# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Pain definition

The International Association for the Study of Pain (IASP) proposed that "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, 1979). It is the most widely used definition which emphasizes that pain is a complex experience that includes multiple dimensions.

Cancer pain, or cancer related pain, in particular, is a complex phenomenon. Its nature is involved with psychological distress and suffering. The pain is usually continuous and tends to worsen as the disease progresses (Cleeland et al., 1994).

## 2.2 Classification of cancer pain

Cancer pain can be classified in several ways. Its classification are based on many approaches such as source of pain, neurophysiological mechanism of pain, temporal pattern of pain, pain intensity and pain characteristics. To understand these classifications is vital because each type of pain is treated differently.

### Cause of pain

Pain in cancer patients can originate from many sources as follows:

1. Pain is caused by the cancer itself, which is by far the most common. About two-thirds of cancer patients have pain directly related to the presence of primary or metastatic disease (Bruera & Kim, 2003). Cancer related pain causes by tumors involvement such as extension into soft tissues, visceral involvement, bone involvement, nerve compression, nerve injury or raising intracranial pressure.

2. Pain is caused by treatment related pain. About one-third of cancer patients develop pain syndromes because of treatment, including post-surgery, post-chemotherapy, post-radiotherapy (Bruera & Kim, 2003).

3. Pain is caused by other causes unrelated to cancer or its treatment. These pains come from a concurrent disorder such as spondylosis, osteoarthritis. This cause of pain can be found by 3%-15% of cancer patients (Foley, 1982).

**Neurophysiological mechanism of pain**

Neural mechanism classification can be divided into 2 types.

**1**. **Nociceptive pain** is the most common in cancer pain. This type of pain is triggered by noxious stimuli at peripheral nociceptors, and then transmitted through peripheral nerve to nociceptors sensory neuron. At spinal cord level, the pain signal pass through various tracts and propagate upward along neural pathway to central nervous system. The result of pain comes from cancer itself or metastatic cancer. Nociceptive pain may be either somatic or visceral in origin. Nociceptive somatic pain involves structural organ and usually clearly define pain position such as skin cancer, oral cavity cancer, mucositis, and bone metastasis or vertebral compression fractures. Nociceptive visceral pain involves internal organ such as liver, pancreas. Nociceptive pain responds to morphine and other opioid analgesics (Portenoy & Lesage, 1999; World Health Organization, 1996).

**2. Neuropathic pain** is less common than nociceptive pain. It is a chronic pain state that arises from disease or injury-evoked damage to the peripheral nerves or the central nervous system. It has various clinical manifestations which could be both spontaneous pain and pain hypersensitivity (Kulkantrakorn, 2006). Typical signs of neuropathic pain are: (a) pain in an area without tissue damage and attributable to compression or injury of a neural structure; (b) pain described as ‘dysaesthetic’ such as burning, pricking or ‘paroxysmal such as stabbing, shooting, electric shock-like; (c) pain associated with sensory, motoric or autonomic dysfunction (Martin & Hagen, 1997; Portenoy, 1992; Twycross, 1994; World Health Organization, 1996). The examples of this type of pain are chemotherapy-induced painful peripheral

neuropathies, neuroma, post-herpetic neuralgias, phantom limb pain (Portenoy & Lesage, 1999; World Health Organization, 1996).

Most cancer patients with advanced disease often have multiple pains at different sites. In prospective study of 2,266 cancer patients, Grond and colleagues found that majority of patients had pain caused by cancer (85%) or anticancer treatment (17%); 9% had pain related to cancer disease and 9% due to aetiologies unrelated to cancer. Pain could be further classified as producing from nociceptors in bone(35%), soft tissue(45%), or visceral structures(33%), or neuropathic pain(34%) (Grond, Zech, Diefenbach, Radbruch, & Lehmann, 1996).

It is important to differentiate nociceptive from neuropathic pain because different pain is treated differently.

**Temporal pattern of pain**

**1. Acute pain** is a well-defined, severe and lasts a relatively short time. It is usually a signal of tissue injury and the acute pain is generally disappears when the injury heals.

**2. Chronic pain** is defined as pain that persists for more than 3 to 6 months, often with a less well-defined onset (Jennings, 2003). It is associated with significant change in personality, lifestyle, and functional ability. Therefore, chronic pain patients are more complex and require not only pain treatment but also treatment of psychological distress.

It is well recognized that cancer patients have both acute pain and chronic pain. Chronic or persistent pain in cancer patients may range from mild to severe and is present for a long time but acute pain referred to as “breakthrough pain”, may range from moderate to severe and is present for a short time. Breakthrough pain can be occurred many times a day, even though the proper dose of pain medicine is being taken for the chronic or persistent pain (Benedetti et al., 2000).

## 2.3 Cancer pain management

There are three basic approaches to cancer pain control include:

1. Modifying the source of the pain by treating the cancer and the inflammatory response of cancer;

2. Altering the central perception of pain such as by using analgesics, antidepressants, anxiolytics, and psychotherapy;

3. Interfering with nociceptive transmission within the central nervous system (CNS) such as, with anesthetic techniques (neuraxial analgesia and spinal neurolysis), neurosurgery procedure (cordotomy and myelotomy) (Ferrer-Brechner, 1985).

The optimal use of these approaches in the control of cancer pain requires a careful assessment of each patient's pain, cancer, concurrent medical problem, and psychosocial status (Jacox et al., 1994). However, most patients with cancer pain can be controlled by using drugs according to the World Health Organization guidelines in more than 80% (World Health Organization, 1986, 1996; Zech, Grond, Lynch, Hertel, & Lehmann, 1995). In the remaining 20%, it is important to use a multidimensional approach that includes a careful reassessment of the pain and use of second line agents and/or non-pharmacological interventions (Zech, Grond, Lynch, Hertel, & Lehmann, 1995). Another study conducted in 1405 patients from 2 oncology centers (Japan, Italy) and a palliative care unit (UK) showed that treatment was effective in 71-100% of the patients (Zech, Grond, Lynch, Hertel, & Lehmann, 1995). whereas only 29% of patients required nerve blocks and neuroablative procedures (Ventafridda, Tamburini, Caraceni, & De Conno, 1987). Therefore, drug treatment is the mainstay of the cancer pain management.

## 2.4 Assessment of cancer pain

Pain assessment is a vital first step in cancer pain management (World Health Organization, 1996). Inadequate pain assessment is one of the most important factors that lead to undertreatment or inappropriate management (Gonzales, Elliott, Portenoy, & Foley, 1991).

The basic steps in the evaluation of cancer pain have been initiated by WHO. Once starting assessment of pain, it is important for health care workers to believe the patient's report of pain. As pain is purely subjective experience, health care workers should specifically ask the patient about pain, rather than relying on spontaneous comment. In addition, the severity of the pain should be evaluated by asking whether daily activities are limited by the pain, whether sleep is disturbed, and whether pain relief is obtained with the previous medication or other pain-relief procedures. Furthermore, a detail history and a careful clinical examination may be all that's necessary to determine the cause of the pain in order that appropriate treatment may begin. After initiating treatment, the results should be monitored continuously. Finally, continuing evaluation and treatment are best achieved by a team approach. The physicians, nurses, and other care-givers should regularly share information about the effects of treatment. The patients who feel and report the pain should also be considered as one of the team members (World Health Organization, 1996).

Pain intensity reported by a patient implies pain that should be used for monitoring and adjusting treatment. Two patients with similar cancer location may experience different levels of nociception from the tumor itself, different levels somatosensory cortex activity, and different expression of pain because of the influence of culture, beliefs, mood, or delirium (Bruera & Neumann, 2003).

There are several commonly used instruments for assessing cancer pain intensity.

1. Visual Analog Scale (VAS) is a straight line corresponding to intensity of pain on a 100-mm line with the left end of the line representing no pain and the right end of the line representing the worst pain. Patients are asked to mark on the line where they think their pain is.

