



RESEARCH ARTICLE

REVISED Factors influencing non-adherence to opioids in cancer patients: a mixed-methods cross-sectional study [version 2; peer review: 2 approved]

Rattaphol Seangrung ¹, Mallika Ahuja², Koravee Pasutharnchat ¹, Rungwipha Mahawan¹

¹Department of Anesthesiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, 10400, Thailand

²Department of Anesthesiology, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000, Thailand

V2 First published: 16 Dec 2020, 9:1471
<https://doi.org/10.12688/f1000research.27725.1>

Latest published: 15 Mar 2021, 9:1471
<https://doi.org/10.12688/f1000research.27725.2>

Abstract

Background: Strong opioids are mainly utilized to attenuate pain in cancer patients. Adherence to analgesic drugs significantly promotes adequate pain management and improves quality of life. We aimed to identify the factors influencing non-adherence to strong opioids in cancer patients.

Methods: A descriptive, cross-sectional, two-phased, mixed methods design was conducted prospectively to evaluate a cohort of 101 cancer patients who are currently prescribed strong opioids from a pain clinic in Thailand between January and March 2018. Participants were asked to complete a questionnaire that included the following sections: general characteristics; the Medication Taking Behavior in Thai (MTB-Thai) for assessing adherence to medications; and factors influencing nonadherence, which were analyzed using multivariate logistic regression. In addition, face-to-face in depth interviews were conducted with patients showing non-adherence to strong opioids (MTB-Thai score ≤ 21) and analyzed using thematic content analysis.

Results: Of 101 cancer pain patients that completed the questionnaire, 39.6% showed non-adherence to strong opioids. Illness understanding ($P=0.047$) and the use of more than three types of pain medication ($P=0.032$) were significant factors influencing non-adherence. Qualitative analysis indicated that fear of long-term outcomes, opioid side effects, ineffective pain control, attempts to make the regimen more acceptable, poor understanding, and non-acceptance of disease related to non-adherence.

Conclusion: Non-adherence to opioids for cancer patients is a common problem. Awareness of patient factors, medication-related factors, and illness-related factors will provide the knowledge and adequate advice that may enhance adherence to medications.

Open Peer Review

Reviewer Status

| | Invited Reviewers | |
|---|-------------------|-------------|
| | 1 | 2 |
| version 2 (revision) 15 Mar 2021 | | report |
| | | ↑ |
| version 1 16 Dec 2020 | report | ? report |

1. **Sasikaan Nimmaanrat** , Prince of Songkla University, Hat Yai, Thailand
 Prince of Songkla University, Hat Yai, Thailand

2. **Noraida Mohamed Shah** , Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Opioid, medication non-adherence, cancer, pain management

Corresponding author: Rattaphol Seangrung (rattaphol_nu@hotmail.com)

Author roles: **Seangrung R:** Conceptualization, Formal Analysis, Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Ahuja M:** Data Curation, Investigation, Methodology, Resources; **Pasutharnchat K:** Methodology, Validation, Visualization; **Mahawan R:** Data Curation, Software

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2021 Seangrung R *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Seangrung R, Ahuja M, Pasutharnchat K and Mahawan R. **Factors influencing non-adherence to opioids in cancer patients: a mixed-methods cross-sectional study [version 2; peer review: 2 approved]** F1000Research 2021, 9:1471 <https://doi.org/10.12688/f1000research.27725.2>

First published: 16 Dec 2020, 9:1471 <https://doi.org/10.12688/f1000research.27725.1>

REVISED Amendments from Version 1

The 1st version was revised because there were issues with clarity in the questionnaire and references. Furthermore, the latest version has corrected the writing method in study results, making it more transparent.

Any further responses from the reviewers can be found at the end of the article

Introduction

Cancer is the one of four non-communicable diseases that makes up the majority of global deaths¹. In Thailand, an average of 170,000 people were newly diagnosed with cancer in 2018, according to the World Health Organization report². More than one-third of cancer patients experienced moderate or severe pain³. Improper pain management can be caused by a multitude of factors, including the clinicians' attitude, patients' perception, caregiver's perspective, and the availability or accessibility of analgesic drugs⁴⁻⁹. Significantly, poor adherence to the analgesic regimen can contribute to ineffective cancer pain management¹⁰⁻¹². Also, it can lead to a substantial worsening of the disease, death, and increased health care costs^{12,13}.

Strong opioids are the mainstay for treatment of cancer pain. The reported incidence of poor opioid adherence is 50–70% of patients with advanced cancer¹⁴. Previous research on the causes of non-adherence has identified various factors, such as illness, drugs, medical personnel, patient characteristics, and socioeconomic factors¹⁵. Notably, poor compliance is associated with young age, smoking, fear of drug dependence and side effects, the experience of adverse events, misunderstanding of prescriber instructions, poor beliefs and perceptions, poor family support, and non-acceptance of illness^{7,16-20}. However, no study in Thailand has explored the issue of opioid non-adherence in patient-related factors, which is one of the most significant barriers and is a severe problem that obstructs pain management goals. Furthermore, non-adherence to opioids remains a significant health problem, and more high-quality studies are needed to assess these aspects. The study aims to explore the factors influencing opioids non-adherence in cancer patients by using mixed-methods design.

Methods

The present study was a descriptive, cross-sectional, two-phased mixed methods study using both quantitative and qualitative approaches. The study was conducted between January and March 2018

Ethical considerations

This study was approved by the Ethics Committee (Chairman Assistant Professor Dr. Chusak Okascharoen) of Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (09-60-05, 11 January 2018). Participants were informed about the study and provided written informed consent to participate in both the questionnaire and the interviews. All data were confidential.

Participants

The sample size for the study was determined using Taro Yamane sample size formula with 95% confidence level²¹. The calculation formula of Taro Yamane is presented as: $n = N / (1 + N(e)^2)$

where: n = sample size required, N = number of people in the population.

In this study cancer pain patients attending a pain clinic at Ramathibodi Hospital, Bangkok, Thailand were the sample population and numbered 134 in the last three months between January and March 2018; therefore, e = allowable error (%) = 0.05. A minimum of 101 cancer pain patients who used strong opioids (fentanyl, methadone, morphine) by oral and transdermal routes of administration were required to meet the sample size. Participants who had the follow-up appointment schedule were selected using simple random sampling by computer generated random list. They were approached during a routine follow up at pain clinic.

The inclusion criteria were patients aged 18 years or older, diagnosed with cancer pain, strong opioid analgesics for cancer pain prescribed for more than one week for around-the-clock use or as needed, and ability to communicate well in Thai. Exclusion criteria were patients who declined to participate, and who had known or suspected psychotic disease.

