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# The effect of analgesic medications on Blood pressure

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## Abstract
The body's stress reaction causes a temporary rise in blood pressure in response to acute discomfort. Persistent hypertension may be a symptom of inadequate control of the cardiovascular and analgesic systems, both of which are common in people with chronic pain. The effects on blood pressure (BP) of analgesics might differ from one medication type to another. Multiple studies suggest that non-steroidal anti-inflammatory medicines (NSAIDs) may raise BP, with celecoxib demonstrating a lower effect, while data on paracetamol remain contentious. It has been shown that opioid medications might cause hypotension. It is possible that some adjuvants, such as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors, might increase blood pressure by strengthening the effects of the beta-adrenergic receptor.
Keywords: Blood pressure, pain, management, analgesic

## Introduction
The intricate relationship between analgesic medications and blood pressure continues to be a matter of intrigue and interest, challenging both clinicians and researchers. Pain therapy is one of the major components of health care, while analgesics encompass an extensive variety of pharmacological agents (1). However, while the pursuit of effective pain relief goes on and extends, there are potential cardiovascular risks that these agents pose to blood pressure and its regulation. Recent studies have supported the need to comprehend the cardiovascular consequences of analgesics (2). For example, Liao et al. found a relationship between nonsteroidal anti-inflammatory drugs and elevated blood pressure, with the latter having a dose-response trend, suggesting the importance of observation during clinical application (3). Moreover, Pour et al. defined the hemodynamic consequences of opioid administration such as hypotensive crises, which require a personalized interpretation. In the recent past, scientific researchers have focused on the mechanisms causing the cardiovascular effects of analgesics (4). Through the cyclooxygenase enzymes' inhibition, NSAIDs cause an imbalance in prostaglandin synthesis processes, leading to sodium retention, vasoconstriction, and disruption in renal perfusion (5). Such mechanisms were further supported by a study conducted by Zhang et al. who performed a meta-analysis to determine the pathways through which NSAIDs might lead to hypertension. Such a study aimed to help in the clinical setting in making decisions and the development of treatment protocols (6). In contrast, the cardiovascular impact of opioids has become more complex and interconnected. Even though opioids such as morphine might promote vasodilation, thus accelerating the reduction of blood pressure, histamine liberation and suppression of the sympathetic nerve may cause hypotensive catastrophes in sensitive individuals (7). These subtleties were enhanced in a systematic review by Shi et al., who compiled existing literature on this topic and called for bespoke consideration of opioid treatment in the setting of blood pressure control (8). In the

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context of this rapidly evolving field, acetaminophen has recently become a growing point of concern due to potential cardiovascular effects. While epidemiological studies published in recent years have presented a possible correlation between acetaminophen use and hypertension, the medication's safety is now increasingly questioned. Specifically, a retrospective cohort study by Xu et al. revealed a slight yet statistically significant increase in blood pressure among chronic acetaminophen recipients. These findings fuelled the current debate on acetaminophen's effect on cardiovascular health and have triggered caution in the prescription of this well-established OTC treatment (9). In the context of the complexities of addressing and assessing pain, accurate knowledge concerning the cardiovascular impacts of analgesic drugs remains essential to clinicians. This review attempted to achieve that goal by integrating the latest evidence and outlining the mechanisms involved. Ultimately, with this knowledge, healthcare practitioners can make decisions that promote ideal patient management and reduce hazardous cardiovascular events.

Acetaminophen(Paracetamol)

Paracetamol is classified as an over-the-counter medicine and is commonly used as an initial treatment for both short-term and long-term pain. Paracetamol is often regarded as a safer option for those with hypertension compared to non-steroidal anti-inflammatory medicines (NSAIDs), as it is believed to have minimal effect on blood pressure levels. However, the available research regarding the impact of paracetamol on blood pressure is lacking in strength and subject to disagreement (10).

Prior observational studies have indicated a greater likelihood of developing hypertension in individuals who take paracetamol compared to those who do not use it. These studies also imply that the risk of hypertension increases as the frequency of paracetamol usage increases (11, 12). In contrast, Kurth et al. did not report any increase in risk among paracetamol users. Nevertheless, the observational design of these investigations restricts the interpretation of causal connections (13).

