvulsants (including carbamazepine, phenytoin and valproate) require careful monitoring, particularly for neutropenia and magablastic anemia (Paice, 2003). Drug choices are now based not only on efficacy but also toxicity and drug interactions. For this reason, Cymbalta and GABA modulators Neurontin (gabapentin, Pfizer) and Lyrica (pregabalin, Pfizer) have become popular, despite demonstrating a lower efficacy than the tricyclic antidepressant drug class.

Therefore, in order to receive uptake among the neuropathic cancer pain population, pharmaceutical companies would benefit by ensuring their analgesic products are differentiated from the traditional treatments by reducing the harmful side effects and improving the safety profile.

Reduced time to onset of action

There is a demand for faster acting drugs in the management of neuropathic pain, as current treatments vary from 8 weeks (gabapentin) to 1 week (pregabalin) for effective pain management. Even though the leading drug in the neuropathic pain market, Lyrica, demonstrates significant improvement in this unmet need over its predecessor, patients would ideally obtain instantaneous pain relief in preference to waiting for 7 days before symptoms are significantly alleviated. There are insufficient data covering the onset of action for many of the other products that are used, such

as the relatively short-acting opioids, including oxycodone and morphine. In general, when those products are used orally, the impression is that the onset of action is usually 20–30 minutes or more.

Fewer drug-drug interactions

Many of the drugs used for neuropathic cancer pain treatment have the potential to interact with other medications which the sufferer may be prescribed. Cymbalta is subject to drug interactions as both the enzymes CYP1A2 and CYP2D6 are responsible for its metabolism. As such, inhibitors of, or drugs metabolized by, these enzymes can exert side effects. In addition, Cymbalta may have clinically important reactions with central nervous system acting drugs and serotonergic drugs.

In the case of carbamazepine, drugs acting on the CYP3A4 enzyme may affect its plasma levels, and hence cause side effects. In contrast, Lyrica and gabapentin are not metabolized, and are therefore not subject to drug interactions. Despite the availability of Lyrica and gabapentin, more drugs are needed in the neurologists' pharmacological arsenal for treating neuropathic cancer pain which are devoid of drug-drug interactions.

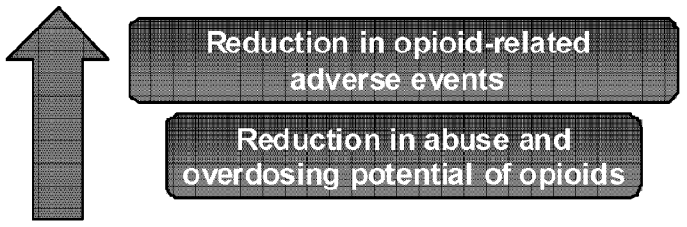
Reduction in pill burden

Two current treatments indicated for neuropathic pain—gabapentin and Lyrica—have a dosing schedule of between two and three times daily. In addition to treatments for pain, cancer patients are administered concurrent medications to treat the cancer itself as well as supportive treatments such as anti-emetics. Therefore, there is currently an unmet need for a once-daily or less frequent drug for neuropathic cancer pain with proven efficacy comparable to Lyrica. This would not have a large impact on the patient's treatment of the disease, but would ease the quality of life.

Clinical unmet needs: non-neuropathic cancer pain

Unmet needs in the management of non-neuropathic cancer pain relate mostly to opioid drugs. Figure 65 illustrates the key unmet needs relating to the treatment of non-neuropathic cancer pain.

Figure 65: Key unmet needs in the treatment of non-neuropathic cancer pain



Source: Datamonitor

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Reduction in opioid-related adverse events

The major adverse effects experienced by patients when using opioids include sedation, respiratory depression and constipation. These side effects arise from the non-specific action of opioids and increase with the dose of drug administered. Opioids are usually administered in increasing doses to find the maximum analgesic effect (titration), with the increases stopping only when side effects become intolerable.

Studies have examined the adverse effects found with various opioids. Out of nearly 61,000 patients receiving opioid medication during surgical hospitalization, 2.7% experienced an opioid-related adverse event. The most common were nausea and vomiting (67%), and rash, hives or itching (33.5%) (Oderda *et al.,* 2003). Another study found that 26% of patients experienced nausea and vomiting and 1.5% suffered respiratory depression after opioid administration. The risk of respiratory depression increased with age. Compared with patients aged 16–45 years, those aged 61–70 years had 2.8 times the risk of development of respiratory depression; those aged 71–80 years had 5.4 times the risk, and those aged older than 80 years had 8.7 times the risk. Men suffered less nausea and vomiting than women, and white participants experienced more nausea and vomiting than black participants (Cepeda *et al.,* 2003). A study looking at rates of constipation found an incidence of 3.7% for transdermal fentanyl, 6.1% for oxycodone controlled-release (CR) and 5.1% for morphine CR (Staats *et al.,* 2004).

A key opinion leader interviewed by Datamonitor regard the reduction in opioid-related adverse events as a key unmet need in the treatment of non-neuropathic cancer pain:

> *"I think it* [the biggest unmet need] *would be an effective analgesic that does not have side effects associated with the chronic opioid administration."*
>
> EU key opinion leader

Reduction in the abuse and overdosing potential of opioids

One of the most frequently cited concerns regarding the therapeutic use of opioids for chronic pain is their potential for abuse, a concern underscored by the classification of opioids as scheduled narcotics (Brennan *et al.,* 2003). In the US, the level of opioid abuse has risen dramatically over the past decade. According to the Substance Abuse and Mental Health Services Administration, the number of individuals abusing pain medications for the first time grew from 628,000 in 1990 to nearly three million in 2000 (Substance Abuse and Mental Health Services Administration, 2004). Indeed, concerns with fentanyl specifically have been fuelled by the media coverage of a number of fatalities due to abuse and overdosing (Washington Post, 2008; www.washingtonpost.com).

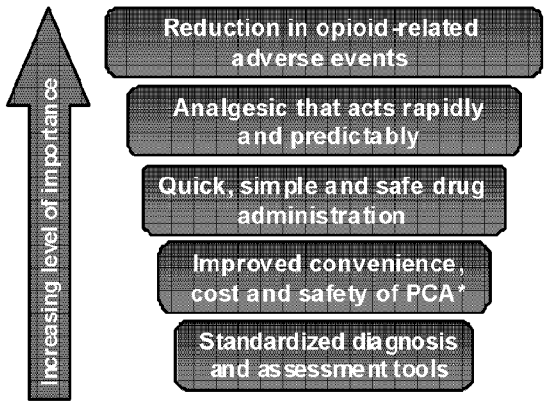
However, opioid addiction in cancer pain patients has been reported to be somewhat rarer. A retrospective review demonstrated that out of 24,000 cancer patients, only seven became addicted (Cancer Pain, 2008; www.cancer-pain.org). Research also suggests that cancer patients can stop taking opioids when the pain stops; they do not crave opioids when they no longer need them for pain relief (American Pain Society, 1992; www.ampainsoc.com). For this reason, Datamonitor regards the need for a reduction in the abuse and overdosing potential of opioids to be of lower importance than the need for reduced opioid-related adverse events.

