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neuroTale

(A CNS Journal)

Issue 1, 2012

Neuropathic Pain Management

Role of Sodium Valproate in Epilepsy

SQUARE

Pharmacologic management of neuropathic pain

Assessment of neuropathic pain (NP) should focus on identifying and treating the underlying disease processes and peripheral or central nervous system lesions, response to prior therapies, and comorbid conditions that can be affected by therapy. Particular attention should be paid to identifying coexisting depression, anxiety, sleep disturbances, and other adverse impacts of NP on health-related quality of life, and both pain and its adverse effects should be reassessed frequently. Patient education and support are critical components of the successful management of NP.

Careful explanation of the cause of NP and the treatment plan are essential. Patient and provider expectations regarding treatment effectiveness and tolerability must be discussed, and realistic treatment goals should be established with patients. Non-pharmacologic methods of coping with pain should be discussed, including the importance of stress reduction, good sleep hygiene, physical therapy, and other potentially useful interventions.

There is insufficient evidence to rank first-line medications for NP by their degree of efficacy or safety. Clinicians must consider several other factors when selecting a specific medication for a patient with NP, including: (1) the potential for adverse outcomes associated with medication-related side effects; (2) potential drug interactions; (3) comorbidities that may also be relieved by the non-analgesic effects of the medication (e.g., sleep disturbance, depression, anxiety); (4) costs associated with therapy; (5) the potential risks of medication abuse; and (6) the risks of intentional and unintentional overdose.

These potentially competing factors must be prioritized according to the specific needs of each patient with NP.

Individual variation in the response to the medications used to treat NP is substantial and unpredictable. Although evidence-based recommendations encourage the use of specific medications, the overall approach should be recognized as a stepwise process intended to identify the medication, or medication combination, that provides the greatest pain relief and fewest side effects for a given patient (see the Table below). If an adequate trial of one medication fails to adequately relieve pain or causes intolerable side effects, treatment should be discontinued and a different medication should be selected for a trial. If a medication is well tolerated and provides partial pain relief, it should be continued and a second medication with a distinct mechanism of action added.

In addition to potential additive analgesic benefits, combination therapy may provide analgesia more quickly by combining a medication with a rapid onset of effect with one that requires several weeks of treatment before maximum benefit is achieved. These potential advantages of combination therapy must be weighed against the possibility of additive adverse effects, drug interactions, increased cost, and reduced adherence to a more complex treatment regimen.

Table-Stepwise Pharmacologic Management of Neuropathic Pain (NP)

Step 1

- Assess pain and establish the diagnosis of NP [Dworkin et al., 2003; Cruccu et al., 2004); if uncertain about the diagnosis, refer to a pain specialist or neurologist.
- Establish and treat the cause of NP; if uncertain about availability of treatments addressing NP etiology, refer to appropriate specialist.
- Identify relevant comorbidities (e.g., cardiac, renal or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy.
- Explain the diagnosis and treatment plan to the patient, and establish realistic expectations.

Step 2

- Initiate therapy of the disease causing NP, if applicable. Initiate symptom treatment with one or more of the following:
  - A secondary amine tricyclic antidepressant (TCA) (nortriptyline, desipramine) or a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) (duloxetine, venlafaxine)
  - A calcium channel alpha 2-sigma ligand, either gabapentin or pregabalin
  - For patients with localized peripheral NP: topical lidocaine used alone or in combination with one of the other first -line therapies
  - For patients with acute neuropathic pain, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with one of the first-line therapies
- Evaluate patient for non-pharmacologic treatments, and initiate if appropriate.

Step 3

- Reassess pain and health-related quality of life frequently.
- If substantial pain relief (e.g., average pain reduced to <3/10) and tolerable side effects, continue treatment.
- If partial pain relief (e.g., average pain remains >4/10) after an adequate trial (see Table 3 in the original guideline document), add one of the other first-line medications.
- If no or inadequate pain relief (e.g., <30% reduction) at target dosage after an adequate trial (see Table 3 in the original guideline document), switch to an alternative first-line medication.

Step 4

If trials of first-line medications alone and in combination fail, consider second-and third-line medications or referral to a pain specialist or multidisciplinary pain center.

First-line Medications

Three medications or medication classes are recommended as first-line treatment for patients with NP (grade A recommendation). In the original guideline document summarizes treatment selection considerations.

