DRUG INDUCED HYPERTENSION

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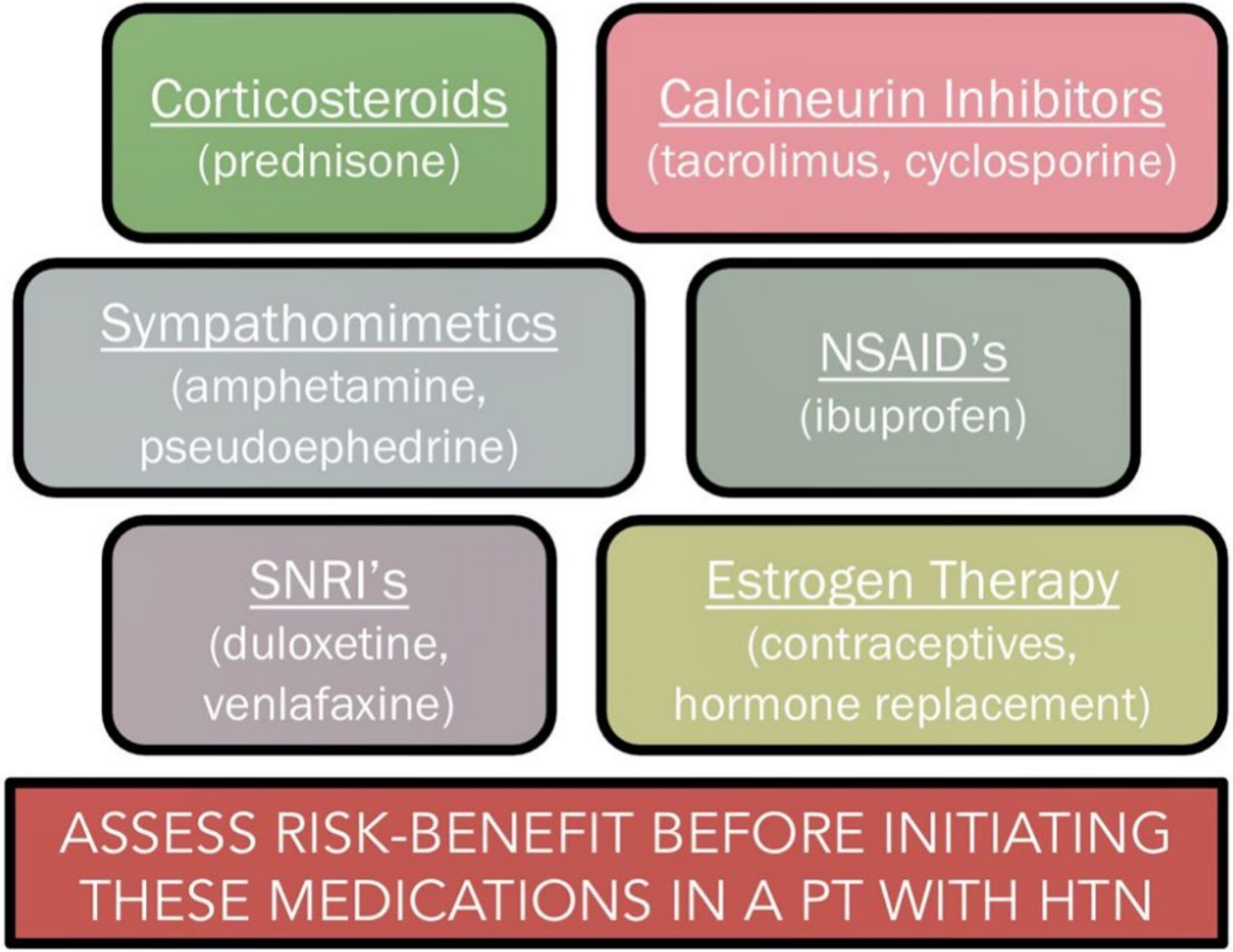
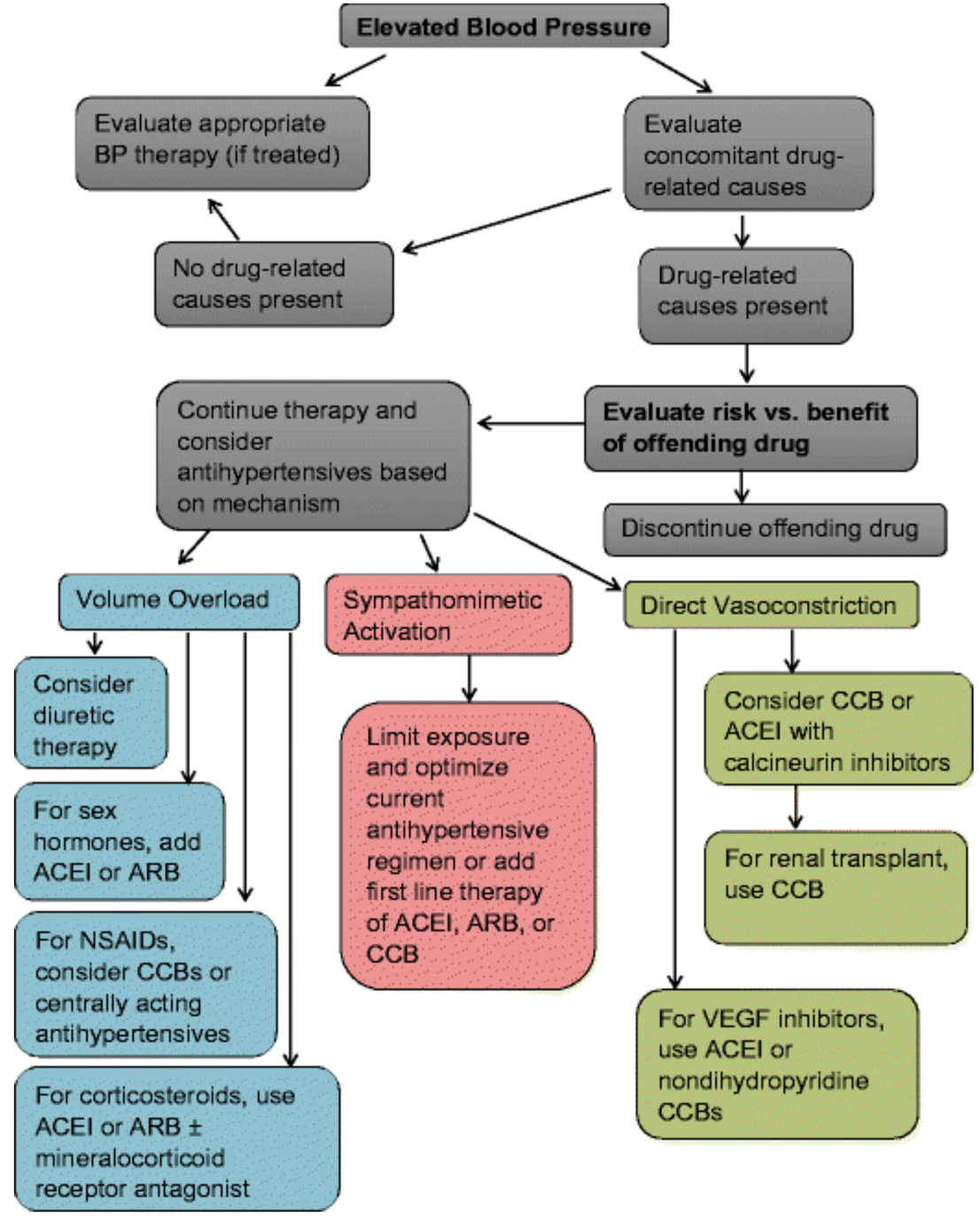
