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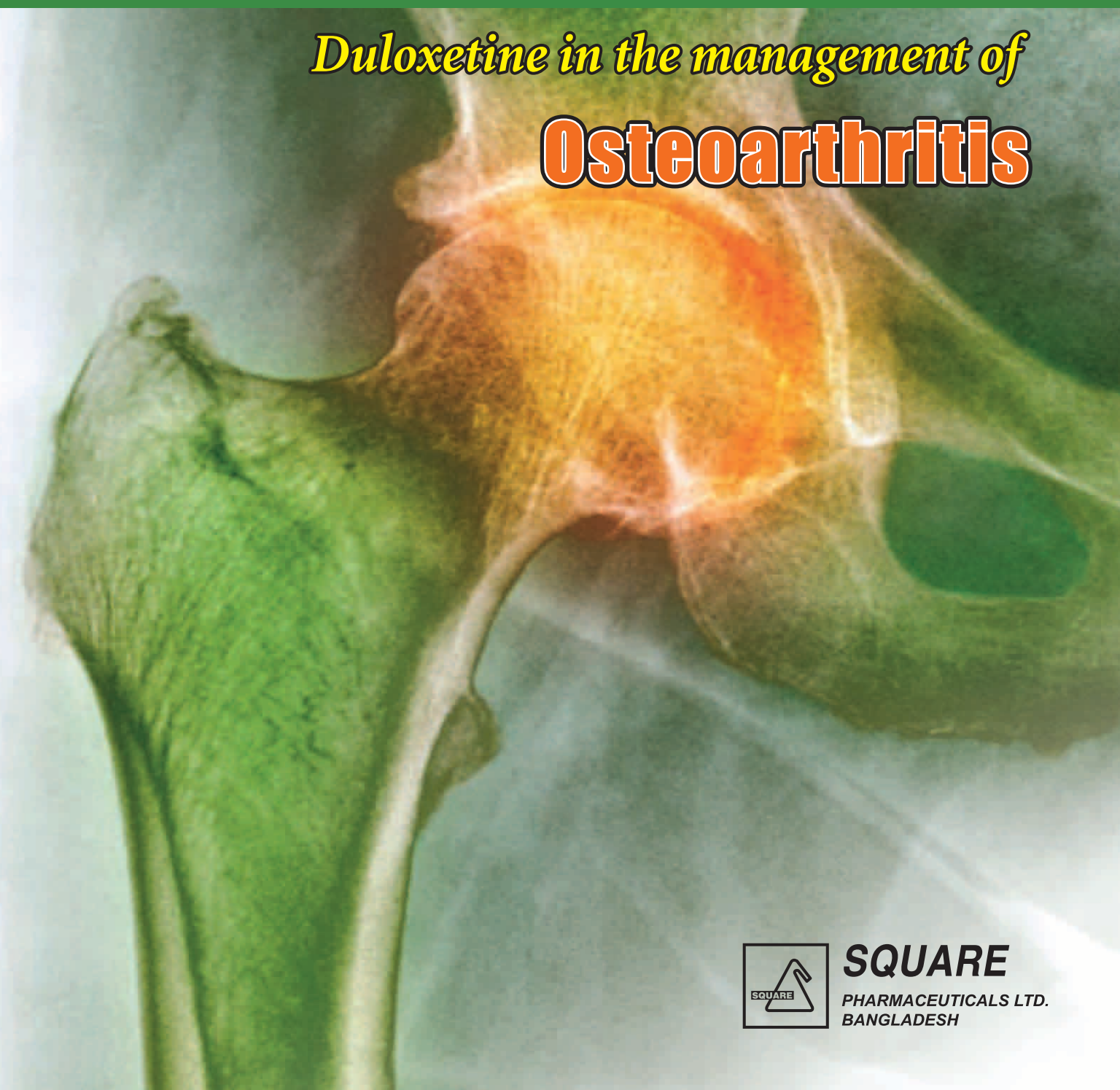
Duloxetine in the management of

Osteoarthritis



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Osteoarthritis

Osteoarthritis (OA) is recognized as one of the most prevalent chronic musculoskeletal diseases worldwide. The joints typically affected are located in the hands, knees, hips, and spine with varying degrees of joint deformity and swelling. Usually beginning when adults are in their 40s, it is estimated that 9.6% of men and 18% of women >60 years of age are affected with symptomatic OA. Since age is a significant risk factor in its development, it is predicted that OA will be the fourth leading cause of disability by 2020. The yearly global economic burden of OA measured by direct and indirect costs is in the tens of billions of dollars annually.

