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Drug-Induced Hypertension: Focus on Mechanisms and Management

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Abstract
Purpose of Review This review is intended to briefly describe the primary mechanistic pathways by which several common drugs can increase blood pressure. We also propose potential management strategies based on the underlying mechanisms responsible for the blood pressure elevation.
Recent Findings As hypertension is a significant risk factor for cardiovascular events, healthcare providers must evaluate patients' concomitant medications that may contribute to elevations in blood pressure. The presence of these medications, if not properly addressed, can lead to consequences such as an inadvertent diagnosis of hypertension, as well as the potential need for unnecessary intensification of antihypertensive regimens in those already treated.
Summary Blood pressure elevation is an unfortunate by-product of multiple medications. The substances discussed in this review can elicit significant and persistent elevations in blood pressure, and health care providers must first evaluate whether the drug is necessary. If one exists, it is best to select a similar agent with lower risk of increasing blood pressure; if unavoidable, then clinicians should select an appropriate management strategy to compensate for the rise in blood pressure.

This article is part of the Topical Collection on *Antihypertensive Agents: Mechanisms of Drug Action*

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Introduction

Hypertension is a chronic medical condition that affects nearly one third of the US population [1] and contributes yearly to 9.4 million deaths worldwide [2]. Although hypertension can be effectively managed with the use of common antihypertensive medications such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, and beta blockers (BBs), blood pressure remains uncontrolled for a large segment of the population. Hypertension may be difficult-to-control because of concomitant drugs, supplements, herbal products, or other substances that patients often co-ingest therapeutically, or recreationally. It is estimated that 58% of patients may be uncontrolled due to other medications that induce hypertension or blunt the effect of an antihypertensive [3]. This elevation in blood pressure can occur through a variety of mechanisms, most notably via volume retention, activation of sympathomimetic pathways, and direct vasoconstriction.

Drug-induced hypertension is an often reversible, or at least manageable, problem that health care providers should consider in every patient presenting with a new elevation in blood pressure and in those with existing treated hypertension but that is not controlled. The purpose of this review is to briefly examine the common medications and other substances that induce hypertension, with a focus on the underlying primary pathophysiologic mechanisms by which they elevate blood pressure. Additionally, an approach to treatment

will be outlined, which is often complicated by the fact that simply stopping the offending agent is not always an option.

Primary Mechanism #1: Volume Retention

Volume retention is one of the most well-known mechanisms responsible for drug-induced elevations in blood pressure. Several commonly used classes of medications can elevate blood pressure via this mechanism, including nonsteroidal anti-inflammatory drugs (NSAIDs), sex hormones, and corticosteroids. Volume retention induced by each of these substances occurs through slightly different pathways which will be discussed below.

Non-steroidal Anti-inflammatory Drugs (NSAIDS)

Blood pressure elevation due to chronic NSAID use is well-recognized. The underlying pathways causing volume retention are complex and multifactorial. NSAIDs inhibit cyclooxygenase-1 and 2, which decreases prostaglandin synthesis. Prostaglandins, particularly PGE2 and PGI2, are responsible for vasodilation and sodium excretion in the kidneys. Upon ingestion of an NSAID, there is decreased production of PGE2 and PGI2 causing lack of vasodilation and increased sodium retention. Sodium balance can be restored by compensatory increased excretion in the kidneys. Although NSAID-induced hypertension can occur in healthy individuals, it may be more pronounced in those with chronic kidney disease because the restoration of sodium balance is impaired. This may lead to complications such as hypertension, edema, and heart failure [4].

A meta-analysis conducted in the 1990s demonstrated that NSAIDs used for greater than 1 week in both uncomplicated hypertensive and normotensive patients elevated the blood pressure by an average of 5 mmHg [5]. The elevation across different agents appears variable. In a prospective cohort studying blood pressure elevations in patients taking NSAIDs vs acetaminophen, NSAID use was associated with a 2 mmHg increase in blood pressure. Ibuprofen, the most widely available over-the-counter NSAID, was associated with a 2.5 mmHg increase in blood pressure compared to naproxen and a 5 mmHg increase compared to celecoxib [6]. Studies have shown that piroxicam produces the largest blood pressure elevation of the NSAIDS, increasing blood pressure by an average of 6.2 mmHg, while aspirin and sulindac caused smaller changes in blood pressure of 0.61 and 2.2 mmHg, respectively [5, 7]. Diclofenac also appeared to minimally elevate systolic blood pressure by 1.6 mmHg [8]. In a study by Pope et al., indomethacin and naproxen were associated with blood pressure elevations of 4.77 and 6.19 mmHg, respectively [7]. In another study, ibuprofen, nabumetone, and celecoxib were shown to cause systolic BP elevations of 6.5, 3.8, and 3.0 mmHg, although nabumetone and celecoxib elevations were not statistically significant. Table 1 summarizes the average blood pressure elevations of specific NSAIDS as gleaned from several sources.

