Ontario Renal Network

Pain

Adapted with permission from the BC Renal Agency's Renal Analgesic Brochure, developed by the agency's Pharmacy & Formulary Committee, and the Kidney Supportive Care Research Group (KSCRG), University of Alberta / Northern Alberta Renal Program. To review original source materials, see www.bcrenalagency.ca and www.ualberta.ca/~kscrg.

Ontario

Chronic Pain Treatment Algorithm for Hemodialysis Patients

Musculoskeletal/Nociceptive Pain

Assessment

- Nociceptive pain is most commonly described as aching, dull, gnawing, throbbing, or cramping but may be intermittently sharp
- Characterize the chronic pain: character (aching, dull, etc.), location, radiation, intensity, timing, duration, aggravating factors, and alleviating factors (including medications used)

Consider Etiology

- Exclude dangerous causes of pain such as angina, fracture, or infection particularly if pain is new or recently changed character or increased intensity
- Nociceptive pain is often due to musculoskeletal issues (low back pain, myofascial pain syndrome, sprains, etc.)

Non-Pharmacologic Measures

- Encourage pain diary
- Consider gentle exercise, yoga, deep breathing exercises, massage, meditation, or physiotherapy as appropriate

Refer to the Ontario Renal Network Pain Patient Self-Management Guide for more information.

Pharmacologic Options – For Non-Severe Nociceptive Pain

- Acetaminophen* (including acetaminophen arthritis formulation): Max. 4 g/day; caution if Hx of EtOH, other liver enzyme inducer (e.g., rifampin), and heart failure. Follow GGT & ALT Q3 months if dose >2.6 g/day
- Duloxetine*: 30 mg/day
- Consider short course of NSAIDs in **anuric** patients (consider gastric ulcer risk): Ibuprofen* 400-800 mg daily, Naproxen* 250-500 mg daily
- For Localized Pain consider:
  - Topical NSAIDs: Apply TID to QID (diclofenac 5 to 25% in Phlojel, diclofenac gel 1.16% [OTC])
  - Capsaicin cream 0.025% or 0.075%: Apply bid to qid (may take >2 weeks for onset of action)

Pharmacologic Options – For Severe Nociceptive Pain

Consider adding an opioid to non-opioid analgesic and or adjuvant after considering risk of opioid abuse (for example, using the Current Opioid Misuse Measure [COMM]).

AVOID MORPHINE, CODEINE AND MEPERIDINE

- Preferred Short Acting Opioid:
  - Hydromorphone IR*: 0.25 to 0.5 mg PO Q4 hours PRN

  Consider regularly scheduled dosing once a stable dose identified for constant pain. Regularly scheduled dosing may also be useful in very severe pain.
- Preferred Long Acting Opioids:
  - Hydromorphone CR*: PO Q12 hours (available in 3 mg increments)
  - Fentanyl patch*: Initial dose: 12 µg/hours patch Q3 days, increase dose to next patch size every 2nd HD run. Consider use only after opioid requirement stable.

  Note: If pain control not optimal before next scheduled CR dose, consider giving ⅓ total daily dose of hydromorphone Q8 hours

  Consider consultation with chronic pain specialist, medical marijuana prescriber, methadone prescriber, family physician comfortable with pain management, and/or palliative care service.

For Refractory Severe Pain

Consider consultation with chronic pain specialist, medical marijuana prescriber, methadone prescriber and/or palliative care service.

*** covered by ODB**

Chronic Pain Treatment Algorithm for Hemodialysis Patients

Neuropathic Pain

Assessment

- Neuropathic pain is most commonly described as pain, pain to cold, electric shocks, tingling, pins and needles, numbness, itchy, increase pain with light touch, decrease sensation
- Characterize the chronic pain: character (aching, dull, etc.), location, radiation, intensity, timing, duration, aggravating factors, and alleviating factors (including medications used)

Consider Etiology

- Exclude dangerous causes of pain such as angina, fracture, or infection particularly if pain is new or recently changed character or increased intensity
- Common causes of neuropathic pain include diabetic neuropathy, herpetic neuralgia, post-stroke pain, nerve compression pain/sciatica, and multiple sclerosis

Non-Pharmacologic Measures

- Encourage pain diary
- Consider gentle exercise, yoga, deep breathing exercises, massage, meditation, or physiotherapy as appropriate

Refer to the Ontario Renal Network Pain Patient Self-Management Guide for more information.