Clinical unmet needs: breakthrough cancer pain

Unmet needs in the management of breakthrough cancer pain relate largely to the opioid drug class since opioids form the mainstay of pharmacological treatment for breakthrough cancer pain.

Figure 66 summarizes key unmet needs in the treatment of breakthrough cancer pain.

Figure 66: Key unmet needs in the treatment of breakthrough cancer pain



*PCA = patient-controlled analgesia

Source: Datamonitor

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Reduction in opioid-related adverse events

As for non-neuropathic cancer pain, a key unmet need in the treatment of breakthrough cancer pain is a reduction in opioid-related adverse events. Table 14 summarizes the opioid-related adverse events for patients enrolled in the Phase III Actiq trial (Farrar *et al.*, 1998). Results found that the two most common adverse events in patients were dizziness (17%) and nausea (14%).

Table 14: Primary opioid-related adverse events for 130 patients initially enrolled in the trial of Actiq for cancer-related breakthrough pain

Typical adverse events*	Number of patients (%)
Dizziness	22 (17)
Nausea	18 (14)
Somnolence	11 (8)
Constipation	7 (5)
Asthenia	6 (5)
Confusion	5 (4)
Vomiting	4 (3)
Pruritus (itching)	4 (3)

* Only adverse events that were considered by the investigator to be at least possibly related to the study drug and that occurred on days when an Actiq unit was used are included

Source: Farrar *et al.*, (1998).

DATAMONITOR

"The problem with Fentora or even with Actiq is that some patients complain of nausea."

EU key opinion leader

"All in all, I would say [the biggest unmet needs are reduction in] *side-effects. It is like a war against side-effects when prescribing medicines. We can prescribe medicine as much as we want but because of the side-effect we have to control the amount of medicine we prescribe."*

Japanese key opinion leader

Need for an analgesic that acts rapidly, predictably and just for the duration of a breakthrough pain episode

Because not all breakthrough pain episodes are predictable, and the time from onset to peak pain intensity is generally only a few minutes, the opioid needs to have a rapid onset of pain relief and a duration of action appropriate for the characteristics of the breakthrough pain (Bennett *et al.,* 2005).

The ideal treatment of breakthrough pain would match its onset and duration and would therefore typically have a rapid onset (within minutes) and a short duration of action (about 30 minutes in most cases) (Bennett *et al.,* 2005). Many non-intravenous medications do not act quickly enough and provide insufficient around-the-clock treatment of breakthrough pain.

An oral analgesic with a sudden onset and relatively short duration would address many of the needs specific to breakthrough pain (Portenoy & Hagen, 1990). However, the speed of onset for ingested oral administration is generally slower than for injected or inhaled methods.

In addition to the fact that opioid formulations do not act fast enough, one of the common problems faced by physicians is not knowing the correct dose on which to start the patient. Without knowing the most effective dose to begin with, physicians will typically start the patient on a low dose and titrate upwards, which further increases the time to meaningful pain relief. One opinion leader cited the lack of guidance for the starting dose as a key weakness of Actiq.

"My population of [cancer] *patients do not like this drug* [Actiq] *very much…probably because we do not know exactly the doses and probably*

because sometimes they have adverse effects. So it [Actiq] *is not a good choice for me."*

EU key opinion leader

Large studies need to be carried out to quickly determine the most effective and safe dose on which to start a patient, although this can be both costly and complicated clinically. Guidelines advocate a fixed proportion of the daily maintenance dose, typically in the range of 5–15% of the total daily dose (World Health Organization, 1996; American Pain Society, 2003, www.ampainsoc.org; Cherny & Portenoy, 1993). However, more recent guidelines suggest fixed proportion dosing is not always effective. Breakthrough pain may vary in cause, severity and duration, and the dose of medication for breakthrough pain may need to be titrated in much the same way as the dose of opioid is titrated for baseline persistent pain (Bennett *et al.,* 2005).

Quick, simple and safe drug administration

"Our patients need to have quicker relief."

EU key opinion leader

As with many conditions requiring pharmaceutical intervention, oral administration of drug therapy is the preferred method in breakthrough pain (Cancer Pain, 2008; www.cancer-pain.org). However, once ingested, the time it takes for oral medications to enter the bloodstream and provide meaningful pain relief is often unsatisfactory for patients. Morphine, hydromorphone and oxycodone are the oral opioids most often used to treat breakthrough pain when they are administered in their immediate-release (IR) forms in tablets, capsules or liquid concentrates (Bennett *et al.,* 2005). However, these agents typically have an extensive first-pass effect and are hydrophilic in nature, which slows the onset of analgesia to 30 minutes or more. According to the consensus panel recommendations from Bennett *et al.* (2005), this makes these three opioids less well suited for severe idiopathic or unpredictable incident breakthrough pain. The panel suggests, however, that oral IR opioids may be appropriate in patients with predictable incident pain when they are given 30–45 minutes before the precipitating event, such as movement.

Some patients may not be able to take an oral drug due to difficulties in swallowing, nausea or other gastrointestinal problems, which can be common in cancer sufferers. Faster acting methods of administration include sublingual (under the tongue), injection (subcutaneous or intravenous), rectal or transmucosally absorbed in the mouth but not swallowed (Mercadante *et al.,* 2002).

Improved convenience, cost and safety of patient-controlled analgesia

One of the key market opportunities is to develop and launch an effective analgesic that can be safely administered and dose titrated by the patients themselves, known as patient-controlled analgesia (PCA). This is especially important for the many cancer outpatients who do not have time to seek a healthcare professional when experiencing a breakthrough pain episode.

When PCA is administered in the hospital setting, it is most often given by intravenous, subcutaneous or epidural routes. Intravenous PCA is the standard for acute postoperative pain management and many authors have reported that patients prefer intravenous PCA to nurse-administered analgesia because it affords them greater control and optimizes their pain relief (Kastanias *et al.,* 2006). PCA is available in the form of a medication-dispensing unit equipped with a pump attached to an intravenous line. By means of a simple push button mechanism, the patient is allowed to self-administer doses of an analgesic (typically a fast-acting opioid) on an 'as needed' basis.

Other advantages of PCA, according to Spinasanta (2000), include the following:

- The patient feels less apprehensive about pain following surgery because they know they have control by simply pushing a button.
- Narcotic addiction can be avoided because the drug is taken on a short-term controlled basis.
- Pain relief is available around the clock and there is no need to wait for a nurse to deliver pain medication.
- Pain is more consistently controlled.
- Prior to expected activity (e.g. getting out of bed) the patient can self-dose to control pain during movement.

However, as a patient recovers, intravenous PCA is routinely discontinued and replaced with nurse-administered oral analgesia. This eliminates much of the patient's control over managing their pain and results in patients waiting, in pain, for a nurse to bring their pain medication. A literature review on oral PCA by Kastanias *et al.* (2006) concludes that this is a simple and low-tech method for providing oral opioids to patients in the hospital setting in a timely and patient-centered fashion.

