

## Critical Points Regarding Chronic Musculoskeletal Pain Management Using Analgesics in Elderly Patients

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**Received:** February 03, 2016; **Published:** February 03, 2016

### Abstract

Chronic musculoskeletal pain such as low back pain affects not only patients, but it also affects caregiver's activity of daily life or quality of life. One approach to management of chronic pain is medication. However, chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) may produce gastrointestinal problems such as erosion or ulcer. NSAIDs also decrease the glomerular filtration rate. Therefore, it is also important to recognize that elderly patients are potentially suffering from chronic kidney disease (CKD), which is increasing in prevalence throughout the world. Furthermore, elderly patients tend to have comorbid diseases, i.e. hypertension, diabetic mellitus, or hyperlipidaemia. Therefore, it is important to consider drug-drug interactions and not just focus on reducing the chronic pain. For example, NSAIDs interfere with antihypertensive medications such as angiotensin-converting enzyme inhibitors (ACEI),  $\beta$ -blockers, and diuretics. The combination of ACEI, diuretics, and NSAIDs comprise the so-called 'triple whammy', which produces clinically significant nephrotoxicity in CKD and is often unrecognized. To reduce NSAID-induced gastrointestinal or kidney problems, opioid analgesics have been more frequently prescribed than before; however, adverse effects, i.e. nausea, constipation, and withdrawal syndrome, are a concern. It is important to make an effort to determine the best "tailor-made" treatment for patients, because the medication needed to relieve the chronic musculoskeletal pain is quite different in each patient.

**Keywords:** *Chronic musculoskeletal pain; Chronic kidney disease; Non-steroidal anti-inflammatory drugs; Opioid; Adverse effect*

**Abbreviations:** CKD: chronic kidney disease; NSAID: non-steroidal anti-inflammatory drug; ACEI: angiotensin-converting enzyme inhibitors

### Progressive aging of society

The population of elders is increasing throughout the world. In particular, Japan is the world's top country for longevity. In a society experiencing progressive aging, there is still about a 10-year gap between the average life expectancy and healthy life expectancy. The number of osteoporosis and osteoarthritis is increasing. Additionally, musculoskeletal diseases are usually associated with chronic musculoskeletal pain. Chronic pain decreases physical activity and leads to locomotive syndrome. Therefore, chronic musculoskeletal pain is an important issue to be solved. Approximately 15% of the Japanese population suffers from moderate-severe chronic musculoskeletal pain persisting for at least 6 months (Nakamura, *et al.*). Furthermore, the number of solitary elderly adults is increasing. Inoue, *et al.* reported that people living alone showed a high score of psychological distress, which may influence the development and maintenance of chronic pain (Inoue, *et al.*).

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**Citation:** Toshihiro Imamura. "Critical Points Regarding Chronic Musculoskeletal Pain Management Using Analgesics in Elderly Patients". *EC Orthopaedics* 1.S1 (2016): S1-S4.

The most important approach to understanding chronic musculoskeletal pain is to understand patients' backgrounds. Listening to patient complaints and sometimes gathering information from the family helps to determine the appropriate treatment. Social factors and related psychological factors (including depression) thus appear to greatly affect chronic musculoskeletal pain (Ushida); vice versa, persistent chronic pain also may interfere with mental health and lead to a depressive state.

### **Consideration of comorbidities to stop the 'Triple Whammy'**

Multiple options are available for the clinical management of pain, most of which are usually centred on pharmacological therapy. However, nonpharmacologic options, i.e. exercise therapy, counselling, physiotherapy, or cognitive behaviour therapy, should also be considered; moreover, attention should be given to indications for surgery as well as to its appropriate timing if it is necessary to treat acute and chronic pain. Elderly individuals usually take more than three medications to treat conditions such as hypertension, diabetic mellitus, or hyperlipidaemia.

Non-steroidal anti-inflammatory drugs (NSAIDs) are analgesic medications that alleviate chronic pain and lead to improvements in the patient's quality of life. However, it is necessary to pay attention to adverse effects, including drug-drug interactions. One adverse effect of NSAIDs is gastrointestinal toxicity, which can be reduced through the use of proton pump inhibitors. In addition, the use of NSAIDs decreased following the implementation of estimated glomerular filtration rate. Recently, a cohort study showed that proton pump inhibitor use was associated with a higher risk of incident chronic kidney disease (CKD) (Lazarus, *et al.*).

