Renal Analgesic Brochure

BC Renal Agency
An agency of the Provincial Health Services Authority

Contents

OPIOID

Buprenorphine (BuTrans patch®)

Indications	For moderate pain requiring continuous opioid analgesia.
Mechanism of Action	Partial agonist of mu receptor.
Pharmacokinetics	Normal half life 25 to 37 hrs; Extensive hepatic metabolism by CYP 3A4 and potential for drug interactions; 1% excreted unchanged in urine; 27% inactive metabolites excreted in urine.
Adverse Effects	Opioid associated adverse drug reactions (sedation, respiratory depression, nausea and vomiting, constipation, itchiness); irritation/erythema, pruritus at application site. Risk of accidental overdose when used in acute pain, non-tolerant individuals, or through careless disposal. Might precipitate opioid withdrawal symptoms if administered before other opioid agonist effects have subsided (within 4 hours of short acting opioid or 24 hours after long acting opioid).
Dosing Guidelines (Normal Renal Function)	Start low and titrate to effect, e.g. 5 mcg/h buprenorphine patch q7d (max. 20 mcg/h q7d). Previous opioid should be tapered over first 12 hrs of buprenorphine as absorption is delayed. Starting dose for non-opioid naive patient: 5 to 10 mcg/h q 7 d. Adequate breakthrough medication should be provided when switching to buprenorphine as predicted doses are sometimes too conservative. Available: transdermal patch.

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

Pharmacare Coverage	No
Cost (30 day supply)	4 patches of Buprenorphine 10 mcg/h patch: $95.76

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OPIOID

Codeine Contin® or combination of Acetaminophen-Codeine (Tylenol #2, 3,® Empracet-15,® Empracet-30®) or combination of ASA-Codeine (282,® 292®);

Indications	For moderate nociceptive or musculoskeletal pain. Acute or chronic pain.
Mechanism of Action	Mu receptor agonist.
Pharmacokinetics	Normal half life 2 to 3 hrs; Oral bioavailability 50%; 10% of the dose is metabolized to morphine; 7–10% population cannot metabolize codeine; Active metabolites (norcodeine and morphine) are excreted in the urine in the free and conjugated forms.
Adverse Effects	Opioid associated adverse drug reactions (see buprenorphine); Not well tolerated with doses > 200 mg/day; Caution with combination products – risk of hepatotoxicity with acetaminophen overdose or GI bleed with ASA.
Dosing Guidelines (Normal Renal Function)	**Not ideal for elderly or patients with renal impairment due to active metabolites.** 30 to 60 mg PO q4h (max of 360 mg/day); Sustained release codeine—30 mg PO bid. Available: PO – immediate release (IR); sustained release (SR) e.g. Codeine Contin;® oral liquid; Parenteral – Intra muscular (IM).

Renal Dosing Guidelines GFR (mL/min)	>50 (mL/min)	10 to 50 (mL/min)	<10 (mL/min)
	100%	75%	50%

Supplemental Dose after	IHD	PD
	None	None

Pharmacare Coverage	Codeine IR – yes; Codeine SR – full benefit for patients in Palliative Program. Special Authority required for patients unresponsive or intolerant of codeine IR.
Cost (30 day supply)	Codeine IR 60 mg PO q4h: $33.40 Codeine Contin 50 mg PO bid: $23.40 Codeine 5 mg/mL liquid 30 mg PO q4h: $37.40

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Fentanyl (Duragesic Patch®)

Indications	For moderate nociceptive or musculoskeletal pain. Acute or chronic pain. Neuropathic pain—in higher doses.
Mechanism of Action	Mu receptor agonist.
Pharmacokinetics	Normal half life 7 to 12hr; Extensive hepatic metabolism; <10% excreted unchanged in urine; No known active metabolites; Subcutaneous fat tissue & skeletal muscles absorb fentanyl. From these deposits, fentanyl is then released into systemic circulation.
Adverse Effects	Opioid related adverse drug reactions (see buprenorphine); 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;** Start low and titrate to effect, e.g. 12 mcg/h fentanyl patch q72h; Previous opioid should be tapered off over first 12 hrs 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 q48h dosing. Available: transdermal patch

Renal Dosing Guidelines GFR (mL/min)	>50 (mL/min)	10 to 50 (mL/min)	<10 (mL/min)
	100%	75%	50%