In a retrospective study of intravenous PCA in outpatients with cancer pain (Schiessl *et al.,* 2006), the authors concluded that, if the indications are correct, this method

results in higher opioid consumption and better pain control. The authors also conclude that home-care PCA requires a lot of human and financial resources, but pain-related hospitalization can be prevented, although the pump can be inconvenient for many patients.

Since high doses of opioids (especially fentanyl) can be fatal, companies developing breakthrough pain products, especially ones that can be self-administered, will need to provide regulators with suitable risk-management plans that address potential abuse and overdosing.

Need for standardized diagnosis and assessment tools for breakthrough pain

There is no globally accepted, standardized method for diagnosing breakthrough pain (WHO Cancer Pain, 2008; www.whocancerpain.wisc.edu). Indeed, the reporting of breakthrough pain across pain specialists from different countries was uneven in the Caraceni *et al.* (2004) international survey and experts from the International Association for the Study of Pain have been calling for more standardization (WHO Cancer Pain, 2008; www.whocancerpain.wisc.edu). This suggests that breakthrough pain is still not commonly recognized, evaluated or treated.

The main problem is that the definition of breakthrough pain is not consistent or clear across the literature. For example, various studies do not report whether patients had controlled baseline pain, and how this was determined.

Moreover, the difficulty in distinguishing between nociceptive and neuropathic breakthrough cancer pain can confound treatment decisions. This is further complicated by the fact that most cancer pain is caused by a mixture of both nociceptive and neuropathic mechanisms (Davis & Walsh, 2004).

There are also no independently validated tools to assess breakthrough pain. Clinical practice guidelines such as the 2005 American Pain Society guidelines, as well as those from the European Association for Palliative Care, recommend a comprehensive pain assessment, including frequency and duration of each episode, intensity, precipitating factors, and previous and current pain treatments for baseline (persistent) pain and their effectiveness (Miaskowski *et al.,* 2005; Mercadante *et al.,* 2002).

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APPENDIX A

Physician research methodology

For more information on Datamonitor Healthcare's primary and secondary research methodology please refer to the Methodology Document, available from your account manager.

Physician sample breakdown

The physician sample breakdown for *Stakeholder Insight: Cancer Pain* is as follows.

US

Table 15: US physician sample breakdown, 2009

Specialty	Number of physicians	Proportion of sample (%)
Oncologist	18	50
Palliative medicine specialist	2	6
Pain care specialist	11	31
Anesthetist (special interest palliative care/pain medicine)	5	14
Total	**36**	**100**
Average experience as specialist (years)	12.97	
Average time in clinical practice per day (hours)	9.61	
Average number of cancer patients with chronic neuropathic pain prescribed pain therapies per month (mean)	49.31	
Average number of cancer patients with chronic non-neuropathic pain prescribed pain therapies per month (mean)	47.64	
Average number of cancer patients with chronic mixed pain (neuropathic and non-neuropathic) prescribed pain therapies per month (mean)	40.97	
Average number of cancer patients with breakthrough pain prescribed pain therapies per month (mean)	46.25	
Average number of cancer patients with mild pain prescribed pain therapies per month (mean)	46.53	
Average number of cancer patients with moderate cancer pain prescribed pain therapies	60	

per month (mean)	
Average number of cancer patients with severe cancer pain prescribed pain therapies per month (mean)	50.97

Source: Datamonitor, Stakeholder Insight: Cancer Pain Survey DATAMONITOR

Japan

Table 16: Japan physician sample breakdown, 2009

Specialty	Number of physicians	Proportion of sample (%)
Oncologist	12	50
Palliative medicine specialist	12	50
Pain care specialist	0	0
Anesthetist (special interest palliative care/pain medicine)	0	0
Total	**24**	**100**
Average experience as specialist (years)	20	
Average time in clinical practice per day (hours)	8.5	
Average number of cancer patients with chronic neuropathic pain prescribed pain therapies per month (mean)	8.13	
Average number of cancer patients with chronic non-neuropathic pain prescribed pain therapies per month (mean)	13.96	
Average number of cancer patients with chronic mixed pain (neuropathic and non-neuropathic) prescribed pain therapies per month (mean)	7.54	
Average number of cancer patients with breakthrough pain prescribed pain therapies per month (mean)	13.79	
Average number of cancer patients with mild pain prescribed pain therapies per month (mean)	6.17	
Average number of cancer patients with moderate cancer pain prescribed pain therapies per month (mean)	9.71	
Average number of cancer patients with severe cancer pain prescribed pain therapies per month (mean)	6.04	

Source: Datamonitor, Stakeholder Insight: Cancer Pain Survey DATAMONITOR

France

Table 17: France physician sample breakdown, 2009

Specialty	Number of physicians	Proportion of sample (%)
Oncologist	12	50
Palliative medicine specialist	2	8
Pain care specialist	6	25
Anesthetist (special interest palliative care/pain medicine)	4	17
Total	**24**	**100**
Average experience as specialist (years)	12.4	
Average time in clinical practice per day (hours)	9	
Average number of cancer patients with chronic neuropathic pain prescribed pain therapies per month (mean)	30.42	
Average number of cancer patients with chronic non-neuropathic pain prescribed pain therapies per month (mean)	32.08	
Average number of cancer patients with chronic mixed pain (neuropathic and non-neuropathic) prescribed pain therapies per month (mean)	34.58	
Average number of cancer patients with breakthrough pain prescribed pain therapies per month (mean)	24.79	
Average number of cancer patients with mild pain prescribed pain therapies per month (mean)	32.5	
Average number of cancer patients with moderate cancer pain prescribed pain therapies per month (mean)	41.46	
Average number of cancer patients with severe cancer pain prescribed pain therapies per month (mean)	32.92	

Source: Datamonitor, Stakeholder Insight: Cancer Pain Survey DATAMONITOR

Germany

Table 18: Germany physician sample breakdown, 2009

Specialty	Number of physicians	Proportion of sample (%)
Oncologist	12	50
Palliative medicine specialist	2	8
Pain care specialist	5	21
Anesthetist (special interest palliative care/pain medicine)	5	21
Total	**24**	**100**
Average experience as specialist (years)	11.38	
Average time in clinical practice per day (hours)	8.63	
Average number of cancer patients with chronic neuropathic pain prescribed pain therapies per month (mean)	28.33	
Average number of cancer patients with chronic non-neuropathic pain prescribed pain therapies per month (mean)	43.96	
Average number of cancer patients with chronic mixed pain (neuropathic and non-neuropathic) prescribed pain therapies per month (mean)	48.54	
Average number of cancer patients with breakthrough pain prescribed pain therapies per month (mean)	27.25	
Average number of cancer patients with mild pain prescribed pain therapies per month (mean)	36.38	
Average number of cancer patients with moderate cancer pain prescribed pain therapies per month (mean)	52.17	
Average number of cancer patients with severe cancer pain prescribed pain therapies per month (mean)	46.25	

