ACE Inhibitors
Angiotensin Receptor Blockers

Perioperative Hypotension
Angioedema

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Agenda

- Discuss Angiotensin Converting Enzyme Inhibitors & Angiotensin Blocking Agents
  - Indications for use
  - Effects on Renin Angiotensin Aldosterone System
    - Primary & Secondary Effects
  - Refractory Perioperative Hypotension During Anesthesia
    - Continue or Hold Agents Perioperatively
  - Risks of Angioedema

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Top 5 Prescribed Medications in 2024

Semaglutide	Ozempic
Adalimumab	Humira
Apixaban	Eliquis
Dulaglutide	Trulicity
Empaglifloxin	Jardiance

- Antihypertensive medication ranking in 2024
  - not in top 50 prescribed medications in US
  - however → total sales in 2024 → $24.5 billion

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Top 5 Prescribed Anti-Hypertensives 2024

Lisinopril	ACE Inhibitor
Losartan	Angiotensin Receptor Blocker
Amlodipine	Calcium Channel Blocker
Hydrochlorothiazide	HCTZ Diuretic
Metoprolol	Beta Blocker

Anti-Hypertensive Agent		2024 Estimated Sales ($ million)
Lisinopril	(ACEI)	$415.5 million
Losartan	(ARB)	$292 million
Amlodipine	(CCB)	$395 million
Benazepril	(ACEI)	$450 million
Amlodipine – Benazepril Combo		Unavailable but significant

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ACE – Inhibitors & Angiotensin Receptor Blocking Agents

- ACE – Inhibitors & ARBs
  - most prescribed antihypertensive agents in US
    - 28.5% patients using antihypertensive meds → use ACE - Inhibitors
  - 40 million individuals use ACE – I worldwide
  - Captopril was 1st ACE – I developed
  - Lisinopril is the most widely used ACE – I
- Renin Angiotensin Aldosterone System
  - need basic understanding of RAAS to appreciate how meds work

Immunol Allergy Clin N Am. 2023; 43: 513

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Renin Angiotensin Aldosterone System

RAAS

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Renin Angiotensin Aldosterone System

- RAAS → major role in management of pathologic conditions
  - #1 Hypertension
  - #2 Heart failure with or without reduced ejection fractions
  - #3 Chronic DM & CKD
  - Medications blocking RAAS pathways will improve outcomes in these disorders
    - ACE – Inhibitors & Angiotensin Receptor Blocking Agents

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Renin Angiotensin Aldosterone System

- Overview
  - Angiotensin Converting Enzyme (ACE)
    - converts → Angiotensin I to Angiotensin II
    - ACE → found in capillaries in lung & kidney endothelium
  - Angiotensin II
    - potent vasoconstrictor
    - metabolizes bradykinin → a vasodilating agent
  - ACE – Inhibitors
    - inhibit conversion → Angiotensin I to Angiotensin II
    - reduces BP by vasodilation & inhibiting release of aldosterone to retain fluid
    - no Angiotensin II to bind to AT – 1 Receptor to vasoconstrict

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Renin Angiotensin Aldosterone System

- RAAS
  - critical regulator of intravascular volume, electrolyte balance, & systemic vascular resistance
  - function → dependent on 3 compounds
    - Renin
    - Angiotensin II
    - Aldosterone

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RAAS

- Renin
  - Activation of juxtaglomerular cells in kidney arterioles cleaves prorenin to renin
  - Stored renin is released by 4 major stimuli
    - Changes in renal perfusion pressures
    - Decreased Na & Cl → in distal convoluted kidney tubules
    - Increased β - 1 sympathetic stimulation secondary to hypotension
    - Hypokalemia

Decreased Renal Perfusion & Reduced Kidney Tubular Sodium → Release Renin in Kidney to Convert Angiotensinogen to Angiotensin I in arterioles of lung and kidney

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RAAS

- Angiotensinogen
  - synthesized & secreted by liver
  - renin → cleaves angiotensinogen to form → Angiotensin I
  - angiotensin I has no biologic activity
- Angiotensin Converting Enzyme (ACE)
  - ACE = Kininase II enzyme
  - found primarily in pulmonary endothelial cells
  - cleaves Angiotensin I → to Angiotensin II

Angiotensin I has no clinical effects

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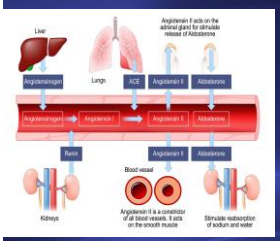
Renin Angiotensin Aldosterone System



- Pro-renin cleaved to Renin in Kidney
- Renin converts angiotensinogen to Angiotensin I
- ACE enzyme converts Angiotensin I to Angiotensin II
- Angiotensin II has multiple effects

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RAAS

- Angiotensin II
  - responsible for the physiologic effect of the renin angiotensin aldosterone system
- Angiotensin II acts on 2 receptors
  - Angiotensin II Type 1 Receptor (AT – 1)
  - Angiotensin II Type 2 Receptor (AT – 2)

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RAAS & Angiotensin II

- Angiotensin II Type 1 Receptor
  - found in multiple tissues
    - Heart, Blood Vessels, Kidney, Adrenal Glands, Pituitary, & CNS
- Physiologic Effects of Angiotensin II on Type 1 Receptor
  - *Vasoconstriction* of arterioles
  - *Release Aldosterone* from Adrenal Cortex
  - *Increase Na reabsorption* & water reabsorption
  - *Increase Sympathetic* mediator release
  - *Release Vasopressin* from posterior pituitary

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RAAS

- End results of Angiotensin II Type 1 Receptor Activation
  - Rapid vasoconstriction → ↑ BP, MAP, & SVR
  - ↑ Cardiac Output
  - ↑ Na & water retention & excretion of K
  - Restore perfusion of organs

Current Opin Anesthiol.2018;31:50 Anesth Analg.1999;89:1143 J Crit Care.2015;30:613

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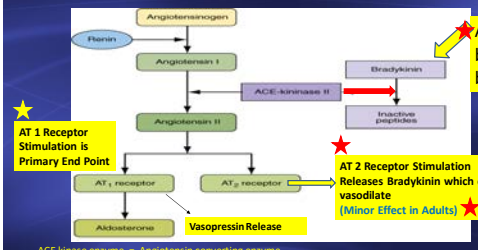
Renin – Angiotensin System



ACE kinase enzyme = Angiotensin converting enzyme
ACE reaction yields Angiotensin II Also breaks down bradykinin to inactive compound

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RAAS

- Angiotensin II Type 2 Receptors
  - found in heart, kidney, adrenal glands, & brain
  - opposite effects of Type 1 Receptors
    - see vasodilation & loss of Na in urine

Angiotensin II Type 2 Receptor Stimulation → Less prominent than Type 1 Receptors → Minor Effects

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ACE & Angiotensin II

- ACE enzyme → acts on kallikrein – kinin pathway to degrade bradykinin
  - prevents vasodilation
- Angiotensin II → can bind to AT 2 receptors → releases bradykinin → causes vasodilation & myocardial depression
  - minor effect → bradykinin is metabolized by ACE enzyme

Anesth Analg.1999;89:1143 J Crit Care.2015;30:613

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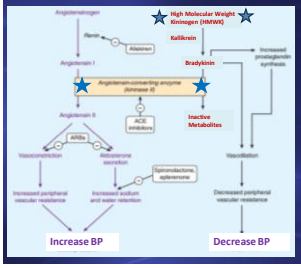
ACE Enzyme & Bradykinin



- ACE converts Angiotensin I to Angiotensin II
- Kallikrein Kinin Contact Pathway
  - High molecular weight kininogen is cleaved by kallikrein
  - Bradykinin is produced
- ACE metabolizes the bradykinin from the contact pathway

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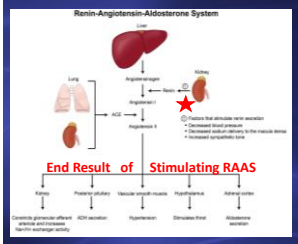
RAAS Reversing Hypotension



- RAAS very responsive to hypotension
  - 1 of 3 mechanisms to restore BP & perfusion of tissue
- ★Factors stimulating Renin Release
  - Decreased Blood Pressure & Perfusion in Kidney
  - Decreased Na levels in kidney tubules
    - want to reabsorb Na & water

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Example: RAAS Reversing Anesthesia Hypotension

- Perioperative Hypotension secondary to interaction of anesthetic agents + Patient's medications
- Angiotensin II reacts to restore BP & perfusion
  - Direct Effects
    - Vasoconstriction, Adrenal Medulla release Epi & Nepi, & reabsorb Na & water
  - Indirect Effects
    - Release aldosterone for reabsorption of Na & water, release ADH – Vasopressin for vasoconstriction & water retention

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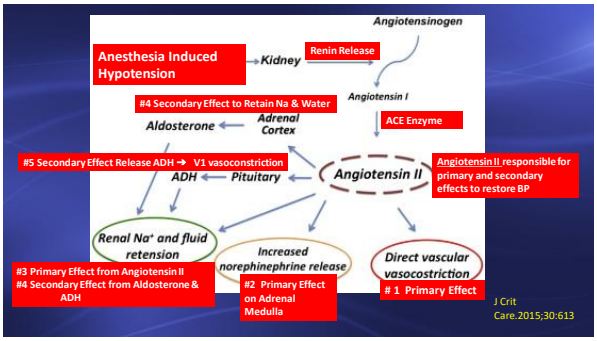

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Angiotensin Converting Enzyme Inhibitors

ACEI

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ACE – Inhibitor Medications

"PRILS"

Brand Name		Generic	
Lotensin		Benazepril	
Capoten	(Typically generic only)	Captopril	1st ACEI
Vasotec		Enalapril	
Monopril	(Typically generic only)	Fosinopril	
Prinivil, Zestril		Lisinopril	Most used ACE-I
Univasc	(Typically generic only)	Moexipril	
Aceon	(Typically generic only)	Perindopril	
Accupril		Quinipril	
Altace		Ramipril	
Mavik	(Typically generic only)	Trandolapril	

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ACE - Inhibitors

- ACE – I → Pharmacokinetic properties
  - 2 types of agents → prodrugs & non-prodrugs
    - prodrugs require hepatic conversion to an active form

ACE – Inhibitor Prodrug →	Active Drug	ACE – Inhibitor Non- Prodrug
Enalapril	Enalaprilat	
Fosinopril	Fosinoprilat	Lisinopril
Benazepril	Benazeprilat	Captopril
Quinapril	Quinaprilat	
Moexipril	Moexiprilat	

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ACE - Inhibitors

- Enalaprilat
  - only available → IV ACE – Inhibitor medication
  - Indication for Use
    - hypertensive urgencies or emergencies
    - rapid onset of action
  - Dose
    - 0.625 to 1.25 mg IV Q6h
    - increase dose as indicated → up to 5 mg IV Q6h

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ACE - Inhibitors

- PO administration
  - peak serum levels within 1 hour
  - dosing → single daily dose
- Liver disease
  - use non-prodrugs due to decreased liver activation

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ACE - Inhibitors

- Contraindications
  - Pregnancy → not used in 2nd or 3rd trimester due to fetal risks
  - Breastfeeding
    - ACE – I have active metabolites with long half lives
    - Breast milk will contain parent drug + metabolites
    - Lisinopril has short half life + no active metabolites
    - No data to support use if breastfeeding

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ACE - Inhibitors

- Adverse Effects

Dry Cough	10 to 20%
Dizziness	12 to 19%
Hypotension	7 to 11%
Increased BUN & Creatinine	2 to 11%
Syncope	5 to 7%
Hyperkalemia	2 to 6%

Key Adverse Effects: Dry Cough & Hyperkalemia

- Hyperkalemia
  - ACE – I → prevent release of aldosterone
    - do not retain Na or water but retain potassium in kidney

Consider K levels preop

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ACE - Inhibitors

- Lithium
  - ACE – I → reduce Lithium clearance by kidney
    - risk of Lithium Toxicity
    - patients on Lithium should get preop level checked
    - be aware of clinical signs of Lithium Toxicity

Lithium Toxicity	Clinical Signs
Mild Symptoms	N/V, Lethargy, Hand Tremors, & Fatigue
Moderate Symptoms	Confusion, Agitation, Delirium, & Tachycardia

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ACE – Inhibitor Dry Cough

- Incidence → 5 to 35% of patients using ACE – I
- Pathology → secondary to → ↑ bradykinin & substance P
- Onset → within 1 week of ACE-I initiation → up to 6 months
  - 1 report → anytime in 1st year of use
- More common in older individuals → Age ≥ 60
- Women 3X more likely than men

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ACE – Inhibitors & Dry Cough

- Greater incidence in East Asian population
- Laboratory findings
  - Normal → C4, C1 – INH levels, C1 – INH functional levels
- Increased risk of airway obstructions & bronchospasm
- Exacerbation of asthma attacks
- Treatment → Stopping the ACE-I

Switch to ARB agent → Lower risk of Cough

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Indications for ACE Inhibitors

- Hypertension
  - HTN is risk factor for developing
    - CAD, HF, Strokes, CHF with reduced ejection fractions, and MI
    - CKD
  - BP 130 to 139 / 80 to 89 → in presence of atherosclerotic heart disease (ASCVD)
    - initiate ACEI or ARB therapy

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Indications for ACE Inhibitors

- Hypertension
  - BP > 140 / 90 without clinical Cardiovascular Disease (CVD)
    - CVD → presence of CAD, CHF, Stroke, or peripheral vascular disease
  - BP > 130 / 90 + any of the following
    - Diabetes I or II, CKD, HF, Stable ischemic disease, age ≥ 65
- History of STEMI in past 24 hours
  - especially in patients with anterior wall MI, HF, EF ≤ 40%

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Indications for ACE Inhibitors

- Patients with Coronary Artery Disease (CAD) + HTN
  - ACEI indicated
  - Especially if there is a history
    - Left Ventricular Dysfunction
    - Diabetes
    - CKD

Contraindications for ACE – Inhibitors
Hereditary Angioedema
Acquired Angioedema

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Other Indications for ACE Inhibitors

- CKD patients + HTN
  - regardless of race or DM status → ACEI improve kidney function
- HTN in Non-Black Diabetic population without CKD
  - initial therapy → ACEI, ARB, CCB, or thiazide diuretic
- HTN in Black Diabetic patients without CKD
  - use thiazide diuretic or CCB → no ACEI or ARB agents

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Off Label Indications for ACE - Inhibitors

- Delay progression of Diabetic Neuropathy in Type I & II DM
- Non-alcoholic Fatty Liver Disease (NALFD)
  - decreases cirrhosis risk and liver cancer risk
- Possible reduced mortality rate in Atrial Fibrillation
- HTN + Alzheimer's Disease
  - prevention of neuromuscular junction degradation + improved muscle strength

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ACE- Inhibitors Mechanism of Action

Renin – Angiotensin – Aldosterone System

Antihypertensive Agent

(Primary Indication)

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Renin Angiotensin Aldosterone System

- Clinical Overactivation of RAAS
  - will increase risk of developing cardiovascular disease
    - results in → hypertension, HF, MI, & reduced ejection fractions
  - medications can correct these abnormalities

Primary Medications → ACE- I & ARBs

  - Angiotensin Converting Enzyme Inhibitors → ACE-I
  - Angiotensin Receptor Blocking Agents → ARBs

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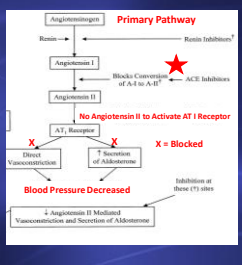
ACE – Inhibitors and RAAS



- ACE – I → block formation of Angiotensin II
  - can not activate AT 1 Receptor
  - end result = ↓ BP
  - no release of Aldosterone
    - increased diuresis of Na & water in kidney
    - less fluid retention → ↓ BP
  - hyperkalemia secondary to retained K in kidney

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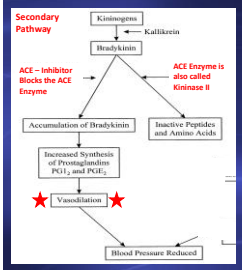
ACE – I & Kallikrein – Kinin Pathway



- ACE – I blocks Bradykinin metabolism by Kininase II (ACE enzyme)
  - accumulation of Bradykinin
- Bradykinin causes vasodilation
- BP is reduced

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Angiotensin Receptor Blocking Agents

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Angiotensin Receptor Blocking Agents

- Indications for ARBs overlap with ACE – I medications
  - Hypertension
  - HF with or without reduced EF
    - EF < 40% → major indication
  - DM nephropathy
  - CKD
  - Recent MI with EF < 40%
  - Patients who can not tolerate ACE – I
    - dry cough or angioedema

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ARB Agents

- Contraindicated
  - pregnancy & breastfeeding
- Drug interactions
  - increased risk for hyperkalemia
    - especially when combined with K sparing diuretics or K supplements
  - do not use in combination with ACE – I
    - develop severe hypotension, acute renal failure, or hyperkalemia

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Angiotensin Receptor Blockers

- Blocks Angiotensin II binding to AT 1 receptor
  - ↓ MAP
  - ↓ release of aldosterone
  - ↓ release of Vasopressin (AVP)
- Angiotensin II can bind to AT 2 receptors
  - ↑ vasodilation
  - ↓ myocardial contractions
  - ↓ decrease HR

ARB Medications do not Block the AT 2 receptors

Curr Opin Anesthiol.2018;31(1):50

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Angiotensin Receptor Blockers

- ARBs → AT 1 receptor blockade >> ACEI AT 1 blockade
- ARBs → Cause more profound hypotension than ACEI
  - especially when combined with diuretics
- Intraoperative hypotension from ARBs
  - less responsive to phenylephrine, ephedrine, and epinephrine
  - even less responsive to Nepi

Curr Opin Anesth.2010;23:687

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Angiotensin Receptor Blockers (ARB)

Losartan	Cozaar
Valsartan	Diovan
Eprosartan	Teveten
Olmesartan	Benicar
Telmisartan	Micardis
Irbesartan	Avapro
Candesartan	Atacand

"sartans"

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Perioperative Hypotension from ACE – Inhibitors and Angiotensin Receptor Blockers

Do you Hold or Continue Medications for Surgery?

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Anesthesia Issues with ACEI & ARBs

- ACEI & ARBs Perioperative Issues
  - #1 Agents continued for Surgery
    - Develop Intraoperative Hypotension IOH → resolved with typical vasopressors → ephedrine or phenylephrine
  - #2 Agents continued for Surgery
    - Develop catecholamine resistant hypotension → resistant to typical vasopressors → ephedrine, phenylephrine, & even epinephrine
    - Intraoperative vasoplegia
      - requires epinephrine infusions, Nepi, vasopressin, methylene blue or glucagon

Curr Opin Anesth.2018;31(1):50-54

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Anesthesia Issues

- ACEI & ARBS → Perioperative Issues
  - #3 Agents Held for Surgery
    - Develop intraoperative Hypertension
    - Exacerbate HF → further reduction of cardiac output
    - Potential Risk of MINS, AMI, or Stroke

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Question: Hold or Continue Perioperatively?

- Current Evidence – Protocols
  - based primarily on inpatient populations not ambulatory populations
- Ambulatory Surgery & Anesthesia
  - minimally invasive surgery → shorter surgical duration
  - negligible fluid loss & shifts
  - less hemodynamic instability
  - shorter acting anesthetic agents → rapid emergence
  - risks should be less than inpatient non-cardiac surgery

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ACEI & ARBs Hold or Continue

- No real consensus → Opinions change every few years
- Majority of literature → based on → inpatient surgery
  - major surgical procedures → cardiac & noncardiac surgery

Non-Cardiac Surgery	Non-Cardiac surgery
ACC/AHA 2014	Reasonable to continue meds If hold agent, restart as soon as possible
Canadian Society Cardiology 2017	Hold agents for 24 hours preop
European Society Cardiology 2014	Well controlled HTN patients: Consider holding agent for surgery Patients with HF or LV systolic dysfunction: Continue agents if patient is stable

Anesth Analg. 2024; 138(4) Eur Heart J. 2014; 35:2383

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ACE – I & ARB Agents: Hold or Continue

- Concerns with ACEI & ARBs
  - Hold the agent → possible HTN and/or cardiac complications
  - Take the agent → cardioprotective but possible hypotension

European Heart Journal SPACE Trial 2024	Holding vs Continuing Agents Perioperatively
	1. Risk of Myocardial Injury Non-Cardiac Surgery (MINS) → Similar in Both Groups
	2. Intraoperative Hypotension (IOH) → Similar in Both Groups
	3. Need for Vasopressors Similar in Both Groups
	4. Increased Risk of Perioperative Hypertension if Hold Agents

Non-Cardiac Surgery → Hold or Continue → Should Have Low tolerance for Treating Intraoperative Hypotension or Hypertension

European Heart Journal. 2024; 45(13): 1146 European Heart Journal. 2024; 45(13): 1156

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ACEI & ARB

Second Study From 2024

- 2024 STOP or NOT Trial → Elective Major Noncardiac Surgery
  - 2 study groups
    - Continue ACEI or ARB until day of surgery
    - Hold ACEI or ARB for 48 hr prior to surgery
  - Studied Mortality & Major complications 0 to 28 days postop
  - Incidence of IOH (MAP < 60) for both groups
  - Need for Vasopressors

JAMA. 2024;332(12):970

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Stop or Not Trial 2024

- NO difference for all cause mortality & major complications
  - MACE → MINS, vascular death, AMI, stroke, & cardiac arrest
  - Identical at 22% for holding or continuing medications

No Difference in MACE if Give or Hold ACEI or ARB

- Incidence of IOH **Higher Incidence of IOH if Continue Meds**
  - 54% if continued medications
  - 41% if stopped medications

JAMA. 2024;332(12):970 Cardiology in Review. 2025 www.cardiologyinreview.com

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Stop or Not Trial 2024

- Conclusions
  - #1 Hold or Continue ACEI or ARB
    - MACE or Mortality → No Difference between Groups
  - #2 Intraoperative Hypotension (IOH)
    - Higher incidence if Continue ACEI or ARB but still happens even if hold the medications

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ACC/AHA 2024 Perioperative Guidelines for Non-Cardiac Surgery

3rd Study 2024

- #1 Well Controlled Hypertensive Patient using ACEI or ARB

✚ **HOLD AGENTS**

- #2 Patient having Elevated Risk Non-Cardiac Surgery
  - Potential for excessive intraoperative blood loss
  - Expect significant hemodynamic abnormalities

Hold the ACEI or ARB for 24 Hours Preop
Prevents Additional Perioperative Hypotension- Tachycardia & Perfusion Abnormalities

Circulation 2024; 150: e351-442

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ACC/AHA 2024 Perioperative Guidelines for Non-Cardiac Surgery

- #1 Patient taking ACEI or ARB → History of Heart Failure
  - HF with mildly reduced EF
  - HF with no reduction of EF
  - HF with significant reduction of EF < 40%
  - All benefit from use of ACEI or ARB medication

CONTINUE AGENTS

✚

- #2 Patient with Severe Hypertension (poorly controlled)

Continue the ACEI or ARB for Surgery
Benefits for HF outweigh risks of Hypotension

Circulation 2024; 150: e351-442

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ACC/AHA Summary for Inpatient Major Surgery

- Well Controlled HTN ± Major Surgery with Potential Significant Cardiovascular Hypotensive Complications
  - Hold the ACEI or ARB medication perioperatively
- Poorly Controlled Significant HTN ± Patients with HF
  - Continue the ACEI or ARB medication perioperatively
  - We do not do office anesthesia on uncontrolled HTN patients

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2025 Stop or Give Meds

- Concerns for Non-Cardiac Inpatient surgery
  - ACEI or ARB continued → may see intraoperative hypotension
  - ACEI – ARB stopped → exacerbate hypertension or heart failure
- Conclusions & Recommendations
  - #1 Continuing medication → ★ significant risk of IOH
  - #2 Hold or Not Hold → ★ no significant difference observed for
    - All cause mortality, MACE, AKI, or Hypertension

J. Cardiothoracic & Vascular Anesthesia. 2025;39: 2057

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Conclusion for Stop or Not 2025

- Conclusions
  - Stop or Hold Agents
    - No difference in Mortality or Morbidity
  - Continue Agent Perioperatively
    - Risk of IOH
      - most respond to typical vasopressors

Up to Practitioner

Probably Continue Meds

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Current Recommendations

- Recent Publications
  - Do not address ambulatory surgery
  - Do not address types of office surgery performed
- Comments found in articles for ambulatory surgery
  - Reasonable approach → Hold ACEI & ARBs for office surgery
    - Cataracts, Endoscopies, Dental Office Surgery

No Data for Statement → Just Opinion

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Ambulatory Surgery

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2010 ACE –I & ARB Ambulatory Surgery

- Incidence of Perioperative Hypotension with Medications
  - #1 ARB + Diuretic → most profound IOH → others follow in order
  - #2 ACEI + Diuretic
  - #3 ARB Agents more frequent & significant IOH than ACEI
  - #4 ACEI Agents

2010 Study

- Incidence of IOH in patients using antihypertensive meds
  - ARB incidence 100%
  - ACEI incidence → 67%
  - β blockers & CCB → 60%

Curr Opin Anesthesiol 2010; 23; 687

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2010 ACE –I & ARB Ambulatory Surgery

- ACEI or ARB + Diuretic
  - hold Diuretic day of Surgery to reduce IOH

2010 Study

- ACEI or ARB as single agent
  - continuing agent → very likely to see IOH
  - holding agent → may still see IOH but not as severe as above
- Holding ACEI or ARB dose day of surgery
  - no adverse cardiac or renal effects detected

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2010 ACE –I & ARB Ambulatory Surgery

- IOH → intraoperative hypotension
  - cases responded to → Fluids and/or Vasopressors
    - Ephedrine, Phenylephrine, & mini bolus epinephrine

2010 Study

- Conclusion of 2010 Ambulatory Study
  - likely to see IOH if hold or continue
  - no CVS or Renal adverse effects if hold 1 dose

2010 Study Consensus Opinion
Maintain Antihypertensive Agents Perioperatively

Curr Opinion Anesthesiol 2010; 23: 687

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2014 Ambulatory Surgery with ACE-I or ARB

- Holding ACEI or ARB day of surgery
  - did not ↑ risks → preoperative HTN, cancelled surgery, admissions, or post operative HTN in PACU

2014 Study

- Continuing ACEI or ARB for surgery
  - Preop BP → No significant difference between holding or giving ACEI or ARB
  - No difference in Post op Hypertension if held or gave the drug

Anest Analg.2014;118:938-44

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2014 Ambulatory Surgery with ACE-I & ARBs

- Patients who are on multiple antihypertensive medications
  - holding the ACE-I or ARB is acceptable
- Patients only taking an ACE-I or ARB
  - continuing the drug is acceptable

2014 Conclusions
Go either way
Hold or Continue

- Patients only taking an ACE-I or ARB
  - discontinuing the day of surgery does not increase adverse hemodynamic outcomes
  - based on review of 526 ambulatory general anesthetics

Anesth Analg. 2014;118:938-44

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2024 Ambulatory Surgery Study 2024

- 537 pts for ambulatory surgery & discharge same day
  - TIVA or inhalation general anesthesia
  - Meds: ACEI, ARB, or combination of (ACEI or ARB) plus another antihypertensive agent

2024 Study

  - IOH definition
    - MAP < 55 for any duration of time
    - SBP decrease > 30% baseline pressure for ≥ 5 minutes
  - Looked at → Early hypotension 0 to 15 mins after induction or hypotension at any point during surgery

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Ambulatory Study 2024

- Important Points to Consider **2024 Study**
  - #1: hypotension is an expected outcome with the use of anesthetic agents regardless of the type of antihypertensive medications
  - #2: hypotension occurs in most patients → more frequent & exaggerated in patients taking antihypertensive medications
  - #3: patients on antihypertensive medications experience more intraoperative variability in pressures (high – low – normal)

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2024 Ambulatory Surgery Study

Antihypertensive Medication	Early IOH 0 to 15 minutes after induction
No Antihypertensive Medications	21% patients IOH due to anesthesia
ACE/ARB < 10 hours before Surgery	30% patients IOH
ACE/ARB > 10 hours before Surgery	41% patients IOH
Another Antihypertensive Med preop	30% patients IOH

- More likely to develop IOH if taking any antihypertensive agent
  - not limited to ACEI or ARB
- Seems reasonable to Continue these agents for surgery

2024 Continue ACEI or ARB for Surgery

Anesth Analg. 2024: 138:763

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Summary for Ambulatory Surgery

- Ambulatory Surgery
  - Consider Continuing the ACEI or ARB perioperatively
    - most hypotension responds to phenylephrine or ephedrine
  - Refractory Hypotension
    - Vasopressin is effective but expensive → not common office medication
    - NEpi is an alternative but rarely used in office
    - Glucagon & Methylene Blue never knew anyone who stocked it in office

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Summary

- Our Surgery is typically elective
- Cause of IOH → Combination of
  - Anesthetic Medications
  - Antihypertensive Agents
  - Other medications with side effect of hypotension
- Rare Cases → Refractory IOH resistant to typical office vasopressors → Phenylephrine, Ephedrine, Epinephrine

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Summary

- Stop the Procedure
- Allow Anesthetic Drugs to redistribute
- Reversal Agents if feel is Indicated to speed recovery
- No further interaction with ACE-I or ARB
- Patient wakes up
- BP returns to normal

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Summary

- BP monitoring → typically Q 5 mins
  - develop IOH → decrease interval to less than Q5min
- BP cuff → right size cuff
- Continuous Finger Cuffs
  - systems can predict hypotensive events
    - can predict if need fluids vs pressors
    - not cost effective for office to date

78

Beta Blockers

- Long term data
  - patients on chronic Beta blockers should continue medications
- Should Beta blockers be started preop for surgical patients
  - did reduce risk of cardiovascular death & AMI
  - problem → increased risk of stroke & total mortality
  - Do Not Start Beta Blockers → Significant Harm

Cardiology in Review 2025

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Management of Hypotension

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Management of Hypotension

- Semi reclined (semi-Fowler) to Trendelenberg position
- Elevate the legs = get 2 liters of fluid return to heart
- Oxygen, ABCs, Vital Signs
- Fluids → increase IV infusion rate with NSS
  - bolus of 250 to 500 mls of LR or NSS
  - healthy patient: 5 to 10 ml/kg → ~ 400 to 500 ml
  - how do you get fluids in???