Questionnaire

All participants filled out the questionnaire by themselves and participated in the interviews at the hospital. The questionnaire assessed demographic characteristics, pain severity (numerical rating scale in the past week and at the moment) with therapeutic outcomes (pain affect working and social activities, routine daily activities and life), and medication adherence using the Medication Taking Behavior in Thai (MTB-Thai) measure (the total score was between 6 and 24, if score ≤ 21 indicated non-adherence)^{22,23}. Other factors associated with non-adherence to strong opioids, including patient factors (knowledge of strong opioid analgesics and patient beliefs about strong opioid analgesics) were assessed using a copyrighted Thai version of the self-report Belief about Medication Questionnaire [Thai-BMQ])^{24,25}. For the questions about knowledge assessment of strong opioid analgesics were created by pain specialist. Socioeconomic factors (family and social support), medical personnel factors (satisfy and confident of medical service and staffs), medication-related factors (taste, cost, type of medicines, frequency of taking and side effects) and illness-related factors were also assessed. Both MTB-Thai and Thai-BMQ were used in the study with permission of the originators of the questionnaires and completely validated. The full questionnaire used in this study was approved by three pain specialists. Content validity was determined by obtaining the item objective congruence (IOC) value for each questionnaire (including general information and pain severity, which influence non-adherence to opioids, MTB-Thai and Thai-BMQ) ranged from 0.80 to 0.92. All were >0.5 , indicating good content validity. Cronbach's alpha coefficient of the questionnaire ranged from 0.702 to 0.788; a score of >0.7 indicates acceptable internal consistency^{26,27}. The

questionnaire was not modified after the pilot with 10 patients. A copy of the questionnaire can be found in the *Extended data*^{26,27}.

In-depth interviews

Open-ended interview questions were included at the end of the questionnaire for patients who had a MTB-Thai score ≤ 21 , in order to provide further commentary and suggest other factors that may influence non-adherence to strong opioids. The open-ended of the interview included four questions related to the experienced of using strong opioids for pain control and outcomes, patients' concern, and healthcare service system^{26,27}. These questions were asked in a face-to-face qualitative in-depth interviews by the second (MA) and the fourth author (RM) that were conducted until data saturation was reached. The interviews were audio-recorded with the patients' permission, and the interviewers also took field notes.

Statistical analysis

SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) was used for quantitative data analysis. Descriptive statistics, such as frequencies, percentages, means, and standard deviations, were used to analyze demographic data. Chi-square test, relative risk, 95% confidence intervals (CI), and p-values were used to measure the association between factors and strong opioid analgesic non-adherence. Multiple logistic regression was performed to identify risk factors for opioid non-adherence and to calculate adjusted risk ratios. P-values less than 0.05 were considered statistically significant.

Interview data (transcribed verbatim from recordings) and the interviewers' memos were subject to thematic content analysis using ATLAS.ti software version 8.0. Using five stages of data analysis in the framework approach included: 1) familiarization or immersion in the raw data to list key ideas and recurrent themes, 2) identifying a thematic framework (all the key issues, concepts, and themes), 3) indexing or applying the thematic framework or index systematically to all the data in textual form by annotating the transcripts with numerical codes, 4) charting or rearranging the data according to the appropriate part of the thematic framework to which they relate, and forming charts, and 5) mapping and interpretation by using the charts to define concepts, map the range and nature of phenomena.

Results

Quantitative survey

All 101 participants completed the questionnaire (Figure 1). Most participants were women (N = 52, 51.49%), and the average age was 60.14 years. In total, 40 patients (39.6%) reported non-adherence; the others reported moderate to high adherence. The mean duration of pain treatment was three months (range: 1–11 months). Table 1 shows the demographic data.

Statistically significant differences between the adherence and non-adherence groups were found in the general-overuse dimension of the Thai-BMQ (P = 0.047), illness understanding (P = 0.028), and use of more than three types of pain medication (P = 0.035) (Table 2).

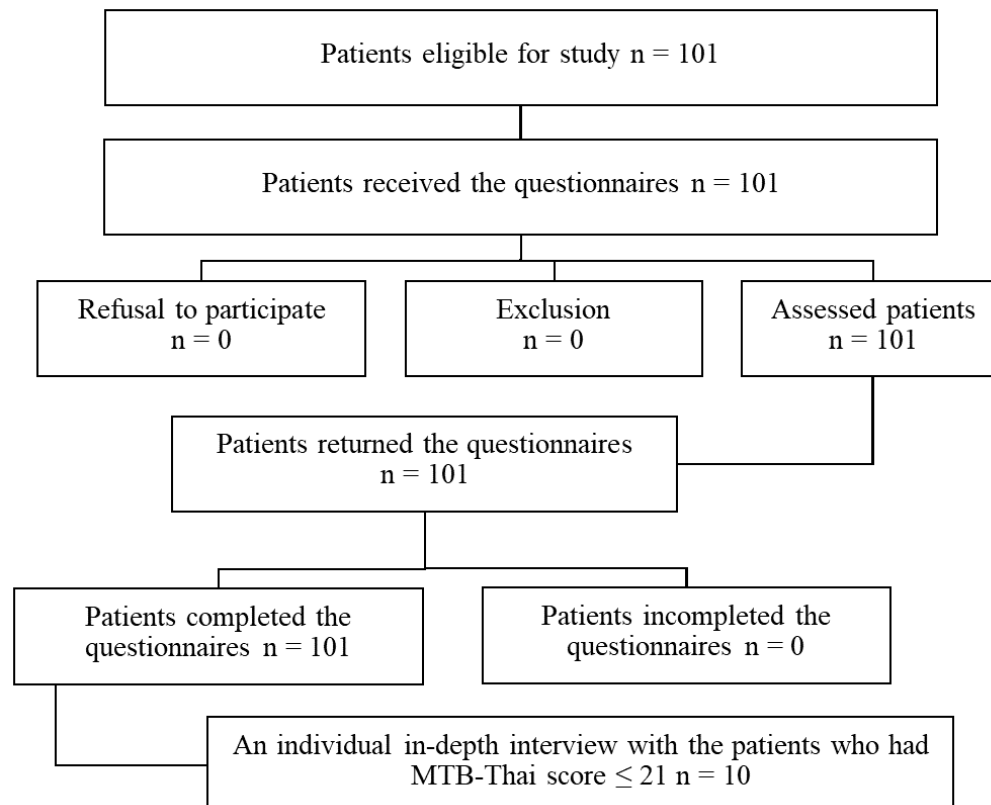


Figure 1. Patient selection flowchart. MTB-Thai score = Medication taking behavior scale in Thai²².

Table 1. Demographic and clinical characteristics of participants (n = 101).

