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Review Article

Updated guidelines for prescribing opioids to treat patients with chronic non-cancer pain in Korea: developed by committee on hospice and palliative care of the Korean Pain Society

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ABSTRACT

There are growing concerns regarding the safety of long-term treatment with opioids of patients with chronic non-cancer pain. In 2017, the Korean Pain Society (KPS) developed guidelines for opioid prescriptions for chronic non-cancer pain to guide physicians to prescribe opioids effectively and safely. Since then, investigations have provided updated data regarding opioid therapy for chronic non-cancer pain and have focused on initial dosing schedules, reassessment follow-ups, recommended dosage thresholds considering the risk-benefit ratio, dose-reducing schedules for tapering and discontinuation, adverse effects, and inadvertent problems resulting from inappropriate application of the previous guidelines. Herein, we have updated the previous KPS guidelines based on a comprehensive literature review and consensus development following discussions among experts affiliated with the Committee on Hospice and Palliative Care in the KPS. These guidelines may assist physicians in prescribing opioids for chronic non-cancer pain in adult outpatient settings, but should not to be regarded as an inflexible standard. Clinical judgements by the attending physician and patient-centered decisions should always be prioritized.

Keywords: Adult; Analgesics; Chronic Pain; Drug Monitoring; Drug Prescriptions; Opioid-Related Disorders; Prescription Drug Misuse; Treatment Outcome.

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INTRODUCTION

An opioid epidemic has emerged as a major social problem in many countries [1,2]. While the socioeconomic burden of opioid misuse in Korea may not be as pronounced as in the United States, concerns have been raised about the safety of long-term opioid use, particularly in patients with chronic non-cancer pain who require high doses. A population-based cohort study based on data from the Korean National Health Insurance Service revealed a 6-fold increase in the number of chronic opioid users, which was associated with an increase in the 5-year mortality rate in the period from 2002 to 2015 [3]. Potentially inappropriate opioid prescriptions, including prescriptions with concurrent use of central-nervous-system-acting agents, for patients with psychiatric diseases, for extended treatment periods, and with high dosages, increased from 13.2% in 2012 to 19.4% in 2018 [4]. Diverse and complex factors have contributed to this increase. A letter to the editor presenting a retrospective review in 1980, stating that only 4 out of 11,882 patients treated with opioids for pain became addicts [5], was widely referenced in the literature in support of opioid prescriptions for chronic non-cancer pain. The recognition of the problem of inadequate pain management in patients with cancer, AIDS, and trauma in the 1990s prompted clinicians to adopt aggressive treatments for pain [6]. The three-step analgesic ladder created by the World Health Organization (WHO), based on the patient's pain severity report, which was originally deployed for cancer pain management, was inappropriately applied to the treatment of chronic non-cancer pain [7]. Step 1 of the ladder advocates the use of non-opioid analgesics for mild pain, and escalations to weak or strong opioids are recommended if pain persists (Steps 2 or 3, respectively). Opioids are helpful for patients with cancer pain, but the drugs may work well for only a limited proportion of patients with chronic non-cancer pain. Therefore, the prescription of opioids for chronic non-cancer pain, following the WHO step ladder guideline, may result in a dose escalation beyond the limited benefit and contributes to inadvertent harmful effects. The widespread misconception that administering opioids for pain seldom leads to addiction, coupled with the commitment to identify and treat pain, and the misapplication of the WHO analgesic ladder, may have resulted in a shift in clinicians' attitudes. This shift toward a more lenient prescription of opioids for chronic non-cancer pains, may have inadvertently contributed to the current opioid epidemics.

To address these issues and guide physicians to prescribe opioids effectively and safely, the Korean Pain Society (KPS) developed guidelines for opioid prescriptions for chronic non-cancer pain [8]. Since then, investigations have provided updated data regarding opioid therapy for chronic non-cancer pain and have focused on initial dosing schedules, reassessment follow-ups, recommended dosage thresholds considering the risk-benefit ratio, dose-reducing schedules for tapering and discontinuation, adverse effects, and inadvertent problems resulting from inappropriate application of the previous guidelines. Herein, we have revised the previous KPS guidelines based on a comprehensive review of current literature and consensus development following in-depth discussions among experts affiliated with the Committee on Hospice and Palliative Care in the KPS (**Box 1**). The recommendations put forward by our guidelines align closely with the latest USA guidelines [9], which have been recently updated to incorporate new clinical evidence.

