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ER/LA OPIOID REMS SUPPLEMENT

Extended-Release and Long-Acting Opioids for Chronic Pain Management

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

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

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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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INTRODUCTION

This educational supplement has been created to educate healthcare professionals on the safe and proper use of Extended Release (ER) and Long Acting (LA) opioids for chronic pain management. Opioids are the cornerstone of modern pain management. They are highly complex molecules which require knowledge and integration of basic science, clinical, pharmacological, psychosocial, abuse, diversion, and public health aspects of opioids. This Opioid Risk Evaluation and Mitigation Strategy (REMS) supplement is a valuable tool that can be utilized daily by everyone in your practice. Continuing Medical Education (CME/CE) credits are available for studying this supplement and completing the online test. The supplement and test can be completed in a little more than three hours, but it will have a lifetime benefit!

TARGET AUDIENCE

The target audience includes all clinicians registered with the DEA, eligible to prescribe schedule 2 or 3 drugs that have written at least one ER/LA opioid prescription in the past year, including primary care (family practice and internal medicine); anesthesiology (including pain management); oncology; neurology; orthopedics; PM&R and palliative care physicians, physician assistants and nurse practitioners. Pharmacists would also benefit from this education.

PROGRAM OVERVIEW

This monograph will evaluate clinical guidelines for the use of opioids, including the FDA Opioid REMS requirements, and their impact on the management of chronic pain. This monograph will also evaluate recommended opioid risk-reduction strategies HCPs can use to detect opioid misuse in a timely manner. Finally, the monograph will identify communication strategies HCPs can use to improve their relationships with their patients to ensure optimal patient outcomes and reduce the risk of opioid misuse and abuse.

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be able to:

- Utilize available screening tools for the effective assessment of patients before initiating opioid therapy (Blueprint sections I and II)
- Implement opioid risk-reduction strategies based on a patient's aberrant behavior (Blueprint sections I and II)
- Apply communication strategies to strengthen relationships with patients and improve patient knowledge of their opioid treatment (Blueprint sections III and IV)
- Properly monitor patients on opioid therapy utilizing available resources, including Patient-Provider Agreements and state Prescription Drug Monitoring Programs (Blueprint sections III and IV)
- Identify potential adverse events in patients on opioid therapy (Blueprint sections V and VI)
- Mitigate drug-drug interactions with patients on opioid therapy (Blueprint sections V and VI)

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Extended-Release and Long-Acting Opioids for Chronic Pain Management

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INTRODUCTION

Chronic pain from both cancer and noncancer sources affects approximately one quarter of the adult population in the United States.[1] In addition to the considerable health burden, there is the burden of the patient suffering, loss of work productivity, and loss of social effectiveness for many patients. Untreated chronic pain has been documented to interfere with sleep patterns, increase anxiety and depression, decrease quality of life, and interfere with social relationships and the ability of a patient to cope with life.[2] Long-term opioid therapy for the management of chronic-nonmalignant pain (CNMP) has been used with a subset of patients and found to be efficacious.[1] Although the treatment of patients suffering from CNMP is viewed as humanitarian, their use has been complicated by side effects such as constipation, dose escalation, sedation, endocrine suppression, inadequate analgesic effect, prescription opioid diversion, and unwanted prescription-opioid-related death.[1] Thus, a healthcare professional taking care of patients using long-term opioid therapy must be extremely well versed in the appropriate assessment, management, and specific pharmacology of opioid analgesic products.

The use of chronic opioids for CNMP was pioneered approximately 20 years ago, and has increased greatly during the past decade. Well-intentioned clinicians, having witnessed the value of long-term opioid therapy for active cancer pain, applied the same principles of opioid therapy to the patient with CNMP. Unfortunately, associated with this increased chronic opioid use for nonmalignant pain came a marked increase in prescription opioid diversion and deaths from prescription opioids. A recent national survey estimated that more than 35 million adult Americans used an opioid analgesic for nonmedical use at some time in their life.[3] Furthermore, over the last decade, there has been a dramatic increase in the number of visits to the emergency department involving nonmedical use of analgesics.[4] For example, in 2008, 36,000 Americans died from drug poisonings, with nearly 18,400 deaths involving opioid analgesics.[5] Thus, the healthcare professional prescribing extended-release (ER) and long-acting (LA) opioid analgesics for CNMP must be fully aware and educated on the risks and benefits involved with long-term opioid therapy. The clinician must be prepared to balance the benefits of opioid analgesics for chronic pain management with the risks of serious adverse outcomes such as addiction, unintentional overdose, and death. As hydrocodone is the most prescribed medication in America, physicians must be completely familiar with its pharmacology, side effects, efficacy, and limitations of use.[6] A recent review of the effectiveness and risks long-term opioid treatment for CNMP found that, compared with nonuse of opioids, long-term opioid therapy was associated with increased risk of abuse, overdose, fracture, myocardial infarction, and markers of sexual dysfunction.[7] Furthermore, several studies show that the risks from long-term opioid therapy is dose dependent. As ER/LA opioid analgesics generally contain a higher milligram dose of opioid than immediate release (IR) formulations, the ER/LA opioid analgesics are the subject of this educational monograph. Every clinician who prescribes ER/LA opioid analgesics for CNMP must be knowledgeable in the assessment, initiation, management, and termination of opioid analgesic therapy, including detailed pharmacology of specific ER/LA opioid products.

Prescribers should also explain specific information regarding the exact prescribed ER/LA opioid product. The patient should be taught how to take the opioid as prescribed and understand the importance of adhering to the dosing regimen. The patient should be instructed to read the specific ER/LA opioid product medication guide. Patients should be instructed to reveal all prescribed and unprescribed medications they are taking and be warned to not abruptly discontinue or reduce their opioid analgesic without physician consultation.

It is common public knowledge that some ER/LA opioid products when manipulated (crushed, chewed) or consumed with concomitant sedatives, alcohol, or illegal drugs may result in serious overdose and death. Patients must be warned to neither tamper with the opioid product, nor consume the opioid with concomitant central nervous system depressants.

All patients should be counseled regarding the safe keeping of ER/LA opioids which must be protected from theft, stored in a safe and secure environment away from children or other household members, and disposed of if no longer needed following the opioid product-specific disposal information. Prescribers should explain that sharing opioid analgesics with others is both illegal and may result in serious side effects. Finally, patients are instructed to call emergency services if they ingest excessive medication, have difficulty breathing, or a child has inadvertently taken the opioid.

In addition, evidence suggests that higher dose strengths (such as seen with the ER opioids) are associated with a higher mortality.[8-11] For these reasons, this article will provide the healthcare professional with an update on guidelines for the use of ER and LA opioid analgesics in the management of CNMP. The use of ER opioids for the management of active cancer pain is not considered in this document. Likewise, the use of chronic ER opioids for the management of chronic pain for the cancer survivor will not be addressed in this document, and the reader is referred to other publications.[12] For the purposes of this educational article, chronic pain is defined as pain lasting for at least 3-6 months, usually beyond the phase of acute or subacute tissue injury, which may be due to demonstrable causes or not, but not related to cancer or cancer therapy. An example of chronic-nonmalignant pain would be low back pain of at least 3 months duration.

It is expected that the student of this educational monograph on long-term opioid analgesics with ER or LA opioids will come to 1) recognize the proper assessment of patients considered for long-term treatment with ER/LA opioids, 2) develop skill with the initiation, dose modification, and possible discontinuation use of ER/LA opioid analgesics, 3) develop skills and knowledge to manage patients on long-term opioid therapy with ER/LA opioid analgesics, 4) recognize the information components required to counsel patients and caregivers about the safe use of ER/LA opioids, and 5) describe the general pharmacology of all ER/LA opioid analgesics as well as individual product-specific drug information.[8]

PATIENT ASSESSMENT FOR LONG-TERM OPIOID ANALGESIC THERAPY

All patients with a history of CNMP and considered by health professionals for opioid analgesic therapy, should first have a complete history and physical examination. The history should include a traditional history of the pain, including onset, duration, character and severity of the pain, location of pain, alleviating as well as aggravating factors, and a review of any previous laboratory or imaging studies. A typical previous medical history as well as review of systems is mandatory, along with a psychosocial history that includes the patient's current living conditions, family relations, work history, as well as drug allergies. This psychosocial history must include an evaluation of individual patient risk of opioid use. This must include a patient history as well as family history of substance abuse of alcohol, illegal drugs, or prescription drugs. Younger patients are more at risk for opioid use as well as patients with a history of sexual abuse, psychological disease such as major schizophrenia or depression. Commonly used tools, available for free on the Internet and validated for current use, include the Opioid Risk Tool and the Revised Screener and Opioid Assessment for Patients in Pain.[13,14] These assessment tools are quickly completed at initial evaluation, and a simple scoring system identifies the patient at low, moderate, or high risk for misuse of long-term opioid analgesics.[13,14] Other tools include the CAGE questionnaire for evaluation of alcohol abuse, and the Current Opioid Misuse Questionnaire which will assess for misuse of prescription opioids. An evaluation of all previous analgesic therapy is mandatory, especially the history of any opioid or nonopioid analgesics currently or previously used. A general and specific physical examination along with history and imaging studies, will help the clinician form an accurate complete evaluation of the patient with an identified pain diagnosis. A treatment plan is then completed and discussed with the patient and relevant family members. The clinician should first treat the patient with all appropriate nonopioid therapies or document such previous treatments. Prior to initiating a trial of opioid therapy, the clinician should complete urine drug testing to check for unacknowledged opioids or illegal drugs. The risks of chronic opioid use, along with the possible benefits, must be explained to the patient and the opioid prescribing agreement with informed consent completed. A prescription monitoring program should be reviewed to verify patient history as well as insure the patient has not been treated by multiple prescribers. It is important that

the clinician completely document the initial patient evaluation as well as all follow-up visits. Prescription opioids for chronic pain should not be prescribed for any family members of the clinician, and cautious prescription to any close friends of the prescriber.

Patients deemed to be a high risk for long-term opioid therapy, such as history of substance abuse, may still be considered for opioid therapy with ER/LA opioid analgesics, but will likely require expert consultation and additional and closely supervised monitoring. High-risk patients, including patients with serious psychiatric issues, serious aberrant drug-related behaviors, and history of previous prescription opioid abuse, should be strongly considered for referral to pain management specialists. One specific opioid formulation, transdermal fentanyl patch, carries a warning that it be used only for patients who are considered opioid tolerant, that is, patients currently receiving long-term opioid therapy for chronic pain.

Many studies of the efficacy of prescription opioids for the management of chronic pain have shown analgesic benefit and safety over clinical trials of 4-12 weeks.[15] However, long-term trials (12 months) using an open, prospective, blinded, placebo-controlled trial format have yet to be completed. Therefore, it is important that the clinician inform the patient for long-term opioid therapy that there are known risks involved with ER/LA opioid analgesics, and that adequate pain relief may be limited or not possible because of these side effects. The patient must be informed of potential serious opioid risks including inadvertent overdose and death. It is common for patients to discontinue long-term opioid therapy because of intolerable opioid-related adverse effects. The ER/LA formulations may give rise to increased opioid risk as most ER opioid dosage units necessarily must contain more opioid than the IR formulation. Side effects from long-term opioid therapy include the typical effects of constipation, and nausea and vomiting. With the initial use of opioids, or an increase in opioid daily dose, sedation is occasionally seen; however, the patient usually becomes tolerant to this side effect. Serious adverse events from long-term opioid therapy include life-threatening respiratory depression, inadvertent death, use of opioids as a tool for suicide, opioid addiction, and opioid misuse situations such as selling the opioid product on the street. Other opioid side effects include tolerance (increased opioid dosage required to produce the same analgesic effect), opioid-induced hyperalgesia (a state of nociceptive sensitization related to opioid exposure), immunosuppression, and hypogonadism.[16] Long-term opioid therapy may be a risk for central sleep apnea, but the data are currently lacking in this area. The patient should also be cautioned that if prescription opioids are not kept in a secure environment, they may be abused by household or family context, including inadvertent ingestion and overdose by children.[8] Women should be counseled that long-term opioid therapy during pregnancy may result in neonatal opioid withdrawal syndrome. All patients should be advised that opioids may interact with other medications such as alcohol and benzodiazepines resulting in increased risk and side effect profile. The concomitant use of benzodiazepines has been seen as a risk factor for opioid-related death.[17] All patients taking regular and chronic opioids will become physically dependent (will show some signs of opioid withdrawal upon sudden discontinuation of opioid therapy); however, most patients can be easily weaned from opioids when clinically indicated without harm. Finally, patients should be cautioned regarding automobile driving when first started on opioid therapy and when an increase in dose has been affected.[18]

LONG-TERM OPIOID THERAPY: INITIAL OPIOID TRIALS

Following careful patient selection including the above history, physical examination, screening tools, imaging studies, trials of nonopioid analgesics, and chronic pain diagnosis, a patient may be considered for a trial of opioid therapy to improve pain relief as well as increased patient functioning. Prior to initiation of opioid therapy, all prescribers should be aware of all Federal regulations and their particular state regulations concerning prescription opioid therapy.

The opioid-naïve patient

Before initiating any opioid therapy, the patient must be informed of all risks, as well as hoped-for benefits, must have an appropriate urine drug screen, and have completed a Patient Treatment Agreement. All patients should understand that the initiation of long-term opioid therapy for the management of chronic pain is a clinical trial therapy. Many patients are convinced that long-term opioid therapy will eliminate all of their pain with very few or minor opioid-related side effects. All patients should be counseled that, in fact, most patients will discontinue opioid therapy when followed for 12 months or longer due to inadequate analgesia or intolerable side effects.[19] Thus, the patient must understand that initial opioid therapy is a trial, which may or may not be successful regarding pain

relief or patient functioning. There are no studies to accurately suggest the length of the initial opioid trial, the authors find a period of 8-12 weeks is typically sufficient.

Multiple ER/LA opioid analgesics are available to the physician in the United States. Thirteen of these products are reviewed in detail in a follow-up article to this manuscript. For the purposes of this monograph, the authors consider that the initial opioid trial is with an ER or LA opioid product. Be aware that certain ER/LA opioids should not be trialed in the opioid-naïve patient, including transdermal fentanyl, ER hydromorphone, Avinza, Butrans, Embeda 100 mg, Kadian 100 mg capsules or greater, MS Contin 100 mg tablets or greater, Oxycontin 40 mg doses or greater, Targiniq ER 40/20 mg or greater, and Zohydro ER 40 mg doses or greater.

