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Critical appraisal of neuropathic pain guidelines in Asia

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ABSTRACT

Neuropathic pain (NP) is type of chronic pain that is common and often difficult to treat. Clinicians may be guided by a number of published guidelines and algorithms for the management of neuropathic pain. It is important for every clinician to know the quality of guidelines. The availability of current guideline in Asian countries is not well understood. Critical appraisal of NP guidelines in Asia has not performed, yet. The aim of this study was to appraise the quality of pharmacological treatment from neuropathic pain guidelines in Asia. Systematic searches were conducted by using combination of keywords i.e NP, Asia, and guideline. Guidelines evaluation was using appraisal of guidelines for research & evaluation II (AGREE II) instrument. The result interpreted as (i) a strongly recommended for use in practice if most domains scored above 50%; (ii) recommended for use with some modification if most domains scored between 30% to 50%; or (iii) not recommended for use in practice if most domains scored below 30%. After matched to inclusion and exclusion criteria there were 5 guidelines left: a guideline from Philippines, China, South Korea, Malaysia and Middle East. All of guidelines are recommended for use with some modification. The guidelines mention that first line treatment for NP are tricyclic antidepressants, selective norepinephrine reuptake inhibitor (SNRI) and alpha 2-delta ligand calcium channel blocker (CCB). Most of the evidences come from peripheral NP. There were limited evidences for the treatment of central neuropathic pain (central post stroke pain and pain after spinal cord injury). All the existing guideline mention, that the first line treatment for neuropathic are the tricyclic antidepressants, SNRI and alpha 2-delta ligand CCB.

ABSTRAK

Nyeri neuropatik (NP) adalah tipe nyeri kronis yang umum dan seringkali sulit diobati. Dokter dipandu oleh sejumlah pedoman dan algoritma yang diterbitkan untuk manajemen NP. Penting bagi setiap dokter untuk mengetahui kualitas pedoman. Ketersediaan pedoman saat ini di negara-negara Asia belum dipahami dengan baik. Penilaian kritis pedoman NP di Asia belum dilakukan. Tujuan dari penelitian ini adalah untuk menilai kualitas pengobatan farmakologis dari pedoman NP di Asia. Pencarian sistematis dilakukan dengan menggunakan kombinasi kata kunci: nyeri neuropatik, Asia, dan pedoman. Evaluasi panduan menggunakan instrumen *appraisal of guidelines for research & evaluation II (AGREE II).* Hasil ini diartikan sebagai (i) sangat direkomendasikan untuk digunakan dalam praktik jika sebagian besar domain mendapat skor di atas 50%; (ii) direkomendasikan untuk digunakan dengan beberapa modifikasi jika sebagian besar domain mencetak antara 30% hingga 50%; atau (iii) tidak direkomendasikan untuk digunakan dalam praktik jika sebagian besar domain mendapat skor di bawah 30%. Setelah dicocokkan dengan kriteria inklusi dan eksklusi ada 5 pedoman yang tersisa: pedoman dari Filipina, Cina, Korea Selatan, Malaysia, dan Timur Tengah. Semua pedoman direkomendasikan untuk digunakan dengan beberapa modifikasi. Pedoman menyebutkan bahwa pengobatan lini pertama untuk NP adalah tricyclic antidepressants, *selective norepinefrin reuptake inhibitor* (SNRI), dan alpha 2-delta ligand *calcium channel blocker* (CCB). Sebagian besar bukti berasal dari NP perifer. Terdapat bukti terbatas untuk pengobatan nyeri neuropatik sentral (nyeri post stroke sentral dan nyeri setelah cedera tulang belakang). Semua pedoman yang ada menyebutkan bahwa pengobatan lini pertama untuk NP adalah antidepresan trisiklik, SNRI, dan alpha 2-delta ligand CCB.

