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TIZANIDINE IN THE MANAGEMENT OF MUSCULOSKELETAL PAIN, WITH PARTICULAR EMPHASIS ON BACK PAIN: MECHANISM OF ACTION, EFFICACY, SAFETY, AND CLINICAL USE – A LITERATURE REVIEW

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ABSTRACT

Musculoskeletal pain, including back pain, is a leading cause of disability worldwide and often coexists with increased paraspinal muscle tension and painful muscle spasm. This narrative review aimed to summarize current knowledge on the mechanism of action, clinical efficacy, safety profile, and clinical use of tizanidine in musculoskeletal pain, with particular emphasis on back pain. The review included clinical trials, systematic reviews, case reports, clinical practice guidelines, prescribing information, and toxicological data concerning tizanidine. Tizanidine is a centrally acting alpha-2 adrenergic receptor agonist that inhibits polysynaptic spinal reflexes and exhibits both antispastic and antispasmodic effects, with possible involvement of imidazoline receptors. Earlier studies suggested that adding tizanidine to nonsteroidal anti-inflammatory drugs may improve outcomes in acute low back pain, whereas more recent randomized trials did not confirm additional clinical benefit. The most common adverse effects include drowsiness, dry mouth, hypotension, dizziness, and weakness. Rare but serious adverse effects include hallucinations, bradycardia, hepatotoxicity, and withdrawal symptoms after abrupt discontinuation. Strong CYP1A2 inhibitors, especially ciprofloxacin and fluvoxamine, markedly increase the risk of hypotension and excessive sedation. Evidence on the efficacy of tizanidine remains inconsistent. Tizanidine is not a first-line treatment but may be considered as short-term adjunctive therapy in selected patients when a muscular component is clinically relevant.

KEYWORDS

Tizanidine, Musculoskeletal Pain, Low Back Pain, Skeletal Muscle Relaxants

CITATION

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Introduction

In 2020, musculoskeletal disorders, including back pain, constituted the second leading cause of non-fatal disability worldwide and affected more than 1.63 billion people. This group comprises five major categories of musculoskeletal disorders, including rheumatoid arthritis, osteoarthritis, low back pain, neck pain, and gout. A sixth category comprises other musculoskeletal disorders, encompassing a broad range of other acute and chronic conditions affecting the musculoskeletal system and connective tissue, including bones, joints, ligaments, tendons, and muscles (Gill et al., 2023). Chronic musculoskeletal pain is defined as pain originating from bones, joints, muscles, or related soft tissues that persists for longer than three months. This condition is one of the leading causes of disability worldwide and affects approximately 22% of the global population. Chronic musculoskeletal pain represents a significant therapeutic challenge, as symptoms persist in 79–92% of patients even 12 years after diagnosis and initiation of treatment. In many patients, chronic pain leads to moderate or severe disability, reduced quality of life, and an increased risk of chronic diseases, including cardiovascular disease, diabetes, and cancer. Acute musculoskeletal pain is common. Pain and the accompanying functional limitation usually resolve within three months, reflecting the recovery of damaged or irritated musculoskeletal structures during this period. The mechanisms underlying chronic musculoskeletal pain differ from those of acute pain. Chronic pain may be underpinned by hypersensitivity of the nervous system, which produces persistent or recurrent pain despite the absence of signs of an ongoing healing process. Despite an increasingly better understanding of the mechanisms of chronic musculoskeletal pain, clinical practice continues to be dominated by an approach focused on musculoskeletal structures as the primary source of pain. Biopsychosocial strategies are typically implemented only after the initial failure of the above treatment methods (Dunn et al., 2024).