81

IV Fluid Administration

- Need at least 18 G catheter
- 20 to 60 ml syringe + Pull – Push syringe fluid bolus

IV Catheter Size	Rate of Fluid Administration
14 G	330 ml/min
16 G	205 ml/min
18 G	105 ml/min
20 G	65 ml/min
22 G	38 ml/min
24 G	20 ml/min

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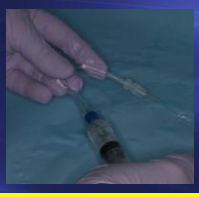
Pull Push IV Fluids



1. Insert Syringe into IV Port → Open up the IV line roller clamp
2. Clamp off the IV line distal to the syringe → Pull back on the syringe plunger for fluid
3. Clamp off the IV line proximal to the syringe → Inject the fluid from the syringe

83

Management of Hypotension

- Fluid challenges often not done especially in office
- Vasopressors are typical 1st line therapy
- Indications → MAP < 65 → baseline MAP drop ≥ 20%
- Office vasopressors typically
  - Ephedrine & Phenylephrine

Personally, treat when MAP < 65 in normotensive patient. Some wait until MAP < 60

84

Ephedrine

- Vasopressor → alpha & beta receptor agonist
  - indirect effects > direct effects
  - ↑ HR, SBP, DBP, & MAP
- Venous effects > arterial effects
  - get ↑ venous return to heart → ↑ preload & CO
  - some increase in afterload
- β – 2 effect → bronchodilation

85

Ephedrine

- Adults → dose is 5 mgs IV to start
  - 5 to 10 mg → every 5 to 10 minutes
  - up to 50 mg total dose in office
- Onset → very rapid → almost immediate
- Peaks → 2 to 5 minutes
- Duration → 10 to 20 minutes

5 mg IV every few minutes to effect

Stanford Manual: 5 to 20 mg IV

Integrated Blood Pressure Control.2014;7:49

86

Ephedrine

- Ampule = 50 mg/ml 1 ml vial
- Dilute 50 mgs in 10 ml fluid
  - 5 mg per ml
- CAD patients & MAOI
  - may cause dysrhythmias & severe hypertension
- Use: **Hypotension & Bradycardia**

87

Phenylephrine

- Vasopressor → direct α – 1 effects → vasoconstriction
  - venous effects > arterial effects
- ↑ MAP, ↑ venous return, ↑ SVR (afterload)
- Reflex bradycardia → can decrease CO
- Increase in coronary perfusion
- Decrease in cerebral perfusion → risk of delirium
- Rare to see dysrhythmia

Anesthesiology. 2024; 140(4): 657 Anesthesiology 2021;135(5); 788

88

Phenylephrine

- Onset < 1 minute
- Peak few minutes
- Duration 15 to 20 minutes
- Dose → 100 mcg IV Q 5 minutes
  - expect 25 mm rise in BP → each 50 to 100 mcg dose
- Infusion → 10 to 200 mcg/min

Stanford Manual: 100 to 300 mcg IV

89

Phenylephrine

- Vial is 10 mg/ml 1 ml vial
  - 10 mgs in 100 ml fluid = 0.1 mg/ml or 100 mcg per ml
  - 10 mgs in 10 mls fluid → 1 ml and dilute in 10 mls of fluid
    - 0.1 mg per ml or 100 mcg per ml (double dilution)
- Use → **Hypotension + Tachycardia**

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Epinephrine

- Vasopressor & Inotrope
  - α 1 , α 2, β 1, and β 2 effects
- Indications for use
  - allergic reactions, severe bronchospasm, cardiac arrest, & refractory hypotension
  - ↑ MAP, CO, SVR, stroke volume, and heart rate

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Epinephrine

- Refractory hypotension → call EMS
  - potential agents = Epi, Nepi, vasopressin, and glucagon
- Epinephrine bolus → 10 to 20 mcg IV Q 5 minutes
- Epinephrine Infusion
  - 2 to 20 mcg/min or 0.1 to 1.0 mcg/kg/min
  - peaks in 3 minutes
  - duration 5 to 10 minutes

Stanford Manual: 10 to 50 mcg IV

Epi ampule = 1000 mcg/ml
Dilute in 100 ml bag
Epi = 10 mcg/ml

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Norepinephrine

- Vasopressor + inotrope
  - α 1, and β 1 effects → α > β effects
  - sepsis & vasoplegia
- Restores BP while maintaining CO & HR
- Dose → 1 to 10 mcg/min or 0.04 to 0.4 mcg/kg/min
- Onset < 1 minute
- Peaks 1 to 2 minutes
- Duration 2 to 10 minutes

J Cardiothoracic Vascular Anesthesia. 2013;27(1): 156

93

Vasopressin System

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Vasopressin System

- Short term effect of vasopressin
  - vasoconstriction & ↑ MAP

Vasopressin Short Term → Vasoconstriction to Increase BP

- Long term effect → water reabsorption in kidney
  - fluid retention & ↑ in MAP

Vasopressin Long Term → Retention of Na & Water to Increase BP

- Mechanism of action
  - stimulation of V receptors in periphery and brain
  - V1, V2, V3

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Vasopressin Control of Hypotension

- Normal physiologic state
  - Vasopressin has minor role (most of the time) in BP control
  - Sympathetic nervous system & RAAS → primary control of BP
- **When Refractory hypotension occurs**
  - endogenous ADH → is depleted
  - **Catecholamine Refractory Vasoplegia**
    - intraoperative hypotension refractory to sympathomimetic agents

Exogenous Vasopressin May be Needed to Correct Hypotension

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Vasopressin

- Ampule = 20 U/ml
- Dilute to 1 U/ml in → D5W or NSS
- Initial bolus → 0.5 to 1.0 units (2 U per 10 mins)
- Infusion → 0.01 to 0.06 U/min
  - increase infusion by 0.005 U/min → increments Q 10 to 15 mins
- Case report 2008 refractory hypotension resistant to phenylephrine, ephedrine, and Epi
  - 0.4 U bolus repeated; 2 U Q 10 min then infusion 0.04 U/min over 90 minutes

J Clin Anesth.2008;20:135 Anest Progress. 2022; 69: 30-35

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V 1 Receptors

- Stimulate vascular smooth muscle contraction
  - vasoconstriction
- Release nitric oxide from coronary & pulmonary vessels
  - vasodilate vessels in these organs → maintain perfusion
- Overall effect → vasoconstriction in non-vital organs like skin, skeletal muscle, and fat
  - ↑ SVR shifts blood back to heart for organ perfusion
  - ↑ MAP

AANA J. 2013;81:133 Korean J Anest. 2017;70(3):245

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Vasopressin

- Metabolism in liver & by kidney vasopressinases
- Side effects
  - increased SVR can decrease perfusion to kidneys, liver, and mesentery
  - myocardial ischemia & arrest at high doses
  - antidiuretic effects can last 2 to 8 hours → water intoxication possible so water restriction considerations

99

Glucagon & Methylene Blue

- Methylene Blue
  - decreases Nitric Oxide formation
  - Nitric Oxide causes vasodilation
- Glucagon
  - increases cyclic AMP which causes increased inotropic & chronotropic effects in heart

100

Drug	Dose	Onset	Duration
Ephedrine	5-10 mg	< 1-3 min	10-20 min
Phenylephrine	100 mcg	< 1-3 min	15-20 min
Epinephrine	10-20 mcg	< 1 min	5-10 min
Vasopressin Bolus	0.1 – 1.0 U 1 – 4 U	< 1 min	30-60 min
Vasopressin Infusion	0.04 U/min	< 1 min	30-60 min

101

Angioedema

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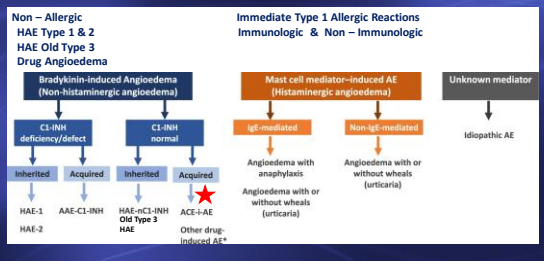
Multiple Types of Angioedema



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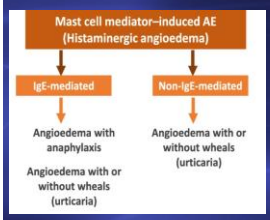
Mast Cell Mediated Angioedema



- Mast cell mediated reactions
- Majority are IgE immediate hypersensitivity reactions
- Urticaria & pruritus common presentation

Reaction	Percentage
Urticaria + Angioedema	50% cases
Isolated Urticaria	40% cases
Isolated Angioedema	10% cases

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Angioedema Comparisons

Clinical Presentation	Mast Cell Angioedema	Bradykinin Angioedema
Onset	Minutes to hour	Hours
Duration	Few Hours	48 to 72 hours
Location	Face, Intraoral, Airway, Extremities, Abdomen, & Chest	Face, Intraoral, Airway, Extremities, Abdomen, & Chest
Urticaria & Pruritus	Common	Rare
Epinephrine, Antihistamines, & Steroid Response	Yes	No

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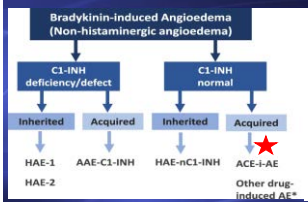
ACE – Inhibitor Angioedema



ACEI & ARB Angioedema are Bradykinin – Induced Angioedema

Drug Induced Angioedema
- ACE – Inhibitor Angioedema
- ARB Induced
- Calcium Channel Induced
- Monoclonal – Biologic Induced

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ACE – Inhibitor Angioedema

- Potentially lethal complication of ACEI use
  - even with laryngeal edema → still see low mortality rate
- Angioedema
  - non-pitting, non-pruritic swelling of submucosal and subcutaneous tissues → lips, tongue, oral cavity, pharynx, and larynx
  - no urticaria or pruritus
  - etiology is bradykinin accumulation
- 1st reported in 1980

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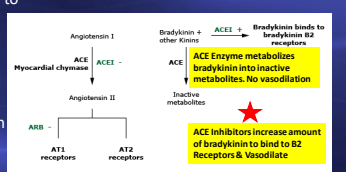
Angiotensin Converting Enzyme

- ACE converts → angiotensin I to angiotensin II
- Angiotensin II causes vasoconstriction of vessels
- ACE is a kininase enzyme that also metabolizes bradykinin
- ACEI blocks bradykinin metabolism



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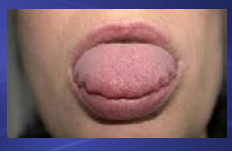
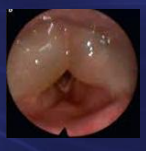
ACE – Inhibitor Angioedema

- Epidemiology of Angioedema
  - over 100,000 ER visits per year for Angioedema
  - Histamine mediated → 40 to 70% of visits
  - ACE – I Angioedema → 30% to 50% of ER visits

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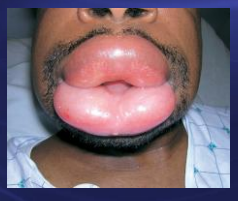
ACE – Inhibitor Angioedema

- ACE – I Angioedema
  - 0.1 to 0.7% of all patients using ACE – I medications
  - Blacks → 5% incidence vs Caucasians
  - Females > Males
  - Smokers > Non-smokers



Curr Opin Anesthesiol.2012:25:1
Immunol Allergy Clin N Am.2023;43:513

110

ACE – Inhibitor Angioedema

- Location
  - predominately lips, tongue, floor of mouth, pharynx, upper airway including the larynx
  - unlike HAE → abdomen & extremities uncommon sites

Location	Frequency
Lips	60.2%
Tongue	39.7%
Larynx	29.5%
Soft Palate & Uvula	17%
Face	12.5%
Floor of Mouth	6.8%

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ACE – Inhibitor Angioedema

- Symptom Onset → over the course of several hours
- Duration → 48 to 72 hours

ACE – Inhibitor	Incidence of Angioedema
Lisinopril	87.2%
Enalapril	4.3%
Benazepril	3.0%

Clin Exp Emerg Med. 2024; 11(1):94-99

112

Initiation of ACE-I vs ACE-I AE Onset

- Literature reports vary
  - first few weeks of therapy
  - first few months of therapy

When Does It Occur?

Weeks, Months, Years

  - case report → 23 years after ACE-I started
  - case report → 10% of all cases in 1st year of use
  - case reports → 33% cases in 1st month

Take Home Message → ACE – Inhibitor Angioedema Can Occur at Any Time
Acute Episode of Angioedema in Office
Always Rule out Allergic Reaction as 1st Step

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ACE-I Angioedema

- Onset Age: Average age is 59.3 years (range 33 to 89)
  - expect older population → Antihypertensive & CVD medication

888 Cases	% Onset over Years 1 to 5
First Month	10%
First Year	35%
2nd Year	15-17%
3rd Year	15-17%
4th Year	15-17%
5th Year	15-17%

Immunol Allergy Clin N Am. 2023; 43: 513

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Airway Management for ACE – I AE

- Major focus for Head and Neck Angioedema
  - Airway Patency
- Angioedema can lead to asphyxiation secondary to airway obstruction
  - even isolated angioedema of lips needs sent to ER for evaluation
    - can progress to involve other structures preventing intubation
  - call EMS & initiate Epinephrine – Antihistamines – Steroids to rule out allergic reaction

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Airway Management

- Physical examination + Symptoms dictate need for airway intervention

Indications for Direct Fiberoptic Nasopharyngoscopy		
Painful Swallowing	Dyspnea	Difficulty Speaking
Hoarseness	Difficulty Swallowing	Drooling
"Feeling Lump in Throat"	Lip & Tongue Swelling	Can't Visualize Pharynx

- Fiberoptic Nasopharyngoscopy
  - exam itself can increase swelling
  - load ET tube on scope for exam → most experienced provider

Relying on Direct Laryngoscopy is Foolish Choice

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Airway Management

- Likelihood of Intubation or Surgical Airway
  - Base of Tongue or Laryngeal Swelling
    - positive swelling → 38% needed intubation or surgical airway
- Chiu Study: Swelling in tongue, floor mouth, pharynx, or larynx
  - 68.5% were ACEI cases

Otolaryngol Head Neck Surg. 2015; 153(4): 544 Laryngoscope. 2011; 121(2): 262

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Chiu Angioedema Study 3 Types

- No Type 1 AE patients → required airway intervention
- Intubation → low incidence even in Type 3
- Only 2 patients required surgical airway

Type of AE	Sites Involved	Discharge from ED	Admit to Floor	Admit to ICU	Intubate	Surgical Airway
1	Face, Oral Cavity but no floor of mouth	69.4%	22.6%	8%	0%	0%
2	Floor of mouth, Uvula, Base Tongue, & Soft Palate	10.7%	28.6%	32.1%	21.4%	7.1%
3	Oropharyngeal + supraglottic + glottic swelling	5.6%	11.1%	50%	33.3%	0%

Immunol Allergy Clin N Am. 2023; 43: 513

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Ishoo Study 4 Stages

- Ishoo Study → 39% cases were ACE – I Patients

Stage	Involved Sites	Outpatients	Floor	ICU	Intervention
I	Face – Lips	48%	52%	0%	0%
2	Soft Palate	60%	40%	0%	0%
3	Tongue	26%	7%	67%	7%
4	Larynx	0%	0%	100%	24%

- All Stage 1 & 2 cases → tx as outpatient or floor management
- Stage 3 → 67% tx in ICU → 7% needed airway intervention
- Stage 4 → 100% tx in ICU → 24% needed airway intervention

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Acute ACE-I AE Management in Office

- #1 → Rule out mast cell mediated angioedema
  - Urticaria + pruritus → not present in ACE – I AE
  - Vital signs → unlike allergic reactions → minor or no changes even with severe swelling
    - no hypotension, tachycardia, or wheezing
  - Medications → no response to Epinephrine, Antihistamines, or Steroids

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Acute ACE-I AE Management in Office

- #2 Call EMS
  - can not predict amount of swelling over time
- #3 No supraglottic devices → No LMA
  - will not correct glottic or laryngeal swelling
  - placement may increase airway swelling
- #4 No CPAP positive pressure
  - barotrauma to induce swelling

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Acute Management

- #5 Intubation
  - Overall 1st Pass Success → 60%
  - All ET tubes had Bougie placed to guide insertion

Technique	% Success on First Pass
Fiberoptic Nasopharyngoscopy	51.1%
Blind Nasotracheal Intubation	22.2%
Video Laryngoscopy	15.6%
Fiberoptic Oral Intubation	6.7%
Direct Laryngoscopy	★ 4.4% Very Poor Choice

Ann Emerg Med. 2017; 69(5): 635

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Acute Management

- #6 Mark out cricothyroid membrane for possible surgical airway
- #7 Glycopyrrolate IV
  - 0.1 to 0.2 mg IV
  - Onset → 3 to 5 minutes Duration → 30 to 60 minutes
- #8 Lidocaine Spray
  - superior to nebulized lidocaine

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EMS Transfer to Hospital

- Swelling of lips & face → no intraoral swelling
  - see uvula & posterior pharyngeal walls
  - keep in ER → 4 to 6 hours
    - monitoring for any progression
- More extensive swelling
  - Ishoo or Chiu Staging for monitoring location & duration of hospital observation

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Treatment of ACE – I Angioedema

- Primary treatment for ACE – I AE
  - continued use of ACE – I → will increase recurrent episodes
  - discontinue use of ACE – I medications
  - episodes may continue for 1 month after stopping the drug
    - rare reports → several months

Allergy, Asthma & Clinical Immunology. 2024; 20 (Suppl) 3: 65
Immunol Allergy Clin N Am 2023; 43: 513

125

ARB Angioedema

- Angiotensin Receptor Blocking Agents
  - do not promote bradykinin accumulation
  - alternative medication for diseases of RAAS
  - risk of developing angioedema is low for ARBs vs ACE – I drugs
    - risk 9.4%
    - risk is similar for CCB or Beta blocker induced angioedema
  - risk of ARB causing angioedema in patients with confirmed ACE-I edema → 3.5%

Imm Allergy Clinics 2023

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Other Agents Causing Angioedema

- NSAIDS
  - ibuprofen & ASA → risk of non allergic angioedema
    - 0.3 to 0.9 % of population
- Calcium Channel Blockers (CCB) + ACE – I combination
  - increase risk of ACE – I angioedema by 57%

Cureus 2023 ACE-I AE International Immunopharmacology 2020

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Other Medications

- Angioedema not limited to just ACEI & ARBS
- Television Adds
  - monoclonal antibody medications + other medications for variety of medical conditions
  - commercials specifically state a potential rare risk
    - angioedema to face, oral cavity, pharynx, and larynx
    - difficulty with breathing

128

Drug Therapy for ACE-I Angioedema

- Fresh Frozen Plasma
  - separate plasma from whole blood then freeze (- 30 C)
  - contents
    - C1 – INH & Factor XII
    - ACE enzyme to metabolize bradykinin
    - HMWK and pre-kallikrein to increase bradykinin
  - ACE enzyme can metabolize bradykinin to reverse angioedema
  - no case reports of refractory ACE – I angioedema

In Theory, FFP should work to reverse edema → Insufficient Data to Support Use

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Drug Therapy for ACE – I Angioedema

- C1 – INH
  - plasma derived and recombinant
    - prophylaxis and treatment for HAE
  - insufficient data to support treatment of ACE – I edema
- Kallikrein Inhibitors → Ecallantide
  - prevents kallikrein from breaking down HMWK to bradykinin
  - insufficient data to support ACE – I management

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Drug Therapy

- Icatibant
  - blocks bradykinin from binding to Bradykinin B2 receptor
    - activation of the B2 receptor will cause vasodilation
  - 2025 report → consider for treatment of ACE – I angioedema
    - efficacy still debated Am J Emergency Med. 2025
- Best management
  - EMS transfer, monitor for extension of swelling
  - Intubate if needed → possible medication interventions

Allergy, Asthma, & Clinical Immunology 2024; 20(Suppl 3): 65 Am J Emergency Medicine. 2025; 93: 237.e1 – 237.e3
International Immunopharmacology. 2020. 78: 10608
Clin Exp Emerg Med. 2024; 11(1): 94 Immunol Allergy Clin N Am. 2023; 43: 513

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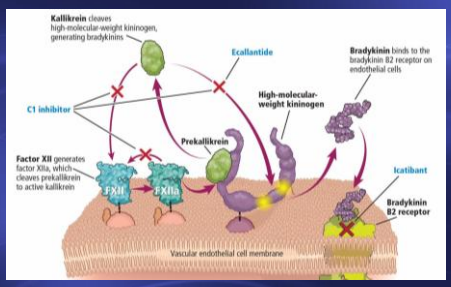

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Thank you

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1

Cannabis

Marihuana – Marijuana

Edward C. Adlesic, DMD
Pittsburgh, Pa

2

Cannabis Terms & Definitions

Term	Definition
Cannabinoids	Refers to chemical compounds found in cannabis or produced by the human body
Endocannabinoid	Ligand to endogenous cannabinoid receptors (CB1-R or CB2-R); examples are AEA and 2-AG
Synthetic cannabinoid	New psychoactive substances derived from laboratory; includes pharmacologic agents and drugs of abuse; examples are dronabinol and nabilone
Phytocannabinoid	Compounds found in or derived from cannabis plants; examples are THC and CBD
Flavonoids and terpenes	Nonphytocannabionid chemicals found in cannabis that exert synergistic effects may enhance bioactivities of phytocannabinoids
Cannabis	Refers to plant material or its extracts

Term Cannabis
THC & CBD from Plant

Cannabinoids
Chemical Compounds in Plant
Pharmaceutical Products

Lecture
Marijuana interchangeable for Cannabis

Anesth Analg. 2024; 138: 16-30

3

Cannabis Plants

- Cannabis Plants
  - Sativa
  - Indica
  - Ruderalis
- Cannabis Sativa
  - Highest concentration of THC
  - Low concentration of CBD

Cardiology & Therapy. 2018; 7: 45

4

Cannabinoid Classification (4 Types)

- Phytocannabinoids (Plants)
  - cannabinoids found in flowers, leaves, stems, and seeds from *Cannabis sativa & indica* plants in US

Flower has highest THC concentration **Plant products called "Flower"**

- Endogenous cannabinoids (AE & 2 – AG)
  - N – arachidonoyl – ethanolamine (Anandamide) (AE)
  - 2 – arachidonoyl glycerol (2 – AG)
  - Bind to endocannabinoid CB 1 & CB 2 Receptors

5

Cannabinoid Classification (4 Types)

- Purified, naturally occurring Cannabinoids
  - plant derived, purified compounds
  - delta – 9 – tetrahydrocannabinol (THC)
  - cannabidiol (CBD)
  - Sativex (CBD + THC) & Epidiolex (CBD) → purified extract medications
    MS pain & spasticity **Epilepsy: Lennox-Gastaut & Dravet**
- Synthetic Cannabinoids
  - synthetic Rx medications → Dronabinol & Nabilone (Rx meds) (CINV & HIV anorexia)
  - synthetic THC (K2 or spice) (Drug of abuse)

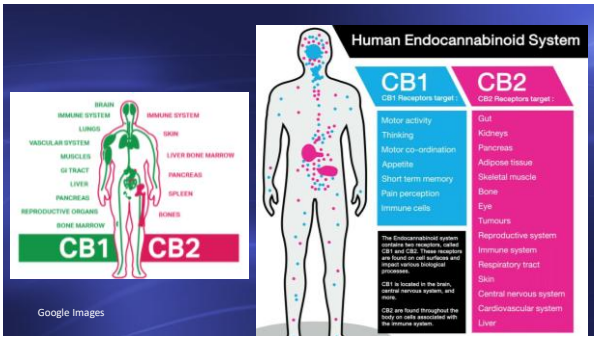
National Institute on Drug Abuse

6

Endocannabinoid System

- Neurotransmission system identified in early 1990s
  - G – protein – coupled cannabinoid receptors (CB 1 & CB 2)
  - endocannabinoids bind to receptors → CB 1 and CB 2
    - N – arachidonoyl – ethanolamine (Anandamide)
    - 2 – arachidonoyl glycerol (2 – AG)
- System is therapeutic target for numerous physiologic conditions
  - appetite stimulation, pain modulation, blood pressure, & N/V
  - memory, learning, coordination, GI motility, and immune response

7



8

Cannabinoid Receptors

- CB 1 Receptors
  - majority found in brain
  - mediate psychoactive properties
  - mood, level of consciousness, memory, & motor control
- CB 1 Receptors also in other organs & tissues
  - Lungs, Vascular System, Gastrointestinal, Reproductive
  - Liver, Pancreas, Muscle, & Bone

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Cannabinoid Receptors

- Activation of CB 1 Receptors
  - reduce release of GABA (inhibitory) neurotransmitter
  - increase release of Acetylcholine, Glutamate (excitatory), Dopamine, Norepinephrine, & Serotonin

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Cannabinoid Receptors

- CB 2 Receptors
  - found primarily in immune system
    - B cells, T cells, macrophages
  - modulates inflammation, pain, & immune function
  - minimal psychoactive effects

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Endocannabinoid System

- Potential treatment target for pathological conditions
  - Parkinson's Disease
  - Huntington's Disease
  - Alzheimers and Multiple Sclerosis
- Any Cannabinoid compound can activate the system
  - Marijuana, THC, CBD, Dronabinol, Nabilone, or K2 & spice

Any Cannabinoid will Activate System: Street Grade Products, "Kitchen Organic Chemistry", Pharmaceutical, Legal, & Illegal

Acta Pharmacologica Sinica. 2019;40:297-299

12

Endocannabinoid System

- THC binds to Cannabinoid Receptors in Brain
  - hippocampus, orbitofrontal cortex, cerebellum, & basal ganglia
  - alters memory, coordination, ability to focus – concentrate
  - alters sensory and time perception
- THC causes release of Dopamine
  - increase in pleasure & relaxation
- Interact with other receptors
  - NMDA, Serotonergic, GABA, Opioid, & Autonomic

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Endocannabinoid System

- CBD
  - antagonist or inverse agonist at CB 1 & CB 2 receptors
  - low affinity for binding to these receptors
- CBD binding to receptors
  - will not cause intoxication
  - causes analgesia & anti -inflammatory effects

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Cannabis
Marijuana

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Federal Government Classification

- Cannabis or Marijuana Plant
  - THC content > 0.3%
- Hemp
  - THC content < 0.3%

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Marijuana

- 2020 Substance Abuse in United States
  - #1 Alcohol
  - #2 Tobacco
  - #3 Marihuana
    - 2018 → 11.8 million young adults used Marijuana
    - 2019 → 22 million Americans over the age of 12
    - 2021 → 19% of Americans ≥ age 12

J Clin Med. 2020;9, 1925; doi: 10.3390/jcm9061925 Proc Bayl Univ Med Center. 2019; 32(3): 364
J Clin Med 2025;14:858

17

Marijuana

- Adults Population → Marijuana Use
  - 2002 to 2014 → 455% increase in US adults → age 55-64
  - 2002 to 2014 → 333% increase in US adults → age > 64
  - 2022 → 44% of Adults ages 19 to 30 → use MJ
- Adolescents 2023
  - 28% used MJ in past year
  - 4.4% 10th graders use it daily

JOMS. 2023;81:1460

18

Marijuana

- Marijuana Use
  - not limited to healthy adults
  - increased use in ages 12 and above
  - older adults with comorbidities → increased MJ use

Cardiovascular & Cerebrovascular Risks Unknown at Present in Senior Population → Increased Risk is Probable

Baylor Proceedings 2019

19

Marijuana

- Cannabis plants → 4 species
  - *Cannabis sativa* plant → common source
  - *Cannabis indica* plant
- Marijuana → entire plant is used
  - flowers, leaves, stems, and seeds → flower is an excellent source of THC → hence the nickname "flower"
- Street Names
  - weed, herb, pot, grass, ganja, & Mary Jane

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Marijuana

- More than 100 Cannabinoids in the plant
- THC is primary psychoactive agent → δ - 9 – tetrahydrocannabinol
- Cannabidiol (CBD) & Cannabinol
  - lack psychoactive properties
  - wide range of other pharmacologic activity
- More than 500 other compounds in plant
  - terpenes, flavonoids, & terpenoids

CBD is a Hemp Product

Hemp can have psychoactive compounds
Delta 8 & 10 THC

Terpenes = Weed Aroma

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How is Marijuana Used

- Delivery systems
  - smoking → "joint" cigarette
  - pipes
  - "bongs" → water pipes
  - "blunts" → cigar wrapper filled with Marijuana
  - vaporizers → eliminate smoke → "dabbing" on heated titanium nail or quartz glass container
  - edibles
  - transoral

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Marijuana Extracts & Concentrates

- Hemp extracts → yield high levels of CBD
  - Delta 10 & Delta 8 → hemp products with euphoria
  - CBD → no euphoria
- Marijuana extracts → yield high levels of THC
- Techniques → grind flowers, leaves, & stems
  - "Kitchen Organic Chemistry"
  - use heat, pressure, or solvents to remove contaminates
  - get a higher concentration of THC & CBD

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Marijuana Extracts & Concentrates

- Trying to remove impurities & increase THC content
- Budder → soft texture "stick of butter"
- Crumble → brittle version of budder "honeycomb"
- Shatter → brittle glass like texture → amber color
  - high THC content → 60 to 90%
- Delivery system → typically vaporization with dab rig or vape pen

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THC Content of Marijuana

- THC in "flower" (plant for smoking)
  - 1980's → 1 to 3%
  - 1990's → 6 to 20%
  - 2020 → up to 33% readily available
- "Flower" Trade names

The Toad	37%	Godfather OG	25 to 34%
GG4	25 to 30%	Bubba Kush	27 to 28%

Proc Bayl Univ Med Cent. 2019;32(3):364

27

Marijuana Distillates

- Using organic chemistry techniques
  - isolate specific compounds in marijuana
- THC concentrations in these products
  - Denver → found 82% THC
  - Pharmaceutical Company Future Involvement
    - expect THC concentrations approaching 95+ %

