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GUIDELINE

Drug listing – enteral and parental

Guidelines for the management of acute pain in specific scenarios 2022

Pain treatment requires an understanding of the physiology and nature of pain and the drugs and interventions available for treatment. The impact thereof on patients is important and applicable to the general practitioner and his or her patients as well.

The following article is a chapter from the Acute pain guidelines published by the South African Society of Anaesthesiologists (SASA). As stated in the foreword: *Pain is inevitable. Suffering is optional*. (Haruki Murakami).

To access the complete guideline, please visit https://ua.medpharm.co.za/journals/sajaa/2022/01/01/00

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Note that while examples of generic drugs are listed below, the list should not be considered comprehensive. Drugs are regularly added and removed by pharmaceutical companies and the latest drug indices should be consulted if necessary.

Opioids – mainly for severe pain

Opioids are grouped into the following categories:

1. Opioid agonists
2. Opioid antagonists
3. Opioid dualists – with agonist and antagonist properties, theoretically cancelling side effects
4. Atypical opioids

Side effects of all opioids include the following:

1. Respiratory depression – opioid patches should not be used for acute pain
2. Sedation (best indicator of incipient respiratory depression)
3. Nausea and vomiting
4. Constipation
5. Pruritis
6. Tolerance
7. Addiction

Table I: Relevant information for opioids

Opioid agonists			
Drug	**Adult**	**Porphyria**	**Relevant information**
Morphine MST Continus • Jurnista (hydromorphone HCl) • Morphine Sulphate-Fresenius • Pharm-Q Morphine injection • Cyclimorph (Morphine + Cyclizine)	**Oral** 10–20 mg q 12-hourly **Intramuscular** 0.1–0.3 mg/kg q 4-hourly **Intravenous** ***Bolus*** 1–5 mg q 1-hourly ***Infusion*** Loading dose followed by titration guided by pain and sedation scale – 3–5 mg/hr **PCA** Bolus 1–2 mg with 5–10 min lockout time	USE	***a. Oral*** morphine • Preparations are used in the treatment of chronic pain • Dosage is dependent upon the severity of pain and patients' previous analgesic history (i.e. opioid naïve or not) ***b. Intravenous*** morphine • IV titrations should be done in ICU • Infusions may readily cause excessive accumulation of the drug with respiratory depression and, if undetected, could lead to **death** • PCA (patient-controlled analgesia) is a safer option • IV opioid PCA provides better analgesia than conventional parenteral opioid regimens • Patient preference for IV PCA is higher when compared with conventional regimens ***c. Neuraxial*** morphine • Neuraxial opioids should be preservative free (PF) • Extreme caution with neuraxial morphine is advised because the onset of respiratory depression only occurs 8–12 hours after administration • Respiratory depression in the elderly is more prevalent and the neuraxial dose of opioids should be drastically decreased

