Dr R Amburajan IMACGP Oration:

“Drug-Induced Hypertension”

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Drug-Induced Hypertension

Outline

Introduction

Mechanisms of Drug-Induced Hypertension (DIH)

Drugs Associated with Hypertension

Clinical Presentation, Diagnosis

Management Strategies

Case Study: Drug-Induced Hypertension

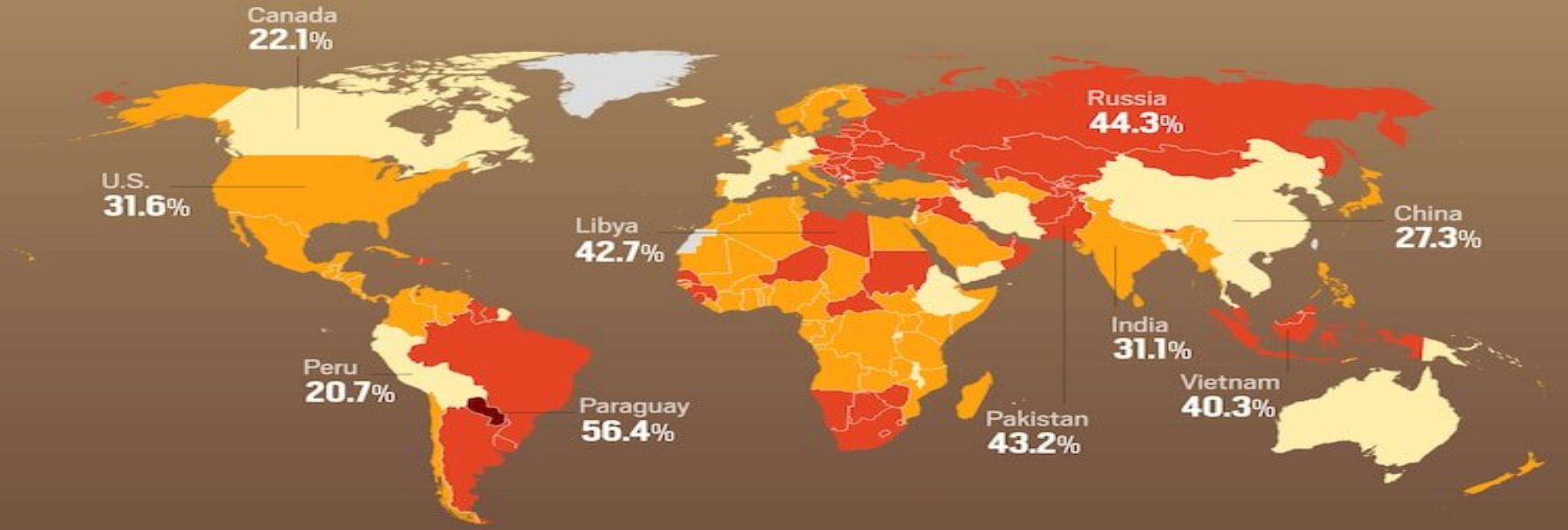
conclusion

Hypertension: A Global Epidemic

INDIA TODAY GROUP

Prevalence of hypertension among people aged 30-79 years

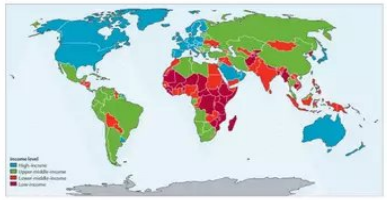
20-30% 30-40% 40-50% 50-60%



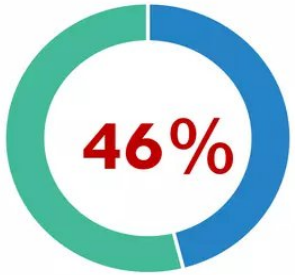
Global Prevalence of Hypertension

World Health Organization

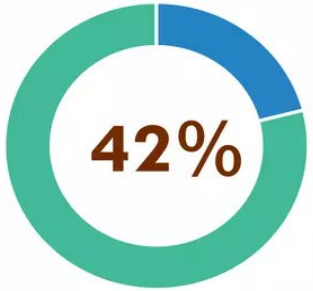
1.28 billion adults aged 30–79 years



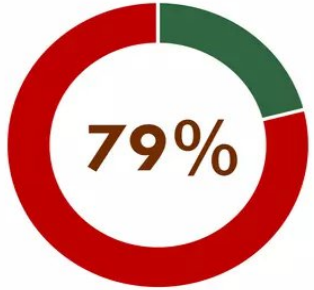
Two-thirds living in low- and middle-income countries