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THC Content in Other Cannabinoids

- Budder 60 to 80%
- Crumble 60 to 90%
- Shatter 70 to 90%
- Distillates 95 to 99%
- Hybrids & Concentrates: THC to CBD ratio is increasing
  - CBD content is far less than THC content
  - CBD content attenuates psychoactive effects of THC
  - Customers want a better "high"

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CBD & THC Commercial Content

- THC & CBD content in "flower"
  - THC content → 8% to 29%
  - CBD content → 0.26 to 10.24%

Hybrid Growing can control THC and CBD content

- Customer has a choice
  - buy 1:1 product → less euphoria
- Shatter
  - THC content → 70 to 90%
  - CBD content → 1.1 to 3.6%

Internet Shopping California & Colorado

30

Inhaled Cannabinoids

- Onset "Immediate" → 1 to 2 minutes
- Peaks 15 to 30 minutes
- Duration 1 to 3 hours depending upon dose

- Elimination half life
  - Occasional User 20 to 30 hours
  - Chronic User 72 hours

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THC Concentration in Blood

- Smoking – Vaporization & Blood concentration depends on
  - #1 THC content of the product used → 20 to 99%
  - #2 Tidal Volume → deep breaths increase THC content
  - #3 Breath Holding → allows time to diffuse into blood
  - ★ #4 Hot temperature of smoking → 13 to 30% available for lung absorption (internet: 40 to 50% available after burning)
  - ★ #5 Vaporization yields lung absorption → > 70% → more effective inhalation technique

JAMA Surgery on line doi:10.1001/jamasurg.2020.5545

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THC Blood Content

Marihuana Product	Weight of Product	THC Concentration And Amount	% Lost To Burn	THC in Blood
Flower Joint	320 mg	20% = 64 mg	40% Loss = 25.6 mg	38.4 mg
Flower Bowl	250 mg	18% = 45 mg	40% Loss = 18 mg	27 mg
Dab Concentrate	500 mg	70% = 350 mg	33% Loss = 115.5 mg	234.5 mg

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Synthetic Cannabinoids

- Pharmaceutical Agents for Legal Use
  - Dronabinol & Nabilone
- Street Grade Products → NPS → New Psychoactive Products
  - "Herbal Smoking Blends" "Herbal Incense"
  - K2 or Spice → Joker, Black Mamba, & Kronic
- Full CB1 & CB2 Agonists

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Synthetic Cannabinoids

- Cannabinoid Receptor Binding
  - Bind to same receptors as THC
  - Binding is 10 to 200 times more potent
- Product is added to "Legal Carriers" for use
  - Spray on Plants to conceal agent
  - At present, legally sold in Smoke Shops & Gas Stations
    - Smoke or Vape
  - Illegal in some states

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"Synthetic Cannabinoids"

- Adverse Effects
  - Psychosis, paranoia, & hallucinations
  - Tachycardia & Hypertension
  - QT Prolongation & AMI
  - Ischemic Stroke & Transient Ischemic Attacks
- Addictive agent
- Not a cannabinoid → has similar structure

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Marijuana Edibles

- Variety of products
  - brownies, cookies, candy bars, & gummy bears
- Onset → 45 to 90 minutes
- Peak → 2 to 5 hours
- Duration → 5 to 10 hours
- Redosing → no effects felt → wait 2 hours before redose

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Marijuana Edibles

- Adding CBD to edibles → enhance medical benefits
  - analgesia and antianxiety
  - decrease elevated heart rate
- CBD to THC ratio → 4:1 or higher
  - decrease likelihood of unwanted effects
  - improve medical benefits
  - significantly decrease euphoria from THC

Euphoria Want High THC Content

Medicinal Want High CBD Content

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Cannabidiol CBD

- CBD
  - no psychomotor effects (Delta 8 & 10 THC exceptions)
  - anti emetic
  - anti convulsant
  - anti psychotic
  - can attenuate THC psychomotor effects
- Found in most marijuana plants
  - hemp has high concentration of CBD

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Delta 8 THC (delta-8-tetrahydrocannabinol)

- "NEW MARIJUANA" → currently legal → no license needed
  - found in gas stations, smoke shops, & marijuana dispensaries
  - higher concentration in hemp plants
  - Farm Bill of 2018 → hemp is legal if THC content is < 0.3%
- "Marijuana Light"
  - relaxation, euphoria, & "feeling high"
  - mostly sold as edibles
    - can be smoked or vaped

Less potent than delta-9-THC

Currently no governmental oversite

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Delta-10-THC

- Another hemp product
- Effects similar to delta-8-THC
  - less potent than delta-8-THC
- No governmental oversite
- OTC product

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Psychoactive Component THC

- Primary psychoactive component is → THC
  - δ - 9 – tetrahydrocannabinol
- Euphoria → "High"
  - varies with dose, mode of administration, & personality of user

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CNS Effects

Euphoria	Heightened sensory perception
Relaxation	Laughing
Drowsiness	Dizziness
Anxiety	Dysphoria
Loss of Control	Impaired short-term memory

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CNS Effects

- Dysphoria
  - not uncommon especially in naïve users
  - severe anxiety & panic, loss of control, fear of dying
  - sometimes euphoria & dysphoria alternate

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"Help Me Get Home"

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Marijuana Physiologic Effects

Cardiovascular
Respiratory
Gastrointestinal

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Perceptions About Marijuana

- Long History of Use
- Common Perception
  - General Public and now Politicians
  - Marijuana is safe → Make it accessible
- Assumptions based on historically low dose of THC
  - THC levels at present → > 20%
  - Senior population → increased risk today vs yesterday
  - Children & Teenagers → ↑ risk of Cannabis Use Disorder

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Acute CVS Effects of Marijuana Naïve User

- Dose dependent: CB 1 mediated
  - ↑ β – 1 sympathetic activity & ↓ parasympathetic activity
  - increase in HR & BP → range of 20 to 50% → up to 100%
  - onset of CVS symptoms → same as onset of euphoria → 1 to 2 minutes
  - duration → at least 1 hour after stop THC use → 1 to 3 hours

J Clin Anesth. 2019; 57: 41-49 J Perioperative Practice. 2025; 35(10): 456

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Acute CVS Effects of Marijuana

- Norepinephrine Levels
  - Peak in first 30 minutes of using THC
  - Stay elevated for → additional 120 minutes
    - prolonged sympathetic effects
- Potential Risks for Patients will be Dependent Upon
  - Young patients with no Cardiovascular Disease
  - Older patients with Cardiovascular Disease

J Clin Anesth. 2019; 57: 41-49 Cardiology & Therapy. 2018; 7: 45 Frontiers Cardiovascular Med. 2024: 1343549

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Acute CVS Effects of Marijuana

- Implications
  - Increased myocardial oxygen consumption vs myocardial oxygen supply
  - Elevated Carboxyhemoglobin Levels from smoking MJ
    - Less Oxygen Binding to Hemoglobin → due to elevated COHb
    - Decreased Coronary Oxygen Supply
  - Decreased Coronary Blood Flow secondary to Tachycardia
  - Prothrombotic Effect from Cannabis in older patients
  - Coronary Vasospasm especially in young patients

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Acute CVS Effects of Marijuana

- Cardiac Dysrhythmias with Cannabis use
  - Atrial Fibrillation or Flutter, AV Blocks, PVCs
  - V Tachycardia, V Fibrillation, Brugada ECG Patterns
  - Typically seen within 2 hours of MJ use
  - Most have been benign findings

To Date → Atrial Fibrillation Most Common Dysrhythmia

J Clin Anesthesia 2019 J. Clin Med. 2020 Frontiers in Cardiovascular Med. 2024; 11: 1343549

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Cardiac Dysrhythmias

- Low to Moderate Dose Marijuana
  - See ↑ Sympathetic Activation
  - Increased Heart Rate
  - ECG → Tachydysrhythmias from normal conduction from SA node to AV node to ventricles
- High Dose Marijuana & Chronic Users
  - See ↑ Parasympathetic Activation
  - ECG → Bradydysrhythmias

Frontiers in Cardiovascular Medicine. 2024

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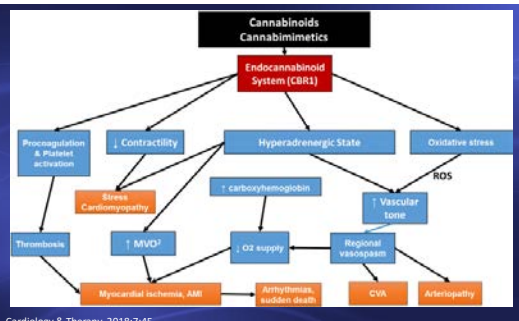

Cardiology & Therapy. 2018;7:45

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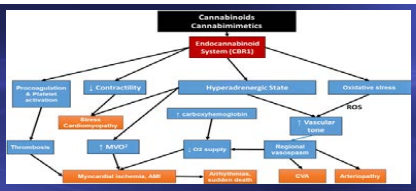

- Naïve User → Increased Sympathetic Activity
  - ↑ Vascular Tone results in Vasospasm + ↑ HR results in ↑ myocardial O2 consumption
  - ↑ Carboxyhemoglobin from smoking → Less myocardial O2 Supply
  - Increased risk of dysrhythmias
  - Increased risk of AMI

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CVS Effects with Chronic Use of MJ

- Parasympathetic Stimulation + Baroreceptor Inhibition
  - Decreased HR & Increased Baroreceptor Inhibition
  - Orthostatic Hypotension

May Need Vasopressors During Surgery

- Anginal Pain Threshold is Reduced in Chronic stable angina
- Coronary Vasospasm or Coronary Thrombosis
  - increased risk of AMI
- LV dysfunction or Failure

Frontiers in Cardiovascular Medicine 2024

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Cardiovascular Issues

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Cardiac Issues with Marijuana

- Tachycardia issue: literature reviews of past based upon lower THC content of cigarettes (4 to 8%)
  - tachycardias were tolerated in healthy and young
- Issue in 2020s: Older patients & Increase THC concentration
  - Unanswered → but needs addressed & should raise concern
  - THC plant content currently → 20 to 30+%
  - Concentrate content > 60%

Increased Cardiovascular Issues in Older Patients All Secondary to Increased THC Content

J Gen Intern Med. 2019;35(3):969-74

58

AMI with Marihuana

- Several reports linking Marijuana use to AMI
  - Young Patients without risk factors → possible → not common
  - National Academy of Science → found limited evidence for link
- Colorado Data
  - 32% increase in admissions for patients > 40 with primary diagnosis of AMI & secondary cannabis use disorder

West J Emerg Med.2019;20(4):557-572 Nature Reviews Cardiology.2018; 15:151

59

AMI with Marijuana

- Mittelman (2001) → 4.8 X increased risk of AMI → 1st hour of marijuana exposure
  - risk decreases to 1.7 X in 2nd hour
  - male patients
    - Age → 44 ± 8
    - Obese Smoker

Patients
40% Patients Used MH Weekly
66% Patients Used MH at least Monthly

- Compared to Cocaine Users
  - 24 X increased risk of AMI in 1st hour

Nature Reviews Cardiology.2018; 15:151 Am Soc Regional Anesthesia & Pain Medicine. (ASRA) 2023
Proc Bayl Univ Med Center. 2019

60

AMI & Marijuana

- Report → Acute AMI In – hospital Mortality
  - 60% increased rate for AMI caused by marijuana use
- Report → Symptoms of AMI secondary to marijuana use
  - most occurred within → 5 hours of MJ use
- Reinforced often quoted misconception
  - "No MJ use for 72 hours before Surgery"

ASRA Guidelines 2023

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AMI or Unstable Angina

- Marijuana use is risk for AMI or Unstable Angina
  - Patients with known CAD
  - Older age patients
  - Heavy users of marijuana & cannabis use disorder patients
  - High THC content products
- Synthetic THC (K2) → risk of AMI in younger patients

Anesthesiology.2020;132:625 Nature Review Cardiology. 2018

62

Angina & Marijuana

- Cannabis → can decrease Anginal Pain Threshold
  - Marijuana decreased threshold by 48%
  - Tobacco decreased threshold by 23%
- Stable Anginal Patients
  - Marijuana + Exercise → MJ caused chest pain faster than exercise alone → ↑ in HR, BP, and myocardial oxygen consumption

ASRA. 2023 ASRA Guidelines for Perioperative Patients using Cannabis Proc Baylor Univ Med Center 2019

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Angina & Marijuana

- Chronic Anginal Patients
  - Assess Patient's Functional Capacity
    - METS prior to Marijuana Use
    - METS after Marijuana Use
- Pain or Inability to achieve METS before MJ use
  - increased risk of myocardial ischemia using MJ

Joshi. Baylor Proceedings 2019

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Cerebrovascular Issues

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CVA & Marijuana

- Ischemic stroke in young, male patients
  - age 25 to 35
  - 2.3 to 2.9 fold increase → for marijuana vs tobacco users
    - 4.7 fold increase → smoke multiple times per week

Mechanism = Cerebral Vasospasm

- Ischemic stroke & TIA → far more common than hemorrhagic stroke
- Heavy users → greater risk than occasional users

Nature Reviews Cardiology 2018 Curr Opin Anesthesiol. 2020;33:318 J Clin Anesth. 2019;57:41

66

Cerebrovascular

- Naïve Cannabis Users
  - CVA risk low with THC → Unless they have additional comorbidities
- Chronic Users - Heavy Users - Synthetic Cannabinoids (K2)
  - Increased Risk of Ischemic Stroke (Cerebral Vasospasm)
  - Increased Risk of Transient Ischemic Attacks (TIA)
  - K2 – Spice increased cerebral thrombosis

Ischemic Stroke & TIA → Most Common Cerebrovascular Events

J. Clin Med. 2025; 14(3): 858 Frontiers in Cardiovascular Med. 2024: 11: 1343549

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Cerebral Vasospasm

- Clinical Signs
  - Severe Headache
  - Nausea & Vomiting
  - Photophobia
  - Confusion
  - Blurred Vision

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Summary of CVS Effects

System	CB Receptor	Use Profile	Physiologic Effects
Cardiovascular	CB 1	Naïve - New	↑ Sympathetic ↓ Parasympathetic ↑ HR, BP, Myocardial Contractility ↑ Tachydysrhythmias (Afib, Aflutter, V tach & fib ↑ Myocardial Oxygen Consumption ↑ Carboxyhemoglobin levels ↓ Coronary Blood Flow
	CB 1	Chronic Use	↑ Parasympathetic + Baroreceptor Inhibition ↑ Coronary Vasospasm in CAD → AMI ↑ Coronary Thrombosis → AMI ↑ LV systolic dysfunction → Heart Failure Reduces Anginal Threshold Pain
	CB 1	Synthetics K2 – Spice	Prolonged QT - Cardiac Arrest LV Dysfunction Myocardial Infarction

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Summary of Cerebrovascular

System	Receptor	Duration of Use	Physiologic Effects
Cerebrovascular	CB 1	Naive	Ischemic Stroke Rare Unless Comorbidites
	CB 1	Chronic Use Heavy Use Synthetics – K2	Ischemic Stroke Cerebral Vasospasm usually Anterior Cerebral Vessels Cerebral Thrombosis (K2, Spice) Transient Ischemic Attacks (TIA)

Frontiers in Cardiovascular Medicine. 2024

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Respiratory Effects Marijuana

- Smoking → exposes airway & lung to
  - high concentration → irritants & carcinogens
    - benzopyrene & benzanthracene (carcinogens)
  - tar content of marijuana
    - 3 X more concentrated than tar from tobacco
    - 33% greater deposition in respiratory tract

Heliyon 2018 accessed online Proc Bayl Univ Cent. 2019 accessed online

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Respiratory Effects of Marijuana

- Smoking
  - marijuana burns at higher temperature than tobacco
  - heat is direct irritant to respiratory mucosa especially with smoking short butts ("roach clip" heat)
- Smoking technique is different than tobacco
  - 66% greater → puff volume
  - 33% greater → depth of inhalation
  - 4 X greater → breath holding

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Respiratory Effect of Marijuana

- Effects of Smoking Techniques
  - 5 X amount of carboxy – hemoglobin in lungs than tobacco
  - Greater diffusion of THC into blood
  - 3 to 4 cannabis cigarettes over the course of time → yields the same amount of lung damage as chronic use of → 20 tobacco cigarettes

West J Emerg Med. 2019 Curr Opin Anesth. 2020; 33:318

73

Respiratory Effects Marijuana

- Bronchodilation
  - non-users of marijuana or new users
  - CB 1 mediated response
  - occurs in smokers or with PO use
  - duration of action → 1 hour
  - likely to produce → ↑ FEV1 & FVC on acute exposure
  - chronic use → no longer seen

Not a Treatment for Asthma

AANA J. 2019;87:451 J Clin Anesth.2019;57:41

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Respiratory Effects of Marijuana

- Chronic Use Respiratory Effects → 6 to 10 weeks of marijuana use
  - Onset of bronchial irritation & hyperactivity
  - ↓ FEV1 & FEV1/FVC ratio
  - FVC & Functional Residual Capacity → no change
  - ↑ Cough, Wheeze, & Mucus production

Prolonged Use → Symptoms of Chronic Bronchitis

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Gastrointestinal Issues with Marijuana

- Marijuana increases gastric emptying time
  - additional delay of 30 to 120 minutes
- Additional GI Disturbances
  - Decreased intestinal motility
  - Increased hyperemesis events
  - Increased PONV

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Summary of Physiologic Effects

	Acute effects	Chronic effects
Cardiovascular	Tachycardia Vasodilation Orthostasis	Atheromatous disease
Pulmonary	Bronchodilation Hyperreactivity Airway edema	Chronic bronchitis Emphysema
Central nervous system	Anxiolysis Anxiety Paranoia/psychosis Euphoria Dizziness Headache Memory dysfunction Analgesia	Similar to acute effects but tolerance develops, requiring higher doses for similar effects
Gastrointestinal	Antinausea Increased appetite Abdominal pain	Hyperemesis

Proc Bayl Univ Med Center. 2019; 32(3): 364

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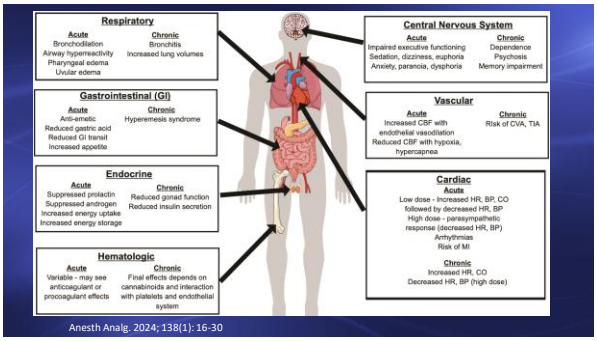

Anesth Analg. 2024; 138(1): 16-30

78

Overdose

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Overdose Deaths

- Marijuana risk of overdose death
  - 4000 years of use → no reports of cannabis overdose????
  - J Opioid Management.2009:5(3): 153
- Synthetic THC (K2) → reports of death
- What about newer hybrids, purified products, & distillates plus older patients with co morbidities ??

80

New Psychoactive Substances Complications

- K2 or Spice + other NPS
- 2016 Report: 3695 individuals with NPS toxicity
- Synthetic Cannabinoid CVS Effects
  - most common is → Tachycardia → 30% Incidence
  - Death → 0.2%
  - Stroke → 0.1%
  - AMI → 0.09%

Australas Psychiatry. 2016;24:598

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New Psychoactive Substances

- 2021 Report → 28,531 ER cases of Synthetic Cannabinoid Toxicity in US
  - 78% of these involved adolescents & young adults (age 12 to 29)
- 2014 to 2020 → Overdose Deaths from Synthetics
  - 327 Overdose deaths in Florida
  - 75 from Cannabis Overdoses
  - 252 from Synthetic Cannabinoids

Synthetic Cannabinoids = New Psychoactive Substances

J. Nurs Sch. 2023;55:623

82

Marihuana & Anesthesia

83

Marijuana & Surgery - Anesthesia

- Controlled Substance Act of 1970
  - Marijuana was classified as a Schedule 1 Drug
- Research Papers
  - most are case reports or retrospective reviews
- Current Strategies for Anesthesia & Surgery
  - mostly based upon anecdotal data from conferences & colleagues

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Marijuana & Surgery - Anesthesia

- University of Mississippi National Center for Natural Products Research
  - US government approved center providing MJ for research
  - THC content → 13 to 14%
- THC concentration was lower than illegal THC on street
  - lower than THC content of current THC dispensaries
- Center approved now for higher THC content

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Current Literature: MJ & Anesthesia

- Majority of publications to date → problematic
  - Little to No information → type of marijuana used
    - flower - concentrate - NPS - medicinal
  - Little to No information → THC concentration of marijuana used
  - Little to No information → frequency of use & time of last dose before surgery
  - Limited data on → age of patient & comorbidities

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Marijuana & Anesthesia

- Medical Marijuana & CBD Research Act 2022
  - research facilities can obtain → highly concentrated THC flower and distillates from licensed marijuana outlets
- Future data will become more relevant

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Preoperative Evaluation

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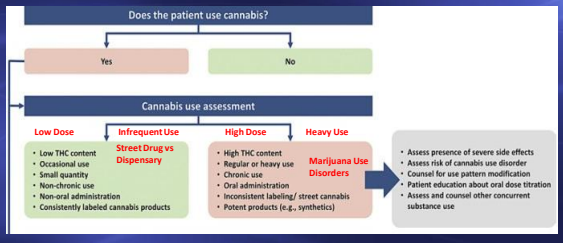
Marihuana Patient Preop Evaluation



Med Cannabis Cannabinoids. 2022;5: 120

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Preoperative Questions

1. Does the patient use Marijuana?
2. How long have they been a user? (Years vs Months)
3. What is the frequency of use?
   - Monthly - Weekly - Daily
   - Quantitate the use for each of these time periods
4. What type of Marijuana do you use?
   - Flower - Concentrates - New Psychoactive Substances - Medicinal
5. Street Weed vs Commercial Weed
   - Commercial → Reliable THC content

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Preoperative Questions

- 6. How do you deliver the Marijuana
  - Smoking - Dab Rigs (Vaporize) - Vape Pen - Edibles
- 7. Chronic Users → Personal History
  - Hyperemesis Events
  - Overdose - ER visits
  - Withdrawal Symptoms
- 8. Additional illicit drugs or prescription drug abuse

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Perioperative Challenges

- Street Weed
  - Unknown THC Content
  - May be other illicit drugs mixed with Marijuana (heroin or fentanyl)
- ***Should you hold Marijuana preoperatively & for how long?***
- Holding marijuana for several days preoperatively
  - Will you create withdrawal & how do you treat that?
- How do you manage the " Rodeo Anesthetic"
  - bolus vs infusion → which TIVA agents are best???

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Preoperative Considerations

Frequency	Technique	Marijuana
Monthly	Smoking	Flower – THC Content
Weekly	Vaporize	Concentrate
Daily	Vape Pen	K2 - Spice
How Many Times per Day	Edibles	Medicinal

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Preoperative Considerations

History	Heart Palpitations
	Irregular Heart Rhythms (PACs, PVCs, AV Block)
	Cough, Dyspnea, Wheeze, Sputum Production
	History of Stroke
	History of Angina or MI
	Asthma, Bronchitis, COPD
	Hyperemesis Episodes
	GERD or Gastroparesis

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Examination

New User	Chronic User
Tachycardia	Bradycardia or Tachycardia
↑ SBP	Postural or Orthostatic Hypotension
Dysrhythmias	Dysrhythmias
Dyspnea & Sputum	Dyspnea & Sputum
Wheeze	Wheeze

95

Marijuana & CVD

- Patients without risk of CVD → MJ use has low risk of MACE
  - adolescents & young adults
    - may see acute hypertension & tachycardia after acute use for several hours
    - MACE possible but rare for occasional users
  - Same holds for Stroke for occasional users

Med Cannabis Cannabinoids. 2022;5: 120

96

Anginal Patients

- Middle aged & older anginal patients
- Ask about anginal free functional capacity both before and after marijuana use
- Elevated risk of AMI → 2 hours after using marijuana
  - lower but continued risk for up to 5 hours with CVD

Proc Baylor Med Center 2019

- Patients with cannabis use disorder (heavy use can't stop)
  - marijuana used perioperatively → ↑ risk of perioperative AMI

Anesthesiology.2020;132:625

97

Airway Reactivity

- Smoking = airway irritability & hyperresponsiveness
- Management → same as chronic tobacco smoking
- Stop smoking → 24 to **72 hours??**
  - carboxy Hb levels 5X greater than tobacco
  - stopping for at least 24 hr will decrease carboxy Hb levels
- Rare reports → severe edema & airway obstruction
  - heat causes swelling → common sense cancel if swollen airway

98

Airway Reactivity

- Marijuana smoking → ↑ risk of laryngospasm, bronchospasm, & airway obstruction for 4 hours after use

Helyion 2018

- Reactive Airway Patients & Marijuana
  - Asthma Patients using Marijuana
  - Chronic Bronchitis Patients using Marijuana

★ Glycopyrrolate to decrease airway secretions

★ IV lidocaine → reduce airway hyperresponsiveness **30 to 50 mg IV**

99

Airway Reactivity

- Reactive Airway Patients
  - Albuterol pretreatment → improves lung function
    - 2 to 4 puffs → 10 minutes preop
  - Dexamethasone → 4 to 8 mg IV preop
  - Wheezing may require preop optimization days in advance
    - Oral Prednisone 40 mg/day (0.5 mg/kg) PO 5 days before surgery

100

Aspiration Risk

- Marijuana increases gastric emptying time
  - delayed additional 30 to 120 minutes
- Consider longer NPO times especially for solids
  - fatty foods: hold for 24 hours???
  - liquids: liquids only the day before surgery???
  - NPO for 4 hours before surgery → time to clear all liquids
  - no data at present

101

Aspiration Risk

- Consider use of famotidine (Pepcid) → H2 blocker
  - 20 mg PO at HS before surgery → 20 mg PO 2-3 hours preop
  - alternative → 20 mg IV preop
  - Alka Setzer Gold (no aspirin or particulates)
    - reduces acid but increases gastric volume → avoid
- Consider Protein Pump Inhibitors - Metoclopramide
  - Omeprazole 20 mg PO day of surgery
  - Metoclopramide 10 mg IV over 1 to 2 minutes (tardive dyskinesia)

102

Aspiration & Vomiting

- Increased Gastric Contents + Pro emetic effect of High Dose Marijuana
  - Increased Risk of PONV
  - Dexamethasone for most OMFS Anesthetics
  - Add Serotonin Antagonist → Ondansetron IV 4 mg IV

103

Marijuana & CYP450 Enzymes

- THC Metabolism
  - primarily by → CYP3A4 & CYP2C9
- CBD Metabolism
  - primarily by → CYP3A4 & CYP2C19
- Drugs that inhibit or induce these enzymes
  - increase or decrease THC & CBD levels

Cannabis & Cannabinoid Research 2019 AANA J. 2020 Anesth Analg. 2020 ASRA 2023

104

CYP Inhibitors & Inducers

- Medications that inhibit or induce THC metabolism

CYP3A4 Inhibitors	CYP2C9 Inhibitors
• Protease Inhibitors • Ketoconazole • Nefazodone • Amiodarone • Verapamil • Cimetidine • Imatinib • Tamoxifen	• Luvoxamine • Fluoxetine • Proton Pump Inhibitors • Ketoconazole • Clopidogrel • Fluconazole • Fluorouracil
CYP3A4 Inducers	**CYP2C9 Inducers**
• Phenytoin • Carbamazepine • Topiramate • Rifampicin • Pioglitazone	• Phenytoin • Carbamazepine • Phenobarbital • Rifampin • St. John's Wort

APSF Newsletter 2025

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Marijuana and Bleeding

Cannabinoids drug interactions with anticoagulants and antiplatelets

Drug	Effect	Intervention
Warfarin	THC and CBD can cause competitive inhibition of CYP2C9 and inhibit metabolism of the S-warfarin isomer, leading to supratherapeutic international normalized ratio levels.	▶ Check INR within 3 days
DOACs (direct-acting oral anticoagulants)	CBD and possibly THC can increase DOACs level due to competitive inhibition of P-glycoproteins, and to a lesser extent CYP3A4.	▶ Close monitoring ▶ Consider using other anticoagulants or discontinue CBD/THC
Clopidogrel	CBD and possibly THC can increase clopidogrel level due to the competitive inhibition of CYP2C19.	▶ Consider using another antiplatelet
Heparin/fondaparinux	No known interactions as these agents are processed by endothelial and renal cells and not metabolized by CYP enzymes, UGT, or P-glycoprotein.	
Platelets	Immune thrombocytopenia with synthetic cannabis.	▶ Unlikely to have significant clinical effects ▶ Immune thrombocytopenia is rare

CBD, cannabidiol; THC, tetrahydrocannabinol.

- Marijuana may increase bleeding in patients using
  - Warfarin, DOACs, & Plavix

106

Temperature & Marijuana

- Perioperative hypothermia → Temperature < 36 C
- Shivering Threshold → Temperature = 35.5 C
- Marijuana users & Perioperative Temperatures
  - hypothermia & shivering common
- Potential Side Effects of Shivering
  - Tachycardia, Hypoxia, Increased Oxygen Consumption, & Myocardial ischemia
    - Monitor Temperature in Marijuana Patients

J. Clin Anesthesia. 2019;57:41

107

Anesthetic Agent Interactions

108

Marijuana as Premedication

- Marijuana produces relaxation & euphoria
- Can we use it as a premedication for office anesthesia?
- 1977 Gregg & Campbell → Preop IV THC → Results
  - Increased anxiety, dysphoria, and paranoia
  - Distorted sense of perception & delusions
  - Dose dependent tachycardia & hypotension as ↑ THC dose
  - NO!!!