Pain is recognized as one of the hallmark symptoms in OA and is the primary reason why patients seek medical attention. It is a significant determinant of functional impairment and disability, even more so than radiographic findings. Therefore, it is necessary to consider other factors which may be involved in the maintenance of pain when it cannot solely be explained by peripheral nociceptive factors. As such, alterations in the central nervous system (CNS) may be implicated and understanding the role of central sensitization in pain modulation is important in conditions of chronic pain since its treatment requires an approach that differs from the treatment of pain in a peripheral context.

Pain in Osteoarthritis: Pain is a prominent component of many rheumatologic conditions and is the result of a complex physiologic interaction of central and peripheral nervous system signalling that results in a highly individualized symptom complex. Pain is frequently categorized as acute or chronic (generally 3 months' duration). Chronic pain is not simply acute pain that has lasted longer; it is more likely to be influenced by input from the central nervous system, whereas acute pain is often attributable primarily to inflammation and/or damage in peripheral structures (i.e., nociceptive input).

OA is a prevalent disorder characterized by the progressive destruction of articular cartilage associated with subchondral bone remodeling, formation of osteophytes, and secondary inflammation of synovial membranes. Amongst other factors contributing to pain, innervation and vascularisation of the articular cartilage may be involved, and compressive forces and hypoxia may stimulate these new nerves, causing pain even after inflammation has subsided. Innervation of the joint tissue and angiogenesis have been described as main pathophysiological pathways causing the deep joint pain described by some OA patients.

The pain of OA includes both nociceptive and non-nociceptive components and is associated with abnormally excitable pain pathways in the peripheral and central nervous systems. Quantitative sensory testing in OA patients reveals that OA patients have lower thresholds for mechanical and thermal pain than healthy controls and increased sensitivity to pressure, ischemia, and innocuous stimuli. OA patients were shown to have lower pain thresholds than control subjects at the forehead, a non-painful area of the body unaffected by OA. Such findings suggest that OA pain is also centrally mediated. Functional magnetic resonance imaging (fMRI) studies have identified several brain regions involved in OA pain processing, indicating the complexity of OA pain mechanisms.

The concept of centralized pain : The term "central pain" was originally used to describe the condition in individuals who developed pain following a stroke or spinal cord lesion. "Central" refers to the fact that the lesion leading to pain occurred within the central nervous system (CNS). More recently, however, the term has been expanded to describe any CNS dysfunction or pathologic condition that may be contributing to the development or maintenance of chronic pain, which includes, but is not limited to, important contributions from psychosocial aspects of pain perception. Another term that has often been used to describe this same phenomenon is "central sensitization." The term "central sensitization" was originally used to describe a state in which the spinal cord amplifies afferent signals out of proportion to peripheral tissue changes. This term has the same problem as the term "central pain" because it originally referred to a specific mechanism, representing only one potential cause of augmented CNS pain processing.

The prominent role of central factors in chronic pain and thereby in OA is highlighted by the fact that there is currently no chronic pain condition in which the degree of tissue inflammation or damage alone (e.g., as measured by radiographs, magnetic resonance imaging [MRI], or endoscopy) accurately predicts the presence or the severity of pain. Central factors alter pain processing by setting the "gain," such that when peripheral input is present, it is processed against a background of central factors that can enhance or diminish the experience of pain. There are very large inter-individual differences in these central nervous system factors that influence pain perception, such that some individuals with significant peripheral nociceptive input (e.g., from joint damage or inflammation) will feel little or no pain, whereas others are very pain sensitive, and they can experience pain with minimal or no identifiable abnormal peripheral nociceptive input. This emerging knowledge has important implications for pain management in individuals with chronic rheumatologic disorders.

Osteoarthritis and Central Sensitization : In last decades, great progress has been made in the knowledge of pain. Majority of chronic musculoskeletal pain conditions are characterized by an alteration in pain processing by the CNS. More specifically, sensitivity of central neurons to inputs coming from the unimodal and polimodal receptors increase, which results in central sensitization, characterized by a general or extended hypersensitivity. However, central sensitization also includes an alteration of sensory processing in the brain, loss of descending anti-nociceptive mechanisms, enhanced facilitatory pain mechanisms, increased temporal summation or wind-up and long-term potentiation of neuronal synapsis in the anterior cingulate cortex. Pathophysiological mechanisms underlying central sensitization are complex and numerous, but the net effect is an amplification of neural signalling within the CNS than elicits pain hypersensitivity.

