Prepared By: Amber Schilling, PharmD

Date:	September 2, 20XX
Requestor's Name:	Dr. XXX, PharmD
Request Classification:	Therapy Evaluation
Verbatim Request:	What is the pain-relieving efficacy of oxycodone compared to hydrocodone?
Interpreted / Detailed Request:	Hydrocodone was recently changed from schedule C-III to C-II. What evidence exists, if any, for keeping both hydrocodone and oxycodone on formulary?
Notes / Search Terms Used:	[PubMed]: oxycodone hydrocodone comparison, oxycodone hydrocodone pain efficacy, oxycodone hydrocodone pain comparison, oxycodone hydrocodone compare, oxycodone hydrocodone analgesia

Response to Question:

- **Pertinent Background Information**: On August 22, 2014 the DEA ruled to move all hydrocodone-combination products from C-III to C-II status (single entity hydrocodone products have been listed as C-II since 1971; Zohydro ER was FDA approved in October 2013 [launched on March 2014] and is currently the only single-entity hydrocodone product available in the US). This change will be effective October 6, 2014.[1] Handling of schedule II drugs requires stricter procedures with regard to prescribing, dispensing, storage, destruction, and record-keeping.

- **Pertinent Patient Factors**: n/a

- **Pertinent Disease Factors**: n/a

- **Pertinent Medication Factors**: Oxycodone and hydrocodone are both ketone derivatives of codeine and differ in chemical structure by the presence of only one –OH group (oxycodone contains a 14-beta-hydroxy whereas hydrocodone contains a hydrogen in that position; see chemical structures below). Both have FDA labeled indications for treatment of moderate to severe pain, are administered PO, have comparable onsets of action (10-20 mins) as well as duration of analgesia (approx. 5-6 hrs), and minimal protein binding (45%). Both are dosed every 4-6 hours. One difference between the two is that hydrocodone-APAP carries FDA approval for use in pediatrics, while oxycodone does not. Both hydrocodone and oxycodone are Pregnancy Category C (risk of harm to fetus cannot be ruled out) and are excreted into breast milk in lactating women. Both come solid and liquid dosage forms. See **Table 1**.

  There are limited studies available that have examined the comparative pain efficacy of hydrocodone versus oxycodone. Three studies that are representative of the literature available on this topic have been reviewed in **Table 2**.

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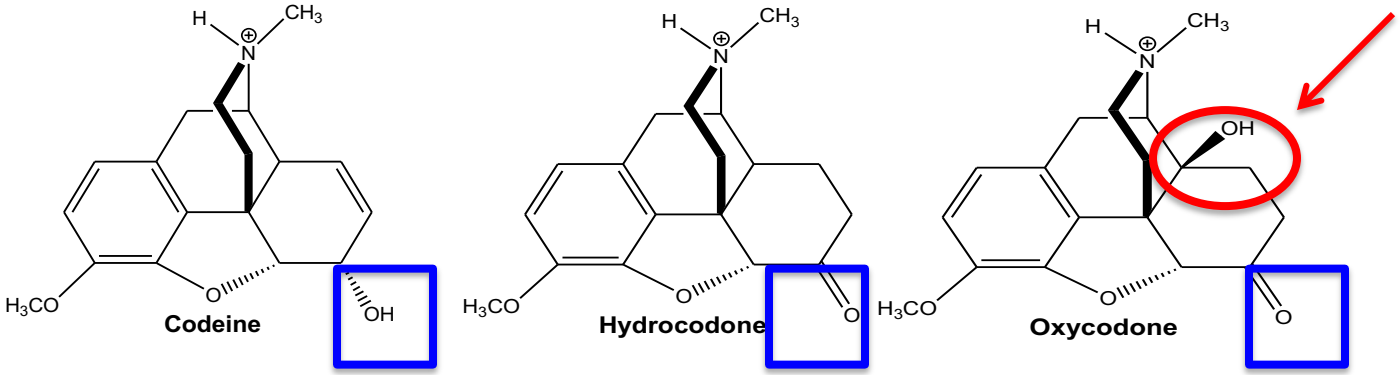

Chemical Structures compliments of Dr. Michael L. Adams, Campbell University College of Pharmacy

Table 1. Selected characteristics of hydrocodone and oxycodone.

