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Review Article

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Prevention, diagnosis, and treatment of opioid use disorder under the supervision of opioid stewardship programs: it's time to act now

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The third opium war may have already started, not only due to illicit opioid trafficking from the Golden Crescent and Golden Triangle on the international front but also through indiscriminate opioid prescription and opioid diversion at home. Opioid use disorder (OUD), among unintentional injuries, has become one of the top 4 causes of death in the United States (U.S.). An OUD is defined as a problematic pattern of opioid use resulting in clinically significant impairment or distress, consisting of 2 or more of 11 problems within 1 year, as described by the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition. Observation of aberrant behaviors of OUD is also helpful for overworked clinicians. For the prevention of OUD, the Opioid Risk Tool and the Current Opioid Misuse Measure are appropriate screening tests before and during opioid administration, respectively. Treatment of OUD consists of 3 opioid-based U.S. Food and Drug Administration-approved medications, including methadone, buprenorphine, and naltrexone, and non-opioid-based symptomatic medications for reducing opioid withdrawal syndromes, such as α_2 agonists, β-blockers, antidiarrheals, antiemetics, non-steroidal anti-inflammatory drugs, and benzodiazepines. There are at least 6 recommendable guidelines and essential terms related to OUD. Opioid stewardship programs are now critical to promoting appropriate use of opioid medications, improving patient outcomes, and reducing misuse of opioids, influenced by the successful implementation of antimicrobial stewardship programs. Despite the lack of previous motivation, now is the critical time for trying to reduce the risk of OUD.

Key Words: Analgesics, Opioid; Antimicrobial Stewardship; Buprenorphine; Methadone; Naltrexone; Narcotic Antagonists; Opioid-Related Disorders; Opium; Prescriptions; Substance Withdrawal Syndrome; United States Food and Drug Administration.

INTRODUCTION

The third opium war may have already started, not only due to illicit opioid trafficking from the Golden Crescent and Golden Triangle on the international front, but also through indiscriminate opioid prescription and opioid diversion at home [1].

The concept of opioid stewardship programs (OSPs) was encouraged by the successful implementation of antibiotic stewardship programs (ASPs). Appropriate use of opioid

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analgesics for terminal patients with painful malignancies has been considered a human right, and the amount of opioid consumption (morphine milligram equivalent per day [MME/d]) per 1,000 inhabitants was also once an indicator of being an advanced country [2].

However, increasing numbers of individuals, over 2 million in the United States of America, have an opioid use disorder (OUD). The number of deaths from unintentional opioid overdose in 2014 was 90 per day, and exceeded deaths from motor vehicle accidents [3]. OUD is deeply related to perioperative opioid over-prescription from all surgical specialties, with half of opioid tablets obtained by surgical patients going unused. Six percent of surgical patients became persistent opioid users compared to 0.4% in a non-surgical control cohort [4].

In addition, indiscriminate adherence to the World Health Organization (WHO)'s 3-step ladder in cancer pain management, jumping up from non-steroidal antiinflammatory drugs (NSAIDs) or acetaminophen to weak or strong opioids, without a dedication to interventions which could get rid of removable sources of pain, is widespread, even though at each step there are adjuvant medications available, including anticonvulsants and antidepressants [5,6].

Nowadays, the 5-year survival rate from malignant diseases is increasing, especially for breast, prostate, uterine cervical, and thyroid cancer, as well as melanoma and Hodgkin's lymphoma [7]. Therefore, increasing numbers of patients who have been cured from malignant disorders receive opioids regularly without any effort towards tapering or discontinuation, regardless of the presence of pain when the opioids were prescribed.

The most serious problem is opioids in chronic noncancer pain (CNCP). Clinicians prescribe opioids to the patients with CNCP for pain relief and improvement of physical and psychological function, hoping for an improvement of lifestyle, reduced environmental stress, and a return to work [8,9]. However, opioids, especially strong opioids, should only be prescribed in CNCP when there is a belief that discontinuation of the opioids within a limited and designated duration can occur.

This review includes prevention, diagnosis, and treatment of OUD based on the various recommended guidelines, under the supervision of OSPs (**Fig. 1**).

MAIN BODY

1. OSPs

"Stewardship" is defined as the act of responsible supervision or careful management of something. "Antimicrobial stewardship", starting from the late 1990s, has been defined as a structured program that improves the correct use of antimicrobials for better patient outcomes, reducing microbial resistance, and lessening the spread of infec-

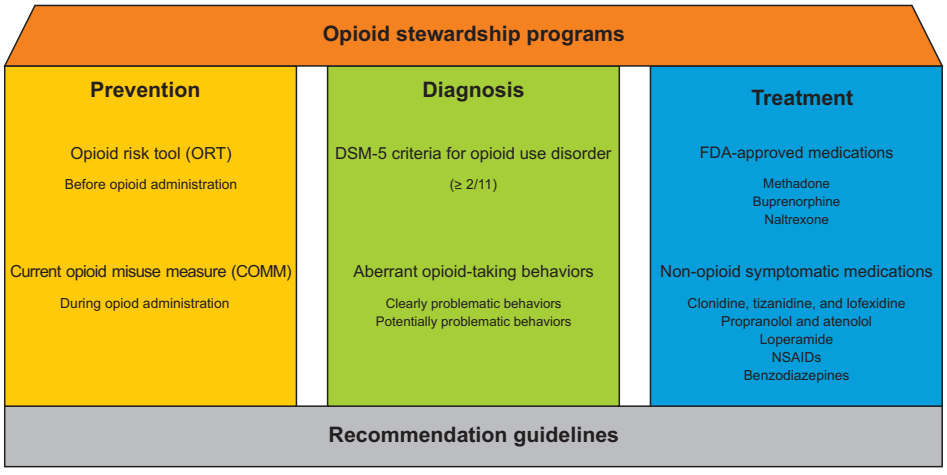

Fig. 1. Schematic illustration of prevention, diagnosis, and treatment of opioid use disorders (OUD). Under the supervision of opioid stewardship programs (roof), prevention, diagnosis and treatment of opioid use disorder (3 pillars) should be performed, based on the various recommendation guidelines (foundation). Prevention of OUD is recommended to use the screening tests, such as opioid risk tool (ORT) before opioid administration and current opioid misuse measure (COMM). Diagnosis of OUD is performed by the Diagnosis and Statistical Manual of Mental Disorders, fifth edition (DSM-5). OUD is suspected if patients have 2 or more among 11 items. For busy clinicians, aberrant opioid-taking behaviors, composed of clearly and potentially problematic behaviors, can be used for suspicion of OUD in a clinical field. Treatment of OUD consists of 3 the U.S. Food and Drug Administration (FDA)-approved medications, including methadone, buprenorphine, and naltrexone and non-opioid symptomatic medications for the treatment of opioid withdrawal syndrome, such as α_2 agonists, β-blockers, antidiarrheals, antiemetics, non-steroidal anti-inflammatory drugs (NSAIDs), and benzodiazepines. These methods for prevention, diagnosis, and treatment are based on the 6 recommendation guidelines from various societies and associations, under the supervision of opioid stewardship programs.

tions due to multidrug-resistant organisms, according to the United States Centers for Disease Control and Prevention (CDC) [10,11].

After the successful implementation of ASPs, the next issue focused on was OSPs for the appropriate use of opioids from the late 2010s. According to the Institute of Safe Medication Practices (ISMP) Canada, "opioid stewardship" is defined as coordinated interventions designed to improve, monitor, and evaluate the use of opioids in order to support and protect human health [12].

The U.S. CDC published guidelines for prescribing opioids for chronic pain in 2016 [13]. The National Quality Forum (NQF) published a book, *Opioid Stewardship*, which included 7 fundamental actions, in 2018 [14].

OSPs are defined as coordinated programs that promote appropriate use of opioid medications, improve patient outcomes, and reduce misuse of opioids. The American Hospital Association (AHA) published "Stem the Tide: Opioid Stewardship Measurement Implementation Guide" in 2020. According to the AHA, opioid stewardship includes judicious and appropriate opioid prescription, appropriate disposal, prevention of opioid diversion, and management of the effects of the use of opioids, such as identifying and treating OUD and reducing opioid overuse mortality. The AHA suggested 6 critical elements in developing an opioid stewardship measurement strategy. They include ① a leadership strategy with patient engagement, ② environmental scans, ③ measurement selection, ④ goal setting and improvement planning, ⑤ policies and team education, and ⑥ patient education and engagement [15].

Strong leadership is essential to initially establish the successful OSPs in a hospital. Pain physicians are eager to devote time and effort to build a suitable policy and guidelines for their hospitals in opioid prescription, such as duration and dosage according to the source of pain and to provide opioid education for other physicians regularly. Pharmacists need to monitor and report the trends, amount, and duration of opioid prescriptions and the combinations of other medications. Nurses can prevent opioid diversion. Psychiatrists can support mental and behavioral health for OUD. The patient, family, and community education team should give information for nonpharmacologic and pharmacologic multimodal therapies, proper opioid storage and disposal, and opioid tapering for OUD. Collaboration with the government can prevent overlapped opioid prescription through the internet. OSP multidisciplinary and multimodal strategy lead a successful prevention, diagnosis, and treatment of OUD [10].

