RESEARCH ARTICLE

BLOOD PRESSURE INCREASES INDUCED BY IATROGENESIS, OVER THE COUNTER SUBSTANCES, AND HERBALS PRODUCTS

Authors
Sarah J. Wang, Gary E Sander, MD, PhD

Affiliation
Division of Cardiology, Department of Medicine, Tulane University Health Sciences Center, 1430 Tulane Avenue, New Orleans, LA 70112

Corresponding Author:
Gary E Sander, MD, PhD
Division of Cardiology, Department of Medicine, Tulane University Health Sciences Center, 1430 Tulane Avenue, New Orleans, LA 70112
gsander@tulane.edu
504-458-5717

AIMS AND GOALS

1. Blood pressure is ever increasingly recognized as a critical, and perhaps most important, factor in predicting cardiovascular morbidity and mortality risk. Risk increases starting from a BP of 115/75 mmHg.
2. It is important for accurate BP measurements to be made using AHA/ACC or similar recommendations and possible changes after new drugs or substances are introduced.
3. Adverse effects on BP resulting from medical personnel actions are referred as "iatrogenesis;" It is however clear that many, perhaps the majority of induced BP increases are due to the actions of the patients themselves; an example of this is increased alcohol use, which is currently being suggested as a risk factor rather than protective, even at small amounts. Thus, patients may themselves be the cause of iatrogenic actions.
4. As outlined in this review, not only approved drugs, but over the counter drugs and environmental toxins, including herbals substances, must been considered. In dealing with herbal substances, it is important to identify the active ingredients that may be present. Also possible exposure to such toxins as lead must be considered.
5. It is only by such physician efforts in correct BP measurement and monitoring can patient welfare be maximized.

ABSTRACT

A number of both prescription and over the counter drugs, herbal supplements, and miscellaneous substances can increase blood pressure in subjects by degrees that vary substantially within drug classes and individual patients; such increases often remain within the normal range but may cause overt hypertension (BP>140/90) mmHg and even precipitate hypertensive crises. Blood pressure increases are often potentiated by co-existing cardiovascular conditions, age, renal disease, diabetes, obesity, and interactions with other concomitant medications. The need to scrutinize for drugs or other substances that may be contributing to elevated blood pressures or impairing responses to anti-hypertensive medications is critically important, particularly in the evaluation of resistant and refractory hypertension. Anti-hypertensive effects of diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers may be blunted. The drugs most commonly associated with blood pressure elevations are non-steroidal anti-inflammatory agents, sympathomimetic amines, estrogen-containing oral contraceptives, certain antidepressants, angiogenesis inhibitors, and ephedra. Although most drug-induced blood pressure increases do not, in fact, lead to overt hypertension, systolic and diastolic blood pressure elevations of as little as 2 mmHg lead to significant increases in the risk of cardiovascular events. When a medication with the potential to increase blood pressure is added to a patient's therapeutic regimen, it is most important to monitor for possible changes in blood pressure even within the normal range. An initial diagnosis of hypertension should not be made until a thorough examination of all over the counter products and herbal substances that a patient may be consuming.

INTRODUCTION

Iatrogenicity is defined in the Merriam Dictionary as the "inadvertent and preventable induction of disease or complications by the medical treatment or procedures of s physician or surgeon;" It is most important that this does not imply an improper action by the medical provider. This is derived from the ancient Greek words ιατρος (physician) and γενεσιξ (origin); this problem of "first do no harm" was first acknowledged by Hippocrates (1). However, for the purpose of this review, other substances that are not drugs but that can also induce blood pressure (BP) increases such as alcohol, herbal supplements, and chemical agents will also be discussed.

It is well recognized that certain approved medications, over the counter (OTC) formulations, herbal supplements, as well as industrial chemicals can elevate BP and impair responses to anti-hypertensive treatments. (2) However, the prevalence and severity of BP changes remain difficult to define. Thus elevated BPs in individuals exposed to such molecules may artificially suggest that their hypertension represents chronic endothelial dysfunction. As such, this increase in BP is iatrogenic or induced and can be "cured" simply by removing the offending substance. It is imperative to consider the role of such substances in the evaluation of BP, particularly hypertension of recent onset, loss of control of previously adequately treated hypertension, and resistant hypertension, as has been emphasized in the JNC reports (3, 4). The so-called "iceberg effect," describes a common situation in which a substance may significantly increase BP despite the BP remaining in the "normal range" by JNC 7 or JNC Committee report

8 criteria. Recent clinical trials have suggested that an ”ideal” BP is ≤ 120/80, making even small changes above this threshold of legitimate concern. (5). For the purpose of this review hypertension will be considered as BP > 140/90 mmHg.

Significant BP increases of 20/10 mmHg, even with BP remaining ≤ 140/90 mmHg, double the cardiovascular event rate (6), and small but significant differences in event rates can be demonstrated between “high normal” and “optimal” BP (7) However, in clinical trials in which BP is not a primary endpoint but rather a safety parameter, measurements are often less carefully performed and generally qualitative rather than quantitative and there is no carefully matched control data. In the presence of a BP ≤ 140/80 recorded in a clinical situation in which BP is not a primary concern, changes within this range are easily overlooked. Even in hypertensive patients, particularly those receiving multiple agents, BP variations can be expected between physician visits and are generally considered to be of limited significance. Yet another consideration is that accentuated BP responses are observed in the presence of older age and cardiovascular or renal disease.