2. Numerical Rating Scale (NRS) is a number assigned to the intensity of pain on a scale of 0 to 10 with 0 reflecting "no pain" and 10 reflecting the "worst pain possible".

3. Verbal Descriptor Scale is a description of pain intensity as no pain, mild pain, moderate pain, severe pain, or worst possible pain.

4. Pain Faces Scale uses six faces with different expressions on each face. Each face is a person who feels happy because he or she has no pain or feels sad because he or she has some or a lot of pain. A patient is asked to choose the face that best describes how he or she is feeling. This rating scale can be used by person age 3 years and older.

All measures correlate highly with one another. For pain assessment in clinical settings, the VAS, Verbal Descriptor Scale and NRS approach equivalency (Jensen, Karoly, & Braver, 1986) so that clarity, ease of administration, and simplicity of scoring become justifiable criteria in response scale selection. In clinical trial, the NRS has proven more reliable than the VAS, especially with less educated patients (Ferraz, Quaresma, Aquino, & et al, 1990).

## 2.5 World Health Organization analgesic ladder

In 1986, WHO proposed a method for relief of cancer pain, based on a small number of relatively inexpensive drugs, particularly morphine (World Health Organization, 1986). This guideline has been translated into 22 languages. The sale and distribution of greater than 500,000 copies reflected the growing awareness of the cancer pain problem. In 1996, the second edition (World Health Organization, 1996). takes into account many of the advances in understanding and practice that have occurred since the mid 1980s.

The WHO analgesic ladder is a simple and effective method with a limited number of potent drugs for controlling cancer pain. The proportion of cancer patients who should receive effective pain relief varied from 75%-90% (Jacox et al., 1994). Zech and colleagues study (Zech, Grond, Lynch, Hertel, & Lehmann, 1995) found that 88% of cancer pain patients had good pain control by the WHO guidelines. Similarly, Schug and colleagues (Schug, Zech, & Don, 1990) estimated that only 11% of cancer pain patients managed with WHO guidelines required alternate methods of pain management. Grond and colleagues (Grond et al., 1991) found that 75% of terminally ill cancer patients received effective management with these guidelines.

Treatment for cancer pain should begin with a straightforward explanation to the patient of the causes of the pains. Many pains are best treated with a

combination of drug and non-drug measures. However, analgesics and a limited number of other drugs is the mainstay of cancer pain management as described in Table 2.1. For practical purposed, the opioid analgesics are divided into those for mild to moderate pain and those for moderate to severe pain. Anticancer treatment and analgesic drug therapy for cancer pain can be given concurrently. Some pains respond well to a combination of a non-opioid and an opioid drug. Others require combining a corticosteroid and an opioid. Neuropathic pains often respond poorly to non-opioids and opioid analgesics, but tricyclic antidepressants and anticonvulsants may prove effective.

Table 2.1

A basic drug list for cancer pain relief (World Health Organization, 1996)

| Category | Basic drugs | Alternatives |
|---|---|---|
| Non-opioids | Acetylsalicylate acid | Choline magnesium trisalicylate |
| | Acetaminophen | Diflunisal |
| | Ibuprofen | Naproxen |
| | Indomethacin | Diclofenac |
| Opioids for mild to moderate pain | Codeine | Dihydrocodeine |
| | | Dextropropoxyphene |
| | | Standardized opium |
| | | Tramadol |
| Opioids for moderate to severe pain | Morphine | Methadone |
| | | Hydromorphone |
| | | Oxycodone |
| | | Levorphanol |
| | | Pethidine |
| | | Buprenorphine |
| Opioid antagonist | Naloxone | - |
| Antidepressants | Amitriptyline | Imipramine |
| Anticonvulsants | Carbamazepine | Valproic acid |
| Corticosteroids | Prednisolone | Prednisone |
| | Dexamethasone | Betamethasone |

The principle of pharmacotherapy suggested by the WHO is as follows:

**1. By month**

When possible, patients should take analgesic medications by month. However, alternative routes such as rectal, transdermal, sublingual, and parenteral (subcutaneous and intravenous) administration may better serve patients with dysphagia, uncontrolled vomiting, or gastrointestinal obstruction.

**2. By the clock**

Patients with continuous pain should take analgesic medication at fixed intervals of time. The dose of analgesic drug should be titrated against the patient's pain such as, gradually increasing dose until the patient is comfortable. The next dose should be taken before the effect of the previous dose has fully worn off.

Some patients may need to take "rescue" doses for incident and breakthrough pain in addition to the regular schedule. Such doses should be 50%-100% of the regular four-hourly dose.

**3. By the ladder**

The WHO analgesic ladder is based on the premise that most patients gain adequate pain relief if health care professionals learn how to use a few effective and relatively inexpensive drugs well as shown in Figure 2.3. The first step of ladder involves the use of non-opioids. If this step does not relieve pain, add an opioid for mild to moderate pain (step 2). When the opioid for mild to moderate pain in combination with a non-opioid fails to relieve the pain, substitute an opioid for moderate to severe pain (step 3). Use only one drug from each of the groups at the same time. Give adjuvant drugs for specific indications.

Adjuvant drugs are necessary for one of three reasons: (a) to treat the adverse effects of analgesic medications such as anti-emetics, laxative; (b) to enhance pain relief, for example a corticosteroid in nerve compression pain; and (c) to treat concomitant psychological disturbances such as insomnia, anxiety and depression, and psychosis.

**4. For the individual**

There are no standard doses for opioid drugs. The "right" dose is the dose that relieves the patient's pain with the minimum of side effects. The range for oral

morphine, for example, is from as little as 5 mg to more than 1000 mg every four hours. Drugs used for mild to moderate pain have a dose limit in practice because of formulation for example, combined with acetylsalicylic acid or paracetamol, which are toxic at high doses, or because of a disproportionate increase in adverse effects at higher doses such as codeine.

**5. With attention to detail**

Carefully outline and monitor the patient's analgesic regimen. Follow up regularly with the patient by monitoring compliance, drug efficacy, and side effects. Anticipate adverse effects and, in some situations, treat them prophylactically.

**The WHO cancer pain relief methods can be summarized as follows:**

1. Cancer pain can, and should, be treated
2. Evaluation and treatment of cancer pain are best achieved by a team approach
3. The first steps are to take a detailed history, and to examine the patient carefully, to determine if the pain is:

a.caused by the cancer, related to the cancer, caused by anticancer treatment or caused by another disorder;

b. part of a specific syndrome;

c.nociceptive, neuropathic, or mixed nociceptive and neuropathic.

4.Treatment begins with an explanation and combines physical and psychological approaches, using both non-drug and drug treatments.

5. It is useful to have a sequence of specific aims , such as:
   a. to increase the hours of pain-free sleep;
   b. to relieve the pain when the patient is at rest;
   c. to relieve pain when the patients is standing or active.

6.Drugs alone usually give adequate relief from pain caused by cancer, provides that the right drug is administered in the right dose at the right time intervals.

7."By month": the oral route is the preferred route for analgesics, including morphine.

8.“By the clock”: for persistent pain, drugs should be taken at regular time intervals and not “as needed”.

9. “By the ladder”: (Figure 2.1)

a.Unless the patient is in severe pain, begin by prescribing non-opioid drugs (eg. Paracetamol, aspirin, NSAIDs, Coxibs) and adjust the dose, if necessary, to the maximum recommended dose.

b.If or when the non-opioid no longer adequately relieves the pain, an opioid drug should be prescribed in addition to the non-opioid.

c. If or when an opioid for mild to moderate pain (e.g. codeine) no longer adequately relieves the pain, it should be replaced by an opioid for moderate to severe (e.g.morphine).

10. “For the individual”: the right dose of an analgesic is the dose that relieves the pain. The dose of oral morphine may range from as little as 5 mg to more than 1000 mg.