Opioid daily dose selection to start the initial trial is crucial, and the practitioner must be aware of potencies and dose range of typical ER/LA opioid analgesics. It is recommended that the lower dose of the therapeutic range be considered as an initial daily dose for the opioid-naïve patient. It is recognized that the opioid dose should be titrated to the individual in every situation. The reasons for this are many, including individual pharmacokinetic differences, individual pharmacodynamic differences, genetic variability for both the new opioid receptor as well as for metabolism of the opioid product, variability with social, psychological, emotional, and anxiety among each patient. The physician must be aware that increasing the ER opioid dose in response to inadequate analgesia (discussed further in this article) should be approached with caution and dose escalation should be done slowly to decrease the risk of opioid overdose. The physician should limit opioid dose increases to a minimum of every five to seven expected elimination half-lives of the ER opioid product. ER opioids should be prescribed on a timed daily schedule. Current guidelines disagree about the addition of IR opioids to the patient on ER/LA opioid analgesics. In the author's experience, IR opioids should only be added to ER/LA opioids to treat well-defined episodes of breakthrough pain. Nonopioid analgesics, such as nonsteroidals, tricyclic antidepressants, or antiseizure drugs, may be continued along with long-term opioid therapy and may augment opioid analgesia. When a maximum daily opioid dose has been reached without any evidence of analgesic efficacy, improved patient function, or there are intolerable side effects, the opioid should be weaned and discontinued.[20] It is unclear what the maximum daily opioid dose should be in the patient with CNMP; however, most current guidelines would classify a dose of morphine equivalent of 80-100 mg daily as high dose, and most suggest there is increased risk of adverse events with the highest dosage.[7,20]

It is important to educate the patient and caregivers to the possibility of significant respiratory depression from long-term opioid therapy, especially at the time of opioid trial initiation, as well as during opioid dose increases. Patients must be monitored closely and recent guidelines for the use of methadone for the treatment of CNMP suggest that patients be seen or called within 3-5 days of opioid initiation or dose increase.[9]

The opioid-tolerant patient

A patient is considered opioid tolerant if they have been receiving opioid treatment on a regular basis for at least 1 week prior to opioid trial initiation. For example, if a patient has a history of long-term opioid therapy but has discontinued all opioids for the past 2 weeks prior to a clinical trial, this patient would be considered opioid naïve. An expert panel of the US Food and Drug Administration (FDA) has defined opioid tolerance as patients receiving, for 1 week or longer, at least 60 mg of daily oral morphine, 25 μg/h of transdermal fentanyl, 30 mg of daily oral oxycodone, 8 mg of daily oral hydromorphone, 25 mg of daily oral oxymorphone, or an equal analgesic dose of any other opioid.[8]

An opioid-tolerant patient is, by definition, currently taking daily opioids. Therefore, it can be assumed that the current opioid regimen is inadequate to produce significant analgesia or improved patient functioning. If the physician judges that this patient is appropriate for additional trials of long-term opioid therapy (see above) then several choices become available. First, the patient on an IR opioid, and having adequate pain relief, may be converted to the same opioid available as an ER/LA opioid formulation and continued at the same daily dose. Second, a patient on an IR opioid with inadequate pain relief can be switched to the ER/LA same opioid family product for purposes of dose escalation. Dose escalation in the opioid-tolerant patient should also be performed with the same diligence and caution as with the opioid-naïve patient. Third, patients on a high dose of opioid (greater than 91 mg oral morphine daily equivalence)[20] may be given a trial of a different opioid as the patient has likely reached the upper limit of safety with that given opioid. This requires that the treating clinician have a good understanding of the principles of opioid rotation and incomplete opioid cross-tolerance.

Opioid rotation occurs when a patient is switched from one opioid to a different opioid in an effort to

improve analgesia, reduce adverse side effects, or improve patient functioning.[21] The concept of opioid rotation, developed for the management of cancer pain near the end of life, was tried for the treatment of CNMP and was found to be helpful for some patients. It has been applied to the long-term opioid patient for CNMP but without adequate research to date. In brief, the clinician calculates the current daily opioid dose of the patient, using an opioid equianalgesic published table, then converts the daily opioid dose to the equivalent daily opioid dose of a different opioid analgesic. Unfortunately, equianalgesic tables are based on population pharmacokinetics, and typically derived from studies of acute pain, volunteer studies, and sometimes on single dose studies.[22] In addition, therapy for the individual is quite variable because of opioid receptor differences, opioid metabolism and pharmacodynamic differences, and pharmacogenetic differences. Some studies have concluded that strict reliance on calculated opioid equivalence for opioid rotation has resulted in preventable fatal outcomes from opioid therapy.[23] The authors use a modified and cautious approach to opioid rotation. Because an individual patient may demonstrate incomplete cross-tolerance when rotating from one opioid to another, the authors use a lower initial dose than suggested by an opioid equianalgesic table. This approach requires calculation of the equianalgesic opioid dose, and then decrease this dose by approximately 50 percent for initial titration. To give an example, if a patient has an oral daily morphine dose of 100 mg, with a calculated equianalgesic hydromorphone dose of 20 mg daily, the patient would be started on a daily hydromorphone dose of approximately 10 mg. Of special note, recent guidelines on the use of methadone for treatment of CNMP recommend that when switching to methadone from another opioid, clinicians initiate methadone at a daily dose of 75-90 percent less than the calculated equianalgesic dose.[9] In addition, these methadone guidelines also indicated that, whatever the calculated equianalgesic opioid dose, the initial methadone daily dose would be no higher than 30-40 mg per day.[9]

Prior to initiation of a long-term opioid therapy trial, clinicians should review and establish analgesic goals as well as functional goals for therapy. Patients should be counseled that the analgesic goal of therapy would be to reduce symptoms sufficiently to allow improvement in quality of life and patient functioning. Patient must be educated to the risks and uncertainty involved with long-term opioid therapy, and the use of an Opioid Treatment Agreement is strongly encouraged. Although Opioid Treatment Agreements (OTAs) have not been documented to decrease serious opioid adverse events, many clinicians believe they are a useful document to outline at the start of opioid therapy, what is expected of the patient, the family, and the prescribing clinician. The OTAs vary in their content, but typically outline the treating clinician as the sole provider of opioids to the patient, educate the patient on the risks of opioid therapy including failure to provide analgesia, outline a patient commitment to return to clinic for follow-up visits and to comply with appropriate monitoring such as drug testing, and a patient commitment to maintain the opioids in a secure and safe environment at all times. The OTA is signed at the time of initiation of opioid therapy with the prescriber and patient. In some states, the OTA is in fact a mandatory requirement.

There is little research information available for the use of ER/LA opioids in special populations such as pregnant women and children. Clinicians should be extremely cautious about the use of opioid analgesics to treat a woman during pregnancy as the opioids will cross over into the fetal circulation. Patients with this special circumstance should be managed by pain specialist clinicians. As long-term opioid therapy in a woman may result in neonatal withdrawal syndrome in the newborn baby, the treating pain physician must alert the obstetrician and neonatology service such that appropriate treatment is available for the newborn.

MAINTENANCE OF LONG–TERM OPIOID THERAPY

Following initiation of the opioid trial, the patient is titrated to a daily opioid dose that achieves a balance between analgesia, opioid-related side effects, and functional activity. Most current guidelines suggest caution when using higher doses of opioids for CNMP, defined often as 100-200 mg of daily oral morphine equivalent.[24]

If an adequate goal of analgesia and improved functioning has been achieved, the patient must be scheduled for regular follow-up visits. These visits are not just for opioid prescriptions but should include a review of current pain history, a focused physical examination, a review of diagnosis, and reassessment of the treatment plan. Some states also advise an annual complete and full checkup. It is the authors' practice to complete a review of the electronic monitored prescription program at each patient visit and to complete random and intermittent urine drug testing to help insure opioid compliance.[25] The urine, or other body fluid, testing allows the clinician to ensure that the patient who is taking the prescribed opioid, is not taking other unprescribed opioids, and does not have street drugs

present in the urine. The clinician should provide good documentation of all these aspects of the follow-up patient visit.

The regular follow-up patient visit therefore documents pain relief, patient functional activity, opioid-related side effect profile, and health-related quality of life. If analgesia has been obtained to patient and physician agreed upon goals, but side effects are troublesome, the opioid may be continued at the present dose and an attempt made to control opioid side effects with specific medications. Constipation should always be suspected and treated adequately, and nausea and vomiting may be treated with antiemetic therapy. The clinician should also assess at the follow-up visit the clinical benefit compared to the side effect profile of the opioids, and whether the analgesic should be continued or tapered. This is a judgment made by the clinician after reviewing all the patient data.

The regular patient follow-up visit is an opportunity to recognize, document, and address any aberrant drug-related behaviors. Aberrant patient behaviors predictive of opioid misuse have been categorized into more, or less, predictive activities.[26] Behaviors highly suggestive of opioid misuse or mismanagement include prescription forgery, selling prescription opioids, stealing opioid analgesics, obtaining prescription or illicit drugs from the street, continuously losing prescription opioids, and altering oral opioid medications for injecting.[26] Less predictive behaviors include drug hoarding, requesting specific opioid analgesics, unsanctioned dose escalation, and aggressive complaining of the need for higher opioid daily doses.[26] All aberrant behavior should be documented in the patient chart, with further history, physical examination, and urine drug testing considered to diagnose the nature of the aberrant behavior. Depending on the severity of the behavior, the long-term opioid therapy may be tapered and discontinued, opioid dose may be reduced, the patient may be referred to a specific pain management specialist, the patient may be referred to an addiction medicine or psychiatry specialist, or the opioid medication may be continued as previously. It is incumbent on the clinician to document the outcome of the investigation to the aberrant behavior and note in the chart what the continued treatment plan will be. Additional responses on part of the clinician to aberrant behavior include shortening the patient follow-up visit and increasing the frequency of drug testing, and intermittent pill counts.

The regular patient follow-up visit allows an opportunity for the clinician to evaluate any changes in the patients underlying medical condition. Any changes to major organ function, such as liver or renal dysfunction, cardiac or pulmonary dysfunction, will result in a critical reevaluation of the risk-benefit ratio of long-term opioid therapy in this specific patient. Any significant new dysfunction in these major organs may result in increased opioid plasma levels or increased patient sensitivity to opioid-related side effects, which could be life threatening.

The use of methadone for the treatment of CNMP requires intimate knowledge of the prescribing clinician with the pharmacology of methadone. Specifics of patient evaluation, pain titration, and follow-up monitoring for patients on long-term methadone therapy is discussed in the section for specific opioid analgesic products. At least one set of recent guidelines has recommended that methadone be used only by clinicians with specific training in methadone therapy and only used following trials and failure of other opioid therapy.[20]

The patient follow-up visits are important to ensure, as much as possible, patient compliance with long-term opioid therapy treatment. There are several reasons for the clinician to seek patient compliance with therapy. First, the clinician needs an accurate knowledge of exactly how much opioid the patient is taking on a daily basis. If the patient is seeking additional opioids from other sources, it may simply reflect that the patient needs a higher regular daily opioid dose to achieve adequate analgesia. Second, if the patient is diverting prescription opioids, this is a serious criminal offense and must be reported. Third, if the patient is using additional sedatives, alcohol, or street drugs, the patient may be at risk for serious opioid overdose. Fourth, a recent review of closed claims physician malpractice associated with opioid management for CNMP revealed that patients with aberrant behavior were more at risk for serious opioid side effects such as death.[27] The investigation reviewed claims (N = 51) over a 3-year period for medication management and found that almost all patients had at least one risk factor for opioid medication misuse, and that 24 percent of patients had three or more of such risk factors.[27] Death was the most common outcome in the malpractice claim, and most (84 percent) such patients did not cooperate in their care. Factors associated with this increased risk of death included LA opioids, concomitant psychoactive drug use, and three or more opioid risk factors for medication misuse. Thus, the patient who is uncooperative in their care is not only burdensome to the healthcare team but also at risk of fatal opioid overdose.

Patients who do not achieve adequate analgesia, have intolerable side effects, or have been found to have aberrant behavior such that discontinuation of therapy is warranted, should have their prescription

opioid dose safely tapered. There are little research data to guide the clinician on the exact protocol for opioid tapering. A recent informal survey of pain physicians at a national meeting (P.A.S., unpublished data, 2013) found that opioid taper among pain physicians varied between 0 days and 3 months. In addition, a few physicians looked to in-hospital weaning of opioids, while most clinicians chose to taper the patient on an outpatient basis. As a rapid tapering of opioid can lead to unwanted symptoms, the authors typically taper the opioid by reducing the total dose to 75 percent, then 50 percent, then 25 percent, and finally to 0, using a 2-week interval for each reduction in dose. This usually results in a satisfactory tapering of the opioid without undue stress on the patient. Other therapies to help with opioid tapering include the addition of medication such as ondansetron or clonidine and also cognitive-behavioral therapy.[28,29]

The clearance of most opioids is affected by liver failure and should be used cautiously in these patients. The presence of renal failure does not change the clearance of morphine but dramatically reduced clearance of the principle metabolites (M3G, M6G). As M6G is a potent μ-receptor agonist, this may lead to prolonged opioid effect with renal failure, and unwanted sedation or respiratory failure. Fentanyl appears to be the opioid least affected by both liver and renal failure.[30]

PATIENT AND CAREGIVER EDUCATION CONCERNING ER/LA OPIOIDS

The FDA REMS education document strongly encourages healthcare professionals to council patients and caregivers regarding safe practices for the administration of ER/LA opioid analgesics.[8] As long-term opioid therapy is associated with the potential for serious adverse outcomes, this seems like very wise advice. Clinicians must document in the chart that they have provided this patient education. Essentially, the counseling includes information on how to take the medicine, consequences for not taking the opioids as prescribed, and advice for the patient should opioid side effects occur. The FDA REMS document does not require clinicians to use an OTA with their patients. The OTA, also referred to in the literature as opioid contract or pain medication agreement, is use by many, but not all physicians, in the management of long-term opioid therapy. The opioid contract usually adds binding statements for the patient such that they must comply precisely with all pain medication prescriptions, attend all scheduled appointments, submit for urine screening and pill counts, and other patient-physician requirements.[31-33] Opioid contracts are not universally endorsed by all pain physicians and some experts suggest that opioid contracts are neither enforceable nor effective and may erode the trust a patient has with his physician.[34]

A patient counseling document should be used to help explain to both patient and caregiver best practices for the safe use of long-term opioid therapy.[35] In addition to the FDA counseling document, other patient education aides can be found on the Internet.[36] Specifically, opioid prescribers should educate patients and caregivers on the common side effects of ER/LA opioids including the risks of falls, working with heavy machinery, and driving limitations when changing daily dose. Patients should be instructed to let the physician know about any side effects and ask for help in managing side effects. Serious side effects, such as overdose and death, must be discussed with all patients including risk factors, signs and symptoms of overdose and respiratory depression, serious gastrointestinal obstruction, and allergic reactions.[8] Any serious adverse events should be reported to the FDA.[37]

Prescribers should also explain specific information regarding the exact prescribed ER/LA opioid product. The patient should learn how to take the opioid as prescribed and understand the importance of adhering to dosing regimen. The patient should be instructed to read the specific ER/LA opioid product medication guide. All patients should be counseled regarding the safe keeping of ER/LA opioids which must be protected from theft, stored in a safe and secure environment away from children or other household members, and disposed of if no longer needed following the opioid product-specific disposal information. Finally, patients are instructed to call emergency services if they ingest excessive medication, have difficulty breathing, or a child has inadvertently taken the opioid.