Central sensitization is present in different chronic musculoskeletal conditions such as whiplash trauma, chronic low back pain, fibromyalgia or more recently, in OA which concerns us here. One of the factors that favour the development of central sensitization in OA is the massive and repetitive nociceptive input coming from peripheral joint nociceptors arriving to dorsal horn neurons in the spinal cord.

Intense and continued nociceptive input proceeding from an OA joint may cause central sensitization, as shown in different studies. Presence of central sensitization entails greater complexity of the clinical picture and less possibilities of achieving positive results with physical therapy treatment. Patients with OA quite often present referred pain and changes in skin sensitivity in remote areas with respect to the affected joint. There are various theories on referred pain, but they all include a higher centers misinterpretation of the peripheral origin of nociception.

Another phenomenon associated with central sensitization is secondary hyperalgesia. While primary hyperalgesia or peripheral sensitization involves an increased sensitivity of peripheral nociceptors in response to tissue damage, secondary hyperalgesia correspond to increased sensitivity of dorsal horn neurons, located in the spinal segments corresponding to the primary nociceptive source.

Peripheral sensitization is a local phenomenon, while secondary hyperalgesia is a central process of the nervous system. Regarding OA, different studies have shown an increase in nociceptive transmission in dorsal horn neurons, typical of secondary hyperalgesia. Recent evidence suggests that OA pain is caused by central sensitization through communication between peripheral OA nociceptors and the central sensory system. It was observed that structural changes in components of the peripheral knee joint correlated with alterations in the central compartments (dorsal root ganglia and the spinal cord) and symptomatic pain assessed by behavioral hyperalgesia.

Apart from referred pain and secondary hyperalgesia, there is further evidence in scientific literature that shows how pain in OA can be modulated through mechanisms related to the CNS. It has been found, for instance, that OA not only causes a decrease in pain thresholds in the affected joint, but also far from it in remote and over extended areas. Loss of descending pain inhibitory mechanisms, increase of temporal summation (increase of painful response to repetitive stimulation) as well as the presence of extended areas of hyperalgesia in patients with OA, further support the role of central sensitization in OA pain. Moreover, it was also noted that patients with chronic musculoskeletal pain conditions usually present generalized hyperalgesia in deep tissues and an increased response to experimental painful stimulation.

One of the characteristics of central sensitization is that, once installed, it can persist in time despite the lack of new painful stimuli from the periphery. In clinical practice, it is common to find patients with OA who show symptoms even after prosthetic substitution. It has been noted that patients suffering from OA with a high degree of pain and low pain thresholds before surgery run a greater risk of continued pain after getting a prosthetic knee, which has been interpreted as an accurate reflection of central sensitization.

