

## Study of Analgesic Intake among Patients with Chronic Low Back Pain and their Side Effects

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### ABSTRACT

**Background:** chronic low back pain is one of the most common causes of chronic pain. Low back pain can have many causes but most cases have nonspecific etiology. There are many approaches in the management of chronic low back pain. **Methodology:** we carried out a systematic review on observational (nonrandomized) of 43 studies using PUBMED. **Aim:** to evaluate the use of analgesics, mainly Non-Steroidal Anti-inflammatory Drugs and opiates, compare their efficacies for symptomatic treatment of low back pain, and study the side effects briefly for both category of drug.

**Conclusion:** management of chronic low back pain aims mainly to improve function, and quality of life, and to decrease level of disability, and therefore, it remains as a big challenge for the general practitioner. More studies must be done to compare efficacies of various lines of management for both short and long term.

**Keywords:** chronic low back pain, analgesic, NSAIDs, Anti-inflammatory Drugs, opioids, side effect of NSAID, side effects of opioids, chronic pain therapy

### INTRODUCTION

Low back pain is a common global health problem, and is one of the leading causes of years lived with disability, with more than 80% of adults experiencing it at least once in their lifetime<sup>(1)</sup>. It is also considered the most common cause of chronic pain<sup>(2)</sup>. It is mostly prevalent among females and people aged 40-80 years, and its prevalence has been increasing in the past few years<sup>(3)</sup>. Low back pain can have many causes, but is mostly nonspecific, with less than 10% of cases with an identifiable cause<sup>(4,5)</sup>. There are many known etiologies of chronic low back pain including: discogenic back pain, spondylolisthesis, fracture, tumor and metastatic disease, infection, aortic aneurysm, sickle cell crisis, osteomyelitis, nephrolithiasis, pyelonephritis, endometriosis, lumbar spinal stenosis, Paget disease, or rheumatologic diseases (e.g. ankylosing spondylitis, Rheumatoid arthritis, Psoriatic spondylitis, etc.). The differential diagnosis of chronic low back pain is very broad, thus proper history taking and physical examination are essential for detecting the presence of a specific medical cause; this is extremely important as some causes - as tumors and metastasis - are serious and may only present initially with back pain. Predisposing factors for developing chronic low back pain include:

sociodemographic factors, psychosocial factors, occupational factors, respiratory disorders, heart disease, rheumatological disorders, and other comorbid conditions<sup>(4,6)</sup>.

Chronic low back pain is defined as low back pain lasting for more than 3 months<sup>(7)</sup>. It is estimated that a large population of patients will develop chronic low back pain after an attack of acute low back pain. A systematic review of 11 studies concluded that only one-third will recover from an acute low back pain attack within the first three months, while the others will have chronic pain and continue to suffer for at least a year after the initial presentation<sup>(6,8)</sup>.

Managing chronic low back pain can be very challenging, most importantly due to its non-specific etiologies; the fact that is causing a large inconsistency among physicians<sup>(4)</sup>. The main target of treatment is to relieve the pain on the long term. Along with treating the cause - if possible - many approaches are important in the treatment of chronic low back pain; Non-steroidal anti-inflammatory drugs (NSAIDs) are most commonly prescribed medications<sup>(9)</sup>. Many guidelines recommend the initial use of acetaminophen followed then by NSAIDs<sup>(6,10)</sup>. Other medications include opioids, antidepressants (TCAs, SNRIs, and SSRIs), skeletal muscle relaxants, benzodiazepines, systemic

corticosteroids, and anti-epileptics<sup>(9)</sup>. There is a strong evidence to support the use of muscle relaxants in acute cases with weaker evidence to use it in chronic cases<sup>(6)</sup>. Humanized anti-nerve growth factor antibody were also examined (and proven effective) in the treatment of chronic low back pain, based on the assumption that this pain may be associated with increased nerve growth<sup>(11)</sup>. Other non-pharmacological approaches, including physical therapy and yoga, have been studied in several trials and systematic reviews, and demonstrate varying results, concluding the need of more studies to reach an answer that whether these approaches are effective, and to what extent<sup>(12, 13)</sup>. Generally speaking, proper treatment of chronic low back pain is extremely important as it can be very distressing and cause a lot of psychological and emotional disturbances. In this paper we aim to review the use of analgesics, mainly non-steroidal anti-inflammatory drugs, for symptomatic treatment of low back pain, and we will focus on their side effects in the long term.

#### METHODOLOGY

We carried out a systematic review on 77 observational (nonrandomized) studies using PUBMED (January 1983 to June 2017), but used 43 of them after exclusion to evaluate the use of analgesics, mainly Non-Steroidal Anti-inflammatory Drugs and opiates, compare their efficacies for symptomatic treatment of low back pain, and study the side effects briefly for both category of drug. The keyword used for this search were: *chronic low back pain, analgesic, NSAIDs, Anti-inflammatory Drugs, opioids, side effect of NSAID, side effects of opioids, chronic pain therapy*.

