Evidence-Based Recommendations on the Pharmacological Management of Osteoarthritis and Chronic Low Back Pain: An Asian Consensus

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The overall burden of chronic musculoskeletal pain in Asian countries will continue to increase as the population ages, as will the demand for safe and effective pain management. Currently available Asian guidelines are mostly outdated and targeted only to primary care. Implementation of international guidelines may be unsuitable for Asian patients due to cultural, local economic and regulatory factors. With the aim of developing Asian-specific consensus recommendations for the pharmacological management of osteoarthritis (OA) pain and chronic low back pain (cLBP), we convened to review and discuss recent available evidence for pharmacotherapy, clinical experiences, and current practice challenges they face in the region, including challenges in opioid use. Taking these into consideration, we provided general recommendations for the overall assessment and management of OA pain and cLBP. The strength of the recommendations regarding the use of pharmacological agents was assessed using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system. Where evidence is conflicting or limited, we made no recommendation pending the availability of further evidence. We recommend topical non-steroidal anti-inflammatory drugs (NSAIDs) as a first-line pharmacological treatment of OA pain, while oral NSAIDs should be considered as a first-line pharmacological treatment of cLBP. Acetaminophen has been commonly used as the first-line treatment for OA pain and cLBP, but its long-term use is not recommended based on recent evidence. These consensus recommendations are not prescriptive, and serve as a guide for decision-making in clinical practice. The optimal management of OA pain and cLBP should ultimately be individualized to each patient.

Keywords: pharmacotherapy, osteoarthritis pain, low back pain, Asian consensus, musculoskeletal pain
Introduction

The International Association for the Study of Pain Task Force defines chronic musculoskeletal pain as "persistent or recurrent pain that arises as part of a disease process directly affecting bone(s), joint(s), muscle(s), or related soft tissue(s)." This definition is limited to nociceptive (peripheral) pain, and includes pain characterized by persistent inflammation such as rheumatoid arthritis and by structural changes that affect bones, joints, tendons, or muscles such as osteoarthritis (OA). Musculoskeletal conditions with causes that are not completely understood, such as nonspecific back pain, are classified under chronic primary pain—defined as "pain in one or more anatomic regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or significant functional disability and that cannot be better explained by another chronic pain condition." Similar to chronic low back pain (cLBP; the abbreviation LBP is used instead when studies do not specify duration of pain), current data seem to support the description of OA as a mixed pain state, where both nociceptive and neuropathic factors may play important roles in some individuals.

The prevalence of musculoskeletal pain is expected to increase in the Asia region due to population aging, highlighting the need for an evidence-based approach to optimally manage chronic musculoskeletal pain in the Asian population. However, some of the available guidelines in Asia on the management of chronic musculoskeletal pain are outdated and targeted only to primary care. Some of the existing international guidelines that are commonly referred to in clinical practice are at least 10 years old and the scientific evidence assessed by these guidelines are at least a few years older than the date of publication. Cultural, local economic, and regulatory factors may render the clinical implementation of European or American guidelines unsuitable for Asian patients.

In view of the above factors, the current manuscript aims to provide an updated consensus on Asian-specific recommendations in the pharmacological management of OA pain and cLBP based on the availability of newer evidence.

Methods

A consensus meeting was held in April 2016 in Incheon, South Korea, to address the need for Asian-specific recommendations on both OA and cLBP as both exhibit similar pathology in chronic pain state. Due to limited Asian-specific pharmacotherapy studies for the management of OA pain and cLBP, clinical recommendations from existing guidelines were adapted to fit into the Asian populations, by updating the recommendations with available evidence and incorporating the cultural, economic, and regulatory factors seen in the daily practice of physician/pain specialists in Asian countries. The meeting was attended by eight experts from four Asian countries (Hong Kong, Japan, South Korea, and Taiwan) and one expert from Canada. During the meeting, we reviewed and discussed recent evidence and pharmacotherapy recommendations from existing guidelines, as well as current practice and local challenges in the pharmacological management of OA pain and cLBP.

A literature search was conducted via PubMed to identify recent systematic reviews, meta-analyses and available Asian randomized controlled trials (RCTs) on OA pain and cLBP published in English. The literature search period was based on the most recent available guidelines that are commonly referred to by the expert panel. For OA, the recent available guidelines are the 2014 National Institute for Health and Care Excellence (NICE) OA guidelines and thus, the search period used was January 2013 to April 2016. For LBP, the recent available guidelines are the 2011 Canadian guidelines and thus, the search period used was January 2010 to April 2016. From the search outcomes, relevant studies of chronic OA and LBP including treatment efficacy and safety, recent systematic reviews or meta-analyses, cost-effectiveness studies, and Asian RCTs were selected. Additional search for available Asian studies included keywords: Asian, China, Japan, Korea, or Taiwan. The exclusion criteria included non-clinical studies, specific LBP studies such as lumbar spinal stenosis, radiculopathy, and lumbar disc herniation, stem cells-related studies, epidemiology studies and studies of exploratory molecules. In the absence of or limited systematic reviews and meta-analyses, recent RCTs and comparative studies were included for review.

