Ph.D. Dissertation of Medicine

Addressing Opioid-Related Chemical Coping in Long-Term Opioid Therapy for Chronic Noncancer Pain

– A Multicenter, Observational, Cross-sectional Study –

마약성 진통제를 장기간 복용하는 만성 비암성 통증 환자에서 마약성 진통제와 연관된 화학적 대처

– 다기관, 관찰, 단면 조사 연구 –

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Abstract

Introduction: Opioid consumption has increased worldwide, which carries the risk of opioid use disorder (OUD). However, the literature on OUD and opioid-related chemical coping (OrCC) in chronic noncancer pain (CNCP) is heterogeneous, with the majority of studies conducted in the United States, a country with high opioid consumption rates.

Objective: To determine the frequency and predictors of OrCC, and the patients' functional and psychiatric characteristics.

Design: This was a multicenter, observational, cross-sectional study. Set at the pain clinics of six tertiary hospitals in South Korea, a country with moderate opioid consumption rates. The patients included had CNCP and were receiving long-term opioid therapy (LtOT). Sociodemographic data, pain characteristics, and opioid information were obtained, and a prospective survey was conducted. Nine pain specialists evaluated OrCC with a questionnaire.

Results: A total of 258 patients were included and among them, fifty-five (21%) patients showed OrCC. The sample had high pain catastrophizing (≥30 points; 66%), moderate-severe insomnia (≥15 points; 63%), low resilience (68 points), and high suicidal ideation (67%). OrCC patients had greater pain interference (85.18% vs. 58.28%, p = 0.017), lower satisfaction with the LtOT (56.4% vs 78.3%, p = 0.002), and higher worst numerical rating scale pain scores (8.75 ± 1.42 vs 7.95 ± 2.06, p = 0.001). In multivariable analysis, alcohol abuse history within one year (OR= 6.84, p = 0.001), prescription drugs abuse within one year (OR= 19.32, p = 0.016), functional pain syndrome (OR= 12.96, p<0.001), head and neck pain (OR= 2.48, p = 0.039), morphine equivalent daily dose (MEDD) ≥ 200mg/d (OR= 3.48,

p = 0.006), and ongoing litigation (OR= 2.33, p = 0.047) were significant predictors of OrCC.

Conclusion: Approximately 21% of CNCP patients receiving LtOT were coping chemically with opioids. The break-out of OrCC in CNCP in South Korea was comparable to those in countries with high opioid consumption, such as the United States, regardless of the country's opioid consumption rate.

Keyword: Chronic noncancer pain; Opioids; Opioid use disorder; Chemical coping; Frequency; Long-term opioids.

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Abbreviations

Abbreviation	Explanation
BMI	Body Mass Index
BPI-SF	Brief Pain Inventory – Short Form
BTP	Breakthrough Pain
CAGE-AID	Cut down, Annoyed, Guilty, Eye-opener – Adapted to Include Drugs
CCI	Chemical Coping Inventory
CI	Coefficient Interval
CNCP	Chronic Noncancer Pain
CNS	Central Nervous System
DSM-5	Diagnostic and Statistical Manual of mental disorders, fifth edition
EMR	Electronic Medical Record
ER	Emergency Room
EU	European Union
HADS	Hospital Anxiety and Depression Scale
IRB	Institutional review board
ISI	Insomnia Severity Index
K-CD-RISC	Korean – Connor-Davidson Resilience Scale
K-IADL	Korean – Instrumental Activities of Daily Living
LtOT	Long-term Opioid Therapy
MEDD	Morphine Equivalent Daily Dose
NRS	Numerical Rating Scale
OECD	Organisation for Economic Co-operation and Development
OR	Odds Ratio
OrCC	Opioid-related Chemical Coping
OUD	Opioid Use Disorder
PCS	Pain Catastrophizing Scale
PGIC	Patient Global Impression of Change
PTSD	Post-traumatic Stress Disorder
ROOs	Rapid Onset Opioids
SD	Standard Deviation
S. Korea	South Korea
U.S.	United States
WHO	World Health Organization

1. Introduction

1.1. Study Background

Chronic pain is a devastating disease that is often treated inadequately [1]. Among a plethora of treatments, opioid agonists are one pharmacotherapy for moderate–severe pain. Opium has been used for thousands of years to relieve pain and suffering, and after the morphine alkaloid was identified in 1806, the pharmacologic production of opioid drugs began [2]. In the 19th century, the increased availability of opioid drugs led to the institution of legal controls to prevent narcotic abuse. The strict regulatory controls on opioids and the reluctance of physicians to prescribe them resulted in the under–treatment of pain [3]. Consequently, towards the end of the 20th century, opioid therapy was reestablished as an invaluable and accepted treatment for acute, cancer, and end–of–life pain.

The recognition that opioid therapy can relieve pain and improve mood and functioning in many patients with chronic pain led experts on pain to recommend opioids to such patients [2]. However, although its consumption by country (mg/capita) has increased in the last two decades [4–6], it may remain under–requirements for managing moderate–severe pain in some regions, including Asian countries [1,6,7]. According to the 2015 opioid consumption data, the medical opioid consumption in the United States (U.S.) was 678 mg/capita while in South Korea (S. Korea), it was 55 mg/capita which was below average (Figure 1); ranking 43rd globally and 30th among thirty–five Organisation for Economic Cooperation and Development (OECD) countries (258 mg/capita average in OECD countries) [6]. However, it is remarkable that the opioid consumption in S. Korea has increased 5–6 times since 2005 (10 mg/capita), ranking third among Asian

countries preceded only by Vietnam (62 mg/capita) and Malaysia (60 mg/capita).

Despite pain experts' recommendations, many clinicians are reluctant to prescribe opioids to treat chronic noncancer pain (CNCP). Some physicians argue that opioids have a minimal effect on functioning and may even worsen the outcome of CNCP patients [2]. Additionally, there are concerns regarding the risk of opioid use disorder (OUD) from long-term opioid therapy (LtOT), secondary to the induced reward responses to the drug [8]. The controversy in the use of LtOT in CNCP is supported by new evidence of increased risk of OUD, rise in all-cause mortality, and poor long-term treatment results in terms of pain relief and quality of life [9-12]. Recently, the rising rates of opioid overdose deaths in countries with high opioid consumption made evident the risk for serious harms and the need to detect OUD early. However, the spectrum of OUD in CNCP is wide and varies greatly from opioid abuse to addiction [13].

The abundance of status included in the OUD spectrum makes it difficult to determine the best way to detect promptly subjects at risk for addiction. Between the extremes of OUD, opioid-related chemical coping (OrCC) is the use of opioids to cope with emotional distress characterized by inappropriate and/or excessive opioid use [14]. OrCC should be distinguished from addiction, a brain disease that involves neuroplasticity and substantial loss of self-control [15]. All addicts are chemical copers, but not all chemical copers are addicts [13]. Although OrCC was first defined in cancer patients [16], the correlation with OUD in CNCP patients is high [17]. Therefore, understanding this intermediate status may prompt the identification of risk factors for severe OUD and prevention of unnecessary opioid toxicity [18].

Nonetheless, the literature on OUD and OrCC is heterogeneous, and an overwhelming majority of the studies took place in the U.S. [9,19–21], a country with high opioid consumption rates [7] and a current opioid epidemic. In the U.S., drug overdose deaths (the majority involving an opioid) have nearly quadrupled since 1999 [4] leading to the development of guidelines to discourage opioid prescribing for CNCP in North America [22,23]. Moreover, growing evidence suggests no benefits of the LtOT over non-opioid therapy in CNCP patients [11]. However, despite the evidence and recent strict regulations in the U.S. and other countries with high opioid consumption, the 'street' availability of illicitly manufactured opioids such as fentanyl keep increasing and opioid-related overdose deaths is not decreasing.

In May 2018, a report calculated the number and the percentage of opioid-related overdose deaths in the U.S. between 2010 and 2016 using death certificates from the National Vital Statistics System [24]. The researchers found that synthetic opioids like fentanyl caused about 46% of the 42249 opioid-related overdose deaths in 2016. That is more than a three-fold increase compared with 2010, when synthetic opioids were involved in about 14% of opioid overdose deaths. Additionally, other studies suggest that CNCP remains undertreated [1,25–28] and stringent regulations to prevent opioid abuse and addiction may result in inadequate pain control [29], especially in countries with low opioid consumption rates [6,7]. Moreover, the lack of studies in countries with low opioid consumption makes it difficult to extrapolate results and guidelines to prevent a possible worldwide opioid epidemic. Consequently, it is necessary to determine the frequency and characteristics of OUD in CNCP patients in countries with low-moderate opioid consumption rates, to ascertain if OUD is indeed correlated with the country's overall consumption rates of opioids (mg/capita).

1.2. Purpose of Research

We performed a national, multicenter, observational study to address OrCC, the intermediate status of OUD, in LtOT for CNCP in S. Korea, a country with moderate opioid consumption rates since 2010 [7]. Addressing OrCC instead of OUD in a country with moderate rates of opioid consumption such as S. Korea may help us to assess a bigger quantity of patients at risk for severe harms in an early stage. The objectives of this study were to estimate the frequency of OrCC in a sample of CNCP patients, to evaluate the patient's functional and psychiatric characteristics, and to determine the risk factors independently associated with OrCC.

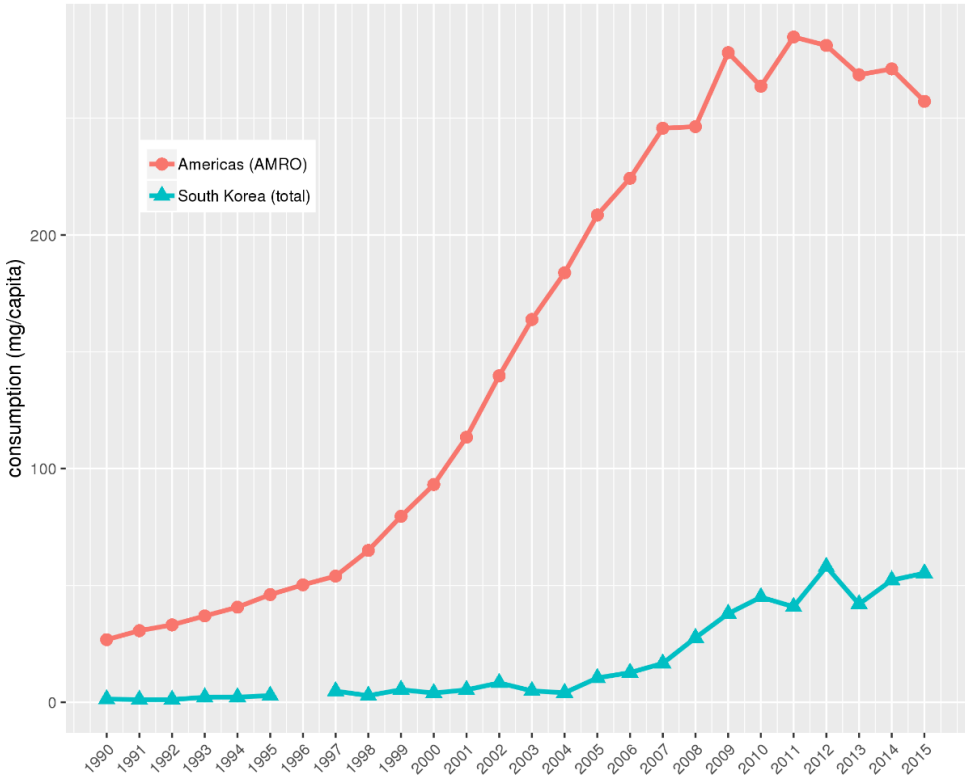

Figure 1. South Korea total opioid consumption

This figure depicts a comparison of the opioid consumption (morphine equivalence mg/capita) in the Americas region versus S. Korea from 1990–2015. Although S. Korea's opioid consumption has increased yearly since 2005, it remains low in comparison to the Americas region. ***Sources:*** *International Narcotics Control Board/ World Health Organization population data.* ***By:*** *Pain & Policy Studies Group, University of Wisconsin/WHO Collaborating Center, 2018.*

2. Materials and Methods

This national, observational, cross-sectional study was conducted in eight tertiary university-based hospitals in S. Korea between April 2017 and January 2018. The study was conducted in accordance with the Declaration of Helsinki, and the Institutional Review Boards (IRB) in each hospital approved the protocol. The protocol of the study was registered and openly shared in ClinicalTrials.gov (NCT03161795) to stress in the transparency of the research conduction.