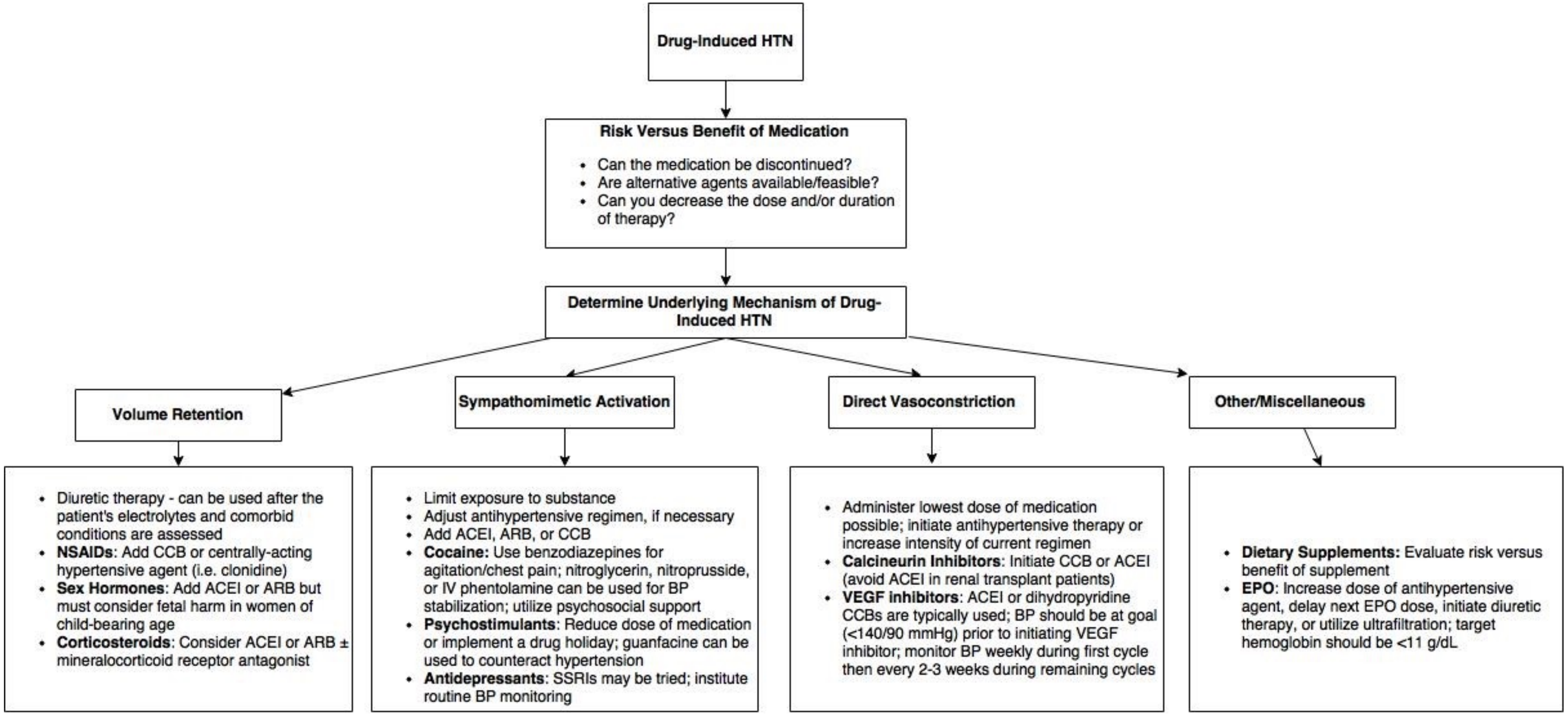
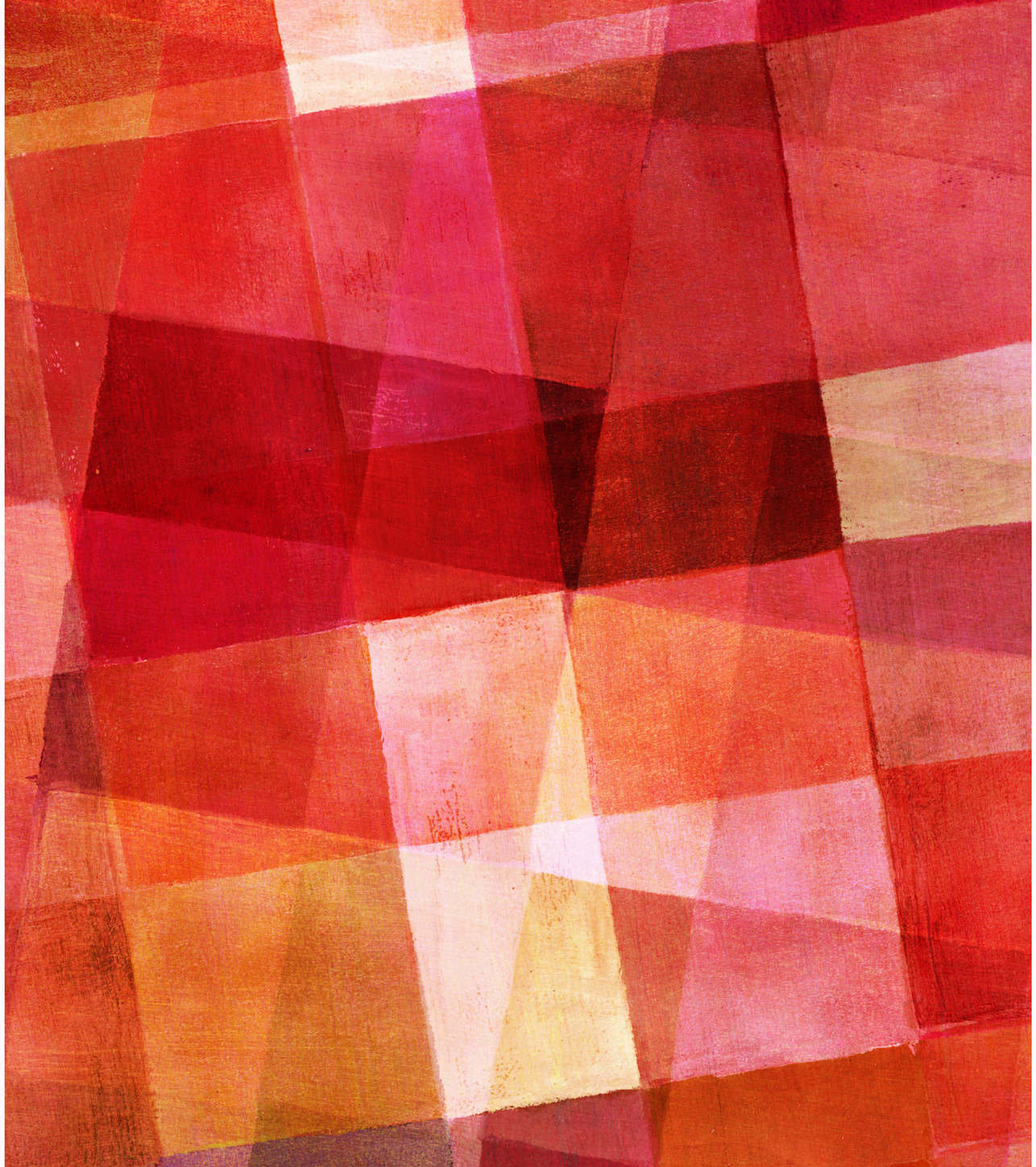
Drug-Induced Hypertension
Common Medications