Supplemental Dose after	IHD	PD
	No data	No data

Pharmacare Coverage	Full benefits for patients in Palliative Program. Special Authority required for pts unresponsive or intolerant to codeine, oxycodone, morphine or hydromorphone.
Cost (30 day supply)	For 10 patches: 12 mcg: $37.40 50 mcg: $128.40 75 mcg: $181.40

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OPIOID

Hydromorphone (Dilaudid® and Hydromorph Contin®)

Indications	For moderate to severe nociceptive or musculoskeletal pain. Acute or chronic pain. Neuropathic pain—in higher doses.
Mechanism of Action	Mu receptor agonist.
Pharmacokinetics	Normal half life 2.5 hrs; Oral bioavailability 50%; Extensive hepatic metabolism; <13% excreted unchanged in urine; Glucuronide metabolites are excreted renally.
Adverse Effects	Opioid related adverse drug reactions (see buprenorphine); 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
Dosing Guidelines (Normal Renal Function)	Start low and titrate to effect, e.g. 0.5 to 1 mg PO q3-4h; sustained release 3 mg PO bid. Available: PO – immediate release(IR); sustained release (SR) e.g. Hydromorph Contin,® oral liquid, suppository, Parenteral – SC/IM/IV

Renal Dosing Guidelines GFR (mL/min)	>50 (mL/min)	10 to 50 (mL/min)	<10 (mL/min)
	100%	75%	50%

Supplemental Dose after	IHD	PD
	No	No

Pharmacare Coverage	Hydromorphone IR – yes; Hydromorphone SR – full benefit for patients in Palliative Program or Special Authority required for patients unresponsive or intolerant of hydromorphone IR or morphine SR.
Cost (30 day supply)	Hydromorphone IR 1 mg PO q3h: $27.40 Hydromorphone SR 3 mg PO bid: $45.40

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OPIOID

Methadone

Indications	For severe nociceptive or neuropathic pain. Chronic pain.
Mechanism of Action	Mu receptor agonist, δ receptor agonist, NMDA receptor antagonist, inhibition of serotonin or norepinephrine re-uptake.
Pharmacokinetics	Normal half life 12 to >150 hrs; 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.
Adverse Effects	Opioid related adverse drug reactions (see buprenorphine); 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.
Dosing Guidelines (Normal Renal Function)	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: powder – compounded as 1 mg/mL oral liquid; as well as 10, 15 and 25 mg/tablet. **Methadone prescribing licence required.**

Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	100%	50–75%

Supplemental Dose after	**IHD**	**PD**
	None	None

Pharmacare Coverage	Yes.
Cost (30 day supply)	Methadone 1 mgr/mL, 15 mg per day: $18.00

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OPIOID

Morphine (MOS,® MS-IR,® Statex,® MS Contin, M-Eslon®)

Indications	For moderate to severe nociceptive or musculoskeletal pain. Acute or chronic pain.. Neuropathic pain—in higher doses.
Mechanism of Action	Mu receptor agonist.
Pharmacokinetics	Normal half life 2 to 3 hrs; Oral bioavailability 30%; Extensive hepatic metabolism; 2 to 12% excreted unchanged; Active metabolites excreted renally.
Adverse Effects	**Not ideal for elderly or patients with renal impairment due to accumulation of active metabolites.** Opioid related adverse drug reactions (see buprenorphine); Myoclonus with high dose.
Dosing Guidelines (Normal Renal Function)	Start low and titrate to effect, e.g. 2.5 to 5 mg PO q3 to 4h; Sustained release 10 mg SR PO bid. Available: PO – immediate release (MOS,® MS- IR,® Statex®); sustained release (SR) e.g. MS Contin,® M-Eslon,® Kaldian® oral liquid; suppository; Parenteral – SC/IM/IV.

Renal Dosing Guidelines GFR (mL/min)	>50 (mL/min)	10 to 50 (mL/min)	<10 (mL/min)
	100%	75%	50%

Supplemental Dose after	IHD	PD
	None	No data

Pharmacare Coverage	Yes.
Cost (30 day supply)	Morphine IR 5 mg PO q4h: $26.40; Morphine SR 10 mg PO bid: $20.40

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OPIOID

Oxycodone (Supeudol,® Oxy- IR®) or combination of Acetaminophen-Oxycodone (Percocet®) or ASA-Oxycodone (Percodan®), Oxycontin®

