ER/LA OPIOID REMS SUPPLEMENT 3

DOI:10.5055/jom.2014.0230

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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