

# WY- DUR

## Wyoming Drug Utilization Review Board

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*Debra Devereaux, R.Ph., M.B.A.*

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*Chair*

*George Zaharas, R.Ph.*

*Vice Chair*

March 8, 2006

Dear Doctor:

You have been identified as a prescriber of one or more of the following medications for patient(s) in the Wyoming Medicaid program: Methadone 40mg, Fentanyl 100 mcg. patch, Oxycodone 80 or 160mg., Avinza (morphine sulfate) 90 or 120mg, Kadian 100mg, MS Contin/Oramorph 100mg or 200mg., hydromorphone 8mg, Palladone 24 or 32mg., or morphine sulfate 100 or 200mg. This letter will provide information about the efficacy and safety of high dose opioids.

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.<sup>1 2 3 4 5</sup>

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.<sup>6 7 8 9</sup> In addition, there is evidence in animal studies that high dose opioids affect growth hormone.<sup>10</sup>

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

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 for you review.

Thank you for your care of Wyoming Medicaid patients. 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 or contact us at [lgm@uwyo.edu](mailto:lgm@uwyo.edu). If you are interested in obtaining more information on this subject, a review article was published in the New England Journal of Medicine 2003.<sup>12</sup>

Sincerely,

Scott Johnston, MD

Scott Johnston, M.D.

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### References

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**Table 1: High Dose Narcotics**

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

## Converting from One Opioid to Another

Kendra Grande, RPh  
Consultant Pharmacist  
WY-DUR Board

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 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.<sup>1</sup>

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%.<sup>1</sup>

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.<sup>1</sup>

Two articles that review equianalgesic calculations are useful to keep on hand for reference. They are:

1. Gordon DB, Stevenson KK, et al. Opioid equianalgesic calculations. *J Pall Med* 1999;2(2): 209-218.
2. Gammaitoni AR, Fine P, et al. Clinical application of opioid equianalgesic data. *Clin J Pain* 2003;19:286-297.

### **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

<b>Table 3: Equi-analgesic doses for Opioid Analgesics</b> <small>adapted from reference 1, 4</small>					
<i>Dose (mg) equi-analgesic to morphine 10mg IM<sup>a</sup></i>					
Drug	PO (mg)	IM (mg)	Half-life (hours)	Duration (hours)	Comment
Morphine	20-30 <sup>b</sup>	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 <sup>2</sup>
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. <sup>3</sup> 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	
<p>a. Equi-analgesic studies have used IM morphine. IM and IV routes are considered equivalent.</p> <p>b. Studies vary for PO:IM ratio from 6:1 (single-dose) to 2-3:1 with repeated administration</p>					
CR=controlled release; IM=intramuscular; IV=intravenous; PO=oral; SC=subcutaneous; SR=sustained release; TS=transdermal system.					

#### References

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2. Dunbar PJ Chapman CR Buckley FP, et al. Clinical analgesia equivalence for morphine and hydromorphone with prolonged PCA. *Pain* 1996;68:269-70.
3. Donner B Zenz M Tryba M, et al. Direct conversion from oral morphine to transdermal fentanyl. *Pain* 1996;64:527-34.
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