Indications	For moderate nociceptive or musculoskeletal pain. Acute or chronic pain. Neuropathic pain—in higher doses.
Mechanism of Action	Mu receptor agonist; kappa receptor agonist (more in females – ? Clinical significance).
Pharmacokinetics	Normal half life 3 to 4 hrs; Oral bioavailability 60%; Metabolized in liver to active metabolites noroxycodone via CYP3A4 and oxymorphone via CYP2D6; 7% of the population cannot metabolize oxycodone to active metabolites; oxycodone and its active metabolites are primarily excreted renally; Neuroleptics, SSRI also inhibit its metabolism.
Adverse Effects	Opioid related adverse drug reactions (see buprenorphine); Increased adverse effects in ultra-rapid CYP 2D6 metabolizers.
Dosing Guidelines (Normal Renal Function)	Start low and titrate to effect, e.g. 2.5 to 5 mg PO q3 to 4h; Sustained release 10 mg SR PO bid. Available: PO – immediate release; sustained release (SR) e.g. OxyContin,® suppository.

Renal Dosing Guidelines GFR (mL/min)	>50 (mL/min)	10 to 50 (mL/min)	<10 (mL/min)
	100%	75%	50%

Supplemental Dose after	IHD	PD
	No data	No data

Pharmacare Coverage	Oxycodone IR – Yes; Oxycodone SR - full benefit for pts in Palliative Program. Special Authority required for patients unresponsive or intolerant to oxycodone IR and morphine SR.
Cost (30 day supply)	Oxycodone IR 5 mg PO q4h: $36.40; Oxycodone SR 10 mg PO bid: $58.40

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OPIOID

Tramadol (Ultram®) Tramadol CR (Zytram XL®); Tramadol ER (Ralivia® and Tridural®) or combination of Acetaminophen 325 mg and Tramadol 37.5 mg (Tramacet®)

Indications	For moderate to moderately severe nociceptive or musculoskeletal pain. Also studied in chronic or neuropathic pain.
Mechanism of Action	Mu receptor agonist by both tramadol and its active M1 metabolite; Weak inhibition of serotonin and norepinephrine re-uptake.
Pharmacokinetics	Normal half life 4 to 6 hrs (tramadol) and 7 hrs (M1 metabolite); Hepatic metabolism via demethylation, glucuronidation, and sulfation; M1 metabolite formed by CYP 2D6; 30% excreted as unchanged drug and 60% as metabolites.
Adverse Effects	Sedation, fatigue, dizziness, nausea and vomiting, constipation, itchiness, seizure (increased risk with higher dose).
Dosing Guidelines (Normal Renal Function)	Tramacet: 1 to 2 TABS PO q4 to 6h PRN (max: 8 TABS/day); **Sustained release TABS NOT recommended in CrCl < 30 mL/min.**

Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	50%	50%

Supplemental Dose after	**IHD**	**PD**
	No	No data

Pharmacare Coverage	No.
Cost (30 day supply)	Tramacet 1 TAB PO bid: $46.30 Tramadol 100 mg PO bid: $76.80

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NON OPIOID

Acetaminophen (Tylenol®)

Indications	For mild to moderate pain and as an adjunct to opioids for severe pain.
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 hrs; 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 q4h 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)**
	q4h	q6h	q8h

Supplemental Dose after	**IHD**	**PD**
	None	None

Pharmacare Coverage	Special Authority required for acetaminophen; See *http://www.health.gov.bc.ca/pharmacare/sa/criteri a/restricted/acetaminophen.html*.
Cost (30 day supply)	$5–10.00 per 100 Tabs

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NON OPIOID

Non-steroidal anti-inflammatory drugs (NSAIDs) e.g. Ibuprofen (Motrin,® Advil®), Diclofenac (Voltaren®), Naproxen (Naprosyn®) COX-2 inhibitors e.g. Celecoxib (Celebrex®)

Indications	For mild to moderate bone pain, inflammatory and rheumatoid conditions, and as an adjunct to opioids for severe pain.
Mechanism of Action	Inhibits the synthesis of prostaglandin peripherally. Inhibits COX-2 enzyme which is activated during inflammation to cause signs and symptoms associated with inflammation.
Pharmacokinetics	Normal half life 2 to 3 hrs for ibuprofen and diclofenac; 12 to 15 hrs for naproxen, Extensive hepatic metabolism, Little excreted unchanged but inactive metabolites are primarily excreted by the kidneys.
Adverse Effects	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.
Dosing Guidelines (Normal Renal Function)	These drugs have a ceiling effect: ibuprofen 200 to 400 mg PO q4 to 6h; 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.**

