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Case Studies of Long-Acting, Extended-Release, and Sustained-Release Opioids for the Treatment of Chronic Nonmalignant Pain

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Chronic pain of nonmalignant nature (CNMP) is often treated with chronic opioid therapy (COT). Although many guidelines exist to help the clinician use COT in a safe and effective manner, many controversies surrounding the exact prescribing practices remain.[1] The purpose of these following brief case studies is to help the practicing clinician consider real patient scenarios and help further understanding of the principles outlined by the US FDA REMS document.[2] The patient case scenarios presented in this article do not represent any one real patient. However, each case scenario is entirely plausible and has presented themselves in some like manner to the author. These discussion and recommendations following each case scenario represent the opinion of the author alone, based on the author's 30-year experience, a review of common published guidelines, review of the US FDA REMS paper, and a review of the literature concerning COT for CNMP.[2-5] Some of the discussion points remain controversial and recommendations for therapy are based on a low level of evidence.[6]

CASE STUDY #1

A 54-year-old male former truck driver with chronic low back pain has been taking oxycodone ER 60 mg twice daily for the past 1 year. He has been compliant with his opioid therapy in addition to prescribed desipramine 25 mg at night. The patient is hoping for improved pain relief and you decide to discontinue the oxycodone and start a COT trial of methadone. How should you proceed with this opioid rotation?

Prior to initiation of methadone therapy, a careful patient history to assess factors affecting a prolonged electrocardiogram QT corrected (QTc) interval, history of a prolonged QTc, history of cardiac dysrhythmia, and patient concomitant medications must be obtained. Next, a current electrocardiogram (ECG) should be reviewed. If the patient's QTc is greater than 450 milliseconds, then an alternative opioid, rather than methadone, should be considered for the opioid rotation. After obtaining an ECG with a normal QTc interval, and following patient education and opioid treatment agreement (OTA), oxycodone ER may be discontinued and methadone therapy initiated. The patients oxycodone dose of 120 mg/d is in the relatively high category, thus opioid rotation should be to 10 percent of the calculated opioid value, resulting in a daily starting dose of methadone 10-15 mg. The clinician must assess for any adverse events within 3-5 days following methadone initiation through a telephone interview. This author would not consider any dose escalation for the first 2 weeks of methadone therapy. It is reasonable to repeat a follow-up ECG after 2-3 months of methadone treatment.

CASE STUDY #2

A 65-year-old woman has a long history of osteoarthritis affecting both hips. Her chronic hip pain has been well controlled with oxycodone ER 30 mg twice daily for the past 1 year. The patient has been compliant with the OTA. Your clinic receives an anonymous phone call stating that your patient is, in fact, a known drug dealer and selling your prescription drugs to the community. The anonymous caller wants you to stop prescribing opioid therapy to your patient. How should you then proceed?

Anonymous information received to the physician office should be taken seriously; however, further action against a patient must be based on further investigation and verification of any claims. This author would carefully review the patient risk factors for opioid therapy, review previous patient compliance with COT, and review previous pill counts and urine drug testing results. Any discrepancy in this patient history may lend more support for the anonymous information. The patient would be told of the call and interviewed in a nonjudgmental and nonthreatening manner as to possible truth to the information. Following this patient interview, and assuming a low index of suspicion of drug diversion, local

law enforcement would nonetheless be informed of the anonymous call, to be investigated further at their discretion. An additional urine drug test (UDT) would be taken, along with careful review of the electronic prescription monitoring program. The patient would be maintained on their opioid regimen if no new information suggested opioid diversion.

CASE STUDY #3

A 48-year-old male executive presents to your office for treatment of chronic low back pain. Medical history reveals the onset of the back pain started following heavy lifting while constructing a deck on his house. At the time of injury, he was evaluated in the local hospital where imaging revealed no obvious spine fracture or deformity. He has been taking only naproxen for pain relief. The pain is interfering with his ability to function at work and he is asking for oxycodone ER to help manage his pain. How should you proceed?