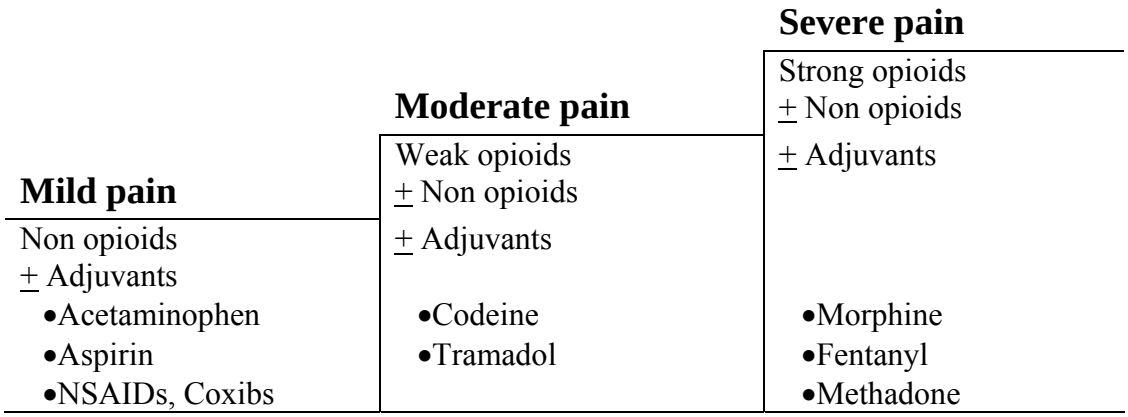
11.Adjuvant drugs should be prescribed as indicated.

12. For neuropathic pain, a tricyclic antidepressant or an anticonvulsant is the analgesic of choice.

13. “Attention to detail”: it is essential to monitor the patient’s response to the treatment to ensure that the patient obtains maximum benefit with as few adverse effect as possible.

Figure 2.1

WHO analgesic ladders (World Health Organization, 1996)



## 2.6 Barriers to Cancer Pain Treatment

A wide range of pain management therapies are available, and evidence shows that 85–90% of cancer pain can be controlled by using the guidelines of the World Health Organization. Nevertheless, only 50% pain control is satisfactorily achieved in cancer patients (World Health Organization, 1996). Barriers that interfere with adequate pain management have been broadly classified as problems related to health care professionals, to patients, and to the health care system (Cherny & Foley, 1994).

### Problems Related to Health Care Professionals

Poor assessment of pain and inadequate knowledge on the part of clinicians has been identified as major barriers to cancer pain treatment (Bruera et al., 2005). Physicians and nurses make decisions that play a major role in cancer pain management, and improvements in their assessment of their patients' pain may result in adequate analgesic prescription and better pain management (Cleeland, Cleeland, Dar, & Rinehardt, 1986). Anxiety about regulation of controlled substances, concerns about the side effects of analgesics, and fear of patients becoming addicted or tolerant to analgesics have also been identified as inappropriate attitudes (Von Roenn, Cleeland, Gonin, Hatfield, & Pandya, 1993).

Comparing to physician with anesthesiology specialty, those with a medical specialty in surgery, medicine, or oncology would be inclined to have inadequate knowledge of opioid prescribing (Ger, Ho, & Wang, 2000). Insufficient physician knowledge and inappropriate attitudes in cancer pain management have been suggested as major factors contributing to inadequate pain relief throughout the world (Marks & Sachar, 1973; Stjernsward, 1985).

### Problems Related to Patients

Patients may not complain of pain because they want to be a "good" patient, or they are reluctant to distract the physician from treating the primary disease. They may think of pain as an inevitable part of having cancer, or they may not want to recognize that their disease is progressing (Hodes, 1989). Many patients

also fear that early pain control will preclude pain control later in the course of disease because of concerns (which their physicians often share) that they will become tolerant to pain medications (Jones, Rimer, Levy, & Kinman, 1984). Patients are often reluctant to take pain medication, and some fear addiction or being perceived as an addict (this fear may be more pronounced in minority patients) (Anderson et al., 2002). Worries about unmanageable side effects can result in poor adherence to the prescribed analgesic regimen (Mystakidou et al., 2001).

A recent survey study assessed patients' misconception that may lead to under-treatment of pain using factor analysis and revealed four factors, including fear of side effect (physiological effect), fatalism about the possibility of achieving pain control (fatalism), fear of distracting physicians from treating cancer (communication) and belief that pain is indicative of progressive disease (harmful effect) (Gunnarsdottir, Donovan, Serlin, Voge, & Ward, 2002).

**Problems Related to the Health Care System**

A strict regulatory environment that closely monitors physicians' prescribing practices further contributes to under-treatment of cancer pain. Restrictive regulation of controlled substances and unavailability of treatment may constitute barriers to patient care. A survey of Wisconsin physicians in the United State found that, due to concerns about regulatory scrutiny, most respondents reduced the drug dosage or the quantity of pills prescribed, limited the number of refills, or chose a drug in a lower schedule (Weissman, Joranson, & Hopwood, 1991). Low priority is given to cancer pain treatment in the health system and in the training curriculum of health professionals. Major medical and nursing textbooks devote only a few pages to current pain and symptom control guidelines (Caron, Lynn, & Keaney, 1999). Health policy issues related to pain, including cost, access to care, regulatory perspectives, and ethical and legal issues, have likewise been neglected (Ferrell & Griffith, 1994). Although the World Health Organization has had an immense impact in changing policies on cancer pain relief, still today, in many parts of the world, even simple analgesics are not available for cancer pain, let alone morphine (World Health Organization, 1996). The most appropriate treatment may not be reimbursed or may be too costly for patients and their families in many countries. The available evidence

suggests that lack of coverage and uneven reimbursement policies for healthcare—including prescription drugs, medical equipment, and professional services—inhibit access to acute and cancer pain management for millions of people, in particular the poor, elderly, and minorities (Joranson, 1994).

## 2.7 Consequences of inadequate pain treatment

### 2.7.1 Quality of life

Intractable pain is a complication dreaded by many cancer patients. Cancer pain comprises acute pain, chronic pain, tumor-specific pain, and treatment related pain. Pain is a major cause of impaired quality of life, included decreased patient functionality and caregiver burden, in cancer patients, and intensifies the distress and suffering commonly evoked in patients with cancer onwards.(Bonica, 1990). Cancer pain treatment is strongly associated with quality of patient's life and has been suggested as an important indicator for quality of life of cancer patients (American Society of Clinical Oncology, 1996). Previous study showed a strong correlation between pain worsening and lessening of quality of life. It was found that a 30% change of pain scores can lead to a significant change meaningful to quality of patient's life (Thienthong et al., 2006). Therefore, inadequate pain control has a significant impact on the overall quality of cancer patient's life by influencing physical, psychological and spiritual aspects (Ahmedzai, 1995).

The assessment of QOL has become known as a standard component in the overall care of cancer. As a result, any tool designed to assess should be multidimensional, subjective, useful in setting, valid, and reliable (Cella, 1995; Elwood, 1988). Its multidimensional assemble reflects an individual's physical, emotional, and social well-being resulting from disease and its treatment (Fisch et al., 2003). An increasing number of published researches have shown QOL outcomes as facilitating clinical decision-making and of good predictive value in oncology (Velikova et al., 2004). A number of validated QOL evaluation tools are now available (Ganz, 1994) such as European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire (EORTC-QLQ), Functional Assessment

of Cancer Therapy (FACT-G), Functional Living Index-Cancer (FLIC), Medical Outcomes Short Form Health Survey (SF-36), Cancer Rehabilitation Evaluation System (CARES). One of the commonly used QOL tools in oncology is the FACT_G. It is sensitive to important characteristics of cancer including staging, location of service and changes in a patient's clinical condition over time (Cella et al., 1993).

### 2.7.2 Depression

Depression is the mood disorder most often observed among patients with chronic pain in general and among patients with cancer in particular (Spiegel, Sands, & Koopman, 1994). Depression or depressive disorder is a set of symptoms with specific signs and treatments. It is more than just sadness and difficult to distinguish from symptoms of the underlying disease in cancer patients. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) defines depression as having at least five of the following symptoms for at least 2 weeks.