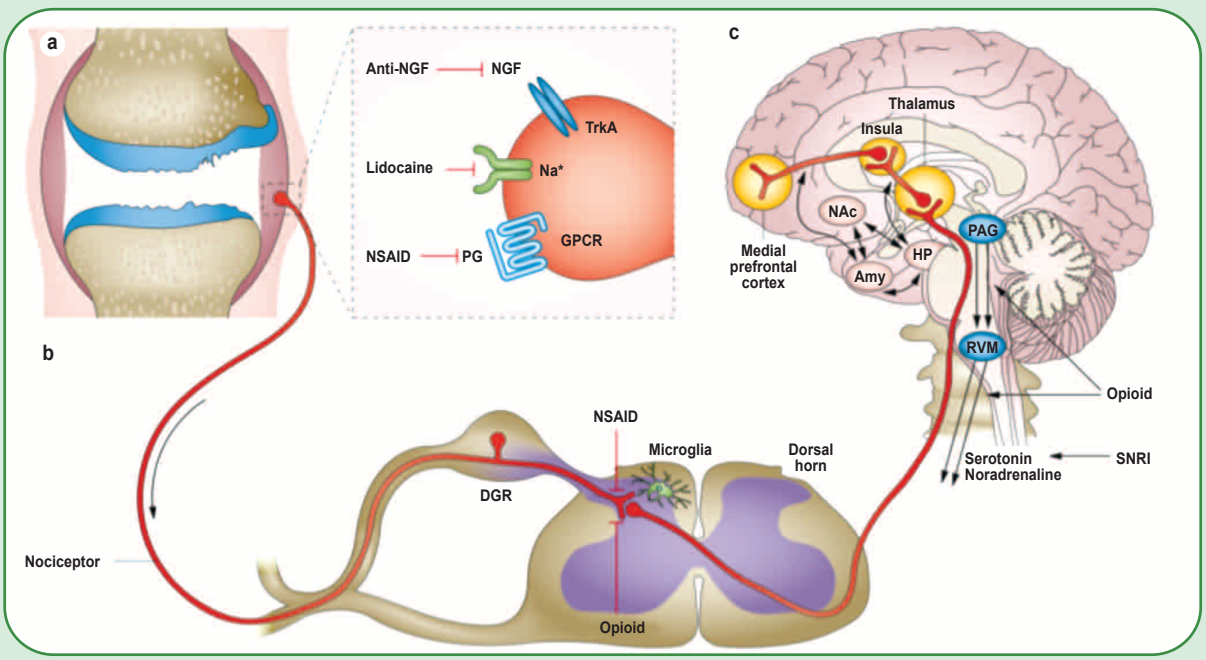

Figure 1: Neuroanatomy of the pain pathway and analgesic targets in OA.

a. Pain signals are detected by nociceptors in the periphery and carried to the dorsal horn of the spinal cord. Various analgesics that are efficacious against joint pain act in the periphery by targeting receptors expressed at nociceptor peripheral terminals.

b. The central terminals of the afferent nociceptors synapse with second-order neurons in the dorsal horn, in a stratified pattern that is anatomically very precisely organized. Second-order neurons are either interneurons (not shown) or projection neurons that cross to the contralateral side and carry the signal up the spinal cord. Central sensitization can occur through the strengthening of synapses and through the loss of inhibitory mechanisms. In addition, the activation of microglia contributes to enhanced pain sensitivity. Prostaglandins can also have a sensitizing effect in the dorsal horn, and NSAIDs can thus exert central analgesic actions, in addition to their peripheral actions. Opioids can inhibit incoming pain signals in the dorsal horn.

c. Projection neurons relay pain signals along the spinothalamic tract to the thalamus, and along the spinoreticulothalamic tract to the brainstem. From there, the signals can be propagated to different areas of the brain, including the cortex. Descending pathways (black arrows), both facilitating and inhibitory, modulate pain transmission; descending inhibitory pathways release noradrenaline and serotonin onto the spinal circuits. SNRIs engage these descending inhibitory pathways. RVM neurons are opioid sensitive, and morphine has an analgesic effect through engaging descending inhibition. Abbreviations: Amy, amygdala; DRG, dorsal root ganglion; GPCR, G-protein-coupled receptor; HP, hippocampus; NAc, nucleus accumbens; NGF, nerve growth factor; PAG, peri-aqueductal grey; PG, prostaglandin; RVM, rostral ventromedial medulla; SNRI, serotonin-noradrenaline reuptake inhibitor.

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Pain Management in OA

A wide variety of interventions have been evaluated in the management of OA, with greatest attention focused over the years on the effects of weight loss, exercise, acupuncture, nutraceuticals, paracetamol, NSAIDs, opioids and other centrally_acting drugs (such as antidepressants, and particularly SNRIs), as well as intra_articular therapy with glucocorticoid and hyaluronan preparations. While there is good evidence for the effectiveness of some of these treatments, the effect size of most of these treatments for OA is small. Furthermore, compliance with exercise therapies is low and the effectiveness of some treatments, for example, an intra-articular corticosteroid injection, is short lived. NSAIDs and opioids can have significant associated morbidity, particularly in the elderly population and given the recent concerns over the safety of paracetamol, there is a real lack of safe treatments for those with OA pain.

Clinical studies of NSAIDs have repeatedly demonstrated their efficacy, compared with placebo, in relieving pain and increasing function in people with OA. Their dose-response curve is reasonably flat with regard to pain relief, such that only numerical and not statistically significant differences can be demonstrated for different doses of the same NSAID.