We reviewed relevant evidence and discussed our clinical experience and local factors that may affect the implementation of clinical recommendations in our daily practice. Following the development of the initial draft of the present manuscript, each of us reviewed the evidence for a pharmacological agent for the development of clinical recommendations. The
The subsequent draft incorporated all clinical recommendations, including the strength of recommendations based on the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system that classifies recommendations as either strong or weak. The draft was subjected to repeated detailed reviews to achieve complete consensus. Where evidence is conflicting or limited, we decided to make no recommendation until further evidence is available.

**General Consideration**

The primary goal of pain management is to control pain to a tolerable level that allows the person in pain to maximize activity and function. The optimal management of chronic musculoskeletal pain involves psychosocial factors, non-pharmacological (physical exercise, diet, education, managing mood and sleep disorders, etc.) and pharmacological treatments, given in consideration of the needs, risk factors and preferences of the individual. Based on our clinical experience, we provided general recommendations on the overall management, and the monitoring and assessment of OA pain and cLBP (Table 1).

The complexity of pain necessitates a comprehensive biomedical, psychosocial and behavioral assessment for the proper management of patients with chronic musculoskeletal pain. Multi-dimensional pain assessment tools, such as the Brief Pain Inventory and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), are more useful for chronic pain patients as they capture the characteristics and quality of pain, satisfaction with pain control, and how pain affects mood and activities of daily living.

**Table 1.** General recommendations for the overall management of osteoarthritis pain and chronic low back pain

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall management</td>
</tr>
<tr>
<td>• Pain management should be individualized to each patient and optimized with the goal of improving activity of daily living, quality of life, and ability to carry out rehabilitation exercises.</td>
</tr>
<tr>
<td>• Pain management strategy should be multimodal and multidisciplinary, encompassing physical exercise, pharmacological therapy, surgery, dietary advice, weight management, patient education, and aids and assistive devices.</td>
</tr>
<tr>
<td>• Modification to pain management strategy should be based on the patient’s response to treatment, and with careful considerations for potential side effects.</td>
</tr>
<tr>
<td>• Clinicians should formulate an agreeable pain management plan with the patient.</td>
</tr>
<tr>
<td>• We recommend non-pharmacological and non-surgical treatment, such as physical exercise and exercise therapies, as the primary approach in the management of patients with OA pain and cLBP; advice to stay active should be given to improve disability in the long term.</td>
</tr>
<tr>
<td>• The use of pharmacological treatment as an adjuvant to physical exercise should be based on benefits for each individual patient; the adverse effects of the therapy choice should not affect the general well-being of the patient and should be acceptable to the patient. Previous treatment history, including adverse effect profile, should be carefully recorded.</td>
</tr>
<tr>
<td>Monitoring and assessment</td>
</tr>
<tr>
<td>• Clinicians should regularly assess and monitor patients with OA pain and cLBP, including treatment efficacy and adverse effects; continuous monitoring of adverse effects is important to ensure patient safety and prevent non-adherence to treatment.</td>
</tr>
<tr>
<td>• Referral to a pain management programme should be considered for patients with chronic pain who are unresponsive to recommended pharmacological, physical, and psychological interventions.</td>
</tr>
<tr>
<td>• Clinicians should frequently follow-up patients until the optimal treatment can be determined based on patients’ response; follow-up interval could be adjusted gradually.</td>
</tr>
<tr>
<td>• Clinicians should also assess pain behaviors and pain-associated complaints of the patient, and monitor for objective changes such as bone change, muscle and joint contractures, and presence of red flags (tumor, inflammations, etc.).</td>
</tr>
<tr>
<td>• In addition to the standard multi-dimensional pain assessment, quality of sleep and global impression on improvement may be included as additional assessment criteria.</td>
</tr>
</tbody>
</table>

OA: osteoarthritis; cLBP: chronic low back pain.
daily living. Risks for cardiovascular disease, gastrointestinal (GI), renal and liver function need to be assessed when pharmacotherapies are considered. Drug selection and combination must consider the benefit against the potential risk for individual patient.

Follow-up assessment of patients with OA pain and cLBP is necessary but its frequency may be influenced by patient’s physical condition, patient’s transport/access to the clinics or hospitals, patient load in local clinics/hospitals in public or private sector, patient’s medical shopping, widespread use of alternative medicine, and financial and reimbursement issues. In Japan, the outpatient clinics provide more frequent follow-up than the hospitals; the typical follow-up frequency at the hospitals is once every 1–3 months. In Korea, smaller clinics provide more frequent follow-up compared with bigger hospitals. In Hong Kong, patient load determines the frequency of follow-up in the public sector whereas in the private sector, it is influenced by financial and reimbursement issues.

Table 2 lists the consensus recommendations for pharmacological management of OA pain and cLBP following our review of existing guidelines (Table 3) and available evidence (Suppl. Tables 1–5), which were summarized below. These recommendations serve only as a guide for decision-making in clinical practice and are not prescriptive. As such, these recommendations would not necessarily apply to all patients with OA pain and cLBP.