Eleven pain specialists, one neuropsychiatrist, and one oncologist took part in the study. Written informed consent was obtained from each participant prior enrollment. All methods and results have been reported according to the STROBE recommendations [30].

2.1. Study Participants

Inclusion criteria: (1) age ≥18 years; (2) diagnosis of chronic pain defined by the International Association for the Study of Pain (IASP) as persistent or recurrent pain lasting longer than 3 months or past the time of normal tissue healing [31]; (3) patients with LtOT defined as the current and regular use of one or more opioid prescriptions for ≥ 3 months; and (4) patients who completed the questionnaires administered in the study.

Exclusion criteria: (1) patients with a cancer diagnosis and/or receiving ongoing cancer treatment, palliative care, or end-of-life care; (2) patients who received opioid therapy for < 3 months or intermittently; (3) patients with serious systemic diseases (hepatic or renal failure, acute cardiac ischemic disease,

etc.), or acute psychiatric disorders that required inpatient management (schizophrenia, anxiety, depression, etc.), which compromised their safety or the completion of the study; or (4) patients with intellectual impairment and unable to answer the survey questions.

2.2. Evaluation of Opioid-Related Chemical Coping

Eleven anesthesiologists, one neuropsychiatrist, and one oncologist in the initial expert meeting discussed the evaluation of OrCC. The presence of OrCC was determined through a questionnaire that contained seven behaviors related to OrCC. The questionnaire was based in a previous study of OrCC [14] and the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) diagnostic criteria of OUD [32] (Table 1 and 2).

The questionnaire was reviewed through two additional educational meetings that were held prior to the patient's enrollment to reduce bias between physicians. A pain specialist at each participating hospital evaluated the presence of OrCC using the study's questionnaire. Two or more affirmative answers to the questionnaire were considered positive for OrCC.

There is a previously developed scale to measure OrCC, the chemical coping inventory (CCI) [13]. The CCI asks patients with opioid-treated pain to indicate the extent to which they agree with 15 statements describing nonprescribed use of medications to cope with emotional stress. Although the CCI was pre-validated in one study [13] and showed high internal consistency in another study [17], there are no further validation studies. In our study, pain physicians evaluated OrCC thus the self-administered CCI was not considered.

2.3. Outcome Measurements

Patients' sociodemographic data were obtained from the electronic medical record (EMR) including educational level (<high school graduate or ≥high school graduate) and religion (yes = Christianity, Islam, Buddhism, Hinduism, Taoism, etc.; no = Atheism), pain characteristics including pain intensity using an 11-point numerical rating scale (NRS) [33], co-morbid psychopathologies (depression, anxiety, bipolar disorder, etc.), substance abuse history within one year, and secondary morbid gain (if the patient's pain allows him/her to miss work, avoid military duty, obtain financial compensation, obtain drugs, etc.). We also collected opioid information, which included the duration of administration in months, opioid name and type, administration route (oral, transdermal, intrathecal, intravenous), morphine equivalent daily dose (MEDD, mg/day) [34], initial prescribers of the opioid, number of opioid-seeking visits per year to the opioid provider or the emergency room (ER), and co-prescription of benzodiazepines or other medications (anticonvulsants, antidepressants, topical agents, etc.). The information that was unavailable in the EMR was asked directly to the patient when appropriate using an individualized survey (Appendix 1). The tools and questionnaires administered in this study were divided into patient's and physician's booklets. The physician's booklet included the questionnaire to assess the patient's OrCC (Table 1 and 2) and the patient's booklet contained predictive tools for OUD and questionnaires to address functionality (Appendix 2 and 3).

The risks of LtOT were assessed through a survey in the outpatient setting of each pain clinic. After obtaining written, informed consent, the patients received a patient's booklet and responded to the following questionnaires and forms: (1) Cut down, Annoyed, Guilty, Eye-opener Adapted to Include Drugs

(CAGE-AID) [35]; (2) Brief Pain Inventory-Short Form (BPI-SF) [36]; (3) Pain Catastrophizing Scale (PCS) [37]; (4) Hospital Anxiety and Depression Scale (HADS) [38]; (5) Insomnia Severity Index (ISI) [39]; (6) Korean Instrumental Activities of Daily Living Scale (K-IADL) [40]; (7) Korean Connor-Davidson Resilience Scale (K-CD-RISC) [41]; and (8) Patient Global Impression of Change Scale (PGIC) [42].

Among the four questions in the CAGE-AID, one or more affirmative answers was considered "positive" for OUD [43]. BPI-SF measured pain intensity (Items 3–6) and pain interference (Item 9) [44], which had seven components scored from 0 (no interference) to 10 (interferes completely). PCS had 13 items rated from 0 (not at all) to 4 (all the time); a total score ≥30 was considered "catastrophizing" [37]. HADS scores for anxiety and depression ranged from 0 to 21, with ≥11 points considered "abnormal" [45]. The ISI total score ranged 0–28; scores ranging from 15–21 and 22–28 indicated moderate and severe insomnia, respectively [46]. K-IADL evaluated daily activities with 11 questions rated from 0 (independently performed/normal) to 3 (impossible to perform) [47]. K-CD-RISC had 25 items, rated from 0–4, with higher scores reflecting greater resilience [48]. PGIC was rated from 1 (very much improved) to 7 (very much worse) [49]. Patients' overall satisfaction with their LtOT ranged from 1 (extremely satisfied) to 5 (extremely unsatisfied). A question to evaluate the presence of suicidal ideation in CNCP was also included (yes = previous suicidal attempts, thoughts of ending one's life, planned to commit suicide, wish to be dead; no = never attempted or thought about committing suicide). Additionally, adverse and undesirable effects of opioids were collected.

On the survey day, after answering the patient's booklet, each patient attended a routine visit with a pain specialist. Once

the patient exited the room, the specialist answered the questionnaire to assess the patient's OrCC included in the physician's booklet. The same process was reproduced with all the subjects included in the study and was supervise by a designated research nurse.

2.4. Sample Size Calculation and Statistical Analysis

The precision/absolute error and the significance level were set at 5% and 95%, respectively (Type 1 error of 5%, α = 0.05). According to a published study by Kwon et al. [19], the prevalence of chemical coping was approximately 18%; therefore, the sample size was calculated to be 235 participants. Considering a 10% dropout rate, a group of 258 participants was planned for recruitment.

$$Sample\ size = \frac{Z_{1-\alpha/2}{}^{2}\mathrm{p}(1-\mathrm{p})}{d^2}$$

$$Sample\ size = \frac{1.96^2 \mathrm{x} 0.18(1-0.18)}{0.05^2} = 235$$

The precision/absolute error and the significance level were set at 5% and 95%, Depending on the data distribution, independent t-tests or Wilcoxon rank sum tests were performed to compare two independent groups. A paired t-test was used to compare two means from the same group. Categorical data were analyzed using Pearson's $\chi 2$ test, Fischer's exact test or Chi-square test. The normality distribution for continuous variables was assessed with the Kolmogorov-Smirnov test. The

independent t-test was used to compare normal distribution and the Mann-Whitney U test was used for non-normal distribution.

Univariable analysis was performed to explore variables associated with OrCC, using the presence of OrCC as a dependent variable and clinical variables that included sociodemographic data, pain characteristics, opioid information, and scores of CAGE-AID, K-IADL, PCS, ISI, K-CD-RISC, HADS, BPI-SF, and PGIC as independent variables. Clinical variables with a p-value < 0.1 in univariable analysis were considered for multivariable analysis. The multivariable regression analysis was conducted by manual forward stepwise selection, and variables with a p-value < 0.05 were retained. All parametric data were presented as mean ± standard deviation (SD) and nonparametric data as percentage (%) or odds ratio (OR) with a 95% confidence interval (95% CI). All p-values are two-tailed, and p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 22.0. (IBM Corp., Armonk, NY, USA).

Table 1. Opioid-related chemical coping questionnaire

1. Please read carefully the definition of opioid-related chemical coping:

   "Opioid-related chemical coping is the use of opioids to cope with emotional distress characterized by inappropriate and/or excessive opioid use" [14].

2. The following are aberrant behaviors related to chemical coping with opioids. Please mark all the behaviors which you believe the patient presents:

Behavior	Check
• Use of opioids other than for the prescribed purpose to treat non-nociceptive symptoms (cope with emotional or spiritual distress, anxiety, depression, insomnia, fatigue, anger, etc.).	☐
• Excessive use (more than prescribed according to appropriate titration) of PRN (pro re nata) doses despite no benefits added to pain relief or quality of life.	☐
• The patient has obtained or stolen prescription opioids from another person (family member, friend, etc.).	☐
• The patient asks the physician to prescribe a specific opioid or certain amount of the opioid.	☐
• Impulsive or excessive use of the prescribed opioids despite several and persistent secondary effects (drowsiness, nausea, vomiting, constipation, etc.)	☐
• The patient has insisted aggressively to receive higher doses of an opioid for storage purposes, prevention, fear, etc.	☐
• The patient keeps losing the prescription of opioids and often seeks to visit the opioid provider to get new prescriptions and feel reassured.	☐

Two or more affirmative statements were considered positive for OrCC.

Table 2. 마약성 진통제 관련 화학적 설문지

1. 마약성 진통제 관련 화학적 대처의 정의를 주의 깊게 읽으십시오:
   "마약성 진통제 관련 화학적 대처란 정서적 고통에 대처하기 위해 마약성 진통제를 부적절하거나 과다하게 사용하는 것을 의미합니다." [14].

2. 다음은 마약성 진통제에 대한 화학적 대처와 관련된 비정상적인 행동들입니다. 환자가 보인다고 생각되는 행동에 모두 표시해 주십시오.

행동	표지
• 환자가 처방 받은 마약성 진통제를 통증과 관계없는 증상을 위하여 복용하고 있습니다. (정서적 또는 심리적 고통, 불안, 우울감, 불면, 피로, 분노 등에 대처하기 위하여).	☐
• 환자가 통증의 감소나 삶의 질의 향상에 도움이 되지 않음에도 불구하고 과도하게 PRN으로 처방된 마약성 진통제를 사용하고 있습니다. (적절한 용량 결정에 의해 처방받은 양보다 더 많이).	☐
• 다른 사람 (가족, 친구 등)에게 처방된 마약성 진통제를 얻거나 훔쳐서 복용합니다.	☐
• 환자가 의사에게 특정 약물을 지정하거나 원하는 용량을 처방할 것을 요구합니다.	☐
• 몇 가지 지속적인 부작용들 (졸음, 메스꺼움, 구토, 변비 등)에도 불구하고 처방된 마약성 진통제를 충동적으로 또는 과다하게 사용합니다.	☐
• 환자가 의사에게 약물 보관, 발생할지 모르는 증상의 예방, 두려움의 해소 등을 목적으로 높은 용량의 마약성 진통제를 처방할 것으로 공격적으로 주장합니다.	☐
• 환자가 처방전을 자꾸 잃어버리며 마약성 진통제를 다시 처방받기 위해 여러 병원을 찾아 다니는 양상을 보입니다.	☐

2-개 이상의 긍정적 인 진술은 OrCC에 대해 양성으로 간주되었습니다.

