EFFECTS OF PHARMACY PAIN SERVICE IN CANCER PATIENTS: A RANDOMIZED CONTROLLED TRIAL

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A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

The objective of this study was to assess the impact of pharmacy pain service (PPS) on the quality of pain control in hospitalized cancer patients. This was a stratified, randomized, controlled study conducted at Chiangrai Prachanukroh hospital during April – October 2008. Cancer patients who were hospitalized and rated their pain intensity as $\geq$ 5 on a standard 0-10 numerical rating scale were randomized to receive PPS by clinical pharmacists as the intervention group, or usual care as the control group. Pharmacists' intervention included drug initiation, dosage adjustment and recommendation, monitoring of adverse drug reactions, and patient education. The quality of pain control expressed as a difference of mean pain intensity (MPI) at baseline and discharge in each group and a difference of MPI at discharge between the intervention and control group. Other secondary outcomes were the number of drug related problems, number of pharmacists' interventions, and percentage of acceptance to pharmacists' interventions. Overall, a total of 96 patients were included in the analysis; 48 patients received PPS while 48 patients received usual care. Baseline characteristics such as age, gender, and tumor types were comparable between the two groups. At baseline, MPIs of both groups were comparable (7.8 ± 1.3 for intervention and 7.9 ± 1.1 for control). At discharge, MPI of patients in the intervention group was significantly lower than that of the control group; 2.2 ± 1.2 vs 4.9 ± 1.8 ($P < 0.0001$). Moreover, all patients in the intervention group experienced either improvement in pain control or became free of pain while only 47.9% of patients in the control group experienced improvement in pain control. There were no significant differences in the number of patients experiencing adverse drug reactions ($P = 0.72$). In the intervention group, 251 drug related problems exclusively regarding pain issues were identified. Common problems were need for initiation or addition of drugs for pain treatment and dosage too low. More than 85% of pharmacist interventions were accepted by physicians. These results demonstrated that participation of pharmacists in a healthcare team could lead to positive outcomes of pain control among patients with cancer pain.

KEY WORDS: CANCER PAIN / PAIN / PHARMACIST / PHARMACEUTICAL CARE

114 pages

ผลของการให้บริการจากฝ่ายเภสัชกรรมต่อการควบคุมความปวดในผู้ป่วยโรคมะเร็ง: การศึกษาแบบสุ่มโดยมีกลุ่มควบคุม

EFFECTS OF PHARMACY PAIN SERVICE IN CANCER PATIENTS: A RANDOMIZED CONTROLLED TRIAL

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บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาผลของการให้บริการจากเภสัชกรคลินิกต่อการควบคุมความปวดในผู้ป่วยโรคมะเร็ง การศึกษาเป็นแบบสุ่มโดยมีกลุ่มควบคุม ในผู้ป่วยที่เข้ารับการรักษา ณ โรงพยาบาลเชียงรายประชานุเคราะห์ในระหว่างเดือนเมษายน-ตุลาคม 2551 ผู้ป่วยโรคมะเร็งประเภทผู้ป่วยในซึ่งมีระดับความปวดมากกว่าหรือเท่ากับ 5 (จาก 0-10) ได้รับการสุ่มให้อยู่ในกลุ่มทดลองคือกลุ่มได้รับการบริการจากเภสัชกรหรือกลุ่มควบคุมซึ่งได้รับการบริการตามปกติ โดยเภสัชกรให้คำแนะนำเกี่ยวกับการเริ่มยา ปรับหรือแนะนำขนาดยา ติดตามอาการไม่พึงประสงค์จากการใช้ยา และให้ความรู้แก่ผู้ป่วย โดยผลลัพธ์หลักคือความแตกต่างของระดับความปวดเมื่อแรกรับกับเมื่อจำหน่ายออกจากโรงพยาบาลในแต่กลุ่ม และความแตกต่างของระดับความปวดเมื่อจำหน่ายระหว่างกลุ่ม ผลลัพธ์รองคือจำนวนปัญหาที่เกี่ยวกับยา จำนวนข้อแนะนำและการยอมรับต่อคำแนะนำของเภสัชกร มีผู้ป่วยที่อยู่ในการวิเคราะห์ผลจำนวนทั้งหมด 96 ราย ซึ่งอยู่ในกลุ่มทดลองและควบคุม 48 และ 48 ราย ตามลำดับ พบว่าลักษณะพื้นฐานของผู้ป่วยทั้งสองกลุ่ม เช่น อายุ เพศ และชนิดของมะเร็ง ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติเมื่อแรกรับผู้ป่วยทั้งสองกลุ่มมีระดับความปวดที่เท่าเทียมกัน (7.8 $\pm$ 1.3 ในกลุ่มทดลองเทียบกับ 7.9 $\pm$ 1.1 ในกลุ่มควบคุม) แต่เมื่อจำหน่ายพบว่าผู้ป่วยในกลุ่มทดลองมีระดับความปวดที่น้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (2.2 $\pm$ 1.2 ในกลุ่มทดลองเทียบกับ 4.9 $\pm$ 1.8 ในกลุ่มควบคุม, $P < 0.0001$) นอกจากนี้ ผู้ป่วยในกลุ่มทดลองทุกคนได้รับการประเมินว่าการรักษาอาการปวดดีขึ้นหรือหายจากอาการปวดในขณะที่มีเพียงร้อยละ 47.9 ของผู้ป่วยในกลุ่มควบคุมที่การรักษาอาการปวดดีขึ้น จำนวนผู้ป่วยที่เกิดอาการไม่พึงประสงค์จากการใช้ยาระหว่างสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($P = 0.72$) ในกลุ่มทดลองพบปัญหาจากการใช้ยา 251 ปัญหา ที่พบบ่อย ได้แก่ การจำเป็นต้องเริ่มยาหรือได้รับยาเพิ่ม และการใช้ยาในขนาดที่ต่ำเกินไป แพทย์ยอมรับคำแนะนำของเภสัชกรมากกว่าร้อยละ 85 ผลการศึกษานี้แสดงให้เห็นว่าการมีเภสัชกรเข้าร่วมในการดูแลผู้ป่วยโรคมะเร็งจะช่วยให้ผลลัพธ์ของการควบคุมความปวดดีขึ้น

114 หน้า

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LIST OF ABBREVIATIONS

%	Percent
ADRs	Adverse drug reactions
CI	Confidential interval
DRPs	Drug Related Problems
g	Gram
GI	Gastrointestinal
hr	Hour
ICD-10	The International Statistical Classification of Diseases and Related Health Problems 10th Revision
IM	Intramuscular
IU	International units
IV	Intravenous
JCAHO	The Joint Commission on Accreditation of Healthcare Organization
Kg	Kilogram
mcg	Microgram
MEs	Medication errors
mg	Milligram
ml	Milliliter
No.	Number
NRS	Numerical rating scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OPD	Out-patient department
PPS	Pharmacy pain service
PRN	Pro re nata; as needed
RR	Relative risk
SC	Subcutaneous

LIST OF ABBREVIATIONS (cont.)

SD	Standard deviation
SPSS	Statistical Package for Social Science
U	Units
vs	Versus
WHO	World Health Organizatio

CHAPTER I
INTRODUCTION

Pain is a prevalent and potentially debilitating symptom in cancer patients. Despite major advances in the understanding and treatment of pain, inadequate pain control is an international problem including Thailand [1-4]. Untreated or undertreated pain impairs physical and psychological health, quality of life, and has been shown to be associated with increased medical complications and health care cost. Hence, the standard of quality care requires that pain should be effectively managed [5, 6].

A variety of barriers impede the application of appropriate pain management. The barriers may come from patient/family, professional, or healthcare system. This can range from patients' reluctance to report their pain or take pain medication, fear of addiction, inadequate knowledge of pain management, low priority given to cancer pain treatment, and problems of the availability of treatment [1, 7]. In Thailand, Chaudakshetrin [8] suggested that the shortage of professional healthcare workers, financial resources, and lack of education for the healthcare professional are the mains obstacles to optimal pain management. Over 60% of Thai physicians use analgesic drugs on an as-needed basis. Fear of addiction, respiratory depression, and other side effects are common reasons for narcotic under-prescribing among young physicians, whereas dislike of official forms is common in the older group of physicians.

Based on these findings, pain management especially cancer-related pain may be the area of opportunity for Thai pharmacists. From substantial evidences, pharmacist can play an active role in the improvement of pain management especially in drug therapy issues. Several reports have shown that pharmacists' participation in healthcare teams leads to positive outcomes to patients and institutions. Such participation may range from monitoring of pharmacotherapy, identification of drug

related problems, prevention and management of adverse effects, providing in-service education, and even prescribing and refilling pain medication [9-15].

The studies regarding a role of pharmacist in cancer pain manage care in Thailand were first conducted by Kongtalae and colleagues [16, 17]. Both studies were designed as pre-post comparison to evaluate a reduction of pain intensity in patients with solid tumor after pharmacist recommendations. The results of both studies showed that mean pain scores of cancer patients with baseline pain intensity higher than 5 on 0-10 numerical rating scale were significantly decreased and drug therapy problems were also resolved with high acceptance rate from physicians. However, without a control group, it is difficult to evaluate the level of impact by the pharmacist compared to usual care.

At Chiangrai Prachanukroh hospital, an affiliated teaching hospital located in the north of Thailand, there are 756 beds and 34 wards. To meet Hospital Accreditation (HA) and the Joint Commission on Accreditation of Healthcare Organization (JCAHO) standard, clinical practice guideline for post-operative pain management in Chiangrai Prachanukroh hospital has been developed in 2005. This guideline focuses on pain in post-operative patients, but not cancer-related pain. Although there is presently a provision of pharmaceutical care in cancer patients who receive chemotherapy, the interventions of pharmacists associated with pain treatment are very few and the responsibilities of pharmacists in pain medication management are also limited. Furthermore, from the observation by the research pharmacist in cancer patients who had pain, it was found that inadequate pain treatment and various drug therapy problems related to pain medication were commonly found.

Consequently, the purpose of this study is to improve quality of pain care in a wide range of cancer patients who are admitted in Chiangrai Prachanukroh hospital through pharmacy pain service. With a design of a randomized, controlled trial, the effects of pharmacist interventions on clinical outcomes especially pain intensity will be investigated.

CHAPTER II
LITERATURES REVIEW

Currently, cancer is ranked among the top three causes of death in Thailand. The National Cancer Institute of Thailand has estimated that there were over 120,000 new cases in 2008 [18]. Pain is one of the most common symptoms associated with cancer. The latest systematic review of the past 40 years showed that pain was highly prevalent in cancer patients. The incidences were reported to be 64% in patients with metastatic or advanced stage disease, 59% in patients on anticancer treatment and 33% in patients after curative treatment. Furthermore, among patients suffering with pain, more than one-third graded their pain as moderate or severe [2].

According to the International Association for the Study of Pain, pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [19]. Unsurprisingly, pain is one of the symptoms that patients fear most. Unrelieved pain denies them comfort and greatly affects their activities, motivation, interactions with family and friends, and overall quality of life. There are convincing evidences that inadequate pain relief hastens death by increasing physiologic stress, potentially diminishing immunocompetence, reducing mobility, increasing tendencies toward pneumonia and thromboembolism, and increasing the work of breathing and myocardial oxygen requirements [20]. Moreover, pain may lead to a spiritual despair and significantly decrease in emotional well-being because the individual's quality of life is impaired. The economic costs of undertreated pain approach 80 billion US dollar a year in treatment, compensation, and lost wages [21]. Therefore, it is the professional and ethical responsibility of the healthcare professions to focus on and attend to adequate pain relief for their patients. In 1999, the Joint Commission on Accreditation of Healthcare Organization (JCAHO), an independent, not-for-profit organization that accredits and certifies health care organizations in the United States, mandated that all patients, not just patients with a terminal illness, have the right to suitable pain

assessment and the right to be free of pain [11]. In addition, JCAHO emphasizes the importance of effective pain management and establish it as an essential component of quality patient care [22, 23].

The importance of relieving pain and the availability of effective therapies make it imperative that health care professionals caring for these patients be adept at the assessment and treatment of cancer pain. This requires familiarity with the pathogenesis of cancer pain, pain assessment techniques, and relevant pharmacological, anesthetic, neurosurgical, and behavioral approaches to the treatment of cancer pain [19].

I Pathophysiology of pain and clinical applications

It is generally accepted that clear understanding of the etiology and pathophysiology of cancer pain could facilitates the optional management of cancer-related pain [24, 25]. Different types of pain can occur in cancer patients. A number of attempts have been made to classify pain according to different criteria. Pain classification includes differentiating between pain associated with tumor, pain associated with treatment, and pain unrelated to either. Acute and chronic pain should also be distinguished from each other when deciding what therapy to use. Therapeutic strategy depends on the pain pathophysiology, which is determined by patient examination and evaluation.

There are two predominant mechanisms of pain pathophysiology: nociceptive and neuropathic. Nociceptive pain is the result of injury to somatic and visceral structures and the resulting activation of nociceptors. Nociceptors are present in skin, viscera, muscles, and connective tissues. Nociceptive pain can further be divided into somatic pain and visceral pain. Pain described as sharp, well localized, throbbing, and pressure-like is somatic nociceptive pain. It occurs often after surgical procedures or from bone metastasis. Visceral nociceptive pain is often described as more diffuse, aching, and cramping. It is secondary to compression, infiltration, or distension of abdominal thoracic viscera. Neuropathic pain results from injury to the peripheral or central nervous system. This type of pain might be described as burning, sharp, or shooting. Examples of neuropathic pain include pain due to spinal stenosis or

diabetic neuropathy, or as an adverse effect of chemotherapy (e.g. vincristine) or radiation therapy. [20, 25, 26]

Somatic cancer pain [25]

Somatic cancer pain can be caused by tumor invasion of bone, joint, muscle, or connective tissue. The local tumor mass produces and stimulates local production of inflammatory mediators, causing ongoing stimulation of peripheral nociceptors. Other sources of somatic cancer pain include bone fractures, reactive spasm of muscle overlying an area of tissue damage, postsurgical incisional pain, and radio/chemotherapy-induced pain syndromes. The most prevalent somatic pain syndromes are related to neo-plastic bone involvement. Bone pain may be acute, chronic, or incidental in nature. It is typically dull, exacerbated by weight-bearing or movement.

Bone pain [25, 27, 28]

Direct tumor invasion of bone or the development of osseous metastases may account for persistent bone pain. Not all bone metastases are painful, and the pain is often disproportionate to the radiological findings. Nociceptive afferents are most concentrated in the periosteum, whereas bone marrow and cortex are less sensitive to pain. Some of the mechanisms contributing to neoplastic bone pain include stretching of the periosteum by tumor expansion, local microfractures that cause bony distortion, nerve compression due to either collapsed vertebrae or direct tumor encroachment, and local release of algesic substances from the bone marrow.

Bone pain has been correlated with osteoclastic activity. In normal bone, the net activity of bone resorbing cells (osteoclasts) equals the net activity of bone-forming cells (osteoblasts). In metastatic disease, there is evidence of increased osteoclastic activity. Both tumor and humoral factors, including prostaglandins, cytokines, local growth factors, and parathyroid hormone, enhance osteoclastic activity and act locally to stimulate nociceptors. Despite increased osteoclastic activity, bone formation also increases.

Clinical applications [25-27, 29]

Bone pain remains a significant problem for cancer patients. Opioid analgesics, which form the basis of cancer pain treatment, are used frequently for mild to moderate bone pain and can provide good baseline analgesia. For opioid-

resistant bone pain, adjuvant analgesics and other treatment modalities should be considered. Non-steroidal anti-inflammatory agents (NSAIDs) are particularly useful for bone pain since many of the symptoms are related to local inflammation. NSAIDs act on cyclooxygenases to inhibit prostaglandin synthesis and reduce local edema and prostaglandin-induced sensitization. Bisphosphonate drugs are increasingly being recognized for use in bone pain management. They selectively inhibit osteoclastic bone resorption and may exert a possible anti-inflammatory effect. This could account for some of their analgesic effect.

Visceral cancer pain [25]

Certain clinical characteristics are peculiar to visceral pain. Some viscera are apparently insensitive to pain. Solid organs such as lung, liver, and kidney parenchyma are insensitive, despite gross destruction by malignancy, and pain is signaled only when capsular or adjacent structure is involved. Harmful stimuli such as burning or cutting of visceral tissue do not cause pain, whereas a natural stimulus such as hollow-organ distension readily produces pain. Visceral pain is often diffuse and poorly localized, and it is sometimes referred to other non-visceral structures, making the source of the pain difficult to elucidate.

Pain in visceral structures is not necessarily linked to tissue injury, but rather is dependent on the nature of the provoking stimulus. Adequate stimuli that induce pain are distension, ischemia, and inflammation. Hollow organs such as the colon are very sensitive to luminal distension or inflammation but are totally insensitive to cutting or burning stimuli. Pain induced by colonic distension is dependent on the distending pressure rather than the volume. Hence, a tumor may continue to grow undetected if it fails to exert this intraluminal pressure and may cause pain only at a much later stage when there is complete obstruction of the lumen and a significant rise in intracolonic pressure. Solid organs are least sensitive, whereas the serosal membranes of hollow organs are most sensitive.

Referred pain - Visceral pain may be localized to distant and often superficial somatic structures such as muscle or skin. A common example of referred pain is the shoulder, abdominal, and back pain that occurs with pancreatic carcinoma. When somatic structures are invaded by visceral malignancies, further localized pain may ensue.

Clinical applications [25]

Visceral pain can be managed by both pharmacological and interventional techniques. Combinations of opioids, NSAIDs, and adjuvant medications form the mainstay of therapy. When pharmacological therapies prove ineffective or are limited by side effects, regional anesthesia techniques or neurosurgical techniques should be considered. The former techniques involve the administration of local anesthetics, opioids, or neurolytic agents to the neural axis or visceral plexi. The goals of these interventional procedures are to provide superior analgesia and to allow for a decrease in opioid consumption.

Neuropathic cancer pain [25, 30]

Neuropathic pain results from damage or inflammation of the nervous system, either peripheral or central. In patients with cancer, peripheral neuropathic pain can be caused directly by infiltration or compression of the nerve by the tumor or indirectly by cancer treatments such as radiation therapy and chemotherapy (eg, vincristine).

Neuropathic pain is characterized by the following pain symptoms: spontaneous burning pain with an intermittent sharp stabbing or lancinating character, an increased pain response to noxious stimuli (hyperalgesia), and pain elicited by nonnoxious stimuli (allodynia). The relationship between mechanism and symptomatology is complex. The underlying mechanism can be different for the same symptom, while the same mechanism can result in different symptoms.

Clinical applications [25, 30]

Neuropathic pain normally responds poorly to systemic opioids. Although the insensitivity can be relative, the greater dose of opioids can produce intolerable or unmanageable adverse effects that render opioid therapy undesirable. The problem of opioid responsiveness in neuropathic pain states may not simply be that of a reduced opioid sensitivity, but rather the failure to deliver a sufficiently high concentration of the systemic opioids to the spinal cord in the absence of adverse effect. The widely-used adjuvant analgesics are an important part of our neuropathic pain management.

Breakthrough pain [31-32]

Portenoy et al. have defined breakthrough pain as “a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline (background) pain.

Breakthrough pain may be related to a number of different causes (cancer-related, treatment-related, concomitant illness) and different pathophysilogies (nociceptive, neuropathic, mixed). Breakthrough pain is usually classified into one of two categories:

a. Spontaneous pain (idiopathic pain) – the episodes are not related to an identifiable precipitant, and so are unpredictable in nature
b. Incident pain (precipitated pain) – the episodes are related to an identifiable precipitant, and so are somewhat predictable in nature. Incident pain is usually sub-classified into one of three categories:
    1. Volitional incident pain – is brought on by a voluntary act e.g. walking
    2. Non-volitional incident pain – is brought on by an involuntary act e.g. coughing
    3. Procedural pain – is related to a therapeutic intervention e.g. wound dressing

Clinical applications [31-32]

The cornerstone of the management of breakthrough pain episodes is the use of so-called “rescue medication” which is taken as required, rather than on a regular basis. In most cases the most appropriate rescue medication will be an opioid analgesic, rather than non-opioid or an adjuvant analgesic. Traditionally, the most common form of rescue medication has been the oral immediate release formulations of morphine and it the dose of opioid rescue should be a fixed proportion of the dose of the opioid background medication (10-30% of the total daily dose of sustained released morphine).

II Comprehensive pain assessment [19]

A comprehensive evaluation is essential to ensure proper pain management. Failure to adequately assess pain frequently leads to poor pain control.

All patients with cancer should be screened for pain during the initial evaluation, at regular follow-up intervals, and whenever new therapy is initiated. If pain is present on a screening evaluation the pain intensity must be quantified. If the patient has no pain, re-screening should be performed at each subsequent visit or as requested. Identifying the presence of pain through repeated screening is essential to allow implementation of effective pain management. The endpoint of comprehensive pain assessment is to diagnose the etiology (cancer, cancer therapy or procedures, and coincidental or non-cancer) and pathophysiology (somatic, visceral, or neuropathic) of the pain and individualize pain treatment plan based on mutually developed goals.

