Chapter 6

Predictive Factors for Postherpetic Neuralgia and Recent Pharmacotherapies

Yuko Kanbayashi and Toyoshi Hosokawa

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1. Introduction

Postherpetic neuralgia (PHN) is a form of refractory chronic neuralgia that, despite the importance of prevention, currently lacks any effective prophylaxis. The efficacy of live zoster vaccine in preventing PHN was recently reported [1]. However, this vaccine appeared to be of limited use in prophylaxis[2]. PHN has a variety of symptoms and significantly affects patient quality of life [3-12]. Various studies have statistically analyzed predictive factors for PHN [13-23], but neither obvious pathogenesis nor established treatment has been clarified or established. We designed and conducted a study on the premise that statistical identification of significant predictors for PHN would contribute to the establishment of an evidence-based medicine approach to the optimal treatment of PHN. As a result, we reported our paper "Predictive Factors for Postherpetic Neuralgia Using Ordered Logistic Regression Analysis" [24].

In this review, we discuss predictors for PHN based on our results, and further review recent pharmacotherapeutic results.

2. Predictors for PHN

Previous studies have shown that older age, female sex, presence of a prodrome, greater rash severity, and greater acute pain severity are predictors of increased PHN [14-18, 25]. Some other potential predictors (ophthalmic localization, presence of anxiety and depression, presence of allodynia, and serological/virological factors) have also been studied [14, 18]. We conducted a retrospective study to identify significant predictors of PHN that would

contribute to the establishment of evidence-based medicine approaches to the optimal treatment of PHN [24].

The participants were 73 patients with herpes zoster who had been treated at the pain clinic of our hospital between January 2008 and June 2010. Variables present at the initial visit were extracted from the clinical records for regression analysis of factors related to the occurrence of PHN. The following scores for response were used: 0 = no PHN after 3 months; 1 = PHN present after 3 months, but absent after 6 months; and 2 = PHN present after 6 months. Multivariate ordered logistic regression analysis was performed to identify predictive factors for PHN. Table 1 shows the clinical characteristics of patients and various factors that could be related to the occurrence of PHN. Multivariate ordered logistic regression analysis identified advanced age and deep pain at the initial visit to our outpatient pain clinic as factors predicting the occurrence of PHN. diabetes mellitus (DM) and pain reduced by bathing also showed high odds ratios, but were not significant predictive factors (Table 2). In conclusion, advanced age and deep pain at first visit were identified as predictive factors for PHN. DM and pain reduced by bathing should also be considered as potential predictors of PHN [24]. To improve patient safety and the likelihood of achieving satisfactory outcomes, prospective studies are needed to establish optimal treatments including pharmacotherapy for PHN. Next section we further review recent pharmacotherapeutic results for PHN.

	(0/1) or (0/1/2), median (range)
Demographics	
Significant zoster-associated pain	35/13/25
Age	8/46/19, 69 (27-90)
Sex	37/36
Complication	
Hypertension	44/29
Angina	69/4
Diabetes mellitus	61/12
Malignant tumor	50/23
Autoimmune disease	68/5
Sleep disorder	36/37
Location	
Trigeminal nerves	58/15
Cervical nerves	58/15
Thoracic nerves	42/31
Lumbar nerves	61/12
Sacral nerves	70/3

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	(0/1) or (0/1/2), median (range)
Period of onset, type and extent of pain	
Period before herpes zoster onset (days)	30 (1-3000)
Log (period before herpes zoster onset)	1.477 (0-3.477)
Prodromal rash	39/34
Prodromal pain	34/39
Allodynia	35/38
VAS (mm)	66 (0-100)
Pain reduced when bathing	41/32
Pain (superficial)	35/38
Pain (deep)	38/35
Pain (continuous)	43/30
Pain (breakthrough)	31/42

Binary scales were: female = 0, male = 1 for sex; and absent = 0, present = 1 for others.