3. Results

A total of 258 CNCP patients receiving LtOT, in six of eight hospitals, were included in the study (Figure 2). Patients from two hospitals were excluded due to delayed IRB approval. Based on the pre-defined consensus and the questionnaire for chemical coping, 55 patients (21%) were classified as OrCC.

The patients were divided into two groups according to a positive assessment for OrCC (the coping group (n = 55) and control group (n = 203)). Table 3 demonstrates the patients' sociodemographic data and clinical characteristics. The sample was homogenous in terms of ethnicity (all patients were Asian and only one patient was non-Korean), sex, BMI, marital status, employment, and religion. The average pain duration was 74.55 months (95% CI: 66.68 – 82.43), the shortest was 4 months and the longest 440 months (mode = 16 months). When compared to the control group, patients in the coping group were younger (48.58 ± 12.25 years vs. 53.79 ± 13.54 years; $p = 0.038$) and with an education level greater or equal to high school level (90.9% vs. 73.9%; $p = 0.007$).

Although the reduction of NRS pain score from the initial to final visit was significant within each group ($p < 0.001$ in controls and $p = 0.048$ in copers), it was less than one point in both groups. Pain in the head and neck, functional pain syndrome, and mixed pain were more common in copers (27.3% vs. 13.3%, $p = 0.013$; 18.2% vs. 2.5%, $p < 0.001$; and 18.2% vs. 8.4%, $p = 0.035$, respectively). Alcohol and/or medication abuse, and prescription drug use with alcohol within one year, were remarkably frequent in copers when compared to non-copers (20.0% vs. 3.9%, $p < 0.001$; 9.1% vs. 0.5%, $p < 0.001$; and 22.6% vs. 8.5%, $p = 0.02$, respectively). More copers had co-morbid depression (50.9% vs. 27.6%, $p = 0.001$) and reported ongoing litigation (27.8% vs.

13.9%, p = 0.010). Additionally, an overwhelming 66.7% of the sample (n = 172) had suicidal ideation related to their chronic pain.

The opioid information is shown in Table 4. The duration of opioid administration and number of patients with co-prescription (including benzodiazepines) was not significantly different between groups. Although the opioid types (long-acting vs. short-acting) were similar in both groups, rapid-onset fentanyl and intravenous injections were more frequent in the coping group (14.5% vs. 3.4%, p = 0.005 and 10.9% vs. 3.0%, p = 0.023, respectively). The average MEDD was significantly higher in the copers than the non-copers (169 ± 186 mg/day vs. 119 ± 227 mg/day, p = 0.006). Additionally, patients with MEDD ≥100 and ≥200 mg/day were more frequent in the coping group (32.7% vs. 21.2%, p = 0.033 and 25.5% vs. 9.9%, p = 0.002, respectively). The number of annual visits to an opioid prescriber and the number of patients who visited the ER seeking for opioids was significantly higher in the copers than non-copers (36.35 ± 53.93 visits vs. 19.07 ± 18.86 visits, p = 0.023 and 27.3% vs. 4.4%, p < 0.001, respectively). The first opioid prescriber was not significantly different between groups; and in 81% of the sample, the first opioid prescriber was a pain specialist.

Table 5 shows the questionnaires and predictive tools used in the study. Although the proportion of patients with a positive CAGE-AID was higher in the copers (80.0% vs. 66.5%), it did not reach statistical significance (p = 0.054). The PCS was over 30 in both groups, indicating a "catastrophic" appraisal of pain. The "worst" NRS item of the BPI-SF was higher, and the general activity, mood, and sleep interference were worse in the copers than the non-copers (p = 0.001, p = 0.043, p = 0.013, and p = 0.021, respectively). The K-IADL score and percentages were higher in the coping group (p = 0.031 and p = 0.017, respectively). Both groups reported high anxiety and depression

in HADS, moderate clinical insomnia in the ISI, and low resilience in the K-CD-RISC.

About 74% of the subjects were extremely or somewhat satisfied with their LtOT, and the percent of patients unsatisfied was significantly more prevalent among copers vs. non-copers (n = 24, 44% vs. n = 44, 22%; p = 0.002). A total of 14 patients were extremely unsatisfied and among them 12 replied that the opioids were not effective (“it doesn’t work”, “there is no pain relief”) and 2 patients that they were afraid of addiction. The PGIC was similar in both groups, the patients were moderately better with a slight but noticeable change. Two patients answered that they were much worse after receiving opioids, one in the control and the other in the coping group. There were no differences in the adverse or undesirable effects between groups, and 62% of the patients reported at least one event. The most frequent adverse effect was constipation (n = 105, 40.7%) followed by somnolence (n = 62, 24.0%) and nausea (n = 50, 19.4%).

Figure 3 shows the independent predictors of OrCC identified in multivariable analysis. The risk of OrCC increased in patients with: (1) prescription drugs abuse, Odds ratio (OR) = 19.32, 95% CI = 1.75–213.81, p = 0.016; (2) alcohol abuse, OR = 6.84, 95% CI = 2.26–20.69, p = 0.001; (3) functional pain syndrome, OR = 12.96, 95% CI = 3.47–48.45, $p < 0.001$; (4) head and neck pain, OR = 2.48, 95% CI = 1.05–5.88, p = 0.039; (5) MEDD $\geq$ 200 mg/day, OR = 3.48, 95% CI = 1.43–8.48, p = 0.006; and (6) ongoing litigation, OR = 2.33, 95% CI = 1.01–5.39, p = 0.047. Additionally, age < 55 years, OR = 2.17, 95% CI = 0.99–4.76, p = 0.052 and BPI-SF mood interference $\geq$ 8, OR = 1.84, 95% CI = 0.90–3.77, p = 0.096 remained in the multivariable model.

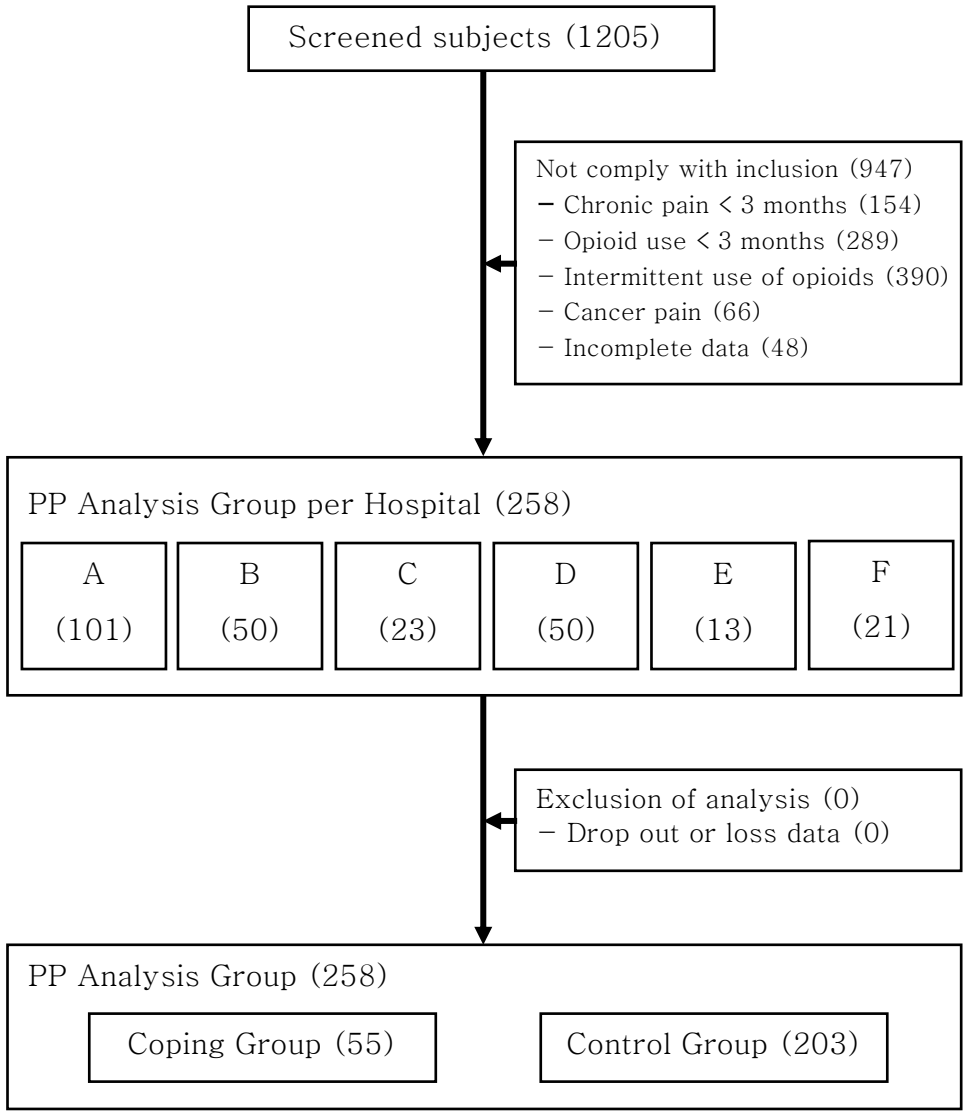

Figure 2. Flow diagram of participants

This figure shows the process of subjects' recruitment for the study.

A, B, C, etc., indicate the hospitals that participated in the study.
PP: per-protocol.