There are several unanswered issues pertaining to chronic pain management, including the lack of long-term studies of pharmacotherapies, when to change pain medication strategy, and availability of other treatment options for patients who do not respond to any of the recommended treatments.

**Acetaminophen**

The existing international and Asian guidelines for chronic pain management have consistently rec-
Table 2. Consensus recommendations for pharmacological management of osteoarthritis pain and chronic low back pain (continued)

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Recommendations</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Opioids should only be considered in patients with OA pain and cLBP whose pain control and ADL is not adequately achieved by simple analgesics, NSAIDs, or antidepressants, and when the patient is committed to participating in a multimodal management program.</td>
<td>Strong</td>
<td></td>
</tr>
<tr>
<td>• Clinicians should inform patients the liability of psychological dependence and potential AEs from chronic long-term use of opioids.</td>
<td>Strong</td>
<td></td>
</tr>
<tr>
<td>• Clinicians should do assess pain, function, AEs, mood and aberrant behaviors at regular intervals during strong opioids use.</td>
<td>Strong</td>
<td></td>
</tr>
<tr>
<td>• The use of opioids should only be continued if there are clinically relevant improvements in both pain and function.</td>
<td>Strong</td>
<td></td>
</tr>
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</table>

**Combination pharmacotherapy**

• Combination pharmacotherapy should be considered in OA and cLBP in order to treat both the nociceptive and neuropathic components of pain. 

• Combination pharmacotherapy should be considered if the combination is more effective and/or associated with fewer side-effects than the component drugs alone. 

• No recommendation could be made with regard to the use of the combination of acetaminophen with NSAIDs, or acetaminophen with tramadol in patients with OA and cLBP. 

• The combination of pregabalin with NSAIDs or transdermal buprenorphine should be considered in patients with a neuropathic component to OA and cLBP. 

• Pharmacological action and interaction of each pharmacotherapy should be considered when prescribing combination pharmacotherapies.

OA: osteoarthritis; cLBP: chronic low back pain; NSAIDs: non-steroidal anti-inflammatory drugs; GI: gastrointestinal; PPIs: proton pump inhibitors; NA: not applicable; AEs: adverse events; ADL: activities of daily living.

ommended acetaminophen as a first-line analgesic (Table 3). The 2014 NICE guidelines for OA management maintain the recommended use of acetaminophen ahead of other oral pharmacotherapies, but also note that there is evidence for a reduced effectiveness of acetaminophen in the management of OA, which should be taken into account in routine prescribing practice.\textsuperscript{10}

Despite being recommended for first-line use, recent data suggests that there is high quality evidence that acetaminophen is ineffective for managing pain and improving the quality of life of people with LBP and OA (Suppl. Table 1).\textsuperscript{18-21} The short treatment duration in these evaluated trials (often up to 6 weeks, with up to 12 weeks of follow-ups) does not allow evaluation of the benefit versus safety of long-term use of acetaminophen.

Although the safety and efficacy of acetaminophen has not been evaluated in Asian populations, the findings of available studies clearly contradict the long-standing recommendation for acetaminophen use as a first-line analgesic in managing chronic pain, as well as the current clinical practice of Asian doctors. Acetaminophen should no longer be recommended as a first-line analgesic based on the lack of efficacy; however, it can be used in specific patient populations, in whom other analgesics may not be suitable.

**Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

NSAIDs are often recommended as a first-line pharmacological agent for OA and LBP management in international and Asian guidelines, with the exception of the Hong Kong clinical guidelines (Table 3). These guidelines generally recommend assessment of patient’s cardiovascular and GI risk prior to prescribing NSAIDs, and short duration use of NSAIDs. Co-prescription of gastro-protective agents are also recommended (Table 3).

Based on the evidence reviewed (Suppl. Table...
<table>
<thead>
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</thead>
<tbody>
<tr>
<td><strong>Acetaminophen</strong></td>
<td>First-line treatment (with acknowledgement of reduced effectiveness of acetaminophen for OA management)</td>
<td>First-line treatment</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>First-line treatment (esp. topical)</td>
<td>First-line treatment (short term)</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>TCAs can be considered as a treatment option in those with no contraindications</td>
<td>As co-medication for pain relief</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td>When acetaminophen or NSAIDs are insufficient for pain relief</td>
<td>Weak opioids for those who do not respond to other treatment modalities</td>
</tr>
</tbody>
</table>

NICE: National Institute for Health and Care Excellence; EULAR: European League Against Rheumatism; ACP/APS: American College of Physicians/American Pain Society; OA: osteoarthritis; NSAIDs: non-steroidal anti-inflammatory drugs; esp. especially; TCAs: tricyclic antidepressants.
2), 20,22-28 NSAIDs are more effective than placebo in OA and LBP management. Although there is no evidence for superiority of a particular type of NSAID over the others for LBP, diclofenac and etoricoxib are more likely to be more effective for OA. There is no evidence that NSAIDs are more effective than acetaminophen for LBP but there is a small effect favoring NSAIDs for OA. Topical NSAIDs provide good pain relief in OA, and their efficacies are comparable with oral NSAIDs for musculoskeletal pain. In terms of safety, non-selective NSAIDs have a higher risk for upper GI events compared with coxibs; there is also evidence for an increase in local adverse events (AEs) with the use of topical NSAIDs. However, these systematic reviews and meta-analyses are not able to address the issues pertaining to long-term use of NSAIDs. 20,22 Head-to-head long-term trials are required for a definite conclusion on the long-term safety of NSAIDs. Intermittent short-term use of NSAIDs in moderate to maximum doses can be considered as required to balance the benefit and potential risk. 20