2. Essential terms related to OUD

The opium poppy was harvested from 3400 BC in Mesopotamia. Opium is a combination of alkaloids from the poppy seed. Opioids are substances which act on the (mu, delta, and/or kappa) opioid receptors agonistically (synergistically), antagonistically, partially agonistically, or agonistically/antagonistically. They can be divided into natural, semisynthetic, and synthetic opioids. Opiates refer to only natural opioids, such as morphine and codeine. Semisynthetic opioids include oxycodone, hydrocodone, hydromorphone, and oxymorphone. Synthetic opioids include methadone, buprenorphine, and fentanyl [16].

According to the International Classification of Diseases, 10th edition (ICD-10), opioid dependence is defined as a grouping of cognitive, behavioral, and physiological features in the presence of at least 3 of 6 features (**Table 1**) [17,18]. In addition, ICD-11 has been officially in effect by the WHO since January 1, 2022, even though it was released on June 18, 2018. The definition of opioid dependence is expressed as a regulation disorder of opioid use from repeated or continuous use of opioids [19].

Similar to opioid dependence, OUD is defined by the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a problematic pattern of opioid use resulting in clinically significant impairment or distress, consisting of 2 or more of 11 problems within 1 year (**Table 1**) [20].

In addition, the 11 criteria of OUD defined by DSM-5 is ambiguous and complicated for clinicians, therefore, it is better to observe the aberrant opioid-taking behaviors associated with OUD. Aberrant opioid-taking or opioid-related behaviors associated with OUD is defined as a behavioral contrast to treatment recommendation (**Table 1**) [21].

Opioid addiction is defined as a primary, chronic neurobiological disease, created by repeated exposure to an addictive opioid, showing loss of control over opioid use. It is supposed to be developed by genetic, psychosocial, and environmental factors [21]. The reward circuits have an important role in compulsive opioid taking. It is deeply related to mesocorticolimbic dopamine systems originating in the ventral tegmental area, and projecting to the nucleus accumbens, amygdala, and prefrontal cortex. Opioids generate dopamine release indirectly by decreasing gamma-amino-butyric acid-inhibition via mu-opioid receptors in the ventral tegmental area, and directly by interacting with opioid receptors in the nucleus accumbens. At least one or more of these four cardinal features of opioid addiction include ① craving, ② obsessive thinking, ③ loss of control, and ④ compulsive opioid taking (**Table 1**) [21–23].

Opioid pseudoaddiction is defined as opioid-seeking due to inadequate pain treatment, relieved by adequate pain management (**Table 1**) [21].

Table 1. Definition of terms for opioid use disorder

Terms	Definition		References
Opioid dependence	A cluster of cognitive, behavioral, and physiological features (≥ 3/6) ① A strong desire or sense of compulsion to take opioid ② Difficulties in controlling opioid use ③ A psychological withdrawal state ④ Tolerance ⑤ Progressive neglect of alternative pleasure or interests because of opioid use ⑥ Persisting with opioid use of despite clear evidence of overtly harmful consequences		ICD-10 [18]
Opioid use disorder (OUD)	Opioid use and the repeated occurrence with 1 year (≥ 2/11), 2–3: mild, 4–5: moderate, and ≥ 6: severe ① Continued use despite worsening physical or psychological health ② Continued use leading to social and interpersonal consequences ③ Decreased social or recreational activities ④ Difficulty fulfilling professional duties at school or work ⑤ Excessive time to obtain opioids, or recover from taking them ⑥ More taken than intended ⑦ Cravings ⑧ Unable to decrease the amount used ⑨ Tolerance a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect. b. A markedly diminished effect with continued use of the same amount of an opioid. ⑩ Use despite physically dangerous settings ⑪ Withdrawal		DSM-5 [20]
Aberrant opioid-taking behaviors related to OUD	Clearly problematic	Potentially problematic	Brady et al. [21]
	① Selling opioids	① Hoarding	
	② Forging prescriptions	② Requesting a certain type of opioid	
	③ Stealing opioids from others	-	
	④ Use by non-prescribed route	-	
	⑤ Doctor shopping	-	
	⑥ Repeated loss of opioids and running out early	③ A single loss of opioid and running out early	
	⑦ Multiple increases in dosage	④ A single increase in dosage	
Opioid addiction	A primary chronic neurobiological disease, produced by repeated exposure to an addictive opioid and characterized by loss of control over opioid use (≥ 1/4) ① A pronounced craving for the opioid ② Obsessive thinking about the opioid ③ Erosion of inhibitory control over efforts to refrain from opioid use ④ Compulsive opioid taking		Ballantyne and LaForge [23]
Opioid pseudoaddiction	An opioid seeking situation due to inadequate pain treatment, relieved by adequate pain management		Brady et al. [21]
Opioid physical dependence	A state of adaptation that is manifested an opioid specific withdrawal syndrome, produced by abrupt cessation, rapid dose reduction, decreasing blood level, and/or administration of an antagonist		Ballantyne and LaForge [23]
Opioid tolerance (insensitivity)	Need for increasing dose of opioid to achieve the same effect or diminished response to a opioid with repeated use		Dowell et al. [13] Ballantyne and LaForge [23]
Opioid withdrawal syndrome (OWS)	A opioid-specific problematic behavioral change, with physiologic and cognitive components, that is due to the cessation of, or reduction in, heavy and prolonged opioid use		DSM-5 [20]
	A group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a psychoactive opioid after persistent use of that opioid		ICD-10 [18]
	A collection of characteristic clinical symptoms and signs, which include hypertension, tachycardia, mydriasis, piloerection, lacrimation, rhinorrhea, yawning, insomnia, nausea, vomiting, and diarrhea		Srivastava et al. [24]
Opioid misuse (non-medical opioid use)	Any use outside of prescription parameters ① Misunderstanding of instructions ② Self-medication for sleep mood, or anxiety regardless of pain ③ Compulsive use driven by OUD		Brady et al. [21] Kosten and Baxter [25]
Opioid abuse	Use of opioids without a prescription		Brady et al. [21]

Table 1. Continued

Terms	Definition		References
Opioid diversion	The intentional transfer of opioid from authorized to unauthorized possession		Inciardi et al. [26]
Morphine milligram equivalent per day (MME/d)	An opioid daily dosage's equivalency to morphine		
	Weak opioids	tramadol (0.1), meperidine (0.1), codeine (0.15)	Dowell et al. [13]
	Moderate opioid	tapentadol (0.4)	
	Strong opioids	morphine (1), hydrocodone (1), oxycodone (1.5), oxymorphone (3), hydromorphone (4), methadone (1–20: 4, 21–40: 8, 41–60: 10, and 61–80: 12), transdermal fentanyl patch (μg, 2.4)	

Methadone shows a different morphine milligram equivalent per day according to its dosage: 1–20 mg/d of methadone is equivalent to 4 mg/d of morphine; 21–40 mg/d of methadone is equivalent to 8 mg/d of morphine; 41–60 mg/d of methadone is equivalent to 10 mg/d of morphine; 61–80 mg/d of methadone is equivalent to 12 mg/d of morphine.
ICD-10: International Classification of Diseases, 10th edition, DSM-5: 5th edition of the Diagnostic and Statistical Manual of Mental Disorders.

Opioid physical dependence is an adapted state showing an opioid withdrawal syndrome (OWS), activated by a decreased blood level due to abrupt cessation or rapid dose reduction of opioids and/or administration of an antagonist (**Table 1**). Even after the cessation of pain, use of opioids continues to prevent OWS [21,24].

Opioid tolerance (insensitivity) exhibits as a requirement for a higher dose of opioid to achieve a similar effect or diminished response to an opioid with repeated use (**Table 1**) [23].

OWS is defined as an opioid-induced problematic behavioral change due to discontinuation or decrease of prolonged and higher dose of opioid use (**Table 1**). This syndrome originates from an upregulation of cyclic adenosine monophosphate and noradrenergic mechanisms in the locus coeruleus [8,18,20,23–25].

Opioid misuse (non-medical opioid use) is a broad term which includes any non-prescription use, self-medication for other causes excluding pain, and uncontrollable use induced by OUD [25]. Opioid abuse is a non-specific term which includes use of opioids without prescription following one's feeling or experience (**Table 1**) [21].

Opioid diversion is defined as the willful transmission of opioids from certified to uncertified possession or the unlawful channeling of managed pharmaceuticals from legal sources to the illegal marketplace (**Table 1**) [26]. Opioid diversion can happen during all steps, from the original manufactures, wholesale distributors, physician's offices, retail pharmacies, and finally to patients. In the U.S., the most common diverted opioid during the 5 years from 2002 to 2006 was hydrocodone, followed by oxycodone [26]. In addition, population-adjusted rates of diversion from 2009 to 2015 were 6.1-fold higher for immediate release (IR) than extended release (ER) opioids [27]. The drugs most frequently diverted by healthcare personnel are also opioids [28]. Typical methods for diverting controlled substances used by healthcare workers include ① removing excessive amounts of as-needed medication, ② taking the wasted portion of the drug, or ③ not administering the prescribed medication or administering a substitute substance to patients [29].