Unaware



Diagnosed & Treated

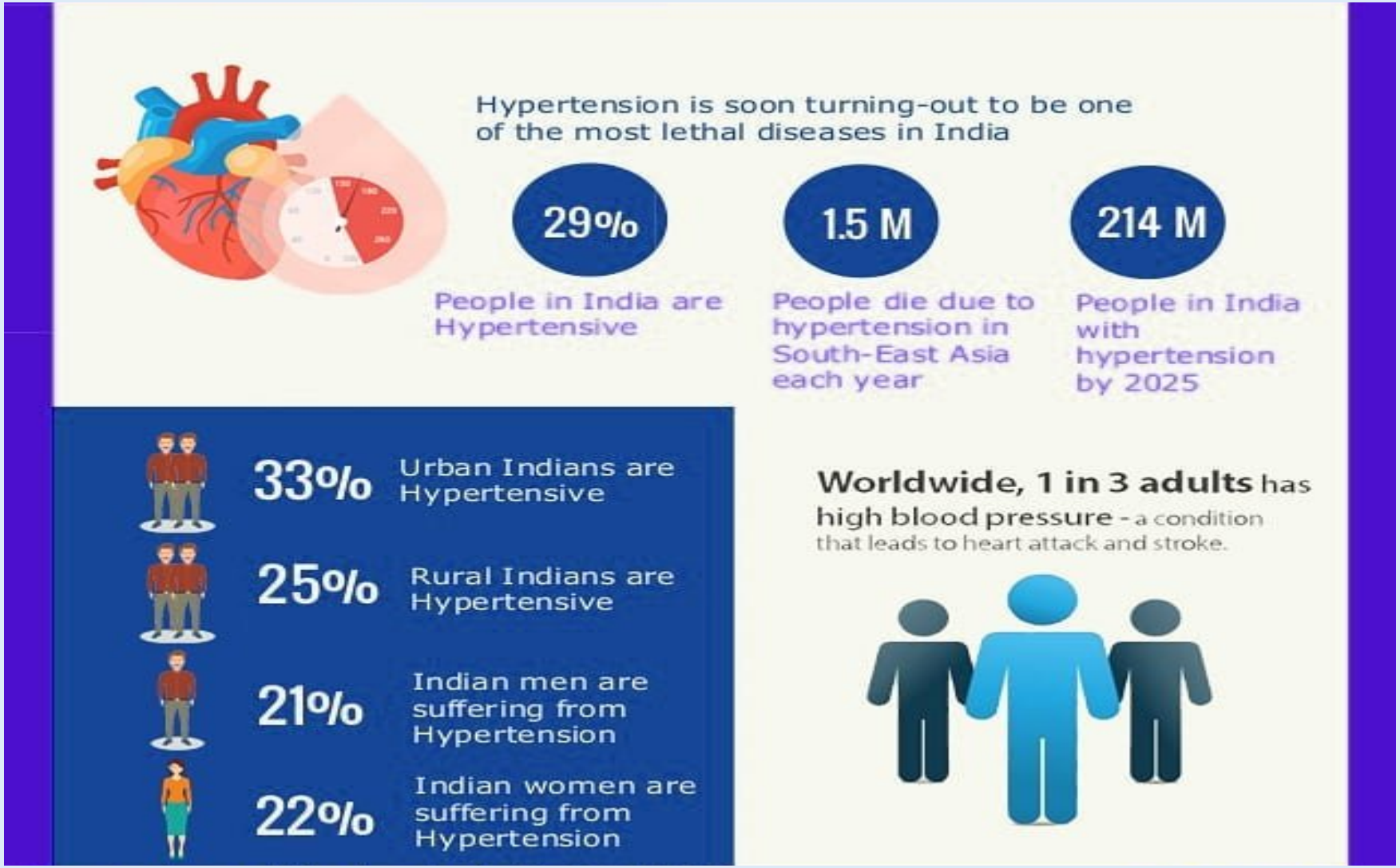


Un-controlled

Lack of awareness is the key

WHO, 16 March 2023 (www.who.int/news-room/fact-sheets/detail/hypertension)

Prevalence of Hypertension in India



Epidemiology

Incidence:

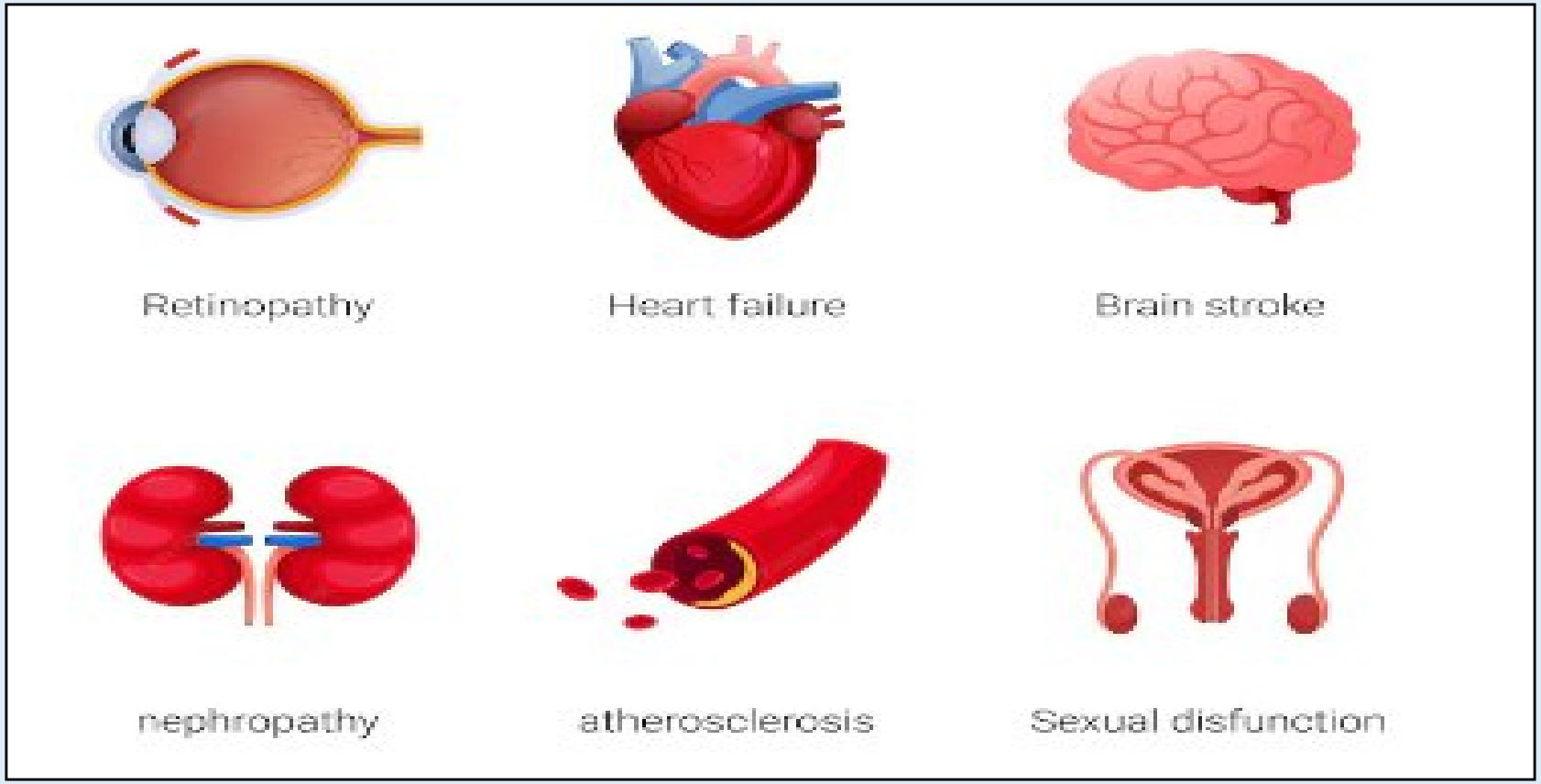
- In nationally representative survey study, 18% of US adults with hypertension reported taking medications that may cause elevated BP.
- It is estimated that 58% of patients may be uncontrolled due to other medications that induce hypertension or blunt the effect of an antihypertensive
- Common in elderly populations due to polypharmacy.

At-Risk Populations:

- Patients with pre-existing hypertension.
- Individuals with renal dysfunction or cardiovascular disease.

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2786014#:~:text=The%20most%20commonly%20reported%20classes,CI%2C%201.4%25%2D2.0%25).

Complications of Hypertension



Introduction

Defined as elevated blood pressure caused by the use of specific medications, substances, or supplements.

Significance:

- Often overlooked in clinical settings.
- Can exacerbate pre-existing hypertension or lead to long-term complications.

Why It Matters:

- Increasing use of prescription drugs linked to rising cases of DIH.
- Highlights the need for awareness and monitoring by healthcare professionals.

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2786014#:~:text=The%20most%20commonly%20reported%20classes,CI%2C%201.4%25%2D2.0%25).

Mechanisms of Drug-Induced Hypertension (DIH)

Volume Retention:

Drugs like nonsteroidal anti-inflammatory drugs (NSAIDs), sex hormones, and corticosteroids

Sympathomimetic Activation:

Nasal decongestants, Caffeine, Cocaine, Psychostimulants, Antidepressants

Direct Vasoconstriction:

Calcineurin Inhibitors- Cyclosporine and tacrolimus, Vascular Endothelial Growth Factor (VEGF) Inhibitors- bevacizumab, lapatinib, sunitinib, and sorafenib

Lovell AR, Ernst ME. Drug-induced hypertension: focus on mechanisms and management. Current hypertension reports. 2017 May;19:1-2.