The ordered scale was: absent after 3 months = 0, present = 1, and present after 6 months = 2 for significant zoster-associated pain; and <50 years = 0, 51-74 years = 1, ≥75 years = 2 for age.

VAS, visual analog scale

Table 1. Clinical characteristics of 73 patients and various factors that could be related to the occurrence of PHN [24]

Variable	EV	SE	χ^2 value	P	OR	CI of OR	
						Lower 95%	Upper 95%
Age	*1.008*	*0.461*	*4.78*	*0.0288**	*2.740*	*1.110*	*6.761*
Prodromal pain	0.442	0.532	0.69	0.4059	1.556	0.549	4.413
DM	1.123	0.693	2.63	0.1049	3.075	0.791	11.952
Allodynia	0.201	0.630	0.10	0.7489	0.818	0.238	2.808
Pain reduced by bathing	1.221	0.745	2.68	0.1014	3.389	0.787	14.601
Deep pain	*1.446*	*0.682*	*4.49*	*0.0341**	*4.244*	*1.114*	*16.163*
Breakthrough pain	0.687	0.598	1.32	0.2506	1.988	0.616	6.418
Sleep disorder	0.146	0.514	0.08	0.7757	1.158	0.423	3.169

EV, estimated value; SE, standard error; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus

*P<0.05

Table 2. Results of multivariate ordered logistic regression analysis for variables extracted by forward selection with addition of prodromal pain and allodynia [24].

3. Recent pharmacotherapy for PHN

To date, no clear predictors of treatment response have been identified in patients with neuropathic pain, including PHN. Various types of drugs have shown consistent efficacy in randomized clinical trials and meta-analysis [9]. The modes of action and information on dosing, precautions, and adverse events (AEs) for the different drug classes are summarized in Table 3 [9]. Numbers needed to treat (NNTs), numbers needed to harm (NNH) [26, 27] and AEs for the different drugs are shown in Table 4 [28].

Among systemic therapies, tricyclic antidepressants (TCAs), calcium channel α2-δ ligands (gabapentin and pregabalin), and extended-release formulations of morphine and oxycodone show good efficacy in patients with PHN. Current guidelines suggest, perhaps to maximize the benefit-risk ratio, that TCAs should be preferred over opioids, and among TCAs, second-generation TCAs such as nortriptyline, desipramine, and imipramine are preferred over the first-generation agent, amitriptyline [29]. Opioids, specifically oxycodone, morphine, methadone, and tramadol, are also effective against PHN. However, addiction and regulatory issues, coupled with the benign adverse event profile of anticonvulsants, make opioids a secondary choice in PHN [28].

The American Academy of Neurology (AAN; 2004), European Federation of Neurological Societies (NeuPSIG; 2007), and European Federation of Neurological Societies (EFNS; 2010) guidelines all recommend TCAs and pregabalin as first-line oral therapies for patients with PHN [11, 30, 31]. The NeuPSIG and EFNS guidelines also recommend gabapentin as first-line therapy for PHN. The NeuPSIG and EFNS guidelines state that secondary amine TCAs should generally be considered instead of the tertiary amine amitriptyline, due to the superior safety profiles [11, 29, 30].

Japan Society of Pain Clinicians (JSPC; 2011) guidelines recommend TCAs (particularly the secondary amines), calcium channel α2-δ ligands, and extract of cutaneous tissue of rabbits inoculated with vaccinia virus (Neurotropin®) as first-line oral therapies [32].