| Characteristics | Data |
|---|-------------------|
| Gender n (%) | |
| Male | 49 (48.51) |
| Female | 52 (51.49) |
| Age (years) Mean \pm SD | 60.14 \pm 12.17 |
| Cancer type n (%) | |
| Head and Neck | 13 (12.87) |
| Breast | 15 (14.85) |
| Lung | 15 (14.85) |
| Gastrointestinal | 28 (27.72) |
| Genitourinary | 13 (12.87) |
| Hematologic | 8 (7.92) |
| Others | 9 (8.91) |
| Metastatic cancer n (%) | |
| Metastasis | 57 (56.44) |
| Without metastasis | 44 (43.56) |
| Duration of Pain (months) Median (IQR) | 12 (5–15) |
| Duration of Pain Treatment (months) Median (IQR) | 3 (1–11) |
| Numbers of analgesics n (%) | |
| >3 | 22 (21.78) |
| \leq 3 | 79 (78.22) |
| Types of analgesics n (%) | |
| Sustained-release opioids | 65 (64.36) |
| Immediate-release opioids | 101 (100) |
| Opioid transdermal patch | 28 (27.72) |
| Anticonvulsants | 69 (68.32) |
| Antidepressants | 47 (46.53) |
| Others | 8 (7.92) |
| Marital Status n (%) | |
| Single | 21 (20.79) |
| Married | 59 (58.42) |
| Divorced/Separated | 8 (7.92) |
| Widowed | 13 (12.87) |
| Education n (%) | |
| None | 6 (5.94) |
| Primary school | 37 (36.63) |

| Characteristics | Data |
|---|------------|
| Junior high school | 8 (7.92) |
| Senior high school/Vocational certificate | 9 (8.91) |
| High vocational certificate | 8 (7.92) |
| Bachelor's degree | 23 (22.77) |
| \geq Master's degree | 10 (9.9) |
| Career n (%) | |
| Unemployed | 40 (39.6) |
| Student | 27 (26.73) |
| Government employee/State enterprises | 3 (2.97) |
| Company employee | 10 (9.9) |
| Business owner | 7 (6.93) |
| Freelance | 6 (5.94) |
| Others | 8 (7.92) |
| Income (Baht/month) n (%) | |
| No income | 38 (37.62) |
| <10,000 | 17 (16.83) |
| 10,001–20,000 | 13 (12.87) |
| 20,001–30,000 | 12 (11.88) |
| 30,001–50,000 | 14 (13.86) |
| 50,001–100,000 | 6 (5.94) |
| >100,000 | 1 (0.99) |
| Health Scheme n (%) | |
| Self-pay | 12 (11.88) |
| Universal coverage scheme | 41 (40.59) |
| Social security scheme | 5 (4.95) |
| Government State Enterprise Office scheme | 38 (37.62) |
| Health insurance | 1 (0.99) |
| Others | 4 (3.96) |
| Smoking n (%) | |
| Never | 54 (53.47) |
| Quit | 42 (41.58) |
| Still smokes | 5 (4.95) |
| Alcohol Drinking n (%) | |
| Never | 52 (51.49) |
| Quit | 47 (46.53) |
| Still drinks | 2 (1.98) |

SD = Standard deviation, IQR = Interquartile range.

Table 2. Factors associated with non-adherence to opioids (MTB-Thai score^a ≤21).

| | Non-adherence | Adherence | P-value |
|-------------------------------------|---------------|---------------|---------|
| Gender n (%) | | | 0.516 |
| Male | 21 (52.5) | 28 (45.9) | |
| Female | 19 (47.5) | 33 (54.1) | |
| Age (years) Mean ± SD | 59.73 ± 11.04 | 60.41 ± 12.94 | 0.184 |
| Cancer type n (%) | | | >0.999 |
| Head and Neck | 5 (12.5) | 8 (13.11) | |
| Breast | 6 (15) | 9 (14.75) | |
| Lung | 6 (15) | 9 (14.75) | |
| Gastrointestinal | 12 (30) | 16 (26.23) | |
| Genitourinary | 5 (12.5) | 8 (13.11) | |
| Hematologic | 3 (7.5) | 5 (8.2) | |
| Others | 3 (7.5) | 6 (9.84) | |
| Metastatic cancer n (%) | | | 0.291 |
| Metastasis | 20 (50) | 37 (60.66) | |
| Without metastasis | 20 (50) | 24 (39.34) | |
| Duration of Pain (months) | | | |
| Median (IQR) | 11.5 (6–13.5) | 12 (5–15) | 0.774 |
| Duration of Pain Treatment (months) | | | |
| Median (IQR) | 2 (1–7.5) | 4 (2–12) | 0.188 |
| Numbers of analgesics n (%) | | | |
| >3 | 13 (32.5) | 9 (14.75) | 0.035* |
| ≤3 | 27 (67.5) | 52 (85.25) | |
| Types of analgesics n (%) | | | |
| Sustained-release opioids | 25 (62.5) | 40 (65.57) | 0.752 |
| Immediate-release opioids | 40 (100) | 61 (100) | - |
| Opioid transdermal patch | 14 (35) | 14 (22.95) | 0.186 |
| Anticonvulsants | 30 (75) | 39 (63.93) | 0.242 |
| Antidepressants | 23 (57.5) | 24 (39.34) | 0.074 |
| Others | 3 (7.5) | 5 (8.2) | >0.999 |
| Marital Status n (%) | | | 0.346 |
| Single | 6 (15) | 15 (24.59) | |
| Married | 25 (62.5) | 34 (55.74) | |
| Divorced/Separated | 5 (12.5) | 3 (4.92) | |
| Widowed | 4 (10) | 9 (14.75) | |
| Education n (%) | | | 0.371 |
| None | 1 (2.5) | 5 (8.2) | |
| Primary school | 12 (30) | 25 (40.98) | |
| Junior high school | 6 (15) | 2 (3.28) | |
| High vocational certificate | 3 (7.5) | 5 (8.2) | |

| | Non-adherence | Adherence | P-value |
|---|----------------------|------------------|----------------|
| Bachelor's degree | 10 (25) | 13 (21.31) | |
| ≥Master's degree | 4 (10) | 6 (9.84) | |
| Career n (%) | | | 0.579 |
| Unemployed | 15 (37.5) | 25 (40.98) | |
| Student | 14 (35) | 13 (21.31) | |
| Government employee/State enterprises | 1 (2.5) | 2 (3.28) | |
| Company employee | 4 (10) | 6 (9.84) | |
| Business owner | 2 (5) | 5 (8.2) | |
| Freelance | 3 (7.5) | 3 (4.92) | |
| Others | 1 (2.5) | 7 (11.48) | |
| Income (Baht/month) n (%) | | | 0.14 |
| No income | 14 (35) | 24 (39.34) | |
| <10,000 | 6 (15%) | 11 (18.03) | |
| 10,001–20,000 | 7 (17.5%) | 6 (9.84) | |
| 20,001–30,000 | 7 (17.5) | 5 (8.2) | |
| 30,001–50,000 | 2 (5) | 12 (19.67) | |
| 50,001–100,000 | 4 (10) | 2 (3.28) | |
| >100,000 | 0 (0) | 1 (1.64) | |
| Health Scheme n (%) | | | 0.847 |
| Self-pay | 6 (15) | 6 (9.84) | |
| Universal coverage scheme | 15 (37.5) | 26 (42.62) | |
| Social Security Scheme | 1 (2.5) | 4 (6.56) | |
| Government of State Enterprise Officer scheme | 16 (40) | 22 (36.07) | |
| Health insurance | 0 (0) | 1 (1.64) | |
| Others | 2 (5) | 2 (3.28) | |
| Smoking n (%) | | | 0.205 |
| Never | 18 (45) | 36 (59.02) | |
| Quit | 21 (52.5) | 21 (34.43) | |
| Still smokes | 1 (2.5) | 4 (6.56) | |
| Alcohol Drinking n (%) | | | 0.712 |
| Never | 18 (45) | 34 (55.74) | |
| Quit | 21 (52.5) | 26 (42.62) | |
| Still drinks | 1 (2.5) | 1 (1.64) | |
| Average pain score last week (0–10) | | | |
| Median (IQR) | 7 (5–9) | 6 (4–8) | 0.058 |
| Mean ± SD | 6.75 ± 2.46 | 5.57 ± 2.76 | |