There is a limited number of well-designed studies that have examined the effects of paracetamol on blood pressure, and the results of these studies are inconsistent (14). Iskander et al. found no significant alteration in blood pressure among hypertension patients who were administered 1 gram of paracetamol thrice daily (15). In a study conducted by Pavlicevic´ et al., the blood pressure effects of ibuprofen (400–600 mg, 3/day) and piroxicam (10–20 mg/day) were compared in hypertensive patients and controls who were also taking either hydrochlorothiazide/lisinopril or amlodipine. This was followed by the administration of paracetamol (1 g, thrice daily). Within the hydrochlorothiazide/lisinopril subgroup, both piroxicam and ibuprofen caused a notable increase in blood pressure, whereas blood pressure decreased during the paracetamol phase, indicating a hypotensive impact (16). Nevertheless, these effects were not validated in the subset of those using amlodipine. A clinical trial conducted on patients with coronary artery disease found that treatment with paracetamol (1 g, 3 thrice daily) for 2 weeks resulted in a notable rise in ambulatory blood pressure. The systolic blood pressure ranged from 122 to 125 mmHg, while the diastolic blood pressure ranged from 73 to 75 mmHg. The observed differences were statistically significant ($p < 0.02$) for both measurements (17). In a study conducted by Spence et al., a randomized, double-blind placebo-controlled experiment found that hypertension individuals who were given paracetamol 1 g thrice daily saw a 4 mmHg increase in systolic blood pressure (11).

Despite its widespread prescription, the pharmacodynamics of paracetamol remains largely unexplored. It is hypothesized that it functions by inhibiting the cyclo-oxygenase (COX) pathway, hence decreasing the production of prostaglandins (PGs) which are responsible for inflammation and pain (18). The potential impact of paracetamol on blood pressure may be attributed to its ability to block the formation of prostaglandins, specifically PGE2 and prostacyclin (PGI2). Both of these

molecules are powerful vasodilators, and a decrease in their levels could lead to an increase in vasoconstrictor chemicals like endothelin. PGI2 and PGE2 also have the additional effects of promoting natriuresis (sodium excretion) and reducing the release of norepinephrine. These effects may help explain the hypertensive effect of paracetamol observed in certain studies (19).

Furthermore, it is worth noting that the sodium bicarbonate present in effervescent formulations of paracetamol can contribute to fluctuations in blood pressure due to its high salt concentration (14). The transition from effervescent formulations to sodium-free tablets consistently resulted in a clinically meaningful decrease in blood pressure in older hypertensive patients. The decrease was 13 mmHg for systolic blood pressure and 2.5 mmHg for diastolic blood pressure, with both results being statistically significant ($p < 0.0001$) (20).

A recent randomized experiment examined the impact of intravenous paracetamol on the circulation of healthy individuals, presenting a distinct situation. The administration of paracetamol resulted in a temporary but notable decrease in average blood pressure (− 1.85 mmHg). This was accompanied by a decrease in systemic vascular resistance and an increase in cardiac index, indicating vasodilation (21). In critically ill patients, there have been reports of hypotension occurring after the administration of paracetamol infusion. Some writers have suggested that this may be due to a decrease in cardiac index (22, 23).

Ultimately, the impact of paracetamol on blood pressure remains a subject of debate and uncertainty. It is necessary to collect randomized data from bigger samples, with a specific focus on hypertension patients, to get relevant information. Furthermore, it is crucial to examine the impact of paracetamol on blood pressure outside of medical settings, as well as its possible interplay with antihypertensive drugs.

Non-steroidal anti-inflammatory Drugs (NSAIDs)

There is a consensus that NSAIDs might raise blood pressure levels, especially in individuals with hypertension (15, 24). A meta-analysis conducted by Bellos et al. involving 1324 individuals revealed that the use of NSAIDs was related to a 3.3 mmHg increase in mean arterial pressure. After accounting for salt intake, indomethacin and naproxen showed the highest increase in blood pressure (+3.7 and +3.6 mmHg, respectively), while piroxicam, ibuprofen, and aspirin had minimal impact on blood pressure (25). Abdu et al. conducted a meta-analysis that found comparable results, indicating that hypertension individuals who took NSAIDs saw an average increase of 5 mmHg in mean arterial pressure. Piroxicam exhibited the most significant increase in blood pressure compared to the placebo, with an increase of 6.2 mmHg. In contrast, aspirin had a negligible impact on blood pressure (26). In a prior trial of 18,790 persons with hypertension, it was consistently demonstrated that a daily dose of 75 mg of aspirin did not have any impact on antihypertensive treatment (27).

