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Oxycodone/naloxone (Targiniq ER®): A new option for chronic pain control

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Chronic pain affects an estimated 100 million adults in the United States.[1] In 2010, the annual economic cost of chronic pain was an estimated $600 billion dollars in the U.S.[1] The healthcare costs and lost productivity associated with chronic pain represent a significant burden on the healthcare system. Commonly prescribed options for chronic pain management include opioid analgesics: over 259 million prescriptions for these drugs were written in the United States in 2012.[2] These medications are effective analgesics, but they have been associated with abuse and misuse. In 2011, over 400,000 emergency room visits were associated with nonmedical use of opioids and 74% of pharmaceutical overdose deaths involved opioid analgesics.[3,4] Prescribers may be hesitant to prescribe opioid analgesics for pain control due to the potential of abuse or diversion.[5]

On July 23, 2014, a new fixed-dose combination, oxycodone/naloxone (Targiniq ER®), was given an approved indication by the FDA for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[6] This new combination product consists of oxycodone, a full μ-opioid agonist, and naloxone, an opioid receptor antagonist, that is intended to provide analgesia while limiting opioid abuse. This article will review the pharmacology, efficacy, adverse reactions, and dosing of oxycodone/naloxone for the treatment of chronic pain.

Pharmacology

Oxycodone is a full opioid agonist that is relatively selective for the μ-opioid receptor, but can bind to other opioid receptors at high doses. The exact mechanism of action by which oxycodone produces analgesia is unknown, but opioid receptors throughout the brain and spinal cord are thought to be involved with the analgesic response. Oxycodone is rapidly absorbed after oral ingestion with a median time to maximal absorption (T_{max}) of 3 to 4 hours and 60% to 87% oral bioavailability.[6] Oxycodone is metabolized by CYP3A4/5 and CYP2D6 to noroxycodone, oxymorphone, and noroxymorphone. These metabolites are present in the blood in lower concentrations than the parent drug. Noroxycodone and noroxymorphone are the major circulating metabolites. Noroxycodone exhibits very weak analgesic potency compared to oxycodone.[7] Noroxymorphone is active at μ-opioid receptors but does not easily cross the blood brain barrier.[8] Oxycodone and its metabolites reach steady state plasma concentrations after ~2 days.[6]

Naloxone is a μ-, κ-, and δ-opioid receptor antagonist that competitively binds to opioid receptors in the brain, spinal cord, and peripheral organs. The oral bioavailability of naloxone is <2%. However, the bioavailability is approximately 31% when naloxone is crushed and administered intranasally. Naloxone is metabolized by UGT1A8 and UGT2B7 to 6β-naloxol, naloxone-3β-glucuronide and 6β-naloxol-3β-glucuronide.[6] These metabolites are inactive, but are present in higher concentrations than the parent drug due to the low plasma naloxone concentrations after oral administration.[6,9] Naloxone and its metabolites reach steady state plasma concentrations after approximately 2 days.[4] The pharmacokinetics of oxycodone/naloxone are summarized in Table 1.

Some noted drug-drug interactions include an interaction between oxycodone and the CYP3A4 inhibitor ketoconazole, whereby oxycodone AUC is increased by 170% and C_{max} is increased by 100%. Concomitant use of oxycodone and the CYP3A4 inducer rifampin decreases oxycodone AUC by 86% and Cmax by 63%.[6] Although clinical studies with other drugs have not been completed, other

Table 1 | Pharmacokinetics of oxycodone/naloxone.

Parameter	Oxycodone	Naloxone
C_{max}[a]	12.1 ng/mL	0.0306 ng/mL
AUC[a]	130 ng•hr/mL	0.136 ng•hr/mL
V_d	245 L	348 L
Metabolism	CYP3A4, 3A5, 2D6	UGT1A8, UGT2B7
Clearance	3.66 to 4.37 L/hour	7.85 to 31.9 L/hour

AUC = area under the curve; **C_{max}** = maximum concentration; **V_d** = volume of distribution.
[a]After a single oxycodone/naloxone 10 mg/5 mg dose.

CYP3A4 inhibitors likely also increase oxycodone plasma concentrations, while other CYP3A4 inducers likely decrease oxycodone plasma concentrations.[7] Naloxone drug interactions have not been studied, but are not likely to be significant due to the low oral bioavailability of naloxone.[6]

Clinical Trials

The safety and efficacy of oxycodone/naloxone was evaluated in a randomized, double-blind, placebo-controlled, multicenter phase 3 clinical trial.[10] This study has yet to be published but results have been made available. The study enrolled 1095 patients over the age of 18 years who suffered from moderate-to-severe chronic low back pain for at least 3 months prior to the study screening period.[6] These patients must have been on a stable opioid analgesic regimen with a total average daily dose of 20 mg to 160 mg of morphine or its equivalent.[10] Study participants were converted from their previous opioid analgesic regimen to an equianalgesic dose of oxycodone/naloxone or placebo. The dose of oxycodone/naloxone could be titrated up to a maximum of 40/20 mg twice daily every 1-2 days or titrated down at any time.[6] During the 4-week titration period, subjects were allowed to take up to 8 capsules per day of immediate-release oxycodone 5 mg for supplemental low back pain relief.[6] Six hundred patients completed the titration period, achieving analgesia and tolerating the study drugs; these patients were then randomly assigned to either the final titrated dose of oxycodone/naloxone or placebo for 12 weeks of double-blind treatment.[6]