Back pain, particularly low back pain and neck pain, is among the most common forms of musculoskeletal pain and represents a significant cause of reduced functional capacity, work absenteeism, and healthcare utilization. Low back pain is an extremely common symptom worldwide and affects all age groups,

from children to the elderly (Hartvigsen et al., 2018). In 2020, the estimated number of low back pain cases worldwide was 619 million, representing a substantial increase compared with earlier data (Ferreira et al., 2023). This condition is currently the leading cause of disability worldwide. In many cases, back pain coexists with increased paraspinal muscle tension, painful muscle spasm, and restricted range of motion. The management of musculoskeletal pain, including back pain, requires a multimodal approach. Key elements of management include patient education, physical activity, physiotherapy, analgesic treatment, nonsteroidal anti-inflammatory drugs, and, in selected cases, skeletal muscle relaxants (Hartvigsen et al., 2018). Muscle relaxants, which aim to reduce muscle tension, do not replace treatment of the underlying cause or non-pharmacological management. They may serve as a component of adjunctive therapy in cases where a muscular component plays a significant clinical role.

Materials and Methods

The PubMed and Google Scholar databases were searched for publications concerning tizanidine in the context of the treatment of musculoskeletal pain and back pain. The search was conducted using the following keywords: tizanidine, musculoskeletal pain, low back pain, skeletal muscle relaxants, mechanism of action, CYP1A2 interaction, adverse effects, and drug safety, used individually and in various combinations. No time restrictions were applied in order to include both classic works on the pharmacology of tizanidine and the most recent clinical studies. The search was limited to publications in English. Randomized controlled trials, systematic reviews, case reports, and clinical practice guidelines relating to the mechanism of action, efficacy, safety, and clinical use of tizanidine were included. Additionally, prescribing information approved by the U.S. Food and Drug Administration and the LiverTox database were used as sources of regulatory and toxicological data.

Mechanism of Action of Tizanidine

Tizanidine is one of the centrally acting skeletal muscle relaxants, exerting its effects primarily on polysynaptic spinal reflexes. The precise mechanism of action of tizanidine has not yet been fully elucidated; however, its effects on the central nervous system appear to be multifaceted. This action results primarily from the agonistic activity of the compound at noradrenergic alpha-2 receptors, although imidazoline receptors may also play a role. Tizanidine occupies a distinctive place among skeletal muscle relaxants, as it exhibits both antispastic and antispasmodic activity (Zhu et al., 2024). This effect may result both from a direct reduction in the release of excitatory amino acids from spinal cord interneurons and from a postsynaptic reduction in the efficacy of released excitatory neurotransmitters. Consequently, this leads to a reduction in the excitatory influence of spinal interneurons on alpha motoneurons and a decrease in their excitability. Tizanidine has also been reported to inhibit descending signal transmission pathways from the locus coeruleus to the spinal cord. Owing to a greater separation between its skeletal muscle-relaxant effect and its inhibitory effect on the central nervous system (CNS) compared with other agents, tizanidine may represent a valuable addition to the pharmacological treatment of back pain, particularly in cases where increased paraspinal muscle tension plays a significant role (Coward, 1994; Wagstaff & Bryson, 1997). Studies conducted in animal models have shown that supraspinal mechanisms may also be involved in the inhibition of spinal reflexes by tizanidine. Kino et al. indicated that this mechanism may involve imidazoline receptors, probably of the I3 type, as well as descending monoaminergic pathways (Kino et al., 2005).

Efficacy of Tizanidine in Musculoskeletal Pain, with Particular Emphasis on Back Pain

Available clinical trials on the efficacy of tizanidine in low back pain differ in terms of design, comparator treatment, and reported endpoints. The key randomized controlled trials evaluating the efficacy of tizanidine in this indication are presented in Table 1.

Table 1. Summary of randomized clinical trials assessing the efficacy of tizanidine in acute low back pain.