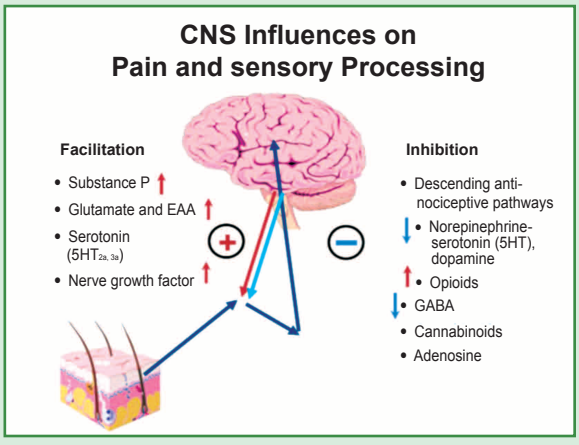

Figure 2. Influences of the central nervous system (CNS) on pain and sensory processing. Recent studies have demonstrated that an individual's "set point" or "volume control setting" for pain is determined by a variety of factors, including the levels of neurotransmitters shown on the left, which facilitate pain transmission (turn up the gain or the volume control), or the neurotransmitters shown on the right, which reduce pain transmission. Thus, high levels of the neurotransmitters on the left or low levels of those on the right would be capable of causing the diffuse hyperalgesia (increased volume control) that is seen in a variety of chronic pain states. EAA= excitatory amino acid; 5-HT 2A= 5-hydroxytryptamine H2A ; GABA= _-aminobutyric acid.

NSAIDs are potent inhibitors of the COX enzymes in humans, and thereby reduce the production of prostaglandins. Prostaglandins effectively sensitize peripheral nociceptors to painful stimuli, resulting in increased sensitivity to pain. NSAID activity in OA might be based on the ability of these drugs to down-regulate the peripheral production of neural sensitizers. In addition, it is now recognized that COX2 expression is up-regulated in painful states not only in the periphery but also in spinal cord neurons; thus, NSAIDs, which can cross the blood-brain barrier, might also have a role centrally in modulating the pain response. Indeed, pilot data have demonstrated a relationship between cerebrospinal fluid COX2 inhibitor levels and change in pain after NSAID treatment in patients with OA. Thus, NSAIDs might have dual sites of action, inhibiting the sensitization of peripheral nociceptors as well as acting centrally at the level of the spinal cord and brain (Figure 1 a, b).

Early anitdepressent drugs, SSRIs have been in use for chronic pain management. In contrast to SSRIs, newer antidepressants, including duloxetine, venlafaxine and milnacipran, inhibit both serotonin and noradrenaline reuptake in the CNS and have shown efficacy in the treatment of major depressive disorder and general anxiety disorder. Subsequent clinical trials with duloxetine also demonstrated its efficacy in reducing pain levels in patients with diabetic peripheral neuropathy as well as in individuals with fibromyalgia. Most recently, duloxetine has been shown to reduce pain in individuals with chronic back pain and in those with OA, leading to its approval in the USA by the FDA for the treatment of chronic musculoskeletal pain.

Duloxetine in OA pain

Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI). The presumed pain-relieving properties of duloxetine stem from its action on descending inhibitory pain pathways (Figure 1c). Previous studies revealed that both norepinephrine and serotonin play important roles in maintaining the function of this mechanism of analgesia. Increasing either neurotransmitter alone is not as effective in producing analgesia when compared with increasing them simultaneously. Any deficiency in this tract may lead to heightened pain or potentially painful responses to normally non-painful stimuli. Duloxetine may play a role in restoring or enhancing the function of this pathway.

Preclinical study suggests that duloxetine might be effective for treating the pain of knee OA, because it had better effects than acetaminophen and ibuprofen. Overall, clinical trials suggest that 50% to 60% of patients with knee or hip OA or with chronic LBP treated with 60 to 120 mg/day of duloxetine experiences a significant clinical improvement. Pooled data from 2 randomized, double-blind, placebo-controlled trials of duloxetine 60 and 120 mg/day in 487 patients with symptomatic knee OA found that duloxetine patients were 33% more likely to respond to treatment than placebo patients ($P < 0.001$; number needed to treat or NNT = 6). Significantly more duloxetine patients than placebo patients reported 30% improvement in pain from baseline to endpoint ($P < 0.001$; NNT = 5) and improvements > 50% occurred more often in the duloxetine group ($P < 0.001$; NNT = 7). Duloxetine patients also had greater improved function ($P = 0.009$; NNT = 9). However, duloxetine patients were more likely than placebo patients to experience a treatment-emergent adverse event ($P = 0.003$, number needed to harm [NNH] = 8).

