HUNTER NEW ENGLAND
NSW HEALTH

PAIN MATTERS

Medical Practice Guidelines
Hunter Integrated Pain Service
Updated July 2007

Use of Oral Antineuropathic Agents

SUMMARY

1. In acute and sub-acute neuropathic pain (≤6 months duration) there is the potential for intervention to stop progression to a persistent pain state.
2. Once neuropathic pain has become persistent (>6 month duration) the likelihood of abolition becomes less. A greater emphasis is placed on helping patients to accept and manage their pain.
3. There is evidence from systematic review of benefit from anticonvulsants and antidepressants in the treatment of neuropathic pain.
4. There is evidence from randomised controlled trials of benefit from opioids in treatment of neuropathic pain.
5. Use of oral therapy is generally the initial treatment strategy for neuropathic pain. Procedural intervention is then considered if response is inadequate. Optimal therapy may include a combination of oral medication, procedural intervention and self-management approaches.
6. Antidepressants and anticonvulsants (often in combination) are first line oral agents. Opioids are usually a later option to consider if therapeutic benefit remains inadequate. Membrane stabilising agents (eg. mexiletine) have a minor role.
7. A 2-4 week trial should be undertaken before considering maintenance therapy.
8. Drug adverse effects, including tolerance, are common.
9. Rotation of therapeutic agents can be used to treat tolerance.

What is the current evidence?

1. There is evidence from systematic review of benefit from antidepressants[1] and anticonvulsants[2] in the treatment of postherpetic neuralgia (PHN) and painful diabetic neuropathy (DN). Carbamazepine has benefit in trigeminal neuralgia (TN)[2].
2. Side effects are common with both antidepressants and anticonvulsants. The NNH for minor side effects is similar to the NNT for ≥50% pain relief.
3. Pregabalin, the latest anticonvulsant agent, has shown efficacy in the treatment of both PHN and DN[3,4,5,6] in several randomised controlled trials.
4. There is evidence from randomised controlled trials of benefit from opioids in persistent neuropathic pain.[7,8,9,10]
5. There are no comparative studies to guide the choice between individual antidepressant and anticonvulsant agents. There is no evidence at this stage that gabapentin and pregabalin are superior in terms of efficacy to the older anticonvulsant agents.
6. Several randomised controlled trials have addressed the role of mexiletine in the treatment of peripheral and central neuropathic pain[11]. The NNT (≥50% pain relief) for mexiletine in peripheral neuropathy is around 10. Mexiletine was no better than placebo in the treatment of spinal cord injury pain.

Table 1 summarises pooled data for numbers needed to treat (NNT) for ≥50% reduction in pain and also numbers needed to harm (NNH)[12]. Only small numbers of patients have been studied in selected groups to derive the data for sodium valproate and carbamazepine whereas gabapentin and pregabalin have been more exhaustively studied.

Table 1: Oral Antineuropathic Therapy

	NNT (95%CI)	**NNH (95%CI)**
TCA	**3.1** (2.7-3.7)	**14.7** (10-25)
SNRI	**5.5** (3.4-14)	Not significant
SSRI	**6.8** (3.4-441)	Not significant
Sodium valproate	**2.8** (2.1-4.2)	Not significant
Carbamazepine	**2.0** (1.6-2.5)	**21.7** (13-79)
Gabapentin	**3.8** (3.1-5.1)	**26.1** (14-170)
Pregabalin	**4.2** (3.4-5.4)	**11.7** (8.3-19.9)
Opioids (morphine/oxycodone)	**2.5** (2.0-3.2)	**17.1** (10-66)
Tramadol	**3.9** (2.7-6.7)	**9.0** (6-18)

