

WYOMING DRUG UTILIZATION REVIEW



Edited by
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Efficacy and Safety of High Dose Opioids

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There is a large amount of evidence on the efficacy of opioids for any number of chronic pain conditions. On the other hand, long-term studies are rare. Numerous manufacturers currently state that there is no opioid ceiling. Opioid doses above 180 mg per day of morphine equivalent have never been assessed for long-term efficacy or safety. Efficacy studies have included only a rare patient in this dose range. Safety studies have never been published for high dose opioids. Table 1 lists doses of opioids considered to be high.

There is good evidence from both animal and human studies that high dose opioids change pain perception, induce numerous hormonal changes, and are possibly immunosuppressive. When high dose opioids are given, pain perception changes through an unknown mechanism, although numerous mechanisms have been postulated. These changes include increasing hyperalgesia and allodynia.^{1,2,3,4,5}

Hormonal changes appear to be mediated through the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis. Specific changes that have been identified include: Increased prolactin, decreased luteinizing hormone, decreased cortisol, decreased follicle-stimulating hormone, decreased testosterone, and decreased estrogen levels.^{6,7,8,9} In addition, there is evidence in animal

studies that high dose opioids affect growth hormone.¹⁰

There is good evidence that high dose opioids are immunosuppressive in HIV infected patients.¹¹

With no evidence that reveals a benefit to high-dose opioids and evidence that it may be harmful to use high-dose opioids, limiting narcotic doses to less than 180 mg morphine equivalent per day may be reasonable. Current information on narcotic equivalency and dosing is included in this newsletter for you review (Converting from One Opioid to Another, Kendra Grande, RPh).

If you need more information or would like to comment on this information, please contact us at: Wyoming DUR, University of Wyoming School of Pharmacy, Dept. 3375, 1000 E. University Ave., Laramie, WY 82071. If you are interested in obtaining more information on this subject, a review article was published in the New England Journal of Medicine 2003.¹²

References

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Converting from One Opioid to Another

Kendra Grande, RPh

Conversion from one oral opioid to another requires diligence. The equi-analgesic dose must be calculated for the new drug. When calculating the starting dose of the new drug, first calculate the total daily dose of the old drug. Do not forget to include “rescue” or “as needed” doses. Table 2 gives a stepped approach for calculating equi-analgesic doses. Table 3 lists known equi-analgesic doses from published studies along with notes and limitations. This table can be used to find the equi-analgesic dose for the

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Morphine	>180mg/day
Oxycodone	>180mg/day
Fentanyl transdermal	>100mcg/hr
Methadone	>60mg/day
Levorphanol	>24mg/day
Hydromorphone	>45mg/day
Actiq	>1600mcg/day

Table 1: High Dose Narcotics

Medicaid/Medicare Dual Eligible Transition to Medicare Part D

From the Wyoming Department of Health perspective, the transition of the dual eligibles to Medicare Part D went fairly well. The Office of Pharmacy Services attributes this smooth transition to several things. The pharmacists in our state stepped up to the plate and worked with these clients to make the transition happen. In addition, all of the stakeholders worked diligently to make the transition as smooth as possible by educating clients and providers. This includes the American Association of Retired People (AARP) local office, Wyoming State Health Insurance Information Program (WSHIIP) offices, provider associations, Department of Health representatives (Office of Pharmacy Services and Aging Division) and many others. This teamwork approach helped prepare Wyoming for the transition to Part D.

While the majority of our dual eligible Medicaid clients have been transitioned, the transition is not over. Smaller numbers of Medicaid clients will become eligible for Medicare each month and be transitioned to a Part D plan. In addition, those clients who are eligible for both Medicare and the Prescription Drug Assistance Program (formerly MMP) will be auto-enrolled into a Part D plan in April/May and will begin receiving their medications from Medicare in May/June.

As we continue this transition, there are a few tips that may help ease the burden.

- First, to find out what plan a client is on, the pharmacy can either call ACS at 1-800-251-1268 (only for dual eligibles), or call 1-800-Medicare. In addition, a pharmacy may use the Eligibility (E1) or TROOP query system developed by CMS.
- Second, when there are problems with a client's copay or low income subsidy, a pharmacy should call the Medicare drug plan or 1-800-MEDICARE. If the issue is not resolved through these sources, the **provider** may contact the CMS Denver Regional Office at 888-795-4683, Den_drughelp@cms.hhs.gov, or by fax at (303) 844-3453. **Please note that this resource is for providers only and should not be given to clients to ensure the best customer service.**
- There are a number of "tip sheets" created by the Centers for Medicare and Medicaid Services (CMS) that give additional information and are available on the CMS website at www.cms.hhs.gov. Click on Medicare and look for Prescription Drug Coverage information and then "Pharmacy". Many of these information sheets have a great deal of useful information.

The Office of Pharmacy Services understands that this was a challenging period for pharmacists and appreciates the extra time and effort given to this vulnerable population.