Table 3. Demographic variables and clinical characteristics

Variable	Overall (n = 258)	Control (n = 203)	Coping * (n = 55)	*p Value*
Gender, n (%)				0.905
Male	153 (59.3)	120 (59.1)	33 (60.0)	
Female	105 (40.7)	83 (40.9)	22 (40.0)	
Age, mean±SD, years	52.89±3.36	53.79±13.54	48.58±12.25	**0.038**
Ethnicity, n (%), Asian	258 (100)	203 (78.7)	55 (21.3)	–
BMI, mean±SD, kg/m^2	24.81±4.03	24.89±3.87	24.51±4.58	0.544
Marital status, n (%)				0.960
Married	64 (24.9)	50 (24.8)	14 (25.5)	
Single	185 (72.0)	146 (72.3)	39 (70.9)	
Divorced/Widowed	8 (3.1)	6 (3.0)	2 (3.6)	
Education level, n (%)				**0.007**
< high school	58 (22.6)	53 (26.1)	5 (9.1)	
≥ high school	200 (77.5)	150 (73.9)	50 (90.9)	
Employment status, n(%)				0.982
Unemployed and students + housewives	192 (75.6)	152 (75.6)	40 (75.5)	
Employed	62 (24.4)	49 (24.4)	13 (24.5)	
Religion, n (%)				0.245
No	130 (50.6)	106 (52.5)	24 (43.6)	
Yes	127 (49.4)	96 (47.5)	31 (56.4)	
Chronicity of pain, mean ±SD, months	74.55±64.25	73.23±66.09	79.44±57.23	0.526
NRS, mean±SD, points				
Initial	7.38±1.61	7.37±1.54	7.43±1.89	0.730
Current	6.55±2.09	6.51±2.10	6.86±2.07	0.309
Absolute change	−0.83±2.29	−0.89±2.41	−0.58±1.74	0.364
P−value of absolute change	**< 0.001**	**< 0.001**	**0.048**	
Percent change	−8.6±32.3	−8.9±22.1	−8.5±34.4	0.936†

Etiology of pain, n (%)				
Trauma	128 (49.6)	96 (47.3)	32 (58.2)	0.152
Surgery	51 (19.8)	43 (21.2)	8 (14.5)	0.273
Degenerative	15 (5.8)	10 (4.9)	5 (9.1)	0.325†
Disease	73 (26.7)	56 (28.1)	17 (32.7)	0.236
Combined	1 (0.4)	1 (0.5)	0 (0.0)	1
Idiopathic	9 (3.5)	6 (3.0)	3 (5.5)	0.407‡
Location of pain, n (%)				
Head & Neck	42 (16.3)	27 (13.3)	15 (27.3)	**0.013**
Chest or Abdomen	35 (13.6)	24 (11.8)	11 (20.0)	0.116
Back	102 (39.5)	77 (37.9)	25 (45.5)	0.311
Extremities	197 (76.4)	155 (76.4)	42 (76.4)	0.999
Others§ or unknown	20 (7.8)	15 (7.4)	5 (9.1)	0.776
Type of pain, n (%)				
Nociceptive	36 (14.0)	29 (14.3)	7 (12.7)	0.767
Neuropathic	197 (76.4)	160 (78.8)	37 (67.3)	0.074
Functional	15 (5.8)	5 (2.5)	10 (18.2)	**< 0.001**‡
Mixed	27 (10.5)	17 (8.4)	10 (18.2)	**0.035**
Substance abuse history within 1 year, n (%)				
Yes	79 (30.6)	52 (25.6)	27 (49.1)	**0.001**
Tobacco	62 (24.0)	46 (22.7)	16 (29.1)	0.322
Alcohol	19 (7.4)	8 (3.9)	11 (20.0)	**< 0.001**
Medication	6 (2.3)	1 (0.5)	5 (9.1)	**< 0.001**
Illicit drugs	0 (0.0)	0 (0.0)	0 (0.0)	–
Multiple	1 (0.4)	1 (0.5)	0 (0.0)	1.00‡
Taken prescription drugs with alcohol within 1 year, n (%)	29 (11.2)	17 (8.5)	12 (22.6)	**0.002**
Concurrent psychopathology, n (%)				
Yes	120 (46.5)	86 (42.4)	34 (61.8)	**0.008**
Depression	84 (32.6)	56 (27.6)	28 (50.9)	**0.001**
Anxiety	25 (9.7)	19 (9.4)	6 (10.9)	0.73
PTSD	52 (20.2)	37 (18.2)	15 (27.3)	0.138

Bipolar disorder	6 (2.3)	4 (2.0)	2 (3.6)	0.611ǂ
Others	22 (8.5)	18 (8.9)	4 (7.3)	1.00ǂ
Secondary morbid gain, n (%)				
Miss work or studies	42 (53.1)	30 (83.3)	12 (92.3)	0.658
Avoid military duty		46 (22.8)	7 (13.0)	0.157
Ongoing litigation	43 (16.7)	28 (13.9)	15 (27.8)	**0.010**
Suicidal ideation, n (%)	172 (66.7)	132 (65.3)	40 (75.5)	0.161

This table depicts the data and statistical analysis of the patients' demographic and clinical characteristics

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* *A physician with the OrCC questionnaire evaluated the presence of OrCC. Two or more affirmative answers were positive for OrCC.*

† *Values from Mann–Whitney U test*

ǂ *Values from Fisher's exact test*

§ *Whole body or genitalia*

BMI: body mass index; NRS: 11–point pain numerical rating scale; PTSD: post–traumatic stress disorder; SD: standard deviation.

Table 4. Opioid-related information

Variable	Overall (n = 258)	Control (n = 203)	Coping * (n = 55)	*p Value*
Duration of opioids, mean±SD, months	16.34±31.08	15.90±28.76	17.85±38.25	0.722
> 12 months, n (%)	65 (25.2)	51 (25.1)	14 (25.5)	0.747
Opioid types, n (%)				
Long-acting	231 (89.5)	184 (90.6)	47 (85.5)	0.265
Oral long-acting	213 (82.6)	170 (83.7)	43 (78.2)	0.335
Transdermal patch	85 (32.9)	63 (31.0)	22 (40.0)	0.210
Short-acting	145 (56.2)	109 (53.7)	36 (65.5)	0.119
Oral	141 (54.7)	107 (52.7)	34 (61.8)	0.229
Rapid onset fentanyl	15 (5.8)	7 (3.4)	8 (14.5)	**0.005**
Intravenous	12 (4.7)	6 (3.0)	6 (10.9)	**0.023**
MEDD, mean±SD, mg/d	129±220	119±227	169±186	**0.006** †
≥100 mg/d, n (%)	95 (36.8)	68 (33.5)	27 (49.1)	**0.033**
≥200 mg/d, n (%)	34 (13.2)	20 (9.9)	14 (25.5)	**0.002**
Number of visits per year to the opioid provider, mean±SD	22.77±30.71	19.07±18.86	36.35±53.93	**0.023**
ER visits seeking opioids, n (%)	24 (9.3)	9 (4.4)	15 (27.3)	**< 0.001**
First opioid provider, n (%)				0.702
Family doctor	2 (0.8)	1 (0.5)	1 (1.8)	0.609
General physician	6 (2.3)	5 (2.5)	1 (1.8)	0.778
Surgeon	20 (7.8)	13 (6.4)	7 (12.7)	0.120
ER physician	2 (0.8)	2 (1.0)	0 (0.0)	0.460

Pain physician	209 (81.0)	166 (81.8)	43 (78.2)	0.547
Others ǂ	18 (7.0)	15 (7.4)	3 (5.5)	0.617
Unknown	1 (0.4)	1 (0.5)	0 (0.0)	0.602
Benzodiazepines, n (%)	120 (46.5)	95 (46.8)	25 (45.5)	0.859
Non-opioid drugs, n (%)				
Antidepressants	134 (51.9)	107(55.4)	27 (51.9)	0.651
Anticonvulsants	182 (70.5)	149 (77.2)	33 (64.7)	0.068
Topical agents	33 (12.8)	24 (12.4)	9 (17.6)	0.333
Physical therapy, n (%)	32 (12.4)	28 (3.9)	4 (7.4)	0.203

This table depicts the data and statistical analysis of the patients' opioid consumption and other treatments information.

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* *A physician with the OrCC questionnaire evaluated the presence of OrCC. Two or more affirmative answers were positive for OrCC.*

† *Values from Mann-Whitney U test*

ǂ *Gynecology, internal medicine, neurology, neuropsychiatry, orthopedics, otorhinolaryngology.*

ER: emergency room; MEDD: morphine equivalent daily dose; SD: standard deviation.

Table 5. Questionnaires and predictive tools

Variable	Overall (n = 258)	Control (n = 203)	Coping * (n = 55)	*p Value*
CAGE-AID, n (%)				
Negative	79 (30.6)	68 (33.5)	11 (20.0)	0.106
Positive (≥1 positive)	179 (69.4)	135 (66.5)	44 (80.0)	0.054
PCS, mean±SD, points	34.22±2.27	34.14±12.33	34.51±12.18	0.843
≥30 points, n (%)	170 (65.9)	134 (66.0)	36 (65.5)	0.939
BPI-SF, mean±SD, points				
Worst NRS	8.12±1.97	7.95±2.06	8.75±1.42	**0.001**
NRS on average	6.63±2.05	6.53±2.05	6.98±2.04	0.152
NRS right now	6.37±2.36	6.29±2.30	6.67±2.58	0.288
Pain relief (%)	48.44±23.47	49.79±22.39	43.45±26.75	0.112
Pain interference				
General activity	6.47±2.48	6.31±2.53	7.07±2.20	**0.043**
Mood	6.59±2.53	6.39±2.56	7.35±2.27	**0.013**
Walking ability	5.85±3.14	5.77±3.14	6.15±3.15	0.437
Normal work	6.38±2.75	6.22±2.79	6.96±2.55	0.076
Relations with other people	6.04±3.26	5.88±3.28	6.62±3.15	0.137
Sleep	6.29±3.09	6.06±3.12	7.15±2.85	**0.021**
Enjoyment of life	6.78±3.00	6.66±3.03	7.22±2.85	0.221
K-IADL, mean±SD, points	7.46±7.18	6.96±6.90	9.31±7.90	**0.031**
Percentage	64.01±74.55	58.28±73.74	85.18±74.35	**0.017**
PGIC, n (%), better	108 (41.9)	89 (43.8)	19 (34.5)	0.215

Satisfaction scale, †				0.002
Satisfied, n (%)	190 (73.6)	159 (78.3)	31 (56.4)	
Unsatisfied, n (%)	68 (26.4)	44 (21.7)	24 (43.6)	
HADS				
Anxiety, mean±SD, points	10.88±4.99	10.72±4.80	11.45±5.66	0.381
≥11 points, n (%)	125 (48.4)	96 (47.3)	29 (52.7)	0.474
Depression, mean±SD, points	11.76±4.71	11.74±4.35	11.80±5.91	0.938
≥11 points, n (%)	160 (62.0)	127 (62.6)	33 (60.0)	0.728
ISI, mean±SD, points	16.83±7.63	16.61±7.62	17.62±7.66	0.386
≥15 (moderate-severe), n (%)	162 (62.8)	124 (61.1)	38 (69.1)	0.276
≥22 (severe), n (%)	88 (34.1)	66 (32.5)	22 (40.0)	0.299
K-CD-RISC, mean±SD, points	67.95±22.06	68.77±22.24	64.91±21.30	0.250

This table depicts the data and statistical analysis of the patients' responses to the questionnaires and predictive tools evaluated in this study.

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* *A physician with the OrCC questionnaire evaluated the presence of OrCC. Two or more affirmative answers were positive for OrCC.*

† *Satisfied = extremely satisfied and somewhat satisfied, unsatisfied = somewhat unsatisfied and extremely unsatisfied.*

BPI-SF: brief pain inventory - short form; CAGE-AID: cut down, annoyed, guilty, eye-opener - adapted to include drugs; HADS: hospital anxiety and depression scale; ISI: insomnia severity index; K-IADL: Korean-instrumental activities of daily living; K-CD-RISC: Korean-Connor-Davidson resilience scale; PCS: pain catastrophizing scale; PGIC: patient global impression of change; SD: standard deviation.