| | Non-adherence | Adherence | P-value |
|---|----------------------|------------------|----------------|
| Average pain score now (0–10) | | | |
| Median (IQR) | 5 (3.5–7) | 5 (3–6) | 0.196 |
| Mean \pm SD | 5.38 \pm 2.68 | 4.62 \pm 2.75 | |
| Effect on work and social life n (%) | 36 (90) | 50 (81.97) | 0.267 |
| Effect on daily routine n (%) | 35 (87.5) | 51 (83.61) | 0.59 |
| Overall effect of pain on life n (%) | | | 0.444 |
| Not at all | 0 (0) | 4 (6.56) | |
| Little impact | 3 (7.5) | 5 (8.2) | |
| Moderate impact | 9 (22.5) | 15 (24.59) | |
| Large impact | 16 (40) | 17 (27.87) | |
| Extremely large impact | 12 (30) | 20 (32.79) | |
| Patient Factors | | | |
| Knowledge Score (0–10) | | | |
| Median (IQR) | 9 (8–9) | 8 (7–9) | 0.788 |
| Mean \pm SD | 8.13 \pm 1.56 | 8.16 \pm 1.4 | |
| Belief about Medication (Thai-BMQ ^b) | | | |
| Specific-Necessity (5–25) | | | |
| Median (IQR) | 20 (17.5–23) | 20 (19–22) | 0.514 |
| Mean \pm SD | 19.85 \pm 3.66 | 20.31 \pm 2.57 | |
| Specific-Concern (5–25) <i>reversed^c</i> | | | |
| Median (IQR) | 14 (11–17.5) | 16 (12–19) | 0.17 |
| Mean \pm SD | 14.38 \pm 4.61 | 15.67 \pm 4.62 | |
| General-Overuse (4–20) <i>reversed^c</i> | | | |
| Median (IQR) | 11 (10–12) | 12 (11–13) | 0.047* |
| Mean \pm SD | 11.05 \pm 2.63 | 11.97 \pm 2.43 | |
| General-Harm (4–20) <i>reversed^c</i> | | | |
| Median (IQR) | 12 (10.5–15.5) | 13 (12–14) | 0.806 |
| Mean \pm SD | 12.33 \pm 3.28 | 12.54 \pm 2.27 | |
| Family and social support | | | 0.898 |
| Caregiver n (%) | | | |
| Self-care | 19 (47.5) | 29 (47.54) | |
| Relatives | 18 (45) | 29 (47.54) | |
| Non-relatives | 3 (7.5) | 3 (4.92) | |
| Help provided if needed n (%) | | | 0.382 |
| No | 3 (7.5) | 2 (3.28) | |
| Yes | 37 (92.5) | 59 (96.72) | |

| | Non-adherence | Adherence | P-value |
|---|---------------|-------------|--------------------|
| Satisfaction with pain clinic n (%) | | | 0.789 |
| Satisfied | 6 (15) | 8 (13.11) | |
| Very satisfied | 34 (85) | 53 (86.89) | |
| Confidence in pain clinic n (%) | | | >0.999 |
| Not sure | 0 (0) | 1 (1.64) | |
| Confident | 40 (100) | 60 (98.36) | |
| Medication-related factors n (%) | | | |
| Drugs taste bad | 6 (15) | 16 (26.23) | 0.181 |
| Drugs too expensive | 7 (17.5) | 17 (27.87) | 0.231 |
| Too many types of drugs | 6 (15) | 11 (18.03) | 0.690 |
| Need to take drugs too often | 5 (12.5) | 7 (11.48) | >0.999 |
| Too many side effects | 11 (27.5) | 9 (14.75s) | 0.207 |
| Illness understanding and acceptance | | | |
| Median (IQR) | 4 (3–4) | 4 (4–4) | 0.028 ^a |
| Mean ± SD | 3.48 ± 0.75 | 3.72 ± 0.64 | |

SD = Standard deviation, IQR = Interquartile range.

^aMTB-Thai score = Medication taking behavior scale in Thai²².

^bThai-BMQ = Belief about Medication Questionnaire, Thai version²⁴.

^cReversed scale.

*P < 0.05 (statistically significant).

The multivariate analysis showed that two variables had significant associations with opioid non-adherence: illness understanding (P = 0.047) and use of more than three types of pain medication (P = 0.032). The illness understanding and acceptance part of the questionnaire contained five statements. Most participants agreed with either “I understand my illness, and I think I received the best treatment” or “I understand my illness, but I think I could have received better treatment.” Patients who chose the former response were less likely to show non-adherence than those who chose the latter answer (RR = 0.53, 95% CI [0.283–0.993]). Participants prescribed more than three types of analgesics had a 3.04 times higher risk of medication non-adherence than participants prescribed three or fewer types of medication (RR = 3.04, 95% CI [1.099–8.411]) (Table 3).

Qualitative results

Saturated data, in total 10 individual in-depth interviews with patients who had MTB-Thai score ≤21 were conducted, which lasted around 30 to 45 minutes. Five themes related to opioid non-adherence emerged from the data: fear of long-term outcomes, desirable or undesirable opioid side effects, ineffective pain control, attempts to make the regimen more acceptable, and poor understanding and non-acceptance of

the disease. Analytic results of the contextual factors associated with non-adherence to opioids in cancer patients are presented in Table 4.

Patient factors

Theme 1: Fear of long-term opioid adverse events

Almost half of the patients were concerned about opioid addiction. Some chose to be in pain to minimize the chance of addiction. As two patients remarked:

“I could get addicted to the medication, so I don’t want to take morphine syrup more than once a day.”

“I feel uncomfortable taking morphine in front of people. They look at me like I am addicted to drugs.”

Many patients were afraid of liver or kidney damage after long-term opioid use and combined with other pain medications, despite their physicians confirming the safety of their opioid dosage. As some patients mentioned:

“Morphine could reduce my pain but if I take as much as I need, I will suffer from liver or kidney disease in the future.”

Table 3. Univariate and multivariate logistic regression results.

| | Non-adherence (n = 40) | Adherence (n = 61) | RR (95% CI) | P-value [#] | Adjusted RR (95% CI) | P-value |
|---|---------------------------|-----------------------|------------------------|----------------------|-------------------------|---------|
| General-Overuse, <i>reversed</i> ^a Median (IQR) | 11 (10-12) | 12 (11-13) | 0.86 (0.725-1.019) | 0.082 | 0.872 (0.729-1.044) | 0.136 |
| Illness understanding and acceptance Median (IQR) | 4 (3-4) | 4 (4-4) | 0.597 (0.332-1.075) | 0.086 | 0.53 (0.283-0.993) | 0.047* |
| Number of drugs >3 n (%) | 13 (32.5%) | 9 (14.75%) | 2.782 (1.056-7.329) | 0.038* | 3.04 (1.099-8.411) | 0.032* |

IQR = Interquartile range, CI = Confidence interval, RR = Risk ratio.

*P < 0.05 (statistically significant).

[#]Results from binary logistic regression analysis (unlike the output from chi-square test in Table 2)

^aReversed scale.

