Principles of Pharmacology in Dentistry

Arash Khojasteh DMD, PhD, MS
Associate Professor of Oral and Maxillofacial Surgery
Director of Basic Sciences Research, Research Institute of Dental Sciences.
Shahid Beheshti University of Medical Sciences, Tehran, Iran

Drug Pharmacology Knowledge

Drug that you prescribe in your practice

Drug that may interfere with the patient used drug

Drug that you prescribe in your practice

- Analgesic
- Antibiotics
- Corticostroids
- Local Anaesthetic
- Muscle Relaxant
- Antifungal
- Prevent Tooth Decay
- Control Gingival Microbial Plaque

Analgesic

- It has been estimated that dentists write approximately 16 million prescriptions for analgesics each year in the United States alone

"Pain as the 5th Vital Sign"

Review of Neuroanatomy and Pathophysiology of Pain

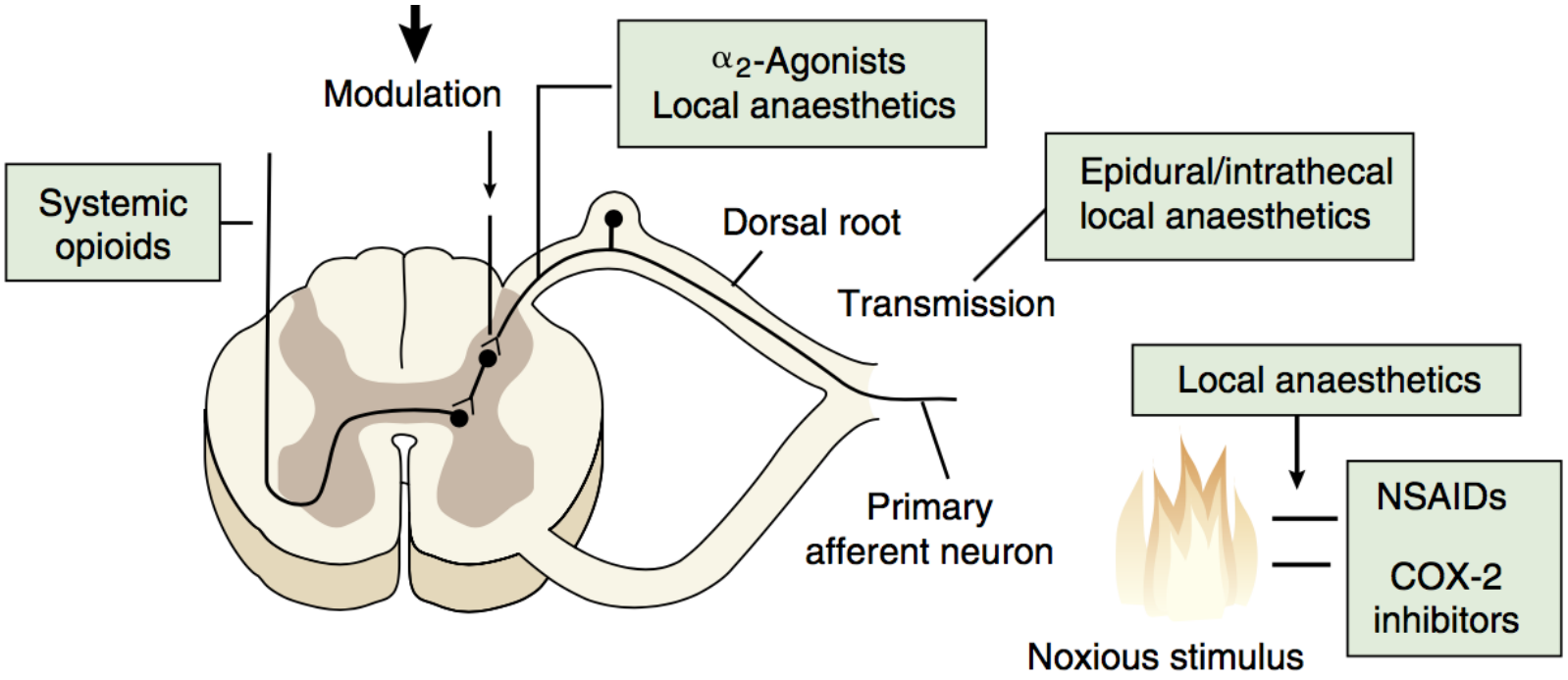
- There are two main afferent nerve fibers associated with pain transmission: A-delta and C fibers

Review of Neuroanatomy and Pathophysiology of Pain

- ***A-delta***
  - lightly myelinated, large diameter, and fast conducting.
  - mechanical stimulaltion
  - sharp or shooting sensation.
- ***C fibers***
  - Thermal, chemical, and mechanical stimuli.
  - Unmyelinated, small diameter, and slow conducting
  - dull or aching sensation.

Review of Neuroanatomy and Pathophysiology of Pain

- Extracranial tissue damage and pain nociception follows a slightly different pathway than pain sensation from the oral and craniomaxillofacial region.
- In the periphery, free nerve endings stimulated by mechanical, chemical, and thermal sensation act as a afferent pain receptors synapsing in the dorsal horn.
- Impulse then crosses to the contralateral ascending spinothalamic tract and travels to the thalamus.
- In the dorsal horn, ascending impulses can be modulated by descending pain-modifying pathways from the cerebral cortex, mid- brain, and brainstem.


Modulation
α_2-Agonists
Local anaesthetics
Systemic opioids
Dorsal root
Epidural/intrathecal local anaesthetics
Transmission
Local anaesthetics
Primary afferent neuron
NSAIDs
COX-2 inhibitors
Noxious stimulus

Review of Neuroanatomy and Pathophysiology of Pain

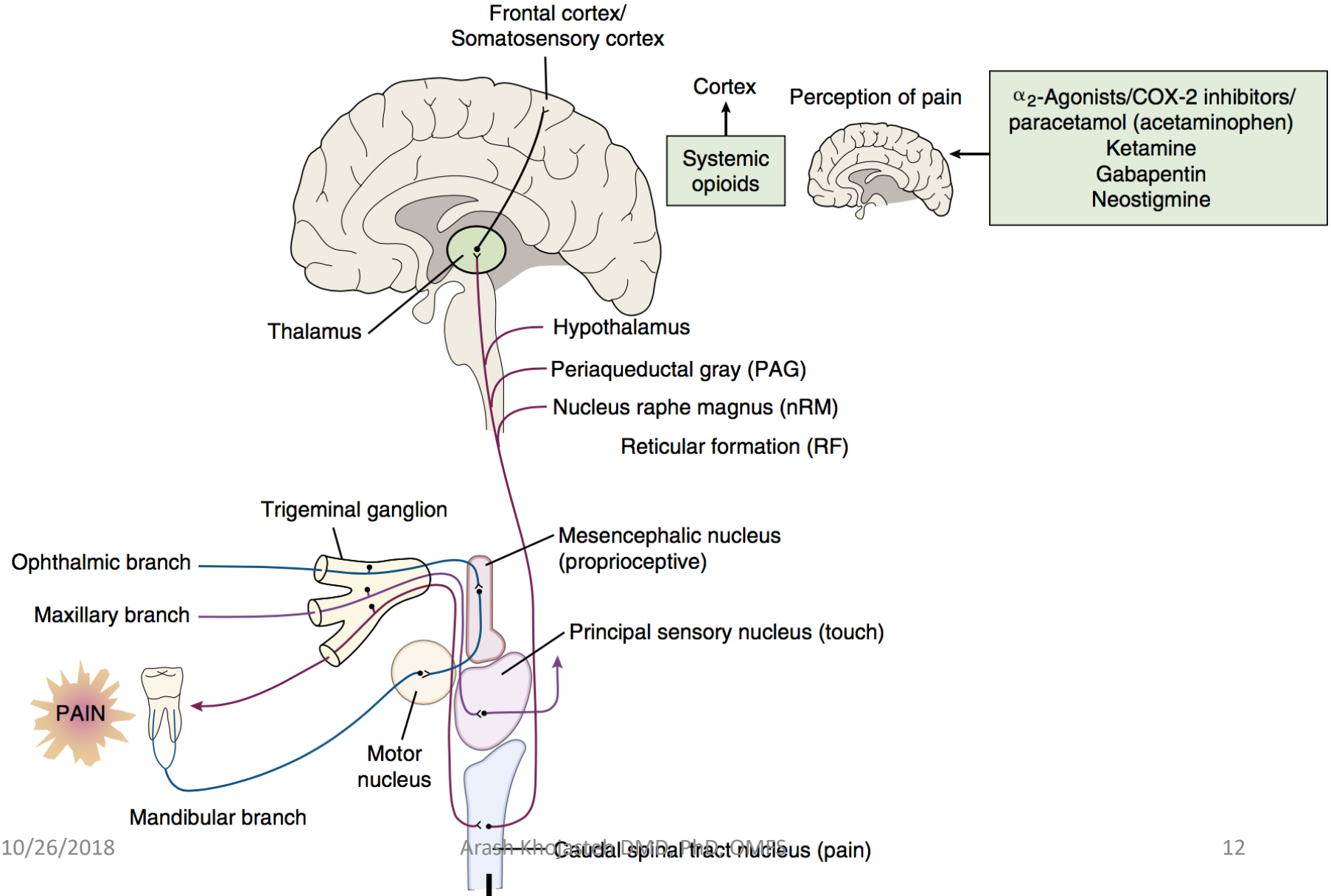
- Painful stimuli in CMF tissue innervated by the trigeminal nerve is transmitted to the central nervous system (CNS) via the Gasserian (trigeminal) ganglion and then through a portion of the brainstem known as the trigeminal brainstem sensory nuclear complex (VBSNC)

Review of Neuroanatomy and Pathophysiology of Pain

- This bilateral, multi-nucleated structure resides in the dorsolateral brainstem extending from the pons to the upper cervical spinal cord

Review of Neuroanatomy and Pathophysiology of Pain

- The peripheral processes of these cells innervate the orofacial structures, whereas the central processes enter the brainstem and synapse with the second-order neurons at various levels of the trigeminal brainstem sensory nuclear complex. This complex may be subdivided into the caudal spinal tract nucleus, which transmits pain, and the rostral principal sensory nucleus, which transmits afferent inputs such as touch. Proprioceptive impulses end in the mesencephalic nucleus, which is connected to the motor nucleus. The subnucleus caudalis extends into the cervical spinal cord and merges with the dorsal horn and peripheral sensory innervation. It possesses gating mechanisms capable of modulating painful stimuli


Frontal cortex/
Somatosensory cortex
Cortex
Perception of pain
α_2-Agonists/COX-2 inhibitors/
paracetamol (acetaminophen)
Ketamine
Gabapentin
Neostigmine
Systemic
opioids
Thalamus
Hypothalamus
Periaqueductal gray (PAG)
Nucleus raphe magnus (nRM)
Reticular formation (RF)
Trigeminal ganglion
Mesencephalic nucleus
(proprioceptive)
Ophthalmic branch
Maxillary branch
Principal sensory nucleus (touch)
PAIN
Motor
nucleus
Mandibular branch
Caudal spinal tract nucleus (pain)

Analgesics

- Opioids
  - Opiates (Morphine,Codeine)
  - Synthetics opiates Oxycodone , dihydromorphinone)
  - Opiate congeners Meperidine , Methadone , Pentazocine , Propoxyphene
- Non – Opioids
  - Salicylic Acid Derivatives
    - Acetylsalicylic acid
    - Salicylamide

NSAIDS

  - Para-aminophenols
    - Acetaminophen
    - Acetophenetidin (Phenacetin)

Opioids Adverse Effects

- Respiratory Depression
- Euphoria
- Impaired Decision Making
- Constipation
- Abuse
- Hypotension
- Pruritis

Opioid Analgesia

01

Decrease in calcium influx at afferent nerve terminals, leading to decreased presynaptic release of neurotransmitter

02

Increased potassium efflux, resulting in hyperpolarization of postsynaptic neurons

03

Inhibition of GABAergic transmission, leading to the excitation of descending inhibitory pathways.

Meperidine

- Meperidine is no longer commonly prescribed because of the neurotoxicity of one of its active metabolites, normeperidine. Meperidine also interacts with monoamine oxidase inhibitors, causing potential hypertensive crisis, hyperpyrexia, and cardiovascular collapse.
- Meperidine is included here because it is often used to reduce shivering in an inpatient anesthesia setting

Codeine

- When prescribing codeine, a weak mu agonist, doses greater than 60 mg are to be avoided because the adverse side effects will dominate the analgesic effects

Tramadol

- A synthetic opioid compound, which is chemically unrelated to the other synthetic agents.
- Mechanisms of action: (1) it is a weak mu agonist, and (2) it inhibits serotonin and norepinephrine reuptake. Because of the distinct chemical structure of tramadol, respiratory inhibition and abuse potential are lower. e equipotency of tramadol compares with that of codeine,
- Prescribed in 50- to 100-mg doses

Non-opioid Analgesia

NSAIDs

Acetaminophen

NSAIDS

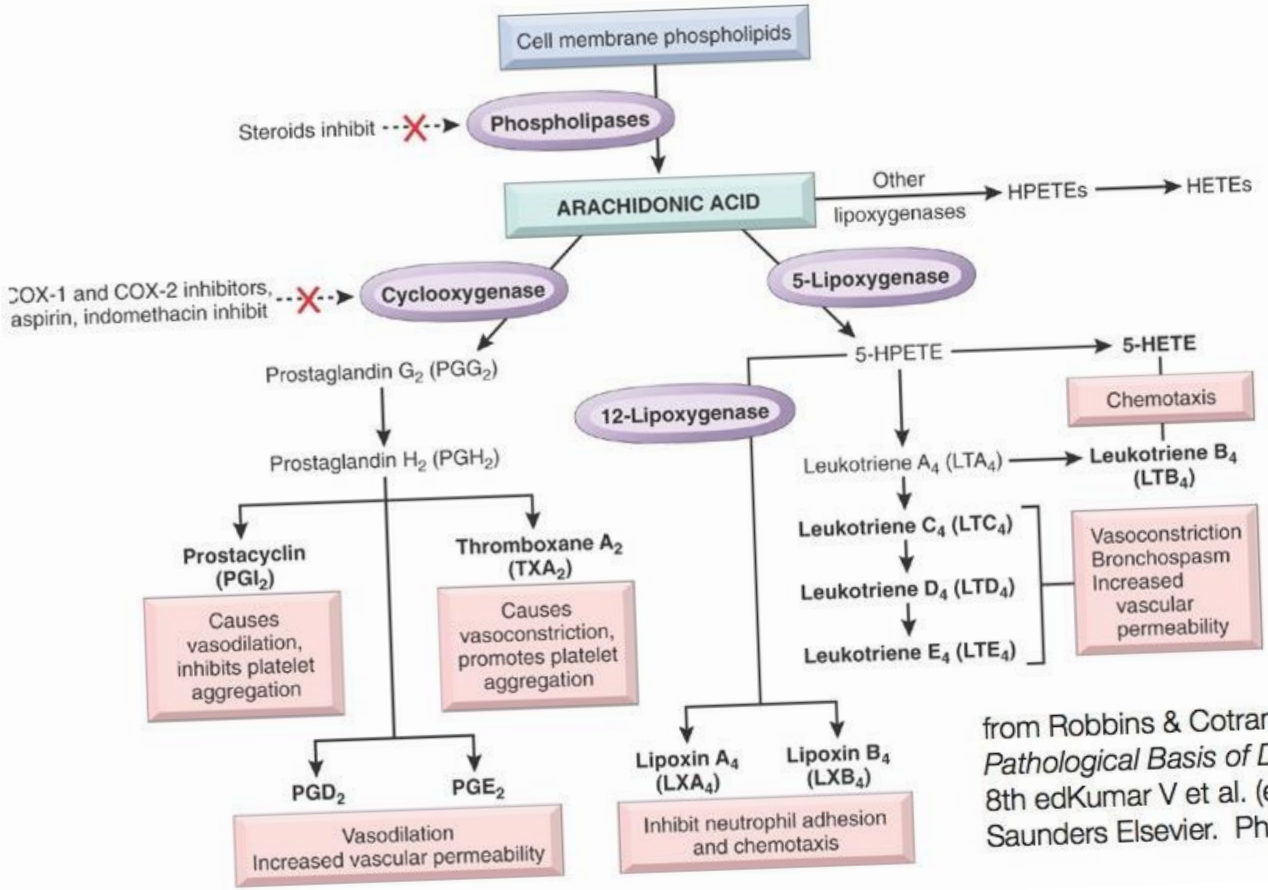
1

Nonsteroidal anti-inflammatory drugs (NSAIDs) are nearly the ideal postoperative analgesic, possessing both anti-in ammatory and antipyretic properties.

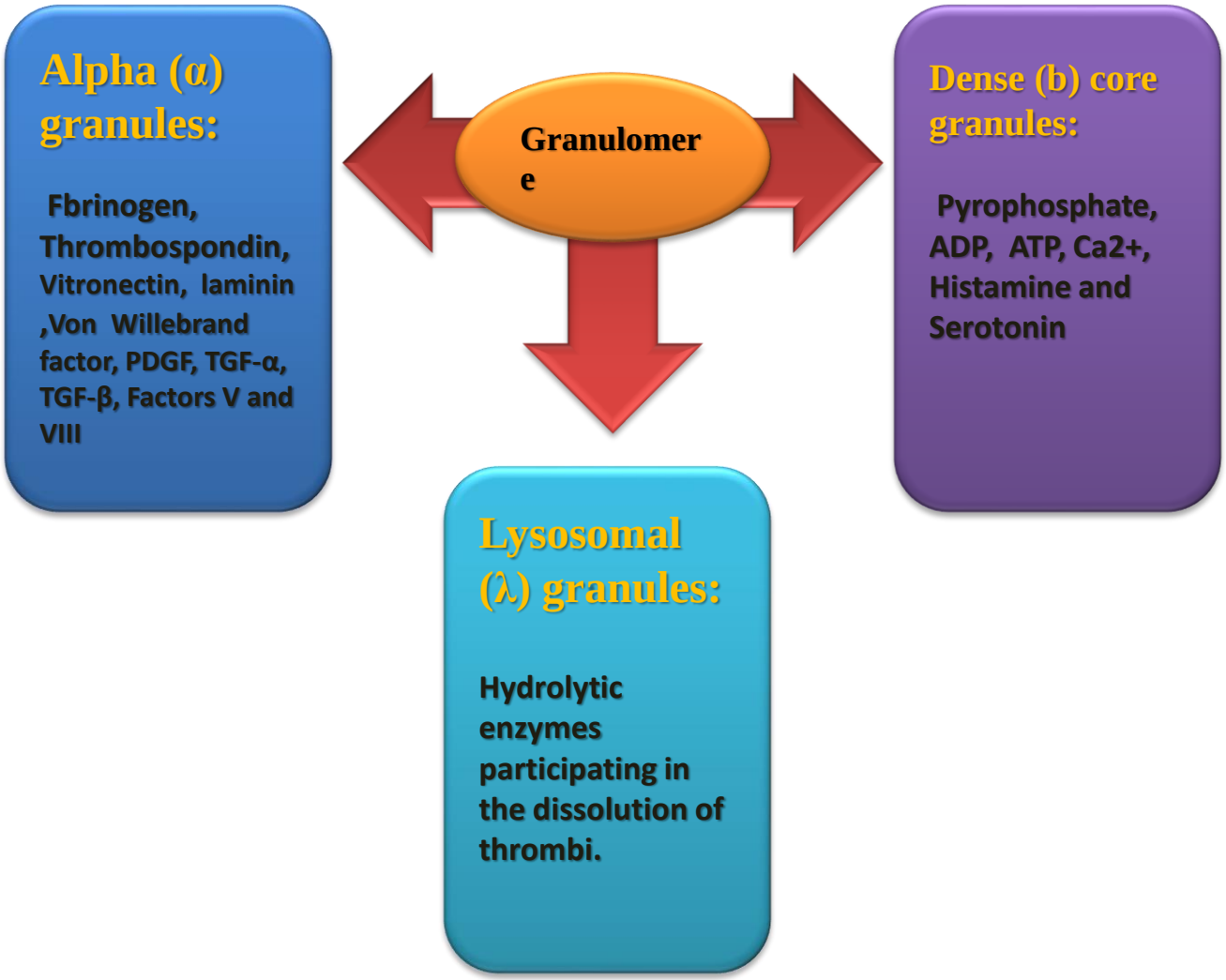
2

The primary mechanism of action is the inhibition of cyclooxygenase (COX), thereby inhibiting the conversion of arachidonic acid to prostaglandin.

Arachidonic acid metabolites and inflammation



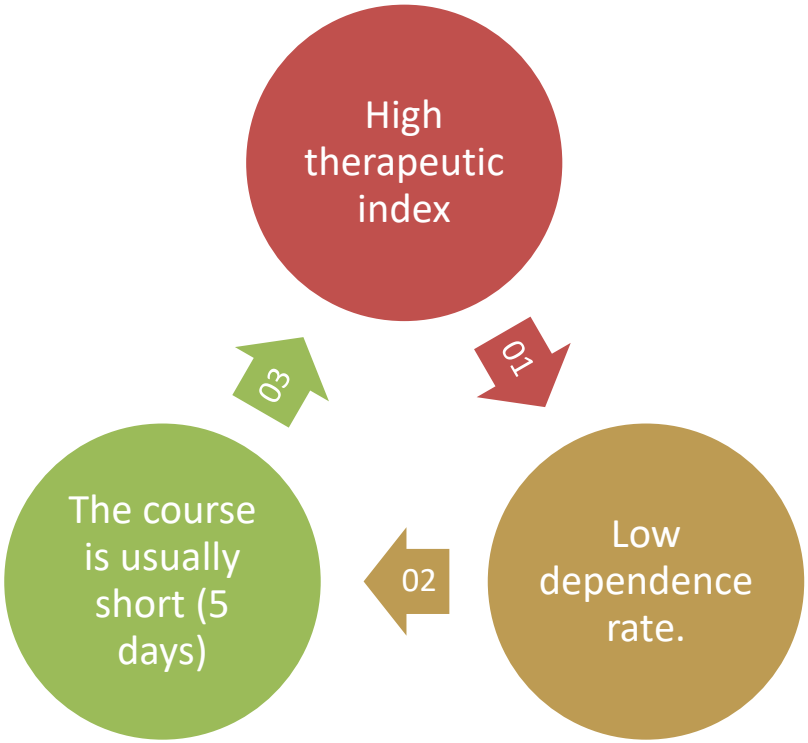
from Robbins & Cotran's *Pathological Basis of Disease* 8th edKumar V et al. (eds). Saunders Elsevier. Philadelphia (2010)


Alpha (α) granules:
Fbrinogen, Thrombospondin, Vitronectin, laminin ,Von Willebrand factor, PDGF, TGF-α, TGF-β, Factors V and VIII
Granulomere
Dense (b) core granules:
Pyrophosphate, ADP, ATP, Ca2+, Histamine and Serotonin
Lysosomal (λ) granules:
Hydrolytic enzymes participating in the dissolution of thrombi.

NSAIDs

- NSAIDs are the first-line choice for management of postoperative pain resulting from tissue injury and inflammation.
- There are two different isoforms of COX: COX-1 and COX-2.

NSAIDs Advantages



NSAIDs Contraindication

PATIENTS WITH KNOWN GI DISEASE (PEPTIC ULCER, KNOWN ALCOHOL ABUSE

PATIENTS WITH CHRONIC HEPATIC AND/OR RENAL DISEASE

NSAIDs

Non Selective NSAIDs

Para- aminophenols derriatives

Acidic Derivatives

- Salycylate
  - Accetylated
  - Non Accetylated
- Propionic Acid
- Acetic Acid
- Enolic acid (oxicams)
- Anthranilic acid (Fenamates)

Non Acidic derriatives

- naphthylalkanone:Nabumetone

Selective NSAIDs

Celecoxib

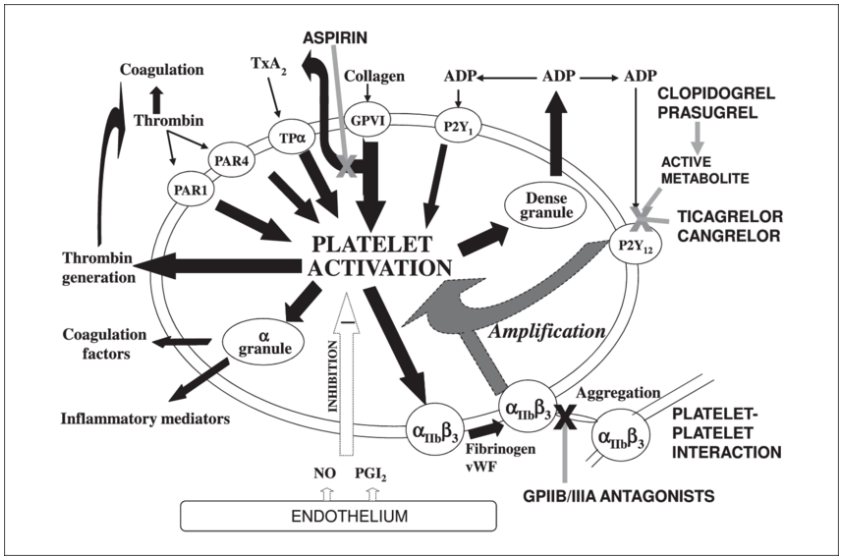
Para-aminopheno Derriatives: Acetaminophen

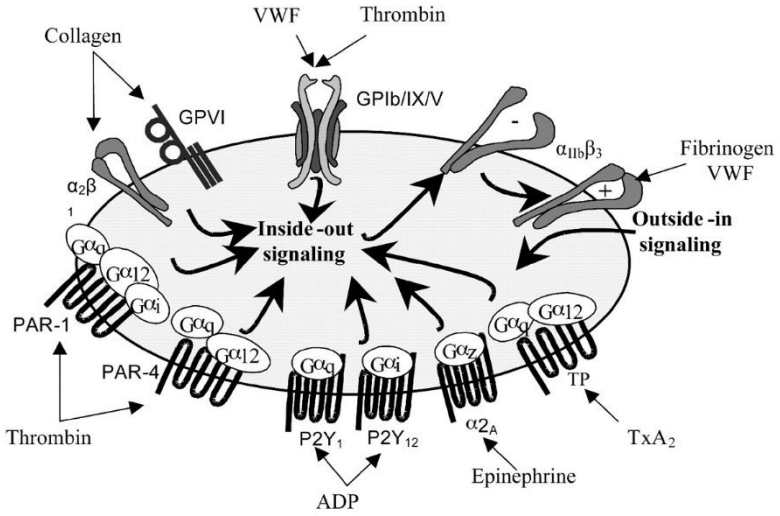
Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Acetaminophen * (paracetamol)	<2600	325 to 1000 mg every 4 to 6 hours	4000	Treatment of mild pain and minor febrile conditions. Lacks significant antiinflammatory effect. Useful adjunct to opioid analgesics and NSAIDs. Lacks antiplatelet effect and gastrointestinal (GI) toxicity. Can cause hepatotoxicity in chronic or acute overdosage. Avoid, or use a lower daily dose, in older adults and patients at risk for hepatoxicity (eg, heavy alcohol use or malnourished). Interacts with warfarin (prolongation of INR) and CYP-450 inducing drugs (elevated risk of hepatic inflammation).

NON-SELECTIVE NONSTEROIDAL ANTIINFLAMMATORY (NSAID) AGENTS

Salicylate (acetylated)

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Aspirin	2600	325 to 650 mg every 4 to 6 hours	4000	Standard for comparison but now used infrequently for treatment of chronic pain and inflammation due to its association with severe gastropathy. Unlike other NSAIDs, irreversibly inhibits platelet function for platelet life (7 to 10 days) and salicylism may occur with high doses or chronic use at analgesic doses. Caution for Rye Syndrome , PUD, Asthma


ASPIRIN
Coagulation
TxA2
Collagen
ADP
ADP
ADP
CLOPIDOGREL
PRASUGREL
Thrombin
TPα
GPVI
P2Y1
PAR4
PAR1
ACTIVE
METABOLITE
Dense
granule
TICAGRELOR
CANGRELOR
P2Y12
Thrombin
generation
PLATELET
ACTIVATION
Amplification
Coagulation
factors
α
granule
INHIBITION
Aggregation
Inflammatory mediators
αIIbβ3
αIIbβ3
αIIbβ3
PLATELET-
PLATELET
INTERACTION
Fibrinogen
vWF
NO
PGI2
GPIIB/IIIA ANTAGONISTS
ENDOTHELIUM


Collagen
VWF
Thrombin
GPVI
GPIb/IX/V
αIIbβ3
Fibrinogen
VWF
α2β1
Inside -out
signaling
Outside -in
signaling
Gαq
Gα12
Gαi
PAR-1
PAR-4
Gαz
TP
Thrombin
P2Y1
P2Y12
α2A
TxA2
ADP
Epinephrine

Salicylates (non-acetylated)

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Diflunisal	1000 once Δ	500 mg every 8 to 12 hours	1500	Treatment of mild to moderate pain and acute or chronic inflammatory conditions. Relatively lower risk of gastropathy compared to aspirin and possibly other NSAIDs. Generally tolerated by patients with asthma. Slower onset and possibly longer duration of action than aspirin or acetaminophen. Do not inhibit platelet function.
Choline magnesium trisalicylate	1500 once Δ	750 mg every 8 to 12 hours	3000	
Salsalate	1500	750 to 1000 mg every 8 to 12 hours	3000	

Propionic acids: Ibuprofen

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Ibuprofen	1600	400 mg every 4 to 6 hours	3200 acute, 2400 chronic	Treatment of mild to moderate pain, minor fever and acute or chronic inflammatory conditions. A 200 to 400 mg dose is comparable in analgesic effect to 650 mg acetaminophen or aspirin. Reversibly inhibits platelet function and increases bleeding time. Can alter cardioprotective effect of low dose aspirin ◊. Minimal risk of severe gastropathy with daily dose ≤2400 mg.

