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Opioids for the treatment of non-cancer pain

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INTRODUCTION

The analgesic ladder was introduced under the auspices of the World Health Organization (WHO) in 1990[1] with the idea of providing health care providers around the world with a tool to help them implement pain therapy in patients with cancer related pain. With the suggestion that opioids could also be used for the treatment of non-cancer related pain[2], the principles of the analgesic ladder were eventually implemented in patients with non-cancer pain[3]. Moreover, recent studies have addressed the potential problems associated with the use of non-steroidal anti-inflammatories (NSAIDs) and cyclo-oxygenase-2 (COX-2) inhibitors in the geriatric population, expanding the indications for opioids in the treatment of non-cancer pain. The objective of this review is to discuss the findings of recent articles published in the literature suggesting that the implementation of opioid therapy in patients with specific co-morbidities and drug-drug interactions may be indicated to avoid significant complications and adverse drug reactions. In fact, adverse drug reactions have been recently linked to polypharmacy[4] and are estimated to incur costs in excess of one billion US Dollars annually just in the United States[5]. Since 28% of adverse drug events are preventable and occur most commonly with cardiovascular drugs, diuretics, opioid analgesics, antidiabetic agents and anticoagulants[6], there is also a negative economic impact of using inappropriate medications in some patients.

In parallel with these findings, the availability of new modes of delivery, such as topical analgesics[7], the development of clinical guidelines for the management of special conditions, such as neuropathic pain[8-10], and the development, and the subsequent critical evaluation of interventional techniques for the management of pain such as neuromodulation[11,12], etc., have significantly change the approach suggested by the WHO step ladder, portending that it may not be appropriate to treat every patient in the same way. Thus, the role and the place of opioid therapy in chronic non-cancer pain are better defined in the 21st century. Likewise the potential complications associated with long-term opioid therapy are better understood at this point.

To facilitate the presentation of the arguments, the discussion will be divided accordingly in distinct clinical conditions where most of the literature has become relevant to support this point of view.

PATIENTS WITH OSTEOARTHRITIS (OA)

The first line agent for the treatment of pain associated with osteoarthritis is acetaminophen[13]. However, as the disease progresses, patients will eventually not respond to this form of therapy and will need a stronger analgesic for the control of pain. According to the analgesic ladder, the choice would be a non-steroidal anti-inflammatory (NSAID), or a cyclo-oxygenase (COX-2) inhibitor. Well established contraindications to the use these drugs are renal failure[14] and a history or current evidence of peptic disease[15]. There is a wide understanding among clinicians of this fact. The incidence of renal dysfunction is the highest in patients 65 years or older; it is dose-related to NSAIDs and COXIBs; ibuprofen, indomethacin, piroxicam are likely to be worse when compared to other NSAIDs; pre-existing evidence of renal disease or gout increases the odds ratio of renal failure to 6; and the combination of pre-existing renal disease and gout increase the odds ratio of renal failure to 82[14]. Consequently, the use of these agents in the presence of renal dysfunction is ill advised.

Patients with PUD receiving NSAIDs will have an incidence of upper gastrointestinal (UGI) ulcer complications 2.9 times greater than those receiving celecoxib, and 2 times

greater incidence of complications and symptomatic ulcers than those treated with the same COX-2 inhibitor[15]. Moreover, risk factors for the development of ulcer complications include[16]:

- History of perforation, ulcer, or bleeding
- Concomitant anticoagulant therapy
- Use of oral corticosteroids
- Longer duration of NSAID therapy
- Advanced age
- Poor general health status

In contrast, it is not as widely recognized that the incidence of congestive heart failure (CHF) in patients 65 years or older who have a history of heart disease is just as high as the incidence of UGI peptic ulcer complications[17,18]. The incidence appears to be the highest with the use of piroxicam, naproxen, and tenoxicam[18]. In fact, when these NSAIDs are used in patients with a history of heart disease, the odds ratio of developing CHF is 25[19]. Consequently, patients with either chronic renal failure or increased plasma creatinine levels, those with a history of PUD or heart disease should not be treated with NSAIDs. In contrast, it appears that celecoxib could be used in those patients with a history of heart disease, as the incidence of CHF after one year of treatment, in a large scale observational study, was no different than those in the control group[19]. However, the risk of thromboembolic phenomenon and myocardial infarction is still a concern, particularly in this population.