Pethidine • Pethidine HCl-Fresenius • Pharma-Q Pethidine	**Intramuscular** 1–1.5 mg/kg q 3–4-hourly **PCA** 10–20 mg bolus with 5–10 min lockout time	USE	• Pethidine has never been shown to be superior to other opioids • It is no longer considered a 'first line' analgesic • Use depends on the preference and experience of the prescriber • Pethidine commonly causes euphoria/dysphoria • Drug interactions with MAOI and SSRI
Papaveratum • Omnopon-Fresenius	**Intramuscular** 0.15 mg q 4-hourly		**Not for children under the age of 1 year**
Dihydrocodeine Tartrate • Df-118	**Oral** 30 mg q 4–6-hourly **Intramuscular** 25–50 mg q 4–6-hourly	USE	**Not for children under the age of 4 years** • 30 mg of DF-118 gives analgesia comparative to 10 mg morphine • May worsen asthma
Codeine • Lennon-Codeine Phosphate	15–60 mg daily p.o.	USE	***Mild to moderate pain*** • Codeine is a prodrug with low receptor affinity • Only 10% is demethylated via CYP2D6 enzymes to morphine • *Ultra-rapid metabolisers* may produce high levels of morphine which in turn may lead to respiratory depression in children • Conversely, *poor metabolisers* may produce such low levels of morphine that no analgesia will be evident • Respiratory depression may also occur in patients with obstructive sleep apnoea (OSA) • The FDA has contraindicated the use in **children under 12 years of age**
Oxycodone • Oxynorm – injection and immediate-release tabs • Oxycontin – prolonged-release tabs • TarginAct – prolonged-release tabs • Oxycorrell – caps	***Oxycontin tablets (sustained-release)*** 5 mg, 10 mg, 20 mg, 40 mg, 80 mg Dose depends on the severity of the pain Recommendation is to start with 5–10 mg p.o. bd in an *opioid naïve* patient ***Oxynorm*** *Injection* 1–10 mg/ml slowly over 1–2 minutes IV For PCA and infusion check package insert *Oral* 5 mg, 10 mg, 20 mg For severe postoperative pain Start with 5 mg p.o. q 4–6-hourly ***TarginAct (prolonged-release)*** 5 mg, 10 mg, 20 mg, 40 mg q 12-hourly ***Oxycorrell*** 5 mg, 10 mg, 20 mg q 4–6-hourly	USE	***Mild to moderate to severe pain*** • Has identical opioid side effect and contraindication profile • Opioid alkaloid thebaine is the main ingredient and works on μ_1-receptor • Pharmacology depends on age of patient; elderly patients have a 15% higher plasma level • Excreted in urine, drastically decrease dose in renal failure • The combination of oxycodone and naloxone in TarginAct® decreases constipation • This combination may also be a deterrent of abuse potential
Fentanyl • ADCO Tenyl • Durogesic • Fendermal	**Transdermal patches**		• These patches are only recommended in chronic pain management

Opioid dualists

Drug	Adult	Porphyria	Relevant information
Tilidine • Valeron	**Drops** 10–20 drops q 6–8-hourly	UWECO	***For moderate to severe pain*** • 1 drop = 2–5 mg • Probably better to calculate dose according to ***weight*** rather than age • **Not for children under the age of 1 year** • **Do not exceed single dose of 1 mg/kg** • Drops are useful in ***adults*** requiring analgesia and having dysphagia
Pentazocine • Sosenol	**Injection** 30–40 mg q 3–4-hourly IM/IV/SC (If IV, only 30 mg/dose) Maximum of 360 mg/24 hours	AVOID	***For moderate to severe pain*** • Not a potent analgesic, but proponents claim superior postoperative analgesia for varicose vein operations • Also increases peripheral vascular resistance that may be detrimental in elderly patients • Respiratory depression is prevalent in children

Buprenorphine • Sovenor (transdermal) • Subutex (high dose for addicts) • Temgesic (sublingual and parenteral for analgesia)	**Transdermal patch** 5, 10 or 20µg/hr **Sublingual** 0.2–0.4 mg q 6–8-hourly (Dose for opioid addiction is higher) **Deep IM/slow IV infusion** 0.3–0.6 mg q 6–8-hourly	USE	***For moderate to severe pain*** • Transdermal patch (Sovenor) recommended for chronic pain • High doses (Subutex) used for weaning patients with opioid addiction • Patients may experience excitation/hallucinations • Contraindications: ◦ Concomitant MAOI ◦ Acute asthma ◦ Not for children under the age of 12 years ◦ IM injection must be 'deep'

Opioid antagonists

Drug	Adult	Porphyria	Relevant information
Naloxone • Naloxone HCl Fresenius • Pharma-Q Naloxone HCl	**IV** 0.006 mg/kg		• May cause pulmonary oedema if entire calculated dose is rapidly administrated • Ampoule contains 0.4 mg; this should be diluted in 10 ml prior to administration • Naloxone reverses all opioid effects • The half-life may only be 15–60 minutes • Unwanted opioid side effects may re-occur, warranting re-administration of naloxone