Case Study: Drug-Induced Hypertension

- **Patient Profile:**
  - **Age:** 60 years
  - **Gender:** Female
  - **History:**
    - Osteoarthritis managed with NSAIDs (Diclofenac 100 mg daily for 3 months).
    - Controlled hypertension on Amlodipine 5 mg daily (baseline BP: 130/80 mmHg).
  - Other conditions: Mild chronic kidney disease (eGFR: 55 mL/min).
- **Presentation:**
  - Complaints of persistent headache and fatigue during follow-up.
  - BP on examination: 160/95 mmHg.
  - No recent changes in diet, exercise, or other medications.
- **Investigations:**
  - **Renal function tests:** Worsened kidney function (eGFR dropped to 48 mL/min).
  - **Electrolytes:** Normal sodium and potassium levels.
  - **Urinalysis:** No proteinuria or hematuria.
- **Diagnosis:**
  - **Drug-induced hypertension due to chronic NSAID use.**

- **Management:**
  - **Drug Discontinuation:**
    - Diclofenac stopped and replaced with acetaminophen for pain management.
  - **Adjustment in Antihypertensive Therapy:**
    - Increased Amlodipine dose to 10 mg daily.
    - Added Losartan 50 mg daily to address potential RAAS activation.
  - **Monitoring:**
    - Weekly BP checks for 1 month.
    - Follow-up renal function after 4 weeks.

- **Outcome:**
  - BP normalized to 135/85 mmHg within 3 weeks.
  - eGFR improved to 53 mL/min after stopping NSAID therapy.
- **Key Takeaways:**
  - **NSAIDs can exacerbate hypertension, especially in patients with pre-existing kidney disease.**
  - Early identification and substitution of the offending drug are critical.

Overview of Drug-Induced Hypertension

Drug-induced hypertension is a condition where high blood pressure is caused by a response to taking or stopping a drug or chemical substance

Differentiating drug-induced hypertension from primary (essential) and secondary hypertension is crucial for appropriate treatment.

Accurate diagnosis ensures that patients receive the correct management strategies and avoid unnecessary interventions.

Estimated prevalence and mechanism of drug-induced hypertension by class

Drug	Prevalence of Hypertension	Proposed Mechanism
VEGF inhibitors	15%–90%[5–8]	VEGFR-2 antagonism with subsequent decreased NO production.
Calcineurin inhibitors	23%–60%[21,22]	Endothelin-1 overproduction with decreased NO production. Renal Na^+ retention through stimulation of thiazide-sensitive NaCl cotransporter via increased WNK kinase activity. Direct postsynaptic excitation via glutaminergic transmission with increased SNS activity.
NSAIDs[a]	14%–20%[45]	Reduced prostaglandin E2 with subsequent decrease in urine Na^+ excretion. Increased intrarenal aldosterone levels secondary to decreased hormone glucuronidation. Reduced prostaglandin I_2 with increased systemic vascular resistance.
Glucocorticoids	20%[50]	Renal Na^+ retention via stimulation of mineralocorticoid receptors. Upregulation of AT1 receptors on vascular smooth muscle with subsequent increased vascular tone.
Erythropoietin stimulating agents	20%–30%[57]	Increased thromboxane and reduced prostacyclin levels with blunted response to NO. Increased endothelin levels with resulting vasoconstriction.
Oral contraceptive pills	Unknown	Increased renin (estrogenic component) leading to RAAS activation and subsequent Na^+ and water retention.
Selective norepinephrine reuptake inhibitors	1%–5%[77]	Activation of the SNS with increased norepinephrine.
Drugs of abuse MDMA PCP Methamphetamine Cocaine	 33%[80] 17%–46%[81]	Increased release and inhibited reuptake of monoamine neurotransmitters with subsequent SNS activation. Increased CNS catecholamine release with decreased neuronal uptake. Cocaine-induced increase in arterial wall stiffness and atherosclerosis.
Stimulants Modafinil Methylphenidate Amphetamines	~7%[99]	Block reuptake of norepinephrine or dopamine. Promote release of catecholamines.

Table 1. Prevalence of Use of Medications That May Raise Blood Pressure (BP) Among US Adults, 2009-2018

	Survey participants, % (95% CI)		
		Adults with	
	US adult population	Hypertension[a]	Uncontrolled hypertension[b]
Unweighted No.	27 599	14 629	10 696
Weighted No.	225 284 279	111 056 498	79 921 633
Use of medications that may raise BP			
Any	14.8 (13.9-15.8)	18.5 (17.5-19.5)	17.4 (16.3-18.5)
1	12.3 (11.7-12.9)	14.9 (14.1-15.8)	14.1 (13.1-15.1)
≥2	2.5 (2.2-2.9)	3.6 (3.1-4.1)	3.3 (2.7-3.8)
Use of classes of medications that may raise BP			
Antidepressants	6.7 (6.2-7.3)	8.7 (8.0-9.5)	7.9 (7.0-8.8)
NSAIDs	4.9 (4.4-5.3)	6.5 (5.8-7.2)	6.2 (5.4-6.9)
Steroids	1.4 (1.2-1.6)	1.9 (1.6-2.1)	1.7 (1.4-2.0)
Estrogens	1.4 (1.2-1.6)	1.7 (1.4-2.0)	1.6 (1.3-1.9)
Stimulants	1.1 (0.9-1.4)	0.9 (0.6-1.1)	1.0 (0.7-1.4)
Testosterones	0.4 (0.2-0.5)	0.4 (0.2-0.6)	0.4 (0.2-0.6)
Antiobesity agents	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.1 (0.1-0.3)
Decongestants	0.2 (0.1-0.4)	0.4 (0.2-0.6)	0.4 (0.1-0.7)
Antipsychotics	0.1 (0.1-0.2)	0.2 (0.1-0.3)	0.2 (0.1-0.4)
Immunosuppressants	0.1 (0.0-0.1)	0.2 (0.1-0.3)	0.2 (0.1-0.3)
α Agonists	<0.01	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Antirheumatics	<0.01	0.1 (0.0-0.1)	0.1 (0.0-0.1)
Use of antihypertensives			
1	13.2 (12.5-13.9)	23.3 (22.2-24.4)	19.8 (18.8-20.9)
2	8.9 (8.3-9.4)	17.0 (16.0-18.0)	13.0 (12.1-14.0)
>3	4.9 (4.5-5.3)	9.8 (9.1-10.6)	7.9 (7.2-8.6)

Drugs commonly linked to Hypertension

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

CNS: central nervous system; NSAID: nonsteroidal anti-inflammatory drug; COX: cyclooxygenase; ERT/HRT: estrogen replacement therapy/hormone replacement therapy; SNRI: serotonin-norepinephrine reuptake inhibitor.

DRUGS CAUSING HYPERTENSION

DRUGS	CLINICAL USE	NOTES
Glucocorticoid	Replacement therapy, rheumatic disease collagen disease, dermatologic disease, allergic state, ophthalmic disease, inflammatory bowel disease	Hypertension occurs more often in elderly patients and in patients with a positive family history of primary HTN. Blood pressure rise is dose dependent, and at low doses, cortisol has less effect on BP.
NSAIDs	Analgesic, anti inflammatory	Mild, dose-dependent increase in BP. Elderly patients, those with pre-existing hypertension, salt-sensitive patients, patients with renal failure and patients with renovascular hypertension are at a higher risk to develop severe HTN
Phenylephrine hydrochloride	Upper respiratory decongestant, ophthalmic drops	Dose-dependent, sustained increase in BP.