Antidepressants and Anticonvulsants

Antidepressants are typically recommended as an alternative or adjuvant option in the guidelines for LBP management (Table 3), 14,15 with no recommendations for anticonvulsant use. In the Japanese LBP guidelines, anticonvulsants could be considered as second-line medication. 25 Both antidepressants and anticonvulsants are not recommended in OA guidelines.

The data reviewed (Suppl. Table 3) 25,29-35 indicates that there is limited evidence for duloxetine in reducing pain intensity for OA pain and LBP when compared to placebo or other oral pharmacotherapies. Compared to placebo, duloxetine was associated with more AEs, including nausea, constipation, dry mouth, diarrhea, fatigue, dizziness, somnolence, and insomnia. 31 Although anticonvulsant gabapentin is prescribed as an analgesic in cLBP, trials supporting this practice are limited. There is conflicting evidence for the efficacy of gabapentinoids for cLBP with associated radicular symptoms. While there are a number of studies of anticonvulsants in cLBP management, their use in OA pain management are not well studied.

Opioids

The recommended use of opioids in the currently available guidelines is generally reserved for when severe disabling pain is not controlled with acetaminophen, NSAIDs, or other treatment modalities, or when NSAIDs are contraindicated (Table 3). The Asian guidelines recommend opioids as second-line therapy for cLBP and OA when NSAIDs are deemed inadequate or ineffective (Table 3).

Based on the available data (Suppl. Table 4), 25,36-44 there is strong evidence that opioids are effective in alleviating pain and improving function in OA and LBP patients; however, with higher incidence of AEs than placebo. Opioids may not be more effective compared with other analgesics. While tramadol and tapentadol are similar in terms of efficacy, their clinical benefit is relatively small. There is limited evidence that the transdermal formulation of opioids offers several advantages compared to the oral formulation. There is no evidence to support the use of one opioid over another with regard to efficacy, route of administration and doses. Opioids-treated patients had significantly higher incidence of AEs compared with patients on placebo. Up to date, evidence for long-term use of opioids at any dose in chronic non-malignant pain remains insufficient to determine long-term benefits, highlighting the need for such trials.

Combination Pharmacotherapy

Available guidelines generally recommend the use of pharmacotherapy combinations when prior treatment is inadequate or ineffective but do not recommend specific combinations. The 2014 NICE guidelines for OA management recommend the addition of stronger analgesics when prior treatments are insufficient based on risks and benefits consideration, but also acknowledges that there is limited evidence on the effects of combination therapies. 10 Likewise, the Hong Kong OA guidelines consider the combination of opioid analgesics and acetaminophen as an option for the treatment of moderate-to-severe pain in patients who are tolerant or unresponsive to NSAIDs. 5 By contrast, the use of combination pharmacotherapy is not included in LBP guidelines. 14,15

The data reviewed (Suppl. Table 5) 26,45-52 suggest that there is limited evidence to support the use of a specific combination pharmacotherapy in OA and cLBP. The recent systematic review and meta-analysis by Abdel Shaheed et al., 36 which included primarily western studies, indicates weak evidence that the combination of acetaminophen and tramadol is not more effective than tramadol alone in improving pain and function, but recent studies in Asian populations
The implementation of these recommendations (Table 2) in each country may be influenced by culture, local regulations, reimbursement/cost issues, and patient’s preference.

Acetaminophen Use

Hepatotoxicity is a key concern in the region due to the prevalence of chronic hepatitis B infection which is estimated to range between 1.02% in Japan to 5.49% in China. Despite so, the overall prevalence of actual liver toxicity due to acetaminophen is reported to be generally low (7.3%), thus acetaminophen is still used as first-line treatment in the region.

While the incidence of acetaminophen-associated hepatotoxicity is low, we noted that there is a lack of patient awareness of the potential risks of high dose or long-term acetaminophen use in the region. Asians tend to underestimate their pain experience, are reluctant to report their complaints, and do not want to spend too much money on treatment. These may prevent them from seeking appropriate treatment and lead to self-medication. Patients may be taking medications at inappropriate dose or in combination with other medications or herbal remedies that may increase the risk of hepatotoxicity.

Acetaminophen use in the region is also influenced by local regulations. For example, the new chronic kidney disease (CKD) guidelines in Japan prohibit the use of NSAIDs in patients at risk for CKD, which leads to the use of acetaminophen in this subgroup of patients.

NSAIDs Use

We noted that there is a preference for the use of NSAID patches in the region. The simpler and non-invasive application, along with the advantage of reduction in systemic AEs, renders NSAID patches a favorable treatment option for patients.