The more important drug classes and individual drugs that increase BP are listed in Table 1. It is critically important to recognize that many drugs within the same pharmacologic class may have very different effects on BP; one of the best examples of this are the nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)) specific inhibitors Categorization of these drugs may be rendered more difficult by the observation that certain drugs may be represented in clinical or therapeutic classes rather than pharmacological categories or appear in multiple classes; as an example, sympathomimetic agents may be considered as decongestants, stimulants, and/or weight loss medications. The major classes of drugs that may increase BP are discussed below.

NSAIDS

Perhaps the best example of drugs causing hypertension are the NSAIDs, and COX-2 inhibitors. There has been considerable discussion as to differences between these drug classes as well as among drugs within each class as to the danger of BP elevations. As early as 1994, a meta-analysis using eight databases from 50 randomized demonstrated that NSAIDs elevated supine mean BP by 5.0 mmHg (95% CI, 1.2 to 8.7 mm Hg), and antagonized the anti-hypertensive effect of beta-blockers (BP elevation, 6.2 mm Hg; CI, 1.1 to 11.4 mm Hg) more so than that of vasodilators and diuretics (8). Among NSAIDs of the COX-1 class, piroxicam produced the most marked elevation in BP (6.2 mm Hg; CI, 0.8 to 11.5 mm Hg), whereas sulindac and aspirin had the least hypertensive effect. The observed BP increases were sufficient to antagonize the BP-lowering effect of anti-hypertensive medication to an extent that may potentially increase BP into the hypertensive range. In an updated metanalysis, with 51 RCTS, it was found that for coxibs versus placebo, there was a RR of 1.49 (1.18-1.88, P = 0.04) in the development of new hypertension. For coxibs versus ns-NSAIDs, the RR was 1.12 (0.93-1.35, P = 0.23). These results were mainly driven by rofecoxib, with a RR of 1.87 (1.63-2.14, P = 0.08) versus placebo, and etoricoxib, with a RR of 1.52 (1.39-1.66, P = 0.01) versus ns-NSAID. (9)

Among 19 randomized controlled trials involving COX-2 inhibitors

published before May 2004, with a total of 45,451 participants, COX-1 and COX-2 inhibitors increased systolic/diastolic (SBP/DBP) BP compared to placebo. The COX-2 drug rofecoxib increased SBP by 2.83 mm Hg and caused a non-significantly higher risk of developing clinically important SBP elevation (RR, 1.50; 95% CI, 1.00-2.26; P = 0.05) compared with celecoxib (10). In yet another trial, celecoxib was compared with rofecoxib with naproxen in type 2 diabetes on stable anti-hypertensive regimens including ACEI or ARB using 24-hour ambulatory BP monitoring. The BP difference between rofecoxib and celecoxib was 3.78 mm Hg (95% confidence interval, 1.18-6.38; P = 0.005); between rofecoxib and naproxen, 3.85 mm Hg (95% confidence interval, 1.15-6.55; P = 0.005). 30% of patients receiving rofecoxib with controlled BP at baseline developed hypertension (p=0.05), compared to 16% on celecoxib (p=NS) and 19% on naproxen arm (p=NS) (11) Rofecoxib was clearly the outlier and has been withdrawn from the market, primarily due to an increase in the cardiovascular event rate (12), and has been included in this discussion only because of results for the agents to which it was compared and to re-enforce the risks than these drugs can present. Celecoxib is now considered to have marginal BP effect. (13)

Naproxen has been found to have the lowest relative risk of association with major vascular events and myocardial death or coronary heart disease death relative to , ibuprofen and diclofenac (14) In contrast to long-term use, short-term use of NSAIDs at low-dose does not affect BP in a meaningful way and will not increase risk of future cardiovascular events.

The BP effects of NSAIDS appear to result from inhibition of renal prostaglandins E_2 and I_2 synthesis, with subsequent sodium and fluid retention on. Elderly patients, diabetics, and patients with CKD are at increased risk of manifesting these adverse effects. Both NSAID sand COX-2 agents can blunt the BP–lowering effect of several anti-hypertensive medication classes, including diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), and β-blockers (12, 15, 16).

SYMPATHOMIMETIC AMINES (DECONGESTANTS/STIMULANTS/DIET DRUGS)

These agents, listed in Table 2, activate α adrenoreceptors, and thus might be expected to increase BP. Sympathomimetic amines pseudoephedrine and phenylpropanolamine effects on BP have been reported from a search on MEDLINE, EMBASE, and the Cochrane Library for English-language, randomized placebo-controlled trials of treatment in adults. Pseudoephedrine (24 trials with 45 treatment arms; 1285 patients) caused a small but still significant increase in SBP of 0.99 mmHg (995% CI, 0.08 to 1.90) and heart rate (HR) of 2.83 beats/min (95% CI, 2.0 to 3.6), with no effect on DBP, (0.63 mm Hg, 95% CI, -0.10 to 1.35). Patients with controlled hypertension experienced a similar SBP increase (1.20 mmHg; 95% CI, 0.56 to 1.84 mmHg) (17). Phenylpropanolamine (33 trials, 48 treatment arms, with 2165 patients) increased SBP 5.5 mmHg (95% CI: 3.1-8.0) and DBP 4.1 mmHg (95% CI: 2.2-6.0) with no effect on pulse. Patients with controlled hypertension were not at greater risk of BP elevation. Eighteen studies contained at least one treated subject≥ having BP elevations ≥ 140/90 mmHg, an increase in SBP ≥ 15 mmHg or