	Mode of action	Major Adverse- events Precautions Other benefits	Starting dose/maximum dose Titration Duration of adequate trial
Nortriptyline Desipramine	Inhibition of reuptake of serotonin and/or noradrenaline, blockage of sodium channels, anticholinergic	Sedation, ant-cholinergic effects (e.g., dry mouth or urinary retention, weight gain) Cardiac disease , glaucoma, seizure disorder, use of tramadol Improvement of depression and	25 mg at bedtime/150 mg daily Increase by 25 mg every 3-7 day as tolerated 6-8 weeks (at least 2 weeks Maximum tolerated dose)

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	Mode of action	Major Adverse- events Precautions Other benefits	Starting dose/maximum dose Titration Duration of adequate trial
		sleep disturbance	
Gabapentin	Decreases release of glutamate, noradrenaline, and substance P, with ligands on α2-δ subunit of voltage-gated calcium channel	Sedation, dizziness, peripheral edema Renal Insufficiency No clinically significant drug interactions	100-300 mg once to three times daily/1200 mg three times daily; reduce if renal function impaired Increase by 100-300 mg three times daily every 1-7 days as Tolerated 4 weeks
Pregabalin	Decreases release of glutamate, noradrenaline, and substance P, with ligands on α2-δ subunit of voltage-gated calcium channel	Sedation, dizziness, Peripheral edema Renal Insufficiency No clinically significant drug interactions, improvement of sleep disturbance and anxiety	50 mg three times daily or 75 mg twice daily/200 mg three times or 300 mg twice daily, reduce if renal function impaired Increase to 300 mg daily after 3-7 days, then by 150 mg daily every 3-7 days, as Tolerated 4 weeks
5% lidocaine patch	Blockage of sodium channels	Local erythema, Rash None No systemic adverse events	1-3 patches/3 patches None 2 weeks
Morphine, oxycodone, methadone, levorphanol	μ-receptor agonism (oxycodone also causes κ-receptor antagonism)	Nausea/ vomiting, constipation, dizziness History of substance abuse, suicide risk, driving impairment Rapid onset of analgesic effect	10-15 mg morphine every 4 h or as needed (equianalgesic doses should be used for other opioids)/no maximum doses After 1-2 weeks convert to long-acting opioids/ transdermal application, use short-acting drug

	Mode of action	Major Adverse- events Precautions Other benefits	Starting dose/maximum dose Titration Duration of adequate trial
			as needed and as tolerated 4-6 weeks

Recommendations are all grading level A = good scientific evidence suggesting that the benefits of the treatment substantially outweigh the potential risks.

Table 3. Recommended first-line treatments for patients with PHN [9]

Drug	NNT (95%CI)	NNH (95%CI)	Specific/Common Adverse Effects
Amitriptyline	1.6 (1.2-2.4) 4.2 (2.13-81.6)	Minor harm: 8 (2.5-22) Major harm: 24 (8-36)	Sedation, dry mouth, tachycardia, constipation, urinary retention, weight gain, prolonged QT interval
Desipramine	1.9 (1.3-3.7)	Minor harm: 4.8 (2.5-36.7) Major harm: 13*	
Nortriptyline	3.7 (2.4-8)	ND	
Gabapentin	4.4 (3.3-6.1)	Minor harm: 4.1 (3.2-5.7) Major harm: 12.3 (7.7-30.2)	Somnolence, dry mouth, weight gain, peripheral edema, ataxia
Pregabalin	4.9 (3.7-7.6)	Minor harm: 4.3 (2.8-9.2) Major harm: ND	Dizziness, somnolence, peripheral edema
Oxycodone	2.5 (1.7-4.4)	Minor harm: 3.6 (2.2-10.2) Major harm: 6.3 (4.2-12.8)	Immune suppression, loss of libido, endocrine dysfunction
Morphine-controlled release or methadone	2.8 (2-4.6)	ND	
Tramadol	4.8 (3.5-6.0)	Minor harm: 7.2* Major harm: 10.8*	Somnolence, constipation, nausea and vomiting, seizures, serotonin syndrome when combined with SSRIs and MAO inhibitors

Values for NNTs and NNHs were adapted from Hempenstall et al. [27] and Wu and Raja [26]. NNTs for amitriptyline were based on studies by Watson et al. [49] and Max et al. [50].

*The 95% confidence interval (CI) could not be determined by Hempenstall et al. [27] or by Wu and Raja [26].

