Journal of Korean Society of
Spine Surgery

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J Korean Soc Spine Surg 2011 Dec;18(4):246-253.
Originally published online December 31, 2011;
http://dx.doi.org/10.4184/jkss.2011.18.4.246

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pISSN 2093-4378 eISSN 2093-4386

Original Article | pISSN 2093-4378 eISSN 2093-4386

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A Treatment Guideline for Neuropathic Pain

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Study Design: A review of literature including definition, diagnosis and treatment of neuropathic pain.
Objectives: To review and discuss the treatment guideline for neuropathic pain.
Summary of Literature Review: Neuropathic pains are characterized by partial or complete somatosensory change caused by various disorders affecting central and peripheral nervous system, and are especially problematic because of their severity, chronicity and resistance to simple analgesics.
Materials and Methods: Review of literature.
Results: Tricyclic antidepressants and the anticonvulsants gabapentin and pregablin were recommended as first-line treatments for neuropathic pain. Opioid analgesics and tramadol were recommended as second-line treatments that can be considered for first-line use in selected clinical circumstances. Other medications such as dual reuptake inhibitors of both serotonin and norepinephrine would be used in severe cases. More invasive interventions (e.g., spinal cord stimulation) may sometimes be helpful.
Conclusions: Treatment must be individualized for each patient and aggressive, combinatory pharmacotherapy and multidisciplinary approach are recommended for the treatment of neuropathic pain.

Key Words: Neuropathic pain, Definition, Diagnosis, Treatment guideline

INTRODUCTION

Neuropathic pain results from damages in peripheral nerve system or dysfunctional central nerve system and is challenging to control with typical analgesia currently using. It is characterized by incurable and severe pain and doesn't respond well to the standard pain management methods which impaired the quality of patients' lives significantly and is also classified as a morbid pain manifesting that it can cause mental disorder such as sleeping disturbance, depression and anxiety and induce social issues such as reduced productivity secondary to the failure of social adaptation.

Adequate early treatments for neuropathic pain prevent the pain from worsening and becoming too chronic and incurable to control satisfactorily. Therefore, it is vital to start established effective treatment at early stage after the diagnosis when neuropathic pain is suspected. For this reason, this study aimed to summarize diagnosis methods and management guideline through literature review and to contribute to the effective management.

REVIEW OF LITERATURE

Definition

Neuropathic pain was defined as pain initiated or caused by a primary lesion or dysfunction in the nerve system by the International Association for the Study of pain (IASP).[1)]

Received: August 12, 2010
Revised: July 25, 2011
Accepted: August 2, 2011
Published Online: December 31, 2011
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본 논문의 요지는 2010년도 대한척추외과학회 춘계학술대회에서 발표되었음.
본 논문은 ㈜한국 얀센의 척추외과학회 학술사업(ULT-KOR-9028)의 지원을 받아 이루어졌음.

Table 1. Classification of neuropathic pain by anatomical location and etiology.

Peripheral	Central
Complex regional pain syndrome	Cervical or thoracic myelopathy
Neural entrapment syndrome	Spinal cord injury
Cervical, thoracic and lumbar radiculopathy	Syringomyelia
Neural compression by tumor	Spinal cord compression (e.g. cancer)
Diabetic neuropathy	

Table 2. Grading system for neuropathic pain.[9]

Criteria to be evaluated for each patient
1. Pain with a distinct neuroanatomically plausible distribution
2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system
3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test
4. Demonstration of the relevant lesion or disease by at least one confirmatory test

Grading of certainty for the presence of neuropathic pain:
Definite neuropathic pain: all (1 to 4)
Probable neuropathic pain: 1 and 2, plus either 3 or 4
Possible neuropathic pain: 1 and 2, without confirmatory evidence from 3 or 4.

