CHAPTER 5

DISCUSSION

The first part of this chapter concerns the methodological considerations and limitations including the study population representatives, design, chance, biases, and confounders. The second part discusses the main findings, implication and recommendation for future research study.

5.1 General methodological consideration

5.1.1 The study population and representativeness of the sample

This is a hospital-based study conducted at two tertiary government hospitals in Bangkok Metropolitan Region (Bangkok and its vicinity). The study population was referred patients. Patients who were being treated in primary or secondary care settings and not referred to the specialized care setting such as a cancer center or a pain clinic were not included in the population under study. Neither were some of the terminally-ill cancer patients, patients living in a remote area and those who had no or limited access to health care. Therefore, the findings of this study cannot be generalized to the entire Thai population of cancer patients with pain. The results can at best reflect the general situations of cancer pain management in pain clinics and specialized cancer care centers in Thailand.

The response rate in this study was sufficiently high; with 228 of the 240 participants successfully completed the interview (95.0%), thus the potential for “response bias” was negligible.

5.1.2 The study design

This is a cross sectional study design, in which type of cancer pain care setting was examined as an exposure which may affect pain treatment outcomes. The advantage of the cross sectional studies are time efficient and less expensive to

conduct. They allow for investigation of multiple exposures and multiple outcome measures which are useful for a study of this kind. Evidence suggests that cancer pain management, one of the main study outcomes, is affected by several clinical factors such as choice of treatment, co-morbidities, type of clinical care setting, phase of illness, etc (Carr et al., 2002). Furthermore, there were several impediments to pain control in terms of the characteristics of the physicians, patients and health care systems. Physicians' knowledge and attitudes relating to cancer pain management and opioids prescribing can determine the adequacy and appropriateness of cancer pain treatment. The attitudes of the patients and their care givers towards pain and analgesic taking (Gunnarsdottir, Donovan, Serlin, Voge, & Ward, 2002; Von Roenn, Cleeland, Gonin, Hatfield, & Pandya, 1993), and barriers within a health system to obtain particular opioids (World Health Organization, 1996) also contribute to the cancer pain treatment outcomes. Depression, another main study outcome, is highly comorbid with chronic pain and illness. It is therefore very common in cancer patients but usually under-diagnosed and under-treated. Effective treatment of depression may influence the disease course and improve cancer pain management (Spiegel, 1996). The other main study outcome was quality of life (QOL) which is an essential part of the evaluation the treatment outcomes in cancer patients. Evidence suggests that pain intensity and depression are negatively correlated with QOL of cancer patients (Rustoen, Moum, Padilla, Paul, & Miaskowski, 2005). Given that these outcomes are correlated, they should therefore be investigated simultaneously for the effects of cancer pain treatment in this study.

The main limitation of the cross sectional design is that it does not permit assessment of direction of causality, because exposure and outcome are ascertained simultaneously. Both have occurred already and only the respondent's account of their timing can establish the sequence of events. Therefore, using this design, it will not be possible to establish a causal etiological association between the clinical setting and risk for inadequately treated pain. The most precise study design should have been a longitudinal cohort, given its ability to assess the temporal sequence between exposures and outcomes. Ideally, for each patient, pain should be measured at baseline since diagnosis and followed throughout the treatment period.

5.1.3 The role of chance

The sample size estimated for this study was at least 340 patients. In this study, only 228 were recruited, including 133 from the pain clinic and 95 from the regional cancer center. This was due to a smaller-than-expected number of eligible patients and the time constraint of the study. However, it turned out that this study had sufficient power not only to provide the acceptable range of the inadequate pain control prevalence (61.4%, 95% CI: 55.1- 67.7) but also to detect the effect of being treated in the cancer center of 2.5 (95%CI: 1.3 - 4.9) for risks associated with inadequate pain control compared to being treated in the pain clinic. We were able to reject the alternate hypotheses with 95% confidence. The use of the appropriate statistical tests in this study made it unlikely that the main findings can be explained by chance (Type 1 error). It should be noted that multiple tests of statistical significance in this study was conducted, the probability of type 1 error would have increased with respect to subgroup analyses.

5.1.4 The role of bias (systematic errors)

Several types of bias can be arising from many sources including the manner in which participants are selected for the study and the way in which information is obtained, reported or interpreted (Hennekens & Buring, 1987). Bias tends to produce results that differ systematically from the truth (Sackett, 1979).

5.1.4.1 Selection bias

Selection bias referred to a distortion in the estimate of the effect as a consequence of the way in which participants are selected for the study population (Kleinbaum, Kupper, & et al, 1982). In analytic study, selection bias always occurs when the investigator has to deal with two or more groups of sample. Selection bias may have occurred in the study as a result of different inclusion criteria (eligibility criteria) used for the two compared groups. The inclusion criteria adopted for the pain clinic group were the cancer patients who had been treated in this clinic for more than one month whereas the criteria for the cancer center group were those who had been

treated as inpatients for more than one week. In general, the hospitalized cancer patients tend to be more seriously ill, have more co-morbidities, and receiving aggressive interventions than the outpatients did. These differences in drug titration time and inclusion criteria between the two settings might have biased the association between the setting and the pain control. Therefore, selection bias is a real possibility. However, it is difficult to anticipate the direction and effect of selection bias on the hypothesized association between the exposure (type of clinical setting) and the outcomes (such as inadequate pain control). Future studies should try to minimize such bias by making the two groups more comparable by using the same inclusion criteria and drug titration period for both groups under study.

