Comparison of the Clinical Outcomes between Short-term and Long-term Opioid Users with Noncancer Pain at Pain Clinics

Asween R. Sani, Che Suraya Zin

Department of Pharmacy Practice, Kulliyyah of Pharmacy, International Islamic University Malaysia (IIUM), Kuantan, Pahang, Malaysia

Introduction: The clinical use of opioids for long-term for noncancer pain indications remains a controversy. More studies are needed for evidence-based guidelines in noncancer pain management involving opioids. The primary objective of this study was to investigate the clinical outcomes of the short-term and long-term opioid use among patients with noncancer pain. Materials and Methods: This is a retrospective cross-sectional study where patients (aged ≥18 years) with noncancer pain treated with opioids were recruited from three pain clinics in Malaysia. Data on patients’ opioid use were collected from prescription records. The individual days covered with opioids per patient were calculated and based on this, patients were classified as short-term (<90 days) or long-term (≥90 days) opioid user. Outcome measures included pain intensity and pain interference with daily activities assessed by Brief Pain Inventory – Short Form (BPI-SF), health-related quality of life (HRQoL) assessed by 36-Item Short Form Health Survey version 2 (SF-36v2). These measures were compared between short-term and long-term opioid users. Results: Of the 61 noncancer pain patients recruited, 49.2% (n = 30/61) were short-term and 50.8% (n = 31/61) were long-term opioid users. There were no statistically significant differences in the mean scores of pain intensity, pain interference with daily activities, and HRQoL between short-term and long-term opioid users in this study. Conclusion: Findings of this study imply that long-term opioid therapy does not provide significant pain relief or improvement in patients’ functional capability and HRQoL in noncancer pain patients. Future prospective studies with larger sample sizes are needed to support the findings of this study.

Keywords: Noncancer pain, opioids, pain, pain management

Submitted : 08-Nov-2019
Revised : 09-Mar-2020
Accepted : 21-Apr-2020
Published : 05-Nov-2020

INTRODUCTION

Opioids are increasingly prescribed to treat noncancer pain for long-term.[1,2] Evidences which indicated that opioids are effective for various chronic pain conditions were mostly based on short-term randomized control trials (RCTs) with the longest duration being 16 weeks.[1,4] Moreover, unusually high attrition rates due to lack of efficacy or adverse effects, and enrichment protocols (patients who do not respond or selected out during the pretrial phase) of RCTs impede the internal validity of these trials.[4,5] However, available long-term studies evaluating the benefits versus risk of long-term opioid therapy for noncancer pain indicate that although a subgroup of noncancer patients significantly benefit from long-term opioid use, the majority do not. A systematic review by Noble et al.[6] concluded that long-term (≥6 months) pain relief only occurs in a small fraction of well-selected noncancer patients with no history of drug
addiction or substance abuse, whereas the evidence for improvement of health-related quality of life (HRQoL) and physical functioning (PF) is inconclusive. In the most recent study conducted among chronic noncancer pain (CNCP) patients attending pain clinics, Saïdi et al.[7] found that only a minority (20%) of long-term (≥12 months) opioid users experienced improvement in terms of pain intensity, pain interference, and mental HRQoL, whereas the majority of them reported higher levels of pain intensity and interference and poorer physical capability compared to nonopioid users and short-term users.

More importantly, evidences of harms related to long-term opioid use are accumulating. In the most recent systematic review of long-term opioid therapy for CNCP, Chou et al.[9] reported that controlled observational studies found that compared to no-opioid use, long-term opioid use is associated with increased risk of overdose, opioid abuse and dependence, fracture, myocardial infarction, and sexual dysfunction.

The clinical use of opioids continues to be limited by the compromise between effectiveness and adverse effects. Clinicians face a challenge in identifying noncancer patients who respond well to opioid therapy in terms of improved pain relief and functional capacity. More studies are needed for evidence-based guidance in noncancer pain management involving opioids. Therefore, the objective of this study was to identify patient characteristics and investigate the clinical outcomes of patients on short-term and long-term opioid therapy in pain clinics.