ND, could not be determined by Hempenstall et al [27]; SSRIs, selective serotonin reuptake inhibitors; MAO, monoamine oxidase

Table 4. NNT, NNH, and adverse effects of selected drugs for PHN [28]

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3.1. Calcium hannel α2-δ Ligands

Gabapentin and pregabalin suppress the release of excitatory neurotransmitters on binding to the α2-δ subunit of potential-dependent calcium channels in the central nervous system (CNS). Both drugs are structurally similar and share similar mechanisms of action, but pregabalin shows a linear pharmacokinetic profile and strong affinity for the α2-δ subunit. Both drugs have been widely studied in peripheral pain syndromes, although pregabalin has been the focus of most studies in central neuropathic pain syndromes. Only a few drug interactions have been reported for both drugs and the agents are well tolerated, but must be used at lower doses in patients with decreased renal function [9, 32]. The EFNS, AAN, and NeuPSIG guidelines recommend the calcium channel α2-δ ligands gabapentin and/or pregabalin for the treatment of PHN [11, 29-31]. In a meta-analysis, NNTs before 1 patient achieves 50% pain reduction for gabapentin (3 trials, 559 patient episodes) and pregabalin (3 trials, 411 patient episodes) for a 50% reduction in pain were 4.4 and 4.9, respectively [27, 29] (Table 4). Subsequent Cochrane reviews for both drugs calculated NNTs of 7.5 for gabapentin [29, 33] and 3.9 for pregabalin 600 mg [29, 34]. Gabapentin and pregabalin are effective and are the most commonly prescribed drugs in PHN because of their efficacy and benign AEs profile.

3.1.1. Pregabalin

Pregabalin is a 3-isobutyl derivative of gamma-amino butyric acid (GABA) with anti-convulsant, anti-epileptic, anxiolytic, and analgesic activities. Although the exact mechanisms of action are unclear, pregabalin selectively binds to α2-δ subunits of presynaptic voltage-dependent calcium channels located in the CNS. Binding of pregabalin to α2-δ subunits of presynaptic voltage-dependent calcium channels prevents calcium influx and the subsequent calcium-dependent release of various neurotransmitters, including glutamate, noradrenaline, serotonin (5-Hydroxytryptamine: 5-HT), dopamine, and substance P, from the presynaptic nerve terminals of hyperexcited neurons; synaptic transmission is inhibited and neuronal excitability is diminished. Pregabalin does not bind directly to GABA-A or GABA-B receptors and does not alter GABA uptake or degradation [35].

Pregabalin has also been associated with dose-related risks of somnolence (5-14%), dizziness (7-28%), and peripheral edema (6-16%) [29, 32, 34]. At a higher dose (600 mg/day), pregabalin has been associated with weight gain (9%), asthenia (9%), dry mouth (6%), and vertigo (5%) [28, 29, 36]. Discontinuations due to these AEs were ≤1% in patients treated with pregabalin at 150 mg/day and 4-15% in patients receiving a 600-mg/day dose. Serious AEs were reported in 2-5% of patients treated with pregabalin at 150, 300, and 600 mg/day, compared with 3% in those assigned to receive a placebo [29, 36]. Symptoms including insomnia, nausea, headache, and diarrhea were reported by some patients following abrupt withdrawal of pregabalin. Pregabalin should therefore be tapered gradually over a minimum of 1 week rather than discontinued abruptly. Weight gain noted in clinical trials of pregabalin was not limited to patients with peripheral edema. Weight gain was related to dose and duration of exposure to pregabalin, but did not appear to be associated with sex, age, or baseline body-mass index. A higher incidence of weight gain and peripheral edema were noted in patients taking both

pregabalin and a thiazolidinedione, compared with patients taking either agent alone. As a result, care should be taken when co-administering pregabalin and one of these agents [37].

JSPC guidelines recommend beginning pregabalin treatment at 75 mg/day once before bed, 150 mg/day as two doses after breakfast and supper, or 150 mg/day as three doses after each meal. Even when renal function is normal, consider a very low dose only just before bed, such as 25 mg/day once before bed, for elderly patients, patients of low body weight, and others prone to AEs [32].