Source: Datamonitor, Stakeholder Insight: Cancer Pain Survey DATAMONITOR

Italy

Table 19: Italy physician sample breakdown, 2009

Specialty	Number of physicians	Proportion of sample (%)
Oncologist	12	50
Palliative medicine specialist	0	0
Pain care specialist	10	42
Anesthetist (special interest palliative care/pain medicine)	2	8
Total	**24**	**100**
Average experience as specialist (years)	15.29	
Average time in clinical practice per day (hours)	8.5	
Average number of cancer patients with chronic neuropathic pain prescribed pain therapies per month (mean)	36.5	
Average number of cancer patients with chronic non-neuropathic pain prescribed pain therapies per month (mean)	34.58	
Average number of cancer patients with chronic mixed pain (neuropathic and non-neuropathic) prescribed pain therapies per month (mean)	41.42	
Average number of cancer patients with breakthrough pain prescribed pain therapies per month (mean)	43.75	
Average number of cancer patients with mild pain prescribed pain therapies per month (mean)	38.88	
Average number of cancer patients with moderate cancer pain prescribed pain therapies per month (mean)	49.88	
Average number of cancer patients with severe cancer pain prescribed pain therapies per month (mean)	46.75	

Source: Datamonitor, Stakeholder Insight: Cancer Pain Survey DATAMONITOR

Spain

Table 20: Spain physician sample breakdown, 2009

Specialty	Number of physicians	Proportion of sample (%)
Oncologist	12	50
Palliative medicine specialist	1	4
Pain care specialist	10	42
Anesthetist (special interest palliative care/pain medicine)	1	4
Total	**24**	**100**
Average experience as specialist (years)	12.17	
Average time in clinical practice per day (hours)	8.13	
Average number of cancer patients with chronic neuropathic pain prescribed pain therapies per month (mean)	27.08	
Average number of cancer patients with chronic non-neuropathic pain prescribed pain therapies per month (mean)	40.63	
Average number of cancer patients with chronic mixed pain (neuropathic and non-neuropathic) prescribed pain therapies per month (mean)	38.13	
Average number of cancer patients with breakthrough pain prescribed pain therapies per month (mean)	34.17	
Average number of cancer patients with mild pain prescribed pain therapies per month (mean)	38.13	
Average number of cancer patients with moderate cancer pain prescribed pain therapies per month (mean)	48.33	
Average number of cancer patients with severe cancer pain prescribed pain therapies per month (mean)	35.21	

Source: Datamonitor, Stakeholder Insight: Cancer Pain Survey DATAMONITOR

UK

Table 21: UK physician sample breakdown, 2009

Specialty	Number of physicians	Proportion of sample (%)
Oncologist	16	67
Palliative medicine specialist	1	4
Pain care specialist	3	13
Anesthetist (special interest palliative care/pain medicine)	4	17
Total	**24**	**100**
Average experience as specialist (years)	12.13	
Average time in clinical practice per day (hours)	8.96	
Average number of cancer patients with chronic neuropathic pain prescribed pain therapies per month (mean)	24.79	
Average number of cancer patients with chronic non-neuropathic pain prescribed pain therapies per month (mean)	26.38	
Average number of cancer patients with chronic mixed pain (neuropathic and non-neuropathic) prescribed pain therapies per month (mean)	25.13	
Average number of cancer patients with breakthrough pain prescribed pain therapies per month (mean)	34.29	
Average number of cancer patients with mild pain prescribed pain therapies per month (mean)	24.58	
Average number of cancer patients with moderate cancer pain prescribed pain therapies per month (mean)	35.71	
Average number of cancer patients with severe cancer pain prescribed pain therapies per month (mean)	28.42	

Source: Datamonitor, Stakeholder Insight: Cancer Pain Survey DATAMONITOR

Contributing experts

This analysis is supported by interviews with the following seven key opinion leaders:

The following key physician opinion leaders were interviewed by Datamonitor during the course of this report:

Dr. Carla Ripamonti, Palliative Care Unit of Day Hospital and Out Patient Clinic. National Cancer Institute of Milan, Italy. Dr Ripamonit is Consultant of the Collaborative Center for Cancer Pain Relief of the World Health Organization; Member of the Steering Committee of the Research Network of the European Association for Palliative Care; Vice Director of 'School of training and updating in Palliative Medicine', National Cancer Institute of Milan; and Professor of Palliative Medicine at the School of Specialization in Oncology of the University of Milan.

Prof. Jean-Pierre Marie, Head of the Hematology and Medical Oncology Department, Hotel-Dieu of Paris, France.

Dr Gary McCleane, Consultant in Pain Management at the Rampark Pain Center, Lurgan, Northern Ireland, United Kingdom. Dr McCleane has over 15 years experience in pain management and has authored over 70 scientific papers and book chapters related to pain management. In addition, he is the author and/or editor of four pain-related books.

Dr. Paul Farquhar-Smith, Consultant in Anesthetics, Pain and Intensive Care at the Royal Marsden NHS Foundation Trust, London, UK.

Dr. Marilène Filbet, Director of the Palliative Care Unit at the University Hospital Lyon Sud, Lyon, France.

US Professor of Anesthesiology – requested total anonymity.

Japanese Professor of Anesthesiology – requested total anonymity.

APPENDIX B

The survey questionnaire

Screener questions

S.1a What is your medical specialty?

Please select one response only

Oncologist	1 CONTINUE
Palliative medicine specialist	2 CONTINUE
Pain care specialist	3 CONTINUE
Anesthetist (special interest palliative care/pain management)	4 CONTINUE
Other	5 CLOSE

S.2 How long have you been practicing in your specialism?

Please enter number of years below

_____ # of years

S.3 On average how many hours do you spend in clinical practice each day?

Please enter number of hours below

_____ # of hours

S.4 Of all your cancer patients (at all stages of the disease), what percentage experience cancer pain?

Please insert % below

_____% of patients

S.5 To how many cancer patients with the following sub-categories of cancer pain do you prescribe pain therapies **per month?**

Chronic pain is defined as pain that lasts longer than 3 months.

Breakthrough pain is defined as a transient flare of pain of moderate or severe intensity arising on a background of controlled pain.

Pain subtype	Number of patients treated per month
Chronic neuropathic pain	
Chronic non-neuropathic pain	
Chronic mixed pain (neuropathic & non-neuropathic)	
Breakthrough pain	

S.6 To how many cancer patients with the following severities of cancer pain do you prescribe pain therapies per month?

Please use the following definitions for this question:

Based on the 10-point Brief Pain Inventory (BPI, ratings of 1 to 4 corresponded to mild pain, 5 to 6 to moderate pain, and 7 to 10 to severe pain)

Pain severity	Number of patients treated per month
Mild	
Moderate	
Severe	

S.7 Do you work for a pharmaceutical company in any capacity, excluding participation in clinical trials?

Please select one response only

Yes	1 CLOSE
No	2 CONTINUE

This questionnaire investigates the management of cancer pain using pharmacological treatments. There are a number of sections which will ask you questions on prevalence, referral patterns, treatment by type of pain and prescribing influences. A number of questions will ask you to provide percentages; please provide your best estimates wherever possible.

Please note: This questionnaire focuses on the use of analgesics and centrally acting drugs to treat cancer pain. Therefore, the use of bisphosphonates in achieving pain relief from bone metastases is not included.