Elevated Blood Pressure
Evaluate appropriate BP therapy (if treated)
Evaluate concomitant drug-related causes
No drug-related causes present
Drug-related causes present
Continue therapy and consider antihypertensives based on mechanism
Evaluate risk vs. benefit of offending drug
Discontinue offending drug
Volume Overload
Sympathomimetic Activation
Direct Vasoconstriction
Consider diuretic therapy
For sex hormones, add ACEI or ARB
For NSAIDs, consider CCBs or centrally acting antihypertensives
For corticosteroids, use ACEI or ARB ± mineralocorticoid receptor antagonist
Limit exposure and optimize current antihypertensive regimen or add first line therapy of ACEI, ARB, or CCB
Consider CCB or ACEI with calcineurin inhibitors
For renal transplant, use CCB
For VEGF inhibitors, use ACEI or nondihydropyridine CCBs


Drug-Induced HTN
Risk Versus Benefit of Medication
Can the medication be discontinued?
Are alternative agents available/feasible?
Can you decrease the dose and/or duration of therapy?
Determine Underlying Mechanism of Drug-Induced HTN
Volume Retention
Sympathomimetic Activation
Direct Vasoconstriction
Other/Miscellaneous
Diuretic therapy - can be used after the patient's electrolytes and comorbid conditions are assessed
NSAIDs: Add CCB or centrally-acting hypertensive agent (i.e. clonidine)
Sex Hormones: Add ACEI or ARB but must consider fetal harm in women of child-bearing age
Corticosteroids: Consider ACEI or ARB ± mineralocorticoid receptor antagonist
Limit exposure to substance
Adjust antihypertensive regimen, if necessary
Add ACEI, ARB, or CCB
Cocaine: Use benzodiazepines for agitation/chest pain; nitroglycerin, nitroprusside, or IV phentolamine can be used for BP stabilization; utilize psychosocial support
Psychostimulants: Reduce dose of medication or implement a drug holiday; guanfacine can be used to counteract hypertension
Antidepressants: SSRIs may be tried; institute routine BP monitoring
Administer lowest dose of medication possible; initiate antihypertensive therapy or increase intensity of current regimen
Calcineurin Inhibitors: Initiate CCB or ACEI (avoid ACEI in renal transplant patients)
VEGF inhibitors: ACEI or dihydropyridine CCBs are typically used; BP should be at goal (<140/90 mmHg) prior to initiating VEGF inhibitor; monitor BP weekly during first cycle then every 2-3 weeks during remaining cycles
Dietary Supplements: Evaluate risk versus benefit of supplement
EPO: Increase dose of antihypertensive agent, delay next EPO dose, initiate diuretic therapy, or utilize ultrafiltration; target hemoglobin should be <11 g/dL

Class	Drugs	Mechanism
Sympathomimetic agents	Amphetamines (dextroamphetamine, methamphetamine, methylphenidate); phenylpropanolamine, ephedrine, pseudoephedrine	Cause dose-related increases in blood pressure; CNS stimulant
NSAIDs and COX-2 inhibitors	Ibuprofen, diclofenac, celecoxib	Block COX-1 and COX-2 enzymes, which leads to a reduction in prostaglandin formation; cause dose-related increases in sodium and water retention
Corticosteroids	Prednisone, fludrocortisone, hydrocortisone	Cause sodium retention, resulting in dose-related fluid retention
CNS stimulants	Caffeine	Stimulant effect
Estrogens and progestins	Oral contraceptives, ERT/HRT	Estrogen stimulates the hepatic production of the renin substrate angiotensinogen; both appear to contribute in a dose-dependent fashion
Dietary supplements	Ginseng, natural licorice, yohimbine	Mild stimulant effect; increase arterial pressure
SNRIs	Venlafaxine, sibutramine	Increase levels of norepinephrine and the subsequent potentiation of noradrenergic neurotransmission
Immunosuppressants	Cyclosporine, tacrolimus	Increase prostaglandin synthesis and decrease water, sodium, and potassium excretion

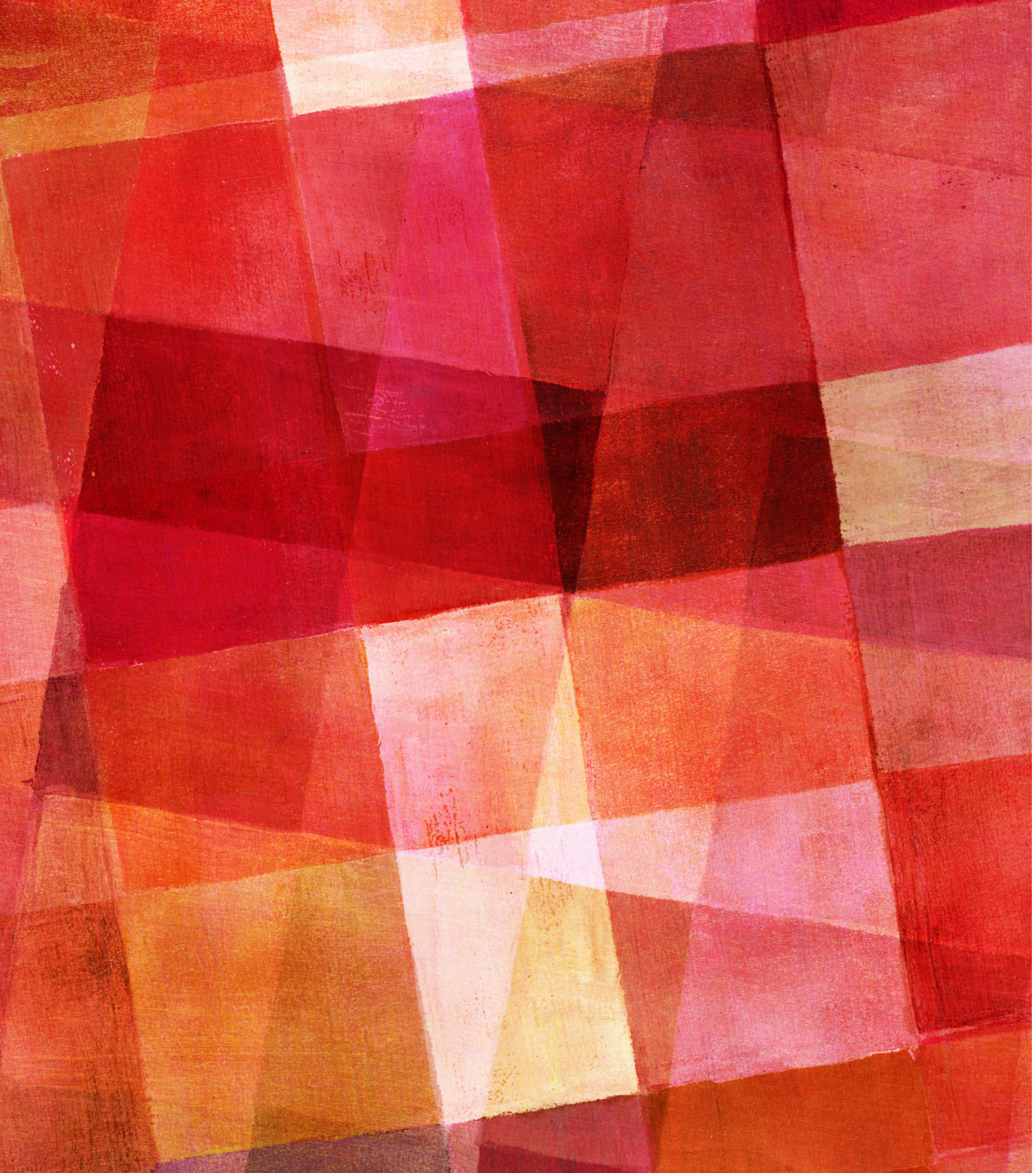


Sympathomimetic Agents

Sympathomimetic amines include amphetamines and similar compounds, such as pseudoephedrine, phenylpropanolamine, and ephedrine