Pharmacologic Options – For Non-Severe Neuropathic Pain

- Gabapentin*****: 100 mg PO hs and titrate weekly by 100 mg/day. Maximum dose: 300 mg/day. Adequate trial duration: 4 to 6 weeks.
- Pregabalin*****: 25 mg PO hs and titrate weekly by 25 mg/day. Maximum dose: 75 mg/day. Dose to be given post-HD on HD days. No data to support use of pregabalin in gabapentin resistant or intolerant patient.
- Duloxetine*****: 30 mg/day
- Capsaicin cream 0.025% or 0.075%: Apply BID to QID for localized pain (may take >2 weeks for onset of action)

Pharmacologic Options – For Severe Neuropathic Pain

- Nortriptyline*****: 10 mg PO daily (usually given hs) and titrate weekly by 10 mg/day. Maximum dose: 100 mg/ day
- Amitriptyline*****: 10 to 25 mg PO daily (usually given hs). Titrate by 10 to 25 mg every week as required. Maximum dose: 75 mg/day

Note: Nortriptyline and Amitriptyline should be used with caution in patients with history of cardiac disease. Consider monitoring QTc. Combination gabapentin + nortriptyline or amitriptyline can provide better pain control for diabetic polyneuropathy and postherpetic neuralgia.

- Nabilone*****: 0.25 to 0.5 mg PO hs and titrate weekly by 0.25 to 0.5 mg/day. Maximum dose: 2 mg/day. Capsule strengths available: 0.25 mg, 0.5 mg and 1 mg
- THC:CBD (Sativex): 1 spray under tongue or toward inside of cheeks daily to BID. May increase by 1 spray/day qHD run. Maximum dose: 12 sprays/day. Limited data in renal failure patients. May worsen orthostatic hypotension.
- Topiramate*****: 25 mg PO daily and titrate every 2 weeks by 25 mg/day. Maximum dose: 200 mg/day (dosed daily or BID).
- Venlafaxine*****: 37.5 mg PO daily, and titrate in 1 week to 75 mg PO daily
- Additional options: clonidine*****, tizanidine, benzodiazepines*****

Consider consultation with chronic pain specialist, medical marijuana prescriber, methadone prescriber, family physician comfortable with pain management, and/or palliative care service.

Pharmacologic Options – For Inadequately Controlled Neuropathic Pain

Consider adding an opioid to non-opioid analgesic and or adjuvant after considering risk of opioid abuse (for example, using the Current Opioid Misuse Measure [COMM]).

AVOID MORPHINE, CODEINE AND MEPERIDINE

- Preferred Short Acting Opioid:
  - Hydromorphone IR*****: 0.25 to 0.5 mg PO Q4 hours PRN

  Consider regularly scheduled dosing once a stable dose identified for constant pain. Regularly scheduled dosing may also be useful in very severe pain.
- Preferred Long Acting Opioids:
  - Hydromorphone CR*****: PO Q12 hours (available in 3 mg increments)
  - Fentanyl patch*****: Initial dose: 12 µg/hour patch Q3 days, increase dose to next patch size every 2nd HD run. Consider use only after opioid requirement stable.

  Note: If pain control not optimal before next scheduled CR dose, consider giving ⅓ total daily dose of hydromorphone Q8 hours

  Consider consultation with chronic pain specialist, medical marijuana prescriber, methadone prescriber, family physician comfortable with pain management, and/or palliative care service.

For Refractory Severe Pain

Consider consultation with chronic pain specialist, medical marijuana prescriber, methadone prescriber and/or palliative care service.