In addition to a complete history of the chronic pain, a complete medical and social history, as well as general and focused physical examination, a careful review of previous analgesic therapies should be obtained. Additional history revealed that this patient had not been treated with other nonopioid analgesic therapies, such as physical therapy, epidural steroid therapy, acetaminophen, adjuvant analgesics such as tricyclic antidepressants, or cognitive behavioral therapy. COT should only be prescribed after patients have completed appropriate nonopioid analgesic therapies. Therefore, this patient should not be started immediately on COT but undergo trials of nonopioid analgesics or appropriate interventional pain therapies.

CASE STUDY #4

A 72-year-old grandfather has a 5-year history of chronic neck pain related to degenerative joint disease. He has been taking oxymorphone ER 20 mg twice daily for approximately 6 months. He has been compliant with his opioid regimen, without any adverse side effects, but rates his pain at 7/10 on a numeric pain rating scale. He desires improved pain relief and is asking for increase in his opioid dose. He has read online that there is no ceiling effect for opioid therapy for chronic pain. Assuming there are no issues with opioid misuse, or opioid-related side effects, should you increase his opioid dose?

First, the clinician should calculate his current opioid dose in daily oral morphine equivalents. Using an opioid conversion table, the oxymorphone dose calculates at 120 mg daily oral morphine equivalent. This put the patient in a relatively high opioid dose category, and further increases in opioid dose should be done with caution. Most published guidelines recommend that higher doses of opioid not be used on a chronic basis for CNMP. This author would consider the addition of any nonopioid analgesic therapy or opioid rotation with a lower starting dose of a new rotated opioid, rather than simply escalating the patient's current oxymorphone dose.

CASE STUDY #5

A 24-year-old male was involved in a motor vehicle crash 5 months ago, with a 3-week hospital course involving pelvic reconstructive surgery. He is now 4 months postinjury and has been discharged from the office of the treating surgeon, taking morphine ER 30 mg three times daily. He presents to your office for a follow-up visit and additional management. He complains of low back and bilateral hip pain that has remained severe since the accident. He rates the pain at 12/10 on a numeric pain scale and is asking for an increase in his opioid therapy. You obtain a urine drug screen which is not only appropriate for morphine but also positive for cocaine metabolites. How will you manage this patient's pain?

Additional history using the opioid risk tool (ORT) confirms that the patient is at high risk for opioid misuse. It is determined that his motor vehicle crash was related to alcohol and street drug use. The patient should be counseled that he is at high risk for drug overdose and death when combining prescribed opioids with alcohol and cocaine. Nonopioid analgesics, such as gabapentin, should be initiated and the patient informed that current opioid therapy will be tapered and discontinued. In addition, the patient should be counseled and referred to an addiction specialist.

CASE STUDY #6

A 48-year-old woman with a long history of painful chronic fibromyalgia has been prescribed oxycodone ER 30 mg twice daily for many months. Apart from depression and chronic anxiety, she has no other significant medical history. A random UDT is positive for oxycodone; however, a random pill count shows that she falls considerably short of the number of tablets she should have on hand. A patient interview reveals that, while she has been taking some oxycodone for pain relief, she has been trading the majority of her prescription opioid tablets for marijuana as an antianxiety therapy. In addition to reporting the sale of prescription opioid

medications to the local enforcement, how will you taper the opioid therapy?

The US FDA document regarding ER opioids recommends a tapering of opioid therapy, when indicated, rather than an abrupt discontinuation.[2] This author would decrease the dose immediately by 50 percent for a 10-day period, then decrease the dose to 25 percent of the initial therapy for another 10 days, and finally reduce the dose to 10 percent of the initial opioid therapy dose for 10 more days, and then discontinue altogether. Some physicians elect to add low-dose clonidine to help control any symptom of opioid withdrawal. This slow tapering does not require any hospitalization. The patient should be advised that, while additional opioid therapy will not be prescribed, the patient will remain as a patient and be managed with nonopioid analgesic therapies alone.