3.1.2. Gabapentin

Gabapentin is a synthetic analogue of the neurotransmitter GABA with anticonvulsant activity. Although the exact mechanisms of action are unknown, gabapentin appears to inhibit excitatory neuron activity. This agent also exhibits analgesic properties [35].

In clinical trials, the most frequent AEs observed with gabapentin were somnolence (16%), dizziness (21%), and peripheral edema (8%) [33]. Twelve percent of patients discontinued gabapentin owing to AEs, compared with 8% who discontinued placebo. Serious AEs with gabapentin and placebo occurred in 4% and 3% of patients, respectively [29].

3.2. Opioids

Opioid analgesics are agonists at presynaptic and postsynaptic opioid receptors. Opioids offer comparable analgesic efficacy to TCAs. Concerns about long-term AEs, such as immunological changes, physical dependency, and misuse or abuse, can limit the use of strong opioids in patients with neuropathic non-cancer-related pain [9].

The place of opioids and tramadol in guidelines for the management of PHN has evolved over time. In the 2004 AAN guidelines, extended-release formulations of oxycodone and morphine were recommended as first-line agents. Guidelines issued by the NeuPSIG (2007) and EFNS (2010) recommend strong opioids and tramadol as second-line therapy, not because of new data on efficacy, but perhaps reflecting concerns about the risks of AEs and abuse [29].

Extended-release formulations of oxycodone [38] and morphine, as well as methadone [39], have shown efficacy in patients with PHN. The NNT for a 50% reduction in pain were 2.5 for oxycodone and 2.8 for morphine or methadone, compared with an NNT of 3.7 for the TCA nortriptyline (Table 4). In a placebo-controlled, active comparator-controlled crossover trial, the majority of patients (53%) preferred the opioids morphine or methadone over TCAs. Opioids tended to provide greater pain relief, although the difference was not significant [40]. A meta-analysis of the 2 trials evaluating oxycodone, morphine and methadone calculated an NNT for opioids of 2.7 [27]. Tramadol has proven less effective than strong opioids. In a randomized controlled trial, tramadol was not significantly better than placebo on a 5-point verbal scale or on measures of quality of life [40]. An analysis of this trial calculated an NNT of 4.8 [27]. Oxycodone, morphine, and methadone were associated with typical opioid-related AEs, including nausea, diarrhea, and constipation [38, 39]. Tramadol was better tolerated, but less effective [40].

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In the JSPC guideline, although multiple clinical studies have demonstrated the analgesic effects of opioid analgesics (narcotics for medical use) in patients with neuropathic pain, opioids are generally recommended as second- or third-line treatment for several reasons. First, opioid analgesics have a high incidence of associated AEs that may persist over the entire course of treatment. Second, the lack of any systematic investigation into the long-term safety of opioid analgesics means that the opioid analgesics may not be fundamentally safer than other drug options. Third, opioid analgesics may cause hyperalgesia. This effect, if present, would adversely modify the risk/benefit profile of long-term treatment in neuropathic pain patients. Finally, opioid abuse and addiction are substantial problems [32].

3.2.1. Morphine

The sulfate salt of morphine is an opiate alkaloid isolated from the plant Papaver somniferum and produced synthetically. Morphine binds to and activates specific opiate receptors (δ, μ and κ), each of which are involved in controlling different brain functions. In the CNS and gastrointestinal system, this agent exerts widespread effects including analgesia, anxiolysis, euphoria, sedation, respiratory depression, and smooth muscle contraction in the gastrointestinal system.