Section 1 – Prevalence of cancer pain

Section 1 will look at the prevalence of cancer pain.

1.4 Of all **your** cancer patients you see in a **month** that suffer from chronic neuropathic pain, what percentage suffers from the following severities of pain?

Chronic pain is defined as pain that lasts longer than 3 months.

Please use the following definitions for this question:

Based on the 10-point Brief Pain Inventory (BPI, ratings of 1 to 4 corresponded to mild pain, 5 to 6 to moderate pain, and 7 to 10 to severe pain)

Please enter % for each pain severity. If the response is 'None' for any of the below, please insert '0'. Your answers must equal 100%.

	Pain severity	**Percentage of patients with chronic neuropathic pain (%)**
1	Mild pain	
2	Moderate pain	
3	Severe pain	
	Total	**=100%**

1.5 Of all **your** cancer patients you see in a **month** that suffer from chronic non-neuropathic pain, what percentage suffers from the following severities of pain?

Please use the following definitions for this question:

Based on the 10-point Brief Pain Inventory (BPI, ratings of 1 to 4 corresponded to mild pain, 5 to 6 to moderate pain, and 7 to 10 to severe pain)

Please enter % for each pain severity. If the response is 'None' for any of the below, please insert '0'. Your answers must equal 100%.

	Pain severity	**Percentage of patients with chronic non-neuropathic pain (%)**
1	Mild pain	
2	Moderate pain	
3	Severe pain	
	Total	**=100%**

Section 2 – Referral patterns

Section 2 will look at referral and management patterns of cancer patients suffering from pain.

Please consider ALL your cancer pain patients of all stages and severities when completing this section.

2.1 Please give the percentage breakdown of your cancer patients whose treatment is initiated and managed by each Healthcare professional.

Please enter % for each Healthcare professional. If the response is 'None' for any of the below, please insert '0'. Your answers must equal 100%.

	Healthcare professional	**A** Percentage of patients with cancer pain who received **INITIATION** of	**B** Percentage of patients whose cancer pain is **MANAGED** by each physician type after initiation (%)

		their treatment by each physician type (%)	
	Primary care physician (PCP)/General practitioner (GP)		
	PCP/GP palliative medicine or pain care specialist		
	Oncologist		
	Oncologist palliative medicine or pain care specialist		
	Neurologist		
	Neurologist palliative medicine or pain care specialist		
	Anesthetist		
	Anesthetist palliative medicine or pain care specialist		
	Nurse		
	Nurse palliative medicine or pain care specialist		
	Patient themselves (Patient controlled analgesia)		
	Hematologist		
	Hematologist palliative medicine or pain care specialist		
	Internal medicine specialist		
	Internal medicine -		

	palliative medicine or pain care specialist		
	Total	**=100%**	**=100%**

Section 3 – Treatment of chronic neuropathic cancer pain

Section 3 will look at **chronic neuropathic cancer pain**.

Chronic pain is defined as pain that lasts longer than 3 months.

Please note: This questionnaire focuses on the use of analgesics and centrally acting drugs to treat cancer pain. Therefore, the use of bisphosphonates in achieving pain relief from bone metastases is not included.

3.1 What percentage of **your** patients with each of the following severities of chronic neuropathic cancer pain receives pharmacological treatment for pain?

Please enter % for each pain severity. If the response is 'None' for any of the below, please insert '0'. Your answers do not need to equal 100%.

	Pain severity	**Percentage of patients receiving pharmacological treatment (%)**
1	Mild	
2	Moderate	
3	Severe	

3.2 Please select your most commonly prescribed **FIRST-LINE** drug (or drugs) which you would prescribe to a ***MILD*** **CHRONIC NEUROPATHIC** cancer pain patient by choosing from the drug class lists below. Please ensure you choose the correct formulation. Also provide the percentage of patients you prescribe this regimen to.

Please note: the focus of this section is on centrally acting drugs. Therefore, please do not add bisphosphinate use in the 'Other class' list.

Please choose "None" from any drop down lists which do not apply. Please scroll all the way to the right to see all options for this question.

Appendix B

DATAMONITOR

A	B	C	D	E	F	G	H
Oral NSAID Celecoxib/ Diclofenac/ Eoricoxib/ Etodolac/ Flavocoxib/ Flurbiprofen/ Ibuprofen/ Indometacin/ Lumiracoxib/ Ketoprofen/ Meloxicam/ Nabumetone/ Naproxen/ Nimesulide/ Piroxicam/ Other (please specify) Topical NSAID Intravenous NSAID	**Opioids:** Buprenorphine (oral)/ Buprenorphine (intravenous)/ Buprenorphine (subcutaneous)/ Buprenorphine (intramuscular)/ Buprenorphine (intrathecal)/ Buprenorphine (rectal)/ Butorphanol (oral)/ Butorphanol (intravenous)/ Butorphanol (subcutaneous)/ Butorphanol (intramuscular)/ Butorphanol (intrathecal)/ Butorphanol (rectal)/ Codeine (oral)/ Codeine	**Opioid fixed dose combinations:** Oxycodone & acetaminophen/ Oxycodone & aspirin/ Oxycodone & ibuprofen/ Hydrocodone & acetaminophen/ Hydrocodone & ibuprofen	**Antidepressants:** SNRIs/ Tricyclics/ Other (please specify)	**Anticonvulsants:** Carbamazepine/ Gabapentin/ Pregabalin/ Other (please specify)	**Other drug classes:** Corticosteroids/ Antispasmodics/ Cannabinoids/ Topical local anesthetics/ Paracetemol (acetaminophen)/ Ketamine/Capsaicin/Lidocaine	**Other class:** Other class &/or brand (please specify).	Percentage of ***MILD*** **CHRONIC NEUROPATHIC** cancer pain patients regimen is prescribed to **(%)**

	(intravenous)/ Codeine (subcutaneous)/ Codeine (intramuscular)/ Codeine (intrathecal)/ Codeine (rectal)/ Dextropropoxyphene (oral)/ Dextropropoxyphene (intravenous)/ Dextropropoxyphene (subcutaneous)/ Dextropropoxyphene (intramuscular)/ Dextropropoxyphene (intrathecal)/ Dextropropoxyphene (rectal)/ Dihydrocodeine (oral)/ Dihydrocodeine (intravenous)/ Dihydrocodeine (subcutaneous)/ Dihydrocodeine						

	(intramuscular)/ Dihydrocodeine (intrathecal)/ Dihydrocodeine (rectal)/ Fentanyl (oral, transmucosal)/ Fentanyl (oral, buccal)/ Fentanyl (transdermal)/ Fentanyl (intravenous)/ Fentanyl (subcutaneous)/ Fentanyl (intramuscular)/ Fentanyl (intrathecal)/ Fentanyl (rectal)/ Hydrocodone (oral)/ Hydrocodone (intravenous)/ Hydrocodone (subcutaneous)/ Hydrocodone (intramuscular)/ Hydrocodone (intrathecal)/						

