

Editorial

Therapeutic Medical Agents' Recent Trend in Treating Diabetic Peripheral Neuropathic Pain

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ABSTRACT

Recently, elder patients tend to have neuropathic pain such as lower back and joints pain, stiff shoulders, besides diabetic neuropathy. Typical peripheral neuropathic pain includes diabetic peripheral neuropathic pain (DPNP), postherpetic neuralgia (PHN) and chronic pain due to herniated disc. Three analgesic agents are described. Pregabalin (Lyrica[®]) has been prevalent worldwide. However, it has been provided for several diseases for off-label administration, which has been one of the clinical problems. Mirogabalin (Tarlige[®]) has revealed efficacy for DPNP in a dose-dependent manner. Duloxetine hydrochloride (Cymbalta[®]) has efficacy for pain and also depression as serotonin and noradrenaline reuptake inhibitor (SNRI).

Keywords

Neuropathic pain; Pregabalin; Mirogabalin; Duloxetine hydrochloride; Diabetic peripheral neuropathic pain (DPNP).

Abbreviations

DPNP: Diabetic peripheral neuropathic pain; PHN: Postherpetic neuralgia; CRPS: Complex regional pain syndrome; FDA: Food and Drug Administration.

In primary care medicine, the number of elderly outpatients has increased in recent years. Regarding common health problems, general medicine region includes non-communicable diseases (NCD) such as diabetes mellitus, and orthopedic region includes low back pain, knee joint pain and shoulder stiffness.¹ Statistic survey of lifestyle revealed the health and medical complaints of people. They include several popular symptoms in order as follows: man showed lower back pain, stiff shoulders, joints pain and woman showed stiff shoulder, lower back pain, joints pain, respectively.¹

Patients often complain of numbness. This includes several situations as follows: i) tingling abnormal sensations that are close to pain, ii) the sensation of the skin is dull, and iii) the movement of extremities are stiff and rigid. Thus, various conditions are observed for the combination of numbness and neuralgia. There

is some difference in the perception between patients and medical professionals.²

The progress situation of numbness and pain has been important.³ For example, low back pain is classified into three types due to persisting period, which are acute less than 4-weeks, subacute for 4-weeks to 3-months, and chronic for more than 3-months. As described above, detail medical interviews, diagnosis and treatment would be crucial for patients with diabetic neuropathy, orthopedic neuropathy and other impaired states.

Recently, comprehensive medical term “neuropathic pain” has been widely prevalent.^{2,3} It is also used in the documents in U.S. Food and Drug Administration (FDA), such as management of neuropathic pain associated with diabetic peripheral neuropathy and spinal cord injury.

Neuropathic pain has a variety of causes, including traumatic, infectious, nutritional metabolism, toxic, neoplastic and compression/strangulation.³ They are also classified according to whether the affected nerves are central (brain or spinal cord) or peripheral (terminals such as limbs). The typical examples of peripheral neuropathic pain would be shown as follows: i) diabetic peripheral neuropathic pain (DPNP), ii) postherpetic neuralgia (PHN), iii) chronic pain due to herniated disc.

In the category of neuropathic pain, there are rare but important diseases. One is allodynia, where pain is caused by a stimulus that does not usually elicit pain. The other is complex regional pain syndrome (CRPS), also known as reflex sympathetic dystrophy (RSD).⁴ CRPS is characterized by continuing regional pain that seems disproportionate in time, degree or region. Regarding the analgesics for reducing pain, three kinds of medicine would be described in this article.