Study	Study design	N (randomized / analyzed)	Tizanidine dose	Intervention	Comparator	Main outcome
Berry & Hutchinson, 1988a	RCT, double-blind, placebo-controlled	112 / 96 completed	4 mg TID for 7 days	Tizanidine	Placebo	Significantly lower rescue aspirin consumption in the tizanidine group ($p = 0.037$); no significant between-group difference in pain intensity (VAS) at rest, at night, or on movement
Berry & Hutchinson, 1988b	RCT, double-blind, multicenter	105 / 97 with evaluable data	4 mg TID for 7 days	Tizanidine + ibuprofen 400 mg TID	Placebo + ibuprofen 400 mg TID	Significantly better treatment helpfulness rating ($p = 0.05$) and faster improvement in pain on walking ($p = 0.029$) and sciatica ($p = 0.039$) at day 3; overall VAS scores for pain at night/rest did not differ significantly
Pareek et al., 2009	RCT, double-blind, double-dummy, multicentric	197 / 185 completed	2 mg BID for 7 days	Aceclofenac 100 mg + tizanidine	Aceclofenac monotherapy	Combination therapy was significantly more effective across all pain measures ($p < 0.05$) and pain relief scores on days 3 and 7 (reported as $p = 0.00$ in the original study)
Friedman et al., 2019	RCT, double-blind, 4-arm	320 / 76 in tizanidine arm	2–4 mg as needed for 1 week	Ibuprofen + tizanidine	Ibuprofen + placebo; additional baclofen and metaxalone arms	No significant difference in RMDQ improvement vs. placebo; mean difference 0.1 points, 95% CI: −2.8 to 3.0
Hung et al., 2024	RCT, double-blind, multicenter	296 / 291 analyzed; 99 in tizanidine arm	2 mg every 6 h for 2 weeks	Diclofenac + tizanidine	Diclofenac + placebo; additional tramadol arm	No significant difference in RMDQ vs. placebo; adjusted mean difference −0.56, 95% CI: −2.48 to 1.37

Abbreviations: BID – twice daily; CI – confidence interval; RCT – randomized controlled trial; RMDQ – Roland-Morris Disability Questionnaire; TID – three times daily; VAS – Visual Analogue Scale.

Malanga et al. demonstrated that tizanidine is effective in the treatment of both acute and chronic myofascial pain syndrome. Pain, functional limitation, and muscle tenderness were substantially reduced. Sleep quality also improved significantly. According to assessments by 89% of patients and 79% of physicians, tizanidine provided good or very good pain reduction. No serious adverse events were reported. These findings suggest that tizanidine may represent a valuable treatment option for patients with myofascial pain (Malanga et al., 2002). In turn, in a systematic review comparing the efficacy and safety of skeletal muscle relaxants for the treatment of spasticity, as well as for musculoskeletal conditions accompanied by pain or muscle spasm, the authors indicated that there is moderate evidence supporting the efficacy of tizanidine compared with

placebo in patients with musculoskeletal conditions, mainly acute back or neck pain. At the same time, the available data do not allow definitive conclusions to be drawn regarding the relative efficacy or safety of tizanidine compared with other muscle relaxants. The quality of the available studies was limited, and the assessment of adverse effects was often inadequate (Chou et al., 2004). Berry and Hutchinson conducted a study involving 112 patients with acute low back pain. Patients were treated for 7 days with tizanidine or matching placebo. Acetylsalicylic acid (300 mg) was taken as needed as "rescue" medication. Patients who had not taken any medication prior to entering the study reduced their acetylsalicylic acid consumption by almost half during the first 3 days of tizanidine treatment compared with placebo. These findings indicate that tizanidine may contribute to faster recovery and reduced consumption of other nonsteroidal anti-inflammatory drugs, which could potentially reduce the risk of adverse effects, particularly gastrointestinal effects. These results suggest that tizanidine may be beneficial as a component of treatment for acute low back pain (Berry & Hutchinson, 1988a). A subsequent study by the same authors involved 105 patients with acute low back pain. The study compared 7-day therapy with tizanidine combined with ibuprofen versus treatment with ibuprofen and placebo. The results showed an advantage of combination therapy over NSAID monotherapy, particularly in terms of treatment helpfulness and faster improvement in pain on walking and sciatica symptoms. Differences in overall VAS scores for pain at night and at rest did not reach statistical significance (Berry & Hutchinson, 1988b). Similar results were obtained in patients receiving a combination of aceclofenac and tizanidine compared with those receiving aceclofenac monotherapy. The combination of an NSAID and a muscle relaxant was significantly more effective than aceclofenac alone in reducing pain intensity and improving spinal mobility (Pareek et al., 2009). A more recent study by Friedman et al. involved 320 patients with low back pain lasting no longer than two weeks, who were randomly assigned to receive either one week of therapy with ibuprofen plus placebo or ibuprofen combined with one of three skeletal muscle relaxants: baclofen, metaxalone, or tizanidine. Based on this randomized trial, the authors concluded that adding tizanidine to ibuprofen provided no additional benefit in terms of improved functioning or pain reduction after one week of therapy in patients presenting to the emergency department with acute low back pain (Friedman et al., 2019). These observations are consistent with the conclusions of a 2024 randomized trial involving 291 patients with acute low back pain and sciatica. Adding tizanidine to another NSAID, diclofenac, was not associated with significant improvement in functional capacity (Hung et al., 2024). Available data indicate that tizanidine may be beneficial in selected patients with musculoskeletal pain, particularly when increased muscle tension or painful spasm plays a significant role. At the same time, more recent randomized trials suggest that routine addition of tizanidine to nonsteroidal anti-inflammatory drugs in acute low back pain does not always translate into additional clinical benefit.