Atypical opioid

Drug	Adult	Porphyria	Relevant information
Tramadol • Austell-Tramadol • Dolotram • Domadol • Synotram • Tamoltra • Tramacet • Tramal • Tramahexal • Tramaspen • Tramazac	**Oral** *Capsules* 50–150 mg q 4–6-hourly to a maximum of 400 mg/day *SR tabs* 100–150 mg q 12-hourly *Drops* (unavailable) 100 mg = 1 ml = 40 drops Start with 20 drops and titrate up if necessary Do not exceed 400 mg/24 hours **Rectal** (unavailable) 100 mg/suppository Do not exceed > 400 mg/24 hours **IV/IM** 100 mg IM IV administration must be slow	USE	**Not for children under the age of 12 years** • It is a prodrug and reduced metabolism via CYP 2D6 may result in reduced *active* metabolite in 10% of the caucasian population • Tramadol acts on µ1-receptors, noradrenaline and serotonin receptors • Avoid/caution using concomitant 5-HT3-antagonists (anti-emetics), SSRIs, antimigraine medication, as serotonergic syndrome may occur • Avoid higher doses and rapid IV administration which may lead to an increased incidence of nausea and vomiting • *Therapeutic range*: moderate to severe pain • Combinations with paracetamol will be discussed in oral combination analgesics
Tapentadol • Palexia	**Oral** 50–100 mg q 4–6-hourly *SR* 50–200 mg q 12-hourly	?	• Recommended for short-term use in moderate to severe pain • This synthetic drug is a single enantiomer and therefore genetic CYP variations do not influence its pharmacokinetic profile • It works on μ_1-receptors and has a degree of selectivity for NRI • There is minimal SRI and, therefore, less chance of serotonin syndrome • There is reduced nausea and vomiting compared to oxycodone • Used for moderate to severe postoperative pain • May be of use for neuropathic pain and chronic pain syndromes • There are decreased 'opioid like' side effects

bd – twice daily, PCA – patient-controlled analgesia, p.o. – per os (orally), IM – intramuscular, IV – intravenous, MAOIs – monoamine oxidase inhibitors, SSRIs – selective serotonin reuptake inhibitors, USE – safe, UWC – use with caution, UWECO – use with extreme caution, may be unsafe, AVOID – unsafe, SR – slow-release, NRI – noradrenaline reuptake

Paracetamol

- Excessive dosage may cause irreversible liver failure.
- Use with caution or decrease the dose for the following:
  - Acute liver disease
  - Alcohol-related liver disease
  - Glucose-6-phosphate dehydrogenase deficiency

Table II: Relevant information on paracetamol

Drug	Adult	Porphyria	Relevant information
Enteral ***Oral*** 500 mg/tab • Actomol • Adco-Napamol • Austell-Paracetamol • Calpol GSK • Feverpain • Painamol • Panado • Parafizz	0.5–1 g q 4-hourly to a maximum of 4 g/day	USE	Mild to moderate pain only • Package insert does not recommend for babies under the age of 3 months
• Painamol • Panado	2 caplets q 8-hourly, maximum 6 caplets/ 24 hours		• Do not crush, chew or dissolve the extended-release caplets
Rectal • Empaped	N/A		• Rectal absorption is inconsistent • Caution in renal and liver disease
Parenteral ***Intravenous*** • Cetafuse IV • Paracetamol Biotech IV • Paracetamol Fresenius IV • Paraspen IV • Perfalgan IV	(> 50 kg) 1 g q 6-hourly to maximum dose of 4 g/24 hours		• Prescribe carefully according to weight, age and comorbidity • Administration of infusion should occur over 15 minutes • Registered use only for 24–48 hours • Hypotension is known to occur and may be due to mannitol in some formulations • *Do not administer any other oral paracetamol concomitantly, check combination analgesics for paracetamol* • An inadvertent IV overdose should be treated with N-acetylcysteine ***Intravenous dose*** • Loading dose = 150 mg/kg over 60 minutes • Followed by a second dose = 50 mg/kg over 4 hours • Third dose = 100 mg/kg over 16 hours ***Oral dose*** • Loading dose = 140 mg/kg, followed by 70 mg/kg every 4 hours for 17 additional doses

N/A – not applicable, USE – safe, UWC – use with caution, UWECO – use with extreme caution, may be unsafe, AVOID – unsafe

Nonsteroidal anti-inflammatory drugs for mild to moderate pain relief

NSAIDs can be divided into the following categories:

1. COX inhibitors
2. Selective COX-2 inhibitors
3. Specific COX-2 inhibitors

Side effects of NSAIDs include:

1. Renal damage, especially if prior renal impairment or hypovolaemia
2. Platelet impairment
3. Gastric erosions and haemorrhage
4. Possible poor wound healing
5. Asthma may be exacerbated in some patients

Sole drug for parenteral administration is parecoxib.