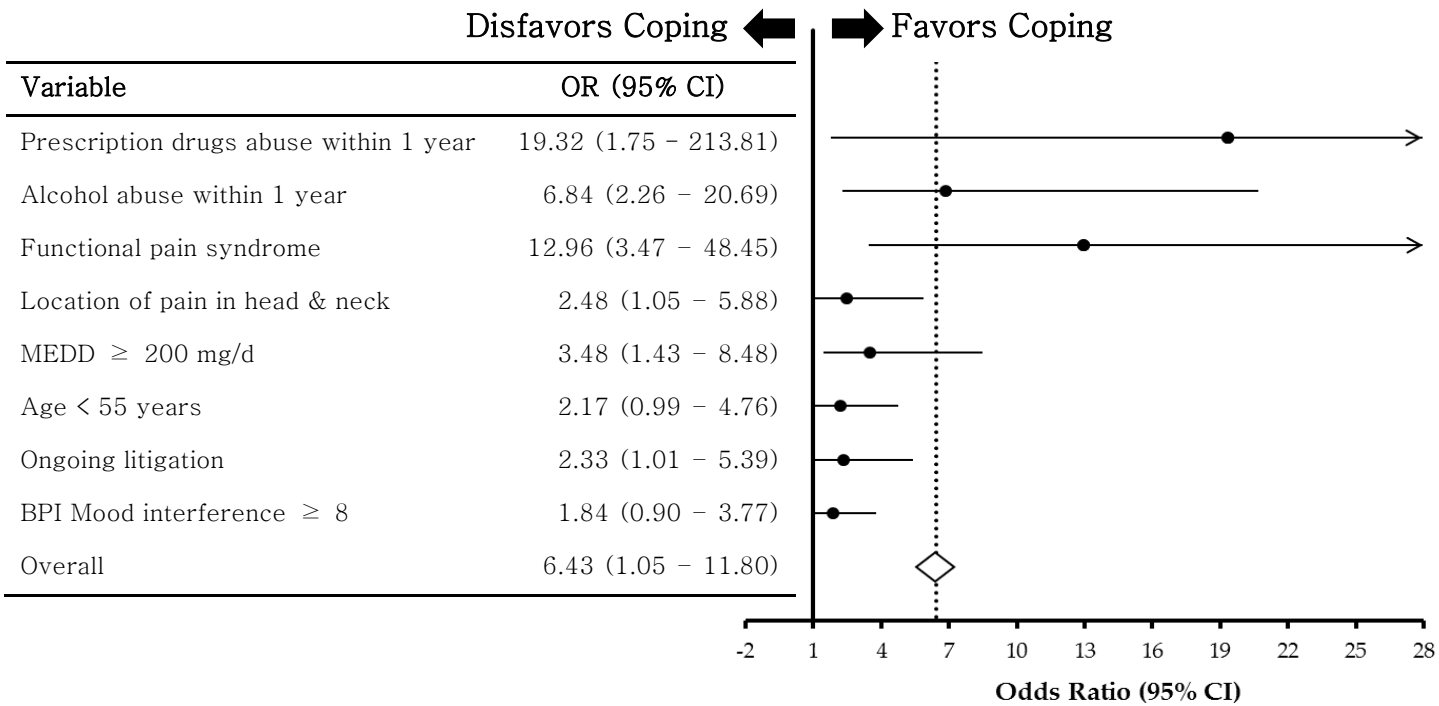

Figure 3. Forest plot of multivariable analysis showing the factors independently associated with opioid-related chemical coping

This figure shows the distribution of risk probabilities per factor associated with OrCC.

BPI: brief pain inventory; CI: coefficient interval; MEDD: morphine equivalent daily dose; OR: Odds ratio.

Chapter 4. Discussion

This study evaluated the rate of OrCC, patient characteristics, and risk factors of OrCC in a group of CNCP patients receiving LtOT. The frequency of OrCC was 21%, which indicates that about one out of every five CNCP patients used opioids to cope with emotional distress. There is a scarcity of research regarding the frequency of OrCC, except for one study [19], which reported a rate of 18% in palliative care patients in the U.S. Therefore, to the best of our knowledge, this is the first study to evaluate the rate of OrCC in CNCP. Our results demonstrate that the frequency of CNCP patients coping chemically with opioids is as high as that found in cancer patients [19]. Furthermore, it is comparable to the rate of misuse (21–29%) determined in a recent systematic review that included 35 studies from the U.S. and three studies from the European Union (EU) [21]. Our results show that OrCC in CNCP is comparably high to OUD rates, even in countries with low–moderate opioid consumption. Therefore, the risk of OUD seems to be independent of the country's opioid consumption rate (mg/capita), and the countries with low–moderate opioid consumption may have an underestimated opioid problematic.

Regarding patients' demographics, previous studies reported that young age and male sex are common risk factors for OUD and dependency [50,51]. In this study, younger patients were more likely to be classified in the coping group and conversely patients 70 years or older were frequently found in the control group. Another survey of 25,864 patients in the U.S. also found that old age was associated with lower rates of OUD [52]. Although the copers were younger, patient sex was not statistically significant, which correlates with another OrCC study [19]. OrCC patients had high level of education compared to the

non−copers, which contradicts previous studies in substance abuse and dependence [53,54]. The discrepancy in our finding may be explained as an interaction effect between age and level of education (correlation coefficient = −0.178, p = 0.005). In our study, younger patients had higher level of education and conversely older patients had lower than high school education level. A recent report found that 66% of Koreans, between the age of 25 and 34 years, attained tertiary education, while only 8% of Korean women aged 55–64 years did it [55]. Therefore, younger patients with an increased liability to OrCC had higher education levels, which may explain our results.

Although there were no differences in the job status between coppers and controls, most of the CNCP patients were informal workers (n = 83, 32.3%) or unemployed (n = 122, 47.3%). Other studies found that chronic pain is negatively associated with an individual's employment, thus job loss is a frequent consequence of the patient's catastrophizing of pain, health care dissatisfaction, and pain disability [56,57]. Another interesting finding was that most of the CNCP patients were single (n = 185, 72%). Marriage has been associated with longer life and better health in both men and women. One study found a strong association of the marital status with emotional suffering but not with negative illness beliefs and concluded that widowed patients have better psychological resilience to chronic pain [58]. However, the population of married people is decreasing yearly, and younger people are inclined to cohabitate or remain single thus studies correlating marital status with chronic pain may prove difficult to conduct. In S. Korea, according to census statistics released on March 2018, the number of marriages recorded in 2017 fell 6.1% from the previous year achieving a rate of 5.5 marriages per 1000 people, the lowest level since 1970 [59]. The trend among young Koreans is to choose a single lifestyle, which has contributed to a low birthrate and converted

the country in the world's fastest-aging developed economy.

In terms of the pain characteristics, the overall patients in this study complained of moderate to severe pain with an NRS pain score over seven points at their initial visits. Despite LtOT, however, their pain improvement on the last measurement was trivial with only 8.6% reduction in the pain severity and only 1 point in the NRS scale. In addition, the prevalence of posttraumatic stress disorder (PTSD) in the study's sample was relatively high (n = 52, 20.2%) without significant differences between the groups. PTSD patients have more risk factors for pain, including higher rates of psychiatric and substance use disorders [60], which may explain the high frequency of the disorder found in this study. Another interesting result in this study was that head and neck pain increased 2.5 times ($p = 0.039$), and functional pain disorders increased 13 times the risk of OrCC ($p < 0.001$) in our multivariable analysis. Functional pain syndromes typically concur with anxiety, depression, and chronic fatigue syndrome [61], conditions for which opioids are usually ineffective [62]. Therefore, the treatment of chronic functional pain should be centered in non-opioid pharmacotherapy with active use of physiotherapeutic and psychological methods to improve coping with pain [63]. Moreover, patients receiving LtOT without improvement in the pain control should be evaluated to assess the real contribution of opioids and to reduce drug toxicity.

Major depression and alcohol or drug abuse are known risk factors for OUD and OrCC [18,63,64] which is concordant with our result. Markou et al. [65] asserted that depression has neurobiological effects similar to those in alcohol or opiate withdrawal syndromes. Hence, patients with underlying depression may self-medicate with opioids to correct their dysfunctional systems. Our sample had high HADS scores without statistically significant differences between groups, which may be

explain by the scale's low specificity (~50%) and sex/age-related biases [66], and due to the high prevalence of anxiety and depression in chronic pain patients with LtOT. In addition, alcohol and prescription drug abuse also increased seven ($p = 0.001$) and 19 times ($p = 0.016$) the risk of OrCC in our results. The concomitant use of alcohol and opioids is associated with OUD, OrCC and worse outcomes [67], which is consistent with our result ($p = 0.002$). Therefore, CNCP patients with alcohol and/or prescription drug abuse history require special attention due to an increased risk of OrCC, opioid toxicity, and poor outcomes.

Similar to previous studies in OUD [68,69], patients with OrCC received significantly higher dosages of opioids ($p = 0.006$) in this study. Interestingly, doses of 100–200 mg/day were not different among the groups ($p = 0.878$). However, dosages ≥200 mg/day almost quadrupled the risk of OrCC ($p = 0.002$). Another study from the U.S. also found increased OUD rates with dosages ≥200 mg/day, without differences at 100 or 120 mg/day [70]. Therefore, dosages ≥200 mg/day should be concerning in CNCP due to a high correlation with OrCC and OUD. In terms of opioid types, rapid-onset opioids (ROOs) were prescribed more frequently in the coping group. ROOs are used for the management of breakthrough pain (BTP) in opioid-tolerant patients with cancer or noncancer pain [70–73]. Although the evidence linking ROOs to OUD is limited [74,75], our results support that ROOs may potentiate OUD. A cautious use of ROOs in CNCP patients is recommended and further studies that evaluate its association with OUD are needed. Additionally, frequent visits to the provider and/or the ER seeking for opioids was correlated with OrCC ($p = 0.001$ and $p < 0.001$, respectively). Therefore, although pseudo-addiction should be initially discarded as a cause of opioid seeking [76], frequent hospital and ER visitors must be evaluated for OUD.

The BPI-SF showed increased pain interference, and the K-IADL indicated an increased compromise of daily activities in the copers. Our results suggest that decreased functionality and high pain interference constitute risk factors of OrCC [77,78]. Ongoing litigation doubled the risk of OrCC. Although previous studies have not linked litigation with OUD, this process causes negative emotions that accentuate the underlying pain with anger, frustration, and helplessness [79], which may induce OrCC. Furthermore, two-thirds of the sample had catastrophic thinking and moderate-severe insomnia. Pain catastrophizing is associated with pain severity, altered CNS pain processing, and exaggerated pain-related interference [80]. Our sample had low resilience (68/100 points), compared to the U.S. general population average (80/100 points) [40]. These findings highlight the role of psychological therapy in improving pain-coping skills and functionality in CNCP patients [81,82].

Contrary to previous studies on chemical coping [19,76], in this study, the CAGE-AID questionnaire was not significantly positive in the OrCC group when compared to the controls ($p = 0.054$). Interestingly, CAGE-AID positives were found in 66.5% of the controls, whereas 20% negatives were copers. This result infers that CAGE-AID is a predictive, but not a diagnostic tool for OUD with a low specificity [19,83]. Moreover, the questionnaire focuses on addiction and may not detect risky use in non-dependent individuals [35], as in our study population. Another distinctive result is that pain specialists were the predominant opioid prescribers. S. Korea's strict regulations on opioids and the difficulties of storage and administration limit their use by primary specialists [84]. Conversely, in the U.S., the primary care specialty groups accounted for nearly half (44.5%) of all dispensed opioid prescriptions during 2007–2012 [85]. Additionally, insufficient training in the management of CNCP and excessive focus on the treatment with opioids may lead to its

over-prescription and the under-detection of OUD [86,87]. Accordingly, the mean amount of opioids prescribed per person in 2015 in the U.S. was 640 mg/day (0.1–5543 mg/day) [4], almost five times the mean in our study 129 mg/day (4.5–2700 mg/day).