It is worth noting that while NSAIDs are known to have a decreased impact on blood pressure in individuals with normal blood pressure (28, 29), certain studies indicate that there is a higher likelihood of developing hypertension when using NSAIDs (30).

Patients who are on selective COX-2 inhibitors, such as rofecoxib and etoricoxib, may experience changes in their blood pressure (31). In comparison, celecoxib appears to have a lesser effect on office and ambulatory blood pressure levels when compared to other selective and non-selective NSAIDs (32-34). The blood pressure effects of NSAIDs are believed to be associated with the suppression of

the COX pathway, similar to paracetamol. There are two kinds of COX enzymes, known as COX-1 and 2. The first gene is expressed continuously in most tissues, whereas the second gene is mostly activated in response to inflammation and cellular damage. Specific NSAIDs selectively block the COX-2 isoform, whilst other NSAIDs may primarily block COX-1 or have an equal impact on both (35). Empirical research on animals verifies that suppressing both COX enzymes can result in an elevation in blood pressure (36). This finding offers a physiological and pathological rationale for the blood pressure effects of NSAIDs. Furthermore, it has been proposed that NSAIDs may cause an elevation in blood pressure through other mechanisms, such as an increase in the synthesis of endothelin-1 and aldosterone levels (37, 38). The hypertensive effects of NSAIDs may be more prevalent in elderly individuals, as they are more susceptible to age-related salt retention, which is further intensified by the suppression of prostaglandin synthesis (39, 40). Celecoxib, unlike other nonsteroidal anti-inflammatory drugs (NSAIDs), hinders the calcium responses in vascular smooth muscle and diminishes vascular tone, without relying on COX-2 inhibition (41, 42). The modest effect of celecoxib on blood pressure may be explained by its pharmacodynamic feature, which likely offsets the vasoconstriction caused by COX-2 inhibition (43).

It is important to note that prostaglandins (PGs) play a role in the way certain antihypertensive medications work. For example, PGs have a natriuretic effect that complements the diuretic effect of some medications. Additionally, the effects of ACE inhibitors are partially influenced by bradykinin, a molecule that causes blood vessels to dilate by inducing the release of PGs (44). Therefore, the co-administration of NSAIDs appears to have the greatest impact on ACE inhibitors, angiotensin receptor blockers, and diuretics (45). There is no evidence to suggest that the antihypertensive effect of calcium antagonists is weakened. However, some writers have noted a potential interaction with NSAIDs. The precise impact of NSAIDs on beta-blockers is still not well understood (29, 46).

To summarize, the existing data suggest that patients should be closely observed for changes in blood pressure while starting NSAID therapy, especially in older adults and those with hypertension. Research on the effects of NSAIDs on blood pressure has been concentrated on young and generally healthy persons with well-managed hypertension. However, there is a lack of data regarding elderly patients with several health conditions and/or uncontrolled hypertension.

Opioids

Regarding the hemodynamic effects of opioid medications, the existing literature primarily focuses on their immediate intravenous use in anesthesia or postoperative pain management. In this particular situation, opioids can lead to significant cardiovascular effects, such as low blood pressure and slow heart rate, especially when benzodiazepines are used together (47). There is a lack of extensive data on chronic opioid treatment. Still, it is generally stated that hypotension, orthostatic hypotension, and syncope are potential side effects of most opioid analgesics, including buprenorphine, morphine, oxycodone, fentanyl, and tapentadol (48). However, the specific process responsible for causing low blood pressure through the use of opioids is still a topic of discussion (49).

