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EDITORIAL



# Pharmacological considerations when treating hypertensive patients for osteoarthritis

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## 1. Introduction

Osteoarthritis (OA) is a degenerative joint disease resulting in significant pain and mobility disability. It is strongly related to age, with an estimated 10–15% of all adults over the age of 60 years old having some degree of OA, although it can affect any age group [1]. An estimated 4 in 10 patients with OA also have concomitant hypertension [2]. Evidence has demonstrated women are more likely than men to experience both conditions simultaneously, especially considering both are age-related conditions and hypertension and OA (especially knee) sex disparities increase with age [3]. Most patients will require treatment for both conditions; however, many OA pharmacotherapy options adversely affect blood pressure (BP) or the efficacy of antihypertensives, complicating treatment in this population. Recent guidelines from Osteoarthritis Research Society International (OARSI) and the American College of Rheumatology (ACR) lay out several treatment options for OA, but do not address alterations in therapy for comorbid disease states like hypertension [4,5]. Non-pharmacologic methods such as exercise, weight loss and dietary improvement are mainstays for both conditions, but drug therapy will often be required for initial and progressive management. Therefore, this review summarizes important considerations for tailoring common OA medications in patients with concomitant hypertension.

## 2. Considerations for analgesic therapies in osteoarthritis

### 2.1. NSAIDs

Oral non-steroidal anti-inflammatory drugs (NSAIDs) are considered first-line therapy for treatment of OA pain. NSAIDs are thought to produce their analgesic effect primarily by inhibiting the cyclooxygenase-2 enzyme (COX-2), resulting in decreased production of prostaglandins involved in pain and inflammation. Regardless of COX-2 isoform selectivity, the analgesic and anti-inflammatory activities of all oral NSAIDs are considered similar at equipotent dosages. Nevertheless, there does appear to be variability across NSAIDs in terms of risk of drug-induced adverse events, including effects on BP. For example, recent studies indicate essentially no meaningful change from baseline in 24-hour ambulatory systolic BP observed in celecoxib-treated patients compared to a 2–4 mmHg increase from baseline in ibuprofen- or naproxen-treated patients [6]. The COX-2 inhibitors valdecoxib and lumiracoxib appear to have similar negligible effects on BP, whereas rofecoxib and etoricoxib have been associated with greater incidence of hypertension compared with nonselective NSAIDs and placebo [7]. The antihypertensive regimen may also factor into decisions regarding oral NSAID therapy. Prostaglandin inhibition and sodium retentive effects caused by NSAIDs may blunt the effects some antihypertensives, particularly diuretics and renin-angiotensin-aldosterone system inhibitors [8], and oral NSAIDs may be less ideal in patients requiring these agents. Conversely, calcium channel blocker efficacy is not substantively affected and such combinations (CCB + NSAID) have recently come to market [8].

Topical NSAIDs such as diclofenac are available over-the-counter and are potentially efficacious alternatives for superficial joint pain (e.g. knees, hands, elbows). When applied appropriately to unbroken skin, these agents provide lower systemic exposure and fewer consequent adverse effects. Data demonstrating direct BP effects of these agents are lacking; however, topical NSAIDs are associated with reduced risk of cardiovascular events, compared to oral NSAIDs [9].

### 2.2. Acetaminophen

Acetaminophen (paracetamol) is another inexpensive and widely available agent, generally recommended as second-line treatment for OA pain. It is thought to work by inhibiting prostaglandin production in the brain and spinal cord, though efficacy in OA has been questioned in recent years. Nevertheless, acetaminophen is commonly regarded as a safe alternative to oral NSAIDs and without noteworthy effects on BP. However, evidence to the contrary dates back half a century. Some of these prior studies indicating a link

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between acetaminophen and elevated BP have had some methodologic shortcomings, but a recent randomized controlled trial clearly implicates acetaminophen in significantly increasing BP (i.e. ~4 mm Hg increase ambulatory systolic BP), after only 2 weeks of daily use. This increase is of a similar magnitude to many NSAIDs [10]. If prostaglandin inhibition does lead to decreased efficacy of certain antihypertensives as mentioned above, then acetaminophen may also exert these blunting effects.

### 2.3. Intra-articular therapy

Intraarticular injections, as an alternative to oral or topical agents, are generally effective at reducing OA pain in the short term. Options for intraarticular therapy include glucocorticoids (primarily methylprednisolone or triamcinolone) and hyaluronic acid, of which the former is preferred in consensus guidelines. Systemically administered corticosteroids are well known to increase BP, particularly with chronic use or high doses. Systemic absorption of glucocorticoids may occur after intraarticular injection and increase BP [11]. However, this effect is typically transitory and resolves within a few weeks. Nevertheless, there is some evidence to suspect that even these transitory effects impart greater risk of coronary events [12].

### 2.4. Non-opioid alternatives (duloxetine, tramadol)

Non-opioid analgesic medications may be used for OA pain and are typically recommended ahead of opioids due to their non-narcotic nature and side effect profiles. The primary two non-opioid alternatives in OA are duloxetine and tramadol.

Duloxetine is a serotonin- and norepinephrine–reuptake inhibitor (SNRI). Moderate doses have been shown to have moderate benefits on pain, function and quality of life. These effects were demonstrated in knee OA patients, but likely extrapolate to other OA joint pain modalities. In contrast to other SNRIs, i.e. venlafaxine, duloxetine appears to have minimal effect on BP, with studies suggesting a 0–2 mm Hg increase in diastolic BP [13]. Although these direct BP effects are of limited clinical significance, duloxetine can inhibit CYP2D6, thereby enhancing effects of β-blockers and, in some cases, causing clinically significant hypotension.