Another remarkable finding in this study is the absence of illicit drug abuse reports. This result may be secondary to deep-rooted cultural and social stigmatization of illicit drugs in Asia [88]. In Asia drugs are ill seen by society and its possession, distribution, and use are severely punished by law. Historically, S. Korea has been viewed as a drug-free country when compared to the U.S., Japan, and other countries [89]. Traditional drugs, including heroin and cocaine, are not commonly used in S. Korea, as reflected by drug seizure and arrest data [90]. However, drug availability has increased since 2006 due to globalization and economic expansion [90]. Nonetheless, it is still difficult and expensive to obtain illicit substances in S. Korea, thus the 'street' use of drugs among young adults and students is limited. In the U.S., the poor results in the reduction of overall overdose deaths with the guidelines in opioid prescription has led to a change of strategies. In 2018, the U.S. government has centered in law enforcement to reduce drug supply, prevention and education by ad campaigns, and job-seeking assistance for individuals fighting addiction [91]. The efforts to combat opioid addiction are directed now to achieve public awareness and to sweep the legislation to include promoting research that find new drugs for pain management and expand the treatment for substance use disorders for Medical patients. The results of the new U.S. government strategies will prove its efficacy in the years to come. In the meantime, the strict laws on illicit drug-use in S. Korea seem to be effective in controlling overdose deaths and maintaining low rates of illicit drug consumption.

There are several limitations to be addressed. First, this study took place only in tertiary hospitals. This may be associated with biases for generalization since the patients in this study may have more challenging pain syndromes than those in primary institutions. Second, the questionnaire used to evaluate OrCC was a result of an expert meeting; however, it is not a validated tool. In addition, although there were three consensus and educational meetings prior to patient enrollment, there might be detection biases between pain specialists. Nonetheless, OrCC is a clinical phenomenon accurately assessed by experienced providers [16], thus, a high predictability of true positives may be expected. Moreover, in this study, OrCC was evaluated immediately after each visit to avoid inappropriate scoring or recall biases. Third, our sample size was relatively large (n = 258); however, a broad CI of some OrCC risk factors in our multivariable analysis, such as prescription drug abuse (OR = 19.32 (95% CI = 1.75–213.81)) or functional pain syndrome (OR = 12.96 (95% CI = 3.47–48.45)), would be a limitation. Another drawback is that the study's data depended on statements from patients. Although there was assurance of confidentiality, patients' responses may not always be reliable. Finally, urine drug test and opiate immunoassay, which are considered "gold standards" to assess OUD [9], were not conducted. Barriers to cost–effectiveness and accessibility restricted their use in this study.

Chapter 5. Conclusion

Approximately 21% of the CNCP patients receiving LtOT are chemically coping with opioids, carrying high intensity of pain, and experiencing severe interference in daily activities. The high rates of OrCC found in this study suggest that the break-out of OUD in CNCP of S. Korea is comparable to those in countries with high opioid consumption, such as the U.S., regardless of the country's opioid consumption rates. Therefore, we should be vigilant about OUD in CNCP patients with LtOT. The independent risk factors of OrCC are prescription drugs and alcohol abuse, functional pain syndrome, pain in the head and neck, MEDD $\geq$ 200 mg/day, and ongoing litigation. Although further validation studies are warranted, the assessment of OrCC may prompt the identification of patients at high risk for severe OUD. Finally, although our result has suggested that, there is no benefit of LtOT in CNCP; more research is needed to establish the rationale of evidence-based opioid prescription that should be limited to short-term use as much as possible.

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Appendix 1. Individual questions to patients

다음 중 질문에 답해 주십시오

1.1. 마약성 진통제를 처음 처방 받은 과(의사)는 어디 입니까?

0 – 가정의학과의사
1 – 일반내과의사
2 – 외과의사
3 – 응급의학과의사
4 – 통증의학과의사
5 – 잘모른다

1.2. 마약성 진통제 복용 후 부작용을 경험한 적이 있습니까? (네 / 아니오)

➔ '네' 라고 대답한 경우 아래 해당 항목에 표시해주세요.

변비	구역/구토	근육긴장이상	졸림	수면 중 무호흡	성기능 장애	비뇨기 기능장애	호흡 억제	그 외의 증상

1.3. 현재 다른 병원에서 받고 있는 통증치료가 있습니까? (네 / 아니오)

➔ 네' 라고 대답한 경우 아래 해당 항목에 표시해주세요.

물리치료	스크램블 치료	수술	한의학	자연치료	신경 차단술	그 외의 치료

1.4. 현재 정신건강의학과 진료를 보고 있습니까? (네 / 아니오)

➔ '네' 라고 대답한 경우 아래 해당 항목에 표시해주세요.

우울증	불안	외상 후 스트레스 장애	경계성 인격장애	이 외에 다른 증상

1.5. 자살에 대해 생각해 본 적이 있습니까?

0 – 한번도 없었다
1 – 한번이상 있다
2 – 한상 있다

1.6. 실패한 자살 행동이 있습니까?

0 – 없다 1 – 있다

1.7. 군 복무를 하였습니까?

0 – 아니오 1 – 네 2 – 해당 없음

1.8. 현재 진행중인 법적 소송이 있습니까?

0 – 없다 1 – 있다

Appendix 2. Questionnaires and scales in Korean

2.1. CAGE-AID Questionnaire (CAGE-AID 질문지):

향정신성 약물(마약성 진통제 포함) 사용에 대해 생각할 때, 불법적인 향정신성 약물 사용 및 처방 받은 (용법)것 이외의 사용을 모두 포함시켜 주시기 바랍니다.

질문	예	아니오
1. 귀하는 귀하의 음주 또는 향정신성 약물 (마약성 진통제 포함) 사용을 줄여야 한다고 느낀 적이 있습니까?	☐	☐
2. 사람들이 귀하의 음주 또는 향정신성 약물 (마약성 진통제 포함) 사용에 대해 비난하여서 귀하를 짜증나게 한 적이 있습니까?	☐	☐
3. 귀하는 귀하의 음주 또는 향정신성 약물 (마약성 진통제 포함) 사용에 대해서 나쁘게 느끼거나 죄의식이 든 적이 있습니까?	☐	☐
4. 귀하는 신경을 안정시키거나 숙취를 제거하기 위해 아침에 첫 번째로 한 일이 음주 또는 향정신성 약물 (마약성 진통제 포함) 사용이었던 적이 있습니까?	☐	☐

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*Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. Wis Med J **1995**, 94(3):135-140.*

2.2. Pain Catastrophizing Scale, PCS (통증파국화 척도):

1. 나는 통증의 끝은 있는 것인가 하고 항상 걱정한다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

2. 나는 앞으로 통증으로 이겨낼 수 없을 것 같다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

3. 통증이 너무나 심각하여 통증이 더 이상 호전될 것 같지 않다는 생각이 든다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

4. 통증이 너무 심하여, 통증이 나를 압도하는 느낌이다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

5. 더 이상 통증을 견딜 수 없을 것 같다고 생각된다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

6. 통증이 더 심각해질까봐 두렵다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

7. 아팠던 상황들에 대하여 계속 생각이 든다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

8. 나는 진정으로 통증이 사라졌으면 좋겠다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

9. 머리 속에서 통증에 대한 생각을 지워버릴 수가 없다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

10. 나는 항상 얼마나 통증이 아팠었는가에 대하여 생각한다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

11. 나는 항상 통증을 멈추게 하고 싶다고 생각한다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

12. 통증의 강도를 줄이기 위해 스스로 할 수 있는 있이 아무것도 없다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

13. 더 심각한 일이 생길까 걱정이다.

● 전혀 그렇지 않다. ● 가끔 그렇다. ● 보통 그렇다. ● 자주 그러한 편이다. ● 항상 그렇다.

주치의 기록란입니다. ▶ 총점 [ ] / 52

Sullivan, M.J.L.; Bishop, S.R.; Pivik, J. The Pain Catastrophizing Scale: Development and validation. Psychol. Assess ***1995****, 7 (4), 524-532.*

2.3. Insomnia Severity Index, ISI (불면증 심각성 척도)

당신의 불면증에 관한 문제들의 현재(최근 2주간) 심한정도를 표시해 주세요.

	없음	약간	중간	심함	매우심함
1. 잠들기 어렵다	0	1	2	3	4
2. 잠을 유지하기 어렵다	0	1	2	3	4
3. 쉽게 깬다	0	1	2	3	4

4. 현재 수면 양상에 관하여 얼마나 만족하고 계십니까?

매우만족	약간만족	그저그렇다	약간불만족	매우불만족
0	1	2	3	4

5. 수면장애로 인한 당신의 삶의 질 손상정도를 다른 사람들은 얼마나 걱정합니까?

전혀	약간	다소	상당히	매우 많이
0	1	2	3	4

6. 당신은 현재 불면증에 대해 얼마나 걱정하고 있습니까?

전혀	약간	다소	상당히	매우 많이
0	1	2	3	4

7. 당신의 수면장애가 어느 정도나 당신의 낮의 활동을 방행한다고 생각합니까?
(낮의 피곤, 직장이나 가사에 일하는 능력, 집중력, 기억력, 기분 등)

전혀	약간	다소	상당히	매우 많이
0	1	2	3	4

1~7번 항목의 점수를 모두 더하세요.

점 수	결 과
0~7	유의할만한 불면증이 없습니다.
8~14	약간의 불면증경향이 있습니다.
15~21	중등도의 불면증이 있습니다.
22~28	심한 불면증이 있습니다.

▲주치의 기록란입니다.

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*Morin CM, Belleville G, Belanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep **2011**, 34(5):601-608.*

2.4. Korean Instrumental Activities of Daily Living Scale, K-IADL (한국형 도구적 일상생활활동 측정도구)

환자의 최근 한달간의 상태를 고려하여 해당 사항에 동그라미 쳐주세요. 원래 하지 않았던 일은 '해당없음'에 표시해 주십시오.

항 목	0	1	2	3	
1. 시장보기 상점에 가서 계획한 물건들을 잊지 않으며 돈 계산에 실수 없이 구매합니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음
2. 교통수단이용 대중교통을 이용하거나 스스로 운전해서 길을 잃지 않고 목적지에 갑니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음
3. 돈 관리 용돈을 관리하고, 은행에 가서 저축을 하는 등의 돈과 관련된 일을 처리합니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음
4. 기구 사용과 집안 일하기 진공청소기, 다리미 등의 기구들을 잘 다루고 일상적인 집안 일(예: 청소, 화포 물주기, 설거지)을 예전처럼 말끔하게 합니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음
5. 음식준비 적절한 식사를 계획하여 재료를 준비하고, 예전과 같이 맛있게 음식을 만듭니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음
6. 전화 사용 필요한 전화번호를 수첩에서 찾거나 기억하여 전화를 겁니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음
7. 약 복용 시간과 용량을 지켜 약을 먹습니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음
8. 최근 기억 약속, 어제의 일 또는 다른 사람에게 전달해야 할 전화 내용 등을 기억합니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음
9. 취미 생활 종교, 독서, 바둑, 장기, 화투, 산책, 등산, 운동 등의 예전에 하던 취미를 그대로 잘 수행합니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음
10. 텔레비전 시청 집중해서 텔레비전을 보며 그 내용을 이해합니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음
11. 집안 수리 못박기나 전구 끼우기 같은 집안 잡일을 수행합니까?	혼자 가능	약간 도움이 필요	많은 도움이 필요	불가능	해당 없음

◆평점(총점/11문항 – '해당 없음' 문항 수): (/)점 ◀ 주치의 평가 란입니다.