A retrospective cohort study conducted in 2012 examined the influence of NSAIDs added to antihypertensive regimens. The adjusted hazard ratios (HR) for the need for hypertension treatment intensification was 1.34 (95% confidence interval (CI) 1.05–1.71) for NSAIDs in general. Diclofenac and piroxicam were associated with higher risks of requiring more intensification of antihypertensive regimens, with hazard ratios of 1.79 (95% CI 1.15–2.78) and 2.02 (95% CI 1.09–3.77), respectively [10].

The risk of blood pressure elevations with COX-2 selective inhibitors does not appear to be much lower than that of nonselective NSAIDs. In a meta-analysis conducted by Chan et al., COX-2 selective NSAIDs had a relative risk (RR) of 1.49 (95% CI 1.18–1.88; $P < 0.04$) for developing new hypertension compared to placebo, and a RR of 1.12 (95% CI 0.93–1.35; $P < 0.23$) compared to nonselective NSAIDs [11]. Of the selective agents, rofecoxib, which has since been withdrawn from the market, had the greatest risk of blood pressure elevations compared to placebo (RR = 1.87 (95% CI 1.64–

Table 1 Summarized potential elevations in blood pressure due to NSAID use

Drug	BP elevation (mmHg)	Source	Patient population
Piroxicam	6.2	[5]	Unknown
Ibuprofen	6.5	[9]	Hypertensive (ACEI)
Naproxen	6.1	[7]	Hypertensive
Aspirin (dose >150 mg/day)	0.61	[7]	Hypertensive
Diclofenac	1.6	[8]	Unknown
Indomethacin	4.77	[7]	Hypertensive
Nabumetone	3.8	[9]	Hypertensive (ACEI)
Sulindac	2.2	[7]	Hypertensive
Celecoxib	3.0	[9]	Hypertensive (ACEI)

2.14; $P < 0.08$)). Celecoxib appeared to have little effect on blood pressure in this study.

Sex Hormones

Estrogens and progestins are common agents that can increase blood pressure. Estrogens and progestins are thought to increase angiotensin synthesis in the liver, therefore enhancing angiotensin II production. This increases aldosterone secretion which activates the mineralocorticoid receptor and causes sodium resorption and water retention [12].

Approximately 5% of women started on hormonal contraceptives experience hypertension. This was found when users took at least 50 mcg of estrogen and 1–4 mg of progestin [13]. Elevations in blood pressure are typically associated with older, higher-dose estrogen contraceptives. However, even the newer, lower-dose combination products containing only 20–35 mcg of estrogen can lead to elevations in blood pressure. In a case-control study comparing women taking low-dose oral estrogen progestin contraceptives with women who had never taken contraceptives, systolic blood pressure in the oral contraceptive group was increased by 8 mmHg [14]. Risk factors for the development of hypertension while on oral contraceptives include a personal history of gestational hypertension, family history of hypertension, occult renal disease, age greater than 35 years, and duration of contraceptive use. Although these risk factors can predispose a patient to hypertension, discontinuation of the contraceptive usually leads to the blood pressure decreasing to baseline within weeks [15].

This increase in blood pressure does not appear to be a feature shared by hormone replacement therapy. In fact, both oral and transdermal hormone replacement therapy in postmenopausal women appear to have no effect or have even reduced blood pressure [16–18].

Testosterone can cause blood pressure elevations via androgen receptor agonism. Activation of the androgen receptor causes increased sodium and water retention. However, in males treated for hypogonadism, systolic and diastolic blood pressures were significantly decreased with testosterone therapy by 23 and 16 mmHg, respectively [19]. This may be, in part, because testosterone deficiency can cause metabolic syndrome, and supplementing with testosterone would decrease this manifestation. Although more data is necessary to determine testosterone's effect on blood pressure, a recent retrospective cohort by Cheetham et al. demonstrated that testosterone therapy was associated with a hazard ratio of 0.67 (95% CI 0.62–0.73) for a cardiovascular event per 1000 patient years compared to those not receiving testosterone [20].