CASE STUDY #7

A 28-year-old moderately obese male suffers with juvenile rheumatoid arthritis. His chronic joint pain has been partly controlled for the last 3 years with methadone 10 mg four times daily. At a scheduled follow-up visit, the patient reveals that he would like to take as little opioid as possible. He explains that he has tried to decrease the dose to 10 mg three times daily in the past few weeks. He explains that he is unable to tolerate the decrease in dose noting an increase in pain. He is concerned that he cannot wean himself off the methadone. He asks you if he has become an opioid addict? How will you answer?

The clinician should review the patient's history for any risks of opioid addiction behaviors, and, finding none, council the patient that the requirement for COT to treat chronic pain does not indicate that he is an opioid addict. The patient should be educated that he has physical dependence on methadone, meaning that an abrupt discontinuation would lead to opioid withdrawal symptoms, but this is entirely different from addiction behavior. He should be told that addiction involves a compulsive use and preoccupation with a substance, despite loss of control and harm to the patient in all spheres of life. A compliant patient who requires a particular opioid dose to maintain adequate pain relief from a chronic debilitating disease must understand that this is not defined as addictive behavior.

CASE STUDY #8

A 70-year-old woman with a history of degenerative joint disease of the cervical spine, and chronic neck and arm pain for 4 years, presents to your office. She has been taking oxycodone IR 10 mg QID to help control her chronic pain. She finds that the oxycodone IR provides pain relief for a couple of hours, but then is inadequate analgesia over the last 2 hours of the dosing interval. You decide to discontinue the oxycodone, starting transdermal buprenorphine at 7.5 μg/h once per week. Two weeks later, she presents to a local hospital with tachycardia, mild fever, diaphoresis, and myalgia. What is your diagnosis?

Buprenorphine transdermal can be an effective and potent analgesic for chronic pain, particularly in the elderly. However, rotating a patient from oral opioids to transdermal buprenorphine has occasionally resulted in symptoms of withdrawal, as with our patient. First, the equipotency ratio of buprenorphine to oral morphine has not been established. Second, volunteer studies on persons receiving methadone demonstrate that sublingual buprenorphine precipitated withdrawal in most subjects.[7] While adding other opioids to a patient receiving buprenorphine therapy appears to be safe and effective, the rotation of a patient to buprenorphine from other opioids should be done with more caution. The rotation from an opioid to transdermal buprenorphine may result in precipitation of withdrawal.[8]

CASE STUDY #9

A 76-year-old retired laborer takes oxycodone ER 20 mg twice daily for control of chronic low and upper back pain. He has no particular risk factors for opioid misuse. He has been followed in your clinic for 12 months, known to be very compliant with COT. You complete a UDT as part of a yearly patient check. The urine is positive not only for the expected oxycodone but also for amphetamines. How should you proceed?

An elderly patient on COT and compliant for more than 1 year is unlikely to abruptly start consuming street drugs. Further history regarding changes in the patient's medical history and medication use should be investigated. A search for medications that may cross-react on a UDT producing a false positive amphetamine signal should be completed. On evaluation, our patient reveals a new diagnosis of Parkinson's with recent treatment of selegiline. This medication is known to produce amphetamine and methamphetamine as a urinary metabolite, thus triggering a positive UDT. No further action regarding COT for this patient needs to occur.

CASE STUDY #10

A 28-year-old woman with two young children has a 12-month history of unresectable cancer of the

cervix. She has failed all therapies and appears to be in the last few weeks of life. She complains of severe bilateral pelvic pain not well controlled with oxymorphone ER 30 mg twice daily. Although the patient is taking a high dose of oral opioid, her hospice nurse is asking for an increase in her baseline opioid, and for additional opioid as needed breakthrough dosing. How will you respond to the request?

The guidelines regarding ER opioids for the treatment of CNMP are not applicable to the active patient with cancer in the last weeks or months of life.[2,3] The clinician, in this situation, is encouraged to titrate opioid analgesics upward until pain relief is achieved or intolerable opioid side effects limit further dosing.

CASE STUDY #11

A 71-year-old recently retired male presents with a long history of chronic neck pain. Previous therapy with nonopioid analgesics, including injective therapy, has been unsuccessful. The ORT reveals a low-risk patient. You plan a trial of hydrocodone ER 10 mg BID. The patient refuses to sign an OTA saying, "I have been a responsible corporate executive for decades, and I do not want to have an OTA like a common street drug addict." Will you proceed with the trial of COT?