Although this definition was thought to be useful to distinguish neuropathic pain from the other types of pain, it was criticized that there was a lack of anatomical accuracy and diagnostic manifestation.[2–7] Therefore, the definition neuropathic pain was revised in recent years and the terms is now described as pain arising as direct consequence of a lesion or disease affecting the somatosensory system. Contrary to nociceptive pain, which is usually acute and reversible, the neuropathic pain progresses to the chronic status and is characterized by allodynia (pain due to a stimulus which does not normally provoke pain), hyperalgesia (an increased sensitivity to pain) and dysesthesia (an unpleasant, abnormal sense of touch).[8]

Classification

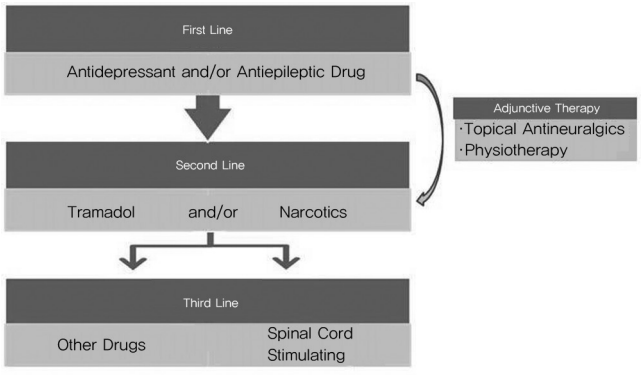

Fig. 1. This algorithm shows the management of neuropathic pain in primary care. Topical antineuralgics such as lidocaine patch is useful for focal neuropathy such as postherpetic neuralgia.

Neuropathic pain is classified as peripheral or central according to the anatomical origins of pain[9] and it can be also caused by following orthopedic or operative spinal diseases (Table 1).

Diagnosis

The accurate clinical diagnosis of neuropathic pain is not easy because it can be caused by a number of different diseases. It is necessary to analyze the anatomical location of the lesions and the cause of the lesions for the diagnosis. First of all, it is necessary to confirm whether the distribution of pain is corresponded to the anatomical location of peripheral nerve or central nerve through the detailed history taking and there should be a causal relationship between the onset of pain and the lesions in central somatosensory system. If neuropathic pain is suspected after this, whether there is muscle weakness, sensory disturbance and pain should be confirmed in the physical examination and in addition to this, neurological disease or lesions should be confirmed via laboratory test, 3 phase-bone scan, radiological investigation and electroneuromyography to diagnose neuropathic pain.

The diagnosis of neuropathic pain can be made according to the correspondence to the following criteria based on the grading system (Table 2). When the symptom includes all 4 criteria, it is a definite neuropathic pain and when the symptom includes criteria 1 and 2 and one of criteria 3 or 4, neuropathic pain is

highly probable. In addition to the grading system, the diagnosis of neuropathic pain can be also made according to the pain scale using S-LANSS basing on the clinical symptoms.[10] There are 7 items (the existence of pricking sensation, changes of skin color in the affected areas, the existence of unpleasant sensation or onset of pain when the affected area was touched, whether there is sudden pain in bursts for no apparent reason, whether there is feeling of skin temperature changes in the painful areas, whether stroking the affected area of skin with a piece of cotton wool produce an unpleasant painful sensation, whether touching the affected area of skin with a sharp needle feel sharper or duller when compared to an area of normal skin) and sensory test and the diagnosis is made when the score is more than 12 out of 24.

Management

Principles of neuropathic pain management

The treatment of neuropathic pain should be started actively at the earliest possible moment considering the causative diseases and the dose of first line drugs should be increased until the pain is controlled as long as the side effects are tolerated and even if the pain is not controlled, continuous treatment is recommended.[11] The use of second line drugs or the combined with other types of drugs may offer if there is not satisfactory improvement with monotherapy and psychological support and comfort should be provided. Providing that the combined drug therapy fails to control the pain, multi-disciplinary approach such as interventional procedures and psychological support will be necessary (Fig. 1).