*** covered by ODB**

Management of Opioid Adverse Effects

Common Adverse Effects:

Constipation, nausea, vomiting, dry mouth, drowsiness, confusion, delirium

Constipation

- Initiate bowel regimen when starting any opioids
  - Senna glycosides +/- PEG +/- lactulose
- If no BM in 48–72 hours, check for impaction and manual removal
  - Administer bisacodyl suppository +/- glycerin suppository
  - Increase PEG, lactulose and senna glycosides as tolerated
- Increase physical activity and consider a consult with Registered Dietitian to assess fiber/ fluid intake

Nausea and vomiting

- Consider switching to a different opioid
- Due to central stimulation:
  - Prochlorperazine 2.5 to 10 mg PO/PR/IV/ subcutaneous QID PRN (note: parenteral preparations may be difficult to obtain)
  - Metoclopramide 5 mg PO/IV/ subcutaneous QID PRN
  - Haloperidol 0.5 to 1 mg PO/subcutaneous BID-TID PRN
  - Ondansetron 4 to 8 mg PO TID PRN
- Due to gastric stasis or delayed gastric emptying:
  - Metoclopramide 5 mg PO/IV/ subcutaneous QID
  - Domperidone 5 to 10mg TID. Maximum 30 mg/ day – Severe renal impairment, may require twice daily dosing instead of TID. Use lowest effective dose.

Drowsiness

Common with initiation of opioid therapy and may lessen with continued therapy. If persists, the opioid dosage should be decreased.

Delirium/Cognitive Impairment

The opioid dosage should be decreased or a different analgesic should be tried

Less Common Adverse Effects:

Urinary retention, myoclonus, respiratory depression

Respiratory Depression

- Administer naloxone 0.1 to 0.2 mg IV Q2 to 3 minutes or naloxone 0.1 to 0.2 mg subcutaneously Q5 to 10 minutes until respiratory rate is more than 10 per minute.
- If no response in 2 to10 minutes, repeat naloxone 0.2 to 0.4 mg Q2 to 3 minutes
- Continue to monitor respiratory rate Q15 minutes until no naloxone given for 1 hour
- **Consider only partial reversal of opioid effects in palliative patients**

Other Issues:

Known or Suspected Overdoses

- Administer naloxone 0.4 to 2 mg IV; if no response, repeat naloxone 0.4 to 2mg Q2 to 3 minutes
- In cases of large narcotic overdoses or methadone overdoses, higher doses may be required
- If no response after 10 mg of naloxone, reassess diagnosis
- May need to repeat doses Q20 to 60 minutes

Hyperalgesia

Too much opioid exposure may result in sensitization and worsening pain state despite high opioid doses. Optimal treatment options include decreasing opioid doses or rotating to different opioid, e.g. methadone.

Renal Analgesic Drug Monographs

Opioid

Fentanyl (Duragesic MAT®transdermal patch)			
Mechanism of Action	Mu receptor agonist		
Pharmacokinetics	Normal half-life 7 to 12hours; extensive hepatic metabolism; <10% excreted unchanged in urine; no known active metabolitaes; subcutaneous fat tissue & skeletal muscles absorb fentanyl. From these deposits, fentanyl is then released into systemic circulation.		
Adverse Effects	• Common: constipation, nausea, vomiting, dry mouth, drowsiness, confusion, delirium, dyspnea • Less common: urinary retention, myoclonus, respiratory depression • Study of Asian patients showed increased dizziness and nausea due to less subcutaneous fat; risk of accidental overdose when used in acute pain, non-tolerant individuals, or through careless disposal		
Dosing Guidelines (Normal Renal Function)	• **NOT recommended in opioid-naïve patients, refer to opioid conversion table in chronic pain treatment algorithm for conversion information/ table.** • Start low and titrate to effect, e.g. 12 mcg/hour fentanyl patch Q72 hours; previous opioid should be tapered off over first 12 hours of fentanyl as absorption is delayed; adequate breakthrough medication should be provided when switching to fentanyl as predicted doses are sometimes too conservative; some patients may require Q48 hours dosing • Withdrawal syndrome may also occur when switching to fentanyl, which responds to tapering dose of previous opioid		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	75% Use with caution, titrate dose carefully	50% Use with caution, titrate dose carefully
Supplemental Dose After	**IHD**	**PD**	
	No data	No data	
Drug Coverage	Yes – covered by ODB (requires Limited Use code)		
Estimated Cost (30-day supply) without dispensing fee (Prices as of October 2018)	For 10 patches (2 pack): • 12 mcg – $40.37 • 25 mcg – $45.55 • 50 mcg – $82.18 • 75 mcg – $114.27		