The other clinical situation to consider in patients with OA is the co-administration of a mini-dose of aspirin (ASA) and NSAIDs or COX-2 inhibitors. There is evidence that suggests that the co-administration of ASA and ibuprofen may result in acetylation of the serine 529 residue in the platelet that results in >95% inhibition of thromboxane A2 (TXA2) production and with this phenomenon, the loss of the anti-aggregation effect of ASA in the platelets[20]. It is not clear if this drug-drug interaction may also occur with other NSAIDs, but al least in theory, based on the mechanism of action, this could occur. Moreover, there is evidence that co-administering a mini-dose of ASA and celecoxib[15] or lumirocoxib[21] may result in the loss of the gastro-protective effects of COX-2 inhibitors. In the case of celecoxib[15], patients not concomitantly receiving ASA and celecoxib 400 mg twice daily had a statistically significant lower incidence of upper gastrointestinal (UGI) complications than those treated with non-specific NSAID (naproxen 800 mg TID or diclofenac 75 mg BID) (0.44 versus 1.27%, p = 0.04) and a significant lower incidence of complications and symptomatic ulcers (1.4 *versus* 2.91%, p = 0.02). In contrast, patients who received ASA and celecoxib 400 mg twice daily did not have neither a lower incidence of UGI complications (2.01 *versus* 2.12%, p = 0.92) nor a significant lower incidence of complications and symptomatic ulcers (4.7 *versus* 6%, p = 0.49) than those treated with non-specific NSAIDs[9]. In the case of lumiracoxib[21], there were also differences in the cumulative one year incidence of peptic ulcer complications between patients receiving lumiracoxib only or non-specific NSAID (naproxen or ibuprofen) (0.20 *versus* 0.92%) and those who received lumirocoxib + ASA or non-specific NSAID (0.69 *versus* 0.88%). The clinical implications of these findings are important as the OA population tends to be 65 years or older, and as a result of that will be frequently receiving mini dose ASA for cardiovascular prophylaxis. Thus, one has the option to switch them from ASA to clopidrogel or ticlopidine and then start therapy with a COX-2 inhibitor, to use topical NSAID therapy (diclofenac)[22,23], or to implement therapy directly with either a short-acting opioid if the patient only needs one or two doses of this medication per day, or a long-acting opioids[24,25] if more frequent dosing of a short-acting opioid is necessary.

Consequently, the WHO analgesic ladder oversimplifies the management of OA pain in patients with complex comorbidities which are typically present in the population affected by this disease. Additionally, the use of topical NSAIDs is not part of the algorithm as this form of therapy did not exist when the guidelines were drafted. These two situations make the analgesic ladder obsolete and even dangerous in some patient populations with OA.

NEUROPATHIC PAIN

Current guidelines for the treatment of peripheral neuropathic pain[8-10] suggest the implementation of therapy with topical lidocaine as the first step. If this is not successful, and there is not a contraindication for the use of a tricyclic antidepressant (TCA), the addition of one of these agents is suggested. Alternatively, a dual re-uptake norepinephrine/serotonine inhibitor may be used. If this combination is still not successful, then the use of an anticonvulsant is suggested, and if despite the use of these three agents at maximum doses is not successful, then the use of an opioid or tramadol is suggested. Current guidelines for the management of central pain suggest following the same algorithm as that outlined for peripheral neuropathic pain, with the exception that topical lidocaine is not recommended.

Consequently, the use of multiple adjuvants in the treatment of neuropathic pain is indicated prior to implementing therapy with opioids, but they are recognized as an important component of a treatment plan. There is no data to suggest which opioid should be used when needed in these patients. There have been suggestions, based on putative mechanisms of action, that tramadol, tapentadol, or methadone would be better choices, but this superiority has not been demonstrated in randomized clinical trials.

