Meperidine(Demerol®): a relic misfit for chronic pain

Meperidine was developed as an atropine analogue initially but soon gained popularity as a pain medication as its analgesic properties were noticed. A lot of its initial popularity stemmed from assumptions and anecdotal evidence rather than scientific evidence. For instance, it was initially thought to have a lower spasmogenic effect and was preferred for use in acute pancreatitis but later research refuted this idea and found all opioids, including meperidine, to have this effect. Another example is the use of meperidine for headaches which was recommended at one time when this was the only opioid studied in headache patients. However, subsequent research showed meperidine to be less effective for acute headache than dihydroergotamine (DHE) or anti-emetics and to be non-superior to an NSAID while carrying more serious risks. At this point in time, there is enough evidence to conclude that meperidine has no advantage to offer over any other opioid. There were over 3000 prescriptions for meperidine in Alberta in 2014 which presents an opportunity for clinicians to positively impact their patient's health and help reduce serious harm by working with these patients to explore safer alternatives and switch and/or taper depending on the clinical situation.

The risks associated with meperidine arise from its unique pharmacological properties. Meperidine is an anticholinergic and serotonergic opioid which is metabolized through hepatic glucoronidation to normeperidine which is then renally cleared. Normeperidine is a non-opioid with limited analgesic potency but has two to three time the neurotoxic potential of meperidine. It has a half-life which is 14-48 hours which is a problem given the short duration of action for meperidine of only 1-2 hours depending on route of administration. This poses a clinical dilemma: to achieve any meaningful analgesia the needed frequency of meperidine dosing would predispose a patient to dangerous accumulation of the toxic metabolite even in the context of normal renal function. Elderly patients are more likely to have compromised renal function in addition to an increased sensitivity to the neurotoxic effects of normeperidine which puts them at an even greater risk of toxicity, neuroexcitation, seizures, agitation and delirium. Naloxone is not effective in reversing the toxic effects of seizures and neuroexcitation unique to meperidine use.

Other pharmacological challenges with this medication is the poor bioavailability with oral use (around 40-60%) and of what escapes first pass metabolism, only 40% of exists as free drug available for pharmacological efficacy. It is no surprise then that in research, oral meperidine has very poor analgesic efficacy (~10 times lower than morphine). Another concern and contributor of serious overdose is the high oral: parenteral conversion ratio for reasons described. Parenteral use is associated with an even lower duration of action and as such the frequent injections required can cause dystrophy and increase the risk of infections.

As discussed, the duration of action of meperidine is short. This coupled with the intense central effects, which only last a few minutes and result in a profound euphoria, reinforces use. In comparison to morphine, meperidine has been linked to a higher elation, greater work impairment and more dizziness.

In addition to the drug interactions which are attributable to opiates as a class, such as CNS and respiratory depression, meperidine has its own set of interactions due to its action at multiple receptor levels. Serotonin syndrome is one such reaction and has been reported with meperidine use in conjunction with other medication and over-the-counter products that affect serotonin levels.

Meperidine is contraindicated in patients with cirrhosis and renal impairment. The elderly and patients with certain medical conditions such as Sickle Cell Disease may be more sensitive to the neurotoxic and anticholinergic action of the medication. This drug is on the Beer's list of potentially inappropriate medication for use in the elderly.

Due to the serious risks with meperidine, the Institute of Safe Medical Practices Canada has issued multiple safety warnings advising against the use of meperidine. In its 2004 bulletin, ISMP recommended:

i) Removal of oral meperidine from formularies;

ii) Restricting use of parenteral meperidine to short-term pain management in patients with normal renal, hepatic and CNS function where alternative opioids are contraindicated while:

a) Not exceeding a daily dose of 600mg/ day; and,

b) Limiting duration of use to 48 hours.

Clinical situations that meperidine may still be considered for include a true allergy to other opioids. This is very rare in practice so when an allergy is suspected, it should be carefully assessed for confirmation. The histamine release following opioid use may cause a rash and itchiness which may be mistaken as an allergic reaction. In the case of a true hypersensitivity reaction, a structurally different opioid class or even switching to a semi-synthetic opioid are available alternatives. Another use for meperidine may be for post-operative shivering.

While there are very rare situations where limited and well deliberated use of this medication may be appropriate, in the majority of clinical situations it is not the best available choice. As a clinician, the well-being of the patient must be the primary consideration and patient-centered care may include refusing patient demands for continued prescribing of a dangerous medication. Being the medical experts and ultimately responsible for their prescribing, clinicians should work with their patients to explore alternatives whenever possible and seriously consider de-prescribing and tapering-off all patients who are chronically using this medication. The Opioid Manager (appended) may help in rotating to another opiate if that is the chosen clinical option following patient assessment.

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OPIOID MANAGER

The Opioid Manager is designed to be used as a point of care tool for providers prescribing opioids for chronic non cancer pain. It condenses key elements from the Canadian Opioid Guideline and can be used as a chart insert.