#### The Efficacy of Non-Steroidal Anti-inflammatory Drugs for Chronic Low Back Pain

NSAIDs work by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, which are responsible of prostaglandin synthesis. Prostaglandins are essential in inflammation, pain, and fever. Thus, NSAIDs reduce the process of inflammation, pain, and fever by disturbing the prostaglandins synthesis process. However, COX-1 inhibition does not only affect prostaglandins responsible of inflammation, but also affects prostaglandins that support platelets, protect the stomach lining, and help maintain kidney functions. This, consequently, causes the adverse events associated with long term NSAIDs use, such as:

bleeding, gastritis, and renal insufficiency<sup>(1)</sup>. Thus, NSAIDs are usually not recommended for long term use, especially in elderly and patients at high risk of developing adverse events<sup>(5)</sup>. The use of NSAIDs in chronic low back pain aims to provide a symptomatic improvement by relieving pain and decreasing disability associated with pain, thus improving quality of life<sup>(6)</sup>.

NSAIDs have been used for chronic low back pain for a long time, and many trials have studied their effect on relieving the pain. In a trial assessing the effect of naproxen on back pain among 37 patients, Berry *et al.*<sup>(14)</sup> after administering naproxen for 14 days, found that it was better compared to placebo in improving global pain, night pain, and pain on movement. Oral naproxen was also found in other two trials to be better than placebo in treatment of chronic low back pain<sup>(15)</sup>. However, it was found to be inferior to tanezumab (humanized anti-nerve growth factor antibody). In another trial, etoricoxib, a cyclooxygenase (COX)-2-specific inhibitor, had a significant positive effect in relieving symptoms and decreasing disability when given daily for 12 weeks<sup>(16)</sup>. Valdecoxib, a cyclooxygenase (COX)-2-specific inhibitor, was assessed in a trial to determine its efficacy in relieving chronic low back pain. It was found to have a positive effect, improve function, and decrease disability, when compared to placebo<sup>(17)</sup>. Some trials were conducted to compare NSAIDs together. One such trial was done to compare the effect of indomethacin versus piroxicam. Both were equally effective for chronic low back pain treatment<sup>(18)</sup>. Zerbini *et al.* found in another trial that etoricoxib and diclofenac were equally effective for pain relief in chronic low back pain<sup>(19)</sup>. However, when compared to home-based exercise, NSAIDs were found to provide less effective in relief of pain<sup>(20)</sup>. Generally speaking, the use of NSAIDs for low back pain relief remains an area of debate. Most of the previously mentioned trials were conducted on small samples that may not have been powered enough. Moreover, the statistically significant efficacy does not necessarily mean clinical significance. A recent systematic review and meta-analysis found that although the improvement in pain and disability associated with NSAIDs was significant, it was still of minimal clinical importance. This review concluded that the evidence that supported the use of NSAIDs was of low quality, and more trials are required to assess this use<sup>(1)</sup>.

### Side Effects Associated with Non-Steroidal Anti-inflammatory Drugs Use

NSAIDs are not usually well tolerated due to high rates of adverse events<sup>(15)</sup>. It is estimated that more than 100,000 patients are admitted to hospitals annually for gastrointestinal symptoms related to NSAIDs use. NSAIDs deplete COX-1 derived prostaglandins which protects the gut. Without those prostaglandins, the mucosa of the gastrointestinal tract (GIT) faces topical injury leading to peptic ulcer diseases, and upper GIT bleeding<sup>(21)</sup>. By a similar mechanism, the NSAIDs also lead to renal damage such as decreased glomerular filtration rate, electrolyte imbalance, and chronic kidney injury. Such incidences are more noted in patients with pre-existing diabetes, renal dysfunction, or heart failure. Trials that were conducted on non-selective NSAIDs showed a significant increase in adverse events rates<sup>(11)</sup>. However, Selective cox 2 inhibitors NSAIDs are more tolerated and associated with less adverse effects than non-selective NSAIDs. Trails on etoricoxib and valdecoxib -both selective cox 2 inhibitors- showed a more tolerable safety profile, with higher levels of compliance when compared to non-selective NSAIDs<sup>(16)</sup>. In other studies, NSAIDs have shown to cause sodium retention leading to hypertension, and overall increased incidence of adverse cardiovascular events such as ischemic heart diseases and congestive heart failure<sup>(15)</sup>.

Unfortunately, serious adverse events rates were not adequately assessed in most of the previously mentioned trials, as most of these trials did not follow up patients for long enough. Generally, all this raises a huge concern regarding the use of NSAIDs for chronic low back pain, especially when it comes to efficacy and safety. More research should be conducted with larger samples to reach more definite conclusions<sup>(11)</sup>.

### Opioids Use for Chronic Low Back Pain

Opioids can be effective in short-term treatment of chronic low back pain. They work on the central and peripheral nervous system causing decreased sensation of pain. However, this may also cause central depression in several centers causing potentially serious adverse events. Another important expected harm is the high probability of developing addiction. We generally classify opioids as weak or strong referring to efficacy of the opioid in relieving the pain<sup>(22)</sup>.