Table 4. Contextual factors associated with non-adherence to opioids in cancer patients.

| Contextual factors | Participants mention (N=10): n (%) |
|---|---------------------------------------|
| <i>Patient factors: fear of long-term opioid adverse events</i> | |
| concern about opioid addiction | 4 (40) |
| concern about opioid and other medication induced organ failure | 8 (80) |
| <i>Medication-related factors: desirable or undesirable opioid side effects</i> | |
| concern about opioid-induced constipation | 6 (60) |
| concern about opioid-induced nausea | 3 (30) |
| concern about opioid-induced sedation | 4 (40) |
| <i>Medication-related factors: ineffective pain control</i> | |
| opioids are unable to control the pain sufficiently | 4 (40) |
| <i>Medication-related factors: attempts to make the regimen more acceptable</i> | |
| applied opioids regimen to suit their lifestyle | 3 (30) |
| <i>Illness-related factors: poor understanding and non-acceptance of the disease</i> | |
| discontinue opioids after better pain relief | 7 (70) |

“I took lots of medication. I think my liver has had to work too hard, so I wait until I had severe pain, I will take morphine.”

“These drugs can relief the pain, but I wondered if just one or two drugs could control everything. I think that taking four types of drugs every day will damage my health.”

Medication-related factors

Theme 1: Desirable or undesirable opioid side effects

Many patients reported opioid side effects. Some found that the side effects were unbearable and affected their quality of life. Commonly reported severe constipation, upset stomach, and drowsiness. As some patients said:

“I am in pain but I chose to use as low a dose of morphine as I could because it made me constipated.”

“Severe nausea made me afraid to use morphine. Throwing up was much worse than living with this pain.”

“I always had to take a nap after taking morphine. So I could only take it before bedtime otherwise I might sleep all day.”

Notably, some participants found specific side effects beneficial, whereas others found them problematic. As one patient said:

“The rescue drug makes me sleep well at night. I take it every night even if the pain does not bother me much.”

Theme 2: Ineffective pain control

Some patients do not adhere to medical regimens because they find pain medication ineffective. Some participants reported not taking opioids because they did not have the intended effect. As one patient remarked:

“I suffered from pain, but the drug did not make me feel as good as I expected. So there was no reason for taking it.”

Some patients increased their basal opioid doses because their pain had worsened and dared not to call to consult the doctor about ineffective pain control. As one patient remarked:

“I did not know what to do with my pain anymore. I felt so hopeless. I took morphine syrup every hour. The effect was too short-lived, so I tried to take more morphine tablets than the doctor had prescribed, but I ended up feeling sleepier all day.”

Theme 3: Attempts to make the regimen more acceptable

Some patients applied their medication regimen to suit their lifestyle and drug reactions. Some reduced the medication frequency, as they felt uncomfortable taking medicine at mid-day. Others changed the regimen from around the clock to after meals, because it was easier to remember. Some took all their drugs at bedtime rather than in the morning because of the sedative effect. As some patients said:

“I go to work every day. It’s not easy to bring the drugs with me, so I changed the schedule from a three times daily regimen to a two times daily regimen. I think this work for me.”

“I take the morphine after meals. It is easier to remember. I used to forget to take the pills at 2 pm, which made the pain worse in the evening.”

“I felt sleepy after I took the pills, so I took it all at night before bedtime. This meant that the pain wasn’t well controlled, but that’s better than feeling drowsy all day.”

Illness-related factors

Theme 1: Poor understanding and non-acceptance of the disease

If doctors can improve patients’ understanding and acceptance of illness, then more collaborative treatment decisions can be

made. If patients insist on seeking complete pain relief or a complete cure and are reluctant to adopt modified life goals and activities, it is difficult to set realistic treatment goals. Acceptance-based pain management may be helpful for cancer patients. Many patients reduced or discontinued opioids by themselves when their pain was decreasing. As two patients said:

“I took the pills everyday as advised and they controlled the pain well. I wondered if I could stop taking these drugs, so I tried to stop and the pain came back. Are these drugs helping me with the disease? Or I should try something else?”

“After taking the drug, I feel better, I stopped taking it on some day. I think the disease is getting better.”

Discussion

The main purpose of this mixed-methods study design was to explore the factors influencing non-adherence to strong opioids in cancer pain patients. Most research has studied the clinical factors associated with adherence to opioids for cancer pain and has not focused the medical non-adherence factor alone. Investigation of non-adherence to opioids in cancer patients is a pro-active useful model for correcting beliefs, attitudes and behavior. This study asked participants about characteristics related to themselves, family and social support, doctor-patient relationships, medication-related factors, and illness-related factors. The incidence of non-adherence of our study was 39.6%, similar to previous study²⁸. Our data indicate that only three out of these five factors were significantly associated with non-adherence: patient factors, medication-related factors, and illness-related factors.

Patient factors

In the quantitative data, patients’ knowledge of strong opioid analgesics and their beliefs about medication were not significantly related to non-adherence. However, the interviews revealed a concern about adverse effects, side effects, opioid addiction and multiple organ failure from long-term usage, as reported in previous work^{29–33}. This was even though most of the patients from this study had a higher education and good knowledge of strong opioids. They may also be concerns about the adverse effects of opioids. Similarly another study found that some patients who were educated about the side effects of medication showed increased concerns about the risk of addiction^{34,35}.

Generally, cancer patients require long-term use of strong opioids. Physicians should educate patients during treatment about the prevention of adverse effects. Although patient education is a key component of adherence, more education may make patients anxious and fearful about opioid adverse effects. Patient beliefs and attitudes regarding the effectiveness of the treatment, and lack of motivation, also affects medication adherence³⁶. Healthcare providers should reassure patients by emphasizing the benefits rather than the risks of opioids, and should identify patients’ concerns. Additionally, involvement of

patients in the treatment decision-making process may help to reduce fear and facilitate adherence^{12,37}.

Family and social support

A previous study³⁸ found an association between medical adherence and family and social support: adherence was 1.74 times higher in patients from cohesive families and 1.53 times lower in patients from families in conflict. The present findings did not show a correlation between adherence and family support. More than 90% of patients in both the adherence and non-adherence groups confirmed that they received the best care from their families when needed. This may be because Thai people live in large families and therefore find it relatively easy to obtain assistance when needed.

Doctor-patient relationships

Almost all patients expressed high satisfaction and confidence in the pain clinic services and staff. Therefore, the doctor-patient relationship was not significantly associated with non-adherence. One previous study³⁹ found a correlation; patients who believed that doctors treat patients as equals, who felt that doctors discuss treatments with patients before making decisions, and who could choose their doctor were more likely to adhere to recommendations.

Medication-related factors

Both the quantitative and qualitative data revealed many medication-related reasons for non-adherence, which reflected previous study findings^{17,40,41}. Our quantitative analysis showed that use of more than three types of drugs was associated with a 3 times higher risk of non-adherence than use of less than three types. Furthermore, the qualitative analysis identified three themes related to medication-related non-adherence factors. Similar to a previous study^{15,40}, we found that some patients reduced their opioid dose to avoid unbearable side effects, such as constipation, nausea, vomiting, dyspepsia, or drowsiness. Despite having poor pain control, they could not take the opioid dose prescribed because of the side effects. Most said that their pain was much more bearable than the side effects. Some did not inform their doctor about their pain owing to limited time, being considerate or shame. Moreover, some patients used opioids for the wrong reasons; for example, taking opioids at night to help them sleep even when they had no pain.