Local guidelines also influence the use of NSAIDs in the region—hospital guidelines in Hong Kong recommend oral over topical NSAIDs, and patients with higher GI risk tend to be prescribed with non-specific NSAIDs in combination with a proton pump inhibitor. In Korea, coxibs are prescribed for higher-risk patients.

Opioids Use

We agreed that there is a need for more high quality trials on opioids use in cLBP and OA patients, with clear inclusion and exclusion criteria and objectives, such as improvement in pain and activities of daily living as well as long-term safety. These will help to provide justification for opioids use in chronic musculoskeletal pain management, and allow eligible patients to benefit from this treatment option.

Local and international guidelines for the use of opioids in chronic non-cancer pain are available, including the 2012 Guidelines for Prescribing Opioid Analgesics for Chronic Non-Cancer Pain published by the Japanese Society of Pain Clinicians; the 2016 Opioid Therapy for Chronic Non-Cancer Pain: Guidelines for Hong Kong published by the Hong Kong Hospital Authority Multidisciplinary Committee on Pain Medicine; the 2017 Guidelines for Prescribing Opioids for Chronic Non-Cancer Pain in Korea published by the Opioid Research Group in the Korean Pain Society; and the 2017 Canadian guideline for Opioids for Chronic Non-Cancer Pain by the National Pain Centre of McMaster University, Canada. Our recommendations on opioid use, while not specific, are consistent with these guidelines.

There is a general concern and fear of addiction in the region that lead to very restrictive policies limiting opioid use for chronic non-cancer pain. In Taiwan, prescription for more than 2 weeks must follow the national guidelines—the process involves three independent interdisciplinary assessments, evaluation of the three assessments by the independent members of a hospital committee, and final approval by the controlled drug committee who conducts review every 4 months. All patients have to be re-evaluated every 6 months. In Japan, patients are reluctant to take opioids due to negative perceptions associated with its use after World War II. There is also no proper system to control or limit the prescription of strong opioids, although they are prescribed as a second-line therapy for cLBP in Japan. Hence, a balanced system that allows for safe prescribing of opioids for chronic musculoskeletal pain management is needed. Patients in Korea are also concerned over the risk of addiction and AEs of opioid, and clinicians have insufficient
experience in prescribing opioids. In Hong Kong, opioids are not widely used for chronic musculoskeletal pain treatment due to inadequate knowledge of the pharmacological properties and indications amongst clinicians, and a lack of local guidelines on early use of opioids. Resources to support the continuous monitoring of opioids use are limited in the public sector and thus, opioids are generally avoided due to AEs and concerns over risk of abuse. Additionally, opioids are relatively more expensive in comparison to simple analgesics or NSAIDs, thus clinicians would defer early use of the more expensive opioids.

**Conclusion**

We developed a set of consensus recommendations for the pharmacological management of OA pain and cLBP (Tables 1 and 2) based on the review of existing guidelines (Table 3), newer evidence (Suppl. Tables 1–5) and expert discussion on current practice and challenges in the Asian region. As part of overall pain management, we agreed that pain management strategy should be tailored to each individual patient, and non-pharmacological treatment, such as exercise, should be the primary approach before considering pharmacotherapy. Regular pain assessment and monitoring during any treatment approach is essential. Where evidence is conflicting or limited, we decided to make no recommendation until further evidence is available.

The implementation of these consensus recommendations in each country will vary depending on cultural and regulatory factors. There are various challenges in different countries in the Asian region pertaining to the use of pharmacological agents in the management of OA pain and cLBP, particularly opioids. A better understanding and knowledge of opioids is thus necessary to improve the pain control of patients with OA and cLBP.

Ultimately, clinicians should take into account the nature and severity of pain, benefit versus risk profile of pharmacotherapy and combination pharmacotherapy, as well as patient preference, when determining the optimal pharmacotherapy in the management of OA pain and cLBP.

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**Author Contributions**

All authors participated in the consensus meeting, made substantial contributions to the review of evidence and formulation of the consensus statements, preparation of the manuscript, provided critical revision for intellectual content and final approval for submission.

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6. Ho PC, Johnson MH. Behaviours and beliefs about pain and treatment among Chinese immigrants and New Z


26. Verkleij SP, Luijsterburg PA, Bohnen AM, Koes BW, Bierma-Zeinstra SM. NSAIDs vs acetaminophen in knee and


### Supplimentary Tables

#### Suppl. Table 1. Acetaminophen

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Study authors’ assessment of quality of evidence reviewed in the study</th>
<th>Study conclusion</th>
</tr>
</thead>
</table>
| Machado et al. (2015)  | Systematic review and meta-analysis (LBP and OA) | High                                                                   | • Acetaminophen is ineffective for reducing pain intensity and disability, or improving the quality of life of people with LBP in the short term.  
• Acetaminophen provides minimal short-term benefit in reducing pain and disability in people with OA.  
• Acetaminophen increased the risk of having abnormal liver function tests. |
| Bannuru et al. (2015)  | Systematic review and meta-analysis (OA) | Moderate                                                               | • Acetaminophen did not show clinically significant improvement in pain intensity.                                                                                                                                  |
| da Costa et al. (2017) | Network meta-analysis (OA)            | High                                                                   | • Acetaminophen as a single agent is ineffective in managing pain.                                                                                                                                                   |
| Ennis et al. (2016)    | Systematic review (OA)               | Low                                                                    | • There is little evidence for the efficacy of acetaminophen in managing patients with OA pain.                                                                                                                                 |

LBP: low back pain; OA: osteoarthritis.