1.Depressed mood most of the day
2.Loss of interest or pleasure
3.Change in appetite and/or change in weight
4.Insomnia or hypersomnia
5.Psychomotor retardation of agitation
6.Loss of energy
7.Feelings of worthlessness or guilt
8.Poor concentration
9.Thoughts of death or suicidal ideation

In order to meet the criteria for major depressive disorder, one of the patient's symptoms must be either depressed mood or loss of interest/pleasure, and the individual must also be experiencing distress or impairment in social, occupational, or other areas of functioning.

However, depression in cancer patients has been under-diagnosed and under-treated partly because of the belief that depression is a normal and universal reaction to serious disease (Massie & Holland, 1990) and partly because the

neurovegetative signs (weight loss, sleep disturbance) or emotional/cognitive signs of depression often are attributed to the medical illness (Rodin & Voshart, 1986) It is estimated that 20 to 25% of all cancer patients will experience depression during the course of their illness (Bottomley, 1998 ). Cancer patients are three times more likely than the general population and almost twice as likely than other medically hospitalized patients to develop depression (Arolt, Fein, Driessen, & et al, 1998; Kessler, McGonagle, Zhao, & et al, 1994 ). The prevalence of depression in cancer patients is even higher in those with the greatest disability and distressing physical symptoms, especially uncontrolled pain. There is great variation in the reported frequencies of depression in cancer populations. These varying estimates of depression in cancer patients may result from differing definitions of "depression," differing assessment tools, and different cancer populations with different significant variables such as timing of the assessment, physical debilitation, and concurrent treatment (Carr et al., 2002).

**The evaluation of depressive disorder**

Although clinical evaluation specifically for psychiatric symptoms is generally thought to be the best assessment, several instruments, both self-report and clinician-administered are being used to assess depressive symptoms. These instruments include three main types as follows: firstly, standard psychiatric assessments such as the Beck Depression Inventory (BDI) or Hamilton Depression Inventory (HDI); secondly, instruments designed to assess symptoms in a medically ill population (such as the Hospital Anxiety and Depression Scale and the Brief Symptom Inventory); and thirdly, rapid assessment instruments (such as The Distress Thermometer). Some of these instruments are currently being used in clinical settings to screen for depressive symptoms.

However, the HADS instrument was a widely used instrument for screening of depression in cancer patients (Snaith & Zigmond, 1986). It is a self-administered instrument with a good validity and reliability for use in Thai cancer patients (Nilchaikovit, Lortrakul, & Phisansuthideth, 1996). Beyond the HADS, the BDI and HDI were also a popular instrument that appeared to be good screening instrument seemed to be good.

## Interrelationship between pain and depression

Pain and depression conditions have biological link. The biochemical theory of depression suggests that depression is the result of a neurochemical imbalance or a dysfunctional serotonin and norepinephrine system. It is suggested that depression and painful symptoms follow the same descending pathways of the central nervous system. Although the ascending nociceptive fibers transmitting pain signals from the peripheral tissues through the dorsal horn to the thalamus and higher brain areas, the pain signals can be modulated by the activity of descending inhibitory fibers. The descending pathway originates from the amygdala and hypothalamus and terminates in the periaqueductal grey (PAG) (Fields, 2000). The PAG is an anatomic relay from limbic forebrain and midbrain structures to the brainstem. The amygdale, hypothalamus, and frontal neocortex all send fibers to the PAG, which connects with relay systems in the pons and medulla (Okada, Murase, & Kawakita, 1999). These relay systems contain serotonergic neurons and noradrenergic neurons (Hirakawa, Tershrer, & Fields, 1999). The serotonergic neurons send projections to the dorsal horn directly, whereas the noradrenergic neurons affect dorsal horn neurons indirectly by its projections to the serotonergic neurons and having direct connections (inhibitory only) to the dorsal horn. The serotonergic neuron has 2 types of cells important in pain perception: “on cell”, which facilitate pain transmission; and “off cells”, which inhibit pain perception (Fields, 2000).

The on and off cells in the serotonergic neurons through data transmitted from the limbic forebrain and other structures transmitted through the PAG may amplify or dampen pain impulses transmitted from the periphery. Activation of the off cells or the noradrenergic neurons may depress the activity of nociceptive neurons in the spinal dorsal horn (Fields, 2000; Hirakawa, Tershrer, & Fields, 1999). Normally, this system has a modulatory effect and tends to dampen pain signals. However, depletion of serotonin and norepinephrine often occurs in patients with depression, this system may lose its modulatory effect and amplifies minor signals from the body. This explanation may tell us why patients with depression describe multiple pain symptoms and why their pain is often associated with increased attention, focus, and negative affect.

## 2.8 Problems of cancer pain treatment

Previous studies using a variety of cancer pain outcome definition have shown that cancer pain management is significant (see Table 2.2). Reported inadequate pain control or moderate to severe pain ranged from 18% to 85% and inadequate pain medication ranged from 27% to 79%. A meta-analysis of fifty-two studies between 1966 and 2005 illustrated the prevalence of cancer pain in several aspects. It was found that the prevalence of cancer pain varied between 13% and 89% depending on the respective study population (Henningsohn, Wijkstrom, Dickman, Bergmark, & Steineck, 2001; Soebadi & Tejawinata, 1996) design, and the definition of cancer pain (van den Beuken-van Everdingen et al., 2007). Interestingly, the prevalence of cancer pain in each subgroup was quite high. For example, the prevalence in patients after curative treatment was 33% (95% confidence interval (CI) 21%-46%), while it was 59% (95%CI 44%-73%) in patients undergoing anti-cancer treatment, and 64% (95% CI 58%-69%) in patients at advanced/metastatic/terminal stage of the disease. In all cancer types, the prevalence of pain was more than 50%, with the highest prevalence in head and neck cancer patients (70%, 95%CI 51%-88%) (van den Beuken-van Everdingen et al., 2007).

Despite the availability of effective cancer pain relief guidelines, under-treatment of cancer pain has still existed. The factors that affect poor pain control can be though of as barriers to cancer pain management. Several studies demonstrate that many physicians continue to manage cancer pain inadequately (Cleeland et al., 1994; Larue, Colleau, Brasseur, & Cleeland, 1995). Von Roenn and colleagues (Von Roenn, Cleeland, Gonin, Hatfield, & Pandya, 1993) conducted a survey on cancer pain management within the Eastern Cooperative Oncology Group (ECOG). The ECOG consists of medical oncologists, hematologists, surgeons and radiation oncologists. Respondents answered questions about the magnitude of their patients' pain, their perceptions of the adequacy of pain management, and whether or not their settings had implemented a management plan for cancer pain. Eighty-six percent of respondents said that pain in their practices was under-medicated. Thirty-one percent said that they would not maximize analgesia unless a patient's life span was less than

6 months. The majority reported not using adjunctive forms of analgesics or having a prophylactic side effect management plan in place. The ECOG survey further identified certain barriers to adequate pain management. The most prevalent single factor (76%) among the respondents was a perceived inability to assess pain appropriately. Sixty-two percent attributed inadequate patient reporting of pain as a significant barrier, and 62% attributed the patients' reluctance to take analgesics as an additional barrier. Sixty-one percent said that the physicians' reluctance to prescribe adequate quantities or doses of opioid analgesics was also a barrier to adequate pain control. In a 1994 follow-up report on the adequacy of outpatient metastatic cancer pain management, Cleeland and colleagues (Cleeland et al., 1994) reported that 67% of patients had pain associated with their cancer, of whom 36% had impaired function of activities of daily living associated with their pain. Forty-two percent of these patients said that their pain was inadequately controlled.