Many OA and chronic LBP patients take NSAIDs for pain. Duloxetine may be effective in combination with an NSAID. In a 10-week, randomized, double-blind, flexible-dose, placebo-controlled trial of 524 patients with knee OA on an optimized NSAID regimen (specific drug, dose, and regimen at the discretion of the investigator), patients who received duloxetine concomitantly with NSAID therapy had significantly greater pain reduction at week 8 ($P < 0.001$) improved physical function ($P < 0.001$), and better global impression of improvement ($P < 0.001$) than patients taking NSAIDs alone.

Table 1: Recent Studies of Duloxetine for Treating Chronic Pain Associated with Osteoarthritis (OA)

Study	Patients	Comparator	Methods/Description	Results	Comments
Chappell	231 knee OA patients	Placebo	13-week randomized, double-blind study	Duloxetine was superior to placebo in weekly mean 24-hour pain scores and function	AEs similar (49.5% duloxetine vs. 40.8% placebo)
Chappell	256 knee OA patients	Placebo	13-week randomized, double-blind study	Duloxetine patients had significantly greater pain reduction at all time points (P 0.001) and better function (P = 0.044) than placebo but a higher rate of treatment-emergent AEs (P 0.05)	
Sullivan	17 knee OA patients	Placebo	12-week, single-blind, placebo-controlled, run-in trial	Duloxetine did not significantly reduce pain intensity on the BPI, but did improve WOMAC pain intensity and function	Physical and functional improvements reported by patients were not observed by investigators
Wise	231 knee OA patients	Placebo	13-week randomized, double-blind study	Duloxetine patients had significantly greater pain reduction vs. placebo patients. Adverse events similar in all 3 groups	

AE, adverse event; BPI, Brief Pain Inventory; mg/d, milligrams per day; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Duloxetine: Practice point

- Starting dose: Since adverse effects, such as nausea, tend to be greater when duloxetine is initiated and then dissipate with continued use, it is advisable to start at a lower dose for at least 1 week, such as 30 mg/day, and then increase the dose to 60 mg/day as tolerated.
- Discontinuing duloxetine: Discontinuation-emergent adverse events have been reported on stopping duloxetine; therefore, a gradual reduction in the dose, rather than abrupt cessation, is recommended.
- Time course of efficacy: Improvement in pain may be seen as early as 1 week. However, to fully evaluate benefit it is advisable for the patient to use the medication for at least 1 month.
- Initial tolerability profile: A number of the adverse events associated with the use of duloxetine, including nausea, tend to be more prominent during the initial weeks of use and may then diminish with continued use. Advising the patient of this and gradual titration to the recommended dose, as well as administration with food, may improve tolerability and compliance.
- Safety with other medications: The optimal treatment of pain conditions often involves combinations of medicines with different and potentially complementary modes of action to achieve an additive effect. Therefore, in practice, it would not be unusual to simultaneously use medicines such as nonsteroidal anti-inflammatory drugs or others with analgesic properties in combination with duloxetine. Although many drugs with analgesic properties were excluded from trials of duloxetine and, thus, the effect of combination therapy has not been formally examined, it may be reasonable to use certain combinations if there appears to be an additive benefit and the drugs are safe in combination. However, an increased risk of bleeding may occur with the concomitant use of duloxetine and nonsteroidal anti-inflammatory drugs, aspirin or other drugs that affect coagulation. It is important to be cautious about the concomitant use of medicines with serotonin-enhancing effects and to not use medication that is contraindicated in combination, such as monoamine oxidase inhibitors.

Chronic painful conditions often coexist with major depressive disorder (MDD), which is another indication for duloxetine. In fact, chronic LBP and MDD can be mutually exacerbating. In an open-label study of duloxetine therapy in 30 community-dwelling older adults (60 years) with both MDD and chronic LBP, all patients who had depression remission also had a pain response; of the patients who exhibited a pain response, 50% had depression remission. In a double-blind, placebo-controlled study of 282 MDD patients, patients treated with duloxetine 60 mg qd had better (but not statistically significant) rates of pain improvement than similar patients on placebo. Improvements in pain severity were independent of the severity of depressive symptoms. A summary of recent large studies of duloxetine in treating OA appears in Table 1.

Safety & tolerability of Duloxetine: The most common treatment-emergent adverse events (5% and twice the rate of placebo in at least one pain condition) for patients with chronic pain treated with duloxetine include nausea, dry mouth, dizziness and somnolence. Adverse events with duloxetine are generally transient in nature, mild to moderate in severity and occur early in treatment.

