

Chronic opioid therapy in patients with chronic noncancer pain in Taiwan

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Abstract

Purpose Our aim was to analyze the physiopsychosocial variables in patients with long-term opioid therapy for chronic noncancer pain (CNCP) in Taiwan.

Methods Patients registered in the database of the National Bureau of Controlled Drugs (NBCD), Taiwan, were interviewed and completed questionnaires on pain assessment and interference in quality of life, using the Taiwanese version of the Brief Pain Inventory, and questionnaires on depressive status, using the Chinese version of the Beck Depression Inventory-II; in addition, they completed questionnaires on the adverse effects of the opioid therapy and the use of complementary and alternative medicine.

Results Of 114 patients registered at the NBCD, Taiwan, in August 2001, 61 completed the interviewing procedures and questionnaires. The durations of pain and opioid administration were 93.6 ± 84.3 months (range, 10–480, median 72) and 54.2 ± 57.6 months (range, 6–240, median 30), respectively. Significantly reduced pain intensity (range, 8.8 ± 2.0 to 3.2 ± 2.5) and pain-induced interference with general activity (8.2 ± 2.6 to 3.5 ± 2.5), in addition to improvements in mood, walking ability, normal

work, relationships with other people, sleep, and enjoyment of life, indicated remarkably improved quality of life after chronic opioid therapy. The major adverse effects of the opioids were constipation (48%), dry mouth (30%), and nausea and vomiting (21%). Almost half of the patients reported decreases in sexual desire and capability. Up to 60% of the patients received alternative medicine, including acupuncture and herbal drugs. Despite the improved quality of life, 31 of the 61 patients stated that they had moderate or severe depression.

Conclusions The long-term use of opioids provided significant improvement of pain relief and quality of life in these patients with CNCP; this therapy is a good solution if other modalities are not effective or useful.

Keywords Chronic pain · Noncancer · Opioid

Introduction

Chronic pain may occur in patients with numerous diseases and syndromes, including cancer pain and common conditions such as back pain, osteoarthritis, fibromyalgia, and headache [1]. According to the clinical guidelines issued by the American Pain Society [1], all chronic pain disorders outside of cancer pain or pain at the end of life are collectively labeled “chronic noncancer pain” (CNCP). CNCP is a leading cause of work disability and can have deleterious effects on functional status and quality of life, accounting for very high costs [2].

Opioids have been accepted as effective therapy for carefully selected and monitored patients with CNCP [1]. However, there are controversies about the diminishing analgesic efficacy, potentially serious adverse effects, and misuse of opioids. The existing evidence [3] suggests that

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analgesic efficacy, although initially good, is not always sustained during long-term opioid therapy (months to years). Therefore, many patients discontinue long-term opioid therapy due to adverse events or insufficient pain relief [4].

In Taiwan, chronic opioid treatment has been strictly regulated since 1996 and patients should be registered with the National Bureau of Controlled Drugs (NBCD), Taiwan, Food and Drug Administration, Department of Health, Taiwan [5]. For these patients, each oral and patch prescription of strong opioids, such as morphine, meperidine, and fentanyl, is limited to 2 weeks, and, in injection form, the dosage is limited to 1 week. Every 4 months, the treating hospital should report all the data of patients with long-term narcotic treatment to the NBCD and local health departments for record-keeping and management. However, there have been few surveys of these patients in Taiwan. Accordingly, in this study we set out to first investigate the effectiveness of opioid treatment (beneficial effects on pain relief, quality of life, and functional capacity) and the adverse effects in these CNCP patients in Taiwan; as well, we investigated the use of complementary and alternative medicine (CAM) in these patients.

Methods

After obtaining the approval of the NBCD, Taiwan, in August 2001, the 114 patients with CNCP registered with the NBCD at that time were included in the study. To protect the patients' privacy, the list from the NBCD, Taiwan, omitted the patients' Chinese middle names and their personal addresses and telephone numbers. In the 6 months after August 2001, the study interviewers (the physician investigator or a trained research assistant) visited the outpatient department of each hospital on the list and requested the appropriate specialist to identify the relevant patients, who were then briefly interviewed to determine eligibility and interest in the study. After signing a written informed consent form, participants completed the questionnaires by themselves, or with verbal help from the interviewer.