Keywords:
systematic review, neuropathic pain, guidelines, Asia

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INTRODUCTION

Chronic pain is the most common reason for visiting the outpatient clinic.[1] Neuropathic pain (NP) is a common type of chronic pain. NP is defined as pain initiated or caused by lesion or disease of the somatosensory system, including peripheral fibres (Aβ, Aδ and C fibres) and central neurons.[2] Previous study showed that 7 to 8% of the population affected by NP. Evidences showed that as much as 5% NP cases may be severe enough and intractable.[3] NP reduces the quality of life significantly.[4] It causes poor impact on the economy such as considerable loss in working days, disability and increasing health care costs. Therefore, NP should be approached as major health problem.[5]

Pharmacological treatment is the main approach in the management of NP.[6] NP is often difficult to treat since due to it is resistant to many medications and/or due to the adverse effects associated with effective medications. Most patients require treatment with more than one drug. Clinicians may be guided by a number of published guidelines and algorithms for the management of NP.[1] Clinical practice guidelines defined as statements that include recommendations intended to optimize patient care that are informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options.[6] Clinical practice guidelines are developed systematically to help practitioners and patients choose the appropriate care for specific clinical situations.[7]

A critical appraisal is a systematic process used to identify the strengths and weaknesses of a research article in order to assess the usefulness and validity of research findings.[8] As treatment is made based on a guideline, it is important to determine the quality of every guideline. The availability of current guideline in Asian countries is not well understood yet. Critical appraisal of NP guidelines in Asia has not performed, yet. The aim of this study was to appraise the quality of pharmacological treatment from NP guidelines in Asia.

MATERIAL AND METHODS

MATERIALS

A systematic search was performed by 2 authors. Guidelines were obtained by reviewing the major medical database (Pubmed and EMBASSE), homepages of international medical institution and other relevant websites. The search was conducted by using combination of keywords: neuropathic pain, Asia and guideline.

The inclusion criteria i.e. (1) guideline from different country in Asia; (2) full text was available; (3) the guidelines were written in English; and (4) the guidelines were published between 2009 and 2017. We decided to only include guidelines written in English so that whosoever can access the guideline. Guidelines were excluded if focused on only one type of neuropathic pain, such as diabetic neuropathic pain. We excluded the guideline or consensus statement that did not represent the view of national pain organization. FIGURE 1 below represents the selection process.

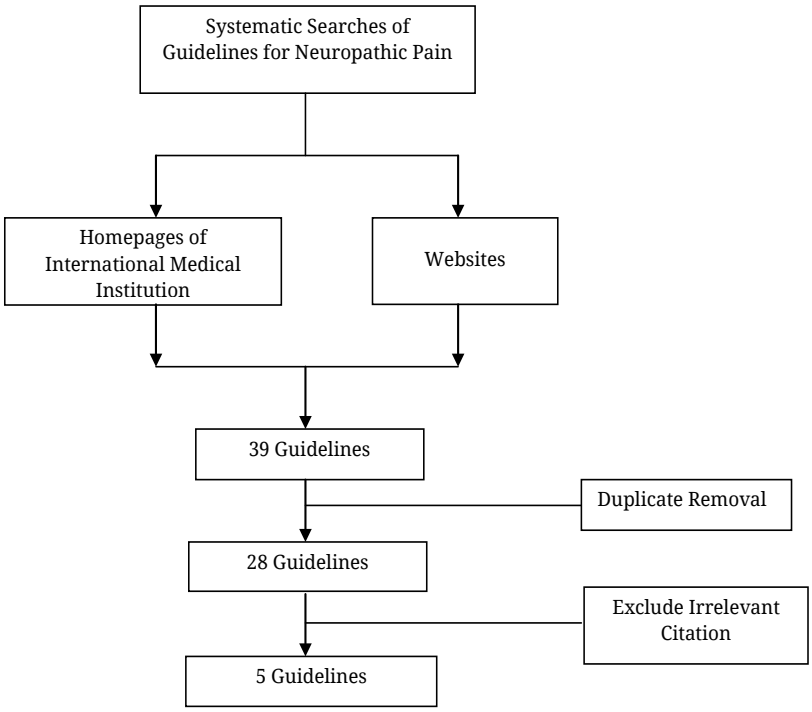

FIGURE 1. Guidelines selection process

There were 39 manuscripts found during systematic search. Nine of them were duplication, as the same manuscript published in the different database. After checking for the content of each manuscript, only 5 manuscripts meet our criteria. Irrelevant manuscripts were published before 2009, written in regional language, or did not meet the criteria of guideline. We expected that every guideline discussed in this critical appraisal can be beneficial by whosoever so that manuscript in regional language would be excluded.