an increase in DBP ≥ 10 mmHg. The hypertensive effects of these sympathomimetic amines were in general more pronounced with shorter-term administration, higher doses of medication and immediate release formulations (18). Phenylethylamine is a commonly used sympathomimetic that mainly cause hyperadrenergic states with different degrees of serotonin toxicity. Beta-ketonated phenethylamines are a member of the cathinone group that is also known as "bath salts". Those with ring-substitution of the 2C and D series are direct serotonin receptor activators with comparatively less stimulant effects. Their cardiovascular effects include hypertension, chest pain, tachycardia and myocarditis.(19) Similar drugs with the potential to increase BP are pseudoephedrine, phenylephrine, oxymetazoline, and naphazoline.

Modafinil, solriamferol, and armodafinil are psychostimulants used to attenuate fatigue and promote wakefulness, particularly in patients with obstructive sleep apnea and narcolepsy. They alter autonomic cardiovascular regulation and increase HR and BP. In 12 healthy normal subjects modafinil increased resting HR (9.2±-2.0 bpm; 95% confidence interval [CI], 4.7 to 13.6; P=0.001), resting SBP (7.3±-3.2 mm Hg; 95% CI, 0.2 to 14.4; P=0.044), and resting DBP (5.3±1.7 mm Hg; 95% CI, 1.4 to 9.1 mm Hg; P<0.012), and increased plasma and urinary catecholamines (20). Solriamferol has been reported to cause hypertensive crisis in patients also receiving monamine oxidase inhibitors.

This review has focused on the propensity of chronic use of the discussed drugs and substances to increase BP, acute drug-induced hypertension, sympathomimetic toxicity, and other hyperadrenergic states can be caused by both drug toxicity as well as withdrawal. Included among these are herbal stimulants, α-2 and baclofen agonist withdrawal, and posterior reversible encephalopathy syndrome (PRES) or acute hypertensive encephalopathy (19). This entity is characterized by headache, seizures, altered mental status, and visual loss, with white matter vasogenic edema affecting posterior occipital and parietal lobes. Additionally, an unopposed central nervous system α-2 driven hypertensive response may result from concurrent use of non-vasodilator beta-1 adrenergic antagonists in the presence α-2 receptor agonists, particularly clonidine.

ANTI-OBESITY DRUGS

Observations of BP changes with the weight loss drug sibutramine, also removed from the market, illustrate the difficulty with BP assessment. Although sibutramine did not augment BP in Stage 1 or Stage 2 hypertension or isolated systolic hypertension, marked standard deviation was noted with several markedly hypertensive responses, thus indicating the variability of individual responses (21).

ORAL CONTRACEPTIVES

Most studies on BP in normotensive women have shown an increase in BP associated with oral contraceptive (OC) use (22). Two studies found an increase in SBP by 7-8 mmHg on average compared with those not using OC (23, 24). Compared with women who had never used OC, the age-adjusted OC produced a significant increase in 24-h ABPM values (from 120±3/75±2 to 128±4/81/± mmHg, P < 0.04) which was particularly evident for night-time values (from 108±/64± to 120±/73± mmHg, P < 0.02) (22). In a prospective cohort study in the United States, 68,297 female nurses aged 25 to 42 years and free of diagnosed hypertension,

diabetes, coronary heart disease, stroke, and cancer at baseline were followed up for 4 years (22). During 231,006 person-years of follow-up, 1567 incident cases of hypertension were diagnosed (23). Mildly hypertensive subjects taking low dosage estrogen-progestogen oral contraceptives exhibited significantly higher daytime and nighttime S BP values as recorded by ABPM compared to hypertensive controls not talking OCs - there was an average 8.3 mm Hg difference (95% confidence interval, 3.0 to 13.7 mm Hg; P = 0.003) for the daytime and 6.1 mm Hg difference (95% confidence interval, 0.4 to 11.8 mm Hg; P = 0.04) for the nighttime (24). These data indicated that hypertensive oral contraceptive users with the same office BP as that in hypertensive non contraceptive users have a significantly higher ambulatory SBP. The newer progestins such as drospirenone, with anti-mineralocorticoid diuretic effect, produce lower BP. In contrast, progestins such as drospirenone, with anti-mineralocorticoid diuretic effect, produce lower BP.