To evaluate pain intensity and interference with quality of life during the past week, the self-reported questionnaire of the Taiwanese version of the Brief Pain Inventory [6] was used, utilizing a numeric scale of 0–10. The pain intensity was evaluated at its worst and least in the past week, along with pain intensity on average and pain intensity 'right now'. In an additional questionnaire, the pain intensity at its onset and the adverse effects of opioid therapy in the past week, including self-reported impacts on sexual desire or capability (increased, unchanged, or decreased), were also evaluated. Also, the use of CAM, including acupuncture, herbal drugs, and chiropractic was investigated. The Beck Depression Inventory-II [7] was

also applied to assess each patient's depressive condition before and after receiving chronic opioid therapy.

The demographic data and results of the questionnaires were entered into SPSS version 10 (SPSS, Chicago, IL) and presented as means \pm SD. Age, pain duration, pain severity, and functioning subdomain scores were analyzed by using a paired *t*-test. Gender, CAM use, adverse effects, decrease of sexual performance, and depression were analyzed as categorical variables by using the χ^2 test. A *P* value of <0.05 was considered statistically significant.

Results

Of the 114 patients registered at the NBCD, Taiwan, in August, 2001, sixty-one completed the interviewing procedures and questionnaires. Seven patients refused to participate in this study, and forty-six withdrew from the follow-up at the outpatient departments before the interviewing procedures began (including twenty-six who lost contact, sixteen who stopped opioid therapy, and four patients who died). The demographic data, details of opioid prescriptions, and data on pain intensity are presented in Table 1. The durations of pain and opioid administration were 93.6 ± 84.3 months (range 10–480, median 72) and 54.2 ± 57.6 months (range 6–240, median 30), respectively. The pain intensity decreased significantly after the patients had been receiving chronic opioid therapy, from worst as 8.8 ± 1.9 to least 3.2 ± 2.5 , with an average of 5.5 ± 2.4 .

Table 2 lists the diagnoses in the patients with chronic noncancer pain and indicates the effectiveness of chronic opioid therapy. As shown in Table 3, the pain-induced interference in general activity, mood, walking ability, normal work, relationships with other people, sleep, and enjoyment of life was significantly reduced after the patients had been receiving chronic opioid therapy.

The major adverse effects of chronic opioid therapy were also examined. Constipation, dry mouth, nausea and vomiting, drowsiness, and itching were common in these patients, with 48, 30, 21, 20, and 5%, respectively, reporting these features (Table 4), in addition to the decrease of sexual desire and sexual capability in 48% and 44% of patients, respectively.

On account of the prevailing availability of traditional Chinese medicine in Taiwan, we also investigated the use of CAM in these patients with chronic opioid therapy (Table 5). Almost 60% of the patients received herbal drugs and acupuncture, with 18% participating in martial art practice and 8% using chiropractic. As well, 43, 16, and 13% of the patients, respectively, reported that they also sought help with worship at a temple, and the use of Taoist magic figures, and incense ash. The Taoist magic figures are writings or paintings symbolizing the magic powers from gods to exorcise evil spirits. The incense ash obtained

Table 1 General data and pain intensity of patients with chronic noncancer pain receiving chronic opioid therapy ($N = 61$, men/women = 36/25)

	Mean \pm SD (range)	Median
Age, years ($N = 61$)	45.3 \pm 16.6 (23–84)	
Pain duration, months ($N = 61$)	93.6 \pm 84.3 (10–480)	72
Opioid therapy, months ($N = 61$)	54.2 \pm 57.6 (6–240)	30
Morphine, oral, mg/day ($N = 21$)	72 \pm 38 (30–180)	60
Morphine sustained release, oral, mg/day ($N = 22$)	134 \pm 90 (60–360)	105
Meperidine, oral, mg/day ($N = 8$)	391 \pm 326 (50–600)	200
Meperidine, intramuscular, mg/day ($N = 5$)	760 \pm 90 (600–800)	800
Fentanyl, transdermal, μ g/h ($N = 3$)	333 \pm 115 (200–400)	400
Codeine, oral, mg/day ($N = 10$)	140 \pm 97 (30–360)	112
Pain intensity		
Onset	8.8 \pm 2.0 (1–10)	10
Worst, in the past week	8.8 \pm 1.9 (2–10)	10
Least, in the past week	3.2 \pm 2.5 (0–8)	3
On average	*5.5 \pm 2.4 (0–10)	5.5
Right now	*5.8 \pm 3.1 (0–10)	7

Combined prescription: morphine + morphine sustained release: 10; morphine + meperidine: 2; morphine + fentanyl: 2; morphine + codeine: 1
 Meperidine, intramuscular, was used in 5 patients with intolerable side effects of previous oral morphine. Only 3 potent opioids (morphine, meperidine, and fentanyl) were available in Taiwan in 2001