IMPLEMENTING THERAPY

Understanding the pharmacokinetics and pharmacodynamics of opioids is imperative to providing patients with effective pain relief and avoiding adverse effects, such as sedation, nausea, and vomiting. The clinician's efforts should be directed at producing opioid plasma concentrations within the therapeutic window to avoid side effects that occur when drug concentrations rise above those necessary for pain relief and loss of efficacy when plasma levels are too low[26]. It is recommended to try to open the therapeutic window to decrease the incidence of sedation, nausea and vomiting that may occur in up to 30% of the patient when first exposed to opioid therapy by prescribing a small dose of a long-acting opioid and then allowing the patient free access to a short-acting opioid[26]. After two weeks of therapy, acute tolerance will typically develop, and with that, the therapeutic window widens, allowing patients to tolerate higher doses of controlled released opioids with a lower incidence of these side effects[26].

BREAKTHROUGH PAIN

Breakthrough pain is defined as a transitory increase of more severe pain over relatively well-controlled baseline pain[27,28]. The reported incidence of breakthrough pain ranges between 16% and 95% in patients with persistent pain[28]. There are three types of breakthrough pain: end-of-dose failure, incidental pain, and spontaneous/idiopathic pain[28]. End-of-dose failure occurs when plasma concentrations fall below the therapeutic window. In order to avoid end-of-dose failure, the dosing interval should be decreased. It is important to talk to patients about patterns of breakthrough pain in relation to the time of administration of the long-acting opioid to determine if end-of-dose failure is responsible for the appearance of breakthrough pain.

Incidental and «true» breakthrough pain both occur despite appropriate opioid plasma concentrations. True breakthrough pain rises quickly in intensity and it is severe, occurring in patients whose pain was previously well controlled. It usually lasts between 30 and 45 minutes before subsiding. A medication with a rapid onset of action such as oral transmucosal fentanyl or a fentanyl buccal tablet is needed to control this type of pain, assuming that the pain is somatic in nature. In contrast, if the pain is neuropathic, it is unlikely that these alternative therapeutic options will be useful. Overall, when dealing with breakthrough pain, it is important to determine first, whether the pain is somatic, visceral or neuropathic, and then if it is due to end-of-dose failure or incidental and treat appropriately.

OPIOID ROTATION

The largest groups of opioids are the morphine-like agonists. Morphine remains a prototypic opioid analgesic against which all other drugs are compared. Despite its clinical utility, the associated side effects led to attempts to develop molecules with similar analgesic action without the management challenges[29]. Over the last hundred years, numerous opiate drugs have been synthesized and the vast majority falls into the mu category; ie, they target the mu opioid receptor (MOR). Initially, all mu opioids were thought to act through a single class of opioid receptors, but subsequent research has identified genetic locations for several mu opioid receptor subtypes. To date, at least 25 variants of the mu receptor have been identified in mice, 8 in rats, and 11 in humans[30]. Although mu opioids share many pharmacological characteristics, there are differences[29].

The concept of multiple mu receptors may help explain the variability in individual response to various opioids, the differences in side effects among patients, incomplete cross tolerance among various mu opioid analgesics, and the clinical utility of opioid rotation[3,26,28]. Opioid rotation is now a widely accepted approach to poorly responsive pain patients in whom a neuropathic pain component has been adequately treated or ruled out. If side effects with one opioid are significant, an improved balance between analgesia and side effects might be achieved by changing to an equivalent dose of an alternate opioid[26]. Rotation between 2 or 3 opioids is often required to obtain satisfactory long-term pain control[31]. A systematic review of existing literature on opioid rotation performed in 2006 found that opioid switching results in clinical improvements in greater than 50% of patients with chronic pain who experience a poor response to one opioid[32]. However, an important problem raised in the opioid literature is the conversion rate among the various opioid medications. Most conversion data presented in reference tables are derived from older studies that were not designed for determining relative potencies[32]. Yet, an understanding of equianalgesic doses is important when both titrating long-acting opioids and performing opioid rotations. One practical approach is the «rule of 2»[26] *(Table I)*. Assuming a morphine dose of 100 mg/24 h and dividing it by two, one arrives at a dose equivalent of 50 mg/24 h for oxycodone/hydrocodone. Dividing it by four, one reaches the fentanyl (25 µg/h) and oxymorphone (25 mg/24 h) dose equivalents. Dividing it by eight, one obtains the equianalgesic dose of 12 mg/24 h for hydromorphone. This method allows

Table I. Equianalgesic doses: Rule of two (Based on a morphine dose of 100 mg/24 h)[26].