The primary outcome in the study was average pain over the last 24 hours, measured at week 12 of the double-blind period. The pain outcome was measured on an 11-point scale where 0 was "no pain" and 10 was "pain as bad as you can imagine."[10] Secondary outcomes included sleep disturbance at weeks 4, 8, and 12, and patient global impression of change at week 12. Of the 600 subjects who entered the randomized double-blind treatment phase, average age was 53.2 years, 56% were women, and 77% were white. The baseline characteristics were similar between the treatment and placebo groups with regards to age, sex, and race.[10]

Table 2 | Adverse effects reported in ≥2% of subjects during double-blind period.

Adverse Effect	Oxycodone/naloxone (N=298)	Placebo (N=302)
Nausea	8%	5%
Headache	3%	3%
Constipation	3%	1%
Abdominal Pain	3%	2%
Vomiting	5%	2%
Pruritus	2%	1%
Anxiety	3%	0%
Drug Withdrawal	3%	2%
Insomnia	2%	1%
Back Pain	3%	1%

The mean baseline pain scores were 7.0 in the oxycodone/naloxone group and 7.1 in the placebo group at baseline. The mean pain scores at week 12 of the double-blind period were significantly lower in the oxycodone/naloxone group (3.86) than in the placebo group (4.32), for a between group difference of 0.45 (95% CI 0.13 – 0.77). However, the clinical significance of this difference is unclear since it was small relative to the full range of the 11-point scale and the comparison group was treated with placebo. Sleep disturbance scores at week 12 were also lower in the oxycodone/naloxone group (31.1) compared to the placebo group (36.4; p=0.019), as were patient global impression of change scores (153 in oxycodone/naloxone group vs. 109 in the placebo group; p=0.0002).

Studies evaluating the abuse deterrence properties of oxycodone/naloxone were also conducted. In a randomized, double-blind, controlled, 3-period crossover study, 23 non-dependent opioid abusers were administered, intranasally, finely crushed tablets of oxycodone/naloxone 40 mg/20 mg, oxycodone 40 mg powder, and placebo treatments.[6] Participants were surveyed about drug-liking on a scale of 0 to 100, where 0 represented maximum disliking of the drug, 50 represented a neutral response, and 100 represented maximum liking of the drug. Participants were also surveyed about if they would take the drug again on a scale of 0 to 100:0 represented the strongest negative response and 100 represents the strongest positive response.[6] Intranasal administration of crushed oxycodone/naloxone was associated with lower maximum drug liking scores (59.1 for oxycodone/naloxone vs. 94.8 for powdered oxycodone) and lower maximum taking drug again scores (42.6 for oxycodone/naloxone vs. 93.6 for powdered oxycodone).[6]

Adverse Events

The adverse effects associated with oxycodone/naloxone are summarized in Table 2. Although not observed in the phase 3 trial of oxycodone/naloxone, the individual components may cause respiratory depression or arrest, apnea, circulatory depression, hypotension, or shock.[6]

Oxycodone/naloxone is classified as Pregnancy Category C based on data from the individual components. Prolonged use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome.[4] The safety and efficacy of oxycodone/naloxone has not been evaluated in patients under aged <18 years. In a study to assess age effects of oxycodone/naloxone, patients aged >65 years demonstrated higher steady state oxycodone and naloxone AUCs than younger patients. Therefore, oxycodone/naloxone use should be monitored carefully in those aged >65 years.[6]

Dosing and Administration

Oxycodone/naloxone is intended to be taken orally and is available in three tablet strengths with a 2:1 ratio of oxycodone to naloxone: 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg. For opioid-naïve patients, initial dosing recom-

Table 3 | Equianalgesic opioid doses.

Current Oral Opioid	Conversion Factor[a]
Morphine	1
Codeine	0.3
Hydrocodone	1.8
Hydromorphone	8
Methadone	3
Oxycodone	2
Oxymorphone	4
Tramadol	-[b]
Tapentadol	0.3

[a]Multiply dose of current oral opioid by the conversion factor to determine the equivalent morphine dose. Use Table 4 to determine initial oxycodone/naloxone dose based on the equivalent morphine dose.

[b]Patients on tramadol should be initiated at a oxycodone/naloxone dose of 10 mg/5 mg every 12 hours, regardless of the tramadol dose.

mendations are 10 mg/5 mg orally every 12 hours. For non-opioid-naïve patients, the dosing regimen should be individualized based on the patient's previous analgesic use. Specifically, equianalgesic dosing conversions should be applied to determine morphine equivalents (Table 3); the total daily morphine equivalents can then be used to identify the recommended oxycodone/naloxone starting dose (Table 4). The dose should be adjusted thereafter, until an appropriate balance between analgesia and adverse effects is achieved.[6]

Plasma concentrations of both oxycodone and naloxone are elevated in patients with hepatic impairment and in patients with renal impairment. In patients with mild hepatic impairment, the initial dose should be reduced to between one third and one half of the normal dose (i.e., a 50% to 67% reduction from standard dosing); patients should also be monitored for signs of respiratory depression due to elevated oxycodone levels, and for signs of withdrawal due to elevated naloxone levels. This drug is contraindicated in patients with moderate-to-severe hepatic impairment.

