Pharmacological approach for the management of chronic low back pain

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ABSTRACT

Chronic low back pain is a common condition affecting a high percentage of the general population. Affected people report diminished quality of life due to pain and disability. In terms of pharmacological treatment, physicians have a wide variety of options to choose from non-steroidal anti-inflammatory drugs (NSAIDS), opioids, non-opioids, muscle relaxants, antidepressants, antiepileptic drugs and biologic agents. However, there is no consensus as far as the optimal treatment is concerned.
A review of the current literature was performed to assess the efficacy and possible side effects of the different pharmacological treatments used in chronic low back pain and possibly give some guidelines about their use. The Pubmed and Cochrane databases were used to identify studies regarding the pharmacological treatment of chronic low back pain.

Key Words: chronic low back pain, medications, doses, effect

Introduction

Low back pain or lumbosacral pain refers to pain and discomfort, localized below the costal margin and above the inferior gluteal folds with or without leg pain [1]. Chronic low back pain (CLBP) lasts longer than 12 weeks. Non-specific low back pain includes symptoms that cannot be attributed to a known condition as infection, tumor, osteoporosis, ankylosing spondylitis, fracture, inflammatory process and cauda equina syndrome [2]. Pain is a multidimensional sensory experience that is unpleasant and may differ in intensity (mild, moderate, severe), quality (sharp, burning, dull), duration (transient, intermittent, persistent) and referral (superficial, deep, localized, diffuse). In addition, it has a strong emotional component. Pain is associated with avoidance, motor reflexes and alterations in autonomic output [3]. Low back pain is a common complaint among the general population with a subgroup of patients developing chronic and disabling symptoms generating large societal costs. In developed countries, about 70% of people develop low back pain at some time in their life, which usually improves at 2 weeks, but 10% of them are not able to work and 20% of them report sustainable symptoms for 1 year [4]. Low back pain occurred in 63.5% of workers at Kosovo energetic corporation [5]. Most primary care physicians can expect to see at least one patient with low back pain per week. The extended loss of function

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is also a financial burden for the social security systems since it results in loss of work productivity, treatment costs and disability payments [6]. It is estimated that the range of costs is about $ 12.2 to $ 90.6 billion, annually [7].

Generally, conditions causing CLBP can be categorized as: a) non-specific or idiopathic (70%): lumbar sprain or strain, b) mechanical (27%): degenerative process of disk, facets, fracture, spondylosis, c) referred pain (2%): diseases of pelvic organs, gastrointestinal disease, pancreatitis, d) non-mechanical (1%): neoplasia, multiple myeloma, spinal cord tumors, Paget disease of bone [6,8].

The main goal of physicians is to alleviate pain. Conservative treatment can be applied through several pharmacological factors, including acetaminophen, non- steroidal anti-inflammatory drugs (NSAIDS), opioids, non-opioids, muscle relaxants, antidepressants, antiepileptic drugs, biologic drugs and steroid epidural injections. However, there is no consensus as far as the optimal treatment is concerned. For this reason, a review of the current literature was performed to assess the efficacy and possible side-effects of the different pharmacological treatments applied in chronic low back pain and possibly provide guidelines on their use. The Pubmed and Cochrane databases were used to identify studies regarding the pharmacological CLBP treatment. The key words "chronic low back pain", "medications", "doses" and "effect'' were used.

Discussion

A wide variety of studies for CLBP were found (n= 1572). Most of them were excluded because of the different approach of treatment that was recommended (n= 1226). Remaining articles assessed for eligibility were 346. However, a great number of articles were also excluded for different reasons. Finally, 49 studies were included in the review (Table 1).