Ehud Grossman, Franz H. Messerli, Drug-induced Hypertension: An Unappreciated Cause of Secondary Hypertension, The American Journal of Medicine, Volume 125, Issue 1, 2012, Pages 14-22,

DRUGS CAUSING HYPERTENSION

DRUGS	CLINICAL USE	NOTES
Dipivalyl adrenaline hydrochloride	Ophthalmic drops	Severe HTN has been reported.
Cocaine	Local anesthetics	Cocaine use is associated with acute but not chronic HTN. Transient severe increase in BP, especially when used with beta-blockers.
Ketamine hydrochloride	Anesthetic agent	Transient severe increase in BP has been reported.

Ehud Grossman, Franz H. Messerli, Drug-induced Hypertension: An Unappreciated Cause of Secondary Hypertension, The American Journal of Medicine, Volume 125, Issue 1, 2012, Pages 14-22,

DRUGS CAUSING HYPERTENSION

DRUGS	CLINICAL USE	NOTES
Yohimbine hydrochloride	Impotence	Acute, dose-dependent increase in BP.
Sibutramine	Weight loss	Mild increase in BP.
Venlafaxine	Antidepressive and anti-anxiety agents	At dose above 300 mg/day.

Ehud Grossman, Franz H. Messerli, Drug-induced Hypertension: An Unappreciated Cause of Secondary Hypertension, The American Journal of Medicine, Volume 125, Issue 1, 2012, Pages 14-22,

DRUGS CAUSING HYPERTENSION

DRUGS	CLINICAL USE	NOTES
Monoamine oxidase inhibitors	Antidepressive agents	Mainly with sympathomimetic amines and with certain food containing tyramine. Tranylcypromine is the most hazardous because of its stimulant action, whereas moclobemide and brofaromine are the least likely to induce hypertensive reaction.
Tricyclic antidepressants	Antidepressive agent	More common in patients with panic disorders.
Buspirone	Anxiolytic agent	Mild dose-dependent increase in BP.

Ehud Grossman, Franz H. Messerli, Drug-induced Hypertension: An Unappreciated Cause of Secondary Hypertension, The American Journal of Medicine, Volume 125, Issue 1, 2012, Pages 14-22,

DRUGS CAUSING HYPERTENSION

DRUGS	CLINICAL USE	NOTES
Thioridazine hydrochloride	Psychotic and depressive disorders	Massive overdose may cause severe HT.
Ritodrine hydrochloride	Inhibition of preterm labor	Hypertensive crisis has been reported.
Disulfiram	Management of alcoholism	Slight increase in BP. Severe HT may occur in alcoholic-induced liver disease.

Ehud Grossman, Franz H. Messerli, Drug-induced Hypertension: An Unappreciated Cause of Secondary Hypertension, The American Journal of Medicine, Volume 125, Issue 1, 2012, Pages 14-22,

DRUGS CAUSING HYPERTENSION

DRUGS	CLINICAL USE	NOTES
Cyclosporine A	Immunosuppressive agent, prophylaxis of organ rejection, autoimmune disease, dermatologic disorders	Dose-dependent mild to moderate increase in BP.
Rapamycin	Prophylaxis of organ rejection	Produces little BP increase.
Bevacizumab	Metastatic cancers of the colon, rectum, kidney, breast and glioblastoma multiforme	The incidence of HTN is dose related and is more pronounced in elderly patients, in those with preexisting HTN, and in those with renal cell carcinoma.

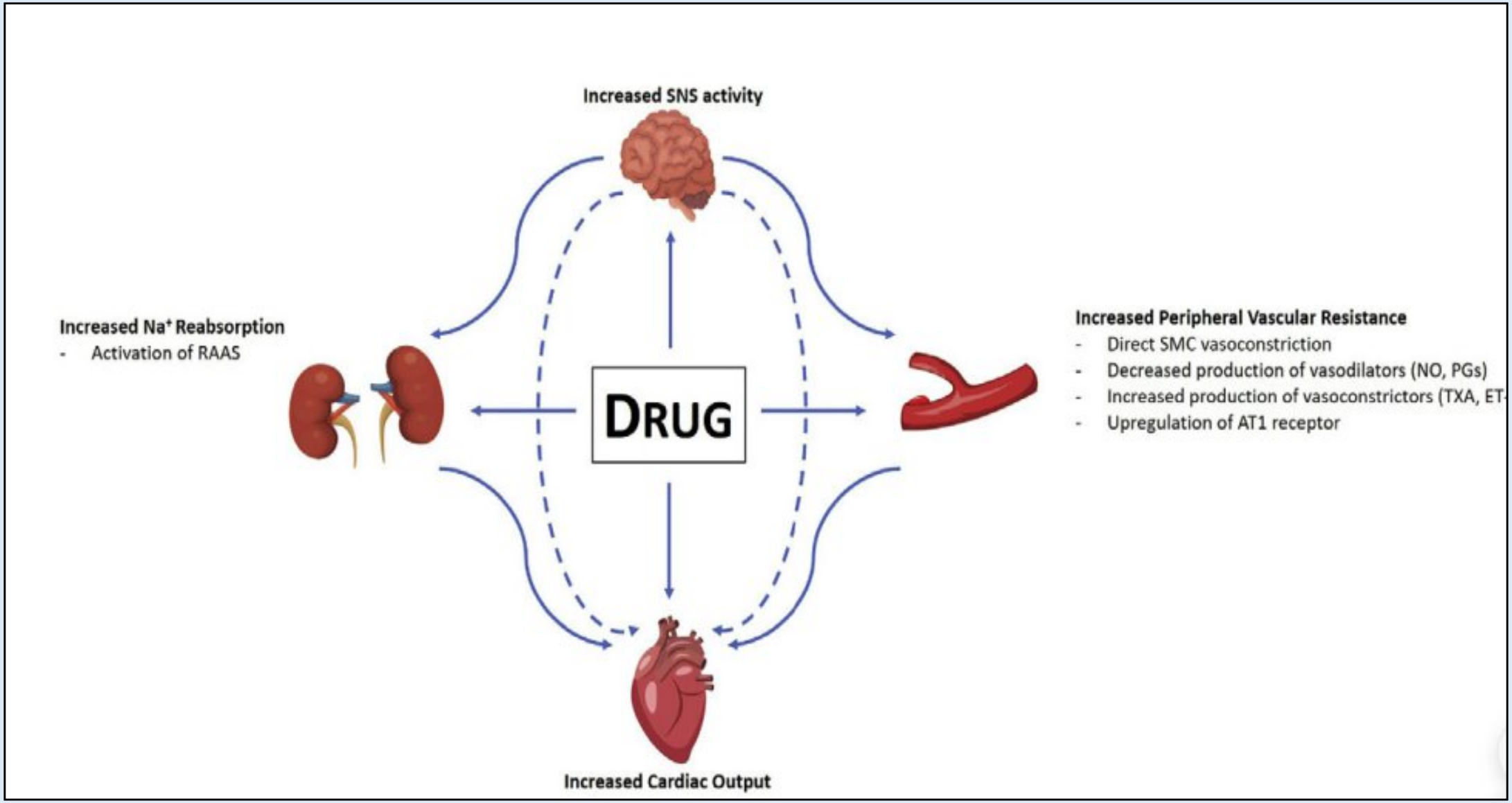
Ehud Grossman, Franz H. Messerli, Drug-induced Hypertension: An Unappreciated Cause of Secondary Hypertension, The American Journal of Medicine, Volume 125, Issue 1, 2012, Pages 14-22,

