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The Medication Guidelines for Neuropathic Pain Including Fibromyalgia is justified from a Scientific Viewpoint, However, it does Not Necessarily Agree with Clinical Priority

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Abstract

The medication guidelines for fibromyalgia (FM) and neuropathic pain (NP) were mainly based on scientific evidence of analgesic efficacy in the literature. From a scientific viewpoint, it is justified, however, it does not necessarily agree with clinical priority. Adverse effects slightly affect these guidelines. Most adverse effects that were considered in the development of guidelines for NP including FM were short-term adverse effects such as drowsiness, nausea, vomiting, diarrhea, constipation, dysuria, and dry mouth. However, the long-term adverse effects such as cognitive dysfunction, dependence or abuse, sexual dysfunction, fracture, and osteoporosis also should be considered in medication. The adverse effects of pregabalin are cognitive dysfunction, dependence or abuse, obesity, marked drowsiness (sometimes loss of consciousness), and an expensive drug price. The adverse effects of duloxetine are cognitive dysfunction, dementia, sexual dysfunction, and bleeding and the drug price is expensive. Tricyclic antidepressants are safer than serotonin noradrenaline reuptake inhibitors in terms of dementia or cognitive dysfunction. The price of amitriptyline is inexpensive and most adverse effects except obesity disappear as soon as it is discontinued. Many studies have shown the analgesic effect of amitriptyline in FM and NP. However, scientific evidence of efficacy is low, because they are old studies. In clinical practice, efficacy based on personal experience, adverse effects based on personal experience and scientific evidence, drug price, and degree of off-label use in addition to scientific evidence of efficacy should be reflected in the order of priority. Pregabalin and duloxetine should be administered after amitriptyline in medication treatment for NP including FM.

Key words:

Fibromyalgia; Neuropathic pain; Medication guideline.

Introduction

The medication guidelines for fibromyalgia (FM) [1] and NP [2] were mainly based on scientific evidence of analgesic efficacy in the literature. From a scientific viewpoint, it is justified, however, it does not necessarily agree with clinical priority.

(1) Many pharmaceutical companies provide huge amounts of economic assistance to studies that show the efficacy of expensive medicine that substantially benefits the companies. Therefore, studies of such medicines are frequently published, which enhances scientific evidence. Conversely, scientific evidence of inexpensive medicine does not increase. In my experience, nortriptyline is effective for FM; however, limited scientific evidence shows its efficacy. I believe that the low drug price is the major cause. Faked study is beside the question. No association of industry funding or the authors' financial conflicts of interest with the study outcomes was seen in FM drug therapy randomized controlled trials [3]. However, many reports including systematic reviews show that pharmaceutical company sponsorship is strongly associated with results that favor the sponsors' interests [4-9].

(2) In clinical practice, efficacy based on personal experience, adverse effects based on personal experience and scientific evidence, drug price, and degree of off-label use in addition to scientific evidence of efficacy should be reflected in the order of priority. Adverse effects slightly affect these guidelines. Most adverse effects that were considered in the development of guidelines for NP including FM were short-term adverse effects such as drowsiness, nausea, vomiting, diarrhea, constipation, dysuria, and dry mouth. These adverse effects have a clear causal connection and are easy to identify. They disappear as soon as the causative drug is discontinued. However, the long-term adverse effects such as cognitive dysfunction, dependence or abuse, sexual dysfunction, fracture, and osteoporosis also should be considered in medication. These adverse effects have an obscured causal relationship and are difficult to identify. Improvement of these long-term adverse effects is impossible or difficult after the causative drug is discontinued. These long-term adverse effects cannot be applied to "the analgesic effect and the adverse effects were compared to determine the optimum dosage." Patients have to compare the analgesic effect with the adverse effects to determine the optimum dosage. They are usually not reflected in the medication guidelines for NP including FM. Pregabalin, duloxetine, and milnacipran are the only drugs approved by the FDA for the clinical treatment of FM [10].

Pregabalin

Pregabalin is an excellent medicine with a strong analgesic effect based on both the literature and my experience on actual use. Some systematic reviews and/or meta-analyses [11-16] and Cochrane review [17] showed that pregabalin showed the analgesic effect in patients with FM. Some systematic reviews and/or meta-analyses showed that pregabalin showed the analgesic effect in patients with several kinds of NP [18-20]. However, the adverse effects of pregabalin are cognitive

dysfunction [21, 22], dependence or abuse [23-27], obesity [28], marked drowsiness (sometimes loss of consciousness), and an expensive drug price. Two short-term studies reported cognitive dysfunction [21, 22] due to pregabalin. Cognitive dysfunction may continue for a long time. It is almost impossible to detect long-lasting cognitive dysfunction at the individual patient level. It is unknown whether long-lasting cognitive dysfunction improves after the discontinuation of medication. In my experience, sleepiness caused by antidepressants occurs gradually, and sleepiness caused by pregabalin sometimes occurs suddenly (loss of consciousness). Loss of consciousness caused by pregabalin is described in drug package inserts. From the viewpoint of traffic accidents and falls, loss of consciousness is far more dangerous than gradual sleepiness.