Corticosteroids

Corticosteroids include both mineralocorticoids and glucocorticoids, both of which can increase blood pressure through volume retention. Mineralocorticoids such as aldosterone and fludrocortisone regulate the fluid and electrolyte balance by increasing sodium resorption in the kidney. Glucocorticoids such as prednisone, methylprednisolone, and hydrocortisone can have some, although lower, mineralocorticoid activity, but enough to result in similar effects—mineralocorticoid receptor activation and increased sodium resorption leading to increased blood pressure [21•].

Corticosteroids increase blood pressure in a dose-dependent fashion, and it has been reported that oral cortisol at doses of 80–200 mg/day can elevate systolic blood pressure by as much as 15 mmHg [22]. A retrospective cohort study examined patients with and without hypertensive medications within a year before they were exposed to a minimum of 3 months of glucocorticoid use. For the first 3 months after initiation of the steroid, those on hypertensives did not have a significant increase in blood pressure compared to the year prior to exposure. In those not receiving antihypertensives in the year prior to glucocorticoid initiation, they had a small but significant (1 mmHg) increase in systolic blood pressure [23•]. This may suggest that prolonged use (greater than 1 month) is not associated with increases in blood pressure. However, a study comparing glucocorticoid users to non-users found the rate of cardiovascular events to be significantly higher in patients prescribed high glucocorticoid doses (≥7.5 mg/day of prednisone or equivalent) compared to those who had not received glucocorticoids. The adjusted relative risk was 2.56 per 1000 patient years (95% CI 2.18–2.99). It is important to note that cardiovascular risk was not increased in patients using less than 7.5 mg of prednisone or its equivalent daily [24].

Management of Drug-Induced Hypertension Mediated Through Volume Pathways

Although the exact pathways behind how they cause volume retention differ slightly, the management of drug-induced hypertension occurring through volume mechanisms should begin with some simple considerations. These are basic considerations and are a shared feature of all drugs elevating blood pressure, regardless of mechanism. First, is the offending drug really necessary? If the patient clearly benefits from the medication, and alternative agents are not feasible, then it is important to use the lowest dose and shortest duration possible, particularly if it is an acute condition being treated. Secondly, if there is an agent within-class that has the least reported effects, such as sulindac or diclofenac in the NSAID class, it should be used preferentially. This is particularly important if the exposure to the drug will likely be chronic. Figure 1 describes a basic approach to the evaluation of drug-induced elevations in blood pressure, as well as suggesting an appropriate management strategy based on the supposed underlying mechanism responsible.