<table>
<tr><th colspan="4">Hydromorphone (Dilaudid® and Hydromorph Contin®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Mu receptor agonist</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">Normal half-life 2.5 hours; oral bioavailability 50%; extensive hepatic metabolism; <13% excreted unchanged in urine; Glucuronide metabolites are excreted renally</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">• Common: constipation, nausea, vomiting, dry mouth, drowsiness, confusion, delirium, dyspnea
• Less common: urinary retention, myoclonus, respiratory depression
• May have less adverse effects than morphine in some patients, e.g., sedation, confusion, nausea, constipation
• Ideal for elderly and pts with renal impairment due to less active hydromorphone 6–glucuronide metabolite</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">• Start low and titrate to effect, e.g. 0.5 to 1 mg PO Q3 to 4 hours. Available: PO – immediate release(IR); e.g. Hydromorph Contin, oral liquid, suppository, Parenteral – SC/IM/IV</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>75%
Use with caution, titrate dose carefully</td><td>50%
Use with caution, titrate dose carefully</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">No</td><td>No</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">• Hydromorphone: Yes – regular release tablet, oral liquid covered by ODB
• Hydromorphone SR: Yes – Hydromorph Contin 3mg to 18 mg covered by ODB
• NOTE: Hydromorphone SR 24mg and 30 mg NOT covered (delisted off ODB Jan 2017)</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">• Hydromorphone 1 mg PO Q3 hours – $17.26
• Hydromorphone SR 3 mg PO BID – $36.14</td></tr>
</table>

<table>
<tr><th colspan="4">Methadone (Methadose®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Mu receptor agonist, δ receptor agonist, NMDA receptor antagonist, inhibition of serotonin or norepinephrine re-uptake</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Normal half-life: 12 to >150 hours; oral bioavailability 80%; metabolized primarily by CYP3A4, and secondarily by CYP2D6, CYP2C and CYP1A2
• Numerous drug interactions (consult Pharmacist)
• Excreted by glomerular filtration and undergoes renal reabsorption; reabsorption decreases as urinary pH decreases
• Urinary excretion is dose dependent and comprises the major route of excretion when dose >55mg per day</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">• Common: constipation, nausea, vomiting, dry mouth, drowsiness, confusion, delirium, dyspnea
• Less common: urinary retention, myoclonus, respiratory depression. Prolonged QTc. ECG recommended at baseline, within 30 days and annually. Additional ECG is recommended at doses >60 mg/day or if patient has unexplained syncope or seizures. Monitor and review risks vs benefits if QTc 450-500 ms; discontinue or reduce methadone dose if QTc >500 ms.</td></tr>
<tr><td>Dosing Guidelines
(Normal Renal Function)</td><td colspan="3">• Not ideal for elderly or patients with renal impairment due to active metabolites. Initial dose should not exceed 15 mg/day; caution with dose titration due to prolonged and variable half-life.
• When switching from morphine to methadone, 10:1 initial conversion ratio is recommended for most patients. However, extreme caution is necessary and a higher ratio may be required when switching from high doses of other opioids. Available: 1 mg/mL oral solution; 10 mgl/mL oral concentrate; 1,5,10, and 25 mg/tablet. Methadone prescribing license required.</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>100%</td><td>50–75%
Use with caution,
titrate dose carefully</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">None</td><td>None</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">Yes – only 10 mg/ mL oral liquid concentrate covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">Methadone 10 mg/mL, 15 mg per day – $6.75</td></tr>
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Non Opioid

Acetaminophen (Tylenol®)			
Mechanism of Action	Inhibits the synthesis of prostaglandin, which causes inflammation and increases pain receptor firing centrally but has relatively little effect on peripheral prostaglandin synthesis		
Pharmacokinetics	Normal half-life 2.5 hours; hepatic metabolism to sulphate and glucuronide metabolites, with a small amount metabolized via cytochrome P450 (CYP2E1, CYP1A2, CYP3A4) to a reactive intermediate (acetylimidoquinone) which is inactivated through glutathione conjugation; urinary excretion of glucuronide and sulphate conjugates; 9% excreted unchanged in urine		
Adverse Effects	Hepatotoxicity with large doses		
Dosing Guidelines (Normal Renal Function)	325 to 650 mg PO Q4 hours to max of 4 g/day for chronic use with normal liver function; **Max of 2.6 g/day for patients at risk (e.g., alcoholism, malnourished, fasting states, chronic hepatitis).**		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	Q4 hours	Q6 hours	Q8 hours
Supplemental Dose After	**IHD**	**PD**	
	None	None	
Drug Coverage	Yes – covered by ODB		
Estimated Cost (30-day supply) without dispensing fee (Prices as of October 2018)	100 caplets – $11.99 (price for 325 mg tabs)		