Duloxetine

Duloxetine is an excellent medicine with a strong analgesic effect based on both the literature and my experience on actual use. Some systematic reviews and/or meta-analyses [13,14, 29,30] and Cochrane review [31] showed that duloxetine showed the analgesic effect in patients with FM. Some systematic reviews and/or meta-analyses [18,30,32,33] and Cochrane review [31] showed that duloxetine showed the analgesic effect in patients with several kinds of NP. The adverse effects of duloxetine are cognitive dysfunction [34-36], sexual dysfunction [37], and bleeding [38] and the drug price is expensive. Long-term studies [39,40] and a systematic review and meta-analysis [35] showed that serotonin noradrenaline reuptake inhibitors (SNRI) increased the risk of dementia.

Milnacipran

Milnacipran is an SNRI that is licensed for the treatment of FM in some countries, including Canada, Russia, and the United States [41]. Milnacipran is an excellent medicine with a strong analgesic effect based on both the literature and my experience on actual use. Some systematic reviews and/or meta-analyses [13,29] and Cochrane review [41] showed that duloxetine showed the analgesic effect in patients with FM. No studies provided head-to-head comparison of analgesic effect and adverse effects between milnacipran and duloxetine in FM. However, analgesic effect and adverse effects of both medicines are similar based on my experience on actual use. Milnacipran is considerably more inexpensive than duloxetine at least in Japan. One of the reasons is that we can use generic milnacipran, but we cannot use generic duloxetine in Japan. From a viewpoint of clinical practice, I believe that milnacipran should be administered before duloxetine.

Amitriptyline

Amitriptyline is said to be difficult to use because it frequently causes adverse effects. Most adverse effects except obesity occur early in medication and are easy to identify. The price of amitriptyline is inexpensive and most adverse effects except obesity disappear as soon as it is discontinued. Obesity is an adverse effect and it does not disappear immediately after the discontinuation of medication. However, it is easy to identify obesity if the body weight is measured. A large German cohort showed that amitriptyline was associated with patients with severe cognitive impairment [42], a population-based case-control study showed that tricyclic antidepressants (TCA) had no association with the dementia risk [40], and a population-based, retrospective case-control study showed that TCA reduced the risk of dementia [34]. A systematic review and meta-analysis showed that TCA may be associated with a reduced risk or no risk of dementia, and SNRI have been reported to show an intermediate risk [35]. Therefore, TCA is safer than SNRI in terms of dementia or cognitive dysfunction [34-36,40,43]. In fact, amitriptyline is an easy-to-use medicine and it is safe for patients. All patients who would like to receive medication underwent an electrocardiogram in my hospital. If the electrocardiogram showed an abnormality, the patients were referred to a cardiologist to confirm whether amitriptyline could be administered. A meta-analysis of observational studies in subjects with no history of coronary heart disease suggests that neither selective serotonin reuptake inhibitor nor TCA use is associated with an increased risk of coronary heart disease [44]. A retrospective cohort study reported that current users of TCA had a dose-related increase in the risk of sudden cardiac death and the rate ratios was 0.97 (95% confidence interval, 0.72-1.29) for doses lower than 100 mg (amitriptyline or its equivalent) [45]. Therefore, if the cardiotoxicity of amitriptyline was a concern due to an advanced age, etc., I decreased the maximum dosage from 150 to 95 mg. Many studies have shown the analgesic effect of amitriptyline in FM [46, 47] and NP [48]. However, scientific evidence of efficacy is low, because they are old studies. Moreover, pharmaceutical companies are unlikely to fund the studies that show the analgesic efficacy of amitriptyline, because the drug price of amitriptyline is not expensive. Therefore, evidence of analgesic efficacy of amitriptyline will be rarely strengthened in the future.

Nortriptyline

Nortriptyline is a main metabolite of amitriptyline [49]. The International Association for the Study of Pain Neuropathic Pain Special Interest Group declared as follows in "Pharmacologic management of NP: Evidence-based recommendations": Secondary amine TCA (nortriptyline and desipramine) are preferred because they are better tolerated than tertiary amine TCA (amitriptyline and imipramine) but have comparable analgesic efficacy [50]. In my experience, nortriptyline is effective for NP including FM.

Conclusion

The medication guidelines for NP including FM based on scientific evidence of analgesic efficacy in the literature is justified from a scientific viewpoint. However, it does not necessarily agree with clinical priority. In clinical practice, efficacy based on personal experience, adverse effects based on personal experience and scientific evidence, drug price, and degree of off-label use in addition to scientific evidence of efficacy should be reflected in the order of priority. An immediate analgesic effect is not necessary in NP including FM. Pregabalin and duloxetine should be administered after amitriptyline (if possible after nortriptyline) in medication treatment for NP including FM. Duloxetine should be administered after milnacipran in medication treatment for FM.

Declaration

The author has no conflicts of interest relevant to this report.

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