1 Pharmacological management

Neuropathic pain is commonly progressed to the chronic status and subsequently, long-term and high dose of medication will be required. Hence, it is important to fully acknowledge about the type of possible drugs, their dose, the use and the side-effects (Table 3).

First line pharmacologic treatment

Tricyclic antidepressants (TCAs)

The great advantages of tricyclic antidepressants (TCAs) are that it is cost-effective and also manages comorbid depression which is highly prevalent to the patients with neuropathic pain. It also had the equipotentiality in both neuropathic pain patients with depression and without depression. On the other hand, anti-cholinergic effects such as thirst, constipation and micturition disorder can be presented and there is also possible cardiotoxicity even though the prevalence is extremely low. Therefore, it cannot be used in the cardiac patients such as arrhythmia or ischemic heart disease and it might not be appropriate to use in the elderly patients. However, secondary amine tricyclic anti-depressant such as nortriptyline and desipramine can be used for elderly patients instead because they have significantly low cardiotoxicity and anti-cholinergic effects. Amitriptyline should be started at low dose (25mg) at night and increased 25mg every 3-7 day up to 150mg over 2 weeks and can be used for 6-8 weeks.[12]

Gabapentin/Pregabalin (calcium channel α 2-δ ligand)

Gabapentin/Pregabalin exerts their beneficial effects by binding to calcium channels inducing changes in neurotransmitter. Side-effects such as dizziness and sedation can be presented in proportion to the dose but these side effects can be minimized as long as the drug is started with low dose and carefully titrated. Interaction with other drugs is rare but the reduced dose is recommended in renal failure.

Gabapentin is instructed to start 300mg three times a day and can be increased up to 3600mg per day. It usually takes about 2 month to take an effect as the analgesic effect is slowly expressed. The effect of pregablin is similar to that of gabapentin and it is recommended to start 75mg twice a day and increase 300mg within 3-7 days. Depending on the efficacy of the dose, it can be increased up to 600mg per day every 1 week.

Local lidocaine products

5% lidocaine patch is usually used in postherpetic neuralgia and it is reported that 5% lidocaine patch is effective to manage allodynia and peripheral neuropathic pain but also showed tolerance and can be only used in the local areas. Lidocaine gel is reported to be easier to use and has similar effects. Local lidocaine products hardly cause side effects apart from local skin irritation.[12]

Second line pharmacologic treatment

Opioid analgesics/Tramadol

The effects of opioid analgesics and tramadol have been

Table 3. Neuropathic pain medications.

Drug	Starting dose	Titration	Usual maintenance dose (and maximum)	Adverse effects	Duration of adequate trial	Comments
Tricyclic antidepressants						
amitriptyline Imipraine Nortriptyline desipramine	10-25 mg/day	increase weekly by 10 mg/day	50-150 mg/day	Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrthythmia	6-8 weeks with at least 1-2 week at maximum tolerated dosage	Amitriptyline more likely to produce drowsiness and anticholinergic side effects; contraindicated in patients with glaucoma, symptomatic prostatism and significannt cardiovascular disease
Calcium channel α_2-δ ligand						
Gabapentin	100-300 mg at bedtime or 100-300 mg three times daily	Increase by 100-300 mg three times daily every 1-7 days as tolerated	300-1200 mg three times daily	Drowsiness, dizziness, peripheral edema, visual blurring	3-8 weeks for titration plus 2 weeks at maximum dosage	Dosage adjustments required in renal failure
Pregabalin	50 mg tid or 75 mg bid	Increase to 300 mg daily after 3-7 days, then by 150 mg/d every 3-7 days as tolerated	150-300 mg twice daily	Drowsinee, dizziness, peripheral edema, visal blurring	4 weeks	Similar adjustments in renal failure
Topical lidocaine						
5% lidocaine patches or gel	Maximum of 3 patches daily for a maximum of 12 h	None needed	Maximum of 3 patches daily for a maximum of 12 -18 h	Local erythema, rash	3 weeks	None