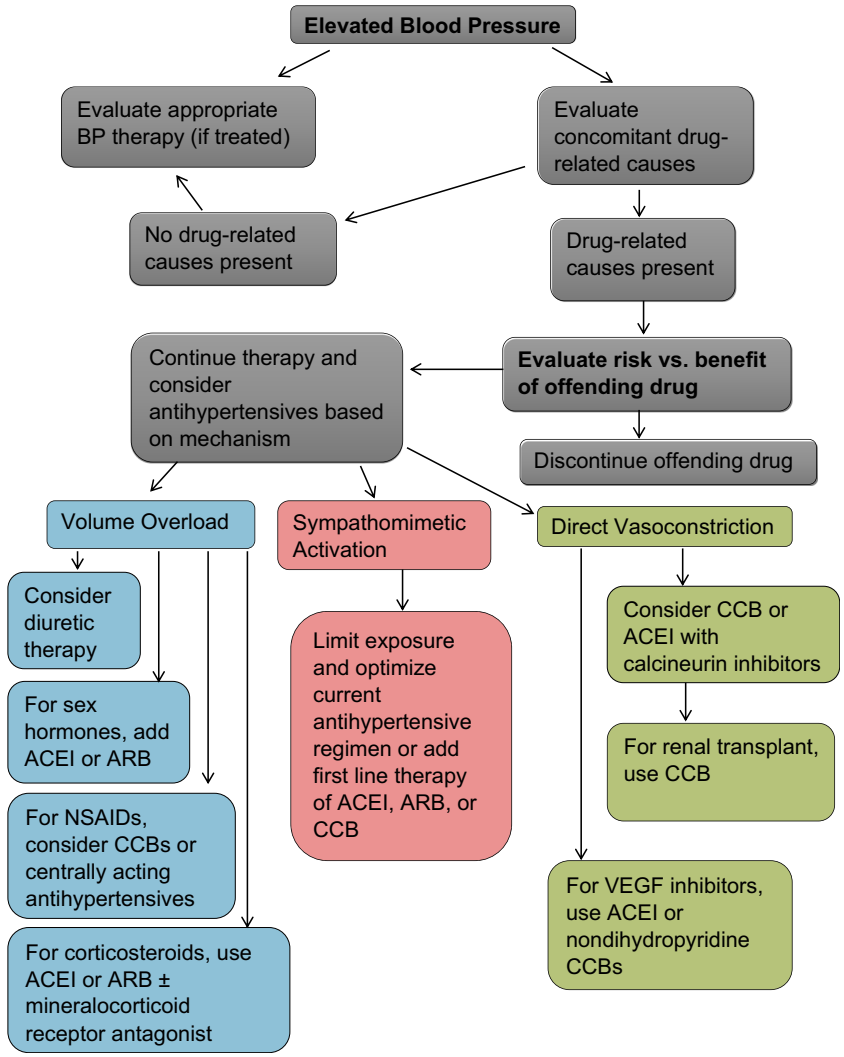

Fig. 1 Suggested algorithm for the management of drug-induced elevations in blood pressure

If it is clear that the patient will need to remain on the suspected medication or class of medications contributing to their increased blood pressure, then it may become necessary to add medication to minimize the volume retention effects. Because volume expansion is the underlying mechanism, one obvious approach to drug-induced hypertension via this mechanism is to decrease the amount of volume in the cardiovascular system. Mechanistically, this can be done by using diuretics such as chlorthalidone or hydrochlorothiazide. Any attempts at lowering volume must also be balanced with the potential risks of contributing to acute renal insufficiency through the possible hypoperfusion that may occur when NSAIDs and diuretics are used in combination. Careful assessment of electrolytes and underlying frailty of the patient can help determine the risk/benefit ratio of adding a diuretic in these patients.

If NSAID exposure is chronic and contributing to the patient's hypertension, other antihypertensive medications such as CCBs or centrally acting antihypertensives like alpha-2 agonists [4, 25] may be necessary. NSAIDs can blunt the effect of ACEIs, ARBs, and beta blockers, making them a poor first-line option for NSAID-induced hypertension [8, 26, 27]. However, they may be useful add-on agents. Choosing a CCB or a drug like clonidine may be a potential antihypertensive strategy when discontinuing the NSAID is not an option, or coadministration of a diuretic does not lower blood pressure effectively. Peripheral alpha-1 antagonists like doxazosin can be added as well, but due to their propensity to cause fluid retention themselves, should not be used as a monotherapy but ideally added if blood pressure remains uncontrolled despite adequate diuretic therapy.

In the case of drug-induced hypertension from contraceptives, the enhanced angiotensin II production they cause may make it appropriate to consider antihypertensives like ACEIs or ARBs for management. However, this strategy must recognize the potential for fetal harm if pregnancy were to occur from oral contraceptive failure, and women of child-bearing age should be counseled accordingly.

For corticosteroids, use of an antihypertensive targeting the renin-angiotensin-aldosterone system and/or the

mineralocorticoid receptor can be used in addition to diuretic therapy. Although aldosterone antagonists as monotherapy have been tried with steroids, improvements in blood pressure have not been shown with spironolactone alone [28].

Primary Mechanism #2: Sympathomimetic Activation

Decongestants

Nasal decongestants activate the sympathomimetic nervous system by stimulating the alpha-1 adrenergic receptors on vascular smooth muscle causing vasoconstriction [25]. Two common agents that increase blood pressure by this mechanism are phenylephrine and pseudoephedrine. It has been estimated that doses of 45 mg of phenylephrine can increase the systolic blood pressure by as much as 20 mmHg. It has also been shown that the bioavailability of phenylephrine is increased with coadministration of acetaminophen [29]. This poses a potential risk because many nonprescription cold remedies contain this combination.

Pseudoephedrine is a popular decongestant that is widely available over-the-counter. In a meta-analysis by Salerno et al., there appears to be a dose-dependent increase in systolic blood pressure, diastolic blood pressure, and heart rate. Pseudoephedrine use in normotensive patients caused a 0.99 mmHg increase in systolic blood pressure, compared to a 1.20 mmHg increase in hypertensive patients [30]. Interestingly, the immediate-release formulation increased systolic blood pressure by 1.53 mmHg, while sustained-release preparations had no significant effect. Longer study duration was associated with less effect on systolic blood pressure, suggesting the development of tolerance. There is evidence to suggest that standard doses of pseudoephedrine in those with well-controlled hypertension have no significant effect on blood pressure [31, 32]. Although decongestants have the potential to increase blood pressure, their use in controlled hypertensive patients is generally thought to be safe.