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

Pharmacare Coverage	Special Authority required for celecoxib; See *http://www.health.gov.bc.ca/pharmacare/sa/criteria/genericbrandtable.html*.
Cost (30 day supply)	Ibuprofen 400 mg PO q4h: $10.00 Diclofenac 50 mg PO tid: $41.00 Naproxen 500 mg PO bid: $18.00 Celecoxib 100 mg PO od: $46.40

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ANTICONVULSANT

Gabapentin (Neurontin®)

Indications	For neuropathic pain – first line for lancinating or paroxysmal pain.		
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 hrs; 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 PO tid, titrate gradually to effect and as tolerated to a max of 3600 mg/day (in 4 divided doses).		
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 daily	usual max of 300 mg/day
Supplemental Dose after	**IHD**	**PD**	
	100 mg or dose after HD	300 mg q2d	
Pharmacare Coverage	Yes		
Cost (30 day supply)	Gabapentin 200 mg PO od: $17.60		

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ANTICONVULSANT

Pregabalin (Lyrica®)

Indications	For neuropathic pain (expensive and minimal advantage over gabapentin).		
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 hrs; Oral bioavailability 90%; Limited hepatic metabolism, 90% excreted unchanged in the urine.		
Adverse Effects	Sedation, confusion, incoordination, peripheral edema.		
Dosing Guidelines (Normal Renal Function)	Start with 25 mg PO qHS, titrate to effect and as tolerated to a max of 300 mg PO bid.		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	25 to 150 mg/day	25 to 75 mg/day
Supplemental Dose after	**IHD**	**PD**	
	25 mg or dose after HD	No data	
Pharmacare Coverage	No		
Cost (30 day supply)	Pregabalin 50 mg PO qHS: $54.80		

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ANTICONVULSANT

Topiramate (Topamax®)

Indications	For neuropathic pain – third line.		
Mechanism of Action	Inhibition of GABA-ergic pathways and blocks AMPA/glutamate pathways.		
Pharmacokinetics	Normal half life 6 hrs, Limited hepatic metabolism, 55 to 97% excreted unchanged in urine.		
Adverse Effects	Sedation, confusion, agitation, tremors, paresthesia, speech disorders, weight loss, narrow angle glaucoma, non-anion metabolic acidosis, kidney stones.		
Dosing Guidelines (Normal Renal Function)	Start with 25 mg PO od, titrate gradually to effect and as tolerated up to 200 mg PO bid.		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	50%	25%
Supplemental Dose after	**IHD**	**PD**	
	Dose after HD	50%	
Pharmacare Coverage	Yes		
Cost (30 day supply)	Topriamate 50 mg PO qHS: $48.80		

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ANTICONVULSANT

Tricyclic Antidepressants e.g.Amitriptyline (Elavil®), Desipramine (Norpramin®), Nortriptyline (Aventyl®)

Indications	For neuropathic pain or chronic pain complicated by depression or insomnia.
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; Enhance 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 hrs depending on the agent; Extensive hepatic metabolism; little excreted unchanged but inactive metabolites are primarily excreted by the kidneys.
Adverse Effects	**Nortriptyline and desipramine are 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, desipramine, 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

Pharmacare Coverage	Yes
Cost (30 day supply)	Desipramine 50 mg PO qHS: $16.40 Nortriptyline 50 mg PO qHS: $20.40

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ANTIDEPRESSANT

Duloxetine (Cymbalta®)

Indications	For neuropathic pain associated with diabetic peripheral neuropathy; fibromyalgia .		
Mechanism of Action	It inhibits neuronal serotonin, norepinephrine and dopamine reuptake.		
Pharmacokinetics	Normal half-life from 8 to 17 hrs; extensive liver metabolism by CYP 1A2 and 2D6; 70% excreted renally (mainly metabolites).		
Adverse Effects	Diaphoresis, constipation, nausea, dizziness, headache, fatigue, hepatotoxicty. **Contraindicated if CrCl< 30 ml/min.**		
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	No data
Supplemental Dose after	**IHD**	**PD**	
	No data	No data	
Pharmacare Coverage	No		
Cost (30 day supply)	Duloxetine 60 mg PO daily: $118.20		

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ANTIDEPRESSANT

Venlafaxine (Effexor XR®)