A Before You Write the First Script

Patient Name: _____

Pain Diagnosis: _____

Date of Onset: _____

Goals decided with patient:

_____

_____

_____

_____

_____

_____

_____

Initiation Checklist

	Y	N	Date
Are opioids indicated for this pain condition			
Explained potential benefits			
Explained adverse effects			
Explained risks			
Patient given information sheet			
Signed treatment agreement (as needed)			
Urine drug screening (as needed)			

Opioid Risk Tool

By Lynn R. Webster MD

Item (circle all that apply)	**Item score if female**	**Item score if male**
1. Family History of Substance Abuse:		
Alcohol	1	3
Illegal Drugs	2	3
Prescription Drugs	4	4
2. Personal History of Substance Abuse:		
Alcohol	3	3
Illegal Drugs	4	4
Prescription Drugs	5	5
3. Age (mark box if 16-45)	1	1
4. History of Preadolescent Sexual Abuse	3	0
5. Psychological Disease Attention Deficit Disorder, Obsessive-Compulsive Disorder, or Bipolar, Schizophrenia	2	2
Depression	1	1
Total		

Total Score Risk Category:
Low Risk: 0 to 3, Moderate Risk: 4 to 7, High Risk: 8 and above

Overdose Risk

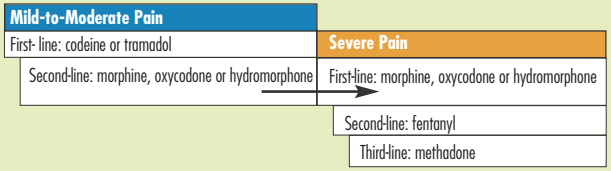
Patient Factors
- Elderly
- On benzodiazepines
- Renal impairment
- Hepatic impairment
- COPD
- Sleep apnea
- Sleep disorders
- Cognitive impairment

Provider Factors
- Incomplete assessments
- Rapid titration
- Combining opioids and sedating drugs
- Failure to monitor dosing
- Insufficient information given to patient and/or relatives

Opioid Factors
- Codeine & Tramadol - lower risk
- CR formulations - higher doses than IR

Prevention
- Assess for Risk Factors
- Educate patients /families about risks & prevention
- Start low, titrate gradually, monitor frequently
- Careful with benzodiazepines
- Higher risk of overdose - reduce initial dose by 50%; titrate gradually
- Avoid parenteral routes
- Adolescents; elderly - may need consultation
- Watch for Misuse

Stepped Approach to Opioid Selection



B Initiation Trial

A closely monitored trial of opioid therapy is recommended before deciding whether a patient is prescribed opioids for long term use.

Suggested Initial Dose and Titration (Modified from Weaver M., 2007 and the e-CPS, 2008) Notes: The table is based on oral dosing for CNCP. Brand names are shown if there are some distinct features about specific formulations. Reference to brand names as examples does not imply endorsement of any of these products. CR = controlled release, IR = immediate release, NA = not applicable, ASA: Acetylsalicylic Acid

Opioid	Initial dose	Minimum time interval for increase	Suggested dose increase	Minimum daily dose before converting IR to CR
Codeine (alone or in combination with acetaminophen or ASA)	15-30 mg q.4 h. as required	7 days	15-30 mg/day up to maximum of 600 mg/day (acetaminophen dose should not exceed 3.2 grams/day)	100 mg
CR Codeine	50 mg q.12 h.	2 days	50 mg/day up to maximum of 300 mg q.12 h.	NA
Tramadol (37.5 mg) + acetaminophen (325 mg)	1 tablet q.4-6 h. as needed up to 4/day	7 days	1-2 tab q. 4-6 h. as needed up to maximum 8 tablets/day	3 tablets
CR Tramadol	a) Zytram XL®: 150 mg q. 24 h. b) Tridural™: 100 mg q. 24 h. c) Ralivia™: 100 mg q. 24 h.	a) 7 days b) 2 days c) 5 days	Maximum doses: a) 400 mg/day b) 300 mg/day c) 300 mg/day	NA
IR Morphine	5-10 mg q. 4 h. as needed maximum 40 mg/day	7 days	5-10 mg/day	20-30 mg
CR Morphine	10-30 mg q.12 h. Kadian®: q.24 h. Kadian® should not be started in opioid-naïve patients	Minimum 2 days, recommended: 14 days	5-10 mg/day	NA
IR Oxycodone	5-10 mg q. 6 h. as needed maximum 30 mg/day	7 days	5 mg/day	20 mg
CR Oxycodone	10-20 mg q.12 h. maximum 30 mg/day	Minimum 2 days, recommended: 14 days	10 mg/day	NA
IR Hydromorphone	1-2 mg q. 4-6 h. as needed maximum 8 mg/day	7 days	1-2 mg/day	6 mg
CR Hydromorphone	3 mg q. 12 h. maximum 9 mg/day	Minimum 2 days, recommended: 14 days	2-4 mg/day	NA