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

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LONG–ACTING OPIOIDS: PROMISE VERSUS REALITY

Both short-acting (SA) opioids and long-acting (LA) opioids have been used for chronic pain (defined as pain lasting >3 months). SA opioids have a duration of action ranging between 2 and 4 hours, result in rapidly fluctuating drug levels and are suitable for acute, unstable, intermittent, breakthrough, and procedure-related pain.[1] End-of-dose failure pain is not considered a breakthrough pain by some investigators, but suboptimal around-the-clock (ATC) dosing, and is managed by increasing the ATC dose.[2,3] LA products are sustained-release/extended-release (SR/ER) potent opioid formulations which slowly release opioid over 8-24 hours or are particular opioids which have a long half-life and duration of action of >8 hours (buprenorphine, levorphanol, and methadone).[1,4,5] There are several potential reasons to prefer LA over SA opioids. Analgesia is associated with maintaining plasma opioid levels; each individual has a minimally effective plasma opioid concentration.[5-7] LA opioids theoretically maintain analgesic opioid levels better compared with SA opioids, depending on how SA opioids are dosed.[8] If patients take their SA opioid ATC, there appears to be no particular benefit to LA opioids.[9-11] Another proposed advantage to LA opioids is reduced side effects. Side effects are also related to plasma levels of opioids and SA opioids produce wider peak to trough levels leading to a greater risk of side effects at peak times. The transient high levels with SA opioids may increase side effects relative to LA opioids.[11-14]

Other proposed benefits to LA relative to SA opioids are improved sleep, less end-of-dose failure, less risk of addiction, and improved health-related quality of life.[4] However, in reality, there is insufficient evidence to substantiate claims of benefits to LA over SA opioids.[15,16] None of the comparison trials have demonstrated a reduced need for rescue analgesics with LA opioids. Sleep improved to a greater extent in only one of three studies with LA opioids. Function as an outcome, measured in only a minority of studies, was not different between opioid formulations. Side effects in general did not differ between formulations. One study demonstrated reduced nausea with LA opioids and another reduced depression and confusion with SA opioids.[15-17] These findings have not changed to date. No study to date has compared the risk of addiction with SA relative to LA opioids.[15,16,18] A study was done on the risk of aberrant behavior based on opioid formulation. "Drug-liking" effects were greater with SA than the LA opioids; however, this study was done in recreational drug users and not in individuals with chronic noncancer pain (CNCP) and so in reality is not applicable.[4] Trial heterogeneity in design and patient population prevent meta-analysis, but taking this into account, pain intensity outcomes between SA and LA opioids do not appear to differ.[15] Although some guidelines recommend LA opioids for CNCP, this is not based on analgesia, side effects, improved function, quality of life, or reduced risk of aberrant opioid behaviors.[19-21] Most comparison studies are of moderate to poor quality by present standards. While most focused on analgesia, none have systematically collected adverse events using a validated questionnaire but rather depended on patient spontaneous reports or diaries. It is estimated that opioid-related side effects are eight times more frequent when side effects are collected systematically rather than by patient volunteered reporting or diaries.[22,23] As a result, true differences in side effects between SA and LA opioids are largely unknown.

There are several drawbacks to using LA opioids. Pharmaceutical limitations of LA opioids are such that the lowest dose available with some LA opioids formulations may be too high for opioid-naïve individuals, the elderly, those with comorbidities, or those with organ failure.[14] In this setting, starting with an SA opioid then converting to an LA opioid once pain is controlled is a better strategy. For example, transdermal fentanyl 25 μg/h patch is contraindicated in opioid-naïve individuals and in the

postoperative setting. This dose of fentanyl is equivalent to 60 mg of morphine a day.[14] Another advantage of SA opioids is that these products can be more rapidly titrated to an effective dose more rapidly than LA opioids. The ATC dose should not be adjusted until steady state and steady state is reached more quickly with SA opioids due to the short half-life.[14] LA opioids have been used for initial dosing and titration but require close observation for adverse effects.[24] In at least one study, there was greater risk of side effects when initially using an LA opioid with titration than an SA opioid.[25] While individuals are on an LA opioid, many will require an SA opioid as rescue for breakthrough pain. This is relatively well established for cancer pain, more so than in CNCP. Two different opioids for pain management increase the risk for dosing errors. Methadone is particularly problematic when used in the opioid naïve. Methadone should not be increased for 4-5 days and has several disadvantages including the risk for corrected electrocardiographic QT (QTc) interval prolongation and Torsade de Pointe.[26-28] Buprenorphine has a long half-life and requires coupling with a SA opioid for breakthrough pain.[29]

ADDICTION AND ABUSE OF LA ANALGESIC PRODUCTS

LA opioid products are scheduled under the Controlled Substances Act and can be misused and abused. Misuse and addiction have paralleled the increase of prescriptions for LA opioids over recent years.[30] Evidence from observational studies suggest that long-term opioid analgesics for chronic pain increase the risk for opioid abuse.[31] No study to date has assessed the risk of abuse, addiction or related outcomes with long-term opioid therapy versus placebo or nonopioid analgesics. In uncontrolled studies, rates of abuse vary substantially based on strict inclusion criteria, even when controlling for care setting (primary care vs pain clinic).[32-39] Some of the variability in prevalence may be due to differences in ascertaining opioid addiction. Family and personal history of addiction and a psychiatric disorder increase the risk for opioid addiction. Certain genes involving dopamine neurotransmission, opioid receptors, and neurotrophic factors may increase the risk for addiction.[40] Risk mitigation strategies which include prediction questionnaires and urine drug screens are associated with reduced opioid misuse behaviors.[41,42]

Two studies have demonstrated a relationship between the total daily opioid dose measured as morphine equivalent doses (MED) and opioid overdose and mortality. In two studies, the hazard ratio (HR) was as high as 11 for individuals on >100 mg MED per day.[43,44] Another study demonstrated that overdose deaths were related to the maximum daily opioid dose. The adjusted HR was 4.5 for those on a MED >100 mg per day and was even higher for those with chronic pain and opioid doses >100 mg MED per day (HR 7.2).[45] Causes of opioid-related deaths are multifactorial. Root causes are physician error due to opioid knowledge deficits, patient nonadherence, unanticipated medical and mental health comorbidities, and payer policies that mandate methadone as first-line therapy without taking into account prescriber expertise or experience with methadone.[46] There are different patient demographics associated with opioid deaths depending on the location of overdose or death. Patient characteristics described in the emergency room include middle-aged male, public insurance, lower income, comorbid chronic pulmonary disease or neurologic disease, and history of sleep apnea. Overdoses which occur at home are associated with a college degree, female gender, and combined opioid and benzodiazepines.[47,48]

Methadone is a particular risk factor. Although methadone accounts for 4.5-18.5 percent of opioids distributed by state, it accounts for nearly 40 percent of single opioid-related deaths.[49] Also, deaths from fentanyl have doubled between 2013 and 2014 in certain states. Most deaths are from injections of illegally produced acetyl fentanyl.[50]

At least two methods have successfully reduced opioid-related deaths. Reformulation of oxycodone ER to an abuse-deterrent pharmaceutical which has reduced deaths from oxycodone by 82 percent.[51] Second, state supported overdose education and nasal naloxone distribution programs have reduced opioid deaths in communities.[52,53]

RESPIRATORY DEPRESSION

Respiratory depression is the most important and feared serious opioid adverse effect which is immediately life threatening. The type of opioid and patient characteristic associated with respiratory depression has changed over the decade. In a systematic review of opioid-related respiratory depression in patients with chronic pain, morphine and cancer pain were most commonly associated with respiratory depression prior to the year 2000. After the year 2000, methadone or fentanyl and patients with noncancer pain where the most often associated respiratory depression.[54] Specific root causes contributing to respiratory depression prior to 2000 were increased plasma morphine levels, renal failure, and sensory deafferentiation. In the years following 2000, elevated opioid plasma levels and drug interactions with

cytochrome P450 enzymes were factors associated with respiratory depression. Other factors are pharmacodynamic interactions between opioids and benzodiazepines which lead to synergistic respiratory depression.[55] Long-term maintenance methadone decreases hypoxemic as well as hypercapnic ventilatory responses.[56] This may place patients with sleep apnea at risk for respiratory depression.[57,58] All phases of the respiratory cycle are influenced by opioids. At low doses, there is decreased tidal volume and at high doses decreased respiratory rate.[59] As a result, rapid dose titration in an opioid-naïve individual who has not developed tolerance is a strong risk factor for respiratory depression.[60] The degree to which opioids suppress peripheral and central chemoreceptors depends on the characteristics of the particular opioid.[61] In animal models, single opioid doses produce variable durations of respiratory depression. Respiratory depressive effects were short lived for fentanyl and oxycodone as single doses whereas morphine, morphine-6-glucuronide, and buprenorphine produced prolonged respiratory depression.[62] The route of administration also plays a role. Oral opioids have less effect on hypoxic and hypercapnic ventilatory drive than parenteral opioids.[63] There also may be a genetic predisposition to opioid-related respiratory depression.[64]

Part of the difficulty of defining respiratory depression with opioids is that there are different definitions of respiratory depression which involve sensorium, respiratory rate, hypoxemia, and hypercapnea. Oxygen desaturation has been used in the past as the hallmark of respiratory depression.[65,66] Not infrequently, respiratory rate has been used on hospital wards. However, the respiratory rate may decrease while the tidal volume compensates thus maintaining oxygen saturation.[67,68] This compensatory mechanism may fail during an acute illness leading to reduced respiratory rate, tidal volume, and oxygen desaturation.[69]

Naloxone is an allyl derivative of noroxymorphone, first synthesized in 1960. It is a nonselective competitive opioid antagonist for all three major opioid receptors (mu, delta, and kappa).[70] It has a high first past hepatic clearance (>95 percent) and thus low oral bioavailability. Metabolism is primarily through glucuronidation to naloxone-3 glucuronide, 70 percent is excreted in urine as the conjugate metabolite, and 30 percent unchanged.[70-73] The extent and duration of naloxone-induced reversal of opioid-associated respiratory depression is variable and related to the opioid dose, the mode of administration, coadministered medications, underlying disease, pain, state of arousal, genetic makeup of the patient, and exogenous stimulating factors.[74,75] Naloxone rapidly gains access to the central nervous system (CNS). Its' elimination half-life from plasma is quite short, 33 minutes, such redosing of naloxone may be needed, particularly for LA opioids.[76] The onset to effect is <2 minutes. Naloxone should be given at a rate of 20-100 μg (intravenous) IV every 2 minutes to reverse respiratory depression but not analgesia. An IV infusion may be needed for individuals on LA opioids.[69,77] Buprenorphine will require large doses of naloxone, 2-4 mg IV, and an infusion to reverse respiratory depression.[75,76] Intranasal (recently approved by the Food and Drug Administration for use in opioid overdose) and subcutaneous naloxone are also effective and as effective as parenteral naloxone in reversing respiratory depression. This is particularly important if patients do not have IV access.[78]

CONSTIPATION AND NARCOTIC BOWEL SYNDROME

Constipation is the most common long-term side effect with opioids and should be anticipated. Unfortunately, very little tolerance develops to opioid effects on bowel function. Adverse effects are due to μ-receptors on enteric neurons but also arise from activation of the CNS μ-receptors.[79,80] Constipation can occur with spinal opioids. Opioids reduce peristalsis by inhibiting longitudinal smooth muscle, increasing segmentation by disinhibiting circular muscle, reduce bowel secretions, and increase water absorption. Sphincter function is also adversely affected.[81-83] Opioid-induced constipation can be accompanied by straining at stool, colic, nausea, abdominal distention, bloating, anorexia, and vomiting.[83]

The narcotic bowel syndrome is the paradoxical development of abdominal pain while on opioids and is frequently under recognized as an opioid side effect.[82,84] The narcotic bowel syndrome is estimated to occur in 6 percent of individuals on long-term opioid.[85] Pain is described as burning or colicky. There can be an overlap of symptoms of opioid-induced constipation; both include bloating, distention, nausea, and constipation as well as anorexia.[86] The syndrome bears a remarkable similarity to the irritable bowel syndrome and functional abdominal pain syndrome.[87] A common differential diagnosis includes pain from chronic pancreatitis, partial bowel obstruction, peptic ulcer disease, abdominal angina, renal calculi, uterine fibroids, and ovarian cysts.

Management of constipation associated with opioids is primarily preventative with the use of stimulating and osmotic laxatives, stool softeners, and suppositories. Osmotic laxatives include lactulose, sorbitol, polyethylene glycol, and magnesium

hydroxide. Stimulating laxatives include bisacodyl or senna derivatives.[88-92] There does not appear to be an advantage of one laxative over another.[93-95] Laxatives should be initiated at the time opioids are prescribed to prevent constipation and titrated to effect which is highly variable. A minority will require suppositories or enemas to treat constipation and/or fecal impaction. Oral naloxone has been used in the past; presently in certain countries (not the United States), there is a combination formulation of SR oxycodone and naloxone which is reported to reduce constipation relative to oxycodone alone.[96,97] Methylnaltrexone, which does not cross the blood-brain barrier, has been used for refractory constipation unresponsive to laxatives.[98-100] Lubiprostone has recently been approved to treat opioid-induced constipation.[101-103]

Management of the narcotic bowel syndrome requires first an "index of clinical suspicion" and a careful history.[104] Patients may not understand the reasoning behind opioid reduction or withdrawal in the face of increasing abdominal pain; an empathetic discussion and patient education is a necessity. Patient concerns and fears about opioid withdrawal should be addressed.[82] Abdominal radiographs can be misleading as they may show evidence of a "partial intestinal obstruction," secondary pseudo-obstruction or ileus.[82,86,105,106] Clonidine and parenteral continuous infusion metoclopramide have also been used to treat the narcotic bowel syndrome.[85,107,108]

DRUG–DRUG INTERACTIONS

Drug-drug interactions vary among different products and opioids. Knowledge of particular opioid-drug interactions and underlying pharmacokinetic and pharmacodynamic mechanisms is important before initiating opioids or switching opioids and allows safer administration. Approximately 6 percent of patients with CNCP on LA opioids are exposed to potential major drug-drug interactions.[109]

Pharmacodynamic interactions between CNS depressants (alcohol, sedatives, hypnotics, tranquilizers, and tricyclic antidepressants) and opioids potentiate sedation and respiratory depression of both drug classes. Benzodiazepines are involved in 31 percent of opioid deaths.[110] There is an increased risk for motor vehicle accidents when individuals drive while on both a benzodiazepine and an opioid.[111] Although in healthy individuals, the combinations of benzodiazepines and opioids do not increase the abuse liability of an opioid, the combination does enhance behavioral toxicity of either drug class.[112]

Alcohol increases the positive "liking" effects of opioids while adversely affecting physical function and cognition.[113] The prevalence of alcohol-related disorders in individuals on oral potent opioids is 5.5 percent and is twice that of the general population which is 2.2 percent.[114] There are major pharmacokinetic interactions between LA opioids and alcohol. Alcohol is linked to dose-dumping of certain SR/ER opioids.[115-118] Therefore, clinicians who prescribe LA opioids to patients need to warn them about the danger of using alcohol while on opioids.