<table>
<tr><th colspan="4">Non-steroidal anti-inflammatory drugs (NSAIDs) e.g., Ibuprofen (Motrin®, Advil®), Diclofenac (Voltaren®), Naproxen (Naprosyn®) COX-2 inhibitors e.g., Celecoxib (Celebrex®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Inhibits the synthesis of prostaglandin peripherally. Inhibits COX-2 enzyme, which is activated during inflammation to cause signs and symptoms associated with inflammation.</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Normal half-life: 2 to 3 hours for ibuprofen and diclofenac; 12 to 15 hours for naproxen
• Extensive hepatic metabolism, little excreted unchanged but inactive metabolites are primarily excreted by the kidneys</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">• Confusion, dizziness, headaches, tinnitus, bronchospasm, indigestion, peptic ulcers, melena stool, edema including pulmonary edema, CHF; HTN, nephrotoxicity
• Contraindicated in patients who have coagulopathies or at risk of bleeding</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">• These drugs have a ceiling effect: ibuprofen 200 to 400 mg PO Q4 to 6 hours; diclofenac 25 to 50 mg PO TID; naproxen 250 to 500 mg PO BID; celecoxib 100 to 200 mg PO daily to BID.
• Best for short term use only (~2 wks) in elderly; best avoided in CKD pts due to risk of worsening kidney function or increased bleeding</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>100%
Best avoided in CKD patients</td><td>100%
Best avoided in CKD patients
Short courses may be used in anuric patients</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">None</td><td>None</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">• Yes – some covered by ODB (e.g., diclofenac, ibuprofen, celecoxib, naproxen)
• Note: Celecoxib requires Limited Use code</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">• Ibuprofen 200 mg PO Q4 hours – $9.18
• Diclofenac 25 mg PO TID – $7.03
• Naproxen 250 mg PO BID – $6.42
• Celecoxib 100 mg PO BID – $7.67</td></tr>
</table>

Anticonvulsant

Gabapentin (Neurontin®)			
Mechanism of Action	• Selective, high affinity for voltage-gated calcium channels in the brain and dorsal horn of the spinal cord • Reduces influx of calcium, thus inhibiting the release of excitatory neurotransmitters such as glutamate, noradrenaline, substance P and calcitonin gene related peptide		
Pharmacokinetics	• Normal half-life: 5 to 6.5 hours • Saturable oral bioavailability (900 mg-60%; 1200 mg-47%; 2400 mg-34%) • Limited hepatic metabolism, 70 to 80% excreted unchanged in the urine		
Adverse Effects	Sedation, confusion, incoordination, peripheral edema		
Dosing Guidelines (Normal Renal Function)	• Start with 100 mg PO daily, then 100 mg TID, titrate gradually to effect and as tolerated to a max of 3600 mg per day (in 4 divided doses) • Start at minimum dose and titrate up as required		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	400 mg PO TID	300 mg PO Q12 to 24 hours	Usual max of 300 mg per day
Supplemental Dose After	**IHD**	**PD**	
	Yes for HD patients – 100 mg after dialysis *consider additional dose post dialysis if usual dose given pre-dialysis	No evidence available	
Drug Coverage	Yes – covered by ODB		
Estimated Cost (30-day supply) without dispensing fee (Prices as of October 2018)	100 mg PO QHS – $1.25		