	Hydrocodone (rectal)/ Hydromorphone (oral)/ Hydromorphone (intravenous)/ Hydromorphone (subcutaneous)/ Hydromorphone (intramuscular)/ Hydromorphone (intrathecal)/ Hydromorphone (rectal)/ Oxycodone (oral)/ Oxycodone (intravenous)/ Oxycodone (subcutaneous)/ Oxycodone (intramuscular)/ Oxycodone (intrathecal)/ Oxycodone (rectal)/ Morphine (oral)/ Morphine (intravenous)/ Morphine						

	(subcutaneous)/ Morphine (intramuscular)/ Morphine (intrathecal)/ Morphine (rectal)/ Levorphanol (oral)/ Levorphanol (intravenous)/ Levorphanol (subcutaneous)/ Levorphanol (intramuscular)/ Levorphanol (intrathecal)/ Levorphanol (rectal)/ Meperidine (oral)/ Meperidine (intravenous)/ Meperidine (subcutaneous)/ Meperidine (intramuscular)/ Meperidine (intrathecal)/ Meperidine (rectal)/ Methadone (oral)/						

	Methadone (intravenous)/ Methadone (subcutaneous)/ Methadone (intramuscular)/ Methadone (intrathecal)/ Methadone (rectal)/ Oxymorphone (oral)/ Oxymorphone (intravenous)/ Oxymorphone (subcutaneous)/ Oxymorphone (intramuscular)/ Oxymorphone (intrathecal)/ Oxymorphone (rectal)/ Pethidine (oral)/ Pethidine (intravenous)/ Pethidine (subcutaneous)/ Pethidine (intramuscular)/ Pethidine						

	(intrathecal)/ Pethidine (rectal)/ Sufentanil (oral)/ Sufentanil (intravenous)/ Sufentanil (subcutaneous)/ Sufentanil (intramuscular)/ Sufentanil (intrathecal)/ Sufentanil (rectal)/ Other (please specify molecule and formulation) ……						

3.3 Please select your most commonly prescribed **FIRST-LINE** drug (or drugs) which you would prescribe to a **MODERATE CHRONIC NEUROPATHIC** cancer pain patient by choosing from the drug class lists below. Please ensure you choose the correct formulation. Also provide the percentage of patients you prescribe this regimen to.

Please note: the focus of this section is on centrally acting drugs. Therefore, please do not add bisphosphinate use in the 'Other class' list.

Please choose "None" from any drop down lists which do not apply. Please scroll all the way to the right to see all options for this question

Drug selection table as per question 3.2

3.4 Please select your most commonly prescribed **FIRST-LINE** drug (or drugs) which you would prescribe to a **SEVERE CHRONIC NEUROPATHIC** cancer pain patient by choosing from the drug class lists below. Please ensure you choose the correct formulation. Also provide the percentage of patients you prescribe this regimen to.

Please note: the focus of this section is on centrally acting drugs. Therefore, please do not add bisphosphinate use in the 'Other class' list.

Please choose "None" from any drop down lists which do not apply. Please scroll all the way to the right to see all options for this question.

Drug selection table as per question 3.2

3.5 What is the **relative importance** of the following factors when deciding to **progress** patients with **chronic neuropathic cancer pain** to **second line therapy?** Please distribute 100 points across the following attributes to indicate their relative importance, allocating more points to the more important attributes. If an attribute is of no importance please allocate zero points.

	Factor	Weighting
1	Failure to achieve pain relief	
2	Slower than required onset of action	
3	Shorter duration of action than required	
4	Lack of flexible dosing frequency	

5	Development of tolerance/addiction to drug	
6	Side effects – gastrointestinal (GI) related	
7	Serious side effects e.g. kidney failure, liver failure, ulcer, prolonged bleeding after an injury or surgery	
8	Serious adverse events – heart attack or stroke	
9	Patient non-adherence	
	Total	**=100**

3.6 What percentage of the following subgroups of patients with **chronic neuropathic cancer pain** fail on first-line treatment and progress to second line treatment?

Please enter % for each pain severity. If the response is 'None' for any of the below, please insert '0'. Your answers do not need to equal 100%.

	Severities of chronic neuropathic cancer pain	**Percentage of patients progressing to second line analgesia (%)**
1	Mild	
2	Moderate	
3	Severe	

Section 4 – Treatment of chronic non-neuropathic cancer pain

Section 4 will look at **chronic non-neuropathic cancer pain**.

Chronic pain is defined as pain that lasts longer than 3 months.

Please note: This questionnaire focuses on the use of analgesics and centrally acting drugs to treat cancer pain. Therefore, the use of bisphosphonates in achieving pain relief from bone metastases is not included.

4.1 What percentage of **your** patients with each of the following severities of chronic non-neuropathic cancer pain receives pharmacological treatment for pain?

Please enter % for each pain severity. If the response is 'None' for any of the below, please insert '0'. Your answers do not need to equal 100%.

	Pain severity	**Percentage of patients receiving pharmacological treatment (%)**
1	Mild	
2	Moderate	
3	Severe	

4.2 Please select your most commonly prescribed **FIRST-LINE** drug (or drugs) which you would prescribe to a ***MILD*** **CHRONIC NON-NEUROPATHIC** cancer pain patient by choosing from the drug class lists below. Please ensure you choose the correct formulation. Also provide the percentage of patients you prescribe this regimen to.

Please note: the focus of this section is on centrally acting drugs. Therefore, please do not add bisphosphinate use in the 'Other class' list.

Please choose "None" from any drop down lists which do not apply. Please scroll all the way to the right to see all options for this question.

Drug selection table as per question 3.2

4.3 Please select your most commonly prescribed **FIRST-LINE** drug (or drugs) which you would prescribe to a **MODERATE CHRONIC NON-NEUROPATHIC** cancer pain patient by choosing from the drug class lists below. Please ensure you choose the correct formulation. Also provide the percentage of patients you prescribe this regimen to.

Please note: the focus of this section is on centrally acting drugs. Therefore, please do not add bisphosphinate use in the 'Other class' list.

Please choose "None" from any drop down lists which do not apply. Please scroll all the way to the right to see all options for this question

Drug selection table as per question 3.2

4.4 Please select your most commonly prescribed **FIRST-LINE** drug (or drugs) which you would prescribe to a **SEVERE CHRONIC NON-NEUROPATHIC** cancer pain patient by choosing from the drug class lists below. Please ensure you choose the correct formulation. Also provide the percentage of patients you prescribe this regimen to.

Please note: the focus of this section is on centrally acting drugs. Therefore, please do not add bisphosphinate use in the 'Other class' list.

Please choose "None" from any drop down lists which do not apply. Please scroll all the way to the right to see all options for this question.

Drug selection table as per question 3.2

4.5 What is the **relative importance** of the following factors when deciding to **progress** patients with **chronic non-neuropathic cancer pain** to **second line therapy?** Please distribute 100 points across the following attributes to indicate their relative importance, allocating more points to the more important attributes. If an attribute is of no importance please allocate zero points.