Tricyclic Antidepressants (TCAs) and Selective Serotonin and Norepinephrine Reuptake Inhibitors (SSNRIs)

TCAs are typically inexpensive and usually administered once daily. The presence of depression is not required for the analgesic effects of these medications, although they may be particularly useful in patients with inadequately treated depression. The most common side effects of TCAs include sedation, anticholinergic effects (e.g., dry mouth, constipation, and urinary retention), and orthostatic hypotension. Secondary amine TCAs (nortriptyline and desipramine) are preferred because they are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) but have comparable analgesic efficacy. Amitriptyline in particular should be avoided in elderly patients.

The decision to start a TCA should also consider the possibility of cardiac toxicity. Data suggest that the lowest effective dosage of a TCA should be used in all patients with NP, and that TCAs should be avoided in patients who have ischemic heart disease or an increased risk of sudden cardiac death. A screening electrocardiogram (ECG) is recommended before beginning treatment with TCAs in patients over 40 years of age. TCAs should be used cautiously in patients at risk for suicide or accidental death from overdose. They can cause or exacerbate cognitive impairment and gait disturbances in elderly patients, and may predispose to falls. Toxic TCA levels may result if TCAs are administered together with medications that inhibit cytochrome P450 2D6, such as selective serotonin reuptake inhibitors (SSRIs).

Starting doses of TCAs should be low, and the dosage should be titrated slowly until pain is adequately controlled or side effects limit continued titration (see Table 3 in the original guideline document). Although monitoring medication levels is not usually necessary, it may reduce the risk of cardiac toxicity at dosages greater than 150 mg/day.

Duloxetine is an SSNRI that inhibits the reuptake of both serotonin and norepinephrine. It has demonstrated significantly greater pain relief compared with placebo in patients with painful diabetic peripheral neuropathy (DPN) but it has not been studied in other types of NP. Duloxetine has a generally favorable side effect profile and dosing is simple. Nausea is the most common side effect, but it occurs less frequently if treatment is initiated at 30 mg/day and titrated after one week to 60 mg/day, an efficacious dosage at which pain relief can occur within one week. As a new medication, there is limited long-term safety information and efficacy data are limited to studies of painful DPN.

Venlafaxine is an SSNRI that inhibits serotonin reuptake at lower dosages and both serotonin and norepinephrine reuptake at higher dosages.

Randomized clinical trials (RCTs) in patients with painful DPN and painful polyneuropathies

of various types including DPN demonstrated efficacy at dosages of 150 to 225 mg/day. RCTs in other populations, including those with post-mastectomy pain, various peripheral and central NP conditions, and post herpetic neuropathy (PHN), demonstrated inconsistent or negative results. In one RCT, 5% of venlafaxine-treated patients developed ECG changes, and monitoring is therefore recommended in patients with cardiovascular risk factors. Venlafaxine is available in both short- and long-acting formulations. Two-to-four weeks is often required to titrate to an effective dosage, and patients should be tapered gradually from venlafaxine because of the risk of discontinuation syndrome.

Calcium Channel alpha 2-delta Ligands

Gabapentin is generally safe, has no clinically important drug interactions, and is available in generic formulations. The main dose-limiting side effects are somnolence and dizziness, which are reduced by gradual dosage titration, and peripheral edema. In some patients, particularly the elderly, gabapentin can cause or exacerbate cognitive or gait impairment. Several weeks can be required to reach an effective dosage, which is usually between 1800 and 3600 mg/day (administered in three divided doses, increasing the night-time dose preferentially). Dosage reduction is necessary in patients with renal insufficiency. The onset of activity can be seen as early as the second week of therapy when titration is rapid, but peak effect usually occurs approximately two weeks after a therapeutic dosage is achieved. Therefore, an adequate trial may require two months or more.