5.1.4.2 Information bias

Another inherent weakness in cross sectional design is the potential for measurement bias. Errors in measurement may be introduced by the observer (observer bias), by the study individual (responder bias) or by the instruments. In this study, observer bias was minimized by 1) using structured interviewer administered questionnaire and 2) carefully training the interviewers in structured interview, and 3) blinding the participants to the specific study hypotheses. However, it was not feasible to blind the interviewers to the exposure (i.e. type of clinical setting), so it was impossible to know whether the interviewers forced the participants to answer in a way that they might, consciously or unconsciously, have expected. Regarding responder bias, it was also possible that some participants in the pain clinic would feel better after having been referred to a pain specialist and given ‘extra’ pain management - a kind of placebo effect. All these possibilities of information may have inflated the hypothesized associations between the exposure and the pain outcomes. They should have had, however, no effects on depression and quality of life outcomes.

Secondly, regarding the measure of the physicians’ knowledge of and attitudes towards opioids prescribing, it was found that there were no significant differences in the knowledge and attitudes between the physicians in the two settings. This may simply have been due to the inability of the instrument to measure such

attributes. The questionnaire used in the study is rather simple, consisted of only 8 questions for measuring the knowledge and 8 questions for measuring the attitudes. The proper measure should be more sophisticated and comprehensive, and be validated in order to evaluate whether the physicians' knowledge and attitudes meet the standards of pain control management.

Thirdly, regarding the barriers to obtain a variety of opioids within the health care setting, such barriers were not reported to be different between the two study institutions. This may have been due to the very limited sources of information that we managed to obtain. In this study, we could only complete interview with 2 pharmacists at the two hospitals, and 3 physicians in the pain clinic, whereas the physicians in the cancer center were unavailable for interview. Lack of complete information and opinions from health professionals involved made us unable to assess the differences in the barriers between the two settings. Future studies are needed to acquire such information from a variety of sources, which may come from the hospital's drugs lists, health professionals, health authorities and policy makers.

. Finally, regarding the patients barriers measured by the modified BQ-II in this study. Although special attention was given to selecting instruments with strong psychometric properties, the reliability coefficient of the physiological effects subscale of the modified BQ-II in this study was only 0.37. Careful interpretation was therefore warranted when interpreting the results involving this subscale. Nevertheless, measuring the patients' barriers to pain treatment based on their belief or attitudes may not reflect the real behavior of patients regarding the treatment. Future studies should try to directly measure the patients' reported behavior or their drug adherence.

5.1.5 The role of confounding

Confounding is a distortion of an exposure-outcome association brought about by the association of another factors with both outcome and exposure. Ignoring confounding when assessing the association between an exposure and an outcome variable can lead to an overestimate or underestimate of the true association between

exposure and outcome and even change the direction of the observed effect. In the present study, several potential confounding factors were planned to collect on patients' demographic (gender, age), clinical factors (stage of cancer, the presence of bone metastasis, number of pain sites, duration of pain, dosage of opioid prescribed per day), and the patients' barriers variables which were felt likely on the basis of previous research to be associated both with the exposure (clinical setting) and with the outcome (pain intensity).

5.1.5.1 Patients' demographic: Gender and age

Gender and age factors are usually practically included in all studies as potential confounders. These factors were entered in the multivariate regression analysis as the potential confounders in this study.

Previous studies revealed that female gender (Cleeland et al., 1994; Uki, Mendoza, Cleeland, Nakamura, & Takeda, 1998) and age [older(Cleeland et al., 1994), younger (Larue, Colleau, Brasseur, & Cleeland, 1995)] are significant predictors of inadequate cancer pain treatment whereas a previous study in Thai cancer patients revealed that male subjects tended to report greater pain intensity than female subjects (Lukkahatai, 2004).

5.1.5.2 Clinical factors

Five clinical factors were purposed as potential confounder in this study.

Stage of cancer

The stage of cancer has been found as a factor influencing the pain complaint (Twycross, Harcourt, & Bergl, 1996). Studies support the finding that 15% of patients with non-metastatic disease had pain associated with their tumor at the time of diagnosis. When disease progresses with the diagnosis of metastatic disease, the percentage of patients having pain increased to 74% (Daut & Cleeland, 1982). Another study also reported that more than 80% of all advanced cancer patients with end stage disease reported pain with increasing frequency and severity (McKegney, Bailey, & Yates, 1981).

Bone metastasis

Skeleton involvement is a frequent and troublesome complication affecting cancer patients. It is the third most common metastatic site after the lung and liver (Tubiana-Hulin, 1991). Metastatic cancer may invade bone in 30% to 70% of patients (Wagner, 1984). The percentages of pain vary by primary site of disease, with patients who have bone cancers most frequently having pain (Cleeland, 1984; Twycross, Harcourt, & Bergl, 1996). Patients with metastatic disease, especially those with bone metastases reported cancer pain significantly more often than with local or regional disease (Ahles, Ruckdeschel, & Blanchard, 1984).