DRUGS CAUSING HYPERTENSION

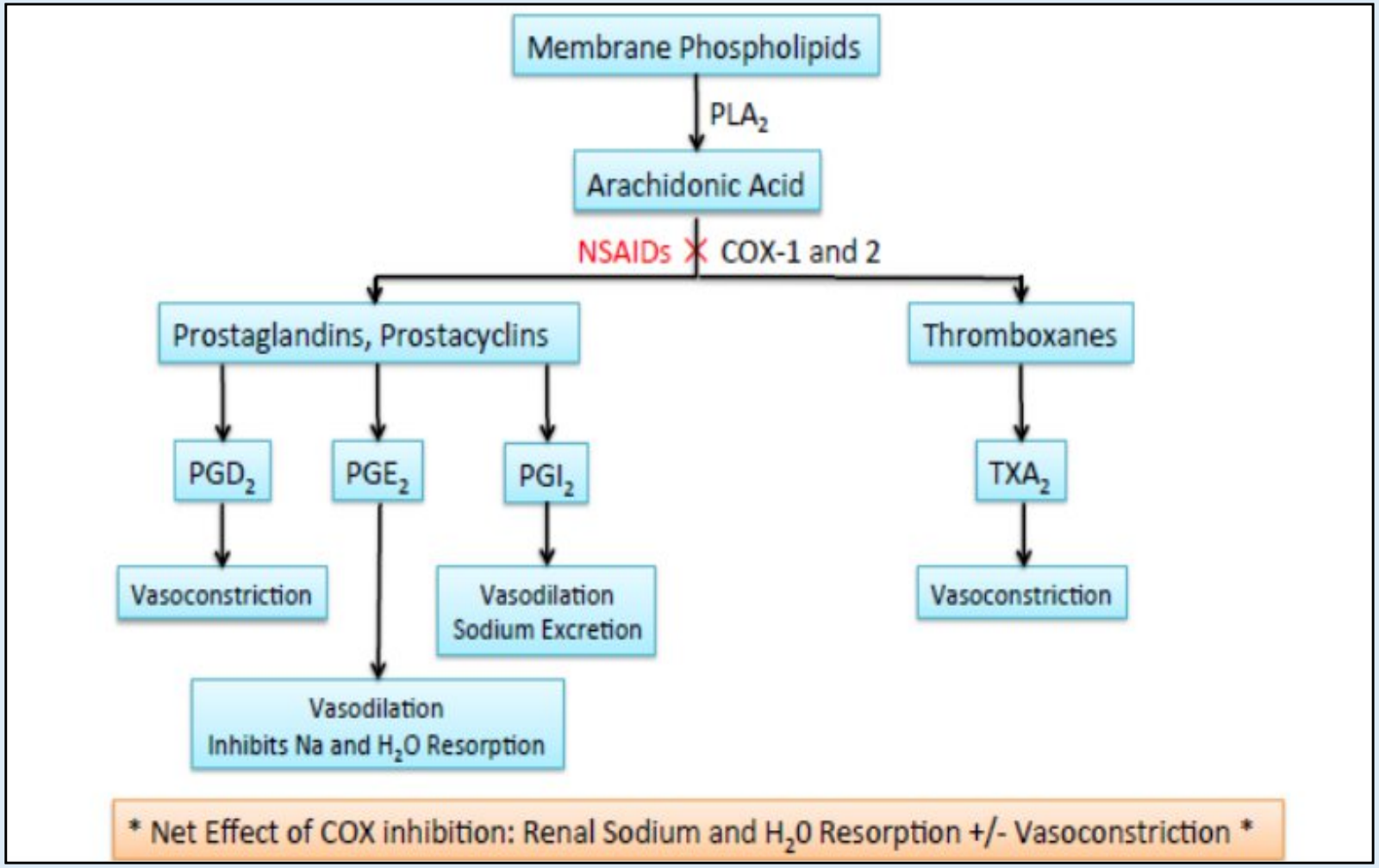
DRUGS	CLINICAL USE	NOTES
Naloxone hydrochloride	Opioid overdose	Transient BP elevation
Metoclopramide	Antiemetic	Transient increase in BP in association with cancer.
Bromocriptine mesylate	Suppression of lactation, and prolactin inhibition in prolactinoma	Severe HTN with stroke has been reported following the use for suppression of lactation. Patients with pregnancy-induced HTN are at increased risk to develop HTN.

Ehud Grossman, Franz H. Messerli, Drug-induced Hypertension: An Unappreciated Cause of Secondary Hypertension, The American Journal of Medicine, Volume 125, Issue 1, 2012, Pages 14-22,