In accordance with previous findings^{40,41}, we found that ineffective pain control was a key reason why some patients refused to take prescribed medication. Some patients increased the prescribed opioid dose for maximal pain relief. Some obtained opioids from many different hospitals to control the pain without discussing this with their doctor. Patients reported many reasons for non-adherence. Some felt that their doctor had insufficient time to listen to their problems. Others were afraid that the doctor would abandon them because they did not use the drugs as prescribed.

One of the medication-related factors we identified was the attempt to make the drug regimen more acceptable; this has also

been reported in previous work⁴⁰. Patients changed the drug schedule to suit their lifestyle. Some patients reduced the dose frequency as they were not comfortable taking drugs at certain times of the day. Some changed the interval from around the clock to after meals, as it was easier to remember. Some patients took all their medications at bedtime rather than in the morning because of the sedative effects.

Illness-related factors

Previous studies of patients with chronic nonmalignant pain indicate that illness acceptance predicts increased psychological, social, and physical functioning^{42,43} and that acceptance-based pain management may be helpful for cancer patients⁴⁴. The present quantitative and qualitative data show that patients with poor illness understanding and non-acceptance of the disease show medication non-adherence. In our study, patients misunderstood their situation and believed that they could be fully cured and become pain free. Some patients believed that there were better treatment options than the treatment they had received. The results suggest that enhancing the acceptance of pain and cancer may be a clinically relevant management goal.

Although many factors were not statistically significant in the quantitative study, such as the patient's belief about opioid side effects or adverse effects; however, more than three types of pain medication may be the critical factor of non-adherence that might raise their concern about long term adverse effects as opioid addiction or multiple organs failure. Also, taking multiple drugs may be a factor that causes patients to adjust their medication as appropriate, which causes inadequate pain relief. From the in-depth interviews, it was clear that concerns about medication side effects, fear of adverse events and poor pain control were barriers for opioid use in cancer pain management.

Recommendations

Mainly, the various opioids are very different in bioavailability, metabolism, and response between individual patients. Appropriate opioid use must be selected for each cancer patient, and the dose must be individually titrated. Effective and safe titration of opioids has a significant impact on patient comfort. Obviously, several complex factors affect opioids non-adherence in cancer patients. Therefore, we recommend the following strategies to improve adherence to strong opioid medication for cancer pain.

1. Understanding patients' reasons for non-adherence to opioids could help doctors to identify how these patients may present clinically, address patients' concerns about opioids, and encourage doctors to offer patients alternatives to opioid treatment.
2. Reviewing the number of medications because of drug interactions can be managed by reviewing the patient's medication profile for duplicate or unnecessary medications.
3. Good patient-doctor communication may reduce anxiety, and also improves pain control⁴⁵. For example,

discussing a patient's concerns about the risk of addiction may help the patient and doctor to set up plans to monitor misuse or identify less risky or more acceptable alternative pain management strategies.

Limitations

We only measured non-adherence to strong opioid analgesic medicine. The patients might have been taking other medicines for pain control prescribed simultaneously. As these medicines could have affected pain control, they might have confounded the present results.

Conclusion

Almost half of cancer pain patients prescribed opioids showed non-adherence to the medical regimen. Three factors were significantly associated with medication non-adherence: patient factors (fear of long-term outcomes), medication-related factors (use of more than three types of drugs, side effects, ineffective pain control, attempts to make the regimen more acceptable), and illness-related factors (poor illness understanding and non-acceptance of the disease).

Data availability

Underlying data

The recordings and transcription of interviews are not openly available in order to conserve the confidential information of participants. All document files were eradicated immediately following data analysis. Themes and quotes from the data analysis are available in Thai. This data can be obtained by application to the Ethical Committee of Faculty of Medicine Ramathibodi Hospital. To apply, please contact the corresponding author at rattaphol_nu@hotmail.com, who will facilitate this process.

Figshare: Data of factors influencing non-adherence to opioids in cancer patients.xls., <https://doi.org/10.6084/m9.figshare.13336691.v2>⁴⁶.

Extended data

Figshare: Questionnaire and open ended questions in English.doc., <https://doi.org/10.6084/m9.figshare.13336754.v1>²⁶.

Figshare: Thai version of the questionnaire and open ended questions.docx., <https://doi.org/10.6084/m9.figshare.13336766.v2>²⁷.

Reporting guidelines

Figshare: STROBE checklist for 'Factors influencing non-adherence to opioids in cancer patients: a mixed-methods cross-sectional study', <https://doi.org/10.6084/m9.figshare.13336778.v1>⁴⁷.

Figshare: COREQ checklist for 'Factors influencing non-adherence to opioids in cancer patients: a mixed-methods cross-sectional study', <https://doi.org/10.6084/m9.figshare.13336793.v1>⁴⁸.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license \(CC-BY 4.0\)](https://creativecommons.org/licenses/by/4.0/).

Acknowledgments

The authors would like to thank the participants in the study and particularly thank Rojnarin Komonhirun who provided assistance and coordination support. The authors also thank Diane Williams, PhD, from Edanz Group (www.edanzediting.com/ac) for editing the English text of a draft of this manuscript.