Number of pain sites

Multiple pains at different sites are often found in the patients with advanced disease (Twycross, Harcourt, & Bergl, 1996). This is because when the tumor becomes larger and invades nearby organ, it can cause pain (Bonica, 1990). Moreover, it can metastasize to distant organs in the body and create pain at the site of metastasis.

The relationship among the number of pain site and pain outcomes have been reported. A study revealed that number of pain site, frequency of worst pain, pain intensity, and mood explained 52% of the variance in functional outcome as measured by the BPI (Portenoy et al., 1992). A study in Thai cancer patients reported that higher number of pain site was found to have a significant on pain intensity, mood disturbance, and pain interference (Petpichetchian, 2001).

Duration of pain

The duration of pain is the period of time patients have experienced their current pain episode. A study of 2,266 cancer patients, 17% of the patients suffered from pain more than 6 months, 44% for 1 to 6 months, and 36% for less than 1 month (Grond, Zech, Diefenbach, Radbruch, & Lehmann, 1996). This finding indicated that more patients have a longer duration of pain than those of a short duration of less than 1 month. Most patients who have experienced pain of longer period were in advanced stage of disease (15% in stage 3 and 55% in stage 4).

Another study found that the duration of pain was positively associated with pain intensity and difficulty in emotional expression (Dalton & Feuerstein, 1989).

Dosing opioids

There is no optimal or maximal dose of opioid analgesic drugs for patients with cancer pain (Jacox et al., 1994). The appropriate dose for individual patient depends on the balance between pain relief and the side effects. On the basis of the steady-state pharmacokinetics of morphine, patients with severe unrelieved chronic pain should have their total daily dose of morphine increased by 50% to 100% every day whereas moderate unrelieved pain can be treated with daily increases of 25% to 50% (Levy, 1996). A study revealed that most advanced cancer patients require less than 200 mg of oral morphine per day and 10%-20% may require 300 mg or more of daily morphine (Bercovitch, Waller, & Adusky, 1999). Since there is no apparent ceiling doses to morphine's analgesic effect (Tuttle, 1985), a wide range of morphine dose taking in individual patient may affect pain treatment outcomes in clinical practice.

5.1.5.3 The Patients' barriers

Patients' beliefs can act as barriers to optimal management of cancer pain. Previous studies suggested that patients' reluctant to report pain and to use available analgesics are major obstacles to optimal pain management (Du Pen et al., 1999; Gunnarsdottir, Donovan, Serlin, Voge, & Ward, 2002).

The Barriers Questionnaire-II (BQ-II) is a reliable and valid measure of patient-related barriers to cancer pain management (Gunnarsdottir, Donovan, Serlin, Voge, & Ward, 2002). However, the finding revealed that the BQ-II total scores were positively related to only least pain and time spent in moderate to severe pain.

It should be noted that there may be unknown confounders not to be controlled for the effect of exposure on the outcome in this study.

5.2 The findings

5.2.1 Study aims

The prevalence of inadequate pain control in the two settings

The prevalence of inadequate pain control was 61.4% (95% CI: 55.1 - 67.7). Stratified by the clinical setting, the prevalence of inadequate pain control in the pain clinic and in the cancer center were 54.1% (95% CI: 45.7 – 62.6) and 71.6% (95%CI: 62.5 – 80.6) respectively. A recent comparable study in several centers in Thailand (Thienthong et al., 2006), using the same measure (reporting the worst pain in the past 24 hours of the BPI instrument), pain severity classification [as mild pain (score 1-3), moderate pain (score 4-6), and severe pain (score 7-10)] and similar type of clinical settings (pain clinics, radiology and medical oncology clinics) reported a similar proportion of patients with inadequate pain control (61.5%, mean pain score 4.8) after receiving care at the study sites for two weeks. Note that inadequate pain control (pain scores $\geq$4 out of 10) in the present study is equivalent to having moderate to severe pain (pain score 4-10) reported in other studies. The prevalence of inadequate pain control in previous studies varied widely from 18% to 85% (Table 2.2). The wide variation may have been due to differences in study design, outcomes definition, cancer population, timing of the assessment, type of treatment settings etc. For example, a multicenter study in the United State and France found that 62% and 69% of the cancer patients suffered significant pain (worst pain $\geq$ 5 out of 10 score) respectively (Cleeland et al., 1994; Larue, Colleau, Brasseur, & Cleeland, 1995). A study in a palliative care unit in the United Kingdom and Hong Kong reported 41.6 % and 74% of the patients had moderate to severe pain respectively (Sze et al., 1998; Williams, Chandler, Ranwala, DeSilva, & Amarasinghe, 2001). Interestingly, a study in a pain clinic in Sri Lanka found that only 18% of the patients had moderate to severe pain. However, it could be argued that the high proportion of the participants who still rated their pain as significant in this study may have been overestimated. This may be due to the duration for pain assessment being too short. Studies with cross sectional survey design like this study included both incident and prevalent cases. Those with inadequate pain control were more likely to be recruited whereas those with adequate pain control or those with curable cancer could have been back

home and were not recruited. A prospective cohort study design would have been better to estimate the effect of cancer pain management. Individual patients would need to be tracked from their first admission throughout the treatment period.