Table III: Relevant information on NSAIDs

	COX-1 and COX-2 inhibitors		
Drug	**Adult**	**Porphyria**	**Relevant information**
Aspirin • Disprin • Dr Du Toit's Pain Expeller tablets • Ecotrin	300–900 mg q 4–6-hourly to a maximum of 4 g daily	USE	• Associated with Reye's syndrome • Caution in: ◦ elderly ◦ renal function ◦ gastric bleeds

Diclofenac • Adco-Diclofenac • Austell-Diclofenac Sodium • Bio Diclofenac injection • Catafast D • Cataflam • Diclofenac SR Biotech • Dicloflam • Fortfen • K-Fenak • Mylan Diclofenac • Panamor suppositories + tabs • Veltex • Voltaren • Voltaren Acti-Go • Arthrotec • Diclofenac 75 mg + misoprostol 200 µg	**Oral** 25–50 mg q 8-hourly to a maximum of 150 mg/day **Drops** (only Voltaren) 15 mg = 1 ml 1 drop = 0.5 mg 1 ml = 30 drops 100 mg in 2–3 divided doses Daily max = 150 mg **Intramuscular** 75 mg q 12-hourly to a maximum of 150 mg/day for 2 days only **Suppositories** 100 mg daily The maximum by all routes is 150 mg/day 1 tab q 12-hourly	UWECO	***Mild to moderate pain*** • Available as drops • **Not for children under the age of 2 years** via any route • Good COX1:COX2 ratio • Avoid in the following: ◦ Asthma ◦ GIT/renal disease ◦ Intra- and postoperative hypovolaemia ***Intramuscular injections*** • Must be deep intragluteal • May cause necrotising fasciitis – therefore, change to oral therapy ASAP • Inadvertent injection into nerve may cause irreversible neural damage • Suppositories can cause proctitis, avoid use for longer than 5 days • Controversial for posttonsillectomy use • Swallow tablet whole with food; do not chew • Combination with prostacyclin may decrease NSAID side effects
Ibuprofen • Advil • Betagesic • Betaprofen • Bren-400 • Brufen • Ibucare • Ibugesic Fever and Pain • Nurofen • Pedea	200–400 mg q 4–6-hourly to a maximum of 1 200 mg/day	USE	• Beware of GIT bleeds • Beware of asthma • For moderate pain
Indomethacin • Arthrexin • Betacin • Flamecid • Mediflex	25–50 mg q 6–8-hourly to a maximum of 200 mg/day	USE	• Take with food/antacid/milk • GIT bleeds/asthma/renal insufficiency • CNS disturbances
Ketoprofen • Fastum Gel	5–15 cm to affected area q 12-hourly	USE	
Mefenamic acid • Adco-Mefenamic Acid • Ponac • Ponstan • Ponstel	500 mg q 8-hourly		• Not for children under the age of 6 months or weighing less than 10 kg • Do not administer for longer than 5 days
Lornoxicam • Xefo	8–16 mg/day in 2–3 divided doses		• Not for children under the age of 18 years • GIT, renal and platelet concerns
Naproxen • Adco-Naproxen • Aleve • Bio-Naproxen • Litha Naproxen • Mylan Naproxen • Nafasol • Napflam • Vimovo + esmeprazole	500 mg q 12-hourly	USE	• Not for children under the age of 5 years • Caution if: ◦ Diathesis for GIT bleeding ◦ Renal compromise ◦ Asthma • Drug interactions with hydantoins/anticoagulants/ sulphonylureas • For mild to moderate pain
Piroxicam • Brexecam • Piroxicam Actor DT • Pixicam • Pyrocaps • Rheugesic • Xycam	20–30–40 mg daily		• Not recommended for children • Usual concerns with NSAIDs • Caution if hepatic insufficiency • Long half-life, may be given as a single daily dose • For moderate pain