Opioid	*Available Products and Dosage Forms*	*Dosing Frequency*	*FDA Labeled Indication*	*PK data*	*Metabolism*	*FDA approved for Pediatric use?*	*Pregnancy Category*	*Lactation*	*Max Daily Dose*
Hydrocodone (as Bitartrate salt)	**Hydrocodone-APAP products:** Vicodin Norco Lortab Lorcet Anexsia (Tablet, Elixir, Soln) • 2.5-325mg • 5-300mg • 5-325mg • 7.5-300mg • 7.5-325mg • 10-300mg • 10-325mg **Hydrocodone-Ibuprofen products:** Vicoprofen Reprexain (Tablets) • 2.5-200mg • 5-200mg • 7.5-200mg • 10-200mg **Hydrocodone-only**	HYD-APAP or HY-IBU • q4-6 hrs Zohydro ER • q12hrs	Moderate-severe pain	Onset of action: 10-20 mins Time to Peak (plasma): 1.3-1.7 hrs[3,5] Duration: 4-8 hrs Half-life (elim): 3.3-4.4 hrs Protein Binding: 19-45% Bioavailability: ? Zohydro ER Time to Peak: 5 hrs (incr w/ high-fat meal) Half-life (elim.): 8 hrs	(Hydrocodone) 2D6 3A4 O-demethylation to hydromorphone (2D6) → major, active metabolite (higher binding affinity to mu-opioid receptors) *Poor metabolizers will have decreased conc. *Extensive metabolizers will have increased conc. N-demethylation to norhydrocodone (3A4) → major metabolite 40%occurs via non-CYP pathways	Yes Age 2 and older: oral soln	C	Enters breast milk	HDY: 60 mg APAP: 4g

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Opioid	*Available Products and Dosage Forms*	*Dosing Frequency*	*FDA Labeled Indication*	*PK data*	*Metabolism*	*FDA approved for Pediatric use?*	*Pregnancy Category*	*Lactation*	*Max Daily Dose*
	products: Zohydro ER (Capsules) • 10, 15, 20, 30, 40, 50 mg								
Oxycodone	**Oxycodone-APAP products:** Percocet Endocet Roxicet Primlev Xartemis (XR) (Tablets, Soln) • 2.5-325mg • 5-300mg • 5-325mg • 7.5-300mg • 7.5-325mg • 10-300mg • 10-325mg **Oxycodone-Ibuprofen products:** Generic (Tablets) • 5-400mg **Oxycodone-only products:** Roxicondone (IR) (Capsule, Tablet, Soln) • 5mg • 5mg/5mL • 10mg • 15mg • 20mg • 30mg • 100mg/5mL OxyCONTIN (CR) (Tablet) • 10, 15, 20, 30, 40, 60, 80 mg	IR: q4-6 hrs Oxycontin: q12 hrs	Moderate-severe pain	<u>For IR products:</u> Onset of action: 10-15 mins Time to Peak (plasma): 1.2-1.9hrs Duration: 3-6 hrs Half-life (elim.): 2-4 hrs Protein binding: 45% Bioavailability: 60-87% Vd: 2.6L/kg <u>For CR products:</u> Duration: 12 hrs Half-life (elim.): 5 hrs Time to peak (plasma): 4-5 hrs	(Oxycodone) 3A4 2D6 Noroxycodone (active, major metabolite) Oxymorphone (active, minor metabolite)	No (unlabeled use)	C	Enters breast milk	OXY: ?