J Oral Surgery. 1976; 34: 301

109

Anesthetic Agents

- Anecdotal reports are abundant
  - anesthetic agents → patients require significant increased doses
  - excessive intraoperative → movement & restraint issues
  - bizarre emergence reactions
- Growing evidence → regular cannabis use → resistant to sedative hypnotics
- Require ↑ induction dose → maintenance dose varies

Proc Baylor Med Center. 2019 Curr Opin Anesth. 2020

110

Anesthetic Agents

- Marijuana used weekly for 6 months
  - required increased doses of propofol to place LMA
  - no difference between groups to get to BIS < 60
- Cannabis → increase tolerance to sevoflurane & isoflurane
- Postoperative Opioids → increased doses not uncommon

J Clin Anest. 2020. 67 109980 Curr Opin Anesth.2020;33:832 Heliyon.2018
Anesth Analg. 2024; 140(6): 1401

111

Anesthetic Agents

- Imasogie et al. 2021 : Propofol for endoscopy
  - Cannabis users: young, male tobacco smokers
  - 53% reported daily Marijuana use
  - needed higher propofol dose for marijuana users
    - 0.33 mg/kg/min vs 0.18 mg/kg/min
  - daily MJ use required more propofol → than weekly or monthly use

Marijuana Users Needed More Propofol than Nonusers

Daily Users required more than weekly or monthly users

Digestive Diseases and Sciences. 2022;67:5371

112

Anesthetic Agents

- King 2021: Sedation for Endoscopy
  - No difference in propofol for cannabis vs no cannabis
  - Fentanyl & Ketamine
    - higher doses needed for cannabis users
- Lee 2021: Sedation for Endoscopy
  - Daily Marijuana Users vs Nonusers
  - Cannabis users required higher doses → propofol & fentanyl

Digestive Diseases and Sciences. 2022;67:5371

113

Marijuana & Sedation

- Moderate & Deep Sedation for Endoscopy

Sedative	Non-Cannabis User 255 pts	Cannabis User 25 pts	Greater Requirements %
Fentanyl mcgs	109.91	125.93 (25 mcg)	14%
Midazolam mg	7.61	9.15 (3 mls)	19.5%
Propofol mg	13.83	44.81 (This is a difference of ~ 3 mls. Let's get real)	220.5 (Really????)

J. Am Osteopath Assoc. 2019;119(5):307

114

Cannabis Ambulatory OMFS Surgery

Table 3. CANNABIS USE VERSUS INTRAVENOUS ANESTHETIC AGENTS ADMINISTERED

Covariates	Propofol	Midazolam	Ketamine	Fentanyl
No cannabis use	117.9 mg ± 71.5	4.7 mg ± 1.0	40.1 mg ± 15.7	75.2 μg ± 26.3
Cannabis use	152.5 mg ± 101.8	5.1 mg ± 1.5	46.0 mg ± 16.9	88.6 μg ± 32.8
P value	.004[a]	.01[a]	.01[a]	.02[a]

- Cannabis Users Required More Agents for Deep Sedation – General
  - More Propofol, Midazolam, Ketamine, & Fentanyl

Agent	THC + Patients Increased Dose
Propofol	29.3%
Midazolam	8.5%
Ketamine	14.7%
Fentanyl	17.8%

JOMS. 2023;81:1460

115

Anesthetic Agents

- Marijuana users vs non – users → drug doses
  - Intraoperative fentanyl → no difference
  - Postoperative fentanyl → marijuana users required more
  - Propofol, ketamine, & dexmedetomidine → no difference

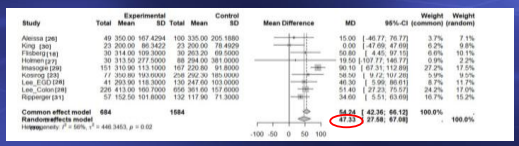
J Clin Anesth. 2020: 67

- Tachycardia, Hypertension, Dysrhythmias secondary to drug
  - avoid ketamine & sympathomimetics → synergistic effects
  - why are you still doing the case??
  - Let's Use Common Sense

Curr Opin Anesth. 2020;33:832

116

Propofol Sedation for MJ Patients

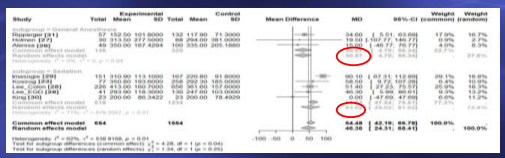


- IV Sedation + GA Propofol Doses → 9 Studies
  - (THC +) patients → Required 47.33 mg more Propofol

J Clin Med. 2025; 14: 858

117

IV Sedation vs GA in MJ → Patients



- MJ Users
  - IV Sedation for THC + patients required → 53.02 mg more Propofol
  - GA for THC + patients required → 30.57 mg more Propofol

J. Clin Med. 2025; 14:858

118

JOMS 2026

- Chronic cannabis use
  - down regulates CB 1 Receptors
    - reduces effectiveness of GABA mediated TIVA agents → (Propofol & Midazolam)
  - up regulates CYP enzymes that metabolize propofol
    - reduces effectiveness of propofol
  - interferes with GABA neurotransmission
    - reduces effectiveness of propofol & midazolam

JOMS 2026; 84: 641 - 648
Anesth Analg. 2024;140(6):1401 Curr Opinion Anaesth 2025; 38(5): 660

119

JOMS 2026

- Classified Marijuana use for third molar surgery
  - Low Risk vs Moderate Risk vs High Risk
  - Concluded that chronic use correlates with increased propofol doses

Risk from Marijuana Use	Total Propofol Dose
Low Risk < 2 to 3 years of use	169 mg
Moderate Risk > 2 to 3 years of use	216 mg
High Risk > 2 to 3 years of use Multiple times a day	262 mg

JOMS. 2026; 84:641

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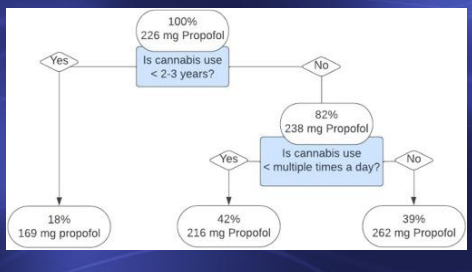
JOMS 2026



121

Propofol & Marijuana

- Cannabinoids decrease the effectiveness of Propofol and Benzodiazepines
  - promotes formation of → CB 1 / GABA-A complex
    - decreases GABA - A neurotransmission
  - decreases effectiveness of inhalation agents, midazolam, & propofol
    - must increase the anesthetic dose
- Cannabinoids induce CYP enzymes
  - accelerates metabolism of propofol & midazolam

Frontiers in Cardiovascular Medicine. 2024 J Clin Med. 2025

122

Cannabis Ambulatory OMFS Surgery

- Unknown Factors found in many publications
  - Type of MJ used → Flower or Distillates
  - Route of Administration → Smoke, Vape, or Edible
  - THC concentration of MJ
  - Frequency of Use → Occasionally, Monthly, Weekly, Daily, & how many times per day
  - Last dose prior to surgery

123

Postoperative Issues

- Postoperative pain requirements
  - acute pain required higher doses of opioids
- Reports of increased pain & sleep disturbance postop
- Cannabis use → may experience hyperalgesia
  - ketamine useful agent

Eur J Anaesthesiol. 2019;36:623 Eur J Anaesthesiol.2019;36:705 J Clin Anest 2020:66

124

Post operative Pain

- To date → majority of studies → cannabinoids for acute ` surgical pain → not effective
- Chronic cannabis users → may have greater baseline levels of pain & hyperalgesia
  - post operative pain more difficult to manage

Advances in Anesthesia. 2024; 42: 85

125

Recommendations – Suggestions for Perioperative Marijuana Users

Anesthesia Patients

Not Local Anesthetic Cases

126

Elective Anesthesia & Marijuana

- Acute Intoxication = Cancel Elective Surgery for all patients
  - same guideline as alcohol or other drug intoxications
  - excessive sympathetic stimulation
  - increased cardiac risks (Angina, AMI, or Arrest)
    - tachycardia, hypertension, dysrhythmias, bradycardia or hypotension
  - increased cerebrovascular risk
  - respiratory risks (obstruction, laryngospasm, bronchospasm)

Digestive Diseases and Sciences. 2022;67:5371

127

Elective Anesthesia & Marijuana

- How long do you hold marijuana preop??
- Multiple articles → All Patients Should Hold for 72 hours.
  - Heliyon 2018; J Clin Anest 2019; AANA J 2019
  - can't find evidence to support these recommendations
  - most effects of acute cannabis persist for up to 6 hours
  - increased risk of AMI for up to 5 hours after acute ingestion
  - increased risk of airway obstruction for 4 hours after acute use

Why Wait 3 Days?

Preop Guideline for Cannabis & Elective Sx. J PeriAnesthesia Nursing 2022 Trends Cardiovasc Med.2020:30:298

128

Elective Anesthesia & Marijuana

- Infrequent Users → Marijuana 2 to 3 times per week
  - Adjusting Use for 48 hours → marijuana anesthetic interaction should be eliminated
  - Infrequent users → abstinence withdrawal risk → **low**
  - "Rodeo anesthetic" risk → **low**
  - Resume Marijuana use after surgery

Very Reasonable Request → Easy to Comply

J PeriAnesth Nursing . 2022. doi.10.1016/j.jopan.2022.10.002 Stover. Preop Guidelines fro MH Elective /sx

129

Suggestion for Infrequent Users

- Goals for the Occasional User of Marijuana
  - Adjust patient's marijuana use
  - No marijuana use for at least 2 days preop →
  - Vaping is preferred over smoking
  - Edibles preferred over Vaping
  - Postop: Edibles or vaping → avoid hot temperatures of smoking

Less Carboxy Hb in Lungs
Less CVS Stimulation

- Makes patient compliance easier
- To Date: Patient acceptance exceptional
  - If I can believe the patients.

130

Elective Surgery & Anesthesia

- 2022 Nursing Study: Developed Preoperative Marijuana Abstinence Plan
  - no marijuana for 72 hours preop
  - actual abstinence was 36 hours on average → not 72 hours
  - no surgery cancelled regardless of when the patient stopped
  - no complications reported

Don't expect Daily Users or Marijuana Use Disorder Patients to Hold for 72 Hours

J PeriAnesth Nursing . 2022. doi.10.1016/j.jopan.2022.10.002 Stover. Preop Guidelines fro MH Elective /sx

131

Elective Surgery & Marijuana

- Daily or heavy user → Can they hold for 72 hours?
  - What about → Emotional and Physical Complications
  - Marijuana Withdrawal???
  - Unrealistic Expectation by the Practitioner
  - Would you consider doing this for chronic pain opioid users ?
- Need a new plan

132

Elective Surgery

- Does patient know the THC content of their product?
  - Flower product → street weed vs commercial dispensary
  - Concentrates → should know THC content from dispensary
- What is risk of withdrawal symptoms?
  - Marijuana Use Disorder Patients → Expect Symptoms in 24 hours

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Elective Surgery

- High Doses of MJ or Cannabis Use Disorder patients
  - multiple uses per day
  - holding drug for 72 hours → almost certain to experience withdrawal → starts within 24 hours
    - Increased Sympathetic Activity: HR, BP, Anxiety, Irritable, & Uncooperative
  - more likely to see → "Rodeo Anesthetic"
    - thrashing around in chair
  - will need ↑↑↑ doses of anesthetic agents
  - may not be able to prevent "rodeo anesthetic"
  - intermittent bolus anesthesia → poor choice here → need pumps

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High Doses of Cannabis

- Is There a Better Way than Holding for 72 hours?
- How about reducing the dose over several days preoperatively?
- How about THC → "Gummy Bears" or Hard Candy
  - reduce the dose over several days preoperatively
  - eliminate the smoking for lung function as well

135

Elective Surgery for Heavy Users

- Gets "baked" every day…….. Will not stop
- Marijuana reduction protocol
  - reduce total dose per day by 25 to 50% several days preop
  - no marijuana morning of surgery → restart in afternoon – evening
  - resume normal dosing postoperatively
  - no smoking THC → use edibles or vaping as alternative

No Proof. Just Common Sense

136

Weaning Cannabis Preoperatively

British J Anaesthesia. 2021; 126(1): 304-318

Published after my suggestions on Marijuana Weaning

137

Perioperative Management of Cannabis

- Significant Cannabis Consumption Requirements
  - 1.5 grams/day of inhaled cannabis
  - 300 mg/day of CBD oil
  - 20 mg/day of THC oil
  - cannabis product with unknown CBD or THC concentration
    - consumed more than 2 to 3 times per day

Typical Joint has 500 mg of Cannabis

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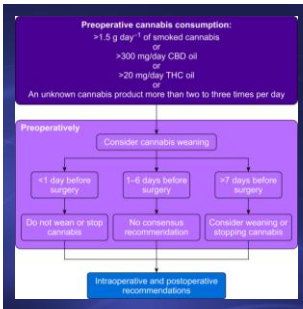

- More than 7 days before Sx
  - Patient uses 2 grams per day
  - Reduce to 1.5 grams per day
  - May go lower if patient cooperates
  - Safe & may benefit the patient
- No consensus if 1 to 6 days before surgery
- Tapering < 1 day before Sx may induce withdrawal symptoms

They started with 25% reduction

Br J Anaesth. 2021;126(1):304

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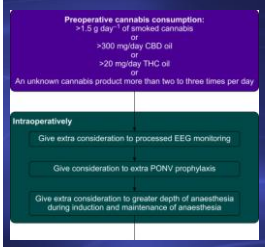
Intraoperative Considerations



- High dose cannabis patients
  - have increased incidence of N/V
- Consider Extra PONV prophylaxis
  - dexamethasone + ondansetron
- Increased doses of anesthetic agents
  - consider infusion pumps to maintain anesthetic agent concentrations

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Office Anesthetic Protocols

- Benzodiazepines → Anxiolysis & Sedation
  - Midazolam → 1 to 5mg at beginning of case
- Propofol → infusion preferred over bolus bumping
  - 100 mcg/kg/min to start → increase as needed
  - Expect increased dosing vs non marijuana users
- Opioids
  - Low dose Fentanyl boluses → total dose within 0 to 2 mcg/kg
  - Remifentanil infusions

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Office Anesthesia Protocols

- Ketamine boluses
  - excellent adjunct
  - sedation & pain control especially with potential hyperalgesia
- Dexmedetomidine
  - sedation & control of hypertension – tachycardia
  - control of → hyperactivity & emergence reactions
  - mini bolus doses of 4 mcg/ml prn

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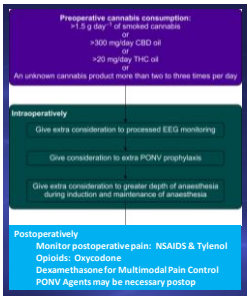
Summary of Intraoperative Considerations

- May require higher doses of → TIVA & Inhalation Agents
  - to avoid "Rodeo Anesthesia"
  - Infusion Pumps
- Cannabis use → No contraindications to using
  - NSAIDs, Opioids, or Ketamine
  - Dexmedetomidine, Local Anesthetics, or Tylenol
- Chronic High Dose Cannabis
  - increased risk of PONV → use additional PONV prophylaxis

Br J Anaesth. 2021

143



Postoperative

- High dose cannabis patients
  - have greater postoperative pain
  - cannabis is not effective for acute pain relief
- Employ multimodal Analgesia
- Opioids may be needed
- Remember your Dexamethasone
- PONV agents

144

Patient Smoked Marijuana Before They Came Into the Office

Can we treat the Patient??

Local Anesthetic Cases in Office vs Office Anesthesia

145

Smoked Marijuana Before Office Visit

- Patient is not intoxicated
  - awake & alert → is oriented → no apparent impairment
- Can you treat the patient under local anesthesia
- ASA 1 Adult or Adolescent → No tachycardia or HTN
  - No history of CVS or Cerebral Vascular Disease
  - Risk of AMI or CVA due to excessive oxygen consumption is low
    - tell patient about risk → low → possible → not probable

146

Smoked Marijuana Before Office Visit

- Proceed with surgery under Local Anesthesia
  - consider limiting Epi in Local
- Compare this to the patient that told you
  - "Doc, I had a couple of drinks before I came to the office"
  - Did you refuse them treatment?

Frontiers in Cardiovascular Medicine. 2024
ASRA recommendation: Wait at least 2 hours if used THC that day
Frontiers suggested 5 hours for consent???

147

Smoked Marijuana Before Office Visit

- Adults with history of CVS disease or CVA history
  - Local Anesthesia Procedure
  - Not intoxicated
  - Risk for complications do exist
  - CVS issues can persist for up to 5 hours → highest risk 1st 2 hours
- Would defer treatment for up to 5 hours
  - ASRA say defer for at least 2 hours

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Smoked Marijuana Before Office Visit

- Explain potential risks of not waiting few hours
  - AMI or Stroke
  - Document → BP & Pulse
- Most likely to reschedule if you insist on delaying for a few hours
- Patients may just deny use on next visit or not come back

149

Smoked Before Came Into Office

- Treatment planned for IV anesthesia in Office
- Not intoxicated
- ASA 1 → No CVS or Stroke History & No airway disease
  - ASRA says wait at least 2 hours before proceeding
  - Personally → would defer at least 5 hours or reschedule
  - Patient will probably leave office → may never return
  - Need to discuss this with patient on preop visit

150

Smoked Before Came In

- Treatment planned for IV anesthesia in Office
- Not intoxicated
- History of CVS & Cerebral Disease + Airway Disease
- Reschedule Patient is Best Option

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Marijuana Testing

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THC Testing

- THC Testing Methods
  - Urine, Hair, Saliva, Serum
    - Urine is most common → 50 ng/ml is positive test
  - Testing for THC-COOH metabolite

Tests	Detection Capability
Urine	Up to 3 days for Occasional User Up to 30 days for Chronic, heavy users
Saliva	24 to 72 hrs
Blood	Few hours up to 24 to 48 hours

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Cannabinoid Hyperemesis Syndrome

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Case Presentation

- 25 y.o. male
- PMH: no significant history except marihuana use
- Chief Complaint
  - pain in tooth #30
- Secondary complaint
  - cyclic episodes of severe N/V
  - multiple vomiting episodes per day
  - lasts for several days then stops then recurs in few months
  - severe abdominal pain
  - only relief is taking hot showers

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Cannabinoid Hyperemesis Syndrome (CHS)

- Cyclic episodes of emesis
- 1st reported in Australia in 2004
- Colorado → since legalization → ER visits have doubled
- Often requires admission for hydration & analgesia
- Most cases → cannabis inhalation is cause
- Usually unresponsive to typical antiemetics

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CHS

- Onset → Requires at least 1 year of Marijuana use
  - most cases → range is 1 to 5 years
- Cannabis Frequency of Use

< Weekly	2.4%
Weekly Use	19.4%
Daily Use	47.9%
Greater Than Daily	23.7%

Daily Use Most Common

J. Med Toxicol.2017;13:71

157

Signs & Symptoms

Severe N/V	100%
Cyclic Vomiting	100%
Resolution when stop cannabis	96.8%
Symptoms ↓ with Hot Shower/Bath	92.3%
Abdominal Pain	85.1%
Caucasian	80%
Males	72.9%

Many Patients Report Cannabis Use Started as Teenager

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4 Phases of CHS

- Inter – episodic phase
  - No symptoms
- Prodromal
  - Onset → Need at least 1 year of Marijuana Use
  - Triggers → stress, noxious stimuli, & infections
  - Develop nausea, anorexia, & abdominal discomfort
  - Still able to eat
  - Can tolerate oral anti-nausea agents

159

4 Phases

- Vomiting Phase
  - may be < 12 hours of vomiting
  - duration 1 to 2 days → can persist for 7 to 10 days
  - abdominal pain
  - hot showers/bath will relieve pain
- Recovery Phase
  - vomiting stops
  - resume oral intake
  - duration = days to months

Vomiting on Empty Stomach → More Painful Than Full Stomach

PO Fluid Intake → Watery – Foamy Vomit

160

Management of CHS

- Hot showers or hot bath
- Anxiety issues → benzodiazepines in ER or hospital
- IV Proton Pump Inhibitors (PPI) to reduce acid
- H2 Blockers or Antacids
- Analgesics including opioids
- Saline IV for hydration
  - 1 to 2 Liters in ER then 150 to 200 ml/hr
- Typical antiemetics → may be ineffective
- Solution = stopping the use of cannabis = most effective

161

TRPV 1 Receptors

- Transient Receptor Potential Vanilloid 1 Receptors
  - TRPV 1 Receptor
  - found in the endovanilloid system → system interacts with endocannabinoid system
- TRPV 1 and CB 1 receptors
  - located on same neurons in CTZ & VC of medulla
  - located on same peripheral enteric & vagal sites
  - both receptors are activated by cannabinoids
  - TRPV 1 is also found in skin

J.Med Toxicol.2017;13:71

162

Mechanism of Action

- Cannabis activates TRPV 1 receptors
  - result = antiemetic
  - prolongs gastric emptying time
- Cannabinoids activate CB 1 receptors
  - act as antiemetic
  - prolongs Gastric Emptying Time

Low Dose Cannabinoids = Antiemetic
High Dose Cannabinoids = Pro-emetic

163

Mechanism of Action

- Excessive cannabinoid use
  - Gastric Emptying Time → additional emptying delays
  - down regulates or desensitizes → CB 1 receptors
  - desensitizes or downregulates → TRPV 1 receptors
  - acts as a pro-emetic
- Develop Cyclical Vomiting

No Case Reports Linking CHS to Increased PONV

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Capsaicin Topical Cream

- Capsaicin → plant extract from chili peppers
  - medical use → topical pain relief
  - topical cream → 0.025%, **0.075%,** & 0.1%
  - activates TRPV 1 receptors found in skin
- Apply 1 inch strip on abdomen → 3 to 4 times day
  - relief after 1 or more doses
  - prevents admission to hospital
  - side effects → burning & erythema skin

J Pharmacy Practice.2020; 1-8. doi: 10.1177/0897190020934289

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Capsaicin & TRPV 1 Receptors

- Prolonged marijuana exposure inactivates TRPV 1 receptors
  - receptors in CTZ, VC, enteric, and vagal neurons
  - gastric emptying time increased + nausea & vomiting
- Capsaicin or heat → temperatures > 43 C
  - activate TRPV 1 receptors in skin
  - restore anti emetic effects & normalizes gastric motility

81% Success Rate

Clin Toxicol.2020;58(6):471 J Pharm Practice2020

166

Capsaicin Topical Cream

- 11 Reports (2014 – 2020) Capsaicin in ER for CHS
  - Resolution of N/V & cramping → within 20 to 45 minutes
  - Decreases Pain
  - Dosing → 1 to 3 doses
  - ER length of stay → most were shortened, some no change

Am J Em Med. 2021;49:343

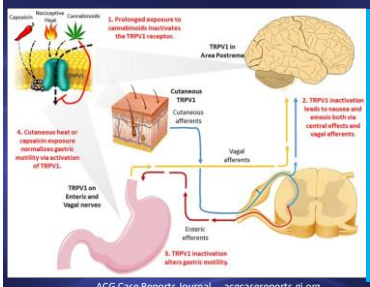
- 2020 Report
  - 67% got pain relief → Average ER stay of 3 hours

Clin Tox. 2020;58:471

- 2022 Report
  - 42% got pain relief → Average ER stay of 8 hours

Ann Pharmocotherapy. 2022;56(2):51

167



1. **High Dose Marijuana Will Downregulate CB1 & TRPV1 Receptors**
2. **CB1 & TRPV1 Receptors now promote N/V**
3. **CB1 & TRPV1 Receptors now decrease gastric motility & gastric emptying**
4. **Capsaicin or Heat will reactivate TRPV1 Receptors to increase gastric motility & decrease N/V**

ACG Case Reports Journal. acgcasereports.gi.org

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Haloperidol for CHS

- Haldol → Dopamine antagonist in CTZ D2 site
  - 1 to 5 mg IV → most case reports → 5 mg IV
  - relief of symptoms in about 1 hour (11 patients in study)
  - relief of symptoms in 1 to 2 hours (4 patients)

82% Success Rate

- Haldol for PONV relief
  - 0.5 to < 2 mg IV or IM 2020 Consensus Guidelines PONV
  - 0.5 to 1 mg IV SAMBA
- Could consider droperidol 0.625 mg IV

Am J Therapeutics.2017;24:e64 Am J Emerg Med.2013;31:1003e5

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CHS Treatments Summary

Drug	Total # Patients	Positive Response
Capsaicin	94	80.6%
Haloperidol	11	81.8%
Lorazepam	36	58.3%
Promethazine	24	8.3%
Ondansetron	64	6.3%
Diphenhydramine	13	7.7%
Morphine	20	15.0%

J. Pharmacy Practice.2021;34(5): 786

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Thank you

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Cannabis Withdrawal

Cannabis Withdrawal Symptoms
CWS

Br J Anaesthesia. 2021;126(1): 304

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Cannabis Use Disorder

- DSM – 5 Criteria: Drug for at least 1 year + 2 of following
- Repeatedly tried to stop
- Used larger amts over longer time than intended
- Cravings & obsession for drug
- Kept using despite negative consequences
- Drug more important than other aspects of life
- Developing tolerance

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Cannabis Withdrawal

- Abrupt cessation of → Heavy & Prolonged Marijuana Use
  - Use of High THC Content
  - Daily – Multiple Daily Use
  - Patients with Marijuana Use Disorders
- Cannabis Consumption Risks
  - > 1.5 grams/day of inhaled product
  - > 20 mg/day of THC oil
  - > 2 or 3 THC products of unknown concentration per day

Br J Anaesthesia. 2021;126(1): 304

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Cannabis Withdrawal

- Incidence → 47% of individuals with increased risks
- Onset → 24 to 72 hours after cessation
- Duration → 1 to 2 weeks

- Unlikely to occur if consume < 300 mg/day of cannabis
  - 1 "joint"

- Can occur if withhold Cannabis for surgery
  - " HOLD for 72 HOURS" → Needs Rethought

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Cannabis Withdrawal

- DSM – 5 Criteria → Heavy Use or Cannabis Use Disorder

- Cessation of Agent + 3 or more of the following
  - irritability, anger, or aggression
  - nervousness or anxiety
  - sleep disorders
  - appetite or weight disturbance
  - restlessness or depressed mood
  - HA, Diaphoresis, N/V, Tremors, Fever – Chills, or Abdominal Pain

Reg Anesth Pain Med. 2023; 48: 97

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Withdrawal Symptoms

Variable	Description
Signs and symptoms	Irritability/anger
	Anxiety/depressed mood
	Insomnia
	Altered dreams
	Anorexia
	Abdominal cramping
	Headaches
	Tremors
	Fevers/chills
Onset	<1 day for high-dose, chronic users
Duration	Up to several weeks
Treatment	Symptomatic therapy, synthetic THC

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Treatment by Addiction Specialist

- These patients require management by a specialist

- Medications that have been found useful
  - Nabiximols
    - plant derived: CBD + THC 1:1 oral preparations
  - Nabilone
    - synthetic pharmaceutical THC

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Thank you

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JOMS. 2026;84:641
Anest Analg. 20245;140(6):1401
Curr Opin Anaesth. 2025;38(5): 660

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Table 3 Summary of cannabinoid-drug interactions used with permission from Samer Narouze, MD, PhD [63-67]

Enzyme	Drugs	Effects and interventions
CYP2C9		
CYP2C9 inducers	▶ Antiarrhythmics: amiodarone ▶ Anticonvulsants: valproic acid ▶ Antidepressants: fluoxetine ▶ Fluconazole, metronidazole, sulfamethoxazole	▶ Decrease THC level ▶ Unlikely to have significant effect on CBD
CYP2C9 inhibitors	▶ Carbamazepine, rifampin	▶ Increase THC level ▶ Unlikely to have significant effect on CBD
CYP2C9 substrates	▶ Warfarin ▶ **Buprenorphine** ▶ Non-steroidal anti-inflammatory drugs (NSAIDs): celecoxib, naproxen, ▶ Anticonvulsants: phenobarbital, phenytoin ▶ Fluvastatin, rosiglitazone, rosuvastatin, sulfonylureas, losartan, valsartan	▶ CBD and possibly THC may increase drug levels *Interventions:* ▶ Decrease dose of substrate ▶ Monitor for toxicity and side effects ▶ Check INR within 3 days
CYP2C19		
CYP2C19 inducers	▶ Anticonvulsants: carbamazepine, phenytoin, phenobarbital ▶ Rifampin, rifampicin, ketoconazole, St. John's wort	▶ Decrease CBD and THC levels
CYP2C19 inhibitors	▶ Antidepressants: fluoxetine, fluvoxamine ▶ Chloramphenicol, felbamate, isoniazid ▶ Protease inhibitors	▶ Increase CBD and THC levels
CYP2C19 substrates	▶ Antidepressants: amitriptyline, citalopram, bupropion ▶ Anticonvulsants: diduscan, diazepam, phenytoin, phenobarbital ▶ Antiplatelets: clopidogrel ▶ Proton-pump inhibitors: omeprazole, pantoprazole	▶ CBD and THC may increase drug levels *Interventions:* ▶ Decrease dose of substrate ▶ Monitor for toxicity ▶ Consider using alternative antiplatelet instead of clopidogrel

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CYP2D6		
CYP2D6 Substrates	▶ **Opioids: codeine, morphine, hydrocodone, tramadol** ▶ Anticonvulsants: valproate ▶ Antidepressants: amitriptyline, citalopram, nortriptyline ▶ Antipsychotics: clozapine, haloperidol, risperidone ▶ Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone ▶ β-blockers: carvedilol, metoprolol	▶ CBD>THC may increase drug levels. *Interventions:* ▶ Decrease dose of substrate ▶ Monitor for toxicity and side effects ▶ Monitor for opioids augmentation ▶ Monitor QTc for antidepressants and antiarrhythmics
CYP3A4		
CYP3A4 Inducers	▶ Anticonvulsants: carbamazepine, phenytoin, phenobarbital, topiramate ▶ Cimetidine, pioglitazone, rifampin, St. John's wort	▶ Decrease CBD and THC levels
CYP3A4 Inhibitors	▶ Antiarrhythmic: amiodarone, dronedarone, quinidine, diltiazem, verapamil ▶ Anticonvulsants: valproate ▶ Antifungals: ketoconazole, itraconazole, posaconazole ▶ Macrolides: clarithromycin, erythromycin ▶ Protease inhibitors ▶ Tyrosine kinase inhibitors	▶ Increase CBD and THC levels
CYP3A4 Substrates	▶ **Opioids: fentanyl, alfentanil, methadone** ▶ • Benzodiazepines: midazolam ▶ Calcium channel blockers: amlodipine, felodipine ▶ Calcineurin inhibitor: cyclosporine, tacrolimus ▶ PDE5 inhibitors: sildenafil ▶ Propafenone ▶ Statins ▶ Zaleplon, zopiclone, zolpidem	▶ Increase CBD and THC levels

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UGT1A9 (Phase II)		
UGT1A9 Substrates	▶ Analgesics/NSAIDs: acetaminophen, ibuprofen, diflunisal ▶ Anesthetics: propofol ▶ Anticonvulsants: valproate ▶ Antipsychotics: haloperidol ▶ DOACs: dabigatran ▶ Canagliflozin, dapagliflozin, irinotecan, mycophenolate mofetil, regorafenib, sorafenib	▶ CBD increases substrate levels *Interventions:* ▶ Consider decreasing substrate dose ▶ Monitor for side effects or toxicity
UGT2B7 (Phase II)		
UGT2B7 substrates	▶ **Opioids: hydromorphone, morphine, buprenorphine** ▶ NSAIDs: ibuprofen, naproxen. ▶ Benzodiazepines: lorazepam ▶ Anticonvulsants: carbamazepine, valproate, lamotrigine ▶ Statins: lovastatin, simvastatin ▶ Ezetimibe, losartan	

Table 3 Continued

Enzyme	Drugs	Effects and interventions
P-glycoprotein substrates	▶ DOACs: dabigatran, apixaban, rivaroxaban ▶ Digoxin, loperamide	▶ CBD and possibly THC may be a substrate and inhibitor of P-glycoprotein *Intervention:* ▶ Decrease dose of substrate ▶ Monitor for toxicity and side effects

CBD, cannabidiol; INR, international normalized ratio ; THC, tetrahydrocannabinol.