Table 2.2

Studies reporting the cancer pain

| Author | City/Country | Participants | Number of participants | Measure | Pain severity category | % Pain severity | Other findings |
|---|---|---|---|---|---|---|---|
| Cleeland et al (1994) | United State | 54 Oncology clinics, outpatients | 1308 | BPI worst pain in the past week | 8-10 = severe<br>4-7 =moderate<br>1-3=mild<br>0=no pain,<br>> 5 =significant pain | Among patients who had pain (n=597),<br>62% Significant pain | 42% (-) PMI |
| Larue et al (1995) | France | 20 Cancer servises | 605 | BPI worst pain in the past week | 8-10 = severe<br>4-7 =moderate<br>1-3=mild<br>0=no pain,<br>> 5 =significant pain | Among patients who had pain (n=270),<br>69% Significant pain | 51% (-) PMI |
| Twycross et al, (1996) | United Kingdom | a specialist palliative care with medical school ,<br>outpatients | 111 | BPI worst pain at the last 24 hours | 8-10 = severe<br>5-7 =moderate<br>1-4=mild<br>0=no pain | At 4 weeks follow up (n=36)<br>8.3% Severe pain,<br>33.3% Moderate pain,<br>33.3% Mild pain<br>25.0% No pain | |
| Saxena et al (1998) | New Delhi, India | Cancer center:<br>Monolingual patients: | 200 | BPI worst pain at the last 24 hours | 7-10 = severe<br>5-6 =moderate<br>1-4=mild<br>0=no pain | 70% Severe pain ,<br>14% Moderate pain,<br>14% Mild pain,<br>2% no pain | 79% (-) PMI<br>28% Pain relief |
| | | Bilingual patients | 100 | | | 48% Severe pain,<br>37% Moderate pain,<br>15% Mild pain | 65% Pain relief |

Table 2.2 (Continued)

| Author | City/Country | Participants | Number of participants | Measure | Pain severity category | % Pain severity | Other findings |
|---|---|---|---|---|---|---|---|
| Beck and Falkson (1998) | Republic of South Africa | Oncology setting in 2 health care facilities, inpatients and outpatients | Phase 1: 263 | | | 35.7% cancer related pain | |
| | | | Phase2 : 426 | BPI worst pain at the last 24 hours | 8-10 = severe<br>4-7 =moderate<br>1-3=mild<br>0=no pain | 32.6% Severe pain ,<br>41.8% Moderate pain, | 30% (-) PMI |
| Ger et al. (1998) | Taiwan | The Tri-service General Hospital | 296 | BPI | $\geq$ 5 = significant pain | Among patients who had pain (n=113)<br>65% Significant pain | 69% (-) PMI |
| Uki et al (1998) | Saitama, Japan | cancer center | 121 | BPI worst pain at the last 24 hours | | | 27%(-) PMI, Mean scores of pain worst=4.9, average=3.8, current=2.9 , least=1.9 |
| Sze et al (1998) | Hong kong | Palliative care unit | 218 | NRS, VAS 0-10 scores | | 20% Severe pain,<br>54% Moderate pain, | 64% Moderate to severe disabilities in basic daily activities |

Table 2.2 (Continued)

| Author | City/Country | Participants | Number of participants | Measure | Pain severity category | % Pain severity | Other findings |
|---|---|---|---|---|---|---|---|
| Williums et al (2001) | Maharagama, Sri Lanka | Pain clinic, outpatient and inpatient | 100 | BPI | | One week after pain clinic treatment<br>7-9 score =1%<br>4-6 score =17%<br>0-3 score =82% | |
| Shvartzman et al, (2003) | Israel | Outpatient clinics at 3 oncology centers | 218 | BPI<br>worst pain in the past week | 8-10 = severe<br>4-7 =moderate<br>1-3=mild<br>0=no pain | 40% Severe pain,<br>40% Moderate pain,<br>20% Mild pain,<br>77% Significant pain | 75% (-) PMI,<br>68% reported moderate to high relief from pain. |
| Yun et al (2004) | Seoul, Korea | University hospital, outpatients and inpatients | 132 | BPI<br>worst pain at the last 24 hours | 7-10 = severe<br>5-6 =moderate<br>1-4=mild<br>0=no pain | 43.9% Severe pain,<br>31.1% Moderate pain,<br>25% Mild pain | 74% (-) PMI |
| Okuyama et al (2004) | East, Japan | Cancer center, outpatient | 138 | Anderson Symptom Inventory (MDASI) | 7-10 = severe<br>5-6 =moderate<br>1-4=mild<br>0=no pain | 59.4% Severe pain,<br>18.8% Moderate pain,<br>21.7% Mild pain | 70.3% (-) PMI |
| Hsieh (2005) | Taipei, Taiwan | 15 Oncology clinic outpatients | 480 | | | Among patients who had pain (n=257)<br>35% Severe pain,<br>35.4% Moderate pain, | |

Table 2.2 (Continued)

| Author | City/Country | Participants | Number of participants | Measure | Pain severity category | % Pain severity | Other findings |
|---|---|---|---|---|---|---|---|
| Reyes-Gibby et al (2006) | Hanoi, Vietnam | Tertiary cancer center, outpatient and inpatient | 178 | BPI<br>worst pain at the last 24 hours | 7-10 = severe<br>5-6 =moderate<br>1-4=mild<br>0=no pain | Among patients who had pain (n=118),<br>24.6% Severe pain,<br>14.4% Moderate pain,<br>33% Mild pain,<br>28% no pain | |
| Roelien et al (2007) | Rotterdam, Netherlands | Outpatient cancer center | 915 | BPI<br>worst pain in the past week | 7-10 = severe<br>5-6 =moderate<br>1-4=mild<br>0=no pain | 54% Severe pain,<br>26% Moderate pain, | 65% (-) PMI |

Table 2.2 (Continued)

| Author | City/Country | Participants | Number of participants | Measure | Pain severity category | % Pain severity | Other findings |
|---|---|---|---|---|---|---|---|
| Petpichetchian ( 2001) | Thailand | 5 tertiary hospitals (age 19-84 years) Outpatient oncology clinic | 300 | BPI worst pain at the last 24 hours | | | Mean scores of pain, worst =6.77, average=4.93, current =3.75, least=2.5 |
| Lukkahatai (2004) | Thailand | 3 tertiary hospitals (age 19-84 years) Inpatient=72.5% | 265 | BPI worst pain at the last 24 hours | | | Mean scores of pain, worst =4.5, average=3., current =1.9, least=1.3 |
| Thienthong et al (2006) | Thailand | 3 departments (pain clinic, radiology and medical oncology) from 7 university hospital and 3 tertiary care centers | 520 | BPI worst pain at the last 24 hours | 7-10 = severe<br>4-6 =moderate<br>1-3=mild<br>0=no pain | 32.9% Severe pain,<br>28.6% Moderate pain,<br>28.3% Mild pain,<br>10.2% no pain | |
| Vatanasapt et al (2008) | Thailand | University hospital, inpatients | 335 | BPI worst pain at the last 24 hours | 8-10 = severe<br>4-7 =moderate<br>1-3=mild<br>0=no pain | Among patients who reported pain (n=139) within 24 hours of admission<br>45.3% Severe pain,<br>33.1% Moderate pain,<br>21.6% Mild pain | 75.5% reported improvement before discharge |

## 2.9 Pain Treatment facilities

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The desirable characteristics for pain clinic suggested by the IASP task force should be as follows (International Association for the Study of Pain, 1990):

1.A pain clinic should have access to and regular interaction with at least three types of medical specialties or health care providers. If one of the physicians is not a psychiatrist, a clinical psychologist is essential.

2. The health care providers should communicate with each other on a regular basis both about individual patients and programs offered in the pain treatment facility.

3. There should be a director or coordinator of the pain clinic. If he or she is not a physician, there should be a director of medical services who is responsible for the monitoring of medical services which are provided to the patients.

4. The pain clinic should offer both diagnostic and therapeutic services.

5. The pain clinic should have designated space for its activities.

6. The pain clinic should maintain records on its patients so as to be able to assess individual treatment outcomes and to evaluate overall program effectiveness.