Propionic acids: Naproxen

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Naproxen	500 once$^{\Delta}$(naproxen base)	250 mg every 8 hours or 500 mg every 12 hours (naproxen base)	1250 acute, 1000 chronic (naproxen base)	Treatment of mild to moderate pain, minor fever and acute and chronic inflammatory conditions. 250 mg dose (base) comparable in analgesic effect to 650 mg aspirin. In the treatment of rheumatologic disorders, total daily dose may be increased to a maximum of 1500 mg base (1650 mg naproxen sodium) when needed for added effect. Reversibly inhibits platelet function and increases bleeding time. Can alter cardioprotective effect of low dose aspirin . Appears to have the greatest relative cardiovascular safety profile among nonselective COX-2 inhibitors.

Propionic acids: Ketoprofen

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Ketoprofen	100	25 to 50 mg every 6 to 8 hours	300 mg	For treatment of mild to moderate pain and acute or chronic inflammation. 25 mg dose comparable to analgesic effect of 400 mg ibuprofen.

Propionic acids: Flubiprofen

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Flurbiprofen	100	50 to 100 mg every 6 to 12 hours	300 mg	For treatment of mild to moderate pain and acute or chronic inflammation. In some countries it is available as a lozenge for throat pain and as an intravenous injection.

Propionic acids: Oxaprozin

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Oxaprozin	600	1200	26 mg/kg up to 1800 mg	For treatment of chronic pain and inflammation, osteo- and rheumatoid arthritis. Once daily dosing may be useful.

Acetic acids : Diclofenac

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Diclofenac	75 or 100 mg once$^{\Delta}$	50 mg every 8 hours	150 mg	For treatment of mild to moderate pain and acute or chronic inflammation. Also available as a topical patch for pain due to trauma and as a gel for treatment of painful joints.

Acetic acids : Etodolac

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Etodolac	600	200 to 400 mg every 6 to 8 hours	1200 mg	For treatment of mild to moderate pain and acute or chronic inflammation. 200 mg dose has a comparable analgesic effect to 400 mg of ibuprofen.

Acetic acids : Tolmetin

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Tolmetin	600	400 to 600 mg every 8 hours	1800	For treatment of chronic pain and inflammation, osteo- and rheumatoid arthritis.

Acetic acids : Sulindac

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Sulindac	300	150 to 200 mg every 12 hours	400	For treatment of acute and chronic pain and inflammatory conditions. More frequently implicated in hepatotoxicity than other NSAIDs. Parent drug and metabolites can accumulate with hepatic insufficiency. Drug and metabolites have been identified in renal calculi.

Acetic acids: Indomethacin

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Indomethacin	75	25 to 50 mg every 8 to 12 hours Controlled release: 75 mg every 12 hours	150	An alternate, non first-line option for treatment of mild to moderate pain and acute or chronic inflammatory conditions. GI and central nervous system adverse effects may be more frequent or severe than with other NSAIDs. Intravenous formulation not indicated for pain.

Acetic acids: Ketorolac

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Ketorolac (intravenous and intramuscular)	<65 yrs 60 mg IV or IM once	15 to 30 mg every 6 hours	120	Short term treatment of moderate acute pain when oral administration of an NSAID is not available and as an adjunct to other analgesics for the treatment of moderate to severe postoperative pain. Not indicated for treatment of chronic cancer pain. Risk of gastropathy is increased when use exceeds five days. An oral preparation of ketorolac is available but offers no advantage over other oral NSAIDs.

Oxicams (enolic acids): Meloxicam

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Meloxicam	7.5	7.5 to 15 mg every 24 hours	15	For treatment of chronic pain and inflammation, osteo- and rheumatoid arthritis. Once daily dosing may be useful. While reported to be selective for COX-2 at lower dose of 7.5 mg, overall adverse effects are similar to other NSAIDs.

Oxicams (enolic acids): Piroxicams

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Piroxicam	10	10 to 20 mg every 24 hours	20	An alternate, non first-line option for treatment of chronic pain and inflammation poorly responsive to other NSAIDs. Comparatively high incidence of gastropathy in daily dose above 20 mg and in older adults. Concurrent pharmacologic gastroprotection is suggested.

Fenamates (anthranilic acids)

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Mefenamic acid	500 once	250 mg every 6 hours	1000	For acute pain and dysmenorrhea. Anti-inflammatory efficacy is comparatively low. Not indicated for treatment of chronic cancer pain.

NON-ACIDIC NSAIDS

naphthylalkanone:Nabumetone

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Nabumetone	1000 once	500 to 750 mg every 8 to 12 hours or 1000 to 1500 mg once daily	2000	For treatment of chronic pain and inflammation, osteo- and rheumatoid arthritis. While reported to be comparatively selective for COX-2 at the lower dose of 500 mg twice daily, the overall adverse effects when dosed in the usual range are similar to the other NSAIDs. Once daily dosing may be useful.

SELECTIVE COX-2 INHIBITORS

Celecoxib

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Celecoxib	400 once	200 mg daily or 100 mg every 12 hours	400	An option for patients requiring chronic NSAID treatment who may be at risk for gastropathy. Demonstrated efficacy and relative reduction in GI toxicity compared to non-selective NSAIDs. No effect on platelet function. Dosage above 200 mg daily associated with increased cardiovascular risk.

Parecoxib

Drug	Initial dose per day (mg)	Usual analgesic dose and interval	Maximum dose per day (mg)	Role in therapy
Parecoxib (intravenous and intramuscular)	40 once	20 to 40 mg every 6 to 12 hours	80	For short-term treatment of postoperative pain where oral route of administration is not available. Not indicated for treatment of chronic cancer pain.

Typical pain	Type of Procedure	Protocol
Mild	Forceps extraction	Paracetamol 1 g every 6 hours regularly (maximum 4 g/24 h)
Moderate	Surgical removal of tooth	Ibuprofen 400 mg every 6 hours regularly (maximum of 2.4 g/24 h) and paracetamol 1 g every 6 hours as necessary (maximum of 4 g/24 h)
Severe	Surgical removal of tooth involving bone removal	Ibuprofen 400 mg every 6 hours regularly (maximum of 2.4 g/24 h) and paracetamol 1 g/codeine 60 mg combination
Severe for inpatient	More difficult surgical removal of teeth or major surgery	Morphine by intravenous titration or intermittent intramuscular injection

ACUTE PAIN MANAGEMENT STRATEGIES

- Numerous clinical trials have investigated the effectiveness of initiating NSAID therapy prior to surgery. Most often 400 mg oral (PO) ibuprofen was administered 30 minutes before surgery
- Additionally, patients treated with preoperative 30 mg of intravenous (IV) ketorolac reported signifcantly lower pain intensity scores when compared with those receiving ketorolac postoperatively

Corticostroids

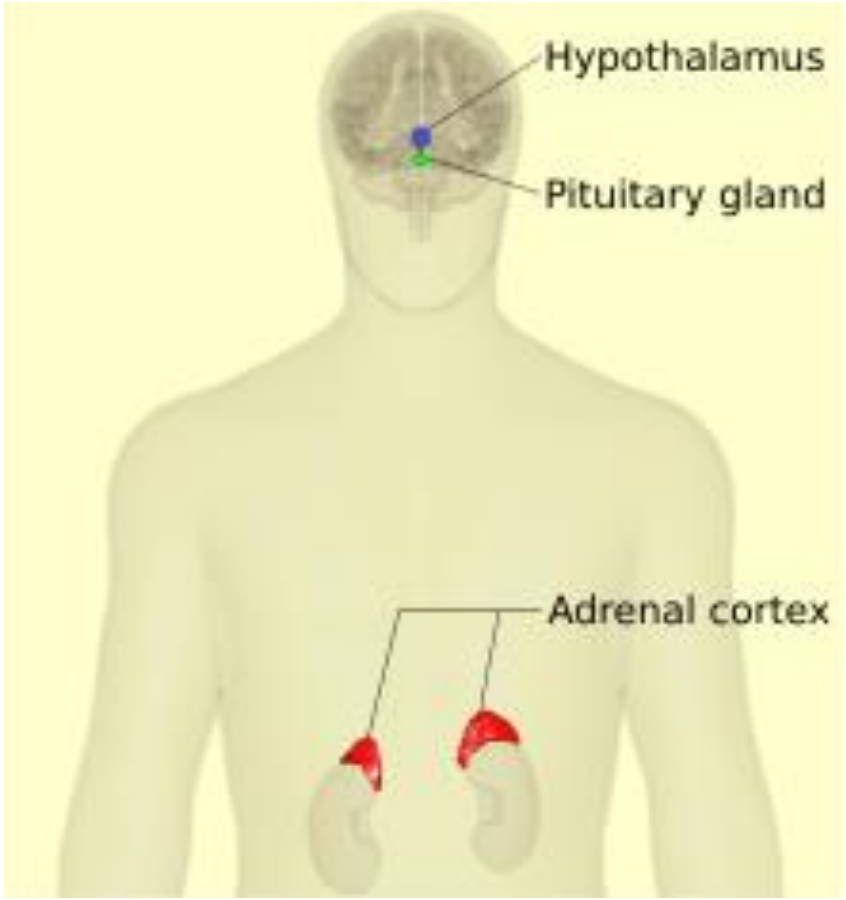
Tissue Damage

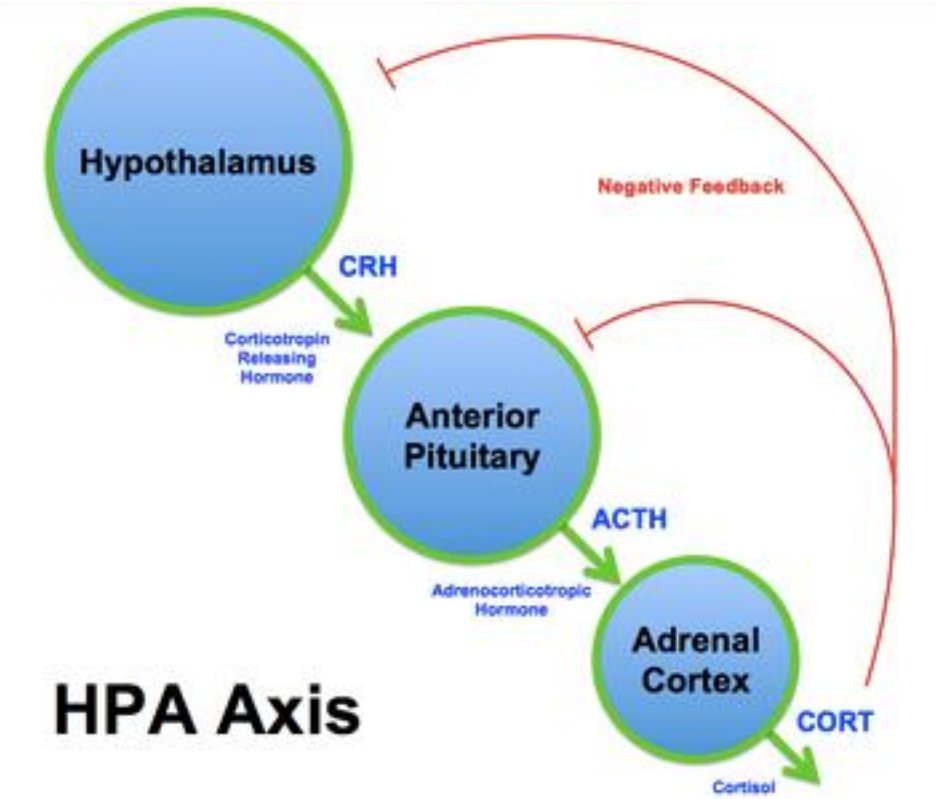
Arachidonic Acid Release

Lipooxygenase

Cyclooxygenase

Produce Prostaglandins


Hypothalamus
Pituitary gland
Adrenal cortex


Hypothalamus
Negative Feedback
CRH
Corticotropin Releasing Hormone
Anterior Pituitary
ACTH
Adrenocorticotropic Hormone
Adrenal Cortex
CORT
Cortisol
HPA Axis

Corticostroids

Pharmacologic doses of glucocorticoids are used to treat patients with inflammatory, allergic, immunological disorders.

If chronic, this supra-physiologic therapy has many adverse effects, ranging from suppression of the hypothalamic-pituitary-adrenal axis and Cushing's syndrome to infections and changes in mental status.

Comparison of representative glucocorticoid preparations

	Approximate equivalent dose* (mg)	Relative anti-inflammatory activity	Relative mineralocorticoid activity	Duration of action (hours)
Cortisol •	20	1	1	8 to 12
Cortisone acetate	25	0.8	0.8	8 to 12
Hydrocortisone	20	1	1	8 to 12
Prednisone	5	4	0.8	12 to 36
Prednisolone	5	4	0.8	12 to 36
Methylprednisolone	4	5	0.5	12 to 36
Triamcinolone	4	5	0	12 to 36
Fludrocortisone (see NOTE)	-	10	125	12 to 36
Dexamethasone	0.75	30	0	36 to 72

HPA axis suppression

Both endogenous and exogenous glucocorticoids exert negative feedback control on the hypothalamic-pituitary-adrenal axis by suppressing hypothalamic corticotropin-releasing hormone (CRH) production and pituitary corticotropin (ACTH) secretion.

This leads to adrenal atrophy and loss of cortisol secretory capability.

Not suppressed

Any patient who has received any non-parenteral dose of glucocorticoid for less than three weeks

Patients treated with alternate-day glucocorticoid therapy at physiologic doses

Supressed

Anyone who has received more than 20 mg of prednisone a day for more than three weeks

Any patient who has clinical Cushing's syndrome

Corticostroid Prescription

Reduce edema during the first 48- 72 hours

Should not exceed more than 3 days

Bone formation divided to 4 phases

Immediate Phase

Hypoxia which consists signaling molecules for healing phase

Hematoma formation

Early Phase

- Recruitment of inflammatory cells
- bFGF, VEGF
- O2 saturation
- MSCs to PHO

Regenerative Phase

New woven bone formation

Remodeling phase

Early phase is a critical phase in normal bone regeneration process

COXI

COX-2

PGE-2 is necessary for bone formation

NSAID decrease the amount of PGE2

Post op Management

NSAIDs + Acetaminophen Codein

Dexamethasone

Neuropathic Targeted Medications

- In the case where the inferior alveolar nerve has been stretched, bruised, or damaged, the patient may also have neuropathic pain
- Neuropathic pain does not often respond well to standard NSAID and opioid postoperative therapy
- Agents such as antidepressants (tri- cyclic) and anticonvulsants (gabapentin, pregabalin) have been shown to reduce continuous and episodic pain

Antibiotics

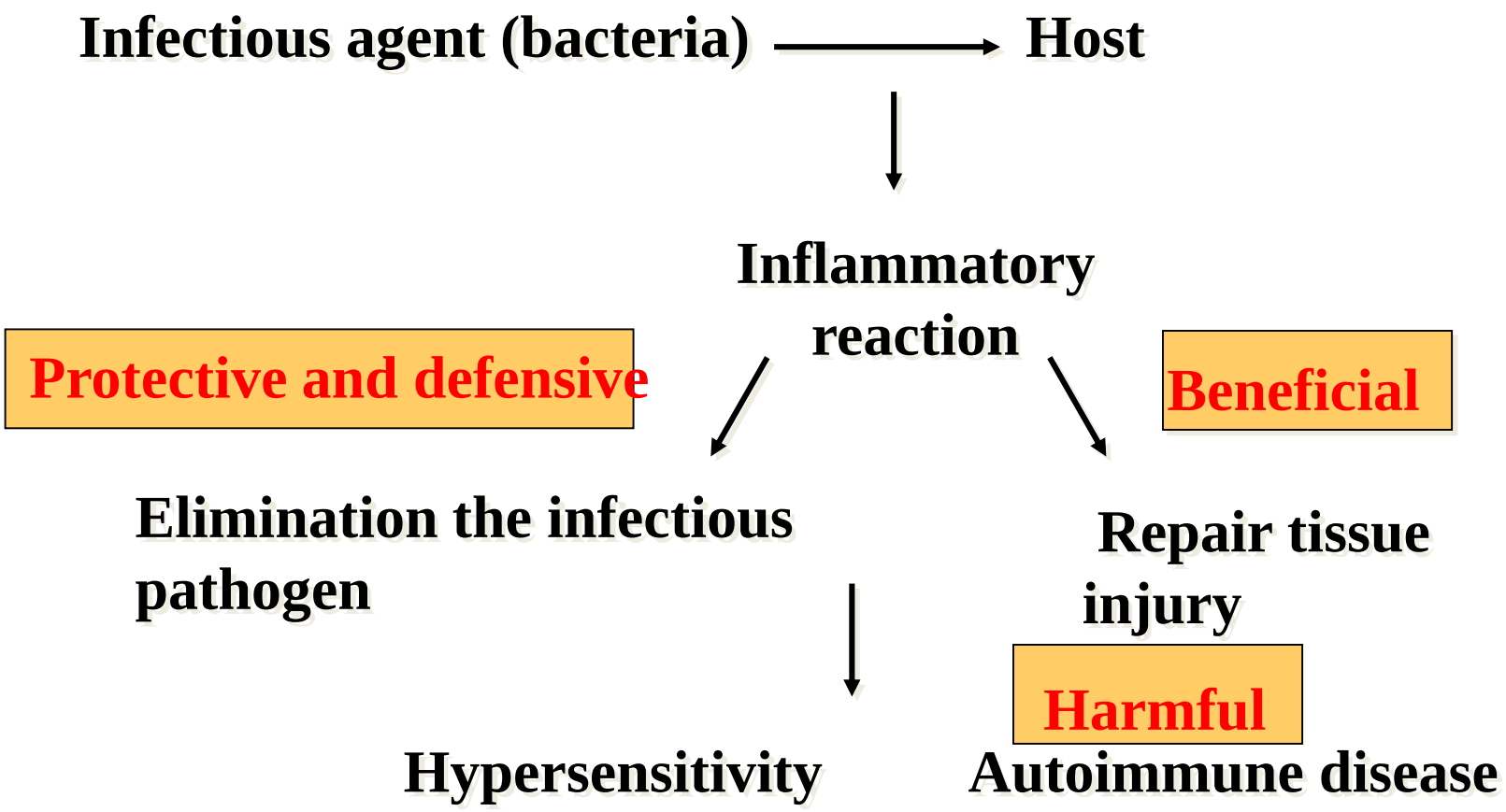
Antibiotics

What?

When?

How?

Infection

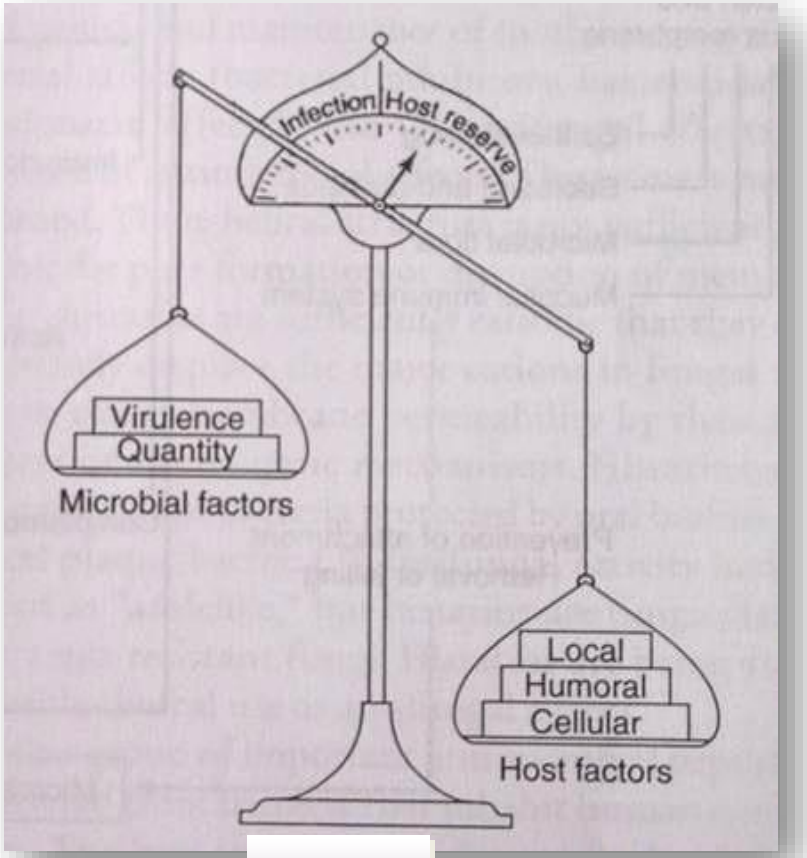

Infectious agent (bacteria)
Host
Inflammatory reaction
Protective and defensive
Beneficial
Elimination the infectious pathogen
Repair tissue injury
Harmful
Hypersensitivity
Autoimmune disease

Infection---Arising

- **Host--- defense system**
- **Microbe---virulence**

  quantity
- **Local circumstance**

Balance ⟶ Imbalance



Scale

Indication

Host Factor

- Sys factor
  - ASA III Immunecompromised patients
- Local Factor
  - Damage to the normal vascularization of the maxillomandible
  - Oral Microbial count

Surgical Factor

- Sterile Vs Clean Surgery
- Surgical Time
- Foreign body Insertion

Major Pathogens of Head and Neck Infections

TYPE OF INFECTION		MICROORGANISMS
Odontogenic cellulitis/abscess		*Streptococcus milleri* group Peptostreptococci *Prevotella* and *Porphyromonas* Fusobacteria
Rhinosinusitis	Acute	*Streptococcus pneumoniae* *Haemophilus influenzae* Head and neck anaerobes (*Peptostreptococcus, Prevotella, Porphyromonas, Fusobacterium*) GABHS (group A beta-hemolytic streptococci) *Staphylococcus aureus* *Moraxella catarrhalis* Viruses
	Chronic	Head and neck anaerobes
	Fungal	*Aspergillus* *Rhizopus* spp. *(Mucor)*
	Nosocomial (esp. if intubated)	Enterobacteriaceae (esp. *Pseudomonas, Acinetobacter, Escheria coli*) *Staphylococcus aureus* Yeasts (*Candida* spp.)
Osteomyelitis of the jaws	Acute	Odontogenic flora *Staphylococcus aureus* and skin flora in trauma Salmonella in sickle cell disease
	Chronic	*Actinomyces* spp.
Necrotizing fasciitis		Streptococcal (Groups A, C, G) Polymicrobial (aerobes + anaerobes) Clostridial Community-associated MRSA
Fungal	Mucosal or disseminated Soft tissue	*Candida* spp. *Histoplasma* spp. *Blastomyces* sp.
	Sinus	*Aspergillus* *Rhizopus (Mucor)*

What is the Normal Flora in Mouth?