MME/d is an opioid daily dosage's equivalency to morphine. In order to avoid accidental overdose resulting from incomplete cross-tolerance and interpersonal variability, the new opioid recommended dose is considerably lower than the calculated MME dose when converting opioids. Caution should be used, especially for a higher dose of methadone with a high dose conversion factor (from methadone to morphine: 1–20 mg/d = 4 MME/d, 21–40 mg/d = 8 MME/d, 41–60 mg/d = 10 MME/d, and 61–80 mg/d = 12 MME/d). Fentanyl patches should be used with great caution when converting into/from other opioids, due to using a different dosage unit (μg/h) and showing a different absorption rate due to temperature (**Table 1**) [13].

Opioid switching or opioid rotation is performed for getting better pain relief with a lower dosage or different formulation, or for reducing adverse reactions. The dosage of the new opioid is generally accepted as a 25%–50% MME/d reduction. This reduction is made due to incomplete cross-tolerance and inter-individual variation [30,31].

3. Problems in opioid use for pain

1) Problems in opioid use for acute pain

(1) Intraoperative infusion of remifentanil

Remifentanil is a potent, ultrashort-acting synthetic opioid. Acute tolerance against intraoperative remifentanil infusion at the maintenance dose of 0.25–0.5 μg/kg/min remains controversial. There are conflicting results, from no evidence of acute tolerance from the volunteers and those who received gynecologic surgery to increased postoperative pain and opioid requirement, associated with

acute opioid tolerance and hyperalgesia [32–35].

Acute opioid tolerance refers to lowering the effects of the opioid and desensitization to opioids. An increased dose of opioid can solve this problem. The tolerance develops not only to the analgesia but also to adverse reactions. Opioid-induced hyperalgesia refers to increased pain from a stimulus that normally provokes pain after opioid use. Here, it is not helpful to increase the opioid dose. This condition is characterized by a paradoxical increase in pain, related with hyperalgesia and allodynia. It may be prevented by N-methyl-D-aspartate receptor antagonists, such as ketamine, magnesium sulfate, and amantadine [36–38]. Infusion rates of remifentanil above 0.25 μg/kg/min are associated with tolerance, requiring increased postoperative opioid requirement; however, an infusion rate above 0.2 μg/kg/min is related to hyperalgesia, characterizing lower mechanical/pressure/cold/pain threshold [34].

Dexmedetomidine may be a solution for acute opioid tolerance and opioid-induced hyperalgesia. It is a highly selective α2-adrenergic agonist which has sympatholytic, sedative, amnestic, and analgesic properties [39]. It can also upregulate the expression of excitatory amino acid transporters by increasing the release of N-methyl-D-aspartate receptors [40]. Compared with remifentanil, intraoperative dexmedetomidine infusion shows lower pain and opioid requirement at 2 and 24 hours postoperatively, and fewer adverse reactions, including hypotension, shivering, nausea, and vomiting, even though exhibiting similar episodes of bradycardia [41].

(2) Patient-controlled analgesia for postoperative pain

Patient-controlled analgesia is a common practice for postoperative analgesia. NSAIDs are administered at the lowest effective dose owing to an increased bleeding tendency. Most surgical patients are naïve to opioids, and OUD begins in many patients with perioperative pain treatment [3]. On the other hand, patients may choose to discontinue the patient-controlled analgesia due to intractable itching and nausea/vomiting. The patient-controlled analgesia syringe filled with a large amount of opioid intended for at least 3-day use should be disposed of in an approved controlled drug disposal kit for reducing the risk of opioid diversion by health care personals.

Available non-opioid intravenous analgesics for patient-controlled analgesia without increasing the risk of bleeding include acetaminophen, nefopam, ketamine, and dexmedetomidine according to the pain characteristics and source of the pain [42]. In addition, ketorolac does not influence the prothrombin time and partial thromboplastin time, however, it shows clinically irrelevant change in the platelet count reduction in volunteers [43].

2) Problems in opioid use for chronic pain

(1) Problems in opioid use for CNCP

Pain chronification comes from intense nociceptive pain from actual tissue damage and/or neuropathic pain from a lesion or disease of the somatosensory nervous system [9]. Well-established postherpetic neuralgia (PHN), which has lasted over 6 months, shows radiating pain from scars on the dorsal root ganglia, dorsal horns or trigeminal ganglia, and remaining neuropathic pain. Before paying attention to OUD, such as misuse, dependence, overdose, and addiction [44], in chronic neuropathic pain, opioids were reported to show better pain relief and less initial adverse reaction in cognitive function [45]. Sometimes, PHN patients apply fentanyl or buprenorphine transdermal patches or take a short-acting oxycodone with patient referral. While tapering these opioids and up-titration of anticonvulsants and antidepressants simultaneously, most patients visit a clinic before their scheduled appointment, complain of generalized pain and going cold turkey, and demand a specific opioid, even though they have received extensive warnings, cautions, and made agreements related to dose-reduction of an opioid. It is also difficult for PHN patients who are tapering a moderate or strong opioid to keep their own tapering schedule of 6 months or 1 year.

Incidence of OUD in patients hospitalized with chronic pancreatitis as a representative of visceral pain was known to be 3-times higher than that in general hospitalized patients [46]. Even after complete pain relief from celiac plexus alcohol neurolysis and injections for co-morbid facet joint syndrome, patients with chronic pancreatitis sometimes resist tapering an opioid because of general aching and a depressed mood. Patients with chronic pancreatitis may suffer from alcoholism as a kind of substance use disorder (SUD). Frequency of pain was increased associated with increasing intake of alcohol [47].

When prescribing an opioid for CNCP, the physician should have confidence that it can be discontinued. Even the CDC has recommended to begin with an IR opioid, but that the IR opioid should be changed to an ER opioid after confirmation of the daily dose. Patients with OUD commonly request a specific IR opioid which they can keep in their pocket, due to its rapid onset, similar to that of intravenous opioid administration. Generally, maintenance with an ER opioid over an IR opioid is recommended [48].

Medications for complex regional pain syndrome (CRPS) are divided into first- to fourth-line analgesics: the first-line analgesics include NSAIDs or acetaminophen, anticonvulsants, and antidepressants. The second- to third-

line analgesic is tramadol, a weak opioid. The third- to fourth-line analgesics include strong opioids. Even though short-term use in the early phase is necessary for function and quality of life, high-dose long-term opioid therapy (LTOT) should be avoided due to the risks of death, dependency, tolerance, overdose, and opioid-induced hyperalgesia [49]. In addition, opioid-induced adrenal insufficiency can be found 9%–29% in LTOT due to suppression of the hypothalamus-pituitary-adrenal axis. The symptoms, such as fatigue, nausea/vomiting, weight loss, dizziness, and myalgia before cardiovascular collapse, sometimes overlap those of chronic pain syndrome. Cortisol, corticotropin, and synthetic corticotropin stimulation testing is recommended [50].

For the successful removal of spinal cord stimulators in CRPS after complete relief of pain, moderate and strong opioids should be removed [51]. To make matters worse, an intrathecal opioid pump, followed by failed spinal cord stimulators implantation in patients with CRPS, makes them lifetime opioid users [52].

(2) Problems in opioid use for cancer pain

Inappropriate opioid prescription for new-development somatic or neuropathic pain in visceral cancers is frequently found in cancer patient referrals. Patients have already covered their entire bodies with fentanyl patches, with no bare skin to apply more. It is better to treat the correctable deep somatic lesions rather than to increase unnecessary opioid dosage. First of all, correctable painful bony metastatic lesions can be treated by percutaneous osteoplasties or percutaneous vertebroplasties instead of unnecessary and ineffective dose-up titration of opioids. Second, it is also common to find cervical or thoracic facet joint pain syndrome due to an incapacity to lie down on the back, even at night, from both abdominal pain in advanced or inoperable abdominal cancers and dyspnea in lung cancer [53]. Third, do not forget hidden benign degenerative musculoskeletal disorders in cancer patients which may or may not be cancer-related. There are often combined osteoporotic and osteolytic vertebral compressive lesions in elderly cancer patients [54]. In breast cancer patients, radical mastectomy with extensive lymph node dissection, ipsilateral frozen shoulder due to long-standing pain, and limitation of shoulder motion are also commonly found [55]. Neuropathic pain from uncorrectable metastatic lesions is treated by anticonvulsants and antidepressants rather than dose-up titration of opioid.

OUD is very common in cancer patients and cancer survivors. Chemical (or opioid) coping describes an excessive or inappropriate use of medication (opioid) to control psychological distress associated with having cancer [56]. Dual diagnosis for major depression or anxiety in cancer patients is very common in young male patients. While opioid misuse was found similarly in both cancer survivors and the general population, and opioid abuse is higher in cancer survivors than the general population [57,58].