Fentanyl, transdermal patch, was first introduced in Taiwan in 2001

Pain intensity, 0 = no pain and 10 = pain as bad as you can imagine

* $P < 0.001$, compared with onset (before opioid therapy)

Table 2 Diagnoses of patients with chronic noncancer pain and pain intensity before and after receiving chronic opioid therapy ($N = 61$)

Diagnosis	No.	Pain intensity		Interference in quality of life	
		Before	After	Before	After
Chronic pancreatitis	13	9.2	3.7	8.1	2.6
Spinal cord injury	12	7.8	7.9	7.9	4.3
Neuralgia	8	8.9	5.3	6.7	3.4
Back pain after failed spinal surgery	7	8.5	7.1	7.3	3.7
NIDDM with neuropathic pain	3	9.3	2.2	9.0	3.1
Complex reflex pain syndrome	3	9.5	5.8	8.9	2.9
Pelvic pain	2	8.5	8.5	8.9	3.2
Porphyria	2	9.5	2.0	9.0	2.2
Others	11	9.4	6.3	8.6	4.9
Total	61	8.8	5.5	8.0	3.6

The data are presented as means

Pain intensity, 0 = no pain and 10 = pain as bad as you can imagine; Interference, 0 = does not interfere and 10 = completely interferes

NIDDM noninsulin-dependent diabetes mellitus

from temples is dissolved in water for drinking or spraying on the body to help cure diseases or discomfort.

Despite the generally improved quality of life in these 61 patients, 31 patients still reported moderate or severe depression, as assessed by the Beck Depression Inventory score (Table 6).

Discussion

The present study is the first investigation of the effects of chronic opioid therapy, using a self-reported questionnaire format, in officially registered patients with chronic non-cancer pain (CNCP) in Taiwan. The results demonstrated

Table 3 Chronic noncancer pain-induced interference in quality of life in patients receiving chronic opioid therapy (N = 61)

	Before	After	P value
General activity	8.2 ± 2.6 (0–10), 10	3.5 ± 2.5 (0–10), 3	<0.001
Mood	7.8 ± 3.0 (0–10), 9.5	2.8 ± 2.5 (0–10), 2.5	<0.001
Walking ability	7.9 ± 2.9 (0–10), 9.5	4.3 ± 3.5 (0–10), 4	<0.001
Normal work	8.6 ± 2.2 (0–10), 10	4.5 ± 3.6 (0–10), 4	<0.001
Relationships with other people	6.4 ± 3.9 (0–10), 7.5	2.7 ± 3.1 (0–10), 2	<0.001
Sleep	9.1 ± 1.5 (3–10), 10	3.8 ± 2.6 (0–10), 4	<0.001
Enjoyment of life	8.1 ± 2.6 (0–10), 9.5	3.6 ± 2.6 (0–10), 3.5	<0.001

The data are presented as means ± SD (ranges), medians
Interference, 0 = does not interfere and 10 = completely interferes

Table 4 Adverse effects of chronic opioid therapy in patients with chronic noncancer pain (N = 61, men/women = 36/25)

Adverse effect	No. of patients	Men/women	With morphine N = 33	With meperidine N = 13	With fentanyl N = 3	With codeine N = 10
Constipation	29 (48%)	20/9	18 ^a	6	2	4
Dry mouth	18 (30%)	11/7	9	5	1	2
Nausea and vomiting	13 (21%)	8/5	7	3	0	0
Drowsiness	12 (20%)	7/5	9	2	2	1
Itching	3 (5%)	2/1	2	1	0	0
None	15 (25%)	8/7	9	1	0	4
Decreased sexual desire	29 (48%)	18/11	18	4	2	5
Decreased sexual capability	27 (44%)	16/11	18	4	1	4

^a Combined prescription: morphine + meperidine: 1; morphine + fentanyl: 2; morphine + codeine: 1

Table 5 Complementary and alternative medicine use in patients with chronic noncancer pain receiving chronic opioid therapy (N = 61, men/women = 36/25)

	No. of patients (%)	Men/women
Herbal drugs	36 (59)	20/16
Acupuncture	35 (57)	18/17
Martial art practice	11 (18)	7/4
Chiropractic	5 (8)	4/1
Worship ^a	26 (43)	15/11
Taoist magic figures ^a	10 (16)	5/5
Incense ash ^a	8 (13)	3/5
None	11 (18)	7/4

^a See text for explanations

remarkable improvements in pain relief and quality of life after the patients had been receiving long-term opioid treatment. CAM, including herbal drugs, acupuncture, and some Chinese folk therapies, was used in up to 60% of these CNCP patients in Taiwan.