References

- World Health Organization: **Global Health Observatory**. Geneva: World Health Organization. 2018; Accessed June 21, 2018. [Reference Source](#)
- Bray F, Ferlay J, Soerjomataram I, et al.: **Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries**. *CA Cancer J Clin*. 2018; **68**(6): 394–424. [PubMed Abstract](#) | [Publisher Full Text](#)
- van den Beuken-van Everdingen MHJ, de Rijke JM, Kessels AG, et al.: **Prevalence of pain in patients with cancer: a systematic review of the past 40 years**. *Ann Oncol*. 2007; **18**(9): 1437–49. [PubMed Abstract](#) | [Publisher Full Text](#)
- Jamison RN, Sheehan KA, Scanlan E, et al.: **Beliefs and attitudes about opioid prescribing and chronic pain management: survey of primary care providers**. *J Opioid Manag*. 2014; **10**(6): 375–82. [PubMed Abstract](#) | [Publisher Full Text](#)
- Potter VT, Wiseman CE, Dunn SM, et al.: **Patient barriers to optimal cancer pain control**. *Psychooncology*. 2003; **12**(2): 153–60. [PubMed Abstract](#) | [Publisher Full Text](#)
- Liang SY, Yates P, Edwards H, et al.: **Factors influencing opioid-taking self-efficacy and analgesic adherence in Taiwanese outpatients with cancer**. *Psychooncology*. 2008; **17**(11): 1100–07. [PubMed Abstract](#) | [Publisher Full Text](#)
- Gunnarsdottir S, Donovan HS, Serlin RC, et al.: **Patient-related barriers to pain management: the Barriers Questionnaire II (BQ-II)**. *Pain*. 2002; **99**(3): 385–96. [PubMed Abstract](#) | [Publisher Full Text](#)
- Lee BO, Liu Y, Wang YH, et al.: **Mediating Effect of Family Caregivers' Hesitancy to Use Analgesics on Homecare Cancer Patients' Analgesic Adherence**. *J Pain Symptom Manag*. 2015; **50**(6): 814–21. [PubMed Abstract](#) | [Publisher Full Text](#)
- Reid CM, Gooberman-Hill R, Hanks GW: **Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer**. *Ann Oncol*. 2008; **19**(1): 44–8. [PubMed Abstract](#) | [Publisher Full Text](#)
- Miaskowski C, Dodd MJ, West C, et al.: **Lack of adherence with the analgesic regimen: a significant barrier to effective cancer pain management**. *J Clin Oncol*. 2001; **19**(23): 4275–79. [PubMed Abstract](#) | [Publisher Full Text](#)
- Valeberg BT, Miaskowski C, Hanestad BR, et al.: **Prevalence rates for and predictors of self-reported adherence of oncology outpatients with analgesic medications**. *Clin J Pain*. 2008; **24**(7): 627–36. [PubMed Abstract](#) | [Publisher Full Text](#)
- Osterberg L, Blaschke T: **Adherence to medication**. *N Engl J Med*. 2005; **353**(5): 487–97. [PubMed Abstract](#) | [Publisher Full Text](#)
- Cutler RL, FernandezLlimos F, Frommer M, et al.: **Economic impact of medication non-adherence by disease groups: a systematic review**. *BMJ Open*. 2018; **8**(1): e016982. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Abbas SQ, Abbas Z: **Is opiate compliance a problem in cancer pain? A survey of health-care professionals' views**. *Int J Palliat Nurs*. 2003; **9**(2): 56–63. [PubMed Abstract](#) | [Publisher Full Text](#)
- Pound P, Britten N, Morgan M, et al.: **Resisting medicines: a synthesis of qualitative studies of medicine taking**. *Soc Sci Med*. 2005; **61**(1): 133–55. [PubMed Abstract](#) | [Publisher Full Text](#)

16. Jin J, Sklar GE, Min Sen Oh V, et al.: **Factors affecting therapeutic compliance: A review from the patient's perspective.** *Ther Clin Risk Manag.* 2008; **4**(1): 269–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. Ingersoll KS, Cohen J: **The impact of medication regimen factors on adherence to chronic treatment: a review of literature.** *J Behav Med.* 2008; **31**(3): 213–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. Alhewiti A: **Adherence to Long-Term Therapies and Beliefs about Medications.** *Int J Family Med.* 2014; **2014**: 479596.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
19. Kleinsinger F: **The Unmet Challenge of Medication Nonadherence.** *Perm J.* 2018; **22**: 18–033.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Nguyen LMT, Rhondali W, De la Cruz M, et al.: **Frequency and predictors of patient deviation from prescribed opioids and barriers to opioid pain management in patients with advanced cancer.** *J Pain Symptom Manage.* 2013; **45**(3): 506–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Yamane T: **Statistics, An Introductory Analysis.** Harper and Row, New York, NY, USA, 2nd edition, 1967.
[Reference Source](#)
22. Sakthong P, Sonsa-Ardjit N, Sukarnjanaset P, et al.: **Development and psychometric testing of the medication taking behavior tool in Thai patients.** *Int J Clin Pharm.* 2016; **38**(2): 438–45.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Sooksai N, Rittirod T, Pachanasoontorn N, et al.: **The Guardian's Beliefs on Psychotropic Medications Adherence of Autistic Pediatric Patients.** *Srinagarind Med J.* 2019; **34**(6): 595–601.
[Reference Source](#)
24. Leangsomnana Y, Leangsomnana S, Promproh S, et al.: **Confirmatory factor analysis of beliefs about medicine questionnaire in Thai version.** *J Prapokklao Hosp Clin Med Educat Center.* 2014; **31**: 297–310.
25. Sriwarakorn S, Krittiyanunt S, Sakulbumrungsil R: **Sensitivity and Specificity of Thai-Version Brief Medication Questionnaire.** *J Health Res.* 2018; **24**(3): 129–34.
[Reference Source](#)
26. Seangrung R: **Questionnaire and open ended questions in English.doc.** *figshare.* Dataset.
<http://www.doi.org/10.6084/m9.figshare.13336754.v1>
27. Seangrung R: **Thai version of the questionnaire and open ended questions.docx.** *figshare.* Dataset. 2020.
<http://www.doi.org/10.6084/m9.figshare.13336766.v2>
28. Chou WC, Chen JS, Hung CY, et al.: **A nationwide survey of adherence to analgesic drugs among cancer patients in Taiwan: prevalence, determinants, and impact on quality of life.** *Support Care Cancer.* 2019; **27**(8): 2857–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Tzeng JL, Chang CC, Chang HJ: **Assessing analgesic regimen adherence with the Morisky Medication Adherence Measure for Taiwanese patients with cancer pain.** *J Pain Symptom Manage.* 2008; **36**(2): 157–66.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Berry PE, Ward SE: **Barriers to pain management in hospice: a study of family caregivers.** *Hosp J.* 1995; **10**(4): 19–33.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Cherny NI, Portenoy RK: **The management of cancer pain.** *CA Cancer J Clin.* 1994; **44**(5): 262–303.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Ho RC: **Pain in the cancer patient.** *CA Cancer J Clin.* 1994; **44**(5): 259–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Ward SE, Hernandez L: **Patient-related barriers to management of cancer pain in Puerto Rico.** *Pain.* 1994; **58**(2): 233–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Davis MP, Walsh D: **Epidemiology of cancer pain and factors influencing poor pain control.** *Am J Hosp Palliat Med.* 2004; **21**(2): 137–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Sun VC, Borneman T, Ferrell B, et al.: **Overcoming barriers to cancer pain management: an institutional change model.** *J Pain Symptom Manage.* 2007; **34**(4): 359–69.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
36. Horne R, Chapman SC, Parham R, et al.: **Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework.** *PLoS One.* 2013; **8**(12): e80663.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
37. Haynes RB, McDonald HP, Garg AX: **Helping patients follow prescribed treatment: clinical applications.** *JAMA.* 2002; **288**(22): 2880–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. DiMatteo MR: **Social support and patient adherence to medical treatment: a meta-analysis.** *Health Psychol.* 2004; **23**(2): 207–18.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Stavropoulou C: **Non-adherence to medication and doctor-patient relationship: Evidence from a European survey.** *Patient Educ Couns.* 2011; **83**(1): 7–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Lewis ET, Combs A, Trafton JA: **Reasons for under-use of prescribed opioid medications by patients in pain.** *Pain Med.* 2010; **11**(6): 861–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Crosby FE, Colestro J, Ventura MR, et al.: **Survey of pain among veterans in Western New York.** *Pain Manag Nurs.* 2006; **7**(1): 12–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. McCracken LM, Eccleston C: **A prospective study of acceptance of pain and patient functioning with chronic pain.** *Pain.* 2005; **118**(1–2): 164–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. McCracken LM, Spertus IL, Janeck AS, et al.: **Behavioral dimensions of adjustment in persons with chronic pain: pain-related anxiety and acceptance.** *Pain.* 1999; **80**(1–2): 283–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
44. Xu X, Cheng Q, Ou M, et al.: **Pain acceptance in cancer patients with chronic pain in Hunan, China: A qualitative study.** *Int J Nurs Sci.* 2019; **6**(4): 385–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. Banja JD: **Empathy in the physician's pain practice: benefits, barriers, and recommendations.** *Pain Med.* 2006; **7**(3): 265–75.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Seangrung R: **Data of factors influencing non-adherence to opioids in cancer patients.xls.** *figshare.* Dataset. 2020.
<http://www.doi.org/10.6084/m9.figshare.13336691.v2>
47. Seangrung R: **STROBE checklist cross-sectional study of factors influencing non-adherence to opioids in cancer patients.docx.** *figshare.* Dataset.
<http://www.doi.org/10.6084/m9.figshare.13336778.v1>
48. Seangrung R: **COREQ Checklist for factors influencing non-adherence to opioids in cancer patients.pdf.** *figshare.* Dataset.
<http://www.doi.org/10.6084/m9.figshare.13336793.v1>