Oxycodone-hydrocodone/oral	50 mg/24 h
Fentanyl transdermal	25 µg/h
Oxymorphone	25 mg/24 h
Hydromorphone/oral	12 mg/24 h
Methadone/oral	10-60 mg/24 h

for relatively quick conversions. Although on the conservative side, these quick conversions should place the patient's plasma levels in the therapeutic range. However, the patient should be contacted within a day or two to determine if further titration is required. Although methadone is a very effective, and inexpensive, medication, it provides a unique challenge because there are no good dosing guidelines and no easy conversion rates[32,33]. Although there are several conversion protocols for methadone, for patients on a moderate opioid dose (400 mg of morphine), we usually convert to 10 mg of methadone every 8 hours for the first two weeks of treatment and then titrate the dose, based on pain scores, psychosocial functioning, rescue opioid use, etc. If the patient is on higher opioid doses, the starting methadone dose is 20 mg every 8 hours. Patients on methadone need to be monitored closely. One study found a correlation between the daily dose of methadone and the QTc interval in 17 patients who experienced torsade de pointes[34]. Of note, the relationship persisted after adjusting for the clinical variables known to be associated with QT-segment prolongation. In patients who receive methadone doses greater than 100 mg per day, it is imperative that baseline EKG testing be performed and then repeated every 3 months[26]. In addition, if patients are receiving medications known to prolong the QTc segment, a consideration to switch to a different opioid should be made[35].

In November 2006, the FDA released an alert about this information (FDA, 2006). The alert resulted in the addition of a black box warning to the product labeling for methadone manufactured as Dolophine® Hydrochloride CII (Roxane Laboratories, Columbus, OH).

IMPORTANT CONSIDERATIONS IN THE LONG-TERM USE OF OPIOIDS

There are four long-term concerns with the use of opioids: endocrine changes, opioid abuse and diversion, those related to the central effects and metabolism of these agents, and opioid-induced hyperalgesia.

Endocrine changes: Long-term opioid use decreases cortisol levels, which may be why patients experience lassitude and lack of energy after long periods of therapy. It is important not to confuse these symptoms with those seen when opioid therapy is implemented acutely[26]. The diagnosis is made by performing an adrenocorticotropin (ACTH) stimulation test and if a flat cortisol response is seen, consideration to withdrawing opioid therapy or implementing corticosteroid replacement therapy is indicated. Additionally, opioids decrease prolactin, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, and estrogen levels, which in turn can cause sexual impotence and eventually osteoporosis[3,36,37]. This problem can easily be overcome in men by prescribing testosterone in either intramuscular or the gel form. However, reduced sex hormones are more problematic in women because of the increased risk of breast cancer after estrogen/progesterone replacement. Thus, a consult with an endocrinologist may be warranted to address the risk of osteoporosis with the use of bisulphonates, calcium and vitamin D therapy.

Opioid abuse and diversion: Based on the 2003 position paper from the College on Problems of Drug Dependence, there is a «need to strike a balance between risk management strategies to prevent and deter prescription opioid abuse and the need for physicians and patients to have appropriate access to opioid pharmaceuticals for the treatment of pain»[38]. Although opioids should be a tool in the analgesic armamentarium, it is essential that all health care providers approach pain management using opioids with the necessary due diligence, including a complete initial evaluation, followed by appropriate monitoring (random urine testing), and documentation throughout treatment. At the outset of therapy with opioids, obtaining a signed agreement should be considered wherein the patient's expectations and the clinician's responsibilities are detailed.

Likewise, universal precautions should be implemented for other drug with a misuse potential such as certain antidepressants and psychotropic agents (i.e., benzodiazepines). Misuse includes usage of inappropriate drug combinations due to poor patient education or misinformation, as well as abuse and diversion. Appropriate education in an understandable vernacular is essential to successful pain management. A strong predictor of the potential to opioid misuse is other medication misuse, or alcohol and/or illicit drug abuse[39]. Because patient reporting of both prescribed and other drugs is highly unreliable at best, and because in the United Stated, 43% of patients on long-term opioid therapy misuse their medications, routine urine toxicity screens for a wide range of substances are considered the cornerstone of pharmacological vigilance at this point[39,40]. When opioid therapy is initiated, and there is a high index of suspicion for opioid abuse, a baseline urine drug screen can be used to assess if there has been any drug misuse, even before opioid therapy is begun. Evaluations of patients should also involve noting and documenting slurred speech, sleeping, or weaving while walking, including observations gathered before the patient has even entered the examination room.