A sustained-release tablet formulation contains the sulfate salt of the opiate alkaloid morphine to provide analgesic activity. Morphine binds to and activates μ-opioid receptors in the CNS, thereby mimicking the effects of endogenous opioids. Binding of morphine to opioid receptors stimulates exchange of guanosine 5'-triphosphate for guanosine 5'-diphosphate, inhibits adenylate cyclase, and decreases intracellular cyclic adenosine monophosphate. This inhibits the release of various nociceptive neurotransmitters, such as substance P, GABA, dopamine, acetylcholine, noradrenaline, vasopressin, and somatostatin. In addition, morphine closes N-type voltage-gated calcium channels and opens calcium-dependent inwardly rectifying potassium channels, causing hyperpolarization of neuronal membranes and reductions in neuronal excitability, with subsequent analgesia and sedation [35].

3.2.2. Oxycodone hydrochloride

The hydrochloride salt of oxycodone is a methylether of oxymorphone and a semisynthetic opioid agonist with analgesic and antitussive properties. Oxycodone binds to μ-receptors in the CNS, thereby mimicking the effects of endogenous opiates as well as morphine. In addition to analgesia and a depressive effect on the cough center in the medulla, this agent may cause euphoria, anxiolysis, miosis, sedation, physical dependence, constipation, and respiratory depression, depending on dosage and variations in individual metabolism [35].

3.2.3. Tramadol

A synthetic codeine analogue, tramadol has central analgesic properties with effects similar to opioids, such as morphine and codeine, acting on specific opioid receptors. Used as a narcotic analgesic for severe pain, this agent can be addictive. Tramadol is used to treat moderate-to-severe pain in adults, and binds to opioid receptors in the CNS[41]. Tramadol also weakly inhibits noradrenaline and 5-HT reuptake and can therefore interact with serotonergic drugs (selec-

tive noradrenaline reuptake inhibitors [SNRIs] and selective serotonin reuptake inhibitors [SSRIs]), causing serotonin syndrome, although this risk seems to be low in clinical practice [9].

3.3. TCAs

Clinical data support the efficacy of TCAs for PHN. In a 2005 meta-analysis of 4 clinical trials (248 patient episodes), the NNT for 1 patient to achieve a 50% reduction in pain with the TCAs amitriptyline, nortriptyline, and desipramine was 2.6 [27]. A 2007 Cochrane review of 4 clinical trials (244 patients) calculated an NNT of 2.7 [41]. Although effective, TCAs have been associated with significant systemic AEs, most notably anticholinergic AEs [43, 44], and have been associated with cardiotoxicity [45-47]. Electrocardiography (ECG) before the start of treatment is mandatory and careful dose titration is needed [9]. Individual trials of amitriptyline and desipramine in patients with PHN suggest that the second-generation TCA desipramine produces fewer anticholinergic side effects than amitriptyline [48, 49].

3.3.1. Amitriptyline hydrochloride

The hydrochloride salt of the tricyclic dibenzocycloheptadiene amitriptyline with antidepressant and antinociceptive activities. Amitriptyline hydrochloride is the hydrochloride salt of the tricyclic dibenzocycloheptadiene amitriptyline, and shows antidepressant and antinociceptive activities. Amitriptyline inhibits the re-uptake of noradrenaline and serotonin by the presynaptic neuronal membrane in the CNS, thereby increasing synaptic concentrations of noradrenaline and serotonin. Due to constant stimulation of these receptors, amitriptyline may produce a downregulation of adrenergic and serotonin receptors, which may contribute to the antidepressant activity. In the CNS, the antinociceptive activity of this agent may involve high-affinity binding to and inhibition of N-methyl-D-aspartate (NMDA) receptors and/or enhancement of the action of serotonin at the spinal terminals of an opioid-mediated intrinsic analgesia system [35].

Amitriptyline has an NNT of 2.2 for PHN, but the AEs, lack of recommendations for use in the elderly, and small sample sizes of studies have relegated this agent behind antiepileptics for certain PHN cases [30, 42, 50, 51]. Nortriptyline, maprotiline, and desipramine have also proven effective, but less so than amitriptyline.