Caffeine

Caffeine can increase blood pressure through several mechanisms. Not only does it increase sympathetic activity but it also increases catecholamine release and antagonizes endogenous adenosine which is responsible for vasodilation of coronary vessels [33]. In a meta-analysis by Mesas et al., those that consumed 200–300 mg of caffeine had an average rise in systolic and diastolic blood pressure of 8.1 and 5.7 mmHg, respectively [34]. This increase was observed in the first hour after consumption and lasted greater than 3 h. However, when looking at those who drank coffee for 2 weeks, there were no significant differences in blood pressure at baseline and after 2 weeks. This suggests that habitual caffeine intake promotes tolerance to blood pressure elevations. Hypertensive patients are at a higher risk of worsening their blood pressure if they start consuming caffeine, but consistent intake is not associated with worse outcomes.

Cocaine

Cocaine prevents the peripheral re-uptake of norepinephrine, leaving the neurotransmitter in the synapse to excessively stimulate adrenergic receptors causing potent vasoconstriction and increased blood pressure. In a study comparing otherwise healthy regular cocaine users with non-users, regular cocaine users had an 8 mmHg higher mean systolic blood pressure [35]. In a study of non-treatment seeking cocaine users, the effect of cocaine was found to be dose-dependent. Increasing doses resulted in increased blood pressure, but subsequent administrations of the same dose did not produce increased blood pressure elevations [36]. In this same study, the blood pressures of the cocaine users started to fall towards baseline 15 min after administration. Interestingly, the route of administration can have different effects on blood pressure elevation. Intrabrachial infusion causes small changes in blood pressure while intranasal administration may cause up to an 11% increase in blood pressure [37].

Psychostimulants

Similar to cocaine, medications used to treat attention deficit hyperactivity disorder (ADHD) can cause hypertension by increasing the amount of norepinephrine in presynaptic nerve terminals causing adrenergic activation and vasoconstriction. In a study conducted in children, methylphenidate increased diastolic blood pressure by 3.9 mmHg and did not significantly affect systolic blood pressure [38]. In adults, both systolic and diastolic blood pressure may increase by 3.5 and 2.4 mmHg, respectively [39, 40]. Although stimulants are the gold standard of treatment for ADHD, little is known about the long-term cardiovascular effects of these medications. The American Heart Association (AHA) recommends periodic cardiovascular monitoring, including blood pressure, in children using methylphenidate and dextroamphetamine [41].

Antidepressants

Tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are two classes of antidepressants that have been associated with elevations in blood pressure through an increase in norepinephrine and sympathetic activity [42]. TCAs have been shown to increase both systolic and diastolic blood pressure by up to 8 mmHg compared to controls not using an antidepressant [43]. Venlafaxine, a

commonly used SNRI, has been shown to cause a dose-related increase in blood pressure. Patients taking doses of greater than 300 mg per day are three times more likely than those taking 100–200 mg per day to have diastolic blood pressures greater than 90 mmHg [44]. In a recent study in healthy volunteers, venlafaxine titrated up to 150 mg per day over 3 weeks resulted in an average increase in systolic and diastolic blood pressure of 9.1 and 4.3 mmHg as measured on day 21 [45]. Blood pressures returned to baseline once venlafaxine was discontinued.

Bupropion is another common antidepressant that has shown increases in blood pressure, in this case through dopaminergic pathways. Although there is a warning about use in those with hypertension in the package labeling, data is conflicting and recent studies have actually shown a decrease in systolic and diastolic blood pressure after initiation of bupropion. After 4 weeks of therapy with bupropion SR 150, 300, or 400 mg per day, average systolic blood pressure decreased by 6.46, 4.20, and 4.87 mmHg, respectively. Likewise, average diastolic blood pressure decreased by 2.27, 1.95, and 1.55 mmHg [46].

Although use of these agents is uncommon now, it is important to note that ingesting tyramine rich foods while on a monoamine oxidase inhibitor (MAOI) can cause hypertensive crisis. Tranylcypromine is the most likely to cause hypertension, while meclobemide, which is not approved in the USA, is least likely [47]. In a study in healthy volunteers, those taking phenylzine required only 15 mg of tyramine to increase systolic blood pressure by 30 mmHg [48].