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Marijuana & Chronic Pain

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Marijuana & Chronic Pain

- 1661 patients: Chronic Pain & Marijuana
  - 25.9% used MJ for pain in past 12 months
  - 23.2% used it in past 30 days
  - 94% used marijuana & at least 1 other pharmacologic for pain
  - 50% reported decrease in opioid & OTC analgesics since used MJ
  - 1% reported increased need for opioids since started on MJ

JAMA Open. 2023; 6(1): e2249797

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Chronic Pain

- Chronic Pain Relief
  - THC was better than CBD
  - Use PO or Oral Sprays → Do not smoke
- Indications for Use
  - Monotherapy, Replacement Therapy, or Adjunctive Therapy
- Moderate Evidence to Support
- Strong Recommendation for Use

Cannabis and Cannabinoid Research. 2023
Clinical Practice Guidelines for Cannabis Management of Chronic Pain
Bell et al. Doi 10.1089/CAN.2021.0156

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Cannabis

- Multiple Sclerosis
  - THC 10 to 15 mg doses
  - Pain relief & Muscle spasm relief
  - Strong Recommendation & Moderate Evidence
- Arthritic Pain
  - Use THC/CBD oral mucosal liquid 15mg/15mg
  - Strong Recommendation Low Evidence
  - ?? CBD cream to knees

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Cannabis

- Cannabis & Opioid Sparing for Chronic Pain
  - Adjunct cannabis can help decrease need for chronic opioids
    - patients using opioids > 50 morphine equivalents will benefit
  - Strong Recommendation but Low Evidence

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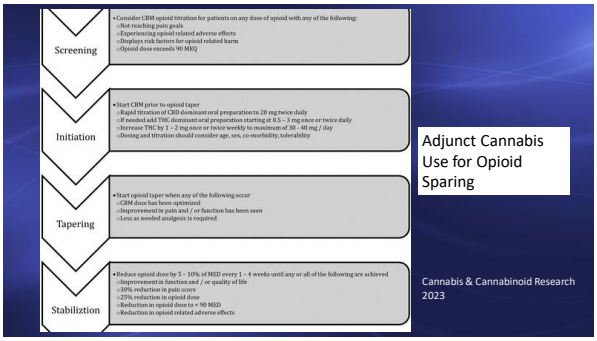

Adjunct Cannabis Use for Opioid Sparing

Cannabis & Cannabinoid Research 2023

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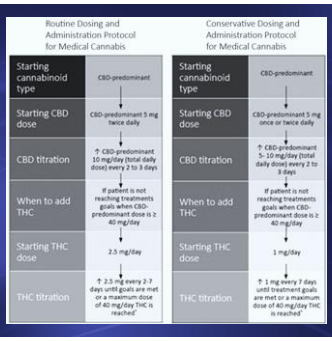

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1

Perioperative Allergic Reactions

Hives to Anaphylaxis

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2

Key Concepts for Discussion

- #1 Allergic reactions in the office: Diagnosis & Management
  - Mild Reactions to Anaphylaxis
- #2 Clinical Presentation
  - Awake versus Unconscious
- #3 Epinephrine
  - IM or IV
  - Risk versus Benefit
  - Epinephrine versus Antihistamines & Steroids

3

Allergic Reactions

- Reactions are rare but potentially life-threatening
  - minor skin reactions → urticaria & pruritus

    OR
  - severe reactions → angioedema & anaphylaxis
    - Cardiovascular compromise → hypotension & perfusion abnormalities
    - Respiratory compromise → bronchospasm & hypoxia
    - Laryngeal edema → asphyxiation

4

Perioperative Allergic Reactions

- Perioperative Allergic Reactions
  - estimates vary in literature reports → wide ranges reported
  - most sources claim → perioperative allergic reactions are rare
- Journal Allergy Clinic Immunol. 2022; 2(1): 88
  - worldwide incidence
    - allergic reactions → 1: 355 to 1: 18,600 surgeries
    - anaphylaxis → 1: 1250 to 1: 20,000 surgeries
    - anaphylaxis → less common than mild & moderate allergic reactions
  - US → anaphylaxis in 1: 6537 cases
  - Europe → anaphylaxis in 1:736 to 1: 2297 cases

5

Allergic Reactions

Hypersensitivity Reactions

6

Hypersensitivity Reactions

- Exaggerated or inappropriate response to an "allergen or antigen" resulting in localized or generalized tissue damage
- World Allergy Organization 2003
  - Reproducible symptoms and signs initiated by exposure to a stimulus at a dose tolerated by normal individuals
- Allergy → type of hypersensitivity reaction initiated by an immunologic mechanism

Van Cuilenborg. Best Practice & Research Clinical Anaesthesiology. 2021; 35: 11

7

Hypersensitivity Reactions

- Hypersensitivity can be "allergic" or non-allergic
  - in other words → immunologic or non-immunologic
- Cross Reactivity
  - risk of allergic reaction to 2 or more medications with similar chemical structures

8

Hypersensitivity Reactions

- 4 Types of hypersensitivity reactions
- Type I Immediate Hypersensitivity Reactions
  - majority of allergic reactions → IgE immunologic reaction
  - exposure to previously encountered Antigen → cross links → 2 IgE antibody complexes on mast cell (primary cell) or basophil
  - release mediators
    - histamine, tryptase, platelet activating factor, & leukotrienes

Wilkerson. Immunol Allergy Clin N Am. 2023;43:473

9

Type I Immediate Reaction

- Histamine mediator → dictates majority of signs & symptoms
  - contracts smooth muscle in airway & GI tract
  - increases vascular permeability & vasodilation
  - increases mucus production, pruritus, & gastric acid secretion
- Histamine Clinical Signs & Symptoms
  - flushing, pruritus, urticaria, rhinorrhea, & sneezing
  - stridor, cough, wheezing, dyspnea, hypoxia
  - hypotension, tachycardia, & increased vascular permeability
  - angioedema to anaphylaxis

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Type I Immediate Reaction

- Type I Immediate Reactions
  - most relevant hypersensitivity reaction in perioperative setting
  - most common
  - mild, moderate, or anaphylactic reactions
- 15 to 25% of the US population are affected
  - 4.5% from allergic asthma
  - 4% from insect bites
  - 5% from medications
  - Other causes → food, latex, disinfectants, pollen, environmental and occupational allergens

11

Type I Immediate Reactions

- Type I Immediate Reactions
  - majority occur within 1 hour of drug exposure (5 to 30 mins)
    - IV route onset → seconds to minutes
    - PO route empty stomach → 3 to 30 minutes
    - PO route full stomach → 10 to 60 minutes

IV Medications → Rapid Reaction → As early as 5 minutes → Majority in 1st 30 mins after Injection

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Remaining Hypersensitivity Reactions

Type	Reactant	Mechanism	Clinical
Type II Cytotoxic	IgG, rare IgM	Activates Complement Pathway to lyse cells	Autoimmune Hemolytic Anemia Fatigue, pallor, tachycardia & hypotension, Thrombocytopenia
III Immune Complex Disease	IgG & IgM	Immunoglobulins bind to Antigens to Activate Complement Pathway	Serum Sickness SLE, Glomerulonephritis,
IV Cell Mediated	T Cells	Inflammatory process	Contact dermatitis

Type II, III, & IV Reactions → Not Involved with Immediate Allergic Reactions

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Mechanisms for Immediate Reactions

- 3 Mechanisms for Type 1 Immediate Reactions
  - IgE Dependent, IgE Independent, & Non- immunologic (Anaphylactoid)
- Most frequent → IgE Dependent Reaction
  - "Classical Immediate Pathway"
  - Mechanism for mild, moderate, & anaphylactic reactions
- IgE antibody complex binds to high affinity receptor on mast cell or basophil
  - FcεRI receptor

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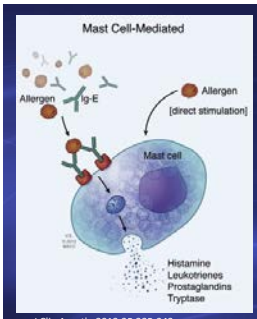
IgE Dependent Reaction

- Cross link Antigen to 2 or more of these IgE complexes
  - mast cell – basophils degranulate
  - release mediators
- Beta lactam antibiotics & NMB agents are primary antigens for the IgE dependent pathway
  - perioperative allergic reactions

15



Ab binds to mast cells and basophils

Antigen cross links 2 IgE – Ab complexes

Release mediators

Some mediators can be measured in laboratory to diagnose IgE reaction

J Clin Anesth. 2013;25:335-343 J. Allergy Clin Immunol.2017;140:335

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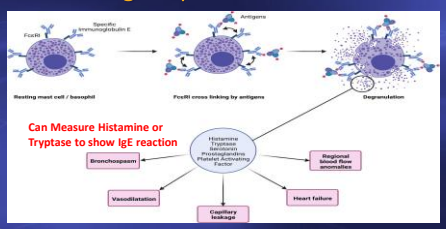
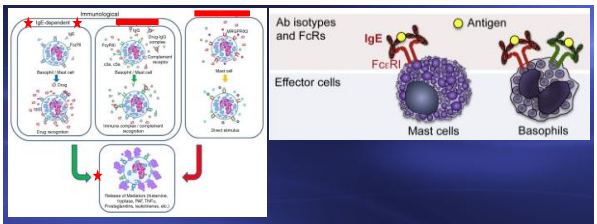
IgE Dependent Reactions



- Antigen cross links the IgE antibody complexes
- Degranulate Mast Cells → Followed by Clinical Effects

Anesthesiology. 2023; 138:100

17



- IgE Dependent Pathway → Primary pathway for perioperative allergic reactions
- 50 to 60% of reactions → Mild, Moderate, or Anaphylactic

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IgE Independent Reaction

- Mediated by IgG antibodies or by complement
- IgG antibody complexes binds to → FcεRIII receptor on basophils
  - release Platelet Activating Factor (PAF)
- IgG antibody complexes can activate Complement as well
- Xray contrast dye is common trigger

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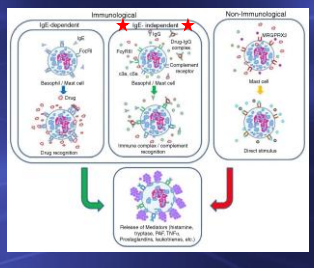
IgG or IgE Independent Reaction



20

Non – Immunologic Reaction

- Immune System is not involved (Anaphylactoid)
- Direct Stimulation of Mast Cells by Antigen
  - degranulate cells → release mediators
  - antigen binds to → MAS – Related G Protein – Coupled Receptor X2
    - MRGPRX2 receptor
- Drugs → xray contrast, opioids, NMB, & vancomycin

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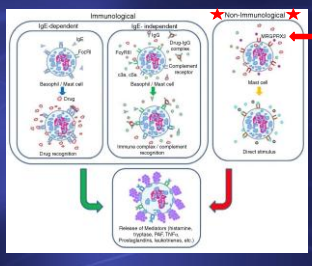
Non - Immunologic



MRGPRX2 RECEPTOR

Brazilian Journal of Anesthesiology. 2020;70(6):642

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Clinical Presentation of Mild to Moderate Allergic Reactions

23

Clinical Signs of Mild to Moderate Allergic Reaction

- Clinical presentation Mild Reaction
  - Urticaria (hives)
  - Pruritus (itching)
  - Cutaneous Flushing

Mild Reactions → 1 Organ System Involved → Skin

  - Angioedema (non pruritic swelling of skin and mucosal tissue)
    - Seen more in moderate allergic reactions
  - Cutaneous lesions more common in mild reactions

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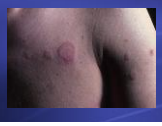
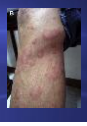
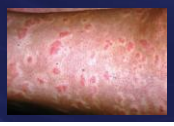
Uticaria (Hives)

- Transient blanchable, raised, smooth pink to red papules on skin
- "classical presentation of wheal"
  - pale, raised lesion of skin surrounded by erythematous flare
- Pruritus is common finding
- Resolve within 24 hours after allergen removed

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Mild Reaction: Urticaria & Pruritus

- Antihistamines → 1st Line of Therapy
  - urticaria, pruritus, flushing, & rhinorrhea
- H1 antihistamine → Diphenhydramine (Benadryl)
  - Adults → 25 to 50 mg → IV over 5 mins → can be dosed IM or PO
  - Peds → 1 mg/kg for weight < 40 kg → IV over 5 mins
  - Crosses Blood Brain Barrier
    - sedates & anticholinergic effects

Adult Max/Day = 400 mg **Peds Max/Day = 200 mg**

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Mild Reaction: Urticaria & Pruritus

- H1 antihistamines → 2nd Generation
  - Do not cross Blood Brain Barrier
    - No sedation or Anticholinergic Effects
  - Cetirizine (Zyrtec)
    - Adults → 10 mg IV over 1 to 2 minutes → can be PO dosed
    - Peds → **< age 6** → give 2.5 mg PO or IV
    - Peds → **ages 6 to 11** → give 5 to 10 mg PO or IV

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Mild Reaction: Urticaria & Pruritus

- Antihistamines
  - no effect on UAO, hypotension, or cardiovascular collapse
  - do not inhibit mast cell mediator release
- Hives & Itching can persist for 24 hours
  - continue H1 antihistamine until relieved
  - Diphenhydramine 25 to 50 mg PO Q6h
    - inform patient about sedation
  - Cetirizine → Maximum dose 10 mg/day

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Antihistamines

- IV antihistamines
  - takes up to 1 hour to see maximum therapeutic effect
- PO antihistamines
  - takes 60 to 120 minutes to see peak effect orally
- Mild Reactions
  - IV med → keep in office at least 1 hour before declared stable
  - PO med → delay discharge at least 1.5 hours

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Mild Reaction: Urticaria & Pruritus

- H2 antihistamine → Famotidine (Pepcid)
- Adult Dose → 20 mg IV/PO
- Peds Dose → 0.25 mg/kg → IV/PO → Max dose 20 mg
- H1 + H2 antihistamine combination
  - more improvement in urticaria size & resolution
  - not much of an effect on pruritus
  - combination more effective in anaphylactic reactions

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Moderate Allergic Reactions

Urticaria ± Angioedema

Moderate Reactions → Skin + 1 Other Organ System → CVS or Respiratory

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Angioedema

- Transient swelling of deep dermis, subcutaneous, or submucosal tissues
- Non pitting edema → any body location
  - arms, legs, abdomen, and chest
  - head, neck, lips, tongue, mouth, pharynx, or larynx
  - isolated area or spread to all of these sites
  - can be painful & limit mobility
- Non pruritic → unlike urticaria

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Angioedema Moderate Reactions

- Moderate Allergic Reactions
  - most common presentation → urticaria + angioedema **50% of Cases**
  - 2nd most common → isolated urticaria **40% of Cases**
  - 3rd most common → isolated allergic angioedema **10% of Cases**
- Isolated Angioedema
  - Usually not due to Histamine (Immediate Hypersensitivity Rxns)
  - More likely ACE – Inhibitor Reaction, HAE, Other medications, or Acquired Angioedema

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Angioedema

- 2 Mediators for angioedema

IgE Mediated Reaction
→ Histamine Allergic Reaction
- **→ swelling occurs in minutes**
- **→ resolves < 24 hours**

Bradykinin reaction
→ Non allergic reaction
- **→ swelling onset in hours**
- **→ resolves in 48 to 72 hr**

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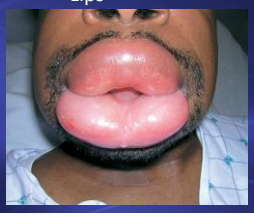
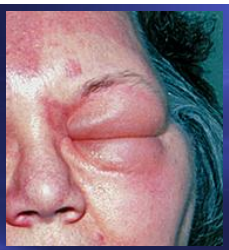
Angioedema

Lips





Periorbital

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Angioedema from Allergic Reactions

- #1 Assumption for Angioedema
  - Swelling is secondary to an allergic reaction

Most fatalities are from allergic reactions
→ Respiratory compromise – Airway Obstruction
→ Cardiovascular collapse

- #2 Assess the Airway for Swelling
  - Inspect lips, tongue, floor of mouth, uvula, & pharynx
    - can you see the posterior pharynx??

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Angioedema from Allergic Reactions

- # 3 Assess Glottic Opening, Vocal Cords, Laryngeal Swelling, & Neck Swelling
  - " Any difficulty in speaking, swallowing, or breathing?"
  - " Do you feel like you have a lump in your throat ?"
  - Positive response → Need to secure airway

Upper Airway Swelling, Glottic Swelling, Laryngeal Edema, Neck Swelling
Thankfully only occur → 20% of All Allergic Reactions

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Angioedema from Allergic Reactions

- # 4 Prepping to secure Airway
  - LMA inappropriate → glottic closure will prevent ventilation
  - Need to intubate before swelling causes glottic closure
  - How are you going to accomplish intubation?
  - Staff → Retrieves Airway Tray
- #5 Other Staff preps Epinephrine at the same time
  - need Epinephrine to Decrease Mucosal Edema

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Angioedema from Allergic Reactions

- # 5 Epinephrine
  - No IV in place → 300 mcg IM
  - IV in place → Moderate Reaction
    - mild hypotension, tachycardia, bronchospasm
    - urticaria + angioedema
    - Epinephrine dose → 20 mcg IV → escalate to 50 - 100 mcg as per symptoms
- #6 EMS called whenever Epinephrine given

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Angioedema from Allergic Reactions

- # 7 Intubation

1. Direct Laryngoscopy → Oral, Tongue, & Pharyngeal Swelling can prevent seeing Vocal Cords

2. Check Ego at Door → Video Laryngoscopy + Small Oral ET tube with Bougie in Place to Enter Trachea

3. Induce GA or Awake Intubation after Spray Throat with Lidocaine + Propofol for Sedation

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Lidocaine for Intubation

Lidocaine Preparations

Application	Dose*	Technique
Atomized	10 ml of 4% Lidocaine Solutions or Spray with 1% Lidocaine	Commercial devices: EZ Atomizer (Alcove Medical Inc.), mucosal atomized device. Spray into the back of the oropharynx prior to procedure, and spray down to vocal cords during the procedure.
Nebulized	4 mL of 4% lidocaine solution at 4 L/min	Nebulizer with mask
Direct application		
Oropharyngeal	2% viscous lidocaine, 5% lidocaine ointment	Lidocaine lollipop—apply a blob of viscous or lidocaine ointment to a tongue depressor, insert the tongue depressor as posterior into the oropharynx as possible; instruct patient to hold it but not to swallow; lidocaine drips down into the trachea
Nasal	4% lidocaine solution, 2% viscous lidocaine	For nasal intubation; soak multiple cotton swabs or nasal airway in solution and insert into the nose. Alternatively, may inject viscous into nasal passage using 10-mL syringe and have patient sniff back into throat.

1. Lidocaine is preferred local anesthetic
2. Nebulizer takes additional time → delays treatment
3. Lidocaine Spray → Easy to use → preferred treatment

Immunol Allergy Clin N Am. 2023;43:453

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Intubation Medications

Adjunct Medications for Awake Intubation

Medication	Initial Dose*	Dose in Average Adult	Use	Comments
Ketamine	0.1–0.3 mg/kg IV	20 mg, may repeat 10-mg boluses	Sedation, analgesia	Preferred agent, does not cause hypotension, preserves respiratory drive, may increase secretions
Propofol	0.5–1 mg/kg IV	50–100 mg	Sedation	Caution if hypotensive, can cause over-sedation or respiratory depression
Midazolam	20–40 μg/kg IV/IM	2–4 mg	Sedation	Benzodiazepine of choice due to rapid on and off, can cause over-sedation and respiratory depression
Fentanyl	0.5–2 μg/kg IV	50–100 μg	Analgesia	Rapid on and off, can cause respiratory depression, reversible with naloxone

Doses are not for GA → Sedate Patient after Local for ET tube but maintains spontaneous breathing

Immunol Allergy Clin N Am. 2023;43:453

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Urticaria vs Angioedema

- Urticaria is not life threatening
  - angioedema involving the airway is life threatening
- Urticaria + angioedema at same time → more severe reaction
  - ↑ duration of swelling
  - ↓ response to treatment
    - add epinephrine especially for laryngeal edema
      (will not respond in all cases → ACEI, ARBs, or HAE)

50% cases	→	urticaria + angioedema
40% cases	→	isolated urticaria
10% cases	→	isolated angioedema

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Perioperative Anaphylaxis (POA)

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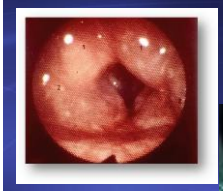
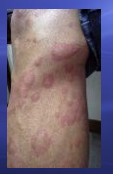
Anaphylaxis



Laryngeal edema courtesy of Dr. Bosack



Other signs: angioedema & urticaria

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Definition of Atopy

- Atopy
  - Inherited predisposition to produce IgE antibodies in response to small amounts of common environmental allergens like
    - pollen, dust mites, foods, and animals
  - More prone to suffer allergic reactions

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Perioperative Anaphylaxis

- Incidence → varies by publications
  - General agreement → uncommon reaction
  - Adults → 1:10,000 to 1:20,000 cases
  - Adults → 1: 353 to 18,600 cases
  - United States → 15.3 cases per 100,000 surgeries
  - Incidence in children → 1: 37,000 cases

J Allergy Clin Immunol Pract.2019;7:2134 Immunol Allergy Clin N Am.2022;42:145 UptoDate accessed 2022
Br J Anesth.2019;123:e50 Clin Review Allergy & Immunol,2022;62:383 Clinical Reviews in Allergy & Immunology. 2022;62:383

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Perioperative Anaphylaxis

- Mortality → 1.4 to 4.8% to 9% by author
  - 2% of survivors developed anoxic brain injury
  - US → 2% cases fatal → 5% were near fatal
- IgE mediated → greater risk of severe reactions on re-exposure than non - IgE mediated reactions

Anesthesiology. 2023; 138: 100

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Perioperative Anaphylaxis (POA)

- Mechanism of Perioperative Anaphylaxis
  - IgE dependent → 50 to 60% cases of perioperative anaphylaxis
  - IgE independent → IgG
  - Non immunologic
- IV medication onset time
  - as fast as → 1 minute
  - usually within 30 minutes → rare cases → > 30 minutes to 1 hour
- Stage of Anesthesia and Medication determine onset
  - Induction, Maintenance, Recovery

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Medications and Pathways

- IgE Dependent
  - Beta lactam antibiotics → Amoxicillin is most common
    - Amox + Clavulanic Acid and Cefazolin
  - NMBA, quinolones, vancomycin, sulfonamides, and some NSAIDs
- IgE Independent
  - Contrast dyes, dextran, and some NSAIDs
- Non-Immunologic
  - quinolones, opioids, vancomycin, contrast dye, and some NSAIDs

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Risk Factors and Diagnostic Challenges of Perioperative Anaphylaxis

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Risk Factors for Perioperative Anaphylaxis

- Primary risk → previous episode of POA
- Other risks
  - elderly patients & female
- Comorbidities that increase risk
  - COPD, coagulopathy, malignancy, obesity, coronary artery disease
  - ASA III or IV

Clin Review Allergy Immunol.2022;62:383

52

Diagnostic Challenge of POA

- What is causing the signs & symptoms of this reaction?
- Is it anaphylaxis?
- Is it just side effects of the anesthetic agent?
- Which drug is causing the reaction?
- Where are the skin signs: urticaria and flushing?
- Do we need Epinephrine? How much? IM, IV, or SC??
- Do we just use an antihistamine?

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Diagnostic Challenge of Anaphylaxis

- Awake patients → can report early signs of anaphylaxis
  - malaise, pruritus, dizziness, wheeze, & dyspnea
- Anesthesia cases → can have delay in diagnosis
  - patient can not report symptoms → deep sedation or GA
  - TIVA agents → cause hypotension → possible to see tachycardia
  - Inhalation agents → hypotension & tachycardia
  - Airway manipulation → possible bronchospasm
  - Anaphylaxis = can see all of above

Curr Opin Anesthesiol. 2020

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Predictive Criteria of Perioperative Anaphylaxis Severity

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Predictive Criteria for Anaphylaxis Severity

- #1 → The more rapid the onset of anaphylaxis → the greater the severity, the morbidity, and mortality
- #2 → Cutaneous signs in perioperative anaphylaxis may be absent in rapidly developing anaphylaxis
  - vasodilation causes fluid loss in central circulation
  - blood shifted from skin to central circulation
  - cutaneous signs return once circulation restored
  - Awake Patients: Skin signs seen in 80 to 90% of cases

Anesthesiology.2009;111:1141

56

Predictive Criteria of Anaphylaxis Severity

- #3 → Bradycardia instead of tachycardia
  - seen in severe anaphylaxis secondary to massive hypovolemia
  - result of → Bezold – Jarisch Reflex
    - cardioinhibitory reflex in left ventricle
    - transmitted by unmyelinated Vagal nerve fibers
    - response to the hypovolemia in central circulation
    - allows ventricle adequate filling time to try and restore cardiac output
    - seen in 10% of perioperative anaphylaxis (POA)

Bradycardia instead of Tachycardia **Protective mechanism for fluid loss**

Anesthesiology. 2009

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Grading Anaphylaxis

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Ring & Messmer Anaphylaxis Grading Scale

Grade	Definition	Signs & Symptoms
Grade I	Minor Skin ± Mucosal Lesions	Cutaneous: Flushing, Urticaria, Pruritus, ± Angioedema & Mucosal Lesions No Cardiovascular, Respiratory, or Abdominal Symptoms
Grade II	Moderate Skin and Multi-organ Involvement	Cutaneous: Flushing, Urticaria, Pruritus, ± Angioedema & Mucosal Lesions Nausea & Cramping Rhinorrhea, Hoarseness, Dyspnea, Bronchospasm Tachycardia ≥ 20 bbm rise Hypotension ≥ 20 mm fall

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Ring & Messmer Anaphylaxis Grading Scale

Grade	Definition	Signs & Symptoms
III	Severe Reaction Life-Threatening Multi-Organ	CVS: Hypotension, Tachycardia, or Bradycardia Possible Dysrhythmias Resp: Bronchospasm, Dyspnea, High Airway Pressures, Desaturations, Low End tidal GI: N/V, diarrhea, & abdominal pain Cutaneous Signs: ± urticaria, rash, angioedema possible swelling upper airway tissues
IV	Cardiac Arrest	Pulseless Electrical Activity
V	Fatal Anaphylaxis	Death

J. Allergy Clin Immunol Pract.2019;7:2134 Curr Opin Anesthesiol.2020;33:448
Clin Review Allergy Immunol.2022;62:383

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Ring and Messmer Grading

- Grades I
  - not life threatening
  - should not need Epinephrine → use antihistamines
- Grade II
  - angioedema, bronchospasm, even mild hypotension & tachycardia
  - low dose Epinephrine IV → 20 mcg then escalate as needed

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Ring & Messmer

- Grade III
  - life threatening anaphylaxis
  - early use of Epinephrine
    - anesthesia cases → IV access → use IV Epinephrine not IM
  - antihistamines & steroids → secondary value only → Epi, Epi,Epi
    - antihistamines little proven benefit
    - steroids used to reduce severity & prevent biphasic
      - little to no data to support

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Immediate Hypersensitivity Grading Scale

- Ring Messmer Grading Scale
  - diagnosis of anaphylaxis has been made
  - grading the severity to outline best treatment
- 2 Newer Grading Scales available to aid in Diagnosis
  - Manion 2022
  - Hopkins 2019

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Manion Alternative Grading

- Skin signs often missing at onset of anaphylaxis due to poor perfusion
- Key to diagnosis
  - Hypotension & Tachycardia
  - Bronchospasm, Desaturation, & Difficulty in Ventilation
  - Timing: most cases 10 minutes after IV injection

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Alternative Grading Scale for Moderate POA