Pregabalin produces dose-dependent side effects similar to those of gabapentin. It has also demonstrated anxiolytic effects in RCTs of generalized anxiety disorder, which may provide additional benefit in patients with chronic pain. Like gabapentin, it has no clinically important drug interactions but requires dosage reduction in patients with renal impairment. Studies indicate that treatment can be initiated at 150 mg/day (in either two or three divided doses), although a starting dose of 75 mg at bedtime is used by some clinicians to reduce the likelihood of early side effects in elderly patients and in others especially prone to side effects. The potential for twice daily dosing and the linear pharmacokinetics of pregabalin may contribute to relatively greater ease of use compared with gabapentin, but the overall efficacy and tolerability of these two medications appear similar. However, onset of pain relief with pregabalin can be more rapid than with gabapentin because its starting dosage of 150 mg/day is efficacious. Upward dosage titration can reach 300 mg/day within one to two weeks, and the maximum benefits typically occur after two weeks of treatment at

target dosages of 300 to 600 mg/day. Because it is a new medication, long-term safety of pregabalin is not as well established as it is for gabapentin. Starting dose of 75 mg at bedtime is used by some clinicians to reduce the likelihood of early side effects in elderly patients and in others especially prone to side effects (see Table 3 in the original guideline document). The potential for twice daily dosing and the linear pharmacokinetics of pregabalin may contribute to relatively greater ease of use compared with gabapentin, but the overall efficacy and tolerability of these two medications appear similar. However, onset of pain relief with pregabalin can be more rapid than with gabapentin because its starting dosage of 150 mg/day is efficacious. Upward dosage titration can reach 300 mg/day within one to two weeks, and the maximum benefits typically occur after two weeks of treatment at target dosages of 300 to 600 mg/day. Because it is a new medication, long-term safety of pregabalin is not as well established as it is for gabapentin.

Topical Lidocaine

As a topical preparation, lidocaine patch 5% is recommended for patients with localized peripheral NP but not for patients with central NP. When used as recommended, the only side effects that occur with the lidocaine patch 5% are mild skin reactions (e.g., erythema and localized rash). Blood levels are minimal with the approved maximum dosing of three patches/day applied for 12 h and also when four patches/day are applied for 18 h. Nonetheless, use of the lidocaine patch 5% should be avoided in patients receiving oral Class I antiarrhythmic medications (e.g., mexiletine) and in patients with severe hepatic dysfunction, in whom excessive blood concentrations are theoretically possible.

The efficacy of lidocaine gel was demonstrated in patients with PHN and allodynia, but not in patients with human immunodeficiency virus (HIV) neuropathy. Because of its safety and ease of use, lidocaine gel can be considered when the lidocaine patch 5% is not available, application of a patch is problematic, or the cost of the lidocaine patch 5% precludes its use.

Second-line Medications That Can Be Used for First-line Treatment in Select Clinical Circumstances

Opioid analgesics and tramadol have demonstrated efficacy in multiple RCTs in patients with NP, and when patients do not have a satisfactory response to the first-line medications alone or in combination, opioid agonists can be used as second-line treatment alone or in combination with the first-line medications (grade A recommendation). In select clinical circumstances, opioid analgesics and tramadol can also be considered for first-line use (see the Table below).

Table – Circumstances in Which Opioid Analgesics and Tramadol Can Be Considered for First-line Treatment of Neuropathic Pain.

- During titration of a first-line medication to an efficacious dosage for prompt pain relief
- Episodic exacerbations of severe pain
- Acute neuropathic pain
- Neuropathic cancer pain

Opioid Analgesics

Treatment of chronic NP with opioid agonists should generally be reserved for patients who have failed to respond to or cannot tolerate the first-line medications. This recommendation is consistent with published guidelines for the use of opioids in chronic non-cancer pain that have been prepared by various groups. Opioids can be considered for first-line use in select circumstances (see Table above). Typically, such first-line use of opioids should be reserved for circumstances in which suitable alternatives cannot be identified and should be on a short-term basis to the extent possible.

Before initiating treatment with opioid analgesics, clinicians should identify and address risk factors for abuse, which include active substance abuse, prior history of opioid or other drug abuse, other major psychiatric pathology, and family history of substance abuse. Response to treatment, side effects, and signs of opioid misuse or abuse should be monitored on a regular basis, as has been described in guidelines for opioid use in chronic non-cancer pain. It is recommended that clinicians without opioid expertise obtain consultation from appropriate specialists in developing a treatment plan for challenging patients.

The most common opioid-related side effects are nausea, constipation, and sedation. Although nausea and sedation typically decrease after several weeks of treatment, constipation may not; it usually requires concurrent management, especially in the elderly or other groups with risk factors for this problem. Opioids should be used cautiously in patients at risk for suicide or accidental death from overdose. In elderly patients, opioids can also cause or exacerbate cognitive impairment and gait disturbances, increasing the risk of falls. In contrast to abuse or addiction, physical dependence develops in all patients chronically treated with opioid analgesics, and patients must be advised that they should not discontinue these medications on their own.