These updated guidelines are intended to aid physicians in prescribing opioids for chronic non-cancer pain in adult outpatient settings. However, the guidelines should not be misapplied as an inflexible standard, especially concerning dosage thresholds and follow-up schedules. The primary consideration should always be the clinical judgement of the physician overseeing pain treatment and patient-centered decision-making. These guidelines should not be used to restrict prescription of opioids by doctors or as a basis for evaluating health insurance adequacy or making judicial decisions regarding the prescription of opioids for a specific patient.

MAIN BODY

1. Considerations prior to the initiation of opioid administration

1) Evaluation of pain and functional status

To provide appropriate and effective pain management to patients, a detailed history with a thorough physical examination to identify the cause and characteristics of pain are fundamental. The patient's medical history, including previous episodes of pain, and any underlying medical conditions should be considered during this process. Assessing the patient's medication history, especially concerning the recent administration of opioids or other pain-relieving medications is essential. Knowledge of any previous interventional procedures for pain is also

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important to evaluate their effectiveness and to guide future treatment decisions. Identifying specific situations that relieve or exacerbate pain can provide valuable insights. The use of assessment tools such as a numeric rating scale (NRS) and a visual analog scale (VAS) is valuable for quantifying pain intensity. Additionally, various other assessment tools can be applied to measure functional status and the impact of pain on a patient's daily life [10].

2) Psychological assessment and prescription drug monitoring

Before considering opioid-therapy prescription, physicians should thoroughly document a patient's psychosocial history and screen for current or past psychiatric disorders. This is essential because individuals with mental-health issues, such as depressive and anxiety disorders or substance use disorders, may be at higher risk for opioid misuse [8]. In addition, physicians should determine whether patients are receiving high opioid doses or taking concomitant medications that may increase the risk of an overdose [9]. This step is crucial to ensure patient safety and reduce the potential for opioid-related harm. In Korea, checking a patient's prescription opioid medication history is feasible using the "Network System to Prevent Doctor-Shopping for Narcotics (https://www. data.nims. or.kr)". This system can help healthcare professionals make informed decisions regarding opioid prescriptions and identify potential issues with overuse or misuse [11]. Moreover, physicians can access the Korean real-time drug utilization review (DUR) system to detect duplicated prescriptions or interactions with drugs prescribed by other doctors [12].

3) Establishing treatment goals based on patient-centered decisions

When treating chronic non-cancer pain, it is important to measure treatment effectiveness. This can be done by assessing pain intensity using tools such as an NRS or a VAS and functionality using questionnaires such as the Oswestry disability or neck-disability indices. Complete pain relief is uncommon; therefore, achieving a significant reduction in pain intensity (*e.g.*, 30% or more) and/or improving function (30% or more) should be the treatment goals [8]. Before initiating opioid therapies for non-cancer pain, physicians should establish treatment goals in accordance with patients' preferences. These goals should be realistic, encompassing improvements in function, quality of life, and pain management. Planning how to discontinue opioid therapy if the benefit-risk ratio is not favorable to the patient is also important. Opioid therapy should continue only in the presence of a meaningful and beneficial change in both pain levels and function that justifies the potential risk to the patient's safety [9].

2. Initiation of opioid treatment

1) Maximization of non-opioid therapy use

Physicians should be aware that, in many cases, the effectiveness of non-opioid therapies for acute pain is equivalent to that of opioids [13] and that non-opioid treatments are the first-line treatment for non-cancer pain [14,15]. Therefore, physicians should maximize the use of non-pharmacological treatments such as exercise, physiotherapy, and psychological therapies and non-opioid pharmacotherapy as appropriate for specific situations and patients [9,16]. Opioid treatments should be considered only if established non-pharmacological treatments and non-opioid analgesics fail, are not tolerated, contraindicated, or unavailable [2]. Concurrent non-opioid therapies may be indicated even when opioids are deemed necessary depending on specific clinical situations [8].