WHO has advocated the Pain Management Index (PMI) to assess the appropriateness of analgesic medication. Negative PMI is indicative of under-treated pain due to inappropriate analgesic medication. In this study, the negative PMI figures found in the pain clinic (7.5%) and the cancer center (11.6%) were very low, compared with similar studies in other countries (Hyun et al., 2003; Okuyama et al., 2004), which reported the negative PMI were 41%-70%. Our figures appear to be acceptable and consistent with that recommended in the guideline used by the physicians in the two settings. Yet, approximately sixty percent of patients (59.9%) who were receiving supposedly appropriateness analgesic prescriptions still experienced inadequate pain control. The reason may be that the PMI only provides a rough estimation of how well pain is treated. It does not take into account other aspects of cancer pain management such as dosing requirement, patient compliances, and route of administration of the analgesic drugs (Cleeland et al., 1994; Mercadante, Dardanoni, Salvaggio, Armata, & Agnello, 1997; Ward et al., 1993). Therefore, the PMI should be considered together with those aspects for a proper evaluation of the quality of cancer pain management. Another reason may be that since opioid analgesics are the cornerstone treatment of moderate to severe pain, patients' compliances to prescribed analgesic regimen is also the key to successful pain control. Previous studies showed that poor compliance contributes to ineffective cancer pain treatment. Du Pen SL, et al (Du Pen et al., 1999) found that patient compliances to prescribed opioid (62% to 72%) was lower than patient compliances to adjuvant therapy (74% to 84%).Thus, the assessment of patient compliances and preference to analgesic regimens should be emphasized among healthcare providers.

The findings indicated that pain treatment in the majority of patients remained unsatisfactory. This may partially be explained by the use of suboptimum doses of pain medication. Most of the patients in this study (98.2%) were receiving pain medication. However, over half of the patients with neuropathic pain in this study, for example, received antidepressants or anticonvulsants in lower doses than the usual effective ones. We found that the median doses of amitriptyline,

nortriptyline, venlafaxine, gabapentin, and pregabalin received in this study were 25 mg/day,17.5 mg/day, 37.5 mg/day, 600 mg/day and 225 mg/day, which were lower than the recommended doses at 50-150 mg/day, 50-150 mg/day, 150-225 mg/day, 1800-3600 mg/day, and 300-600 mg/day respectively (D' Arcy, 2007; Gilron, 2007; Guay, 2001). Moreover, morphine has no ceiling dose and its dose requirements depend on the balance between analgesia and side effects (Biancofiore, 2006). The average equianalgesic oral morphine doses prescribed (this does not include rescue doses, with the mean dose of 62 mg/day (SD = 71) or the median dose of 40 mg/day with a range of 1.5 to 360 mg/day) in this study was rather low whereas previous studies suggested that opioid dosage could be up to 1000 mg/day to control pain (Coley, Adelhardt, Foley, & Portenoy, 1990). This finding suggest that higher doses of opioids and adjuvant drugs may be necessary to satisfactorily relieve the symptom.

Another explanation for the high proportions of significant pain in both settings may lie with the treatment of neuropathic pain. One of the most effective antidepressant group used to treat neuropathic pain are TCAs, which have been used to manage such pain for over 30 years (Chong & Bajwa, 2003), although it is often associated with treatment limiting adverse events. Anticonvulsants are also an important treatment of choice for neuropathic pain (Grond et al., 1999). In this study, a high proportion of patients' with neuropathic pain in the pain clinic (50%) were having significant pain, whereas 76% of those with neuropathic pain in the cancer center were suffering from significant pain. A high proportion of patients with neuropathic pain in the whole sample were receiving antidepressants and/or anticonvulsants, including 95.7% of the pain clinic patients and 61.9% of the cancer patients. This finding suggest that patients with neuropathic pain as a whole may be undertreated. Higher doses of antidepressants and/or anticonvulsants may be required to tackle this problem. In some cases, the management of chronic intractable pain with a combined therapy may also help in providing better pain relief.

Alternative forms of analgesic, such as oral forms, are less expensive, easier to use and have less adverse effects. They may help improve pain outcomes in many cases (Twycross, 1994). If a patient cannot swallow tablets or liquids,

transdermally administered fentanyl is an excellent alternative for patients with chronic cancer pain (Payne, 1992), despite its relatively high cost, In this study, there were 34 cases (25.6%) in the pain clinic who received fentanyl transdermal patch whereas only 2 cases (2.1%) were receiving it in the cancer center. The advantages of the fentanyl transdermal are, for example, reduced gastrointestinal toxicity, constipation, nausea and better patient's tolerance as well as acceptance. It might increase compliance to treatment and result in better pain relief.