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<tr><th colspan="4">Pregabalin (Lyrica®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Selective, high affinity for voltage gated calcium channels in the brain and dorsal horn of the spinal cord. Reduces influx of calcium, thus inhibiting the release of excitatory neurotransmitters such as glutamate, noradrenaline, substance P and calcitonin gene related peptide.</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Oral bioavailability: 90%
• Limited hepatic metabolism, 90% excreted unchanged in the urine
• Normal half-life: 5 to 6.5 hours</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">Sedation, confusion, incoordination, peripheral edema</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">• Start with 25 mg PO HS, titrate to effect and as tolerated to a max of 300 mg PO BID
• Start at minimum dose and titrate up as required</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>• CrCl 30-60 ml/min: Maximum 300mg/day, dosed BID or TID
• CrCl 15-30 ml/ min: Maximum 150mg /day, dosed BID or once daily</td><td>25-75 mg/day, dosed once daily</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">• 50% Pregabalin removed by HD
• Ideally, give post HD. If dosing before HD, consider supplemental dose post HD.</td><td>No data</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">Yes – covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">25 mg PO QHS – $27.17</td></tr>
</table>

<table>
<tr><th colspan="4">Topiramate (Topamax®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Inhibition of GABA-ergic pathways and blocks AMPA/glutamate pathways</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Normal half life 6 hours; limited hepatic metabolism, 55 to 97% excreted unchanged in urine
• In renal failure or HD patients, may take 10 to15 days to reach steady-state compared to 4 to 9 days patients with normal renal function
• Topiramate is cleared by hemodialysis</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">Sedation, confusion, agitation, tremors, paresthesia, speech disorders, weight loss, narrow angle glaucoma, non-anion metabolic acidosis, kidney stones</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">Start with 25 mg PO od, titrate gradually to effect and as tolerated up to 200 mg PO BID</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>50%</td><td>25%</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">• Dose after HD
• May need supplemental dose (50-100 mg)</td><td>50%</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">Yes – covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">Topiramate 50 mg PO qHS – $14.60</td></tr>
</table>

Antidepressant

Tricyclic Antidepressants e.g., Amitriptyline (Elavil®), Nortriptyline (Aventyl®)			
Mechanism of Action	Inhibits the reuptake of serotonin and norepinephrine which, in turn, inhibits the transmission of pain signals down the descending pathways from the brain stem to the dorsal horn. Enhances the plasticity of the nervous system via the activation of glial cells to release neurotrophins and the activation of neurological stem cells.		
Pharmacokinetics	• Long half-life: 24 to 40 hours depending on the agent • Extensive hepatic metabolism; little excreted unchanged but inactive metabolites are primarily excreted by the kidneys		
Adverse Effects	**Nortriptyline is better tolerated** than amitriptyline – sedation; anticholinergic effects, e.g., delirium, dry mouth, constipation, urinary retention; orthostatic hypotension; cardiotoxicity		
Dosing Guidelines (Normal Renal Function)	• Low initial dose: titrate slowly—start at 10 to 25 mg PO qHS • Usual dose for amitriptyline, nortrptyline: 50 to 100 mg PO qHS		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	100%	100%
Supplemental Dose After	**IHD**	**PD**	
	None	None	
Drug Coverage	Yes – covered by ODB		
Estimated Cost (30-day supply) without dispensing fee (Prices as of October 2018)	• Nortriptyline 50 mg PO qHS – $37.45 • Amitriptyline 25 mg PO qHS – $3.78		

Duloxetine (Cymbalta®)			
Mechanism of Action	It inhibits neuronal serotonin, norepinephrine and dopamine reuptake		
Pharmacokinetics	• Normal half-life: from 8 to 17 hours • Extensive liver metabolism by CYP 1A2 and 2D6; 70% excreted renally (mainly metabolites)		
Adverse Effects	• Diaphoresis, constipation, nausea, dizziness, headache, fatigue, hepatotoxicty • **Canadian monograph: Contraindicated if CrCl< 30 mL/min. Controversy over safety in patients with severe renal dysfunction/dialysis dependent.**		
Dosing Guidelines (Normal Renal Function)	Start at 30 mg PO daily and titrate after 1 to 2 weeks to 60 mg PO daily		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	100%, but no data for CrCl< 30 mL/min	No data
Supplemental Dose After	**IHD**	**PD**	
	No data	No data	
Drug Coverage	Yes – covered by ODB		
Estimated Cost (30-day supply) without dispensing fee (Prices as of October 2018)	Duloxetine 30 mg PO daily – $14.40		