Pseudoephedrine

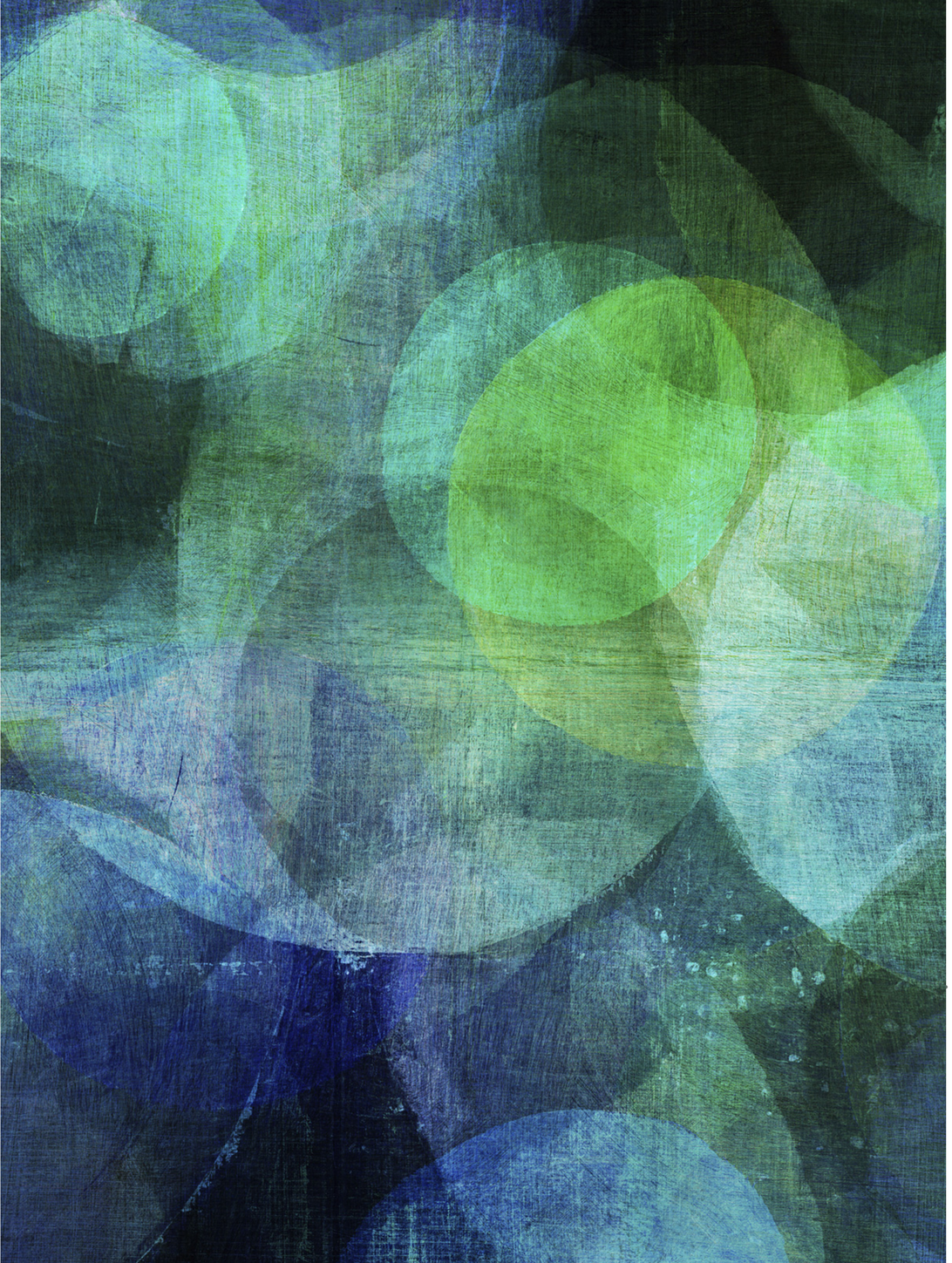
Twenty-four clinical trials had extractable vital sign information and included a total of 1,285 patients. This analysis demonstrated that pseudoephedrine causes a small mean increase in systolic blood pressure (approximately 1 mmHg), with no significant effect on diastolic blood pressure, and a slight increase in heart rate (about 3 beats per minute).



Amphetamine Derivates

These central nervous system (CNS) stimulants include dextroamphetamine, methamphetamine, and methylphenidate.

As a general rule, amphetamine-related compounds (i.e., CNS stimulants) should be avoided in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that increase the risk of sudden death.