ANABOLIC ANDROGENIC STEROIDS (AAS)

The effects of AAS administration in combination with resistance training on BP and rate pressure product, assessed in male amateur bodybuilders and compared with the results in a morphologically matched, resistance trained control group before, during, and after the AAS cycle, included significant increases in both DBP ($P<0.01$) and mean arterial BP ($P<0.05$) from before to after training in the AAS group. Increases in BP occurred within a normal BP range, and returned to normal baseline measurements between 6 and 8 weeks post cycle. The findings indicate that the AAS group exhibited significant increases in standard cardiovascular measurements compared with the control bodybuilders (25). Other studies have shown no association between BP and AAS use. (26-28) In terms of reversible hypertension observed post-AAS use, this is most likely due to the water-sodium retention in kidney induced by AAS. In terms of irreversible hypertension, this most likely due to the atherosclerosis induced by AAS use (29)

ERYTHROPOIETIN

Recombinant human erythropoietin (rHuEPO) is yet another drug reported to induce hypertension. Of forty-one patients receiving hemodialysis (HD) and 36 patients with pre-dialysis (CRF) receiving intravenous injection of rHuEPO, mean BP was increased significantly in HD patients, but not in CRF patients (HD: 103±5 to 105±6 mmHg, $p<0.05$; CRF: 103±4 to 103±6, NS). The percentage of patients with increased mean BP of more than 10 mmHg after rHuEPO injection was significantly larger in the HD than in the CRF group (27.0% vs. 5.5%, $p<0.01$). A positive correlation was found between changes in endothelin-1 level and mean BP in the HD ($r=0.43$, $p<0.01$) but not in pre-dialysis chronic renal failure (30).

HERBAL SUPPLEMENTS

There is a most definite lack of adequate clinical information concerning efficacy and safety of herbal products. This is likely due to the fact that the majority of herbal preparations often contain differing amounts of the named herb as well as contaminating products. Herbal agents reported to increase BP are listed Table 3. Of these bitter orange, ephedra, caffeine, guarana, maté, kola, areca, lobelia, and khat appear to be the more common offenders causing not only BP elevations but a variety of additional adverse cardiovascular effects as well. Ephedra alkaloids (ma-huang) appear to

have the greatest potential to increase BP (31). Herbal supplements are used by many people with hypertension and cardiovascular diseases, and unfortunately, physicians are frequently not aware that patients are using these preparations or of what cardiovascular effects they may have. (32). . Ginseng, goldenseal, licorice, bitter orange, guarana, yohimbine, and St. John's wort have been reported to increase BP (33-35). Yohimbine, an alkaloid with stimulant and aphrodisiac effects, is an α_2-adrenergic receptor antagonist that increases BP by increasing plasma norepinephrine release from sympathetic nerve terminals and epinephrine release from the adrenal. Unmodified licorice, obtained directly from the licorice plant, contains glycyrrhizinic acid, a common ingredient in oral tobacco products, can raise BP by suppressing the metabolism of cortisol, resulting in increased stimulation of the mineralocorticoid receptor (36). Individuals with preexisting hypertension and heart disease are more sensitive to this effect. It is important to separate this product from many popular candies labeled as "licorice" that either contain no true licorice or have the glycyrrhizinic acid removed, and thus have no BP effects. Hoodia gordonii, an appetite suppressant, is widely used as an ingredient in many food supplements despite little supporting scientific evidence. Use of these products has been reported to increase BP and pulse rate, a finding that was confirmed in a placebo controlled trial (37) in which subjects receiving H. gordonii had significantly higher SBP (5.9 to 15.9 mm Hg, $p < 0.05$) and DBP (4.6 to 11.5 mm Hg, $p < 0.05$) from days 2 to 14 relative to placebo ($p < 0.05$). The mechanism appears through sympathetic nervous system activation. Arnica, a member of the sunflower family also known as mountain tobacco or leopard's bane and available OTC in pill formulation, has been used for anti-inflammatory properties, analgesic and antiseptic properties. In a randomized study, arnica has demonstrated reduction in swelling, while having the adverse effects of hypertension, cardiotoxicity, GI disturbances and muscle paralysis. Ma-huang, also known as ephedra, used for weight loss, to increase energy and for respiratory conditions such as asthma and bronchitis, contains potent alkaloids, primarily. It acts on the sympathetic nervous system and thus causes positive inotropic and chronotropic responses, increases BP and HR. One of the main adverse effects of ginseng, a common herbal supplement claimed to promote vitality and longevity, is hypertension. St. John's wort, used to treat depression and anxiety, inhibits serotonin, norepinephrine, and dopamine and acts as an MAO inhibitor. The potential side effects include hypertension from MAO activity, which can lead to hypertensive crisis when consumed with foods containing tyramine (38) and soliamfetol.

ANTI-DEPRESSANTS

Anti-depressant drugs act by altering brain catecholamine concentrations, the result of which may be an increase in BP. BP effects of anti-depressants vary widely among classes (Table 3); drugs most commonly associated with hypertensive responses include venlafaxine, bupropion, desipramine, and phenelzine A study that reviewed data from 2028 depressed subjects reported that users of tricyclic antidepressants had higher mean SBP/DBP and were more likely to have hypertension stage 1 (odds ratio: 1.90; 95% CI: 0.94 to 3.84; P=0.07) and stage 2 (odds ratio: 3.19; 95% CI: 1.35 to 7.59; P=0.008). (39) Users of noradrenergic and serotonergic working antidepressants were more likely to have hypertension stage 1.