Another possible explanation for the unsatisfactory pain control may be related to a lack of opioids alternatives. A critical component in the management of pain is the availability of various forms of opioids (Joranson, 1993). Although morphine is the drug of choice for managing moderate to severe cancer pain (Quigley, 2005), patients who are intolerant to the adverse effects of morphine should be able to switch to an alternative opioid, such as oxycodone, hydromorphone, or fenternyl patch. In a prospective study, 20% of patients needed two or more switches to alternative opioids before a satisfactory outcome was achieved (Cherny et al., 1995). In Thailand opioids currently available (Table 2.4) were very basic and limited (Table 2.1). Other alternative opioids such as oxycodone and hydromorphone were not available. This account was also in line with the opinions given by the pain clinic physicians in the qualitative and quantitative study, stating "Inadequate types and fewer varieties of analgesic opioids are one of the most important barriers to optimum pain management. The more varieties of opioid drugs would serve the different needs of each patient. The unavailability of opioids analgesics was also experienced by many other developing countries (Laudico, 1996; Reyes-Gibby et al., 2006; Sun, Hou, & Li, 1996). Also in many countries, even when opioids are available, there were limitations to their use (e.g., they cannot be used for more than a certain period of time), imposed by government policies and regulations (Sun, Hou, & Li, 1996). In Thailand, physicians, dentists and veterinarians in hospital or clinic can obtain the license to sale or possess narcotic category 2 and then are authorized to prescribe opioid drugs in a sufficient amount for pain treatment, whereas pharmacists is only entitled to dispense opioid drugs according to the prescription. This regulation implies that the use of prescribed opioid depends on each institution's policy, but it is not

imposed by government. With regard to a lack of opioids alternatives, the Thai FDA, the sole agent provider of medical opioids should revise the policy on provision of medical opioids to provide a wider variety of opioids type and form. More alternatives to current opioids analgesics may help improve the effectiveness of pain control.

The World Health Organization (WHO) suggested that the relaxation of laws and regulations to improve the opioid availability is one of the three foundation measures improving the pain treatment (World Health Organization, 1996). In Thailand, the restriction of opioid for medical use and the inaccessibility of opioid analgesics were addressed as an important problem for the cancer patients with pain (Chaudakshetrin, 1993). The opioid analgesics are usually not available in the community hospitals due to legislation constraints and fear of burglaries by drug addicts (Vatanasapt et al., 1992). A number of efforts have been made to solve these inaccessibility problems. Since 2006, the amended Ministerial Notification of Ministry of Public Health No 197 B.E.2549 (2006) has allowed a significant increase in the maximum amount per year of the opioid analgesics possessed by a single hospital across the country, a change from the previous law in 1993. For example, the amount of prescribed morphine for each government hospital was increased from 400 gram to 4000 gram per year. Two years after the amended law was introduced, however, high proportions of patients in our study still experienced inadequate pain control. Compared with the prevalence figures reported in a recent multicenter study by Thienthong S, et al (Thienthong S et al., 2006) in 2006, this may suggest that had been no improvement in the quality of cancer pain treatment over the 2-year period. Nevertheless, this policy needs to be properly evaluated for its failures and successes. A way forward may be a new policy on provision of a wider variety of opioids type and form. Opioid analgesics supplied by the Thai FDA are of much fewer varieties compared to other developed countries. More alternatives to current opioids analgesics may help improve the effectiveness of pain control and the patients' compliance to the drugs.

The prevalence of depression

Depression is one of the most common psychological distresses experienced by cancer patients. In the present study, the prevalence of depression was 20.6% (95%CI: 15.4 – 25.9) for the whole sample. In a subgroup analysis of the two study settings, the pain clinic group (prevalence 26.3%, 95%CI: 18.8- 33.8) had a higher risk of depression than the cancer center group (prevalence 12.6%, 95%CI: 6.0-19.3). The high proportion of depression in the pain clinic patients may have been explained by a larger proportion of patients with the most advanced cancer (stage 4), bone metastasis, and higher number of pain sites. A recent comparable study in breast cancer patients by the Thai-HADS at the Surgical Outpatient Department of university hospital (9.0%) (Lueboonthavatchai, 2007) reported a slightly lower prevalence of depression than that in the cancer center whereas a study using the health-related self–report (HRSR) in an gynecologic oncology unit of university hospital in Thailand (13.4%, 95%CI: 7.9 – 18.9%) (Hengrasmee, Padungsutt, & Boriboonhirunsarn, 2004) reported a similar prevalence of depression to that in the cancer center. One previous studies reviewed more than 100 studies of cancer patients and reported that the prevalence of depression varies significantly, with a major depression of 0% to 38% and a depression spectrum syndromes of 0% to 58% (Massie, 2004). The study also noted that it was difficult to compare the findings between studies because of different definitions of depression, cancer type or stage, time since diagnosis, varying cancer treatments, personal history of depression, and treatment for depression (McDaniel, Musselman, Porter, Reed, & Nemeroff, 1995; Newport & Nemeroff, 1998). In general, the more narrowly the term ‘depression’ is defined, the lower the prevalence of depression reported (Massie, 2004).

In general practice, depression is treatable. Untreated and under-treated depression in patients with pain is associated with more pain complaints and greater impairment (Bair, Robinson, Katon, & Kroenke, 2003). Depression and certain types of pain respond to similar treatments and exacerbate one another (Gallagher & Verma, 1999). Although most of the cancer patients in this study were receiving antidepressants, particularly amitriptyline, they were only being put on suboptimum effective doses for depression.