2) Opioid selection

For the initial prescription of opioids for non-cancer pain, we recommend immediate-release (IR) opioids rather than extended-release/long-acting (ER/LA) opioids. We found no evidence supporting the superiority of ER/LA opioids for short-term pain relief and functional improvement [1]. Additionally, there is no evidence indicating that continuous time-scheduled use of ER/LA opioids reduces opioid-related harms (including opioid use disorder) compared to intermittent use of IR opioids [17]. The long half-life of ER/LA opioids may prolong both the duration of their analgesic effect and any adverse events (including respiratory depression) [9,17]. Compared with IR opioids, ER/LA opioids have been associated with an increased risk of overdose, especially in the first two weeks of therapy [18]. Therefore, IR rather than ER/LA opioids should be the first choice for the initial treatment of non-cancer pain. However, in specific situations, such as the presence of resting rather than activity-related pain, ER/LA opioids may be favored over IR opioids [16]. European guidelines recommend a patient-centered approach for choosing between IR and ER/LA opioids, emphasizing

that the decision should be based on the individual patient's circumstances and clinical symptoms [19]. Still, ER/LA opioids should be reserved for appropriately indicated and opioid-tolerant patients who have received at least 1 week of a daily IR opioid at a specific dose [1,9].

3) Dosage for initial prescription and titration

The opioid dose for initial prescription should be the lowest effective one. Physicians may use the drug label dosage as a starting point and adjust it as needed based on pain severity and other clinical considerations, such as kidney or liver function, or concomitant use of other central-nervous-system-acting agents. The recommended starting dose is a single administration of 5–10 morphine milligram equivalent (MME) or daily dose of 20–30 MME [9].

Opioid dosage increases, if necessary, should be prescribed after careful evaluation of individual benefits and risks, in a stepwise manner. Doses should not be increased beyond a level at which the benefits are unlikely to outweigh the risks [9]. A comparative study investigating liberal dose escalation based on patients' reports of pain severity versus maintaining current doses as a threshold, revealed no favorable outcomes regarding pain, function, or quality of life [20]. In a meta-regression of moderate-quality studies assessing different opioid doses, no dose-response effect was observed for pain relief and functional recovery [16]. Conversely, there is a substantial increase in the risk of opioid-related harms, such as misuse, and non-fatal and fatal overdose (including death) as opioid dosage increases [2,9]. To ensure the effective and safe prescription of opioids for non-cancer pain, current guidelines recommend specific dosage thresholds within a varying range (*e.g.*, 120 MME/day in France [21], 90 MME/day in Canada [16], or 50 MME/day in USA [9]). In a study categorizing opioid dosages as lower than 50 MME/day, 50–90 MME/day, and higher than 90 MME/day, the effects of increasing opioid doses on the mean pain improvement were significant, but a plateau was reached at approximately 50 MME/day [17]. In other words, opioid dosages higher than 50 MME/day were associated with a negligible improvement in pain intensity and functional status compared to dosages lower than 50 MME/day [17]. Therefore, in a significant proportion of patients with non-cancer pain, the benefit of increasing opioid doses beyond 50 MME/day may be relatively small. By contrast, the risk of adverse opioid therapy outcomes, which is relatively low in patients prescribed less than 50 MME/day, increases substantially in those prescribed doses of 50–90 MME/day [16]. Dosages higher than 90 MME/day further increase the risk of opioid-related harms [16]. Based on these observations and in alignment with the USA guideline, we recommend a careful reevaluation of benefits and risks when considering prescription of opioid dosages above 50 MME/day [9]. Importantly, the opioid dosage threshold recommended here is intended as a guideline for clinical practice, but not as the basis for government healthcare policies or legal decision-making. Physicians should consider individual circumstances and apply the guidelines based on their clinical judgment for effective and safe management of chronic pain.

When initiating treatment for a patient already on opioid therapy from another doctor, especially with a dosage higher than 50 MME/day, a thorough risk-benefit assessment based on the patient's individual circumstances is crucial. Physicians should engage in a comprehensive and open discussion with the patient about their existing opioid therapy, treatment goals, and the potential risks associated with continued use. If concerns arise regarding the current opioid regimen, and a dose reduction or discontinuation is deemed beneficial, physicians should develop a tapering plan in collaboration with the patient. Suggestions for opioid tapering schedules will be presented later in this article.