- Aerobic Gr + Cocci
- Anearobic Gr+ Cocci
- Anearobic Gr- Bascillus

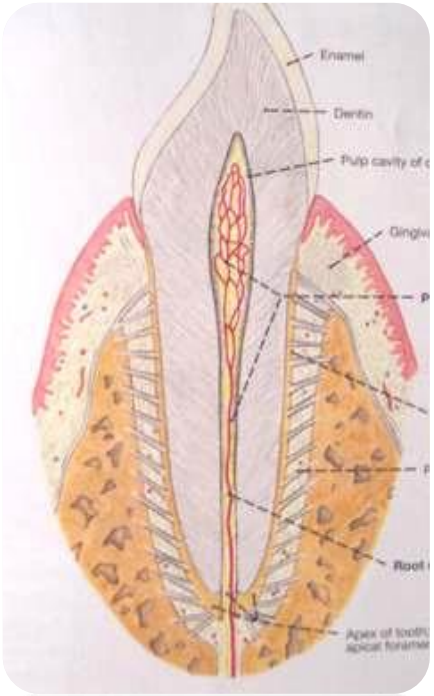
Caries

↓

Pulpitis

↓

Apical infection



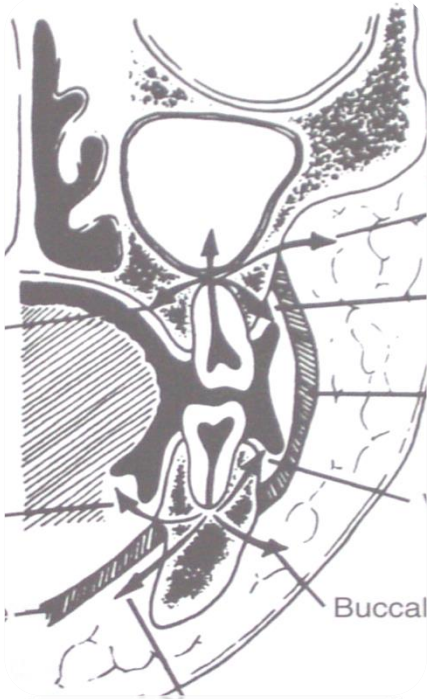
Alveolar bone

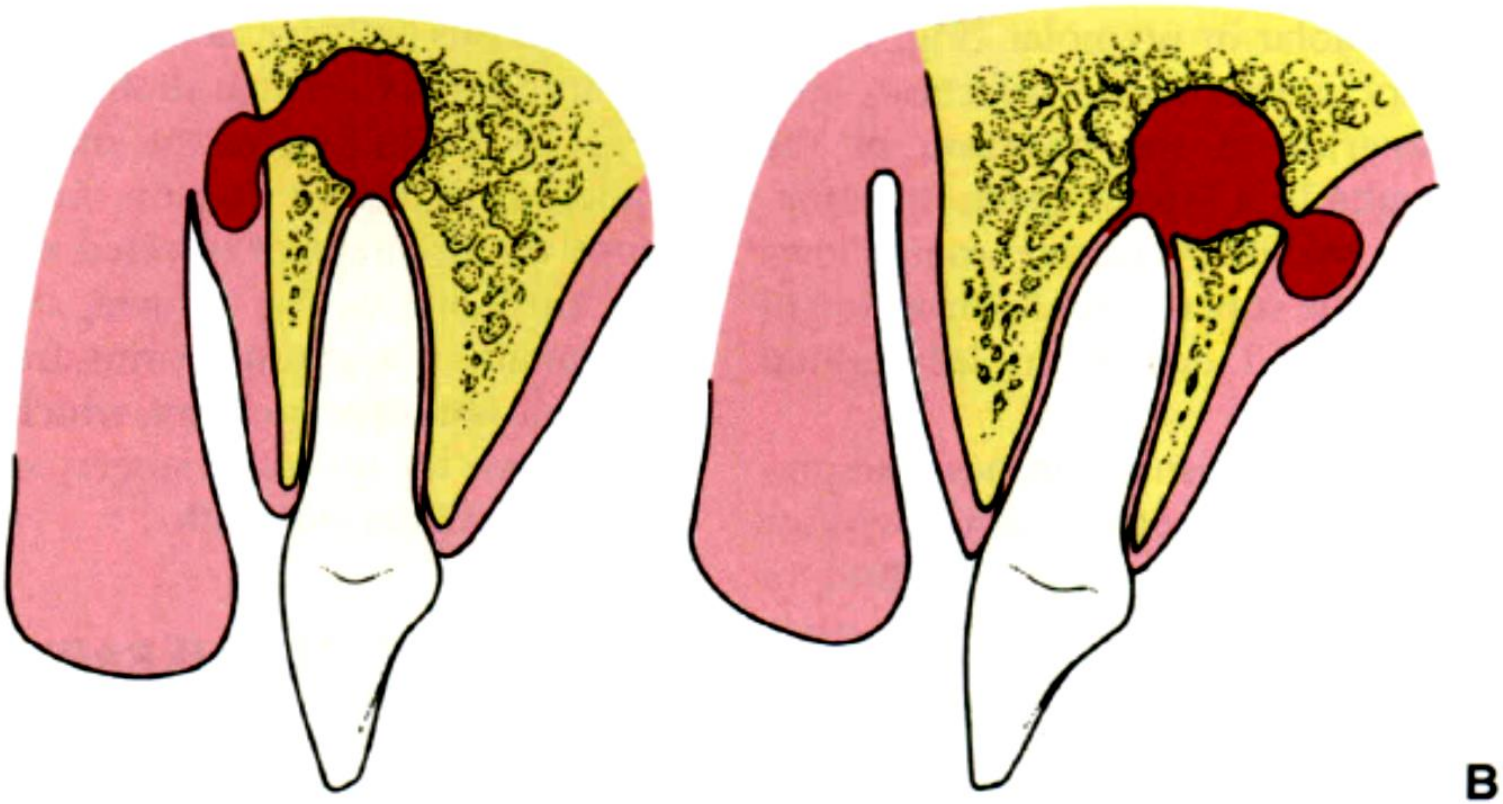
↓

Soft tissue

↓

Fascial space




A
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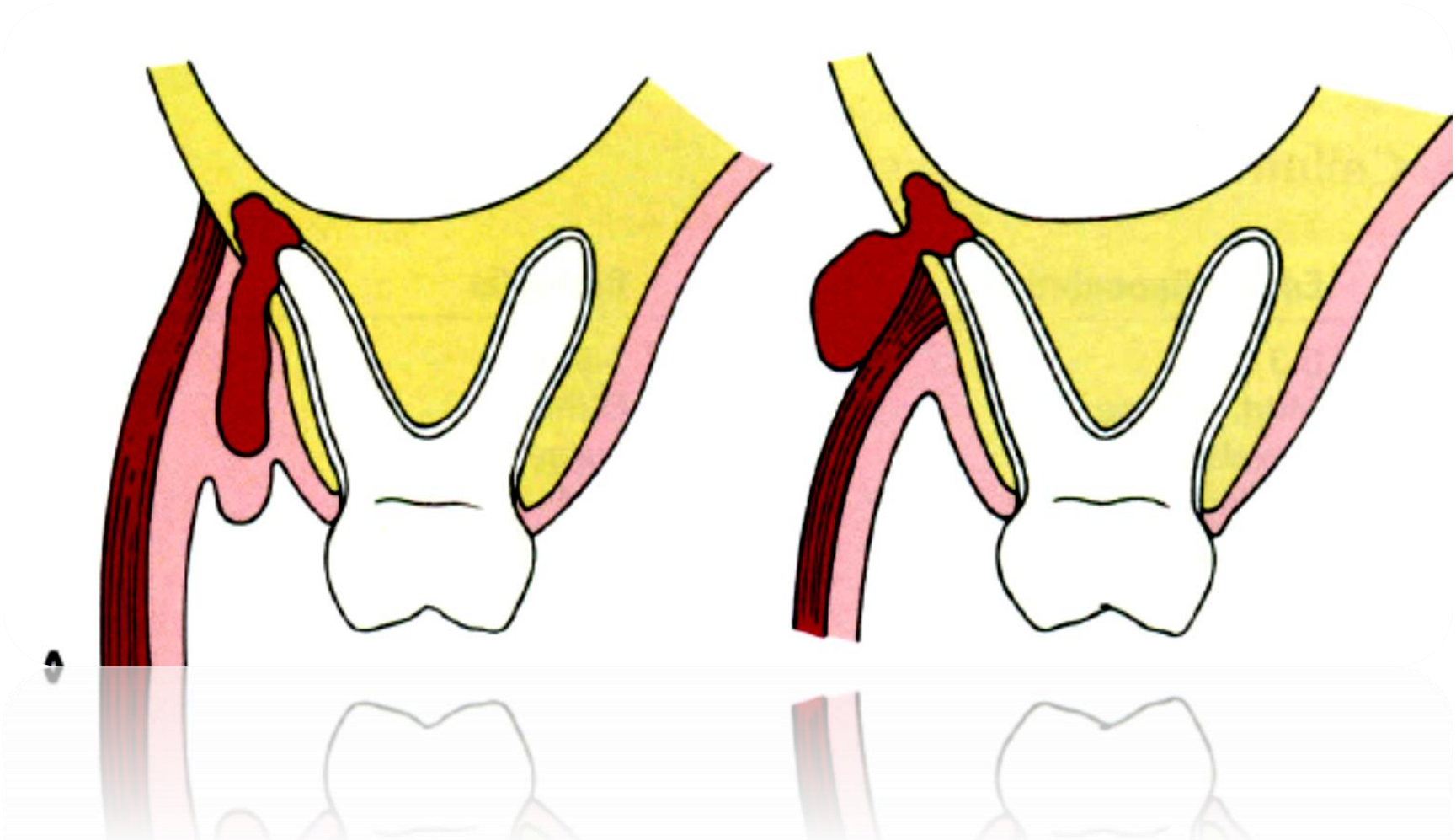
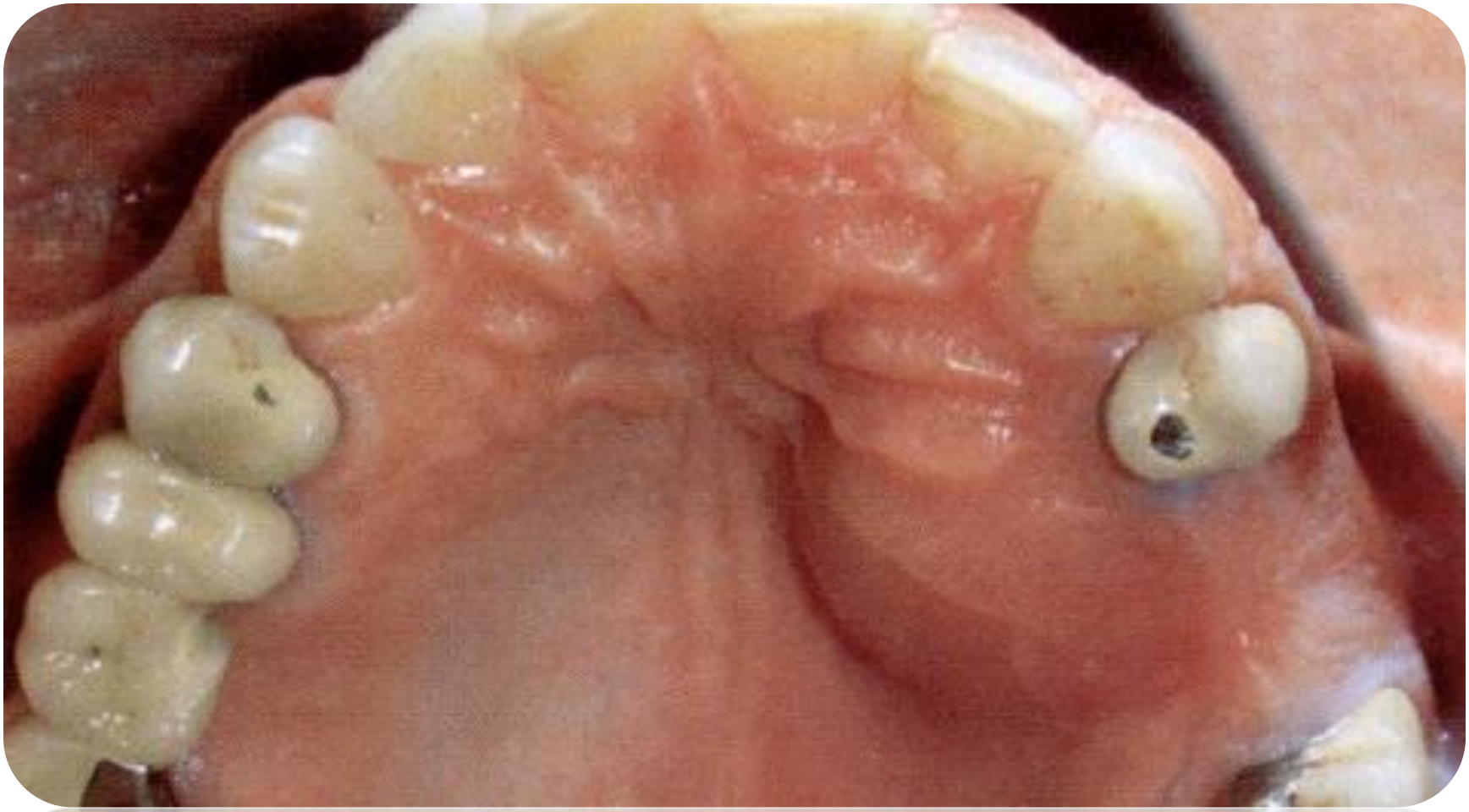
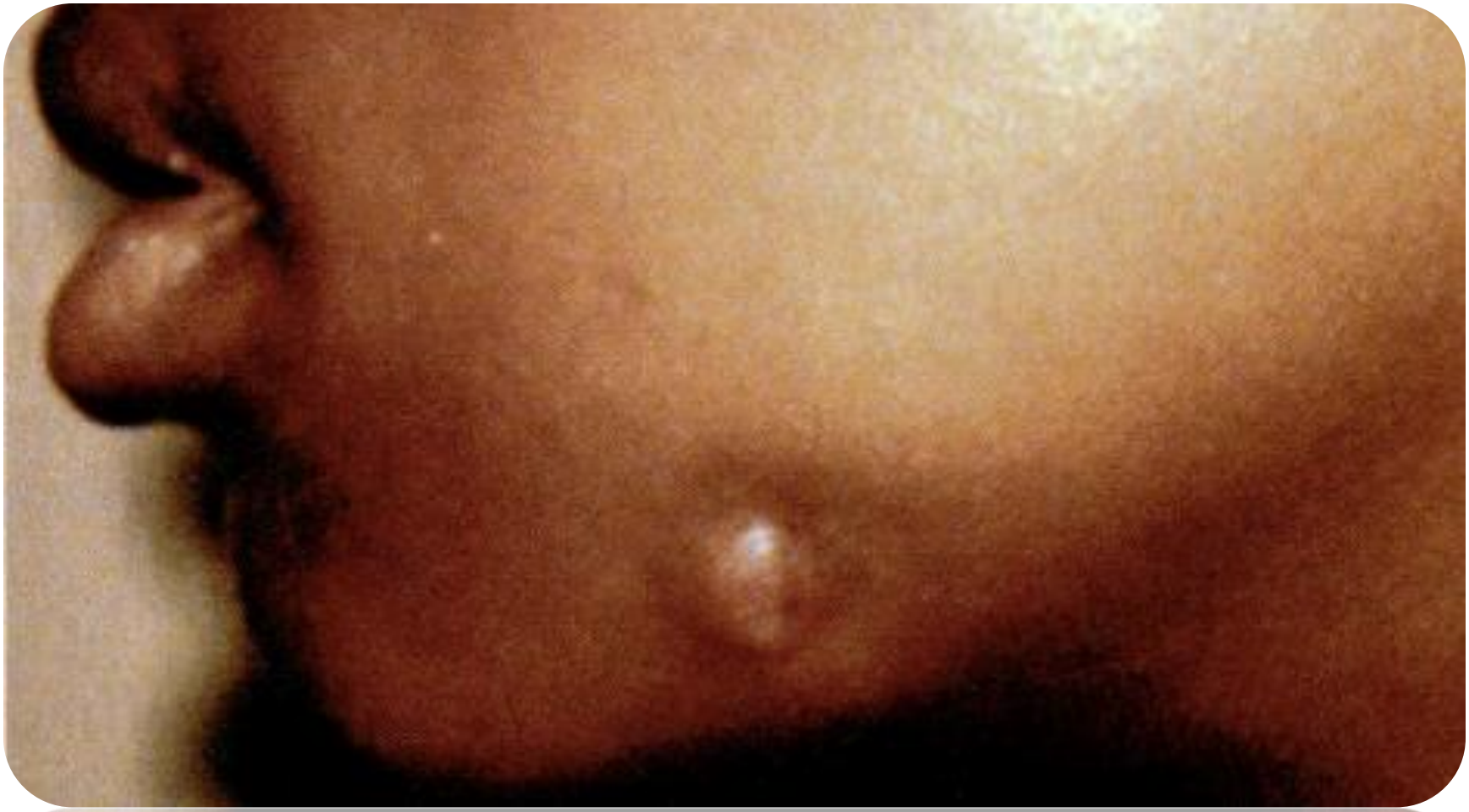
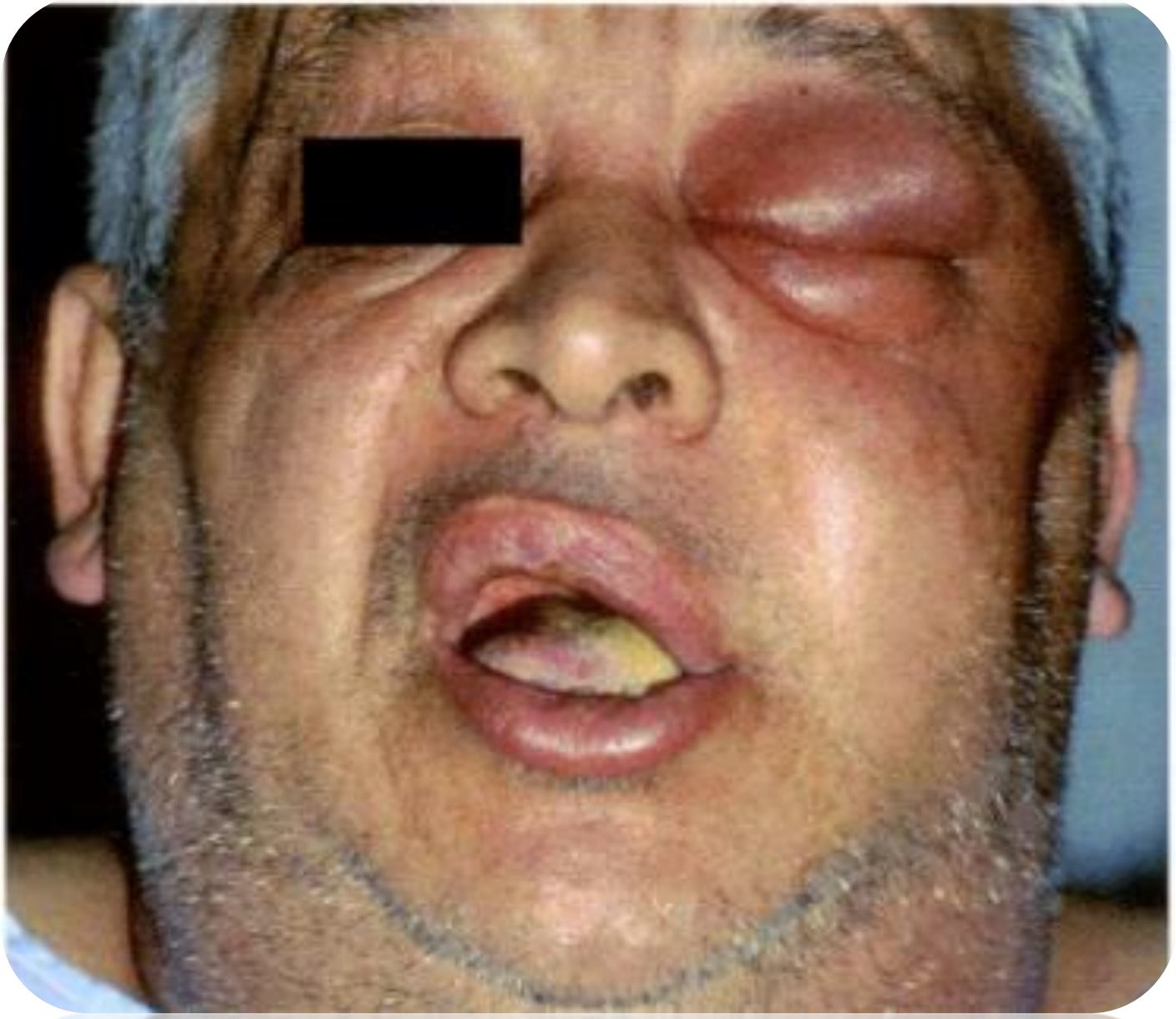
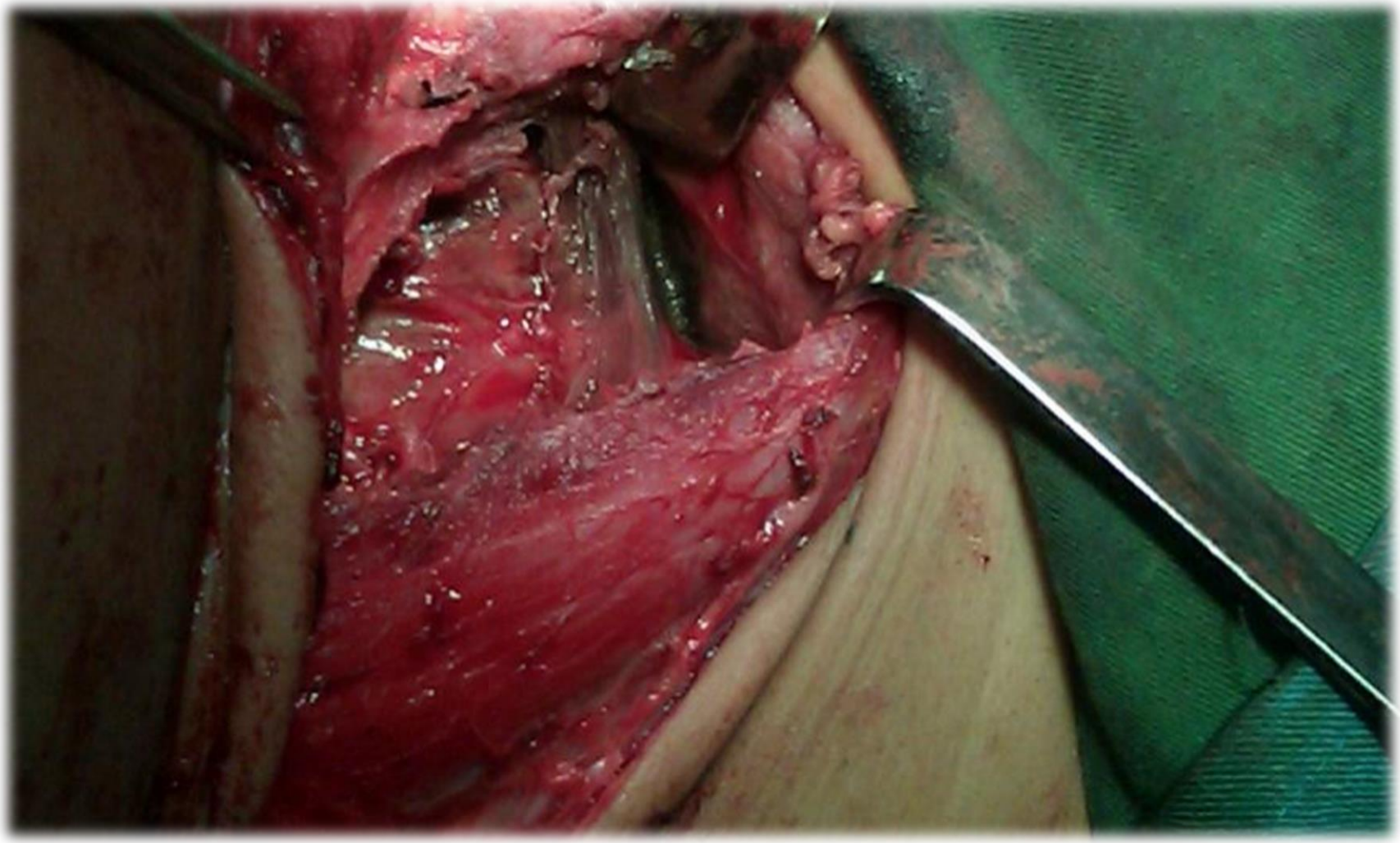
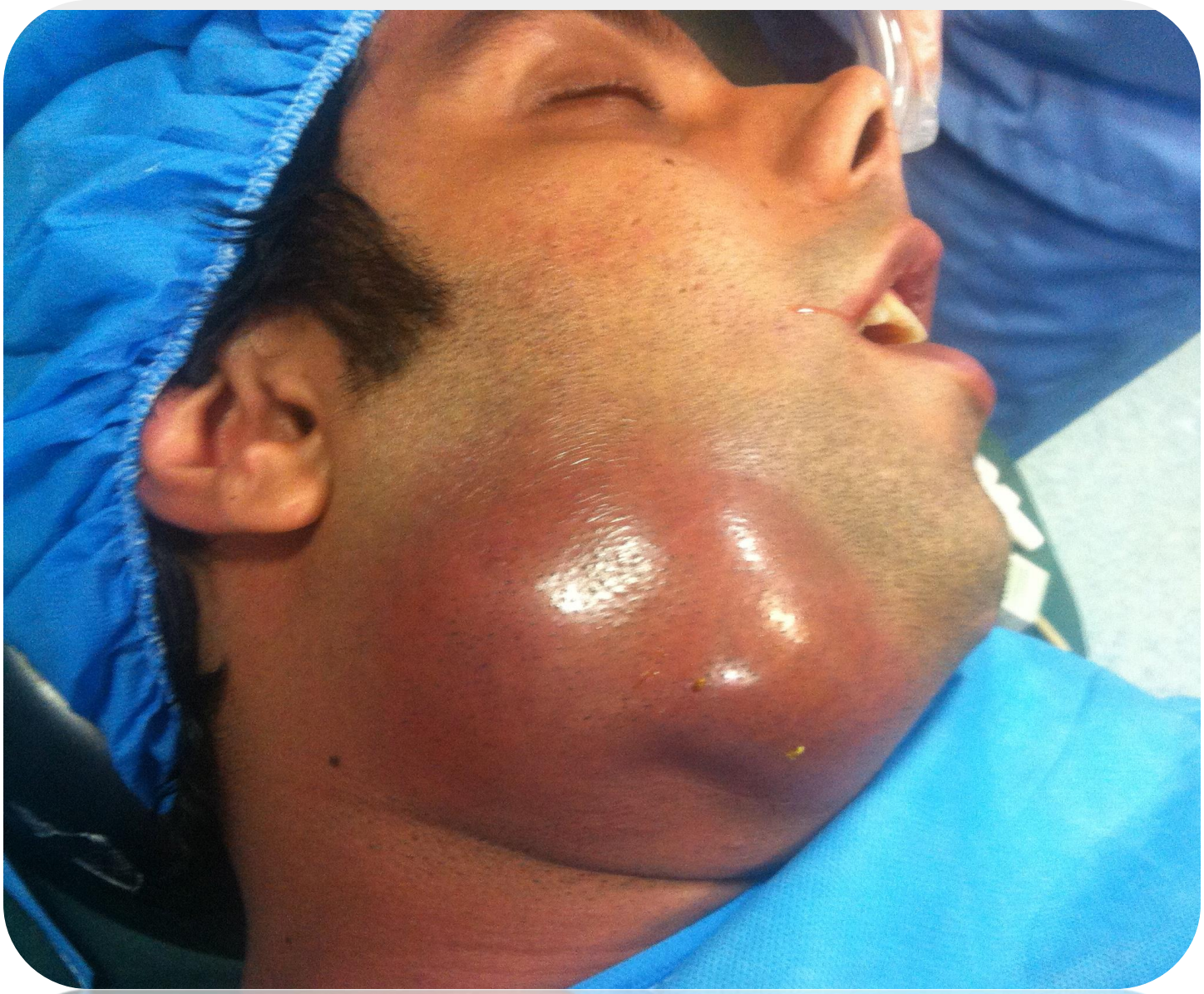


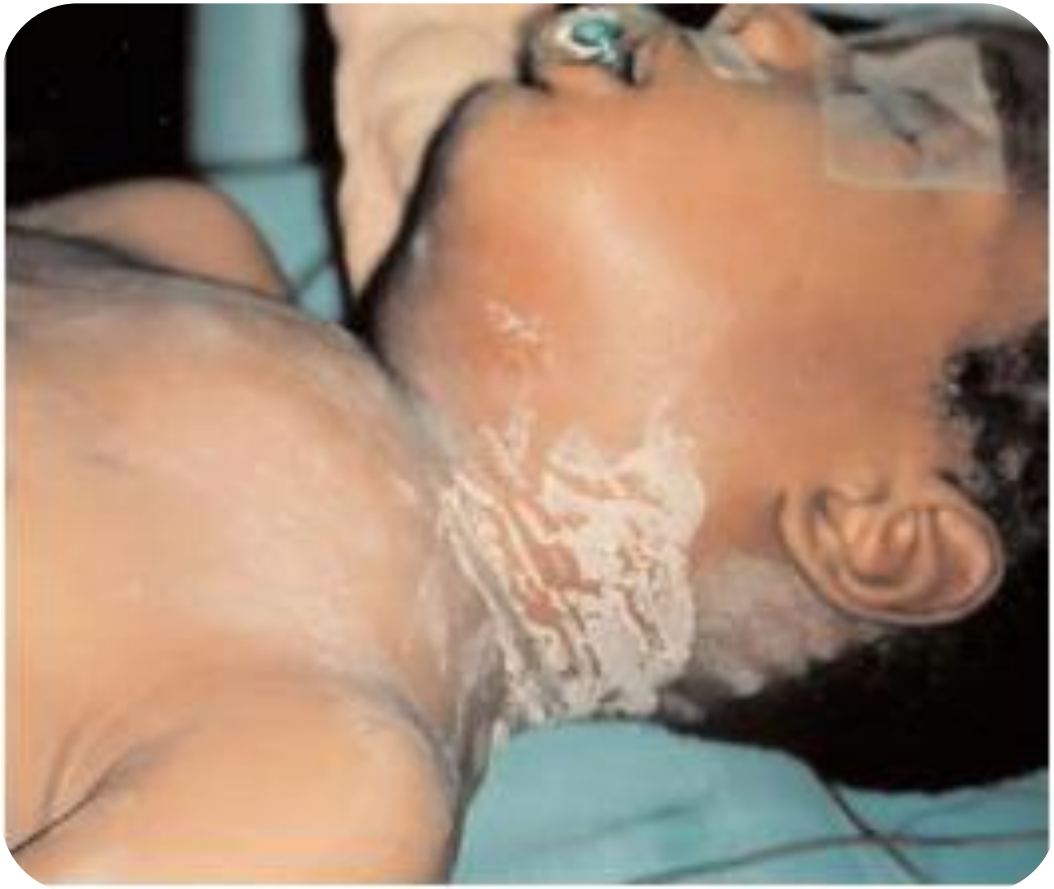


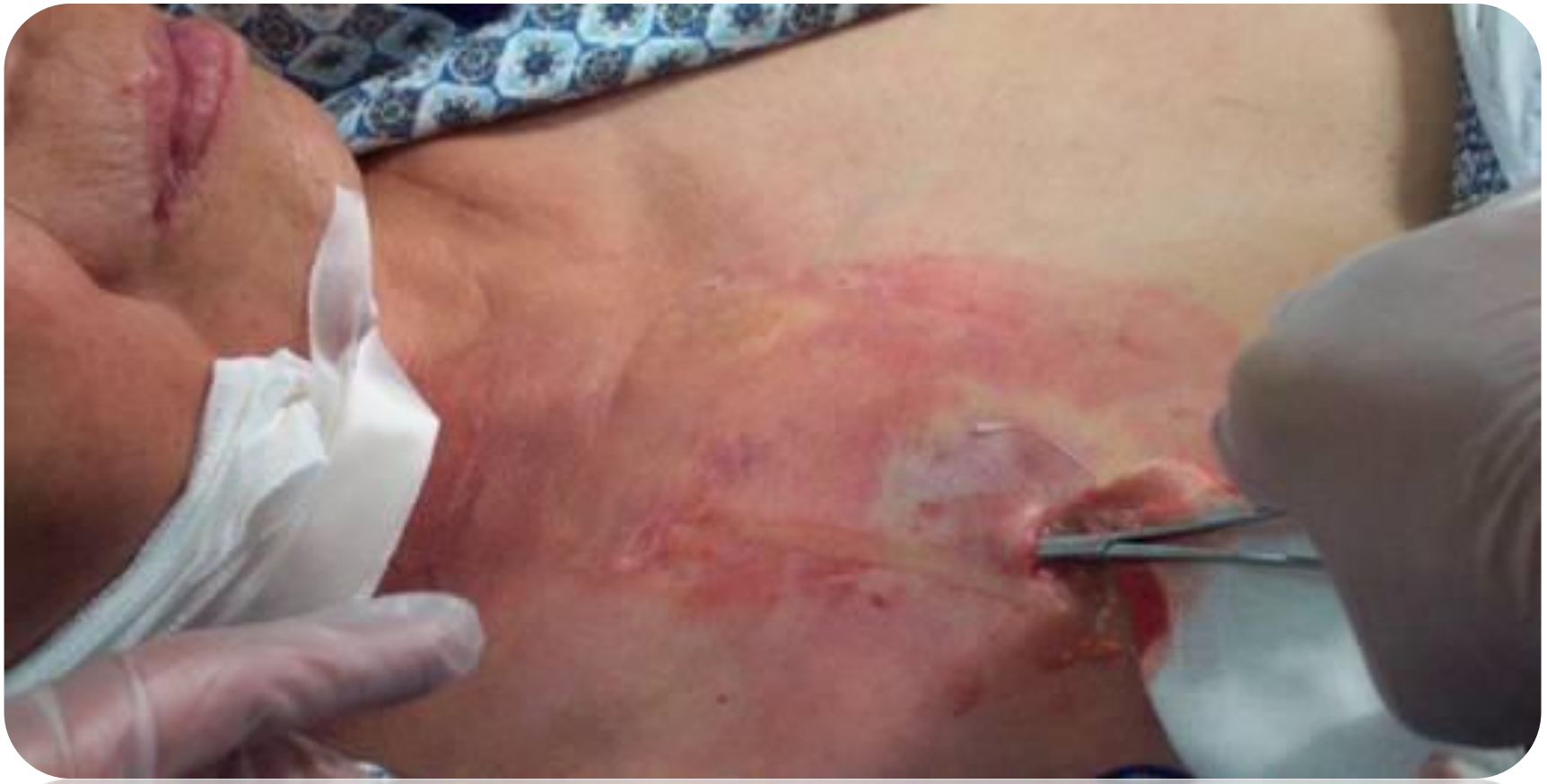












Penicillin

- Penicillin is the drug of choice for odontogenic infections
- gram-positive cocci (except staphylococci) and oral anaerobes.
- Penicillin G is the form given parenterally
- penicillin V is preferred for oral administration.
- Penicillin has Little toxicity except for allergic reactions, which occur in about 3% of the population.