Quality of life (QOL) in cancer patients with pain

Quality of life is one of the most important outcomes for cancer patients (Ferrell, Wisdom, & Wenzl, 1989). Evidence suggests a strong correlation between pain deterioration and a reduction in QOL. The worsening of pain by more than three points on the BPI had a significant impact on the patients' QOL, measured by the FACT-G (Thienthong et al., 2006). Using the same measure, the patients' QOL mean score in this study (total mean = 67.8) was slightly higher than that reported by Thienthong et al's study (total mean = 61) (Thienthong et al., 2006), but lower than that reported by the study of Ratanatharathorn et al (total mean = 72.5) (Rattanatharathorn et al., 2001). Furthermore, the finding that QOL impaired with a more advanced stage of cancer was consistent with a previous study (Rattanatharathorn et al., 2001). When compared between the two settings, the patients' QOL reported in the cancer center was significantly better than that in the pain clinic. It should be noted that in our sample patients with poor quality of life were also more likely to be suffering from depression, which was in line with the fact that QOL tends to have a strong negative correlation with depression (Rustoen, Moum, Padilla, Paul, & Miaskowski, 2005).

5.2.2 Hypotheses

Being treated in a non-pain specialist setting (i.e. cancer center) would be independently associated with reporting higher levels of significant pain

The multivariate analysis revealed that being patients in the cancer center was associated with a higher risk of having significant pain, in other words, inadequate pain control, even after controlling for gender, age, presence of bone metastasis, opioids dosages per day, number of pain sites, and duration of pain (OR 2.5, 95% CI: 1.3 – 4.9). Note that variables related to physicians' characteristics (knowledge of and attitudes toward opioid prescribing) and health system barriers were not included in the multivariate model because the differences in these factors between the two settings were not found in this study. Moreover, the patients' barriers factor was not entered in the multivariate model in this study because the participants with less attitude barriers (the BQ-II mean score $\leq$ 1.5) was not associated with

inadequate pain control compared with those with higher attitude barriers (the BQ-II mean score > 1.5) (OR = 1.1, p-value=0.716) and only 140 participants (61.4%) completed the BQ-II in this study. The association was therefore not accounted for by the physicians' knowledge and attitude, the health system, and the patients' characteristics.

It is understandable that patients in the cancer center (represented as non-pain clinic) were under-treated for pain, compared with those in the pain clinic. Physicians in a cancer center may overlook the patients' pain symptoms because they are more concerned with the treatment of cancer itself (cure or recurrence, etc) or because they do not have skills, knowledge or resources to deal with pain effectively. In contrast to a pain clinic, where there are pain specialists available. They also provide the patients with comprehensive and detailed pain assessments, which are undertaken on a routine basis. Because 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 under-treatment or inappropriate management (Gonzales, Elliott, Portenoy, & Foley, 1991). A standard pain assessment tool may be helpful and should be included in the patients' medical records. This ensures that the doctors or nurses assess pain on a regular basis without waiting for the patients to complain.

5.2.3 Other findings

In this study, exploratory parsimonious models with inadequate pain control, depression, and poor QOL as the main outcomes (dependent variable) were performed to determine which factors were the best predictors. Note that these associations did not mean to reflect the causal relationships between these predictors and the outcomes.

5.2.3.1 Inadequate pain control

In the final model after adjustments, being treated in the cancer center remained significantly associated with risk of inadequate pain control (OR 2.8 95%CI

1.6-5.2). Other factors in the model included having depression (OR 2.2 95%CI 1.0-4.5), which was in line with previous studies (Carr et al., 2002; Spiegel, Sands, & Koopman, 1994) and taking higher opioid dosages (equianalgesic oral morphine dosages more than 30 mg/day) (OR 2.0 95%CI 1.1-3.5) (Table 4.28). It should be noted that taking higher doses of opioids may have been a consequence of inadequate pain control, rather than a cause.

Experiment studies have shown that peripheral pain signals were blocked by either morphine given at any sites of the descending pain modulatory system (limbic cortex, midbrain, medulla, or dorsal horn) or serotonin and norepinephrine given intrathecally (Fields, 2000; Hirakawa, Tershrer, & Fields, 1999). With increasing availability and activity of the monoamine neurotransmitter serotonin and/or norepinephrine in the synaptic cleft have also modulated pain signals (Lynch, 2001). It is known that depression is associated with depletion of serotonin and norepinephrine, which may decrease the modulatory effect of the descending pain system (Bair, Robinson, Katon, & Kroenke, 2003). Antidepressants medication may result in dual effects for improving pain and depression by increasing availability of serotonin and norepinephrine. Therefore, assessment and treatment of depression and pain simultaneously are likely to improve pain outcomes (Bair, Robinson, Katon, & Kroenke, 2003). Although most of the cancer patients in this study were receiving antidepressants, particularly amitriptyline, they were only being put on suboptimum effective doses for depression.

5.2.3.2 Depression

In the final model, two remaining factors that predicted depression in this study were; having a higher number of pain site (OR 2.7 95%CI 1.3-5.9) and being male (OR 2.1 95%CI 1.1-4.0) (Table 4.31). The number of pain site as one of the best predictors for depression was in line with previous studies (Petpichetchian, 2001), reported that the number of pain site was a significant predictor of higher degree of mood disturbance. This may be explained by the impact of pain on the participants' daily life in the BPI measure. In this study, the participants with 2-5 pain sites reported significantly pain interference on activity, mood, walking ability, work, and

enjoyment of life higher than those with only one pain site. These interferences in daily activities may contribute to depression. ,

The finding that being male was found to be an important predictor in this study is quite surprising, although the reason for this is not clear. A previous research reviewed 49 studies (DeFlorio & Massie, 1995) showed that 23 studies found no gender differences in the prevalence of depression in individuals with cancer with a particular gender differences and 10 studies group found either gender differences in subsets of patients. A study in ambulatory patients with head and neck cancer found increased depression in women with early-stage disease and in men with late-stage disease (Baile, Gilbertini, Scott, & Endicott, 1992). A one-year prospective study by Kulkantrakorn and Jirapramukpitak (Kulkantrakorn and Jirapramukpitak, 2007) on post-stroke depression also reported that men were at increased risk of developing depression after stroke than females.