7. The pain clinic should have adequate support staff to carry out its activities.

8. Health care providers working in a pain clinic should have appropriate knowledge of both the basic sciences and clinical practices relevant to pain patients.

9. The pain clinic should have a trained health care professional available to deal with patient referrals and emergencies.

10. All health care providers in a pain clinic should be appropriately licensed in the country and state in which they practice.

The IASP task force is strongly recommended that a multidisciplinary approach to diagnosis and treatment is the preferred method of delivering health care to patients with chronic pain of any etiology. Although not every patient referred to a pain treatment facility is in need of multidisciplinary diagnosis or treatment, the facility should have those resources available when they are appropriate.

## 2.10 Cancer pain in Thailand

### Cancer in Thailand

Cancer has been a major health problem throughout the world because of its high mortality rate. For Thailand, its mortality rate has increased more than four folds during the last three decades, from 12.6 per 100,000 in 1967 to 51.7 in 1996 (WHO, 1999). Although several programmes for cancer control were implemented, the cancer incidences still have not decreased. For example, the estimated age-adjusted incidence rates for all cancer sites during 10 years were 149.6, 150.4, and 149.2 per 100,000 for males and 125.2, 123, and 125 for females during 1988 to 1991, 1992 t0 1994, and 1995-1997 respectively (Deerasamee et al., 1998; Deerasamee et al., 1993; Sriplung et al., 2005). However, if comparing with other countries, the incidence rates are similar to those in Asian countries and about half of those in Western countries (Vatanasapt, Sriamporn, & Vatanasapt, 2002).

Due to a geographical variability, cancer incidences are greatly dissimilar from region to region. For example, lung cancer was the most prevalent in the northern region in Thailand, whereas liver cancer frequently observed in the northeastern region. For the whole country, the leading type of cancer included liver, lung, colon& rectum, cervix, breast as shown in Table 2.3. Similar to Bangkok, lung cancer was the most important cancer in men and breast cancer was in women (Sriplung et al., 2005).

### Cancer pain management in Thailand

In the past, the main aim of cancer treatment in Thailand was generally to lessen tumor size and improve the results of laboratory testing. This often neglected the pain in cancer patients (Vatanasapt, Sriamporn, & Vatanasapt, 2002). Several survey studies were conducted in Thailand in the 1990s and found that 62%-89% of cancer patients had moderate to severe pain. More than 30% of cancer patients had not received pain medication while most of them received inadequate pain treatment based on the WHO's guidelines (Chaudakshetrin, 1993; Chukkul Luengsukcharoen, 1998; Petpichetchian, 1998; Ratanathai, 1998; Vatanasapt et al., 1992). Previous

studies suggested that the reason for under-treating pain in Thailand may be due to insufficient knowledge and resources, the strict regulations during the drugs war, physicians' reluctance to prescribe opioids or physicians' reluctance to adjust doses to meet each patient needs because of fear of addiction (Chaudakshetrin, 1993; Paiboonvorachart & Boonsong, 2000). In 2001, a study of Petpichetchian (Petpichetchian, 2001) found that most cancer patients were not receiving adequate pain medication. The average amount of pain medication taken in the past 24 hours was only 10.49 milligrams (morphine analgesic dose), indicating inadequate pain management for Thai cancer patients. The other reasons may be due to the limited availability of pain medications, particularly opioids (i.e., morphine) in the Thai health care system. Moreover, the drugs were always in short supply at the end of year. The Palliative Care Taskforce of the Ministry of Public Health also reported that the national narcotic drugs control policy of 400 grams of morphine per year for a single government hospital is insufficient (Palliative Care Taskforce, 1999). This limited availability of morphine-like substances for cancer patients in Thailand has been acknowledged and the Taskforce has been working to improve the situation by implementing a corrective action plan within the healthcare system. As a result, since 2006, Ministerial Notification of Ministry of Public Health No. 197 B.E.2549 (2006) has allowed the amount of available and accessible opioids to raise by 10 to 20 folds for medical purposes in all hospitals in Thailand. This notification has been expected to be helpful for cancer pain treatment in Thailand.

**Opioid policy in Thailand**

It is vital that a country should have enough opioids to meet the demand for treatment of patients in pain. Especially, opioids for moderate to severe pain such as morphine, methadone, oxymorphone, oxycodone, levophanol, fentanyl, and pethidine are the substances under strict control by the law. According to the Narcotics Act B.E. 2522, opioids for medical use in Thailand are classified as narcotic category II. No person shall produce, import or export the narcotic category 2 unless he has obtained the license from the Thai Food and Drug Administration (Thai FDA). Any person who violates the law shall be liable to imprisonment for a term of one

year to ten years and to a fine of one hundred thousand to one million baht. Furthermore, no person shall sell or possess the narcotic category 2 unless he has the license. Any person, who violates the law, sells or possesses for sale, shall be liable to imprisonment for a term of one year to ten years or to a fine of twenty thousand to two hundred thousand baht or to both. The Thai FDA has the responsibility to provide the opioids for medical use, scientific purpose, and manufacture; and to control these opioids as well as prevent their misuse or abuse through the measures as following:

**1. Requirements to apply for the license to sell or possess the narcotics category 2.**

1.1 There are 3 types of the applicants who could apply for the license to sale or possess narcotic category 2 as following:

Type A: Ministry, Sub-Ministry, Department, local administrative organization including Bangkok Metropolitan Administration, Thai Red Cross Society or Pharmaceutical Organization;

Type B: Person engaging in the international public transport;

Type C: Medical profession, pharmaceutical practitioner, dental practitioner, first-class veterinary practitioner,

1.2 The qualification of the applicants should be as following:

(a) Having residence in Thailand.

(b) Not having been convicted by a final judgment of the law on narcotics, the law on psychotropic substances, the law on Controlling the Use of Volatile Substances, the law on measures for the suppression of offenders in an offence relating to narcotics and the law on medicine.

(c) Not having his license to engage in the medical profession or license to engage in pharmaceutical practitioner, license to engage in dental practitioner or first-class veterinary practitioner or license under the Narcotic Act B.E. 2522 suspended or revoked and the period of suspension or revocation has not been elapsed.

(d) Not being a person of unsound mind or mental infirmity

(e) Not being an in competent or quasi-incompetent.

Furthermore, the FDA has assigned the authority in issuing the license to the provincial health service department throughout Thailand in order to facilitate their administration.

**2. Providing the opioids for the licensees across the country.**

After obtaining the license to sell or possess the narcotic category II, the licensee should apply for the purchasing of opioid analgesic to the FDA. The amount of opioids supplied to the licenser will be based on case by case consideration as the necessity and appropriateness, but not exceeding the annually quantity notified in the Ministerial Notification (Table 2.5). However, the licensee could apply and submit the following documents for additional quantity of such narcotic. The consideration of Thai FDA will be based on case by case consideration of the Thai FDA.

2.1 The necessity and the appropriateness to use opioids

2.2 The amount of patients to be used per month

2.3 The amount of narcotic category II per month

2.4 The number of beds of each hospital

2.5 The data of narcotics utilization of the hospital for at least 6 months

2.6 The remained amount of the such narcotic products

The Thai FDA will consider on case by case basis for the approval of such additional amount of narcotic category II, but could not allow more than 2 folds of the quantity specified in such ministerial notification.

**3. Monitoring and examining the opioid utilization toward the objective of the license.**

The licensees have a duty to submit the monthly and annually record of the opioid drugs utilization for the Thai FDA.

**4. Providing and preparing the opioid products for sale**

There are 2 methods for providing opioid products as following:

4.1 Importing the raw material and employing the local manufacture for the production including morphine injection, pethidine injection, codeine tablet and methadone tablet

4.2 Importing finished products such as fentanyl injection, sustained released morphine tablet/capsule, fentanyl patch, etc.