Selective COX-2 inhibitors

Drug	Adult	Porphyria	Relevant information
Meloxicam • Adco-Meloxicam • Coxflam • Coxitec • Flamaryx • Flexocam • Loxiflam • Medoxicam • Meloxicam • Melzy • Mobic	7.5 mg q 12-hourly or 15 mg daily Maximum dose 15 mg/day	USE	• Give with food • Selective COX-2 inhibitor – however, in very high doses may have COX-1 inhibition as well

Selective COX-2 inhibitors (COXIB)			
Etoricoxib • Adco-Etoricoxib • Arcoxia • Coricib • Exinef • Extrib	60 mg, 90 mg and 120 mg q 24-hourly 100–200 mg q 12-hourly to a maximum of 400 mg/day		• Moderate to severe pain
Celecoxib • Celebrex • Celecoxib Unicorn • Coxleon		USE	• Not for children under the age of 18 years • Contraindicated for sulphonamide allergy • Selective COX-2 inhibitor (COXIB), i.e. only has COX-2 effects even at very large doses
Parecoxib • Rayzon	40 mg q 6–12-hourly IV/IM, maximum 80 mg/day		• Not for children under the age of 18 years • Contraindicated for sulphonamide allergy

COX – cyclo-oxygenase, GIT – gastrointestinal tract, CNS – central nervous system, NSAIDs – nonsteroidal anti-inflammatory drugs, USE – safe, UWC – use with caution, UWECO – use with extreme caution, may be unsafe, AVOID – unsafe

Approach to oral combination analgesics

Combinations of all the above **oral** drugs are used extensively in South Africa. It is, therefore, not possible to include all combinations in this section. The rationale for drug combination is to reduce the dose of each drug and, hence, improve the side effect profile. The list below gives some components in these combination preparations and highlights specific effects or side effects.

1. Paracetamol
   - The dose is usually lower in combination preparations.
   - Always check that the patient has not received paracetamol via the intravenous (IV) or the rectal route, as overdose may occur.
2. Caffeine hydrate
   - This has a vasodilatory effect and may be good for migraines.
3. Codeine phosphate
   - This has a mild analgesic effect and has to be metabolised to morphine. In a subset of patients, excessive sedation is problematic (see above).
4. Aspirin
   - Use caution if patient has prior history of dyspepsia or bleeding diathesis.
5. Propoxyphene napsylate
   - This has a weak analgesic effect, but some sedation.
6. NSAIDs
   - Use caution if a patient has prior history of dyspepsia or bleeding diathesis and renal impairment.
7. Meprobamate
   - It is a weak analgesic.
   - Probable addiction after 10 days of use; this is a physical as well as emotional addiction.
8. Doxylamine succinate
   - There is not a clear rationale for inclusion in analgesic drugs.
9. Promethazine
   - Phenothiazine with anti-emetic and sedatory effects.
   - 'Blackbox' in the USA due to ↑QT interval.
10. Orphenadrine
    - This has an antimuscarinic effect.
11. Diphenhydramine
    - Antihistamine with sedatory effect (blackbox).

Table IV: Relevant information to the approach to combination analgesics

NMDA receptor antagonists (excitatory amino acid antagonists)			
Drug	**Adult**	**Porphyria**	**Relevant information**
Ketamine	**Oral** 0.25 mg/kg **PCA** May be added to PCA in combination with morphine	USE	• Side effects: ◦ hallucinations ◦ excessive salivation • Synergism with opioids as supposedly decreases opioid tolerance • No decrease in opioid side effects • May give some pre-emptive analgesia • May reduce opioid requirements in opioid-tolerant patients