**Materials and Methods**

**Study design and study population**

Participants were prospectively recruited at pain clinics in three Malaysian outpatient tertiary hospital settings, namely Hospital Tengku Ampuan Afzan (HTAA) Kuantan, Hospital Kuala Lumpur (HKL), and Hospital Selayang. Patients’ medical records were reviewed, and patients were selected for assessment if they have a recent prescription for opioid analgesics in their medical records. Patients were included in this study if they were on opioids at the time of recruitment, have a non-cancer pain diagnosis, were aged ≥18 years old, and gave their informed consent. Cancer patients were excluded from this study. All recruited patients’ clinical outcomes were assessed by a single study researcher and research instruments were filled in by the same study researcher throughout the study to minimize information bias.

Patients’ demographic data such as age, gender, diagnoses, and comorbidities were retrieved from patients’ medical records. The severity of patients’ comorbidities was assessed using the Charlson Comorbidity Index (CCI).

**Ethical approval**

This study was ethically approved by the Medical Research Ethical Committee, Ministry of Health Malaysia (NMRR-14-1837-19898).

**Assessment of clinical outcomes**

Standardized questionnaires were used to evaluate clinical outcomes. Patients’ pain intensity and pain interference with daily activities were assessed with the Brief Pain Inventory – Short Form (BPI-SF). HRQoL and functional outcomes were assessed with the 36-Item Short Form Health Survey version 2 (SF-36v2). The 36 items yield 8 domain scales of health status: physical functioning (PF), role participation with physical health problems (role-physical [RP]), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role participation with emotional health problems (role-emotional [RE]), and mental health (MH). All health domain scales are scored such that higher scores indicate better health. The SF-36v2 can be summarized into two components: the physical component summary (PCS) which reflects the respondent’s physical health, and the mental component summary (MCS) which reflects the respondent’s MH.

**Opioid user classification**

All opioid prescriptions dispensed to participants from January 1, 2013 until the date of clinical outcome assessments were retrieved from prescription records from outpatient pharmacies. The individual days covered with opioids were calculated for each patient. This was calculated by summing the opioid days’ supply of all prescriptions within the study timeframe of each patient. Overlapping days between opioid prescriptions were taken into account and were considered as 1 day. Subsequently, patients were classified into either short-term or long-term opioid user group.

Long-term opioid users were defined as patients who were continuously prescribed (allowing a 60-day gap between refills) opioids for ≥90 days preceding the date of patient clinical outcomes assessment. On the contrary, short-term opioid users were defined as patients who were continuously prescribed opioids (allowing a 60-day gap between refills) for <90 days preceding the date of patient clinical outcomes assessment. The refill gap of more than 60 days between opioid prescriptions was chosen as an indicator of discontinuation of opioid use in this study as pharmacists will not dispense opioids for more than 60 days in each opioid dispensing in Malaysia.
**Statistical analysis**

Means, standard deviations (SD), and frequency tables were used to describe patient demographics and clinical outcomes. Two independent samples $t$ test and chi-square test of independence were used to compare the clinical outcomes between short-term and long-term opioid users. Fisher’s exact test was used to compare noncancer pain diagnosis grouping between short-term and long-term opioid users as one of the cells in its contingency table has an expected frequency of less than 5 (Rabe-Hesketh and Everitt, 2004). All data analyses were performed using Stata version 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, Texas: StataCorp LP). A value of $P < 0.05$ was considered significant in this study.

**RESULTS**

**Patient characteristics**

A total of 61 patients who were on opioids for their noncancer pain at pain clinics gave their informed consent and were recruited into the study [Table 1]. Less than half of them (49.2%) were short-term opioid users, and 50.8% were long-term opioid users. There were no statistically significant differences in the proportions of men and women ($P = 0.912$), as well as the mean age ($P = 0.608$) between short-term and long-term opioid users in this study [Table 1]. Short-term opioid users were aged $53.0 \pm 17$ years on average, whereas long-term opioid users were aged $51.0 \pm 16$ years on average. Chronic back pain and neuropathic pain were the most common pain diagnosis among short-term (33.3% and 23.3%, respectively) and long-term (25.8% and 19.4%, respectively) opioid users. The majority of participants had CCI scores of at least two among both short-term (46.7%) and long-term (48.4%) opioid users [Table 1].