Management of Drug-Induced Hypertension Mediated Through Sympathomimetic Activation

The most appropriate method to manage hypertension caused by sympathomimetic medications is to limit exposure (Fig. 1). In the case of decongestants where their role is typically in the acute situation, this may be relatively easy. Patients should be educated to only use decongestants for the least amount of time possible. In addition, decongestants should not be used in those with hypertension, unless their blood pressure is well-controlled. Although tolerance develops to caffeine consumption, it would be prudent for hypertensive patients to drink caffeinated beverages in moderation.

The only approved therapeutic indication for cocaine use is as a topical anesthetic; however, illicit use is a common cause for emergency department visits. Management of a patient with cocaine-induced hypertension is multifactorial. Acutely, these patients should be treated with benzodiazepines to decrease agitation and chest pain and for hemodynamic benefits. Then, nitroglycerin, nitroprusside, or intravenous phentolamine may be used if the patient's blood pressure remains elevated [49]. It is recommended to avoid beta blockers in this population until cocaine is completely cleared from the body due to unopposed alpha adrenergic stimulation which can lead to increased blood pressure and increased mortality. Once the patient is stable, cocaine cessation with psychosocial support should be initiated.

Management of ADHD and elevated blood pressures becomes complex due to the young patient population and lack of data. The European Child and Adolescent Psychiatry guidelines recommend reducing the dose or implementing a drug holiday [50]. Unfortunately, this may lead to poorly controlled ADHD. Guanfacine, and alpha-2 agonist, is a medication commonly added on to the treatment regimen in ADHD patients when psychostimulants do not sufficiently reduce symptoms. One of the side effects of guanfacine is hypotension. There have been pharmacokinetic studies showing that coadministration of guanfacine and methylphenidate results in lower blood pressures than methylphenidate alone [51]. Also, when guanfacine was used in combination with dexmethylphenidate, there was no significant increase in systolic blood pressure [52•].

Significant heterogeneity exists in response to antidepressants; thus, they are often prescribed on a trial and error basis, which can complicate the management of any drug-induced elevations in blood pressure that may result. Selective serotonin reuptake inhibitors (SSRIs) which do not have significant sympathetic activation [42] may be tried first. However, it is well known that depression is strongly correlated with coronary heart disease [53], and treating the patients' cardiovascular disease risk factors may be inevitable. Thus, the focus becomes less on the antidepressant least likely to induce blood pressure elevations and more so on controlling their multiple co-morbidities with the appropriate medications. Routine blood pressure monitoring should be done for all patients receiving antidepressants.

Primary Mechanism #3: Direct Vasoconstriction

Calcineurin Inhibitors

Cyclosporine and tacrolimus elevate blood pressure through many complex pathways. They reduce the amount of nitric oxide production, thus inhibiting vasodilation. Although the mechanisms are not fully understood, they also cause systemic and renal vasoconstriction as well as sodium retention in the kidneys [54]. In a cohort of 1267 patients who received cyclosporine after kidney transplant, 32.7% were diagnosed with hypertension 1 year post transplant [55]. Many studies have demonstrated that patients receiving cyclosporine are approximately 5–21% more likely to develop hypertension than those on tacrolimus [56–58]. According to a Cochrane review, there appears to be a dose-related effect of cyclosporine. Lower doses of 1–4 mg/kg/day increased the mean blood pressure by an average of 5 mmHg, while higher doses of

>10 mg/kg/day increased mean blood pressure by 11 mmHg on average [59].

The type of transplant also seems to have an effect on the incidence of hypertension. In bone marrow transplant patients, it has been reported that 57% of patients treated with cyclosporine experienced hypertension [60]. Furthermore, the incidence of hypertension in heart transplant patients is almost 100% [47]. This may be related to the different serum target levels and immunosuppressive doses required for each type of transplant.

Vascular Endothelial Growth Factor (VEGF) Inhibitors

One of the most common adverse effects of vascular endothelial growth factor (VEGF) inhibitors is hypertension [22]. They cause hypertension by decreasing nitric oxide production and stimulating endothelin-1 receptors which promotes vasoconstriction [61]. Common VEFG inhibitors include bevacizumab, lapatinib, sunitinib, and sorafenib. Bevacizumab, a monoclonal antibody commonly used to treat colon, rectum, kidney, and breast cancer, caused the onset of hypertension greater than 180/110 mmHg in 23% of patients [62]. When the drug was discontinued, a study in gynecologic cancers showed a median of 87 days for 82% of patients to return to baseline blood pressure [63].