4. Various recommendations related to OUD

There are 5 classes of controlled substances according to the Controlled Substances Act: narcotics, depressants, stimulants, hallucinogens, and anabolic steroids. Narcotics are also classified by the Drug Enforcement Administration as follows: schedule I (high additive non-medical narcotics, such as heroin, marijuana, and phencyclidine), schedule II (highly additive medical narcotics, such as morphine, oxycodone, methadone, fentanyl, and amphetamine), schedule III (moderately additive medical narcotics, such as hydrocodone, codeine, and anabolic steroids), schedule IV (low abuse potential medical narcotics, such as benzodiazepines, meprobamate, butorphanol, pentazocine, and propoxyphene), and schedule V (low abuse potential medical narcotics, such as buprenorphine and promethazine with codeine) [59,60].

1) Twelve recommendations from the U. S. CDC for prescribing opioids for chronic pain in 2016

The U. S. CDC published 12 recommendations related to prescription of opioids for chronic pain, excluding active cancer, palliative, and end-of-life care, as follows [13].

(1) Determination for initiation or continuation of opioids for chronic pain

① Begin with non-pharmacologic and non-opioid pharmacologic therapy. Opioid therapy should be appropriately added to non-pharmacologic and non-opioid pharmacologic therapy. If benefits for patient's pain management and physical functions can be expected to outweigh the risks, then opioid therapy should be considered.
② Create realistic opioid treatment goals prior to administration, and give attention to methods for discontinuation when benefits do not outweigh risks.
③ Discuss with patients the benefits and risks before and during the opioid therapy.

(2) Selection, follow-up, and discontinuation of opioids

④ Start from IR rather than ER/long-acting opioids.
⑤ Start from the lowest effective dosage. Use caution if the dosage is reaching 50 MME/d, and avoid a dosage

above 90 MME/d.
⑥ Start IR opioids only for 3 days or less and limited to 7 days, for acute pain.
⑦ Reevaluate the benefits/harms or dose escalation for chronic pain within 1 to 4 weeks and at least every 3 months. Consider tapering or discontinuing whenever benefits do not outweigh harms.

(3) Evaluation of risk factors and treatment

⑧ Evaluate risk factors, such as history of opioid overdose, other SUD, higher opioid dosage ≥ 50 MME/d, or concurrent use of benzodiazepine.
⑨ Review the history of controlled substances when starting opioids and periodically at every 3 months, using State Prescription Drug Monitoring Program (PDMP) data.
⑩ Use urine examination for prescribed medications, controlled prescriptions, and illicit drugs at least annually.
⑪ Avoid prescribing concurrent administration of benzodiazepines.
⑫ Offer medication-assisted treatment (MAT) and behavioral therapies for OUD.

In the clinical field, it is a wonder how many patients who have already taken an opioid agree to discontinue when benefits do not outweigh risks. In cases of complaints of insomnia due to pain, it is not easy to determine whether to increase the dosage of the opioid or to choose non-benzodiazepines sedatives and hypnotics. It is also hard to decide how many kinds of non-benzodiazepines can be used safely for sleep without adverse reactions. Non-benzodiazepine sleeping sedatives and hypnotics include gamma-aminobutyric acid agents, such as zolpidem or zaleplon; antihistamines, such as diphenhydramine; antidepressants, such as tricyclics, trazodone, mirtazapine, or nefazadone; and antipsychotics, such as quetiapine [61].

2) Ten recommendations from the Canadian guideline for opioid therapy for CNCP in 2017 [62]

① Start with non-opioid medication and non-pharmacologic therapy, rather than opioid therapy in CNCP.
② Avoid opioid therapy in patients with a history of SUD, active psychiatric disorders, and persistent problematic pain despite appropriate non-opioid therapy.
③ Exclude patients with an active SUD.
④ Stabilize psychiatric disorders before administration of opioids.
⑤ Continue non-opioid medication in CNCP patients with a history of SUD for persistent problematic pain.
⑥ Prescribe an opioid at less than 90 MME/d. When setting an upper limit, 90 MME/d, is better than no limitation.
⑦ Prescribe an opioid at less than 50 MME/d in patients who can understand the risk of an increased dose of opioids.
⑧ Switch to other opioids in patients who have persistent problematic pain and/or adverse reactions.
⑨ Taper opioids to the minimal effective dose in patients who are currently using over 90 MME/d.
⑩ Send patients who have trouble in tapering opioids to a formal multidisciplinary program.

Contraindications suggested for opioid therapy in CNCP include a history of SUD, active psychiatric disorders, and persistent problematic pain. Problematic pain is defined as any pain associated with potential to cause significant pain related morbidity (disability and/or distress). The risk factors of problematic pain include high intensity and long-duration of pain, high disability, and pain related distress, including depression, anxiety, and catastrophizing, and multiple site pain [63].

3) Five recommendations from the European Pain Federation position paper in 2017 [30]

According to the directions for proper opioid use for chronic pain by the European Pain Federation position paper in 2017, a gradual initiation of opioid analgesia was suggested. The steps include ① evaluation of the suitability for opioid use, ② choice of an opioid and its type of duration with timing, such as IR, ER, and/or *pro re nata* (PRN), ③ initiation of a short-term trial with the lowest dosage, ④ reviewing outcomes, including therapeutic effects and adverse reactions, for the decision to continue or increase dosage and for treatment of the adverse reactions, and ⑤ reevaluation of outcomes every 12 weeks.

4) Fourteen recommendations from the American Pain Society (APS) and the American Academy of Pain Medicine (AAPM) in 2009 [64]

① Consider a trial of opioids when benefits outweigh harms. A benefit-to-harm evaluation is performed by history taking, physical examination, and a risk evaluation for substance abuse, misuse, and addiction. Moderate to severe pain produces decreased function and quality of life.
② Informed consent for opioid therapy includes objectives, expectations, adverse reactions, and other

treatment options. A written opioid plan should include responsibilities and expectations for the patient and clinician, as well as patient education.

③ Clinicians and patients should determine whether opioids should be used. Initiation and titration of the opioid should be individualized. There is a lack of evidence for recommending IR versus ER formulations and for as-needed versus around-the-clock dosing.

④ Methadone has confusing and fluctuating pharmacokinetics and pharmacodynamics, requiring careful initiation and titration by physicians who are familiar with its dosage and adverse reactions.

⑤ After opioid medication, intensity of pain, function and quality of life, progression of therapeutic goals, adverse reactions, and adherence, as well as, if necessary, periodic urine drug screening should be monitored and reassessed. Progression notes include the current analgesic regimen, pain and pain relief, daily living activities, adverse reactions, aberrant behaviors, and analgesic plans for opioid therapy.

⑥ More frequent and tighter monitoring, consultation with psychiatry or addiction specialists, and discontinuation of opioids are required in high-risk patients with a history of drug abuse, psychiatric issues, or serious aberrant behaviors.

⑦ Reevaluate the causes of the benefits-to-harms in repeated opioid dose escalations. Consider more frequent follow-up visits when showing adverse reactions with poor health status and adherence to the opioid therapy. Consider opioid rotation for intolerable adverse effects or inadequate benefits despite dose increases. Taper or stop opioid administration in cases of repeated aberrant opioid-related behaviors, opioid diversion/abuse, lack of progress towards therapeutic goals, or intractable adverse reactions.

⑧ Prevent, diagnose, and treat adverse reactions.

⑨ Integrate interdisciplinary or multidisciplinary pain management routinely for CNCP.

⑩ Discuss cognitive impairment owing to opioid therapy with patients.

⑪ Consult and communicate with other clinicians.

⑫ Consider an IR opioid prescription for breakthrough pain during ER opioid therapy for continuous pain after analysis of therapeutic benefit versus risk.

⑬ Persuade pregnant women not to use opioids or to use a minimal dosage of opioids during the intrapartum and postpartum period. Prepare and treat risks to the patient and newborn. OWS can be expected in over 50% of newborns of opioid-dependent mothers.

⑭ Be familiar with laws, regulatory guidelines, and policy statements.

Most guidelines recommend that the use of an opioid in CNCP was permitted when benefits outweigh harms. In an ideal world this might be a good recommendation, but it is impractical for those who know how difficult the tapering and discontinuation of strong opioid are. A correction of the WHO 3-step analgesic ladder for CNCP is suggested. Interventional treatment, such as muscle injections, myofascial injections, joint injections, intraosseous injections, and epidural injections, should be included in all 3 steps (1st step: non-opioid medication with adjuvant medication, 2nd step: 1st step + weak opioid, and 3rd step: 2nd step + strong opioid) for the correctable causes of CNCP, and can reduce opioid consumption actively, similar to the 4-step analgesics ladder [5].

5) The American Society of Addiction Medicine (ASAM) National Practice Guideline for treatment of OUD in 2020

The ASAM published a voluminous, updated, professional national practice guideline for the treatment of OUD in 2020, replacing the old 2015 version [65]. They also published an executive summary focusing on the revisions [66]. They suggested a master guideline, including a 14-part diagnosis and treatment regimen for OUD with terminology.

① Assessment and diagnosis of OUD: Appropriate referral to an emergency or psychiatric department, general evaluation of the patient for establishment of treatment, history taking, physical examination, laboratory tests with tests for infectious diseases as well as testing for pregnancy, mental health status, and psychiatric disorders, the coexistence of other SUDs, and multidimensional assessment are essential to assess patients with OUD.