Penicillins		
Amoxicillin	500 mg	8 hr
Penicillin V	500 mg	6 hr
Augmentin	875 mg	12 hr
Augmentin XR	2 g	12 hr
Dicloxacillin	500 mg	6 hr

Penicillins		
Penicillin G	2 m.u.	4 hr
Ampicillin	1 g	6 hr
Unasyn	3 g	6 hr
Oxacillin	2 g	6 hr
Ticarcillin	3 g	4 hr
Timentin	3 g	4 hr

Cephalosporins

- Beta-lactam antibiotics that are effective against gram-positive cocci and many gram-negative rods.
- Three generations, based on their activity against gram-negative organisms.
- The first-generation antibiotics have a similar activity, including activity against grampositive cocci, *Escherichia coli, Klebsiella* organisms, and *Proteus mirabilis.*

Cephalosporins (Generation)		
Cephalexin caps (1st)	500 mg	6 hr
Cefadroxil (1st)	500 mg	12 hr
Cefuroxime (2nd)	500 mg	8 hr
Cefaclor ER (generic)	500 mg	12 hr
Cefdinir (3rd)	600 mg	24 hr

Cefazolin (1st)	1 g	8 hr
Cefotetan (2nd)	1 g	12 hr
Cefuroxime (2nd)	1.5 g	8 hr
Ceftazidime (3rd)	2 g	8 hr
Ceftriaxone (3rd)	1 g	24 hr
Cefepime (4th)	2 g	12 hr

Clindamycin

- The antibacterial spectrum of clindamycin includes the gram positive cocci and almost all anaerobic bacteria.
- Clindamycin is effective for streptococci, staphylococci, and anaerobic infections.
- The drug is more expensive than penicillin and erythromycin and may have increased gastrointestinal toxicityin susceptible patients.

Erythromycins		
Erythromycin base	500 mg	6 hr
Clarithromycin (Biaxin XL)	500 mg	24 hr
Azithromycin (Zithromax)	250 mg	12 hr
Telithromycin (Ketek)	800 mg	24 hr
Antianaerobic		
Clindamycin (generic)	150 mg	6 hr
Clindamycin (2 T generic)	300 mg	6 hr
Clindamycin (generic)	300 mg	6 hr
Metronidazole	500 mg	6 hr

Erythromycin	1 g	6 hr
Azithromycin	0.5 g	24 hr
Vancomycin	0.5 g	6 hr
Vancomycin	1.0 g	12 hr
Antianaerobic		
Clindamycin	0.9 g	8 hr
Metronidazole	0.5 g	6 hr

Metronidazole

Metronidazole is an antibiotic that is effective *only* for anaerobic bacteria.

Metronidazole has no effect on aerobic bacteria such as streptococci.

The drug is primarily used in periodontal disease therapy but may also be useful in the management of anaerobic odontogenic infections alone or in combination with antiaerobic antibiotics such as penicillin.

Tetracyclines

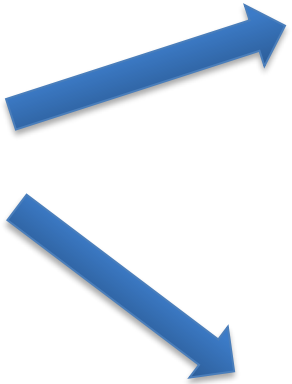
- Broad Spectrum
- Effective against Anaerobes
- Low Toxicities
- Anticollagenase Activity
- Doxycycline 100 mg qd

Fluoroquinolones

- Ciprofloxacin, Moxifloxacin, Levofloxacin, Gemifloxacin
- Anti bacterial DNA activity
- Broad Spectrum, bactericidal, orally taken antibiotics
- Most Activity are against Aerobic Gr- Bacilli (Entrobacteriace and Hemophilus Spp) and Gr- Cocci (Nisseria Spp and Moraxella)
- Unfortunately, these drugs are only marginally effective against streptococci and have little or no effect against anaerobic bacteria
- The third generation of fluoroquinolones has high antistreptococcal and antianaerobic activity.
- These drugs may be especially useful when a bactericidal antibiotic is necessary for a patient with severe penicillin allergy.

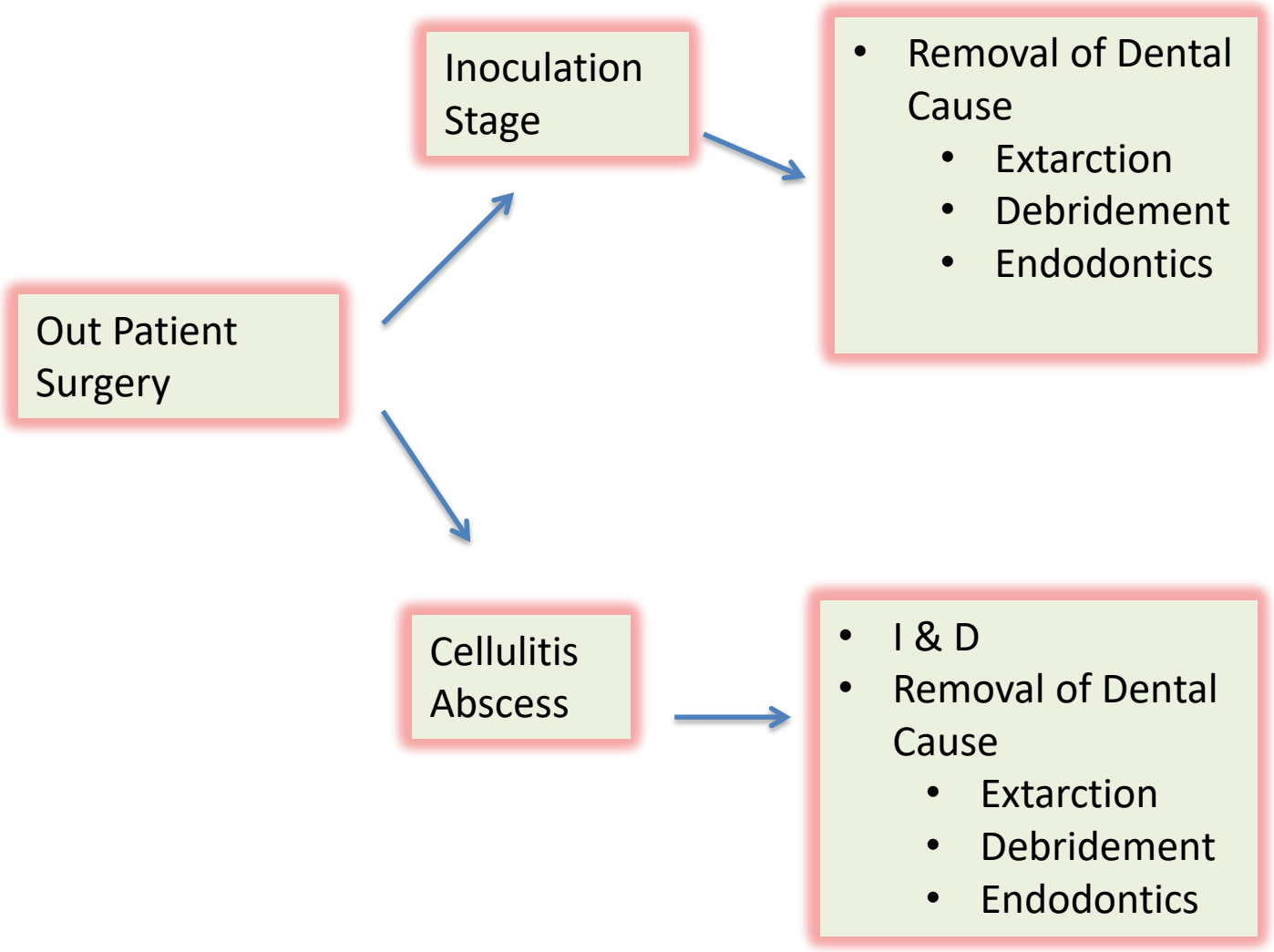
Trimethoprim/sulfameth	160/800 mg	12 hr
Vancomycin	125 mg	6 hr
Ciprofloxacin	500 mg	12 hr
Moxifloxacin (Avelox)	400 mg	24 hr
Doxycycline	100 mg	12 hr
Linezolid (Zyvox)	600 mg	12 hr

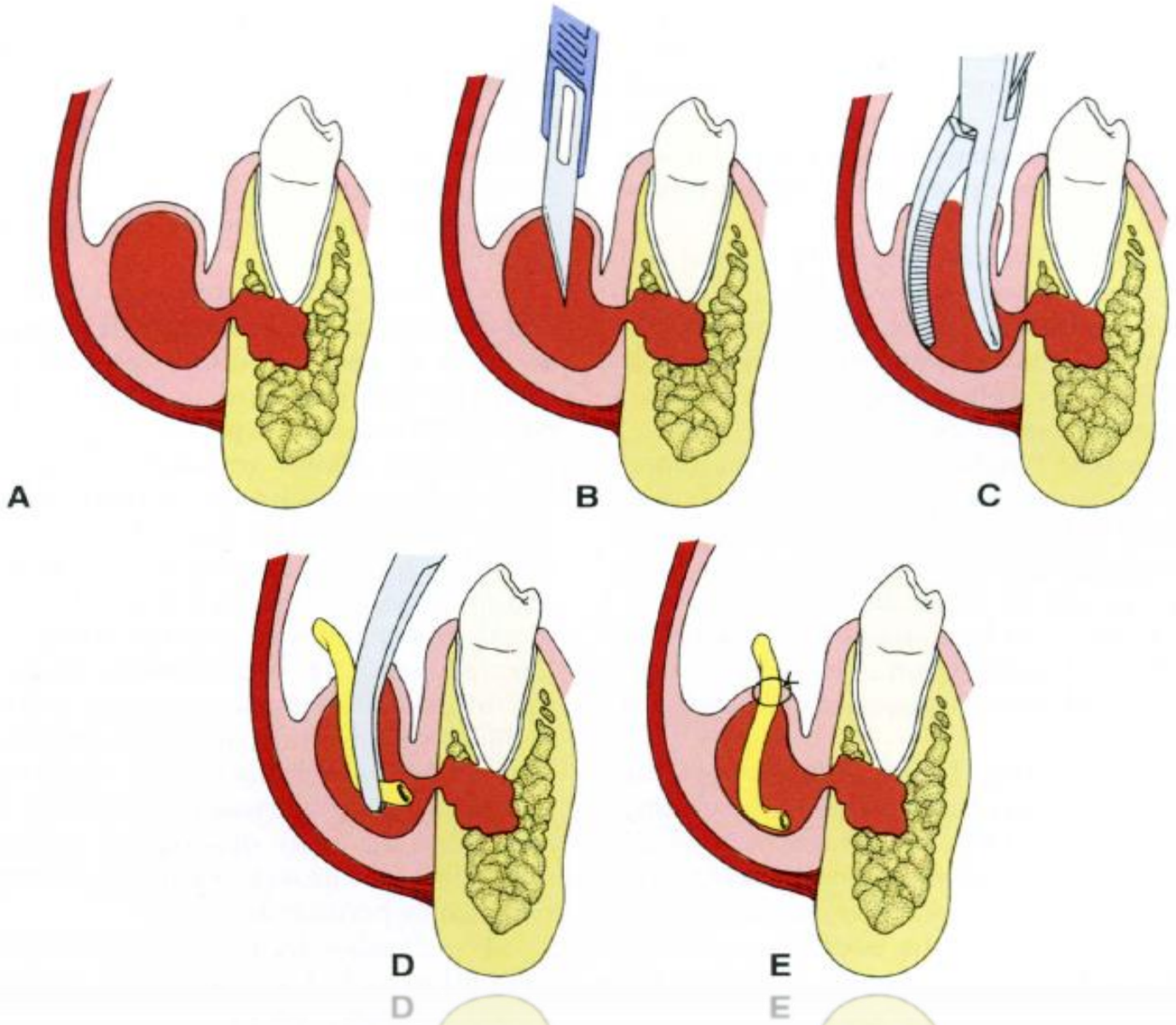
- Assess Severity
  - airway compromise
  - anatomic location
  - rate of progression
  - evaluate host defenses
  - medical comorbidities
  - immune compromise
  - systemic reserve



Out Patient Surgery

Refferal to OMFS


Out Patient Surgery
Inoculation Stage
Removal of Dental Cause
Extarction
Debridement
Endodontics
Cellulitis Abscess
I & D
Removal of Dental Cause
Extarction
Debridement
Endodontics


A
B
C
D
E

PROPHYLACTIC ANTIOBIOTIC USAGE

Five principles of antibiotic prophylaxis

- The surgical procedure should have a significant risk for infection.
- The correct antibiotic for the surgical procedure should be selected.
- The antibiotic level must be high.
- The timing of antibiotic administration must be correct.
- The shortest antibiotic exposure must be used.

Prophylactic Antiobiotic usage

- Prospective RCT revealed significant decrease in complication rate in bone graft cases in Ab Prophylaxis cases with control group

- No significant differences between Clindamycin, Penicilin, Phenethicillin

Prophylactic Antibiotic Regimen

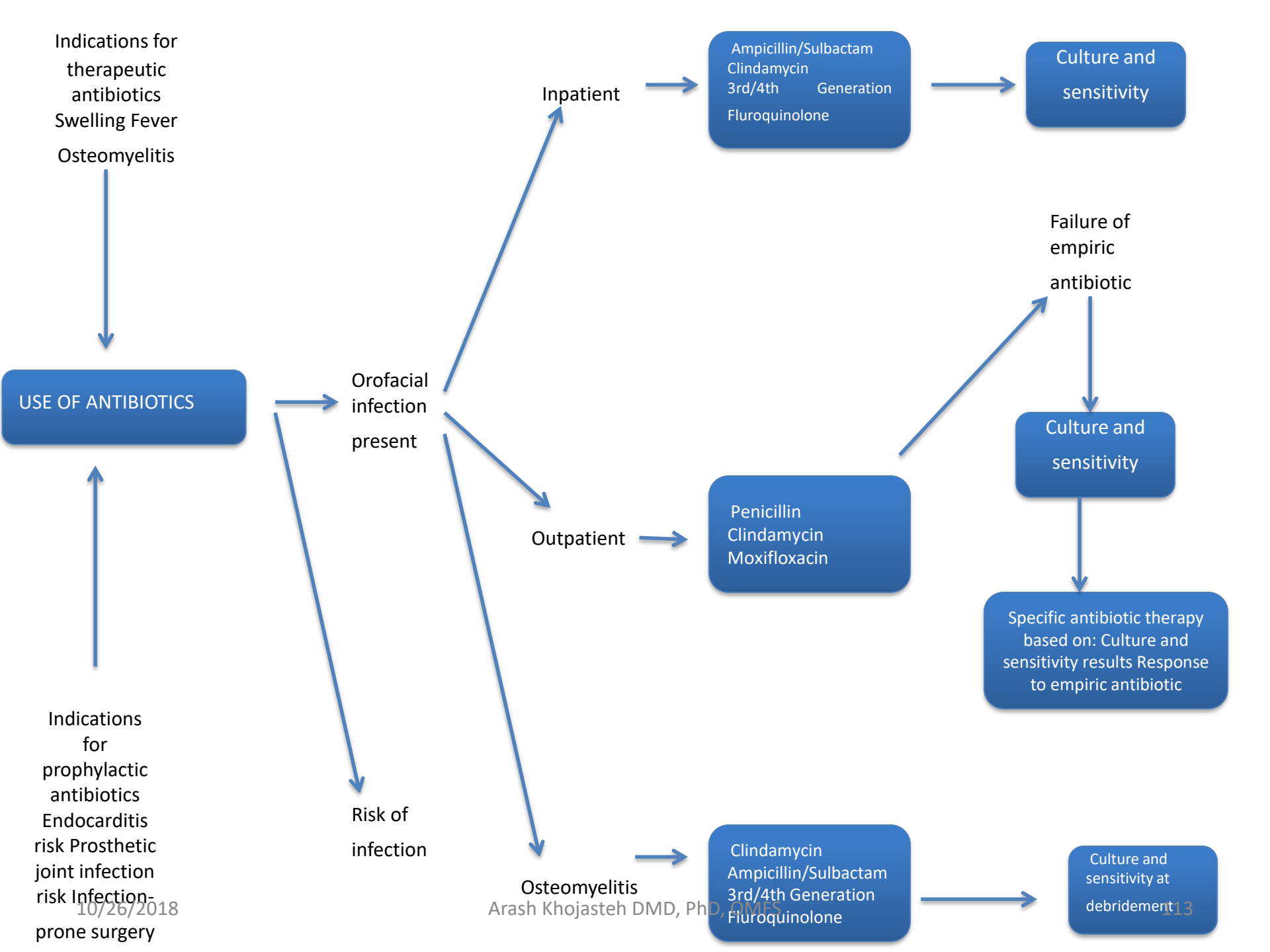
- 4 capsule of Clindamycin 150 mg 1 hour preoperatively
- C.difficile in outpatient surgery is unwarranted

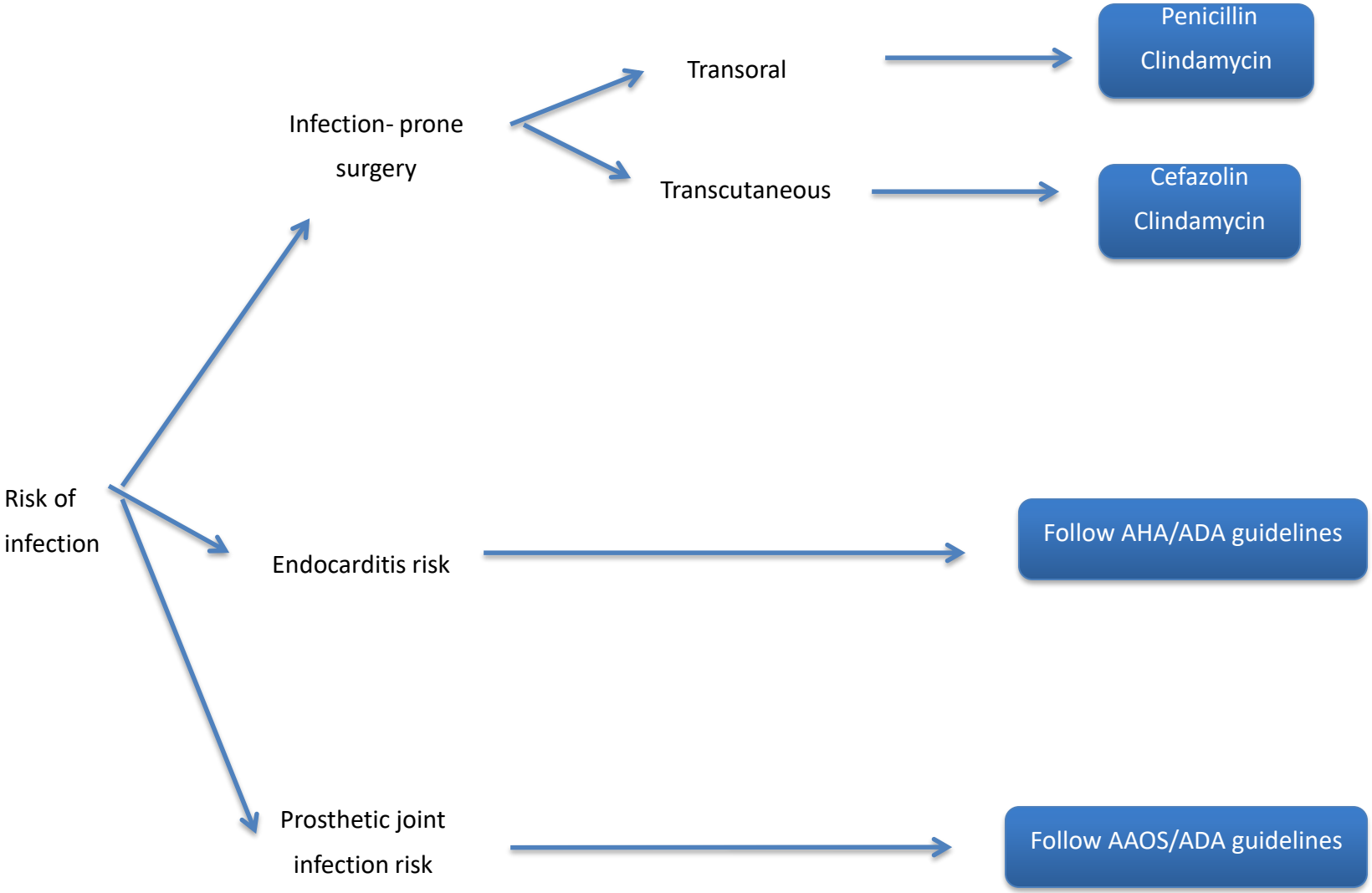
Antibiotic Prophylaxis

In orthognathic surgery, bone grafting, and implant placement, the evidence seems to support at least preoperative antibiotics, although in the case of bone grafting, additional study is warranted.

In third molar extraction, it is clear that partial or full bone- impacted mandibular third molars are most likely to become infected, but the decision for antibiotic prophylaxis should take into consideration the patient's overall risk factors for infection.

The most clear-cut evidence seems to be in support of short-term antibiotics in the management of compound mandibular fractures.


Indications for therapeutic antibiotics Swelling Fever Osteomyelitis
USE OF ANTIBIOTICS
Indications for prophylactic antibiotics Endocarditis risk Prosthetic joint infection risk Infection-prone surgery
Orofacial infection present
Risk of infection
Inpatient
Ampicillin/Sulbactam Clindamycin 3rd/4th Generation Fluroquinolone
Culture and sensitivity
Failure of empiric antibiotic
Outpatient
Penicillin Clindamycin Moxifloxacin
Culture and sensitivity
Specific antibiotic therapy based on: Culture and sensitivity results Response to empiric antibiotic
Osteomyelitis
Clindamycin Ampicillin/Sulbactam 3rd/4th Generation Fluroquinolone
Culture and sensitivity at debridement


Risk of infection
Infection- prone surgery
Transoral
Penicillin
Clindamycin
Transcutaneous
Cefazolin
Clindamycin
Endocarditis risk
Follow AHA/ADA guidelines
Prosthetic joint infection risk
Follow AAOS/ADA guidelines

Drug-Drug interaction

INTERACTIONS ASSOCIATED WITH ANALGESICS

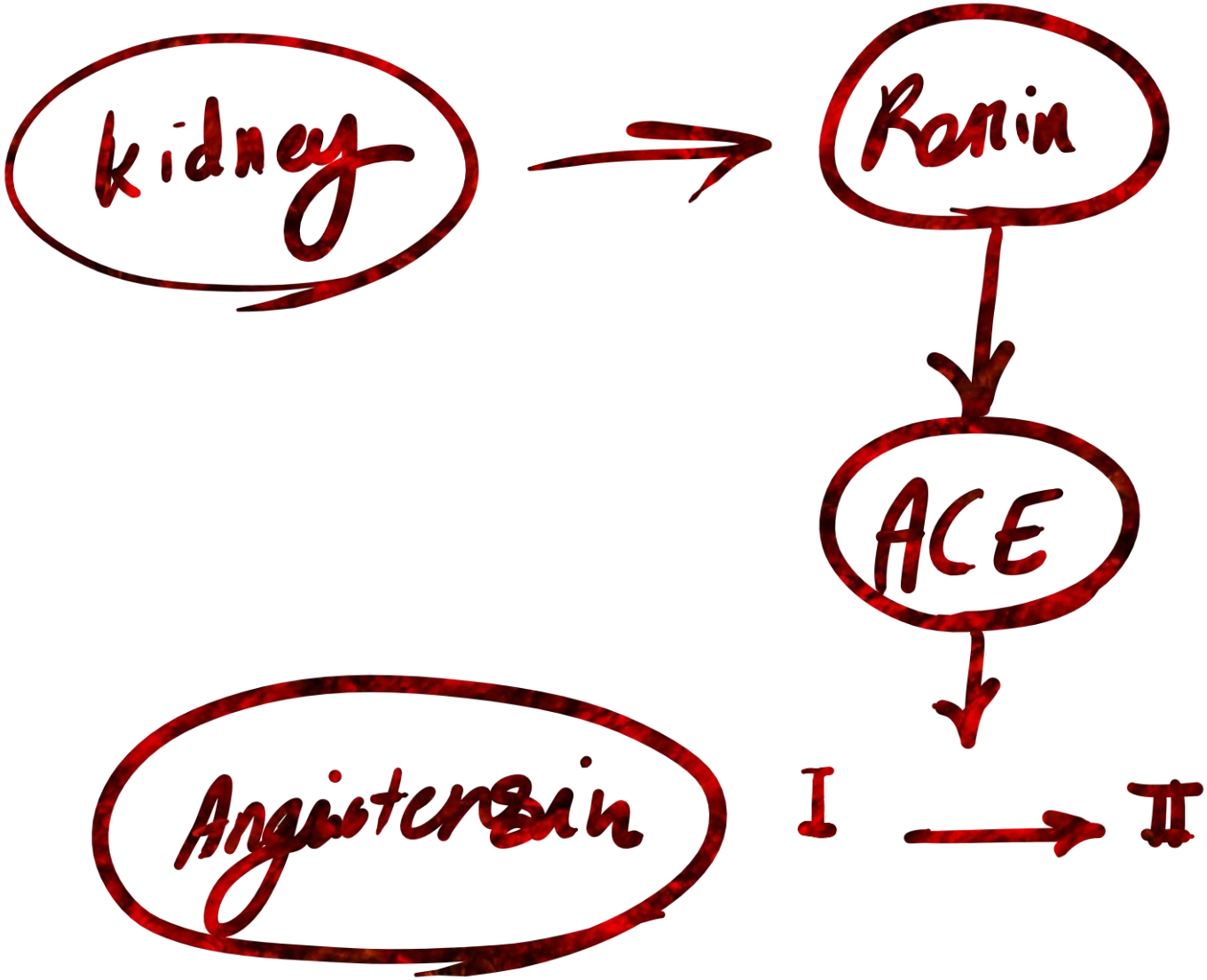
NSAIDs & ACEIs

01

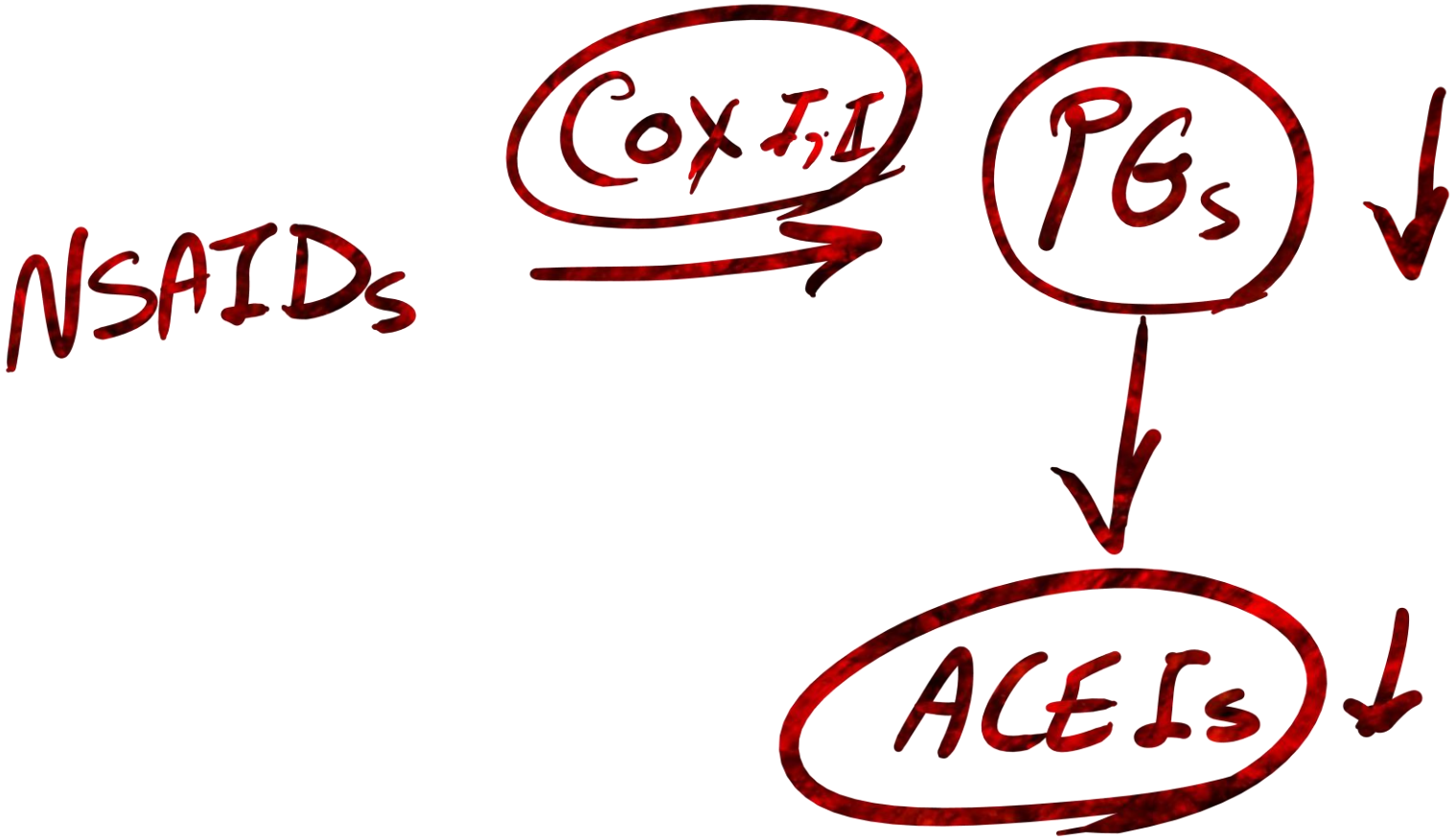
NSAIDs may attenuate ACEI action directly by inhibiting renal prostaglandin synthesis and indirectly by interfering with ACEI-induced prostaglandin production.