3.3.2. Nortriptyline

A TCA used for short-term treatment of various forms of depression, nortriptyline blocks the noradrenaline presynaptic receptors, thereby blocking reuptake of this neurotransmitter and raising concentrations in the synaptic cleft in the CNS. Nortriptyline also binds to α-adrenergic, histaminergic and cholinergic receptors. Long-term treatment with nortriptyline produces downregulation of adrenergic receptors due to increased stimulation of these receptors [41].

3.4. Selective serotonin and noradrenaline reuptake inhibitors

Patients who are unable to tolerate TCAs may do better with selective serotonin and noradrenaline reuptake inhibitors, such as duloxetine or venlafaxine. Although less effective than

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TCAs, the selective 5-HT and noradrenaline reuptake inhibitors (SSNRIs) offer efficacy for both pain and depression with fewer AEs. SSRIs effectively relieve depression symptoms but they do not specifically relieve neuropathic pain. Nevertheless, some patients with chronic pain due to PHN will experience clinical depression, and the use of SSRIs can be useful for the management of depressive symptoms [5].

SNRIs are safer and easier to use than TCAs and represent a better option for patients with heart disease. The mechanism of SNRI analgesia is likely associated with activation of the descending inhibitory system of pain.

3.4.1. Paroxetine hydrochloride

The hydrochloride salt form of paroxetine is a phenylpiperidine derivative and a SSRI with antidepressant and anxiolytic properties. Paroxetine binds to the pre-synaptic serotonin transporter complex, resulting in negative allosteric modulation of the complex and thereby blocking reuptake of serotonin by the pre-synaptic transporter. Inhibition of serotonin recycling enhances serotonergic function through serotonin accumulation in the synaptic cleft, resulting in long-term desensitization and downregulation of 5-HT receptors and leading to symptomatic relief of depressive illness [35].

3.4.2. Duloxetine hydrochloride

The hydrochloride salt of duloxetine is a fluoxetine derivative belonging to the class of SSNRIs and exhibiting antidepressant activity. Duloxetine selectively prevents reuptake of 5-HT and noradrenaline via transporter complexes on the pre-synaptic membrane, thereby increasing the levels of these neurotransmitters within the synaptic cleft. As a result, this agent potentiates serotonergic and noradrenergic activities in the CNS, alleviating depression and neuropathic sensations such as pain and tingling. Furthermore, duloxetine does not show significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamatergic, or GABAergic receptors [35].

Duloxetine is recommended for painful diabetic neuropathies [11, 29, 30], but not for PHN; little clinical trial data has been accumulated supporting use in PHN. SNRIs are also associated with a number of systemic AEs, including nausea, vomiting, somnolence, anorexia, constipation, dizziness, fatigue, insomnia, increased sweating, and dry mouth [52-54].

3.5. Other oral therapies

Several other oral agents have been investigated in the treatment of PHN. Specifically, the NMDA antagonists dextromethorphan and memantine [55, 56] and the benzodiazepine lorazepam [56] have not shown good efficacy in clinical trials.

In treatment guidelines, therapies described as lacking sufficient evidence of efficacy include anticonvulsants that target sodium channels (carbamazepine and oxcarbazepine), other anticonvulsants (lamotrigine, topiramate, and valproic acid), other antidepressants (bupropion, citalopram, paroxetine), and the oral lidocaine analog, mexiletine [11, 30, 31]. For other

neuropathic pain syndromes, mexiletine has only shown efficacy at doses that produce systemic AEs, including proarrhythmic effects [43]. This suggests that the benefits of sodium channel antagonism for PHN may be better achieved via local lidocaine administration.

JSPC guidelines also recommend extract of cutaneous tissue from rabbits inoculated with vaccinia virus (Neurotropin®) as a first-line oral therapy[32].

3.5.1. Carbamazepine

Carbamazepine is a tricyclic compound chemically related to TCAs with anticonvulsant and analgesic properties. This agent exerts anticonvulsant activity by reducing polysynaptic responses and blocking post-tetanic potentiation. The analgesic activity is not understood, but carbamazepine is commonly used to treat pain associated with trigeminal neuralgia [35].

