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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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