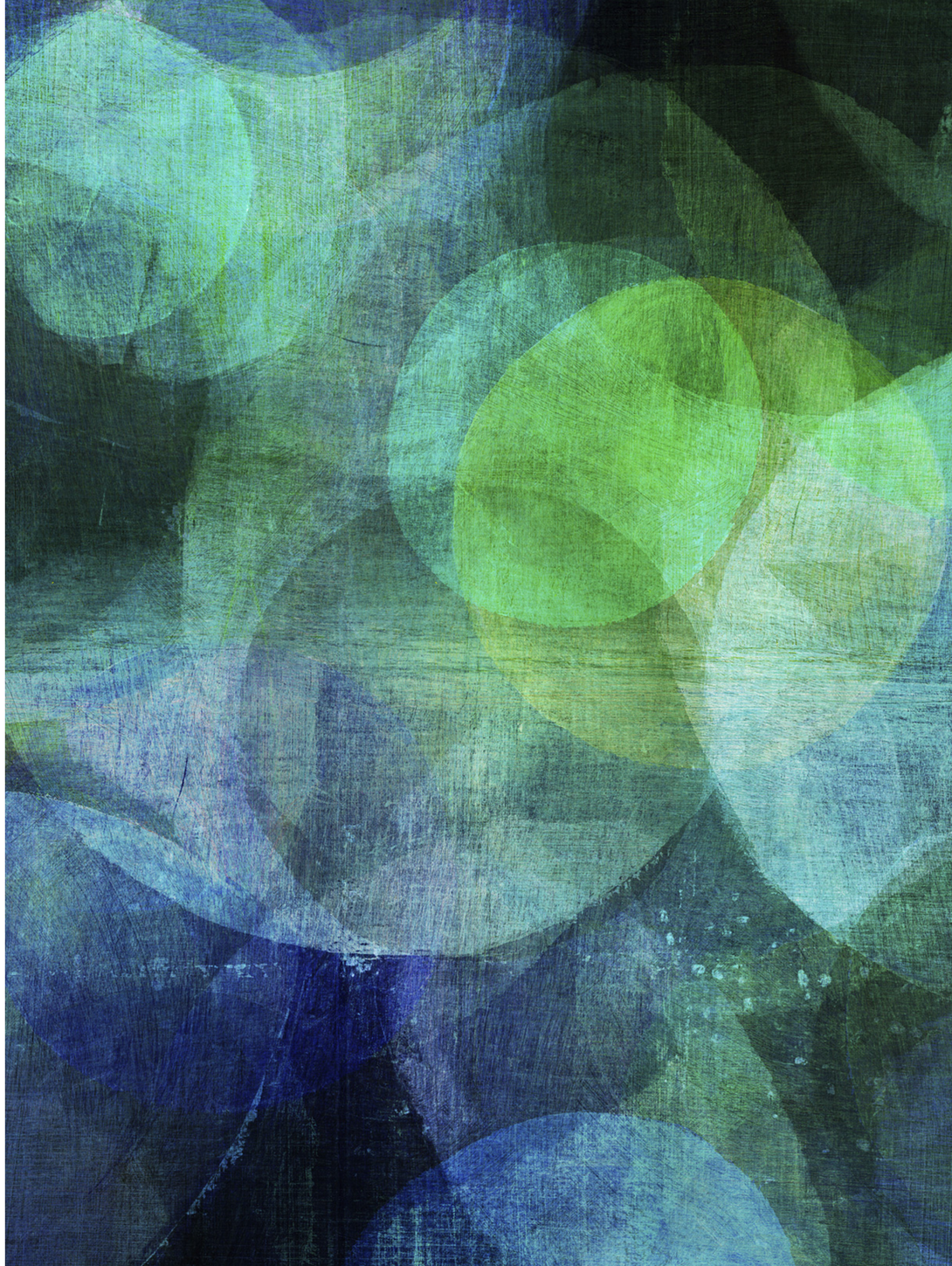
NSAIDs and COX-2 Inhibitors

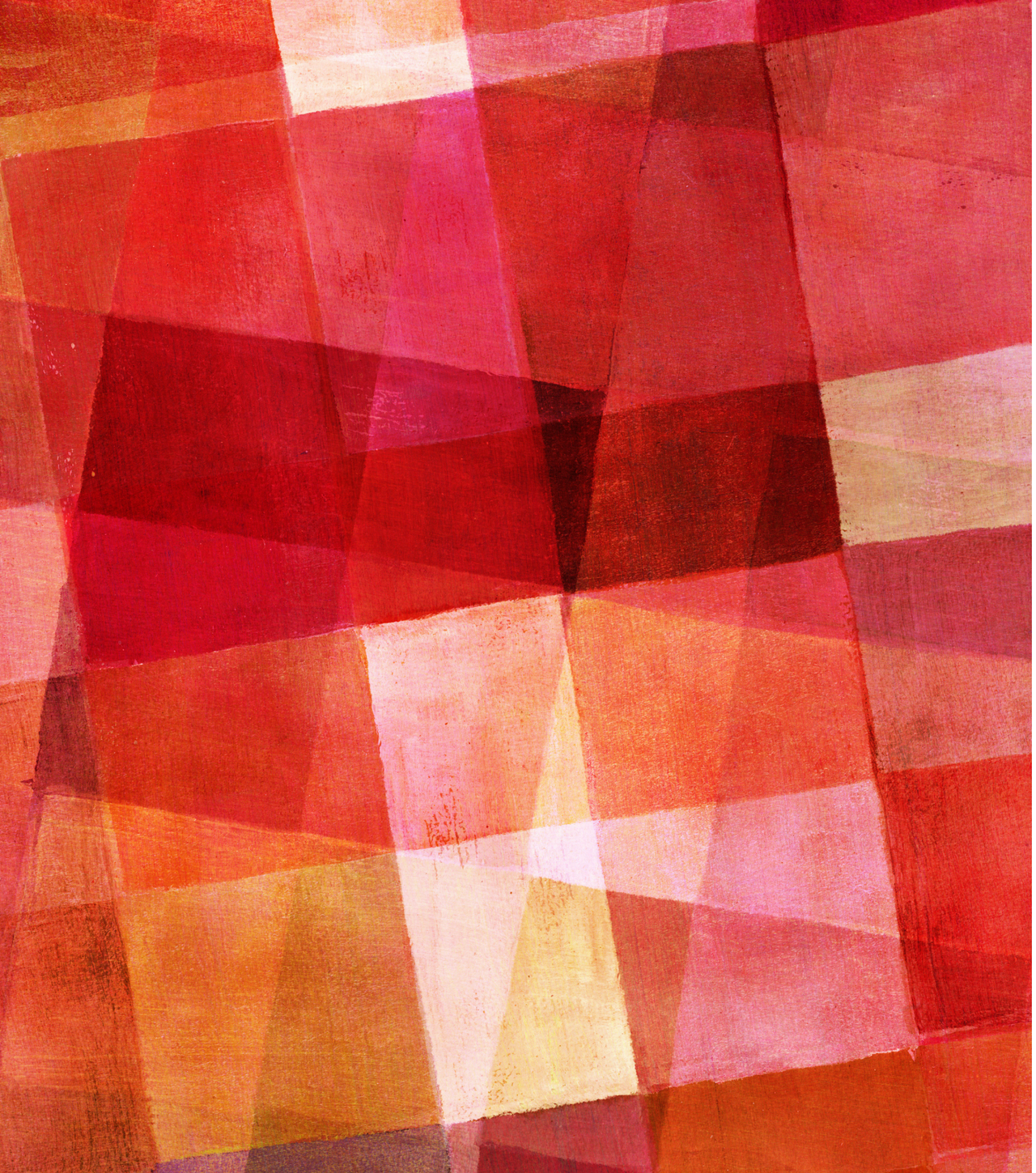
NSAIDs block both cyclooxygenase-1 (COX-1) and COX-2 enzymes, which leads to a reduction in prostaglandin formation.

The COX-1 and COX-2 isoforms are both expressed within the normal adult kidney, with COX-1 in the glomerulus and afferent arteriole and COX-2 in the afferent arteriole, the podocytes, and macula densa.

The prostaglandins produced by COX-1 primarily affect renal homeostasis by promoting vasodilation in the renal vascular bed, reducing renal vascular resistance, and consequently increasing renal perfusion. Prostaglandins produced by the COX-2 isoenzyme have diuretic and natriuretic effects.

In a comparison of celecoxib with diclofenac conducted in 287 patients with arthritis,there was no significant difference



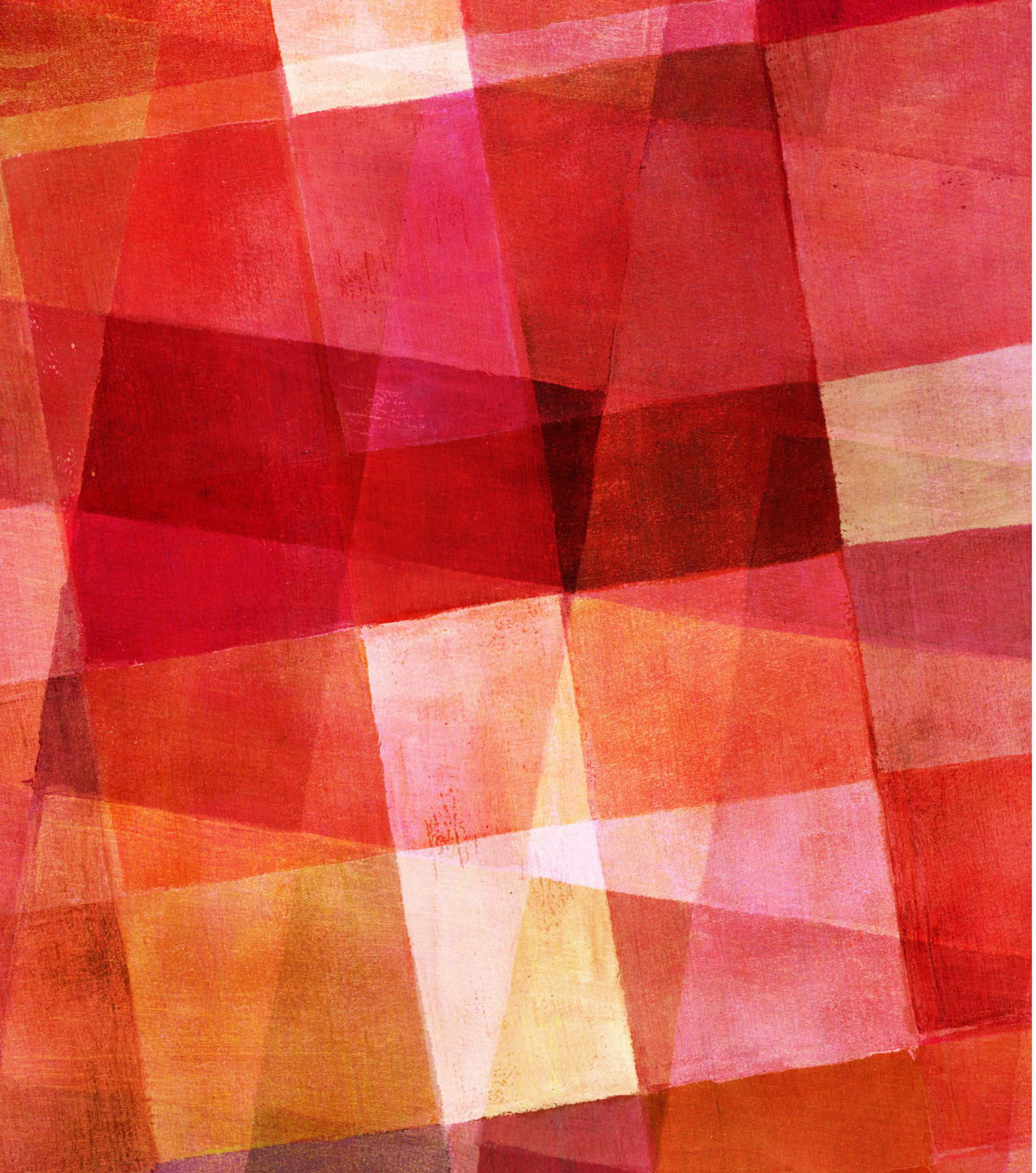


CORITOCSTEROIDS

All corticosteroid drugs, including prednisone, can cause sodium retention, resulting in dose-related fluid retention.