In patients with renal impairment, the initial dose should be reduced to one half of the usual dose with close monitoring for signs of respiratory depression or withdrawal. Alternative products without naloxone should be considered in patients with severe renal impairment due to an increased risk of withdrawal.[6]

Summary

Oxycodone/naloxone, marketed under the trade name Targiniq ER®, is a combination opioid agonist/opioid antagonist granted an FDA-approved indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The addition of naloxone is intended to deter crushing and snorting or injecting these tablets. In a phase 3 trial, oxycodone/naloxone was shown to be more effective than placebo at controlling low back pain. Adverse effects associated with oxycodone/naloxone are primarily gastrointestinal (i.e., nausea, constipation) or CNS-related. The dosing of this medication should be individualized based upon patient factors such as opioid tolerance, renal function, hepatic function, and age. This medication provides a unique alternative for the management of chronic pain, particularly in patients at risk for abusing oral opioid analgesics.

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Table 4 | Initial oxycodone/naloxone dose in non-opioid-naïve patients based on total daily morphine equivalent dosing.

Equivalent Daily Oral Morphine Dose[a]	Recommended Oxycodone/naloxone Starting Dose
70 to <110 mg	20 mg/10 mg every 12 hours (i.e., 40 mg oxycodone daily)
110 to <150 mg	30 mg/15 mg every 12 hours (i.e., 60 mg oxycodone daily)
150 to 160 mg	40 mg/20 mg every 12 hours (i.e., 80 mg oxycodone daily)

[a]Daily oral morphine equivalents can be derived from the conversion factors and equation summarized in Table 3.

Personalized Medicine Corner

My patient complains that "opioids are not working." Should I consider a genetic reason?

The analgesic effects of some opioids result from metabolism through the cytochrome P450 (CYP450) enzyme system. For example, codeine by itself is basically inactive. Unless the CYP2D6 enzyme converts codeine to morphine, there is little to no pain relieving activity. The gene that encodes for CYP2D6 is highly variable and leads to a wide range of enzyme expression. This genetic variability can contribute to clinical differences in the effects of codeine and some other opioids.

In the case of codeine, approximately 5% to 10% of individuals have no CYP2D6 activity. These "poor metabolizers" will not metabolize codeine into morphine and therefore have insufficient pain relief from codeine-containing analgesics. At the other end of the spectrum, another 5% of patients have too much CYP2D6 activity. These "ultrarapid metabolizers" quickly convert codeine to morphine, which can lead to toxic morphine levels with usual codeine doses. There have been reports of children and adults who developed serious adverse events including death after taking usual codeine doses. These individuals were later found to be ultrarapid metabolizers. A 2006 case describes the death of a breastfed infant of a mother taking codeine who was an ultrarapid metabolizer.[1] In 2013, the FDA released a safety communication regarding the use of codeine in children to help avoid toxicity.[2]

Tramadol also depends on CYP2D6 for conversion to its primary active form with similar clinical effects in poor and ultrarapid metabolizers. Hydrocodone and oxycodone are also metabolized to more active forms by CYP2D6, but the impact of genetic variability on these agents is less clear.

Based on this information, could genetic variability in CYP2D6 be affecting pain control in your patient? It depends. Codeine and tramadol have the most evidence supporting clinically relevant effects caused by CYP2D6 genetic variability. With these agents, approximately 10% to 15% of patients are at risk for getting too much or too little of the drug based on their CYP2D6 activity. This is also a possibility with hydrocodone and oxycodone, but the evidence is not as strong for these agents.

The question at this time is when should one order a pharmacogenetic test? Clinicians can consider pharmacogenetic testing if a patient complains of inadequate pain relief, especially with codeine and tramadol.

Pharmacogenetic testing is offered by a number of commercial laboratories. There are clinical guidelines that can help with interpreting and applying test results.[3] Guidelines advise against using codeine or tramadol in poor or ultrarapid metabolizers. Oxycodone and hydrocodone may not be good alternatives in these patients. A nonopioid (i.e., acetaminophen or an NSAID) may be best for mild pain in CYP2D6 poor or ultrarapid metabolizers; morphine or other opioids not affected by CYP2D6 variability are preferred for moderate-to-severe pain.

Codeine use has decreased in recent years. However there were still nearly 2 million prescriptions written for codeine-containing drugs in 2011, and many expect these numbers to increase with the recent hydrocodone's switch to a Schedule II.

Want to know more about ordering and reimbursement for CYP2D6 testing? Email UF Health Personalized Medicine Program at PMP-HELP@ctsi.ufl.edu. You can also request our *CYP2D6-Opioids Clinical Summary* for a short review of the most relevant studies in this area.

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