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) INHIBITORS

VEGF pathway dysregulation has been implicated as a key mediator of neo-angiogenesis and tumor development and progression (40). VEGF signaling pathway inhibitors target the VEGF molecule, its receptor, or downstream pathways. Agents that block VEGF pathway signaling through either a monoclonal mechanism that binds to a VEGF-A isoform (eg bevacizumab) or as TKI have been demonstrated to have antitumor effects. The FDA has approved an ever-increasing number of antiangiogenic agents including bevacizumab, sunitinib, sorafenib and pazopanib. Hypertension is among the most common toxicities of this therapeutic class Table 4). Controlled trials of angiogenesis inhibitors vs placebo are not feasible due to the nature of the drugs and the disease states being treated; however, the absolute risk of developing or worsening hypertension appears to be substantial among these angiogenesis inhibitors (37, 38, 39). With recent meta-analyses reporting the incidence of hypertension induced by a single antiangiogenic agent to approximately 20% to 50% (41-44). As just one example of this, a meta-analysis evaluating a total of 4,999 patients from 13 clinical trials treated with sunitinib between 2004 through 2007 developed hypertension (42); the incidence of >140/90 mmHg and >180/110 mmHg hypertension was 21.6% (95% CI: 18.7-24.8%) and 6.8% (95% CI: 5.3-8.8%), respectively. Sunitinib was associated with a significantly increased risk of high-grade hypertension (RR=22.72, 95% CI: 4.48 to 115.29, p<0.001) relative to similar patients not receiving this drug. The incidence of hypertension associated with high-dose bevacizumab is reported as 25.4% (95% CI: 21.3–30.1%) by a meta-analysis (45);, of hypertension associated with sorafenib is 23.4% (95% CI: 16.0–32.9%) (41) and of hypertension with sunitinib is 22.5% (95% CI: 19.5–25.9%) (42). Therefore, it appears that the incidences of hypertension associated with these angiogenesis inhibitors are remarkably similar. However, single studies have reported an incidence rate as high as 87% (45).

BISPHENOL A (BPA)

BPA is a chemical used in the production of polycarbonate plastic and epoxy resins, which are used in a wide range of products, including plastic bottles, food containers, optical discs, dental fillings, and on the inner coating of cans. Urinary BPA levels were analyzed in 1380 subjects from the National Health and Nutritional Examination Survey (NHNES) 2003-2004. A positive association was observed between increasing levels of urinary BPA and hypertension independent of confounding factors such as age, gender, race/ethnicity, smoking, body mass index (BMI), diabetes mellitus and total serum cholesterol levels. Compared to tertile 1 (referent), the multivariate-adjusted odds ratio of hypertension associated with tertile 3 was 1.50 (95% CI 1.12-2.00); P_{trend} = 0.007). consistently regardless of race/ethnicity, smoking status, BMI, and diabetes mellitus. To further establish a relationship, (46) 60 adult participants were entered into a randomized crossover trial and were given the same beverage in 2 containers on a randomized sequence. Urinary BPA concentration increased after consuming canned beverages by > 1600% compared with that after consuming glass bottled beverages and SBP increased by ≈ 4.5 mmHg ($p< 0.05$), and the difference was statistically significant, demonstrating that consuming canned beverage and

consequent increase of BPA exposure increase BP acutely.

ALCOHOL

The relationship between excessive alcohol intake and increased BP has been well documented, with the initial report over 100 years ago in French soldiers drinking over 3 liters of wine daily (47), and this has since been supported by numerous epidemiologic investigations (48-50). Not surprisingly, findings are inconsistent, perhaps because of differences in duration of alcohol use and the timing of BP measurements as well as, more practically, the accuracy of patient reporting of what actually constitutes a "drink," and the type of alcohol consumed. A review published in 1987 reviewed 30 cross-sectional population studies; the majority reported small but significant elevations in BP in subjects consuming three drinks or more per day in comparison with nondrinkers (48). In 25% of studies, elevations in BP were also reported at lower levels of consumption. Paradoxically, in about 40%, the BP of nondrinkers was greater than that of those consuming one to two drinks per day. In two studies, the maximum contribution to the prevalence of hypertension of alcohol consumption greater than two drinks per day was estimated to be 5 to 7%; the contribution in men (11%) was greater than that in women because of their greater alcohol consumption. Perhaps the largest single study of BP in relation to known drinking habits was performed on 83,947 Kaiser-Permanente men and women of three races (83.5 per cent white). (48) Individuals were classified based upon health-check-up questionnaire responses as nondrinkers or according to usual daily number of drinks: two or fewer per day, three to five per day, or six or more per day. As compared to nondrinkers, BP of men taking two or fewer drinks per day were similar. Women who took two or fewer drinks per day had slightly lower pressures. Men and women who took three or more drinks per day had higher DBP in white men and in white women, and substantially higher prevalence of BP $\geq$ 160/95 mmHg. The associations of BP and drinking were independent of age, sex, race, smoking, coffee use, former "heavy" drinking, educational attainment and adiposity. A more recent systematic review reported results from trials that measured BP after a period of sustained alcohol intake (defined as daily intake of at least one alcoholic drink daily) in one group and that also had a control group of individuals who consumed no alcohol (48). Nine studies met the entrance criteria. The review demonstrated a significant rise in SBP and DBP of 2.7 mm and 1.4 mm Hg, respectively, after alcohol intake. An early effect of alcohol leading to a reduction BP (in the hours after exposure) and a later effect (next day) of raising BP led to smaller differences in the net effect of alcohol on BP when ABPM monitoring measurements were compared with casual office- or clinic-based measurements. Both "J" and "U" shaped patterns have been observed between the amount of alcohol consumed and the BP response (51).

