Clinical Resource Guide:
Neuropathic Pain Management

INTRODUCTION TO NEUROPATHIC PAIN

Neuropathic pain can result from a number of causes leading to damage of the peripheral and/or central nervous system. Painful neuropathy is frequently experienced by patients in the palliative care and hospice settings, and it is estimated that up to 40% of all individuals with cancer experience this type of pain. In addition to patients with cancer, it is also prevalent in other serious, life-limiting illnesses, such as:

- Acquired immune deficiency syndrome (AIDS)
- Multiple sclerosis
- Amyotrophic lateral sclerosis (ALS)
- Sickle cell disease
- Cerebrovascular disease

Untreated or undertreated neuropathic pain may contribute negatively to patient quality of life by exacerbating insomnia, depressed mood, fatigue, and psychosocial distress. Therefore, this Pharmacist Corner was created to serve as a resource for hospice clinicians and administrators addressing the challenges of managing neuropathic pain.

Pharmacist Corner Objectives

1. Describe the role of adjuvant analgesics in the management of neuropathic pain in the hospice setting
2. Understand the role in therapy of different classes of adjuvant analgesics pending pain reported
3. Identify characteristics of adjuvant analgesics that influence utilization when creating a patient-specific pain management plan
4. Create appropriate monitoring plan to assess safety and efficacy of newly initiated adjuvant analgesic

PATHOPHYSIOLOGY

The term neuropathic pain is often used to describe a variety of conditions resulting from an injury or dysfunction of the peripheral or central nervous system. Unfortunately, multiple factors may have contributed to the painful neuropathy experienced by the hospice patient, and classification of the exact cause or incident can be difficult. However, having a general

understanding of the neuronal changes that occur as a result of such an injury can help to develop an effective treatment plan.

Peripheral Neuropathy

Proposed Mechanisms:
Following the initial injury or insult, which may include compression, surgery, or trauma, abnormal nerve regeneration and formation of nerve sprouts can produce spontaneous activity. The neuron becomes more sensitive, and the threshold to painful stimuli is lowered. Additionally, the inflammatory cascade, often including prostaglandins and substance P, can result in the activation of nearby nociceptors, exacerbating the pain experienced by the patient. Another mechanism is the formation of ectopic neuronal pacemakers, which can be formed as a result of injury sustained. Alterations in ion channel expression can result in irregular depolarization of the neuron.

Examples of Peripheral Neuropathic Pain Syndromes	▪ Post-mastectomy pain ▪ Post-thoracotomy pain ▪ Brachial plexopathy due to lymph node mets ▪ Cervical plexopathy due to H&N tumor extension ▪ Lumbosacral plexopathy due to extension of cervical or colorectal tumor

Central Neuropathy

Proposed Mechanisms:
Interruption of afferent neuronal activity can result from either a peripheral or central nervous system injury. Sensitization of neurons can occur, resulting in lowered activation thresholds. The N-methyl-D-aspartate (NMDA) receptor and excitatory amino acids are integral to the mediation of central sensitization. Decrease levels of gamma-aminobutyric acid (GABA) receptors in the spinal cord may also contribute to this neuropathic pain experience.

Examples of Central Neuropathic Pain Syndromes	▪ Thalamic syndrome (post-stroke pain) ▪ Phantom pain ▪ Post-herpetic neuralgia ▪ Complex regional pain syndrome ▪ Spinal cord injury

ASSESSMENT

Patients with severe, life-limiting conditions are likely to experience muti-factorial pain, and the utilization of a comprehensive pain assessment is essential to the development of a viable, patient-centered treatment plan. One indication the pain experienced by the patient is neuropathic in nature is in how it is reported. Patients with neuropathic pain often describe the pain they are experiencing as having one of the following characteristics: burning, tingling, numb, shooting, or electrical in nature. This presentation differs from other types of pain, as noted below.

SOMATIC	VISCERAL	NEUROPATHIC
▪ Originates from muscle, skin or bone ▪ Well localized ▪ Described as **dull, achy, throbbing** ▪ Usually constant ▪ Directly related to underlying pathology	▪ Originates from bowel, lungs, liver, reproductive tract ▪ Generalized location ▪ Described as **aching, gnawing, cramping, sharp or pressure** ▪ Constant or intermittent ▪ Usually result of metastasis	▪ Originates from the nervous system ▪ Usually diffuse, radiating ▪ Described as **burning, tingling, numbness, sharp, shooting, electrical** ▪ Constant or intermittent ▪ Usually the result of neuronal injury

Additionally, if the patient reports the pain seems to radiate from one area to another, this can also be an indicate the presence of neuropathic pain.

TREATMENT

The management of neuropathic pain in the hospice setting can be challenging, as effective treatment often requires the utilization of a combination of analgesics, employing multiple mechanisms of action. This approach may be challenging logistically for the patient and caregivers from a pill burden and compliance standpoint, as a titration schedule may be required. Financial and logistical barriers may also exist for the agency, due to increased number of prescriptions and monitoring required with initiation and titration. This resource is intended to serve as an evidence-based guide to analgesic selection and dosing strategies for hospice patients presenting with neuropathic pain.

Despite the availability of adjuvant analgesics, in the hospice setting, opioids and anti-inflammatories should be optimized prior to the considering the addition of adjuvant

analgesics. This is due to some adjuvants requiring time and/or titration to achieve desired effect, which may not be viable for a patient with a limited life expectancy. Additionally, the versatility of opioids allows options for rotation, titration, and/or transition to a formulation suitable for the specific needs of the patient. As the end of life draws near, a patient may no longer be physically able to take the adjuvant, and/or these agents may not be effective or appropriate to manage increasing pain requirements.