Nowadays, the Thai-FDA is the sole agent provider of opioids throughout the country. The number items of opioid availability, therefore, were based on the Thai-FDA supply. It should be noted that there were no immediate oral form of morphine or fentanyl supplied as described in Table 2.4

Effort was made to assure each hospital should have enough opioids for medical use to meet the demand for treatment of patients in pain. The Thai FDA has been working to improve the pain management by implementing a corrective action plan within the healthcare system. As a result, since 2006, Ministerial Notification of Ministry of Public Health No. 197 B.E.2549 (2006) has allowed the amount of available and accessible opioids to raise by 10 to 20 folds, comparing with the previous ministerial notification as shown in Table 2.5.-2.6

**5. Regulation of health care workers related to opioid availability**

**5.1 Legal ability**

According to the law above, this means that every hospital in Thailand has ability to apply for being such a licensee. Every physician of such hospital is also entitled to prescribe and administer opioid analgesics to their patients**.** Pharmacists in that hospital are also entitled to dispense such analgesics to patients based on prescription. Decisions about the type of drug, the strength, number of dosage units, and duration of therapy are made by medical professionals based on the individual needs of patients. These decisions are not based on government regulation.

**5.2 Accountability**

Individuals who handle opioids must be accountable for providing them only for medical purposes. Opioids should be distributed only between duly

authorized individuals. Opioids should be stored in a secure place and appropriate inventory records must be kept. Such accountability requirements are reasonable to assure the appropriate use for medical purposed and prevent from illegal use.

**5.3 Prescriptions**

A prescription for opioids must be written and contain at least the following information: namand address of the patient; date of issue; drug name, dosage strength and form, and quantity; directions for use; and physician's name, address, and original signature.

Table 2.3

Cases and ASR of leading type of cancer in 1996

| Males | | | Females | | |
|---|---|---|---|---|---|
| Type of cancer | cases | ASR* | Type of cancer | cases | ASR* |
| Liver | 9,031 | 37.6 | Cervix | 6,228 | 19.5 |
| Lung | 5,916 | 25.9 | Breast | 5,592 | 17.2 |
| Colorectum | 2,532 | 10.8 | Liver | 4,696 | 16 |
| Oral cavity | 1,576 | 6.8 | Lung | 2,964 | 10 |
| Prostate | 1,019 | 4.8 | Colorectum | 2,215 | 7.3 |

**ASR= age standardized incidence rate per 100,000*

Table 2.4

Availability of opioids analgesics in Thailand (update Dec. 2008)

| Drug | Preparation | Dosage form |
|---|---|---|
| Opioid for mild to moderate pain | | |
| Codeine | Tablet | 15 mg, 30 mg/tablet |
| Opioid for to moderate severe pain | | |
| Fentanyl | Injection | 0.1mg/2ml., 0.5/10 ml./ampule |
| | Transdermal Patch | 12, 25, 50 µg./hr. |
| Methadone | Tablet | 5 mg./tablet |
| Morphine | Injection | 10 mg./ml./ampule |
| | Sustained release tablet | 10, 30, 60 mg./tablet* |
| | Sustained release capsule | 20, 50, 100 mg./capsule** |
| Pethidine | Injection | 50 mg./ml./ampule |

* Duration of action 12 hours, ** duration of action 24 hours

Data from the Narcotics Control Division, Thai FDA.

Table 2.5

The annually quantity of opioids notified in the Ministerial Notification of Ministry of Public Health No.197 B.E.2549 (2006) (Effective on July 8, 2006 up to present)

| Sale or possess licensee of narcotic category II | The quantity of opioids base (gram) | | | | |
|---|---|---|---|---|---|
| | Codeine | Fentanyl | Methadone | Morphine | Pethidine |
| Government hospital* | 200 | 50 | 10 | 4000 | 2gm/bed |
| Private hospital* | 60 | 25 | 5 | 1000 | 2gm/bed |
| Private clinic* | - | 0.1 | 2 | 10 | 10 |
| Dental practitioner | - | 0.1 | - | 10 | 10 |
| Veterinary practitioner | - | 0.1 | - | 10 | 10 |

* Classified as general hospital/clinic

Table 2.6

The annually quantity of opioids notified in the Ministerial Notification of Ministry of Public Health No.121 B.E.2536 (1993) (Valid from July 20, 1993 to July 7, 2006)

| Sale or possess licensee of narcotic category II | The quantity of opioids base (gram) | | | | |
|---|---|---|---|---|---|
| | Codeine | Fentanyl | Methadone | Morphine | Pethidine |
| Government hospital* | 200 | 0.5 | 5 | 400 | 2gm/bed |
| Private hospital* | 60 | 0.5 | 5 | 50 | 2gm/bed |
| Private clinic* | 30 | 0.1 | 2 | 10 | 10 |
| Dental practitioner | 30 | 0.1 | - | 10 | 10 |
| Veterinary practitioner | 30 | 0.1 | - | 10 | 10 |

* Classified as general hospital/clinic

## 2.11 Instruments for the study

### 2.11.1 Pain Intensity (Brief Pain Inventory: BPI)

The Brief Pain Inventory (BPI)(Cleeland, 1988) was used to assess pain intensity and pain interference. It was developed specifically for cancer patients and has been used worldwide (Cleeland, 1988). It is a powerful instrument and has established both reliability and validity across cultures and language (Cleeland & Ryan, 1994). The BPI-SF assesses the multidimensional nature of cancer pain. It consists of two pain assessment scales: (1) pain intensity and (2) pain interferences with life activities. The first scale, pain intensity, is measured on the last 24 hours at its worst, least, average, and now on an 11-point scale with the number 0-10. The numbers are placed on a horizontal line, with 0 on the left and labeled “no pain” and 10 on the right, labeled “pain as bad as you can imagine”. The worst pain has been demonstrated to be a reliable and valid measure of pain intensity with a test-retest reliability of 0.93 in 20 inpatients with cancer over a 2-day period (Lin, 1998). The second scale, pain interference, is measured by using the same 0-10 scale described as pain intensity, with 0 being ”does not interfere” and 10 being ”completely interferes”. Patient is asked for ratings of how much the pain interferes with general activity, mood, walking, working, relations with others, sleeping, and life enjoyment. The averaging of items produces an interference score. Good internal consistency for the pain interference scale (0.92 for low back pain samples and 0.93 for cancer pain samples) has been reported (Lin, 1998).

The BPI has been translated into many languages such as Chinese (Wang, Mendoza, Gao, & Cleeland, 1996), Italian (Caraceni et al., 1996), Vietnamese (Cleeland, Landinsky, Serlin, & Thuy, 1998), Japanese (Uki, Mendoza, Cleeland, Nakamura, & Takeda, 1998), Hindi (Saxena, Mendoza, & Cleeland, 1999), German (Radbruch et al., 1999), and Greek (Mystakidou et al., 2001), and has been used successfully across cultures because these translated versions measured similar aspects of pain compared to those measured by the original English version (Cleeland & Ryan, 1994). All studies of translated versions of the BPI have reported that the two factor solution of pain intensity and pain interference is interpretable and provides an adequate fit for the data. The two factor solution found in all original and translated

versions provides evidence that this instrument is consistent in terms of the two factors and items loading on each factor. These translated versions have been studied to prove that they were reliable and valid instruments to measure pain by showing high internal consistency (Cronbach's alpha 0.75-0.91).

Additionally, for the purpose of this study, the BPI patients scores were classified into four pain categories as none (score 0), mild (score 1-3), moderate (score 4-6) and severe (score 7-10) (Benedetti et al., 2000). The single item of worst pain is categorized into 2 levels of pain control as adequate (score 0-3) vs inadequate (score 4-10).