	Factor	Weighting
1	Failure to achieve pain relief	
2	Slower than required onset of action	
3	Shorter duration of action than required	
4	Lack of flexible dosing frequency	
5	Development of tolerance/addiction to drug	
6	Side effects – gastrointestinal (GI) related	
7	Serious side effects e.g. kidney failure, liver failure, ulcer, prolonged bleeding after an injury or surgery	
8	Serious adverse events – heart attack or stroke	
9	Patient non-adherence	
	Total	**=100**

4.6 What percentage of the following subgroups of patients with **chronic non-neuropathic cancer pain** fail on first-line treatment and progress to second line treatment?

Please enter % for each pain severity. If the response is 'None' for any of the below, please insert '0'. Your answers do not need to equal 100%.

	Severities of chronic neuropathic cancer pain	Percentage of patients progressing to second line analgesia (%)
1	Mild	
2	Moderate	
3	Severe	

Section 5 – Treatment of breakthrough cancer pain

This section will look at **breakthrough pain**.

Breakthrough pain is defined as a transitory flare of pain that occurs on a background of relatively well-controlled baseline pain.

This questionnaire focuses on the use of analgesics and centrally acting drugs to treat cancer pain. Therefore, the use of bisphosphonates in achieving pain relief from bone metastases is not included.

5.1 What percentage of all your cancer pain patients experiences breakthrough pain?

Please enter percentage below.

_____ % of patients

5.2 What percentage of all your breakthrough pain patients receives pharmacological treatment for this pain?

Please insert percentage below

_____ % of patients

5.3 Please select your most commonly prescribed FIRST-LINE drug (or drugs) which you would prescribe to a BREAKTHROUGH cancer pain patient by choosing from the drug class lists below. Please ensure you choose the correct formulation. Also provide the percentage of patients you prescribe this regimen to.

Please note: the focus of this section is on centrally acting drugs. Therefore, please do not add bisphosphinate use in the 'Other class' list.

Please choose "None" from any drop down lists which do not apply. Please scroll all the way to the right to see all options for this question.

Drug selection table as per question 3.2

5.4 Please estimate the percentage of all your cancer patients with breakthrough pain who receive patient controlled analgesia (PCA).

Please insert percentage below

_____ % of patients

5.5 What is the **relative importance** of the following factors when deciding to **progress** patients with **breakthrough cancer pain** to **second line therapy?** Please distribute 100 points across the following attributes to indicate their relative importance, allocating more points to the more important attributes. If an attribute is of no importance please allocate zero points.

	Factor	Weighting
1	Failure to achieve pain relief	
2	Slower than required onset of action	
3	Shorter duration of action than required	
4	Lack of flexible dosing frequency	
5	Development of tolerance/addiction to drug	
6	Side effects – gastrointestinal (GI) related	
7	Serious side effects e.g. kidney failure, liver failure, ulcer, prolonged bleeding after an injury or surgery	
8	Serious adverse events – heart attack or stroke	

9	Patient non-adherence	
	Total	**=100**

5.6 What percentage of patients with breakthrough cancer pain fail on first-line treatment and progress to second line treatment?

Please insert percentage below

_____ % of patients

Section 6 – Prescribing influences and product profiles

Please now focus on the factors that influence your prescribing behaviour when treating patients with cancer pain (of all subtypes and severities).

6.1 When treating patients with cancer pain, do you adhere to the three-step "analgesic ladder" approach as published by the World Health Organization (WHO)?

Please select one response only

Yes	□
No	□

6.2 What is the **relative importance** of the following factors in your **decision to prescribe** treatments for cancer pain? Please distribute 100 points across the following influences to indicate their relative importance, allocating more points to the more important influences. If an attribute is of no importance please allocate zero points.

	Influences	**Weighting**
1	Published guidelines	
2	Published journal articles	
3	Opinion leaders	
4	Conferences	
5	Pharmaceutical representatives	

	Total	**=100**

6.3 What is the **relative importance** of the following clinical attributes when **prescribing drug therapy** for **each type of cancer pain?** Please distribute 100 points across the following attributes to indicate their relative importance, allocating more points to the more important attributes.

Please enter points for each clinical attribute. If an attribute is of no importance, please insert '0'. Your answers must equal 100 points.

	Clinical Attributes	**Neuropathic pain points allocation**	**Breakthrough pain points allocation**
A	Overall efficacy demonstrable by reduction in pain		
B	Onset of action		
C	Lack of drug-drug interaction		
D	Duration of action		
E	Overall side-effect profile		
F	Flexible dosing frequency (e.g. dose quantity)		
G	Cost issues (e.g. reimbursement status)		
H	Physician product familiarity		
I	Recommended in treatment guidelines		
J	Convenient/less invasive route of administration		
	Total	**= 100**	**= 100**

6.4 Please rate the **performance, or predicted performance** (i.e. please give your opinion even if the drug is not yet available to you), of the following branded drug therapies. Please rate each drug therapy on each attribute on a scale of 1 to 100 where 1= low performance and 100 = high performance.

A. Lyrica (pregabalin) for the treatment of neuropathic cancer pain;

B. Actiq (oral transmucosal fentanyl) for the treatment of breakthrough pain;

C. Fentora (fentanyl buccal tablet) for the treatment of breakthrough pain in patients with cancer who are already receiving and who are tolerant to around-the-clock therapy for their underlying persistent cancer pain.

If unable to answer for a specified therapy, tick DK/NS/NA got 'Overall efficacy demonstrable by reduction in pain' and you will not be asked to rate this drug on any other attribute. Please enter rating for all clinical attributes within each therapy/column, the same rating can be used more than once.

	Attributes	A. Lyrica (pregabalin) for the treatment of neuropathic pain	B. Actiq (fentanyl) for the treatment of breakthrough pain	C. Fentora (fentanyl buccal tablet) for the treatment of breakthrough pain
1	Overall efficacy demonstrable by reduction in pain Good efficacy = high			
2	Onset of action Rapid onset = high score			
3	Lack of drug-drug interaction Low drug-drug interaction = high score			
4	Duration of action Long duration = high score			
5	Overall side-effect profile Favorable side effect profile = high score			

6	Flexible dosing frequency e.g. dose quantity Flexibility in dose quantity = high score			
7	Cost issues (e.g. reimbursement status) e.g. Full reimbursement = high score			
8	Physician product familiarity Familiarity with brand or company = high score			
9	Recommended in treatment guidelines Recommended as first line = high score			
10	Convenient / less invasive route of administration Convenient /less invasive route = high score			
		DK/NS/NA	**DK/NS/NA**	**DK/NS/NA**

Section 7 – Treatment outcomes

This section looks at treatment outcomes and unmet needs.

7.1 Overall, how effective do you think currently available prescription pain medicines are at controlling the following types of cancer pain using a scale of 1-10, where **1 = very ineffective and 10 = very effective?**

Please select one rating for each type of cancer pain.

	Effectiveness rating (1 = very ineffective & 10 = very effective) *Please select one only for each type of cancer pain*									
Type of cancer pain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
A. Chronic neuropathic pain										
B. Chronic non-neuropathic pain										
C. Breakthrough pain										

Thank you for completing this survey. Please proceed with a few questions about your medical practice before submitting your responses.

Demographics

D1. In an average month, what percentage of your time do you spend in office based practice vs. hospital practice?