The effective opioid dosage varies widely among patients, and either of two strategies for the initiation of treatment can be used depending on the specific clinical circumstances. For opioid-naive patients, treatment can be initiated with an oral immediate-release opioid at a dose equivalent to 10–15 mg of morphine every 4 h or on an as needed basis, with conversion to a long-acting opioid after a few days, when the approximate daily dosage has been identified. Treatment can also be initiated with a long-acting opioid (e.g., oral morphine or oxycodone, or transdermal fentanyl). Fixed-schedule dosing with a long-acting opioid is generally preferred, although RCTs in patients with NP are needed to compare the efficacy and safety of short versus long-acting opioids. Titration should continue until satisfactory pain relief is achieved or unacceptable side effects persist despite attempts to improve tolerability (e.g., laxatives for constipation).

Treatment with a short-acting opioid on an as needed basis may be appropriate to continue in selected patients with NP who have episodes of markedly increased pain; until the role of such "rescue" treatment has been more adequately characterized for patients with NP, treatment approaches used for patients with other types of chronic pain, including cancer pain, can be followed. As with all of the medications recommended for NP, the lowest effective dosages of opioid analgesics should be used. If an adequate trial of therapy has not produced clinically meaningful pain relief, patients should be tapered off their opioid analgesic and an alternative treatment administered.

Tramadol

As with opioids, tramadol is associated with abuse potential; although rates of tramadol abuse have remained very low despite new branded and generic formulations, some recent reports suggest that the rate of recreational tramadol use may be rising.

The most common side effects of tramadol are somnolence, constipation, dizziness, nausea, and orthostatic hypotension, which occur more frequently with rapid dosage escalation. Tramadol can cause or exacerbate cognitive impairment and gait disturbances in elderly patients. It can also precipitate seizures in patients with a history of seizures or in those receiving medications that reduce seizure threshold.

Concurrent use of other serotonergic medications (including SSRIs and SSNRIs) may increase the risk of serotonin syndrome, and combination therapy with these medications must be undertaken cautiously. As for opioid analgesics, tramadol is recommended primarily for patients who have not responded to the first-line medications but it can also be considered for first-line use in select clinical circumstances .

Tramadol is available in both short- and long-acting formulations; for the short-acting formulation, the starting dosage is 50 mg once or twice daily, with gradual titration to a maximum of 400 mg/day. Dosage reduction is necessary in patients with renal or hepatic disease and in the elderly.

Generally Third-line Medications

There are a number of other medications that would generally be used as third-line treatments but that could also be used as second-line treatments in some circumstances (e.g., when treatment with an opioid agonist is not indicated or when the patient's treatment history suggests greater potential for their effectiveness). These medications include certain other antiepileptic (carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid) and antidepressant (bupropion, citalopram, paroxetine) medications, mexiletine, N-methyl- D-aspartate (NMDA) receptor antagonists, and topical capsaicin. Recommendations for their use are based on efficacy in a single RCT or inconsistent results from multiple RCTs and the clinical experience of the authors (grade B recommendation). Refer to the original guideline document for information regarding third-line medications.

Additional Recommendations for Central NP

Based on the results of a small number of RCTs, the following specific medications should be considered for patients with central NP: TCAs for central post-stroke pain; calcium channel alpha 2-delta ligands for spinal cord injury pain; and cannabinoids for NP associated with multiple sclerosis (grade B recommendation). Lack of long-term follow-up data, limited availability, and concerns over precipitating psychosis or schizophrenia, especially in individuals with environmental or genetic risk factors, restrict the use of cannabinoids to second-line therapy for patients with multiple sclerosis NP at present, and additional trials are needed to further establish their efficacy and safety.

Many patients with central NP either do not have one of these diagnoses or require alternative therapy. In these situations, the first- and second-line medications recommended for peripheral NP can be considered for the treatment of central NP (except for topical lidocaine). However, it must be acknowledged that the evidence base for such treatment is limited.