Using tools to interview and collect observations of patients are another important strategy to monitoring and documenting a patient's management with opioids *(Table II)*. Screening tools can provide information that can lead to the detection of early warning signs of drug misuse and indicate the need for more thorough monitoring and in-person patient interactions. These instruments can help indicate which patients may be more prone to non-adherence to therapeutic protocols, as well as to demonstrate due diligence in monitoring prescription

Table II. Tools for assessing drug misuse potential.

Interview and observational tools
• Aberrant behaviors identified by clinicians (Portenoy, 1990)
• Checklist of risk behaviors (Chabal, Erjavec, et al, 1997)
• Prescription drug use questionnaire (PDUQ; Compton et al, 1998)
• Physician opioid therapy questionnaire (POTQ; Michna et al, 2004)
• Addiction behaviors checklist (ABC; Wu et al, 2006)
Self-report Questionnaires
• The screening tool for addiction risk (STAR; Friedman & Mehrotra, 2003)
• The screening instrument for substance abuse potential (SISAP; Coambs et al, 1996)
• Screener and opioid assessment for patients with pain (SOAPP; Butler et al, 2004)
• Opioid risk tool (ORT; Webster & Webster, 2005)
• Current opioid misuse measure (COMM; Butler et al, 2007)
• Pain medication questionnaire (PMQ; Adams et al, 2004)
• CAGE-AID (Brown et al, 1998)

use for potential US Food and Drug Administration audits. In addition, the results from these tools, such as the Pain Medication Questionnaire (PMQ), can be used to tailor the treatment program to the specific needs of patients. Still, they can be limited by their time-consuming nature, psychometric (un)reliability, and specificity for only one type of alcohol or drug abuse (i.e., non-generalizable results).

The variety of pain medication questionnaires available is listed in *table II*. For example, chronic pain patients being considered for long-term opioid therapy can be administered the Screener and Opioid Assessment for Patients with Pain (SOAPP) or the Opioid Risk Tool (ORT) to screen for substance abuse potential[41,42]. The SOAPP is a 14-item tool with established reliability and predictive validity. Alternatively, the Diagnosis, Intractability, Risk, and Efficacy (DIRE) score can be used to predict whether a chronic non-cancer pain patient will achieve effective analgesia and adhere to a long-term opioid maintenance treatment regimen[43].

The PMQ is another self-report measure that can be administered quickly to broadly survey a patient's misuse potential for a range of pain medication types prescribed for chronic pain. Higher PMQ scores have a positive association with measures of substance abuse, psychopathology, and physical/life-functioning[44]; in other words, high-risk patients tend to have difficulties controlling their medication use concurrent with significant psychosocial issues, such as poor stress management and deteriorating work and/or home environments. These patients often self-medicate to «deal» with their stressors, as well as to control their pain. In fact, according to a long-term follow-up study, patients with high PMQ scores were 2.6 times more likely to have a known substance-abuse problem, 3.2 times more likely to request early refills of prescription medications, and 2.3 times more likely to drop out of treatment than patients with initially low PMQ scores[45]. Furthermore, patients who completed an interdisciplinary pain management program had significantly lower PMQ scores 6 months following discharge, compared to those patients who discontinued the treatment. Patients with PMQ scores over 32.83 should be closely monitored, as they have a high potential for misusing controlled substances. The PMQ can be a good resource that can be combined with other assessment techniques in order to gather a full understanding of a chronic pain patient, leading to better individualization of therapy, and ultimately, better outcomes.

Other important considerations: The use of morphine in patients with severe renal or hepatic insufficiency is not advisable because they may experience myoclonus and/or hyperalgesia due to morphine-3-glucoronide (M3G) accumulation. M3G, in contrast to the other metabolite of morphine, morphine-6-glucoronide (M6G), is neurotoxic[26].

Moreover, opioids in general should be used with caution in patients with Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients[26].