Guide for comprehensive pain assessment [19, 26, 31]

Pain Experience

1. Location, referral pattern, radiation of pain
2. Intensity
    2.1 Last 24 hours and current pain
    2.2 At rest and with movement
3. Interference with activities: General activity, mood, relationship with others, sleep, and appetite
4. Timing: onset, duration, course, persistent, or intermittent
5. Description or quality
    5.1 Aching, stabbing, throbbing, pressure often associated with somatic pain in skin, muscle, bone
    5.2 Gnawing, cramping, aching, sharp often associated with visceral pain in organs or viscera
    5.3 Sharp, tingling, ringing, shooting often associated with neuropathic pain caused by nerve damage
6. Aggravating and alleviating factors
7. Current pain management plan, both pharmacologic and non-pharmacologic. If medications are used, determine
    7.1 What medications, prescription and/or over the counter?
    7.2 How much?
    7.3 How often?

7.4 Current prescriber?

8. Response to current therapy

8.1 Pain relief

8.2 Patient adherence to medication plan

8.3 Medication side effects such as constipation, sedation, nausea, others

9. Prior pain therapies

Reason for use, length of use, response, reasons for discontinuing

10. Special issues relating to pain

10.1 Meaning of pain for patient and family

10.2 Patient and family knowledge and beliefs surrounding pain and pain medications

10.3 Cultural beliefs toward pain

10.4 Spiritual or religious considerations

10.5 Patient goals and expectations regarding pain management

Psychosocial

1. Patient distress

2. Family and other support

3. Psychiatric history including current or prior history of substance abuse

4. Risk factors for aberrant use or diversion of pain medication: Patient factors, environmental, and social factors

5. Risk factors for undertreatment of pain

Pediatric, geriatric, minorities, female, communication barriers, history of substance abuse, neuropathic pain, and cultural factors

Medical history

1. Oncologic treatment including current and prior chemotherapy, radiation therapy, and surgery

2. Other significant illnesses

3. Pre-existing chronic pain

Physical examination and relevant laboratory and imaging studies to evaluate for disease progression

A thorough physical examination and review of appropriate laboratory and imaging studies are essential for a comprehensive pain assessment. This evaluation should enable caregivers to determine if the pain is related to an underlying cause that requires specific therapy. For example, it is inappropriate to provide only opioids to a patient suffering pain from impending spinal cord compression. Without glucocorticoids and local radiation therapy, the pain is unlikely to be well controlled, and the patient will remain at high risk for spinal cord injury.

Pain intensity rating [19, 26, 31, 32]

Since pain is inherently subjective, patients' self-report to pain is the current standard of care for assessment. Intensity of pain should be quantified using a 0-10 numerical rating scale, a categorical scale, or a pictorial scale (e.g. The Faces Pain Rating Scale). The Faces Pain Rating Scale may be successful with patients who have difficulty with other scales, for example, children, the elderly, and patients with language or cultural differences or other communication barriers. If the patient is non-verbal an alternative method to obtain pain rating and pain assessment is used. If the pain rating scale score is above 0, a comprehensive pain assessment should be initiated.

Numerical rating scale:

Verbal: "What number describes your worst pain in the past 24 hours from 0 (no pain) to 10 (worst pain you can imagine)?"

Written: "Circle the number that describes your worst pain in the past 24 hours."

0 1 2 3 4 5 6 7 8 9 10

No pain Worst pain you can imagine

Patients will be asked to rated the intensity of their pain, and the number reported by each patient is the pain intensity, which is further classified in to 3 levels that are:

Pain intensity of 1-4 corresponds to mild pain

5-6 corresponds to moderate pain

7-10 corresponds to severe pain

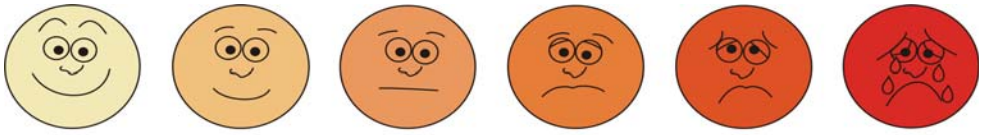
Pain that is rated 5 or higher on a scale of 0-10 NRS interferes substantially with the quality of life.

Categorial scale:

"What is the worst pain you have had in the past 24 hours?"

None (0), Mild (1–4), Moderate (5–6), or Severe (7–10)

The faces pain rating scale:



0 2 4 6 8 10

Instructions: "These faces show how much something can hurt. This face (point to the left-most face) shows no pain. Each face shows more and more pain (point to each face from left to right) up to this one (point to the right-most face) - it shows very much pain. Point to the face that shows how much you hurt (right now)."

Clinically important change in pain intensity

Pain intensity is frequently measured on an 11-point NRS. However, it is difficult to interpret the clinical importance of changes from baseline on this scale (such as a 1- or 2-point change). To date, there has been no standard definition for clinically important change in pain intensity specifically for chronic cancer pain studies. Nevertheless, data derived from studies conducted among patients with diabetic neuropathy, post-herpetic, neuralgia, chronic low back pain, fibromyalgia, and osteoarthritis suggested that, on average, a reduction of approximately two points or a reduction of approximately 30% in the NRS after treatment represents a clinically important difference [33].

Considerable research has demonstrated that pain intensity ratings of 1 to 3 or 4 on a 0 to 10 NRS (mild pain) are associated with less interference with physical and emotional functioning than higher ratings (moderate and severe pain). A reduction of pain to a mild intensity would likely be considered a substantial response to

treatment by both patients and clinicians. In 2007, there was a consensus provided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) about a provisional benchmark for identifying clinically important changes in pain intensity measures that can be used for outcome studies of treatments for chronic pain. It was recommended that reductions in chronic pain intensity in individuals of at least 10% to 20% appear to reflect minimally important changes. Reductions of 30% appear to reflect at least moderate clinically important differences. In addition, because reductions in chronic pain intensity of 50% appear to reflect substantial improvements, it is also recommended that the percentages of patients responding with this degree of improvement should be reported [34].

III Pharmacological management of cancer pain

Among various means to manage cancer pain, drug therapy is the cornerstone because it entails relatively little risk, is usually inexpensive, and as a rule works quickly [35].

In 1986, World Health Organization (WHO) established a stepladder approach for the treatment of patients with cancer pain uses the three categories of pain to guide analgesic-drug therapy (figure 1). Patients receiving no analgesic therapy who have mild-to-moderate pain should be treated with non-opioid analgesics (NSAIDs or paracetamol) for step 1. If a patient has mild-to-moderate pain despite taking a non-opioid analgesic, the dose of the non-opioid analgesics should be maximized and weak opioids (codeine, tramadol) should be added. Patients who have moderate-to-severe pain despite therapy with weak opioids require an increase in the dose of the opioids or, if that is not feasible, a change to a strong opioids (morphine, fentanyl). This method can effectively relieve pain in 80 to 90 percent of patients. Many experts recommend weak opioids as initial therapy for patients with moderate pain and may initiate therapy with strong opioids when pain is severe. Patients who have mild-to-moderate pain while taking strong opioids should have the dose of that opioids increased to an effective level [36, 37]. However, experience reported since its application more than 20 years ago suggests the utility of strong opioids for first line treatment of pain in patients with terminal cancer could be better, especially for patients with moderate to severe cancer pain [38].

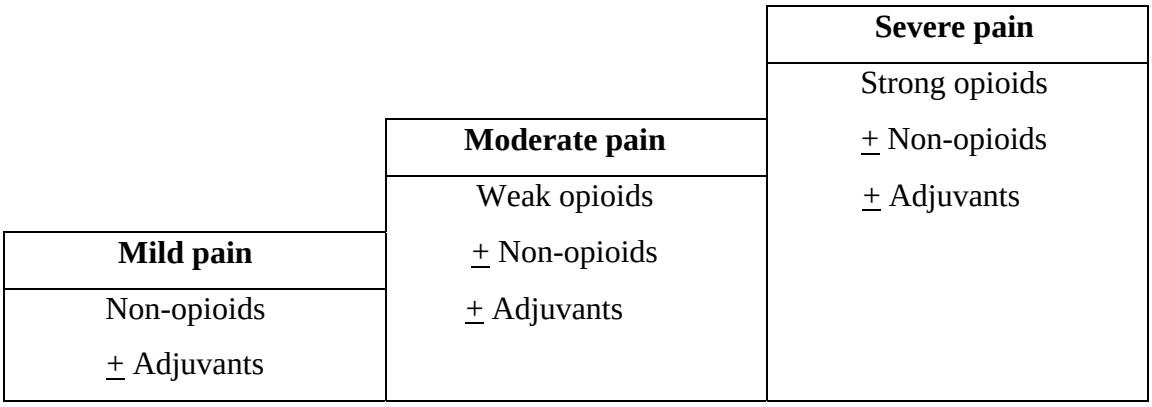


Figure 2.1 Three-step analgesic ladder of WHO [36]

Opioid principles, prescribing, titration, and maintenance

General principles [19, 39-41]

1. The appropriate dose is the dose that relieves the patient's pain throughout the dosing interval without causing unmanageable side effects.

2. Calculate dosage increase based upon total opioid dose (around the clock/scheduled and as needed) taken in the previous 24 hour

3. Increase both around the clock and as needed doses. The rapidity of dose escalation should be related to the severity of the symptoms.

4. Switch from preparations of opioid combined with other medications (such as aspirin or acetaminophen) to pure opioid preparation to excessive or inadequate dosing of the non-opioid component of combination.

5. If patient is experiencing unmanageable side effects and pain intensity is less than 4, consider downward dose titration by approximately 25% and reevaluate. Patient would require close follow-up to make sure pain did not escalate.

6. Equilibrium is achieved in about 5 half lives.

7. Consider opioid rotation if pain inadequately controlled or persistent side effects from current therapy.

8. To convert or rotate from one opioid to another:

8.1 Total the amount of current opioid(s) taken in a 24-hour period that effectively controls pain.

8.2 Calculate the equianalgesic dose of the new opioid.

8.3 If pain was effectively controlled, reduce the dose by 25-50% to allow for incomplete cross-tolerance between different opioids. During the first 24 hours, titrate liberally and rapidly to analgesic effect. If previous dose was ineffective, may begin with 100% of equianalgesic dose or increase that by 25%.

8.4 Lastly, divide the total daily dose of new opioid needed by the number of doses per day to determine the individual dose

Principles of maintenance opioids therapy [19, 39-41]

1. For continuous pain, it is appropriate to give pain medication on a regular schedule with supplemental doses for breakthrough pain.

2. Consider converting from short-acting opioids to extended release opioids for control of chronic persistent pain when 24 hour opioids requirement is stable.

3. Provide rescue doses of short-acting opioids for pain not relieved by extended release opioids including breakthrough pain or acute exacerbations of pain, activity or position related pain, or pain at the end of dosing interval:

3.1 For rescue doses, use short-acting formulation used for regular-scheduled dosing.

3.2 Allow rescue doses of short-acting opioids of 10% to 20% of 24 hours oral dose (mg) every 1 hour as needed

6. Increase dose of extended release opioid if patient persistently needs doses of as needed opioids or when dose of around the clock opioid fails to relieve pain at peak effect or at end of dose.

7. Pethidine or meperidine is not recommended for long term or high dose use because of CNS toxic metabolites (norpethidine, norpropoxyphene)

8. Partial agonists (buprenorphine) and mixed agonist-antagonists (pentazocine, nalbuphine) have limited usefulness in cancer pain. They should not be used in combination with opioids agonist drugs.

Conversion or rotation from other opioids to transdermal fentanyl [19, 40, 41]

1. Pain should be relatively well-controlled on a short acting opioid prior to initiating the patch. Patches are not recommended for unstable pain requiring frequent dose changes.

2. Determine 24 hour parenteral morphine equivalent requirement using the table 1

3. Select the mcg per hour dose according to the ranges listed below.

4. The patch duration is usually 72 hours. Duration in some may be only 48 hours; thin body habitus, fever, or topical application of heat (such as heat from heat lamps, electric blankets, etc.) may accelerate transdermal fentanyl absorption and are contraindications for transdermal fentanyl.

5. An as needed (prn) dose of morphine or other short-acting opioid should be prescribed and may be needed particularly during the first 8-24 hours. Increase the patch dosage based on the average amount of additional opioid required over the 72 hour period. Continue breakthrough medication once the patch dose is stabilized.

Table 2.1 Recommended dose conversion from other opioids to transdermal fentanyl [19]

Transdermal fentanyl (mcg/hour)	Morphine		Codeine	
	IV/SC (mg/day)	Oral (mg/day)	IV/SC (mg/day)	Oral (mg/day)
20	20	60	130	200
50	40	120	260	400
75	60	180	390	600
100	80	240	520	800

Note: Due to patient variability the doses suggested in this guide are approximate and clinical judgment must be used to titrate to the desired response.

Management of opioid side effects [19, 24, 41]

1. Side effects should be promptly identified and assessed, and appropriate should be offered. Opioids should not be withheld from cancer patients for fear of producing respiratory depression, tolerance, physical dependence, or addiction.

2. Tolerance generally develops, except with constipation. Maximize non-opioids and non-pharmacologic interventions to limit opioid dose and treat side effects. If side effects persist, consider opioid rotation.

3. Multisystem assessment is necessary.

4. Recognize that pain is rarely treated in isolation in cancer. Symptoms need to be evaluated as contributing factors.

Constipation [19, 20, 24, 36]

1. Preventive measures:

1.1 Prophylactic medications

1.1.1 Use stimulant laxative and stool softener (eg, senna with docusate, 2 tablets every morning maximum 8-12 tablets per day).

1.1.2 Increase dose of laxative when increasing dose of opioids.

1.2 Maintain adequate fluid intake

1.3 Maintain adequate dietary fiber intake. Compounds such as Metamucil are unlikely to control opioid induced constipation and are not recommended.

1.4 Exercise, if feasible

2. If constipation develops:

2.1 Assess for cause and severity of constipation

2.2 Rule out obstruction

2.3 Treat other causes

2.4 Titrate stool softener / laxatives as needed with goal of one non-forced bowel movement every 1-2 day

2.5 Consider co-analgesic to allow reduction of the opioid dose

3. If constipation persists:

3.1 Reassess for the cause and severity of constipation, rule out bowel obstruction

3.2 Check for impaction

3.3 Consider adding another agent, such as magnesium hydroxide 30-60 ml daily, bisacodyl 2-3 tablets PO daily or 1 rectal suppository daily, lactulose 30-60 mL daily, sorbitol 30 mL every 2 hours for 3 days, then as needed, or magnesium citrate 8 ounce PO daily

3.4 Fleet, saline, or tap water enema

3.5 Consider use of a prokinetic agent (e.g. metoclopramide 10-20 mg per oral four times a day)

3.6 Consider neuraxial analgesics or neuroablative techniques to potentially reduce opioid dose

Nausea [19, 24, 36]

1. Preventive measures

Persistent nausea is rare. For patients with a prior history of opioid induced nausea, prophylactic treatment with antiemetic agents is highly recommended.

2. If nausea develops

2.1 Assess for other causes of nausea (e.g. constipation, central nervous system pathology, chemotherapy, radiation therapy, hypercalcemia)

2.2 Consider prochlorperazine 10 mg PO every 6 hours as needed or haloperidol 0.5-1 mg PO every 6-8 hours, or metoclopramide 10-20 mg PO every 6 hours as needed

2.3 If nausea persists despite as needed regimen, administer antiemetics around the clock for 1 week, then change to as needed

2.4 Consider adding a serotonin antagonist (e.g. granisetron 2 mg PO daily or ondansetron 8 mg PO three times a day, or palonosetron 300 mcg/kg IV). Use with caution as constipation is a side effect.

2.5 Dexamethasone can be considered in some patients.

3. If nausea persists for more than 1 week

3.1 Reassess cause and severity of nausea

3.2 Consider opioid rotation

4. If nausea persists after a trial of several opioids and above measures

4.1 Reassess cause and severity of nausea

4.2 Consider neuraxial analgesics or neuroablative techniques to potentially reduce opioid dose

Pruritus [19, 20]

1. If pruritus develops

1.1 Assess for other causes (other medications, etc.)

1.2 Consider antihistamines

2. If pruritus persists

2.1 Consider changing to another opioid if symptomatic management has failed.

2.2 Consider adding to analgesic regimen: small doses of mixed agonist-antagonist, nalbuphine, 0.5-1 mg IV every 6 h as needed

2.3 Consider continuous infusion of naloxone, 0.25 mcg/kg/hour and titrate up to 1 mcg/kg/hour for relief of pruritus without decreasing effectiveness of the analgesic.

Delirium [19]

1. Assess for other causes of delirium (e.g. hypercalcemia, CNS metastases, other psychoactive medications, etc.)

2. If one cannot determine other possible causes of delirium, consider changing the opioid

3. Consider non-opioid analgesic to allow reduction of the opioid dose

4. Consider haloperidol 0.5-2 mg PO or IV every 4-6 hour or olanzapine 2.5-5 mg PO every 6-8 hour or risperidone 0.25-0.5 mg 1-2 times/day

Motor and Cognitive Impairment [19]

Studies have shown that stable doses of opioids (more than 2 weeks) are not likely to interfere with psychomotor and cognitive function but these functions should be monitored during analgesic administration and titration. The addition of low

dose haloperidol occasionally may be necessary for confusion states induced by opioids. Psychostimulants can be administered to reverse mental clouding in the absence of sedation but should not be administered to agitated patients.

Myoclonus jerk [20, 24]

Myoclonus jerk is not usually a clinical problem, and reassurance should be given to patients regarding its benign nature. However, if myoclonus impairs function, prevent sleep, or increase pain, clonazepam or valproate should be administered. A reduction in opioids should be considered in the face of refractory or severe myoclonus.

Urinary retention [20, 24]

Urinary retention is also rare with chronic opioids administration and should be treated by administration of a direct cholimimetic agents.

Sedation [19, 20, 24]

1. If sedation develops and persists for more than 1 week after initiating opioids

1.1 Assess for other causes of sedation (e.g. CNS pathology, other sedating medications, hypercalcemia, dehydration, sepsis, hypoxia)

1.2 Decrease the dose of opioid if pain control can be maintained at a lower dose

1.3 Consider changing the opioid

1.4 Consider non-opioid analgesic to allow reduction of the opioid dose

1.5 Consider a lower dose of opioid given more frequently, to decrease peak concentrations

1.6 Consider the addition of methylphenidate 5-10 mg 1-3 times per day. When using CNS stimulants for sedation, limit dosing to morning and early afternoon to avoid insomnia at night.

2. If sedation persists despite several changes of opioids and the above measures

2.2 Reassess cause and severity of sedation

2.3 Consider neuraxial analgesics or neuroablative techniques to potentially reduce opioid dose

Respiratory depression [19, 20, 24]

1. Use reversing agents cautiously. If reversing an opioid with a long half life such as methadone, consider naloxone infusion.

2. If respiratory problems or acute changes in mental status occur, consider naloxone administration. Dilute one ampule of naloxone (0.4 mg/1 ml) into 9 ml of normal saline for a total volume of 10 ml Give 1-2 mL (0.04-0.08 mg) every 30-60 seconds until improvement in symptoms is noted. Be prepared to repeat this process (the half-life of opioids is generally longer than that of the naloxone). If the patient is not responsive within 10 minutes and total naloxone dose of 1 mg, consider another reason for the change in neurological status.

Opioid switching [40, 41]

Oral morphine has been widely used for treating pain of moderate to severe intensity and remains the opioids of choice. However, a substantial minority of patients treated with oral morphine (10-30%) do not have a successful outcome because of excessive adverse effects, inadequate analgesia, or a combination of both adverse effects along with inadequate analgesia. It is now recognized that individual patients vary greatly in their response to different opioids. Patients who obtain poor response to one opioid will frequently tolerate other opioids. Sequential opioid trials, also opioids rotation, or opioids switching may be needed to identify the drug that yields the most favorable balance between analgesia and adverse effects.

The need to change opioids occurs in the following clinical conditions:

a. Pain is controlled but the patient experiences intolerable adverse effects.
b. Pain is not adequately controlled, but it is impossible to increase the dose due to adverse effects.
c. Pain is not adequately controlled by rapid increasing the dose of opioids

Non-opioid analgesics: Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol

Principle of NSAIDs and paracetamol used for cancer pain management [19, 20, 29, 39]

1. Use NSAIDs with caution in patients at high risk for renal, GI, cardiac toxicities, thrombocytopenia, or bleeding disorder.

2. Use any NSAIDs that the patient has found effective and tolerated well in the Compounds that do not inhibit platelet aggregation:

3. Other non-opioid analgesics: Acetaminophen, 500 mg every 4 hours or 1 g every 6 hours (daily maximum 4 g/day) (use caution with combination opioid-acetaminophen products to prevent excess acetaminophen ingestion)

4. Patients at high risk for:

4.1 Renal toxicities: age more than 60 year, compromised fluid status, interstitial nephritis, papillary necrosis, and concomitant administration of other nephrotoxic drugs (including cyclosporin, cisplatin) and renally excreted chemotherapy

4.2 GI toxicities: age > 60 years, history of peptic ulcer disease or excess alcohol use, major organ dysfunction, high-dose NSAIDs given for long periods

4.3 Cardiac toxicities: history of cardiovascular disease or at risk for cardiovascular disease

5. Monitoring for toxicities:

5.1 Baseline blood pressure, BUN, creatinine, CBC, and fecal occult blood

5.2 Repeat every 3 month to ensure stability

6. Treatment of toxicities:

6.1 Renal toxicities: discontinue NSAID if BUN or creatinine doubles or if hypertension develops or worsens

6.2 GI toxicities: if patient develops gastric upset or nausea, consider discontinuing NSAIDs or changing to selective COX-2 inhibitor. Consider adding antacids, H_2 receptor antagonists, misoprostol, omeprazole. If patient develops peptic ulcer or gastrointestinal hemorrhage, discontinue NSAIDs.