Monoamine oxidase (MAO) inhibitors can increase respiratory depression of certain opioids. Using certain opioids with antidepressants and MAO inhibitors may also cause the serotonin syndrome.[119,120] Phenylpiperidine opioids (meperidine, tramadol, methadone, and dextromethorphan) are weak serotonin reuptake inhibitors and have been most often associated with the serotonin syndrome when combined with MAO inhibitors. Morphine, codeine, oxycodone, and buprenorphine appear to have little serotonin reuptake inhibition and are less likely to precipitate a serotonin syndrome.[120] Tramadol has been reported to increase the risk for the serotonin syndrome when combined with selective serotonin reuptake inhibitors (SSRIs). The risk is particularly greater in older individuals, those on high doses of tramadol, and those using medications which inhibit cytochrome CYP2D6.[121]

Opioids reduce the efficacy of diuretics by increasing the release of antidiuretic hormone (ADH).[122] As a result, morphine used in acute decompensated heart failure worsens outcomes of acute heart failure and doubles mortality (11 percent vs 5 percent) as well as doubles the odds for in-hospital death.[123] Opioids reduce the clearance of acidosis related to severe cardiogenic pulmonary edema.[124] In addition to systemic opioids, spinal opioids are also associated with increased ADH levels and impaired diuresis.[125] Therefore, morphine should not be used as a symptom treatment for acute cardiogenic pulmonary edema.[126]

Methadone and buprenorphine are associated with prolongation of the QTc interval. Since 2002, methadone-associated arrhythmias have been disproportionately represented in the US Food and Drug Administration Adverse Event Reporting System (FAERS).[127] Prolongation of the QTc interval with methadone correlates with respiratory arrest and the need for intubation.[128] Female gender, those with cardiac channel congenital abnormalities, and those with low magnesium or potassium are at increased risk for prolonged QTc intervals with methadone.[129-134] Genetic polymorphisms of the cytochrome CYP2C19 have been associated with QTc prolongation. Extensive

metabolizers require higher methadone doses; have altered methadone enantiomer clearance (defined as the R-methadone/methadone ratio) and greater QTc changes.[135] Also individuals with congenital long QTc syndrome mutations are at risk for methadone-induced arrhythmias.[136]

Buprenorphine effects on the QTc interval are 100 times less than methadone when adjusted for therapeutic plasma concentrations.[137] Within the opioid maintenance population, QTc interval prolongation is much less frequent with buprenorphine than with methadone.[138] Individuals on methadone with a dangerously prolonged QTc interval (>500 ms) can be switched to buprenorphine with resolution of the prolonged QTc interval.[139-141] Nevertheless, buprenorphine has been associated with QTc prolongation if combined with a CYP3A4 inhibitor.[142]

Recommendations have been recently published on the safe use of methadone for pain by the American Pain Society and College of Problems on Drug Dependency which should be read by clinicians prescribing methadone for pain.[27,28] Specific recommendations include patient education, counseling patients on methadone safety, use of electrocardiograms to identify individuals at risk for complications related to methadone, use of alternative opioids in patients at high risk for methadone-induced arrhythmias, careful dose initiation, titration and diligent monitoring with follow-up.[28]

DRUG INTERACTIONS AND CYTOCHROME P450

Drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can cause higher or lower than expected blood levels of certain opioids, leading to either opioid toxicity or withdrawal. Inhibitors of certain cytochromes delay clearance leading to opioid toxicity or prevent activation of an opioid prodrug leading to poor analgesia.

Cytochrome CYP2D6 metabolizes a large number of medication classes (antidepressants, antipsychotics, beta blockers, and opioids) and is responsible for metabolizing 25 percent of current drugs.[143,144] CYP2D6 is not inducible but the gene allele can be amplified leading to ultra-rapid metabolism. Poor metabolizers have two alleles with reduced function or are nonfunctional. Individuals are classified as ultra-rapid metabolizers with allele amplification, extensive metabolizers with both alleles functional, intermediate metabolizers with one functional allele, and poor metabolizers with two nonfunctional alleles.[143,144] CYP2D6 metabolizes codeine, tramadol, oxycodone, and hydrocodone. Poor metabolizers have reduced analgesia with tramadol (which requires o-demethylation to o-desmethyl-tramadol) and codeine (which requires o-demethylation to morphine).[143,144] Ultra-rapid metabolizers can have life-threatening toxicity with codeine or tramadol.[145,146] An updated version of Clinical Pharmacogenetics Implementation Consortium guidelines recommend that codeine be used based on CYP2D6 gene type for reasons of safety and efficacy.[147] Drugs which block CYP2D6 interfere with codeine and tramadol analgesia and delay clearance of hydrocodone and oxycodone.[148-152]

Both hydrocodone and oxycodone metabolism is also dependent on CYP3A4.[148-153] Hydrocodone is metabolized to hydromorphone through CYP2D6 and norhydrocodone, a weak but active metabolite, through CYP3A4. The clearance of hydrocodone is determined by both enzymes.[154] Oxycodone metabolized through CYP2D6 to oxymorphone and through CYP3A4, the weak active metabolite noroxycodone. Drug interactions at both enzymes have an effect on oxycodone analgesia and safety.[150,153,155]

Transdermal fentanyl is commonly used for chronic pain. There are large patient-to-patient variations in transdermal fentanyl pharmacokinetic parameters.[156,157] Fentanyl clearance at steady state is dependent on CYP3A4. CYP3A4 levels are influenced by liver disease, drug inhibitors such as ketoconazole and inducers such as rifampin.[158,159]

Methadone is extensively metabolized through multiple cytochromes (CYP2B6, CYP3A4, CYP1A2, CYP2D6, CYP2C9, and CYP2C19).[160] Methadone is subject to multiple drug interactions. Methadone induces its own metabolism through induction of CYP2B6 and CYP3A4.[161] Induction of both enzymes may result in "analgesic tolerance" over time due to increased clearance of methadone. Estradiol during pregnancy increases methadone clearance through induction of CYP2B6.[162] More than 50 drug-drug interactions are reported with methadone.[160] Methadone prescribers should inquire about any new medications including complementary and over-the-counter medications periodically and particularly if patients on stable doses of methadone develop withdrawal or opioid toxicity.[160]

DRUG INTERACTIONS AND EFFLUX PUMPS

Cerebral endothelial cells contain energy-dependent efflux transporters which function as a blood-brain barrier. These efflux pumps are also located in the brain parenchyma, astrocytes, and microglia.[163] P-glycoprotein, the major efflux pump, functions to prevent harmful compounds from entering the CNS. Multiple opioids are P-glycoprotein substrates (morphine, oxycodone, methadone,

and fentanyl).[164] Polymorphisms of the P-glycoprotein pump gene (ABCB1) influence analgesia and opioid side effects.[165-170] The ABCB1 gene can be upregulated by chronic morphine exposure causing analgesic tolerance.[171] Drugs which inhibit P-glycoprotein (verapamil) increase opioid toxicity and drugs which introduce P-glycoprotein (rifampin) diminish opioid responses or cause withdrawal symptoms.[172-174] P-glycoprotein is also found along the gastrointestinal tract, induction of P-glycoprotein in the gastrointestinal tract will reduce drug absorption.[175] This leads to opioid toxicity when rotating from a P-glycoprotein substrate opioid to an opioid which is not subject to P-glycoprotein efflux if one only relies on opioid equivalent tables.[175]

The risk of drug-drug interactions increases with age, the number of prescribed drugs, and comorbidities. A large observational study found that >70 percent of individuals on long-term opioids had drug-drug interactions.[176] Very few involved serious contraindicated drug combinations. Interactions were usually drugs with additive CNS depressant effects, inducers and inhibitors of CYP3A4, inhibitors of CYP2D6 and combinations of tramadol with SSRIs, tricyclic antidepressants, and antipsychotics.[176]

OPIOID TOLERANCE

Tolerance to sedation and respiratory depression is critical to the safe use of certain opioid products, certain dosing units, and strengths. For example, patients must be opioid tolerant before using transdermal fentanyl 25 μg/h or rapidly acting fentanyl products for breakthrough pain. Patients are considered opioid tolerant if on morphine 60 mg/d, oxycodone 30 mg/d, hydromorphone 8 mg/d, fentanyl 25 μg/h, or oxymorphone 25 mg/d for a minimum of 1 week. Starting maximal daily doses for those who are opioid naïve are morphine 30 mg, fentanyl 12 μg/h, methadone 2.5-7.5 mg, oxycodone 20 mg, and oxymorphone 10 mg. The same starting dose should be used regardless of the initial pain severity; high pain severity does not warrant starting individuals who are opioid naïve on greater than recommended initial opioid doses.

OTHER ISSUES

ER/LA opioids should be swallowed whole. ER/LA opioids in capsules should be swallowed intact or when necessary the pellets from the capsule can be sprinkled on applesauce and swallowed without chewing. Transdermal products should not be exposed to external heat. Fever or exertion increases fentanyl absorption leading to opioid toxicity or fatal overdose.[177]

When converting patients from one opioid to another, one should use instructions for conversion written in the Dosage and Administration instructions of individual product information pamphlets. Incomplete cross-tolerance and great interindividual variability in opioid responses requires conservative dosing when switching from one opioid to another. It is recommended that dosing start with half the calculated equianalgesic dose and titrate the new opioid to effect. Doses may also need to be tailored based on comorbidity, organ failure, and coadministered medications that have potential for drug interactions.[178]

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ER/LA OPIOID REMS SUPPLEMENT 3

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

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INTRODUCTION

Opioid products, specifically long-acting (LA), extended-release (ER), and sustained-release (SR) formulations, are used for the treatment of a subset of patients with chronic noncancer pain (CNCP).[1] This article will review the specific pharmacology and risks associated with specific LA, ER, and SR opioid formulations that have been used in the treatment of chronic pain. This article will not address the indications for, evidence for and against, or general controversy regarding the use of any form of long-term opioid therapy for the treatment of chronic nonmalignant pain (CNMP), as this has been presented in other published works.

AVINZA

Avinza® (Pfizer Inc., New York, New York) is an extended release (ER) morphine sulfate formulation which became commercially available in 2002. Avinza consists of a hard gelatin capsule which contains immediate release (IR) (10 percent) and SR (90 percent) beads of morphine sulfate. The gelatin capsule dissolves in the gastrointestinal (GI) tract releasing both sets of beads. SR beads contain spheroidal oral drug absorption system (SODAS) technology. This technology involves soluble and insoluble polymers surrounding the morphine-coated core. Fumaric acid acts as an osmotic wick which draws GI fluid into the beads, the polymer swells which creates a pore releasing morphine in a controlled release manner over 24 hours. This results in a minimum peak to trough variation in plasma morphine levels over the 24 hours.[1] Avinza comes in 30, 60, 90, and 120 mg capsules; the 60, 90, and 120 mg dosage forms should be used only in opioid-tolerant individuals.

Avinza pharmacokinetics has been compared with IR morphine elixir. Avinza 60 milligrams (mg) once daily was compared with 10 mg of IR morphine every 4 hours in healthy individuals. The maximum plasma concentration (C_{max}) and the area under the curve (AUC) for morphine were similar.[1] Avinza has also been compared with MS Contin®. Dosing intervals were MS Contin every 12 hours and Avinza every 24 hours for 7 days, at which time pharmacokinetics were measured. The AUC over 24 hours was equivalent while peak to trough fluctuations in morphine levels were 50 percent less with Avinza. Morphine concentrations at 30 minutes, C_{max}, and AUC were similar.[2]

Avinza has also been compared with OxyContin® in 35 healthy males. As these are dissimilar opioids, plasma concentrations were reported in relative concentrations. Avinza had a 23 percent greater relative C_{max} and 20 percent less variation in peak to trough levels compared with OxyContin.[1] Avinza has not been compared with the other 24-hour SR morphine formulation, Kadian®.

In an open label study of CNCP who were opioid naïve, Avinza 30 mg/d could be titrated to 60 mg/d depending on response. Outcomes were pain control as determined by patient diary of numerical rated pain intensity scores (NRS; 0, no pain; 10, severe pain). Of 491 evaluable patients, 90 percent adhered to daily assessment. Pain severity diminished by two points on average (7.83-5.77) through the 3-month study period. In addition to improved pain, sleep and activity also improved.[3]

Avinza has been compared with OxyContin for chronic moderate-to-severe low back pain (CLBP). This 8-week randomized trial enrolled 392 individuals. Morphine equivalent doses (MED) needed to control pain were less with the Avinza (69.9 mg vs 91 mg/d). Avinza-treated patients required fewer

rescue doses, experienced greater reductions in pain and better sleep quality. Side effects were similar between the opioids.[4,5]

Avinza in an open label prospective study involved patients with CNCP who were on short-acting opioids (SAO). Avinza 38, 60, 90, or 120 mg was started based on the SAO doses. This 4-week trial used highest, lowest, and usual pain, as well as unpleasantness, measured by visual analog scales. Of 129 patients entered, 84 completed the study (32 percent dropout rate). The average Avinza dose was 59.1 mg/d (range, 15-360 mg); 83 percent required <60 mg/d. Rescue SAO, used for breakthrough pain, dose requirements diminished while on Avinza from 50 mg MED per day to 24 mg MED per day. Depression, anxiety, frustration, anger, and pain behaviors diminished also.[6] An abbreviated (4 weeks) trial compared Avinza 30 mg/d with MS Contin 15 mg every 12 hours in patients with osteoarthritis pain. Avinza 30 mg daily produced equivalent relief as MS Contin 15 mg every 12 hours.[7]

Avinza has a dose-response with titration to pain control in CNCP. Long-term trials have demonstrated a gradual increase in dose requirements (baseline 120 mg) to 180 mg at 6 months which is followed by stabilization at 1 year.[1,8,9]

Avinza gelatin capsules can be opened and the beads sprinkled on applesauce and immediately swallowed whole. C_{max} and AUC of sprinkled Avinza are similar to swallowed capsules. One should never chew the beads.[1] There is an important dose-ceiling effect with Avinza at 1,600 mg/d. Fumaric acid in the polymer is released and absorbed, and at 1,600 mg there is an increased risk for renal failure due to fumaric acid.[1] Alcoholic beverages or medications containing alcohol can rapidly release morphine and will potentially cause overdose or death. Morphine is a P-glycoprotein substrate; thus, P-glycoprotein inhibitors such as verapamil can also increase the distribution of morphine into the central nervous system (CNS) and increase absorption twofold. Itraconazole, a potent P-glycoprotein inhibitor, will increase morphine C_{max} and AUC without delaying clearance.[10] Morphine is also subject to Multidrug Resistant Associated Protein (MRP) efflux pumps which is part of the blood-brain barrier.[11] Upregulation of P-glycoprotein or MRP leads to reduced analgesia with morphine or analgesic tolerance. Drugs that block P-glycoprotein such as verapamil, quinidine, and Itraconazole may lead to opioid toxicity.[12-16] Because morphine is largely glucuronidated in the liver by UGT2B7, there will be fewer drug-drug interactions compared with opioids metabolized through the cytochrome enzyme system.[17]