Diagnosis of OUD must be obtained from history taking and before pharmacotherapy. It is necessary to perform drug testing for evaluating adherence to prescribed medications as well as for detecting other SUDs.

② Treating OUD: FDA-approved medications and psychological referral can be available based on the PDMP. Methadone is prescribed in opioid treatment programs (OTPs) and acute care settings. Buprenorphine is prescribed by approved clinicians in any setting. However, naltrexone can be prescribed by any clinicians in any setting. Naloxone is also used for reversal of opioid overdose in OUD. MME/d is not applicable to medications for the treatment of OUD.

③ Treating OWS: Methadone or buprenorphine is also

used for OWS resulting from abrupt cessation of opioids. Detoxification is to manage acute OWS for the prevention of relapse and overdose of opioids. In addition to detoxification, continuing maintenance medication with psychosocial therapy is the standard treatment for OWS.

The initial dose of methadone withdrawing from short-acting opioids is 20–30 mg daily, and tapering off may be completed in 6–10 days. The initial dose of 2–4 mg/d of buprenorphine, followed by titrating up as needed to suppress the OWS, should be used when objective signs of OWS are found. Methadone and buprenorphine, rather than alpha-2 agonists (FDA-approved lofexidine and off-label clonidine), are more effective for OWS.

④ Methadone: After getting informed consent, the initial dose of methadone starts from 10 to 30 mg. The first dose may be reduced 2.5 to 10 mg for patients with low or no opioid tolerance. Usual daily doses range from 60 to 120 mg after increasing the dose 10 mg every 5 days under monitoring and psychosocial treatment, in order to prevent it leading to misuse or diversion.

Initial dosing and titration are also needed for re-initiation. Prevention of relapse is an essential goal of addiction treatment. Transition from methadone to another medication is a difficult challenge owing to intractable, dangerous adverse reactions, resulting in relapse. Transitioning from less than 30–40 mg per day of methadone to buprenorphine is tolerable. However, transition from methadone to naltrexone requires complete cessation of methadone or other opioids before administration of naltrexone. There is no deadline for methadone therapy. Patients should know the risk of overuse of other opioids or overdose death from illicit opioid use when discontinuing methadone for the treatment of OUD.

⑤ Buprenorphine: Buprenorphine is a partial mu opioid agonist. It is used for treatment for both OUD (with a similar effect to methadone) and OWS (with a better effect than lofexidine or clonidine). Contraindications include hypersensitivity and severe hepatic impairment. Other SUDs, hypovolemia or use of antihypertensive agents, and severe cardiovascular disorders need attention for the use of buprenorphine. Drug interaction may develop with central nervous system depressants and agents which affect CYP3A4 activity, such as ketoconazole (antifungal agents), erythromycin (macrolide antibiotics), and human immunodeficiency virus protease inhibitors.

FDA warnings on use of all opioids including methadone and buprenorphine include respiratory depression in concomitant use with benzodiazepines, serotonin syndrome in interaction with antidepressants and migraine medicines, Addison's disease, and decreased sex hormone levels with decreased libido, impotence, or infertility [67].

Various FDA-approved buprenorphine formulations are available, including daily sublingual tablets of buprenorphine (monoproduct), daily sublingual tablets or a film combination of buprenorphine and naloxone, monthly or weekly injection of buprenorphine ER, and subcutaneous implants of buprenorphine hydrochloride every 6 months.

Initiation starts with a dose of 2–4 mg, increasing the dosage in increments of 2–8 mg. A daily dose of 16 mg or more has been shown to be effective. However, higher doses of more than 24 mg per day do not show greater effectiveness, but instead increase the risk of diversion.

Psychosocial treatment is also helpful in the treatment of OUD with buprenorphine. Drug testing is monitored for adherence to buprenorphine and other controlled substances. A transition from buprenorphine to naltrexone needs 7–14 days when there is no longer any physical dependency on opioids.

A transition from buprenorphine, a partial agonist, to methadone, a full agonist, does not require a time delay. Buprenorphine can be used any time during the treatment of OUD. Tapering and discontinuation take several months and ongoing monitoring after discontinuation is also essential.

⑥ Naltrexone: Intramuscular ER naltrexone is more effective for prevention of OUD relapse than oral naltrexone. Oral naltrexone is only effective in some highly motivated and compliant patients under the supervision of their family. Oral naltrexone is administered from 25 mg on the first day, increasing to 50 mg daily from the second day, and followed by a 3-day per week regimen (100-0-100-0-150-0-0 mg, a total of 350 mg weekly).

ER naltrexone is commonly administered by intramuscular injection every 4 weeks with a dose of 380 mg. It is helpful to administer it every 3 weeks in rapid metabolizers. There are 4 goals in naltrexone therapy for OUD: prevention of OUD relapse in detoxified patients who are no longer physically dependent on opioids, blocking illegal opioids, reducing opioid craving, and encouraging patient attendance in recovery programs.

Compared to agonist therapy with buprenorphine or methadone, naltrexone can be used in cases of contraindications to buprenorphine or methadone therapy, in those highly motivated to taper off bu-

prenorphine or methadone therapy, in those who have had unsuccessful results with buprenorphine or methadone therapy, and those who refuse buprenorphine or methadone therapy.

Before starting naltrexone, administration of IR and ER opioids should be stopped for 6 and 7–10 days, respectively. Because of uncertainty regarding physical dependency on opioids, a short-acting opioid antagonist, naloxone hydrochloride, or a low-dose oral naltrexone, can be initiated.

Common adverse reactions of naltrexone include sleeplessness, nervousness, lethargy/sedation, nausea/vomiting, abdominal cramps, chills, headache, arthralgia/myalgia, and injection site pain.

Urine drug testing is recommended for the evaluation of adherence for medication and illegal drug use. The frequency of the urine test (at least 8 times a year) is determined by the adherence of the patients with their different medication in their different treatment settings.

Transition from naltrexone to buprenorphine or methadone is applied in cases of intolerable adverse reactions, maintenance of unsuccessful treatment goals, and at the demand of the patient.

⑦ Psychosocial treatment: Psychosocial treatment helps patients reduce craving and relapse, so as to cope with the psychosocial challenge. The therapeutic goals of psychosocial treatment are to modify the underlying processes, to encourage participation and adherence to the treatment plan, and to treat any other psychiatric disorders which may make OUD worse or trigger a relapse. Psychosocial treatment includes evaluation of psychosocial requirements, advice, connection to existing support systems, and referral. In patients receiving methadone, buprenorphine, or naltrexone, psychosocial needs are assessed, and referrals are also provided.

⑧ Special populations of pregnant women: Obstetrical complications related to OUD include preeclampsia, abortion, premature delivery, and fetal growth retardation and death. Neonatal abstinence syndrome (NAS) is defined as a group of withdrawal signs in infants after exposure to substances (often opioid agonists) prenatally. Neonatal opioid withdrawal syndrome (NOWS) refers to withdrawal signs in infants who have had uterine opioid exposure. The infants may have hyperactive central and autonomic nervous systems, affecting the gastrointestinal and respiratory systems. Symptoms may start from minutes to 2 weeks after birth, but usually within 3 days. The treatment is opioid agonist medication in tapering half doses.

Physical examination in pregnant women includes objective opioid intoxication and OWS. The pregnant women with OUD may seek antenatal care late, show missed appointments, and have insufficient weight gain. Injection drug users may show punctured skin evidence, cellulitis, or abscesses. Laboratory tests includes HIV and viral hepatitis.

Pregnant women with active OUD start with methadone or buprenorphine as the choice of treatment, as soon as possible, during pregnancy. It is recommended for them to be hospitalized at the beginning of methadone or buprenorphine treatment to avoid the potential adverse reactions, especially during the third trimester. It is better to start opioid agonist therapy as early as possible because there is little confirmation that methadone or buprenorphine produces higher rates of NOWS. An experienced clinician in both OUD treatment and obstetric care should manage pregnant women with OUD.

The initial dose of methadone starts from 10–30 mg, and incremental doses of 5–10 mg every 3–6 hours is recommended for managing OWS. The maximum dose on the first day is 30–40 mg. Every 5 days, the dose can be limited to increase by 10 mg to control OWS with the lowest dose. Plasma levels of methadone progressively decrease but clearance increases, as gestational age advances. Therefore, split doses may be needed as pregnancy progresses. Reduced doses are needed postnatally.

Naltrexone should be discontinued after pregnancy. Naloxone is also not recommended. However, breastfeeding mothers are recommended to take methadone or buprenorphine.

⑨ Special populations of individuals with pain: Alternative treatments, including non-opioid medications (acetaminophen or NSAIDs), behavioral approaches, physical therapy, or regional anesthesia, should be sought first before the use of opioids.

It is advised for patients with pain who have active OUD to use methadone or buprenorphine. Temporarily increasing the dose or dosing frequency is helpful. Patients who treat moderate to severe acute pain with a regular dose of methadone for the treatment of OUD may require a higher dose of a supplemental short-acting full agonist opioid.