Safety Profile and Tolerability of Tizanidine

The safety profile of tizanidine results directly from its central mechanism of action, primarily its agonistic activity at alpha-2 adrenergic receptors. Adverse effects of tizanidine include drowsiness, dry mouth, hypotension, bradycardia, dizziness, fatigue, weakness, hallucinations, hepatic dysfunction, and hepatotoxicity (Zhu et al., 2024). The most commonly reported adverse effects in patients treated with tizanidine are dry mouth, drowsiness, weakness, and dizziness. Rare but serious adverse effects reported by patients include visual hallucinations and hepatic dysfunction, including hepatotoxicity (Wallace, 1994; Wagstaff & Bryson, 1997). These symptoms may limit treatment tolerability, particularly in elderly patients and those receiving multiple concomitant medications. For this reason, tizanidine should be used with caution, taking into account individual patient tolerability, comorbidities, and the risk of drug interactions. The most clinically significant adverse effects and drug interactions of tizanidine are discussed in detail below.

Drug interactions related to the metabolism of tizanidine by cytochrome P450, primarily the CYP1A2 isoenzyme, deserve particular attention. Concomitant use of tizanidine with strong CYP1A2 inhibitors, such as fluvoxamine and ciprofloxacin, should be avoided, as this may increase the risk of hypotension, psychomotor impairment, and sedation (Zhu et al., 2024). Concomitant use of tizanidine with ciprofloxacin substantially increases plasma tizanidine concentrations and may dangerously potentiate the above-mentioned adverse effects. This effect was observed particularly when ciprofloxacin was administered one hour before tizanidine (Granfors et al., 2004a). Another strong CYP1A2 inhibitor, fluvoxamine, has a similarly important effect, significantly influencing the pharmacokinetics of tizanidine by increasing both the intensity and duration of its action. Given the potentially dangerous consequences of concomitant use of this drug combination, particularly regarding the risk of hypotension and excessive sedation, their combined use should be avoided. The authors extended this recommendation to other commonly used drugs and compounds that

inhibit CYP1A2 activity, such as oral contraceptives and rofecoxib, which has since been withdrawn from the market (Granfors et al., 2004b). Villa-Zapata et al., analyzing the FAERS database, suggested that concomitant use of tizanidine and a CYP1A2 inhibitor may lead to serious health consequences resulting from a sudden decrease in blood pressure, including falls and fractures (Villa-Zapata et al., 2022). These data are corroborated by a retrospective cohort study involving 1,626 patients prescribed tizanidine and 5,012 patients prescribed cyclobenzaprine concomitantly with a strong CYP1A2 inhibitor. The study demonstrated an increased risk of hypotensive episodes, including severe hypotension, resulting from the concomitant use of tizanidine with strong CYP1A2 inhibitors in clinical practice. Cyclobenzaprine was selected as the control drug because it is a commonly used skeletal muscle relaxant with indications similar to those of tizanidine, but with a different mechanism of action and metabolism largely independent of CYP1A2 (Chaugai et al., 2019). Concomitant use of tizanidine, particularly with strong CYP1A2 inhibitors, may cause adverse effects even at standard drug doses.