Mechanisms contributing to drug-induced hypertension



NSAIDS Induced Hypertension: Mechanism of action

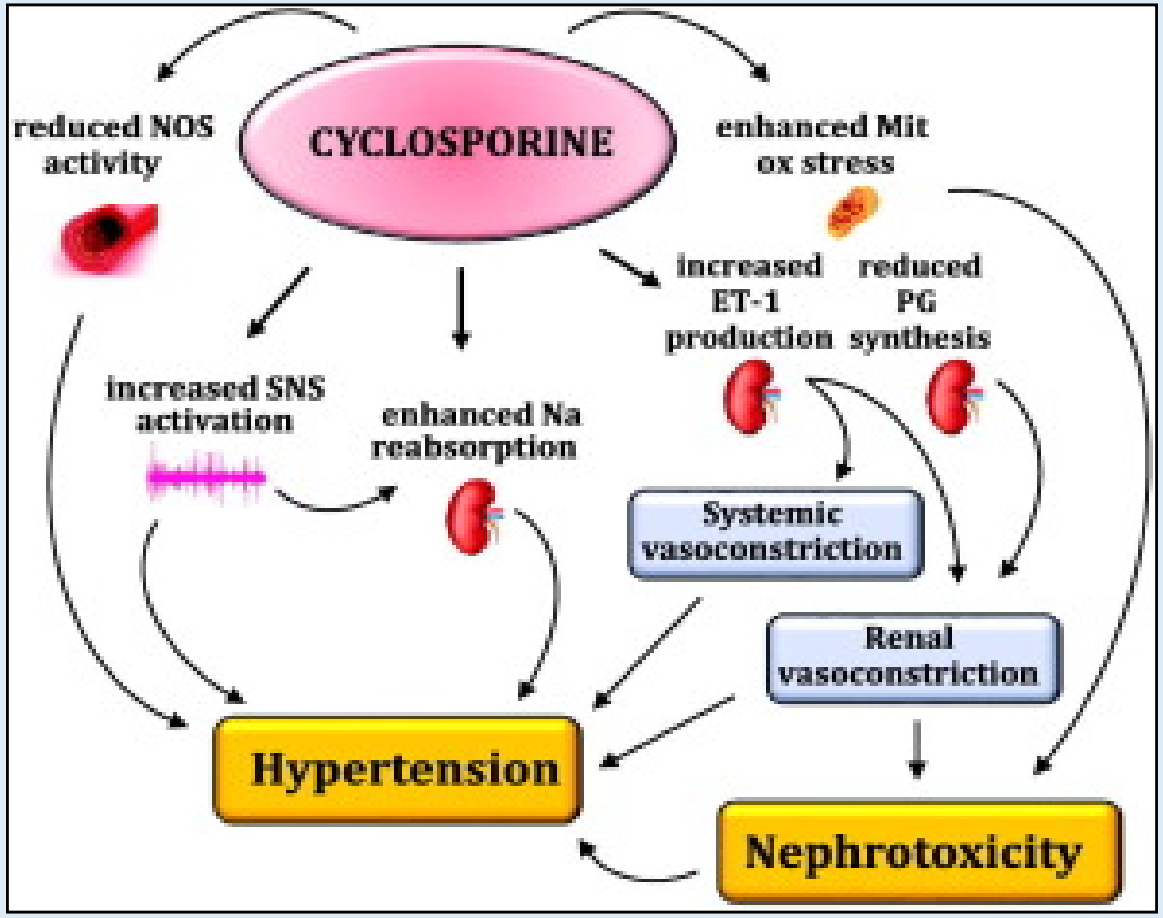


- NSAIDs inhibit the production of prostaglandins, which are important for vasodilation and sodium excretion. This inhibition can lead to sodium and water retention, resulting in increased BP
- Elderly individuals, those with chronic kidney disease (CKD), and diabetics are particularly susceptible to the hypertensive effects of NSAIDs

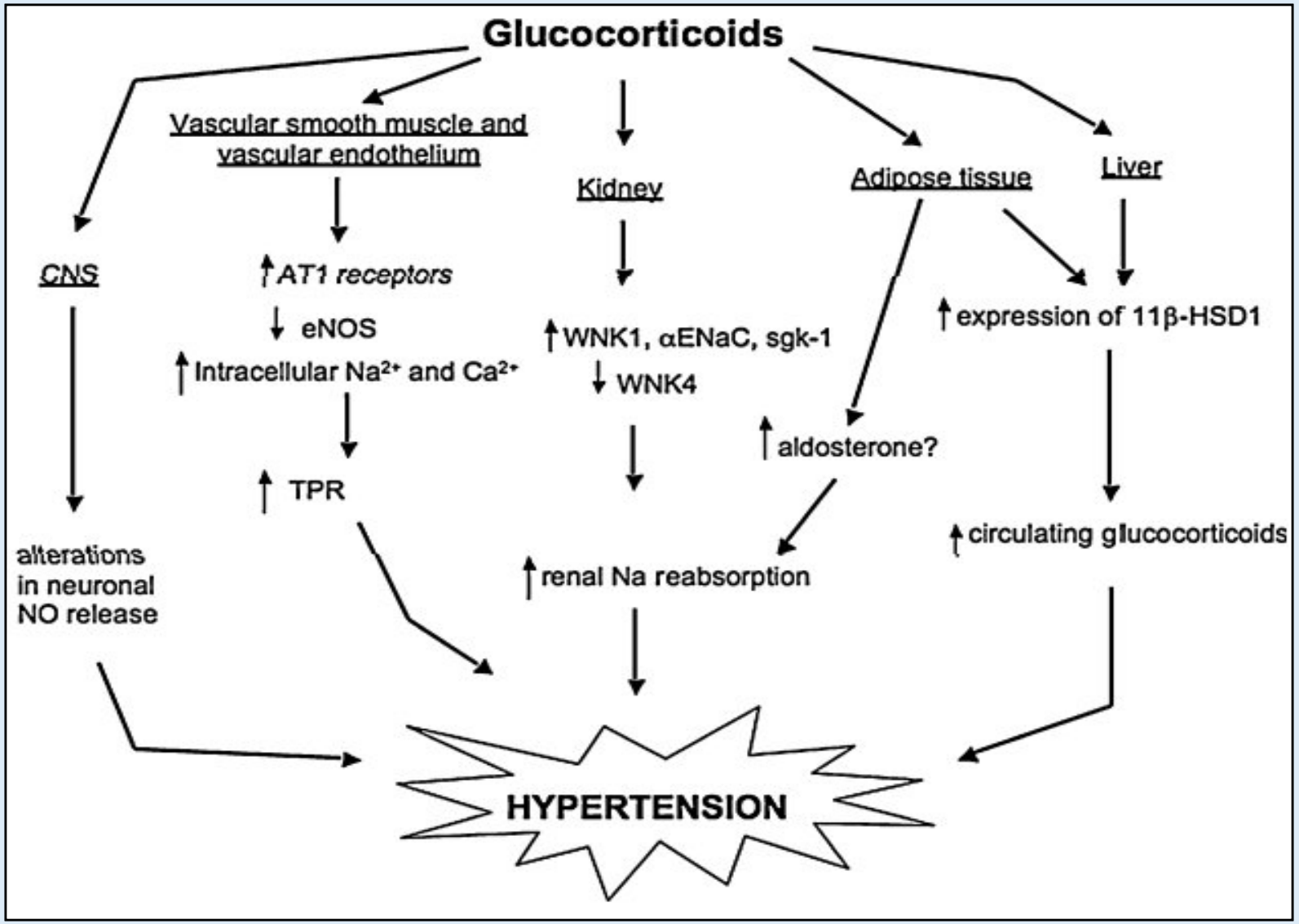
potential elevations in blood pressure due to NSAID use

Drug	BP elevation (mmHg)
Piroxicam	6.2
Ibuprofen	6.5
Naproxen	6.1
Aspirin (dose >150 mg/day)	0.61
Diclofenac	1.6
Indomethacin	4.77
Nabumetone	3.8
Sulindac	2.2
Celecoxib	3.0