Table 2. Studies relating to comparative efficacies of hydrocodone versus oxycodone

What was compared	*Study Type*	*Study Population*	*Sample Size*	*Agents and Doses*	*Duration*	*Study Endpoints*	*Items Measured*	*Results / Conclusions Reached*	*Notes / Issues*
Psychopharmacological profiles Zacny et al (2009)	Randomized Placebo-controlled Double-blind Cross-over (pts served as own controls)	Non-drug abusing volunteers Mean age: 24+/-3yrs	20 total • 10 male • 10 female	Oxycodone/APAP (PO capsule) • 10/487mg • 20/975mg Hydrocodone/APAP (PO, capsule) • 15/487mg • 30/975mg Doses chosen based on degree of miosis ("equi-miotic" dosing) • surrogate marker for plasma concentrations (standard measure in abuse testing)	7 sessions 1 week apart Each session lasted 5.75 hrs	None specifically stated	Tests performed before med ingestion (baseline), and then at every 30 mins or 1 hr, depending on the test Subjective effects (scale of 1 to 10) • extent subject felt various sensations (difficultly concentrating, dizzy, dreamy, dysphoria, drug high, heavy or sluggish, lightheaded, nauseated, sleepy, tingling, etc.) • dry mouth, flushing, itching, sweating, etc. • like / dislike of drug feeling • how much would want to take the drug again Psychomotor/Cognitive • logical reasoning test • eye-hand coordination • auditory rxn time • recall of 15-word list Physiological effects: • HR • BP • O2 sats • RR • Pupil size • Exophoria (eye drift outward)	Dose required to produce equal degree of miosis 1.5 times higher for hydro compared to oxy Equi-miotic doses produced similar psychopharmacological / pharmacodynamic effects No concluding statement could be made about one agent having higher abuse potential over the other	Issues: -No primary / secondary outcomes specifically defined -Unclear whether the study was adequately powered (no overall differences found, so this must be considered as a possibility)

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What was compared	*Study Type*	*Study Population*	*Sample Size*	*Agents and Doses*	*Duration*	*Study Endpoints*	*Items Measured*	*Results / Conclusions Reached*	*Notes / Issues*
Analgesic efficacy (Marco et al 2005)	Randomized Prospective Double-blind 80% power (26 pts needed per group to detect a 2-point pain scale difference → 2 point different considered a priori to be clinically signif.) alpha 5%	Patients with acute fractures reporting to ED Age 12 and older (mean age = 36 yo) No statistically significant difference btw tx groups WRT baseline pain scores or fx type	67 total • 35 oxy • 32 hydro • (met power criteria)	Oxycodone/APAP (PO, liquid) • 5/325mg Hydrocodone/APAP (PO, liquid) • 5/325mg	34 months	Primary outcome: • pain scores at 30 min, 60 min post medication	Pain ratings at baseline, 30 min, 60 min (scale of 1 to 10) Vital signs at baseline, 30 min, 60 min Side effects (presence and severity) at any time while in ED or within next 2 days • n, v • itching • drowsiness • constipation	Raw pain scores at 30 min were not statistically different btw OXY and HYD Raw pain scores at 60 mins not statistically different; however, not enough subjects included in HYD to reach statistical power (request for early discharge) CHANGE in pain score at 30 mins for OXY group WAS statistically significant • Δ3.7 vs 2.5, 95% CI 0.1-2.3 (CI does not include 0 so statistically signif.) • Could be due to slightly higher initial pain score at baseline in this group (mean 7.7 OXY vs 7.1 HYD) and / or OXY being slightly more potent CHANGE in HR at 30 mins statistically significant (more lowering in OXY group), perhaps due to higher pain at baseline in this group and slightly higher HR 2/2 pain RR significantly lower in OXY group at 60 mins No other vital signs at 60 mins showed	Many subgroup analyses performed; investigators did not specify whether alpha spending functions were used to control

