WATAG Advisory Note

GUIDELINES FOR THE PHARMACOLOGICAL TREATMENT OF NEUROPATHIC PAIN (2017)

Purpose
The purpose of this Advisory Note is to provide WA public health services with a 2017 version of guidelines for the treatment of neuropathic pain.

Scope
Neuropathic pain is defined as pain caused by a disease or lesion of the somatosensory nervous system. The disease or lesion can be located in the peripheral (e.g. diabetic neuropathy) or central nervous system (e.g. after spinal cord injury or stroke).
The treatment options presented in these guidelines are for different conditions within the spectrum of neuropathic pain. It is recommended that therapeutic agents should be selected and trialed according to the recommendations provided in these guidelines.

Background
Neuropathic pain is often refractory or inadequately managed by common analgesics; in particular paracetamol and NSAIDs are usually ineffective. Therefore the guidelines provided here should guide choice of therapeutic agents.
It is suggested that patients with neuropathic pain be referred to a pain specialist when second-line treatments have failed.
For consultation, Pain Clinics are located at major metropolitan teaching hospitals.
Consider referring patients with neuropathic pain due to malignant disease to a palliative care physician.

The Therapeutic Guidelines: Neurology also provides information on the treatment of neuropathic pain.

WATAG acknowledges the contribution of Professor Stephan Schug and Associate Clinical Professor Roger Goucke in developing these guidelines.

Signed by:

Associate Professor Christopher Etherton-Beer
Chairman WATAG

Guidelines for the Pharmacological Treatment of Neuropathic Pain

Therapeutic Options		Notes
Peripheral neuropathy (e.g. postherpetic neuralgia (PHN), painful peripheral diabetic neuropathy) and central sensitisation pain syndromes (CRPS, CVPS, CWPS - see glossary on page 6 for definitions)		
First-line in localised peripheral neuropathic pain (e.g. PHN)	Topical lignocaine 5% patch (Versatis®)	• Use on area of pain and allodynia for 12 hours per day • Trial for 3 to 4 weeks, if no clinical benefit then cease • Ideal in elderly or frail due to few systemic side effects and interactions • Not covered by PBS and may be costly
First-line in all other conditions	Tricyclic antidepressants (TCAs): - amitriptyline - nortriptyline or - imipramine	• Start at low dose (5-10 mg) and increase slowly to optimise acceptability • Effective doses vary widely between 10 and 100 mg in individual patients • Slow onset of effect and should be trialed for at least 2 weeks (ideally 6-8 weeks) • Amitriptyline given at night is superior if sleep disturbance also needs treatment • Nortriptyline is less sedating and may have fewer adverse effects • TCAs have significant adverse effects including: dry mouth, constipation, sweating, dizziness, sedation, drowsiness, palpitation, orthostatic dysregulation and urinary retention • Use in elderly patients and those with cardiovascular risk factors should be avoided
	Serotonin/noradrenaline reuptake inhibitors (SNRIs): - duloxetine or - venlafaxine	• Start duloxetine at 30 mg daily, increase as tolerated to 60 mg (maximum 120 mg daily) • Start venlafaxine at 37.5 mg, increase as tolerated to 75 mg (maximum 225 mg daily) • Precaution in hepatic, renal and cardiac co-morbidity • Venlafaxine can cause withdrawal reactions with rapid discontinuation; titrate down carefully

Second-line	Alpha-2-delta subunit modulators: pregabalin or gabapentin	• Use is indicated if TCAs are contraindicated, not tolerated, ineffective or if a rapid onset of effect is needed in acute neuropathic pain states • Pregabalin is preferable to gabapentin due to more predictable dose-response relationship, twice daily dosing and ability to titrate quickly at comparable prices (and being PBS listed) • Starting dose for pregabalin is 75 mg bd, (25-50 mg in the elderly and frail), maximum dose 300 mg bd • Reduce dose in renal insufficiency
Third-line	Tramadol	• Start at 50 mg slow release twice daily; increase as needed and tolerated up to 400 mg/day • Rapid onset of effect • Precaution in seizure disorder and potential interaction with TCAs/SNRIs/SSRIs Contraindicated with MAOIs
	Tapentadol	• Start at 50 mg slow release twice daily; increase as needed and tolerated up to 500 mg/day • Rapid onset of effect • Less GI adverse effects (nausea and vomiting) than tramadol • Controlled medication (S8)
Fourth-line	Opioids (e.g. buprenorphine, oxycodone, morphine or methadone)	• Rapid onset of effect • Only fourth-line treatment in view of limited long-term data on efficacy and safety • Consider usual precautions with regard to prescribing long-term opioids (i.e. endocrine and immunological effects, risk of addiction, abuse and diversion)
Fifth-line	Sodium valproate	
	Sublingual ketamine	• Use in highly selected patients by pain medicine and palliative care specialists only • Currently not a registered drug, requires individual patient consent (see hospital protocol) • Limited data on safety with long-term use (i.e. cognitive or hepatic effect) • Consider risk of abuse and diversion
General comment: Combinations of gabapentin or pregabalin with opioids, antidepressants and lignocaine medicated plasters have been documented in clinical trials; these studies suggest that combination therapies maybe effective, enable dose reductions and/or reduce adverse effects.		