02

Prostaglandins are even more important in mediating the actions of ACEIs in hypertensive patients who have low renin production.

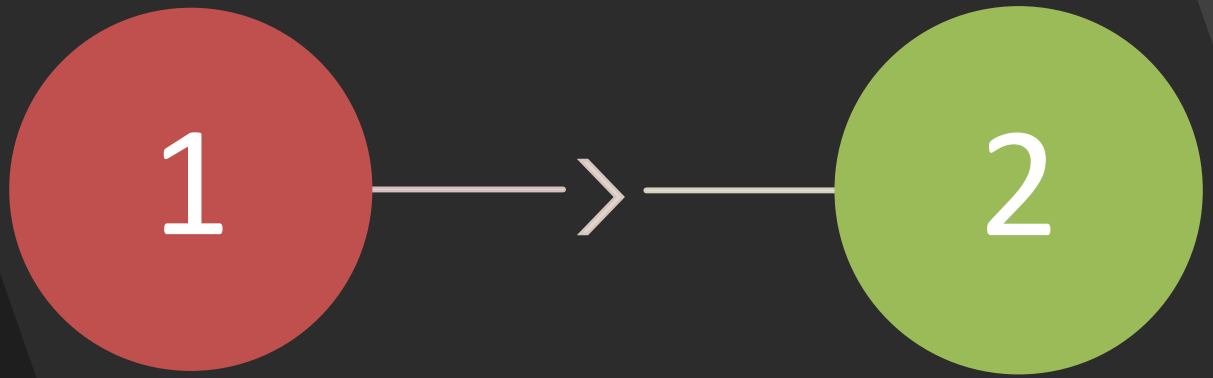

kidney
Renin
ACE
Angiotensin
I
II


Angio II
$Na^+ \uparrow$ + $H_2O \uparrow$
$K^+ \downarrow$


NSAIDs
COX I, II
PGs
ACEIs


ACEIs ↓
HTN ↑

NSAIDs & ACEIs



Patients who are elderly, have severe congestive heart failure or have low concentrations of renin.

In these cases, use of acetaminophen is most appropriate.

NSAIDs & ß-blockers

- ß-blockers reduce blood pressure by a number of mechanisms, including an increase in circulating prostaglandins.

NSAIDs & ß-blockers

- One meta-analysis showed that **indomethacin** was associated with a statistically significant increase in blood pressure, whereas aspirin and ibuprofen had negligible effects.

To what degree do NSAIDs inhibit antihypertensive action?

- One meta-analysis has shown that, on average, NSAIDs raise mean blood pressure by 5 millimeters of mercury.

To what degree do NSAIDs inhibit antihypertensive action?

- Other studies have shown that an increase of 5 mm Hg in diastolic pressure over a number of years increases the risk of stroke by 67 percent and coronary artery disease by 15 percent

What period of NSAID administration is required to affect antihypertensives?

- An assessment of the agents used in dentistry shows that the minimum time for an effect has been 8 days for ibuprofen, **7** days for flurbiprofen and seven days for naproxen

NSAIDs and lithium

01

The effective dose is close to the toxic dose.

02

Side effect: Polyuria, Polydipsia, Nausea, Vomiting, Diarrhea, Tremors and Sedation.

03

NSAIDs increase the serum concentration of lithium and thereby predispose the patient to toxicity.

NSAIDs and lithium

- The mechanism is not known with certainty, but it may involve inhibition of renal prostaglandins that leads to increased lithium reabsorption, which is relevant because lithium is excreted primarily by the kidneys

NSAIDs and lithium

01

Indomethacin is reported to have the greatest effect, whereas Aspirin do not alter lithium levels.

02

In the interim, it may be best to prescribe NSAIDs for only very short durations, if at all, to patients taking lithium, especially if they are elderly

NSAIDs and Anticoagulants.

01

Upper gastrointestinal bleeding is the most common serious adverse event associated with NSAIDs

02

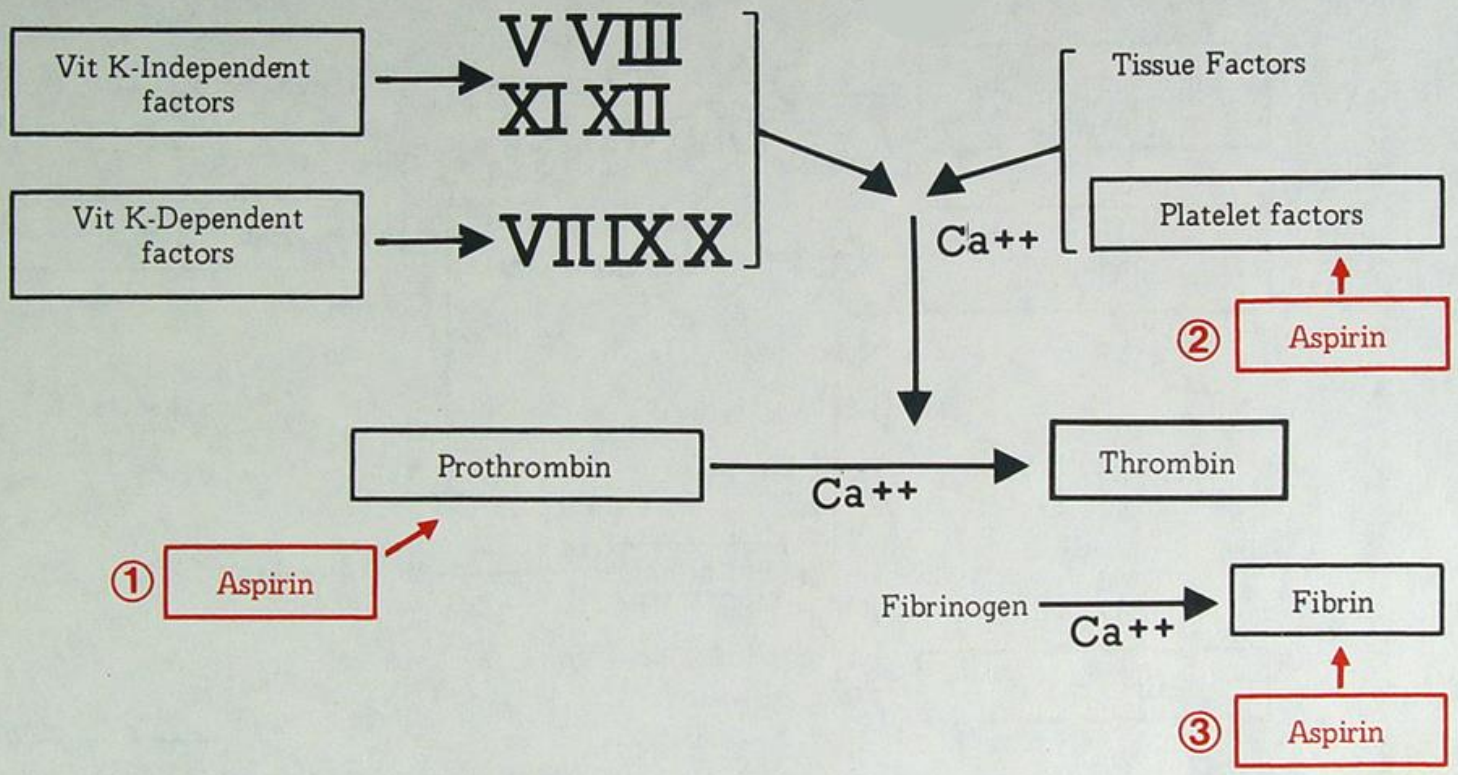
when an NSAID is combined with an anticoagulant such as warfarin (Coumadin), there clearly is potential for excessive bleeding.

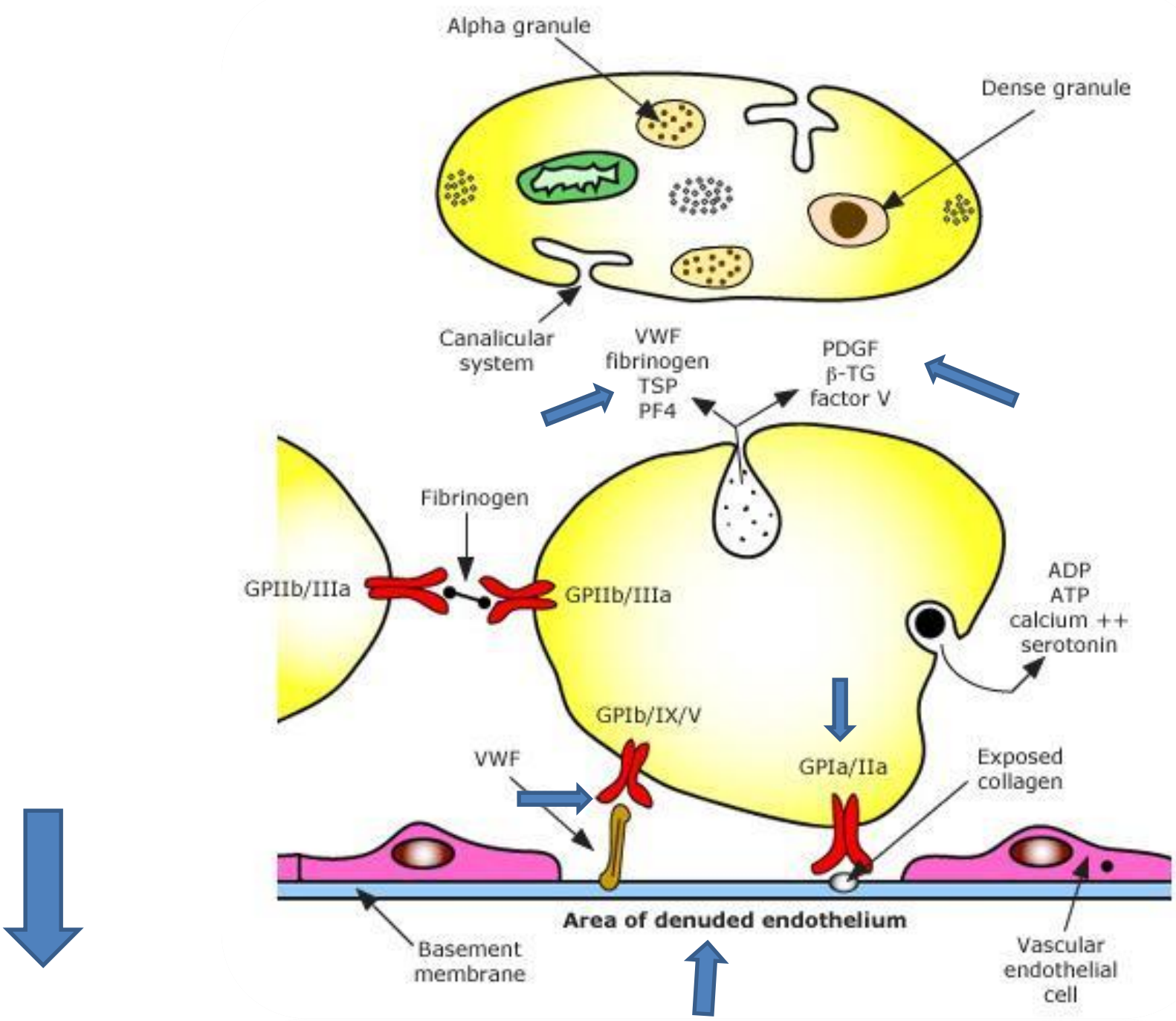
NSAIDs and Anticoagulants

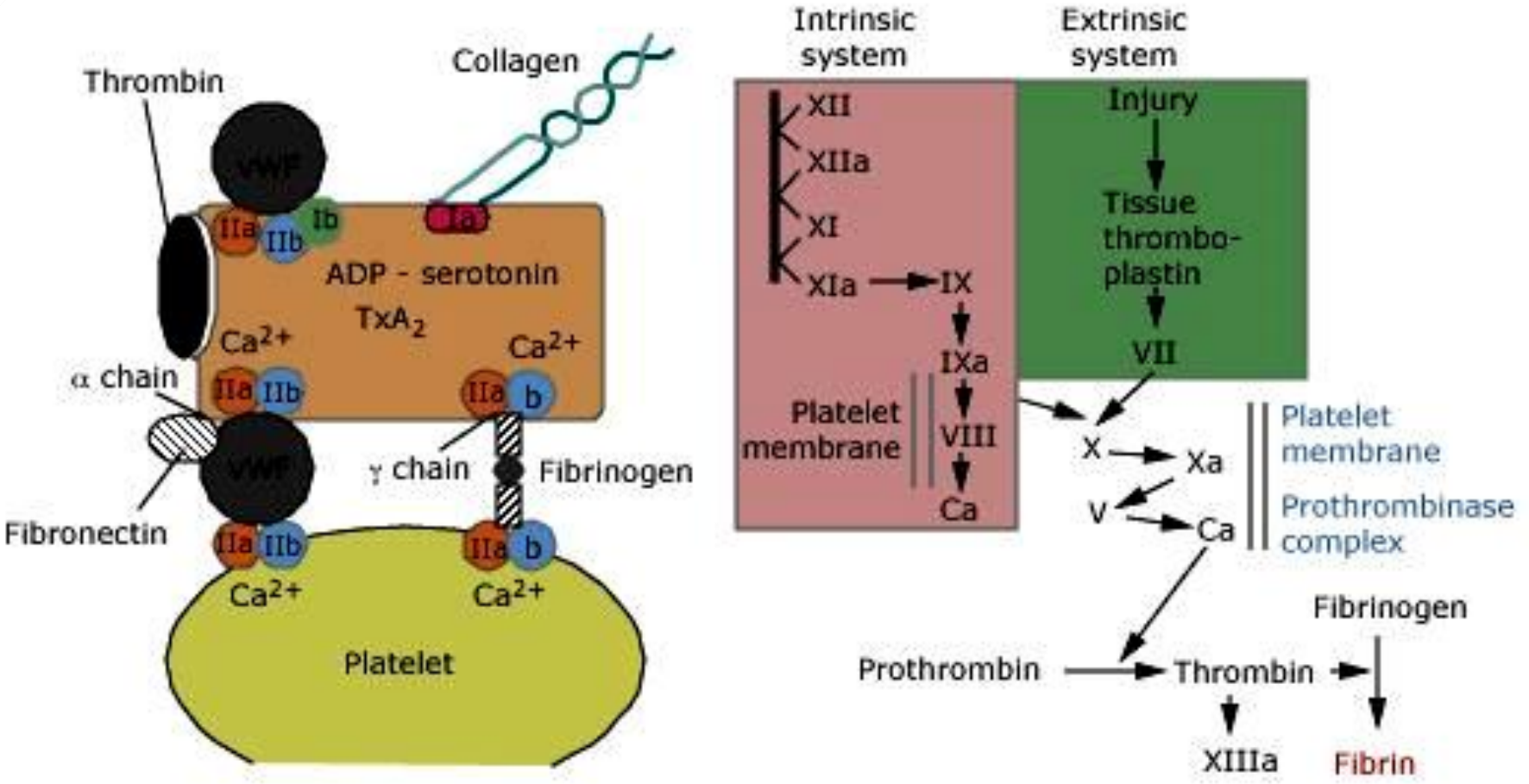
- Moreover, higher dosages of aspirin (for example, more than 3 grams per day) can lead to reduced levels of prothrombin, which will further exacerbate the bleeding problems already mentioned.

Potentiation of Coumarin Anticoagulants by Aspirin

B. Mechanism Of Aspirin-induced Anticoagulation




Alpha granule
Dense granule
Canalicular system
VWF
fibrinogen
TSP
PF4
PDGF
β-TG
factor V
Fibrinogen
GPIIb/IIIa
GPIIb/IIIa
ADP
ATP
calcium ++
serotonin
GPIb/IX/V
VWF
GPIa/IIa
Exposed collagen
Area of denuded endothelium
Basement membrane
Vascular endothelial cell


Thrombin
Collagen
VWF
IIa
IIb
Ib
Ia
ADP - serotonin
TxA2
Ca2+
Ca2+
α chain
IIa
IIb
IIa
b
VWF
γ chain
Fibrinogen
Fibronectin
IIa
IIb
IIa
b
Ca2+
Ca2+
Platelet
Intrinsic system
Extrinsic system
XII
XIIa
XI
XIa
IX
IXa
VIII
Ca
Platelet membrane
Injury
Tissue thrombo-plastin
VII
X
Xa
V
Ca
Platelet membrane
Prothrombinase complex
Fibrinogen
Prothrombin
Thrombin
XIIIa
Fibrin

NSAIDs and Anticoagulants

- In particular, high-dose aspirin, mefenamic acid and ketoprofen should be avoided in patients receiving warfarin.

NSAIDs and Methotrexate.

01

NSAIDs reduce the renal clearance of methotrexate, which can lead to toxicity when the latter drug is used in much higher dosages,

02

renal failure and pancytopenia can result

NSAIDs and Ethanol.

01

Both ethanol and NSAIDs, particularly aspirin, damage the gastric mucosal barrier

02

It has been recommended to separate the ingestion of aspirin and alcohol by at least 12 hours.

NSAIDs and Digoxin.

01

Digoxin a drug used for the treatment of congestive heart disease, has a low therapeutic index

02

It is cleared primarily by the kidneys, and a potential interaction may occur owing to the NSAIDs' ability to reduce renal function.

Acetaminophen

Acetaminophen

- Acute overdoses of acetaminophen typically, 15 g or more in an adult frequently result in hepatotoxicity

Acetaminophen

- Acetaminophen antidote= *N-acetylcysteine*

Acetaminophen and Alcohol.

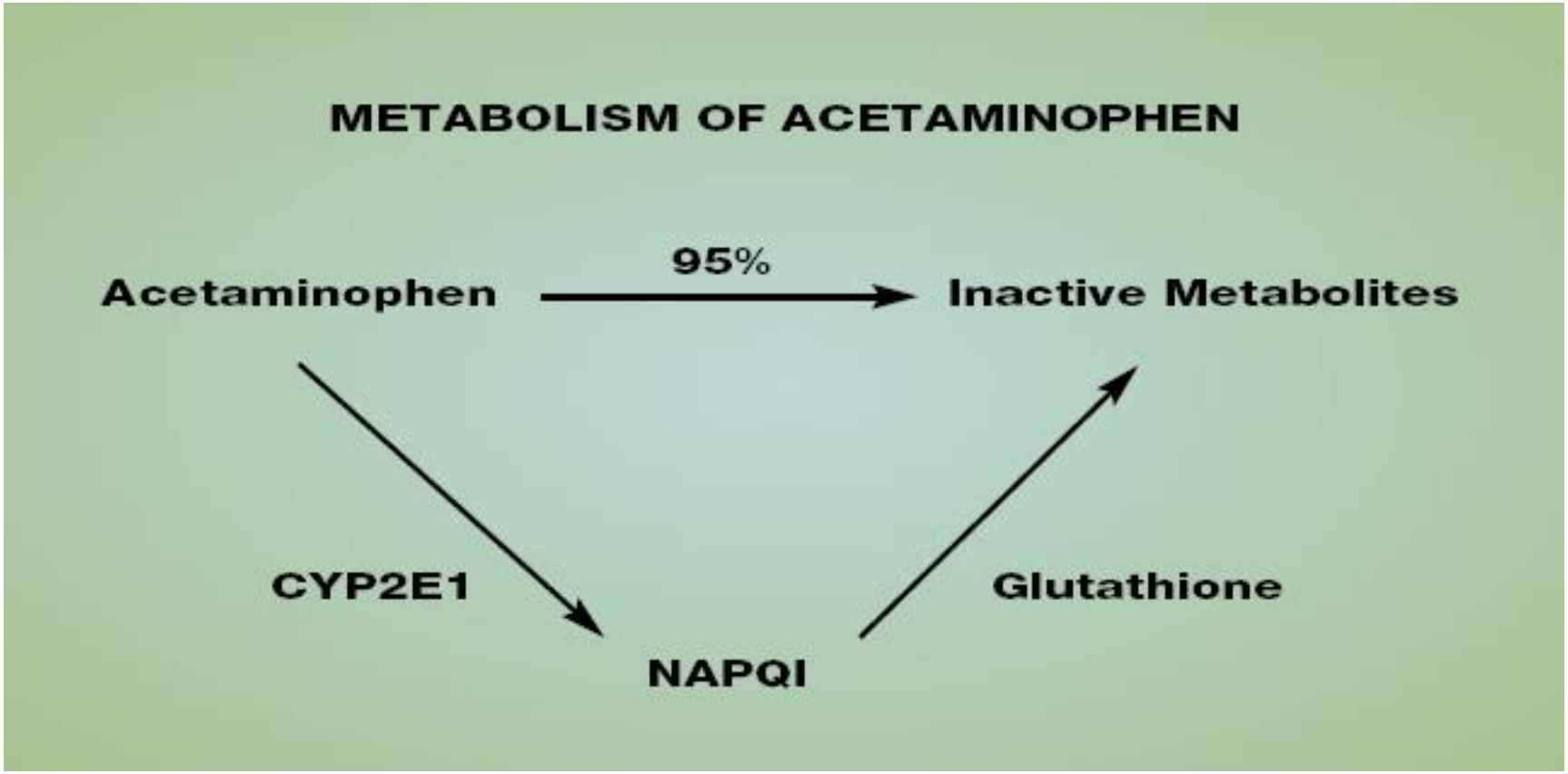
01

The interaction with alcohol arises because the enzyme CYP2E1 is also involved in the metabolism of Ethanol

02

limit the maximum daily dose of acetaminophen to only 2 g in patients with alcoholism to avoid additional liver damage that is already present due to alcohol

Simplified summary of the metabolism of acetaminophen. The hepatotoxic potential of *N-acetyl-p-benzoquinone imine,* or NAPQI, is prevented by rapid breakdown by glutathione



Ester Local Anesthetics With Sulfonamide Antibiotics

- Procaine with sulfamethoxazole
  - Procaine is used infrequently; the procaine metabolite *p-amino benzoic acid* may transiently reduce sulfonamide antibiotic efficacy.

Amide Local Anesthetics With Inhibitors of Metabolism

Lidocaine with cimetidine

lidocaine with propranolol

Inhibition of local anesthetic metabolism will have little effect on peak plasma levels of anesthetic when given as a single injection.

Antihistamines and LA

- Diphenhydramine and Chlorpheniramine impaired lidocaine metabolism in rodent hepatocytes

Local Anesthetics With Opioid Sedation

- Mepivacaine with meperidine
  - Sedation with opioids may increase the risk of local anesthetic toxicity, particularly with children; local anesthetic dose should be reduced.

Local Anesthetic-Induced Methemoglobinemia

- Prilocaine with dapsone
  - Methemoglobinemia usually results from prilocaine dosing in excess of MRD; increased risk may be possible when similar oxidizing drugs are administered.

Mycins and LA

- Four doses of erythromycin ethylsuccinate 600 mg given over two days modestly increased the half-life of an intravenous lidocaine infusion from 2.2 to 2.8 hours.

Vasoconstrictor Interaction

Antidepressants

Classification	Generic name	Trade name
MAOI	Isocarboxazid	Marplan
TCAs	Amitriptyline, Protriptyline Imipramie	Amitril Sinequan Adapin
SSRIs	Fluoxetine	Prozac

MAO +High Level Tyramine
Food & Beverages
(Cheese , Fish ,Beer,Red wine,Liver..)
Hypertensive Crisis,Intracranial bleeding
Excessive Fever , death

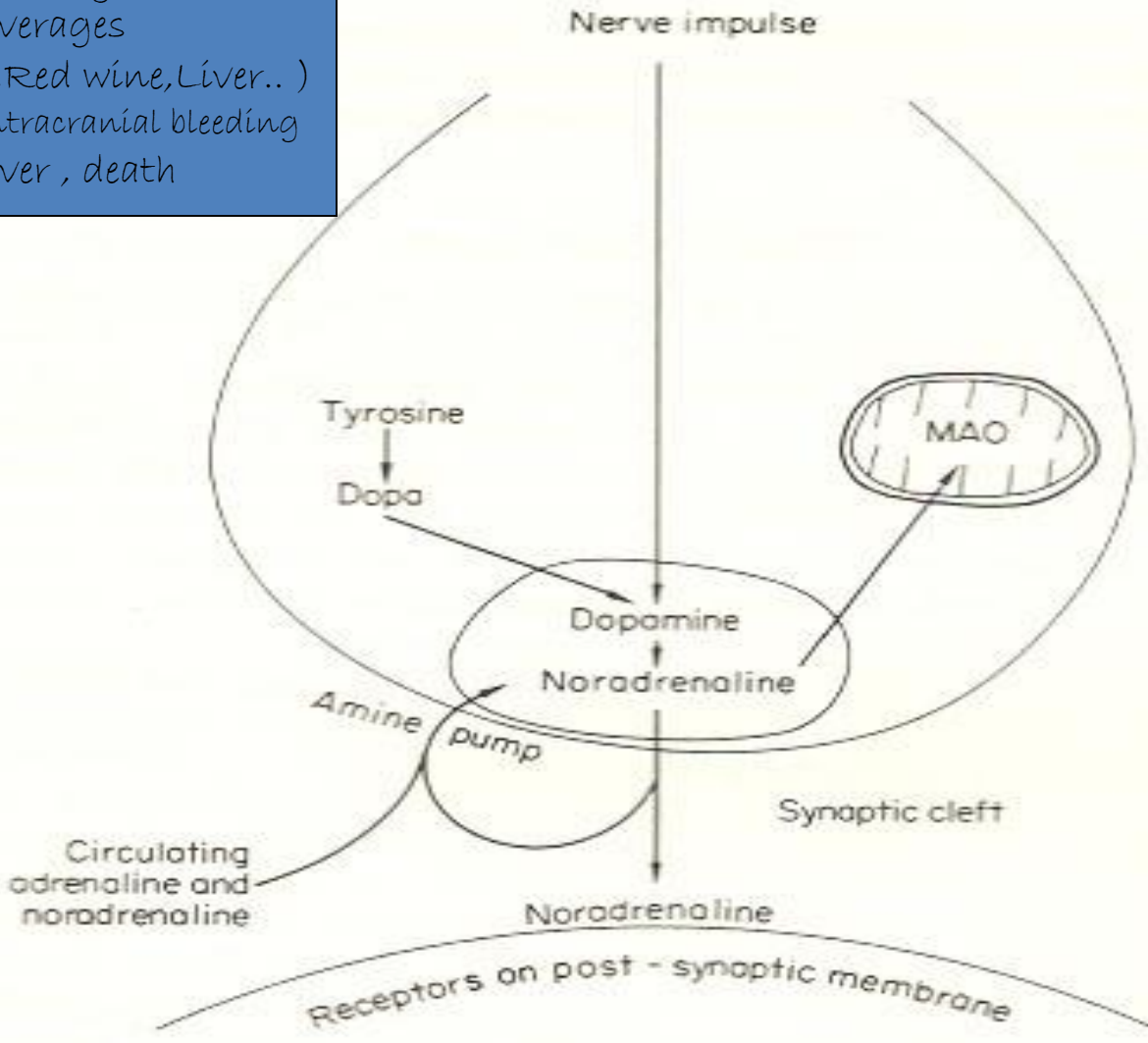


Fig. 3.4 The synthesis, release, and removal of noradrenaline from

TRICYCLIC ANTIDEPRESSANTS (imipramine, amitriptyline, doxepin)

The tricyclic antidepressants block the active reuptake of biogenic amine neurotransmitters by nerve terminals from which they were released.