LEAD (Pb)

Numerous observations have indicated a relationship between moderate or heavy lead exposure and high BP but inconsistency in the relationships reported. When this relationship between blood lead levels and BP was examined using data from the second National Health and Nutrition Examination Survey, a direct relationship was found between blood lead levels and systolic and diastolic BP for men and women and for white and black

persons aged 12 to 74 years. Blood lead levels were significantly higher in younger men and women (aged 21 to 55 years) with high BP, but not in older men or women (aged 56 to 74 years) (52). Significant correlations were found between blood lead and BP for each race-gender group, and blood lead levels were significantly higher in groups with DBP greater than 90 mm Hg. After adjusting for age, race, and body mass index, blood lead levels were significantly related to SBP/DBP pressures in males but not in females. These findings and those from other studies confirm the relationship of blood lead and BP at relatively low levels commonly observed in the general population. (53). Evaluation of a larger group of subjects in the Third National Health and Nutrition Examination Survey. further clarified these relationships. Data from 14 952 whites and blacks aged 18 years or older who participated indicated that mean blood lead levels were significantly higher for black men and women (5.4 and 3.4 μg/dL, respectively) compared with white men and women (4.4 and 3.0 μg/dL, respectively). Each standard deviation higher blood lead (3.3 μg/dL) was associated with a 0.82 (95% confidence interval [CI], 0.19 to 1.44) mm Hg and a 1.55 (95% CI, 0.47 to 2.64) mm Hg higher SBP among black men and women, respectively. In contrast, blood lead level was not associated with BP among white men or women. The multivariate-adjusted odds ratio (95% CI) of hypertension associated with a 1-SD higher level of blood lead was 1.08 (95% CI, 0.99 to 1.19) for black men and 1.39 (95% CI, 1.21 to 1.61) for black women. These findings suggest that increased levels of blood lead remain an important environmental risk factor for elevated BP in blacks. (54)

However, in a later review of 519 subjects with no history of definite hypertension at baseline, cross-sectional analyses revealed positive associations between SBP and bone lead levels (55). Of the 474 subjects who were free from definite hypertension at baseline and had follow-up data, 74 new cases of definite hypertension were reported. Baseline bone, but not blood, Pb levels were positively associated with incidence of hypertension. In proportional hazards models that controlled for age, age squared, body mass index, and family history of hypertension, an increase in patella (trabecular) lead from the midpoint of the lowest quintile to that of the highest quintile was associated with a rate ratio of definite hypertension of 1.71 (95% CI: 1.08 to 2.70), supporting the hypothesis that cumulative exposure to Pb, even at low levels sustained by the general population, may increase the risk of hypertension.

CONCLUSION

Many substances, including approved and over the counter drugs, herbal supplements, alcohol, and environmental toxins have been demonstrated to increase BP by a variety of mechanisms as has been described. Increases and lability in BP are often potentiated by and attributed to co-existing cardiovascular conditions and lifestyle changes such as stress. Most increases remain under the radar and within the "normal" range (<140/90 mmHg). The increasing recognition of BP as a critically important cause of cardiovascular morbidity and even mortality makes recognition of factors negatively impacting BP control of great importance in patient management. It has been established that increases in SBP/DBP beginning at 115 mmHg/75 mmHg lead to increased risk, so

even small increases that would in most circumstances go unnoticed may have negative impacts on outcomes. The so called "iceberg effect" calls attention to the observation that most induced changes remain "within normal limits," a range that has been significantly lowered with recent guidelines and may well go lower. Induction of clinical hypertension and even hypertensive crises have been reported, as outlined above. Thus it is imperative for the treating physician to carefully assess all prescribed medications, over the counter agents, alcohol use, and environmental exposures for potential effects upon BP, to monitor for possible changes in BP when a medication with the potential to increase BP is added to a patient's therapeutic regimen, and to access for interfering substances when previously stable and well controlled BP becomes less well controlled Careful attention to possible "iatrogenic" or patient induced effects upon BP is essential to optimal patient care.

REFERENCES

1. Gussak IB and Kostis JB. The concept of Iatrogenicity.. In Iatrogenesis. (ed I B Gussak and J B Kostis) RUPMNN-.
2. Giles TD SG, Fernandez C. . Iatrogenicity of Blood Pressure measurement in the Diagnosis of Hypertension. Rutgers University Press Medicine. 2018(2018):889-100.
3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42(6):1206-52.
4. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):e510-26.
5. Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015;373(22):2103-16.
6. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.
7. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med. 2001;345(18):1291-7.
8. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med. 1994;121(4):289-300.
9. Chan CC, Reid CM, Aw TJ, Liew D, Haas SJ, Krum H. Do COX-2 inhibitors raise blood pressure more than nonselective NSAIDs and placebo? An updated meta-analysis. J Hypertens. 2009;27(12):2332-41.
10. Whelton A, White WB, Bello AE, Puma JA, Fort JG. Effects of celecoxib and rofecoxib on blood pressure and edema in patients > or =65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol. 2002;90(9):959-63.
11. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352(11):1092-102.
12. Radack KL, Deck CC, Bloomfield SS. Ibuprofen interferes with the efficacy of antihypertensive drugs. A randomized, double-blind, placebo-controlled trial of ibuprofen compared with acetaminophen. Ann Intern Med. 1987;107(5):628-35.
13. Muscará MN, Vergnolle N, Lovren F, Triggle CR, Elliott SN, Asfaha S, et al. Selective cyclo-oxygenase-2 inhibition with celecoxib elevates blood pressure and promotes leukocyte adherence. Br J Pharmacol. 2000;129(7):1423-30.
14. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013;382(9894):769-79.
15. Conlin PR, Moore TJ, Swartz SL, Barr E, Gazdick L, Fletcher C, et al. Effect of indomethacin on blood pressure lowering by captopril and losartan in