An off-label indication of bevacizumab is for age-related macular degeneration. There is conflicting data with regard to systemic blood pressure elevation after intravitreal administration. Rasier et al. found increases in systolic blood pressure up to 11 mmHg in patients already diagnosed with hypertension and up to 5 mmHg in those without hypertension [64]. Lee et al. found no significant difference in blood pressure before and up to 3 weeks after administration [65].

Sorafenib, which is used to treat renal cell carcinoma and hepatocellular carcinoma, has been shown to increase systolic and diastolic blood pressure by an average of 10.8 and 8 mmHg, respectively [66]. The elevation in blood pressure was seen in the first 24 h after administration. Furthermore, in a meta-analysis, sorafenib was shown to have an overall incidence of hypertension in 23.4% of patients and severe hypertension in 5.7% of patients [67]. Sunitinib has a similar incidence of hypertension and severe hypertension as described by Zhu, et al. Hypertension and severe hypertension were found in 21.6 and 6.8% of patients [68].

Management of Drug-Induced Hypertension Mediated Through Direct Vasoconstriction

Because of the severe risks associated with rejection, discontinuing immunosuppressive therapy is not a viable option for transplant patients. Administering the lowest possible dose is preferred, but concomitant use or intensification of an antihypertensive medication may be necessary. Calcium channel blockers and ACEIs are the first line antihypertensive in patients with calcineurin-induced hypertension in cardiac transplant patients (Fig. 1) [69]. In a study in cardiac transplant patients, diltiazem both reduced blood pressure as well as the required doses of cyclosporine necessary for recommended serum levels [70]. For renal transplant patients, the recommended first-line therapy is CCBs, due to ACEI's detrimental effects on renal function [71].

Management of hypertension associated with VEGF inhibitor therapy is necessary. VEGF inhibitors are used in the treatment of certain types of cancer, so discontinuing the drug is not an option. The National Cancer Institute released a recommendation that antihypertensives should be added and titrated to a goal blood pressure of <140/90 mmHg [72]. It is advisable to reach goal blood pressure before initiation of a VEGF inhibitor. The National Cancer Institute also recommends monitoring blood pressure weekly for the first cycle of VEGF inhibitor therapy and then every 2–3 weeks for the duration of treatment. There are no specific guidelines on choice of antihypertensive, but ACEI and dihydropyridine CCBs are often used [73•].

Other Miscellaneous/Unknown Mechanisms

Dietary Supplements

The accessibility of many over-the-counter supplements has led to self-treatment for a variety of health conditions. One in seven patients admits to taking at least one herbal supplement on a weekly basis [74]. Although these products can be purchased without a prescription, they may still have serious adverse effects. Ephedra, bitter orange, and licorice, among others, are dietary supplements that have been shown to increase systolic blood pressure up to 10 mmHg [75]. Although mechanisms behind blood pressure elevation remain unknown for many dietary supplements, ephedra and bitter orange are agonists for the alpha-1 adrenergic receptor [76].

Other supplements like licorice produce increases in blood pressure by different means. The main active ingredient in licorice is glycyrrhizic acid. Glycyrrhizic acid inhibits 11-beta-hydroxysteroid dehydrogenase. This enzyme is responsible for converting cortisol to cortisone. The inhibition of 11-beta-hydroxysteroid dehydrogenase causes an excess of cortisol in the blood [22], which binds to the mineralocorticoid receptor with the same affinity as aldosterone just as in the mechanism for steroid-induced hypertension.

The most appropriate management of hypertension due to supplements is to evaluate the risk to benefit ratio. Most supplements do not have robust data to suggest that they are effective. In most cases, discontinuation of the product is necessary and blood pressure will return to baseline.

Erythropoietin (EPO)

Hypertension can develop in 20–30% of patients receiving EPO [77] and can manifest 2 weeks to 4 months after initiation of treatment [78]. Because blood pressure increases can subside after the increase in hematocrit, blood volume, and viscosity, it is thought that the mechanism behind the EPO-induced hypertension is much more complex [79]. Suggested mechanisms include rise in cytosolic calcium content in vascular smooth muscle cells, activation of the local RAS system, increased ET-1 production, decreased nitric oxide synthesis, and increased vasoconstriction. EPO increased the mean blood pressure by more than 10 mmHg and was more common in dialysis patients rather than predialysis. Forty-four percent of hemodialysis patients and 31% of chronic renal failure patients showed an increase in mean BP of ≥5 mmHg within 30 min after a single EPO injection [80].