Clin Review Allergy Immunol.2022;62:383 Manion	Grade A: Non-Life Threatening Perioperative Anaphylaxis Moderate Anaphylactic Reaction Multi – System Reaction
Cardiovascular	Hypotension, Tachycardia, possible bradycardia Cardiac Dysrhythmias
Respiratory	Cough, Bronchospasm, Difficulty in Ventilation, Desaturations, Rhinorrhea
Other Systems	Change in Level of Consciousness, Agitation, GI symptoms
Cutaneous Signs	Flushing, urticaria, ± angioedema

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Alternative Grading Scale for Severe POA

Clin Review Allergy Immunol.2022;62:383 Manion	Grade B: Life Threatening Anaphylaxis Cardiovascular & Respiratory Distress Cutaneous signs: Variable presentation
Cardiovascular	Systolic BP < 60 Life threatening tachydysrhythmias or bradydysrhythmias
Respiratory	Oxygen Saturation < 90 Inspiratory pressures > 40 Severe difficulty in ventilating lungs Airway Angioedema
Cutaneous	May be absent until circulation restored Urticaria, flushing, + angioedema

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Onset Times for Perioperative Anaphylaxis

- NAP6 study in UK
  - Onset time → 10 minutes after exposure to most allergens
- First 30 minutes after IV allergen exposure
  - 95% of POA cases → 30 minutes after induction
  - NMBA, Antibiotics, and Hypnotics

Clin Reviews All Immunol. 2022
Immunol Allergy Clin N Am. 2022;42:145

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Onset of Anaphylaxis

- Symptoms after first 30 minutes
  - Chlorhexidine, Latex, Dyes, Blood Products, Colloids
  - Sugammadex
- Anaphylaxis to Cardiac Arrest by triggering agent
  - Food → 30 mins
  - Venom → 15 mins
  - Medications → 5 mins

Immunol Allergy Clin N Am. 2023; 43:453

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Fatal Perioperative Anaphylaxis

- Incidence → 1.4 to 4.8% to 9% of POA events
- Median Time from symptom onset to cardiac arrest
  - 5 minutes → IV antigens
  - 15 minutes → SC antigens
  - 30 minutes → PO antigens

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Signs of Perioperative Anaphylaxis

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Anaphylaxis Signs & Symptoms

System	Symptoms	Signs
Cardiovascular	Diaphoresis	Cardiac arrest
	Dizziness	Hypotension or cardiovascular collapse
		Decrease in $Etco_2$
	Palpitations	Tachycardia/bradycardia
		Dysrhythmias
Respiratory	Acute hoarseness	Acute respiratory failure
	Chest discomfort	Bronchospasm/increased inspiratory pressures during ventilation
	Short of breath	Decreased pulmonary compliance
	Wheezing	Laryngeal edema
		Stridor
Mucosa/skin	Burning	Flushing
	Itching	Diffuse erythema
	Tingling	Cutaneous/mucosal edema
		Urticaria (hives)
Neurologic	Sense of impending doom	Loss of consciousness
	Malaise	Confusion
Gastrointestinal	Abdominal cramps	Diarrhea
	Nausea	Vomiting

Office Anesthesia Manual
"Anaphylaxis Triad"
1. **Hypotension**
2. **Tachycardia**
3. **Bronchospasm**

Anesthesiology. 2023;138:100

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When to Suspect Perioperative Anaphylaxis

- Unexplained Hypotension
- Unexplained Tachycardia → even Bradycardia
- New onset Angioedema
- Unexplained Bronchospasm
- Cutaneous Flushing associated with 1 or more of above
- Sudden Cardiac Arrest

- Old anesthesia tenet → after injection of medication → sudden onset of hypotension & tachycardia = anaphylaxis until proven otherwise

Anesth Intensive Care Med.2019;20:702

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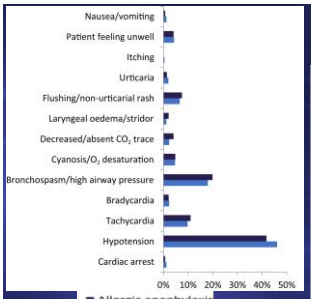

POA Initial Signs

Hypotension	46% cases
Non urticarial Rash	Rare
Bronchospasm	18%
Tachycardia	9.8%
Cyanosis	4.7%
Bradycardia	3%
Arrest	1.2%

Br. J. Anaesth.2018;121(1):159

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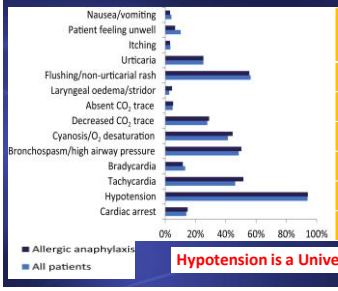

POA Signs Throughout the Reaction

Hypotension	100% cases
Non urticarial Rash	56%
Bronchospasm	48%
Tachycardia	46%
Cyanosis	41%
No Capnograph	33%
Arrest	18%

Hypotension is a Universal Sign of POA

Br. J. Anaesth

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Perioperative Anaphylaxis

- Common Signs
  - Hypotension
  - Tachycardia far more frequent than bradycardia
  - Bronchospasm → more common in patients with underlying airway hyperactivity (asthma, COPD, and obesity)
  - Ventilating patient → ↑ resistance to bag ventilation
  - SpO2 desaturations & ↓ end tidal CO2

Anesthesia Intensive Care Med.2019

75

Perioperative Anaphylaxis Cutaneous Signs

- Cutaneous → flushing, rash, urticaria, and pruritis
  - non perioperative anaphylaxis → 80 to 90% cases → ++ Skin Signs
  - ★ – perioperative anaphylaxis → typically not an early sign ★
  - NAP6 study England → seen in 56% cases → not presenting sign
  - US cases → 50 to 76% of cases
- POA cutaneous signs
  - more prevalent in non severe reactions (Grade I or II) & non IgE reactions

Immunol Allergy Clin N Am.2022;42:145

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Perioperative Anaphylaxis

- Most frequent and Reliable Signs seen in POA
  - Cardiovascular & Respiratory
- ★ Diagnosis of Perioperative Anaphylaxis ★
  - Hypotension & Tachycardia
  - Bronchospasm, Dyspnea, Difficulty in Ventilating Patient, Low Saturations, and Low Capnography
  - Make Perioperative Anaphylaxis High on Differential
  - Especially if these signs are unresponsive to therapy

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Anaphylaxis vs Other Differential Diagnosis

- Hypotension & Tachycardia
  - Anesthesia Induction medications
  - Perioperative antihypertensive medications
  - Other maintenance medications used by patient
  - Myocardial Ischemia
  - Dysrhythmias
- Respiratory Signs
  - Asthma
  - Obesity – OSA – Airway Obstruction
  - Hypoventilation
  - Aspiration

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Management of Anaphylaxis

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Epinephrine

- Drug of choice for treatment of anaphylaxis
  - early use yields better outcomes
  - all other medications are secondary at best except for IV fluids
- Benefits from use
  - ↓ mediator release from mast cells & basophils
  - prevents or reverses angioedema in upper airway
  - prevents or reverses bronchospasm
  - prevents or reverses CVS collapse

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Epinephrine

- α_1 adrenergic agonist
  - ↑ vasoconstriction, BP, & peripheral vascular resistance
  - ↓ mucosal edema in airway
- β_1 adrenergic agonist
  - ↑ inotrope & chronotrope
- β_2 adrenergic agonist
  - ↑ bronchodilation
  - ↓ mediator release from mast cells & basophils

UpToDate. accessed 8/22 Immunol Allergy Clin N Am.2022;42:65

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Epinephrine

- Epinephrine is first line therapy for anaphylaxis
- No absolute contraindication for use in anaphylaxis
- Must be given in timely manner
  - Study → only 16% of anaphylactic cases received Epi for anaphylaxis
  - Delays decrease effectiveness & increase morbidity & mortality

Immunol Allergy Clin N Am. 2023

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Epinephrine IM

- IM dosing is the standard of care for anaphylaxis
  - better & faster absorption than SC route
  - IM in anterolateral thigh (vastus lateralis) is absorbed better than arm (deltoid)
  - considered "safer than IV route???"

Patient	IM Dose	Dosing Interval
Adult	0.01 mg/kg 0.3 to 0.5 mg	Q 5 minutes
Children	0.01 mg/kg Max Dose: 0.5 mg	Q 5 minutes
1. Most Cases Respond to Single Dose of Epinephrine 2. May need a second Dose → Rare to Require 3 Doses for Anaphylaxis		

Immunol Allergy Clin N Am. 2023;43:453

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Epinephrine Auto Injector Pens

Patient & Weight (kg)	Autoinjector Dose (mcg)
Infants ≤ 10 kg	100 mcg or 150 mcg pen
Children 10 to 25 kg	150 mcg
Teens & Adults ≥ 25 kg	300 mcg

Immunol Allergy Clin N Am.2022;42:65

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Epinephrine

- Anaphylactic Reactions
  - Office, Home, ER
  - Use IM dosing → Don't wait to start IV
- Anaphylactic Reactions
  - Office Anesthesia & Operating Room
  - IV in Place → what are your options - Do you ignore IV & inject IM?
- Is Intravenous Epinephrine Contraindicated for Anaphylactic Reactions - Is it unsafe???

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Epinephrine IV

- IV in place → Is it safe to use Epinephrine IV
- Faster onset with IV versus IM
  - Peak plasma levels IM → 8 minutes ± 2 minutes
  - Peak plasma levels SC → 34 minutes ± 14 minutes
  - IV will peak faster than either SC or IM
  - IV easier to start at low dose & escalate as needed
- What are the risks of IV Epinephrine?

Immunol Allergy Clin N Am.2022;42:65

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Safety of Epinephrine IV

- IV route vs IM route
  - IV had 13% greater overdoses than IM
  - IV had 8% greater cardiovascular events than IM
  - IV route side effects
    - tachydysrhythmias, severe HTN, AMI, and stroke
- Perioperative Anaphylaxis
  - Use IM or IV by experienced providers
  - Current reports → IV Epi in United States and elsewhere

Resuscitation.2021;163:86 Immunol Allergy Clin N Am.2022;42:145

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Complications using IV Epinephrine

- IV Epinephrine for Anaphylaxis

World J Emerg Med.2013;4(4):2013

Patient & Age	Event	Dose	Complication
23 female	PCN Anaphylaxis	300 mcg	Severe myocardial ischemia
37 female	Amox Anaphylaxis	500 mcg 500 mcg 1000 mcg	Severe myocardial infarction
43 female	floxacillin	1000 mcg 1000 mcg	ST depression & pain Resolved in 30 mins No MI
34 female	seafood anaphylaxis	1000 mcg	VT that spontaneously resolved
60 female	NSAID anaphylaxis	300 mcg	Intermittent VT

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Complications with IV Epinephrine Data from 2 Reports

- Major adverse events for IV Epinephrine
  - Epi injected too fast? or used excessive dose
  - Did conclude: Indicated for unresponsive anaphylaxis

BMJ.2003;327 December

- IV Epinephrine for Anaphylaxis

J. Allergy Clin Immunol Pract.2015;3:76

  - overdose was common → no overdose for IM or SC
  - overdoses → 1000 mcg, 750 mcg, 500 mcg (4 patients)
  - 3 ischemic events & 1 dysrhythmia → no deaths

Used IV Doses that exceeded recommended IM Doses

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IV Epinephrine for Anaphylaxis

Grade	IV Epinephrine	IV Fluids NSS
Grade II → Moderate Hypotension or Bronchospasm	1. Initial: 10 to 20 mcg Epi 2. Inadequate response in 2 mins 3. Escalate to 50 mcg Epi 4. Repeat Q 2 minutes 5. No IV access: 300 mcg IM	1. 500 ml NSS rapidly 2. Repeat as needed for BP and perfusion
Grade III → Life Threatening Hypotension or Bronchospasm	1. Initial: 50 mcg Epi 2. Or 100 mcg if patient did not respond to other pressors or bronchodilators 3. Inadequate Response in 2 mins 4. Escalate to 200 mcg 5. Repeat Q 2 minutes	1. 1000 ml NSS rapidly 2. Repeat as needed up to 30 ml/kg
Grade IV → Cardiac Arrest	1. 1 mg of Epinephrine 2. ACLS	Chest Compression if SBP < 50 or End tidal CO2 ≤ 20

Br J Anaesthesia. 2019. 123: e50

90

IV Epinephrine 3 Options

- 1: 1000 epinephrine 1ml = 1 mg
- Dilution for intravenous use
  - TB syringe: draw 0.1 ml from the 1: 1000 → 0.1 ml = 100 mcg
  - dilute this 0.1 mg to full 1 ml in syringe = 10 mcg per 0.1 ml
- 1: 1000 epinephrine 1ml = 1 mg = 1000 mcg
  - add 1000 mcg to 100 ml of saline
  - now have 10 mcg per ml

BEST WAY

- 1: 1000 epinephrine: add 1 mg to 250 ml or 500 ml bag
  - get 4 mcg per ml or 2 mcg per ml respectively

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Intranasal Epinephrine

- Neffy nasal spray
  - approved for anaphylaxis
  - 1 mg dose
    - Age ≥ 4 years
    - Weight: 15 to 30 kg or 33 to 66 lb
  - 2 mg dose
    - Weight ≥ 30 kg or 66 lb
  - Repeat 2nd dose after 5 mins
    - No need to inhale
    - Don't spray onto Septum

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IV Fluids

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IV Fluids

- Anaphylaxis
  - lose up to 73% of blood volume into interstitial spaces in 15 minutes
  - need to replace volume
- Adults → NSS 1 to 2 Liters as rapid infusion (30 ml/kg)
  - 5 to 10 ml/kg in first 5 minutes
  - allow Epinephrine to increase cardiac output and perfusion
- Children
  - 20 ml/kg bolus NSS → repeat as needed

UptoDate accessed 8/22 BJA Education.2019;19(10):2019

95

IV Fluid Administration

- Need at least 18 G catheter in adults
- 60 ml syringe + Pull – Push syringe fluid bolus

IV Catheter Size	Rate of Fluid Administration
14 G	330 ml/min
16 G	205 ml/min
18 G	105 ml/min
20 G	65 ml/min
22 G	38 ml/min
24 G	20 ml/min

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Pull Push IV Fluids

1. Insert Syringe into IV Port → Open up the IV line roller clamp
2. Clamp off the IV line distal to the syringe → Pull back on the syringe plunger for fluid
3. Clamp off the IV line proximal to the syringe → Inject the fluid from the syringe

97

Glucocorticoids

- Secondary Medication
- May not prevent biphasic reactions
- Hydrocortisone → fastest onset
  - 1 to 2.5 mg/kg IV (250 mg IV in adult)
- Methylprednisolone
  - 1 mg/kg IV (80 to 125 mg in adult)
- Decadron
  - 6 mg IV in adult

98

Refractory Anaphylaxis

Biphasic Anaphylaxis

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Refractory Anaphylaxis & Management

- Inadequate response after 10 mins & EMS not arrived

Refractory Anaphylaxis	**1. Inadequate response after 10 minutes of treatment**
Definition	**2. Unresponsive to 3 Epinephrine Doses**
Anaphylactic symptoms persist despite fluids and 3 doses of Epinephrine	**3. Double the Epinephrine Dose → 400 mcg bolus**
Anaphylaxis lasting longer than 4 hours	**4. Start Epi Infusion → Dose: 0.05 to 0.1 mcg/kg/min**
Incidence 4% cases	**5. Bronchospasm nebulizer therapy** **6. Vasopressin or Glucagon for Hypotension**

Immunol Allergy Clinics N Am. 2023; 43: 467

100

Vasopressin & V 1 Receptors

- Stimulate vascular smooth muscle contraction
  - vasoconstriction
- Release nitric oxide from coronary & pulmonary vessels
  - vasodilate vessels in these organs → maintain perfusion
- Overall effect → vasoconstriction in non-vital organs like skin, skeletal muscle, and fat
  - ↑ SVR shifts blood back to heart for organ perfusion
  - ↑ MAP

AANA J. 2013;81:133 Korean J Anest. 2017;70(3):245

101

Vasopressin

- Ampule = 20 U/ml
- Dilute to 1 U/ml in → D5W or NSS
- Initial bolus → 0.5 to 1.0 units (2 U per 10 mins)
- Infusion → 0.01 to 0.06 U/min
  - increase infusion by 0.005 U/min → increments Q 10 to 15 mins
- Refractory Anaphylaxis Hypotension
  - 0.4 U bolus repeated; 2 U Q 10 min then infusion 0.04 U/min over 90 minutes

J Clin Anesth.2008;20:135 Anest Progress. 2022; 69: 30-35

102

Biphasic Anaphylaxis

- Recurrence of Anaphylaxis hours after 1st episode
  - 2nd episode of anaphylaxis → 1 to 72 hrs after initial reaction
    - Majority occur in 4 to 6 hours after the initial event
  - Does not require re-exposure to the trigger
- Incidence
  - wide range reported → 0.4 to 4.5 to 23% of anaphylactic reaction
  - 5% incidence currently
  - anaphylactic recurrence → less severe than initial event
  - No Deaths reported

Immunology Allergy Clinics N Am. 2023; 43: 453 Immun All Clin N Am. 2023;43: 467

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Biphasic Anaphylaxis

- Risk Factors
  - #1 Initial Dose of Epinephrine was delayed
  - #2 Initial Reaction was severe
  - #3 Initial Reaction required several doses of Epinephrine
  - #4 Initial Epi dose was delayed → 60 to 90 mins after symptom onset
  - #5 Prior History of Anaphylaxis
  - #6 Onset of Symptoms was not immediate after trigger exposure
    - onset was > 30 minutes after trigger exposure

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Biphasic Anaphylaxis

- Glucocorticoids
  - steroids used to prevent Biphasic Reactions
  - No proof of effectiveness
- Antihistamines & Steroids for Anaphylaxis (all types)
  - Epi is drug of choice
  - Antihistamines & Steroids
    - no proof of effectiveness → will not cause harm

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Agents Causing Perioperative Anaphylaxis

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Agents Causing Perioperative Anaphylaxis 2003 to 2015

Agent	1	2	3	4	Incidence
NMBA	58%	70%	62%	23%	#1
Anesthetic Agents	---------	-------	7.4%	--------	#4
Antibiotics	15.1%	15%	4.7%	59%	# 2 & 3
Latex	16%	23.3%	16.5%	18%	#2 & 3
Opioids	---------	-------	1.9%	--------	Rare

1. Anesthesiology. 2003;99:536
2. Anesth Int Therapy.2012;44:104

Hippokratia.2011;15:138
J Allergy Clin Immun Pract. 2015; Jan

107

Agents Causing Perioperative Anaphylaxis 2016 to 2020

Antibiotics	47 to 55%
NMB Agents	33%
Chlorhexidine	9%
Patient Blue Dyes	5%
Latex	Low risk
Anesthetic Agents	Low risk

J Allergy Clin Immunol Pract 2019 Br J Anesth. 2019 Curr Opin Anesth 2020

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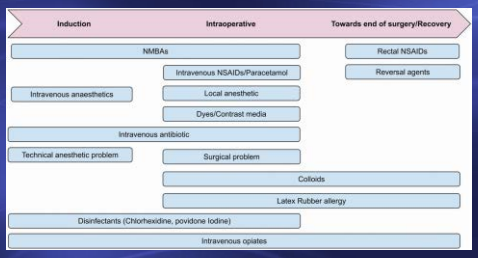
Medications – Anaphylaxis – Onset

- 1st 30 minutes of Anesthetic
  - NMBA, Antibiotics, Hypnotics
  - Induction Agents most likely culprit
- Medications used after induction > 30 mins into Anesthetic
  - Chlorhexidine, Latex, Dyes, Blood Products
  - Sugammadex for reversal of Rocuronium

109

When Do Medication Reactions Occur



Clin Rev Allergy Immunol. 2022;62(3):383

110

Antibiotics

111

Antibiotics & All Allergic Reactions

- Beta lactam antibiotics
  - US → 70% of all antibiotic allergic reactions
  - US → 40 to 55% of all anaphylactic reactions → Allergic & Anaphylactic Reactions from all Sources Not Just Surgery
  - 75% of all fatal anaphylaxis cases
- Penicillin allergy → 10% of the US population
  - risk of anaphylaxis → 0.04 to 0.2%
  - risk decreases over time for Beta Lactam Ab
    - over the course of 10 years → 80% of allergic patients tolerate agent

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Antibiotics & Perioperative Anaphylaxis

- In United States → Antibiotics are #1 medication risk for POA
- Antibiotics account for 20 to 50% of all perioperative allergic reactions
- Cefazolin (Ancef) → #1 cause of POA in United States
- Amoxicillin & Amoxicillin – Clavulanic Acid
  - most likely agent in Europe

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Antibiotics & Perioperative Anaphylaxis

- Mechanism for Antibiotic Anaphylaxis
  - IgE immunologic reactions → most common & most severe
  - Non – Immunologic reactions → direct release of mast cell mediators → not as severe
- Antibiotics for surgery → 2 Choices
  - immediately prior to induction
  - soon after induction

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Beta Lactam Antibiotics

- Timing of Reaction → Important Component of POA
  - Rxns Immediately after injection → more severe & increase risk of death

Anaphylaxis (POA) Onset Time	% Cases
1 to 5 mins	74%
6 to 10 mins	18%
11 to 15 mins	5%
16 to 30 mins	3%

92 % in 10 mins

- Penicillin allergy → 10% of the population
  - risk of anaphylaxis → 0.04 to 0.2%

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Beta Lactam Antibiotics

- 1980s – 2000s
  - Prophylactic antibiotics given either on floor or holding area
- Today
  - Given on OR table either before induction or soon after

Anaphylactic Onset Time for Beta Lactam Ab	Percentage of Cases
5 minutes	74 %
10 minutes	92% of all cases in 10 minutes
Within 30 minutes	All POA Cases

Questions??
1. In Office: Why IV Antibiotics → Why not PO at Home with other Medications?
2. IV Ab Office: Why can't you wait 10 minutes before Induction to see if Reaction Occurs?

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Other Antibiotics and POA

- Non Beta Lactam
  - Vancomycin & Quinolones
  - 75% of patients allergic to fluroquinolones develop POA
- Vancomycin & Red Man Syndrome
  - non allergic reaction
  - flushing secondary to direct mast cell activation
  - too rapid an infusion
- Penicillin Cross Reactivity with Cephalosporins
  - was 10% now 1%

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Antibiotic Test Dosing

- Why a test dose?
  - you either have an allergy – anaphylaxis or you don't
- Reaction is not dose dependent
  - 1 mcg same reaction as → 1 mg or 1 gram
    - think about Bee Sting → very little product but ability for fatal anaphylaxis
  - Ancef 1 gram in 10 ml saline
    - if anaphylactic → same reaction for → 1 ml (100mg) or 10 ml (1000mg)

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Antibiotic Test Dosing

- NAP6 study and others
  - Anaphylaxis after test dose is no less severe than after a full dose
  - Test dose caused → 20% of the POA reactions
- Test dosing has no proven benefit
  - 33% of British anesthetists still do it despite NAP6 data
  - Would think same occurs here in US

Br. J. Anaesth. 2018;121(1): 159 Anesth Intensive Care Med.2019;20:12

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Suggested Protocol IV Antibiotics

- #1 Recommend switch to PO antibiotics preop
- #2 If insist on IV Antibiotics
  - ★ Administer to an Awake Patient
  - ★ Your Choice → Test Dose or Full Dose
    - Medication is given 10 minutes before GA induction
    - Monitor for Urticaria – Pruritus – Hypotension – Tachycardia – Respiratory
  - ★ Patient is awake and can report any "symptoms of concern"
  - ★ Wait 10 minutes to rule out allergic reaction

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Anesthetic Agents & Perioperative Anaphylaxis

121

Agents & Allergic Reactions

Table 1. Country-specific percentage of causative agents of perioperative allergic reactions.[a]

	France [16]	Norway [18]	Belgium [26]	USA [20]	Spain [2]	UK [21]
NMBA	58.1%	66.2%	61.8%	23%	28.4%	38%
Antibiotics #1 in US	12.9%	X	14.5%	59%	34.4%	8%
Opioids Low Risk in US	1.7%	X	X	X	X	X
Hypnotics Low Risk in US	2.3%	X	2.6%	X	X	X
Latex	19.7%	3.6%	9.2%	18%	5.6%	X
Chlorhexidine	X	X	5.2%	X	X	5%

Best Practice & Research. Clinical Anaesthesiology. 2021; 35: 11

122

Neuromuscular Blocking Agents (NMBA)

- NMBA → was #1 in Europe → still significant risk
- NMBA incidence in US → 30% cases
- Females > males 3:1

- Onset within 30 minutes after induction
  - 95% cases → 5 minutes after injection

- IgE mediated anaphylaxis → majority of cases
- MRGPRX2 mast cell activation is minor mechanism

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NMBA

- NMBA perioperative anaphylaxis cases
  - 15 to 30% report no previous exposure to NMBA
  - cross reactivity with → tertiary & quaternary ammonium cpds in OTC cosmetic products, disinfectants, food
  - Pholocodine → quaternary cpd to cross react (Cough Suppressant)

- Cross reactivity between NMBA
  - 36 to 70% cross reactivity in same class
  - 5% cross reactivity between classes

Anesthesiology.2015;122(1) AANA J.2012;80:129 J All Clin Immun Pract.2019

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NMBA Anaphylaxis	Cross-reactivity: Number of patients (%)					
	No cross-reactivity	Rocuronium (%)	Vecuronium (%)	Pancuronium (%)	Suxamethonium (%)	Cisatracurium (%)
Rocuronium (n=48)	12 (27%)	X	20 (42%)	9 (19%)	13 (27%)	3 (6%)
Vecuronium (n=4)	1 (25%)	3 (75%)	X	2 (50%)	1 (25%)	1 (25%)
Suxamethonium (n=9)	6 (67%)	3 (33%)	2 (22%)	1 (11%)	X	0 (0%)

- Succinylcholine
  - can have cross reactivity with → Rocuronium & Vecuronium

- Rocuronium
  - can cross react with → Vecuronium & Succinylcholine

Best Practice & Research. Clinical Anaesthesiology. 2021; 35: 11

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NMBA and Anaphylaxis

- Succinylcholine → 2 times risk versus non-depolarizing agents

- NMB agents Anaphylaxis Risk
  - succinylcholine > rocuronium → most likely allergic risk
  - atracurium > cisatracurium → low allergic risk
  - Succinylcholine accounts for up to 60% of NMBA anaphylactic cases

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Sugammadex

- Reversal agent for non-depolarizing NMBA
  - Rocuronium
- Perioperative anaphylaxis with Sugammadex
  - IgE mediated reaction
  - Incidence 1st reported → 1:1000 to 1:20,000 cases
  - Current incidence → 1: 64,000 cases
  - Onset → as fast as → 5 mins after injection

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Sugammadex

- Rocuronium – Sugammadex complex
  - when bound together → allergenic quaternary ammonium chain is exposed → complex can cross link the IgE antibody complexes
  - anaphylactic reaction is to the complex → not necessarily the sugammadex

Clin Review Allergy & Immunol. 2022;62:383 Anesthesiology. 2023; 138:100 Br J Anaesth. 2019 Brazilian J Anesthesiology. 2020; 70(6):642

128

Sugammadex

- Rocuronium anaphylactic reaction
  - "Can Sugammadex reverse the anaphylaxis"
  - commonly used in Japan for rocuronium allergy
  - review of 13 anaphylactic cases
    - sugammadex did not reverse the reaction
- Sugammadex by itself can cause an allergic / anaphylactic reaction

No Data at Present to Support Use of Sugammadex to Reverse Rocuronium Anaphylaxis

Clin Review Allergy & Immunol. 2022;62:383 Anesthesiology. 2023; 138:100 Br J Anaesth. 2019 Brazilian J Anesthesiology. 2020; 70(6):642
Curr Allergy Asthma Rep 2021;21:4

129

Other Agents

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Latex

- IgE – Ab immediate reaction to protein in natural rubber
- Onset → 30 + minutes after exposure → rarely seen on induction
- Historically → 2nd or 3rd leading cause of anaphylaxis
- Currently on decrease
  - better purification of product & replacement by nitrile products
  - 2005 → incidence was 18%
  - 2021 → incidence was 5%

Best Pract & Research Clinical Anesthesiology.2021;35:11

131

Chlorhexidine

- Chlorhexidine → IgE immediate allergic reaction
  - Reactions → Mild to Anaphylaxis
  - Onset → Minutes to Hours
- Chlorhexidine Products
  - Gels for Mucus Membranes & Oral Rinses
  - Skin washes & Skin preps
  - CVP catheter coatings

Clinical Reviews in Allergy & Immunol.2022;62:383 Br J Anaesth. 2019:;123:95

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Chlorhexidine

		Onset of symptoms after exposure		Severity of reaction		
Route of exposure	Example	Immediate	Delayed	Localised (urticaria)	Generalised (urticaria)	Systemic anaphylaxis
Topical cutaneous	Preoperative whole body wash	Yes	Yes	Yes	Yes	Rare
	Preoperative skin preparation	Yes	Rare	Yes	Yes	Rare
Mucous membrane	Transurethral	Yes	Yes	Rare	Rare	Yes
	Rectal	Yes	Yes	Rare	Rare	Yes
	Vaginal	Yes	Yes	Rare	Rare	Yes
	Oral (mouthwash)	Yes	Rare	Yes	Rare	Rare
	Ophthalmic	Yes	Rare	Yes	Rare	Rare
Parenteral	I.V. cannula preparation	Rare	Yes	Yes	Rare	Rare
	CVC, arterial and epidural catheter insertion	Yes	Yes	Yes	Yes	Yes

Immediate Rxns: Mins to 1 hour Delayed Reactions: Hours to Days

Br J Anaesth. 2019

- Post extraction mouth rinses → 2 anaphylactic deaths in UK
  - 3 other cases in article → 1 anaphylaxis & 2 cases of urticaria

British Dental Journal. 2012; 213:547

133

Betadine

- Povidone-Iodine (Betadine)
  - anaphylaxis is rare
  - allergen is povidone not iodine
  - more contact dermatitis (Type IV cell mediated reaction)
  - can be used if have shellfish allergy
    - allergen in shellfish is not iodine → tropomyosin (muscle protein)
- Iodine is not an antigenic molecule