Rescue doses of buprenorphine in supervised settings, rather than in ambulatory care settings, during hospitalization may have better results in patients receiving buprenorphine for OUD who have moderate to severe acute pain which is refractory to other treatments. It is not necessary to discontinue administration of methadone or buprenorphine

preoperatively. It is also allowable to use intravenous strong opioids intraoperatively. Postoperative daily doses can be restarted 3 days after operation.

In patients who are taking naltrexone and did not respond to opioid analgesics for their somatic pain, non-opioid analgesics are recommended in cases of mild pain, and higher potency NSAIDs, such as ketorolac, are recommended in moderate to severe pain on a short-term basis. High potency full agonist opioids can overcome a blocking effect of mu opioid receptors from naltrexone.

⑩ Special populations of adolescents: Methadone, buprenorphine, and antagonists can also be used in OUD in adolescents. It is appropriate for patients and their parents to participate the treatment of OUD by both pharmacotherapy and psychosocial treatment. Blood-born infections and sexually transmitted infections should be controlled.

⑪ Special populations with current psychiatric disorders: Suicidal or homicidal ideation in OUD patients with psychiatric disorders should be recognized.

⑫ Special populations in the criminal justice system: It is easy to ignore the forced OWS in individuals entering the criminal justice system. Three FDA-approved medications can be provided to individuals within the criminal justice system and even after release. Naloxone kits are prepared within the criminal justice system.

⑬ Naltrexone for treatment of opioid overdose: Naltrexone for opioid overdose is given in both general patients and pregnant women with OUD. Naloxone can be given by trained family members.

⑭ Areas for further research: Personalized medication with new treatment methods may be advantageous in future studies.

The cost for the treatment of OUD in a certified OTP in the United States in 2016 was $126/week or $6,552/year for methadone, $115/week or $5,980/year for buprenorphine, and $1,176.5/month and $14,112/year for naltrexone, respectively [68].

6) OTPs suggested by the United States Substance Abuse and Mental Health Services Administration (SAMHSA) in 2015

A new version of the federal guidelines for OTPs in 2015 was published to replace the old 2007 version [69]. Medications for OUD include methadone, levo alpha-methadyl acetate (LAAM), buprenorphine, or buprenorphine combination products. The upper limitation of initial dose and total first daily dose of methadone are 30 mg and 40 mg, respectively. Therapeutic goals for MAT are prevention of the onset of opioid abstinence syndrome for opioid agonists at least for 1 day, reduction of drug craving for opioid agonists or antagonists, and blockage of their euphoric effects.

LAAM is considered a second-line treatment for OUD, next to methadone or buprenorphine. It is administered 3 times in a week: 75–115 mg on Monday and Wednesday and 105–161 mg (a 40% higher dose) on Friday [70].

5. Screening tests for prevention of OUD

There are 3 types of assessment instruments for opioid and non-opioid risk, designed for anticipating different risks: (1) opioid misuse before opioid medication, (2) opioid misuse during opioid medication, and (3) non-opioid substance abuse (**Table 2**) [71].

1) Screening tests for opioid misuse before initiation of LTOT

They include ① the Opioid Risk Tool (ORT) [72], ② the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) [73], and ③ the Screening Instrument for Substance Abuse Potential (SISAP) [74] used by patients themselves or ④ the Diagnosis, Intractability, Risk, and Efficacy (DIRE) score by clinicians [75].

2) Monitoring methods for detection of opioid misuse during LTOT

It is helpful for clinicians to monitor problematic drug-related behaviors (PDRB), OUD, and LTOT lasting over 90 days [72]. Monitoring methods can be divided into patient self-administered instruments and clinician-administered instruments. The patient self-administered instruments include the Prescription Drug Use Questionnaire-Patient version (PDUQ-p) [76], the Current Opioid Misuse Measure (COMM) [77], and the Patient Medication Questionnaire (PMQ) [78]. Clinician-administered instruments include the Prescription Drug Use Questionnaire-clinician version (PDUQ-c) [79] which was developed from the PDUQ-p, the Pain Assessment and Documentation Tool (PADT) [80], and the Addiction Behavior Checklist (ABC) [81].

3) Screening for non-opioid general substance abuse

When initiating and continuing opioid therapy, it is also important to screen for SUD, such as illegal or non-prescribed drug use and alcohol misuse/abuse.

Feeling you should cut down on drinking or drug use, feeling annoyed by criticism of your drinking or drug use,

Table 2. Risk evaluation before and during opioid administration for prevention of opioid use disorder

Pre-administration opioid risk evaluation methods				
1. Opioid Risk Tool by patients [71]				
			Man	Woman
Family history of substance abuse	Alcohol		1	3
	Illegal drugs		2	3
	Prescription drugs		4	4
Personal history of substance abuse	Alcohol		3	3
	Illegal drugs		4	4
	Prescription drugs		5	5
Age between 16 and 45 years old			1	1
History of pre-adolescent sexual abuse			3	0
Psychological diseases	Attention deficit disorder, obsessive compulsive disorder, bipolar disorder, or schizophrenia		2	2
	Depression		1	1
Total score (26)	Low risk (0–3)			
	Moderate risk (4–7)			
	High risk (≥ 8)			
2. The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) by patients [72]				
3. The Screening Instrument for Substance Abuse Potential (SISAP) by patients [73]				
4. The Diagnosis, Intractability, Risk, and Efficacy (DIRE) score by clinicians [74]				
(1) Diagnosis	1 = Benign chronic condition with minimal objective findings or no definite medical diagnosis		Fibromyalgia, migraine, or non-specific back pain	
	2 = Slow progressive condition concordant with moderate pain, or fixed condition with moderate objective findings		Failed back surgery syndrome, back pain with moderate degenerative changes, neuropathic pain	
	3 = Advanced condition concordant with severe pain with objective findings		Advanced neuropathy, severe spinal stenosis	
(2) Intractability	1 = Trial of few therapies and a passive role in patient's pain management process			
	2 = Trial of most customary treatments, but partially engaged in patient's pain management process			
	3 = Trial of appropriate treatment, but inadequate response			
(3) Risk	Psychological	1 = Serious personality dysfunction or mental illness interfering with care	Personality disorder, severe affective disorder, or significant personality issues	
		2 = Moderate personality or mental health	Depression or anxiety disorder	
		3 = Good communication with clinic	No significant personality dysfunction or mental illness	
	Chemical health	1 = Active or very recent use of illicit drugs, excessive alcohol, or prescription drug abuse		
		2 = Chemical coper or history of chemical dependency in remission		
		3 = No chemical dependency history		
	Reliability	1 = History of numerous problems: medication misuse, missed appointments, rarely follows through		
		2 = Occasional difficulties with compliance, but generally reliable		
		3 = Highly reliable patient with medications, appointments, and treatment		
	Social support	1 = Life in chaos, little family support and few close relationships, loss of most normal life roles		
		2 = Reduction in some relationships and life roles		
		3 = Supportive family/close relationships. Involved in work or school and no social isolation.		
(4) Efficacy	1 = Poor function or minimal pain relief despite moderate to high doses.			
	2 = Moderate benefit with function improved in a number of ways or insufficient information			
	3 = Good improvement in pain and function and quality of life with stable doses over time			
Total DIRE score (21)	Score 7–13	Not a suitable candidate for long-term opioid analgesia		
	Score 14–21	A suitable candidate for long-term opioid analgesia		

feelings of guilt regarding drinking, and use of drinking or drugs as a morning eye-opener are 4 components which have been adapted to include drugs (CAGE-AID) questionnaire [82].

The SBIRT includes screening for cigarettes, drink, and illegal drugs, a brief motivational intervention, and referral to SUD treatment [83].

The RAFFT includes relaxing with drink or drugs, drinking or drug use alone, drinking or drug use with your closest friends, a problem with alcohol or drugs with a close

Table 2. Continued

Intra-administration opioid risk evaluation methods		
1. Prescription Drug Use Questionnaire-patient version (PDUQ-p) by patients [75]		
2. Current Opioid Misuse Measure (COMM) by patients in the past 30 days [76]		
6 Concept Map Clusters	17 Items	Never (0), Seldom (1), Sometimes (2), Often (3), or Very Often (4)
(1) Signs and symptoms of drug misuse	Trouble with thinking clearly or memory problems	
(2) Emotional problems/psychiatric issues	Complaints from others about incompletion of necessary tasks	
	Serious thought about self-harm	
	Arguing with others	
	Trouble managing your anger	
	Experiencing anger with people	
(3) Poor response to medications		
(4) Evidence of lying and illicit drug use	Taking medications differently from being prescribed,	
	Time spent thinking about opioid medications	
	Taking others' pain medication	
	Concern about managing your medications	
	Others' worry about your handling your medications	
(5) Inconsistent appointment patterns	Visiting multiple providers to get sufficient pain relief	
	Making an emergency call or showing up at the clinic without an appointment	
	Visiting an visiting emergency room	
(6) Medication misuse/abuse as well as noncompliance with medication	Needing to take more of your medication than prescribed	
	Borrowing pain medication from others	
	Using pain medication for non-prescribed symptoms	
Total score		/68
A score of 9 or greater out of a total score of 68 is suggestive of current problematic drug-related behaviors.		
3. Patient Medication Questionnaire (PMQ) by patients [77]		
4. Prescription Drug Use Questionnaire-clinician version (PDUQ-c) by clinicians [78]		
5. Pain Assessment and Documentation Tool (PADT) by clinicians [79]		
6. Addiction Behavior Checklist (ABC) by clinicians [80]		

family member, and trouble from drinking or drug use [84].