If no time is spent in one area, please insert 0%

1. Office based	%
2. Hospital based	%

TOTAL=100%

D2. How many other physicians with the same specialty are there in your office practice, excluding yourself?

_____# of physicians with the same specialty in the practice

D3. What type of hospital do you work in?

Please select one response only.

- ❑ 1. General hospital (i.e., City or State Hospital)
- ❑ 2. University/teaching hospital (i.e., Harvard, University of PA, etc)
- ❑ 3. Private hospital (privately funded or philanthropic hospital)
- ❑ 4. Combined Private/Public (combined public and private funds)
- ❑ 5. Specialty clinic/hospital (specializes on specific therapy)
- ❑ 6. Don't know the category of the hospital
- ❑ 7. Others (please specify):_____

Thank you for your valued participation.

Please submit your responses now.

About Datamonitor

Datamonitor is a leading business information company specializing in industry analysis.

Through its proprietary databases and wealth of expertise, Datamonitor provides clients with unbiased expert analysis and in-depth forecasts for six industry sectors: Healthcare, Technology, Automotive, Energy, Consumer Markets, and Financial Services. The company also advises clients on the impact that new technology and eCommerce will have on their businesses.

Datamonitor maintains its headquarters in London, and regional offices in New York, Frankfurt and Hong Kong. The company serves the world's largest 5,000 companies.

About Datamonitor Healthcare

Datamonitor Healthcare provides a total business information solution to the pharmaceutical and healthcare industries. Its key strength is its in-house analysts and researchers, who have strategy, market, disease and company expertise. Datamonitor Healthcare's services are based on specialist market analysis teams covering the following areas:

- Cardiovascular Disease;
- Central Nervous System;
- Immune Disorders and Inflammation;
- Infectious Disease;
- Respiratory;
- Oncology;
- Women's Health;
- Pharmaceutical strategy (publishing under the 21st Century Insight brand);
- eHealth (publishing under the eHealthInsight brand);
- Competitive intelligence (publishing under the PharmaVitae brand);

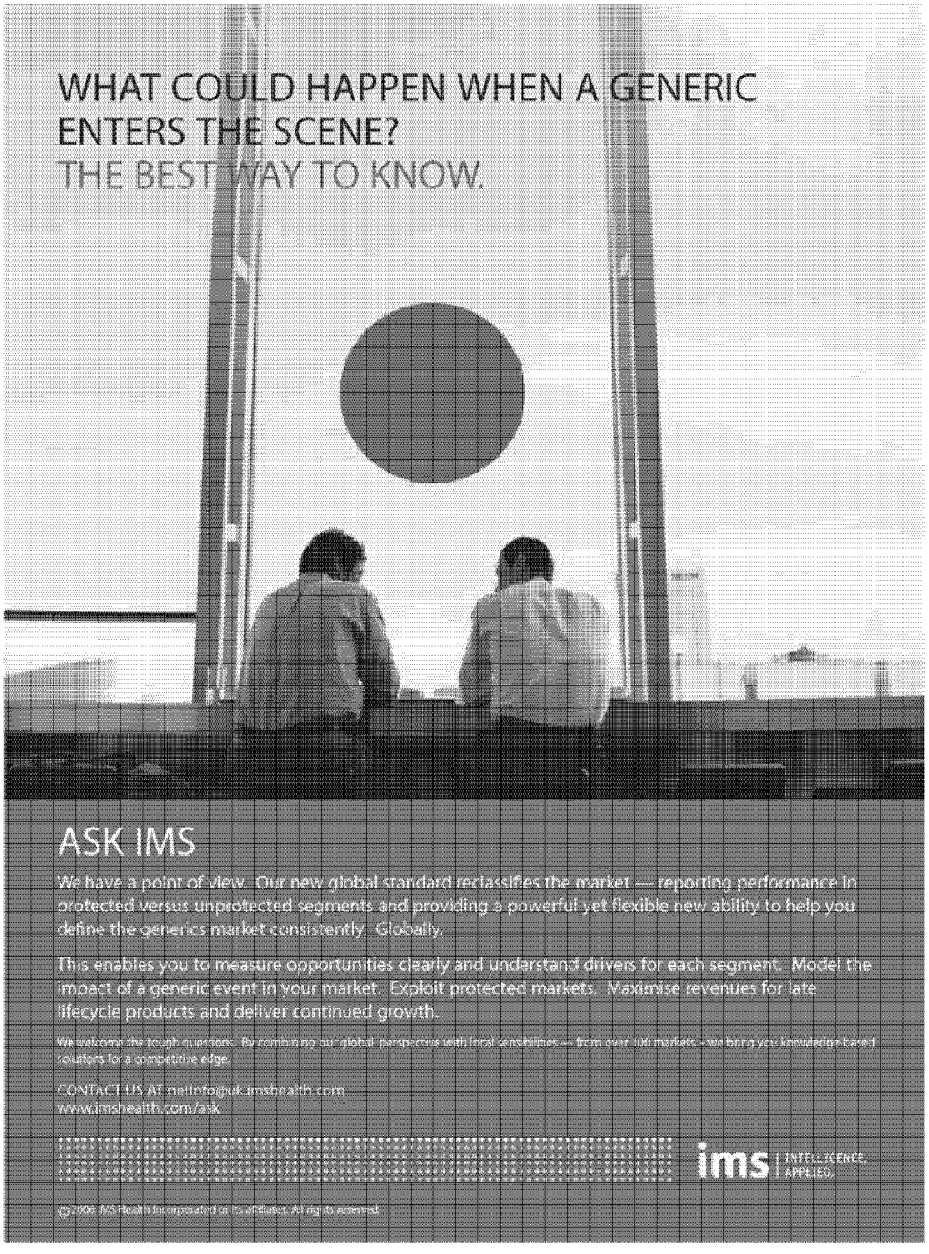
- Medical technologies;
- Healthcare consulting;
- Forecasting and modeling.

Team members are regularly interviewed by, for example, the Wall Street Journal, the BBC, Washington Post, Financial Times, In Vivo, Pharmafocus and MedAdNews, and frequently present at industry conferences in the US and Europe. Below is a brief overview of Datamonitor's analysis capabilities in the CNS area.

About the Central Nervous System pharmaceutical analysis team

Datamonitor's Central Nervous System team studies patient potential, treatment patterns, current and future market dynamics, development pipeline and strategic issues in the market, highlighting latest trends and new opportunities in the Central Nervous System therapy area. The team supports the following products:

- **Pipeline Analysis**: insight into the 'Drugs of Tomorrow', developmental drugs set to enter the market, and their impact on clinical practice and the use of existing therapeutics;
- **Commercial Analysis**: in-depth analyses of changing market dynamics, developing commercial strategies, and the impact of market events on commercial opportunities;
- **Stakeholder Analysis**: analysis of what the key stakeholders in the healthcare sector expect from the pharmaceutical industry—how practicing physicians really prescribe drugs and their expectations of the next generation of therapeutics, and analysis of issues driving prescribing behavior.


WHAT COULD HAPPEN WHEN A GENERIC ENTERS THE SCENE?
THE BEST WAY TO KNOW.
ASK IMS
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