Indications	For neuropathic pain or chronic pain complicated by depression.		
Mechanism of Action	Inhibits neuronal serotonin, norepinephrine and dopamine reuptake.		
Pharmacokinetics	Normal half-life of 5 hrs, extensive hepatic metabolism through CYP 2D6, active metabolites O-desmethylvenlafaxine (normal half-life 11 hrs), mainly renally eliminated; half-life prolonged in renal failure, not dialyzable.		
Adverse Effects	Hypertension, excessive sweating, weight loss, constipation, nausea, dizziness, feeling nervous, headache, impotence.		
Dosing Guidelines (Normal Renal Function)	Start at low dose (37.5 mg PO daily) and titrate weekly up to 150 mg/day.		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	75%	50%	50%
Supplemental Dose after	**IHD**	**PD**	
	None	None	
Pharmacare Coverage	Yes		
Cost (30 day supply)	Venlafaxine 75 mg PO qHS: $29.40		

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MUSCLE RELAXANT

Baclofen (Lioresal®)

Indications	Acute musculoskeletal pain; throbbing, aching and spasm (grabbing type pain); spasticity associated with multiple sclerosis or other diseases of the spinal cord, esp. traumatic lesions; pain associated with strokes.		
Mechanism of Action	GABA receptor agonist– binds to the GABA receptors located in the substantia gelatinosa (lamina II) and lamina III in the spinal cord to block mono- and polysynaptic reflexes.		
Pharmacokinetics	Normal half-life 3 to 7hrs; Oral bioavailability 100%; Limited hepatic metabolism; 85% excreted unchanged in urine.		
Adverse Effects	Sedation, weakness, cognitive impairment.		
Dosing Guidelines (Normal Renal Function)	Start with low dose and titrate to effect e.g. 5 to 20 mg PO tid to qid.		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	Start with 2.5 to 5 mg PO bid	Start with 2.5 mg PO bid
Supplemental Dose after	**IHD**	**PD**	
	No data	No data	
Pharmacare Coverage	Yes		
Cost (30 day supply)	Baclofen 10 mg PO tid: $31.40		

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MUSCLE RELAXANT

Benzodiazepines (e.g. Diazepam (Valium®), Lorazepam (Ativan®), Clonazepam (Rivotril®))

Indications	Acute muscle spasm, lancinating or paroxysmal neuropathic pain.		
Mechanism of Action	GABA receptor agonist.		
Pharmacokinetics	Extensive hepatic metabolism.		
Adverse Effects	Sedation; confusion; addictive potential; withdrawal symptoms (taper slowly after long term use).		
Dosing Guidelines (Normal Renal Function)	Start with low dose/drug specific dosing. Not recommended for long term use.		
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	
Pharmacare Coverage	Yes		
Cost (30 day supply)	Lorazepam 1 mg PO daily: $4.40 Clonazepam 0.5 mg daily: $6.40		

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MUSCLE RELAXANT

Tizanidine (Zanaflex®)

Indications	Acute musculoskeletal pain; throbbing, aching and spasm (grabbing type pain); multiple sclerosis; pain associated with strokes.		
Mechanism of Action	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.		
Pharmacokinetics	Normal half life 2 hrs. Extensively metabolized to inactive metabolites. 60% excreted as parent drug and metabolites in urine.		
Adverse Effects	Sedation, confusion, xerostomia.		
Dosing Guidelines (Normal Renal Function)	Start with low dose and titrate to effect e.g. 2 to 8 mg PO tid.		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	50 to 75%	Start with 2 mg PO daily
Supplemental Dose after	**IHD**	**PD**	
	No data	No data	
Pharmacare Coverage	Special Authority required for treatment of spasticity in patients unresponsive or intolerant of Diazepam or Baclofen.		
Cost (30 day supply)	Tizanidine 4 mg PO tid: $73.00		

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OTHERS

Clonidine (Catapres®)

Indications	Second line agent for patients with chronic pain refractory to NSAIDs and antidepressant.		
Mechanism of Action	Central alpha-2 adrenoreceptor agonist – inhibit 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 hrs; 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)**
	q12h	q12 to 24	q24h
Supplemental Dose after	**IHD**	**PD**	
	dose after HD	q24h	
Pharmacare Coverage	Yes		
Cost (30 day supply)	Clonidine 0.05 mg PO bid: $27.40		

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OTHERS

Nabilone (Cesamet®)

Indications	For patients with neuropathic pain refractory to standard agents.		
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 hrs (parent drug), metabolites (35hrs); 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	
Pharmacare Coverage	Yes		
Cost (30 day supply)	Nabilone 0.5 mg PO qHS: $108.40		