The drug abuse screening test (DAST) includes 20 yes/no questions [85]. The alcohol consumption questions from the alcohol use disorders identification test (AUDIT-C) contains 10 with 5 degrees from 0 to 4 [86].

The self-report Drug Use Disorders Identification Test: Extended (DUDIT-E) is composed of 17 questions, performed by patients [87].

6. Diagnosis of OUD

For identifying OUD, a single screening question, the frequency for use of an illegal opioid or a legal prescription opioid for nonmedical reasons over 1 year, has a sensitivity of 85.1% and specificity of 88.6% [88].

1) DSM-5 criteria for OUD

OUD is impaired control over the risky use of opioids, leading to physical, psychological, and social harms. According to the DSM-5 criteria, at least 2 of the 11 criteria should be present. The 11 criteria can be divided into 4 clusters from the definition. The degree of OUD is further divided into mild (2–3 items), moderate (4–5), or severe (6 and more) (**Table 3**) [20].

2) Aberrant behaviors of OUD

Physicians may consider aberrant behaviors of OUD easier to apply in the clinical field, instead of using the complicated diagnostic DSM-5 criteria. These aberrant behaviors are divided into clearly and potentially problematic behaviors (**Table 3**) [21].

7. Treatment of OUD

For the treatment of OUD, detoxification using opioid agonist maintenance treatments (including opioid detoxification, using either methadone or buprenorphine) or alpha-2 adrenergic agonist detoxification (using clonidine) for reducing OWS, followed by the long-acting opioid antagonist naltrexone and short-acting opioid antagonist naloxone, can prevent relapse or reverse opioid intoxication and overdose [89].

Table 3. Comparison between Diagnostic and Statistical Manual of Mental Disorders. 5th ed (DSM-5) criteria for opioid use disorder and aberrant opioid-taking behaviors [20,21]

DSM-5 criteria for opioid use disorder (OUD)		Aberrant opioid-taking behaviors	
1. Impaired control	① Use of large amounts or longer duration of opioid use,	Clearly problematic	Potentially problematic
	② A persistent desire or multiple unsuccessful attempts to discontinue opioids	Selling	Hoarding
	③ Time-consuming efforts to get opioids or to recover from their effects	Forging prescriptions	
	④ Intense desire or craving for the opioid.	Stealing opioids from others	
2. Risky use	⑤ Recurrent use in physically hazardous situations	Using by non- prescribed route	
	⑥ Interpersonal problems	Doctor shopping	Specific types of drug requested
	⑦ Continuous use despite negative physical or psychological consequences	Repeated losing and running out early	Single loss and running out early
3. Social harms due to opioid use	⑧ Failure to fulfill obligations at work, school, or home, as well as interpersonal problems	Multiple dosage increases	Single dosage increase
	⑨ Abandoning or reducing important social, occupational, or recreational activities		
4. Pharmacologic physical dependence	⑩ Tolerance		
	⑪ Withdrawal		
Mild OUD	2–3		
Moderate OUD	4–5		
Severe OUD	≥ 6		

According to the 2017 Canadian guideline for opioid therapy for CNCP, strategies for opioid tapering include ① a gradual reduction of 5% to 10% of MME/d every 2–4 weeks, ② switching from IR to ER opioids on a fixed-dosing regimen, ③ collaboration with a pharmacist for dose reductions, and ④ rapid dose reduction under the supervision of a withdrawal center or gradual tapering after switching to methadone or buprenorphine/naloxone [62].

There are 3 FDA-approved medications for the treatment of OUD, including methadone, buprenorphine, and naltrexone (**Table 4**) [88,89].

Opioid substitution treatment using methadone and buprenorphine reduces opioid-craving and illegal opioid use, as well as increasing treatment retention and overall survival. Using only methadone or only buprenorphine reduces all-cause mortality from 3.61% to 1.13% and from 0.95% to 0.43% for 1 year, respectively [90]. When choosing methadone or buprenorphine for opioid maintenance or detoxification, methadone can be used with all degrees of opioid dependence, however, buprenorphine should be selected with mild to moderate degree opioid dependence due to its efficacy. Methadone rather than buprenorphine is recommended due to known difficulty in supervision of the consumption of buprenorphine in cases of high risk for opioid diversion. Switching from methadone to buprenorphine is not recommended when the daily dosage of methadone is more than 30 mg [91]. Precipitated OWS is characterized with rapid onset of OWS within 1–2 hours after the first dose of buprenorphine and subsides within 6–24 hours. Risk factors for precipitated OWS include switching from long-acting opioids (methadone) to buprenorphine, recent benzodiazepine use, and a low initial dose of buprenorphine. Treatment includes symptomatic medication, adding buprenorphine, or reverting to methadone treatment [92]. In conclusion, methadone reduces mortality, resulting from reduced opioid use, opioid overdose, and infection; buprenorphine, an opioid partial agonist, produces a low incidence of respiratory depression and opioid overdose [91,93].

Treatment-resistant OUD is considered a resistant condition to usual OUD treatment, which is related to a brain disorder resulting from irreversible change of opioid and dopamine systems [94].

Non-opioid symptomatic medications for attenuating OWS include α_2 agonists, β-blockers, antidiarrheals, antiemetics, benzodiazepines, and NSAIDs. Alpha-2 agonists, such as clonidine, tizanidine, and lofexidine, reduce inordinate autonomic activities, including anxiety, chilling/piloerection, and tachycardia/hypertension. Beta-blockers, such as propranolol and atenolol, decrease the sympathetic nervous system in OWS due to β receptor sensitization after LTOT. Loperamide is used for the treatment of diarrhea with an oral daily dose less than of 4–16 mg, however, a euphoric effect may develop at a daily dose of 200–400 mg. Ondansetron, a 5-hydroxytriptamine-3 antagonist, is administered per os or intramuscularly for the control of nausea/vomiting [88].

There are acute and protracted OWSs. Acute withdrawal (or simply withdrawal) commonly develops as predictable, opposite symptoms and signs of the intoxication

Table 4. Food and Drug Association (FDA)-approved medications to treat opioid use disorder [87–92]

Medication	Mu-opioid receptor intrinsic activity and binding	Pharmacology affecting MOR activation at the therapeutic dose	Recommendation dosing for induction and maintenance	Available formulary
Methadone	Full agonist High affinity Ki = 3.4 nM	Long half-life up to 120 hours poses increased MOR toxicity risk during induction phase	Start from 5–10 mg every 4 hours up to 40 mg in the first day per os (tablet or liquid form) and titer up to 60–200 mg daily over 2 weeks	Generic 5, 10 mg Methadone hydrochloride tablet 10 mg Methadone sugar-free oral concentrate 10 mg/mL Methadone hydrochloride Intensol oral concentrate 10 mg/mL
Buprenorphine	Partial agonist High affinity Ki = 0.2 nM	Once to thrice-weekly sublingual administration due to slow MOR dissociation	Start from 2–4 mg up to 16 mg in the first day per os (sublingual tablet or liquid form) and titer up to 4–24 mg daily for maintenance	Sublingual tablet 2, 8 Buprenorphine with naloxone Sublingual tablet: Zubsolv 1.4/0.36 5.7/1.4 Sublingual film: Suboxone film 2/0.5, 4/1, 8/2, 12/3 Buccal film: Bunavail 2.1/0.3, 4.2/0.7, 6.3/1
Naltrexone ER	Antagonist High affinity Ki = 0.26–0.34 nM	Delayed stabilization of opioid craving due to lack of MOR	Start from 380 mg intramuscular injection monthly, if necessary, oral naltrexone 50 mg daily	Vivitrol 380 intramuscular injection monthly, if necessary oral naltrexone (ReVia) 50 mg daily

Ki: equilibrium dissociation constant, ER: extended release, MOR: mu-opioid receptor.

effects, for example, mydriasis in acute OWS after miosis in OUD. OWS commonly lasts for 4–10 days (methadone for 2–3 weeks, exclusively). Protracted OWS is defined as prolonged substance-specific symptoms and signs beyond those generally expected in acute OWS. Protracted OWS produces anhedonia, anxiety, insomnia, dysphoria, irritability, problems with short-term memory, concentration, and decision-making, persistent fatigue, impaired executive control, unexpected physical complaints, and alcohol or drug cravings [95].