hypertensive patients. Hypertension. 2000;36(3):461-5.
16. White WB, Kent J, Taylor A, Verburg KM, Lefkowith JB, Whelton A. Effects of celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibitors. Hypertension. 2002;39(4):929-34.
17. Salerno SM, Jackson JL, Berbano EP. Effect of oral pseudoephedrine on blood pressure and heart rate: a meta-analysis. Arch Intern Med. 2005;165(15):1686-94.
18. Salerno SM, Jackson JL, Berbano EP. The impact of oral phenylpropanolamine on blood pressure: a meta-analysis and review of the literature. J Hum Hypertens. 2005;19(8):643-52.
19. King A, Dimovska M, Bisoski L. Sympathomimetic Toxidromes and Other Pharmacological Causes of Acute Hypertension. Curr Hypertens Rep. 2018;20(1):8.
20. Taneja I, Diedrich A, Black BK, Byrne DW, Paranjape SY, Robertson D. Modafinil elicits sympathomedullary activation. Hypertension. 2005;45(4):612-8.
21. Jordan J, Scholze J, Matiba B, Wirth A, Hauner H, Sharma AM. Influence of Sibutramine on blood pressure: evidence from placebo-controlled trials. Int J Obes (Lond). 2005;29(5):509-16.
22. Chasan-Taber L, Willett WC, Manson JE, Spiegelman D, Hunter DJ, Curhan G, et al. Prospective study of oral contraceptives and hypertension among women in the United States. Circulation. 1996;94(3):483-9.
23. Cardoso F, Polónia J, Santos A, Silva-Carvalho J, Ferreira-de-Almeida J. Low-dose oral contraceptives and 24-hour ambulatory blood pressure. Int J Gynaecol Obstet. 1997;59(3):237-43.
24. Narkiewicz K, Graniero GR, D'Este D, Mattarei M, Zonzin P, Palatini P. Ambulatory blood pressure in mild hypertensive women taking oral contraceptives. A case-control study. Am J Hypertens. 1995;8(3):249-53.
25. Shufelt CL, Bairey Merz CN. Contraceptive hormone use and cardiovascular disease. J Am Coll Cardiol. 2009;53(3):221-31.
26. Palatini P, Giada F, Garavelli G, Sinisi F, Mario L, Michieletto M, et al. Cardiovascular effects of anabolic steroids in weight-trained subjects. J Clin Pharmacol. 1996;36(12):1132-40.
27. D'Andrea A, Caso P, Salerno G, Scarafile R, De Corato G, Mita C, et al. Left ventricular early myocardial dysfunction after chronic misuse of anabolic androgenic steroids: a Doppler myocardial and strain imaging analysis. Br J Sports Med. 2007;41(3):149-55.
28. Lenders JW, Demacker PN, Vos JA, Jansen PL, Hoitsma AJ, van 't Laar A, et al. Deleterious effects of anabolic steroids on serum lipoproteins, blood pressure, and liver function in amateur body builders. Int J Sports Med. 1988;9(1):19-23.
29. Liu JD, Wu YQ. Anabolic-androgenic steroids and cardiovascular risk. Chin Med J (Engl). 2019;132(18):2229-36.
30. Grace F, Sculthorpe N, Baker J, Davies B. Blood pressure and rate pressure product response in males using high-dose anabolic androgenic steroids (AAS). J Sci Med Sport. 2003;6(3):307-12.
31. Vora CK, Mansoor GA. Herbs and alternative therapies: relevance to hypertension and cardiovascular diseases. Curr Hypertens Rep. 2005;7(4):275-80.
32. Miyashita K, Tojo A, Kimura K, Goto A, Omata M, Nishiyama K, et al. Blood pressure response to erythropoietin