Acetaminophen

The first line of treatment of low back pain is usually acetaminophen (paracetamol). Paracetamol has been available for more than 100 years. In a recent study, the authors collected the clinical guidelines from different countries concerning the use of paracetamol in low back pain since 2016 [9]. In 2016, in Australia. paracetamol was initially prescribed for acute low back pain. In 2017, clinicians in Belgium did not recommend paracetamol as single pain medication, however on the same year in Canada acetaminophen was the first-choice medication for acute and chronic back pain, with NSAIDS being the second. Interestingly, on the same year both in the United Kingdom and United States, the use of acetaminophen was not recommended. However, in the Netherlands paracetamol may be prescribed as regularly as needed, while NSAIDS are not considered to be more effective than paracetamol [10,11]**.** Although many researchers express doubt about the efficacy of acetaminophen in individuals with chronic non-specific low back pain [9], others consider the drug as a first-line therapy, mainly due to its high safety profile [6]**.** There is high quality evidence that tramadol with or without paracetamol in comparison with placebo can decrease the pain coming from CLBP within 3 months [12]**.** Finally, the American College of Physicians recommends as first line option of medication for low back pain acetaminophen or non-steroidal anti-inflammatory drugs [13].

Non-steroidal anti-inflammatory drugs (NSAIDS)

Another medication that is usually recommended for CLBP is NSAIDS. These drugs block COX-enzymes and as a result inflammation is inhibited. European Guidelines suggest that NSAIDS can be used for a short period of time, as far as chronic non-specific low back pain is concerned [14]. In Japan, the outcomes of a study about the most prescribed medications in patients with CLBP and osteoarthritis showed that approximately 90% of the patients received NSAIDS and that the less prescribed drugs were weak opioids (10,7% patients with OA and 20,6% patients with low back pain). Japanese guidelines also recommend COX-2 inhibitors and acetaminophen for chronic low back pain [15]. Typical doses of NSAIDS are: aspirin (40-80mg/day), indomethacin (25mg 2-3 times/day), celecoxib (100mg 1-2 times/day), naproxen (250mg 4 times/day), diclofenac (50mg 3times/day) and piroxicam (20mg/day) [16]. In a recent study, patients with CLBP were separated in 2 groups. The first group was treated with 400mg ibuprofen and the other with placebo. Twenty minutes post-treatment, the group of patients treated with ibuprofen had an important re-

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duction of nitric oxide metabolites in their serum. In both groups, there was a significant analgesic effect compared to baseline [17]. In another 6-week study, a comparison of the analgesic effect and safety of celecoxib (200mg twice/day) and tramadol (50mg/ 4 times per day) in individuals with CLBP took place. The study was performed twice including initially 796 subjects and 802 subjects in the second study. In both studies the groups of celecoxib demonstrated greater pain relief and less adverse effects than the group of tramadol (study 1: celecoxib group 63.2% and tramadol group 49.9%, study 2: celecoxib group 64.1% and tramadol group 55,1%) [18]. In another study, the cost utility of the most common treatments for CLBP was investigated. The two most common treatments were electro-acupuncture (EA) and NSAIDS. The group of patients that were treated with EA had a mean age of 41 years and the group of patients treated with NSAIDS had a mean age of 38 years. For the study, clinicians used the EuroQol five-dimension questionnaire. Finally, they reported that NSAIDS had greater cost than electro-acupuncture (497.77$ ± 85,2$ versus 461,48$ ± 57,8 $) for the year 2016 [19]. In a study, investigating the effects of NSAIDS on CLBP, the authors concluded that six of their included randomized controlled trials showed that NSAIDS were superior in decreasing pain than placebo, but not effective as far as the disability was concerned. Another study comparing NSAIDS and home exercise showed that the group of patients that exercised regularly had better results in decreasing disability, but not in pain reduction [20]. Although, NSAIDS are usually prescribed for CLBP, there are reports that these agents cause serious side effects such as gastrointestinal bleeding and cardiovascular irritations and thus a short-term use is recommended [16].