Immunosuppressant induced Hypertension: Mechanism of action



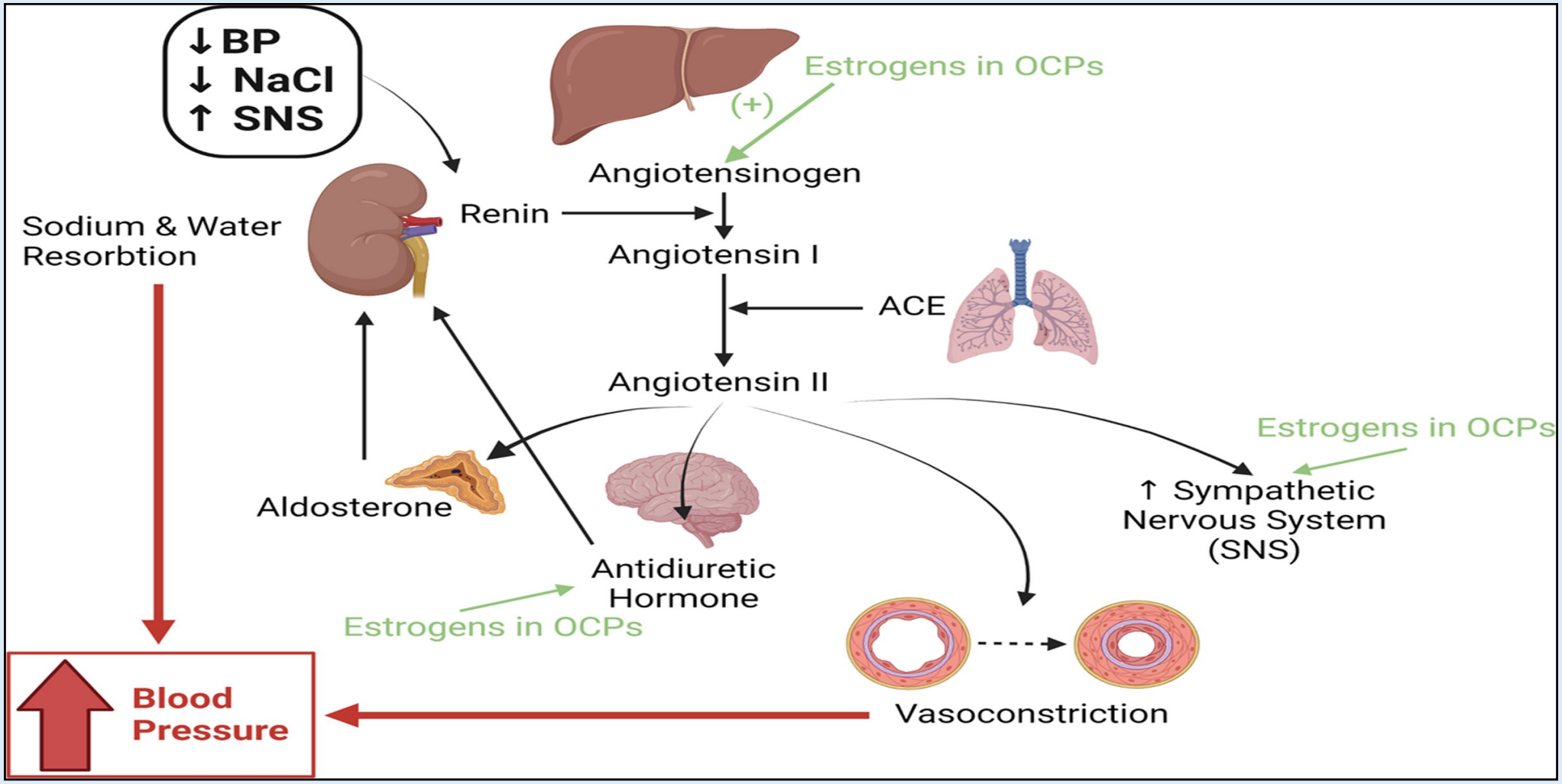
Glucocorticoid-induced hypertension: Mechanism of action



- Approximately 80% of patients with Cushing's syndrome have hypertension
- 20% of patients receiving chronic pharmacological treatment with glucocorticoids have hypertension
- Mediated through promiscuous activation of the mineralocorticoid receptor by excess glucocorticoid

Goodwin, J. E., & Geller, D. S. (2011). Glucocorticoid-induced hypertension. Pediatric Nephrology, 27(7), 1059–1066