Table 3. Neuropathic pain medications. (Continued)

Drug	Starting dose	Titration	Usual maintenance dose (and maximum)	Adverse effects	Duration of adequate trial	Comments
Opioid agonists						
Morphine	15 mg every 12 h	After 1-2 wk, convert total daily dosage to long-acting opioid analgesic and continue shortacting medication as needed	30-120 mg every 12 h	Respiratory depression ataxia, nausea, vomiting, sedation, dizziness, urinary retention, constipation	4-6 weeks	History of substance abuse, suicide risk, driving impairment during treatment initiation, constipation requires concurrent bowel regimen
Oxycodone	10 mg every 12 h	After 1-2 wk, convert total daily dosage to long-acting opioid analgesic and continue shortacting medication as needed	20-60 mg every 12 h	Respiratory depression ataxia, nausea, vomiting, sedation, dizziness, urinary retention, constipation	4-6 weeks	History of substance abuse, suicide risk, driving impairment during treatment initiation, constipation requires concurrent bowel regimen
Fentanyl	12-25ug/h patch	After 1-2 wk, convert total daily dosage to long-acting opioid analgesic and continue shortacting medication as needed	25-100 ug/h patch	Respiratory depression ataxia, nausea, vomiting, sedation, dizziness, urinary retention, constipation	4-6 weeks	History of substance abuse, suicide risk, driving impairment during treatment initiation, constipation requires concurrent bowel regimen
Tramadol	50mg once or twice daily	Increase by 50-100 mg daily in divided doses every 3-7 days, as tolerated, until pain relief	50–100 mg 2–3_ daily, maximaum 400 mg/d (100 mg 4 times daily); in patients older than 75 y, 300 mg/d in divided doses	Respiratory depression, ataxia, sedation, constipation, seizures, nausea, orthostatic hypotension	4 weeks	May lower seizure threshold, use with caution in epilepsy, history of substance abuse, suicide risk, driving impairment during treatment initiation, concomitant use of SSRI, SSNRI, TCA or acetaminophen, keep maximal dose of acetaminophen at 4 g to avoid hepatic toxicity,

Table 3. Neuropathic pain medications. (Continued)

Drug	Starting dose	Titration	Usual maintenance dose (and maximum)	Adverse effects	Duration of adequate trial	Comments
Selective serotonin noradrenaline reuptake inhibitors						
Venlafaxine	37.5 mg once or twice daily	Increase weekly by 37.5 mg/day	150-225 mg/day	Nausea, headache, dizziness, drowsiness, hyperhidrosis, hypertension, constipation, worsening depression	4-6 weeks	Use with caution in concomitant use of tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation
Duloxetine	30 mg once daily	Increase to 60 mg once daily after one week	60-120 mg/day	Sedation, nausea, somnolence, dizziness, constipation, ataxia, drymouth	4 weeks	Use with caution in hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol

proved in a number of randomized controlled trials with different types of neuropathic pain. However, these drugs are usually recommended to the patients who are poorly responded to the first line pharmacologic treatment due to the safety issue relating to the long-term use (comparing to the first line pharmacologic treatment). Opioid analgesics has a similar analgesic effects to tricyclic anti-depressant and gabapentin but the prevalence of the side-effects is higher.[13,14] It is necessary to consider prescribing gastrointestinal drug at the same time for side effects such as nausea/vomiting and constipation and it should be carefully observed for any misuse, abuse or addition when it is used in long-term. Opioid analgesics is usually prescribed 10-15mg every 4 hourly and conversion from short-acting agents to long-action agents may require. Tramadol is less efficient than morphine or oxycodone[15] but the effects in neuropathic pain have been proved as an opioid μ receptor agonist. Tramadol is recommended to start 50mg once or twice a day and can be increased up to 400mg if the patient doesn't suffer from renal failure and up to 300mg in elderly patients. The effect of tramadol is similar to that of opioid analgesia but tramadol, unlike opioid analgesics, interacts with selective serotonin-norepinephrine reuptake inhibitors or selective serotonin re-uptake inhibitors resulting in fatal condition such as serotonin syndrome. Therefore, tramadol should not be used with these drugs at the same time.