6.3 Cardiac toxicities: discontinue NSAIDs if hypertension develops or worsens

7. Further NSAID decisions:

7.1 If NSAIDs are effective but treatment is limited by toxicities that are not deemed serious, consider trial of another NSAIDs. COX-2 inhibitors are associated with lower incidence of GI side effects and do not inhibit platelet aggregation, however, they have not been demonstrated to have reduced renal side effects.

7.2 When systemic administration is not feasible, consider topical NSAID preparations.

7.3 Toxicity of anti-cancer treatment may increase the risk profile of anti-inflammatory treatment

Co-analgesics

Principles of co-analgesic use [19, 20, 29, 39, 42, 43]

1. Antidepressant and anticonvulsants are first-line co-analgesics for the treatment of cancer-related neuropathic pain.

2. These drugs can be helpful for patients whose pain is only partially responsive to opioids.

3. Effective use is predicated on an assessment that clarifies the nature of the pain.

4. As with opioids, it is likely that response to different co-analgesics may vary among types of neuropathic pain and individual patients.

5. Drug selection may be influenced by the presence of certain non-pain symptoms and co-morbidities. For example, a sedating drug may be useful in a patient in whom insomnia is a problem.

6. Patient education should emphasize the trial and error nature of the treatment so patients do not get discouraged.

7. Doses should be increased until the analgesic effect is achieved, side effects become unmanageable, or the conventional maximal dose is reached.

8. For antidepressant, Analgesic effectiveness is not dependent on its antidepressant activity. Effective analgesic dose is often lower than that required to

treat depression. The onset of analgesic action is usually earlier. Frequently used as a co-analgesic in combination with an opioid for the neuropathic component of the pain.

Tricyclic antidepressants (e.g. amitriptyline, imipramine, nortriptyline, desipramine): Start with low dose and increase every 3- 5 days if tolerated. The tertiary amines (amitriptyline, imipramine) may be more efficacious but secondary amines (nortriptyline, desipramine) are better tolerated. Anticholinergic adverse effects such as sedation, dryness of mouth, urinary hesitancy are more likely to occur with amitriptyline and imipramine.

9. Anticonvulsants are frequently used as a co-analgesic in combination with an opioid for the neuropathic component of the pain. For examples:

Gabapentin - Starting dose 100- 300 mg nightly, increase to 900- 3,600 mg daily in divided doses two times a day to three times a day. Dose increments of 50-100% every 3 days. Slower titration for the elderly, medically frail, or those with renal insufficiency.

Pregabalin - Starting dose 50 mg three times a day, increase to 100 mg three times a day. Lower doses in elderly and those with renal insufficiency. Pregabalin more efficiently absorbed through the GI tract than gabapentin. Titration to the analgesic dose requires just 2 or 3 steps, rather than the multiple steps frequently required with gabapentin.

Consider other anticonvulsant agents, many of which have been shown to have efficacy in non cancer neuropathic pain.

10. Topical agents, for example, diclofenac gel 1% act locally and may be used as a co-analgesic in combination with an opioid, antidepressant, and/or an anticonvulsant.

11. Corticosteroids: Long half-life of these drugs allows for once daily dosing. Useful in the acute management of a pain crisis when neural structures or bones are involved.

Guide for management of specific cancer pain syndromes [19, 29, 32, 39]

1. Pain associated with inflammation:

Trial of NSAIDs or glucocorticoids

2. Nerve compression or inflammation:

Trial of glucocorticoids

3. Bone pain without oncologic emergency:

- NSAIDs and titrate analgesic to effect

- Local bone pain: consider local radiation therapy or nerve block

- Diffuse bone pain: consider trial of bisphosphonates, hormonal or chemotherapy, glucocorticoids and/or systemic administration of radioisotopes

- Consider physical medicine evaluation

- For resistant pain, consider referral to a pain specialist and/or the use of interventional strategies.

4. Neuropathic pain:

- Trial of anticonvulsant: start with low dose and increase every 3-5 days if tolerated or lengthen interval up to 14 days (e.g. gabapentin 100-1,200 mg three times a day, carbamazepine, 100-400 mg two times a day, pregabalin 100-600 mg/d divided in 2-3 doses, or other anticonvulsants and/or

- Trial of antidepressant: start with low dose and increase every 3-5 days if tolerated or lengthen interval up to 14 days (e.g. nortriptyline 10-150 mg/day, doxepin 10-150 mg/day, desipramine 10-150 mg/day, venlafaxine 37.5-225 mg/day divided in 2-3 doses, duloxetine 30-60 mg/day and/or

5. Painful lesions that are likely to respond to antineoplastic therapies:

Consider trial of radiation, hormones, or chemotherapy

Table 2.2 Recommendations for optimizing analgesic management in cancer patients [44]

Optimize assessment / documentation - Routine use of validated, culturally and linguistically appropriate standard scales to minimize reporting bias and discern information patients may hesitate to volunteer - Follow-up after analgesic modifications - Rule out disease progression prior to ascribing analgesic dose escalation to tolerance or addiction - Identify and monitor patients at high risk for inadequate pain control
Adopt a holistic treatment approach - Ensure familiarity with current pain management guidelines - Search for underlying causes and reverse the reversible - Ensure analgesic of appropriate potency for reported pain severity is prescribed - Tailor analgesic to putative pain mechanism - Constant pain requires around-the-clock analgesic with breakthrough doses available - Initial opioid dose should be based on pain severity and known response to prior analgesic therapy, preferably with immediate-acting formulations - Common side effects should be proactively addressed (‘the hand that writes the opioid prescription writes the bowel regimen’) - Long-acting formulations may increase compliance but are harder to titrate - Liberal use of co-analgesics and adjuvant analgesics allows opioid-sparing to decrease associated side effects - A multidisciplinary approach encompasses non-pharmacological measures, such as surgical, interventional, and radiotherapeutic options, rehabilitative strategies and other supportive care disciplines - Refer to specialized pain or palliative care programs as necessary for complex cases - Treat emotional distress to maintain quality of life as psychological factors modify perception of pain - Complementary or alternative modalities may enhance a patients’ sense of well being

Table 2.2 Recommendations for optimizing analgesic management in cancer patients [44] (cont.)

Optimize opportunities for education/communication
- Encourage patients or caregivers to maintain a pain diary which is brought to all appointments - Patients and caregivers should be informed of their right to effective pain management - Encourage collaboration for an optimal patient-centered approach - Comprehension of instructions by patients and caregivers should be confirmed - Reinforce information as often as necessary - Ensure caregivers are educated about proper analgesic administration to increase self-reliance and proper decision-making - Instances where a new analgesic or new dose is prescribed can be opportunities for teaching - Ensure it is clear who is responsible for ongoing analgesic provision especially at transition points in care such as discharge from active treatment - Communicate medication changes promptly to those involved in the patient's pain control e.g., primary-care physician, home-nursing support, to increase continuity of care

IV Pharmaceutical care in cancer pain management

Nowadays many cancer pain management guidelines are available, and up to 90 percent of patients with cancer pain can be efficiently controlled by a variety of means, nevertheless, undertreatment of cancer pain is common [35, 45]. Studies of pain control in cancer patients consistently reveal that up to half of patients receive inadequate analgesia and 30% do not receive appropriate drugs for their pain [6]. The barriers to optimum pain relief may come from patient/family, professional, or system barriers. This can range from patients' reluctance to report their pain or take pain medication, fear of addiction, inadequate knowledge of pain management, low priority given to cancer pain treatment, and problems of the availability of treatment [7].

As stated by many guidelines and the pain society, effective pain management should be based upon interdisciplinary co-operation of the health care professional [24, 35, 46]. Based on the clinical and pharmacological expertise of a pharmacist, optimum pain control with appropriate pharmacological strategies could be achieved by the provision of clinical pharmacy service related to pain management.

From previous publications, the value of pharmacists' interventions in pain management has been described. This may indicate that pharmacists have crucial and ever-growing roles in this area. According to the published studies (table 2.3), pharmacists could involve with pain management in different aspects. Even though the characteristic of a service in each setting addressed here may differ based on institutions and patient populations, the results of all models revealed that clinical pharmacists have value and substantial roles in pain management.

Table 2.3 Study of pharmacist participation in pain management

Country, Year	Patients	Study design	Interventions	Results
Puerto Rico, 1999 [15]	33 advanced cancer patients with average worst pain intensity of 5.5 on 0-10 scale	Pre-post intervention study	- Assessment of pain intensity - Identification of drug related problems and intervention with patients and physician to solve problems	- Reduction of pain, increased knowledge about therapy, improved compliance and change in cost of medication. - Drug related problems were subtherapeutic dosage 24.2%, lack of treatment 18.2%, adverse drug reactions 12%, improper drug selection 9.1%, and not taking the prescribed drug 3%
USA, 1999 [47]	941 hospitalized cancer patients	Prospective intervention study	Established pharmacist-based pain management analgesic dosing service (ADS).	- Reduction of average pain score from 2.1 to 1.3 on the 5-point scale - 44% of patients were discharged with a pain score of 0 - 45% reduction of pethidine used - Increased used of oral extended released morphine and topical fentanyl

Table 2.3 Study of pharmacist participation in pain management (cont.)

Country, Year	Patients	Study design	Interventions	Results
The Nether-lands, 2002 [10]	318 patients who received a strong opioids for the first times from 26 community pharmacies	Prospective intervention study	Promoted the use of laxatives in patients starting opioids	Increased the probability of concomitant laxative use 1.9 times [95% CI 1.1-3.3]
USA, 2004 [11]	22 patients with a wide range of diagnosis and received at least 1 dose of as-needed analgesics with pain score more than 4 on NRS	Prospective intervention study	- Changed analgesic orders from as needed to around the clock - Modified non-analgesic orders - Discontinued inappropriate or excessive analgesics - Increased analgesic dosage - Changed route of administration - Modified dosages and administration schedules	- Pain score decreased from 7 to 4 - Median number of as-needed analgesic doses decreased from 3 to 0 - 64% of patients expressed satisfaction about their pain relief

Table 2.3 Study of pharmacist participation in pain management (cont.)

Country, Year	Patients	Study design	Interventions	Results
USA, 2004 [12]	87 patients who were referred to the pain clinic	Prospective intervention study	Established the pharmacy pain clinic as the part of pain management center in the hospital	- Decreased waiting time for an appointment in the pain center - Eliminated unscheduled visits for narcotic prescriptions
USA, 2007 [13]	564 chronic non-cancer related pain patients	Prospective intervention study	Prescribed, modified, and monitored drug therapy in accordance with a written protocol	- Highly significant reduction of pain score ($P < 0.0001$) with continued visit - Generated $ 107,550 of actual revenue and saved the health plan over $ 450,000
USA, 2008 [14]	Patients using Patient-Controlled Analgesia (PCA) in a community hospital	Prospective intervention study	Addition of full time pain management pharmacist (PMP) for providing service to all patients receiving PCA	Increased the number of PCA patients more than 50% from approximately 1,200 patients/year in 1999 to 1,710 patients/year in 2007

Table 2.3 Study of pharmacist participation in pain management (cont.)

Country, Year	Patients	Study design	Interventions	Results
Thailand, 2008 [16]	Patients with solid tumors who had pain intensity score $\geq$ 5 on 0-10 NRS, and must be taking pain medication	Pre-post intervention study	Performing a pharmacist round with pain assessment and the activity of identifying, resolving, and preventing DRPs	- Mean pain score was significantly decreased from 7.4 $\pm$ 1.5 to 1.9 $\pm$ 1.4 - 14% of patients were pain free and 48% of patients had pain score < 3 on NRS - Performing of 9.7 intervention per patients with highly acceptance rate (91%) of physicians

CHAPTER III
MATERIALS AND METHODS

Materials

1. Computer software which was specially developed for this study in order to:

    - Detect admitted patients with history of cancer and print out the list of patients (Appendix A).

    - Access to patient information in the hospital computerized database and obtain medication and laboratory profiles, history of diagnosis and history of drug allergy, and print out their brief profiles (Appendix B).

    - Record additional history of patients which are obtained from medical charts, OPD cards and patients interview (Appendix C).

    - Record drug related problems and medication errors of each patient, and interventions or pharmaceutical care activities of the research pharmacist (Appendix D).

    - Summarize and report the desired data for further analysis.
2. Data collection form for patients' demographic data, medical history, oncologic history and performance status. (Appendix E)
3. Data collection form for current vital signs, laboratory parameters, and medication profiles (Appendix F)
4. Data collection form for pain assessment (Appendix G)
5. Data collection form for daily pain intensity and pain medication (Appendix H)
6. Data collection form for drug related problems and medication errors (Appendix I)
7. Guide for identification and categorization of drug related problems and medication errors (Appendix J)
8. Patients' medical charts and OPD cards

Methods

1. Definition of terms

1.1 Pain [19]

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

1.2 Cancer pain

For this study, cancer pain was defined as pain that is attributable to cancer or its therapy that includes chemotherapy, radiation therapy, and surgery.

1.3 Pain rating scales [48]

Pain rating scales are tools used to measure or assess patients' pain intensity and interpret clinical pain into objective data which is represented as the number of pain intensity. In this study, the Numerical Rating Scales was utilized.

1.3.1 Numerical Rating Scale (NRS) [36, 48]

NRS is a discrete numeric 11 point scale from 0 to 10, which 0 equals no pain while 10 represents the worst imaginable pain. Patients will be asked to rated the intensity of their pain, and the number reported by each patient is the pain intensity, which is further classified in to 3 levels that are:

Pain intensity of 1-4 corresponds to mild pain

5-6 corresponds to moderate pain

7-10 corresponds to severe pain

Pain that is rated 5 or higher on a scale of 0-10 NRS interferes substantially with the quality of life.

1.4 Pain intensity at baseline

Pain intensity at baseline means pain intensity that was assessed in the first visit of the research pharmacist.

1.5 Pain intensity at discharge

According to the recommendation of the Agency for Health Care Policy and Research (AHCPR) in the guideline of management of cancer pain, the quality of cancer pain management should be evaluated at points of transition in the provision of services (i.e. from the hospital to the home) to determine that optimal pain management is achieved and maintained [49].

For this study, pain intensity at discharge was operationally defined as pain intensity that was lastly assessed within 24 hours before discharge or no more than 24 hours after discharge which might be obtained by phone.

1.6 Drug related problem (DRPs) [50]

According to Cipolle et al, drug related problem (DRP) is defined as "any undesirable event experienced by a patient which involves, or is suspected to involve, drug therapy, and that interferes with achieving the desired goal of therapy".

In this study, only DRPs that related to pain treatment were recorded. Categories of DRPs and their causes were identified and categorized as follows:

1. Indication

1.1 Unnecessary drug therapy

1.1.1 There is no valid medical indication for the drug therapy at this time.

1.1.2 Multiple drug products are being used for a condition that requires single drug therapy.

1.1.3 The medical condition is more appropriately treated with nondrug therapy.

1.1.4 Drug therapy is being taken to treat an avoidable adverse reaction associated with another medication.

1.1.5 Drug abuse, alcohol use, or smoking is causing the problem.

1.2 Needs for additional drug therapy

1.2.1 A medical condition requires the initiation of drug therapy.

1.2.2 Preventive drug therapy is required to reduce that risk of developing a new condition.

1.2.3 A medical condition requires additional pharmacotherapy to attain synergistic or additive effects.

2. Effectiveness

2.1 Ineffective drug

2.1.1 The drug is not the most effective for the medical problem.

2.1.2 The medical condition is refractory to the drug product.

2.1.3 The dosage form of the drug product is inappropriate.

2.1.4 The drug product is not an effective product for the indication being treated.

2.2 Dosage too low

2.2.1 The dose is too low to produce the desired response.

2.2.2 The dosage interval is too infrequent to produce the desired response.

2.2.3 A drug interaction reduces the amount of active drug available.

2.2.4 The duration of drug therapy is too short to produce the desired response.

3. Safety

3.1 Adverse drug reaction

3.1.1 The drug product causes an undesirable reaction that is not dose-related.

3.1.2 A safer drug product is required due to risk factors.

3.1.3 A drug interaction causes an undesirable reaction that is not dose-related.

3.1.4 The dosage regimen was administered or changed too rapidly.

3.1.5 The drug product causes an allergic reaction.

3.1.6 The drug product is contraindicated due to risk factors.

3.2 Dosage too high

3.2.1 Dose is too high.

3.2.2 The dosing frequency is too short.

3.2.3 The duration of drug therapy is too long.

3.2.4 A drug interaction occurs resulting in a toxic reaction to the drug product.

3.2.5 The dose of the drug was administered too rapidly.

4. Compliance

4.1 Non compliance

4.1.1 The patient does not understand the instructions.

4.1.2 The patient prefers not to take the medication.

4.1.3 The patient forgets to take the medication.

4.1.4 The drug product is too expensive for the patient.

4.1.5 The patient cannot swallow or self-administer the drug product appropriately.

4.1.6 The drug product is not available for the patient.

1.7 Medication error (MEs) [51, 52]

According to National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), a medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."

MEs can occur throughout the entire medication processes including:

- Prescribing process
- Transcribing process
- Dispensing process
- Administration process

In this study, only MEs related to pain treatment was focused on and recorded.

For a categorization of errors, the NCCMERP classifies an error according to the severity of the outcome as follows

No error

Category A: Circumstances or events that have the capacity to cause error

Error, No Harm

Category B: An error occurred but the error did not reach the patient (An "error of omission" does reach the patient)

Category C: An error occurred that reached the patient but did not cause patient harm

Category D: An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm

Error, Harm

Category E: An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention

Category F: An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization

Category G: An error occurred that may have contributed to or resulted in permanent patient harm

Category H: An error occurred that required intervention necessary to sustain life

Error, Death

Category I: An error occurred that may have contributed to or resulted in the patient's death

1.8 Responses to pharmacist interventions/recommendations [16, 53]

Responses to pharmacist interventions/recommendations were recorded in three categories:

1. Fully acceptance - Defined as recommendations by the research pharmacist were accepted and drug therapy was adjusted or changed according to pharmacist recommendations.

2. Partially acceptance - Defined as recommendations by the pharmacist were accepted but drug therapy was partially adjusted, or recommendations by the pharmacist were accepted but drug therapy was not changed at the time of study.

3. Rejection - Defined as recommendations by the pharmacist were rejected and drug therapy was not adjusted according to pharmacist recommendations.

1.9 Pain status at discharge [18, 36]

Pain status at discharge in this study was classified into 4 categories as follows:

Pain free – Defined as pain intensity at discharge was rated as 0 on NRS

Improved – Defined as pain intensity at discharge was rated as 1 to 3 on NRS, or pain intensity at discharge decreased from baseline pain intensity equal or more than 3 points on NRS

Stable – Defined as pain intensity at baseline decreased from baseline pain intensity less than 3 points on NRS

Worsened – Defined as pain intensity at discharge was higher than pain intensity at baseline

2. Study design [54]

This study was designed as a stratified, randomized, controlled trial. Study subjects were recruited according to the inclusion criteria from every ward in Chiangrai Prachanukroh hospital. The recruited patients were randomly assigned to the intervention or control group with a 1:1 ratio, stratified by baseline pain intensity and gender with a block-of-four randomization to achieve balance between groups in size and characteristics.

All participants were stratified based on their baseline pain intensity as moderate pain (pain intensity 5–6 on NRS) and severe pain (pain intensity 7–10 on NRS), and their gender as male and female. Hence, the participants were divided into the following 4 categories: moderate pain/male, severe pain/male, moderate pain/female, and severe pain/female. In each stratum, each individual was numbered consecutively. These numbers were previously randomized to the intervention or control group equally by a 1:1 block-of-four list. The block was generated by using a permuted block design and drawing lots. Determination of whether a patient would be received pharmaceutical care or usual care was made by reference to a series based on sequence in each block drawn up by a research pharmacist. Consecutive patients according to sequential order of admission time were assigned to the sequence of each block.

3. Study population

3.1 Inclusion criteria

3.1.1 Patients aged equal or more than 15 years, who were admitted into Chiangrai Prachanukroh hospital, with a clinical or histological diagnosis of solid tumor or hematologic malignancy.

3.1.2 Patients who rated their pain intensity as 5 or greater on 0-10 NRS.

3.1.3 Patients who understood the numeric and counting system.

3.2 Exclusion criteria:

3.2.1 Patients who suffered from confusion or reduced level of consciousness and unable to communicate efficiently

3.2.2 Patients who denied participating in this study

3.3 Termination criteria:

Patients who were discharged from the hospital or passed away within 72 hours after admission

3.4 Sample size determination

The sample size was based on a desire to detect a clinically significant difference in the pain intensity at discharge between the intervention and control group. The change of intensity of at least 2 points on 0-10 NRS was considered both statistical and clinical significance [33]. A previous study in similar patients by Caraceni et al [55] demonstrated a standard deviation of 1.3-3.8 in the recruited patients. For this study, within-group standard deviation was assumed to be 3.0.