Clinical Features Suggestive of Neuropathic Pain

1. History of nerve injury or dysfunction
2. Pain in the absence of ongoing tissue damage
3. Pain within (but not necessarily confined to) an area of sensory deficit
4. Character: often burning, shooting, stabbing or pulsing
5. Pattern: paroxysmal or spontaneous pain
6. Allodynia (pain in response to normally non-painful stimuli)
7. Secondary hyperalgesia (hyperalgesia = increased pain in response to normally painful stimuli; secondary hyperalgesia occurs in a non-inflamed area and is due to central sensitisation)
8. Hyperpathia (increasing pain with repeated stimulation and "after response")
9. Dysaesthesias (unpleasantly altered sensation)
10. Associated autonomic features (swelling, change in colour, temperature or sweating)

Trial versus Maintenance Therapy

1. A 2-4 week trial is recommended.
2. Analgesic benefit and functional gains need to be weighed against side effects in determining whether or not to proceed to maintenance therapy.
3. A drug holiday may be worth considering every 6-12 months whilst on maintenance therapy. If pain increases significantly as the drug is tapered then the agent can be restarted. Otherwise the drug can be withdrawn.
4. Development of tolerance may be an issue with antidepressants and anticonvulsants, as with opioid therapy. There may be value in rotating antineuropathic agents.

Choice of Agent

1. Antidepressants
   a. The reuptake inhibition of noradrenaline is an important contributor to the analgesic effect of antidepressants.
   b. Tricyclics and venlafaxine which act on both noradrenergic and serotonergic pathways are therefore preferred to SSRI agents.
   c. Although amitriptyline is the “classic” antidepressant for neuropathic pain, nortriptyline has fewer sedative and anticholinergic side effects.

2. Anticonvulsants
   a. Carbamazepine blocks sodium channel activation in the central nervous system (CNS) and may have a specific role in trigeminal neuralgia.
   b. Sodium valproate blocks sodium channel activation and also increases GABA inhibitory activity in the CNS. It is often preferred to carbamazepine because it is better tolerated.
   c. Gabapentin acts to block the alpha-2-delta subunit of the N-calcium channel. It is well tolerated with less toxicity and fewer drug interactions than other anticonvulsants. It is often used as a 2nd line agent due to the high cost and lack of PBS listing for pain. Gabapentin is renally eliminated with no hepatic metabolism. Hence it can be useful in hepatic dysfunction. Dose reduction is required in renal impairment.
   d. Pregabalin is a new anticonvulsant with similar site of action and efficacy to gabapentin. It is not PBS listed for neuropathic pain.
   e. Other agents such as clonazepam and lamotrigine can also be considered.

3. Opioids
   a. Opioids are generally reserved for cases of inadequate response to antidepressant/anticonvulsant combinations.
   b. Opioids can be combined with antidepressants and anticonvulsants.
   c. Oxycodone and methadone may be preferable to morphine in neuropathic pain due to their specific mechanisms of action (see opioid guidelines).
   d. The dual mechanism of tramadol effects both opioid receptors and descending inhibitory monoamine systems (noradrenergic/serotonergic pathways). Tramadol may have specific benefit in neuropathic pain.

4. Membrane stabilising agents
   a. Mexiletine has a local anaesthetic like action to block sodium channel activation. It has a role in the treatment peripheral neuropathic pain refractory to antidepressants and anticonvulsants but is often poorly tolerated with a high incidence of nausea.