Opioids

Another pharmacological agent that doctors oftenly prescribe, is opioids. For CLBP, oral or transdermal weak (tramadol, codeine, tilidin) or strong opioids (morphine, oxycodone, hydromorphine) can be administered [14]. It is generally believed that opioids should be considered as second- or third-line option in controlling CLBP and should only be administered for a short period of time [21]. There is high-quality evidence that sustained-release tramadol (200-300mg) is more effective than placebo in reducing CLBP at 12 weeks [22]. Another study showed that short-term treatment (<4 months) can improve pain levels but does improve function of individuals with CLBP [23]. However, six trials including 1887 patients comparing strong opioids (morphine, hydromorphine, oxycodone and tapentadol) with placebo, showed that opioids were more efficient than placebo in reducing pain and improving function in patients with CLBP [23]. Another high-quality study comparing tramadol with placebo in patients with CLBP, concluded that tramadol was more efficient in managing pain and disability and in reducing VAS pain scores [24]. The NICE (National Institute for Health and Care Excellence) recommends weak (e.g. codeine) and strong opioids use only for a short period of time. In addition, the American College of Physicians recommends tramadol, if NSAIDS are not effective enough for pain relief in CLBP [25]. However, there is no evidence that opioids improve the quality of life and it is underlined that doctors should prescribe them in low dosages (e.g. not more than 50-100mg morphine per day). Another study compared the effect of opioid and non-opioid medications (NSAIDS, acetaminophen) in 234 patients with CLBP, hip and knee osteoarthritis, focusing on pain-related function and pain intensity over 12 months. The authors announced that opioids were non-superior than non-opioid medications; moreover they caused more adverse effects than the other drugs [26]. Adverse effects as tolerance, hyperalgesia, allodynia, dependence, constipation, dizziness, sweating and sexual impotence in long term use are usual during opioid treatment [14,27]. The American Society of Interventional Pain Physicians recommends that clinicians should assess pain and improvement of function periodically, in case they have prescribed opioids. They suggest that methadone should be given only if other opioids have failed. It is also underlined that long-acting or high dose drugs should be prescribed for unmanageable pain and adverse effects such as constipation should be monitored [28]. In a study of 50 patients with CLBP treated with intravenous naloxone (8mg), morphine (0.08 mg/kg) and placebo, it was shown that morphine was superior in pain relief compared to the other drugs. The authors concluded that morphine provided acute relief of chronic back pain in patients with lower

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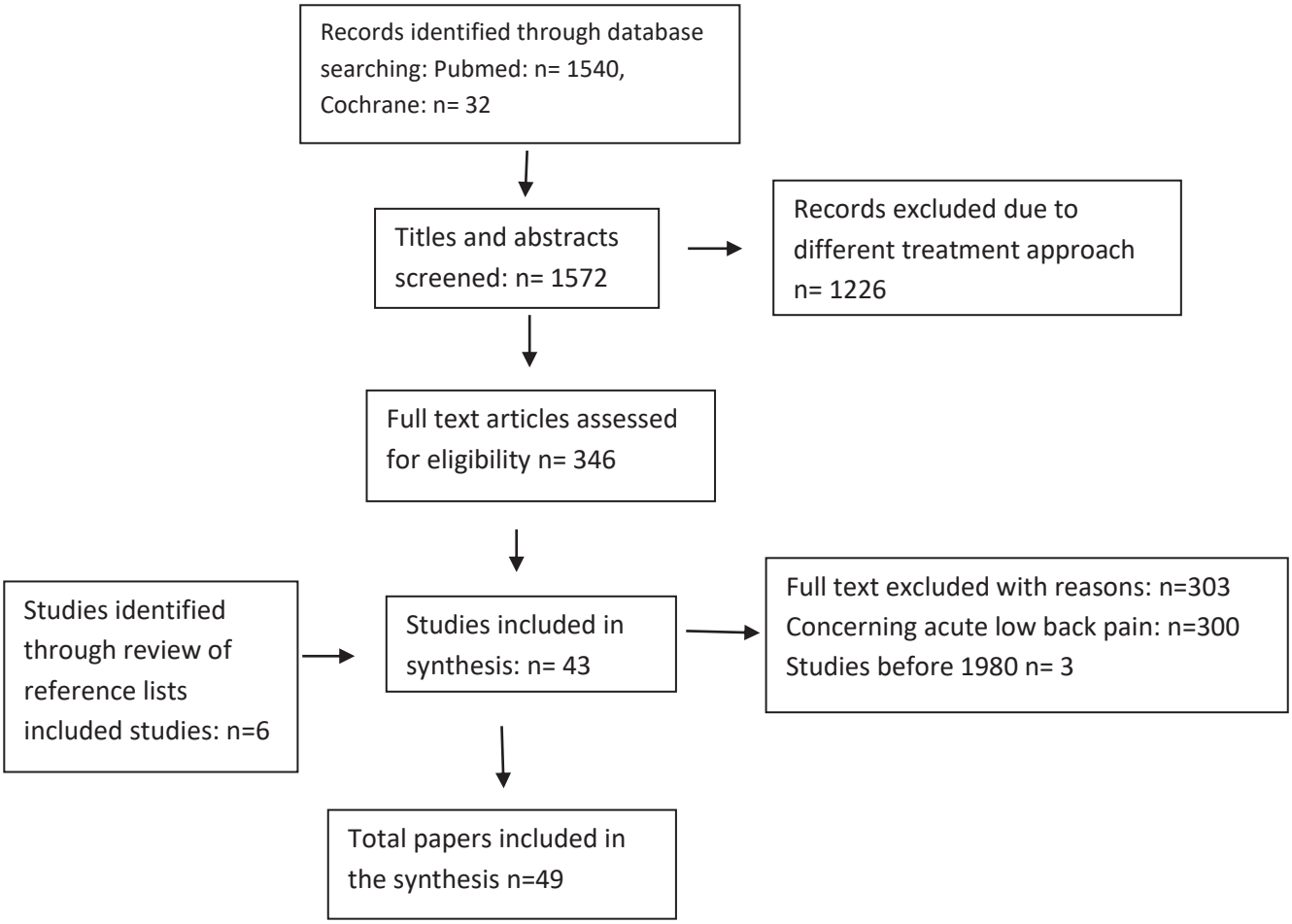