BUTRANS–TRANSDERMAL BUPRENORPHINE

The Butrans®-transdermal system consists of a patch which contains a backing layer furthest from the skin, an overlap adhesive film next to the backing is next, then a separating layer between the overlap adhesive film and the drug polymer adhesive matrix. Next to the skin is a peel off release layer which is removed prior to placing the transdermal patch. The concentration of buprenorphine within the adhesive matrix is the same for all five strengths. The amount of buprenorphine released from each system per hour is proportional to the active surface area of the system attached to the skin. The skin is the limiting barrier to diffusion from the transdermal patch to the bloodstream. The Butrans system provides a controlled release of buprenorphine which lasts 7 days.[18-20] Butrans patches are available in 5, 7.5, 10, 15, and 20 μg/h patches. Once the patches are applied, there is a gradual increase in plasma buprenorphine levels over 2 days. Plasma levels are 143.5 pg/mL at 24 hours with a 20 μg/h patch, which then reaches steady-state levels in 48 hours at 300 μg/mL plasma levels. These levels are maintained for 160 hours.[19,20] Steady-state levels are reached therefore with the first application. Once the patches are removed, buprenorphine plasma levels decrease by 50 percent on average in the first 12 hours (range, 10-24 hours), with a terminal half-life of 26 hours. The AUC is dose proportional indicating no limit to absorption through the skin. However, absorption is influenced by application site. Transdermal patches should be placed on the upper outer arms, upper chest, upper back, or side of chest. Buprenorphine plasma levels are 26 percent higher when applied to the upper back compared with the side of the chest in healthy volunteers though this is not clinically significant.[20] Application to nonapproved sites such as the abdomen and extremities will lead to a dramatic reduction in absorption. Patients can mistake patches for lidocaine transdermal patches and apply the patch at the site of pain. Application, for instance, to the patella produced blood levels which are only 29 percent of those achieved by placing the patch on the upper back.[20] Also, if the same skin application site is continuously used, buprenorphine levels will double. Hence, the same skin site should not be used for 3-4 weeks. Low body fat as occurs with cachexia reduces buprenorphine absorption by 20 percent; the clinical relevance of this is unknown. Exposing Butrans to heat, or sunbathing or entering a sauna with Butrans applied will increase buprenorphine plasma concentrations by 55 percent and can lead to opioid toxicity. However, the patch can be worn during a shower or tepid bath.[18-22]

Buprenorphine is 96 percent protein bound, mostly to α-1 acid glycoprotein. Buprenorphine has a large volume of distribution (430 L) with extensive tissue distribution. Cerebrospinal fluid levels are 15-25 percent of plasma levels. Buprenorphine is metabolized to norbuprenorphine by cytochrome CYP3A4. Both the parent drug and norbuprenorphine are rapidly glucuronidated to buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide. Buprenorphine and norbuprenorphine are biologically active at the μ- and/or κ-receptor.[23] Nor-buprenorphine affinity for the μ-receptor is 40-fold lower than that of buprenorphine but norbuprenorphine, unlike buprenorphine, is a full agonist for G-protein activation.[23-25] Glucuronidated metabolites produce very small antinociceptive effects when tested in mice and probably do not affect buprenorphine analgesia.[23]

Because buprenorphine is metabolized through cytochrome CYP3A4, there is the potential for drug-drug interactions. However, this is not always observed clinically, perhaps because of the rapid glucuronidation of both buprenorphine and norbuprenorphine prevents potential drug interactions at CYP3A4.[26-30] Certain protease inhibitors, however, such as Atazanavir that inhibit both CYP3A4 and UGT1A1 enzymes, important to buprenorphine clearance, will significantly increase buprenorphine blood levels and delay clearance.[31,32]

Respiratory depression associated with buprenorphine is largely due to the metabolite, norbuprenorphine.[33] Buprenorphine protects individuals from norbuprenorphine-related respiratory depression.[34] P-glycoprotein effluxes norbuprenorphine from the CNS to a greater extent than buprenorphine.[35] Drugs which block P-glycoprotein may lead to respiratory depression due to accumulation of norbuprenorphine within the CNS.[36-39]

Butrans pharmacokinetics are not different in the elderly (>72 years) compared with younger individuals (<32 years).[40] Transdermal buprenorphine pharmacokinetics are absolutely unchanged in renal failure.[41] Buprenorphine pharmacokinetics are also unchanged in Child-Pugh class A and B hepatic impairment. However, it is advised to use buprenorphine with caution in those with severe liver impairment.[20]

Single arm studies and randomized trials comparing Butrans to placebo have frequently used a run-in (enrichment enrollment) phase, and some trials have used a randomized withdrawal design after enrichment enrollment. Enrichment enrollment trials tend to under-report side effects.[42] In an open label study involving patients with CLBP, Butrans 5-20 μg/h were used to treat opioid-tolerant individuals. Butrans was associated with improved physical domain of quality of life at 52 weeks.[43] A double-blind, placebo-controlled trial with open extension involved individuals with CLBP. Butrans doses ranged up to 40 μg/h (an acceptable dose in Europe but not Food and Drug Administration [FDA] approved in the United States). Approximately 30 percent of individuals withdrew from study largely due to adverse effects. There was an approximate 25 percent reduction in pain intensity relative to placebo, which was associated with improved sleep and reduced disability. There were no reported opioid withdrawal symptoms with discontinuation of the patch. Five individuals on Butrans were reported to have a significant prolonged QT corrected (QTc; >60 ms compared with baseline); one patient on placebo also had a prolonged QTc.[44] Side effects were nausea (37.5 percent), pruritus or rash with the patch (30 percent), somnolence (20 percent), constipation (12.5 percent), and headache or dizziness (10 percent). A second randomized controlled trial involved a run-in phase of Butrans (10 or 20 μg/h) produced better pain control at 12 weeks (standard mean difference, −0.58) than placebo. Adverse effects were stated to be no different than placebo, and no unanticipated electrocardiogram (ECG) changes were observed.[45]

A third study with a similar design involved patients with CNCP. This trial used an unusual outcome, the proportion of ineffective treatment and the amount of escape acetaminophen used by participants. Ineffective therapy was 1.79 times greater than with placebo.[46] Application site adverse effects occurred in 9 percent. Headaches with Butrans occurred in 3.9 percent and with placebo 2.2 percent.[46]

Butrans has been reported to be tolerable in the elderly. In an open label study (mean age, 72.8 years) of patients with CNCP, Butrans 5 or 10 μg/h reduced pain from 6.8 to 1.7 (NRS) and improved anxiety, depression, disability, and quality of life.[47,48] A second study of patients with arthritis compared Butrans in individuals aged between 50 and 60 years with those >75 years. Doses ranged between 5 and 40 μg/h. The Western Ontario and McMasters University Osteoarthritis Index (WOMAC) score improved equally in both groups as did pain, sleep, and quality of life. The use of rescue analgesics was not different nor were there differences in side effects between the groups.[49]

Butrans has been compared with sublingual buprenorphine, tramadol, hydrocodone plus acetaminophen, oxycodone, fentanyl, codeine, morphine, and dihydrocodeine. In a head-to-head comparison with tramadol in individuals with osteoarthritis, buprenorphine was equally effective in reducing

pain but was preferred by patients over tramadol. Tramadol was discontinued prematurely significantly more often. Butrans was associated with nausea in 30 percent, 19 percent had constipation, and 16 percent head dizziness.[50] Butrans improved pain control in individuals with CNCP and pain was not well controlled with tramadol. Pain improved at rest (5.7-2.9), with activity (7.3-3.8), and at night (5.2-2.3) by NRS rated mean pain severity.[51] In a retrospective cohort study involving individuals older than 65 years with CNCP, Butrans with an average dose of 10 μg/h resulted in less discontinuation at 6 and 12 months compared with codeine, hydrocodone, and tramadol.[52]

Butrans 5, 10, and 20 μg/h for 7 days was compared with sublingual buprenorphine 0.2 mg every 8 hours, 0.2 mg every 6 hours, and 0.4 mg every 8 hours, respectively, in a double-blind randomized study of individuals with osteoarthritis. The mean age was 64 years. More than half withdrew from the study. All outcomes, pain intensity, WOMAC score, sleep, and need for rescue acetaminophen, were equally improved with both treatments. Butrans was associated with less nausea, dizziness, and vomiting

Table 1. Recommendations for transdermal buprenorphine therapy

1. Transdermal buprenorphine is indicated for individuals 18 years or older.
2. The initial dose of transdermal buprenorphine should be 5 μg/h in the opioid naïve.
3. Apply transdermal patch to the upper outer arms, upper chest, upper back, or sides of the chest.
4. Titration should not be sooner than 3 days after initiating therapy.
5. No more than two patches should be placed at one time.
6. Provide a short-acting analgesic during titration for breakthrough pain.
7. Patches should be worn for 7 days continuously.
8. The dose limit in the United States is 20 μg/h.
9. Rotate applications sites. The same site should not be used for 3-4 weeks. Hair at the site of application should be cut to facilitate placing the patch but should not shaved to avoid skin abrasions.
10. No dose reduction is necessary for the elderly.
11. There are no recommendations for echocardiographic monitoring.
12. Avoid exposing transdermal patches to heat. This includes heating pads, saunas, and sun bathing. Patches can be worn while bathing or showering.
13. Transdermal patches should not be cut when adjusting doses.
14. To dispose of transdermal patches, fold the adhesive sides together and flush down the toilet. Check with local officials to be sure this is allowed. Buprenorphine patches as well as all opioids should be kept in a locked box which is secured and locked.
15. Buprenorphine should not be used concurrently with monoamine oxidase inhibitors or for individuals with severe or respiratory impairment.
16. The use of benzodiazepines and sedatives when individuals are on transdermal buprenorphine should be avoided.
17. Use transdermal buprenorphine with caution in severe hepatic impairment and with drugs which inhibit or induce CYP3A4, as well as class IA and III antiarrhythmics.
18. Buprenorphine equal potency to oral morphine has not been established. Daily equivalent morphine doses of 80 mg or more exceed Butrans highest equivalent ceiling doses in the United States. One study did find buprenorphine 20 μg/h produced similar analgesia to oxycodone 40 mg/d.
19. Transdermal buprenorphine 5 μg/h should be used when converting from morphine doses of <30 mg/d or if individuals have mild or moderate pain or if individuals are on weak opioids.
20. Several transdermal medication patches contain metal such as aluminum or titanium dioxide which is problematic if patients are to undergo magnetic resonance imaging (MRI).

compared with sublingual buprenorphine. Skin irritation from Butrans occurred in 25 percent.[53]

A systematic review compared morphine to transdermal buprenorphine. Transdermal buprenorphine significantly decreased pain intensity to a greater extent (mean difference, −16.20; 95% confidence interval [CI], −28.92 to −3.48 by visual analog scale) while morphine was associated with more constipation (odds ratio [OR], 7.50; 95% CI, 1.45-38.85).[54] A larger number of morphine patients discontinued opioid therapy due to adverse events (OR, 5.80; 95% CI, 1.68-20.11). All other outcomes were not significantly different.

A 14-day double-blind, randomized trial compared hydrocodone plus acetaminophen with Butrans 10 and 20 μg/h. Individuals with osteoarthritis were on stable doses of hydrocodone ranging between 15 and 30 mg/d prior to study. Both analgesics resulted in similar efficacy and tolerability.[55] An enrichment enrollment, followed by a double-blind, randomized trial lasting 84 days in patients with CLBP, compared Butrans 5 and 20 μg/h with oxycodone 40 mg/d. Butrans 20 μg/h and oxycodone 40 mg/d were superior to Butrans 5 μg/h. Butrans 20 μg/h produced similar analgesia to oxycodone 40 mg/d. Side effects occurred in 59 percent of patients on Butrans 5 μg/h, 77 percent on Butrans 20 μg/h, and 73 percent on oxycodone.[45]

A systematic review has compared transdermal buprenorphine and transdermal fentanyl (TF) side effects.[56] There were 56 publications, with 49 unique studies. Fentanyl was associated with more constipation. Dizziness, somnolence, nausea, and treatment discontinuation were similar between transdermal opioids. Transdermal buprenorphine was favored in the elderly, those with renal failure and those who were immunosuppressed.[56] There is some evidence that fentanyl clearance is decreased in the elderly unlike buprenorphine which may account for the preference for buprenorphine in the elderly.[57] Fourteen unique trials (17 publications) were included in a second systematic review. TF, in comparison with transdermal buprenorphine, was associated with significantly more nausea (OR, 4.66; 95% CI, 1.07-20.39), and significantly higher number of treatment discontinuations due to adverse events (OR, 5.94; 95% CI, 1.78-19.87).[54] There was a nonsignificant difference with all other outcomes, including pain measures.[54]

Butrans has been used in special populations. In a small open labeled study, buprenorphine reduced neuropathic pain related to AIDS and provided stable CD4 lymphocyte counts, more stable than observed on TF.[58] In a single arm study involving individuals with cancer pain, TF 17.5 μg/h reduced pain within 1-5 days after initiating therapy. However, most patients in this study required dose titration; the average daily dose was doubled by 4 weeks.[59] Recommendations for use of transdermal buprenorphine therapy are given in Table 1.[60,61]

EMBEDA

Embeda® was approved by the FDA in 2009 for moderate-to-severe pain requiring 24-hour analgesia. Embeda contains pellets of morphine surrounding a central core of sequestered naltrexone. The ratio of morphine to naltrexone is 100:1. The outer polymer layer allows release of SR of morphine while preventing the release of naltrexone. Chewing, crushing, or cutting Embeda releases naltrexone, thus inhibiting the opioid effect, acting as a tamper-resistant formulation.

In randomized controlled trials, Embeda had similar bioavailability as MS Contin.[62] Embeda every 12 hours has the same bioavailability and pharmacokinetics as Kadian given once daily.[63] The bioavailability of crushed Embeda has similar pharmacokinetics as equivalent doses of IR morphine. The C_{max} of a crushed capsule is 314 percent higher than seen with intact Embeda; however, the total AUC is the same as whole Embeda. Once naltrexone is released in crushed Embeda, the naltrexone C_{max} and AUC are similar to IR naltrexone liquid taken by mouth.[63,64] Plasma levels of naltrexone and 6-β-naltrexol are low to nonquantifiable in individuals who take the drug as directed and swallow intact Embeda. These low levels do not interfere with pain responses nor are associated with any effect on the morphine analgesia.[62] A high-fat diet alters Embeda pharmacokinetics with the T_{max} delayed from 7.5 to 10 hours, and the C_{max} reduced from 16 to 12 ng/mL. Administration of alcohol (40 percent alcohol in 240 mL) doubles morphine C_{max} without compromising naltrexone sequestration.[65]

Embeda was developed as an abuse-deterrent opioid analgesic. Crushing Embeda reduces the "liking" effect compared with the same dose of intact Embeda.[66] Individuals who ingested crushed Embeda had a 69 percent reduction in euphoria compared with equivalent doses of IR morphine.[67] Conversion of Embeda into an injectable form resulted in reduced euphoria relative to equivalent dosages of morphine.[67] Pharmacodynamics of crushed Embeda was compared with crushed MS Contin; Embeda produced less euphoria than equivalent doses of MS Contin but more than placebo. When crushed Embeda is taken, both naltrexone and 6-β-naltrexol become measurable in plasma.[68]

Embeda has been compared with placebo in an enrichment enrollment, randomized controlled trial

involving individuals with osteoarthritis. Of those entered, 63 percent completed the titration phase. More than half (54 percent) reported greater than a 40 percent reduction in pain with Embeda.[69] A 12-month safety study involved 465 individuals with CNCP who received an average dose of 58.6 mg/d of Embeda (maximum dose, 860 mg/d).[70] As seen with other opioid studies, 30 percent discontinued their opioid analgesic within 30 days largely due to side effects. The Brief Pain Inventory improved at all four assessment periods during the study. Naltrexone was detectable in 11 percent of patients but levels were an order of magnitude lower than clinically relevant concentrations. Typical opioid side effects were recorded.