In the past two decades, opioids have been increasingly used worldwide to treat chronic pain, and millions of Americans now receive opioid therapy for CNCP [8]. The use of opioids had been prohibited in Chinese history since the Sino-British Opium War in the 1840s, and subsequently these compounds were strictly regulated for medical use. Taiwan has an extremely high coverage (99%) of national

Table 6 Self-reported depression, by Beck Depression Inventory score, in patients with chronic noncancer pain receiving chronic opioid therapy (N = 61, men/women = 36/25)

Depression score	No. of patients	Men/women	Pain intensity on average (range)
0–9	14 (23%)	9/5	4.9 ± 2.6 (1–9)
10–18 (mild to moderate)	16 (26%)	8/8	5.2 ± 2.5 (3–10)
19–29 (moderate to severe)	18 (30%)	14/4	6.0 ± 2.1 (3–10)
Over 30 (severe)	13 (21%)	5/8	5.7 ± 2.5 (0–10)

health insurance for its 23-million population. Chronic opioid therapy is strictly regulated in Taiwan [5]. All patients with CNCP who require strong opioids continuously for more than 14 days or intermittently exceeding 28 days within 3 months should be referred to a medical center (tertiary hospital) or teaching hospital (secondary hospital) with an established Narcotics Management Committee. After concomitant consultations with anesthesiologists (or pain specialists), psychiatrists, and other relevant specialists to exclude psychological dependence, each patient signs a written informed consent and then receives an oral or patch prescription, limited to 2 weeks; and/or an injection dosage form, limited to 1 week. Every 4 months, the hospitals have to report all the data of patients with long-term narcotic treatment to the NBCD and local health departments for record-keeping and management.

Consequently, we could obtain the patient list to evaluate the effectiveness and adverse effects of chronic opioid therapy for at least 6 months in these registered patients with CNCP, but not in those with newly developed CNCP.

In regard to pain relief, the existing evidence, first reviewed by Ballantyne and Shin [3], suggested that analgesic efficacy, although initially good, was not always sustained during continuous and long-term opioid therapy (months to years). However, it is important to make a distinction between opioid efficacy (beneficial effects of treatment delivered to a targeted group in a controlled trial) and opioid effectiveness (beneficial effects of treatment for a population when delivered under real-world conditions) [9]. In general, a controlled trial is set up to test specific drugs for short-term effects in specific disease states, or the initiation of therapy, rather than testing over prolonged periods. The successful outcomes of chronic opioid therapy should include analgesia-improved function, enhanced wellbeing, and high patient satisfaction. Denmark is among the most liberal countries in prescribing opioids for chronic pain, and has the highest per capita usage of prescription opioids in the world, most being used for CNCP [3]. In a representative national random sample of 10,066 Danish individuals [10], a total of 1,906 patients with CNCP were investigated with a self-administered questionnaire. Among them, opioid users ($n = 228$) were compared with a matched cohort of patients with chronic pain not receiving opioids. The results demonstrated that opioid usage was significantly associated with the reporting of moderate/severe or very severe pain, poor self-rated health, and a higher use of the healthcare system. The authors of that study [10] also found that long-term opioid treatment did not seem to fulfill any key goals of pain relief or improved quality of life and functional capacity, compared with findings in nonopioid users. In our patients, not only was pain intensity significantly reduced, but also quality of life, including daily activity, return to normal work, mood, sleep pattern, social relationships, and enjoyment of life, was significantly improved. The prescribed doses of morphine sustained release, 60–360 mg/day, used in our study subjects were similar to those used in other, randomized-controlled, trials [3]. Without a control group of nonopioid users, our results could only demonstrate the current status, compared with that before opioid treatment, in a highly-selected group of patients with ongoing long-term use of opioids in Taiwan.