Table 1: Flowchart

natural opiodergic inhibition of chronic pain intensity [29]. Other clinicians investigated the effect of opioid treatment in Negative Affect (NA: distress, anxiety, depression) in a period of six months. Patient sample included 31 patients with chronic discogenic back pain with pain intensity >3/10 and was separated into 2 groups: a) high levels of Negative Affect b) low levels of Negative Affect. The authors concluded that hyperalgesia changes the pain inflection and affects patients' distress and that this process may not be beneficial to high NA patients [30].

Muscle Relaxants

These agents affect skeletal muscles by reducing muscle tone. Some examples of muscle relaxants are benzodiazepines, carisoprodol and dantrolene. It is generally believed that muscle relaxants are effective for a short-term use in the management of CLBP; however, their long-term use is not suggested due to adverse effects as dependency [31]. In a low-quality study, benzodiazepines (tetrazepam 50mg/3 times daily) were compared with placebo showing that benzodiazepines would be effective following treatment for 10-14 days**.** However, adverse central nervous system effects such as dizziness and drowsiness were reported [32]. European Guidelines suggest short-term use of muscle relaxants for controlling CLBP; however, they should be administered with caution because of multiple adverse effects such as addiction, allergies, reduction of liver function and gastrointestinal complications [14].

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Antidepressant and Antiepileptic drugs