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OTHERS

Tetrahydrocannabinol: Cannabidiol (THC-CBO) (Sativex®)

Indications	Adjunctive treatment for patients with neuropathic pain.		
Mechanism of Action	Action on receptors CB1 and CB2 in CNS and peripheral nervous system.		
Pharmacokinetics	Normal initial half life 1 to 2 hrs for parent drug and main metabolite; because highly liposoluble, terminal half life between 24 to 36 hrs. Terminal half life prolonged in renal failure. No PK data available in CKD patientss.		
Adverse Effects	Sedation, euphoria, poor concentration, vertigo, nausea, dysgeusia, dysphoric mood, hypotension, dry mouth, visual disturbances; orthostatic hypotension.		
Dosing Guidelines (Normal Renal Function)	Start at 1 spray bid (ideally 12 hours apart) and increase by 1 spray/day every 2nd to 3rd day. Max 12 sprays/day.		
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**	
	No data	No data	
Pharmacare Coverage	No		
Cost (30 day supply)	THC-CBD 1 bottle (51 doses): $138.51		

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TOPICAL

Diclofenac gel (Voltaren Emulgel®), Diclofenac 5 to 10% in Phlojel

Indications	For the relief of aches and pain associated with acute, localized muscle or joint injuries.		
Mechanism of Action	Inhibits the synthesis of prostaglandin peripherally.		
Pharmacokinetics			
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)	Rub a small amount to affected area(s) tid to qid. Available = 1.16%, Emulgel, 5 to 10% in Pholjel		
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	
Pharmacare Coverage	No		
Cost (30 day supply)	Voltaren Emulgel $9.99 for 30g Voltaren Emulgel $12.99 for 100g Diclofenac 5% in Phlojel $21.50 for 25 g Diclofenac 10% in Phlojel $25.00 for 25 g		

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TOPICAL

Capsaicin cream or ointment (Zostrix®)

Indications	For the relief of localized neuralgia, e.g. diabetic neuropathy, post-herpetic neuralgia, osteoarthritis, rheumatoid arthritis.		
Mechanism of Action	Depletes sustance 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 7 to 14 days in arthritic disorders or 14 to 28 days in neuralgias with peak effect after 4 to 6 wks.		
Adverse Effects	Local burning, stinging or erythema in 44 to 81% of patients (most prominent in the first wk and diminishes with continued use); Coughing 5 to 12% of patients 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) bid to qid. Available as 0.025% or 0.075% cream ointment.		
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	
Pharmacare Coverage	No		
Cost (30 day supply)	Capsaicin cream or ointment $15.00 for 60 g		

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TOPICAL

Lidocaine/Prilocaine cream or patch (EMLA®)

Indications	For minor procedures, e.g. needle insertion.		
Mechanism of Action	Eutetic mixture of amide-type local anesthetics. Stabilize neuronal membrane by preventing the initiation and conduction of nerve impulses.		
Pharmacokinetics	Local analgesia of intact skin is achieved after 60 min of application under occlusive dressing. Efficacy and depth of skin analgesia increase with application time up to 120 min. Duration of analgesia is at least 2 hrs.		
Adverse Effects	Transient local reactions, e.g. paleness, erythema, edema. Mild burning, itching, tingling sensation at application site. Allergic reactions (rare).		
Dosing Guidelines (Normal Renal Function)	Apply 1.5g (10cm^2) or 1 patch under occlusive dressing for a minimum of 1 hr.		
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	
Pharmacare Coverage	No		
Cost (30 day supply)	Lidocaine 2.5%/Prilocaine 2.5% cream $47.99 for 30 g		

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INJECTABLES

Bupivacaine (Marcaine®)

Indications	For procedures, e.g. needle insertion.		
Mechanism of Action	Stabilizes neuronal membrane by blocking the fast voltage gated sodium channels in the neuronal cell membrane and preventing the initiation and conduction of nerve impulses.		
Pharmacokinetics	Duration of action: 2 to 3 times longer than Lidocaine.		
Adverse Effects	Burning at injection site, rare allergic reactions.		
Dosing Guidelines (Normal Renal Function)	0.3 to 0.5 mL Intradermal/subcutaneous pre-cannulation.		
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	
Pharmacare Coverage	N/A		
Cost (30 day supply)	Bupivacaine $2.16 per dose (polyamp)		

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INJECTABLES

Lidocaine (Xylocaine®)