Open Peer Review

Current Peer Review Status:  

Version 2

Reviewer Report 19 March 2021

<https://doi.org/10.5256/f1000research.55051.r81445>

© 2021 Mohamed Shah N. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Noraida Mohamed Shah 

Centre of Quality Management of Medicines, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Thank you for the opportunity to review the revised article. I have no further comments for this paper.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Pharmacy, medication adherence

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 11 January 2021

<https://doi.org/10.5256/f1000research.30656.r76208>

© 2021 Mohamed Shah N. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Noraida Mohamed Shah 

Centre of Quality Management of Medicines, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Thank you for the opportunity to review this article. It is an interesting read. Non-adherence to

opioids for cancer pain is well known in the literature. However, the mixed method employed in this study further explore reasons behind non-adherence specific to the Thai population.

Suggestions/comments related to the article are as follows:

1. English editing is required for this article.
2. Introduction: *"A mixed-methods study is required to study the effects of compliance in enhancing the impact of treatment"* – this sentence is unclear. Was this investigated in this study?

Method

1. Please explain simple random sampling used in this study.
2. Please state if Medication Taking Behavior in Thai (MTB-Thai) and Belief about Medication Questionnaire (Thai-BMQ) are validated questionnaires.
3. How were these questionnaires scored? E.g. How did you classify patients as non-adherent based on MTB-Thai? Similarly, for the other questionnaires.
4. *"item objective congruence (IOC) value for each questionnaire...ranged from 0.80 to 0.92. All were <0.5, indicating good content validity."* - Please check if this statement is correct.
5. Cite references used for values indicating good content validity and acceptable internal consistency as stated in the method section.

Results

1. Would the result be different if number of painkillers is analysed as a continuous variable rather than categorical (< 3 and ≥ 3)? (Table 2).
2. Under Table 2, for Patient Factors, Knowledge score (0-10), which questionnaire was used to assess this? Please elaborate under methods section.
3. Why only 10 patients interviewed for qualitative analysis? What were the questions asked in the interviews (can explain this under method section: in depth interviews).
4. Was the patient who had a desirable opioid effect (*"The drug makes me sleep well at night. I take it every night even if the pain does not bother me much"*) non-adherent to the pain killer? This seems strange as patient would take the medication if it is producing the desired effects.

Discussion

1. Under medication-related factors, it was stated that *"Some did not inform their doctor about their pain owing to limited time, being considerate or shame"*. However, this was not stated under results section. Please clarify.
2. For the statement under illness-related factors: *"Sometimes, patients misunderstood their situation and believed that they could be fully cured and become pain free. Some patients believed that there were better treatment options than the treatment they had received."* Are these based on your assumption or from the literature?
3. *"however, more than three types of pain medication was the critical factor of non-adherence that might raise their concern about long term adverse effects."* – how did you relate taking > 3

types of pain medication with concern about long term side effects? Was this shown in your study? Similarly, for the next statement “Also, taking multiple drugs may be a factor that causes patients to adjust their medication as appropriate, which causes inadequate pain relief”. How did you relate taking multiple drugs with medication adjustment? Was this seen in your study?

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Pharmacy, medication adherence

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 06 Mar 2021

Rattaphol Seangrung, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Thank you, the reviewer, for your thoughtful suggestions. I have edited the last version under your comments as follows:

Introduction: It was written clearly about the sentence of the aims of the study.

Method:

1. The sampling method was simple random by a computer-generated random list of the cancer patients who had the follow-up appointment schedule in the study periods.

2. Already state that MTB-Thai and Thai-BMQ are completely validated.
3. If the total score of MTB-Thai ≤ 21 indicated medical non-adherence, as follows of reference No. 22.
4. Edited the correct symbol.
5. Added the references that indicate the internal consistency of the questionnaire.

Results:

1. Cause of cancer pain is very complicated. In our clinical practice, we prescribed sustained and immediate-release opioids combined with (or without) other adjuvants analgesics in cancer pain treatment, for example, anticonvulsants, antidepressants, Non-steroidal Anti-inflammatory drugs, or acetaminophen.
2. In the section, the patient factors in the part of knowledge score of the questionnaire. A pain specialist created the knowledge assessment of strong opioid analgesics that were completely mentioned in the method section.
3. In the part of face-to-face in-depth interviews by the co-authors. The interviews were audio-recorded, and the interviewers also took field notes. The study was conducted until data saturation was reached that approved by primary and secondary authors.
4. A result of medication-related factors, the patients mentioned using the rescue opioids for sleep well rather than for analgesic effects.

Discussion:

1. The authors elaborate on the study results so that it is clear in the description of the second theme (ineffective pain control). Some patients increased their basal opioid doses because their pain had worsened and dared not to call to consult the doctor about ineffective pain control by many reasons. Among the interviews, some patients expressed thoughtfulness.
2. In our study, the patients mentioned as following the results in theme 1: Poor understanding and non-acceptance of the disease.
3. In table 3. Univariate and multivariate logistic regression results. In our study, more than three types of pain medication had significant associations with opioid non-adherence ($P = 0.032$), which related to the quantitative study that the patients mentioned about adverse effects and multiple organ failure if using medications in the long-term.

Competing Interests: No competing interests were disclosed.

Reviewer Report 23 December 2020

<https://doi.org/10.5256/f1000research.30656.r76209>

© 2020 Nimmaanrat S. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Sasikaan Nimmaanrat 

¹ Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand

² Department of Anesthesiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand

This study used a mixed method of a survey and an in-depth interview to evaluate factors affecting opioid non-adherence in cancer patients. The questionnaire survey was to identify adherence and non-adherence patients, followed by an in-depth interview in patients with non-adherence until data were saturated. Using the mixed method makes the study more informative and attractive. The flow of the study was clearly presented.

Adequate pain management in cancer patients is mandatory. It is useful to know which factors lead to poor pain control. The authors have found factors which can be classified into patient factors, medication-related factors and illness-related factors. Knowing the contributing factors for inadequate cancer pain management can lead to strategic planning to modify these factors resulting in better pain relief.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pain management including acute, cancer and chronic non-cancer pain.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 28 Dec 2020

Rattaphol Seangrung, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Thank you very much.

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research