<table>
<tr><th colspan="5">Venlafaxine (Effexor XR®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="4">Inhibits neuronal serotonin, norepinephrine and dopamine reuptake</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="4">• Normal half-life of 5 hours
• Extensive hepatic metabolism through CYP 2D6, active metabolites O-desmethylvenlafaxine (normal half-life 11 hours), mainly renally eliminated; half-life prolonged in renal failure, clearance is reduced in dialysis, not dialyzable</td></tr>
<tr><td>Adverse Effects</td><td colspan="4">Hypertension, excessive sweating, weight loss, constipation, nausea, dizziness, feeling nervous, headache, impotence</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="4">Start at low dose (37.5 mg PO daily) and titrate weekly up to 150 mg/day</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td colspan="2">10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>75%</td><td colspan="2">50%</td><td>50%</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td colspan="2">PD</td></tr>
<tr><td colspan="2">None</td><td colspan="2">None</td></tr>
<tr><td>Drug Coverage</td><td colspan="4">Yes – covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="4">Venlafaxine 75 mg PO qHS – $8.70</td></tr>
</table>

Muscle Relaxant

<table>
<tr><th colspan="4">Benzodiazepines e.g., Lorazepam (Ativan®), Clonazepam (Rivotril®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">GABA receptor agonist</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">Extensive hepatic metabolism</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">Sedation; confusion; addictive potential; withdrawal symptoms (taper slowly after long term use)</td></tr>
<tr><td>Dosing Guidelines
(Normal Renal Function)</td><td colspan="3">• Start with low dose/drug specific dosing
• NOT recommended for long-term use
• Use with caution in the elderly</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>100%</td><td>100%</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">None</td><td>None</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">Yes – covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">• Lorazepam 1 mg PO daily – $1.50
• Clonazepam 0.5 mg daily – $1.20</td></tr>
</table>

<table>
<tr><th colspan="4">Tizanidine (Zanaflex®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Central alpha-2-adrenoreceptor agonist – acts presynaptically at the spinal cord or supraspinal levels, resulting in reduction of the postsynaptic release of excitatory amino acids thought to be responsible for hypertonicity and spasticity</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Normal half-life: 2 hours
• Extensively metabolized to inactive metabolites; 60% excreted as parent drug and metabolites in urine.
• Half-life increased in renal impairment and clearance reduced by 50%</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">• Sedation, confusion, xerostomia, dizziness
• In renal impairment, monitor closely for adverse reaction (e.g., asthenia, dizziness, dry mouth, somnolence), which are indicators of potential overdose</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">• Start with low dose and titrate to effect e.g. 2 to 8 mg PO TID
• Caution in renal impairment – use reduced doses. If higher doses needed, increase dose instead of increase dosing frequency.</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>50 to 75%</td><td>Use with caution. Start with 2 mg PO daily, increase by 2mg increments. Refer to Dosing section.</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">No data</td><td>No data</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">No – not covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">Tizanidine 2 mg PO daily – $13.50</td></tr>
</table>

Others

Clonidine (Catapres®)			
Mechanism of Action	• Central alpha-2 adrenoreceptor agonist – inhibits painful impulses in the dorsal horn of the spinal cord • Enhanced activity in endogenous pain modulating pathways that use norepinephrine as a neurotransmitter		
Pharmacokinetics	• Normal half-life: 12 to 16 hours (in dialysis half-life significantly prolonged to approximately 41 hour) • 50% hepatic metabolism; 58% excreted unchanged		
Adverse Effects	Sedation, hypotension, dry mouth; abrupt discontinuation may lead to rebound hypertension		
Dosing Guidelines (Normal Renal Function)	Start with low dose – 0.05 mg PO BID		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	Q12 hours	Q12 to 24 hours	Q24 hours
Supplemental Dose After	**IHD**	**PD**	
	None	None	
Drug Coverage	Yes – covered by ODB (0.1 mg dose only)		
Estimated Cost (30-day supply) without dispensing fee (Prices as of October 2018)	Clonidine 0.05 mg PO BID – $2.00		