Several difficulties with Embeda occurred following approval. A Black Box warning was given regarding potential opioid withdrawal if Embeda was inadvertently crushed and consumed.[71,72] It was noted that injection of dissolved Embeda could lead to opioid overdose, withdrawal, and/or embolic events secondary to insoluble particulate matter.[67] Finally, drug stability became an issue which led to multiple recalls of the product. In 2011, Embeda was withdrawn from the market and remains unavailable today.[73]

Embeda was packaged in capsules of 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, and 100/4 mg (morphine/naltrexone). Capsules can be opened and pellets spread on applesauce and immediately eaten uncrushed. Initial doses should be 20/0.8 mg in opioid-naïve individuals. The 100/4 mg capsules should be used in opioid-tolerant patients only. Doses should not be titrated faster than 48 hours. P-glycoprotein inhibitors (as with all morphine products) will increase morphine exposure and absorption twofold.[16,74-77] Morphine is largely cleared by glucuronidation; therefore, drugs which inhibit glucuronidation, such as ketamine, will delay morphine clearance leading to increased risk of opioid toxicity.[78-81]

KADIAN

Kadian consists of morphine-embedded polymer beads contained within a capsule. It is designed as a once daily SR morphine preparation that also is FDA approved for 12-hour dosing intervals.[82] Kadian is available in 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, and 200 mg capsules. Kadian 100, 130, 150, and 200 mg capsules should only be used in opioid-tolerant individuals.

Kadian pharmacokinetics differ compared to other morphine products. Dose-adjusted C_{max} is about one fourth that of equivalent IR oral morphine.[83] T_{max} is 8.5 hours while IR morphine T_{max} is about 1 hour. Kadian has a longer T_{max} and extended C_{max} relative to MS Contin.[84,85] In a volunteer trial of Kadian compared with Embeda, 100 mg/d of both preparations were bioequivalent.[63] Kadian every 24 hours showed AUC and C_{max} equivalent to MS Contin every 12-hour dosing.[86-89] Kadian demonstrates dose-proportional plasma levels between 30 and 100 mg.[90] Forty percent alcohol ingestion with Kadian does not change Kadian pharmacokinetics.[91] Patients older than 65 years have the same clinical benefits with Kadian but usually require lower dosing. In one study, patients aged 65 years and older required an average dose of 72 mg/d versus 105 mg/d for younger individuals with CNCP.[92] Morphine clearance and pharmacodynamics may be altered in older individuals, thus the need for lower doses.[93,94]

Kadian has been compared with OxyContin in a 24-week trial of patients with CNCP.[82] Both analgesics had similar outcomes which included improved pain intensity, sleep, and quality of life. Typical opioid-related side effects were seen. Approximately two thirds of individuals remained on once daily Kadian; the other one third were converted to twice daily. These differences may be due to higher baseline pain scores among patients requiring twice daily dosing.[95]

A large study of 1,428 individuals with CNCP and treated with Kadian compared morning versus evening dosing.[96] Seventy percent completed the 4-week study. Of those remaining on Kadian, all outcomes, pain intensity, sleep, and quality of life improved; 55 percent were maintained on once daily Kadian. Dosing in the morning or evening did not make a difference in pain control.

Kadian has been compared to MS Contin in a double-blind, randomized trial of patients with chronic cancer pain.[85] Patients were stabilized on IR opioids before switching to ER opioids. The mean daily dose requirement was 138 mg. Time to remedication with rescue analgesic was longer ($p < 0.01$) with Kadian (16 hours) compared with MS Contin (8.7 hours), and more patients on MS Contin required rescue medications (55 percent) than those on Kadian (46 percent). Side effects were not different between the two analgesics.[85]

Very little is known about the abuse potential of Kadian[85]; however, it is reasonable to take the same precautions as with other ER morphine products. P-glycoprotein inhibitors can increase absorption and distribution leading to opioid toxicity. Alcohol should be avoided and certain medications that inhibit morphine conjugation should be used with caution.[97-99] As with other morphine products,

individuals with a history of morphine sulfate allergy should not be given Kadian. If naloxone is required to reverse morphine-induced respiratory depression, repeated doses are likely to be necessary due to the very long half-life of Kadian.[100]

MS CONTIN

MS Contin is a morphine ER formulation with tablets releasing morphine over a 12-hour dosing interval. In comparison with IR morphine every 4 hours, MS Contin every 12 hours has equivalent AUC and C_{max}.[101] The mean T_{max} for MS Contin is 3.6 hours and for IR morphine is 1.3 hours.[102] MS Contin pharmacokinetics are dose proportional and not altered by diet.[103] MS Contin every 12 hours is bioequivalent to Avinza once daily based on C_{max} and AUC.[104]

In a large review of MS Contin trials, 93 percent of individuals with chronic pain achieved satisfactory pain relief using MS Contin at 12-hour intervals; while 7 percent required MS Contin at 8-hour intervals.[103] MS Contin was stated to be significantly more effective than prestudy opioids and with fewer side effects, though this review was published in 1989 when other morphine ER formulations were not yet available.[103] MS Contin has been compared to TF in opioid-tolerant patients with CLBP. Fentanyl 25 μg/h was compared with MS Contin 30 mg every 12 hours.[105] Outcomes were weekly diaries of pain intensity and bowel function. Final doses on average were fentanyl 75 μg/h and MS Contin 180 mg/d. Both opioids produced the same degree of pain relief. Fentanyl was associated with reduced constipation.[105] In a pooled analysis of studies which compared TF with MS Contin, fewer side effects (constipation and somnolence) occurred with TF.[106] In another study, more individuals discontinued MS Contin than TF because of side effects even though efficacy was similar.[107] However, not all trials found fentanyl more tolerable than MS Contin.[108] Although constipation is consistently less prevalent with fentanyl, sleep disorders have been reported to be greater with fentanyl.[109]

Many patients fear cognitive impairment related to opioids. In a study which looked at long-term ER morphine in patients with CNCP, cognitive function as well as pain relief actually improved, as did mood. This 12-month trial found that pain, quality of life, subjective memory, and side effects measured at 3, 6, and 12 months were consistently improved compared to baseline. This patient population was screened for addiction risk, mood change was not the euphoria associated with addiction.[110]

MS Contin can be given per rectum; however, this route has greater pharmacokinetic variability than oral dosing. Morphine absorption through the inferior hemorrhoidal vein bypasses the hepatic portal system, thus reducing morphine hepatic clearance which may account for the greater variability in morphine levels.[111,112] MS Contin contains talc thus illicit conversion of MS Contin into an injectable form can lead to microemboli to the lung.[113,114]

Opioids in ER formulation may cause hormonal changes and sexual dysfunction. SR opioids cause hypogonadism in 74 percent of individuals. This high incidence is independent of body mass index and does occur at relatively low doses. The occurrence of hypogonadism is much more frequent with ER than IR (34 percent) opioids.[115] Hypogonadism may be related to sustained opioid levels from the ER product which does not allow recovery of gonadotropin release and function.[116-118] Another concern with the use of MS Contin is in the patient with renal failure. In general, there is a lack of useful information provided in most package drug information pamphlets which can be used to adjust morphine doses in renal failure.[119] Descriptions of renal failure are in general terms such as mild, moderate, severe renal failure which are inadequate for dose adjustments. Therefore, prescribers who wish to use opioids in renal failure should be familiar with published literature on the subject and not depend solely on drug information pamphlets provided with the drug.

OXYCONTIN

OxyContin was originally FDA approved in 1995 but became associated with rising opioid abuse and drug deaths. It was therefore reformulated and re-released in August 2010.[120,121] The original formulation could be chewed, cut, ground, then sniffed or solubilized for injection which resulted in high doses of systemic drug.[122,123] The reformulated product uses the same polymers but manufactured to a plastic-like property which limits oxycodone extraction. The crushed reformulated OxyContin now forms only large particles or a gel which is difficult to misuse.[73]

OxyContin has biexponential absorption kinetics. There is a rapid absorption phase with an oxycodone half-life of 37 minutes (accounting for 38 percent of the drug) and a second peak at 6.2 hours (62 percent of the drug).[124] Pharmacokinetics of two tablets of 10 mg is equivalent to 20 mg OxyContin.[125] OxyContin pharmacokinetics are not changed with food, unlike IR oxycodone.[126] OxyContin every 12 hours has been compared to oxycodone IR every 6 hours as equivalent daily doses. C_{max} was the same for both but T_{max} was

twice as long with OxyContin (3.2 hours) compared with IR oxycodone (1.4 hours).[127] OxyContin every 12 hours in patients with chronic cancer pain produced equivalent analgesia at steady state compared with the same daily dose of oxycodone divided and given every 6 hours.[128] The variability of OxyContin pharmacokinetics was compared with MS Contin in fasting males aged 18-45 years. The coefficient of C_{max} variation was 33 percent less with OxyContin than with MS Contin. Minimum to maximum plasma concentrations were two to threefold less variable with OxyContin.[129]

A randomized, open label study compared hydromorphone ER with twice-daily OxyContin in subjects with CNCP.[130] More than 500 patients were randomly assigned between the two analgesics. OxyContin and hydromorphone ER were noninferior as measured by changes in pain scores. Equianalgesic doses were 16 mg of hydromorphone ER and 40 mg of OxyContin. Tramadol ER was compared to OxyContin after surgery for breast cancer.[131] OxyContin 20 mg was clinically equivalent to 200 mg of tramadol ER. Side effects such as nausea, vomiting, and pruritus did not differ between groups.[131] OxyContin 20-50 mg twice daily was compared with tapentadol ER 100-250 mg twice daily in patients with osteoarthritis.[132] Tapentadol ER use resulted in a significantly higher percentage of patients with 50 percent or greater improvement in pain intensity (32 percent) than OxyContin (17 percent). Opioid side effects were similar to OxyContin, except tapentadol was associated with lower GI-related side effects.[132]

Oxycodone is metabolized in the liver to noroxycodone by CYP3A4, and to oxymorphone by CYP2D6. Oxycodone analgesia is largely dependent on oxycodone with some contribution from oxymorphone.[133] All rapid metabolizers (due to CYP2D6 gene amplification) and poor metabolizers (due to nonfunctioning genes) are at increased risk of toxicity or side effects with oxycodone. Drug-drug interactions at both cytochromes will alter oxycodone pharmacokinetics and can lead to opioid toxicity or withdrawal symptoms.[133-138] There is some interest in developing personalized oxycodone dosing based on pharmacogenetics testing though this is not standard practice at the present time.[139]

Oxycodone, unlike morphine, is actively transported into the brain by the pyrilamine transporter.[140] As a result, CNS oxycodone levels are three times higher than levels in plasma.[141-143] For the same unbound concentrations of morphine and oxycodone in plasma, the concentration of opioid in the brain is six times higher with oxycodone than morphine.[144] Despite reduced oxycodone affinity for the μ-receptor relative to morphine, the selective uptake of oxycodone contributes to its greater analgesic potency. Drugs like naloxone, diphenhydramine, lidocaine, and propranolol will compete for this transporter which may influence CNS drug levels.[145,146]

Oxycodone, like morphine, is a substrate for P-glycoprotein and can induce P-glycoprotein expression leading to analgesic tolerance.[141,147-149] Polymorphisms of the P-glycoprotein gene, ABC B1, influence oxycodone adverse reactions.[150] Oxycodone is also subject to cytochrome drug interactions involving CYP2D6 and CYP3A4 enzymes.[150,151] Interactions occur with azole antifungal drugs, mycin antibiotics, antiretroviral medications, and rifampin.[133,135,136,152-156] Over-the-counter medications such as St John's wort and grapefruit juice will interact with oxycodone.[134,137,157] Individuals lacking analgesia, developing tolerance, or sudden opioid toxicity with OxyContin should be queried about dietary changes, the use over-the-counter medications, or new medications prescribed for them.[136,137,157]

Certain populations have increased sensitivity or a narrow therapeutic index with oxycodone due to altered pharmacokinetics and delayed clearance.[93,158-160] Oral bioavailability of oxycodone in the elderly (76-89 years) is similar to younger patients, but clearance is reduced leading to increased plasma concentrations of opioid for the same given dose to a younger patient.[93,158-160] In addition, oxycodone half-life at steady state is increased in the elderly, from 3.8 to 4.6 hours.[161] Thus, oxycodone ER in the elderly should be given at lower doses and with an increased dosing interval.

Individuals with advanced cancer are often on multiple medications and likely to have organ compromise secondary to metastases. Dose adjustments need to be made particularly in those with liver dysfunction.[162] In this context, starting with IR oxycodone would be preferable to starting with oxycodone ER. Cancer cachexia also delays oxycodone metabolism and clearance.[163,164] Individuals with advanced cirrhosis have a delayed and prolonged half-life (from 3.4 to 13.9 hours) with IR oxycodone. OxyContin should not be used in advanced liver disease for this reason.[165,166] Oxycodone accumulates in renal failure and is also variably dialyzed. Hence, oxycodone can be used cautiously in individuals on hemodialysis but dosing will need to be carefully individualized.[167-169]

Reformulated OxyContin, compared with the original OxyContin, when crushed and given intranasal, has a reduced C_{max} and prolonged T_{max} compared with the original drug formulation, and

thus has a reduced addiction potential index (C_{max}/T_{max}).[170] Following release of the reformulated OxyContin in 2010, it was found that abuse with OxyContin was reduced by 36 percent, and it was hoped that the newest OxyContin formulation would lead to reduced medical costs.[171-173] However, it appears that some abusers found a way to use the new formulation, while most switched to alternate opioids, including IR opioid products.[121,171,174,175] OxyContin, though reformulated, reduces but does not eliminate abuse. The same precautions for addiction screening and urine drug testing should be done when prescribing any tamper-resistant opioid product.