The literature also describes cases of bradycardia induced by tizanidine administered as monotherapy. A particularly noteworthy case report was presented by Kikuchi et al. The authors described a 37-year-old woman who presented to the hospital with loss of consciousness. The patient had been taking 2 mg of tizanidine for two months for nocturnal neck muscle pain. On admission, electrocardiography revealed sinus bradycardia with a heart rate of approximately 30 beats per minute and a prolonged QTc interval of 495 ms. Following hospital admission, tizanidine was discontinued, and within 12 hours the heart rate normalized to a range of 70–100 beats per minute, with concurrent normalization of the QTc interval. Tizanidine-induced bradycardia was diagnosed. Although cases of tizanidine-induced bradycardia are rare, its central agonistic activity at alpha-2 adrenergic receptors may lead to a reduction in heart rate. Therefore, caution is warranted when using tizanidine, even as monotherapy (Kikuchi et al., 2024).

Another rare but serious adverse effect is hepatic dysfunction, including hepatotoxicity and, in rare cases, death. Transient, asymptomatic elevation of plasma liver enzyme activity exceeding three times the upper limit of normal occurs in approximately 5% of patients treated with tizanidine. Available review articles report cases of severe hepatotoxicity, acute liver failure, and death resulting from tizanidine use, although the number of published case reports is small. The mechanism underlying tizanidine-induced acute liver injury remains unknown but is likely idiosyncratic, resulting from individual patient hypersensitivity. Notably, recurrence of liver injury has been observed upon reintroduction of tizanidine; therefore, the drug should not be readministered in patients with a documented history of idiosyncratic tizanidine-induced liver injury (National Institute of Diabetes and Digestive and Kidney Diseases, 2017).

When deciding to initiate tizanidine therapy, particularly in the context of long-term analgesic treatment or high-dose regimens, its action as a modulator of central nervous system neurotransmitters should be taken into consideration. Abrupt discontinuation of the drug may result in withdrawal symptoms caused by excessive catecholamine release, such as increased blood pressure, tachycardia, or worsening spasticity. An individualized approach is therefore necessary, taking into account patient-specific tolerability and the risk of adverse effects (Escobar Gil et al., 2024). From a practical standpoint, tizanidine therapy should be initiated at the lowest effective dose, with cautious up-titration according to clinical response and patient tolerability. Patients should be informed about the potential for drowsiness, dizziness, and psychomotor impairment, which may limit their ability to drive or operate machinery. In cases of prolonged treatment or the emergence of symptoms suggestive of liver injury, monitoring of liver enzyme activity and reassessment of the need for continued therapy are warranted.

Clinical Use of Tizanidine in Musculoskeletal Pain

According to prescribing information, tizanidine is used primarily in the treatment of conditions involving increased muscle tone and spasticity. In the management of musculoskeletal pain, including back pain, tizanidine should be considered as short-term adjunctive therapy in selected patients, particularly in cases involving painful muscle spasm or increased muscle tension. According to prescribing information, treatment should be initiated at low doses, typically 2 mg orally every 6 to 8 hours as needed, with cautious dose escalation according to clinical response and patient tolerability. It is recommended that the dose be increased by 2–4 mg per dose every 1 to 4 days, with a maximum of three doses per 24 hours. The maximum total daily dose is 36 mg. Owing to the short duration of action of tizanidine, its administration should be timed to coincide with periods of greatest symptom severity or functional limitation. This approach helps reduce the risk of adverse effects. With prolonged use or higher doses of tizanidine, abrupt discontinuation should be avoided because of the risk of withdrawal symptoms. In patients with renal and/or hepatic impairment, caution is

warranted, and lower starting doses should be considered. If treatment intensification is required, the individual dose should be increased rather than the interval between doses shortened. Renal impairment is more common in elderly patients; therefore, caution should be exercised when selecting the dose of tizanidine in this population. Monitoring of renal function may be useful, as it can help guide appropriate selection of the starting dose and reduce the risk of adverse effects (U.S. Food and Drug Administration, 2024).