Indications	For procedures, e.g. needle insertion.		
Mechanism of Action	Stabilizes neuronal membrane by blocking the fast voltage gated sodium channels in the neuronal cell membrane and preventing the initiation and conduction of nerve impulses.		
Pharmacokinetics	Onset of action: 1 to 3 min; duration: within 10 min; Elimination half-life ~ 1.5 to 2 hrs in most patients.		
Adverse Effects	Burning at injection site. Rare allergic reactions.		
Dosing Guidelines (Normal Renal Function)	0.3 to 0.5 mL Intradermal/subcutaneous pre-cannulation.		
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	
Pharmacare Coverage	N/A		
Cost (30 day supply)	Lidocaine $1.71 per dose (polyamp)		

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BCPRA Guidelines and Drug Choices for Chronic Pain in Hemodialysis Patients

BC Renal Agency
An agency of the Provincial Health Services Authority

Musculoskeletal/Nociceptive Pain

Pain score 1 to 4 out of 10

Non opioid analgesics are first line of treatment.

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 q3months if dose >2.6 g/day.

Topical NSAIDs: Apply tid to qid for localized pain (diclofenac 5 to 25% in Phlojel, diclofenac gel 1.16% (OTC)).

Capsaicin cream 0.025% or 0.075%: Apply bid to qid for localized pain (may take >2 weeks for onset of action).

Pain is not controlled or initial pain score is ≥5 out of 10

Add an opioid to non-opioid analgesic and or adjuvant:
AVOID MORPHINE AND MEPERIDINE

Complete opioid abuse risk assessment scale.

Dosage can be titrated qHD run based on pain assessment.

Hydromorphone IR: 0.25 to 0.5 mg PO q3-4 hours PRN (Note: neurotoxic metabolite H3G accumulates if HD D/Ced)

Oxycodone IR: 1.25 to 2.5 mg PO q3-4 hours PRN

Percocet (acetaminophen 325 mg-oxycodone 5 mg) can be used to reduce pill burden once pain control is optimized.

Regular opioid dosing (e.g. hydromorphone 0.5 mg PO q3hours regularly) should be considered for patient with severe pain (pain score of 7 to 10 out of 10).

Once analgesic requirement is stable, consider conversion to long-acting opioid agent. Continue providing short-acting opioid agent for breakthrough pain (1/10th total daily dose q2 hours PRN)

Hydromorphone CR: PO q12 hours (available in 3 mg increments)

Oxycodone CR: PO q12 hours (available in 10 mg increments)
Note: If pain management not optimal before next scheduled SR dose, consider giving 1/3 total daily dose of hydromorphone or oxycodne CR q8 hours.

Fentanyl transdermal patch: Initial dose: 12 µg/h patch q3 days, increase dose to next patch size every 2nd HD run. Caution in opioid naïve patient. Fentanyl patch strengths available: 12 µg/h, 25 µg/h, 50 µg/h, 75 µg/h, 100 µg/h.

Alternative agents:

Tramadol (Ultram®): Option for moderate pain (5 to 6 out of 10 without opioid). It has opioid activity (binds to µ receptor) and inhibits reuptake of serotonin and norepinephrine. Initial dosage: 25 mg PO daily to bid (max. daily dose 100 mg PO bid) (Tramadol CR (Zytram XL®) is contraindicated for CrCl <30 ml.min.

Acetaminophen 325mg and tramadol 37.5 mg (Tramacet®): 1 TAB PO bid. Maximum daily dose: 2 TAB PO bid.

Buprenorphine transdermal patch: Option for moderate pain (5 to 6/10 without opioid). Minimal renal elimination. Initial dosage: 5 to 10 µg/h patch q7 days, even for patients not naïve to opioid. Dose can be increased q7 days. Max dose: 20 µg/h q7 days. Acetaminophen should be used for breakthrough pain. Caution for withdrawal symptoms if switching from other opioids.

Methadone: Option for opioid allergy, adverse effects/refractory pain not controlled by other opioids or **if patient taken off HD.**

Required authorization from CPSBC to prescribe methadone for analgesia. Baseline QTc and repeat EKG if daily dose >60 mg. Many drug interactions (e.g. macrolides, fluoroquinolones, fluconazole etc.) Initial dose: 1 or 2 mg PO or SL tid and titrate dose gradually every 2nd HD run.