#### Suppl. Table 2. Non-steroidal anti-inflammatory drugs

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Study authors’ assessment of quality of evidence reviewed in the study</th>
<th>Study conclusion</th>
</tr>
</thead>
</table>
| Enthoven et al. (2016) | Systematic review and meta-analysis (cLBP) | Low                                                                    | • NSAIDs were more effective in reducing pain intensity and disability when compared with placebo, but the effect sizes are small.  
• There was no difference in efficacy between different types of NSAIDs.  
• There was no difference in efficacy or AEs between NSAIDs and paracetamol and pregabalamin. |
| Wong et al. (2016)     | Systematic review of systematic reviews (LBP) | High                                                                  | • Oral NSAIDs are more effective than placebo for cLBP but not for acute LBP.  
• For LBP, there was no difference in treatment outcomes between different oral NSAIDs.  
• NSAIDs-related AEs (dyspepsia and GI bleeding) may be more frequent than placebo. |
| da Costa et al. (2017) | Network meta-analysis (OA)            | High                                                                   | • NSAIDs (diclofenac, etoricoxib, celecoxib, rofecoxib) lead to a clinically relevant improvement of pain compared with placebo.  
• Diclofenac (150 mg/day) is the most effective NSAID in improving pain and function. |
Suppl. Table 2. Non-steroidal anti-inflammatory drugs (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Study authors’ assessment of quality of evidence reviewed in the study</th>
<th>Study conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Walsel et al. (2015) 24</td>
<td>Network meta-analysis (Chronic arthritis [OA, RA])</td>
<td>Not available</td>
<td>• NSAIDs (diclofenac, celecoxib, etoricoxib, naproxen) provide clinically meaningful improvement for pain relief and physical function in patients with chronic arthritis compared with placebo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Diclofenac (150 mg/day) was more likely to have a clinically relevant effect in reducing pain than celecoxib (200 mg/day), naproxen (1,000 mg/day), ibuprofen (2,400 mg/day), and was similar to etoricoxib (60 mg/day).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Non-selective NSAIDs have a higher risk for upper GI events compared to coxibs.</td>
</tr>
<tr>
<td>Chung et al. (2013) 25</td>
<td>Systematic review and meta-analysis (LBP)</td>
<td>Not available</td>
<td>• There were no statistically significant differences between traditional NSAIDs and coxibs in reducing pain intensity.</td>
</tr>
<tr>
<td>Verkleij et al. (2011) 26</td>
<td>Systematic review (OA)</td>
<td>Not available</td>
<td>• NSAIDS may be more effective than acetaminophen for pain management although the treatment effect is small.</td>
</tr>
<tr>
<td>Derry et al. (2016) 27</td>
<td>Systematic review and meta-analysis (OA)</td>
<td>Moderate</td>
<td>• Topical, gel formulations of diclofenec and ketoprofen provides good pain relief in a minority of people with OA.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Topical diclofenec is associated with mild skin reactions compared with carrier or oral NSAIDs, but not with topical ketoprofen.</td>
</tr>
<tr>
<td>Klinge and Sawyer (2013) 28</td>
<td>Comprehensive review (musculoskeletal pain)</td>
<td>Not available</td>
<td>• There was no difference in efficacy between topical and oral NSAIDs.</td>
</tr>
</tbody>
</table>

NSAIDs: non-steroidal anti-inflammatory drugs; cLBP: chronic low back pain; AEs: adverse events; LBP: chronic low back pain; GI: gastrointestinal; OA: osteoarthritis; RA: rheumatoid arthritis.