Management for patients requiring EPO injections consists of increasing doses of current antihypertensives, delaying the next dose of EPO, adding diuretic therapy, or ultrafiltration [22]. It is important to note that it is contraindicated to initiate EPO in patients with uncontrolled hypertension. In addition, the target hemoglobin levels should be less than 11 g/dL. Erythropoiesis-stimulating agents increased the risk of serious cardiovascular events, myocardial infarction, stroke, venous thromboembolism, vascular access thrombosis, and mortality in clinical studies when administered to target hemoglobin levels >11 g/dL [81].

Alcohol

Hypertension is linked to alcoholism. The mechanism behind alcohol-induced hypertension is uncertain. It is thought that alcohol stimulates the sympathetic nervous system, activating RAAS, or abnormal calcium-mediated vasoconstriction [82]. There is a dose-dependent increase in blood pressure [83]. In the study by Yoshita et al., the systolic blood pressure increase was greater in those that consumed more than 300 g per week of alcohol (about 21 standard drinks) than in nondrinkers. The diastolic blood pressure was significantly higher in those who drank more than 200 g per week (14 standard drinks) compared to nondrinkers [83]. In those with hypertension, however, alcohol can have blood pressure lowering effects in the first 4 h after drinking, but then increases blood pressure 10–15 h later [84]. A genetic component may exist which could explain the wide variability in blood pressure elevations, but more research needs to be done.

Table 2 Drug classes causing hypertension and their primary underlying mechanism

Drug	Mechanism of hypertension
NSAIDs	Inhibit cyclooxygenase-1 and 2, which decreases prostaglandin synthesis, preventing vasodilation and sodium excretion.
Sex hormones	Increase angiotensin synthesis in the liver, therefore enhancing angiotensin II production and aldosterone secretion which activates the mineralocorticoid receptor and causes sodium resorption and water retention
Corticosteroids	Act on mineralocorticoid receptors increasing sodium resorption and fluid retention
Decongestants	Stimulate the alpha-1 adrenergic receptors on vascular smooth muscle and causing vasoconstriction
Caffeine	Increases catecholamine release, and antagonizes endogenous adenosine which is responsible for vasodilation of coronary vessels
Cocaine	Prevents the peripheral re-uptake of norepinephrine, leaving the neurotransmitter in the synapse to excessively stimulate adrenergic receptors causing potent vasoconstriction
Psychostimulants	Increase the amount of norepinephrine in presynaptic nerve terminals causing adrenergic activation and vasoconstriction
Antidepressants	Increase in norepinephrine causing adrenergic activation and increased sympathetic activity
Calcineurin Inhibitors	Reduce the amount of nitric oxide production, inhibiting vasodilation and causing systemic and renal vasoconstriction as well as sodium retention in the kidneys
VEGF Inhibitors	Decreasing nitric oxide production and stimulating endothelin-1 receptors promoting vasoconstriction
Dietary Supplements	Many mechanisms are unknown, but ephedra and bitter orange are agonists for the alpha-1 adrenergic receptor increasing sympathetic activity
EPO	Raise the cytosolic calcium content in vascular smooth muscle cells, activate the local RAAS system, increase ET-1 production, decrease nitric oxide synthesis, and increase vasoconstriction
Alcohol	Stimulates the sympathetic nervous system, activating RAAS, or abnormal calcium mediated vasoconstriction

Conclusions

Blood pressure is the most modifiable risk factor that contributes to stroke risk, and even slight increases in blood pressure can have a significant effect on cardiovascular event rates. In middle-aged adults, lowering systolic blood pressure by 2 mmHg results in about 10% lower stroke mortality and about 7% lower mortality from ischemic heart disease or other vascular causes [85]. Thus, it is imperative to examine all aspects of a patient's concomitant medications for their potential contribution to increases in blood pressure. Table 2 summarizes the mechanisms leading to hypertension of the substances discussed in this review.

In general, there are a few principles to consider when encountering use of medications that increase blood pressure (Fig. 1). First, it is important to evaluate if the drug is necessary or if there is an alternative agent that would not cause blood pressure elevation. Second, if the medication is needed, it is recommended to use the lowest effective dose as many of the blood pressure elevations are dose-dependent. Third, it is important to consider the underlying mechanism producing the blood pressure elevations. Depending on the mechanism or the drug, there may be certain antihypertensives that are better options than others, such as diuretics for volume-mediated hypertension and CCBs or ACEIs for calcineurin inhibitors.

Compliance with Ethical Standards

Conflict of Interest Drs. Lovell and Ernst declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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