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*Kang SJ, Choi SH, Lee BH, Kwon JC, Na DL, Han SH. The reliability and validity of the Korean instrumental activities of daily living (K-IADL). J Korean Neurol Assoc **2002**, 20(1):8-14.*

2.5. Connor-Davidson resilience scale, CD-RISC (회복력 측정도구)

문 항		전혀 아니다	거의 아니다	때때로 그렇다	자주 그렇다	매우 그렇다
1.	변화에 잘 적응한다.	1	2	3	4	5
2.	가깝고 안정적인 인간관계가 있다.	1	2	3	4	5
3.	때로는 운명이나 신이 도울 수 있다.	1	2	3	4	5
4.	어떤 상황에도 잘 대처할 수 있다.	1	2	3	4	5
5.	성공적으로 마쳤던 과거의 경험이 새로운 일을 도전하는데 있어 자신감을 갖게 해준다.	1	2	3	4	5
6.	어떠한 상황에서도 유머스러운 면모를 본다.	1	2	3	4	5
7.	스트레스 극복이 날 강하게 한다.	1	2	3	4	5
8.	병이나 어려움을 잘 극복 할 수 있다.	1	2	3	4	5
9.	어떤 일이든 이유가 있어서 일어난다.	1	2	3	4	5
10.	어떤 상황에도 최선을 다 한다.	1	2	3	4	5
11.	자신이 정한 목표를 달성한다.	1	2	3	4	5
12.	비록 희망적이지 않더라도 포기하지 않는다.	1	2	3	4	5
13.	필요한 때, 어느 곳에서 도움(혹은 조언)을 청해야 할지 알고 있다.	1	2	3	4	5
14.	압박감 속에서도 현명하게 생각하고 집중한다.	1	2	3	4	5
15.	문제 해결을 주도하는 것을 좋아한다.	1	2	3	4	5
16.	실패에 쉽게 낙담하지 않는다.	1	2	3	4	5
17.	스스로를 강인한 사람이라 생각한다.	1	2	3	4	5
18.	일반적이지 않은 어려운 일에서도 결정을 내릴 수 있다.	1	2	3	4	5
19.	불쾌한 감정을 잘 다스린다.	1	2	3	4	5
20.	행운이 올 것 같은 예감이 든다.	1	2	3	4	5
21.	강한 목적 의식을 가지고 있다.	1	2	3	4	5
22.	나의 인생을 통제할 수 있다.	1	2	3	4	5
23.	도전을 지향한다.	1	2	3	4	5
24.	나는 목표를 성취하기 위해 일한다.	1	2	3	4	5
25.	자신이 이루어낸 성취물 혹은 결과들에 자부심을 가지고 있다.	1	2	3	4	5

Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson resilience scale (CD-RISC). Depress Anxiety **2003**, *18(2):76-82.*

2.6. Brief Pain Inventory – Short form, BPI-SF [통증 평가지 (축소판)]

PAIN COMPONENT

연구번호: _____ 위의 내용은 기록하지 마십시오 병원번호: _____

간이통증조사지(축소판)

병증평가일자: ____/____/____ 시간: _____

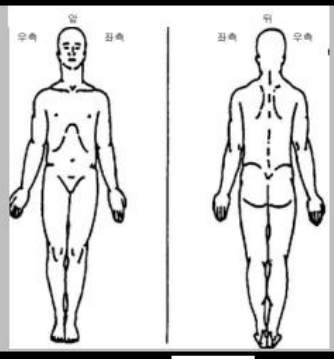
이름: _____ _____ _____

성 이름 중간 이름

1. 우리들 대부분은 살아가는 동안 이따금 통증(가벼운 두통, 염좌, 치통)을 경험합니다. 이러한 일상적인 통증 외에 다른 통증을 오늘 느낀 적이 있습니까?

1. 예 2. 아니오

2. 다음 그림에 귀하가 통증을 느끼는 부위에 음영으로 처리해 주십시오. 그중에서 가장 아픈 부위에 X 표를 하십시오.



3. 귀하의 통증이 지난 24 시간 동안 가장 심했을 때 그 정도를 가장 잘 나타내는 숫자에 동그라미 표시를 하십시오.

0 1 2 3 4 5 6 7 8 9 10
통증이 없음 상상할 수 없을 정도의 심한 통증

4. 귀하의 통증이 지난 24 시간 동안 가장 약했을 때 그 정도를 가장 잘 나타내는 숫자에 동그라미 표시를 하십시오.

0 1 2 3 4 5 6 7 8 9 10
통증이 없음 상상할 수 없을 정도의 심한 통증

5. 귀하가 느끼는 통증의 평균 정도를 가장 잘 나타내는 숫자에 동그라미 표시를 하십시오.

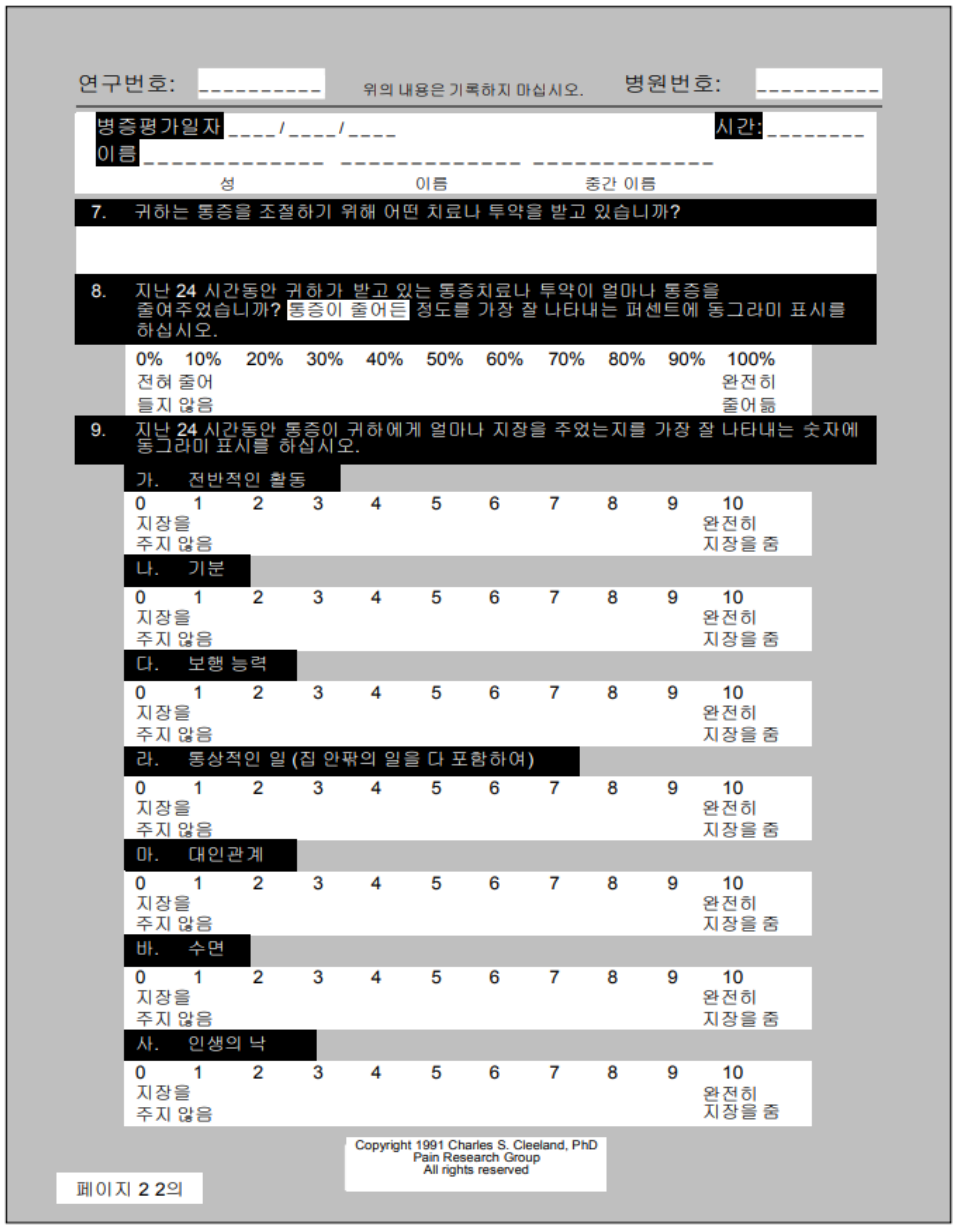
0 1 2 3 4 5 6 7 8 9 10
통증이 없음 상상할 수 없을 정도의 심한 통증

6. 귀하가 바로 지금 느끼는 통증의 정도를 가장 잘 나타내는 숫자에 동그라미 표시를 하십시오.

0 1 2 3 4 5 6 7 8 9 10
통증이 없음 상상할 수 없을 정도의 심한 통증

페이지 1 2의

INTERFERENCE COMPONENT



연구번호: _____ 위의 내용은 기록하지 마십시오. 병원번호: _____

병증평가일자 ____/____/____ 시간: _____

이름 _____ _____ _____

성 이름 중간 이름

7. 귀하는 통증을 조절하기 위해 어떤 치료나 투약을 받고 있습니까?

8. 지난 24 시간동안 귀하가 받고 있는 통증치료나 투약이 얼마나 통증을 줄여주었습니까? 통증이 줄어든 정도를 가장 잘 나타내는 퍼센트에 동그라미 표시를 하십시오.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
전혀 줄어 들지 않음 완전히 줄어듦

9. 지난 24 시간동안 통증이 귀하에게 얼마나 지장을 주었는지를 가장 잘 나타내는 숫자에 동그라미 표시를 하십시오.

가. 전반적인 활동

0 1 2 3 4 5 6 7 8 9 10
지장을 주지 않음 완전히 지장을 줌

나. 기분

0 1 2 3 4 5 6 7 8 9 10
지장을 주지 않음 완전히 지장을 줌

다. 보행 능력

0 1 2 3 4 5 6 7 8 9 10
지장을 주지 않음 완전히 지장을 줌

라. 통상적인 일 (집 안팎의 일을 다 포함하여)