5.2.3.3 Poor quality of life

In the final model, three remaining factors that predicted the poor QOL in this study were the presence of bone metastasis, level of pain control, and depression as shown in Table 4.33. It is not so surprising that the presence of bone metastasis is a predictor for poor quality of life. This may be explained by higher levels of suffering associated with disease progression. A previous study revealed that the stage of cancer has a strong correlation with the patients' quality of life (Rattanatharathorn et al., 2001). Inadequate pain control and depression as predictors for poor quality of life may be due to their close associations with the components of quality of life measure. QOL is often viewed as having a multidimensional construct that encompasses several domains, including health, physical functioning, psychological status, spiritual well-being, and social functioning (Rustoen, Moum, Padilla, Paul, & Miaskowski, 2005). The finding of the strong association between depression and poor QOL is consistent with the previous study (Rustoen, Moum, Padilla, Paul, & Miaskowski, 2005).

5.3 Conclusions

The multi-dimensionality of pain was addressed in this study. The majority of the cancer patients rated their pain control as inadequate in both pain clinic group (54.1%) and cancer center group (71.6%). Otherwise, most of them were prescribed appropriateness analgesics medicine in accordance with the WHO ladder. A higher proportion of patients in pain clinic (26.3%) were diagnosed with depression than that of the cancer center (12.6%), but conversely, the quality of life fared better among at the cancer center patients (51.6%) than those in the pain clinic (45.9%). Inadequate pain treatment was independently associated with the cancer center patients (OR 2.5, 95% CI: 1.3 – 4.9). The association was not accounted for by the physicians' knowledge and attitude, the health system, and the patients' characteristics. In exploratory parsimonious models, the factors that best predicted inadequate pain control were type of clinical setting, depression, and opioid dosages. The most important factors that predicted depression were male gender and higher number of pain sites. The factors that best predicted poor quality of life were the presence of bone metastasis, inadequate pain control, and depression.

5.4 Implications for public health intervention

5.4.1 The high proportions of patients with inadequate pain control in both the pain clinic and the cancer center that should be addressed. These findings suggested that much more needs to be done to improve the quality of pain treatment. Awareness should be raised among policy makers and health care providers. In clinical practice, more comprehensive and intensive approach to pain assessment and management should be adopted. For example, regular assessments of pain should be made to ensure that the patients are free from substantial pain throughout the day(Benedetti et al., 2000). Higher daily dosages of opioids and adjuvant drugs may be necessary to satisfactorily relieve the symptom. Previous studies suggest that opioids dosage could be up to 1000 mg/day for controlling pain (Coley, Adelhardt, Foley, & Portenoy, 1990). Common cancer comorbidities such as depression should be detected and adequately treated. Ample evidence suggests that depression is highly

associated with pain (Patrick et al., 2003). It is also a condition that is often overlooked and under-treated by physicians.

5.4.2 High proportions of the cancer patients were diagnosed with depression, particularly in the pain clinic. In addition, the high correlations between depression and the two other main outcomes were found, suggesting that pain is highly comorbid with depression and poor quality of life. In practice, therefore, it is not possible to treat cancer pain effectively without taking account of its comorbidities. Depression in cancer patients should be detected and treated concurrently with pain management. The better depression improves, the more likley the patients' pain is controlled. This, in turn, contributes to better quality of life. Increased awareness and early detection of depression is, thus, essential for better pain management. Comprehensive pain assessment and management should include routine screening and treatment for depression.

5.4.3 In this study, more than half of the cancer patients with neuropathic pain were receiving antidepressants or anticonvulsant at lower than effective doses for neuropathic pain, suggesting that neuropathic pain in cancer patients were inadequately treated. This may be due to inadequate knowledge and skills related to neuropathic pain management. More attention should be drawn of pain specialists and physicians, involved in the caring of cancer patients, to this kind of pain. Standard guidelines or protocols for neuropathic pain management may be helpful.

5.4.4 A lack of regular pain assessment may also be an important barrier to effective pain management. It is suggested that pain should be routinely evaluated as if it is a fifth vital sign (Merboth & Barnason, 2000) whenever health providers see cancer patients. The evaluation of cancer pain is often difficult and troublesome because of its subjective nature, complexity, and its psychological component. Although numerous assessment tools have been developed to assess pain in many countries, specific tools should be developed, if possible, for Thai patients given the cultural differences in pain expressions. Recording the results of such assessment should be done and incorporated into the medical records to facilitate regular assessments at each visit.

5.4.5 Disseminating the finding of this research to policy makers involved is essential in order to facilitate a policy review. In this study, many of the physicians suggested that hospitals have more varieties of opioid analgesics as those in developed countries to better meet the needs of the patients. The more drugs the Thai authorities (e.g. FDA) could supply, the better treatment the patients would be likely to receive. The Thai FDA should periodically revise the essential opioid drug list.