As noted by See and Ginzburg, according to the 2007 low back pain guidelines issued by the American Pain Society and the American College of Physicians, acetaminophen or nonsteroidal anti-inflammatory drugs are recommended as first-line treatment for most patients. This is based primarily on the favorable adverse-effect profile of these agents compared with other treatment options, rather than on greater efficacy. Only when first-line treatment fails should skeletal muscle relaxants, including tizanidine, as well as benzodiazepines or opioids, be considered as options that may provide additional, short-term pain relief. The available literature indicates that skeletal muscle relaxants are more effective than placebo for the short-term treatment of acute low back pain; however, there is insufficient evidence to allow a definitive comparison of their efficacy with that of first-line treatment. It has also not been clearly established which skeletal muscle relaxants should be preferred. Available evidence supports their use only in acute low back pain; therefore, these drugs should be used exclusively on a short-term basis to relieve pain. When a skeletal muscle relaxant is required, drug selection should take into account symptom severity and duration, prior treatment response, potential adverse effects, abuse potential, risk of drug interactions, expected benefits, comorbidities, and cost of treatment. The choice of a specific skeletal muscle relaxant should be individualized. When muscle tenderness or trigger points are identified on physical examination, an agent from this class may serve as a valuable adjunct to analgesic treatment of low back pain. These drugs may represent an alternative to nonsteroidal anti-inflammatory drugs in patients at high risk of gastrointestinal or renal complications (See & Ginzburg, 2008; Witenko et al., 2014).

However, the risk of central nervous system adverse effects, particularly sedation, should be borne in mind. According to the 2017 American College of Physicians clinical practice guidelines, in patients with acute or subacute low back pain, clinicians and patients should first select non-pharmacological treatment methods. These include the application of heat, massage, and acupuncture. This is consistent with rehabilitation-oriented literature emphasizing that non-pharmacological interventions, including manual therapy and massage techniques, may play a supportive role in the management of low back pain (Badyin & Khomutets, 2025). When pharmacological treatment is required, nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants should be considered. At the same time, updated data indicate that acetaminophen was not more effective than placebo in reducing pain. In patients with chronic low back pain, initial treatment should include non-pharmacological methods, including exercise, multidisciplinary rehabilitation, acupuncture, stress reduction, and motor control exercises. Non-pharmacological methods are preferred as first-line treatment for chronic low back pain because of their lower risk of adverse effects compared with pharmacological treatment (Qaseem et al., 2017).

Limitations of the Review

This paper takes the form of a narrative review. Unlike a systematic review, no structured protocol for study selection or risk-of-bias assessment of individual publications was applied. This carries a risk of subjective literature selection. In addition, the available clinical trials on the efficacy of tizanidine are characterized by considerable heterogeneity with respect to patient populations, dosing, treatment duration, and reported endpoints, which complicates direct comparison of results and precludes meta-analysis. Some of the cited studies, particularly older trials on acute low back pain, date back several decades and were conducted in relatively small patient populations, which limits the strength of the conclusions that can be drawn from them compared with more recent, methodologically rigorous randomized trials. A further limitation is the relatively small number of randomized trials directly comparing tizanidine with other skeletal muscle relaxants, which makes it difficult to clearly determine the therapeutic position of tizanidine relative to other agents in this class. Findings regarding rare but serious adverse effects, such as bradycardia and hepatotoxicity, are largely based on individual case reports, which precludes an accurate estimation of their true incidence in the general population.

Conclusions

Available data on the efficacy of tizanidine in musculoskeletal pain are inconsistent – earlier studies suggested a benefit from adding tizanidine to nonsteroidal anti-inflammatory drugs in acute low back pain, whereas more recent, larger randomized trials did not confirm this benefit. Tizanidine is not currently a first-line treatment but may be considered as short-term adjunctive therapy in selected patients, particularly when a muscular component plays a significant clinical role. The decision to use it should take into account the individual risk of adverse effects, such as drowsiness, hypotension, and, less commonly, hepatotoxicity, as well as the risk of drug interactions related to CYP1A2 metabolism. Treatment should be conducted with cautious dosing and avoidance of abrupt discontinuation.

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