Suppl. Table 3. Antidepressants and anticonvulsants

Antidepressants

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Study authors’ assessment of quality of evidence reviewed in the study</th>
<th>Study conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>van den Driest et al. (2017)</td>
<td>Systematic review (LBP)</td>
<td>Not available</td>
<td>• Very few studies are available, with clinical heterogeneity across studies assessed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Amitriptyline may improve pain and function compared with pregabalin.</td>
</tr>
<tr>
<td>Chung et al. (2013) 25</td>
<td>Systematic review and meta-analysis (nonspecific LBP)</td>
<td>Not available</td>
<td>• Antidepressants have limited effects when compared with placebo.</td>
</tr>
</tbody>
</table>
### Antidepressants and Anticonvulsants (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Study authors’ assessment of quality of evidence reviewed in the study</th>
<th>Study conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williamson et al. (2014)³⁰</td>
<td>Narrative review of meta-analyses (cLBP)</td>
<td>Not available</td>
<td>- Duloxetine demonstrated a statistically significant improvement in pain scores when compared with placebo.</td>
</tr>
<tr>
<td>Wang et al. (2015)³¹</td>
<td>Meta-analysis (OA)</td>
<td>High</td>
<td>- Duloxetine resulted in a significantly greater reduction of pain intensity and improved function when compare with placebo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- No difference in serious AEs when compared with placebo, although duloxetine was associated with more AEs, treatment emergence AEs and discontinuations.</td>
</tr>
<tr>
<td>Cawston et al. (2013)³²</td>
<td>Indirect comparison of randomized trials (cLBP)</td>
<td>Moderate, high</td>
<td>- No difference in efficacy between duloxetine and coxibs, tramadol, tapentadol, oxycodone, oxymorphone, hydromorphone, SSRIs, and glucosamine.</td>
</tr>
<tr>
<td>Myers et al. (2014)³³</td>
<td>Systematic review and meta-analysis (OA)</td>
<td>High</td>
<td>- No difference found between duloxetine and other post-first line oral treatments in patients who failed acetaminophen.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- When adjusted for baseline pain score, duloxetine was superior to both tramadol and hydromorphone, but not to other oral treatments.</td>
</tr>
</tbody>
</table>

### Anticonvulsants

<table>
<thead>
<tr>
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<th>Type of study</th>
<th>Study authors’ assessment of quality of evidence reviewed in the study</th>
<th>Study conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkinson et al. (2016)³⁴</td>
<td>Randomized controlled trial (cLBP)</td>
<td>Not applicable</td>
<td>- Gabapentin is ineffective for cLBP, with no difference between radiating and non-radiating pain.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Some AEs were significantly more likely to be experienced by those who received gabapentin (fatigue, dry mouth, difficulties with mental concentration, memory, or visual accommodation, and loss of balance), but the frequency of specific AEs was in general comparable to placebo.</td>
</tr>
<tr>
<td>Sakai et al. (2015)³⁵</td>
<td>Randomized controlled trial (cLBP)</td>
<td>Not applicable</td>
<td>- The efficacy of pregabalin was similar in older Japanese patients when compared to tramadol-acetaminophen.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Pregabalin was more effective for cLBP with neuropathic component and with lower limb symptoms, while tramadol-acetaminophen was more effective for non-neuropathic cLBP and for those without lower limb symptoms.</td>
</tr>
</tbody>
</table>

LBP: chronic low back pain; cLBP: chronic low back pain; OA: osteoarthritis; AEs: adverse events; SSRIs: selective serotonin reuptake inhibitors.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Study authors’ assessment of quality of evidence reviewed in the study</th>
<th>Study conclusion</th>
</tr>
</thead>
</table>
| Chung et al. (2013)   | Systematic review and meta-analysis (cLBP)     | Not available                                                         | • Opioids had statistically significant treatment effects in relieving pain and improving global functioning compared with placebo.  
• There were fewer AEs in the placebo groups compared with opioids group.                                                                                                                                  |
| Abdel Shaheed et al. (2016) | Systematic review and meta-analysis (cLBP) | Moderate                                                              | • Opioids provide pain relief in the short and intermediate term although treatment effects were small.  
• The magnitude of effects from higher doses of opioids is not likely to be clinically important.                                                                                                         |
| da Costa et al. (2014) | Systematic review and meta-analysis (OA)      | High                                                                   | • Opioids were also more effective in pain reduction compared with placebo albeit to differing extents.  
• Opioids-treated individuals had greater improvement in function compared with placebo-treated individuals.  
• There were no differences in efficacy between the different type of opioids, analgesic potency, route of administration, and daily dose.  
• Opioids-treated patients experienced more AEs compared with patients on placebo.                                                                                                                  |
| Chaparro et al. (2013) | Systematic review and meta-analysis (cLBP)     | Very low to moderate                                                   | • There is low quality evidence for tramadol in relieving pain.  
• There is moderate quality evidence for tramadol in improving functioning compared to placebo.  
• There is very low quality evidence that transdermal buprenorphine alleviates pain.  
• There is very low quality evidence that it does not improve functioning.  
• AEs are more common with opioids compared with placebo but here were insufficient data to conclude on the AE profile of opioids compared to other analgesics.  
• Opioids are not more effective than non-opioid analogesics.                                                                                                                                  |
| Santos et al. (2015)  | Systematic review and meta-analysis (musculoskeletal pain) | Moderate                                                              | • Extended release tapentadol was associated with pain reduction in comparison to placebo and oxycodone.  
• The overall clinical benefit of tapentadol was relatively small in moderate-to-severe chronic pain.  
• Tapentadol was associated with a more favorable safety profile and tolerability than oxycodone.                                                                                                  |
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Study authors’ assessment of quality of evidence reviewed in the study</th>
<th>Study conclusion</th>
</tr>
</thead>
</table>
| Mercier et al. (2014)         | Model-based meta-analysis (chronic non-cancer pain) | Not available                                                          | • the overall benefit-risk profiles of tramadol (300 mg qd) and tapentadol (100–250 mg bid) were comparable.  
• Tramadol was found to be slightly more effective in pain reduction compared with tapentadol.  
• Tapentadol was associated with lower risks of constipation and nausea compared with tramadol.                                                                                                                                                                                                                                                                                        |
| Mitra et al. (2013)           | Feasibility study (chronic non-cancer pain)        | Not applicable                                                          | • Both transdermal buprenorphine and transdermal fentanyl resulted in clinical improvement in the first 6 months.  
• Patients with transdermal buprenorphine benefited significantly in depression symptoms compared to transdermal fentanyl.                                                                                                                                                                                                                                                                                |
| Wolff et al. (2012)           | Systematic review (chronic pain)                   | Not available (quality variation across studies assessed was noted)     | • Transdermal buprenorphine and fentanyl were comparable in terms of pain measures for the treatment of moderate-to-severe chronic pain.  
• Transdermal buprenorphine had significantly lower AEs compared with transdermal fentanyl.                                                                                                                                                                                                                                                                                |
| Lauche et al. (2015)          | Systematic review and meta-analysis (chronic non-cancer pain) | Low, moderate                                                          | • Transdermal opioids were not superior to oral opioids with regard to pain reduction, physical function improvements or frequency of serious AEs.  
• There is moderate quality evidence that there is no significant difference between opioids.  
• There is very low quality evidence that the compared opioids were similar in improving physical function.  
• There is no rational for preferring a particular opioid and/or administration route over another.  
• There is no differential effectiveness between NSAIDs, less potent opioids and potent opioids.  
• Opioids and NSAIDs offer similar pain relief.  
• There is no differential effectiveness between NSAIDs, less potent opioids and potent opioids.  
                                                                                                                                                                                                                                                                                                                                                                                                   |
| Smith et al. (2016)           | Systematic analytic review (OA)                   | Not available                                                           |                                                                                          |