Third line pharmacologic treatment

Other drugs

It is possible to prescribe other types of anti-depressants additionally if it is judged to be beneficial and other types of anti-convulsants apart from gabapentin and pregabalin can also be used as third line drugs. Among these, duloxetine, the serotonin-norepinephrine reuptake inhibitor, is usually used for anxiety or depression but it also known to be significantly effective to control pain of diabetic peripheral neuropathy (DPN). Venlafaxine is also reported to be effective in DPN and other types of peripheral neuropathic pain excluding postherpetic neuralgia.[12] Duloxetine can be started with 30mg and increased to 60mg after a week and increased maximum dose of up to 120mg. Venlafaxine is recommended to start 37.5mg twice a day and can be increased up to 225mg a day but a care should be taken as it may cause hypertension if the maximum dose is used.

2 Interventional procedures

Spinal cord stimulation

Spinal cord stimulation is one of effective management methods for the pain which is poorly responded to the conservative management. The pain can be controlled effectively and it reduces the use of pharmacologic treatment hence, the quality of life can be improved and it facilitates the return to work. Although the initial inserting device can be costly, it is still considered to be cost-effective in the view of long-term effects.[16-18] Failed back surgery syndrome,[19] peripheral vascular disease,[20,21] complex regional pain syndrome,[22, 23] chronic peripheral neuropathy[24,25] and ischemic heart disease[20,26] are known as indications for spinal cord stimulation but it is documented that spinal cord stimulation is less successful to manage central pain originated from brain or spinal cord.[17,25]

CONCLUSION

Neuropathic pain requires active early treatment because it can be easily progressed to the chronic pain due to challenging diagnosis and severity of the symptom. Tricyclic anti-depressants or anti-convulsants (gabapentin or pregabalin) are usually used as the first line treatment and opioid analgesics or tramadol can be added or converted to when the symptom is persistent. Additional drug therapies may initiate if the pain is still not controlled. Furthermore, multi-disciplinary approach such as interventional procedures or psychological approach may be necessary if there is no satisfactory improvement with combined drug therapies.

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신경병증성 통증의 치료 지침에 대한 고찰

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연구 계획: 신경병증성 통증의 정의, 진단과 치료 방법에 대한 문헌 고찰
목적: 신경병증성 통증에 대한 문헌을 고찰하고 치료 지침을 논의하고자 한다.
선행문헌의 요약: 신경병증성 통증은 말초 신경계나 중추 신경계의 질환에 의해 유발된 체성감각계의 부분적 혹은 완전한 변화로, 통증의 정도가 심하고 만성적 경과를 보이며 일반적인 진통제에 반응하지 않는 특성을 지니는 병적 통증으로 분류된다.
대상 및 방법: 문헌 고찰
결과: 일차 약제로 삼환계 항우울제나 가바펜틴이나 프리가바린 같은 항전간제를 사용하며 이차 약제로 마약성 진통제나 트라마돌을 사용할 수 있다. 조절이 잘 되지 않을 경우 세로토닌-노르에피네프린 동시 재흡수 차단제 등 기타 약제를 사용할 수 있으며, 증상에 따라 척수 자극술 등 중재적 시술이 도움이 되는 경우도 있다.
결론: 신경병증성 통증의 치료는 환자에 따라 개별화 되어야 하며, 적극적으로 복합 처방을 통한 통증 조절을 고려해야 하고, 다학제적 접근과 치료가 필요하다.

색인 단어: 신경병증성 통증, 정의, 진단, 치료 지침
약칭 제목: 신경병증성 통증의 치료