The overall discontinuation rate owing to adverse events from the placebo-controlled trials across all chronic pain conditions (duloxetine: n=2423; placebo: n=1469) was 16.4% in duloxetine-treated patients compared with 8% in placebo-treated patients ($p<0.05$). The most common adverse events leading to discontinuation in the duloxetine group included nausea (2.6%), somnolence (1.2%), fatigue (0.9%), dizziness

(0.8%), insomnia (0.8%) and vomiting (0.6%). The rates in the placebo group were not statistically significantly different from the duloxetine group for dizziness and insomnia.The overall rate of serious adverse events was not statistically significantly different between duloxetine (2.6%) and placebo (2.5%) in the combined chronic pain studies.

Patients with chronic pain often take analgesics that may affect coagulation (e.g., NSAIDs and aspirin). A post hoc analysis of studies allowed to continue a stable regimen of NSAIDs along with Duloxetine found that the rate of all bleeding events (duloxetine: 2.34%; placebo: 2.22%) and gastrointestinal bleeding events (duloxetine: 0.29%; placebo: 0.25%) did not statistically significantly differ between patients taking duloxetine and an NSAID compared with patients taking placebo and an NSAID. However, there may be a risk of increased bleeding with the concomitant use of duloxetine and NSAIDS, aspirin or other drugs that affect coagulation.

Conclusion

Despite the wealth of analgesic options, treating arthritis-related pain is still a challenge for clinicians balancing efficacy with safety aspects. Growing understanding of the multiple mechanisms of arthritis pain has given clinicians greater appreciation for a multi-mechanistic approach. NSAIDs are effective pain relievers and helpful as add-on treatment for the painful flares of arthritis. They are not safe at high doses or for long-term use, especially in the frail and elderly. Current evidence supports the idea that OA pain is generated and maintained through continuous nociceptive input from the arthritic joint. During the progression of OA, chronic pain is modulated at different levels in the periphery and the CNS. Intervention by SNRIs, such as Duloxetine offers a novel approach in managing chronic pain due to its efficacy in age related chronic pain conditions. Malfait, A. M., & Schnitzer, T. J. (2013). Towards a mechanism-based approach to pain management in osteoarthritis. Nature Reviews Rheumatology, 9(11), 654-664.-664. Pergolizzi, J. V., Raffa, R. B., Taylor, R., Rodriguez, G., Nalamachu, S., & Langley, P. (2013). A Review of Duloxetine 60 mg Once_Daily Dosing for the Management of Diabetic Peripheral Neuropathic Pain, Fibromyalgia, and Chronic Musculoskeletal Pain Due to Chronic Osteoarthritis Pain and Low Back Pain. Pain Practice, 13(3), 239-252.

OA is a prevalent disorder characterized by the progressive destruction of articular cartilage associated with subchondral bone remodeling, formation of osteophytes, and secondary inflammation of synovial membranes. Amongst other factors contributing to pain, innervation and vascularisation of the articular cartilage may be involved, and compressive forces and hypoxia may stimulate these new nerves, causing pain even after inflammation has subsided. Innervation of the joint tissue and angiogenesis have been described as main pathophysiological pathways causing the deep joint pain described by some OA patients.

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Clinical Characteristics of Central Pain

- ❑ Pain in many different body regions
- ❑ Higher personal lifetime history of chronic pain
- ❑ Multiple somatic symptoms (e.g., fatigue, memory difficulties, sleep problem, mood disturbance)
- ❑ Sensory stimuli sensitivity (e.g., bright light, loud noises, odors, other sensations in internal organs enhanced)
- ❑ More common in women
- ❑ Strong family history of chronic pain
- ❑ Pain triggered or exacerbated by stressors
- ❑ Generally normal physical examination except for diffuse tenderness and nonspecific neurological signs

It is proposed that the classification of CS pain entails two major steps: the exclusion of neuropathic pain and the differential classification of nociceptive versus CS pain. Neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" . Neuropathic pain can be both peripheral (i.e., located in a nerve, dorsal root ganglion, or plexus) and central (located in the brain or spinal cord). Neuropathic pain is characterized by sensitization as well; peripheral and central (segmentally related) pain pathways are hyper-excitable in patients with neuropathic pain. However, on the classification of non-neuropathic CS pain, exclusion of neuropathic pain is required as the first step. Typical CS conditions like fibromyalgia, or any other chronic pain condition not due to a lesion or disease of the somatosensory system, do not satisfy the criteria for the classification of neuropathic pain. Likewise, some patients with chronic low back pain, tennis elbow, or osteoarthritis may show features of CS, but do not fit into the diagnostic criteria for neuropathic pain. The main criteria for differentiating between neuropathic and non-neuropathic CS pain are presented in Table 1.