Tramadol is a centrally acting synthetic opioid analgesic that may also indirectly inhibit serotonin and norepinephrine reuptake [14]. Few data exist directly quantifying these BP effects of tramadol, but it is generally regarded to have little or no hypertensive effect.

### 2.5. Opioids

Opioid analgesics are reserved for later-line treatment options for severe OA pain in which alternative agents have proven ineffective. Collectively, they are not known to induce hypertensive effects directly, although they may have indirect effects through pain modulation (discussed further below). Combination products with acetaminophen have not been explicitly studied for hypertensive effects, but caution may be warranted in patients with or at risk of hypertension, given the known hypertensive effect of acetaminophen.

## 3. Expert opinion

Osteoarthritis and hypertension are common comorbidities, and the prevalence of both appears to be increasing. Unfortunately, the most frequently prescribed medications for OA are also the worst offenders in terms of direct effects on BP or interfering with antihypertensive efficacy (Table 1). Both oral NSAIDs and acetaminophen increase ambulatory systolic BP by up to 4 mmHg, on average. In general, risk of cardiovascular events increases linearly with systolic BP above 115 mmHg, and even minor elevations in systolic BP – similar to those observed with NSAIDs and acetaminophen – are associated with significant excess risk of stroke, ischemic heart disease, and other vascular mortality [15].

Considering their known efficacy for pain, relative inexpensiveness and versatility in being used on an as-needed basis, NSAIDs will continue to see use as a preferred agent in OA, even in a substantial proportion of patients with hypertension. Therefore, strategies to mitigate their BP effects should be prioritized when possible. Topical NSAIDs should be employed when feasible (e.g. superficial joints) as they have negligible BP effects. If an oral NSAID is required, COX-2 selective agents

Table 1. Common osteoarthritis therapies and their known effects on blood pressure or antihypertensive efficacy [5–7,10–12].

| Osteoarthritis treatment | Average effect on BP | Known antihypertensive interactions |
|---|---|---|
| NSAIDs | | |
| Oral, nonselective | +2-4 mmHg (SBP) | Potential for ↓ antihypertensive efficacy, (especially diuretics and RAAS inhibitors) |
| Oral, COX-2-selective | | |
| Celecoxib, valdecoxib, lumiracoxib | None | Potential for ↓ antihypertensive efficacy, (especially diuretics and RAAS inhibitors) |
| Rofecoxib, etoricoxib | +2-4 mmHg (SBP) | Potential for ↓ antihypertensive efficacy, (especially diuretics and RAAS inhibitors) |
| Topical | None | None |
| Acetaminophen | +4 mmHg (SBP) | Unknown, but possible ↓ antihypertensive efficacy (diuretics and RAAS inhibitors) |
| Intra-Articular Therapy | +4-5 mmHg (SBP) | None known |
| Duloxetine | + ≤2 mmHg (DBP) | Moderate CYP2D6 inhibition (hypotension with β-blockers) |
| Tramadol | None | None known |
| Opioids | Unknown | None known |

NSAID, non-steroidal anti-inflammatory drug; DBP, diastolic blood pressure; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

not associated with BP increases, e.g. celecoxib, may be preferred. If costs or other considerations prohibit use of these NSAIDs, then patients should be monitored closely for BP changes, with the antihypertensive regimen adjusted accordingly for the duration of NSAID therapy. Antihypertensives that do not interact with NSAIDs, such as calcium channel blockers, may also be preferred. Of note, a fixed-dose celecoxib/amlodipine combination product (Consensi) is now being marketed, but most patients are likely to be poor candidates for such therapy owing to its high costs and limited flexibility in dosing adjustments.

Acetaminophen is likewise inexpensive and widely available. However, although it has previously been considered a first-line agent for OA pain, recent guidelines have downgraded it based on lack of strong evidence of efficacy. Moreover, there is increasing concern regarding acetaminophen's adverse effects. In addition to the increased BP previously discussed, several lines of evidence suggest it may also increase risk of CV events [16]. And, there are growing concerns over acetaminophen overdose and liver toxicity, particularly given the common use of this agent in over-the-counter products and fixed-dose combination analgesic products. In general, we see relatively little upside to the continued widescale use of acetaminophen for OA, particularly at the high doses (e.g. 3–4 g/day) often recommended. Nevertheless, some individuals may find benefit with acetaminophen, and for these patients, BP should be monitored closely and relatively early after acetaminophen initiation because the hypertensive effect can manifest in as early as 1–2 weeks.

Other second-line options generally have fewer concerns with regard to hypertension. Nevertheless, even patients using these agents may require careful BP monitoring during OA therapy modification because of the complex interplay of pain (and its treatment) and BP. For example, higher severity OA knee pain has been associated with greater prevalence of hypertension [17]. Specific antihypertensive treatment recommendations, in the context of OA pain severity, have not been established. However, increased arterial stiffness may be associated with greater severity of OA pain [18], suggesting that agents with demonstrated effects on arterial stiffness (e.g. calcium channel blockers, angiotensin converting enzyme inhibitors, some β-blockers) may be considered in the setting of severe OA pain [19].

In summary, comorbid OA and hypertension requires careful attention to pharmacotherapy regimens. Prescribers must work with patients to balance between effective pain control and potential drug–drug and drug–disease interactions that often adversely affect BP control. Such balancing remains critical during ongoing management, particularly when OA regimens are substantively modified, to avoid periods of excessively high or low BP.

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