The use of opioids is a huge area of debate, many physicians support its use and believe that it can offer

good efficacy in the management of chronic low back pain<sup>(22)</sup>. Moreover, the American Geriatrics Society Guidelines suggested that they can be used as a first-line treatment for management of patients with high risk of NSAIDs-related adverse events<sup>(23)</sup>. On the other hand, some physicians are against its use due to concerns related to poor function, dependence, and risk of abuse<sup>(22)</sup>. A study on Canadian physicians showed that about half of physicians are against the use of opioids even in severe chronic pain<sup>(24)</sup>.

Schnitzer *et al.*<sup>(25)</sup> studied the effect of tramadol on chronic low back pain, and found that it was effective for providing pain relief<sup>(25)</sup>. In another trial, Vorsanger *et al.*<sup>(26)</sup>, studied the efficacy of extended-release tramadol on chronic low back pain and found it to have a favorable effect in lowering the discomfort. Moreover, this relief was maintained with continuation for 12 weeks. The other two trials studied the combination of tramadol and acetaminophen, and its efficacy in treating chronic low back pain. It was found in both trials that the combination was effective with a relatively good safety profile and tolerability<sup>(27)</sup>. However, in another trial comparing tramadol to celecoxib (a selective NSAID), although the pain was reduced in both groups when comparing with placebo, the results showed tramadol to be inferior to celecoxib, but with a higher risk of adverse events. Specifically, more GI and CNS related adverse events were reported in the tramadol group<sup>(5)</sup>.

When studying morphine, Khoromi *et al.*<sup>(28)</sup> found it to be effective in treatment of chronic low back pain when compared to placebo, but with a less effect when compared to nortriptyline. In another study, oral morphine was found to have a significant effect in improving pain associated with chronic low back pain. However, patients developed tolerance after one month of use<sup>(29)</sup>. Extended-release oxycodone was also tested in several trials and was found to be effective in pain relief and was relatively tolerable. Oxycodone has also been tested and was shown to cause a strong relief of pain with relatively less dependence and withdrawal symptoms<sup>(30)</sup>.

### Side Effects with Chronic Use of Opiates

Among many side effects of chronic opiates therapy for pain, the most common one is constipation as it decreases the gastrointestinal motility. More concerning adverse effect is cognitive impact, such as delirium in elderly, which is more seen in morphine than fentanyl<sup>(31)</sup>. Opiates are also

known to cause nausea with or without vomiting, which can sometimes be so distressing that it leads to non-compliance. The mechanism is not clearly understood, but may be primarily due to chemoreceptor trigger zone, and also due to delayed gastric emptying as gastrointestinal motility is delayed<sup>(27)</sup>. Some new studies have demonstrated ill effect of opiates on hypothalamic-pituitary-gonadal axis, thereby causing hypogonadism leading to decreased libido, sexual dysfunction, infertility, and mood disorders<sup>(23)</sup>. As mentioned earlier, there is always a risk of abuse of opiate medications by the patient, as well as by friends and family of patients. It is evident by the fact that abuse of prescription medication increased in the past ten years, which is the same period in which primary care physicians started using opiate therapy<sup>(31)</sup>. Lastly, discontinuing opiate can be dramatic because of the withdrawal symptoms like tremors, restlessness, vomiting, rhinorrhea, abdominal cramps, and muscle twitches<sup>(32)</sup>. A large systematic review and meta-analysis that was published recently concluded that the use of tramadol and other opioids can result in a short term improvement in symptoms of chronic low back pain<sup>(22)</sup>. However, these results are still not definite due to many limitations in conducted trials. Most trials were conducted for a short period, and with no large enough samples. The high drop rate is also a problem that happened in most trials. The use of opioids is still considered an area of debate, and more research is needed to reach better conclusions, especially when it comes to dependence and risk of abuse<sup>(33)</sup>.

#### Other lines of Low Back Pain Management

Apart from acetaminophen, NSAIDs, and opiates, there are other forms of chronic low back pain management that can assist in pain reduction, help gain maximum functions, and reduce the dependency of medication alone. Exercise therapy, rehabilitation programs, yoga, massage, and behavior therapies are some examples that have shown to improve symptoms by 11-24%<sup>(13)</sup>. Suggested mechanisms for this improvement include the increased physical and mental relaxation<sup>(12)</sup>.

A recently published clinical trial suggested that yoga was as effective as physical therapy in relieving pain associated with chronic low back pain<sup>(13)</sup>. Moreover, a systematic review concluded that patients with chronic low back pain who practiced yoga were more likely to have clinical improvement than patients who do not. This improvement extended to as long as six months<sup>(12)</sup>. However, there is still a

need for many further studies to confirm this effect. Acupuncture has also displayed pain control for short period of time, while surgery hasn't shown much promising results. More studies are being carried out to note the benefits of epidural steroid injections<sup>(12)</sup>.

#### CONCLUSION

The management of chronic low back pain remains a challenge for physicians. This management aims mainly to improve function, and quality of life, and to decrease level of disability. Both NSAIDs and opiates have incredible amount of benefit in overall quality of life with patients of chronic low back pain, but also have several (sometimes serious) adverse events. Many of these adverse events can be controlled with the help of other medications and with better follow-up. However, there is still a need for more studies that must be done to compare the various lines of therapy with respect of their outcomes on patients' health in short as well as long term.

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