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Anesthetic Agents & POA

- Methohexital
  - IgE immediate reaction
  - Women > Men
  - Replaced by propofol
- Etomidate
  - may be the most immunologically safe TIVA agent in use
  - do not worry about anaphylaxis
  - not used in office surgery due to myoclonus → patient moving

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Anesthetic Agents

- Propofol
  - IgE immune perioperative anaphylaxis has been reported
  - Etiology → reaction to 2-isopropyl group on propofol
  - Incidence → 2.3 to 2.6% of POA reactions
  - Egg, Soy, & Peanut allergy → no cross over with propofol
    - safe to use → even if the food allergy was anaphylaxis

J. Allergy Clin Immunol.2019;7: 2134

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Other Anesthetic Agents

- Benzodiazepines
  - allergic reactions of any kind are rare
- Ketamine
  - allergic reactions of any kind are rare
- Volatile Gases
  - no reports of anaphylaxis

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Allergy Testing

- Histamine & Tryptase Levels → Identify IgE reactions
- Histamine
  - serum half life → 20 minutes
  - peaking during the reaction → no time to get sample
- Tryptase
  - peaks → 1 to 2 hours
  - draw sample → 1 to 4 hours

Tryptase Level: 2 mcg/L + (1.2 X Baseline Tryptase Level)
Levels > 11.4 mcg/L → IgE reaction 85% positive

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Allergy Testing

- Allergist in 6 weeks
- Skin Prick Test
- Intradermal injection

- Serum IgE assay testing
- Provocation Testing

139

References

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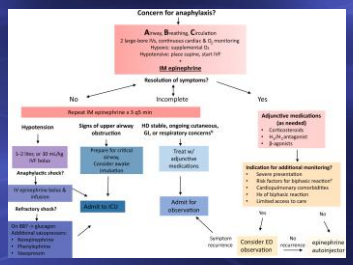
2. Anesthesiology. 2023;138:1:100
3. Best Practice & Research. Clinical Anesthesiology. 2021;35:11
4. Br J Anaesthesiology. 2019;123(1): e29
5. Br J Anaesthesiology. 2019;123(1): e50
6. Clinical Reviews in Allergy & Immunology. 2022;62:383
7. Immunol Allergy Clin N Am. 2023; 43: 435
8. Immunol Allergy Clin N Am. 2023; 43: 453
9. Immunol Allergy Clin N Am. 2023; 43: 467
10. Immunol Allergy Clin N Am. 2023; 43: 473
11. Rev Bras Anestesiol. 2020; 70(6): 342

140

Thank you

141



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Propofol Induced Neuroexcitation

Edward C. Adlesic, DMD

1

Propofol Induced Neuroexcitation

- Literature Terminology
  - Propofol Seizure Like Phenomena → Propofol SLP
  - Propofol Frenzy
    - very descriptive term for patient symptoms & staff involvement
- Incidence → uncommon reaction with broad spectrum of neurologic symptoms
  - 1: 4700 propofol anesthetics
  - 1% of propofol TIVA anesthetics
  - female to male ratio → 2:1

J. Emerg Med.2005;29(4):447
A&A Practice.2022;16:e01569
Acta Anaesthesiology Scand.2000;44:144

2

Propofol Neuroexcitation

- Definition → Recurrent, nonepileptic event
- Symptoms
  - rhythmic or semirhythmic clonus (fine tremors) of extremities
  - thrashing of extremities
  - Pelvic Thrusting
  - intense side to side head movements
  - extreme agitation
  - irregular eye movements with forceful eyelid closure

3

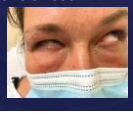
Propofol Neuroexcitation

- Other symptoms
  - loud vocalizations by patient during event
  - unresponsive to verbal or touch in many cases
  - typically requires staff assistance to prevent patient injury from movement in chair
- Vital Signs
  - tachypnea, hypertension, & tachycardia common
  - SpO2 → watch for desaturations

4

Propofol Frenzy

- Dystonic Posturing
  - involuntary muscle contractions that cause repetitive movement of arms, legs, and head → typically into an abnormal position
- Oculogyric Crisis
  - spasmodic eye movement into a fixed upper gaze in one or both eyes → lasts few seconds to hours



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Propofol Frenzy

- Ballismus
  - violent involuntary rapid and irregular movement of proximal limb musculature
  - causes a jerking or flinging movement of extremities
- Torticollis
  - head turns to one side into an abnormal position
  - painful muscle spasm

6

Propofol Frenzy

- Opisthotonus
  - tetanic disorder where spine & extremities are hyperextended
    - head is bent backwards & heels of the feet are bent backwards
    - rest of the body is bowed or arched upwards
    - patient looks like they are lifting themselves up and out of the chair or off the table
    - body is resting on the head & heels of feet

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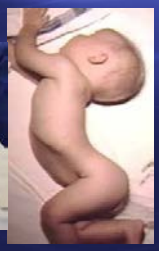
Opisthotonus

- non anesthetic cases: patients are awake & bent





Google Images 2024

8

Propofol & Opisthotonus

- very uncommon event
- most cases involve propofol + opioid
- can occur with just propofol
- seen during emergence & recovery
  - typical onset → within the 1st hour of recovery
- patient has a brief episode of spasm that recurs every few minutes

Can J Anesth. 1994;41(5): 414-9

9

Propofol Frenzy

- Other signs seen in "Frenzy"
- Intermittent Tongue Thrusting
- Common initial presentation → fine rhythmic clonus of 4 extremities → resembles "shivering"
  - " patient is cold" → check temperature → not hypothermic

10

Classification of Symptoms

- #1 → Increased tone in extensor muscles of spine
  - opisthotonos
- #2 → Rhythmical involuntary movements
  - myoclonus
  - muscle twitching
  - jerky movements
- #3 → Epileptiform seizures
  - tonic – clonic or convulsions
  - EEG does not show any epileptic foci

Acta Anesthesiol Scand. 2000;44:144

11

Propofol Frenzy Timeline

- Most case reports
  - emergence is most common time
    - immediately post op or within 30 mins after propofol stopped
  - induction
    - not as likely as emergence
    - especially if using NMB agents → which prevent muscle activity
  - maintenance
    - very rare → especially with infusion techniques that control plasma concentrations of propofol → bolus techniques possible but unlikely

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Clinical Picture

- Clinical Symptoms
  - may be continuous without any pauses
  - may have symptoms for given period of time → followed by a pause of several minutes → then symptoms recur
  - pauses are usually → secondary to medications given to stop the reaction

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Duration of Clinical Symptoms

- Duration is unpredictable
- Short Durations most common → 66% of cases
- Long Durations account for the rest
- Duration Times
  - Few minutes to few hours
  - Case reports → days to weeks (1 report → lasted 7 weeks)

Acta Anaesthesiol Scand. 2000;44:144-149

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Propofol Mechanism of Action

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Propofol Mechanism of Action

- Propofol sedative properties
  - activates GABA A Receptors
  - inhibits NMDA receptors

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Propofol Frenzy Mechanism

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Mechanism of Propofol Frenzy

- No definitive mechanism → just theories
- Many feel that rapid changes in propofol concentration may be the cause
- #1 → Propofol induces an imbalance between excitatory & inhibitory pathways in brain
  - imbalance between the cortex & subcortical structures like spinal cord
  - get selective increased activity of spinal extensor motor neurons
  - opisthotonos is result

The Neurohospitalist. 2021;11(1): 49

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Mechanism

- #1 imbalance of excitatory and inhibitory pathways
  - GABA receptors are desensitized by propofol
    - results in excitation symptoms seen in reaction
  - inhibit NMDA receptors
    - see behavioral and movement abnormalities similar to ketamine emergence

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Mechanism

- #2 → Glycine is primary inhibitory neurotransmitter in the subcortical centers and spinal cord
  - glycine inhibits neuroexcitatory component
  - glycine will inhibit propofol frenzy
  - at low propofol doses → acts as a glycine antagonist
  - glycine antagonism → see ↑ myoclonus = propofol frenzy on emergence
  - at high doses → propofol acts as glycine agonist
  - glycine agonist → no propofol frenzy

Anesthesiology.1991;74:24
Neurology2002;58:1327
Mayo Clin Proc.2017;92(11):1682

20

Case Presentations

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Case #1

- Deep sedation – general anesthesia in the office → common medications that we use
  - midazolam
  - fentanyl
  - propofol
  - ketamine
  - dexamethasone
  - less common → glycopyrrolate, atropine, remifentanil, dexmedetomidine, & vasopressors

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Case #1

- 21 y/o Female → Surgery with nerve block + deep sedation
- ASA 1 patient → 68 kg
- Midazolam 2 mg → Fentanyl 150 mcg → Ketamine 10 mg
- Propofol infusion → 125 – 150 mcg/kg/min
  - total dose = 990 mg
- Intraop vitals stable
  - HR 60 – 70; RR 12 – 16; MAP 55 – 65; SpO2 100

23

Case #1

- OR to PACU → appears to be shivering
  - given meperidine 12.5 mg for shivering
  - see extremity rhythmic clonus
- PACU presentation
  - intense whole body shaking
  - side to side head movement
  - involuntary thrashing of 4 extremities
  - irregular eye movement & forceful eye closure
  - unresponsive to verbal and touch

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Case #1

- No rigidity
- Temperature 36 C → HR 140 – 150 → BP too much movement to get reading
- Staff needed to restrain patient
- Episodes lasted several minutes each time → then quiet period of no movement → recurrent cycles

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A&A Practice. 2022;16(3):e01569

1. Head Side to Side
2. Upper extremity Clonus
3. Myoclonus of Upper Torso & Head
4. Jerking of Lower Extremities

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Case 2

- 18 y/o Male for outpatient third molars
- PMH: Depression → Fluoxetine & Trazodone
- Preop: HR 94 to 105 → RR 14 → BP 128/78
- SpO2 → 97 on room air EtCO2 40
- Lungs Clear Patient afebrile
- Monitors → BP, HR, RR, ECG, EtCO2, SpO2, wireless stethoscope over trachea

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Case 2

- ECG → NSR at rate of 94 to 100
- Lungs clear
- IV → 22 G angiocath in Dorsum R Hand
- IV fluids → NSS
- Anesthetic Medications
  - Fentanyl 100 mcg Midazolam 3 mg
  - Propofol 20 IV + additional as needed 160 mg total

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Case 2

- Surgery completed
- In recovery, became tachycardic, tachypneic, other vitals stable & then became unresponsive
  - lasted for 5 minutes, then recovered, then happened again in 10 minutes
- Was treated with Midazolam 2 mg IV and responded
- 15 mins later → rhythmic shaking of lower extremities and irregular eye movements
- Would localize to pain

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Case 2

- During Reactions
  - HR 100 - 110
  - RR 28 - 35
  - BP, SpO2, EtCO2, and temperature remained stable
  - Afebrile throughout entire case
- Lorazepam 2 mg IV given Q5mins for 2 doses
  - no further reactions
  - 6 hours later back to preop values

30

- 1. See clonus in lower extremities
  - fine, rhythmic leg movement
- 2. Do not see myoclonus, jerking of extremities, or head side to side
- 3. Looks like the "Propofol Shakes" most of us see on occasion
- 4. Need to rule out shivering
- 5. Most cases short duration < 10 mins
- 6. Most of these go untreated, resolve quickly, and discharged from office

Mayo Clin Proc.2017;92(11):1682

31

Mayo Clin Proc.2017;92(11):1682

32

Differential Diagnosis

33

Possibilities

- Post Operative Shivering
- LAST
- Seizure Disorder
- Central Anticholinergic Reaction
- Serotonin Reaction
- Propofol Seizure Like Phenomena
- Drug – Drug interactions → ingestion of illicit drug before surgery

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Differential Diagnosis

- Post Operative Shivering
  - usually all 4 extremities
  - fine, rhythmic movements = clonus not myoclonus
  - we should be monitoring temperatures for cases
    - greater than 30 minutes
    - use of triggering agents

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Differential Diagnosis

- Seizure Disorder
  - patient's medical history → yes or no
  - local anesthetic overdose → correlate with dose used & other signs of LAST
  - interaction of anesthetic agents + illicit drugs patient may have used
  - no patient history but this is your diagnosis → call EMS & initiate midazolam

36

Central Anticholinergic Syndrome

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Central Anticholinergic Syndrome (CAS)

- Caused by anticholinergic medications that cross the blood brain barrier
  - competes with ACh for muscarinic - cholinergic receptor binding
- Terminology in use
  - CAS → Central Anticholinergic Syndrome
  - postoperative delirium
  - anticholinergic syndrome
  - atropine toxicity

38

Central Anticholinergic Syndrome (CAS)

- Agents that cause CAS must be lipophilic to cross the blood brain barrier
- Anticholinergic effects in CNS are due to
  - decreased synthesis of ACh
  - decreased release of ACh
  - block or modulate the ACh receptors

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Perioperative Drugs for CAS

- Volatile anesthetics & nitrous oxide
  - suppress cholinergic pathway
- Opioids
  - competitive antagonists at muscarinic sites
  - inhibit ACh in portions of the brain
  - meperidine, fentanyl, & morphine
  - meperidine & normeperidine are more likely to cause delirium CAS
    - serotonergic & anticholinergic effects

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Perioperative Drugs for CAS

- **Propofol**
  - some of its anesthetic effect is by blocking central cholinergic transmission
- Benzodiazepines
  - chronic use has been associated with increased risk of CAS
  - in nondependent patients → doses used for anxiolysis and sedation are unlikely to induce CAS

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Other Medications associated with CAS

- Tertiary amine anticholinergics → atropine & scopolamine
- Antihistamines → H1 & H2 blockers
- TCA → especially amitriptyline (Elavil)
- Antiparkinson medications & SSRI
- Phenothiazines
- Typical & atypical neuroleptic drugs
  - Mellaril - thioridazine (typical)
  - Clozaril - clozapine (atypical)

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Central Anticholinergic Syndrome
2 Types of CAS

- Hyperactive → Delirium Type
  - myoclonus & agitation
  - hallucinations & delirium
  - convulsions & ataxia

Hyperactive CAS → Similar Symptoms to Propofol Frenzy

- Hypoactive → Depressed Activity
  - somnolence
  - stupor
  - respiratory depression → leading to coma

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CVS Signs of CAS

- Tachycardia
- Hypertension
- Dysrhythmias
  - SVT, Afib – flutter, AV Blocks, Torsades, & QT prolongation
- Our 2 cases
  - Tachycardia was present
  - No hyperthermia → hyperthermia is a definite component of CAS

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CAS

- Physostigmine → "antilirium"
  - tertiary amine anticholinesterase → inhibits acetylcholinesterase breakdown of ACH
    - get increase in ACH to reverse CAS
- Dose → 10 to 30 mcg/kg IV
  - about 1 to 3 mg in adult
  - inject at 1 mg per minute
  - onset → 3 to 5 mins peaks → 5 to 10 mins
  - should see neurologic improvement in 6 to 11 minutes

45

Serotonin Syndrome

46

Serotonin Syndrome (SS)

- Rare but potentially fatal event
- Result of → Increased Serotonergic Activity in CNS and PNS
- Serotonin (5-HT) receptors involved with Serotonin Syndrome
  - 5HT1A & 5HT2A post synaptic receptors
- Serotonergic drugs are commonplace
  - dietary, medicinal, or recreational
  - serotonin syndrome reactions are rare but increasing in frequency

47

Serotonin Syndrome Receptors

- 2 receptors stimulated → 5 – HT1A & 5 – HT2A
  - no single receptor is solely responsible for serotonin reaction
- 5 – HT1A receptors
  - higher affinity for serotonin
  - fully occupied at low levels of serotonin
  - accounts for milder symptoms of serotonin syndrome

48

Serotonin Syndrome Receptors

- 5 – HT2A receptors
  - classical explanation for life threatening severe SS
    - 5-HT2A receptors are activated at high concentrations of 5-HT
    - 5-HT1A + 5-HT2A activation
    - more likely to occur when patient is taking multiple serotonergic agents

Int J Tryptophan Research. 2019

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Serotonin Syndrome

- Typical Precipitating Factors
  - Single serotonergic agent → increasing the dose
  - Overdose of the single serotonergic agent
  - Addition of a second or more serotonergic agents
  - Drug Interactions
    - anesthetic medications + patient's serotonergic medication
    - other prescription medications + patient's serotonergic medications
    - illicit drugs + patient's serotonergic medication

50

Clinical Presentation of Serotonin Syndrome

51

Serotonin Syndrome

- Symptom Onset → usually within 24 hours
- Most patients report symptoms in < 6 hours
- Study: 60% of patients reported symptoms within 6 hours
  - 25% had symptoms after 24 hours
  - Study Criteria: (Large doses of single agent or overdose) or (multiple agents)

BMC Neurol. 2016;16:97

- Onset → expect faster onset with multiple agents & select agents
  - MAOIs & Tramadol

52

Serotonin Syndrome

- Clinical Diagnosis
  - no definitive laboratory test
  - serum serotonin levels → no correlation to clinical findings
  - need to document patient's preoperative medication list
    - identify serotonergic medications
  - must know the signs & symptoms of serotonin reactions
- Consult with Clinical Toxicologist → most reliable diagnosis
- Hunter Criteria for SS

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Hunter Criteria

- Document use of serotonergic agents in past 5 weeks
- If yes → Check for any of the following symptoms
  - Tremor & Hyperreflexia
  - Spontaneous Clonus of Extremities
  - Muscle Rigidity, Temperature > 38 C (100.4 F), and either
    - Ocular Clonus or Inducible Clonus
  - Ocular Clonus + agitation or diaphoresis
  - Inducible Clonus + agitation or diaphoresis

If Yes → Serotonin Syndrome

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SS Clinical Triad of Symptoms

- Altered Mental Status
- Autonomic Instability
- Neuromuscular Hyperactivity

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Signs & Symptoms of SS

Mental Status Changes	Autonomic Instability	Neuromuscular Hyperactivity
Confusion	Hyperthermia	Hyperreflexia
Agitation	Diaphoresis	Ankle & Ocular Clonus
Anxiety	Sinus Tachycardia	Extremity Clonus
Lethargy	Hypertension	Shivering
Seizures	Tachypnea	Extremity rigidity
Coma	Mydriasis	Ataxia
Death	Diarrhea	Tremor

56

Signs & Symptoms

- Ankle & Ocular Clonus
  - slow, continuous horizontal eye & ankle movement
  - definitive sign of SS
- Clonus vs Myoclonus
  - Clonus is rhythmic contractions of extremities
  - Myoclonus is sudden, jerky movements of extremities
  - SS typically → CLONUS

57

Signs & Symptoms

- Temperature
  - mild cases → may not be present
  - no consensus linking temperature to severity
  - Hunter criteria guidelines → temperature > 38C (100.4F)
  - Moderate SS → temperature 40C (104F)
  - Life threatening SS → temperature > 41.1C (106F)
  - Severe temperatures can lead to DIC

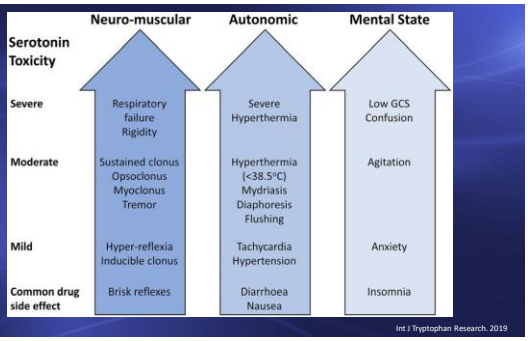
58

Signs & Symptoms

- Muscle rigidity
  - more common in lower extremities
  - rigidity may mask clonus
  - rigidity is poor diagnostic criteria for SS
    - more common in Neuroleptic Malignant Syndrome
- Best Diagnostic Clue for Diagnosis of Serotonin Syndrome
  - Symptoms in the presence of Serotonergic Agents

Clinical Toxicology. 2021;59:89-100

59



Int J Tryptophan Research. 2019

60

Serotonin Syndrome vs Propofol Frenzy

- SS requires presence of serotonergic medication
  - propofol is not one → look for SSRI or SNRI
- Common Features
  - extremity clonus
  - tachycardia, tachypnea, & hypertension
  - agitation
- Propofol Frenzy
  - no muscle rigidity or hyperreflexia
  - no severe hyperthermia

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Serotonin Syndrome SS

- Patient did have tachycardia & tachypnea
  - serotonin syndrome has both
  - no hypertension in either → SS has hypertension
- No hyperthermia, inducible clonus, ankle or ocular clonus
- No hyperreflexia or muscle rigidity
- All of those are part of SS reactions
- **Unlikely a serotonin reaction**

62

How do you manage Propofol Frenzies??

63

Management

- Most cases are self limiting
  - occurs during emergence
  - frequently seen symptoms
    - " extremity shivering" → clonus
    - myoclonus → extremity jerking movements
    - may or may not respond verbally
  - may see continuous movement until resolves
  - may occur in cycles with symptom free periods

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Management

- Most reactions last several minutes then resolve
  - 5 to 10 minutes
  - protect the patient from harming themselves
  - no medications needed
- What if it continues or patient appears in distress??
- What medications are useful??

65

Medications

- Propofol Bolus
  - bolus therapy will increase the concentration of propofol
    - dose up to practitioner → 20 mg to 50 mg
  - neuroexcitation will stop
    - ↑ propofol concentration ↑ glycine agonist actions ↓ symptoms
  - as propofol redistributes from central component
    - neuroexcitation recurs
    - back to beginning

Don't Rebolus Propofol

66

Management

- Midazolam
  - case reports for its use
  - 2 mg IV bolus → 2 to 3 minutes for onset
    - no effect → bolus additional → 1 to 2 mg IV
    - not effect → switch to another treatment
    - if effective but recurs → try lorazepam 1 to 2 mg IV for longer duration

Mayo Clin Proc. 2017;92(11):1682

67

Management

- What about Dexmedetomidine for Propofol Neuroexcitation Reactions?
- Dexmedetomidine Uses
  - ICU sedation
  - Office Moderate Sedation
  - Adjunct for Deep Sedation
  - Adjunct therapy for intraoperative hypertension – tachycardia
  - Primary therapy for Emergence Delirium

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Demedetomidine

- Dexmedetomidine Bolus Therapy
  - Bolus therapy for sedation in office
    - 0.25 to 0.5 mcg/kg → divide total dose into 2 injections → each given over 5 minutes
  - Bolus therapy for emergence delirium
    - Prophylactic dosing → 0.25 mcg/kg in two divided doses intraoperatively
    - If develop emergence delirium → give another 0.25 mcg/kg

Dex 4 mcg/ml IV → Typical Dose Range → 4 to 12 mcg per dose → Titrate to your needs

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Management

- Dexmedetomidine for Emergence Delirium
  - no prophylactic dose given
  - 0.5 mcg/kg IV slowly
- Propofol Frenzy
  - Dexmedetomidine bolus → 20 mcg IV Q 5 minutes as needed to control
  - if persists → start infusion 1.5 mcg/kg/hr

A&A Practice.2022;16:e01569 Mayo Clin Proc.2017:92(11):1682

70

Management

- Dexmedetomidine
  - 20 mcg bolus → stopped the frenzy
  - Followed by infusion → 0.8 mcg/kg/hr → for several hours to prevent possible recurrence → discharged next day

Can J Anesth.2017;64:783

- Intralipid infusion to inactivate propofol by lipid sink
  - 2 case reports using 100 or 250 ml of 20% intralipid
  - 1 case nothing → 2nd case worked

A&A Practice.2022;16:e01569 Eur J Anaesthesiol.2019;36;618

71

Management

- Central Anticholinergic Syndrome vs Frenzy
  - both have agitation & clonus – myoclonus
  - both can present with tachycardia & hypertension
  - CAS → need hyperthermia
    - Frenzy unlikely
- Physostigmine
  - 10 to 30 mcg/kg IV (1 to 3 mg)
    - 1 mg per minute Onset 3 to 5 minutes
    - Clinical improvement in 6 to 10 minutes

Not First Line Treatment

Secondary Line of Therapy

72

Propofol Extrapyramidal Side Effects

- Propofol Extrapyramidal Muscle Excitation
  - involuntary muscular movements uncontrolled by patient
  - same as "frenzy"
- Diphenhydramine 50 mg IV resolved symptoms
  - similar to its use in Tardive Dyskinesia

Pediatrics. 2017;129(2)

No Other Reports Found

73

Benzotropine

- Benzotropine (Cogentin)
  - antimuscarinic agent competing with Ach in CNS & muscles
  - anticholinergic agent to reduce central cholinergic activity in Parkinson patients
- IV route reserved for extrapyramidal drug effects
  - 1 to 2 mg IV
  - has reversed Propofol Neuroexcitation reactions

Inconsistent Results - No current data

Anesth Analg. 2002;94(5):1237

74

Resident Clinic Case

- 36 y/o Female 6 ft: 180 lb: MP 2: for third molars
- PMH: Anxiety, Migraines, Asthma
- Past Sx: Gastric Sleeve, Podiatric Surgery, and Shoulder Surgery
- Meds: Migraine, SSRI, Albuterol
- Allergies: Demerol
- Reports that she "woke up" during her first surgery and requested deeper anesthesia for second surgery after which she had no recollection of surgical events.

75

Resident Case

- Social History: Denies any recreational drugs
- Family History: Non contributory
- Open Airway Deep Sedation General Anesthetic
- Meds:
  - 0.2 mg Glycopyrrolate
  - 8 mg dexamethasone
  - 3 mg midazolam

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Resident Case

- Propofol: Infusion + Bolus → 260 mg total dose
  - infusion at 100 mcg/kg/min
  - intraoperative infusion range → 100 to 250 mcg/kg/min
- Uneventful intraoperative course
- Emergence
  - patient begins to experience what appeared to be bilateral upper and lower extremity shivering.

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Resident Case

- Emergence
  - Patient was continuously monitored. Maintained peripheral perfusion but cuff pressures unreliable due to movement. Tachycardia up to 130's. Apparent shivering continues
- Is this truly shivering??
  - check forehead temperature strip
  - rule out hypothermia

78

Resident Case

- Differential Diagnosis
  - Seizure Disorder → No history → benzodiazepine + propofol on board → unlikely a seizure
  - Propofol Neuroexcitation Syndrome → becomes primary
  - Other potential diagnosis
    - emergence delirium, serotonin reaction
- Propofol "Frenzy"
  - often short course & resolves by itself
  - Plan → currently in no distress → watch & see if it resolves

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Resident Case

- After 10 minutes → no decrease in symptoms
- Patient developed new onset
  - violent head turning → side to side → very rapid
  - arms started to demonstrate dystonia jerking
- Patient now awake
- Complaining about pain in neck secondary to head movement
- Now at 15 minutes → What are you going to do?

80

81

Medications

- Need an intervention
- Medications
  - midazolam?? (propofol frenzy or serotonin reaction)
  - physostigmine?? (anticholinergic reaction)
  - diphenhydramine or Cogentin?? (extrapyramidal muscle reaction)
  - dexmedetomidine??

82

Resident Case

- Dexmedetomidine bolus → 12 mcgs IV bolus
- Over next 5 minutes → improvement
  - head turning slowed down
  - generalized rhythmic clonus decreasing
- Patient now had rhythmic pelvic thrusting
- Dexmedetomidine 8 mcg IV added
- Over next 5 minutes → resolved completely
- Total reaction time → about 30 minutes → DC stable

83

Resident Case

- Patient tells me → this is second time this has happened to her
- Patient says she told residents on consult visit
- Summary → Inexperienced practitioner unfamiliar with anesthetic reactions on consult visit
- Delay by attending to start to treat??
- Dexmedetomidine may be treatment for these cases

84

Summary

- Need to be aware of these signs & symptoms
- Is Propofol contraindicated in Patients with seizure disorders?
- No → Propofol is a treatment for prolonged seizures
  - benzodiazepine then barbiturate then propofol
- Should this patient get Propofol for future cases?

85

Summary

- Future Propofol Anesthetics
- #1 Discussion with patient
  - likely to happen again with propofol anesthetic
  - may be minor reaction → short duration in office
    - responds to medications & discharge to home
  - could be prolonged reaction refractory to interventions
    - transfer to hospital

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Summary

- #2 Medication
  - Dexmedetomidine bolus therapy
  - Dose depends upon severity of reactions
    - Extremity Clonus → No acute distress → Evaluate Vital Signs
    - 8 to 20 mcg IV bolus → repeat or escalate Q5 minutes
  - Dose for more severe reaction
    - Evaluate Vital Signs → 16 to 20 mcg IV bolus Q5 minutes
    - ↑↑↑ dosing → ↑↑↑ recovery time

87

Thank you

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Mayo Clin Proc. 2017;92(11):1682
Acta Anesth Scand.2000;44:144
The Neuorhospitalist. 2021;11(1):49
Korean J Anesth.2021;74(1):70
Medicine.2019;98:27 e16257
Ann Indian Academy Neurology. 2023;26(1)
Neurology.2002;58:1327
Eur J Anaesthesiol.2019;36:612
Can J Anesth.2017;64:783
AA Practice. 2022;16(3)

89

Serotonin Syndrome
Serotonin Toxicity

Edward C. Adlesic, DMD
University of Pittsburgh

1

Serotonin Syndrome (SS)

- Rare but potentially fatal event
- Result of → Increased Serotonergic Activity in CNS and PNS
- Serotonin (5-HT) receptors involved with Serotonin Syndrome
  - 5HT1A & 5HT2A post synaptic receptors
- Serotonergic drugs are commonplace
  - dietary, medicinal, or recreational
  - serotonin syndrome reactions are rare but increasing in frequency

2

Serotonin Syndrome

- 1st case report → 1960
  - coadministration → L – Trytophan + MAO inhibitor (MAOI)
- Low incidence → many practitioners unaware of existence
- 1999 UK study
  - 85% of PCP unfamiliar with Serotonin reactions

Personal Note

Int J Tryptohan Research 2019 Br J Gen Practice 1999

3

Serotonin Syndrome

- 2018 FDA Adverse Event Reporting System
  - 50% of reported serotonin syndrome cases due to single agent
    - surprising report → common perception is → SS etiology is exposure to multiple serotonergic drugs

Int J of Tryptophan Research. 2019

- True incidence of SS is unknown
  - US estimate 0.07% to 0.19%

Basic Clin Pharmacol Toxicol.2023;133: 124

- Practitioners must become aware of signs, symptoms, and medications responsible for these reactions

4

Tryptophan & Serotonin

5

Tryptophan

- Tryptophan → essential amino acid → (1 of 8) essential AA
  - only source is dietary tryptophan
  - principal role is protein synthesis
  - precursor of serotonin
- Dietary Tryptophan
  - decarboxylated and hydrolyzed to form → 5 – hydroxytryptamine
    - 5HT → Serotonin
  - Serotonin is found in CNS and PNS

6

Serotonin

- Serotonin → 5 – hydroxytryptamine → 5 HT
- 5 HT
  - identified in 1948
  - monoamine neurotransmitter
- Peripheral 5 – HT
  - 90% found in enterochromaffin cells of GI tract
  - peripheral 5 – HT will not cross blood brain barrier

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Peripheral 5 - HT

- Regulates GI motility
- Vasoconstricts vessels
- Enhances platelet aggregation & platelet plug
- Causes bronchoconstriction & uterine contractions
- Medications: SSRI will inhibit platelet aggregation
  - possible increased bleeding → interactions with NSAIDs
  - potential benefit in AMI → prevent thrombus????