<table>
<tr><td colspan="3">Trigeminal neuralgia</td></tr>
<tr><td>First-line</td><td>Carbamazepine</td><td>• Should be started at low dose and titrated according to effect/adverse effects in a range of 200-1200 mg
• Has several adverse effects, but is highly effective
• Enzyme inducer; may interact with other drugs</td></tr>
<tr><td>Second-line</td><td colspan="2">Procedural pain management, neurosurgery or radiosurgery (gamma knife)</td></tr>
<tr><td rowspan="3">Third-line (if surgery is contraindicated)</td><td>Pregabalin/gabapentin</td><td rowspan="3">• Baclofen may be used as add-on therapy with carbamazepine
• For each medication, commence at a low dose twice daily and increase every 3 days according to effect/adverse effects</td></tr>
<tr><td>Baclofen</td></tr>
<tr><td>Clonazepam</td></tr>
<tr><td colspan="3">Spinal cord injury (SCI) pain at and below lesion</td></tr>
<tr><td>First-line</td><td colspan="2">Alpha-2-delta subunit modulators (see notes above):
- pregabalin or gabapentin</td></tr>
<tr><td rowspan="2">Second-line</td><td colspan="2">TCAs (possibly combined with first line treatment)</td></tr>
<tr><td colspan="2">Tramadol/tapentadol (possibly combined with first-line treatment)
Baclofen (if associated with muscle spasms)</td></tr>
<tr><td colspan="3">Central post-stroke pain (CPSP)</td></tr>
<tr><td rowspan="2">First-line</td><td colspan="2">TCAs</td></tr>
<tr><td colspan="2">Alpha-2-delta subunit modulators (see notes above):
- pregabalin or gabapentin</td></tr>
<tr><td>Second-line</td><td colspan="2">Lamotrigine</td></tr>
</table>

Acute neuropathic pain conditions requiring parenteral treatment (Acute SCI, acute plexus injury, Guillain-Barré Syndrome, severe CRPS)		
First-line	IV/SC ketamine	• Use initial bolus titration in 5 mg steps to effect or adverse effects • Maintain effect by continuous IV or SC infusion at an average rate of 0.1 mg/kg/hr • Adverse effects are rare at these rates and special monitoring is not required (see local protocol) • If rare psychomimetic adverse events are experienced by patient the addition of low dose midazolam may be effective
Second-line	IV lignocaine	• Use initial slow bolus of 1-1.5 mg/kg • Maintain effect by infusion of 1-2 mg/minute
Phantom limb pain		
First-line	IV/SC calcitonin	• Use 100 IU daily as SC injection or IV infusion (in 100 mL saline over 1 hr) • Give metoclopramide 20mg prior as prophylactic anti-emetic • Repeat daily for at least 3 days
Second-line	All other neuropathic pain treatment options including tramadol, tapentadol or opioids	
General comments: Calcitonin may also be considered by specialist Pain Medicine Services in selected cases of CRPS, CVPS and CWPS (and pain caused by vertebral body fractures)		

Glossary	
The abbreviations CRPS, CVPS and CWPS used in this document summarise pain states thought to be caused by central sensitization processes as a dysfunction of the CNS and fulfill the current IASP definition of neuropathic pain	
CRPS	Complex Regional Pain Syndrome (previously commonly called RSD (Reflex Sympathetic Dystrophy or Causalgia)
CVPS	Complex Visceral Pain Syndrome (summarizing states such as interstitial cystitis, post-cholecystectomy syndrome and IBS)
CWPS	Complex Widespread Pain Syndrome (reflects a suggested more appropriate nomenclature for the previous term fibromyalgia)

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Also see - Therapeutic Guidelines: Neurology Version 4, 2011