From the study design and outcomes of interest, the sample size was calculated by using the following equation [56, 57]

$$n \text{ (per group)} = \frac{2[(Z_{\alpha/2} + Z_{\beta})\sigma]^2}{d^2}$$

Where; n = The number of patients (sample size)

α = Probability of type I error

= 0.05 (2-sided)

$Z_{\alpha/2}$ = 1.96

β = Probability of type II error

= 0.2 (power = 0.80)

Z_β = 0.842

σ = Population standard deviation

= 3.0

d = Difference in mean change between 2 groups that is considered clinically important

= 2

Hence, $n = \frac{2[(1.96 + 0.842)\ 3]^2}{2^2}$

$= 35.3 \simeq 36$

Allowing for 20% dropout rate, therefore, a sample size of at least 43 patients per group was required to detect a difference of 2 points pain intensity between the groups, with 80% power at the significance level of 0.05.

4. Outcome measurement

4.1 Primary outcomes

4.1.1 Differences of the mean pain intensity at discharge between the intervention and control group

4.1.2 Differences of the mean pain intensity between at baseline and discharge in each group of patients

4.2 Secondary outcomes

4.2.1 Differences of the categories of pain status at discharge between the intervention and control groups

4.2.2 Differences in the proportion of patients with $\geq$ 30% and $\geq$ 50% reduction in NRS according to the recommendation of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) between the intervention and control groups [34]

4.2.3 The number of drug related problems and medication errors in both groups

4.2.4 Responses to pharmacist interventions/recommendations in the intervention group.

5. Period of study

The study was performed during April to October 2008.

6. Study protocol

6.1 Patients who were admitted in Chiangrai Prachanukroh hospital were screened for eligibility by using the developed computer software. The list of patients, who had the history of cancer (according to The International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10] chapter II, block C00 to C97 and D00 to D48) in the computerized database of the hospital, were shown. Then the research pharmacist reviewed the medical profile of each patient in the list through the computerized database and printed out the brief medical profiles of patients that were expected to have pain (Appendix A, B).

6.2 Another method to obtain subject patients was the case notification from nurses at wards or other clinical pharmacists.

6.3 For the next step, the research pharmacist briefly reviewed medical charts and OPD cards of targeted patients at wards and assessed or interviewed those patients to decide whether to recruit them into the study according to the inclusion and exclusion criteria.

6.4 The recruited patients were randomly allocated to the intervention or control group with a 1:1 ratio, stratified by baseline pain intensity and gender with a block-of-four randomization. All participants were stratified based on their baseline pain intensity as moderate pain (pain intensity 5–6 on NRS) and severe pain (pain intensity 8 – 10 on NRS), and their gender as male and female. Hence, the participants were divided into the following 4 categories: moderate pain/male, severe pain/male, moderate pain/female, and severe pain/female. In each stratum, each individual was numbered consecutively. Their numbers were previously randomized to the intervention or control group equally by a block-of-four list.

6.5 After allocation, the medical charts and OPD cards of all recruited patients were comprehensively reviewed for details, and the important data that are patient demographics, general medical and oncologic history, and other baseline clinical characteristics were recorded in the data collection form (Appendix E). Current vital signs, laboratory parameters and list of medication used were also

recorded (Appendix F). Additional required data were obtained from interview patients or care givers. Some acquired data were translated into a computerized database by the developed software (Appendix C)

6.6 The research pharmacist then initiated a comprehensive pain assessment including history of pain (i.e. onset and duration), characteristics, location, exacerbating and alleviating factors, pain pattern, and also behavioral manifestations and the impact of pain to daily activities. All data were recorded as the baseline pain characteristics (Appendix G). For quantification of pain intensity, patients were asked to rate their pain intensity as the number using a standard 0-10 NRS.

6.7 From all acquired data, the research pharmacist identified drug related problems (DRPs) and medication errors (MEs) exclusively in pain management issues.

For the intervention group, the point of problems were discussed with the relevant person, i.e. physicians, nurses, pharmacists, patients or care givers, and the research pharmacist proposed the appropriate recommendations or interventions for those problems. All identified DRPs and MEs, pharmacist interventions/ recommendations, and responses to the interventions were recorded in the data collection form (Appendix I), and entered into the computer for the convenience of summarization at the end of study (Appendix D).

For the control group, the research pharmacist only recorded the identified DRPs and MEs in the data collection form. Since the control group was determined to receive the conventional treatment or usual care without providing of pharmacy pain service, the research pharmacist didn't propose any interventions in this group. However, according to the ethic consideration, in case of MEs in category B to I were identified, the research pharmacist would notify the relevant person.

6.8 To identify DRPs in each patient, the research pharmacist would find the following components adapted from Cipolle et al [50]:

An undesirable event or risk of an event experiences by the patients. The problem can take the form of a medical complaint, sign, symptom, diagnosis, disease, or abnormal laboratory.

The drug therapy involved.

The relationship that exists (or is suspected to exist) between the undesirable event and drug therapy. This relationship can be the consequence of

drug therapy or to require the modification of drug therapy for resolution or prevention.

In addition, the research pharmacist identified DRPs by using the IESAC principle: Indication, Effectiveness, Safety, Adherence and Cost in every drug used.

For MEs identification, because the main purpose of this study was to investigate a primary outcome as pain intensity, MEs, one of the secondary outcomes, in each medication process were not observed thoroughly in every step. MEs were detected in the possible ways of the research pharmacists as follows:

- Prescribing and transcribing process: The pharmacist detected the errors by checking the medication order sheet of each patient at ward.
- Dispensing process: The pharmacist detected the errors by checking whether there were discrepancies between the physician order in the medication order sheet at ward and computerized pharmacy order entry, and the discrepancies between dispensed drugs and the physician order.
- Administration process: The pharmacist detected the errors by checking the medication administration record (MAR) of nurses.

6.8 For ongoing assessment, the research pharmacists performed a pharmacy pain service round to assess and monitor all patients in both groups at least once daily until patients were discharged from the hospital or dead. The major points monitored by the pharmacist were pain intensity and characteristics, DRPs such as adverse drug reactions, and MEs. Daily progression in each patient was noted.

6.9 To focus on the progression of pain management, pain intensity and pain medication in everyday were recorded separately in another data collection form (Appendix H). In addition, daily plan for pain therapy management were noted. All of recorded intensity was used for pain management plan.

6.10 Because the goal of this study was to improve patients' outcomes in terms of reduction of pain severity and minimization of DRPs and MEs (pain intensity was equal to or less than 3 on NRS without DRPs and MEs), hence this following scheme was implemented:

6.10.1 In the event of pain intensity was still more than 3 on NRS or new pain or worsening pain, the research pharmacist then analyzed possible

causes of problems and evaluated current drug regimen. The recommendations generated by the pharmacist to solve those problems were discussed with the relevant person.

6.10.2 In the event of pain intensity was equal to or less than 3 on NRS with identified DRPs or MEs, the research pharmacist analyzed possible causes of problems, proposed the recommendations and discussed with the relevant person to solve those problems.

6.10.3 In the event of pain intensity were equal to or less than 3 on NRS without any DRPs or MEs, the research pharmacist assessed and monitored patients every day until discharge to assure that the goal of therapy was maintained and the patient was not at a risk of developing any new problems.

6.11 For routine work, the research pharmacist accessed the computerized database via the developed software to search and screened for new subject patients, and the processes since 6.1 were repeated.

6.12 In case of discharge planning by physicians, the research pharmacist also proposed a pain management plan for discharge.

6.13 On discharge day, the research pharmacist assessed patients especially pain characteristics and DRPs, and recorded pain intensity before discharge. In addition, patients and/or care givers only in the intervention group received discharge counseling from the pharmacist.

Figure 3.1 Study protocol I

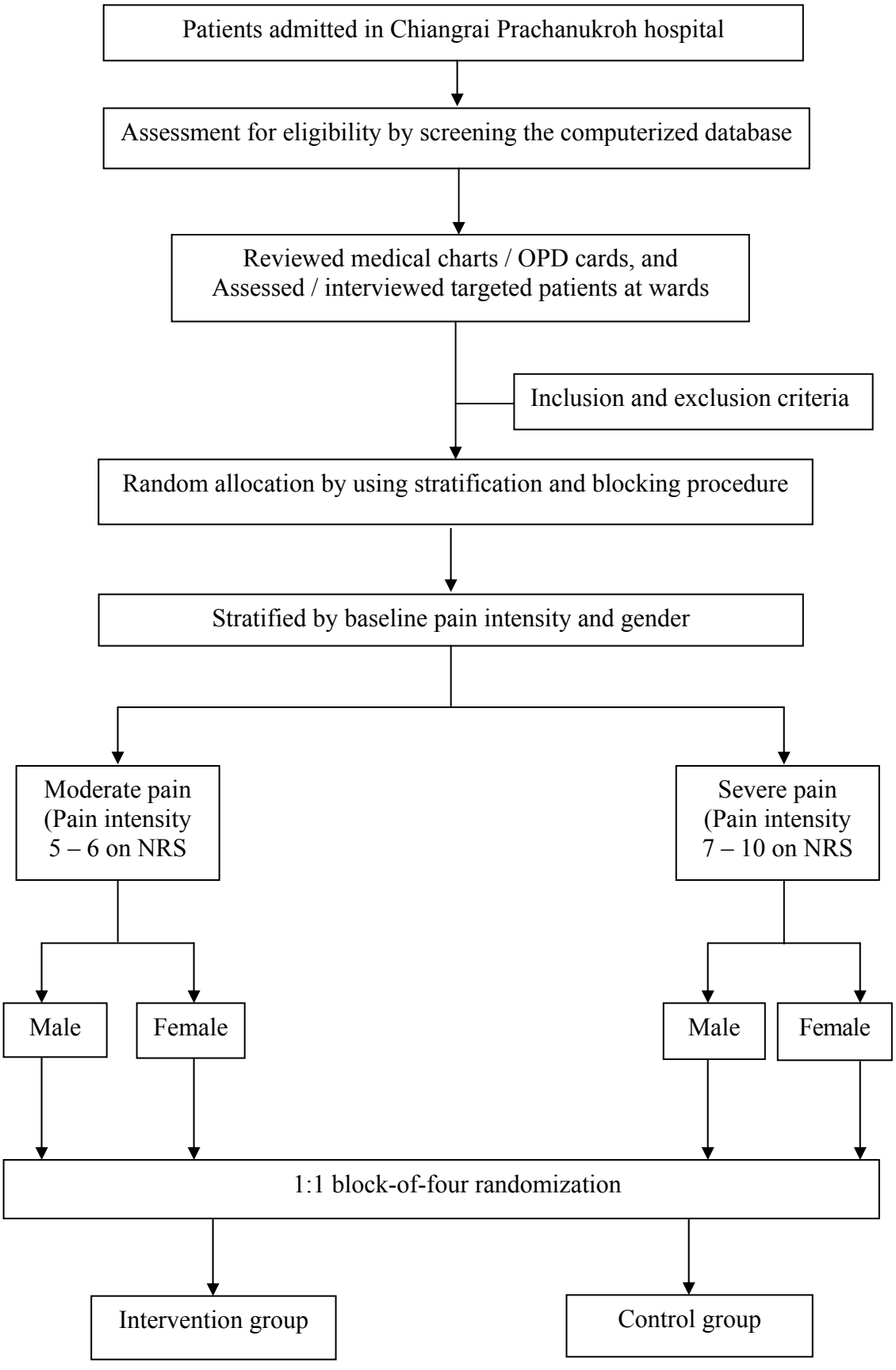


Figure 3.2 Study protocol II

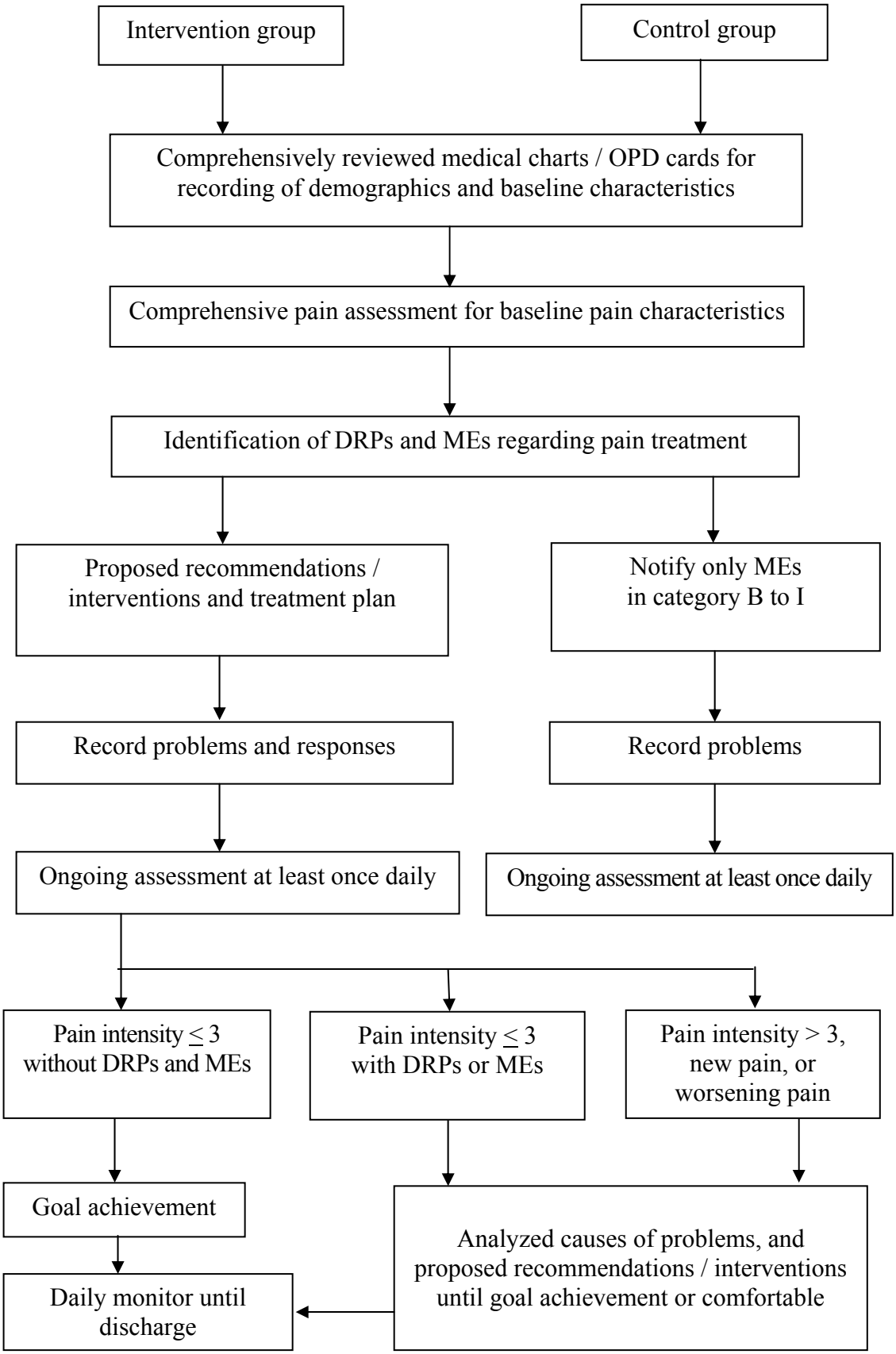
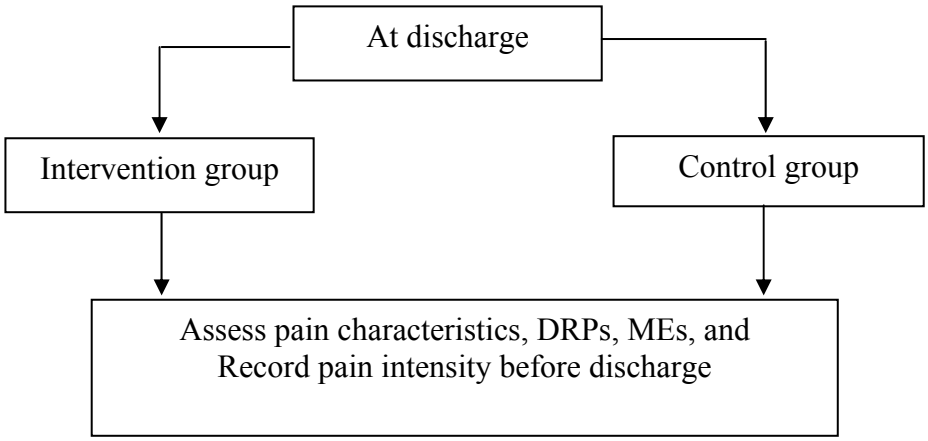


Figure 3.3 Study protocol III



7. Data presentation and analysis

The main analysis was per protocol analysis which was restricted to only participants who fulfilled the protocol in terms of eligibility, interventions, and outcome assessment [54]. For continuous variables, test of normality was performed by using Shapiro-Wilk test. In the event of normal distribution, the variables in each group were summarized by the mean and standard deviation. When continuous data had an asymmetrical distribution, the median and range was used instead. P value less than or equal 0.05 was considered statistically significant. All statistical analyses were conducted with the use of SPSS software 16.0 version (SPSS, Inc., Chicago, Ill, US).

7.1 Demographics and baseline characteristics of patients

7.1.1 Demographic data of patients in each group including gender, age, marital status, education, occupation, payment scheme were presented and analyzed by descriptive statistics

7.1.2 Data of medical and oncologic history in each group including type of tumor, primary tumor site, stage of cancer, prior cancer treatment, current or concomitant cancer treatment, ECOG performance status were presented and analyzed by descriptive statistics

7.1.3 Data of pain characteristics at baseline in each group including causes and types of pain, pain category, number of pain site were presented and analyzed by descriptive statistics

In addition, unpaired t-test, Chi Square test and Mann-Whitney U test were used to determine whether there are differences in any demographics, diseases, and baseline pain characteristics between patients in the intervention and control group.

7.2 Primary outcomes

7.2.1 The difference of the mean pain intensity at discharge between the intervention and control group (between-group comparison) was analyzed by using Mann-Whitney U test.

7.2.2 The difference of the mean pain intensity between at baseline and discharge in each group of patients (within-group comparison): In case of normal distribution, two mean pain intensity was analyzed by using Wilcoxon Signed-Rank test.

7.3 Secondary outcomes

7.3.1 The difference of the categories of pain status at discharge between intervention and control group was analyzed by using Chi-square test.

7.3.2 The differences in the proportion of patients with $\geq$ 30% and $\geq$ 50% reduction in NRS according to the recommendation of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [34] between intervention and control groups was analyzed by using Chi-square test.

7.3.3 The number of drug related problems and medication errors in both groups were presented and analyzed by descriptive statistics.

7.3.4 The number of pharmacist interventions / recommendations in the intervention group were presented and analyzed by descriptive statistics.

7.3.5 Responses to pharmacist interventions/recommendations in the intervention group were presented and analyzed by descriptive statistics.