Neuropathic Pain (Defined by ≥ to 4 of the following symptoms: burning pain, pain to cold, electric shocks, tingling, pins and needles, numbness, itchy, increase pain with light touch, decrease sensation)

Pain score 1 to 4 out of 10

Gabapentin: 100 mg PO hs and titrate weekly by 100 mg/day. Maximum dose: 300 mg/day. Adequate trial duration: 4 to 6 weeks.

Capsaicin cream 0.025% or 0.075%: Apply bid to qid for localized pain (may take >2 weeks for onset of action).

Intolerable adverse effects (e.g. sedation, dizziness)

Pain control is inadequate at target dose for 2–4 weeks or initial pain ≥5 out of 10

Taper off Gabapentin

Nortriptyline/Desipramine: 10 mg PO daily (give dose at hs for nortriptyline) and titrate weekly by 10 mg/day. Maximum dose: 100 mg/ day. Should be used with caution in patients with history of cardiac disease. Combination TCA + gabapentin 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.

Topiramate: 25 mg PO daily and titrate every 1 to 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

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.

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.

Additional options (see chart): clonidine, tizanidine, benzodiazepines, baclofen.

Inadequate response

OPIOID CONVERSION TABLE (for patients on chronic opioids)*

Drug	Parenteral	Oral
Morphine	10 mg	20 mg to 30 mg
Hydromorphone	2 mg	4 mg
Oxycodone	N/A	20 mg
Codeine	120 mg	200 mg
Fentanyl	100 µg (0.1 mg)	N/A
Fentanyl Patch	** see below	
Buprenorphine Patch	** see below	
Methadone	N/A	variable – start at 1/10th morphine dose

* As per PHC/VCH opioid conversion table (last update Jan 15/2010)
** Recommended conversion from PO daily hydromorphone equivalent to fentanyl and buprenorphine:

Hydromorphone (mg/24 hrs)	Fentanyl (µg/hr/)	Buprenorphine (µg/h)
< 6		5
6–12		10
12–26	25	20
27–35	37	
36–44	50	
45–53	62	
54–62	75	
63–71	87	
72–80	100	

Pain Management Agents Cost Coverage

Drugs covered under BCPRA
Drugs covered under Pharmacare
Drugs needing a special authority request to be covered under Pharmacare

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BC Renal Agency
An agency of the Provincial Health Services Authority

Drug Cost Comparison

Drug Name	Estimated Daily Dose	Estimated Daily Cost
Acetaminophen Extra Strength 500 mg/TAB	4 g/day	$ 0.23 (OTC*) $0.14 (S.A.*)
Acetaminophen CR formulation (Tylenol Arthritis,® or generic)	3.9 g/day	$ 0.56
Buprenorphine patch	20 µg/h q7days	$ 6.84 ($47.88 for 2 patches of 10 µg/h)
Desipramine	50 mg/day	$ 0.72
Fentanyl patch	25 µg/h q3days	$ 1.88 ($5.64/patch)
Gabapentin	300 mg/day	$ 0.66
Hydromorphone IR	6 mg/day	$ 0.46
Hydromorphone CR	6 mg/day	$ 1.40
Methadone	6 mg/day	$ 1.08
Nabilone	2 mg/day	$13.28
Nortriptyline	50 mg/day	$ 0.48
Oxycodone IR	20 mg/day	$ 0.56
Oxycodone CR	20 mg/day	$ 1.82
Pregabalin	75 mg/day	$ 1.70
THC: CBD (Sativex®)	10 sprays/day	$27.15 ($138.51 for 1 vial of 51 doses)
Topiramate	200 mg/day	$ 1.91 (1 TAB of 200 mg) $ 2.56 (2 TABS of 100 mg)
Tramadol	200 mg/day	$ 2.56
Tramadol-Acetaminophen (Tramacet®)	2 TABS/day	$ 1.50
Venlafaxine	75 mg/day	$ 0.98

Topical Agents	Usual Format	Cost for Specific Format
Diclofenac 1.16% Emulgel	30 g	$ 9.99
Diclofenac 5% in Phlojel	25 g	$21.50
Diclofenac 10% in Phlojel	25 g	$25.00
Capsaicin cream 0.025%	25 g	$ 8.50
Capsaicin cream 0.075%	25 g	$ 9.50

Drugs covered under BCPRA

Drugs covered under Pharmacare

Drugs needing a special authority request to be covered under Pharmacare

All prices listed are as of October 2011

*OTC: Over the counter medication
*S.A.: Pharmacare special authority

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