The economic impact of OxyContin is related, in part, to opioid side effects. Most individuals (82 percent) will experience at least one side effect, and most (78 percent) will be bothered by that side effect. The most frequent side effects are drowsiness (41 percent), constipation (37 percent), fatigue and daytime sleepiness (37 percent), and dizziness (27 percent). Unscreened and under-reported side effects include hypogonadism. Total payer cost per month associated with these side effects are reported to be $238 above the cost of OxyContin itself.[176]

OxyContin is available in 10, 15, 20, 30, 40, 60, and 80 mg tablets. Initial doses are 10 mg every 12 hours in the opioid-naïve individual. Upward titration should be not <48 hours. OxyContin should be used with caution in those with hepatic impairment. Doses should be reduced by one half to one third with liver dysfunction, and with severe liver impairment oxycodone ER should be discontinued and the IR formulation used instead. OxyContin should be used cautiously in renal failure. Individuals should be started on one half the usual dose for creatinine clearance of <60 mL/min, and IR oxycodone used as needed for patients with severe renal failure or on dialysis. Patients who cannot swallow tablets due to nausea, dysphagia, or bowel obstruction, should be treated with an alternative opioid such as a TF or buprenorphine. Tablets should be swallowed whole and not cut, chewed, or crushed. Drugs which induce or inhibit CYP3A4 or inhibit CYP2D6 may alter OxyContin clearance and lead to either opioid toxicity (including respiratory depression) or opioid withdrawal symptoms. OxyContin doses >40 mg as a single dose, or 80 mg as a total daily dose, should be used only for opioid-tolerant patients. The relative potency of morphine to oxycodone ranges between 2:1 and 1.5:1. It is important that when rotating to OxyContin, an appropriate equianalgesic table is consulted and that also the clinical context be considered when adjusting doses.[177-183]

TARGINIQ ER

Targiniq™ ER is a single formulated tablet of oxycodone and naloxone, in a 2:1 fixed dose ratio, designed primarily to prevent opioid-induced constipation.[184] Targiniq ER has been labeled by the FDA in 2013 as an abuse-deterrent opioid. The 2:1 ratio (oxycodone to naloxone) was identified as the most optimal ratio, balancing constipation, diarrhea, and analgesia.[184,185] Oxycodone release from Targiniq ER is biphasic, similar to OxyContin. The elimination half-life is 4.5 hours. The oxycodone release mechanism is designed for a 12-hour dosing interval.[186] The bioavailability of oxycodone is not altered by the naloxone. Naloxone delivery is also by extended release. Oral naloxone IR at high doses will override first pass liver clearance leading to opioid withdrawal, whereas naloxone ER does not have this effect.[185,187,188] Bioavailability of the oral naloxone is minimal (approximately 2 percent) and thus naloxone binds and blocks GI μ-receptors leading to reduced constipation, but without reversing analgesia.[189] Naloxone has a greater affinity for μ-receptors compared with oxycodone and thus naloxone successfully reverses oxycodone-related constipation.[190-192]

Naloxone is metabolized in the liver by UGT1A8 and UGT2B7, and to a lesser extent CYP3A4. Principal metabolites are the glucuronide conjugate of 6-α-naloxol, an active metabolite.[193-195] Oxycodone absorption through the rectum is about the same as by mouth.[196] Rectal administration of Targiniq ER would result in the same amount of oxycodone and bioavailability but naloxone bioavailability per rectum increases to 15 percent secondary to absorption through the inferior hemorrhoidal vein which bypasses the liver.[193,197] Targiniq ER administered per rectum is likely to lead to an analgesic ceiling at high doses or even precipitate withdrawal symptoms.

GI transit has been measured in healthy volunteers receiving 10 and 20 mg of OxyContin, and 10/5 and 20/5 of Targiniq ER. OxyContin 20 mg caused an increased GI transit time while for Targiniq ER 20/10 the time was the same as placebo.[191] Targiniq ER has been shown to reduce opioid-induced constipation in multiple trials. In a randomized trial comparing OxyContin with Targiniq ER involving individuals with CLBP, 20-40 mg of either analgesic produce similar pain relief but Targiniq ER was associated with less constipation and reduced laxative consumption.[190] In a 12-week trial involving patients with CNCP, 20-50 mg of OxyContin or Targiniq ER, Targiniq ER produced less constipation as measured by the Bowel

Function Index (BFI).[198] In a third randomized trial also involving individuals with CNCP, 60-80 mg of either OxyContin or Targiniq ER produced similar analgesia; however, Targiniq ER was associated with reduced constipation symptoms.[199] A randomized controlled trial involving patients with CNCP with opioid-induced constipation despite laxatives found that Targiniq ER 10-20 mg/d for 12 weeks significantly improved constipation and 36 percent were able to stop laxatives.[200] An open label extension study of Targiniq ER 20-60 mg daily maintained improved bowel function as measured by the BFI without evidence of tolerance to the effect.[201] Many studies, however, did not include detailed descriptions of the method used to collect side effects and adverse events, rather depending on patient self-report.[202] Targiniq ER was reported to have reduced nausea, vomiting, abdominal pain, and dyspepsia relative to oxycodone ER. However, there were more serious adverse events (abdominal pain) noted in one Targiniq ER trial involving patients with cancer.[203]

In contrast to CNCP, the benefits of Targiniq ER in patients with cancer appear to be marginal. In a 4-week trial involving patients with cancer pain randomized to OxyContin or Targiniq ER, there was a statistical reduction in BFI scores compared with OxyContin but the benefits did not seem to be clinically significant.[203] Quality of life was the same for both analgesics. A second trial found that Targiniq ER had no adverse effect on bowel function but did not influence laxative use in patients with cancer.[204] There may be several reasons for the different anti-constipation effect between patients with cancer and patients with CNCP: 1) patients with cancer frequently require higher doses of opioids (Targiniq ER at high doses provides poor analgesia) and 2) patients with cancer have multiple causes of constipation.[186,205,206]

Targiniq ER is classified as an abuse-deterrent opioid by the FDA even though there are no peer-reviewed studies published with this as the primary outcome.[207] However, combining an opioid receptor antagonist with an agonist, as with Targiniq ER, should deter converting the drug to unapproved routes (intranasal and parenteral). Of course this does not preclude the misuse of oral Targiniq ER.[171,208,209] Clinicians should still screen individuals for drug addiction risk and use urine drug screens periodically when prescribing Targiniq ER.

Targiniq ER is available in 10/5, 20/10, and 40/20 mg tablets. Dosing intervals are 12 hours and opioid-naïve patients should be started on 10/5 mg tablets every 12 hours. Titration intervals should not be less than every 48 hours. Doses should not exceed 80/40 mg/d. Single doses >40/10 mg or daily doses of 80/40 mg should be used only in individuals who are opioid tolerant. Targiniq ER may be taken with food without loss of efficacy. Tablets should be swallowed whole and not cut, chewed, or crushed. Oxycodone clearance is delayed in hepatic impairment. Shunting due to cirrhosis may increase naloxone bioavailability. With hepatic impairment, starting doses should be one third to one half the usual dose or patient should be started on IR oxycodone and titrated to response before converting to Targiniq ER. Targiniq ER is contraindicated in moderate-to-severe hepatic impairment. There are no standard guidelines for dose adjustments in hepatic impairment, only general recommendations. Patients with creatinine clearance <60 mL/min should be started on half of the usual dose or initially started on IR oxycodone at reduced doses and titrated to pain control. Conversion to Targiniq ER would then be based on the effective IR oxycodone dose. There are no standard guidelines to adjusting doses in renal impairment, only general recommendations. Drug-drug interactions are largely based on oxycodone studies. Individuals on inhibitors or inducers of CYP3A4, or inhibitors of CYP2D6, will have altered oxycodone clearance. This may lead to opioid toxicity or withdrawal symptoms. When rotating to Targiniq ER from another opioid, physicians should review a conversion table published in the literature. Doses should be adjusted based on clinical context.[177,180,182,183,210,211]

METHADONE

Methadone has been available in America for almost 70 years, often used for opioid maintenance of addicted opioid patients, and used occasionally in the early decades for the treatment of perioperative pain. It is now used in oral formulation for the treatment of chronic pain. The past two decades have seen an increase in the use of methadone for the treatment of CNMP. It is available in a tablet formation of 5 and 10 mg.

Methadone is a very unique synthetic opioid whose pharmacology should be completely understood by the prescriber. It is structurally unrelated to morphine and has three known mechanisms of analgesia.[212] As with other opioids, it binds to the μ-opioid receptor but is also an NMDA antagonist and a norepinephrine reuptake inhibitor at the spinal cord level. It is perhaps these unique mechanisms of analgesia, in addition to opioid antagonist activity, that make methadone such a powerful analgesic. In America, methadone is available as a racemic mixture of stereoisomers, while in Europe it is available

as a levoisomer, in addition to the racemic mixture. The levoisomer appears to have most of the μ-opioid receptor antagonist activity.[213]

The clinician must understand some basic pharmacokinetics unique to methadone. Methadone is almost completely absorbed on oral administration; however, the elimination half-life of the drug varies between 9 and 47 hours among patients.[214] This high variability among patients is due in part to weight, gender, age, genetics, and drug-drug interaction.[215,216] Thus, it is extremely important to start with low initial doses of methadone, and titrate upward doses with caution, and very slowly. For example, an elderly patient who might have an elimination half-life of 3-4 days would not reach steady-state plasma levels for 2 weeks or longer. Thus, if dose escalation occurs before steady state has been reached, delayed respiratory depression as a life-threatening event may occur. Methadone metabolism occurs almost exclusively in the liver with excretion of inactive metabolites.[217] Methadone is not dialyzable and therefore caution should be used in the treatment of renal failure patients on dialysis.

Recent guidelines have been published to improve patient safety when using methadone therapy for chronic pain management.[218] There are three unique areas of caution with the use of methadone for chronic pain: 1) with initial dosing and dose escalation, 2) with elevated QTc interval, and 3) related to drug-methadone patient interaction. Methadone dosing is recommended at every 8-12 hours only, with dosage increases (titrated up to improve analgesia) occurring not more frequently than 1 week intervals. It is important to assess whether an alternative opioid may be safer for individual patients who are opioid naïve. Suggested doses for opioid-naïve patients, or patients currently taking <60 mg of daily oral morphine equivalent, start at 2.5 mg three times daily. Patients being switched from methadone, from a dose of daily morphine equivalent >60 mg, should be started at a methadone dose of only 10 percent of the calculated equianalgesic dose, with a maximum dose of 40 mg of methadone per day.[218] Restated for clarity, the calculated equianalgesic dose should be reduced by 90 percent in this population.[179] The reason for this is that analgesic dosing tables may overestimate the amount of methadone a patient should be converted to, and clinical experience suggests that patients on high daily oral morphine doses require much less conversion equivalent for methadone. If clinicians do not greatly diminish the equianalgesic dose calculated from the equianalgesic dosing tables, the result may be overdose and death. New for these guidelines is the recommendation to make phone assessments for adverse events within 3-5 days following methadone initiation or after any methadone dose increase.[218]

Methadone, like many medications, may prolong the QTc interval as measured on the ECG.[212,219,220] Because of this unique property, it is suggested that the clinician consider a baseline ECG for every patient started on methadone, and certainly obtain an ECG for patients at high risk for QTc prolongation. High-risk patients include those with factors for prolonged QTc, a history of prior ECG >450 milliseconds, or a history of prior ventricular dysrhythmia.[218] It is recommended to not use methadone if the QTc is >500 milliseconds, and consider an alternative opioid if the QTc is measured between 450 and 500 milliseconds.[218] Clinical use suggest that methadone appears to be associated with risk of increased QTc and malignant dysrhythmias such as Torsade de Pointes.[219] Finally, many commonly used medications may either increase or decrease the methadone level within an individual patient because of interaction with the cytochrome P450 enzyme in the liver, the enzyme responsible for methadone metabolism. The clinician must evaluate concomitant medications among each individual patient. In general, selective serotonin uptake inhibitors may increase plasma methadone level, and tricyclic antidepressants may prolong the QTc interval. Benzodiazepines have been associated with overdose involving methadone and thus clinicians should generally avoid the use of benzodiazepines in patients prescribed methadone for chronic pain.[221] Antibiotics may increase or decrease the effect of methadone, anticonvulsants such as carbamazepine decrease plasma methadone level, common antihistamines such as diphenhydramine may increase the sedative or respiratory depressive effects of methadone, and common HIV medications have a variable effect on methadone levels.[218] Other common agents such as cimetidine and grapefruit juice may increase the methadone level in individual patients.[218]

This article concerns the use of methadone for the treatment of patients with chronic pain, and the clinician must understand that the use of methadone to treat opioid detoxification or maintenance treatment of opioid addicted patients must be provided only in a federally certified opioid addiction treatment program.[222] The ongoing use of methadone to treat chronic pain in a pregnant woman should be carefully considered and the benefits and harms of methadone information provided to the patient, as well as the potential risk to the newborn for neonatal abstinence syndrome.[218] All patients should be

monitored to ensure compliance with methadone therapy. However, it should be noted that false-positive results for urine testing of methadone have been reported and attributable to metabolites of verapamil, diphenhydramine, and other agents.[223]

TRANSDERMAL FENTANYL

Fentanyl is a so-called designer opioid developed by Dr. Janssen in the early 1960s with a potency 100 times that of morphine.[224] For the next three decades, it was used mostly as an intraoperative analgesic and anesthetic, until the development of a TF patch 20 years ago.[225] The early use of fentanyl transdermal system concentrated on patients with cancer pain; however, the past decade has witnessed the successful use of TF for the treatment of CNMP. Fentanyl, normally a relatively fast onset and moderately rapid offset opioid when given by the intravenous route, has completely different pharmacokinetics when given by the TF route of administration.[225] Upon first application of TF, the minimum effective fentanyl concentration will take approximately 6 hours, and the maximum serum concentration peak will vary between 12 and 48 hours.[226] Thus, steady state is not reached until the third day of use and the patches should be rotated only at a 72-hour interval. The TF patches, available in doses of 12, 25, 50, 75, and 100 μg/h, are proportional to the surface area of the patch.[226] The clinician should also be aware that when the TF patch is removed (eg, for intolerable side effects), fentanyl will continue to be absorbed from the depo of drug in the skin, with ongoing absorption into the systemic circulation. Thus, if respiratory depression is experienced as a result of TF patch, simply removing the patch will not result in a meaningful decline in fentanyl plasma levels for perhaps 1-3 days. A significant advantage of a TF system is that opioid delivery is continuous and without the need for any special equipment.[225] In addition, the ability to maintain relatively stable plasma levels of fentanyl may result in more stable analgesia and perhaps less opioid-related side effects.[225]

A TF patch should only be used in the treatment of chronic pain and in those patients who are opioid tolerant. The patch should be removed from its protective pouch only at the time of application and should be applied to intact and nonirritated skin, typically on the chest, back, flank, or upper arm. The skin may be prepped by clipping hair, cleaning the area with water only, and patting the skin completely dry. Soaps, lotions, or alcohol should not be used to clean the skin area. The patch is rotated every 72 hours to a new and suitable skin location. Patches removed after 72 hours contain approximately 50 percent of the initial starting milligram dose of TF, and thus careful disposal of the TF system is mandatory. It is recommended that the patch be folded in half and flushed down a toilet. In addition, patients must be advised to not cut the patch, avoid exposure to heat (which may result in increased absorption and relative overdose), avoid contact of the patch with others, and to report any opioid-related side effects.

As the TF system may take 18-36 hours to reach steady state, upward titration of opioid using a TF patch should occur not more frequently than every 72 hours. Several estimates of conversion from oral morphine to TF have used ratios of 50-100 mg of oral morphine equivalent to a 25 μg/h TF patch.[225] However, there is great interindividual variability of plasma concentrations among patients, and therefore it is recommended to use 50 percent of the estimated dose following opioid conversion.