Table 2 : Prescribing Recommendations

Drug	Usual adult starting regime	Usual adult dose range	Drug interactions	Side effects
Amitriptyline	10mg nocte ↑10mg/wk	10-100mg nocte	MAOI	Sedation, dry mouth, blurred vision, constipation, postural hypotension, cardiac conduction abn, weight gain
Nortriptyline	10mg nocte ↑10mg/wk	10-100mg nocte		
Venlafaxine	37.5mg bd	37.5-75 mg bd	MAOI, other drugs affecting serotonergic activity	Dry mouth, sedation, hypertension
S. valproate	200mg bd (100mg bd in elderly),↑ by 200mg/d every 3 days	600-1200mg daily in 3 divided doses	CNS depressants, Hepatic enzyme inducers	Sedation, weight gain, haematological & hepatic dysfn. Check FBC, LFT's every 3-6/12
Carbamazepine	200mg bd (100mg bd in elderly),↑ by 200mg/d every 3 days	600-1200mg daily in 3 divided doses	CNS depressants, Hepatic enzyme inducers	Sedation, weight gain, haematological & hepatic dysfn. Check FBC, LFT's every 3-6/12
Gabapentin	300mg nocte day 1 (100mg nocte in elderly or renal impairment), 300mg bd day 2, 300mg tds day 3	900-2400mg daily in 3 divided doses	CNS depressants, Antacids may ↓ absorption	Sedation, ataxia, accumulation in renal impairment
Pregabalin	75mg nocte day 1, 75mg bd day 2	150-600mg daily in 2 divided doses	CNS depressants,	Sedation, ataxia, accumulation in renal impairment
Mexiletine	50mg tds	Up to 200mg tds	Anti-arrhythmics, Hepatic enzyme inducers	Nausea, cardiac arrhythmias

Notes

1. Lower starting doses and more conservative rates of increase are required in elderly patients.
2. Combination therapy is often helpful.

References

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Appendix 1

MEDICATION SHEET

Instructions on how to take your medication in increasing doses:

Medication: **Sodium Valproate** 200mg tablet
Also known as: Epilim or Valpro

Day	Morning	Afternoon	Evening
1	1	-	1
2	1	-	1
3	1	-	1
4	1	1	1
5	1	1	1
6	1	1	1
7	1	1	2
8	1	1	2
9	1	1	2
10	1	1	2
From day 10 onwards, continue on this maximum dose as tolerated			

Side effects:

The most common side effect is drowsiness.

If you experience any troublesome side effects please reduce your medication to a lower level.

Please telephone ______________________ during business hours if you have any significant problems whilst taking this medication.

Prescribing Information:

Tablets: 100 mg 100 x 2 repeats

200 mg 100 x 2 repeats

500 mg (EC) 100 x 2 repeats

Appendix 2

MEDICATION SHEET

Instructions on how to take your medication in increasing doses:

Medication: **Gabapentin** 300mg capsule
Also known as: Neurontin, Pendine, Gantin

Day	Morning	Afternoon	Evening
1	-	-	1
2	1	-	1
3	1	1	1
4	1	1	1
5	1	1	1
6	2	1	1
7	2	1	1
8	2	1	1
9	2	2	1
10	2	2	1
11	2	2	1
12	2	2	2
From day 12 onwards, continue on this maximum dose as tolerated			

Side effects:

The most common side effects are feeling drowsy or off-balance.

If you experience any troublesome side effects please reduce your medication to a lower level.

Please telephone ______________________ during business hours if you have any significant problems whilst taking this medication.

Prescribing Information:

Capsules: 100 mg 100 x 5 repeats
300 mg 100 x 5 repeats
400mg 100 x 5 repeats

Tablets: 600 mg 100 x 5 repeats
800mg 100 x 5 repeats

NB: Not PBS listed for neuropathic pain

Appendix 3

MEDICATION SHEET

Instructions on how to take your medication in increasing doses:

Medication: **Pregabalin** 75mg capsule
Also known as: Lyrica

Day	Morning	Evening
1	-	1
2	1	1
3	1	1
4	1	1
5	2	2
6	2	2
7	2	2
From day 7 onwards, continue on this dose as directed. Consider increase to 300mg twice daily from day 14.		

Side effects:

The most common side effects are drowsiness and feeling off balance.

If you experience any troublesome side effects please reduce your medication to a lower level.

Please telephone ______________________ during business hours if you have any significant problems whilst taking this medication.

Prescribing Information:

Tablets: 75mg caps x 56

150mg caps x 56

300 mg caps x 56

NB: Not PBS listed for neuropathic pain