Review Process

Selected guidelines were evaluated by 2 appraisers. Appraisal of guidelines for research and evaluation II (AGREE II) instrument was used as guidelines for evaluation. AGREE II is an instrument to assess the quality of guidelines.[9] There were 23 key items organized within 6 domains: (1) scope and purposes, (2) stakeholder involvement, (3) rigour of development, (4) clarity of presentation, (5) applicability, and (6) editorial independence. Each key item was rated on a 7-point scale; 1-strongly disagree to 7-strongly agree. The key item scored 1 if there is no information that is relevant o AGREE II criteria and scored 7 if the key items fulfill the criteria. Score between 2 and 6 were assigned when the key items do not meet the full criteria. Scores in each domain calculated into a single quality score using the following formula: (obtained score – minimum possible score / maximum possible score – minimum possible score) x 100%. The result interpreted as (i) a strongly recommended for use in practice if most domains scored above 50%; (ii) recommended for use with some modification if most domains scored between 30% to 50%; or (iii) not recommended for use in practice if most domains scored below 30%.

The information retrieved about pharmacological treatment for each guideline. The treatment were summarized in a table, based on condition and recommendation level. The discussion was focused in the quality of each guideline.

RESULT

A total 39 manuscripts were collected during the guidelines search. After matched to inclusion and exclusion criteria there are 5 guidelines left: a guideline from Philippines, China, South Korea, Malaysia and Middle East. The information about those guidelines summarized in TABLE 1.

TABLE 1. Neuropathic pain guidelines in Asia

Guidelines Name	Organization or Institute	Short Name	Country or Region	Release Time
Neuropathic Pain Syndromes[10]	Pain Society of the Philippines	PSP	Philippines	2009
Handbook of Neuropathic Pain Management Guidelines, 2nd Edition[11]	Multidisciplinary Panel on Neuropathic Pain	MPNP	China	2011
A Treatment Guideline for Neuropathic Pain[12]	Korean Society of Spine Surgery	KSSS	South Korea	2011
Management of Neuropathic Pain, 2nd Edition[13]	Malaysia Association for the Study of Pain	MASP	Malaysia	2012
Guidelines for the Pharmacological Treatment of Peripheral Neuropathic Pain: Expert Panel Recommendations for the Middle East Region[14]	Square Pharmaceuticals Limited	SPL	Middle East	2014

Those five guidelines were evaluated using the AGREE II instrument. All of guidelines are recommended for use with some modification. TABLE 2 shows a summarized of the guidelines score for each domain. Guidelines from Philippines, China, Malaysia and Middle East show a specific recommendation for each condition. Korean guideline is the only one, which is, shows a general recommendation for all kind of neuropathic pain. The highest score was obtained by domain 4 and the lowest score was obtained by domain 5 and domain 6.

TABLE 2. Domain scores of neuropathic pain guidelines

Organization or Institute	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
PSP[10]	55,56%	61.11%	29.17%	94.44%	29.17%	16.67%
MPNP[11]	83.33%	83.33%	37.5%	94.44%	29.17%	33.33%
KSSS[12]	55.56%	61.11%	29.17%	94.44%	25%	25%
MASP[13]	77.78%	66.67%	18.75%	100%	37.5%	41.67%
SPL[14]	61.11%	55.56%	33.33%	94.44%	33.33%	16.67%

PSP: Pain Society of the Philippines; MPNP: Multidisciplinary Panel on Neuropathic Pain, KSSS: Korean Society of Spine Surgery; MASP: Malaysia Association for the Study of Pain; SPL: Square Pharmaceuticals Limited, Domain 1: scope and purposes, Domain 2: stakeholder involvement, Domain 3: rigour of development, Domain 4: clarity of presentation, Domain 5: applicability, Domain 6: editorial independence