3.5.2. Valproic acid

Valproic acid is a synthetic derivative of propylpentanoic acid with antiepileptic properties and potential antineoplastic and antiangiogenesis activities. In epilepsy, valproic acid appears to act by increasing concentrations of GABA in the brain. The antitumor and antiangiogenesis activities of this agent may be related to the inhibition of histone deacetylases and nitric oxide synthase, resulting in the inhibition of nitric oxide synthesis [35].

3.5.3. Extract of cutaneous tissue from rabbits inoculated with vaccinia virus

Extract of cutaneous tissue from rabbits inoculated with vaccinia virus (Neurotropin®) has been shown to exert analgesic effects in a Japanese clinical study in PHN as one type of neuropathic pain. Producing no serious AEs, the drug product was very well tolerated, in addition to conferring analgesic effects. The drug product has been clinically used in patients 20 years old and older and is very safe [32, 57, 58].

3.5.4. Antiarrhythmics (mexiletine)

Mexiletine hydrochloride is a class 1B antiarrhythmic, and works by blocking sodium channels. A local anesthetic and antiarrhythmic (Class IB) agent structurally related to lidocaine, mexiletine exerts antiarrhythmic effects by inhibiting the inward sodium current in cardiac cells, thus reducing the rate of increase in the cardiac action potential (phase 0) and decreasing automaticity in Purkinje fibers. This slows nerve impulses in the heart and stabilizes the heartbeat. The anesthetic activity is due to the ability of mexiletine to block sodium influx in peripheral nerves, thereby reducing the rate and intensity of pain impulses reaching the CNS [41].

3.5.5. Lidocaine patch 5%

Lidocaine relieves pain through non-specific blockage of sodium channels on ectopic peripheral afferent fibers without causing numbness of the treated skin. Topical application without

a relevant systemic absorption offers a good benefit-to-risk ratio only with local AEs, such as erythema or rash [9].

The transdermal patch contains a 5% aqueous base solution of the synthetic amide-type anesthetic lidocaine with analgesic activity. Upon topical application and transdermal delivery, the active ingredient lidocaine binds to and blocks voltage-gated sodium channels in the neuronal cell membrane; lidocaine-mediated stabilization of neuronal membranes inhibits the initiation and conduction of nerve impulses and produces reversible local anesthesia [34]. The lidocaine 5% patch is recommended as first-line therapy in the AAN [31], NeuPSIG [30], and EFNS [11] guidelines [29].

3.6. Combination therapy

In clinical practice, a combination of two or more drugs is often needed to achieve satisfactory pain relief, although few trials have been conducted to support this clinical observation. However, combination therapy with gabapentin or pregabalin and extended-release morphine in patients with PHN achieved higher pain relief with lower doses compared to administration of one drug alone. These results have also been confirmed for the combination of nortriptyline and gabapentin as well as for pregabalin and topical lidocaine in patients with PHN. Taken together, these results substantiate the usefulness of combination therapies in patients with PHN [9].

4. Conclusion

Neither obvious pathogenesis nor an established treatment have been clarified or established for PHN. Our study indicated that advanced age and deep pain at the first visit were shown to be predictive factors for PHN. DM and pain reduced by bathing should also be considered as potential predictors of PHN. We further reviewed recent pharmacotherapeutic results for PHN. To improve patient safety and the likelihood of achieving satisfactory outcomes, prospective studies are needed to establish optimal treatments including pharmacotherapy for PHN.

Author details

Yuko Kanbayashi[1,2*] and Toyoshi Hosokawa[2,3,4]

*Address all correspondence to: ykokanba@koto.kpu-m.ac.jp

1 Department of Hospital Pharmacy, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

2 Pain Treatment & Palliative Care Unit, University Hospital, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

3 Department of Anaesthesiology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

4 Pain Management & Palliative Care Medicine, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

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