8

CNS 5 – HT

- 10% of 5 – HT → stored in platelets & CNS
- CNS serotonin
  - modulates wakefulness, attention, mood, and appetite
  - sexual behavior, depression, anxiety, and pain perception
  - motor tone, thermoregulation and emesis

Drug & Therapeutic Bulletin. 2022;June 60(6): 88

9

5 – HT Receptors

- 5 – HT receptors
  - 7 families → 5 HT 1 to 5 HT 7
  - Each family can have subtypes
  - 5 – HT 1 → 5 subtypes
    - 5 – HT 1 (A, B, C, D, F)
  - 5 – HT 2 → 3 subtypes
    - 5 – HT 2 (A, B, C)

5 – HT 3 receptors: PONV

10

Serotonin Syndrome Receptors

- 2 receptors stimulated → 5 – HT1A & 5 – HT2A
  - no single receptor is solely responsible for serotonin reaction
- 5 – HT1A receptors
  - higher affinity for serotonin
  - fully occupied at low levels of serotonin
  - accounts for milder symptoms of serotonin syndrome

11

Serotonin Syndrome Receptors

- 5 – HT2A receptors
  - classical explanation for life threatening severe SS
    - 5-HT2A receptors are activated at high concentrations of 5-HT
    - 5-HT1A + 5-HT2A activation
    - more likely to occur when patient is taking multiple serotonergic agents
- Some studies indicate a possible role for 5-HT2A receptor antagonism by serotonin
  - serotonin shunts back to 5-HT1A receptors for overstimulation

Int J Tryptophan Research. 2019

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Serotonin & Neurotransmission

13

Serotonin and Neuron Stimulation

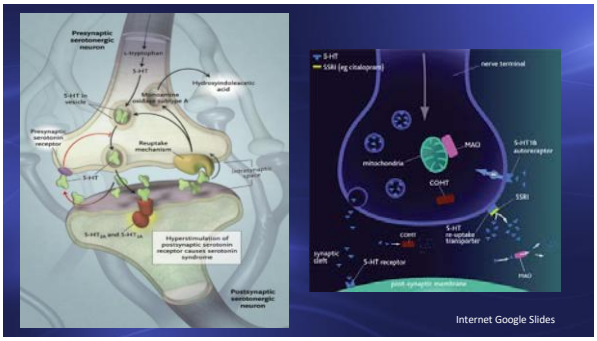
- 5 – HT is stored in presynaptic vesicles
  - presynaptic depolarization releases 5-HT into the synaptic gap
  - binds to 5-HT receptors on postsynaptic neuron
- Primary termination of 5-HT signal in synaptic gap
  - reuptake by serotonin reuptake transporter proteins (SERT) on presynaptic membrane
- Secondary termination by enzymes in synaptic gap
  - MAO – A enzyme
  - COMT enzyme → catechol-O-methyltransferase

14

Neuron Stimulation

- Serotonin returning to presynaptic neuron
- Repackaged into the serotonin vesicles
- Or metabolized by MAO – A into → 5 – hydroxyindoleacetic acid (5 – HIAA)

15



Internet Google Slides

16

Serotonin Syndrome

17

Serotonin Syndrome

- Typical Precipitating Factors
  - Single serotonergic agent → increasing the dose
  - Overdose of the single serotonergic agent
  - Addition of a second or more serotonergic agents
  - Drug Interactions
    - anesthetic medications + patient's serotonergic medication
    - other prescription medications + patient's serotonergic medications
    - illicit drugs + patient's serotonergic medication

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Mechanisms for Serotonin Syndrome

- Increased serotonin synthesis
- Inhibit serotonin metabolism
- Increased release of serotonin
- Inhibit reuptake of serotonin
- Activation of 5 – HT1A receptors
- Antagonism of 5 – HT2A receptors

Pediatric Emerg Care.2012;28(8):817
Drugs and Therapeutic Bulletin.2022 60(6):88
Int J Tryptophan Research.2019

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Additional Mechanisms for SS

- Besides Serotonin
  - Can other neurotransmitters contribute to a serotonergic reaction?
- 5-HT can cause release of Nepi from anterior hypothalamus
  - cause CNS hyperexcitability & contribute to clinical symptoms
- Severe SS → GABA, NMDA, & Dopamine systems may be recruited as well
  - no firm data → further research

20

Clinical Presentation of Serotonin Syndrome

21

Serotonin Syndrome

- Symptom Onset → usually within 24 hours
- Most patients report symptoms in < 6 hours
- Study: 60% of patients reported symptoms within 6 hours
  - 25% had symptoms after 24 hours
  - Study Criteria: (Large doses of single agent or overdose) or (multiple agents)

BMC Neurol. 2016;16:97

- Onset → expect faster onset with multiple agents & select agents
  - MAOIs & Tramadol

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Serotonin Syndrome

- Clinical Diagnosis
  - no definitive laboratory test
  - serum serotonin levels → no correlation to clinical findings
  - need to document patient's preoperative medication list
    - identify serotonergic medications
  - must know the signs & symptoms of serotonin reactions
- Consult with Clinical Toxicologist → most reliable diagnosis
- Hunter Criteria for SS

23

Hunter Criteria

- Document use of serotonergic agents in past 5 weeks
- If yes → Check for any of the following symptoms
  - Tremor & Hyperreflexia
  - Spontaneous Clonus of Extremities
  - Muscle Rigidity, Temperature > 38 C (100.4 F), and either
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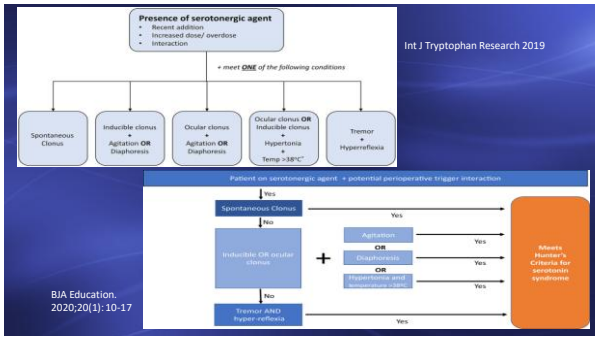
  - Ocular Clonus + agitation or diaphoresis
  - Inducible Clonus + agitation or diaphoresis

If Yes → Serotonin Syndrome

24



25

SS Clinical Triad of Symptoms

- Altered Mental Status
- Autonomic Instability
- Neuromuscular Hyperactivity

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Signs & Symptoms of SS

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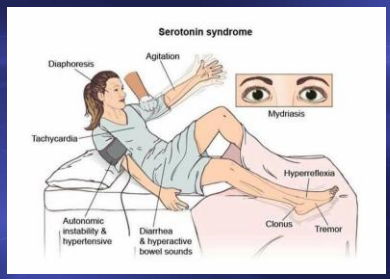
Anxiety	Sinus Tachycardia	Extremity Clonus
Lethargy	Hypertension	Shivering
Seizures	Tachypnea	Extremity rigidity
Coma	Mydriasis	Ataxia
Death	Diarrhea	Tremor

27



Google Images

28

Signs & Symptoms

- Ankle & Ocular Clonus
  - slow, continuous horizontal eye & ankle movement
  - definitive sign of SS
- Clonus vs Myoclonus
  - Clonus is rhythmic contractions of extremities
  - Myoclonus is sudden, jerky movements of extremities
  - SS typically → CLONUS

29

Signs & Symptoms

- Temperature
  - mild cases → may not be present
  - no consensus linking temperature to severity
  - Hunter criteria guidelines → temperature > 38C (100.4F)
  - Moderate SS → temperature 40C (104F)
  - Life threatening SS → temperature > 41.1C (106F)
  - Severe temperatures can lead to DIC

30

Signs & Symptoms

- Muscle rigidity
  - more common in lower extremities
  - rigidity may mask clonus
  - rigidity is poor diagnostic criteria for SS
    - more common in Neuroleptic Malignant Syndrome
- Best Diagnostic Clue for Diagnosis of Serotonin Syndrome
  - Symptoms in the presence of Serotonergic Agents

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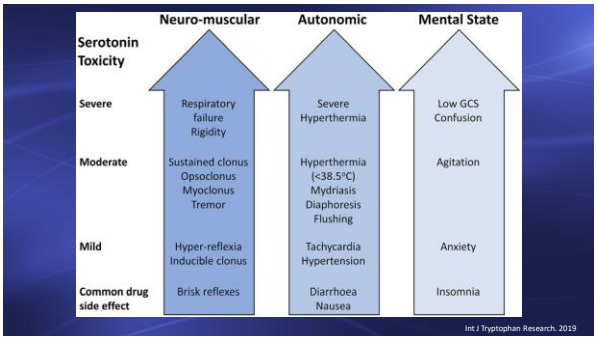

Int J Tryptophan Research. 2019

32

Severe Cases of Serotonin Syndrome

- Temperature > 41.1C
- Autonomic instability
  - Tachycardia, Hypertension, Hyperactive Bowel Sounds
- Muscle rigidity now commonplace
- Complications
  - Seizures
  - Metabolic Acidosis, Rhabdomyolysis, Renal Failure
  - DIC, ARDS, Respiratory Failure, even Death

33

Laboratory Values in Severe Cases

- Transferred to Hospital
- CBC, Electrolytes, CK, Blood Gases, Creatinine
- Liver function tests
- Myoglobin in urine
- Core Temperatures
- Similar to MH monitoring

Drugs and Therapeutic Bulletin. 2022

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Mild Serotonin Reactions

Mental Status Changes	Autonomic Instability	Neuromuscular Hyperactivity
Restless	Afebrile	Hyperreflexia
	Tachycardia	Intermittent tremor
Anxiety	Shivering	Clonus not myoclonus
	Diaphoresis	
	Mydriasis	

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Moderate Serotonin Reactions

Mental Status Changes	Autonomic Instability	Neuromuscular Hyperactivity
Agitation	Tachycardia	Hyperreflexia
	Hypertension	Clonus lower limbs Not myoclonus
Easily startled	Hyperthermia $\leq 40^0$ C	Inducible clonus
	Mydriasis	Ocular clonus
	Hyperactive bowel sounds	Ankle clonus
	Diaphoresis	
	Diarrhea	

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Severe Serotonin Reaction

Mental Status Changes	Autonomic Instability	Neuromuscular Hyperactivity
Agitated Delirium	Hypertension Tachycardia Hyperactive Bowel Sounds	 Muscle Rigidity in lower limbs
Coma	Shock	
	Hyperthermia ≥ 41.0 ^{0}C	

New Eng J Med. 2005;352(11):1112 UpToDate. Accessed 2023 J. Integrative Neuroscience. 2020 Dec

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Management of Serotonin Syndrome

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Management of Serotonin Syndrome

- Intensity and type of management depends on the clinical situation
- Mild cases may resolve on their own with little intervention
- Moderate & Severe Cases demand hospital care
- Management of Agitation, Hyperthermia, & Autonomic Instability are mainstays of therapy

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Management of SS

- 1st Step → Remove serotonergic agents if possible
- 2nd Step → Standard Monitors, IV line, Temperature, Oxygen
  - maintain SpO2 ≥ 94
- 3rd Step → Agitation managed with benzodiazepines
  - Agitation, Anxiety, & Combativeness
- Mild cases of SS → may be all that is indicated

Pain Physician. 2015; 18: 395

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Management Continued

- 4th Step → Clonus and/or Muscle Rigidity → Benzodiazepines
  - physical restraints increase isometric muscle contractions
    - increase damage to muscles
    - patient could develop lactic acidosis or hyperthermia
  - benzodiazepine will blunt this response
    - may also decrease tachycardia & hypertension from agitation

Benzodiazepines → Reverse Mild Mental Disturbances → Decrease Muscle Damage → Can Improve Vitals

Avoid Droperidol or Haloperidol if Hyperthermic → Have anticholinergic properties → inhibit dissipation of body heat

UpToDate 2023

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Management

- Step 5 → Autonomic Instability
- Hypertension & Tachycardia
  - Office medications → Esmolol or Labetalol
    - Vital signs dictate best drug to use
    - Want short acting agents
    - Best drugs for hypertension are IV Calcium Channel Agents
      - Infusion Agents not found in office → Nicardipine or Clevidipine

Hydralazine Contraindicated → has significant inhibitory effect on MAO enzyme → may exacerbate the SS

BJA Education. 2020; 20(4): 139

42

Management

- Hypotension
  - Initial management = IV fluids
    - need appropriate size catheter → not 22 G IV
  - Medications
    - Use direct acting sympathomimetics
      - Epinephrine, Phenylephrine, or Norepinephrine
  - Indirect vasopressors → Ephedrine or Dopamine
    - Avoid if serotonergic agents inhibited MAO enzyme
    - Indirect amines → exaggerated Hypertension

Int J Tryptophan Research 2019

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Hyperthermia & SS

- Step 6 → Hyperthermia (mediated by muscle hyperactivity)
  - animal studies → lower temperatures → downregulates 5HT2A
- Active Cooling Measures
  - Fans, Ice Packs, Chilled IV Fluid, or Cooling Blankets
- Temperatures > 40C
  - may lead to metabolic acidosis, rhabdomyolysis, & DIC
  - paralysis (nondepolarizing) + intubation
    - succinylcholine & rhabdomyolysis → K increase = dysrhythmias

Dantrolene??

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Dantrolene

- Severe Serotonin Toxicity (Serotonin Syndrome)
  - Hyperthermia, Hypertension, Metabolic Acidosis, Rhabdomyolysis, and DIC
- Sounds like Malignant Hyperthermia to me
  - SS is a mimic of malignant hyperthermia
- Rhadbomyolysis, Hyperthermia & hyperkalemia are from muscle breakdown
- Dantrolene in Hospital may be needed

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Hyperthermia & SS

- Hyperthermia is due to muscle activity
  - Temperature rise is not due to an alteration in hypothalamic temperature set point
- No role for antipyretic agents
  - no acetaminophen
- Use external cooling and/or chilled IV fluids

UpToDate. 2023 Cureus. 2022

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Dexmedetomidine

- α - 2 adrenergic agonist
- α – 2 Receptors stimulation in serotonergic neurons
  - can inhibit the release of serotonin
- Dexmedetomidine
  - produces sedation without respiratory compromise
  - can treat hypertension & tachycardia

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Cyproheptadine

- Histamine – 1 receptor antagonist
  - nonspecific 5HT1A & 5HT2A receptor antagonist
  - also has weak anticholinergic properties
- Initial Dose → 12 mg PO or crushed via nasogastric tube
  - 2 mg Q2h → until you see clinical improvement
  - 8 mg Q6h → once symptoms are controlled

Max Dose Day 32mg

- Side effect → Hypotension but controlled with fluids
  - mild sedation as well

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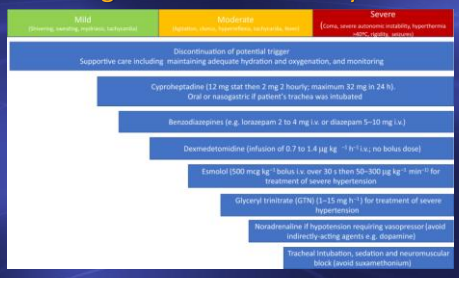
Management of Serotonin Syndrome



BJA Education. 2020;20(4):139

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Drugs Associated with Serotonin Syndrome

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Drugs & Serotonin Toxicity

- Mechanism
  - 1. Increase the Dose of a Single Agent
  - 2. Single Agent + addition of 1 or more serotonergic agents
  - 3. Overdose of Agents: Accidental or Intentional
  - 4. Recreational Serotonergic Drugs: solo or combined with above
  - 5. Serotonergic Drugs + Anesthetic Agents

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"Bad Actors"

- MAOI medications were the first associated with SS
  - no longer 1st Line Psychiatric medications
  - incidence of SS is decreasing
- Most severe cases of Serotonin Toxicity
  - MAOI + another serotonergic drug
- Today → Most frequent cause of Serotonin Toxicity
  - Tramadol + SSRI

Basic Clin Pharm Toxicol. 2023;133:124

53

Most Publicized Case of SS

- LZ 1984
  - seen in ER for possible flu → Temp 103.5F + rigors
  - using MAOI Nardil (phenelzine) for depression
  - chlorpheniramine for flu
  - had taken oxycodone for dental procedure in past
  - Resident gives 25 mg IM meperidine for rigors
  - 45 min later, patient thrashing in bed & combative
  - Temp rose to 107; followed by cardiac arrest

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LZ Case

- Postmortem report possible cocaine metabolites in tissues
- Serotonin reaction from MAOI + Meperidine + Oxycodone + Chlorpheniramine + possible cocaine metabolites
- Outcome most likely the same if there was just MAOI + Meperidine
- Similar event on NBC TV "ER"
  - resident attempted to give Meperidine to patient on serotonergic agent

www.epmonthly.com Accessed 8/14/23

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Tramadol

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Tramadol

- Opioid Medication
  - analogue of codeine
- Central Opiate Agonist
  - mu activity → 10 times less than codeine

Worst Binding Affinity of Any Opioid

- Indications for Use
  - relief of moderate to moderately severe pain unresponsive to other oral medications
  - patients with contraindication to selective COX 2 inhibitors or non - selective COX inhibitors

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Tramadol & Serotonin Toxicity

- Serotonin Mechanism
  - inhibits the SERT protein reuptake of 5HT in synaptic gap
  - inhibits the reuptake of Norepinephrine
  - larger doses → causes release of Serotonin
- CYP450 Enzymes
  - inhibition of CYP2D6 Enzyme
  - tramadol remains active longer if enzyme is inhibited

Tramadol acts to increase serotonin for 5HT1A & 5HT2A receptors

Pain Physician. 2015;18:395 J Pak Med Assoc. 2022; 72(4): 758

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Tramadol

- As a single serotonin agent → can precipitate a Serotonin reaction with large doses or overdose
- Combination of Tramadol + SSRI
  - now most frequently reported cause of SS
  - synergistic serotonergic action from combination
  - inhibition of CYP450 enzymes by SSRI

MAOI use decreased

Basic Clin Pharmacol Toxicol. 2023; 133: 124 Pain Physician 2015; 18: 395

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Tramadol

- Serotonergic Agents that interact with Tramadol to ppt SS
  - SSRI & SNRI
  - Tricyclic Antidepressant (TCA)
  - Triptans
  - Antipsychotics, Anticonvulsants, Antiparkinsonian Agents
  - Dextromethorphan
  - St John's Wort
  - MAOI

Anesth Analg. 2017; 124(1): 44

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Tramadol Recommendation

- Poor analgesic medication
  - other alternatives are better for perioperative pain
- In presence of serotonergic medications → avoid Tramadol perioperatively

Two Solo Agents → Known Causes of Serotonin Toxicity
Tramadol & MAOI

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Phenylpiperidine Opioids

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Phenylpiperidine Opioids

Phenylpiperidine Opioids
Meperidine
Fentanyl
Alfentanil
Sufentanil
Remifentanil

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Phenylpiperidine Opioids

Meperidine	Tramadol
Methadone	Dextromethorphan
Remifentanil	Fentanyl
Alfentanil	Sufentanil
Propoxyphene (no longer used)	

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SS caused by Opioid + Serotonergic Agent

Opioid	*Serotonergic Agent*
Meperidine	MAOIs, SRI agents (SSRIs & SNRIs), linezolid
Dextromethorphan	SSRIs, bupropion, chlorpheniramine, & co opioids (tramadol & methadone)
Fentanyl	SSRIs, SNRIs, trazadone, granisetron, & dihydroergotamine
Oxycodone	SSRIs (escitalopram, sertraline, fluvoxamine, citalopram)

Anesthesiology. 2011; 115: 1291 Can J Anaesth. 2008;55(8): 521
Ann Pharmacotherapy. 2006; 40: 155 Br. J. Anaesth. 2005; 95(4):434

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Phenylpiperidine Opioids

- Inhibitors of SERT protein reuptake of Serotonin
  - Methadone (greatest inhibition)
  - Meperidine
  - Tramadol
  - Dextromethorphan
- Other minor mechanisms
  - increase the release of serotonin
  - act as an agonist at 5HT1A receptors

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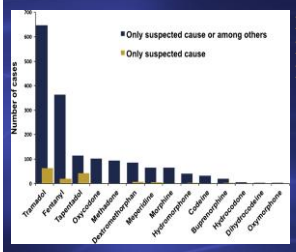
Serotonin Reactions



- Tramadol has most cases of SS
- Fentanyl is #2
- Opioids most associated with SS
  - Tramadol
  - Fentanyl
  - Methadone
  - Meperidine (no longer used)
    - Otherwise, would be high on list

British J Anaesthesia. 2020

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Fentanyl

- Fentanyl is 5HT1A agonist
  - causes a flood of serotonin to bind to receptor
  - weak 5HT reuptake inhibitor
- Fentanyl SS reactions → always need a second serotonergic drug (SSRI, SNRI, TCA, Methadone, Meperidine, or MDMA)
  - fentanyl by itself will not cause SS
- MAOI + Fentanyl → reaction is possible but rarely reported
  - avoid this combination → pick another opioid (remifentanil)

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Fentanyl

- Should we stop using Fentanyl in our office anesthetics???
- Patients with history or SS or using MAOI
  - possible reaction → be alert for signs & symptoms
  - or switch to remifentanil or sufentanil
- Patients on SSRIs or any serotonin reuptake inhibitor
  - rare to react

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Other Phenylpiperidines

- Alfentanil, Sufentanil, & Remifentanil
  - shorter half life than fentanyl
  - if a patient was on an MAOI, these agents may pose less of a risk of SS → not much data found
- No case reports for remifentanil
- Mass General: 112,045 pts using serotonergic med
  - 4538 received Fentanyl
  - 23 had symptoms of SS
  - 4 pts (0.09%) had SS by Hunter Criteria

British J Anaesthesia. 2020;124(1): 44

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IV Sufentanil

- Ultra-potent agent
- 5 mcg sufentanil = 50 mcg fentanyl
- Drug comes: 50 mcg/ml ampule
  - 1 ml and dilute to 10 ml → now 5 mcg/ml
  - use just like you would fentanyl
- Context Sensitivity Half Time > Alfentanil
  - mcg/kg/hr vs mcg/kg/min

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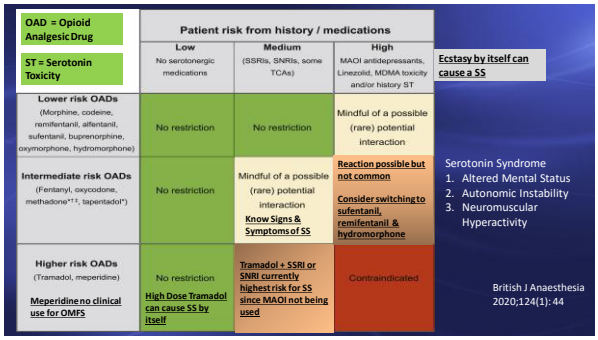
Oxycodone

- Oxycodone has a few case reports of SS
  - not as a solo agent
  - always associated with another serotonergic drug
  - can cause release of 5 – HT

Similar risk as Fentanyl

Anesthesiology. 2011; 115: 1291
J. Clin Pharmacol. 2001; 41(2): 224
Ann Pharmacotherapy. 2006; 40: 155
Br. J Anaesth 2005; 95(4): 434

72



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MAOI Agents

- Introduced in 1952
- Currently
  - used when patients are unresponsive to other agents
  - UK → < 1% of patients
  - Europe → primary treatment in 0.3% of patients
  - Canada → 3rd Line Agent
- 1st Case Report of Serotonin Syndrome → MAOI

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MAO Inhibitors

- Selective or Non-selective
  - Specific for MAO-A or MAO-B or Block both enzymes
- Reversible vs Nonreversible
  - reversible agents allow faster recovery of enzyme activity
    - only drug = Moclobemide (not used in US)
  - irreversible agents bind for the → Life of the Enzyme
    - 2 to 4 weeks → long duration

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MAOI

Drug		Selective	Reversible
Isocarboxazid	MARPLAN	NO	NO
Moclobemide	MANERIX	YES for MAO-A	YES
Phenelzine	NARDIL	NO	NO
Selegiline	ELDEPRYL	YES for MAO-B at low dose NO at higher doses	NO
Tranylcypromine	PARNATE	NO	NO
Rasagline	AZILECT	YES for MAO-B	NO

Selegiline at high doses is nonselective → will Inhibit MAO-B + MAO-A

UpToDate 2023 CNS Drugs. 2021;35: 703 Health Psychology Research. 2022; 10(4)

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MAOI Agents

- MAO – B Enzyme breaks down
  - Dopamine
- MAO – B Inhibitor is used to treat Parkinson Disease
- MAO – A Enzyme breaks down
  - Norepinephrine, Serotonin, & Dopamine
- MAO Inhibitors are used to treat anxiety and depression

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MAOI Complications

- MAO-A will metabolize → 5HT + Nepi
  - prevents buildup of 5HT & NEpi in synaptic gap
- Non-selective MAOI → prevents metabolism of 5HT & NEpi
  - result → possible Serotonin Toxicity + Hypertensive Crisis
- Non-selective MAOI → greatest risk of severe SS & Hypertensive Crisis
  - fortunately, MAOI are rarely used today

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MAOI & Serotonin Toxicity

- MAOI + Tramadol, Meperidine, or Serotonin Reuptake Inhibitor (SSRI or SNRI)
  - most severe reactions
- MAOI + TCA
  - TCA blocks reuptake → MAOI prevents metabolism
- MAOI + Methylene Blue
  - Methylene Blue is a reversible monoamine oxidase inhibitor
  - 2 Agents will ↑↑↑↑ serotonin levels

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MAOI & Serotonin Toxicity

- MAOI + Fentanyl, Methadone, Dextromethorphan, or Oxycodone
  - be alert for reaction → less common than Tramadol
  - opioids are reuptake inhibitors
- MAOI + Morphine, Remifentanil or other phenylpiperidine Opioids, Hydromorphone
  - possible but rare

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MAOI & Serotonin Syndrome

- MAOI + Ecstasy (MDMA)
  - get release of 5HT from ecstasy
  - ecstasy alone can cause a Serotonin Reaction

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MAOI & Hypertensive Crisis

- MAOI + Cold Medications
  - Decongestants → oxymetazoline, phenylephrine, pseudoephedrine, & ephedrine
    - overstimulate α 1 receptors
    - will increase BP
    - MAOI will also increase BP
  - Hypertensive Crisis

Health Psychology Research. 2022; 10(4): Drug Interactions with MAOI

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Cheese Reactions & Hypertensive Crisis

- Dietary tyramine → Amino Acid found in foods
  - metabolized & inactivated by MAO-A in gut & liver
  - minor metabolism by MAO-B
- Nonselective MAOI
  - inhibits MAO-A & MAO-B
  - can not deaminate tyramine to inactive form
  - tyramine concentrations increase
  - tyramine is absorbed into circulation & crosses blood brain barrier

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Cheese Reaction

- Tyramine
  - causes release of NEpi into the synaptic gap
- Result is the "cheese reaction"
  - severe HA, confusion, nausea, & diaphoresis
  - tachycardia, hypertension, dysrhythmias, cardiac failure, & death
- MAO Inhibitor use requires dietary restrictions on Tyramine

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MAOI Diet

- Limit or avoid the following foods
  - aged cheese & air- dried aged meats
    - salami, sopressata, prosciutto, mortadella
    - cheddar, swiss, provolone, fontinella, blue cheese
  - tap beer, home brew, & some red wines
  - sauerkraut, pickled herring, fava beans, & soy
- 10 mg dietary tyramine causes hypertension
- 25 mg results in hypertensive crisis
- MAOI diet → < 6 mg dietary tyramine per day

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Thank you

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Tables of Interest

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MAOI & Hypertensive Crisis

Agent	Adverse Reaction	Comments
Additional MAOIs	Hypertensive Crisis	Increased complications – seizures
Oxymetazoline	Hypertensive Crisis	OTC α 1 stimulant
Phenylephrine	Hypertensive Crisis	OTC α 1 stimulant
SNRI	SS + Hypertensive Crisis	Hypertension + SS

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SSRI Drugs

Prozac	Fluoxetine
Paxil	Paroxetine
Zoloft	Sertraline
Celexa	Citalopram
Lexapro	Escitalopram
Luvox	Fluvoxamine

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Serotonin Norepinephrine Reuptake Inhibitors SNRI

Effexor	Venlafaxine
Cymbalta	Duloxetine
Pristiq	Desvenlafaxine
Savella	Milnacipran

- SNRI have same risks for developing SS as the SSRI agents

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Triptans

Imitrex	Sumatriptan
Maxalt	Rizatriptan
Zonig	Zolmitriptan
Axert	Almotriptan
Relpax	Eletriptan
Frova	Frovatriptan

American Headache Association: Risk of SS is low but be aware if used with other serotonergic agents

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Health Psychology Research. 2022; 10(4)
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Cureus. DOI10.7759/cureus.22805

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Thank you

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