Tricyclic antidepressants also block muscarinic and α1-adrenergic receptors and directly depress the myocardium.

Adrenergic vasoconstrictors are subject to the same uptake process

TRICYCLIC ANTIDEPRESSANTS (imipramine, amitriptyline, doxepin)

The potentiation of epinephrine by imipramine and related tricyclic antidepressants administered acutely is about threefold

Greater potentiating, six to eightfold, occur with norepinephrine

TRICYCLIC ANTIDEPRESSANTS (imipramine, amitriptyline, doxepin)

- Epinephrine should be used cautiously; use of levonordefrin should be avoided

Vasoconstrictor with nonselective β-adrenoceptor antagonist (epinephrine with propranolol)

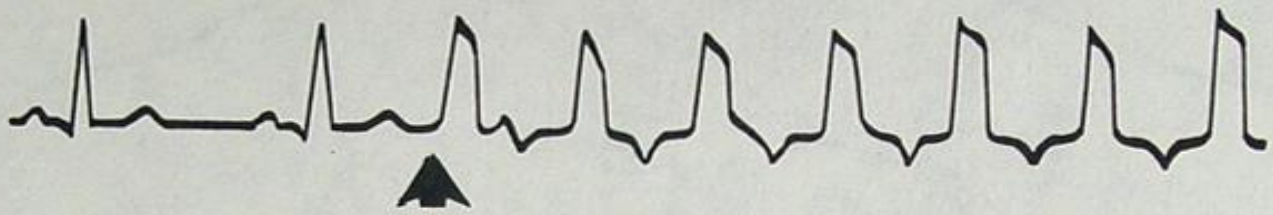
- Hypertensive and/or cardiac reactions are possible. Vasoconstrictor should be used cautiously; blood pressure and heart rate should be monitored.

Vasoconstrictor with general anesthetic (epinephrine with halothane)

- Increased possibility of cardiac arrhythmias exists with some general anesthetics. Consultation with anesthesiologist is recommended.

Sensitization Of The Myocardium By Combination Of Halothane And Epinephrine

Lead II



Onset Ventricular Tachycardia from Halothane and Epinephrine

Normal EKG

Premature Contraction from Halothane and Epinephrine

VT
PVC

Vasoconstrictor with cocaine (epinephrine with cocaine)

- Arrhythmias and hypertensive responses possible. Concurrent use should be avoided

Vasoconstrictor with antipsychotic or other α-adrenoceptor blocker (epinephrine with chlorpromazine)

- Hypotension resulting from overdose of antipsychotic agent may be worsened. Vasoconstrictor should be used cautiously.

Antipsychotic agent
(have as a side effect the ability to block α-adrenergic receptors and cause orthostatic hypotension.)

- Chlorpromazine
- Thioridazine
- Risperidone

α-adrenergic Blocker

- Prazosin
- Phenoxybenzamine

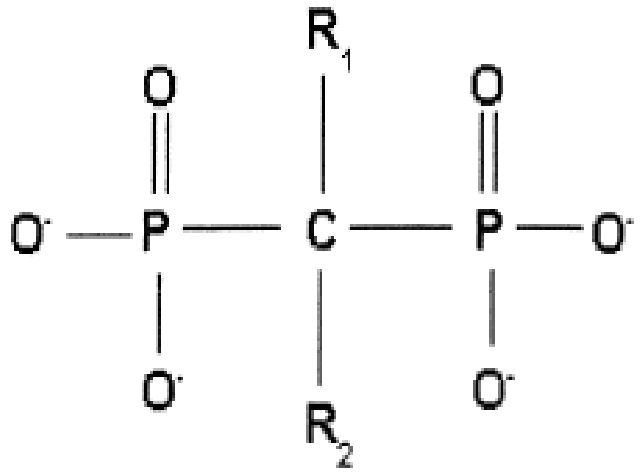
Vasoconstrictor with thyroid hormone (epinephrine with thyroxine)

- Summation of effects possible when thyroid hormones are used in excess. Vasoconstrictor should be used cautiously if signs of hyperthyroidism are present

Bisphosphonates

Osteoprotic Women Drugs

- HRT (Estrogen)
- Supplement Ca
- Pulsed Rh PTH (Triparatide)
- BPs
- Melatonin
- Vit K
- Vit B12
- GH



- P-C-P band is extremely resistant to hydrolysis
- BPs has high affinity for hydroxyapatite
- Negatively charged *O* band to Calcium

BPs

- Non Nitrogenous BPs (NNBPs)

- Nitrogenous Bisphosphonates(NBPs)

NNBPs

- First generation drugs
- Cause apoptosis of the osteoclasts
- Etidronates, colodronates, tiludronate

NBPs

- Second generation drugs
- Inhibit mevalonate Pathway(HMG-CoA reductase pathway) specially at the site of the enzyme Farnesyl diphosphate synthetase(FPPS)
- Inhibition of FPPS lead to decrease level of the Intracellular proteins such as Ras, Rho, Rac which are responsible for the cytoskeleton attachment
- Inhibit the ruffled border of the osteoclasts
- Pamidronate, Alendronate , Ibandronate, Residronate, Zoledronate

NBPs

- Osteoprosis
- Skeletal Metastasis
- Multiple Myeloma
- Padjet Disease
- Osteogenesis Imperfecta

NBPs

- 3% resorped from gut
- 1% resorped in Bone
- 12 to 13 year half life

Bone turn over marker

- Deoxypyridoline- Urine(DPD)
- Type I Collagen cross-linked N telopeptide (NTX)-urine or serum
- Type collagen cross-linked C-telopeptide (CTX)- urine or serum
- ALP

CTX

- CTX<100
- 100<X<150
- X>150

3 significant risk factor in Osteoprotic patients

- Decreased level of Mg
- Decreased level of Vit D
- Increased Level of PTH

ALP

- When the kidney function is normal:

- 50 % of ALP is derived from liver and 50% derived from Bone

Anxiolytic, Analgesic, Hypnotic

PHARMACOLOGY OF DRUGS IN AMBULATORY ANESTHESIA

Fear Can be Visible


EXTERNAL FACTORS
Attitude of dentist
Environment
Sensory Stimuli
Culture
Time
BEHAVIOUR
Expectation
Genetic Influence
Emotional State
Prior Conditioning
Past Experience
INTERNAL FACTORS

Level of Consciousness

General Anesthesia

Deep Sedation

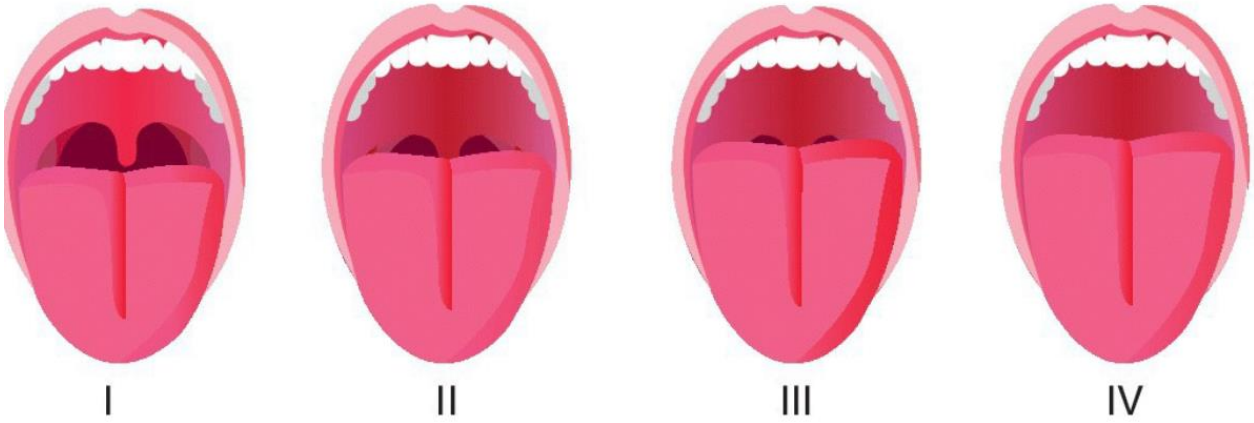
Conscious Sedation

ASA Classification	Definition	Examples, including but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild disease only without substantive functional limitations, Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled diabetes/hypertension, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled diabetes/hypertension, COPD, Morbid obesity (BMI ≥ 40), active hepatitis, alcohol dependence or abuse, implanted pace maker, regular dialysis, history (>3months)of MI, CVA, TIA or stents
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but are not limited to): recent (<3 months) MI, CVA, TIA or Stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but are not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel, multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purpose.	

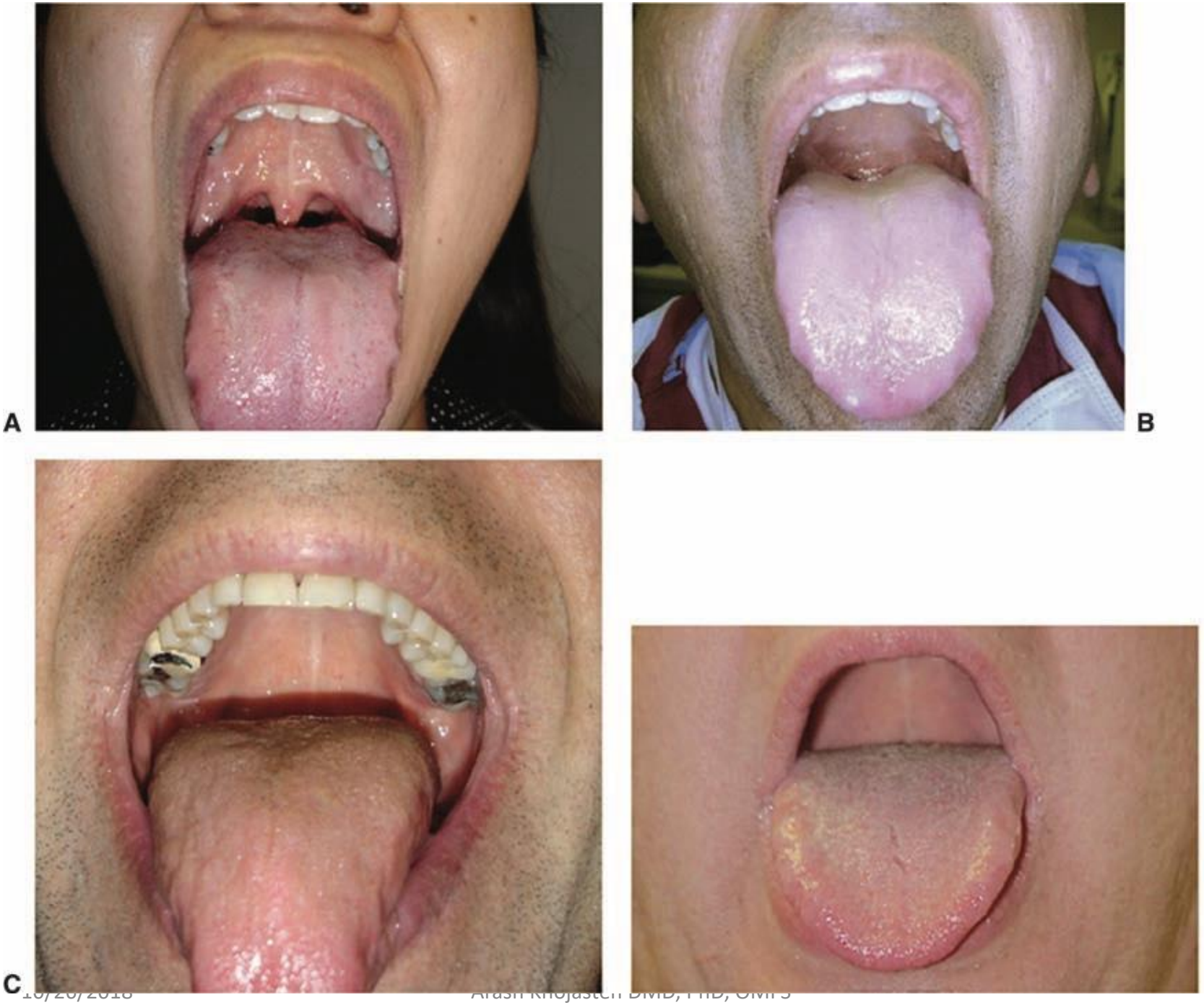
Blood pressure	ASA class
Less than 140/90	I
From 140/90 – 159/94	II
From 160/95 – 199/114	III
Over 200/115	IV

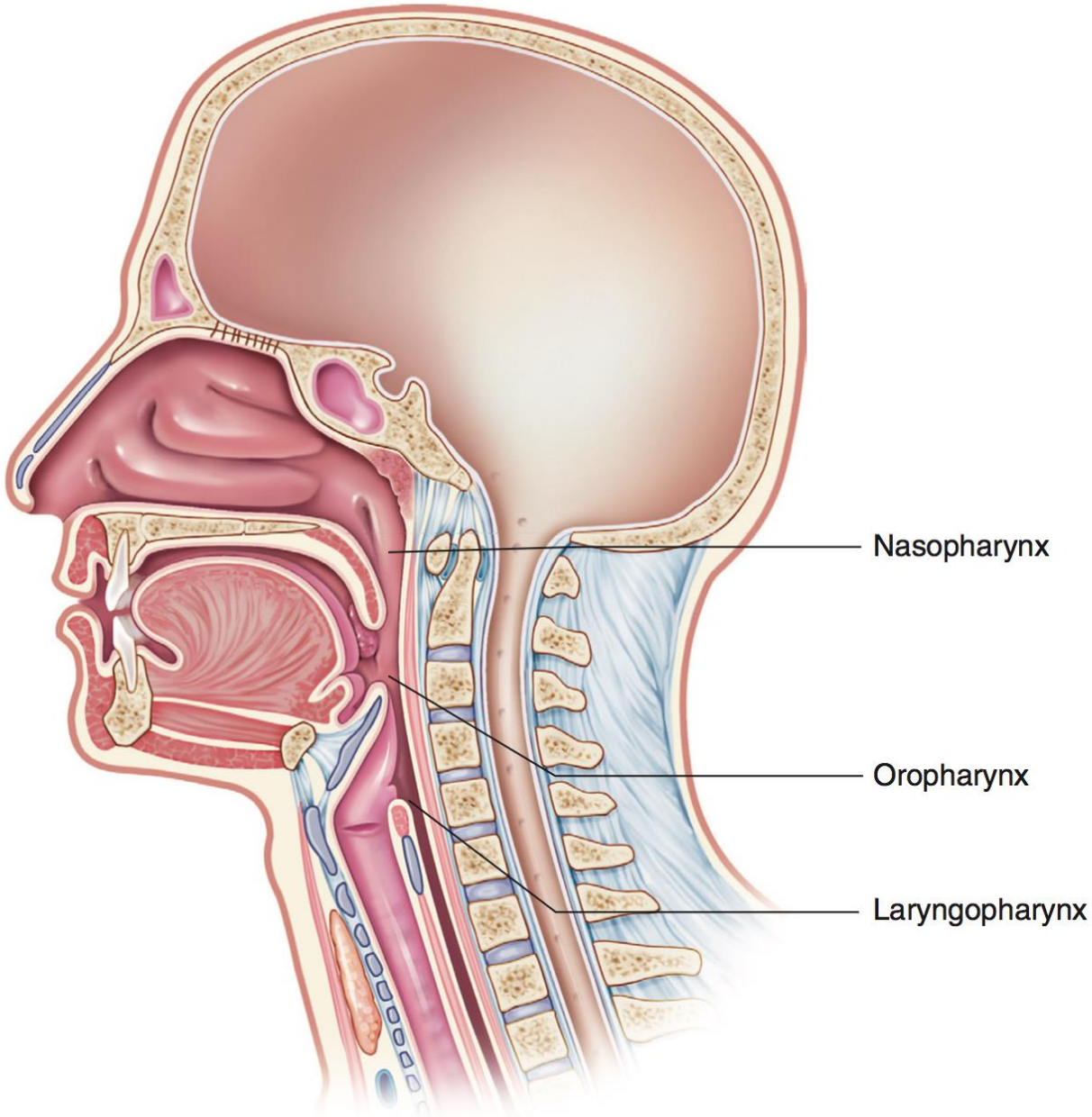
BMI	Classification
<18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Overweight
30.0–34.9	Class I obesity
35.0–39.9	Class II obesity
≥40.0	Class III obesity

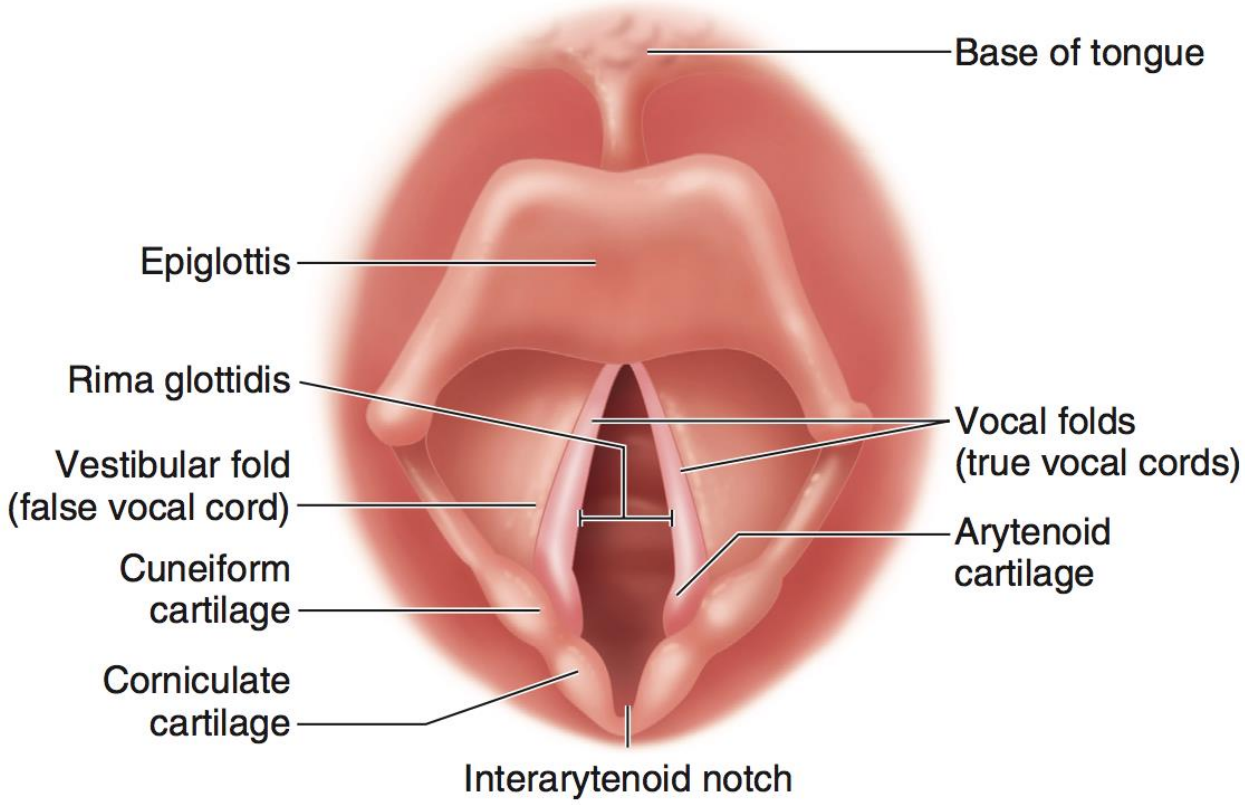
Mallampati Score

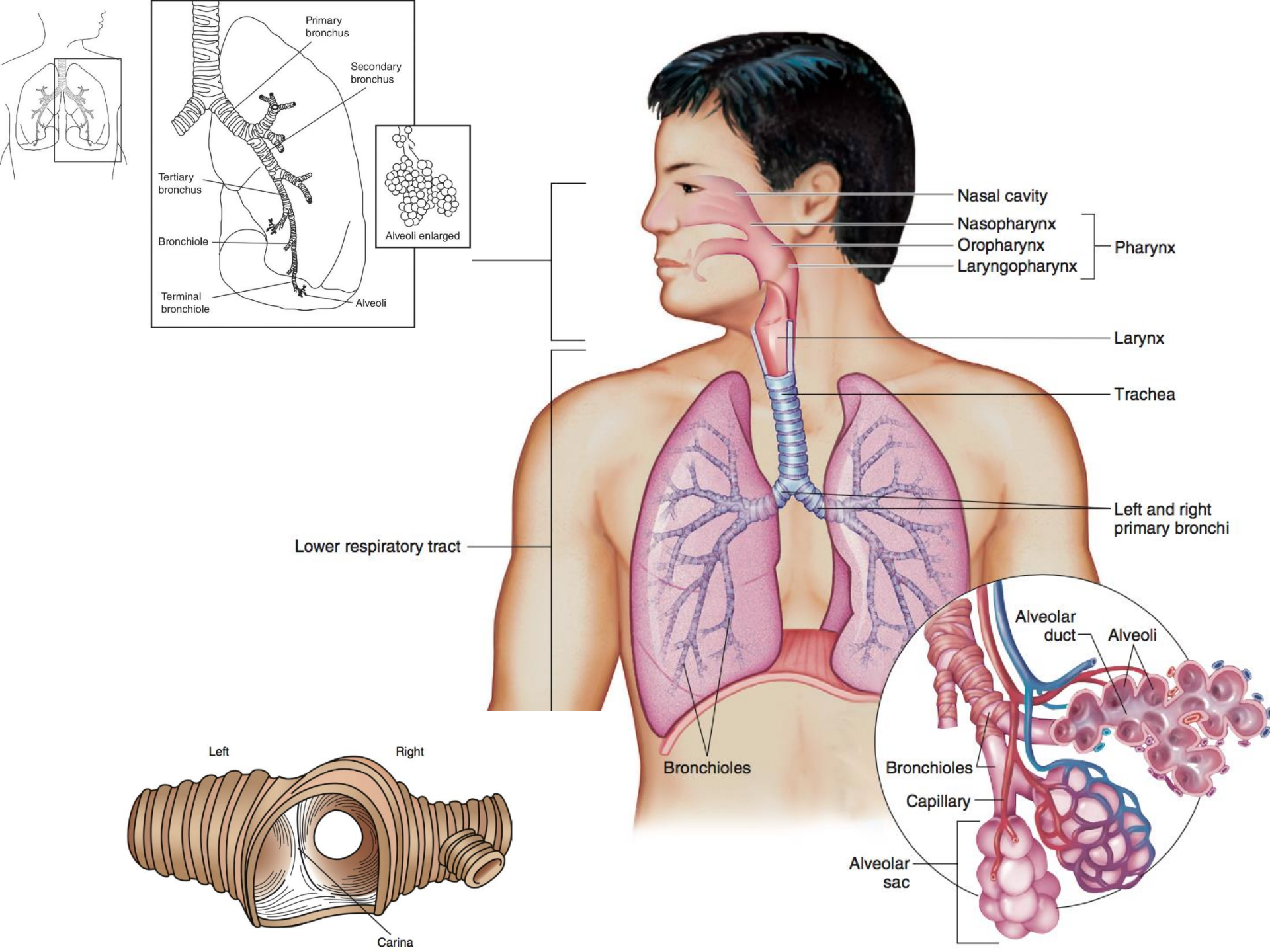


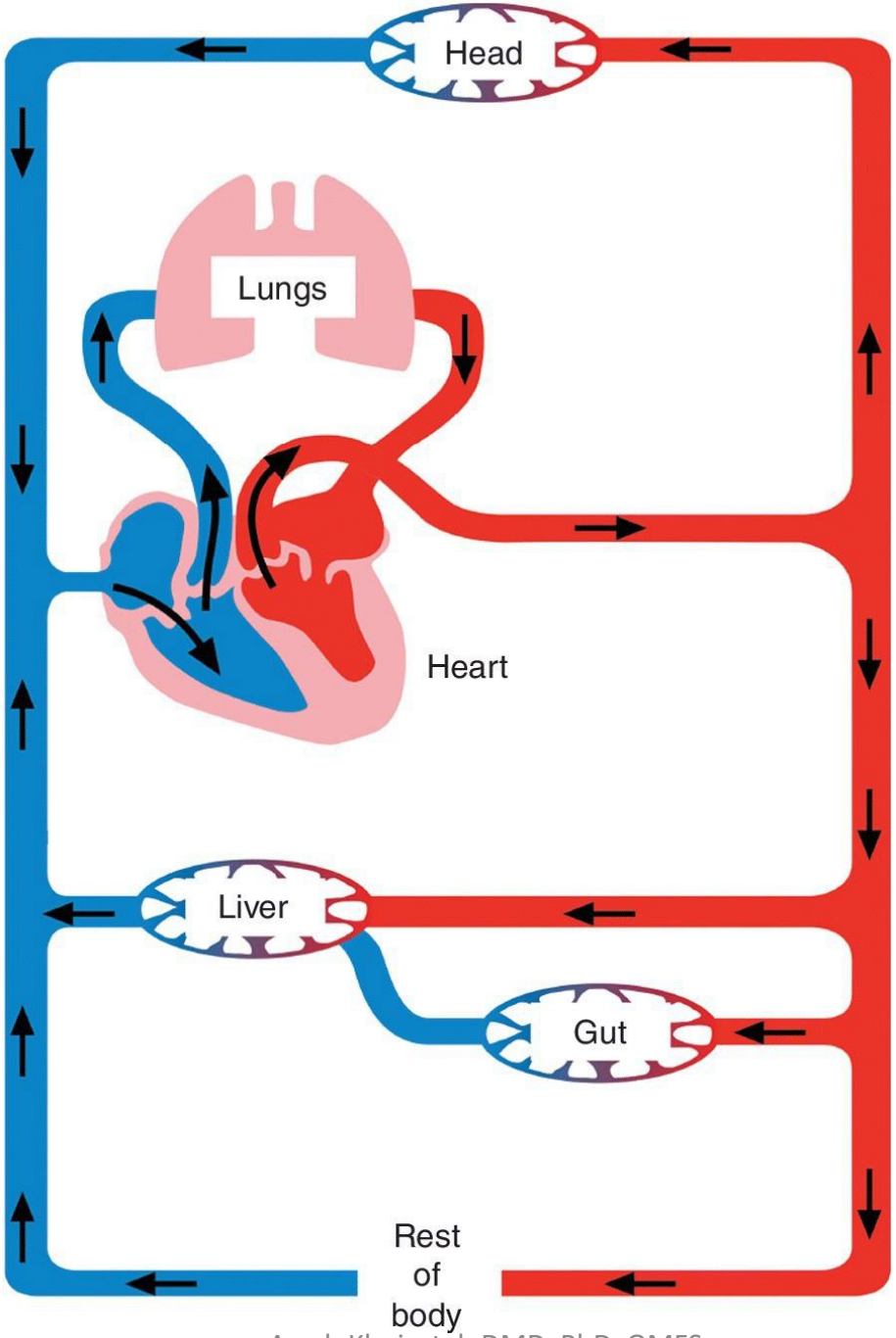
Classification	Description
I	Soft palate, uvula, fauces, pillars visible
II	Soft palate, uvula, fauces visible
III	Soft palate, base of uvula visible
IV	Only hard palate visible