Magnesium	30 mg/kg at start of induction and then 25 mg/kg/hr	USE	• Concern regarding potentiation of muscle relaxation • Decrease in blood pressure, which is usually easily managed
Nitrous oxide • Entonox	Nitrous oxide (N_2O) 50%/ Oxygen (O_2) 50%	USE	• Do not store cylinders in temperatures below 7 °C • Used in labour for analgesia • Used in dental chair • Appropriate monitoring should always be applied • Bone marrow depression occurs with ***prolonged*** use
Dextrometorphan Benylin Original Benylin Dry Cough Benylin	45 mg p.o. preoperatively		• Use as premedication for *pre-emptive analgesia* • Said to decrease use of other analgesics posttonsillectomy in adults • **Addiction potential as no prescription is required**
		α2-agonists	
Clonidine	**Oral** 2.5 µg/kg as a premedication **Intravenous** 2.5 µg/kg slow injection **Epidural/caudal** 2–10 µg/kg epidurally in 10 ml saline	?	• Premedication ◦ sedation ◦ pre-emptive analgesia • Partial agonist, therefore hyper/hypotension may manifest • Bradycardia may be problematic
Dexmedetomidine • Precedex	**LD** = 1 µg/kg slowly over 30 minutes **MD** = 0.2–0.7 µg/kg/hr		***For moderate to severe pain*** • Expensive • Loading dose should be given slowly over 10–30 minutes • Patients on an infusion *should always* go to ICU for monitoring of level of sedation, bradycardia and hypotension • Arterial line is essential for monitoring if drug is given as an infusion • Side effects: ◦ Hypotension ◦ Sedation ◦ Bradycardia • Bonus: analgesia

PCA – patient-controlled analgesia, LD – loading dose, MD – maintenance dose, NMDA – N-methyl-D-aspartate, USE – safe, UWC – use with caution, UWECO – use with extreme caution, may be unsafe, AVOID – unsafe

Local anaesthetics

LAs are divided into short-acting (e.g. lignocaine) or long-acting (e.g. bupivacaine, ropivacaine) anaesthetics.

The following are possible side effects:

1. Toxic doses
2. Cardiotoxicity
3. Neurotoxicity

Table V: Relevant information regarding local anaesthetics

Drug	Adult	Porphyria	Relevant information
Lignocaine 2% • Lignocaine-HCl B Braun • Lignocaine HCl Fresensius Vials • Remicaine • Xylotox	**Toxic dose** *Without adrenaline* 5 mg/kg *With adrenaline* 7 mg/kg *Topicalisation of mucous membranes* 9 mg/kg	UWC	• Neurotoxicity occurs before cardiotoxicity • Do not use intrathecally as toxicity to spinal cord and nerves are a concern • Continuous perineural infusions of lignocaine result in less effective analgesia and more motor block than long-acting LAs • Postoperative systemic administration for analgesia is an option. After abdominal surgery doses, an LD (1.5 mg/kg over 15 minutes) followed by continuous infusion (2 mg/kg/hr) has shown to shorten duration of ileus and decrease nausea and vomiting as well as need of analgesia
Bupivacaine • Macaine • Pharma-Q Bupivacaine	**Toxic dose** 2 mg/kg	USE	• Cardiotoxicity occurs before neurotoxicity • Intralipid may be used for cardiotoxicity 1–1.5 ml/kg IV stat • More potent than isomers as described below and thus motor block and cardiotoxicity may be more pronounced • However, there are no consistent differences between ropivacaine and bupivacaine when given in low doses for regional analgesia in terms of quality of analgesia or motor blockade
Ropivacaine • Adco-Ropivacaine • Naropin	**Toxic dose** 2 mg/kg	UWC	

Volatile agent – self-inhalation			
Methoxyflurane • Penthrop	Inhaler is known as the 'green whistle' It is handheld, single-use, portable and disposable **Maximum adult dose** 6 ml/day, i.e. two 3 ml doses LD = 6–10 breaths/minute 3 ml will last 25 minutes with continuous breathing but with intermittent use can last up to an hour	Avoid	• This was a popular volatile agent in the 1960s but was withdrawn due to nephrotoxicity in doses required for general anaesthesia • Generally used by paramedics at the roadside or in casualty • For moderate to severe pain • May be used in paediatrics, but use caution in children under the age of 5 years, as deep sedation has been reported • Should never be used on consecutive days due to threat of renal failure and disturbances of hepatic metabolism • Contraindications include: ◦ renal and hepatic impairment ◦ head injuries ◦ respiratory failure • Sevoflurane should be avoided if prior use of MOF inhaler, as high concentrations of fluoride ions may be a concern

MOF – methoxyflurane, LD – loading dose, USE – safe, UWC – use with caution, UWECO – use with extreme caution, may be unsafe, AVOID – unsafe

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