Table 3: Equi-analgesic doses for Opioid Analgesics adapted from reference 1,4
Dose (mg) equi-analgesic to morphine 10mg IM^a

Drug	PO (mg)	IM (mg)	Half-life (hours)	Duration (hours)	Comment
Morphine	20-30 ^b	10	2-3	2-4	Standard
Morphine CR	20-30	10	2-3	8-12	Various formulations are not bioequivalent
Morphine SR	20-30	10	2-3	24	
Oxycodone	20-30	15	2-4	2-4	
Oxycodone CR	20	-----	2-3	8-12	
Hydromorphone	7.5	1.5	2-3	2-4	One study suggests a morphine: hydromorphone ratio of 3:1 rather than 6.7:1 for prolonged use ²
Methadone	20	10	12-190	4-12	
Oxymorphone	10 (rectal)	1	2-3	2-4	Rectal or injectable formulations
Levorphanol	4	2	12-15	4-6	
Fentanyl	-----	-----	7-12		Continuous IV or SC infusion. Clinical experience shows 100mcg/hr is roughly equi-analgesic to morphine 4mg/hr
Fentanyl TS	-----	-----	16-24	48-72	One study shows oral morphine: transdermal fentanyl 70:1. ³ The recommended converted ratio was 100:1.
Codeine	200	130	2-3	2-4	
Propoxyphene	100	-----		2-4	
Meperidine	20	10	15-20	4-8	
Tramadol	120	100	3-4	4-6	
Phenazocine	5	-----	3	4-6	
Buprenorphine	0.8	0.4	2-3	3-4	
Pentazocine	100	35	2-3	3-4	
Nalbuphine	-----	10	5	3-8	
Butorphanol	-----	1 (nasal)	2.5-3.5	4-6	

a. Equi-analgesic studies have used IM morphine. IM and IV routes are considered equivalent.
b. Studies vary for PO:IM ratio from 6:1 (single-dose) to 2-3:1 with repeated administration
CR=controlled release; IM=intramuscular; IV=intravenous; PO=oral; SC=subcutaneous; SR=sustained release; TS=transdermal system.

new drug. The starting dose of the new drug should be reduced by 25-50% from the calculated equi-analgesic dose. This will accommodate both potential tolerance of the old drug along with limitations of the equi-analgesic data. The exception to this rule is methadone. Methadone dosing should be reduced by 75-90% of the calculated equi-analgesic dose.¹

After the new drug therapy is initiated, patients should be monitored for pain relief along with adverse effects. Titration is almost always required. "As needed" or "rescue" doses should be made available to help with the transition. Rescue doses are typically 5-15% of the total daily dose. Titration should occur only after steady-state is reached for the new drug (2 to 3 days for controlled release oral drugs). Titration amounts vary and can be calculated by the frequency of the rescue doses used. One published rule of thumb is an increment of 30-50%.¹

Opioid therapy must be individualized for each patient. While these tables give general guidelines, each patient

must be monitored and assessed on a regular basis and their opioid dosages adjusted appropriately to achieve proper pain relief from opioids. Patients should also be monitored for adverse effects. They may need supplemental treatment for constipation, nausea or other side effects to optimize opioid therapy.¹

The following two articles review equianalgesic calculations and are useful to keep on hand for reference: Gordon DB, Stevenson KK, et al. Opioid equianalgesic calculations. *J Pall Med* 1999;2(2): 209-218 and Gammaitoni AR, Fine P, et al. Clinical application of opioid equianalgesic data. *Clin J Pain* 2003;19:286-297.

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Table 2: Calculating Equi-analgesic Doses for Oral Opioid Conversion adapted from reference 1

Always Round Down When Doing Dosage Conversions

1. Calculate total 24h dose of current opioid. Include "rescue" or "as needed" doses.
2. Convert 24h dose to new 24h dose using equi-analgesic dosing table.
3. Decrease the converted equi-analgesic dose by proper percentage for the type of drug (e.g. 25-50% for most opioids, 75-90% for methadone).
4. Determine the administration interval of the new drug.
5. Calculate the rescue dose using the formula: 5-15% of the total 24h dose of the new drug.

Prescription Drug Cost Containment Report

The following table summarizes the actual cost savings achieved by the Wyoming Department of Health for State Fiscal Year (July 1, 2004 - June 30, 2005). Unless otherwise noted, all savings are net administrative costs.

Program	Cost Savings
Pharmacy Prior Authorization + PDL	\$562,131
OTC / DME Coverage Review	\$100,000
Pharmacist Fraud and Abuse (position vacancy)	\$0
State Maximum Allowable Cost	\$1,216,879
Total	\$1,879,010

Partnership for Prescription Assistance

Partnership for Prescription Assistance (PPA) helps qualifying patients who lack prescription coverage get the medicines they need through a public or private program. PPA offers a single point of access to more than 475 public and private patient assistance programs, including more than 150 programs offered by pharmaceutical companies. To find out more about PPA visit the PPA website at www.pparx.org or call toll free 1-888-4777-2669.

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