4) Follow-up schedule for reassessment after initial prescription

One-week follow-ups are recommended after the initial prescription of opioids and for dose-titration in patients with non-cancer pain [8], although the timing can be individualized according to clinical circumstances. For acute pain, physicians should prescribe opioids for the time period when the pain is expected to be high enough to warrant them, usually for a few days or less [9]. We recommend that patients wishing to continue opioid treatment for acute pain should be reassessed every 2 weeks to consider benefit versus risk. Physicians should strive to address potential reversible causes of chronic pain in patients complaining of acute pain severe enough to require opioids for longer than 1 month. During the initial follow-up sessions, identifying opioid-treatment responders and non-responders is important to avoid ineffective long-term treatments and inadvertent side effects. Many common causes of nonsurgical, nontraumatic acute pain can be managed effectively without the use of opioids, and non-opioid treatments should be considered for continuation as well as initiation of opioid therapy.

3. Maintenance or discontinuation of opioid treatment

1) Considerations prior to opting for long-term opioid treatment

The recommended opioid trial period before opting for long-term opioid treatment varies from 1 month in the USA guidelines of 2022 [9], followed by 1–3 months in the European guidelines of 2021 [2], to 6 months in the Canadian guidelines of 2017 [16]. A study on predictive factors of favorable response and tolerability for long-term opioid therapy in opioid-naïve patients revealed that participants who had not experienced pain relief within 1 month of the trial were unlikely to obtain subsequent improvement [22]. Limiting the duration of opioid trials provides several benefits including minimizing the risk of dependence, reducing the need for tapering, limiting unused opioids, and lowering the overall risk [9]. Therefore, we recommend that the decision as to whether to continue or stop opioid therapy should be made within the first month of therapy. The decision to continue opioid treatment should be based on the pain relief achieved and on the patient's function and overall quality of life. Factors such as achievement of pre-defined therapeutic goals, changes in daily physical and social activities, comorbidities or psychiatric-health status, and the presence of adverse effects and addictive behaviors should be considered in determining the progression toward long-term opioid treatment [23,24]. Optimal use of nonopioid medications (including acetaminophen, non-steroidal anti-inflammatory drugs, and selective antidepressants and anticonvulsants) should also be reassessed. If opioid prescriptions need to be continued, the patient's benefits and risks should be weighed, and the decision should be made after thorough discussions with the patient [9].

2) Follow-ups for long-term opioid treatment

We found no studies assessing the effectiveness of specific monitoring intervals on the risk of overdose and opioid use disorder. The evidence for an increased likelihood of long-term opioid use after extended opioid use for acute pain is strong [25-28]. Moreover, placebo-controlled studies showed that the effects of opioid therapy on relief of pain and on function were better after 1–3 months than after 3–6 months [29]. In an observational study, opioid treatment for longer than 3 months was an important risk factor for opioid use disorder [30]. Evidence from another study identified the first 3 months after opioid therapy initiation as an overdose risk periods, providing an opportunity for mitigation strategies to reduce this risk [31]. These observations imply that the benefit-to-risk ratio of opioid treatment for non-cancer pain can change over time, which warrants regular monitoring during long-term opioid treatment. For patients on long-term opioid therapy, we recommend monitoring intervals of 3 months or less to reassess the benefits and risks associated with opioid treatment. However, patients with mental-health issues that can increase the risk of opioid use disorder, receiving high opioid doses (≥ 50 MME/day), or taking concomitant medications that can increase their risk of overdose, need to be followed up more frequently. After dose increments or reductions, or a switch to alternative opioids, we recommend that the patients should be followed up within 1–2 weeks. Increased opioid dosages, as described above, should be prescribed only after careful evaluation of individual benefits and risks, in a stepwise manner. Physicians should exert special caution and re-evaluate the benefits and risks when considering prescribing opioid dosages above 50 MME/day.

3) Dose reductions and discontinuation of opioid administration

(1) Opioid dose reductions

Physicians should carefully assess the benefits and risks of opioid continuation and tapering. When the benefits of continuing opioids outweigh the risks, non-opioid therapy should be optimized while maintaining opioid use. If there is little benefit from continued opioid therapy, dosage reductions or discontinuation depending on the patient's individual circumstances should be considered while optimizing another therapy (*e.g.*, non-pharmacological treatment, non-opioid therapy) [9].