0 1 2 3 4 5 6 7 8 9 10
지장을 주지 않음 완전히 지장을 줌

마. 대인관계

0 1 2 3 4 5 6 7 8 9 10
지장을 주지 않음 완전히 지장을 줌

바. 수면

0 1 2 3 4 5 6 7 8 9 10
지장을 주지 않음 완전히 지장을 줌

사. 인생의 낙

0 1 2 3 4 5 6 7 8 9 10
지장을 주지 않음 완전히 지장을 줌

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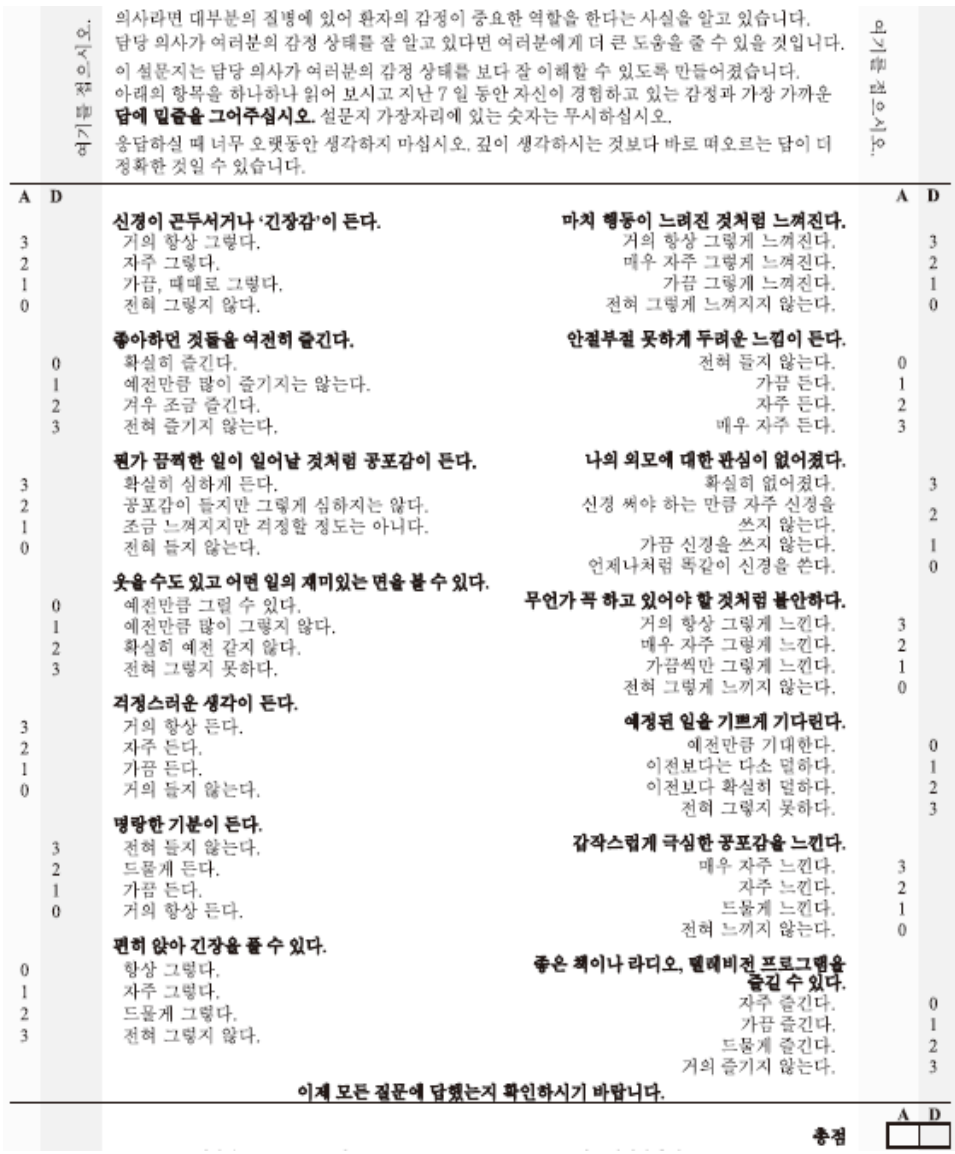
*Yun YH, Mendoza TR, Heo DS, Yoo T, Heo BY, Park HA, et al. Development of a cancer pain assessment tool in Korea: a validation study of a Korean version of the brief pain inventory. Oncology **2004**, 66:439-444.*

2.7. Hospital Anxiety and Depression Scale, HADS (병원 정신 불안 및 우울증에 관한 설문지)



의사라면 대부분의 질병에 있어 환자의 감정이 중요한 역할을 한다는 사실을 알고 있습니다.
담당 의사가 여러분의 감정 상태를 잘 알고 있다면 여러분에게 더 큰 도움을 줄 수 있을 것입니다.
이 설문지는 담당 의사가 여러분의 감정 상태를 보다 잘 이해할 수 있도록 만들어졌습니다.
아래의 항목을 하나하나 읽어 보시고 지난 7 일 동안 자신이 경험하고 있는 감정과 가장 가까운 **답에 밑줄을 그어주십시오.** 설문지 가장자리에 있는 숫자는 무시하십시오.
응답하실 때 너무 오랫동안 생각하지 마십시오. 깊이 생각하시는 것보다 바로 떠오르는 답이 더 정확한 것일 수 있습니다.

여기에 적으십시오.

여기에 적으십시오.

A	D		A	D
		신경이 곤두서거나 '긴장감'이 든다.		
3		거의 항상 그렇다.		
2		자주 그렇다.		
1		가끔, 때때로 그렇다.		
0		전혀 그렇지 않다.		
		즐아하면 것들을 여전히 즐긴다.		
	0	확실히 즐긴다.		
	1	예전만큼 많이 즐기지는 않는다.		
	2	겨우 조금 즐긴다.		
	3	전혀 즐기지 않는다.		
		뭔가 끔찍한 일이 일어날 것처럼 공포감이 든다.		
3		확실히 심하게 든다.		
2		공포감이 들지만 그렇게 심하지는 않다.		
1		조금 느껴지지만 걱정할 정도는 아니다.		
0		전혀 들지 않는다.		
		웃을 수도 있고 어떤 일의 재미있는 면을 볼 수 있다.		
	0	예전만큼 그럴 수 있다.		
	1	예전만큼 많이 그렇지 않다.		
	2	확실히 예전 같지 않다.		
	3	전혀 그렇지 못하다.		
		걱정스러운 생각이 든다.		
3		거의 항상 든다.		
2		자주 든다.		
1		가끔 든다.		
0		거의 들지 않는다.		
		명랑한 기분이 든다.		
	3	전혀 들지 않는다.		
	2	드물게 든다.		
	1	가끔 든다.		
	0	거의 항상 든다.		
		편히 앉아 긴장을 풀 수 있다.		
0		항상 그렇다.		
1		자주 그렇다.		
2		드물게 그렇다.		
3		전혀 그렇지 않다.		
		마치 행동이 느려진 것처럼 느껴진다.		
		거의 항상 그렇게 느껴진다.		3
		매우 자주 그렇게 느껴진다.		2
		가끔 그렇게 느껴진다.		1
		전혀 그렇게 느껴지지 않는다.		0
		안절부절 못하게 두려운 느낌이 든다.		
		전혀 들지 않는다.	0	
		가끔 든다.	1	
		자주 든다.	2	
		매우 자주 든다.	3	
		나의 외모에 대한 관심이 없어졌다.		
		확실히 없어졌다.		3
		신경 써야 하는 만큼 자주 신경을 쓰지 않는다.		2
		가끔 신경을 쓰지 않는다.		1
		언제나처럼 똑같이 신경을 쓴다.		0
		무언가 꼭 하고 있어야 할 것처럼 불안하다.		
		거의 항상 그렇게 느낀다.	3	
		매우 자주 그렇게 느낀다.	2	
		가끔씩만 그렇게 느낀다.	1	
		전혀 그렇게 느끼지 않는다.	0	
		예정된 일을 기쁘게 기다린다.		
		예전만큼 기대한다.		0
		이전보다는 다소 덜하다.		1
		이전보다 확실히 덜하다.		2
		전혀 그렇지 못하다.		3
		갑작스럽게 극심한 공포감을 느낀다.		
		매우 자주 느낀다.	3	
		자주 느낀다.	2	
		드물게 느낀다.	1	
		전혀 느끼지 않는다.	0	
		좋은 책이나 라디오, 텔레비전 프로그램을 즐길 수 있다.		
		자주 즐긴다.		0
		가끔 즐긴다.		1
		드물게 즐긴다.		2
		거의 즐기지 않는다.		3

이제 모든 질문에 답했는지 확인하시기 바랍니다.

	A	D
총점		

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*Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand **1983**, 67:361-370.*

Appendix 3. Other questions to patients

3.1. Patient's Global Impression of Change (PGIC)

귀하의 마약성진통제 효과에 대한 질문입니다. 다음 중 하나에 표시해 주십시오.

마약성 진통제 복용을 통해 나의 통증은:

1 – 아주 많이 나아진다
2 – 많이 나아진다
3 – 아주 조금 나아진다
4 – 변화가 없다
5 – 아주 조금 나빠진다
6 – 많이 나빠진다
7 – 아주 많이 나빠진다

3.2. Other sociodemographic characteristics

다음 중 질문에 답해 주십시오

1) 나는 (미혼, 기혼) 이다
2) 나는 (한국인, 외국인) 이다
3) 나는 (중졸, 고졸, 대졸, 대졸이상) 이다
4) 나는 종교가 (있다, 없다)
5) 나는 흡연가 (이다, 아니다)
6) 나의 직업은 (　　) 이다

Abstract in Korean

마약성 진통제를 장기간 복용하는 만성 비암성 통증 환자에서 마약성 진통제와 연관된 화학적 대처
– 다기관, 관찰, 단면 조사 연구 –

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서론: 전세계적으로 증가하고 있는 마약성 진통제의 소비는 마약성 진통제 사용장애의 위험을 야기하고 있다. 그러나 만성 비암성 통증 환자에서 마약성 진통제 사용장애와 마약성 진통제와 연관된 화학적 대처에 관한 대부분의 연구는 미국과 같이 마약성 진통제 소비율이 높은 나라에서 주로 이루어지고 있어 일반화하여 적용하기 어려운 실정이다.

방법: 마약성 진통제와 연관된 화학적 대처의 빈도와 예측인자를 알아보고 환자들의 기능적, 정신적 특성을 살펴본다. 이 연구는 다기관 관찰 단면 조사 연구이다.

대한민국에서 중등도의 마약성 진통제 소비율을 보이는 여섯 개 3차 병원의 통증 클리닉의 환자들을 대상으로 연구가 이루어졌다.

장기간 마약성 진통제를 복용하고 있는 만성 비암성 통증 환자.

사회인구학적 정보, 통증의 특성, 마약성 진통제에 대한 자료를 얻고 전향적 설문조사를 시행한다. 9명의 통증 전문가가 설문지를 통해 마약성 진통제와 연관된 화학적 대처에 대해 평가하게 된다.

결과: 총 258명의 환자들 중 55명 (21%)의 환자가 마약성 진통제와 연관된 화학적 대처 양상을 보였다. 이 환자들의 조사에서는 높은 정도의 극단적 통증 인지 (≥30 points; 66%), 중등도 이상의 불면증 (≥15 points; 63%), 낮은 회복력 (68 points), 높은 자살 사고 (67%)가 특징적으로 관찰되었다. 마약성 진통제와 연관된 화학적 대처를 보이는 환자들은 높은 정도의 통증 간섭을 보이고 (85.18% vs. 58.28%, p = 0.017), 장기간의 마약성 진통제 사용에 대한 만족도가 낮으며 (56.4% vs 78.3%, p = 0.002), 가장 극심한 통증 정도를 표현한 숫자통증등급에서 더 높은 수치를 보였다 (8.75 ± 1.42 vs 7.95 ± 2.06, p = 0.001). 다변량 분석 결과 1년 이내 알코올 남용이 있었던 경우 (OR= 6.84, p = 0.001), 1년 이내 처방 받은 약의 남용이 있었던 경우 (OR= 12.96, p<0.001), 두경부의 통증 (OR= 2.48, p = 0.039), 일일 모르핀 환산 용량이 200mg 이상인 경우 (OR= 3.48, p = 0.006), 법률적 문제가 지속되는 경우 (OR= 2.33, p = 0.047) 등이 마약성 진통제와 연관된 화학적 대처를 유의하게 예측할 수 있는 인자로 나타났다.

결론: 장기간 마약성 진통제를 처방 받는 만성 비암성 통증 환자의 약 21%에서 마약성 진통제와 연관된 화학적 대처를 보이는 것으로 나타났다. 이 연구에서 나타난 마약성 진통제와 연관된 화학적 대처의 높은 발생률은 만성 비암성 통증 환자의 마약성 진통제 사용장애의 발생이 해당 국가의 마약성 진통제 소비율과는 독립적인 관계임을 보여주고 있다.

주요어: 만성 비암성 통증; 마약성 진통제; 마약성 진통제 사용장애; 화학적 대처; 빈도; 장기간 마약성 진통제 사용.

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