Side effects of TF include all the typical opioid-related side effects; however, the TF seems to be associated with fewer GI adverse events, particularly a reduced incidence of constipation.[225-229] A specific adverse reaction to the TF system includes skin hypersensitivity, reported by approximately 3 percent of patients.[227,230] The clearance of fentanyl occurs in the liver with the cytochrome CYP3A4.[227] Liver metabolism is thus influenced by liver disease and drug-drug interactions. It is recommended to use 50 percent of the estimated dose for patients with mild or moderate liver or renal impairment, and to avoid the use in severe hepatic or renal dysfunction.[231] The recommendation to limit TF use in patients with severe renal dysfunction likely relates to the possibility of sedation in such patients, as other authors have suggested that the use of TF is safe for use in patients with renal failure.[232]

As with all opioids, use of TF in the elderly should be approached with caution. A TF system has been used among children and found that younger children may require higher doses when compared with adults and may have fewer side effects when compared with other opioids.[6] Specific contraindications to the use of TF include patients who are not opioid tolerant, patients with acute or intermittent pain, the management of perioperative pain, the management of postoperative pain in the outpatient setting, and the management of mild pain.

Because fentanyl is metabolized by the CYP3A4 enzyme in the liver, plasma fentanyl levels following TF application may increase with CYP3A4 inhibitors (such as grapefruit juice) or may be decreased by CYP3A4 inducers (such as rifampin). Severe opioid-induced respiratory depression has been reported in at least two patients, one who died following the

addition of fluconazole to his TF analgesic, and a second patient with CNMP (long term on TF) following addition of clarithromycin to the TF system. The mechanism of action for both these cases is thought to be inhibition of CYP3A4 system which resulted in increased fentanyl blood levels.[233] In addition, unintentional misuse may lead to significant consequences including death.[234] Scenarios that expose patients to increase risk of overdose include patient confusion regarding dosage strengths, forgetting to remove the TF patch, transfer of the TF patch to another person, application of a second patch, fever, use of electric blankets, and intense physical exercise.[235,236] Also, there is one case report of a patient with cancer pain who experienced severe bradycardia within 36 hours of the TF application but without any other signs of opioid toxicity.[237]

OPANA ER

Opana® ER is an ER formulation of oxymorphone hydrochloride available in strength of 5, 7.5, 10, 15, 20, 30, and 40 mg tablets. The recommended dosing interval is every 12 hours; however, some patients may benefit from having a different dose given in the morning, compared with the evening dose. For example, a patient may require a lower evening dose to manage pain while sleeping and require a slightly higher dose in the morning to cope with increased activity in the daytime.

Oxymorphone has been available as an injectable format in America for more than six decades and was developed for an oral ER preparation approved in 2006.[238] Oxymorphone is a synthetic opioid that binds to the μ-opioid receptor but with little activity at the κ-opioid receptor.[239,240] Oxymorphone, as with many opioids, is metabolized in the liver by glucuronidation to oxymorphone-3-glucuronide as well as an active metabolite, 6-hydroxyoxymorphone.[239,241] Oxymorphone ER provides predictable, dose-proportional plasma concentration across the entire dosing range.[242] The time to maximum concentration of oxymorphone ER ranges from 2.5 to 4.0 hours, with steady state being achieved at 3 days following regular 12-hour daily dosing.[242] Oxymorphone metabolism occurs in the liver but without using the cytochrome P450 pathways, and thus there is no drug-drug interaction of the cytochrome enzyme which would affect oxymorphone metabolism.[242,243] However, because of extensive liver metabolism, oxymorphone is contraindicated in patients with moderate-to-severe hepatic impairment, and caution should be used in patients with renal disease as oxymorphone accumulates in renal failure.[240,244]

Oxymorphone is more potent than morphine, and an approximate oral dose ratio of 3:1 and 2:1 has been used to convert patients from morphine ER and oxycodone ER, respectively, to oxymorphone ER.[231,242,245,246] As with all opioid rotation calculations, approximately 50 percent of the calculated new opioid dose should be used as the starting dose for the new opioid medication.

The lowest Opana ER dose, 5 mg every 12 hours, should be the initial dose in opioid-naïve patients, as well as in patients with mild hepatic or renal impairment. Low initial doses with cautious individual dose titration should also be used in the elderly patient.[247] Patients are instructed to swallow the tablet whole, be educated that chewing, crushing, or dissolving the tablet may alter the absorption profile. Upward titration of opioid dose should occur in small doses of 5-10 mg, using a minimum of a 3- to 7-day interval.[231] Interestingly, food can increase the rate of absorption by as much as 50 percent; thus, the tablet should be taken either 1 hour before or 2 hours after a meal.[240] In addition, alcoholic beverages may cause "dose-dumping" when administered with oxymorphone ER and may result in the absorption of a potentially fatal dose of morphine.[231,242]

Typical opioid side effects (nausea, vomiting, constipation, sedation, and dry mouth) have been reported with all clinical trials to date, and usually mild in nature.[246] There is one published report of acute withdrawal from oxymorphone ER after a patient ingested a crushed capsule of morphine ER with sequestered naltrexone (Embeda).[71] This acute opioid withdrawal would be expected with any opioid, and not particular to oxymorphone. One specific safety concern related to Opana ER is to use caution in patients who have difficulty swallowing, or have an underlying GI disorder, may predispose them to obstruction.[231]

ZOHYDRO ER

Hydrocodone bitartrate has been known to have analgesic properties for more than one century.[248] Until 2012, hydrocodone had only been available in America in combination products with acetaminophen. Zohydro® ER provides an opioid analgesic with hydrocodone alone, thus eliminating any concern regarding acetaminophen toxicity to the liver. Although hydrocodone in combination with acetaminophen has been the most prescribed in America in recent years, there is a lack of good clinical trials regarding the drug.[249] Nonetheless, extensive and widespread physician experience with hydrocodone products confirm that it is an excellent opioid

analgesic with many effects and side effects similar to other opioid medications.[248]

Hydrocodone is an opioid analgesic and antitussive that binds to the μ-opioid receptor in the CNS.[248] Hydrocodone is a semisynthetic opioid similar in structure to morphine, differing from morphine at a single bond at carbons 7 and 8, and having a keto group at the 6 carbon.[250] Hydrocodone produces typical opioid effects and side effects with a relative analgesic potency of 0.6 when compared with oral morphine.[248] Hydrocodone ER is available in ER capsules at 10, 15, 20, 30, 40, and 50 mg dosage strength. The time to maximum plasma concentration following oral ingestion is approximately 5 hours, with blood levels decreasing slowly over 15 hours.[251] Therefore, the recommended dosing interval is every 12 hours. Initial dosing for the opioid-naïve patient should only be at 10 mg twice daily. Upward titration, if necessary, must use increments of 10 mg with a minimum of 3-7 days between dose increases. When opioid rotation occurs, a ratio of approximately 1.5:1 of oral morphine to oral hydrocodone is recommended. High-dose administration (single doses >40 mg or total daily dose >80 mg) should be given only to opioid-tolerant patients. Pharmacokinetic calculations, in addition to clearance measured among patients, suggest that hydrocodone concentrations will be increased in patients with decreased renal function.[251] Hydrocodone RT should be used with caution among patients with renal dysfunction, doses should be lowered, and upward titration using intervals greater than every 3 days.

Hydrocodone is metabolized in the liver via, in part, cytochrome P4502D6, producing the active metabolite, hydromorphone.[252] Some have argued that hydromorphone is a prodrug, similar to codeine as a prodrug for morphine, with the metabolite hydromorphone being the active product. However, the amount of hydromorphone produced from hydrocodone administration is typically very low, in the order of 3 percent excreted in the urine.[248,253] The primary metabolism of hydrocodone is via the liver enzyme cytochrome CYP3A4 which results in the active compound norhydrocodone.[254] Cytochrome CYP3A4 inducers (glucocorticoids, nafcillin, etc) may decrease levels of hydrocodone, while cytochrome CYP3A4 inhibitors (erythromycin, fluoxetine, grapefruit juice, etc) may result in increased hydrocodone plasma levels and increased opioid activity.

Hydrocodone ER has been found to be effective, at least over a 12-week randomized control trial for the management of low back pain.[255] Typical opioid side effects have been observed.[248,255] Patients are instructed to swallow the capsules whole without any chewing, crushing, as this alteration of the medication may result in elevated drug effect. In addition, coadministration of alcohol is contraindicated as alcohol may result in more than a twofold increase in the peak concentrations in hydrocodone ER.[254] The use of high-dose hydrocodone has rarely been associated with sensory neural hearing loss.[254,256]

NUCYNTA ER

Tapentadol is a unique opioid with two mechanisms of analgesic action. It was initially approved in America as an IR formulation and is now approved as an ER product, Nucynta® ER. Tapentadol was initially developed and synthesized as an analgesic with both μ-opioid agonist and norepinephrine reuptake inhibition mechanisms of analgesic action.[257] Increased noradrenaline levels at the spinal cord increase binding to α-2 agonist receptors with resultant analgesia. As tapentadol works with two mechanisms of analgesia, it is hoped that analgesia may be improved with a lower opioid dose, and that side effects would be less than traditional opioids.[257-260]

Tapentadol ER should be prescribed every 12 hours and exists as 50, 100, 150, 200, and 250 mg dose tablets. In healthy volunteers, maximum plasma concentrations were seen at 5 hours after dosing with a mean terminal half-life ranging from 4 to 6 hours. Concomitant administration of a high-fat meal slightly reduced the absorption of tapentadol.[261] For the opioid-naïve patient, the smallest dose (50 mg every 12 hours) should be given. Upward dose titration, to treat inadequate analgesia, should occur at a minimum of 3-day intervals and using a relatively small increase of 50 mg. A maximum total daily dose is 500 mg and patients are instructed to swallow the tablets whole without any chewing or crushing behavior. Patients are also instructed not to consume alcohol which may contribute to a rapid release of opioid and a potentially fatal overdose. The equipotent analgesic ratio of tapentadol with oral morphine has not been adequately established.[262] A clinical study among patients with cancer suggested a potency of tapentadol at approximately one third that of oral morphine; however, the limited number of patients in the study does not allow a definite conclusion to be drawn about the dose conversion ratio.[262,263]

Tapentadol, which exists as a single enantiomer, is metabolized almost entirely by glucuronidation in the liver.[257,264] Tapentadol has no active metabolites and does not appear to affect the QT ECG interval.[264] Both hepatic and renal impairment elevate

the plasma levels of tapentadol.[260,264] Thus, patients with severe renal hepatic impairment should avoid the use of tapentadol. In addition, elderly patients should be started on a lower dose range and with more cautious dose escalation. Patients with mild to moderate hepatic impairment may continue with tapentadol; however, the dosing interval should be extended to once per day, and with a maximum dose of 100 mg/d.

Side effects to tapentadol demonstrate the usual opioid-related side effect profile, with the exception that GI adverse events (nausea and vomiting, constipation) appear to be less in many clinical trials.[260,265-267] Because tapentadol inhibits the reuptake of norepinephrine, it should not be used by patients taking monoamine oxidase inhibitors.[8] Tapentadol is a very weak serotonin reuptake inhibitor, however, nonetheless, caution is advised when combining tapentadol ER with serotonergic agents.[264] There has been one reported case of angioedema related to tapentadol therapy.

EXALGO

Hydromorphone, a close analog of morphine, has a long history as a potent opioid analgesic for approximately 90 years.[268] The search for an ER hydromorphone preparation started almost 20 years ago and has evolved into a more stable and more tamper-resistant oral formulation.[269,270] Exalgo® is a once a day ER formulation of hydromorphone available as 8, 12, 16, or 32 mg dose tablets. The osmotic-controlled release oral delivery system used in the product delivers effective plasma concentrations over a 24-hour dosing interval.[271,272] Following dose ingestion, plasma concentrations rise and peak at 6-8 hours, being sustained until 18-24 hours postdosing.[272] The time to maximum concentration ranged from 12 to 16 hours and the terminal distribution half-life is approximately 11 hours.[272] Steady-state concentrations are reached after 3-4 days of dosing and provide therapeutic levels similar to IR hydromorphone, but with less fluctuation in peak and trough.[273-275]

It is very important that Exalgo be used for the treatment of opioid-tolerant patients only. As it is contraindicated for treatment of the opioid-naïve patient, all patients receiving Exalgo will have been rotated from their baseline opioid. An approximate opioid dose equivalent of 5:1 oral morphine to oral hydromorphone is typically used, although the clinician is advised to review the individual product information.[276] Following opioid rotation to hydromorphone ER, upward titration, if medically indicated, should proceed in increments of 4-8 mg with a minimum of 3-5 days between upward dose titration. As with other opioid products, the tablets are to be swallowed whole, never exposed to chewing or crushing.

Hydromorphone undergoes extensive glucuronide metabolism in the liver, with the major metabolite, hydromorphone-3-glucuronide capable of producing neurotoxic symptoms. Several minor metabolites are also produced, with minimal analgesic activity.[272] Moderate hepatic or renal impairment results in increased systemic exposure for patients.[272] Therefore, Exalgo should be used cautiously in patients with hepatic or renal impairment. Specific recommendations are to reduce the dose to 25 percent of what would normally be prescribed, for patients with moderate hepatic impairment. For patients with moderate renal impairment, the hydromorphone ER dose should be reduced by 50 percent, and further reduced for patients with severe renal impairment to 25 percent of the normal dose prescribed for a patient with normal renal function. Studies have shown that the bioavailability of hydromorphone is not affected by food.[277]

Side effects include typical opioid-related side effects. Of note, the product contains a metabisulfite such that patients with a sulfite allergy should not be exposed to Exalgo for concern of an allergic reaction. Concomitant use of hydromorphone ER with CNS depressants such as benzodiazepines or alcohol may result in significant overdose and respiratory depression.[273]

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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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Patient Counseling Document (PCD)

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics
Patient Name:
The DOs and DON'Ts of Extended-Release / Long - Acting Opioid Analgesics
DO: • Read the **Medication Guide** • Take your medicine exactly as prescribed • Store your medicine away from children and in a safe place • Flush unused medicine down the toilet • Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
Call 911 or your local emergency service right away if: • You take too much medicine • You have trouble breathing, or shortness of breath • A child has taken this medicine
Talk to your healthcare provider: • If the dose you are taking does not control your pain • About any side effects you may be having • About all the medicines you take, including over-the-counter medicines, vitamins, and dietary supplements
DON'T: • **Do not** give your medicine to others • **Do not** take medicine unless it was prescribed for you • **Do not** stop taking your medicine without talking to your healthcare provider • **Do not** cut, break, chew, crush, dissolve, snort, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider. • **Do not** drink alcohol while taking this medicine
For additional information on your medicine go to: **dailymed.nlm.nih.gov**

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics
Patient Name:
Patient Specific Information
Take this card with you every time you see your healthcare provider and tell him/her: • Your complete medical and family history, including any history of substance abuse or mental illness • If you are pregnant or are planning to become pregnant • The cause, severity, and nature of your pain • Your treatment goals • All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements • Any side effects you may be having **Take your opioid pain medicine exactly as prescribed by your healthcare provider.**

Source: FDA Opioid REMS Blueprint, Reference ID: 3612128
http://www.er-la-opioidrems.com/IwgUI/rems/pdf/patient_counseling_document.pdf

This form is available in pads of 25 sheets, printed two sides.
Visit: *www.opioidmanagement.com/rems* for details