(2) Dose-reduction methods

To reduce opioid dosages, physicians should agree with their patients on a tapering plan. Physicians should inform patients that slowly and autonomously tapering long-term opioid use has been shown to lead to improvements in function, quality of life, anxiety, and mood, without worsening the pain. Also, behavioral and non-opioid pharmacologic therapy should be maximized before and during opioid tapering [32].

Abrupt discontinuation or rapid reduction of high opioid dosages should be avoided unless signs warning of an impending overdose are apparent (*e.g.*, confusion,

sedation, or slurred speech). Rapid tapering or sudden discontinuation of opioids in physically dependent patients has been associated with acute withdrawal symptoms, pain aggravation, serious psychological distress, and suicidal ideation [33,34]. The opioid dosage reduction should be gradual to allow the patient to adjust to a lower dose, thereby minimizing the development of opioid withdrawal symptoms such as insomnia, generalized myalgia, diarrhea, abdominal pain, nausea, palpitations, diaphoresis, mydriasis, and agitation [9]. The tapering schedule, although individualized, depends on the duration of the previous opioid treatment. A working group of experts from the US Department of Health and Human Services recommended a gradual reduction in dosage; specifically, for patients who have been on opioids for an extended period (*e.g.*, ≥ 1 year), the reduction should be slow, at a rate of 10% or less per month, to enhance tolerance [35]. If a patient has been on opioids for a short period of time (*e.g.*, weeks to months), the dose should be reduced by 10% or less per week until reaching 30% of the original dose, and then the remaining dose should be reduced at a rate of 10% per week. Gradual tapering of doses results in successful weaning, preventing the development of withdrawal symptoms [35]. If the goal of tapering is to discontinue opioid use, after reaching the lowest available dose, the dosing interval may be extended. Opioids taken less than once a day may be discontinued at once. For patients who have been taking opioids for more than 7 days but less than 1 month, the recommended rate of opioid dose reduction is 20% every 2 days. For patients on opioids for acute pain who have taken them for more than 3 days but less than 1 week, the daily dose can be reduced by 50% for 2 days [36,37].

4) Opioid rotation

The degree of analgesic or adverse effects of opioids used in clinical settings may vary depending on individual patients and the medications used. Consequently, opioid rotation, the replacement of one opioid type with another, may enhance pain control quality and reduce adverse effects. Opioid rotation should be considered in the following cases [8].

1. Intolerable adverse effects continue after implementing countermeasures.
2. Poor analgesic efficacy despite appropriate dose increments.
3. Changes in clinical status of the patient (*e.g.*, decreased renal function affecting pharmacokinetics of certain drugs).
4. Administration route change requirement.

When conducting opioid rotation, the total amount of the currently used opioid and the MME dose of the opioid to be replaced should be calculated (**Table 1**) [38]. Administration of the new drug should start at 50%–75% of the calculated dose to account for incomplete opioid cross-tolerance [39]. Similarly, when switching from an IR opioid to an ER/LA opioid, the dosage should be reduced to mitigate potential incomplete tolerance [9]. Physicians should titrate the dosage of the new drug by assessing its analgesic and adverse effects.

5) Management of adverse effects

Opioid-use-related complications include constipation, nausea and vomiting, urinary retention, pruritus, myoclonus, and psychiatric disorders (such as somnolence, cognitive impairment, or hallucinations, and opioid use disorder) [2,9]. Physicians should actively monitor

Table 1. Equianalgesic doses of commonly prescribed opioids

Opioids	Ratio to calculate MME (multiply by)	30 MME dose, mg/day	50 MME dose, mg/day
Morphine	1	30	50
Oxycodone	1.5–2	15–20	25–33
Hydromorphone	4	7.5	12.5
Hydrocodone	1–0.67	30–45	50–75
Codeine	0.15	200	333
Tapentadol	0.4	75	125
Fentanyl transdermal patch (in mcg/hr)	2.4	12[a]	NA

MME: morphine milligram equivalent, NA: not applicable.
[a]By calculation, the dose of transdermal fentanyl patch corresponding to 30 MME/day should be 12.5 mcg/hr, however, it was rounded down to the closest equivalent dose that is commercially available.