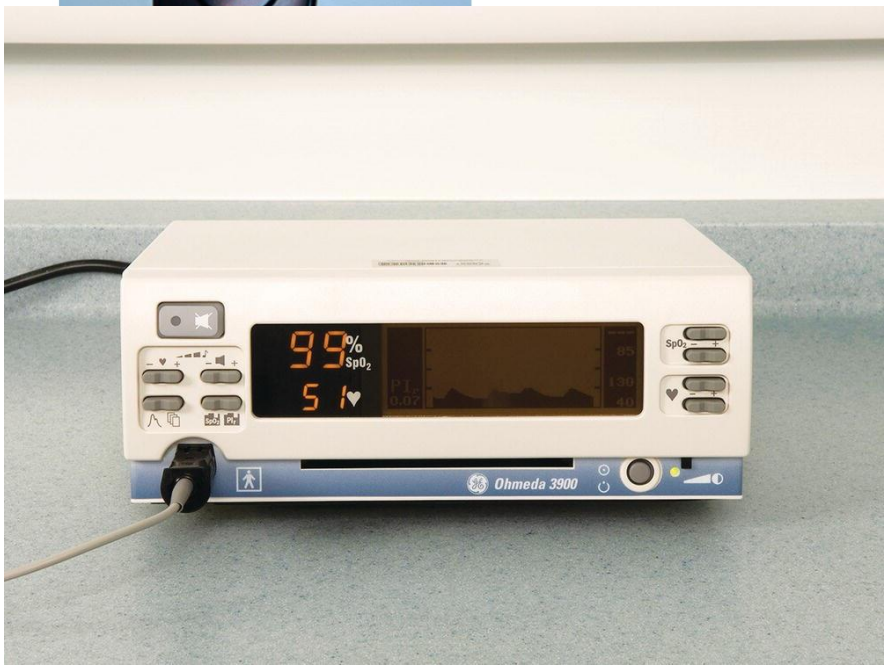

A
B
C
D

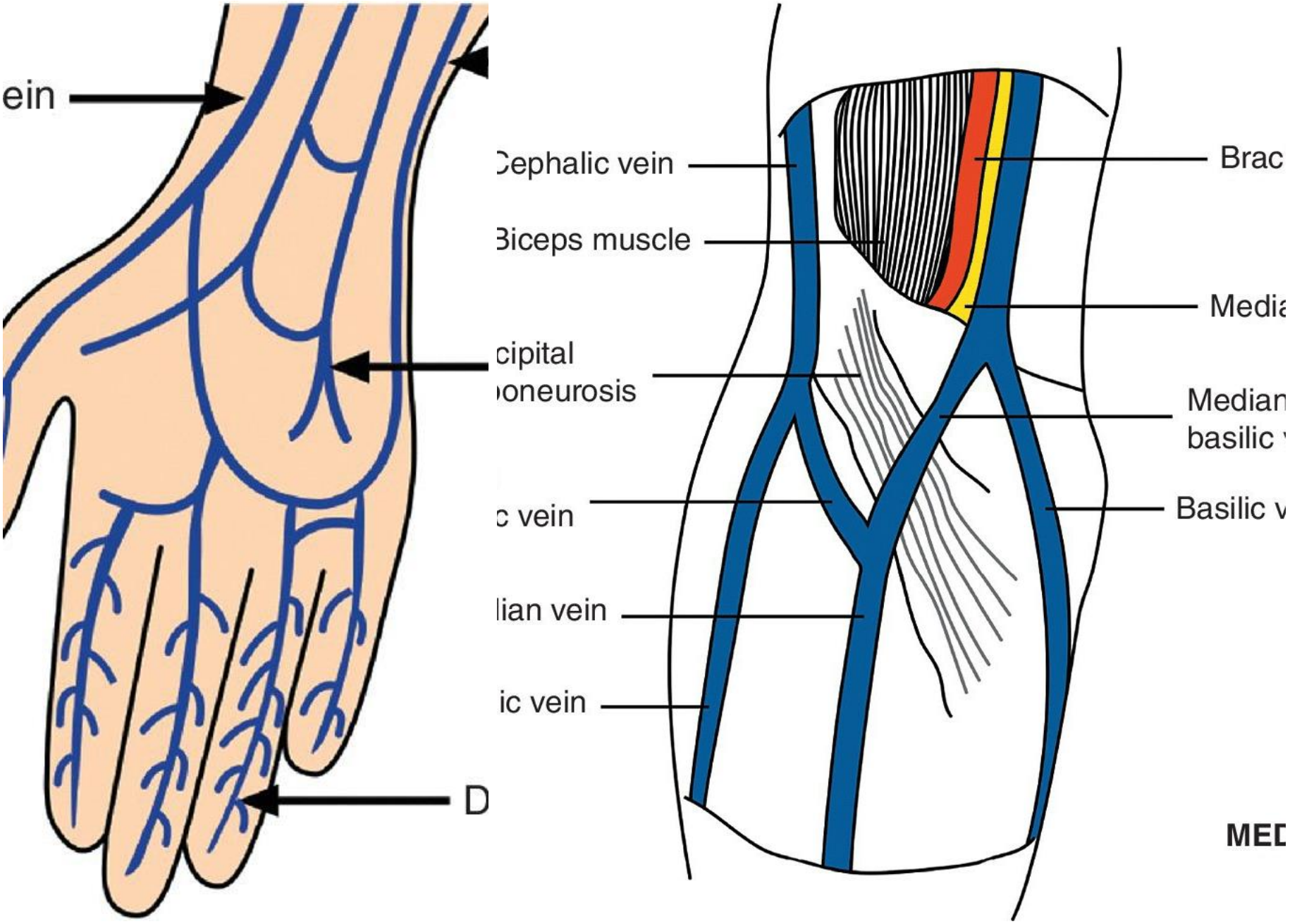

Nasopharynx
Oropharynx
Laryngopharynx

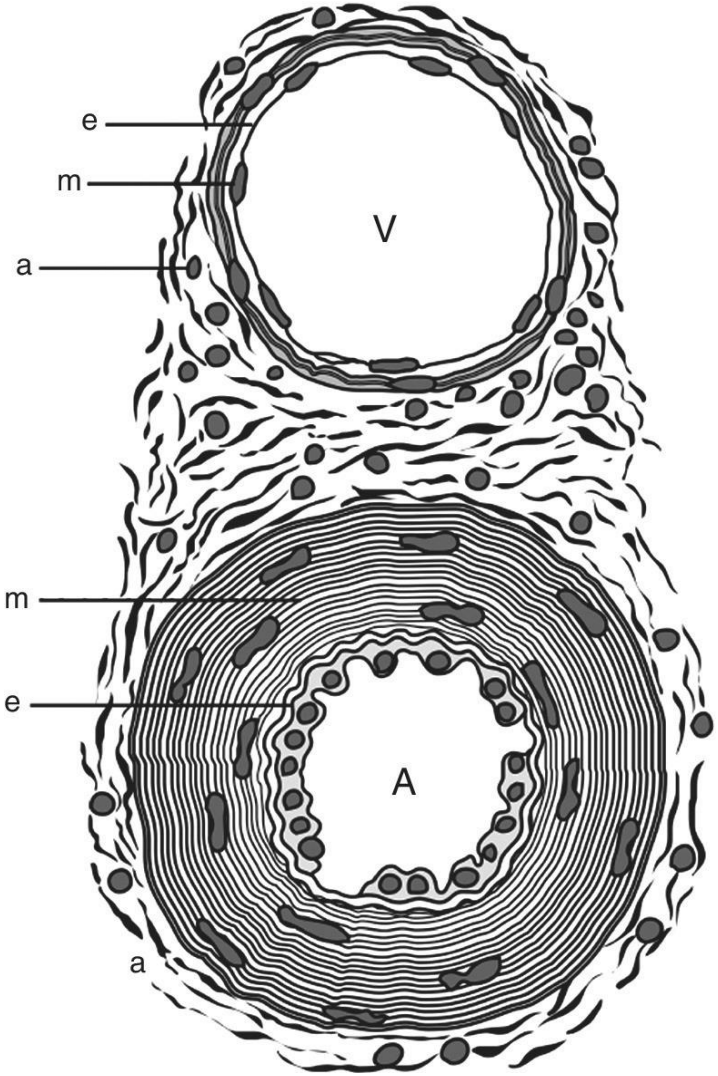

Base of tongue
Epiglottis
Rima glottidis
Vocal folds
(true vocal cords)
Vestibular fold
(false vocal cord)
Arytenoid
cartilage
Cuneiform
cartilage
Corniculate
cartilage
Interarytenoid notch

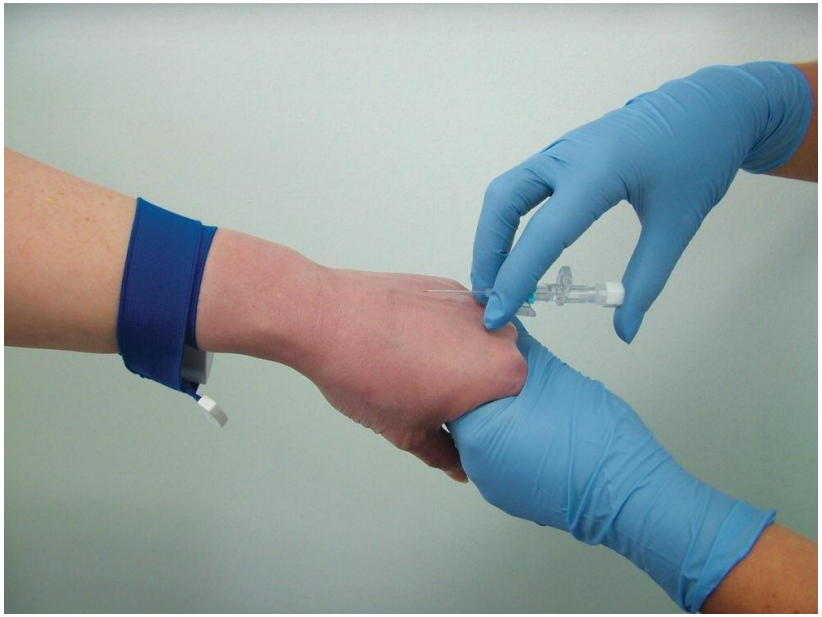

Primary bronchus
Secondary bronchus
Tertiary bronchus
Bronchiole
Terminal bronchiole
Alveoli
Alveoli enlarged
Nasal cavity
Nasopharynx
Oropharynx
Laryngopharynx
Pharynx
Larynx
Trachea
Left and right primary bronchi
Lower respiratory tract
Bronchioles
Alveolar duct
Alveoli
Bronchioles
Capillary
Alveolar sac
Left
Right
Carina

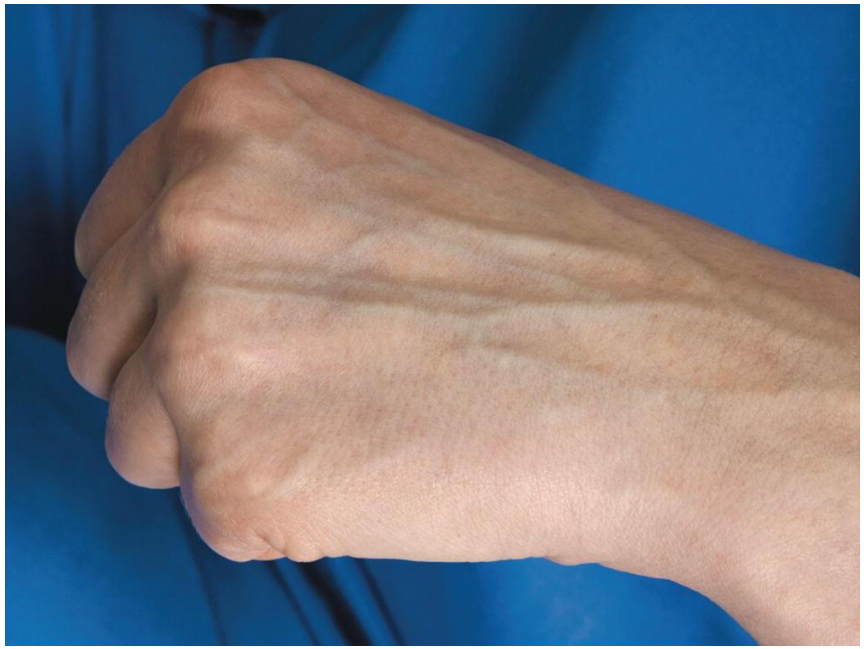

Head
Lungs
Heart
Liver
Gut
Rest
of
body

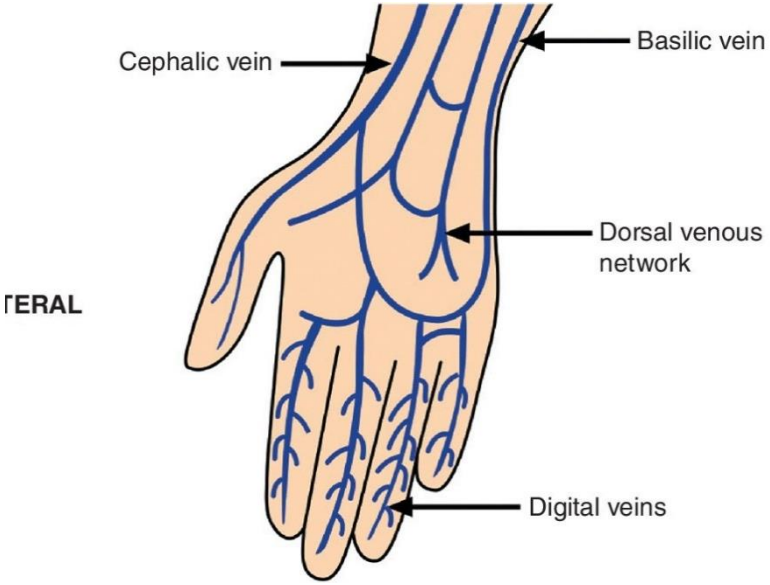

99 %
SpO2
51
Ohmeda 3900

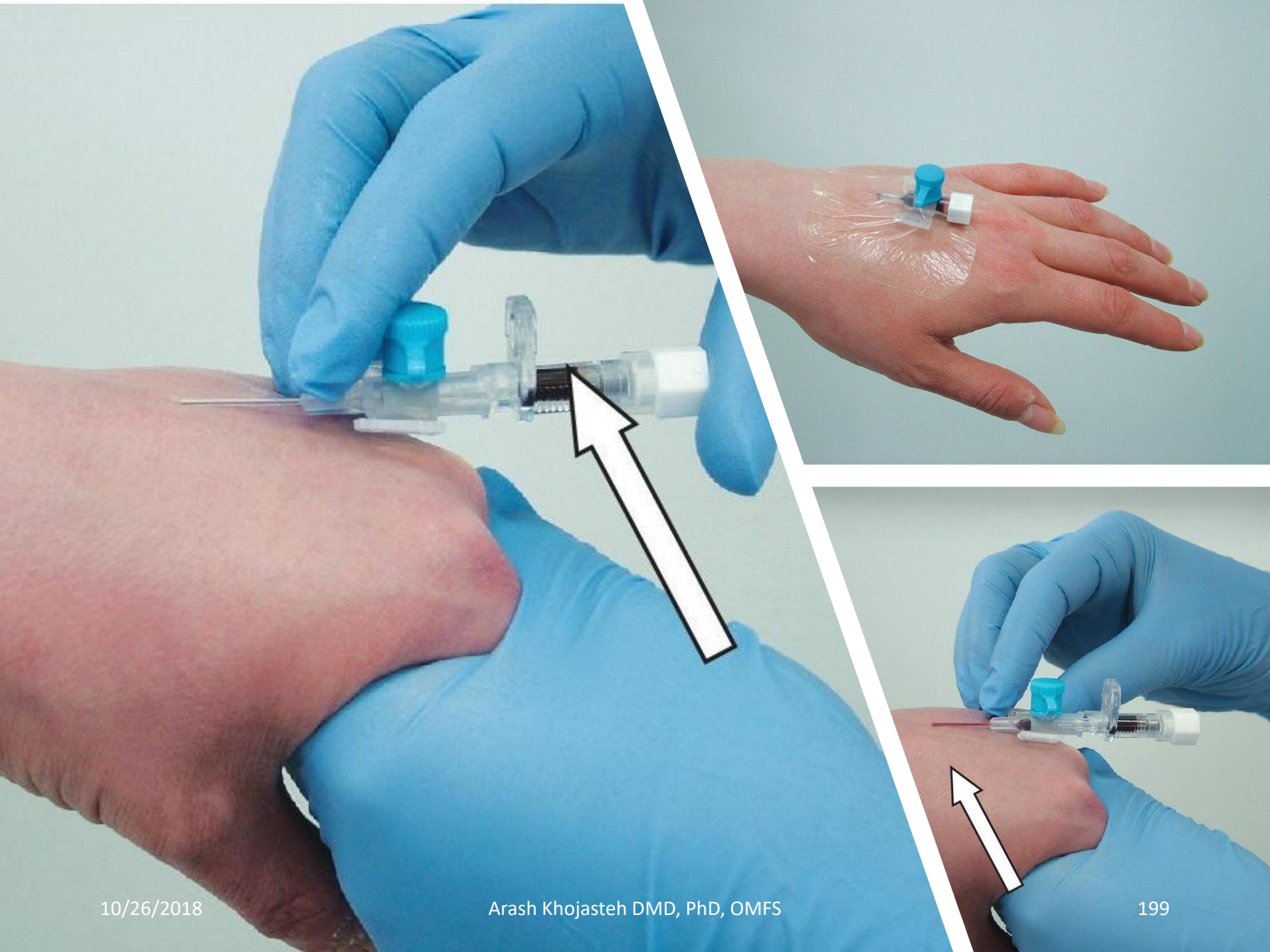

ein
Cephalic vein
Brac
Biceps muscle
Media
cipital
oneurosis
Median
basilic
c vein
Basilic v
lian vein
ic vein
D
MED

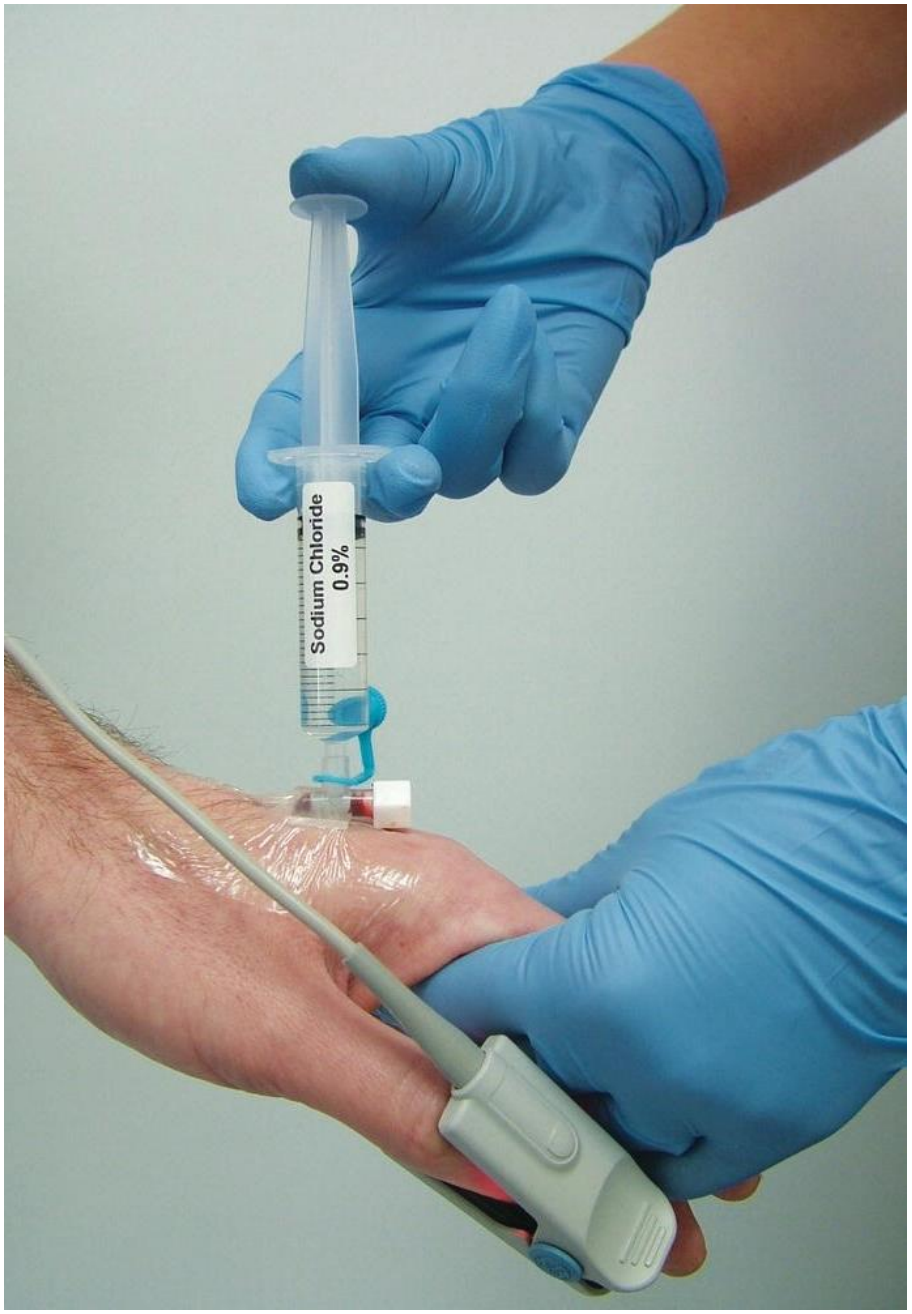

e
m
a
V
m
e
A
a

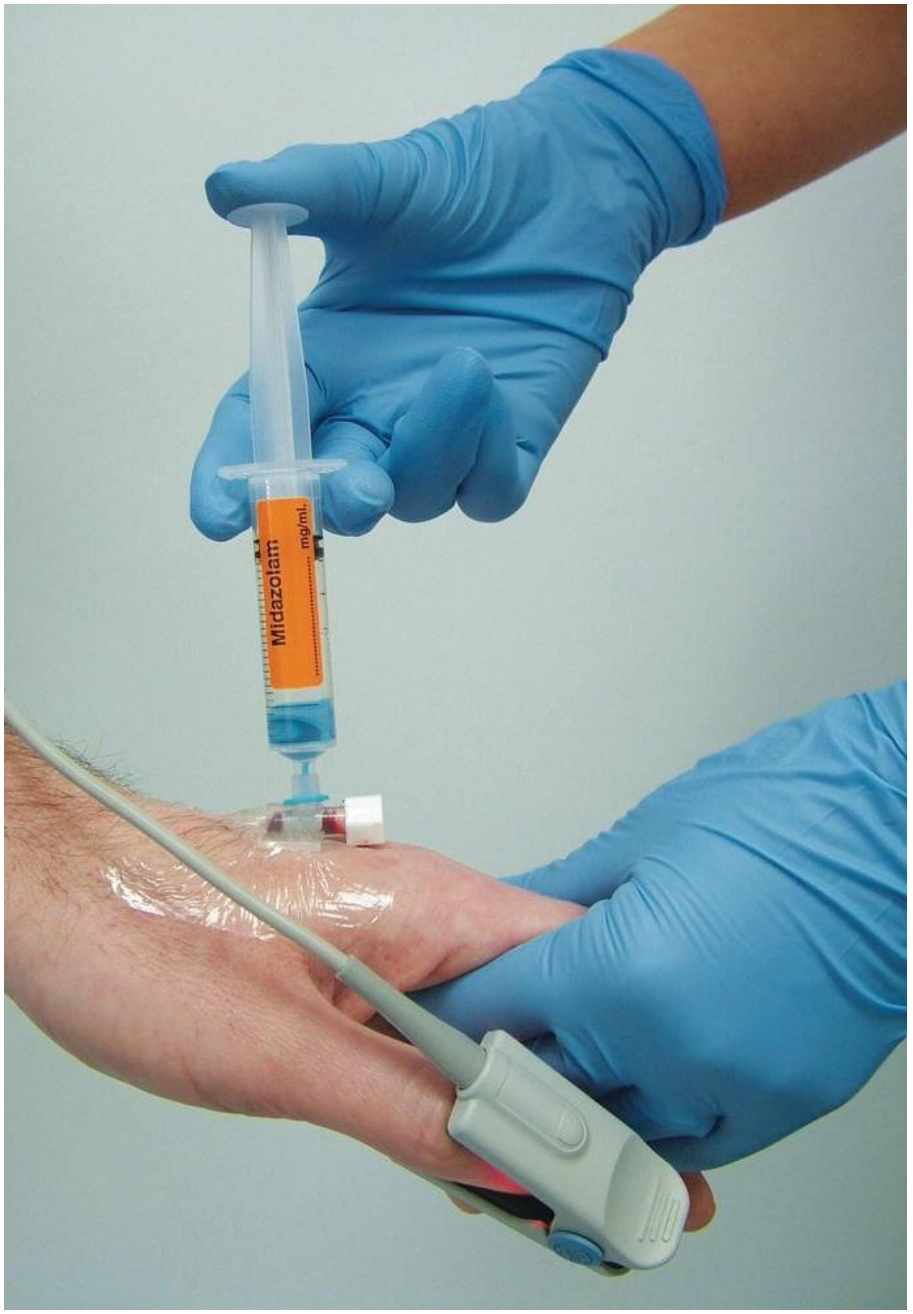


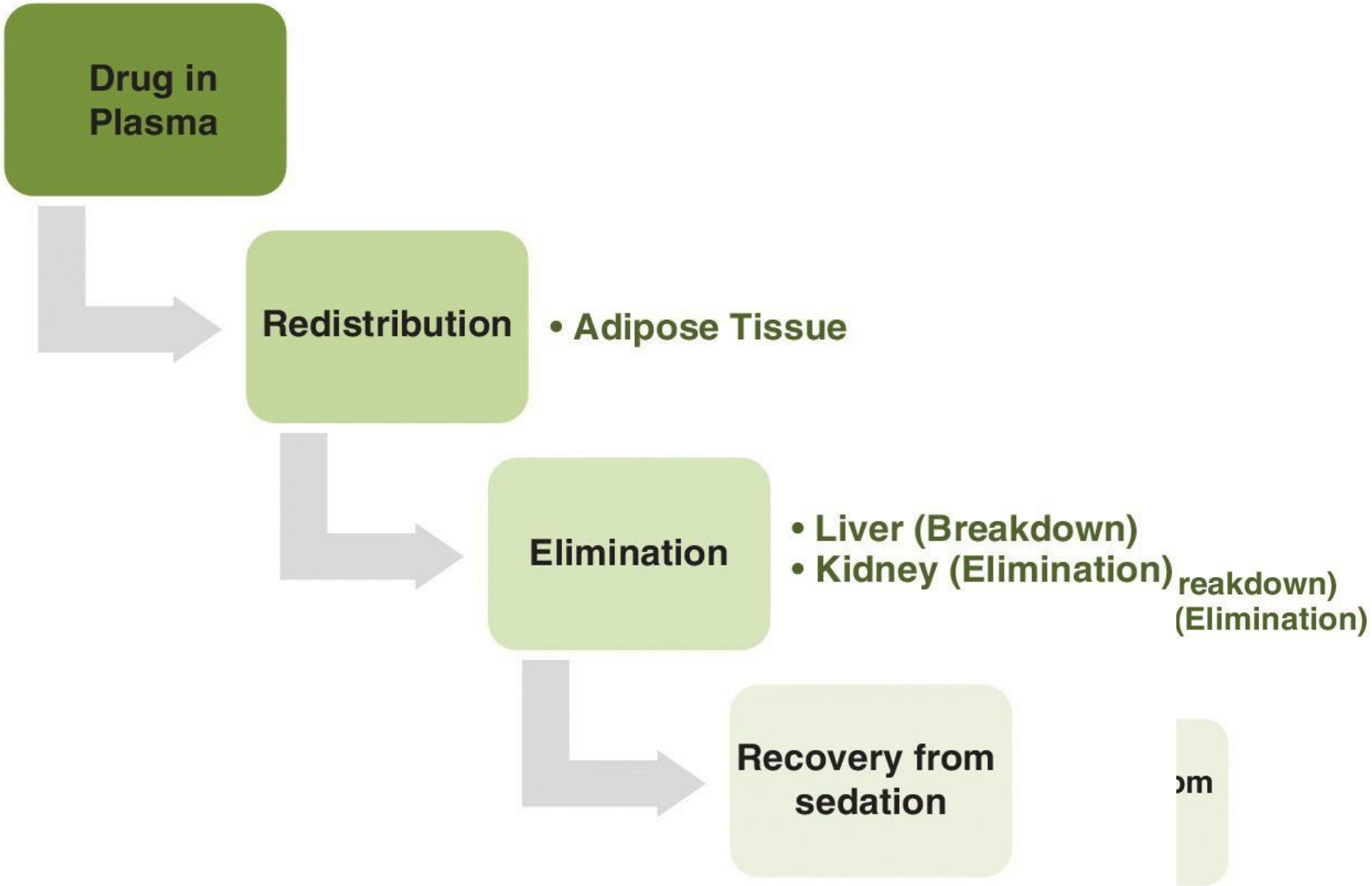



Cephalic vein
Basilic vein
Dorsal venous network
Digital veins




Sodium Chloride
0.9%


Midazolam
mg/mL


Drug in Plasma
Redistribution
• Adipose Tissue
Elimination
• Liver (Breakdown)
• Kidney (Elimination)
reakdown)
(Elimination)
Recovery from sedation
om

Drug	Potential interaction
Alcohol	enhanced sedative effect
Analgesics (opioid)	enhanced sedative effect
Antibacterials	erythromycin inhibits metabolism of midazolam
Antidepressants	enhanced sedative effect
Anti-epileptics	BZDs alter the effect of some antiepileptics e.g. phenytoin
Anti-histamines	enhanced sedative effect
Anti-hypertensives	enhanced hypotensive effect
Anti-psychotics	enhanced sedative effect
Anti-ulcer drugs	cimetidine inhibits metabolism of BZDs