**Clinical outcomes**

There were no statistically significant differences in the average pain intensity ($P = 0.734$) and average pain interference with daily activities ($P = 0.577$) between short-term and long-term opioid users in

---

**Table 1: Patient demographics and clinical outcomes of short-term and long-term opioid users**

| Opioid user type | Description | Short-term opioid users | Long-term opioid users | $P$ Value |
|------------------|-------------|-------------------------|------------------------|-----------|
|                  | No. of patients | $N$ | % | $N$ | % | |
|                  | Gender | | | | | |
|                  | Female | 17 | 56.7 | 18 | 58.1 | 0.912$^a$ |
|                  | Male | 13 | 43.3 | 13 | 41.9 | |
|                  | Age, mean (SD) | 53.03 (16.71) | 50.90 (15.55) | 0.608$^b$ |
|                  | Noncancer pain diagnoses | | | | | |
|                  | Chronic back pain | 10 | 33.3 | 8 | 25.8 | 0.673$^c$ |
|                  | Neuropathic pain | 7 | 23.3 | 6 | 19.4 | |
|                  | Chronic widespread pain | 1 | 3.3 | 4 | 12.9 | |
|                  | Musculoskeletal pain | 5 | 16.7 | 2 | 6.5 | |
|                  | SLE | | | 2 | 6.5 | |
|                  | Arthritis | 1 | 3.3 | 1 | 3.2 | |
|                  | CRPS | 2 | 6.7 | 1 | 3.2 | |
|                  | Postherpetic neuralgia | 1 | 3.3 | 1 | 3.2 | |
|                  | Postsurgical pain | 1 | 3.3 | 1 | 3.2 | |
|                  | Others | 2 | 6.7 | 5 | 16.1 | |
|                  | CCI score | | | | | |
|                  | 0 | 9 | 30.0 | 9 | 29.0 | 0.991$^d$ |
|                  | 1 | 7 | 23.3 | 7 | 22.6 | |
|                  | $\geq2$ | 14 | 46.7 | 15 | 48.4 | |
|                  | Brief Pain Inventory – Short Form | | | | | |
|                  | Pain intensity, mean (SD) | 5.1 (2.4) | 4.9 (1.9) | 0.734$^b$ |
|                  | Pain interference, mean (SD) | 5.7 (2.4) | 5.3 (2.4) | 0.577$^b$ |
|                  | Health-related quality of life | | | | | |
|                  | Physical health (PCS), mean (SD) | 33.5 (7.1) | 34.7 (7.2) | 0.531$^b$ |
|                  | Mental health (MCS), mean (SD) | 42.2 (12.5) | 45.2 (12.6) | 0.360$^b$ |

CCI = Charlson Comorbidity Index, SD = standard deviation, SLE = systemic lupus erythematosus, PCS = physical component summary, MCS = mental component summary

$^a$ Chi-square test of independence

$^b$ Two independent samples $t$ test

$^c$ Fisher’s exact test
Long-term users in this study [Table 1]. There were also no statistically significant differences (results are not shown here) in the mean scores of the eight health domains of the SF-36v2 between short-term and long-term opioid users [Figure 1]. Similarly, there were no statistically significant differences in the mean PCS ($P = 0.531$) and MCS ($P = 0.360$) scores between short-term and long-term opioid users in this study [Table 1].