injection in hemodialysis and predialysis patients. Hypertens Res. 2004;27(2):79-84.
33. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med. 2000;343(25):1833-8.
34. Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. Ann Intern Med. 2002;136(1):42-53.
35. Mansoor GA. Herbs and alternative therapies in the hypertension clinic. Am J Hypertens. 2001;14(9 Pt 1):971-5.
36. Walker BR, Edwards CR. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. Endocrinol Metab Clin North Am. 1994;23(2):359-77.
37. Blom WA, Abrahamse SL, Bradford R, Duchateau GS, Theis W, Orsi A, et al. Effects of 15-d repeated consumption of Hoodia gordonii purified extract on safety, ad libitum energy intake, and body weight in healthy, overweight women: a randomized controlled trial. Am J Clin Nutr. 2011;94(5):1171-81.
38. Jalili J, Askeroglu U, Alleyne B, Guyuron B. Herbal products that may contribute to hypertension. Plast Reconstr Surg. 2013;131(1):168-73.
39. Licht CM, de Geus EJ, Seldenrijk A, van Hout HP, Zitman FG, van Dyck R, et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. Hypertension. 2009;53(4):631-8.
40. Niu G, Chen X. Vascular endothelial growth factor as an anti-angiogenic target for cancer therapy. Curr Drug Targets. 2010;11(8):1000-17.
41. Wu S, Chen JJ, Kudelka A, Lu J, Zhu X. Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. Lancet Oncol. 2008;9(2):117-23.
42. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. Acta Oncol. 2009;48(1):9-17.
43. An MM, Zou Z, Shen H, Liu P, Chen ML, Cao YB, et al. Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: an updated meta-analysis. Eur J Clin Pharmacol. 2010;66(8):813-21.
44. de Jesus-Gonzalez N, Robinson E, Moslehi J, Humphreys BD. Management of antiangiogenic therapy-induced hypertension. Hypertension. 2012;60(3):607-15.
45. Robinson ES, Matulonis UA, Ivy P, Berlin ST, Tyburski K, Penson RT, et al. Rapid development of hypertension and proteinuria with cediranib, an oral vascular endothelial growth factor receptor inhibitor. Clin J Am Soc Nephrol. 2010;5(3):477-83.
46. Bae S, Hong YC. Exposure to bisphenol A from drinking canned beverages increases blood pressure: randomized crossover trial. Hypertension. 2015;65(2):313-9.
47. Lian C. L'alcoholisme cdhaBANMP-.
48. MacMahon S. Alcohol consumption and hypertension. Hypertension. 1987;9(2):111-21.
49. McFadden CB, Brensinger CM, Berlin JA, Townsend RR. Systematic review of the effect of daily alcohol intake on blood pressure. Am J Hypertens. 2005;18(2 Pt 1):276-86.
50. Marchi KC, Muniz JJ, Tirapelli CR. Hypertension and chronic ethanol consumption: What do we know after a century of study? World J Cardiol. 2014;6(5):283-94.

51. Jackson R, Stewart A, Beaglehole R, Scragg R. Alcohol consumption and blood pressure. Am J Epidemiol. 1985;122(6):1037-44.
52. Harlan WR, Landis JR, Schmouder RL, Goldstein NG, Harlan LC. Blood lead and blood pressure. Relationship in the adolescent and adult US population. Jama. 1985;253(4):530-4.
53. Harlan WR. The relationship of blood lead levels to blood pressure in the U.S. population. Environ Health Perspect. 1988;78:9-13.
54. Vupputuri S, He J, Muntner P, Bazzano LA, Whelton PK, Batuman V. Blood lead level is associated with elevated blood pressure in blacks. Hypertension. 2003;41(3):463-8.
55. Cheng Y, Schwartz J, Sparrow D, Aro A, Weiss ST, Hu H. Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension: the Normative Aging Study. Am J Epidemiol. 2001;153(2):164-71.

APPENDIX

TABLE 1
ORAL AGENTS THAT INCREASE BP

Category	**Examples**
Alcohol	Beer, whiskey, wine
Anabolic steroids	norandrolone, oxymetholone, oxandrolone
Anti-depressants	venlafaxine, tricyclics (phenelzine, tranlcypromine), MAO inhibitors (phenelzine, tranlcypromine)
Chemicals	Bisphenol A, lead
Erythropoietin	rHuEPO, darbepoetin
Herbal preparations	ephedra
Immunosuppresants	cyclosporin, tacrolimus
Mineralocorticoids	Licorice (glycyrrhizic acid) , carbenoxolone, fludrocortisone, 9α-fluoroprednisolone
NSAIDS/COXIBS	ibuprofen, piroxicam, indomethacin
Oral contraceptives	estrogen containing
Stimulants	methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil, atomoxetine, dihydroergotamine, sumatriptan
Sulfonylureas	glybenclamide
Sympathomimetic amines	catecholamines and amine analogs such as phenylpropanolamine
VEGF signaling blockers Monoclonal antibodies Tyrosine kinase Inhibitors	 Bevacizumab Sunitinib, sorafenib

TABLE 2. HERBAL PREPARATIONS THAT MAY INCREASE BLOOD PRESSURE	
areca arnica bitter orange blue cohosh dong quai echinacea ephedra ginkgo biloba ginseng goldenseal guarana hootia gordonii kava	khat kola licorice lobelia ma-huang maté pennyroyal oil Scotch broom saw palmetto senna southern bayberry St. John's wort yohimbine

Table 3. THE EFFECTS OF ANTI-DEPRESSANT DRUGS ON BP		
Class	**Examples**	**BP Effect**
SSRIs	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	↔
Tricyclics	Amitriptyline, desipremine, imipramine, nortriptyline	↑
SNRIs	Venlafaxine,desvenlafaxine, duloxetine	↑↑
NDRIs	buproprion	↑
CRIRBs*	Trazodone, nefazodone, maprotiline, mirtazapine	↑↔
MAO	Isocarboxazid, phenelzine, tranlcypromine	↑
Association of hypertension with depression makes these data very difficult to quantitate * Combined reuptake inhibitors and receptor blockers		

TABLE 4. VEGF INHIBITORSTHAT MAY INCREASE BLOOD PRESSURE	
Proprietary name	Generic name
Avastin	Bevacizumab
Caprelsa	Vandetanib
Cometriq	Cabozantinib
Cyramza	Ramucirumab
Lenvima	Lenvatinib
Iclusig	Ponatinib
Inlyta	Axitinib
Nexavar	Sorafenib
Stivarga	Regorafenib
Sutent	Sunitinib
Votrient	Pazopanib
Zaltrap	Ziv-aflib