Corticosteroids with strong mineralocorticoid effects, such as **fludrocortisone** and **hydrocortisone**, produce the greatest amount of fluid retention. However, some corticosteroids that lack significant mineralocorticoid activity (e.g., *dexamethasone*, *triamcinolone*, *betamethasone*) may produce minor fluid retention.

Fludrocortisone causes significant blood pressure increases and, thus, is useful in treating patients with postural hypotension.



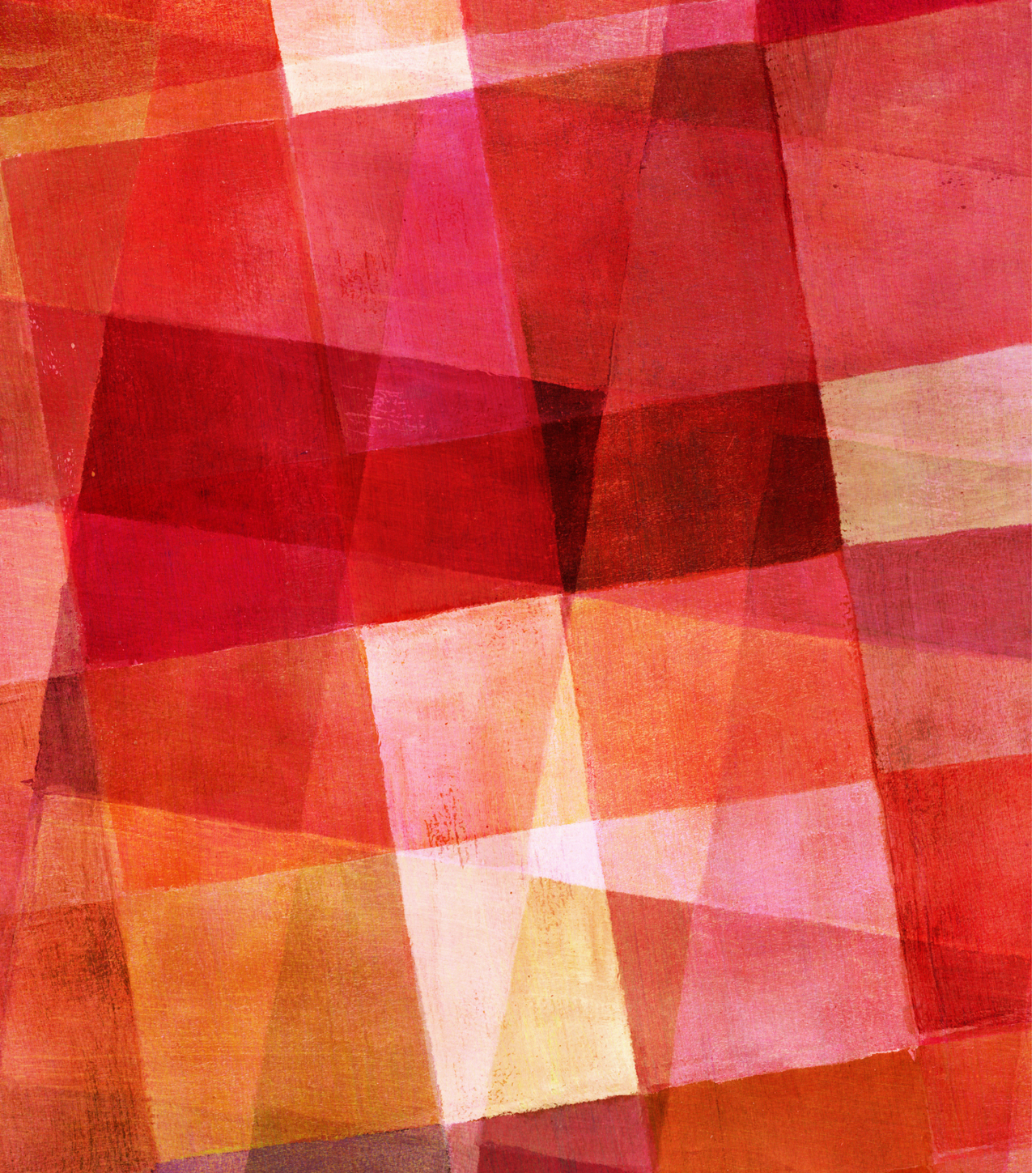
Estrogens and Progestins

Chronic use of oral contraceptives may slightly raise blood pressure in certain women and may have other adverse effects on cardiovascular risk.

mean elevations in blood pressure of 3 to 6 mmHg systolic and 2 to 5 mmHg diastolic, with approximately 5% of women developing new hypertension.

Cessation of therapy typically leads to a return to baseline BP within 2 to 12 months.

The incidence of persistent hypertension is greatest in women over the age of 35 and in those who have coronary risk factors, particularly smoking.



The mechanisms responsible for the hypertensive effect of oral contraceptives are poorly understood. The renin-angiotensin system may be involved, since estrogen stimulates the hepatic production of the renin substrate angiotensinogen

ERT & HRT

Postmenopausal estrogen replacement therapy (ERT, or HRT when combined with a progestin) consists of much lower estrogen doses than in oral contraceptives. It appears to have a neutral effect on blood pressure as illustrated by the following observations from two large randomized trials

The Women's Health Initiative

PEPI trial

CAFFEINE

The effects of caffeine on blood pressure control are not well defined.

An increase of 2.04 mmHg in systolic blood pressure and of 0.73 mmHg in dia stolic blood pressure was found