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								significance, but not enough subjects in HYD group at 60 mins to reach statistical power (request for early discharge) No statistical differences in side effects between OXY and HYD, but not enough patients queried to reach statistical power HYD had significantly more constipation than OXY (all other SE showed no difference between groups)	
Pain efficacy (Litowski et al 2005)	Randomized Double-blind Placebo-controlled Parallel Multicenter 86% power alpha 5% (2-sided) 60 patients needed / study group	Patients with moderate-severe pain after surgery to remove impacted wisdom teeth Mean age=19 yo	248 analyzed in the ITT population • 62 OXY/IBU • 61 OXY/APAP • 63 HYD/APAP (1 withdrew) • 63 Placebo	Oxycodone-APAP • 5/325mg Oxycodone-Ibuprofen • 5/400mg Hydrocodone-APAP • 7.5/325mg Rescue: Ibuprofen		Primary outcomes: • Total pain relief through 6hr after dosing • Sum of pain intensity differences through 6hr after dosing • Adverse Events Secondary efficacy outcomes: • Total pain relief through 3hr after dosing • Sum of pain intensity differences through 3hr after dosing • Peak pain relief • Peak pain intensity difference • Time to onset of pain relief	Patient's perception of pain intensity and pain relief (used Likert-type scales)	Primary outcomes: • OXY/IBU provided significantly greater analgesia compared to all other agents studied for both primary outcomes ($p<0.001$ in all cases) • OXY/APAP and HYD/APAP results similar, but no statistical data provided comparing the two head-to-head (only compared to placebo) Rates of n/v significantly lower with OXY/IBU compared to OXY/APAP Rates of n/v similar	Study compared each agent to placebo and OXY/IBU to other agents, but did not provide statistical data comparing OXY/APAP to HYD/APAP → impossible to tell if it was the oxycodone providing the better pain relief, the ibuprofen, or synergy between the two Ibuprofen may have contributed to

What was compared	*Study Type*	*Study Population*	*Sample Size*	*Agents and Doses*	*Duration*	*Study Endpoints*	*Items Measured*	*Results / Conclusions Reached*	*Notes / Issues*
						• Time to use of rescue medication • Proportion of pts reporting pain half-gone • Patient's global evaluation of study drug		when between OXY/APAP and HYD/APAP groups Secondary outcomes: OXY/IBU significantly more effective compared with all other agents on all secondary endpoints ($p<0.001$)	greater analgesic efficacy and also has anti-inflammatory properties (which may have been important in this patient population) Less n/v with OXY/IBU group may have been due to opioids causing emesis partially through prostaglandin production in the CNS (ibuprofen would have inhibited this)

Other studies

- Susce et al (2006)
  - Case report of a CYP2D6 poor metabolizer; patient was s/p hip surgery; did not tolerate oxycodone well, but had a much better response to hydrocodone
- Palangio et al (2000)
  - Randomized, double-blind, parallel-group, single-dose, active-comparator, placebo-controlled study; hydrocodone-ibuprofen (7.5-200mg) vs oxycodone-APAP (5-325mg); dose was 2 tablets; analgesia assessed over 8hr; gynecological patients; no differences in analgesia found between treatment groups
- Palangio et al (2002)
  - Multi-center, randomized, double-blind, parallel-group, repeat-dose study; analgesia assessed over 8days; hydrocodone-ibuprofen (7.5-200mg) vs oxycodone-APAP (5-325mg); moderate or severe acute lower back pain patients; no differences in analgesia or adverse effects found between treatment groups
- Solomon et al (2010)
  - Propensity-matched cohort, retrospective chart review; Medicare patients; all-cause mortality greater in patients taking oxycodone or codeine compared to hydrocodone

- **Analysis and Synthesis:** Studies comparing the analgesic efficacy of hydrocodone-APAP to oxycodone-APAP are limited. The ones that do exist suggest that there is either no difference or only a slight difference. It could be argued that since there is no clear advantage with respect to analgesia between the two agents that hydrocodone should be dropped from the Hospital X Formulary. In one study, the hydrocodone agent was found to be associated with more constipation compared to

oxycodone, so this would be another reason to consider discontinuing it from formulary. However, hydrocodone has an FDA-approved indication for the pediatric population, whereas oxycodone does not and is used off-label in pediatrics. One study comparing oxycodone-ibuprofen to hydrocodone-APAP and to oxycodone-APAP found that OXY-IBU provided better pain relief than the other two agents, but it is hard to say how much ibuprofen played a role in the increase in pain efficacy, as statistical data comparing the acetaminophen products were not provided (but seemed similar when comparing the raw data). Two other studies comparing hydrocodone-ibuprofen to oxycodone-APAP found no difference; but again, it is hard to say if ibuprofen is providing synergy to hydrocodone's effects when compared to the oxycodone-APAP product. Therefore, until robust studies comparing the two agents are published and one can definitively claim that oxycodone provides more analgesia than hydrocodone, it is recommended to keep the hydrocodone-containing products on Hospital X formulary at this time.

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