The first medicine is Pregabalin (trade name: Lyrica[®]) (D02716). The indication has been neuropathic pain whose effects were demonstrated in fibromyalgia, postherpetic neuralgia, and pain after spinal cord injury. However, in daily medical practice, it has been often used for low back pain, sciatica and joint pain.⁵ From 58 available literatures, clinical abuse potential of pregabalin was suggested and prescribers had to pay attention to this situation especially for patients with abuse of some medicine.⁵

Patients having pain deserve attention, empathy, time and understanding.⁶ Some patients may receive efficacy from trial of gabapentin or pregabalin for off-label indications. However, prescribers do not have to think that these medicines show effect for pain of most pain syndromes.⁶ The comparative study for groups of gabapentin (n=362) and pregabalin (n=362) was conducted.⁷ As a result, clinicians providing these medicines for pain should recognize the limited evidence and explain the patients uncertain benefits for off-label administration.⁷

There have been increasing of intentional gabapentin misuse.⁸ In order to determine the pharmacovigilance abuse signals for gabapentin, FDA adverse events reports from 2005 to 2015 (6 million) were investigated with gabapentin reports (0.1 million). Compared to duloxetine, gabapentin had significantly greater odds of a co-report for an abuse-related and abuse-specific adverse event (AS-AE).⁸

The second is Mirogabalin. This is also ligand for the $\alpha 2\delta$ subunit of voltage-gated calcium channels as Pregabalin.⁹ It has been developed to reduce several pains associated with DPN (diabetic peripheral neuropathy) and postherpetic neuralgia.⁹ Regarding the adequate therapy of Mirogabalin, various doses of 5, 10, 15, 20, 30 mg/day was provided for patients with DPNP.¹⁰ Treatment effect least squares (LS), adverse events (AEs) and other biomarkers were studied. As a result, doses of 15, 20, 30 mg/day had statistically significant reductions in average daily pain score (ADPS) and Mirogabalin may become a promising new option for DPNP.¹⁰ Mirogabalin revealed efficacy for DPNP in a dose-dependent manner.¹¹ Mirogabalin given 30 mg/day showed statistically significant reduced pain in Asian patients. All doses of Mirogabalin tested were well tolerated.¹¹

This medicine Mirogabalin has been known and used widely as Tarlige[®] (DS-5565). This name is from the combination of targeting and ligand. As a matter of fact, a high prevalence of painful DPN has been observed with about one-third of diabetic patients.¹² According to the study of maximum observed effect (Emax) for Pregabalin and Mirogabalin, therapeutic doses of the latter showed limited evidence of abuse potential.¹³

The third is duloxetine hydrochloride (D01179) (Cymbalta[®]).¹⁴ As a standard treatment for administration of the analgesics, the recommended agents for neuropathic pain have been Pregabalin (evidence level 1A), duloxetine hydrochloride (Cymbalta) (1A), and Amitriptyline Hydrochloride (Tryptanol) (1B).¹⁵ Duloxetine is categorized as serotonin and noradrenaline reuptake inhibitor (SNRI), that is effective for depressive state. It has been widely used for diabetic neuropathy.¹⁶

The indication includes diabetic neuropathy, fibromyalgia, chronic low back pain, osteoarthritis and others.¹⁵ In contrast, its contraindications include severe liver and kidney impairment, hypersensitivity, glaucoma, and so on.¹⁷ As for the method of intaking medicine, Pregabalin and Mirogabalin are administered twice a day, while duloxetine is administered once a day. Therefore, compliance and adherence seem to be better in duloxetine.

Pregabalin has been very common medicine in terms of drug sales. In Japan, pregabalin is the number one sales agent among all medical agents sold in Japan. Behind this situation, however, there have been many off-label administrations that deviate from conventional rules. Consequently, drug abuse has been continued for diseases with indeterminate efficacy.

Furthermore, cost-effectiveness analyses (CEAs) would be important in this region. There have been several CEAs for neuropathic pain, in which heterogeneous factors are present such as methodology, design, treatments and perspectives for influencing cost-effectiveness of health condition and pain relief.¹⁸ For initial treatment for DPNP, National Institute for Health and Care Excellence (NICE) shows the recommendation of amitriptyline, duloxetine, pregabalin or gabapentin.¹⁹ However, there was not clear consensus concerning the treatments for neuropathic pain.^{20,21} In the light of CEAs for DPNP, clinically beneficial and tolerated treatment choice has been studied by optimal pathway for treating neuropathic pain in diabetes mellitus (OPTION-DM) study.²² Recent CEAs include systematic reviews focusing on strength and limitation of data and modeling practices.²³

In summary, current topics concerning neuropathic pain and its related medical agents were described in this article. Among them, proper diagnosis and treatment of medical agents would be necessary. This comment will be hopefully useful for adequate therapy in the medical practice.