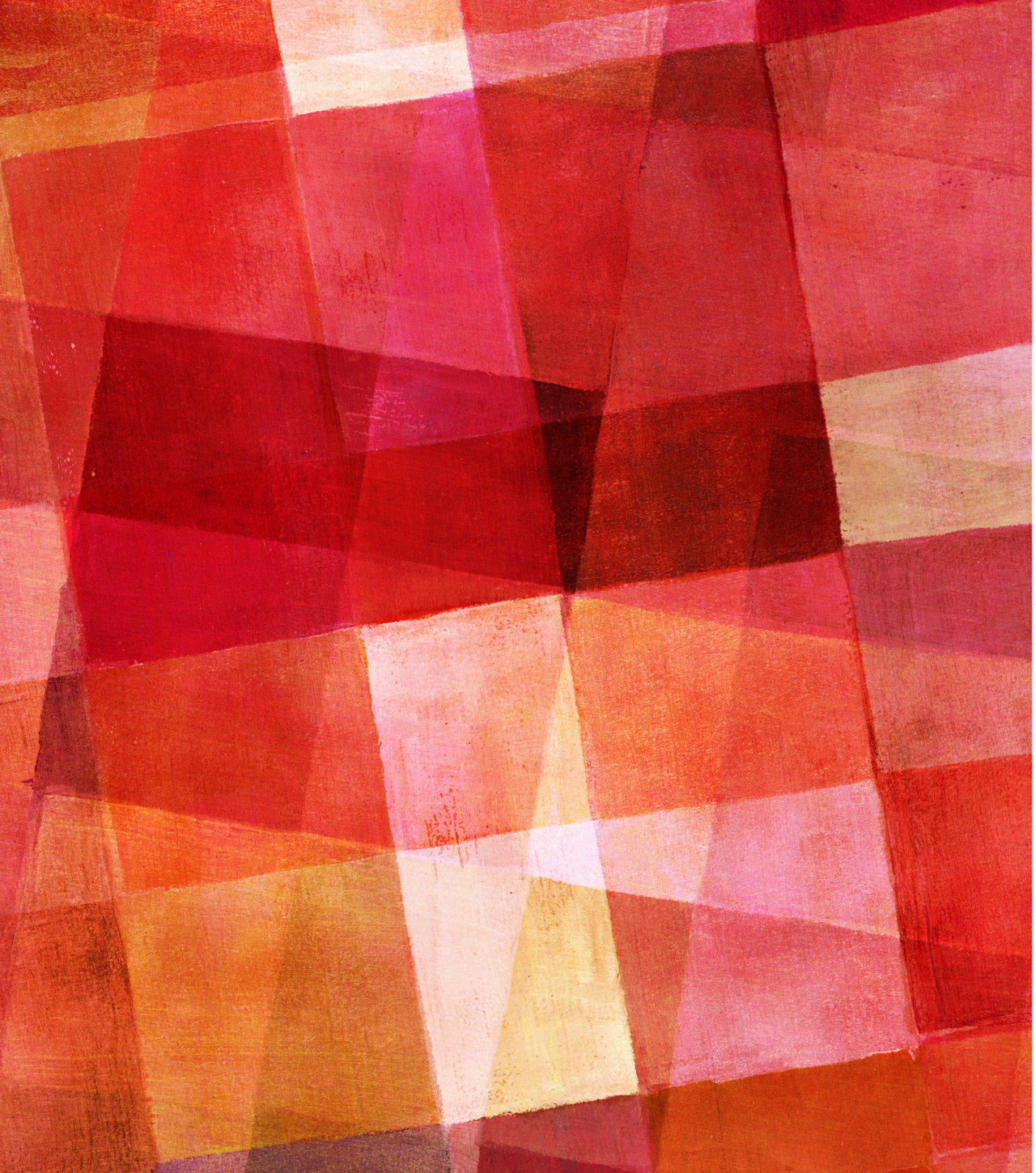
When the coffee and caffeine trials were analyzed separately, the blood pressure elevations induced were larger with caffeine (410 mg/day) than with coffee (725 mL/day). The effects of coffee and caffeine on heart rate were not significant.

Dietary Supplements

Ginseng is generally recognized as safe and has been associated with few serious side effects.

A type of ginseng abuse syndrome, characterized by diarrhea, hypertension, nervousness, dermatologic eruptions, and insomnia, has been described.

Other supplements that may increase arterial pressure include natural licorice and yohimbine.

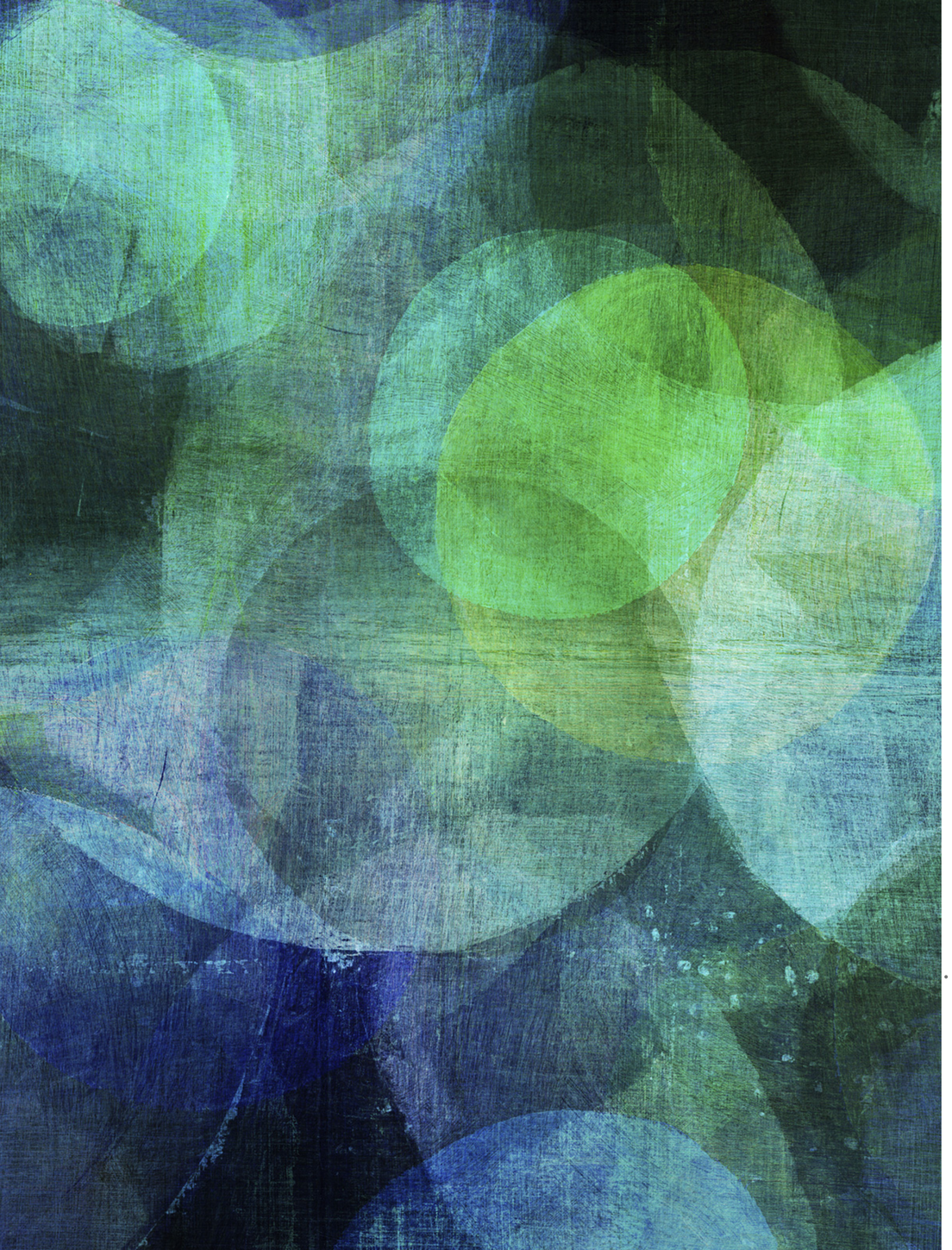


Serotonin-Norepinephrine Reuptake Inhibitors

Venlafaxine:
The likely mechanism of venlafaxine-induced hypertension is the increase in levels of norepinephrine and the subsequent potentiation of noradrenergic neurotransmission.

The extended-release formulation of venlafaxine increases blood pressure in approximately 3% of patients when normal doses (75-150 mg) are used.