patients for these symptoms and provide appropriate interventions to minimize patient discomfort and harms. During opioid treatment initiation or maintenance dose titration, the patients may be at increased risk of developing these side effects [17,31]. Physicians should pay special attention to these risks during these periods and the patient and his or her family should be aware of the risk of falling, prompting avoidance of hazardous activities such as driving or the use of heavy equipment. Additionally, the risk of opioid-related side effects increases when patients take opioids with alcohol or sedative drugs [9,17]. Therefore, when prescribing opioids for a patient with chronic non-cancer pain, physicians should periodically review the patient's prescription records to determine whether they are receiving additional or overlapping prescriptions, or are concurrently being administered sedative medications such as benzodiazepines or other central-nervous-system-acting drugs including gabapentinoids, prescribed by other healthcare providers. The DUR system and the "Network System to Prevent Doctor-Shopping for Narcotics (https://www. data.nims.or.kr)" implemented in Korea since 2010 and 2020, respectively, provide information regarding these issues.

4. Opioid use disorder

Long-term administration of opioids may lead to opioid dependence or problematic use even in patients with chronic pain [30]. This phenomenon was defined as opioid use disorder in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V, **Table 2**) [23]. Opioid use disorder is associated with increased risks of opioid-related morbidity and mortality, but it is a treatable condition [9]. Therefore, when prescribing opioids for patients with chronic pain, physicians should identify patients who develop opioid use disorder and provide or arrange for appropriate interventions. Physicians should not dismiss the potential opioid-related harms or abandon the pain treatment.

1) Terminology and diagnostic criteria controversies

A systematic review revealed a highly variable prevalence of opioid use disorder in patients with chronic pain across different studies, ranging from 0.5% to 26% for dependence and < 1% to 81% for problematic use, including misuse, abuse, and addiction [40]. This variability may stem from different definitions for abnormal opioid use-related conditions. In 1952, the WHO committee review used the term 'addiction' for drugs prone to trigger abuse by their users [41]. Subsequently, they introduced the term 'physiological dependence' to describe normal adaptations that result in tolerance and withdrawal symptoms in response to long-term opioid therapy. The WHO also substituted the term 'addiction' with 'psychological dependence', which in conjunction with physiological dependence, refers to a syndrome of uncontrolled compulsive drug-seeking behaviors [41]. The revised DSM-III by the American Psychiatric Association and the WHO replaced the term 'addiction' with 'dependence' because of the pejorative connotation of the former [42]. They defined the disorder using a set of criteria comprised of

Table 2. DSM-V criteria for opioid use disorder

Opioid Use Disorder Diagnostic Criteria:
A minimum of 2–3 criteria are required for a mild, while 4–5 are for moderate, and ≥ 6 are for severe opioid use disorder diagnosis, occurring within 12 months.
1. Taking the opioid in larger amounts and for longer than intended
2. Wanting to cut down or quit but not being able to do it
3. Spending a lot of time obtaining the opioid
4. Craving for or a strong desire to use opioids
5. Repeatedly unable to carry out major obligations at work, school, or home due to opioid use
6. Continued use despite persistent or recurring social or interpersonal problems caused or made worse by opioid use
7. Stopping or reducing important social, occupational, or recreational activities due to opioid use
8. Recurrent use of opioids in physically hazardous situations
9. Consistent use of opioids despite acknowledgment of persistent or recurrent physical or psychological difficulties from using opioids
10. [a]Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount
11. [a]Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal

[a]This criterion is not counted for the diagnosis of opioid use disorder if the patients are taking opioids appropriately for pain treatment under medical supervision.

nine elements, including not only compulsive uncontrolled drug-seeking behaviors but also tolerance and withdrawal symptoms, which have been thought to be related to the physiological dependence. Unfortunately, this change in terminology may have given rise to confusion because the tolerance and withdrawal symptoms, which are commonly seen in patients with long-term opioid therapy for pain as normal adaptations, were included in the criteria for defining the pathological state previously referred to as addiction [24,43–46]. The DSM-IV, published in 1994, adopted most of the terminology of the DSM-III-R. Stigmatized patients may try to hide potentially abnormal behaviors. To overcome the problems associated with the previous DSM version, the DSM-V proposed a conditional exclusion for the tolerance and withdrawal criteria [23]. In patients taking opioids appropriately for pain treatment under medical supervision, tolerance and withdrawal are not considered symptoms for the diagnosis of opioid use disorder (**Table 2**).