**Discussion**

This study showed that approximately 50.8% of the recruited patients who were receiving opioids for their noncancer pain from pain clinics were found to be on long-term opioid therapy. This proportion was higher than the proportions reported in existing literature. In a recent Malaysian study of 41,091 patients who were prescribed opioids at tertiary outpatient hospital settings, Zin *et al.* reported that only 11.4% of patients were receiving opioids for long-term. In another study, only 21.8% of patients with noncancer pain were on long-term opioid therapy in a Malaysian outpatient hospital setting. It is highly likely that the high proportion of long-term opioid users reported in this study as compared to previous studies is due to the different population and setting. This study was conducted in pain clinics which typically include patients with CNCP and hence increases the probability of patients to be prescribed opioids for long-term due to the chronicity of their pain, whereas previous studies were conducted in tertiary hospital settings which included patients from all clinics who may have been prescribed opioids for acute pain conditions.

This study also showed that compared to short-term opioid users, there were no statistically significant difference in the pain intensity, and pain interference with daily activities on average among long-term opioid users in this study. This indicates that long-term opioid use did not significantly reduce pain intensity and improve functional ability among noncancer pain patients. This finding corroborates the finding of a Norwegian pharmacoepidemiological study which reported that about 75% of CNCP patients on long-term opioid therapy still reported severe or very severe pain in spite of their opioid treatment. Similarly, a Canadian study conducted on a cohort of CNCP patients attending pain clinics reported that long-term (>6 months) opioid users consistently reported high pain intensity scores on average compared to short-term opioid users and nonopioid users.

As anticipated due to chronic pain conditions, the HRQoL of short-term and long-term opioid users in this study was considerably lower than that of the general Malaysian adult population especially with regard to PF, RP, and BP [Figure 1]. This finding is in agreement with a national health survey in Denmark which reported that those with CNCP reported lower scores in all health domain scales of the SF-36 with the largest differences observed in the “RP,” “BP,” and “GH” compared to Danish adults without CNCP.

More importantly, results showed that there were no statistically significant differences in the HRQoL (mental and physical) [Table 1] and in all the SF-36v2 health domains [Figure 1] between short-term and long-term opioid users in this study. This finding is consistent with previous studies which reported that long-term opioid use did not help improve a patient’s HRQoL. Saidi *et al.* indicated that compared to nonopioid users and short-term opioid users, long-term (>6 months) opioid users reported poorer physical HRQoL. Similarly, Birke *et al.* conducted a longitudinal study from 2000 to 2013 of a subsample of 2015 CNCP patients and indicated that long-term opioid users reported lower self-rated health during follow-up. Notably, Rogers *et al.* reported that patients’ self-rated health and self-rated quality of life decreased with increasing treatment intensity (i.e., acute, episodic, and long-term opioid use) in an Australian population-based cohort study of adults aged ≥45 years.

In contrast, a Canadian study of 149 long-term opioid users attending a pain management center for CNCP indicated that 74.1% and 67.6% of patients reported moderate (>40%) pain relief and functional improvement, respectively. This could explain the slightly higher, despite not statistically significant, mean scores of the SF-36v2 health domain scales among long-term opioid users compared to short-term users in this study. The result of this study also implies that only a small proportion of noncancer pain patients on long-term opioid therapy...
benefit from their opioid treatment, whereas the majority do not, as has been shown in previous studies.\textsuperscript{[6,7]}

This study also found no statistically significant differences in patient characteristics such as pain diagnoses, and number and severity of comorbidities (mean CCI score) between short-term and long-term opioid users. This finding supports that of Barnett \textit{et al.},\textsuperscript{[17]} which found similar characteristics and diagnoses between short-term and long-term opioid users but found that long-term opioid users were more likely to be treated physicians with high opioid prescribing rates. This finding merits further investigation into physician prescribing practices in determining the factors of long-term opioid use in noncancer pain patients in future studies.

To the best of our knowledge, this is the first study in Malaysia to evaluate the individual patient-level clinical outcomes among short-term and long-term opioid users attending pain clinics. This study has reduced recall and information bias by using the combination of patient-reported data (outcomes) and data from medical records. The data from medical records were also used to verify information reported by patients in this study.

A limitation of this study is the small study sample size due to difficulties in recruiting patients as the number of patients prescribed opioids was small at each study site. Patient’s refusal to participate, referral to other hospitals, and not showing up for doctor appointments further reduced the probability of patient recruitment for this study.