5.4.6 Develop an action to assist communication and cooperation between health care workers and national regulators in an effort to expand the availability of opioid analgesics that suit different needs of the patients through the following strategies:

- Conduct meetings and workshops, between teams of healthcare professionals, authorities and drug regulatory officials (the Thai FDA) to promote communication and cooperations between regulators and health care professionals. The objectives of the workshop were to discuss the national epidemic of untreated pain, the causes of under-treatment, the role of regulatory and system barriers that undermine opioid availability and access, and strategies to address these barriers.

- Conduct workshops between professionals and the Thai-FDA. Professionals who have data about the extent of the cancer pain problem can help the Thai-FDA to understand the need to increase the national estimate of the amount of opioids used. The Thai-FDA must then arrange for the import or manufacturing of a sufficient supply of opioid analgesics.

- Conduct training in cancer pain control for healthcare providers at the regional hospitals throughout the country.

- Conduct consultation workshops to address the multisectoral concerns over morphine inaccessibility and other pain relief misconceptions.

5.5 Recommendations for future research

Future studies are recommended to establish the findings with larger samples in different settings. In addition, longitudinal cohort study is better to examine the effect of cancer pain management in each setting. More qualitative

research studies should be made to identify barriers to cancer pain among all professionals involved such as nurses and family caregivers.

To minimize the selection bias arising from using different inclusion criteria in this study, future studies should adopt the same inclusion criteria and the same eligible participants regardless of the group to which they belong, or by matching the hospital status of patient of the compared setting.

Owing to very limited resources of information regarding opioid availability and barriers in the institutions under study, future studies should attempt to acquire such information from a variety of sources, which may come from the hospital's drugs lists, health professionals, health authorities and policy makers.

Regarding the questionable reliability and validity of the instrument to measure physicians' knowledge of and attitudes towards opioids prescribing, the proper measure should be more sophisticated and comprehensive, and be validated in order to evaluate whether the physicians' knowledge and attitudes meet the standards of pain control management.

Summary Table: study objectives, key findings, and suggested policy implications, and suggested health professionals implications

Study Aims	Key findings	Suggested policy implications	Suggested health professionals implications
1. To examine the prevalence of inadequate pain control in cancer patients	The proportion of patients with in adequate pain control as a whole was 61.4 % ,with 54.1% in the pain clinic and 71.6%.in the cancer center	Awareness of the importance of undertreated pain in cancer patients should be raised among policy makers (such as Thai FDA) and health professionals involved	A more comprehensive and intensive approach to pain assessment and management should be adopted
			Specific pain assessment tools for Thai patients should be developed and incorporated into the medical records to facilitate regular assessments at each visit
			Higher doses of opioids and adjuvant drugs may be necessary to better relieve the patients' symptoms.
	Other finding: - More than half of the patients with neuropathic pain were inadequately treated		Awareness of this undertreatment should be raised among pain specialists and physicians , involved in the caring of cancer patients with neuropathic pain
			Standard guidelines or protocols for neuropathic pain management may be necessary in clinical practice.

Summary Table: study objectives, key findings, suggested policy implications, and suggested health professionals implications (Continued)

Study Aims	Key findings	Suggested policy implications	Suggested health professionals implications
2. To evaluate the inappropriateness of analgesic medication measured by the Pain Management Index (PMI)	Very low in both settings, 7.5% in pain clinic and 11.6% in cancer center	This index should be considered together with another measures for a proper evaluation of the quality of cancer pain management	
	Other finding: -60 % remained at an inadeqaute pain control level although they were supposedly receiving appropriate analgesic medications		The assessment of patient compliances and preference to analgesic regimens should be emphasized

Summary Table: study objectives, key findings, and suggested health professionals implications (Continued)

Study Aims	Key findings	Suggested health professionals implications
3. To examine the prevalence of depression in cancer patients	20.6 %, predominantly in pain clinic 26.3 %	Awareness of the importance of under-treated depression in cancer patients should be raised among health professionals involved
	Cancer patients with depression reported a relatively higher proportion of inadequate pain control, compared to those with no depression	Special attention to patients with depression with regard to early diagnosis and treatment.
4. To examine the quality of life in cancer patients	Total score of QOL of 67.8 out of perfect score of 108, with functional well-being domain being the most negatively affected among the 4 domains of QOL The QOL fared better among in the cancer center patients than those in the pain clinic.	Special attention to patients with functional disability undergoing pain management.

Summary Table: study objectives, key findings, and suggested health professionals implications (Continued)

Study Aims	Key findings	Suggested health professionals implications
5. Being treated in a non-pain specialist setting would be independently associated with reporting inadequate pain control	Being patients in non-pain specialist setting (cancer center) was associated with a higher risk of having inadequate pain control	A more comprehensive and intensive approach to pain assessment and management should be adopted Specific pain assessment tools for Thai patients should be developed and incorporated into the medical records to facilitate regular assessments at each visit
6. Other findings - Factors associated with inadequate pain control	- Depression - Higher opioids dosages	
- Factors associated with depression	- Higher number of pain site - Being male	
- Factors associated with poor QOL	- Bone metastasis - Inadequate pain control - Depression	