CHAPTER IV
RESULTS

Figure 4.1 depicts the progress of patients through the study period according to the Consolidated Standards of Reporting Trials (CONSORT) recommendations for randomized trials. Over a 7-month period from March to October 2008, 96 patients were recruited, consented and underwent randomization into two groups with 48 patients in each group. After randomization, 45 patients in the intervention group received intervention throughout their hospitalization course. There were 3 patients where interventions were stopped due to severe reduction of consciousness (2 patients) and misdiagnosis (1 patient). For control, there were 2 patients where pain assessment and treatment was stopped due to severe reduction of consciousness. There were 7 and 2 deaths in the intervention and control group during the study period. We performed data analysis based on intention-to-treat principle. Therefore, all 96 patients were included into the data analysis. For patients whose interventions were stopped or patients who died during the study period, the most updated set of data were used. The results of this study were presented as follows:

1. Baseline characteristic of study population
    - 1.1 Demographic and general characteristics
    - 1.2 Medical and oncologic history
    - 1.3 Baseline pain characteristics
2. Primary outcomes
    - 2.1 Mean pain intensity between baseline and discharge in each group of patients
    - 2.2 Mean pain intensity at discharge between the intervention and control groups
3. Secondary outcomes
    - 3.1 Categories of pain status at discharge between the intervention and control groups

3.2 Proportion of patients with ≥ 30% and ≥ 50% reduction in NRS from baseline between the intervention and control groups

3.3 Number of drug-related problems and medication errors in both groups

3.4 Number of pharmacist interventions/recommendations in the intervention group

3.5 Responses to pharmacist interventions/recommendations in the intervention group

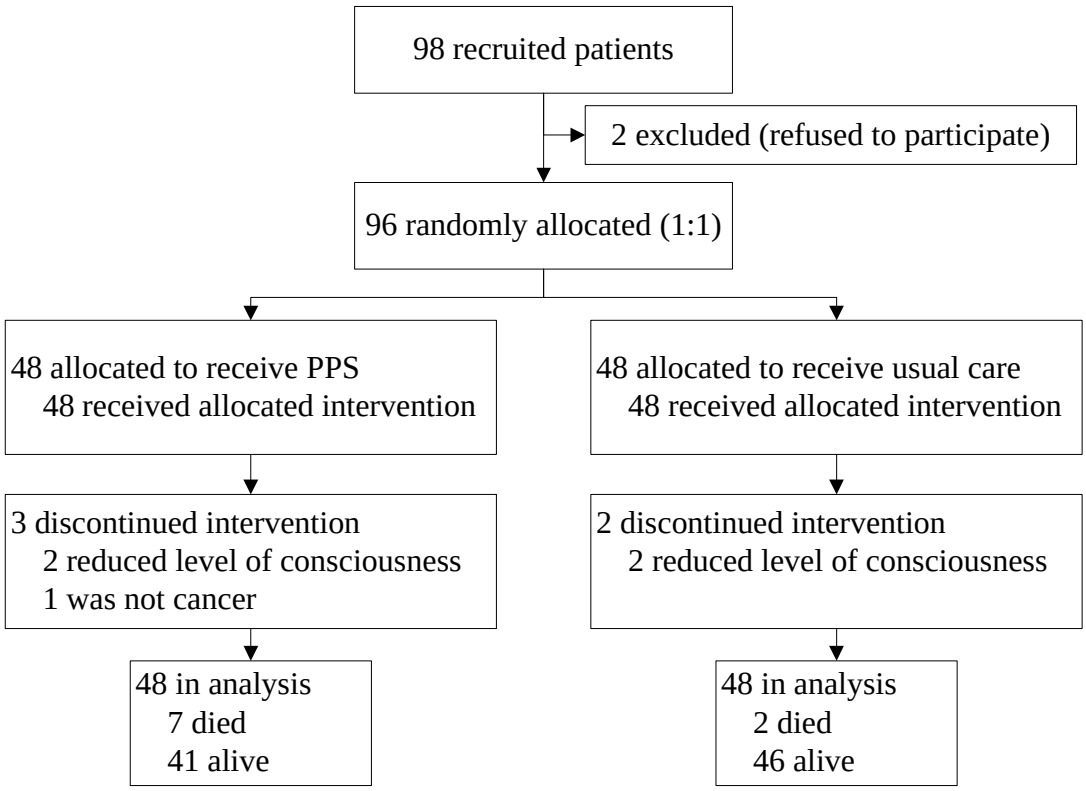


Figure 4.1 Flow diagram of patients through the study period

1. Baseline characteristic of study population

1.1 Demographic and general characteristics

Table 4.1 lists the demographic and general baseline characteristics of patients by group. These characteristics were well-balanced between groups. There were no significant differences between the two groups on any characteristics.

Table 4.1 Demographic and baseline characteristics of the patients

Characteristic	Intervention (n = 48)	Control (n = 48)	P-value
Age, yrs			
Mean ± SD	53.8 ± 11.2	55.9 ± 12.8	0.379[a]
Median (Range)	54 (25-79)	57 (16-80)	
Male gender, n (%)	28 (48.3)	30 (51.7)	0.676[b]
Marital status, n (%)			
Single	5 (10.4)	7 (14.6)	0.836[b]
Married	36 (75.0)	32 (66.7)	
Divorced	1 (2.1)	1 (2.1)	
Widowed	6 (12.5)	8 (16.7)	
Education, n (%)			
None	15 (31.3)	13 (27.1)	0.864[b]
Primary school	24 (50.0)	23 (47.9)	
Secondary school	6 (12.5)	7 (14.6)	
College/university	3 (6.2)	5 (10.4)	
Occupation, n (%)			
None	16 (33.3)	19 (39.6)	0.451[b]
Agricultural	18 (37.5)	17 (35.4)	
Employee	13 (27.1)	10 (20.8)	
Business	1 (2.1)	0 (0.0)	
Civil servant	0 (0.0)	2 (4.2)	
Payment scheme, n (%)			
Universal coverage	43 (89.6)	39 (81.2)	0.466[b]
CSMBS[c]	4 (8.3)	8 (16.7)	
Social security scheme	1 (2.1)	1 (2.1)	

[a] Unpaired t-test was used to compare the means between groups.

[b] Chi-square test was used to compare the proportion of patient between groups.

[c] CSMBS: Civil Servant Medical Benefit Scheme

1.2 Medical and oncologic history

Table 4.2 depicts medical and oncology history of patients by group. Overall, the majority of study population suffered from solid tumors. Types of solid tumors were in concordance with Thailand's statistic of cancer type with gastrointestinal, breast and lung cancers as the most frequent sites. For severity, more than two thirds of study population was with stage 4 cancer. In consistent with the staging of our patient population, most patients received only palliative care. There were statistical differences between the two groups on primary tumor site, ECOG performance score and types of patient ward.

Table 4.2 Medical and oncologic history

Characteristic	Intervention (n = 48)	Control (n = 48)	P-value
Types of tumor, n (%)			
Solid tumor	46 (95.8)	41 (85.4)	0.080[a]
Hematolologic malignancy	2 (4.2)	7 (14.6)	
Primary tumor site, n (%)			
Gastrointestinal	29 (60.4)	27 (56.2)	0.014[a,*]
Breast	10 (20.8)	0 (0.0)	
Lung	3 (6.2)	6 (12.5)	
Urogenital	2 (4.2)	6 (12.5)	
Gynecological	1 (2.1)	4 (8.3)	
Hematological	1 (2.1)	3 (6.2)	
Others	2 (4.2)	2 (4.2)	
Stage, n (%)			
1-2	1 (2.1)	1 (2.1)	0.999[a]
3	12 (25.0)	12 (25.0)	
4	35 (72.9)	35 (72.9)	
ECOG performance status, n (%)			
1	22 (45.8)	11 (22.9)	0.034[a,*]
2	14 (29.2)	25 (52.1)	
3	12 (25.0)	12 (25.0)	

Table 4.2 Medical and oncologic history (cont.)

Characteristic	Intervention (n = 48)	Control (n = 48)	P-value
Current cancer treatment, n (%)			
Surgery	17 (35.4)	7 (14.6)	0.060[a]
Chemotherapy	1 (2.1)	5 (10.4)	
Hormonal therapy	1 (2.1)	1 (2.1)	
No treatment	29 (60.4)	35 (72.9)	
Concomitant other medical problems, n (%)			
Yes	14 (29.2)	22 (45.8)	0.092[a]
No	34 (70.8)	26 (54.2)	
Pain reported on admission			
Yes	28 (58.3)	31 (64.6)	0.529[a]
No	20 (44.7)	17 (35.4)	
Discharge status, n (%)			
Improved	34 (70.8)	36 (75.0)	0.205[a]
Not improved	4 (8.3)	3 (6.2)	
Transferred	3 (6.2)	7 (14.6)	
Dead	7 (14.6)	2 (4.2)	
Length of stay, days			
Median (Range)	9 (3-89)	5 (3-42)	0.034[b,*]
Type of ward			
Surgery	41 (85.4)	27 (56.2)	0.005[a,*]
Medicine	7 (14.6)	19 (39.6)	
Gynecological	0 (0.0)	2 (4.2)	

[a] Chi-square test was used to compare the proportion of patient between groups.

[b] Unpaired t-test was used to compare the means between groups.

[*] Statistically significant at $P < 0.05$

1.3 Baseline pain characteristics

Table 4.3 summarizes baseline pain characteristics of the study population. Most patients suffered pain that were related to tumors itself. Nociceptive pain was prevalent in both groups (68.8% in the intervention group and 91.7% in the control group); the remaining was the combination of nociceptive and neuropathic pain. For pain severity, most patients suffered from severe pain with multiple pain sites. The aggressive modalities such as patient controlled analgesia, intraspinal analgesia, or neurolytic blocks were not used for pain control in this study.

Table 4.3 Baseline pain characteristics

Characteristic	Intervention (n = 48)	Control (n = 48)	P-value
Cause of pain, n (%)			
Tumor only	31 (64.6)	42 (87.5)	0.023[a,*]
Therapy related	2 (4.2)	0 (0.0)	
Combined	15 (31.2)	6 (12.5)	
Pain type, n (%)			
Nociceptive alone	33 (68.8)	44 (91.7)	0.005[a,*]
Nociceptive with neuropathic	15 (31.2)	4 (8.3)	
Pain category on admission, n (%)			
Moderate pain	8 (16.7)	6 (12.6)	
Severe pain	40 (83.3)	42 (87.5)	0.563[a]
Number of pain site, n (%)			
One	14 (29.2)	21 (43.8)	
Two	16 (33.3)	15 (31.2)	0.414[a]
Three	12 (25.0)	9 (18.8)	
More than three	6 (12.5)	3 (6.2)	
Pain site, frequency (%)			
Abdomen	24 (22.2)	39 (41.5)	
Waist	14 (13.0)	9 (9.6)	
Leg	11 (10.2)	11 (11.7)	
Back	10 (9.3)	11 (11.7)	
Wound	9 (8.3)	6 (6.4)	
Others	40 (37.0)	18 (19.1)	

[a] Chi-square test was used to compare the proportion of patient between groups.

[*] Statistically significant at $P < 0.05$

2. Primary outcomes

2.1 Mean pain intensity between at baseline and discharge in each group

For within-group comparisons, mean pain intensity at discharge compared to baseline in both groups were significantly decreased, 7.8 ± 1.3 to 2.2 ± 1.2 ($P < 0.0001$) in the intervention group and 7.9 ± 1.1 to 4.9 ± 1.8 ($P < 0.0001$) in the control group (Figure 4.2). This data indicated significant improvement of pain control in both groups.

2.2 Mean pain intensity at discharge between the intervention and control groups

At baseline, mean pain intensity between the two groups were similar; 7.8 ± 1.3 and 7.9 ± 1.1 in the intervention and control groups, respectively ($P = 0.587$) (Figure 4.2). At discharge, mean pain intensity were 2.2 ± 1.2 and 4.9 ± 1.8 in the intervention and control groups, respectively ($P < 0.0001$) (Figure 4.2). This difference corresponds to a 55.1% reduction in pain intensity. The absolute decrease in mean pain intensity was significantly higher in the intervention group compared to the control group -5.5 ± 1.3 versus -2.9 ± 1.6 ($P < 0.0001$), respectively.

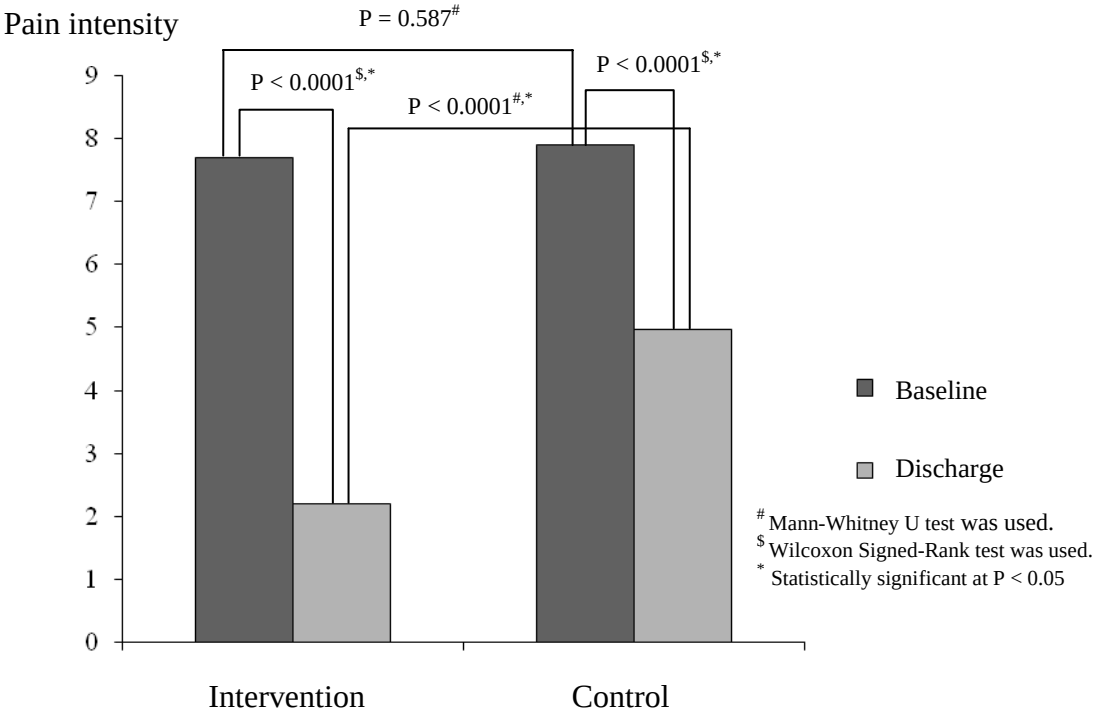
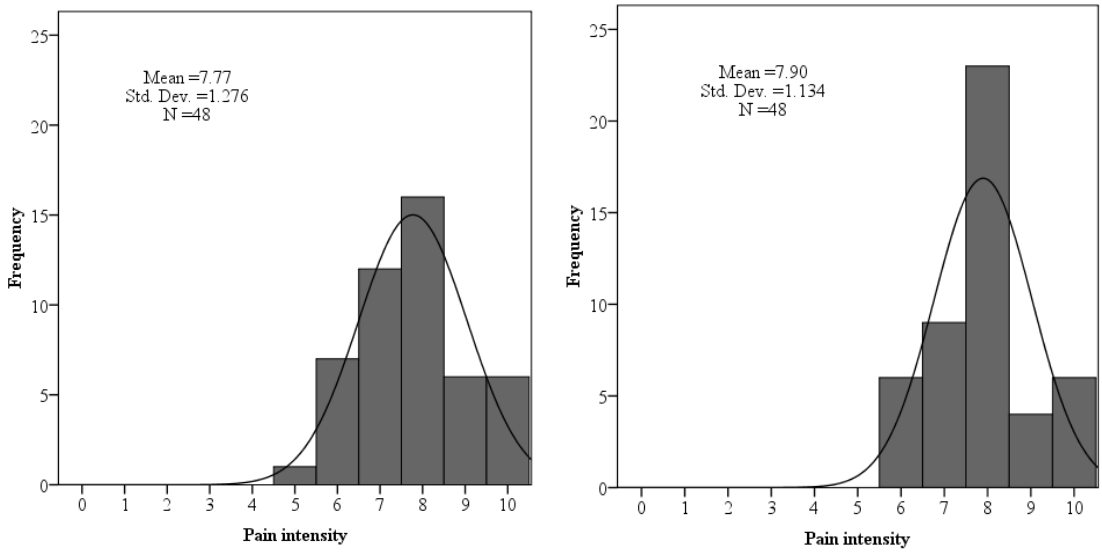


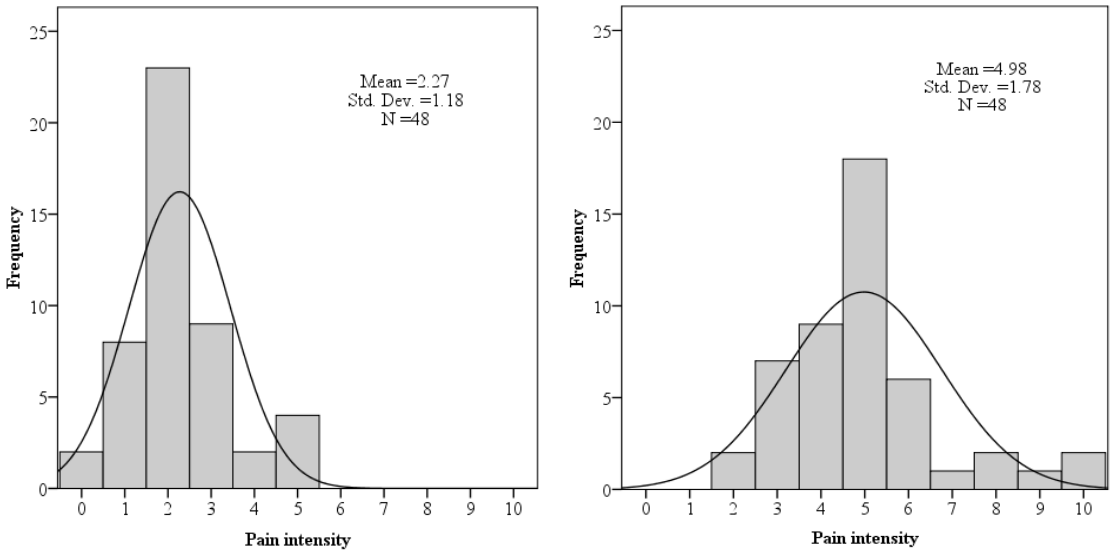
Figure 4.2 Mean pain intensity between at baseline and discharge in each group of patients

Figure 4.3 and 4.4 illustrate the frequency distribution of pain intensity in each group at baseline and discharge.



Intervention Control

Figure 4.3 The frequency distribution of pain intensity in the intervention and control groups at baseline



Intervention Control

Figure 4.4 The frequency distribution of pain intensity in the intervention and control groups at discharge

3. Secondary outcomes

3.1 The difference of the categories of pain status at discharge between the intervention and control group

Pain status at discharge between the two groups is represented in Table 4.4. At discharge, 100% of patients in the intervention group experienced either improvement in pain control or became free of pain. For the control group, there were only 47.9% of patients who experienced improvement in pain control while another 52.1% did not experience changes in their pain control.

Table 4.4 Pain status at discharge

Pain status	Intervention No. (%)	Control No. (%)	P-value
Pain free	2 (4.2)	0 (0.0)	< 0.0001[a,*]
Improved	46 (95.8)	23 (47.9)	
Stable	0 (0.0)	25 (52.1)	
Worsened	0 (0.0)	0 (0.0)	

[a] Chi-square test was used to compare the proportion of patient between groups.

[*] Statistically significant at $P < 0.05$

3.2 Proportion of patients with ≥ 30% and ≥ 50% reduction in pain intensity from baseline between the intervention and control groups

In 2007, a group of pain experts called the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) issued important sets of recommendations related to the conduction of pain clinical trials. One of the recommendations is related to the determination of clinically important differences in pain intensity. The IMMPACT group suggested that a 30% reduction in pain intensity appears to reflect at least moderate clinically important differences. In addition, since a 50% reduction in chronic pain intensity appears to reflect substantial improvements, the proportion of patients responding with this degree of improvement should also be reported.

We therefore conducted analyses based on these recommendations. The results of such analyses are summarized in Table 4.5 and Figure 4.5. Overall,

reduction in pain intensity was significantly higher in the intervention than control groups (P < 0.0001). The average percent reductions in pain intensity were 70.5 ± 13.7% and 38.3 ± 18.1. in the intervention and control groups, respectively. The proportions of patients experiencing at least 30% reduction in pain intensity were 100% and 65.2% in the intervention and control groups, respectively. More than 95% of patients in the intervention group experienced ≥ 50% improvement compared to only 34.8% in the control group.

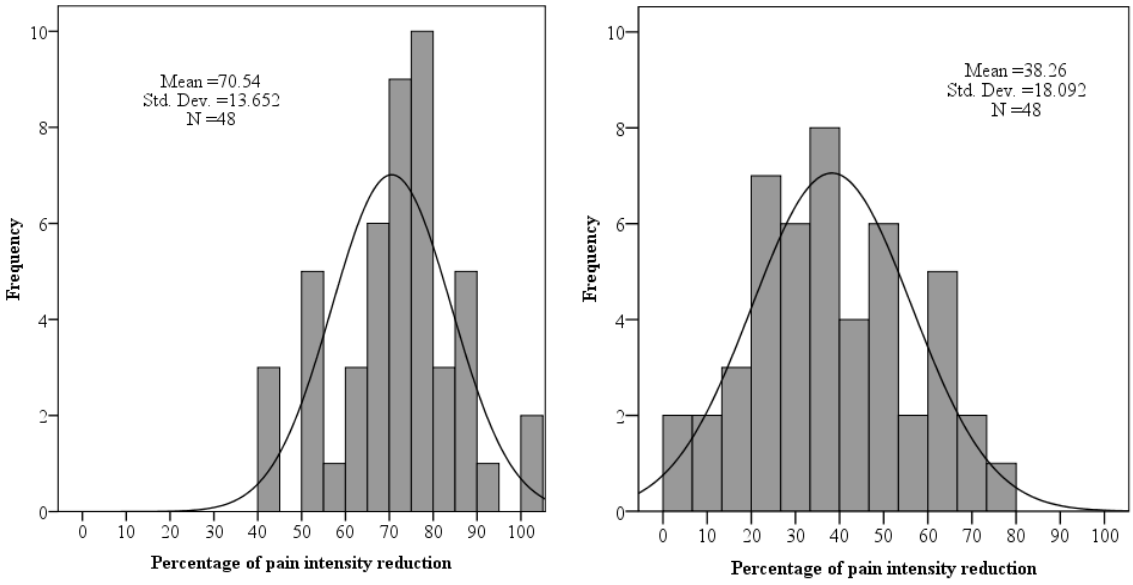
Table 4.5 Proportion of patients with ≥ 50%, ≥ 30%, and < 30% reduction in pain intensity from baseline between the intervention and control groups

Percent reduction in pain intensity	Intervention No. (%)	Control No. (%)	P-value
≥ 50	46 (95.8)	16 (33.3)	< 0.0001[a,*]
≥ 30 - < 50	2 (4.2)	14 (29.2)	
< 30	0 (0.0)	18 (37.5)	

[a] Chi-square test was used to compare the proportion of patient between groups.