Antidepressant and antiepileptic drugs are frequently prescribed for CLBP. The most common antidepressants used are tricyclic antidepressants. Antidepressants influence pain transmission in the spinal cord by inhibiting the reuptake of norepinephrine and serotonin [33]. Antiepileptic drugs, such as gabapentin, constitute an option for neuropathic pain. They act by enhancing the transformation of gamma-aminobutyric acid (GABA) to glutamate and by enhancing the ion channel action and/or the non-synaptic GABA release [14]. It is suggested that low doses of amitryptiline can be effective in reducing pain at 6 months and disability at 3 months in patients with CLBP [34]. In another study, tricyclic antidepressants relieved one in every 2 or 3 patients with peripheral neuropathic pain, serotonin noradrenalin reuptake inhibitors relieved one in every 4 or 5 patients and selective serotonin reuptake inhibitors relieved one in every 7 patients [35]. Fifty patients with non-specific CLBP took part in a study which examined the action of oral imipramine (75mg) in comparison to active placebo (1 mg of tolterodine). It was found that imipramine was not effective in CLBP [36]. In another study, antidepressants were compared with placebo in 504 participants having CLBP. Antidepressant treatment reduced pain level in contrast with the placebo, but it was not efficient enough to improve patients' daily life. About 22% of patients treated with antidepressants faced adverse effects. [37]. There is another mention that noradrenergic-serotoninergic antidepressants can alleviate pain in patients with CLBP [37, 38]. Although there is strong evidence for the action of antidepressants, it is reported that 20% of patients receiving these agents have an adverse reaction such as drowsiness, dry mouth, dizziness and constipation [37]. Another 8-week study which included 74 patients with CLBP compared the effect of 150mg maprotiline (norepinephrine reuptake blocker) with that of 30mg paroxetine (serotonin reuptake blocker) and that of 37.5mg active placebo (diphenhydramine hydrochloride). Pain intensity reduced 45% with maprotiline, 27% with placebo and 26% with paroxetine. In conclusion, noradrenergic agents were found to be superior to selective serotoninergic reuptake inhibitors [39]. Strong evidence supports that tricyclic antidepressants assist in conditions like neuropathic pain, low back pain and fibromyalgia [40]. Another study compared pregabalin (antiepileptic, usually prescribed in neuropathic pain) and celecoxib (selective syclo-oxygenase-2 inhibitor) in 34 patients with CLBP. The authors concluded that the combination of pregabalin and celecoxib showed better results in reducing CLBP, according to the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS score) [41]. In another high-quality study the authors reported that anticonvulsants (gabapentin, pregabalin) are able to help patients handle their CLBP, but the risk of adverse effects is high [42]. However, there is a study which causes second thoughts about the action of pregabalin. In this study, 44 patients with CLBP received pregabalin (35mg/hr) for 3 weeks and then they were randomized in two groups. The first group received 35mg/h transdermal buprenorphine plus 300mg/day pregabalin and the second group received 35mg/h transdermal buprenorphine plus placebo. The results were that the group which received pregabalin with transdermal buprenorphine had significant pain relief and had better quality of sleep [43].

Epidural injections-Cortisone-Biologic Agents

Epidural injections sometimes are used for the management of CLBP. A recent study concluded that epidural injections with steroids or local anesthetic helped patients to reduce CLBP by ≥50% and improve their function by 60% according to the Oswestry Disability Index [44]. However, another study reported that epidural steroid injections should not be in the first line of treatment due to the side effects that may produce, despite the short-term relief of pain and early return to daily life [45]. In a recent study, epidural injections of cortisone were found to be helpful in 82% of patients with acute discogenic pain, but when administered in patients with unstable spine or previous laminectomy (having pain for over 3 months), they were found ineffective [46]. Other researchers tested cortisone injections in combination with other therapies such as manipulation, mobilization, muscle stretching and traction in patients being in the acute and sub-acute phase of low back pain. Patients were randomized in two groups. The first group was treated with conventional therapy by primary health clinicians and the second group was treated with ma-

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nipulation, stretching, mobilization and cortisone injections. The group treated with manipulations and cortisone injections had better results than the group with conventional treatment [47]. Finally, according to the American College of Physicians, systematic corticosteroids do not seem to be effective for the management of low back pain [48].

The last option in the management of CLBP is biologic agents as the anti-tumor necrosis factor-alpha (Anti-TNF-a) and the anti-nerve growth factor (anti-NGF). It has been reported that Anti-TNF-a is able to reduce pain and enhance function but there is no evidence that it is superior to placebo. On the other hand, Anti-TNF-a use has been shown to reduce the number of invasive procedures such as discectomy and radicular block in case of sciatica. Additionally, anti-NFG can alleviate pain intensity and improve function when compared to placebo, although the risk of side effects is high [49]. However, there is need of further research upon anticytokine treatments and how they affect CLBP.

Conclusion

CLBP is a common condition affecting a high percentage of the general population. Affected people report diminished quality of life due to pain and disability. Physicians should choose the right drug in the right dose for each individual patient and always concern about the potential side effects. Further research is needed for promising new drugs to assess their efficacy and safety.

Conflict of interest

The authors declare no conflicts of interest.

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