**CONCLUSION**

This study found no significant differences in the clinical outcomes between short- and long-term opioid users treated for noncancer pain. The similarity in the clinical outcomes between the two groups depicted that there is no benefit of long-term opioid therapy in improving pain relief or HRQoL compared to short-term opioid therapy. This preliminary study warrants further investigation into the effectiveness of long-term opioid therapy among noncancer pain patients using a larger sample size, which may provide valuable evidence for effective pain management involving opioids for noncancer pain patients.

**Financial support and sponsorship**

CSZ was supported by a research grant from the Ministry of Education Malaysia (Fundamental Research Grant Scheme, FRGS 19-010-0618).

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Smolina K, Gladstone EJ, Rutherford K, Morgan SG. Patterns and trends in long-term opioid use for non-cancer pain in British Columbia, 2005–2012. Can J Public Health 2016;107:e404-9.
2. Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. Eur J Pain 2014;18:1343-51.
3. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, \textit{et al.} The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health pathways to prevention workshop. Ann Intern Med 2015;162:276-86.
4. Manchikanti L, Vallejo R, Manchikanti KN, Benyamin RM, Datta S, Christo PJ. Effectiveness of long-term opioid therapy for chronic non-cancer pain. Pain Phys 2011;14:E133-56.
5. Katz N. Methodological issues in clinical trials of opioids for chronic pain. Neurology 2005;65:S32-49.
6. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafo mo C, \textit{et al.} Long-term opioid management for chronic noncancer pain. Cochrane Database of Syst Rev [Internet], 2010 Jan [cited 2019 Oct 10]:1:[about 24 p.]. Available from https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006605.pub2/full.
7. Saidi H, Pagé MG, Boulanger A, Ware MA, Choinière M. Effectiveness of long-term opioid therapy among chronic non-cancer pain patients attending multidisciplinary pain treatment clinics: a Quebec pain registry study. Can J Pain 2018; 2:113-24.
8. Rabe-Hesketh S, Everitt B. A handbook of statistical analyses using Stata. 3rd ed. London: CRC Press LLC; 2004.
9. Zin CS, Alias NE, Taufek NH, Ahmad MM. Sex differences in high opioid dose escalation among Malaysian patients with long-term opioid therapy. J Pain Res 2019;12:1251-7.
10. Zin CS, Rahman NA, Ismail CR, Choy LW. Dose and duration of opioid use in patients with cancer and noncancer pain at an outpatient hospital setting in Malaysia. Pain Pract 2017;17:774-81.
11. Fredheim OM, Mahic M, Skurtveit S, Dale O, Romundstad P, Borchgrevink PC. Chronic pain and use of opioids: a population-based pharmacoepidemiological study from the Norwegian prescription database and the Nord-Trøndelag health study. Pain 2014;155:1213-21.
12. Eriksen J, Jensen MK, Sjøgren P, Ekholm O, Rasmussen NK. Epidemiology of chronic non-malignant pain in Denmark. Pain 2003;106:221-8.
13. Birke H, Ekholm O, Sjøgren P, Kurita GP, Højsted J. Long-term opioid therapy in Denmark: a disappointing journey. Eur J Pain 2017;21:1516-27.
14. Eriksen J, Sjøgren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids for chronic non-cancer pain: an epidemiological study. Pain 2006;125:172-8.
15. Rogers KD, Kemp A, McLachlan AJ, Blyth F. Adverse selection? A multi-dimensional profile of people dispensed opioid analgesics for persistent non-cancer pain. PLoS One 2013;8:e80095.
16. Busse JW, Mahmood H, Maqbool B, Maqbool A, Zahran A, Alwosaibai A, \textit{et al.} Characteristics of patients receiving long-term opioid therapy for chronic noncancer pain: a cross-sectional survey of patients attending the pain management centre at Hamilton general hospital, Hamilton, Ontario. CMAJ Open 2015;3:E324-30.
17. Barnett ML, Olenski AR, Jena AB. Opioid-prescribing patterns of emergency physicians and risk of long-term use. N Engl J Med 2017;376:663-73.