Not only MAT but also real-time information on a current list of the patient's medication is very helpful to reduce the risk of overdose, overlapping, or prescription of contraindicated combination therapy. The Risk Evaluation and Mitigation Strategies (REMS) in the United States is a monitoring program for medications with a high potential for serious adverse effects, since 2007 [96]. The Drug Utilization Review (DUR) of the Korean Institute of Drug Safety and Risk Management (KIDS) has been used for to review medications in a given health care delivery system since 2012 [97]. The Narcotics Handling Reporting System (NHRS) is also operated for data analysis, research and education, risk prevention for opioids and psychotropic drugs since 2015 [98]. "My Prescription Information" of the Health Insurance Review and Assessment Service is very helpful for evaluating the medications the patient has used over the last year since September 16, 2020 [99].

LTOT over 26 weeks in CNCP is deeply associated with not only increased opioid-related mortality in over 200 MME/d but also constipation, sleep disturbance, respiratory depression, osteoporotic fractures resulting from sedation and dizziness with osteoporosis, opioid-induced androgen deficiency (hypogonadism) with sexual dysfunction and infertility resulting from endocrine dysfunction, myocardial infarction and heart failure, pneumonia in the elderly resulting from immune depression, and psychologic problems, such as depression, anxiety, and deactivation apathy [100,101].

1) Methadone

Methadone is an opioid agonist, used for suppressing OWS. Initiation starts with 5 mg every 4 hours up to 30 mg the first day, dosing-up to 60–100 mg per os daily with gradual titration every 3–5 days under monitoring. However, higher doses of methadone over 100 mg/day may induce opioid tolerance or cross tolerance. After stabilization, the dosage should be tapered. After oral administration, a peak concentration is reached at 2–4 hours. Methadone has a long half-life, 15–60 hours, therefore OWS does not develop immediately after the 24-hour period. If patients have not received methadone for more than 72 hours, the described induction process may be necessary. It is bound to α_1-acid glycoprotein and is metabolized in the liver via N-demethylation, by cytochrome P-450 isozyme 2B6, to inactive metabolites [102,103].

It can be used at any time during the course of treatment. However, it takes a long time to achieve an effective

dose in OUD, resulting in drop-outs or accidental overdoses [103].

Not only opioid-related adverse reactions, such as respiratory depression and constipation, but also QT interval prolongation leading to arrhythmia may develop. The electrocardiogram should be checked before, and at 1 month and 1 year after methadone initiation. Magnesium can be given in cases of QT interval prolongation. In addition, hypoglycemia and hypokalemia may also be seen [104].

2) Buprenorphine

Buprenorphine is a mu and nociception (opioid receptor-like 1 [ORL1]) receptor partial agonist (but delta and kappa receptor antagonist), 25–40 times more potent than morphine. However, as a partial agonist, its ceiling effect provides a wider safety margin without euphoria. Various formulations are available with a tablet, an injection, an extended-release injection, and implantable rods [105].

There are various combined oral or sublingual forms with naloxone, such as sublingual tablet form (Zubsolv®; Orexo US Inc., Morristown, NJ) with a ratio of 4:1 (buprenorphine:naloxone = 1.4 mg:0.36 mg and 5.7 mg:1.4 mg) and sublingual film or tablet forms (Suboxone®; Indivior Inc., North Chesterfield, VA) with various doses, such as buprenorphine:naloxone = 2 mg:0.5 mg, 4 mg:1 mg, 8 mg:2 mg, and 12 mg:3 mg [106].

3) Naltrexone

Naltrexone is an opioid antagonist. It can treat SUDs, including both OUD and alcohol use disorder. It reduces euphoria, sedation, and craving for opioids, without abuse or diversion potential [107].

Intramuscular injection of ER naltrexone injectable suspension (Vivitrol®; Alkermes, Waltham, MA) of 380 mg reaches the first peak concentrations within 2 hours and the second peak at 2–3 days. The concentration is decreased at around 14 days, with measurable levels after 1 month of administration. Therefore, it should be administered every 4 weeks or 1 month, but every 3 weeks for rapid metabolizers. Naltrexone ER needs a preparation period of at least 1–2 weeks (1 week for short-acting opioids and 2 weeks for long-acting opioids) to reduce severe OWS, resulting from abrupt discontinuation of the opioid agonist [89].

Patients taking naltrexone should not take opioids, sedatives, tranquilizers, or alcohol. Dosage adjustment is not recommended in hepatorenal dysfunction. Adverse reactions include injection-site reactions, hepatic enzyme abnormalities, nasopharyngitis, insomnia, toothache, eosinophilic pneumonia, depression, suicidality, and OWS/opioid overdose. Opioid overdose may occur at the end of the month after naltrexone injection. It shows low protein binding and is metabolized by dihydrodiol dehydrogenase. The primary metabolite is 6β-naltrexol, excreted in the urine [89].

Precipitated opioid withdrawal may also develop after opioid antagonist administration, such as naltrexone. After stopping previously used opioids and replacing the opioid receptors with opioid antagonist, OWS can occur in patients with physical dependence. Precipitated OWS is treated with buprenorphine as well as conservative treatments, such as fluid therapy, benzodiazepines, antiemetics, and clonidine [108].

The clinical opiate withdrawal scale (COWS) is composed of an 11-items scale administered by clinicians. According to the total score (0–48), the withdrawal scale can be divided into mild (5–12), moderate (13–24), moderately severe (25–36), and severe (≥ 37) degrees [109] (**Table 5**).

4) Current status in the treatment for OUD in South Korea

The number of opioid prescriptions in South Korea was increased over 5 times from 0.07/10,000 in 2002 to 41.23/10,000 in 2015. The MME was also increased 15.06 to 40,727.8 during the same period. Fentanyl had increased most rapidly among prescription opioids (morphine, oxycodone, fentanyl, and hydromorphone) [110]. Chronic weak opioid users increased from 1.03% in 2002 to 9.62% in 2015, and strong opioid users increased from 0.04% in 2002 to 0.24% in 2015 [111].

Fortunately, dispensing opioids increased from 2009 to 2013, however, there was a decrease from 2013 to 2019 [112]. Unfortunately, the prevalence of potentially inappropriate opioid prescription in CNCP rose from 14.8% in 2012 to

Table 5. The clinical opiate withdrawal scale [106]

Items	Score					
Resting pulse rate	0	1	2		4	
Sweating	0	1	2	3	4	
Restlessness	0	1		3		5
Pupil size	0	1	2			5
Bone and joint pain	0	1	2		4	
Running nose or tearing	0	1	2		4	
Gastrointestinal upset	0	1	2	3		5
Tremor	0	1	2		4	
Yawning	0	1	2		4	
Anxiety or irritability	0	1	2		4	
Gooseflesh skin	0			3		5
Total score (0–48)						
Mild (5–12)						
Moderate (13–24)						
Severe (> 36)						

16.8% in 2018. Potentially inappropriate opioid prescription included LTOT, high doses of opioids, a specific drug combinations, and in mental health disorders (bipolar disorder and schizophrenia), or SUD [113].

South Korea's reputation as a drug-free country is in danger now, even though the use of cannabis is strictly forbidden. Although OUD can be reduced through prevention measures in South Korea, the 3 WHO-approved medications, methadone, buprenorphine, and naltrexone ER, are currently not available. The only way to get these medications right now is to fill out and submit the narcotic delivery consent form of the Korean Orphan and Essential Drug Center (KOEDC) [114].

Pain physicians in South Korea should insist on these medications being considered as essential drugs for the treatment of the increasing number of patients with OUD. Pain physicians should actively participate in OSPs in the hospital and control the dosage and duration of opioids in CNCP through the methods of prevention and diagnosis of OUD, which is similar to the role of physicians of the infectious subdivision of internal medicine in the ASPs under the supervision of pharmacists. Under the current circumstances, without these medications in South Korea, opioids should be reduced to the minimal dose available at first and their frequency reduced daily later, with the support of other non-opioid symptomatic medications for attenuating OWS. For the treatment of OUD, collaboration with psychiatrists who specialize in SUD is also essential.

CONCLUSIONS

It is considered a human right for patients with the CNCP and end-of-life malignant disorders to be pain-free in their daily lives through sufficient pain relief by the prescription of opioids. Both the profits of pharmaceutical companies and opinions of physicians who agreed with the policy drove increased consumption of opioids, which led to a misconception that an advanced country has more opioid consumption per person per year.

Despite recovering from malignant disorders with an increased 5-year survival rate, many cancer survivors continue to use opioids daily. In addition, increasing number of CNCP patients who have nociceptive somatic and neuropathic pain have been receiving opioids. LTOT in CNCP increases not only opioid-related mortality but also physical and mental adverse reactions. Most patients who receive surgery in the operating room are opioid naïve, and some patients continue to request opioids even after cessation of acute surgical pain. Intraoperative infusion of remifentanil constantly links with opioid-induced hyperalgesia.

While OUD, among unintentional injuries, has become a major cause of death in the United States, the importance of preventive methods, early detection and diagnosis, and appropriate treatment of OUD while reducing treatment resistant OUD, based on the several recommendations from various societies, under the supervision of OSPs, should be emphasized. In addition, essential terms related to OUD should be acquired. Think twice about prescribing opioids before you have absolute confidence in your patients' cessation of taking opioids, especially for CNCP.

DATA AVAILABILITY

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

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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