Initiation Trial Chart

Date	D / M / Y	D / M / Y	D / M / Y	D / M / Y
Opioid prescribed				
Daily dose				
Daily morphine equivalent				
More than 200 (Watchful Dose > than 200)				
Less than 200				
Goals achieved → Yes, No, Partially				
Pain intensity				
Functional status → Improved, No Change, Worsened				
Adverse effects: Nausea				
Constipation				
Drowsiness				
Dizziness/Vertigo				
Dry skin/Pruritis				
Vomiting				
Other?				
Complications? (Reviewed: Y/N)				
Aberrant Behaviour (Reviewed: Y/N)				
Urine Drug Screening (Y/N)				
Other Medications				

0 = None
1 = Limits ADLs
2 = Prevents ADLs

To access the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain and to download the Opioid Manager visit **http://nationalpaincentre.mcmaster.ca/opioid/**

Feb 2011

C Maintenance & Monitoring

Morphine Equivalence Table

Opioid	Equivalent Doses (mg)	Conversion to MEQ
Morphine	30	1
Codeine	200	0.15
Oxycodone	20	1.5
Hydromorphone	6	5
Meperidine	300	0.1
Methadone & Tramadol	Dose Equivalents unreliable	
Transdermal fentanyl	60 – 134 mg morphine = 25 mcg/h 135 – 179 mg = 37 mcg/h 180 – 224 mg = 50 mcg/h 225 – 269 mg = 62 mcg/h 270 – 314 mg = 75 mcg/h 315 – 359 mg = 87 mcg/h 360 – 404 mg = 100 mcg/h	

Switching Opioids:	
If previous opioid dose was:	**Then, SUGGESTED new opioid dose is:**
High	50% or less of previous opioid (converted to morphine equivalent)
Moderate or low	60-75% of the previous opioid (converted to morphine equivalent)

Maintenance & Monitoring Chart

Date	D / M / Y	D / M / Y	D / M / Y	D / M / Y	D / M / Y	D / M / Y
Opioid prescribed						
Daily dose						
Daily morphine equivalent						
More than 200 (Watchful Dose > than 200)						
Less than 200						
Goals achieved → Yes, No, Partially						
Pain intensity						
Functional status → Improved, No Change, Worsened						
Adverse effects: Nausea						
Constipation						
Drowsiness						
Dizziness/Vertigo						
Dry skin/Pruritis						
Vomiting						
Other?						
Complications? (Reviewed: Y/N)						
Aberrant Behaviour (Reviewed: Y/N)						
Urine Drug Screening (Y/N)						
Other Medications						

0 = None
1 = Limits ADLs
2 = Prevents ADLs

D When is it time to Decrease the dose or Stop the Opioid completely?

When to stop opioids	Examples and Considerations
Pain Condition Resolved	Patient receives definitive treatment for condition. A trial of tapering is warranted to determine if the original pain condition has resolved.
Risks Outweighs Benefits	Overdose risk has increased. Clear evidence of diversion. Aberrant drug related behaviours have become apparent.
Adverse Effects Outweighs Benefits	Adverse effects impairs functioning below baseline level. Patient does not tolerate adverse effects.
Medical Complications	Medical complications have arisen (e.g. hypogonadism, sleep apnea, opioid induced hyperalgesia)
Opioid Not Effective	**Opioid effectiveness = improved function or at least 30% reduction in pain intensity** Pain and function remains unresponsive. Opioid being used to regulate mood rather than pain control. Periodic dose tapering or cessation of therapy should be considered to confirm opioid therapy effectiveness.

How to Stop – the essentials

How do I stop? The opioid should be tapered rather than abruptly discontinued.

How long will it take to stop the opioid? Tapers can usually be completed between 2 weeks to 4 months.

When do I need to be more cautious when tapering? Pregnancy:
Severe, acute opioid withdrawal has been associated with premature labour and spontaneous abortion.

How do I decrease the dose?
Decrease the dose by no more than 10% of the total daily dose every 1-2 weeks. Once one-third of the original dose is reached, decrease by 5% every 2-4 weeks. Avoid sedative-hypnotic drugs, especially benzodiazepines, during the taper.

Aberrant Drug Related Behaviour (Modified by Passik,Kirsh et al 2002).

Indicator	Examples
*Altering the route of delivery	• Injecting, biting or crushing oral formulations
*Accessing opioids from other sources	• Taking the drug from friends or relatives • Purchasing the drug from the "street" • Double-doctoring
Unsanctioned use	• Multiple unauthorized dose escalations • Binge rather than scheduled use
Drug seeking	• Recurrent prescription losses • Aggressive complaining about the need for higher doses • Harassing staff for faxed scripts or fit-in appointments • Nothing else "works"
Repeated withdrawal symptoms	• Marked dysphoria, myalgias, GI symptoms, craving
Accompanying conditions	• Currently addicted to alcohol, cocaine, cannabis or other drugs • Underlying mood or anxiety disorders not responsive to treatment
Social features	• Deteriorating or poor social function • Concern expressed by family members
Views on the opioid medication	• Sometimes acknowledges being addicted • Strong resistance to tapering or switching opioids • May admit to mood-leveling effect • May acknowledge distressing withdrawal symptoms

* = behaviours more indicative of addiction than the others.