Conclusions

TCAs, SSNRIs, calcium channel alpha 2-delta ligands, and topical lidocaine have demonstrated efficacy in NP and are recommended as first-line medications. In patients who have failed to respond to these first-line medications alone and in combination, opioid analgesics or tramadol can be used as a second-line treatment alone or in combination with one of the first-line medications. Opioid analgesics and tramadol can also be considered for first-line use in select clinical circumstances.

Patients who have not responded adequately to these medications used alone and in combination can be treated with one or more other recommended medications. For patients who have not responded adequately to pharmacologic management or those who have pain that is associated with challenging comorbidities or with a high level of disability or distress, prompt consultation with a pain specialist or multidisciplinary pain management center is recommended, including consideration of a broad array of non-pharmacologic therapies and invasive treatments.

It is important to emphasize that pharmacologic management of the patient with chronic NP should be considered an integral component of a more comprehensive approach that also includes non-pharmacologic treatments. Nonpharmacologic treatments for NP require increased attention and evaluation in controlled trials in which they are administered alone and also in combination with pharmacologic therapies.

Role of sodium Valproate in different types of epilepsy

Indication of Sodium Valproate:

Sodium Valproate is used in the treatment of primary generalized epilepsy; as sole or additional therapy in partial (focal) epilepsy; and in the treatment of mania.

Action of Sodium Valproate:

Sodium Valproate works to treat epilepsy by preventing the excessive electrical activity (which causes fits) in the brain. It is thought to achieve this by increasing the activity of a neurotransmitter called GABA in the brain. Neurotransmitters are chemicals that are stored in nerve cells and are involved in transmitting messages between the nerve cells. GABA is a neurotransmitter that helps keep the nerve activity in the brain in balance. Sodium valproate is thought to increase the production and prevent the breakdown of GABA in the brain. This increases the calming activity of GABA in the brain, which stabilises the electrical nerve activity and helps prevents fits. Sodium valproate may also stabilise the electrical nerve activity by preventing sodium from entering the nerve cells when they begin to fire rapid and repetitive electrical signals. A build up of sodium in the nerve cells is necessary for an electrical signal to build up and be passed on, so sodium valproate may also prevent fits in this way.

Dose advice of Sodium Valproate:

Sodium Valproate is available in tablet and liquid formulations. Sodium Valproate tablets should be taken twice daily, and the liquid formulations should be taken in divided doses. Doses should be taken with food.

Epilepsy:

Adults: Dosage should start with 600mg daily, increasing by 200mg/day at 3 day intervals until control of condition is achieved. The usual range is 1-2g/day. If adequate control is not achieved within this dose range, the dose can be increased to 2.5g/day.

Children >20kg: Dosage should start with 400mg/day in divided doses increasing doses gradually until control is achieved. The usual dose range is 20-30mg/kg/day. If the child is <20kg, the usual dose range is 20mg/kg/day. Mania:Initially dosage should start at 600mg/day increasing by 200mg/day at 3 day intervals until control is achieved. The usual range is 1-2g/day. If adequate control is not achieved within this range, the dose can be increased to 2.5g/day.

Common side effects of Sodium Valproate:

Sodium Valproate may cause some of the following common side effects:

- **Nausea and vomiting**
- **Abdominal cramps**
- **Increased appetite**
- **Weight gain**
- **Diarrhoea**
- **Drowsiness**
- **Tremor**

Uncommon side effects of Sodium Valproate:

Sodium Valproate may cause some of the following effects. You should inform your doctor of these.

- **Breast enlargement**
- **Discharge of milk from breasts**
- **Hair loss**
- **Irregular periods**
- **Problems with balance**
- **Double vision**
- **Allergic reactions**
- **Hearing problems**
- **Spontaneous bruising or bleeding**

Congratulations !

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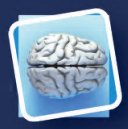

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Oxapro®	Escitalopram 5 mg & 10 mg tablet

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Atypical Antipsychotic

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Please tick the correct answers:

1. Careful explanation of the cause of NP and the treatment plan are essential. ..... Y ☐ / N ☐

1. Two medications or medication classes are recommended as first-line treatment for patients with NP ..... Y ☐ / N ☐

3. TCAs are typically inexpensive and usually administered once daily. ..... Y ☐ / N ☐

4. Duloxetine has a generally favorable side effect profile and dosing is simple. ..... Y ☐ / N ☐

5. Nonpharmacologic treatments for NP not require increased attention..... Y ☐ / N ☐

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