Additionally, chronic NSAID use accelerates the progression of CKD (Imai, *et al.*). There are approximately 13,300,000 patients in Japan, or about 13% of the adult population, who have CKD stage G3a or above. Considering that the number of end-stage renal failure patients and dialysis patients increases annually, it is certainly not a rare pathology. This is especially true in the elderly population, in which there is potentially impaired renal function. Furthermore, the combination of angiotensin-converting enzyme inhibitors (ACEI), diuretics, and NSAIDs comprise the so-called 'triple whammy', which produces clinically significant nephrotoxicity in CKD and is often unrecognized (Boyd, Mathew and Thomas; Onuigbo and Agbasi). This is a preventable condition if recognized.

### **Opioid use should be carefully monitored to avoid serious adverse effects**

Opioid analgesics, such as tramadol and buprenorphine patch, alleviate chronic musculoskeletal pain and disability, while avoiding adverse effects such as gastrointestinal and renal toxicity (Imamura). Buprenorphine also shows a potential benefit in improving neuropathic pain symptoms, possibly owing to its specific pharmacological profile (Pergolizzi, *et al.*). Careful monitoring for toxicity and efficacy is critical, given that advanced age increases the risk for adverse effects. In particular, elderly patients may suffer from extrapyramidal symptoms.

Nausea and vomiting are well-known adverse effects of opioids. To reduce these adverse effects, antiemetic medications are often prescribed. However, certain antiemetic medications may worsen extrapyramidal symptoms; therefore, careful monitoring is required when administering these medications (Moos and Hansen). Moreover, the anticholinergic effect of opioids worsens cognitive function, especially in elderly patients. In addition, other common medications such as antihistamines also contain an anticholinergic agent. Anticholinergic activity is generally thought to cause cognitive dysfunction, which worsens adherence to prescribed medications.

In addition to the anticholinergic effect, withdrawal syndrome should also be considered. This has a high chance of occurring if patients stop taking tramadol suddenly because of adverse effects. The symptoms of tramadol withdrawal include anxiety and restlessness, autonomic dysfunction, abdominal cramping, diarrhoea, sleeplessness, migraine-like headaches, and myoclonic activity of the extremities (Barsotti, Mycyk and Reyes; Thomas and Suresh). Withdrawal of even low doses of tramadol (50 mg) has been associated with uncomfortable restless leg syndrome (Park, *et al.*). Various tramadol extended-releases (once-daily) formulations have been reported to have a lower incidence and severity of adverse events compared to those for immediate-release formulations (Mongin). Presumably, the weekly opioid, transdermal buprenorphine patch would have equivalent or less severity of adverse effects, including withdrawal symptoms.

One of the important keys for orthopaedic surgeons to improve strict patient adherence to prescribed medication is to prescribe as few analgesic medications as possible. Therefore, I personally prefer an extended -release formulation (tablet or patch) rather than an immediate-release opioid. Recently, an interesting paper was published in which transdermal buprenorphine was shown to be cost-effective compared to tramadol (Hirst, *et al.*), especially for female patients age 75 or older in whom there is a high risk of fracture. This is important, as tramadol has a higher risk of fracture than some other opioid analgesics used to treat moderate-to-severe pain.

Hepatic impairment is another point to be considered. Certain opioids such as codeine or tramadol rely on hepatic biotransformation to active metabolites. Accordingly, a possible reduction of their analgesic effect is an expected pharmacodynamic consequence of hepatic impairment. Buprenorphine has also been reported to possibly cause hepatotoxicity, potentially through direct mitochondrial toxicity (Zuin, *et al.*). Therefore, careful monitoring, at least a blood sample, is required, even for asymptomatic patients. For patients with hepatic impairment, I recommend a lower dose of tramadol and/or acetaminophen.

Rigorous research efforts are needed to better understand the clinical risk factors for these adverse drug reactions. Since chronic pain management is not straightforward, it is essential to determine the best way to provide a “tailor-made treatment” for patients.

### Acknowledgements

This research was supported by research funds to promote the hospital functions of the Japan Labour Health and Welfare Organization.

### Conflict of interest

There are no conflicts of interest to declare.

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**Volume 1 Issue S1 February 2016**

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