TABLE 3 shows a summarized of the guidelines treatment recommendations. Guidelines from Philippines, China, Malaysia and Middle East show a specific recommendation for each condition. Korean guideline is the only one which is show a general recommendation for all kind of neuropathic pain. Most guidelines show that most of the evidences come from peripheral neuropathic condition. There are limited evidences in treatment of central neuropathic pain condition (central post stroke pain or spinal cord injury). The evidences about using combination therapy in neuropathic pain are very limited. Most of the recommendation for central neuropathic pain comes from small clinical trial and expert opinions. The combination therapy recommendation comes from expert opinion. There are also limited evidences in radicular pain condition, which is a condition that very common in our daily clinical practice.

TABLE 3. Summary of neuropathic drugs recommendation

Condition and Recommendation Level PSP[10]		Drugs				
		MPNP[11]	KSSS[12]	MASP[13]	SPL[14]	
Post Herpetic Neuralgia	1st line	Gabapentin, Pregabalin	TCA or A2D ligands ± adjunctive local anaesthetic or EMLA cream ± adjunctive TENS		Pregabalin, Gabapentin, Amitriptyline, EMLA cream/ Capsaicin/5% lignocaine patch	Topical lidocaine (patch or 5% gel or cream)
	2nd line	Amitriptyline, Tramadol, Opioids, Oxycodone, Fentanyl, Topical lidocaine	Oral opioids, carbamazepine*		Tramadol	
Diabetic Peripheral Neuropathy	1st line	Pregabalin, Gabapentin, Fentanyl	A2D ligands, TCAs or SNRIs		Pregabalin, Gabapentin Amitriptyline Duloxetine, Venlavaxine	
	2nd line	Duloxetine, Venlavaxin, Oxycodone, Tramadol, Amitriptyline	Tramadol		Tramadol	
Central Post-Stroke Pain	1st line	Lamotrigine	A2D ligands or TCAs	Pregabalin, Gabapentin,	Amitriptyline,	Carbamazepine
	2nd line	Amitriptiline, IV lidocaine	Other anticonvul-sants or opioids		Opioids	
	3rd line		Adjuctive local anaesthetics			
Complex Regional Pain Syndrome	1st line		1. NSAIDs and/ or TCAs or anticonvulsant 2. TCA + anticonvulsant 3. TCA + rotation of anticonvulsant		Antidepressant, Anticonvulsant, or both	
	2nd line		Opioids		Opioids	

	3rd line	Corticosteroids	Lignocaine, Ketamine	
	4th line	1. Lignocaine, capsaicin, or transdermal fentanyl 2. Calcitonin, bisphosphonates		
Neuralgia Trigeminal	1st line	Carbamazepine*	Carbamazepine, Oxcarbazepine	
	2nd line	A2D ligands, other anticonvulsants, antidepressants	Baclofen, Lamotrigine Gabapentin, Pregabalin, Amitriptyline, Duloxetine	
Cancer Pain	1st line	A2D ligand (pregabalin, gabapentin) and/ or TCA		
	2nd line	Other anticonvulsant and antidepressant		
	3rd line	Other agents (systemic ketamine or lignocaine)		
Spinal Cord Pathologies	1st line	A2D ligands, TCAs		
	2nd line	Other anticonvulsant, opioids		
	3rd line	Intravenous ketamine, invasive procedures		
Persistent Post-Surgical Pain	1st line		Pregabalin, Gabapentin, Amitriptyline, Duloxetine	
	2nd line		Tramadol	
1st line		TCAs Gabapentin, Pregabalin, local Lidocaine products		A2D ligand (pregabalin, gabapentin), TCAs (nortriptyline, desipramine)
2nd line		Opioid, Tramadol		SNRI (venlafaxine XR, duloxetine), opioid (tramadol, oxycodone)
3rd line		Duloxetin, Venlavaxine		