cLBP: chronic low back pain; AEs: adverse events; OA: osteoarthritis; NSAIDs: non-steroidal anti-inflammatory drugs.
### Suppl. Table 5. Combination pharmacotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Study authors’ assessment of quality of evidence reviewed in the study</th>
<th>Study conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel Shaheed et al. (2016)</td>
<td>Systematic review and meta-analysis (cLBP)</td>
<td>Moderate</td>
<td>• Tramadol-acetaminophen combination provides short-term pain relief although the treatment effect is small.</td>
</tr>
<tr>
<td>Lee et al. (2013)</td>
<td>Randomized controlled trial (cLBP)</td>
<td>Not applicable</td>
<td>• Extended release of fixed-dose tramadol-acetaminophen was significantly more effective than placebo in reducing pain, improving function and quality of life of Korean patients with moderate-to-severe pain.</td>
</tr>
<tr>
<td>Tetsunaga et al. (2015)</td>
<td>Randomized controlled trial (LBP)</td>
<td>Not applicable</td>
<td>• Fixed-dose tramadol-acetaminophen was effective in reducing pain and depressive symptoms compared with celecoxib in patients with depression, although no difference could be observed in terms of disability.</td>
</tr>
<tr>
<td>Yoshizawa et al. (2015)</td>
<td>Prospective, registry-based (chronic non-cancer pain)</td>
<td>Not applicable</td>
<td>• Tramadol-acetaminophen has a favorable benefit-risk profile in terms of managing pain at the time of observation (12 weeks), in patients who do not respond to non-opioids medications.</td>
</tr>
<tr>
<td>Doherty et al. (2011)</td>
<td>Randomized controlled trial (Knee OA)</td>
<td>Not applicable</td>
<td>• Ibuprofen-acetaminophen combination only confers modest short-term benefits when compared with acetaminophen but not ibuprofen.</td>
</tr>
<tr>
<td>Corsinovi et al. (2009)</td>
<td>Randomized controlled trial (OA)</td>
<td>Not applicable</td>
<td>• Oxycodone-acetaminophen has demonstrated efficacy in reducing pain in elderly women with moderate-to-severe pain.</td>
</tr>
<tr>
<td>Friedman et al. (2015)</td>
<td>Randomized controlled trial (acute LBP)</td>
<td>Not applicable</td>
<td>• The combination of acetaminophen, oxycodone and naproxen is not more effective than naproxen alone in relieving pain or improving functional outcomes.</td>
</tr>
<tr>
<td>Conaghan et al. (2011)</td>
<td>Randomized controlled trial (OA)</td>
<td>Not applicable</td>
<td>• Combinations of transdermal buprenorphine-oral acetaminophen and oral codeine-acetaminophen were equally effective, with comparable AEs.</td>
</tr>
<tr>
<td>Romanò et al. (2012)</td>
<td>Systematic review (cLBP)</td>
<td>Not available</td>
<td>• There is limited evidence that the addition of pregabalin to celecoxib and transdermal buprenorphine improves pain, particularly in subgroups of patients with a neuropathic pain component.</td>
</tr>
</tbody>
</table>

cLBP: chronic low back pain; AEs: adverse events; LBP: chronic low back pain; OA: osteoarthritis.