Table 1: Differential classification between neuropathic and non-neuropathic central sensitization (CS) pain.

Neuropathic pain	Non-neuropathic CS pain
History of a lesion or disease of the nervous system	No history of a lesion or disease of the nervous system
Evidence from diagnostic investigations to reveal an abnormality of the nervous system, or post-traumatic/ postsurgical damage to the nervous system	No evidence from diagnostic investigations, or damage to the nervous system
Often related to an established medical cause like cancer, stroke, diabetes, herpes, or neurodegenerative disease	No medical cause for the pain established
Pain is neuroanatomically logical	Pain is neuroanatomically illogical, i.e., located at sites segmentally unrelated to the primary source of nociception
Pain is often described as burning, shooting, or pricking	Pain is not described as burning, shooting, or pricking, but most often as vague and dull
Location of the sensory dysfunction is neuroanatomically logica	Location of the sensory dysfunction is neuroanatomically illogical, i.e., numerous areas of hyperalgesia at sites outside and remote to the symptomatic site - at segmentally unrelated sites

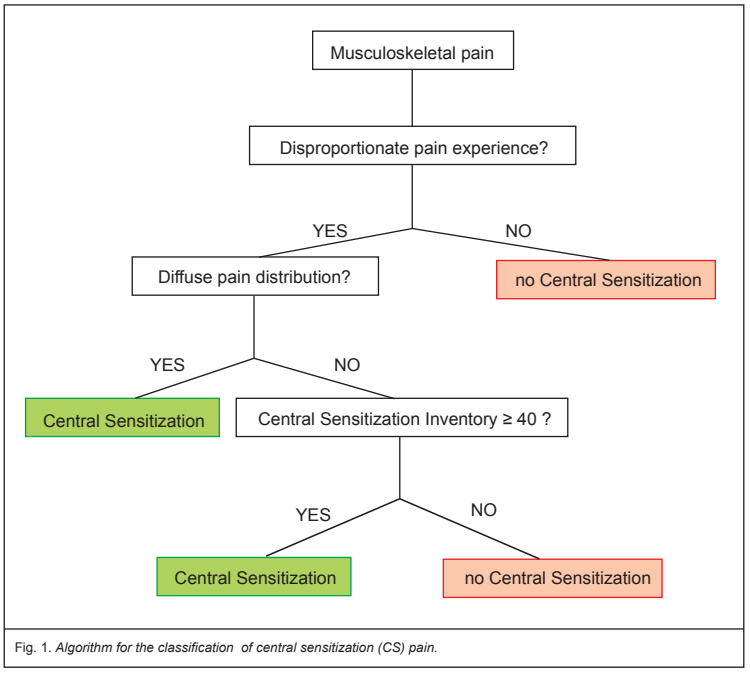

Fig. 1. *Algorithm for the classification of central sensitization (CS) pain.*

Key points

- Current evidence supports the idea that osteoarthritis (OA) pain is generated and maintained through continuous nociceptive input from the joint
- Chronic OA pain is associated with changes in the central nervous system (CNS); these changes are reversible, reflecting the plasticity of the CNS and the requirement for continuous input from the periphery
- Antibodies to nerve growth factor, which do not cross the blood-brain barrier and therefore act entirely through effects in the periphery, are effective at relieving OA pain
- OA pain pathways can also respond to modulation centrally, as exemplified by data from OA pain trials with duloxetine, thus offering opportunity for the identification of new targets for pain relief
- Heterogeneity in the clinical presentation of OA pain and in the response to analgesic therapies suggests that, in the future, distinct mechanism-based therapeutic approaches could be tailored to specific subsets of patients

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For further information: **Product Management Department,** Square Centre, 48 Mohakhali C/A, Dhaka-1212 ***web:*** www.squarepharma.com.bd

Prepared by : **Rains.com,** Dewan Complex (1st Floor), 60/E/1, Purana Paltan, Dhaka-1000, Cell : 01715380902, e-mail: rains.com2013@gmail.com