[*] Statistically significant at P < 0.05

Based on such findings, patients in the intervention group were 1.6 (RR 1.6, 95% CI; 1.3-2.0) and 2.9 (RR 2.9, 95% CI; 1.9-4.3) times more likely than the control group to experience moderate clinically important improvement and substantial improvements, respectively.



Intervention Control

Figure 4.5 Distribution of percent reduction in NRS of the intervention and control groups

3.3 The number of drug related problems and medication errors in both groups

The documentation of DRPs in this study was adapted from Cipolle et al. that defined DRPs as “any undesirable event experienced by a patient which involves, or is suspected to involve, drug therapy, and that interferes with achieving the desired goal of therapy [50]

A wide range of DRPs existed in both groups as shown in table 4.6. There were 240 and 227 problems in the intervention and control group, respectively. Both types and numbers of DRPs between the groups were quite similar. The main issues were needs for additional drug therapy and dosage too low. This may represent the problem of under-treatment of pain. For the control group, 10.4% of patients received non-opioids whereas 22.9% received opioids alone as treatment for moderate to severe level (table 4.7). Dosage too low especially for opioid therapies, (Example: prescribing of as needed analgesics instead of around the clock schedule) were commonly found. Selections of weak opioids or non-opioids for severe pain treatment were also common. Drugs for prophylaxis or treatment of adverse drug reactions (ADRs) were often under-utilized. For unnecessary drug therapy problems, duplication analgesics of

weak and strong opioids were common. In addition, the problems related to compliance including refusal to take medication due to fear of ADRs, lack of understanding for the instructions to take drugs, drug shortage and availability, and drug administration via intramuscular route were identified.

Table 4.6 Type and number of drug related problems and medication errors identified in each group

Problems	Intervention No. (%)	Control No. (%)
Indication		
Needs for additional drug therapy	113 (45.2)	66 (27.9)
Unnecessary drug therapy	20 (7.9)	24 (10.2)
Effectiveness		
Ineffective drug	20 (7.9)	34 (14.4)
Dosage too low	59 (23.5)	53 (22.5)
Safety		
Adverse drug reactions	16 (6.4)	39 (16.5)
Dosage too high	5 (1.9)	5 (2.1)
Compliance	11 (4.4)	12 (5.1)
Medication errors	7 (2.8)	3 (1.3)
Total	251 (100)	236 (100)

Table 4.7 Pattern of opioids usage at baseline and discharge

Opioid usage	Intervention No. (%)	Control No. (%)	P-value
At baseline			
Opioids alone	12 (25.0)	12 (25.0)	0.152[a,]
Opioids combined with NSAIDs or co-analgesics	5 (10.4)	12 (25.0)	
No opioids	31 (64.6)	24 (50.0)	
At discharge			
Opioids alone	6 (12.5)	11 (22.9)	0.002[a,*]
Opioids combined with NSAIDs or co-analgesics	42 (87.5)	32 (66.7)	
No opioids	0 (0.0)	5 (10.4)	

[a] Chi-square test was used to compare the proportion of patient between groups.

[*] Statistically significant at $P < 0.05$

ADRs were common problems in this study and appeared to occur at a similar rate between the two groups. The numbers of patients who experienced ADRs were 10/48 (20.8%) and 18/48 (37.5%) in the intervention and control groups, respectively ($P = 0.81$). The frequency of ADRs occurrences were 16 and 39 in the intervention and control groups, respectively. The most common ADRs in the intervention group were constipation, sedation and nausea/vomiting. The most common ADRs in the control group were constipation, nausea/vomiting and dizziness (table 4.8). There were no severe or life threatening ADRs found in both groups.

Table 4.8 Incidence of ADRs

ADRs	Intervention No. (%)	Control No. (%)	P-value
Patient without ADRs	38 (77.8)	31 (60.9)	0.72[a]
Patient with ADRs	10 (22.2)	18 (39.1)	
Frequency of ADRs			
Constipation	9 (56.3)	15 (38.5)	
Nausea / vomiting	2 (12.5)	9 (23.1)	
Sedation	3 (18.8)	2 (5.1)	
Dizziness	0 (0.0)	4 (10.2)	
Urinary retention	0 (0.0)	2 (5.1)	
Palpitation	0 (0.0)	2 (5.1)	
Dry mouth	1 (6.2)	1 (2.5)	
Confusion	0 (0.0)	1 (2.5)	
Myoclonus jerk	1 (6.2)	1 (2.5)	
Dysphagia	0 (0.0)	1 (2.5)	
Bowel obstruction	0 (0.0)	1 (2.5)	
Total	16 (100.0)	39 (100.0)	

[a] Chi-square test was used to compare the proportion of patient between groups.

Medication errors found in this study were shown in table 4.9 and 4.10. Most of medication errors were categorized as B level (an error occurred but the error did not reach the patient). The pharmacist notified all medication errors to the relevant persons.

Table 4.9 Medication errors

Process	Intervention No. (%)	Control No. (%)
Prescribing	1 (14.3)	2 (66.7)
Transcribing	0 (0.0)	0 (0.0)
Dispensing	0 (0.0)	1 (33.3)
Administration	6 (85.7)	0 (0.0)
Total	7 (100.0)	3 (100.0)

Table 4.10 Categorization of medication errors by level of severity

Level	Intervention No. (%)	Control No. (%)
A	0 (0.0)	0 (0.0)
B	6 (85.7)	2 (66.7)
C	1 (14.3)	1 (33.3)

Example of case synopsis according to drug related problems

Case I Needs for additional drug therapy

A 56 years old Thai male with advanced stage of stomach cancer was admitted due to severe abdominal pain. His pain intensity was rated 7 on 0-10 NRS on admission. He only received pethidine via intravenous injection prn for pain. Consequently, his pain was not controlled adequately. The pharmacist recommended the physician to start around the clock regimen of strong opioids and laxative for the patient. The physician fully accepted pharmacist's recommendations and prescribed around theclock oral morphine (Kapanol®) and Senokot® for prophylaxis of constipation. After around the clock oral morphine was prescribed, the physician discontinued prn pethidine intravenous injection. The pharmacist recommended the physician to prescribe immediate release intravenous morphine for control of breakthrough pain since it was the initial phase of morphine dose titration and background pain was still not well controlled. In addition, the patient complained that

he often had pain at night so amitriptyline 25 mg at bed time was recommended and titrated as the adjuvant to oral morphine. NSAIDs were not recommended because the patient could tolerate only liquid diet. The patient was discharged with pain intensity at 4 on NRS.

Case II Unnecessary drug therapy

A 24 years old Thai male was admitted with stage four head and neck cancer and deep wound at his right eye. He complained that he had pain at his head, neck and wound with overall pain intensity around 9 on NRS. Sustained released oral morphine (Kapanol®) was prescribed for pain control. Unfortunately, his pain was not sufficient controlled so the physician prescribed codeine along with oral morphine. The pharmacist recommended discontinuing codeine and increasing dose of morphine instead. Two days later, another physician prescribed tramadol together with oral morphine. The pharmacist recommended discontinuing tramadol and increasing dose of morphine and amitriptyline. Moreover, the pharmacist found that the patient was prescribed naproxen and ibuprofen together. After recommendation, the physician decided to discontinue naproxen and continue ibuprofen. One day later, another physician ordered fentanyl trandermal patch 25 mcg/hour apply every 72 hours. Because patient also received nevirapine 200 mg every 12 hours for treatment of HIV infection, fentanyl was recommended to discontinue due to drug interaction problems. This patient had pain intensity at 2 on NRS on the day before his death.

Case III Ineffective drug

A 53 years old Thai female with advanced stage of breast cancer with bone and chest wall metastasis was admitted for chemotherapy. She complained about her pain at chest and back with pain intensity at 7 on NRS. She only had paracetamol 500 mg 2 tablet prn for pain. After recommendation, the drug was changed to sustained released oral morphine (Kapanol®) 20 mg once daily combined with diclofenac 25 tablet three times a day and amitriptyline 25 mg tablet once daily at night. The patient had pain intensity at 2 on NRS at discharge.

Case IV Dosage too low

A 56 years old Thai male with stage four of prostate cancer and bone metastasis was admitted due to severe pain at right leg and buttock. His pain intensity was 9 on NRS. He cried all day and every day because of severe pain. He received oral morphine 80 mg/day and pethidine intramuscular injection prn for pain. He required pethidine injection many times per day and sometimes he got normal saline injection instead of pethidine because nurses thought that patient might develop drug addiction. After pain assessment by the pharmacist, dose of oral morphine was titrated for four times to 300 mg/day which pain was adequately control. Pethidine injection was replaced by morphine injection for breakthrough pain with dose increase in accordance to dose of oral morphine. In addition, dose of Senokot® was increased for prophylaxis of constipation due to high dose of morphine utilization. At discharge, patient had pain intensity at 1 on NRS.

Case V Adverse drug reactions

A 43 years old Thai male with advanced stage colorectal cancer was admitted due to diarrhea and severe abdominal pain with pain intensity of 8 on NRS. Because of non-infectious diarrhea, loperamide was prescribed. Sustained released oral morphine (Kapanol®) was also prescribed without laxatives. A few days later, patient developed constipation. The pharmacist recommended adding laxatives for treatment of constipation and prophylaxis of gut obstruction or changing to fentanyl transdermal patch with laxatives because patient had the history of off-and-on constipation. The physician decided to change oral morphine to fentanyl transdermal patch. Because of inadequate pain control, dose of fentanyl was increased to 150 mcg/hr (fentanyl transdermal patch 25 mcg/hr administered 6 patches every 72 hour). Patient notified that he felt more sleepy, the pharmacist then assessed sedation score as 2 (moderate or frequently drowsy but easy to rouse) with normal respiratory rate (18 times/minute) thus patient education and nurse notification for close monitoring was performed. A few days later, he developed myoclonus jerk (sudden contractions of the big body muscles while falling asleep). Because of side effect occurrences together with neuropathic pain components, the pharmacist recommended adding of gabapentin and decreasing dose of fentanyl transdermal patches. A few days later, his myoclonus

jerk got improve and he did not awake because of muscle contractions. The patient had pain intensity at 2 on NRS on the day before his death.

Case VI Dosage too high

A 24 years old Thai male was admitted with stage four head and neck cancer and deep wound at his right eye. Patient was prescribed sustained released oral morphine (Kapanol®) every 8 hours. Pharmacist recommended decreasing dosage interval to 12 hours for prevention of respiratory depression due to high peak level of morphine.

Case VII Compliance

A 53 years old Thai male with advanced stage bladder cancer was admitted due to severe abdominal pain with pain intensity of 8 on NRS. He was prescribed fentanyl transdermal patch with diclofenac intramuscular injection and pethidine intramuscular injection prn for pain. The pharmacist provided patient education about fentanyl usage information and precautions to prevent potential fentanyl related problems. For drug administered via intramuscular injection, the pharmacist recommended changing to intravenous morphine injection because intramuscular was not the preferred route. In addition, chronic pethidine usage might precipitate neurological side effects. In addition, patient was reluctant to request drug for breakthrough pain as he disliked drug administration via intramuscular route. Moreover, the patient thought that pain was the common symptom of cancer and he was willing to stand for cancer pain, but not pain from drug administration. The pharmacist then provided patient education to this issue and patient fully accepted the intervention.

Case VIII Medication errors

A 48 years old Thai male with advanced stage hepatic cancer was admitted due to severe pain at abdomen, waist and back with pain intensity of 8 on NRS. The pharmacist recommended increasing dose of fentanyl transdermal patches. The pharmacist found out later that nurse did not administer fentanyl according to the new dosage regimen (administered 2 patches of fentanyl instead of 3). The pharmacist

notified the nurse and the error was corrected. This medication error was classified as level C (an error occurred that reached the patient but did not cause patient harm).

3.4 The number of pharmacist interventions/recommendations in the intervention group

In the intervention group, the pharmacist made a total of 379 interventions exclusively in pain issues, of which 289 offered to physicians, 50 and 26 offered to patients/caregivers and nurses, respectively. The most common intervention was drug initiation or addition followed by patient education and dose increase as summarized in table 4.11. These were related to the results of DRPs findings. The interventions to nurses were involved with drug administration issues and ADRs monitoring. The mean numbers of interventions per patient was 7.9. And the summary of drug related problems and pharmacist interventions were shown in Table 4.12

Table 4.11 Pharmacist interventions made in the intervention group

Intervention	No.	%
Drug initiation	118	31.1
Dosage increase	52	13.7
Patient education	52	13.7
Drug change	32	8.4
Provision of drug information	31	8.2
Drug discontinuation	29	7.6
Interval/frequency change	20	5.3
Dosage recommendation	17	4.5
Notification	12	3.2
ADRs monitoring	9	2.4
Route change	4	1.1
Dosage decrease	3	0.8
Total	379	100

Table 4.12 Summary of drug related problems and pharmacist interventions

DRPs	Problem details	Pharmacist interventions
Indication: Needs for additional drug therapy	- Required analgesics for pain treatment in patients who did not have any analgesics	- Initiation of analgesics according to WHO analgesic ladder
	- Required immediate released analgesics for breakthrough pain	- Initiation of morphine injection - Notification to nurses for administration of morphine IV injections in case of breakthrough pain episodes during pharmacist round
	- Required other combination drugs to relieve pain, for example, bone pain, neuropathic pain, severe pain	- Initiation of NSAIDs, paracetamol, and adjuvants
	- Required preventive drugs to reduce the risks of developing ADRs	- Initiation of laxatives in case of opioids prescribing or initiation of proton pump inhibitors in case of NSAIDs prescribing
Indication: Unnecessary drug therapy	- Duplication of drug therapy, for example, prescribing of double strong opioids (fentanyl transdermal patch and oral sustained released opiods), prescribing of combination of strong and weak opioids, prescribing of double NSAIDs or double benzodiazepines	- Providing drug information, discontinuation and selection of the drugs that were most suitable for patients, for example, switched from oral morphine to transdermal patch fentanyl because of ADRs or adherence issues, switched from weak opioids

Table 4.12 Summary of drug related problems and pharmacist interventions (cont.)

DRPs	Problem details	Pharmacist interventions
Indication: Unnecessary drug therapy		to strong opioids for patients with severe pain, switched from diazepam to lorazepam since diazepam has a long half-life and may potentiate risk of respiratory depression
Effectiveness: Ineffective drug	- Prescribing of non-opioids or weak opioids for severe pain or breakthrough pain treatment	- Changed drugs to strong opioids or initiation of strong opioids
	- Prescribing or administration of non-analgesics for breakthrough pain control, for example, usage normal saline injection or vitamin B complex injection instead of morphine injection when patients required rescue drugs to relieve breakthrough pain	- Providing drug information and change to strong opioids
Effectiveness: Dosage too low	- The dose of analgesics, especially strong opioids, or co-analgesics were too low to control pain adequately	- Increase dose of drugs until achieving adequate pain control with acceptable ADRs
	- Dosage too low after opioid conversion	- Providing drug information , calculation and recommendation of opioid dosage by using opioid conversion factor
	- The dosage interval is too infrequently to control pain	- Change dosage interval into appropriate interval, for

Table 4.12 Summary of drug related problems and pharmacist interventions (cont.)

DRPs	Problem details	Pharmacist interventions
Effectiveness: Dosage too low	adequately, for example, prescribing of prn (as needed) tramadol or morphine instead of around the clock regimen	example, change tramadol (50) 1 tablet prn for pain to 1 tablet every 6 hours
	- The dose of laxatives too low to prevent opioids related constipation	- Increase dose of laxatives according to patients' status and opioid dosage titration
	- Drug interaction that reduced the amount of active drug available, for example, prescribing of fentanyl and nevirapine which nevirapine decreased fentanyl blood level	- Providing drug information, discontinuation, and selection of most suitable drugs for patients, for example, selection of morphine instead of fentanyl to be used with nevirapine
Safety: Adverse drug reactions	Most of ADRs were related to opioids	- Initiation of drugs for symptomatic treatment, for example, initiation of metoclopramide for control of nausea and vomiting - Opioid rotation, for example, change morphine to fentanyl due to constipation or intolerable nausea/vomiting - Decrease dose, for example, decrease dose of fentanyl because of myoclonus jerk and increase dose of gabapentin instead - Increase dose, for example,

Table 4.12 Summary of drug related problems and pharmacist interventions (cont.)

DRPs	Problem details	Pharmacist interventions
Safety: Adverse drug reactions		increase dose of laxatives for treatment of constipation - Patient education
Safety: Dosage too high	- The dosing frequency were too short that could cause side effects, for example, prescribing of oral sustained released morphine (Kapanol®) 20 mg every 8 hours, or 40 mg twice daily (administered at 8.00 and 17.00)	- Change dosing interval to the appropriate interval of each drug
Compliance	- Patients denied to take medications because of fear of ADRs, addiction, drug tolerance	- Patient education
	- The route of administration was not the preferred route to patients, for example, prescribing of morphine intramuscular injection prn for pain	- Change the route of administration from intramuscular to intravenous injection
	- Patients could not swallow drugs, for example, morphine capsule	- Change to another route of administration. Example: change from oral to transdermal patch
	- Patients did not understand drug instructions, especially transdermal fentanyl patches	- Patient education
	- Some drugs were not in the hospital formulary, for example, gabapentin, morphine syrup	- Asked for permission to use drug from the hospital's director

Table 4.12 Summary of drug related problems and pharmacist interventions (cont.)

DRPs	Problem details	Pharmacist interventions
Compliance	- Lack of continuity of opioid availability	- Change to another opioids by calculation for equivalent dose
Medication errors	- Prescribing error: Prescribing of fentanyl 75 mg subcutaneous injection instead of fentanyl transdermal fentanyl patches 25 mcg/hour	- Notification of physicians
	- Administration error: Did not record of morphine injection prn for pain, Incorrect of record the number of transdermal fentanyl patches, administration of tramadol though it was off by the physician, duplication of record of morphine injection administration, Incorrect dose and time of administration	- Notification and providing drug information to nurses

3.5 Responses to pharmacist interventions/recommendations

Table 4.13 showed responses to pharmacist intervention and percentage of acceptance to pharmacist interventions. The physician fully accepted 258 of 301 recommendations (85.7%) made by pharmacists. Most common reasons for rejection was fear of ADRs when recommendation was to intensify opioid therapy and lack of interest to provide optimal pain control since pain was not at the top priority for the physicians.

Table 4.13 Responses to pharmacist interventions

Response	Physicians No. (%)	Nurses No. (%)	Patients No. (%)
Full acceptance	258/301 (85.7)	26/26 (100.0)	50/50 (100.0)
Partial acceptance	34/301 (11.3)	0 (0.0)	0 (0.0)
Rejection	9/301 (3.0)	0 (0.0)	0 (0.0)

CHAPTER V
DISCUSSION

Cancer related pain is a major issue of healthcare systems worldwide. Pain management remains a great challenge, mainly due to its high prevalence and impairment of cancer patients' quality of life. Despite great advances in the fields of pain management and palliative care, pain directly or indirectly associated with a cancer diagnosis remains significantly undertreated [38]. There is substantial evidence that cancer pain management is often suboptimal [3, 58-61].

This is the first study that investigates the effect Pharmacy Pain Service (PPS) in cancer patients in a randomized, controlled fashion. The scope of services included daily evaluation and provision of recommendations to modify pharmacotherapy plan for optimal pain control and minimization of adverse effects. Communication of recommendations were mostly done through face-to-face discussion on wards and when necessary through telephone consultation and documentation in the progress note of medical charts. Intensive patient education was also an integral part in addition to interventions provided to healthcare professionals. The results of the study have demonstrated that patients suffering from moderate to severe cancer pain obtained benefit from pharmaceutical care service related to pain management.

I Baseline characteristics

This study was designed in a stratified, randomized, controlled trial. With such design, we were able to achieve well-balanced general baseline characteristics between the two groups, proving that randomization process was effective.

Overall, the study population was a representative of most cancer patients in the country. Most patients suffer from advanced stage cancers with high percentages of metastasis. Type of cancer identified in the study population reflects national cancer statistics. However, since we used pain intensity as one of the inclusion criteria, our

study population tends to suffer from solid tumors rather than liquid tumors. Since solid tumors tend to produce pain symptoms more commonly and more severe than liquid tumor, these patients met our inclusion criteria more often than patients with liquid tumors.

Although there was a statistically significant difference in the distribution of ECOG performance scores, we believe that this had no significant impact on our findings. This is because the differences of ECOG scores between two groups were limited to ECOG grade 1 and 2. Since patients with ECOG 1 and 2 can be considered as mild states of physical performance limitation and may not influence much of the pain intensity or pain perception. In addition, since the mean pain intensity score between the two groups at baseline were identical, this small discrepancy in ECOG should not adversely impact our findings.

Length of stay in the intervention group seemed to be longer than the control group. This may be explained by the fact of higher percentage of patients in the intervention group underwent surgical operation (38% versus 15%). These patients therefore required more recovery time. In addition, pharmacist intervention aiming at titrating pain medication to achieve good control may impact discharging decision and resulted in longer length of stay. Nevertheless, future studies need to be designed to investigate the effect of pharmacy pain service on length of stay.