Another important consideration when administering opioids is the effect on cognitive function[31]. Side effects such as sedation, dizziness, and mental clouding interfere with activities that demand alertness, especially driving. Although driving is not advisable at the beginning of treatment, studies have shown that cognitive function, including the ability to drive and operate machinery is often adequate in patients taking stable, moderate doses of opioids for chronic pain[46,47].

When indicated and an opioid drug regimen is chosen, it is important to be cognizant of the potential for drug-drug interactions, as many opioids are metabolized by the enzymes that modify and break down 40 to 50% of all medications. These are the cytochrome P450 (CYP450) isoenzymes, and those primarily involved with opioid metabolism are the CYP2D6, CYP2B6 (methadone), and CYP3A4 (fentanyl) systems[48,49]. Tramadol, oxycodone, hydrocodone, and codeine are converted to active metabolites by CYP2D6. Therefore, drugs that inhibit this enzyme will decrease their effects[50,51]. In addition, other commonly used medications, including fluoxetine, haloperidol, and paroxetine, can inhibit CYP2D6 function resulting in a lack of pain relief[52]. In constrast, morphine, hydromorphone, and oxymorphone are *not* metabolized by the CYP450 enzymes, and therefore, can generally be prescribed with medications metabolized by that enzyme family[50].

***Opioid induced hyperalgesia*:** Sustained exposure to opioids may result in increase sensitivity to pain, potentially by enhancing the descending facilitatory influence of the brain on pain transmission at the spinal cord level[53]. This phenomenon, known as opioid-induced hyperalgesia, can be an outcome of very aggressive opioid dose titration[54]. Likewise, the perioperative use of remifentanyl and fentanyl have been shown to have a higher risk, but all opioids, even methadone, have the capacity to induce this phenomenon when rapidly titrated to higher doses in patients with chronic pain[55]. Pronociception may also result from spinal sensitization due to inappropriate increased brainstem excitatory influences, involving spinal cholecystokinin and dynorphin, descending facilitation of the glutamatergic system, and substance P wind-up (increased central sensitization in response to sustained input from nociceptive afferents)[53-55].

Clinically, it is very important to distinguish between opioid tolerance and opioid-induced pain sensitivity because, despite having similar presentations, they require opposite management approaches[55]. In both cases, patients present with worsening pain. However, in the case of opioid-induced hyperalgesia, the pain intensity is increased above the level of the preexisting pain, despite the absence of disease progression while opioid doses are titrated up[55]. Also, with opioid-induced hyperalgesia, the pain is more diffuse, often affecting areas beyond the original pain distribution. Managing opioid tolerance with a trial of opioid dose escalation can appropriately control the pain, whereas opioid-induced hyperalgesia can be exacerbated with increasing opioid doses[55]. In the latter case, opioid doses should be significantly reduced and acetaminophen and dexamethasone therapy should be implemented[56-58]. For advanced severe cases of opioid-induced hyperalgesia, high-dose intravenous dexamethasone (a loading dose of 20 mg, followed by a course of 6-8 mg every 6 hours for a week) can be used effectively alongside other adjuvant therapies and acetaminophen, while progressively tapering opioid doses. Dexamethasone decreases neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P, that are involved in neurogenic inflammation and opioid-induced hyperalgesia, and it induces the production of kynurenic acid, a post-synaptic NMDA antagonist[56,57].

CONCLUSIONS

Not all patients respond to analgesic regimens, including opioid treatments. For these select patients, the following clinical scenarios should be considered and their treatment correspondingly adjusted: opioid tolerance, opioid-induced hyperalgesia, an alternative disease processes such as myofascial pain, and opioid misuse. Additionally, each patient's unique genetic background can influence the effectiveness and side effects of an analgesic regimen. Therefore, therapies need to be individualized for each patient in order to maximize opioid analgesic effects and minimize side effects, including discontinuing or rotating opioids when appropriate. Given the potential for metabolic issues and drug interactions, and the availability of multiple analgesic options, when prescribing opioids it is also important to use strategies that minimize drug interactions. Especially for individuals on multidrug regimens, such as older adults, an opioid that is *not* metabolized by the P450 enzyme system, such as morphine, hydromorphone or oxymorphone, may be more suitable than other choices.

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