Oral Contraceptive-Induced Hypertension: Mechanism of action

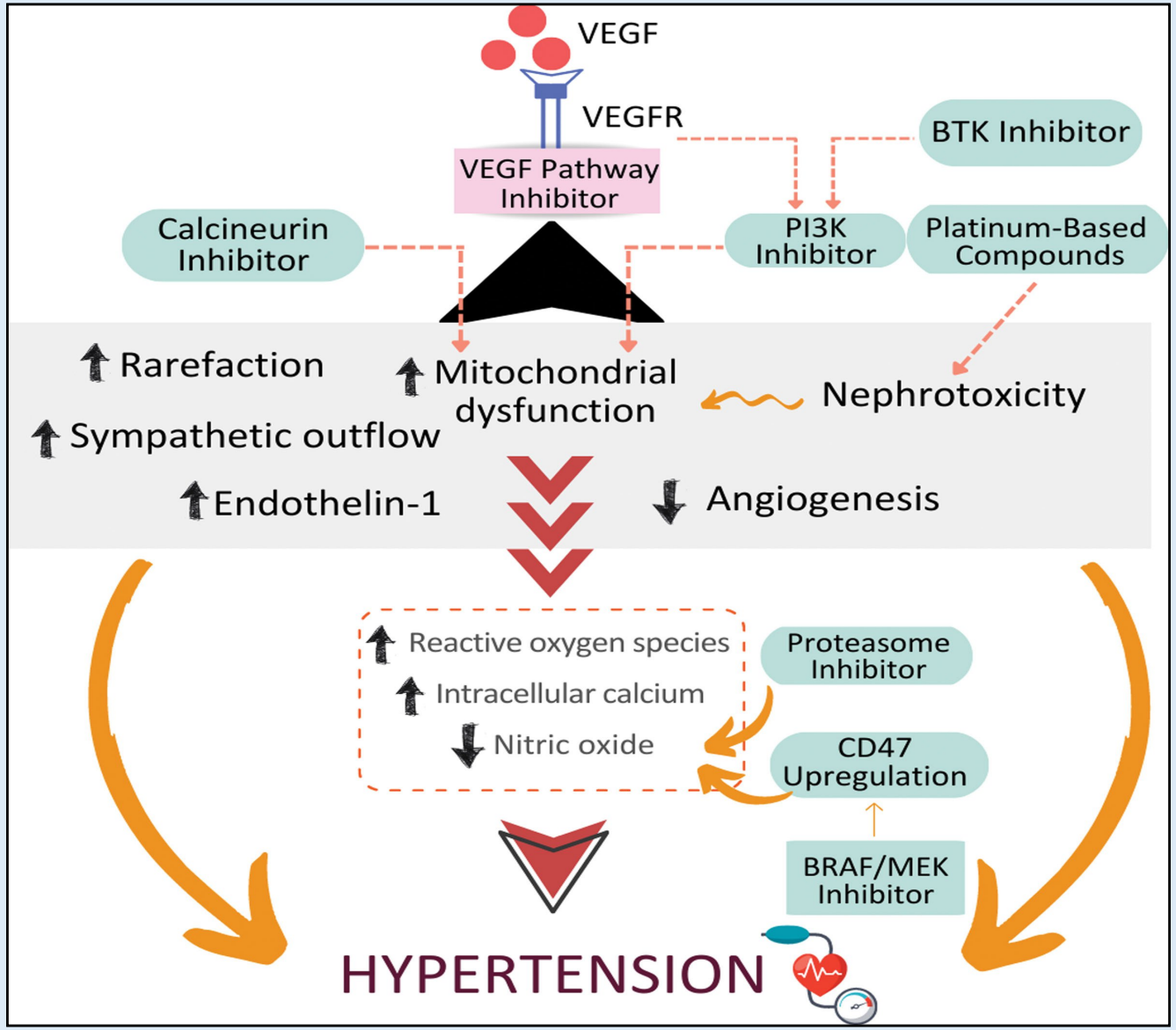


Influence of antidepressant drugs on blood pressure and heart rate

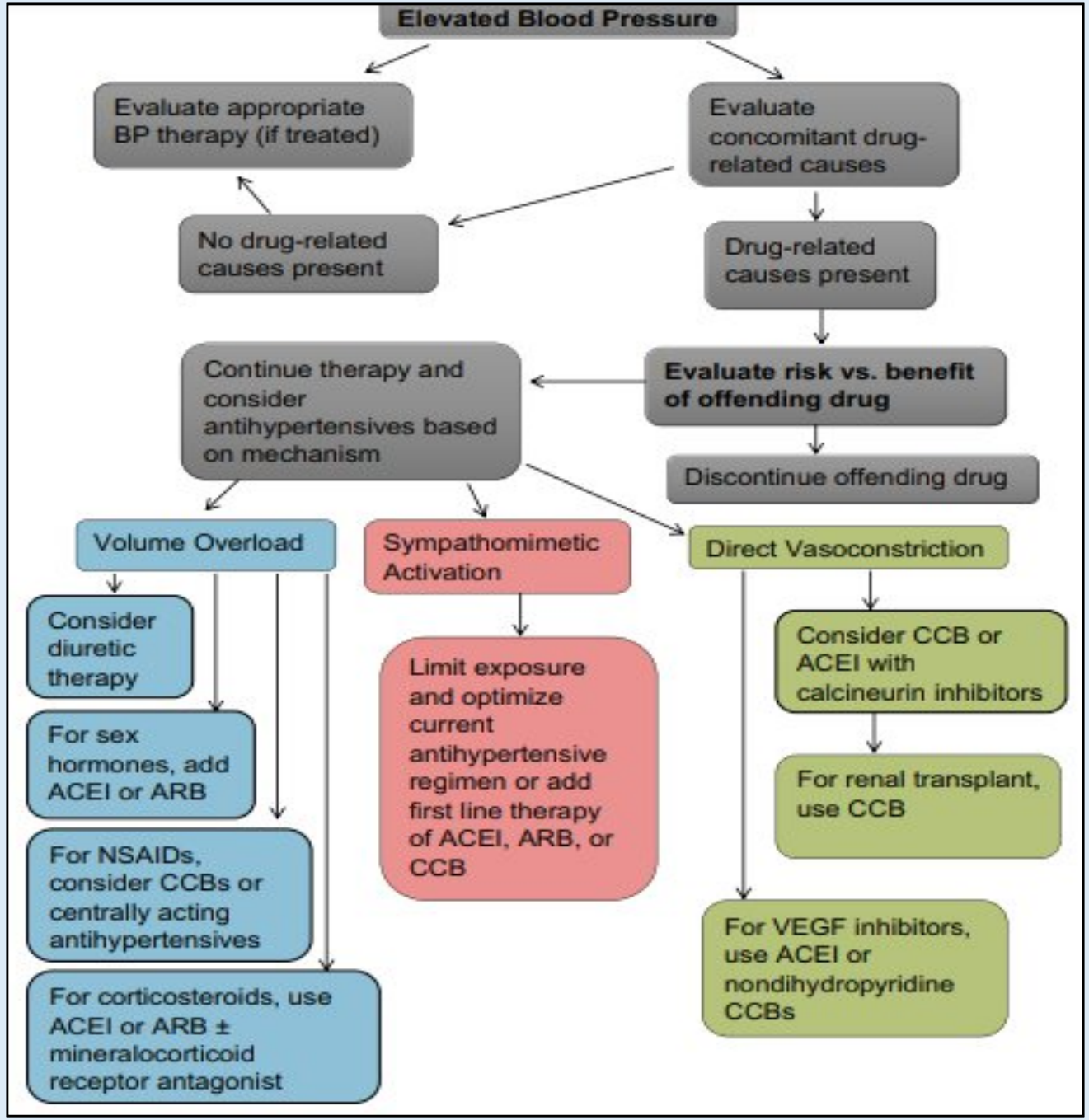
Antidepressant	Hypertension	Orthostatic hypotension	Tachycardia	Bradycardia
SSRI				
Citalopram	0	0	0	+ (53)
Escitalopram	0	0	0	+ (53)
Paroxetine	0	0	0	+ (53)
Fluoxetine	0	0	0	+ (53)
Fluvoxamine	0	0	0	+ (53)
Sertraline	0	0	0	+ (53)
SNRI				
Venlafaxine	++/+++[a]	+ (63–66)	++	0
Desvenlafaxine	++	+ (53)	++	0
Duloxetine	+	+	+	0
Milnacipran	++	0	+	+[b] (67)
Levomilnacipran	++	0	+	0
REBOXETINE	0	0	+	0

Prog Cardiovasc Dis. (2016) 58:514–28. 10.1016/j.pcad.2015.11.003

Anticancer Therapies Causing Hypertension- Mechanism of action



Algorithm for the management of drug-induced elevations in blood pressure



Clinical Presentation

Symptoms:

- Often asymptomatic.
- Can present with headaches, dizziness, or visual disturbances in severe cases.

Key Features of Drug-Induced Hypertension (DIH):

- Onset of hypertension after starting a new medication.
- Exacerbation of pre-existing hypertension without other apparent causes.
- Improvement in blood pressure upon discontinuing the suspected drug.

Diagnosis

Clinical History:

- Detailed drug history: New medications, dosage, and duration.
- Identification of high-risk drugs.

Diagnostic Workup:

- Blood Pressure Monitoring: Document BP changes after starting the drug.
- Lab Investigations: Assess renal function, electrolytes, and hormonal profiles (if RAAS involvement suspected).

Differential Diagnosis:

- Rule out primary hypertension and secondary causes unrelated to medications.

Management Strategies

Discontinuation or Substitution:

- Stop the offending drug, if clinically feasible.
- Substitute with an alternative medication with a lower risk of hypertension.

Lifestyle Modifications:

- Encourage sodium restriction,
- regular physical activity, and
- stress reduction.

Pharmacological Interventions:

- Tailor antihypertensive therapy based on the mechanism:Diuretics for sodium retention.
- Beta-blockers for sympathetic overactivity.
- ACE inhibitors/ARBs for RAAS activation.

Prevention

Patient Education:

- Inform patients about potential side effects of prescribed drugs.
- Encourage adherence to prescribed doses.

Monitoring:

- Regular blood pressure checks for high-risk patients on NSAIDs, corticosteroids, or calcineurin inhibitors.

Prescribing Practices:

- Choose drugs with lower hypertensive risk when possible.
- Avoid polypharmacy in elderly or vulnerable populations.

Conclusion

Drug-induced hypertension is a preventable and treatable condition.

Early identification, regular monitoring, and education are critical to mitigating risks.

Awareness and proactive management of drug-induced hypertension can prevent significant morbidity and improve patient outcomes

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