Although an OTA is often recommended in various COT guidelines, there remains little high-level evidence of its efficacy and safety. Nonetheless, and notwithstanding the retired patient who is indeed at low risk of opioid misuse, the clinician should be aware that most national guidelines recommend the use of an OTA for all patients. This author would insist, for the safety of the patient and safe guarding of the physician, on the completion of an OTA. In addition, the clinician should be aware of all state laws and regulations regarding OTA use for the particular involved location. There may be a law in your state requiring an OTA in place prior to COT.

CASE STUDY #12

A 46-year-old foreman at an automobile factory has been taking methadone 10 mg BID for the past 6 months, for the treatment of post-traumatic upper extremity pain. The foreman has a work injury, resulting in multiple upper extremity surgeries and chronic ongoing pain. At routine follow-up visit, the man reports adequate pain relief and a return to work at 80 percent capacity. However, he does note that he feels less inclined for sexual relations with his partner.

Opioid-induced deficiency of sexual hormone is a common symptom associated with COT for chronic pain. The clinician should recognize this possible side effect, should further investigate the patient testosterone levels, and consider hormonal replacement therapy as treatment. A second option, a judgment call on the part of the clinician, is to consider tapering and discontinuing the methadone therapy. It is unclear whether opioid rotation to a different opioid will have a decreased incident of hormonal deficiency.

CASE STUDY #13

A 55-year-old woman has a long history of chronic abdominal pain related to chronic pancreatitis. Trials of nonopioid analgesics have failed to adequately control her chronic pain. She has no particular risk factors for opioid misuse, and in particular, her pancreatitis has never been related to alcohol use. Following appropriate evaluation, you plan a trial of low-dose COT. You obtain urine for testing as part of your pre-COT assessment. The patient tells you that the urine may likely be positive for marijuana, as she uses marijuana approximately once per week to help manage her abdominal pain. Will you proceed with the COT trial?

The use of COT for CNMP in a patient that admits to marijuana use has resulted in divided opinion among the medical community. An unpublished survey of pain physicians (PAS) revealed a variety of clinician responses. Some physicians feel strongly that any street drug use, including marijuana, is an absolute contraindication to COT for CNMP. Others proceed with COT in a "don't ask, don't tell" manner. Others will accept the marijuana use and carefully monitor the patient on COT per usual therapy. While many states have decriminalized personal marijuana use, the US federal government still considers it an illegal substance. The personal view of this author is that marijuana use is a contraindication to COT unless the marijuana has been prescribed for medical therapy and obtained in a legal dispensary.

CASE STUDY #14

A 38-year-old woman with a diagnosis of fibromyalgia has been taking hydromorphone ER 12 mg once daily for approximately 2 years. Treatment with COT has apparently been stable. The patient shows up at a local emergency department one evening in obvious opioid withdrawal. What is the differential diagnosis?

A patient who is compliant with her COT medications will not spontaneously go into opioid withdrawal. The differential diagnosis includes the possibility that the patient stopped her opioid abruptly, the

patient took buprenorphine off the street, or the patient crushed an opioid tamper-resistant product containing naloxone, and injected this mixture.

CASE STUDY #15

A 72-year-old grandmother suffers with postherpetic painful neuralgia for which nonopioid analgesic therapies have been ineffective. She was started, by an outside physician, on transdermal fentanyl at 50 μg/h every 3 days. Approximately 9 days after initiation of therapy, she presents to the emergency department with sedation, confusion, and a respiratory rate of 6 per minute. How will you manage the patient?

The patient should be in a monitored environment for a minimum of the next 2-3 days. She is obviously diagnosed with respiratory depression, sedation, and confusion from opioid overdose. Low doses of intravenous naloxone may be necessary to treat her symptoms. The fentanyl patch should be removed from the patient. The clinician must be aware that following removal of the fentanyl patch, a significant depot of fentanyl still remains in the underlying skin, such that drug absorption will continue, despite patch removal, for the next 18 hours. Therefore, the patient must be closely monitored during this time period and not discharged early.

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