2) Recommendations to improve outcomes

The DSM-V definition of opioid use disorder has also been controversial [47]. The absence of a recommended term to define the normal adaptation (physiological dependence) to long-term opioid therapy for chronic pain may cause confusion in both clinicians and patients. Inability to carry out major obligations and reduced social or recreational activities, which may be identified as abnormal behavior criteria in the DSM-V (Nos. 5, 6, and 7 in **Table 2**), are common in patients with chronic pain. Craving for, and recurrent use of, opioids (Nos. 4 and 8 in **Table 2**) may represent undertreated pain. Patients undergoing chronic opioid treatment for pain may not exhibit drug-seeking or aberrant behaviors because they are already prescribed opioids, therefore, these patients may develop 'physiological dependence' without 'addiction' [48]. Misapplication of the DMS-V criteria in these clinical scenarios may lead to overdiagnosis of opioid use disorder. For the exact same reason, clinicians may not be able to distinguish a physiological dependence from a pathological addiction, or identify patients in the gray zone between those two states.

Therefore, despite controversies over the terminology, we recommend following the definition of opioid use disorder in the DSM-V. Rather than trying to distinguish between physiological dependence and addiction, physicians should provide appropriate care for all patients, including education and counseling in addition to medical-specialty treatments. Patients showing signs of tolerance and withdrawal without satisfying the diagnosis of opioid use disorder might benefit from education about the condition, its potential harms, and treatment options. Proper management of withdrawal symptoms may prevent progression to a more severe form of the disorder [49] and improve the treatment of the chronic pain itself. Patients diagnosed as having opioid use disorder, particularly moderate or severe cases, should get appropriate treatment for the disorder. The National Center for Mental Health of Korea (www.mentalhealth.go.kr) provides information regarding substance-related disorders, counseling, and mutual help programs such as Narcotics Anonymous, and medical institutions that provide psychiatric addiction services by region in Korea.

CONCLUSIONS

There are growing concerns regarding the safety of long-term treatment with opioids of patients with chronic non-cancer pain. New evidence on opioid-treatment-related outcomes has emerged since 2017, the year the KPS guidelines for prescribing opioids for chronic non-cancer pain were developed. We have updated the previous KPS guidelines based on a comprehensive literature review and consensus development following discussions among experts affiliated with the Committee on Hospice and Palliative Care in the KPS (**Box 1**). These guidelines may assist physicians in prescribing opioids for chronic non-cancer pain, but should not be regarded as an inflexible standard. Clinical judgements by the attending physician and patient-centered decisions should always be prioritized.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

CONFLICT OF INTEREST

Eunsoo Kim is an editorial board member of the Korean Journal of Pain. Woong Mo Kim and Seong-Soo Choi are a section editors of the Korean Journal of Pain. However, they have not been involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Minsoo Kim: Writing/manuscript preparation; Sun Kyung Park: Writing/manuscript preparation; Woong Mo Kim: Writing/manuscript preparation; Eunsoo Kim: Investigation; Hyuckgoo Kim: Investigation; Jun-Mo Park: Study conception; Seong-Soo Choi: Supervision; Eun Joo Choi: Investigation.

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Box 1. Summary of recommendations

I. Considerations prior to the initiation of opioid administration

1. Physicians should try to identify the cause and characteristics of pain through a detailed history including the patient's previous medication and interventional treatment for pain, thorough physical examination, and by using various tools to measure pain intensity and functional status, to provide appropriate and effective pain management to patients. It is also essential to identify the patient's past medical history including mental health issues and substance use disorder. Currently, in Korea, checking a patient's prescription opioid medication history is feasible using the "Network System to Prevent Doctor-Shopping for Narcotics (https://www.data.nims.or.kr)".
2. Physicians should determine the initiation of opioid therapy for chronic pain after a thorough discussion with the patients regarding measurable treatment goals which should be realistic, encompassing improvements in function, quality of life, and pain management. Planning how to discontinue opioid therapy if the benefit-risk ratio is not favorable to the patient is also important.

II. Initiation of opioid treatment

3. Physicians should be aware that the non-opioid treatments are the first-line for the treatment for non-cancer pain, therefore, they should maximize non-opioid treatments first.

3-1. We recommend immediate-release (IR) opioids rather than extended-release/long-acting (ER/LA) opioids for the initial prescription. ER/LA opioids are recommended to be reserved for appropriately indicated and opioid-tolerant patients who have received at least 1 week of a daily IR opioid at a specific dose.