II Differences of mean pain intensity and pain status at discharge

This study attempted to find the magnitude of difference of pain intensity in patients who received pharmaceutical care service and usual care related to pain management. It should be noted that pain intensity used in this study was based on average pain in the last 24 hours.

For within-group comparison, the study results showed that mean pain intensity at discharge were statistically significant lower than at baseline in both groups of patients, 7.8 ± 1.3 to 2.2 ± 1.2 ($P < 0.0001$) in the intervention group and 7.9 ± 1.1 to 4.9 ± 1.8 ($P < 0.0001$) in the control group. A multi-center, prospective cohort study, which recruited 520 patients with cancer pain from 7 university hospitals and 3 tertiary care centers in Thailand, found that mean of maximum pain intensity at the study entry was reduced from 6.6 ± 2.6 to 4.8 ± 3.1 after 2–week period of receiving

medical treatment as judged necessary by responsible physicians (mean difference was -1.8 $\pm$ 3.2, $P < 0.001$) [18]. This might indicate that the result of pain treatment in the control group of our study was not much different from other settings in Thailand. The study of Kongtalae et al. which was designed as pre–post comparison study in 47 patients with cancer pain at medical wards of Ramathibodi hospital, Thailand, found that after providing pharmaceutical care service related to pain managment, mean pain intensity was significantly decreased from 7.4 $\pm$ 1.5 to 1.9 $\pm$ 1.3 ($P < 0.001$) [16]. This finding was similar to the result of the intervention group in our study.

For between-group comparison, mean pain intensity at discharge of patients who received usual care in the control group was higher than the group of patients received PPS (2.2 $\pm$ 1.2 versus 4.9 $\pm$ 1.8). This difference corresponds to a 55.1% reduction in pain intensity. In addition, all patients receiving PPS experienced at least 30% reduction in pain intensity while only 65.2% of the usual care group experienced that. In addition, more than 95% of patients in the intervention group experienced $\geq$ 50% improvement compared to only 34.8% in the control group.

When considered pain status at discharge, three-quarters (73.5%) of patients in the study of Vatanasapt et al. reported an improvement in pain at discharge [4], while this study found that only half of patients received usual care improved. For intervention group, 100% of patients experienced either improvement in pain control or became free of pain. This finding is encouraging and provides a foundation to promote such service for better pain control of cancer patients.

III Drug related problems exclusively regarding pain issue

There were various drug related problems identified during the study period. In consistent with known problems with pain control, common problems reflects inertia to aggressively manage pain. The majority of problems were needs for additional pain medications, lack of prophylaxis drugs to reduce the risk of developing adverse drug reactions, especially laxatives. Underuse of adjuvant therapies such as NSAIDs, antidepressants and anticonvulsants were also very common. The study results showed that one-third (34.8%) of patients in the control group received only non–opioids or opioids alone for severe pain treatment. Prescribing of non–opioids or weak opioids for treatment of severe pain may also contribute to suboptimal pain

management. Combination of weak and strong opioids was also a common practice. These facts may reflect that the principle of WHO analgesic ladder was not widely adopted by physicians of the hospital. Use of inappropriately low dose or prn dosing of analgesics were also common. Furthermore, inappropriate dose conversion of opioids from different dosage forms or different types of opioids was frequently encountered.

Despite more aggressive treatment of pain, the incidences of adverse drug reactions were similar between the two groups. Types of adverse drug reactions found in the study were consistent with known side effects of pain medications and mostly mild and manageable. While numbers of patients experiencing ADRs were similar between the two groups, frequency of ADRs occurrences was higher in the control group, especially constipation. Lack of- or too low dose of laxatives prescribed in the control group might be the contributing factor for this finding. Constipation also occurred in the intervention group though the pharmacist adjusted the dosage regimen of laxatives. This might be explained by the fact that patient with advanced stage of cancer, especially poor ECOG performance status, had limited movement and diet tolerate. These conditions might increase the severity of constipation.

For problems with dosage too high, they were mostly related to inappropriate dosing interval of extended released opioid therapy, especially oral sustained released morphine (Kapanol®). This might reflect the lack of knowledge about drug dosage form and its pharmacokinetic properties.

For compliance to therapy, there were various issues related to this problem. Reasons for non-compliance were dissatisfaction with route of drug administration via intramuscular injection, fear of addiction, fear of becoming tolerant to the effects of analgesics, fear of ADRs, and fear of disturbing healthcare professionals. Some patients did not understand indication and instructions of fentanyl transdermal patch and did not believe that it could relief pain. The pharmacist solved these problems by providing patient education. In addition to patient aspect, the compliance problems also included the problems of drug availability in the hospital and opioids shortage. For example, some patients needed gabapentin as the adjuvant drug for treatment of neuropathic pain, but it was not in the hospital formulary. In the

study period, there was a sudden shortage of sustained released morphine and fentanyl transdermal patch for a while. These all impacted to the outcome of pain control.

Medication errors were infrequently found in this study. Although there was no harm to patients, it affected pain treatment outcomes. The best example for this was the error of omission where patients were not provided pain medication according to medication orders. Incorrect recording of drug administration by nurses could also lead to incorrect dosage titration.

IV Pharmacist interventions and responses

In the intervention group, the pharmacist performed a total of 365 interventions to physicians, nurses and patients/caregivers. The acceptance rate of 86% by physicians was high. This played a major part in the positive findings of the study. It also showed that collaboration between physicians and pharmacist was a key to success in medication management. One of the reasons for high acceptance rate could be related to $\geq$ 15 years history of physician-pharmacist collaboration of the study hospital in various aspects of care. Therefore, if there is a need to replicate this study at other settings, close physician-pharmacist collaboration may be a deciding factor on the success of such study along with the quality of recommendations by responsible pharmacists.

Nevertheless, PPS was a new model of pharmaceutical care services in the study hospital. Skepticism of physicians toward pharmacist's competency in cancer pain management combined with numerous barriers might help explain some of the rejections by physicians. However, some reasons for rejection were related to physician's lack of interest to provide optimal pain control along with fear of ADRs with aggressive treatment.

The majority of pharmacist recommendations were aimed at resolving drug therapy issues. Since needs for additional drug therapy and dosage too low were the major problems (45.4% and 22.9%, respectively), thus drug initiation and dosage increase were the most recommendations given to physicians.

Overall, our findings, similar to results of the recent study in Thailand, suggested that pain is still an invisible problem and a substantial number of cancer patients with moderate and severe pain received suboptimal medication [4]. A number

of barriers impeding pain relief previously reported in the literature were commonly found in our study.

Firstly, based on the authors' consideration, healthcare professionals were the main obstacles for optimum pain control in this study. Failure to adequately assess pain frequently lead to poor pain control [19]. Very few of physicians and nurses in the study hospital employed pain assessment tools to rate the pain of patients. It was found that only 27% (25/91) of study population in both groups received pain assessment as the fifth vital sign using NRS. Other characteristics of pain were not assessed except pain intensity and locations. It is commonly acknowledged that pain assessment is the first step in any strategy of pain management [32]. The recent survey study in pan– European 12–country found that many patients feel that their treating clinicians prioritize the treatment of cancer over the treatment of pain and that this is reflected in the lack of assessment or time devoted to this issue during consultations. Consequently, many patients feel disempowered, that their quality of life is not a consideration for their treating clinician, and that their clinicians do not understand their pain or how to treat it [3]. Unsurprisingly, these problems were also found in our study. Our study clearly shows that a trained pharmacist could perform a comprehensive pain assessment and convey important messages to other health professions.

In addition, it was widely accepted that inadequate knowledge regarding pain management of healthcare professionals led to a negative impact on pain outcomes [1, 8, 23, 62]. As shown in the results, there were various DRPs identified. Pharmacist could provide drug information and recommendations to resolve these problems. For sustainable resolution, however, continuous education system and intensive training in the curriculum of medical/nursing schools are needed to develop knowledge and skills related to pain treatment [4].

Secondly, patients themselves contributed to poor pain control. With regard to low level education and cultural aspects of Thai or Asian people, patience is considered as a moral virtue and they were willing to tolerate pain [4]. Many patients in the study waited for spontaneous decrease of pain intensity before asking for medications. Misconception of pain attitudes (belief that pain related to cancer is inevitable), prioritizing that physicians cure cancer instead of reliving pain, and

reluctance of either patients or caregivers to report their pain to the healthcare professionals hindered adequate treatment. It can also lead physicians or nurses to believe that patients were satisfied with the treatment they received. Some patients denied receiving analgesic drugs because of fear of addiction, tolerance, and ADRs. Patient education has been suggested as a method to overcome these barriers [1, 63]. Pharmacist could help educate patients not only drug therapy issues, but also help convey pain massages from patient to other healthcare professionals. Once pain was accurately reported, the analgesic regimens were altered significantly.

Thirdly, health care system barriers also hamper effective pain treatment. Excessive workload and shortage of staffs may contribute to lack of time to carefully attend to the patients' pain [8, 23]. Moreover, low priority given to cancer pain treatment, lack of drugs in the hospital formulary, and lack of continuity of opioids availability in the hospital were the hindrances of sufficient pain management in this study.

In 2001, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) developed a standard for the assessment and management of pain in accredited hospitals and other healthcare settings. All healthcare institutes must address this standard to provide better pain management even the study hospital. The key concepts of the standard include: [64]

1. Recognize the patient's right to appropriate assessment and management of pain
2. Assess the nature and intensity of pain in all patients
3. Record the results of the assessment in a way that facilitates regular reassessment and follow–up
4. Determine and ensure staff competency in pain assessment and management, and address pain assessment and management in new-staff orientation
5. Establish policies and procedures that support the appropriate prescription or ordering of effective pain medications
6. Educate patients and their families about the importance of effective pain management

7. Address patient needs for symptom management in the discharge planning process
8. Collect data to monitor the appropriateness and effectiveness of pain management.

Overall, the findings from the study together with the international standard of JCAHO suggested numerous areas for institutional improvements and organizational commitment to pain management. The multidisciplinary efforts are needed for this complex and challenging patient care issue [23].

V Limitations of the study

The main strength of our study is the stratified, randomized, controlled design. The differential beneficial effect of pharmacy pain service over usual care can be elucidated in the presence of a control group. However, the study does have several limitations.

The main limitation of the study is non-blind design. Measurement bias is possible, as pain intensity measures were obtained by the research pharmacist, who was not blinded to treatment assignment, and possibly leading to the overestimation of beneficial effect.

In addition, contamination might occur since the physicians who ever had received some recommendations from the pharmacist could remember information related to pain treatment. These physicians might adapt and apply such knowledge in the latter cases.

During the study period, some physicians knew that the study was ongoing. Such awareness may increase their attention to the treatment of pain (Hawthorn’s effect). Moreover, patients in the intervention group might report their pain intensity better than the control group because of knowing that they received the special care from the pharmacist.

Furthermore, inadequate allocation concealment in this study could contribute to selection bias. However, patient allocation was performed based on sequence of admission time, therefore, selection bias should be minimized.

Although the order of interventions varies randomly within each block, a research pharmacist running the study could deduce some of the next treatment

allocations because of the fixed block size. Using larger block sizes and randomly varying the block sizes can ameliorate the problem.

Lastly, individual with cancer who participated in this study might be systematically different from those who were not approached for study participation or those who did not meet study eligibility criteria therefore the results cannot be generalized to all cancer patients with pain**.**

CHAPTER VI
CONCLUSIONS

Pain is one of the most frequent and distressing symptoms experienced by cancer patients with negative impacts on their quality of life [3]. Satisfactory pain relief is thought to be a realistic achievement with conventional analgesic drug therapy for up to 90% of cancer patients experiencing pain [35, 65]. Nevertheless, suboptimal pain management is still a major challenge worldwide including Thailand [3, 4, 65]. Several studies have described the value and positive outcomes of pharmacists' participation in pain management. Such outcomes might range from improved patients' pain relief, decreased drug related problems, decreased cost of care, and increased patients' satisfaction to pain treatment [9-14].

This study was designed to evaluate the effect of pharmacy pain service in cancer patients who were admitted to Chiangrai Prachanukroh hospital. Pharmacist activities in this study included performing a pharmacy pain round, making a comprehensive pain assessment, identifying DRPs, providing appropriate recommendations, patient education, and monitoring outcomes of drug therapy. With a randomized, controlled study, the magnitude of difference of pain management outcomes in terms of mean pain intensity between the patients who received pharmaceutical care services and usual care were elucidated. The results have clearly shown that pain control was significantly better among patients receiving pharmacy pain service compared to usual care. In addition to a significantly lower mean pain intensity score, there were twice more patients in the intervention group who experienced an improvement in their pain status at discharge, compared to the control group. Moreover, ADRs occurrences were not statistical significant difference between the groups of patients even though there were aggressive pain medications in the intervention group. In consistent with previous reports, there were a number of drug-related problems related to pain medications found in the study. Pharmacists under the PPS were able to provide recommendations to solve these DRPs with high

rate of physician's acceptance and led to an improvement in the quality of pain management.

In conclusion, quality of pain management in cancer patients could be improved by optimizing pharmacotherapy and minimizing DRPs by using the PPS model. This may indicate that pharmacists have crucial and ever–growing roles in this area. Therefore, the participation of trained clinical pharmacist to a healthcare team in pain management should be applied nationwide.

Recommendations for further study

Since there are still a variety of means to evaluate the impact of pharmacy pain service, recommendations for future research are as follows:

1. Further studies may study in other settings to increase the external validity, for example, outpatient or multi-center settings.

2. Further studies should evaluate the impact of pharmacy pain service on other clinical, economic, and humanistic outcomes, for example, impact on length of hospital stay, patients' quality of life, patient's satisfaction and healthcare personnel's satisfaction toward the pharmacy pain service.

Recommendations for Chiangrai Prachanukroh Hospital

There is a need to develop effective strategies for translating knowledge into improved clinical practice. Data from our study and others have highlighted potential strategies that could improve pain control in routine practice as follows:

1. Increasing the priority of pain control among health care professionals - which currently focus mainly on curative disease management only.

2. Provide education for physicians and health care professionals to improve their attention and skills in pain assessment. This may help increase their awareness of pain and lead to better pain management.

3. Provide education for physicians to overcome reluctance to appropriately prescribe opioids for patients with cancer pain.

4. Provide education for patients to increase adherence to therapy and help them overcome patient aversion to side effects such as constipation and nausea / vomiting or fears of addiction and tolerance, as well as overcome psychological

barriers e.g. “pain with cancer is inevitable and intractable” or a belief that if they bother physicians or nurse with their pain they are not being good patients.

5. Implementation of simple protocols of oral opioids for pain control. There is a study demonstrating that patients treated according to an oral pain management protocol achieved significantly better reductions in pain compared with those treated with analgesia according to physician discretion [66].

6. In order to provide systematic care for patients with other types of pain, the establishment of pain clinic in the hospital comprising of multidisciplinary health care professionals should be considered.

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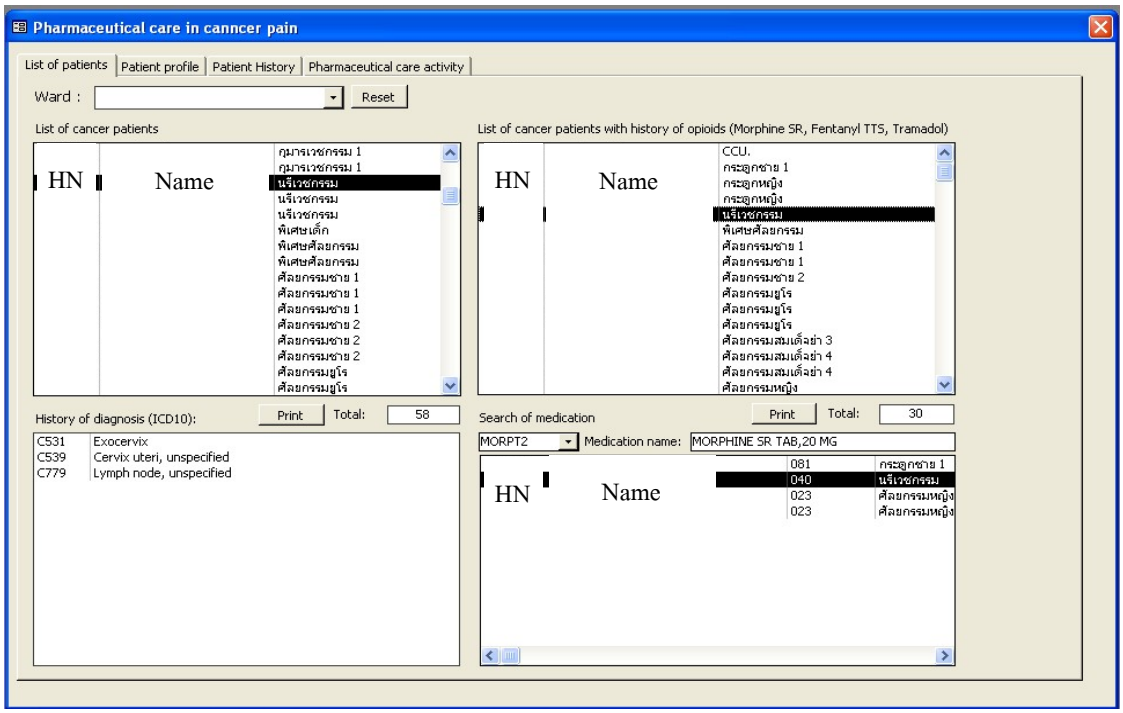
APPENDICES