Due to their ability to release histamine, several opioids can cause a decrease in blood pressure through vasodilation mediated by histamine. Although histamine release has been proven for codeine, morphine, and pethidine (49, 50), it is stated to be minor or non-existent for fentanyl and oxycodone (51, 52). Furthermore, aside from the effects of histamine, opioid-induced hypotension can also result from a reduction in the release of sympathetic alpha-adrenergic signals, which causes the blood vessels in the periphery to widen (53, 54). Alternative mechanisms for the release of nitric oxide and the stimulation of the vagal reflex have been proposed (55, 56). The presence of hypertension may

lead to a heightened sensitivity to opioid receptor agonists or an excessive expression of opioid receptors in hypertensive individuals, which could result in more significant hypotensive effects.

Adjunctive analgesics

Antidepressants are being more commonly utilized as a supplementary treatment for chronic pain, specifically in patients experiencing neuropathic pain, migraines, and fibromyalgia. Antidepressants have been found to have an impact on blood pressure levels, although the specific effects vary depending on the class of medicine being used.

Serotonin-norepinephrine reuptake inhibitors (SNRI) and Tricyclic antidepressants (TCA) are commonly believed to cause high blood pressure and be linked to a higher likelihood of developing hypertension (57, 58). The blood pressure effects of SNRI appear to vary depending on the dosage and become more significant at dosages over the therapeutic range (59, 60). Several investigations have found no significant changes in blood pressure in patients who were given therapeutic doses of venlafaxine or duloxetine (61), providing evidence for this claim.

The increase in blood pressure associated with TCA and SNRI may be explained by the enhancement of adrenergic transmission (62). This is particularly relevant because most of the norepinephrine produced in the heart is reabsorbed by sympathetic nerves. The blocking of the reabsorption of norepinephrine by TCA and SNRI may lead to heightened sensitivity of the heart to sympathetic stimulation (63). Furthermore, the anticholinergic effect of TCA may also lead to an increase in blood pressure (64).

The blood pressure effects of selective serotonin reuptake inhibitors (SSRIs) are still uncertain. Experimental investigations suggest that SSRIs have the potential to reduce blood pressure. Specifically, citalopram, fluoxetine, and sertraline have been found to have a vasodilating impact, likely due to their ability to prevent calcium-induced vasoconstriction (65, 66). In addition, fluoxetine and paroxetine function as inhibitors of the cytochrome CYP2D6 enzyme, which may result in a decrease in the metabolic rate of hypotensive medications such as beta-blockers and nifedipine (67). Some publications propose that SSRIs may reduce sympathetic activity (68). Nevertheless, a recent study and meta-analysis concluded that SSRIs do not have an impact on blood pressure levels (69).

It may be inferred that TCA and SNRI may tend to increase blood pressure, whereas the effect of SSRI on blood pressure still needs further clarification. The investigations that were conducted primarily focused on individuals with depression, a condition that has been linked to a higher likelihood of developing hypertension. This connection complicates the interpretation of the relationship between antidepressants and blood pressure. Future research should focus on investigating the blood pressure effects of antidepressants in persons with chronic pain who have normal blood pressure as well as those who have high blood pressure (70).

In addition to antidepressants, anticonvulsants are a crucial adjunct for managing pain, especially in individuals with neuropathic pain and fibromyalgia. Gabapentinoids, specifically gabapentin, have the most compelling evidence for the treatment of chronic pain (71). On the other hand, carbamazepine is mostly beneficial in treating trigeminal neuralgia. A recent study has shown that gabapentin can cause vasodepression and bradycardia by affecting the nitric oxide pathway. Indeed, gabapentin is recognized for its ability to reduce the increase in blood pressure that occurs during laryngoscopy and tracheal intubation (72).

There is a lack of evidence on the impact of carbamazepine on blood pressure. Carbamazepine can cause severe uncontrolled hypertension, as described in several case reports. This may be due to the blocking of central noradrenergic transmission (73). Furthermore, it is important to note that carbamazepine is a powerful CYP3A4 inducer, which might lead to a reduction in the plasma levels of antihypertensive drugs by cytochrome induction. The latter method may be more significant for calcium antagonists (74).

## Conclusion

There seems to be a direct correlation between pain and blood pressure. Evidence suggests that pain and analgesic treatments may both cause a clinically relevant shift in blood pressure readings. Future research should investigate the ramifications on the prevalence of hypertension and methods of blood pressure management, since they are currently unknown.

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