Long-term opioid therapy was defined by Korff et al. [11] as episodes lasting longer than 90 days with more than 10 opioid prescriptions or more than 120 days' supply of opioids dispensed, 11 in adult members of two health plans serving more than 1% of the United States population. In our patients, the median values for pain onset and opioid administration were 72 and 30 months, respectively,

indicating that the patients had tried many other modalities to resolve their chronic pain, for 42 months in general, but were unsatisfied, before receiving chronic opioid therapy. We believe that more patients with CNCP had come to the pain clinic, but only 114 patients of the total 22.3-million population of Taiwan in 2001 were registered with the NBCD, Taiwan, for chronic opioid therapy, reflecting the fact that patients with CNCP in Taiwan are underestimated in number and are undertreated. The attitude of the physician affects the prescription of opioids for patients with CNCP. In a survey by Lin et al. [12], most physicians strongly agreed that they were hesitant to prescribe opioid analgesics because of concerns about side effects (58%), diversion for illegal use (37%), and causing addiction (31%). In fact, a recent meta-analysis [4] revealed that many patients withdrew from clinical trials due to adverse effects (oral, 32.5%; intrathecal, 6.3%; transdermal, 17.5%). However, signs of opioid addiction were reported in only 0.05% (1/2,042) of the patients and abuse in only 0.43% (3/685). For CNCP patients and their care-providers in Taiwan, more education on chronic opioid therapy will be needed in the future.

Our results also demonstrated the high prevalence of CAM use in the patients with CNCP in Taiwan, with folk therapies such as worship and the use of Taoist magic figures and incense ash also being used as these CNCP patients sought help. A cross-sectional survey [13] in academic medical centers in the United States demonstrated that 52% of primary care patients with chronic nonmalignant pain reported the current use of CAM for the relief of chronic pain. Among them, 54% agreed that nonconventional remedies helped their pain and 14% indicated that their individual alternative remedy entirely relieved their pain. Vitamin and mineral supplements (33%), herbs (15%), and massage (15%) were the most frequently used CAM modalities, despite there being no association between reported CAM usage and pain severity, functional status, or self-efficacy. When asked to choose between conventional therapies and CAM, most patients still preferred conventional therapies for pain relief [13].

Pain-related disability is a burden on the individual, family, and society. Improvements in quality of life, including functions of daily walking, work, and social relationships, in addition to improvements in sleep patterns and the status of depression, receive the majority of attention in the evaluation of the effectiveness of chronic opioid therapy. Chronic pain is frequently associated with depression and anxiety [14]. Meanwhile, persons with a history of depression are more likely to receive long-term opioid therapy for noncancer pain than those without a history of depression [15]. In our results, the pain intensity score varied widely for each depressive status, and did not demonstrate any significant correlations. Clinically, the patients in our study had coped with the difficulty in quality

of life for 10–480 months (median, 72). Consequently, the adaptive pain in many patients might not be correlated with their current depressive status, and vice versa. Besides, a 197-patient analysis by Hirsh et al. [16] indicated that disability was more directly related to pain in men, whereas the effect of pain on disability appeared to operate through negative mood in women. In our limited group of patients, only 36 men and 25 women, the findings did not show any sex differences in the aspects of pain relief, improvements in quality of life and the depression score, or the decrease of sexual desire and performance.

There are some limitations of the present study. First, only patients with long-term use of strong opioids were registered at the NBCD, Taiwan, and this self-reported investigation did not reliably describe all the needed patterns of opioid prescriptions and their impacts. Furlan et al. [17] published a meta-analysis assessing the effectiveness of opioids for chronic pain, which, interestingly, showed that pain relief was improved by strong opioids but not by weak opioids or nonopioids, whereas functional outcome was improved by weak opioids and nonopioids, but not by strong opioids. Second, we did not report the misuse of opioids in the patients in our study. Experts advocate the use of opioid therapy in carefully selected patients. When opioids are prescribed, it is incumbent on the prescriber to monitor patients carefully, documenting changes in symptoms and functioning, as well as aberrant behavior. All of the patients in our study were strictly regulated by the NBCD, Taiwan [5]. Every 4 months, the treating hospitals report all the data of patients with long-term narcotic treatment to the NBCD and local health departments for record-keeping and management. Third, we interviewed the patients at the outpatient departments using lists which did not provide additional contact information. If the patient did not visit a specialist for opioids any more, the underlying causes of withdrawal or loss of contact could not be recorded. In the future, obtaining the official records of long-term opioid prescriptions from the NBCD and combining these with some relevant items, added to the self-reported questionnaire, could help to clarify the differential impacts of chronic opioid therapy on CNCP patients in Taiwan.

In conclusion, this investigation, using patients' self-reported information from questionnaires, demonstrated that chronic opioid therapy provided significant reduction of pain and improvement in quality of life in patients with chronic noncancer pain in Taiwan, and such therapy is a good solution if other modalities are not effective or useful. However, almost half of the patients had constipation, decrease of sexual desire and performance, and moderate to severe depression after receiving long-term opioid therapy. Up to 60% of these patients indicated the concurrent use of CAM and folk therapy, and this factor needs further assessment for its association with better pain management.

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