3-2. The dose of opioids for initial prescription should be the lowest effective one. Physicians may use the drug label dosage as a starting point which may be comparable to a single administration of 5–10 MME or daily dose of 20–30 MME, and adjust as needed based on pain severity and other clinical considerations such as kidney or liver function.

4. After initial prescription of opioids, patients should be followed up in 1 week. For acute pain, an adequate duration of opioid treatment may be a few days or less in most cases. Patients wishing to continue opioid treatment for acute pain should be reassessed every 2 weeks to consider benefit versus risk. When opioid treatment continues for more than 1 month, physicians should try to address potential reversible causes of chronic pain and identify treatment responders and non-responders to opioid, thus avoiding ineffective long-term treatments and inadvertent side effects.
5. We recommend that the decision as to whether to continue or stop opioid therapy should be made within the first month of therapy, after careful evaluation of individual benefits and risks, in collaboration with the patients.

III. Maintenance or discontinuation of opioid treatment

6. Opioid doses should never be increased beyond a level at which the benefits are unlikely to outweigh the risks. We recommend a careful reevaluation of benefits and risks when considering prescription of opioid dosages above 50 MME/day. After dose increments or reductions, or a switch to alternative opioids, patients should be followed up within 1–2 weeks. For patients on long-term opioid therapy, we recommend monitoring intervals of 3 months or less to reassess the benefits and risks associated with opioid treatment.
7. When the benefits of continuing opioids outweigh the risks, non-opioid therapy should be optimized while maintaining opioid use. If there is little benefit from continued opioid therapy, dosage reductions or discontinuation depending on the patient's individual circumstances should be considered while optimizing non-opioid therapy. Abrupt discontinuation or rapid reduction of high opioid dosages should be avoided unless signs warning of an impending overdose are apparent (*e.g.*, confusion, sedation, or slurred speech). Rapid tapering or sudden discontinuation of opioids in physically dependent patients has been associated with acute withdrawal symptoms, pain aggravation, serious psychological distress, and suicidal ideation. The opioid dosage reduction should be gradual to allow the patient to adjust to a lower dose, thereby minimizing the development of opioid withdrawal symptoms such as insomnia, generalized myalgia, diarrhea, abdominal pain, nausea, palpitations, diaphoresis, mydriasis, and agitation.

7-1. The tapering schedule, although individualized, depends on the duration of the previous opioid treatment. For patients who have been on opioids for an extended period (*e.g.*, ≥ 1 year), the reduction should be slow, at a rate of 10% or less per month, to enhance tolerance. If a patient has been on opioids for a short period of time (*e.g.*, weeks to months), the dose should be reduced by 10% or less per week until reaching 30% of the original dose, and then the remaining dose should be reduced at a rate of 10% per week. If the goal of tapering is to discontinue opioid use, after reaching the lowest available dose, the dosing interval may be extended. Opioids taken less than once a day may be discontinued at once.

7-2. For patients who have been taking opioids for more than 7 days but less than 1 month, the recommended rate of opioid-dose reduction is 20% every 2 days. For patients on opioids for acute pain who have taken them for more than 3 days but less than 1 week, the daily dose can be reduced by 50% for 2 days.

8. The degree of analgesic or adverse effects of opioids used in clinical settings may vary depending on individual patients and the medications used. Consequently, opioid rotation, the replacement of one opioid type with another, may enhance pain control quality and reduce adverse effects. When conducting opioid rotation, the total amount of the currently used opioid and the MME dose of the opioid to be replaced should be calculated. Administration of the new drug should start at 50%–75% of the calculated dose to account for incomplete opioid cross-tolerance.

Box 1. Continued

IV. Opioid-related harms

9. When prescribing opioids for a patient with chronic non-cancer pain, physicians should periodically review the patient's prescription records to determine whether they are receiving additional or overlapping prescriptions, or are concurrently being administered sedative medications such as benzodiazepines or other central-nervous-system-acting drugs including gabapentinoids, prescribed by other prescribers.
10. These guidelines may assist physicians in prescribing opioids for chronic non-cancer pain, but should not be regarded as an inflexible standard. Clinical judgements by the attending physician and patient-centered decisions should always be prioritized.