ETHICAL CONSIDERATIONS

As regard to this report, author has established an ethical committee in the Integrative Medicine Japan, Shikoku island division. It included the director, vice-director, expert in the pharmacology, nursing and legal specialties. We have discussed and made confir-

mation that current report was valid and agreed with all members without any problems.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Imagama S, Ando K, Kobayashi K, Seki T, Hamada T, Machino M, et al. Shoulder pain has most impact on poor quality of life among various types of musculoskeletal pain in middle-aged and elderly people: Yakumo study. *Modern Rheumatology*. 2019; 1-5. doi: [10.1080/14397595.2019.1623364](https://doi.org/10.1080/14397595.2019.1623364)
2. Bannister K, Sachau J, Baron R, Dickenson AH. Neuro-pathic pain: Mechanism-based therapeutics. *Ann Rev Pharmacol Toxicol*. 2020; 60(1): 257-274. doi: [10.1146/annurev-pharmtox-010818-021524](https://doi.org/10.1146/annurev-pharmtox-010818-021524)
3. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. *Nat Rev Dis Primers*. 2017; 3: 17002. doi: [10.1038/nrdp.2017.2](https://doi.org/10.1038/nrdp.2017.2)
4. Miller C, Williams M, Heine P, Williamson E, O'connell N. Current practice in the rehabilitation of complex regional pain syndrome: A survey of practitioners. *Disability and Rehabilitation*. 2017; 41(7): 1-7. doi: [10.1080/09638288.2017.1407968](https://doi.org/10.1080/09638288.2017.1407968)
5. Schjerning O, Rosenzweig M, Pottegård A, Damkier P, Nielsen J. Abuse potential of pregabalin. *CNS Drugs*. 2016; 30(1): 9-25. doi: [10.1007/s40263-015-0303-6](https://doi.org/10.1007/s40263-015-0303-6)
6. Goodman CW, Brett AS. Gabapentin and pregabalin for pain — is increased prescribing a cause for concern? *New Eng J Med*. 2017; 377(5): 411-414. doi: [10.1056/nejmp1704633](https://doi.org/10.1056/nejmp1704633)
7. Goodman CW, Brett AS. A clinical overview of off-label use of gabapentinoid drugs. *JAMA Intern Med*. 2019; 179(5): 695-701. doi: [10.1001/jamainternmed.2019.0086](https://doi.org/10.1001/jamainternmed.2019.0086)
8. Vickers-Smith R, Sun J, Charnigo RJ, Lofwall MR, Walsh SL, Havens JR. Gabapentin drug misuse signals: A pharmacovigilance assessment using the FDA Adverse Event Reporting System. *Drug and Alcohol Dependence*. 2019; 206: 107709. doi: [10.1016/j.drugalcdep.2019.107709](https://doi.org/10.1016/j.drugalcdep.2019.107709)
9. Domon Y, Arakawa N, Inoue T, Matsuda F, Takahashi M, Yamamura N, et al. Binding characteristics and analgesic effects of mirogabalin, a novel ligand for the $\alpha 2\delta$ subunit of voltage-gated calcium channels. *J Pharmacol Exp Ther*. 2018; 365(3): 573-582. doi: [10.1124/jpet.117.247551](https://doi.org/10.1124/jpet.117.247551)
10. VinikA, Rosenstock J, Sharma U, Feins K, Hsu C, Merante D. Efficacy and safety of mirogabalin (DS-5565) for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo- and active comparator-controlled, adaptive proof-of-concept phase 2 study. *Diabetes Care*. 2014; 37(12): 3253-3261. doi: [10.2337/dc14-1044](https://doi.org/10.2337/dc14-1044)
11. Baba M, Matsui N, Kuroha M, Wasaki Y, Ohwada S. Mirogabalin for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo-controlled phase 3 study in Asian patients. *Journal of Diabetes Investigation*. 2019; 10(5): doi: [10.1111/jdi.13013](https://doi.org/10.1111/jdi.13013)