In the hospice setting, the most appropriate adjuvant analgesic may be the one that also has efficacy for a comorbid symptom or condition. In addition to neuropathic pain, many hospice patients also experience depressed mood, anxiety, insomnia, and decreased appetite, which may be improved with the utilization of an appropriate adjuvant analgesic.

EFFICACY OF ADJUVANTS FOR TREATMENT OF PAINFUL POLYNEUROPATHY

Medication	Number Needed to Treat	NeuPSIG* Recommendation
Tricyclic antidepressants- tertiary amines: ▪ ***Amitriptyline*** ▪ ***Imipramine***	2.1 (CI 1.8-2.6)	First-line
Tricyclic antidepressants- secondary amines: ▪ ***Nortriptyline*** ▪ ***Desipramine***	2.5 (CI 1.9-3.6)	First-line
Opioids	2.6 (CI 1.9-4.1)	Second-line**
Calcium channel ligands: ▪ ***Gabapentin*** ▪ ***Pregabalin***	3.9 (CI 3.2-5.1)	First-line
Serotonin-norepinephrine reuptake inhibitor: ▪ ***Venlafaxine***	4.6 (CI 3.2-5.1)	Second-line
Serotonin-norepinephrine reuptake inhibitor: ▪ ***Duloxetine***	5.2 (CI 3.2-5.1)	Second-line

*NeuPSIG: Neuropathic Pain Special Interest Group; part of the International Association for the Study of Pain (IASP)

**Except for in end-of-life circumstances when time not available to titrate first-line agents

Tricyclic Antidepressants

Medication	Initial Dose	Target Dose	Estimated Cost/Day
Amitriptyline	10 mg at bedtime	50-150mg at bedtime	$0.24-$0.83
Nortriptyline	10-25mg at bedtime	75-150mg at bedtime	$0.18-$0.36
Desipramine	10-25mg at bedtime	75-150mg at bedtime	$0.41-$0.86

Additional Notes:

- Analgesia is often achieved at a lower dose and more rapidly (3-5 days) than the onset of antidepressant effects (4-6 weeks)
- The pain-relieving properties of antidepressant adjuvant analgesics are independent of effect on mood
- Secondary amines (nortriptyline and desipramine) appear to be as effective as tertiary amines (amitriptyline), and with markedly fewer anticholinergic adverse effects

Serotonin-Norepinephrine Reuptake Inhibitors

Medication	Initial Dose	Target Dose	Estimated Cost/Day
Duloxetine	30mg po daily x 7 days	60mg po daily	$0.43
Venlafaxine	37.5mg po daily	225mg po daily	$0.77

Additional Notes:

- Despite its lower number needed to treat, initiation of **venlafaxine is not recommended** due to multi-step titration process, prevalence of withdrawal with as few as one missed dose, and formulation limitations
- Duloxetine is initiated at lower dose to reduce risk of intolerable GI side effects
- Limited neuropathic analgesic benefit at doses > 60mg/day
- In addition to neuropathic pain, may have benefit on depressed mood, anxiety

Calcium Channel Ligands

Medication	Initial Dose	Target Dose	Estimated Cost/Day
Pregabalin	75mg po BID	25mg - 150mg po BID	$0.28-$1.30
Gabapentin	100mg po QPM	300mg-1200mg po q8h	$0.34-$1.71

Additional Notes:

- Pregabalin now available in generic form, therefore less cost-prohibitive
- Pharmacokinetics of pregabalin allow it to be dosed twice daily without concern for end of treatment failure. Gabapentin often requires every 8-hour dosing to achieve maximal effect
- Pregabalin is approximately 6 times more potent than gabapentin
- Gabapentin is available in solution form for enteral administration
- Doses of pregabalin and gabapentin can be titrated every 3-5 days if tolerated and desired effect not achieved

Topical Lidocaine

Medication	Dosing Guidance	Estimated Cost/Dose
Lidocaine oint/cream	Requires multiple doses per day	$0.39-$1.88
Lidocaine patch	Aspercreme 4% formulation preferred, ½ cost of 5%	$1.11-$2.66
Additional Notes: ▪ Should only be considered for localized pain due to lack of systemic absorption		

RECOMMENDATION SUMMARY

If the patient presentation indicates the presence of neuropathic pain, and the prescribed analgesic regimen is not providing the desired level of relief, the addition of an adjuvant analgesic should be considered:

Comorbid Condition	Recommend Adjuvant Analgesic
Insomnia	Nortriptyline
Depressed mood and/or anxiety	Duloxetine
Diabetic peripheral neuropathy	Pregabalin

The following adjuvant analgesics should be avoided, or used only after careful consideration and consultation when considering broadening the analgesic regimen to manage neuropathic pain:

Medication(s)	Reason to Avoid/Limit Use
Amitriptyline, Imipramine	Significantly higher prevalence of anticholinergic side effects than nortriptyline or desipramine
Venlafaxine	▪ Increased titration requirements compared to duloxetine ▪ Increased risk of experiencing unpleasant withdrawal symptoms if one dose missed
Topical Lidocaine	▪ Limited efficacy for neuropathic pain ▪ Multiple applications/day of cream/oint ▪ Analgesic benefit experienced limited to site of application ▪ Cost

Management of neuropathic pain can be a very complex condition to manage, with multiple patient-specific factors to consider. If you have questions regarding safe effective management for one of your patients, please do not hesitate to contact us for a BetterRX Pharmacy Consultation. Our clinical team is ready to assist.

References

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