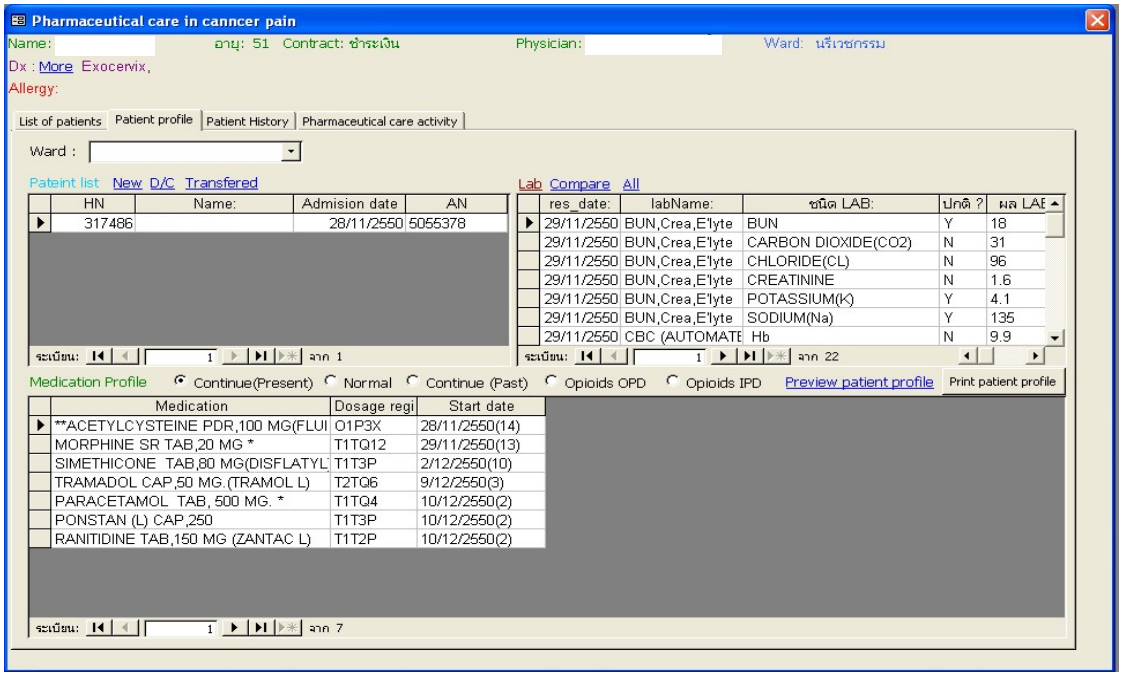
APPENDIX A

On-screen list of patients with history of cancer



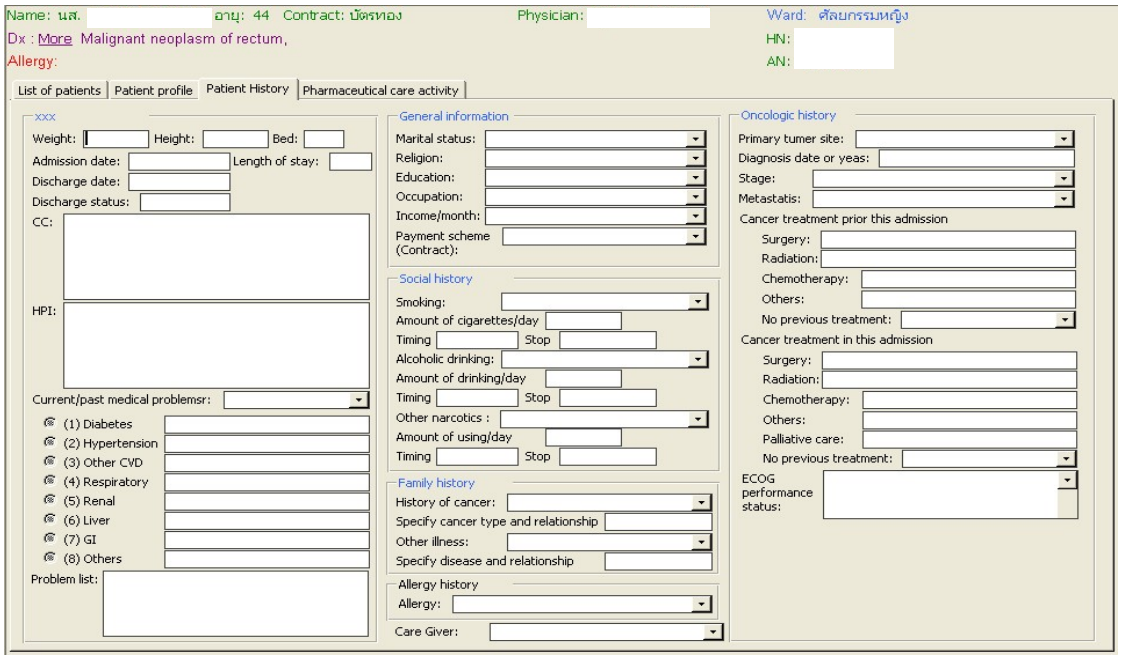
APPENDIX B

On-screen computerized patient profile



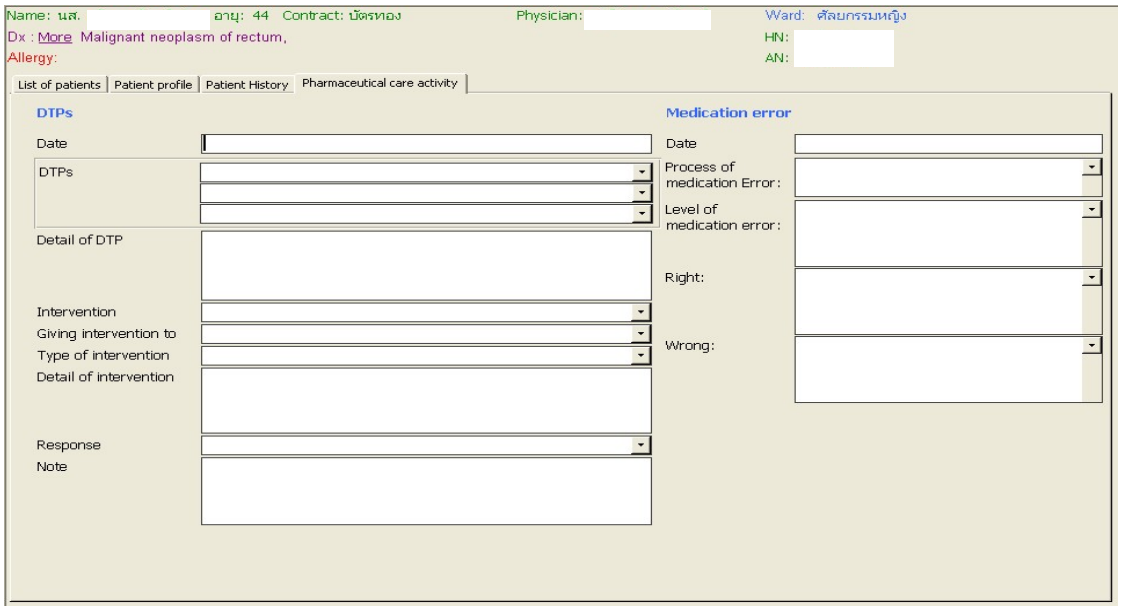
APPENDIX C

Computer screen for recording of additional history of patients



APPENDIX D

Computer screen for recording of drug related problems and medication errors



APPENDIX E

Data collection form for patients' demographics and medical history

Patient's Profile Group I / C

Name…….HN……..AN…….……

Ward……..Bed…….

Gender [1] Male [2] Female Age…….....years Weight……...kg Height…….…..cm

Admission date……..Discharge date…….Length of stay……..

Physician……Discharged status…….

CC:……

HPI:……...

Current/past medical problems: [1] No [2] Yes (please list)

(1) Diabetes……. (2) Hypertension……

(2) Other CVD…… (4) Respiratory……..…….

(5) Renal……. (5) Liver……..……

(6) GI…….. (7) Others……...

Current medications: [1] No [2] Yes (please list drug names and dosage regimen)

1…… 2…….……...…

3……..…….. 4……..…….……..

5……..…….. 6……..…….……..

Physical examination:

……..

Problem list

1…… 2…….……..……

3……..…….. 4……..…..……

5……..…….. 6……..…….……..

General information

Marital status [1] Single [2] Married [3] Divorce [4] Widow

Religion [1] Buddhism [2] Christ [3] Islam [4] Spiritual [5] Others…….

Education [1] None [2] Primary school [3] Secondary school [4] Diploma [5] University

Occupation [1] None [2] Civil servant [3] Business owner [4] Employee [5] Agriculturist [6] Others…….

Income/month (Baht) [1] None [2] < 5,000 [3] 5,000–10,000 [4] > 10,000–20,000 [5] > 20,000

Payment scheme [1] Universal coverage [2] Civil servant medical benefit [3] Social security [4] Out of pocket [5] Others……..

Social history

Smoking [1] No [2] Yes

Amount of cigarettes/day……..Timing……..…….Stop…….

Alcoholic drinking [1] No [2] Yes

Amount of drinking/day……..…..Timing……..…….Stop…….

Other narcotics [1] No [2] Yes (specify type of narcotics)…….

Amount of using……...Timing……...Stop……..

Family history

History of cancer [1] No [2] Yes

Specify cancer type and relationship…….

History of other diseases [1] No [2] Yes

Specify disease and relationship……

Allergy history [1] No [2] Yes (specify details)……

……..

……..

Care givers: [1] No [2] Yes

Name…….Relationship……

Telephone number……

Address……

..

Oncologic history

Primary tumor site [1] Breast [2] Colon/rectum [3] Stomach [4] Liver/pancreas/gallbladder
[5] Lung [6] Head/neck [7] Cervix [8] Lymphoma
[9] Others……

Diagnosed date or year……..

Stage of cancer [1] I [2] II [3] III [4] IV

Metastatis [1] No [2] Yes (specify metastatic site)……..……..

Cancer treatment prior to this admission

[1] Surgery (specify site/extent/time)……

[2] Radiation (specify site/extent/course)…….

[3] Chemotherapy:

3.1 Regimen……..……/……...cycles Time course……..……

3.2 Regimen……..……/……...cycles Time course……..……

[4] Other (specify)……..……..… [5] No previous treatment

Cancer treatment in this admission

[1] Surgery (specify site/extent/time)……

[2] Radiation (specify site/extent/course)…….

[3] Chemotherapy:Regimen……...…… .Cycle…… Start…….

[4] Others……..……

[5] Palliative care [6] No treatment due to remission/other acute medical problems

ECOG performance status: Grade……

0 Fully active, able to carry on all pre-disease performance without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

5 Dead

APPENDIX F

Data collection from for vital signs, laboratory parameters, and medication profiles

Group I / C

Vital Signs: Name…………………….……...……… Ward……………..…..….Bed………..…

Date/ Time	T (°C)	BP (mmHg)	P (BPM)	RR (RPM)	Weight (kg)	Intake (ml)	Output (ml)	Urine (times)	Stool (times)	Progress Note

Group I / C

Laboratory Profile: Name……...……. Ward…….Bed……..…

Biochemistry	**Date**								
FBS mg/dL	**70-110**								
BUN mg/dL	**9-19**								
Scr mg/dL	**0.5-1.5**								
Clcr L/min									
Na mEq/L	**135-150**								
K mEq/L	**3.5-5.0**								
Cl mEq/L	**97-108**								
CO_2 mEq/L	**20-30**								
Ca mg/dL	**8.0-11.5 (corr)**								
P mg/dL	**2.5-5.0**								
Mg mg/dL	**1.6-2.3**								
Uric acid mg/dL	**1.5-7.0**								
TC mg/dL	**150-200**								
TG mg/dL	**0-170**								
HDL mg/dL	**35-95**								
LDL mg/dL	**0-130**								
AST U/L	**16-40**								
ALP U/L	**8-54**								
AP U/L	**36-92**								
LDH U/L	**114-240**								
GGT U/L	**11-51**								
TB mg/dL	**0-1.5**								
DB mg/dL	**0-0.5**								
TP g/dL	**6.6-8.3**								
Albumin g/dL	**3.5-5.0**								
Globulin g/dL	**0-1.5**								

Medication profile (Continue Order)

Group I / C

Name…………………………..…………………………. Ward………..…….Bed…………

Drug	Dosage regimen	Start	Stop	Total (days)	Reason / Indication

Medication profile (One Day Order)

Group I / C

Name…………………………..………………………. Ward……..………Bed……………

Drug	Dosage regimen	Date	Total (doses)	Reason / Indication

APPENDIX G

Data collection form for pain assessment

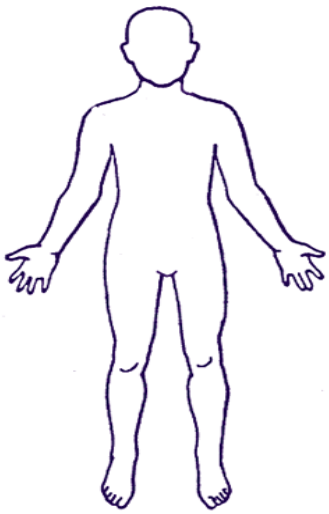
Pain Assessment: Name……. Ward…….Bed……

Pharmacist visit number……..Date……Time……..

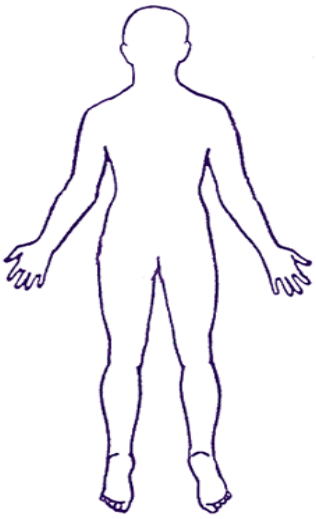
Group I / C

Pain location

Front



Back



Indicate

- Somatic pain in red
- Visceral pain in blue
- Neuropathic pain in green

Remark:

……..

……..……

……..……

Pain type	[ ] Somatic pain	[ ] Visceral pain	[ ] Neuropathic pain
Onset/ Duration of pain			
Pain description			
Pain intensity (specify type of scale)			
Exacerbating factor			
Alleviate factor			
Daily pain pattern*			
Behavioral manifestations of pain			
Impact of pain to daily activities			

* Continuous / Intermittent / Breakthrough / Worse pain in 24 hour

APPENDIX H

Data collection for pain score and pain medication

Group I / C

Pain Score and Medications Profile:

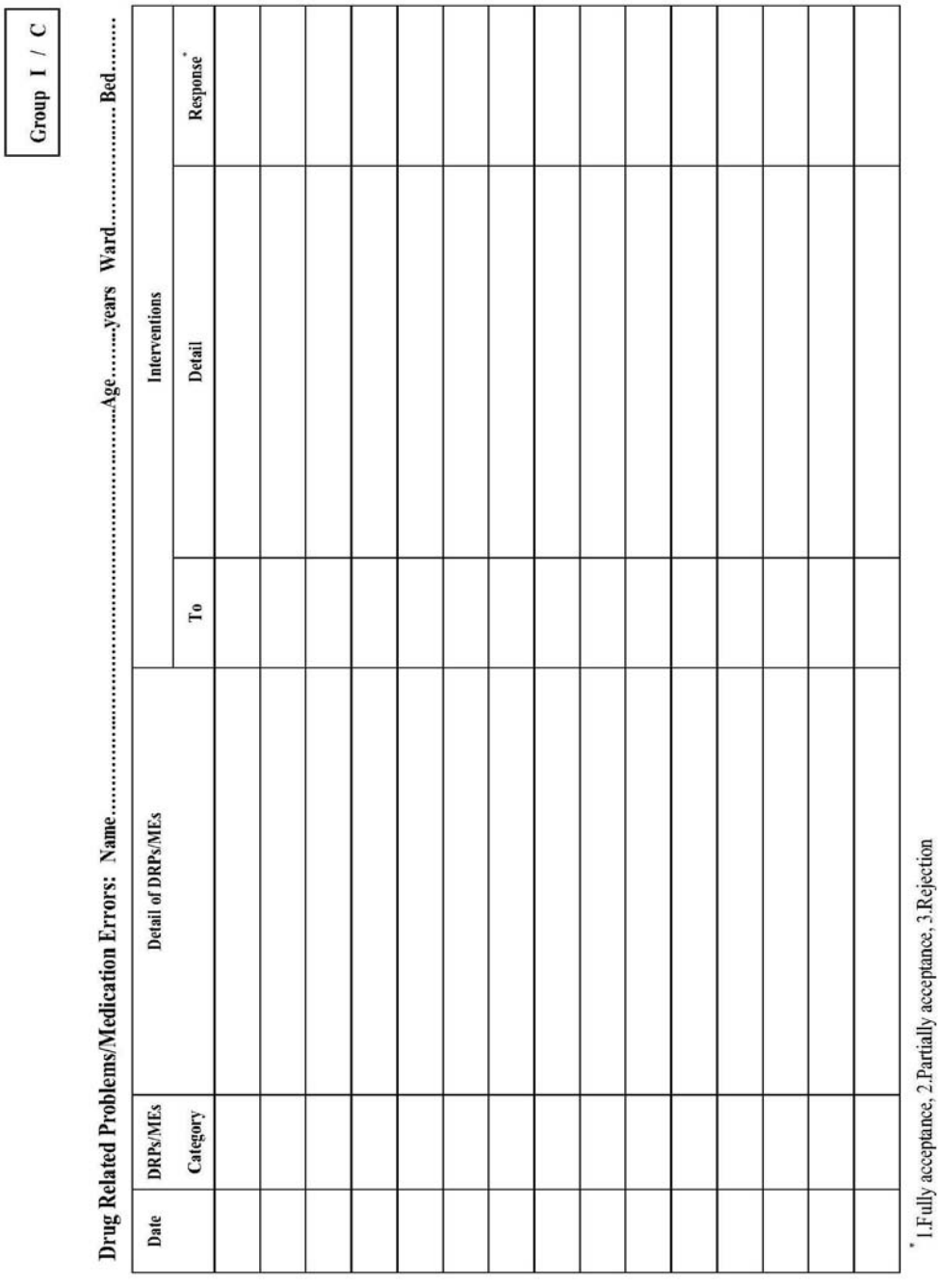
Name……..…..Age……..years Ward……..…Bed…….

Date/Time*				
Score 10	*10*	*10*	*10*	10
9	*9*	*9*	*9*	9
8	*8*	*8*	*8*	8
7	*7*	*7*	*7*	7
6	*6*	*6*	*6*	6
5	*5*	*5*	*5*	5
4	*4*	*4*	*4*	4
3	*3*	*3*	*3*	3
2	*2*	*2*	*2*	2
1	*1*	*1*	*1*	1
0	*0*	*0*	*0*	0
Pain Medication Profile				
Plan and Monitoring				

* Time may be noted above each point of pain score

APPENDIX I

Data collection form for drug related problems (DRPs) and Medication errors (MEs)



Group I / C

Drug Related Problems/Medication Errors: Name.....Age.....years Ward.....Bed.....

Date	DRPs/MEs Category	Detail of DRPs/MEs	Interventions		
			To	Detail	Response*

* 1.Fully acceptance, 2.Partially acceptance, 3.Rejection

APPENDIX J

Guide for identification and categorization of DRPs and MEs

Guide for Identification and Categorization of DRPs and Common Causes		
1. Indication	1.1 Unnecessary drug therapy	1.1.1 There is no valid medical indication for the drug therapy at this time.
		1.1.2 Multiple drug products are being used for a condition that requires single drug therapy.
		1.1.3 The medical condition is more appropriately treated with non-drug therapy.
		1.1.4 Drug therapy is being taken to treat an avoidable adverse reaction associated with another medication.
		1.1.5 Drug abuse, alcohol use, or smoking is causing the problem.
	1.2 Needs for additional drug therapy	1.2.1 A medical condition requires the initiation of drug therapy.
		1.2.2 Preventive drug therapy is required to reduce that risk of developing a new condition.
		1.2.3 A medical condition requires additional pharmacotherapy to attain synergistic or additive effects.
2. Effectiveness	2.1 Ineffective drug	2.1.1 The drug is not the most effective for the medical problem.
		2.1.2 The medical condition is refractory to the drug product.
		2.1.3 The dosage form of the drug product is inappropriate.
		2.1.4 The drug product is not an effective product for the indication being treated.
	2.2 Dosage too low	2.2.1 The dose is too low to produce the desired response.
		2.2.2 The dosage interval is too infrequent to produce the desired response.
		2.2.3 A drug interaction reduces the amount of active drug available.
		2.2.4 The duration of drug therapy is too short to produce the desired response.

Guide for Identification and Categorization of DRPs and Common Causes		
3. Safety	3.1 Adverse drug reaction	3.1.1 The drug product causes an undesirable reaction that is not dose-related.
		3.1.2 A safer drug product is required due to risk factors
		3.1.3 A drug interaction causes an undesirable reaction that is not dose-related.
		3.1.4 The dosage regimen was administered or changed too rapidly
		3.1.5 The drug product causes an allergic reaction.
		3.1.6 The drug product is contraindicated due to risk factors.
	3.2 Dosage too high	3.2.1 Dose is too high.
		3.2.2 The dosing frequency is too short
		3.2.3 The duration of drug therapy is too long.
		3.2.4 A drug interaction occurs resulting in a toxic reaction to the drug product.
		3.2.5 The dose of the drug was administered too rapidly.
4. Compliance	4.1 Non compliance	4.1.1 The patient does not understand the instructions.
		4.1.2 The patient prefers not to take the medication.
		4.1.3 The patient forgets to take the medication.
		4.1.4 The drug product is too expensive for the patient.
		4.1.5 The patient cannot swallow or self-administer the drug product appropriately
		4.1.6 The drug product is not available for the patient.

Guide for Categorization of Medication Error		
No error	A	Circumstances or events that have the capacity to cause error
Error: No harm	B	An error occurred but the error did not reach the patient (An "error of omission" does reach the patient)
	C	An error occurred that reached the patient but did not cause patient harm
	D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm
Error: Harm	E	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention
	F	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization
	G	An error occurred that may have contributed to or resulted in permanent patient harm
	H	An error occurred that required intervention necessary to sustain life
Error: Death	I	An error occurred that may have contributed to or resulted in the patient's death

APPENDIX K

List of analgesic and co-analgesic drugs in Chiangrai Prachanukroh hospital's formulary at the study period

Drug class	Drug	Dosage form / Strength
Strong opioids	Morphine	Injection 10 mg/ml Sustained released capsule (Kapanol®) 20 mg
	Fentanyl	Injection 100 mcg/ 2 ml Transdermal Therapeutic System 25 mcg/hr
	Pethidine	Injection 50 mg/ml
Weak opioids	Tramadol	Capsule 50 mg
	Codeine	Tablet 15 mg
NSAIDs	Diclofenac Sodium	Injection 75 mg/3 ml Tablet 25 mg
	Diclofenac Potassium	Tablet 25 mg
	Mefenamic	Capsule 250 mg Tablet 500 mg
	Aspirin	Tablet 300 mg
	Ibuprofen	Tablet 200, 400 mg Syrup 100 mg/5 ml; 60 ml
	Indomethacin	Capsule 25 mg
	Piroxicam	Capsule 10 mg
	Naproxen	Tablet 250 mg
	Sulindac	Tablet 150 mg
	Nimesulide	Tablet 100 mg
	Ketoprofen	Gel 2.5%; 30 g
Paracetamol	Paracetamol	Injection 300 mg/2 ml Syrup 100 mg/ml;15 ml, 120 mg/5 ml Tablet 325, 500 mg

List of analgesic and co-analgesic drugs in

Chiangrai Prachanukroh hospital's formulary at the study period (cont.)

Drug class	Drug	Dosage form / Strength
Steroids	Dexamethasone	Injection 4 mg/ml Tablet 0.5 mg
	Prednisolone	Tablet 5 mg
Tricyclic antidepressants	Amitriptyline	Tablet 10, 25 mg
	Clomipramine	Tablet 25 mg
	Imipramine	Tablet 25 mg
	Nortriptyline	Tablet 10, 25 mg
Neuroleptics	Olanzapine	Tablet 10 mg
	Pimozide	Tablet 1, 4 mg
Anticonvulsants	Carbamazepine	Tablet 200 mg Controlled released tablet 200 mg
	Valproic acid	Syrup 200 mg/ml; 60 ml Tablet 200 mg
	Phenytoin	Capsule 100 mg
	Topiramate	Tablet 25 mg
Benzodiazepines	Diazepam	Injection 10 mg/2 ml Tablet 2, 5 mg
	Lorazepam	Tablet 0.5, 1 mg
	Clonazepam	Tablet 0.5 mg
Others	Hyoscine	Injection 20 mg/ml Syrup 1 mg/ml; 30 ml Tablet 10 mg
	Orphenadrine citrate	Tablet Orphenadrine 30 mg in combination with Paracetamol 450 mg
	Baclofen	Tablet 10 mg
	Calcitonin	Injection 50 IU/ml Nasal spray 200 IU/dose; 14 doses

BIOGRAPHY

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