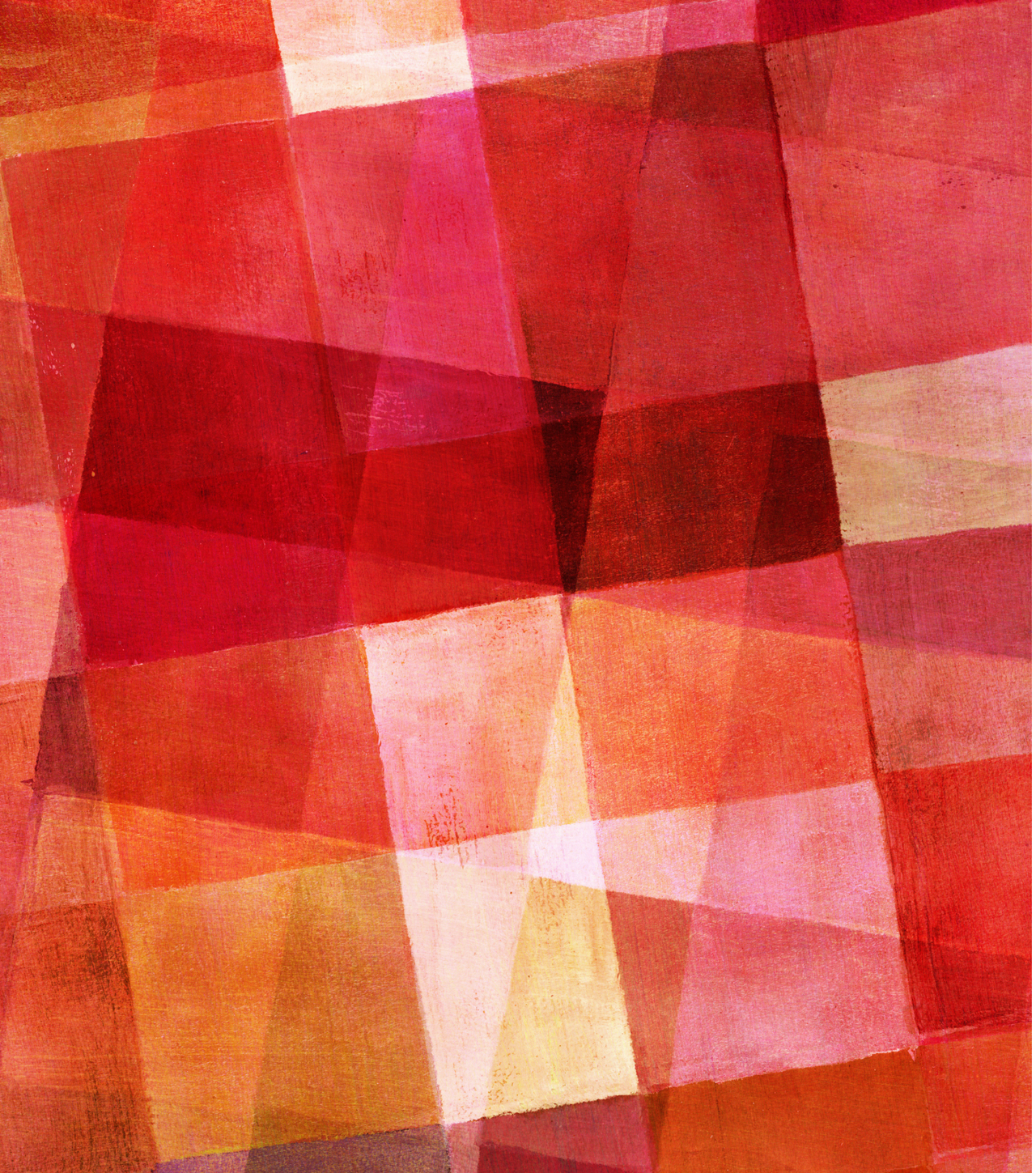
Doses >=300 mg of extended-release venlafaxine demonstrated clinically significant elevations in 13% of patients, with the majority of blood pressure increases between 10 and 15 mmHg.



Sibutramine is an SNRI and is chemically similar to amphetamine.

Sibutramine's likely mechanism of blood pressure elevation in both normotensive and hypertensive patients is the elevated amount of norepinephrine present in the body.

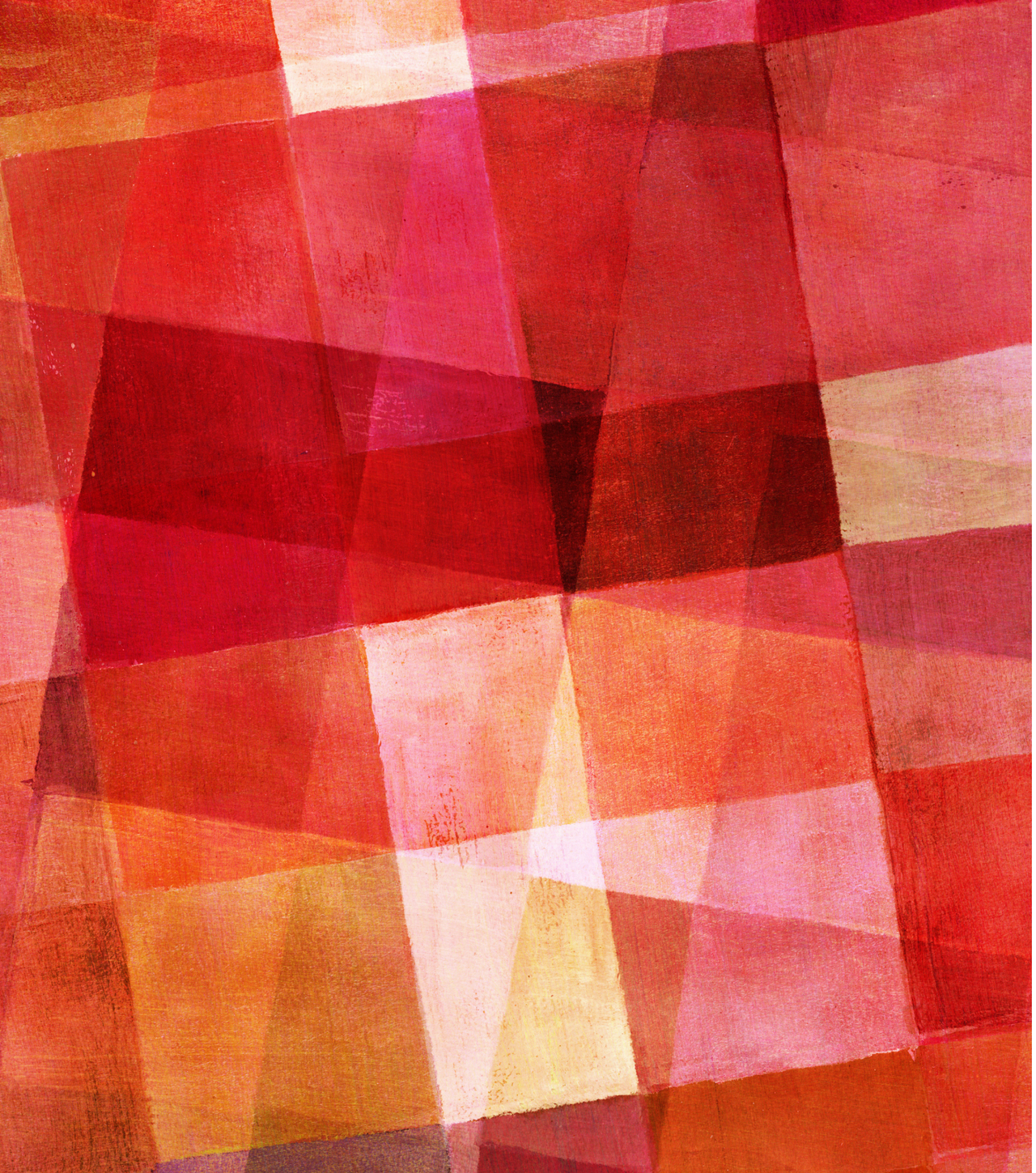
Patients with established hypertension receiving sibutramine experienced significantly higher elevations in blood pressure than patients who had normal blood pressure before medication initiation.



Immunosuppressants

Cyclosporine: The adverse effect of cyclosporine on blood pressure is well known.
several hypotheses have been proposed, including increased prostaglandin synthesis and decreased water, sodium, and potassium excretion.

Treatment of cyclosporine-induced hypertension may be pharmacologic, consisting possibly of calcium channel blockers, diuretics, beta-blockers, or ACE inhibitors, or nonpharmacologic, consisting of reduced sodium intake.



Tacrolimus

The mechanism of tacrolimus-induced hypertension is postulated to be similar to cyclosporine's