### 2.11.2 Pain Management Index (PMI)

The Pain Management Index (PMI) is a conservative method of assessing the adequacy of pain management based on cancer pain treatment guidelines established by the World Health Organization (World Health Organization, 1986) and the Agency for Health Care Policy Research (Jacox et al., 1994). Pain management is considered adequate when there is congruence between the patient's reported level of pain and the potency of the prescribed analgesic drug. The PMI compares the most potent analgesics prescribed to a patient's reported worst pain. This index has been widely employed and allowed researchers to compare the adequacy of pain across countries, races and institutes (Cleeland et al., 1994; Larue, Colleau, Brasseur, & Cleeland, 1995; Mystakidou et al., 2001; Saxena, Mendoza, & Cleeland, 1999; Uki, Mendoza, Cleeland, Nakamura, & Takeda, 1998).

The index was constructed as follows. The most potent analgesic prescribed was categorized at one of four levels: 0=no analgesics, 1=a non-opioid, 2=a weak opioid, 3=a strong opioid. The patient's level of pain from the worst-pain score on the Brief Pain Inventory was also categorized into four pain levels as 0=no pain, 1=mild pain (1-3), 2=moderate pain(4-6), 3=severe pain(7-10) (Benedetti et al., 2000). The PMI was then computed by subtracting the pain level from the analgesic level, range from -3 to 3, with the lower value representing greater under-treatment. Negative PMI scores are considered to indicate inadequate orders for analgesic drugs, scores of 0 or higher are considered to be conservative indicators of acceptable

treatment. However, the PMI does not account for dosage of analgesics, schedule, patient's compliance or adjuvant pain medication.

Previous studies reported that gender (female) (Anderson et al., 2000; Cleeland & Ryan, 1994; Uki, Mendoza, Cleeland, Nakamura, & Takeda, 1998), age [older (Cleeland & Ryan, 1994), younger (Larue, Colleau, Brasseur, & Cleeland, 1995)], education (low) (Wang, Mendoza, Gao, & Cleeland, 1996), physical condition [better ECOG performance status (Cleeland & Ryan, 1994; Larue, Colleau, Brasseur, & Cleeland, 1995), without metastasis (Larue, Colleau, Brasseur, & Cleeland, 1995; Okuyama et al., 2004)], race (minority) (Cleeland et al., 1994), discrepancy between patient and physician estimates of pain severity (greater) (Anderson et al., 2000; Cleeland et al., 1994; Larue, Colleau, Brasseur, & Cleeland, 1995; Uki, Mendoza, Cleeland, Nakamura, & Takeda, 1998), patient reluctance to report pain (Anderson et al., 2000) and lack of staff time (Anderson et al., 2000) are significant predictors of inadequate cancer pain treatment.

**2.11.3 Depression** (Hospital Anxiety and Depression Scale: HADS)

The Thai Hospital Anxiety and Depression Scale (Thai HADS) was translated from the HADS, a widely used instrument for detection of anxiety and depression in hospital medical clinics (Snaith & Zigmond, 1986). The validity and reliability test of Thai HADS showed that it had good validity and reliability for use in Thai cancer patients (Nilchaikovit, Lortrakul, & Phisansuthideth, 1996). It is composed of 14 items; seven items for anxiety subscale (Cronbach's alpha coefficient, $\alpha = 0.86$) and seven items for depression subscale ($\alpha = 0.83$). The total scores of each subscale range from 0 to 21. The scores 0-7 indicate no anxiety or depression, 8-10 indicate anxiety or depressive symptoms (doubtful cases), and 11-21 indicate cases of anxiety or depressive disorders. The sensitivity of the anxiety and depression sub-scales of the Thai HADS were 100% and 85.71% respectively, specificities were 86.0% for anxiety and 91.3% for depression.

**2.11.4 Quality of life** (Functional Assessment of Cancer Therapy-General Scale: FACT-G)

The Thai Functional Assessment of Cancer Therapy-General Scale (Thai FACT-G) was translated from the FACT-G version 4, a widely used instrument for assessing quality of life in cancer patients (Cella et al., 1993). The instrument consists of 27 items. The item scales range from 0 to 4 (not at all – very much) and can be aggregated into four domains: physical, emotional, social and functional well-being. The FACT-G total scores range from 0 -108 with higher scores corresponding to better quality of life. The Thai version shows good reliability with Cronbach's alpha coefficient ranging from 0.75-0.90. Many known groups and factor analysis have confirmed the construct validity of the questionnaire (Rattanatharathorn et al., 2001).

**2.11.5 Patients' satisfaction and expectation**

Satisfaction and expectation of patient to pain management was assessed with the following question: "How satisfied are you with your pain management?" and "Has your pain management met your expectations?" with answer on a 5-point scale ranges from very dissatisfied (1) to very satisfied (5). Scores of 1 and 3 are classified as inadequate pain treatment, while scores of 4-5 are considered adequate treatment. It is indicated as one of the criteria by the American Pain Society (American Society of Clinical Oncology, 1996) and the Agency for Health Care Policy and Research (Agency for Health Care Policy and Research, 1994).

**2.11.6 Patients' barriers** (Barriers Questionnaires - II: BQ- II)

The original Barriers Questionnaires (BQ) (Ward et al., 1993) is originated to measure the patients' barriers to pain control. It has 27 items that reflect two underlying concepts: patients' reluctance to report pain and to use available analgesics. The BQ has been revised to reflect changes in pain management practices, resulting in the Barriers Questionnaire-II (BQ-II), a 27-item, self report instrument (Gunnarsdottir, Donovan, Serlin, Voge, & Ward, 2002). Participants are instructed to rate the extent to which they agree with each item on a 6-point scale, anchored with 0 (do not agree at all) up to 5 (agree very much). The BQ-II consists of 4 subscales. Firstly, Physiological effect consists of 12 items addressing the beliefs that side

effects of analgesics are inevitable and unmanageable, concerns about tolerance, and concerns about not being able to monitor changes in one's body when taking strong pain medications. Secondly, Fatalism consists of 3 items addressing fatalistic beliefs about cancer pain and its management. Thirdly, Communication consists of 6 items addressing the concern that reports of pain distract the physician from treating the underlying disease, and the belief that 'good' patients do not complain of pain. Finally, Harmful effect consists of 6 items addressing fear of becoming addicted to pain medication and the belief that pain medications harm the immune system. The BQ-II total had an internal consistency of 0.89, and alpha for the subscales ranged from 0.75 to 0.85. The BQ-II scores were related to measures of pain intensity and duration, mood and quality of life. Patients who used adequate analgesics for their levels of pain had lower scores on the BQ-II than did patients who used inadequate analgesics (Gunnarsdottir, Donovan, Serlin, Voge, & Ward, 2002).

### 2.11.7 Physicians' knowledge and attitudes

The instrument, which comprised components questionnaires appearing in previous study (Ger, Ho, & Wang, 2000), was designed to assess the knowledge and attitudes of treating physicians in the study on the following aspects:

1. Attitudes toward the optimal use of analgesics for cancer pain management were assessed by 8 questions, including 6 questions all taken from Ger and Wang, 2000 and 2 additional questions regarding assessing pain.

2. Knowledge and attitudes toward opioid prescribing consisted of 16 questions making up two scales. The first scale was for assessing physicians' knowledge to prescribe opioids consisting of 8 items with 6 negative and 2 positive questions. The other scale was for assessing physicians' attitude to prescribe opioids which consisted of 8 items with 7 negative and 1 positive question. A 5- point Likert response format was utilized, ranging from strongly agree to strongly disagree, with a score of 1 to 5 for negative questions and with a score of 5 to 1 for positive questions. Content validity of these two scales was determined by two expert anesthesiologists and two oncology nurses. The coefficient alpha was 0.6133 and 0.8311 for the knowledge scale and the attitude scale respectively. A physician was classified as "knowledge deficits to prescribe opioids" if his/her score was equal to or less than 3.0

on the knowledge scale. Similarly, A physician was classified as “reluctant to prescribe opioids” if his/her score was equal to or less than 3.0 on the attitude scale (Ger, Ho, & Wang, 2000).

3. Perception of barriers to cancer pain management was measured with 14 questions and one open-ended item for additional information that they might have about this issue. Physicians were asked to indicate whether these barriers existed in their current working settings.