PSP: Pain Society of the Philippines; MPNP: Multidisciplinary Panel on Neuropathic Pain, KSSS: Korean Society of Spine Surgery; MASP: Malaysia Association for the Study of Pain; SPL: Square Pharmaceuticals Limited; TCA: Tricyclic Antidepressant; A2D: Alpha-2-delta, EMLA: Eutectic Mixture of Local Anaesthetics; TENS: Transcutaneous Electrical Nerve Stimulation; SNRI: Selective Norepinephiren Reuptake Inhibitor
*Genetic susceptibility for Stevens-Johnson Syndrome (HLA-B1502) should be assessed in Asia patients before commencing treatment with carbamazepine

DISCUSSION

Our result of assessments showed that all guidelines are recommended for use with some modification. The recommendations from all guidelines are specific, unambiguous, clearly presented and easily identifiable.

The AGREE II instrument was used as guidelines for evaluation with 23 key items organized within 6 domains. Domain 1 is "scope and purposes", is concerned with the overall aim of the guideline, the specific health questions, and the target population (items 1-3). Domain 2 is "stakeholder involvement", focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users (items 4-6). Domain 3 is "rigor of development", relates to the process used to gather and synthesize the evidence, the methods to formulate the recommendations and to update them (items 7-14). Domain 4 is "clarity of presentation", deals with the language, structure and the format of the guideline (items 15-17). Domain 5 is "applicability", pertains to the likely barriers and facilitators to implementation, strategies to improve uptake and resource implications of applying the guideline (items 18-21). Domain 6 is "editorial independence", is concerned with the formulation of recommendations not being unduly biased with competing interests (items 22-23).[9]

The highest score was obtained by the domain 4, which means the guidelines had a good description of the recommendations. The recommendations from all guidelines are specific, unambiguous, clearly presented and easily identifiable. The recommendations were summarized in TABLE 3. All guidelines describe the qualifying condition and side effects of each recommendation clearly. The recommendations grouped together in one section and presented as flow charts or a summarized box. A2D ligands (gabapentin and pregabalin) and/or TCAs (amitriptyline) are the first line therapy for almost all type of neuropathic pain. Post herpetic neuralgia, diabetic peripheral neuropathy and central post stroke pain were the most common conditions discussed.

Domain 1 and 2 also had good scores. All guidelines were described the objective(s) specifically. The target population and clinical condition were mentioned clearly, that is neuropathic pain patients. The target user of guidelines was physicians, but the guideline from Philippine and Korea did not mention it clearly. Most of the guidelines's development group was included individual from various professional group, such as physicians, neurologist and anesthesiologist. Middle East's guideline is the only one which didn't describe the development group clearly. All guidelines in this study were used a literature review methods.

Domain 3 is important because it is evaluates the integrity of the guideline development process, but all those five guidelines did not show a high score at the domain 3. Guideline reviewed by external reviewer prior to its publication is necessity and Philippine guideline was the only one guideline mentioned its external reviewer. All guidelines did not describe their details of strategy used to search for evidence, criteria for selecting the evidence, recommendation development process and procedure for updating the guideline clearly.

The lowest score was obtained by the domain 5 and domain 6 which is mean the guidelines have many shortcomings because lack of the related information. Those guidelines had a poor description of barriers and facilitators to implementation, potential resource implications of applying recommendations, monitoring and/or auditing criteria, a statement of not

biased with competing interests.

The treatment recommendations were summarized in TABLE 2. All guidelines describe the qualifying condition and side effects of each recommendation clearly. The recommendations grouped together in one section and presented as flow charts or a summarized box. A2D ligands (gabapentin and pregabalin) and/or TCAs (amitriptyline) are the first line therapy for almost all type of NP. Post herpetic neuralgia, diabetic peripheral neuropathy and central post stroke pain were the most common conditions discussed. There are limited evidences in treatment of central NP condition (central post stroke pain or spinal cord injury).

CONCLUSION

Five Asian guidelines fulfill the satisfying criteria according to AGREE II instrument, eventhough need some modification. The available guidelines describe the medicine recommendations specific, unambiguous, clearly presented and easily identifiable. Tricyclic antidepressant, SNRI, and A2D ligand CCB are the first line treatment for various neuropathic pain condition.

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