12. Alam U, Sloan G, Tesfaye S. Treating pain in diabetic neuropathy: Current and developmental drugs. *Drugs*. 2020; 80(4): 363-384. doi: [10.1007/s40265-020-01259-2](https://doi.org/10.1007/s40265-020-01259-2)
13. Mendell J, Levy-Cooperman N, Sellers E, Vince B, Kelsh D, Lee J, et al. Abuse potential of mirogabalin in recreational polydrug users. *Therapeutic Advances in Drug Safety*. 2019; 10: 204209861983603. doi: [10.1177/2042098619836032](https://doi.org/10.1177/2042098619836032)
14. Wattiez AS, Dupuis A, Privat AM, Chalus M, Chapuy E, Aissouni Y, et al. Disruption of 5-HT 2A -PDZ protein interaction differently affects the analgesic efficacy of SSRI, SNRI and TCA in the treatment of traumatic neuropathic pain in rats. *Neuropharmacology*. 2017; 125: 308-318. doi: [10.1016/j.neuropharm.2017.07.034](https://doi.org/10.1016/j.neuropharm.2017.07.034)
15. Weng C, Xu J, Wang Q, Lu W, Liu Z. Efficacy and safety of duloxetine in osteoarthritis or chronic low back pain: A systematic review and meta-analysis. *Osteoarthritis and Cartilage*. 2020; doi: [10.1016/j.joca.2020.03.001](https://doi.org/10.1016/j.joca.2020.03.001)
16. Shelton RC. Serotonin and norepinephrine reuptake inhibitors. In: Macaluso M, Preskorn S, eds. *Antidepressants*. Experimental Pharmacology, vol 250. New York, USA: Springer, Cham; 2018: 145-180. doi: [10.1007/164_2018_164](https://doi.org/10.1007/164_2018_164)
17. De Oliveira Filho GR, Kammer RS, dos Santos H de C. Duloxetine for the treatment acute postoperative pain in adult patients: A systematic review with meta-analysis. *Journal of Clinical Anesthesia*. 2020; 63: 109785. doi: [10.1016/j.jclinane.2020.109785](https://doi.org/10.1016/j.jclinane.2020.109785)
18. Ruiz-Negrón N, Menon J, King JB, Ma J, Bellows BK. Cost-effectiveness of treatment options for neuropathic pain: A systematic review. *Pharmacoeconomics*. 2019; 37: 669-688. doi: [10.1007/s40273-018-00761-6](https://doi.org/10.1007/s40273-018-00761-6)
19. National Institute for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings. NICE Clin Guidel Webn site. <https://www.nice.org.uk/guidance/cg173>. 2013. Accessed April 19, 2020.
20. Hadley GR, Gayle JA, Ripoll J, Jones MR, Argoff CE, Kaye RJ, et al. Post-herpetic neuralgia: A Review. *Curr Pain Headache Rep*. 2016; 20(3): 17. doi: [10.1007/s11911-6-016-0548-x](https://doi.org/10.1007/s11911-6-016-0548-x)

21. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: A position statement by the American Diabetes Association. *Diabetes Care*. 2017; 40(1): 136-154. doi: [10.2337/dc16-2042](https://doi.org/10.2337/dc16-2042)

22. Selvarajah D, Petrie J, White D, Julious S, Bortolami O, Cooper C, et al. Multicentre, double-blind, crossover trial to identify the Optimal Pathway for Treating neuropathic pain in Diabetes Mellitus (OPTION-DM): Study protocol for a randomised

controlled trial. *BMS*. 2018; 19: 578(2018): 1-16. doi: [10.1186/s13063-018-2959-y](https://doi.org/10.1186/s13063-018-2959-y)

23. Critchlow S, Hirst M, Akehurst R, Phillips C, Philips Z, Sullivan W, et al. A systematic review of cost-effectiveness modeling of pharmaceutical therapies in neuropathic pain: Variation in practice, key challenges, and recommendations for the future. *J Med Econ*. 2017; 20(2): 129-139. doi: [10.1080/13696998.2016.1229671](https://doi.org/10.1080/13696998.2016.1229671)