Nabilone (Cesamet®)			
Mechanism of Action	Synthetic cannabinoid via multiple mechanisms – NMDA receptor antagonist; stimulates serotonergic and norepinephrinergic system; blocks inflammatory action of prostaglandins and substance P		
Pharmacokinetics	• Normal half-life: 2 hours (parent drug), metabolites (35 hours); oral bioavailability 20% • Extensive liver metabolism via multiple isoenzymes; 20 to 24% excreted renally		
Adverse Effects	Sedation, euphoria, poor concentration, vertigo, dysphoric mood, hypotension, dry mouth, visual disturbances		
Dosing Guidelines (Normal Renal Function)	Start with low dose – 0.5 mg PO qHS and titrate to effect		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	100%	100%
Supplemental Dose After	**IHD**	**PD**	
	No data	No data	
Drug Coverage	Yes – covered by ODB		
Estimated Cost (30-day supply) without dispensing fee (Prices as of October 2018)	Nabilone 0.5 mg PO QHS – $23.27		

<table>
<tr><th colspan="4">Tetrahydrocannabinol: Cannabidiol (THC-CBD) (Sativex®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Action on receptors CB1 and CB2 in CNS and peripheral nervous system</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Normal initial half-life: 1 to 2 hours for parent drug and main metabolite
• Because highly liposoluble, terminal half-life between 24 to 36 hours; terminal half-life prolonged in renal failure
• No PK data available in CKD patients</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">Sedation, euphoria, poor concentration, vertigo, nausea, dysgeusia, dysphoric mood, hypotension, dry mouth, visual disturbances; orthostatic hypotension</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">• Start at 1 spray BID (ideally 12 hours apart) and increase by 1 spray/day every 2nd to 3rd day
• Max 12 sprays/day</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>N/A</td><td>Has not been studied; use with caution</td><td>Has not been studied; use with caution</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">No data</td><td>No data</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">No – not covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">THC-CBD 1 bottle – $22.14
Note: May last less than 30 days based on use</td></tr>
</table>

Topical

Diclofenac gel (Voltaren 1.16% Emulgel®, Voltaren 2.32% Emulgel® Extra Strength)			
Mechanism of Action	Inhibits the synthesis of prostaglandin peripherally		
Pharmacokinetics	N/A		
Adverse Effects	• Itchiness, redness, skin irritation; skin rashes; blistering; skin may be more sensitive to sunlight • **Do not apply to cuts or open wounds (systemic absorption will increase)**		
Dosing Guidelines (Normal Renal Function)	• For 1.16% rub a small amount to affected area(s) TID to QID • For 2.32% (extra strength) - 2 gram BID (using dose guide on carton insert) • Available = 1.16%, Emulgel, 5 to 10% in Phlojel		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	N/A	N/A	N/A
Supplemental Dose After	**IHD**	**PD**	
	N/A	N/A	
Drug Coverage	No – not covered by ODB; over the counter		
Estimated Cost (30-day supply) without dispensing fee (Prices as of October 2018)	Voltaren 1.16% Emulgel 50g – $19.99		

Capsaicin 0.025% Cream (Zostrix®)			
Mechanism of Action	Depletes substance P from peripheral sensory C-type neurons which, after repeated application, is presumed to reduce transmission of pain impulses to CNS		
Pharmacokinetics	Onset of action occurs after 14 to 28 days with peak effect after 4 to 6 weeks		
Adverse Effects	• Local burning, stinging or erythema 44 to 81% (most prominent in the first week and diminishes with continued use) • Coughing 5 to 12% due to inhalation of dried capsaicin residue (can be prevented by washing the treated skin 30 to 40 minutes after application)		
Dosing Guidelines (Normal Renal Function)	• Apply sparingly to affected area(s) TID to QID; do not use on broken or irritated skin • Hands should be washed immediately after application, unless hands and fingers are being treated; should not be applied near the eyes		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	N/A	N/A	N/A
Supplemental Dose After	**IHD**	**PD**	
	N/A	N/A	
Drug Coverage	No – not covered by ODB; over the counter		
Estimated Cost (30-day supply) without dispensing fee (Prices as of October 2018)	0.025% cream 60g – $14.14		

The Ontario Renal Network gratefully acknowledges the contributions of the many patients, caregivers, and providers that were involved in preparing this Symptom Management Resource. In addition, a special thank you to the BC Renal Agency and Dr. Sara Davison and the Kidney Supportive Care Research Group (KSCRG), University of Alberta / Northern Alberta Renal Program.

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