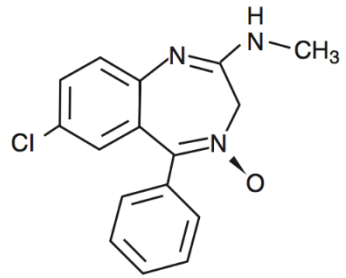
Sedation

IV Sedation

Inhalational Sedation

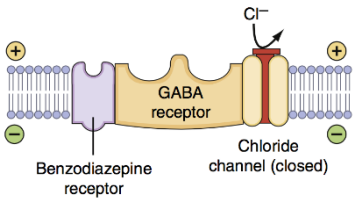
Oral and Intranasal

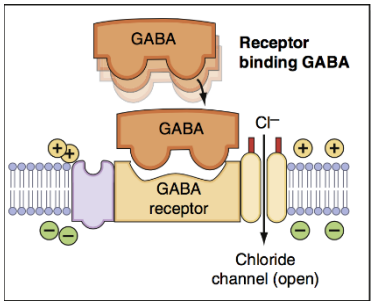
Banzodiazepine



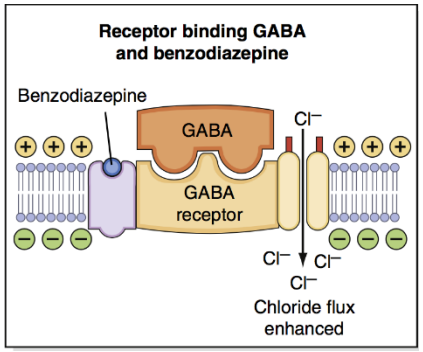
Chlordiazepoxide

- BZDs bind to benzodiazepine receptors presynaptically and postsynaptically, which facilitates the binding of GABA and potentiates its activity, causing CNS inhibition.
- Antidot: Flumazeni

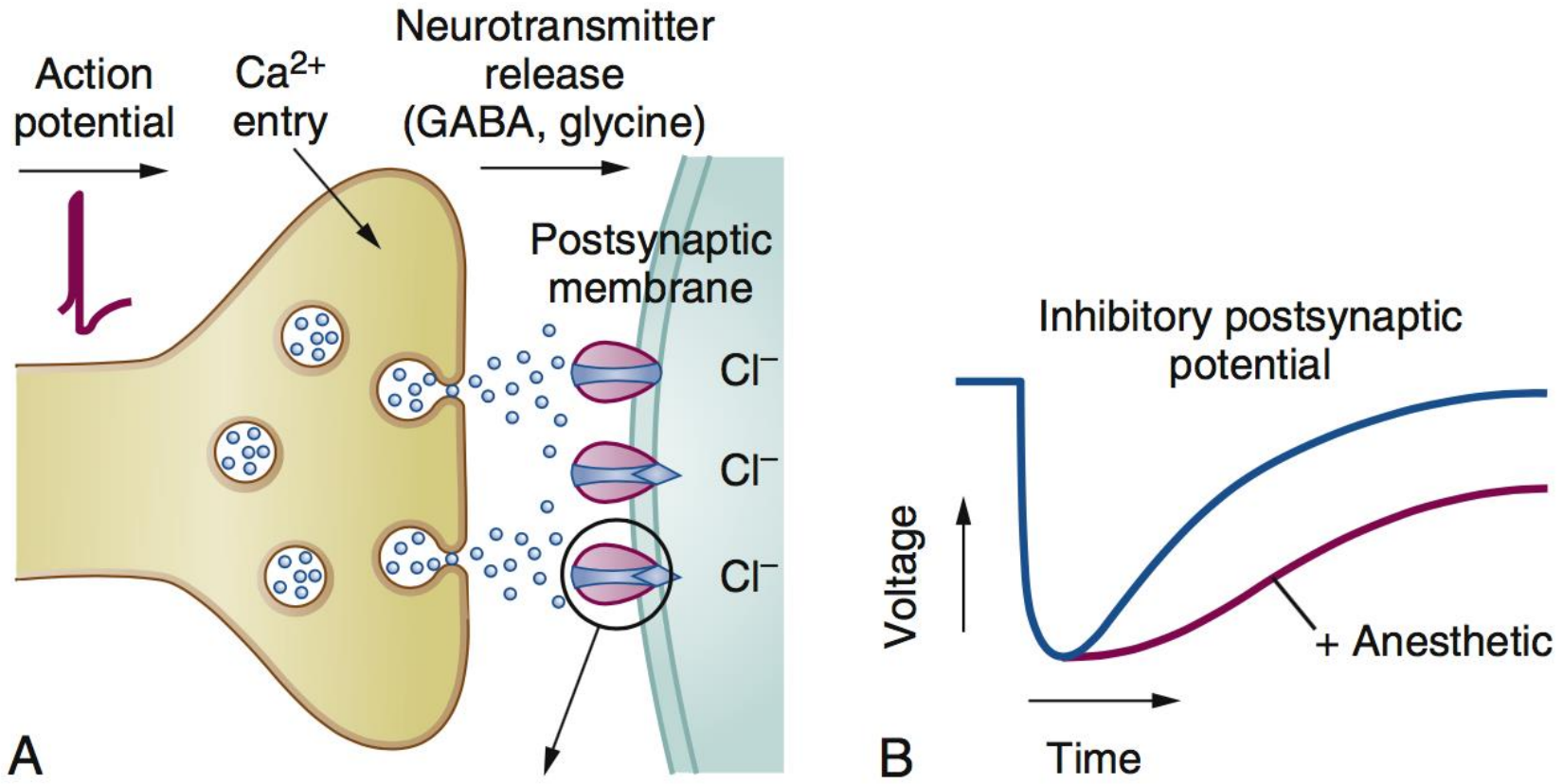


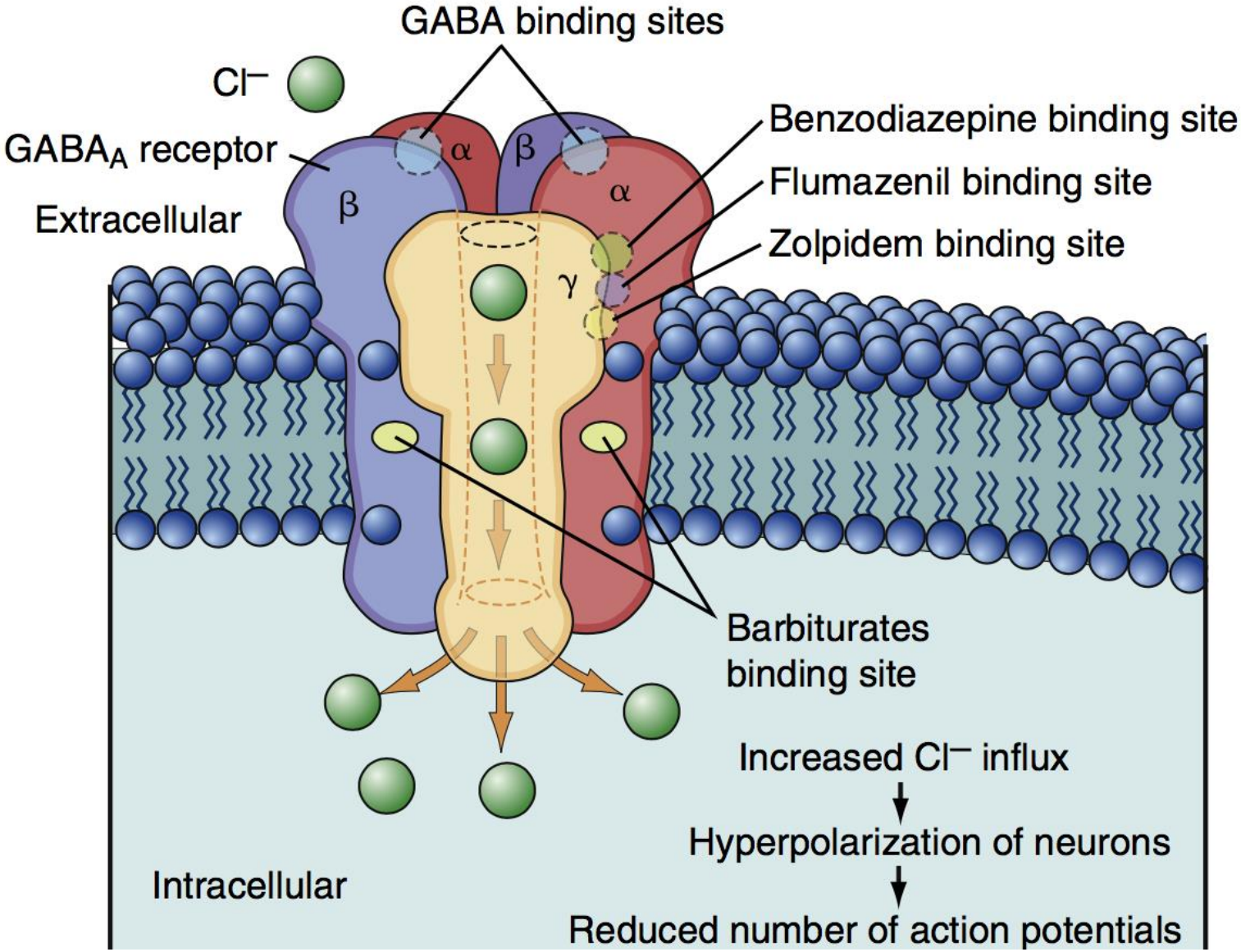


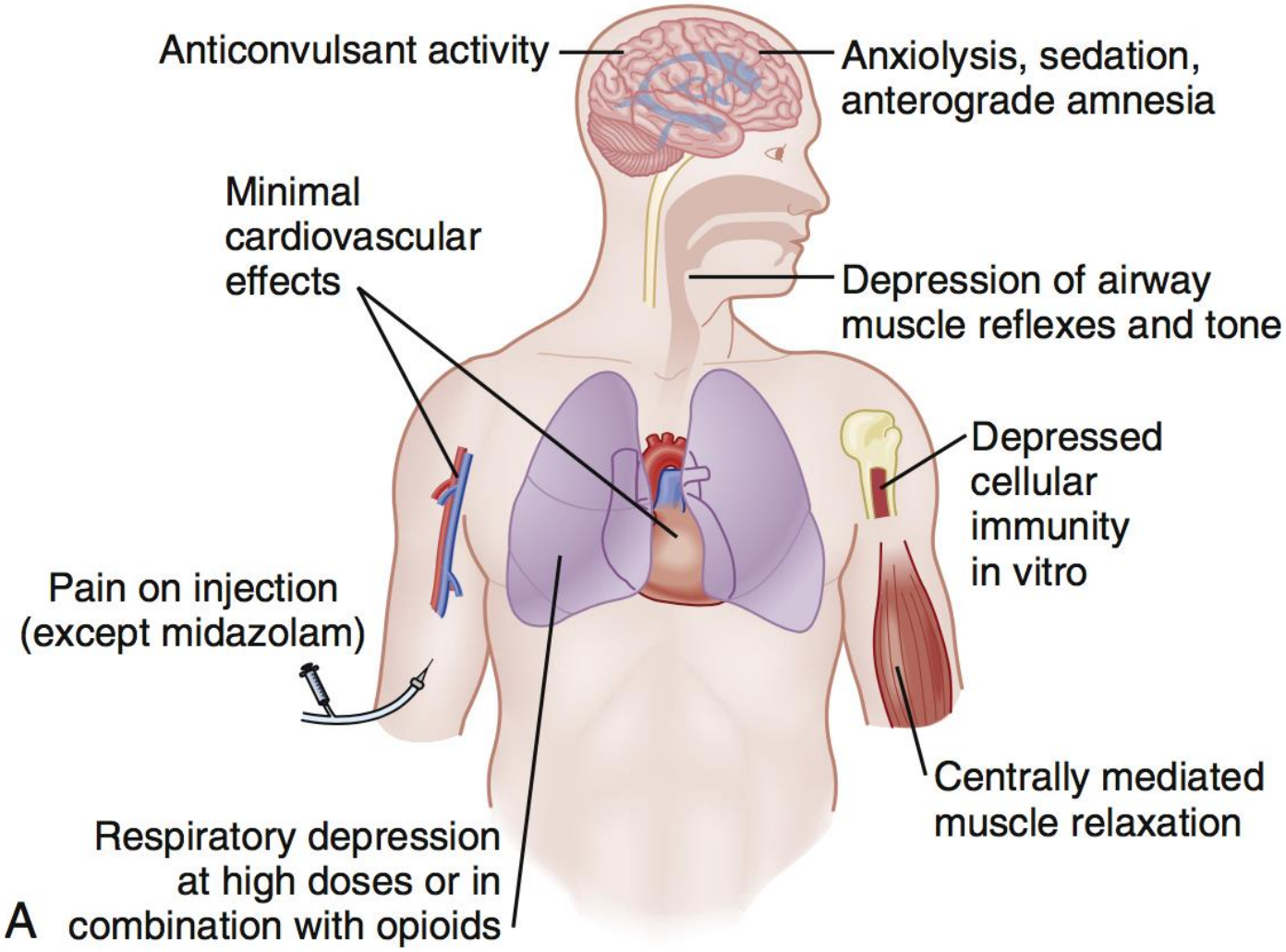
GABA



- GABA exerts its inhibitory effect by opening the chloride ion channel on neuronal membranes, thus hyperpolarizing the cell membrane and making it less likely to depolarize .
- It is still unknown why a BZD receptor exists, because to date no endogenous BZD- like chemicals have been identified.


Action potential
Ca^{2+} entry
Neurotransmitter release (GABA, glycine)
Postsynaptic membrane
Cl^-
Cl^-
Cl^-
A
Inhibitory postsynaptic potential
Voltage
+ Anesthetic
Time
B


GABA binding sites
Cl⁻
GABA$_A$ receptor
Extracellular
α
β
β
α
γ
Benzodiazepine binding site
Flumazenil binding site
Zolpidem binding site
Barbiturates binding site
Increased Cl⁻ influx
Hyperpolarization of neurons
Reduced number of action potentials
Intracellular


Anticonvulsant activity
Anxiolysis, sedation, anterograde amnesia
Minimal cardiovascular effects
Depression of airway muscle reflexes and tone
Depressed cellular immunity in vitro
Pain on injection (except midazolam)
Centrally mediated muscle relaxation
Respiratory depression at high doses or in combination with opioids
A

BZD

Concomitant administration of certain drugs can also increase elimination time; this includes erythromycin, oral contraceptives, and calcium channel blockers.

BZDs have among the widest toxic-therapeutic ratios of any agent used for sedation and anesthesia, making them a safe drug class.

Diazepam

pH of diazepam ranges from 6.2 to 6.9, and it has an elimination half-life of more than 40 hours.

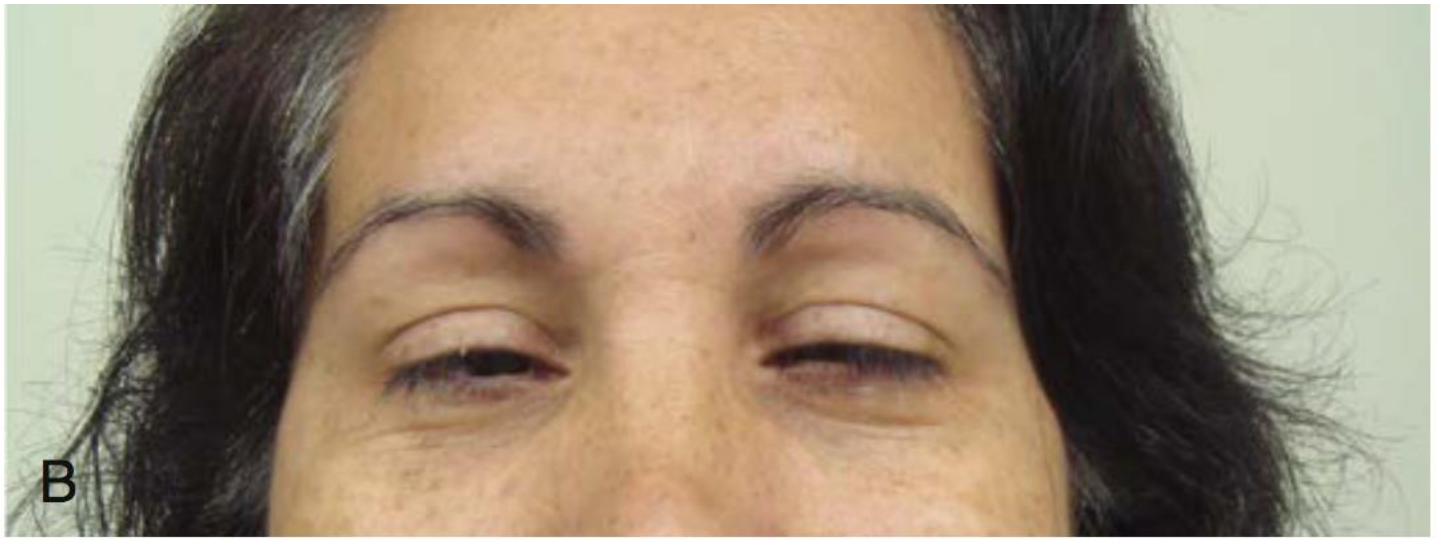
It is not water soluble

The solvent propylene glycol, whose irritating properties cause the risk of phlebitis and venous thrombosis

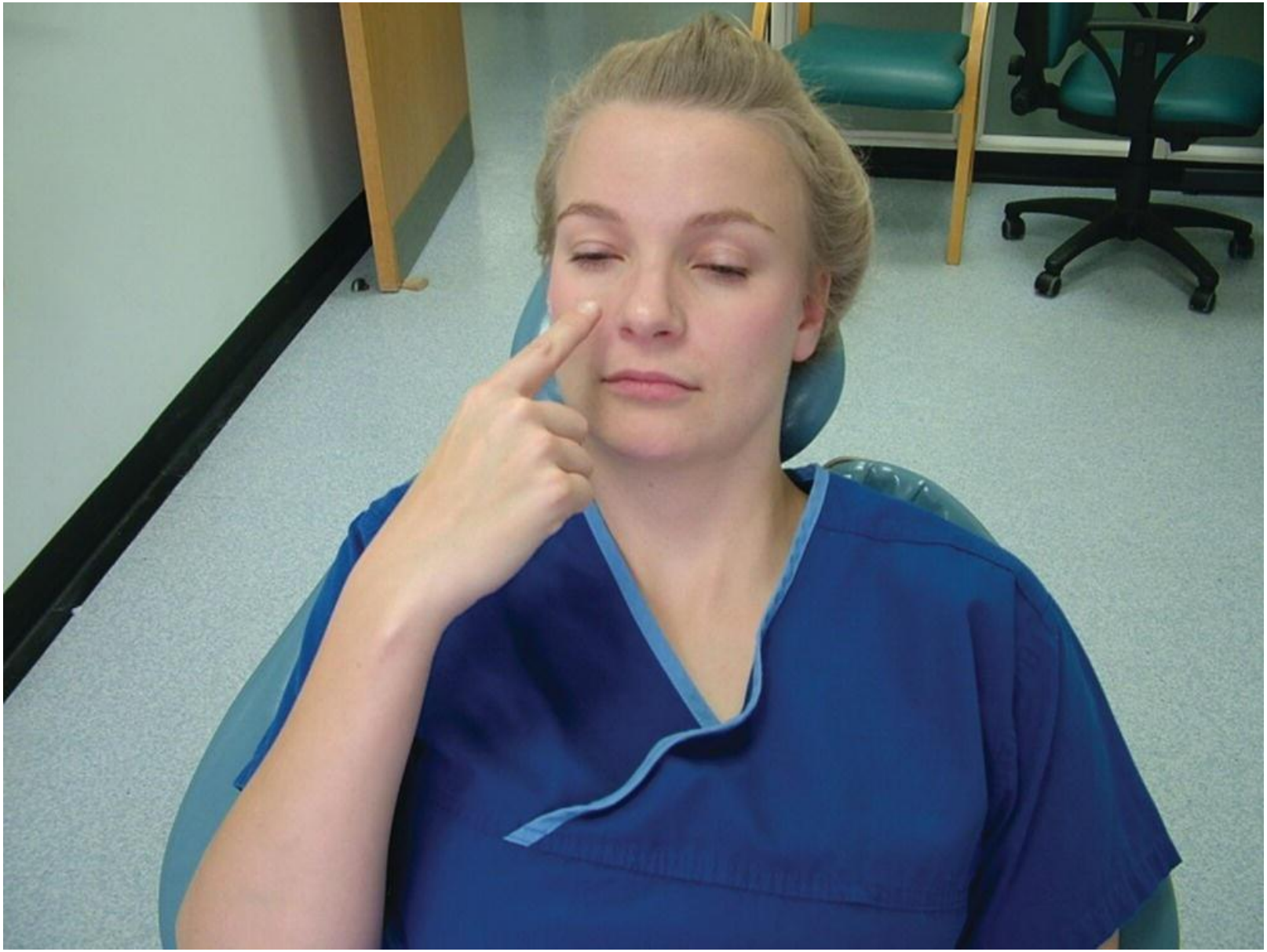
drug must be administered slowly—no more than 1 mL (5 mg) per minute

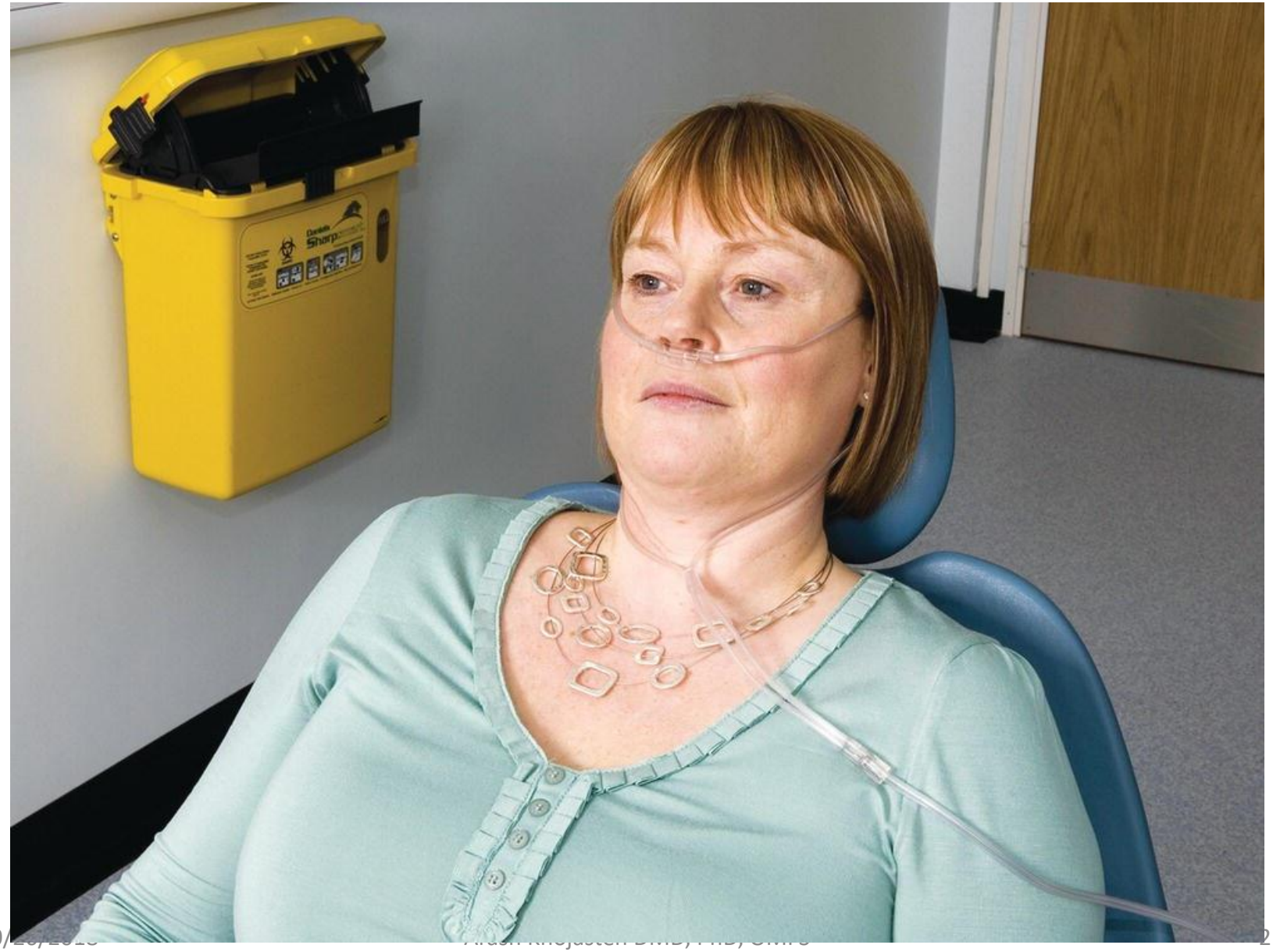
It should not be injected into small veins, such as the dorsum of the hand or the wrist

Veril Sign



Anxiolysis is produced when less than 20% of receptors are occupied; sedation occurs when there is 30% to 50% occupancy; and unconsciousness when more than 60% of receptors are occupied.





Midazolam

It had a much shorter half-life and did not have active metabolites

water soluble

This provided shorter recovery time for patients and avoided the injection of solvents that were irritating to vein

Its water solubility has permitted midazolam liquid to be administered intramuscularly, nasally, rectally, and orally, routes that were not available for use with diazepam

Lorazepam

Frequently used in intensive care units for prolonged sedation,

Does not have a favorable profile for ambulatory anesthesia.

It has a short distribution half-life and a long elimination half-life.

As a result of its lower lipid solubility, its effects do not reach a peak until 30 to 60 minutes after the initial IV dose.

It is more effective at producing amnesia than diazepam, and the amnestic effects may last many hours after administration.

Flumazenil

Flumazenil is an imidazobenzodiazepine that interacts with the GABA-BZD complex and competitively displaces the BZD

It is not protein bound, and its half-life is roughly 1 hour, making resedation a risk when a longer-acting BZD or high doses have been administered.

	Elimination Half-Life (hr)	% Protein Bound
Midazolam	1-5	95
Diazepam	20-40	97
Lorazepam	10-20	88-92
Triazolam	1-5	85-90
Alprazolam	9-15	70
Flumazenil	0.7-1.3	54-64

Modified from Smith RB, Corey SE, Kroboth PD: Pharmacokinetics of benzodiazepines. In Bowdle TA, Horita A, Kharasch ED, editors: *The pharmacologic basis of anesthesiology*, New York, 1994, Churchill Livingstone, p 263.)

OPIATES AND OPIOIDS

Morphine

Three major receptors (mu, delta, kappa) with as many as eight subtypes

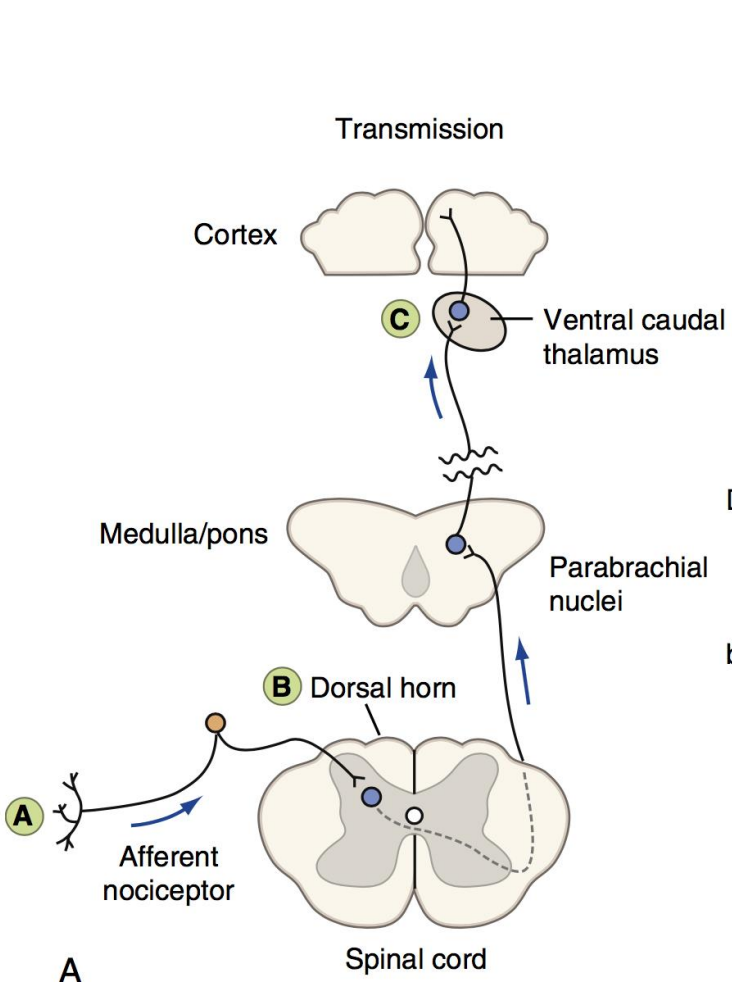
The primary desirable effect of opioids is analgesia

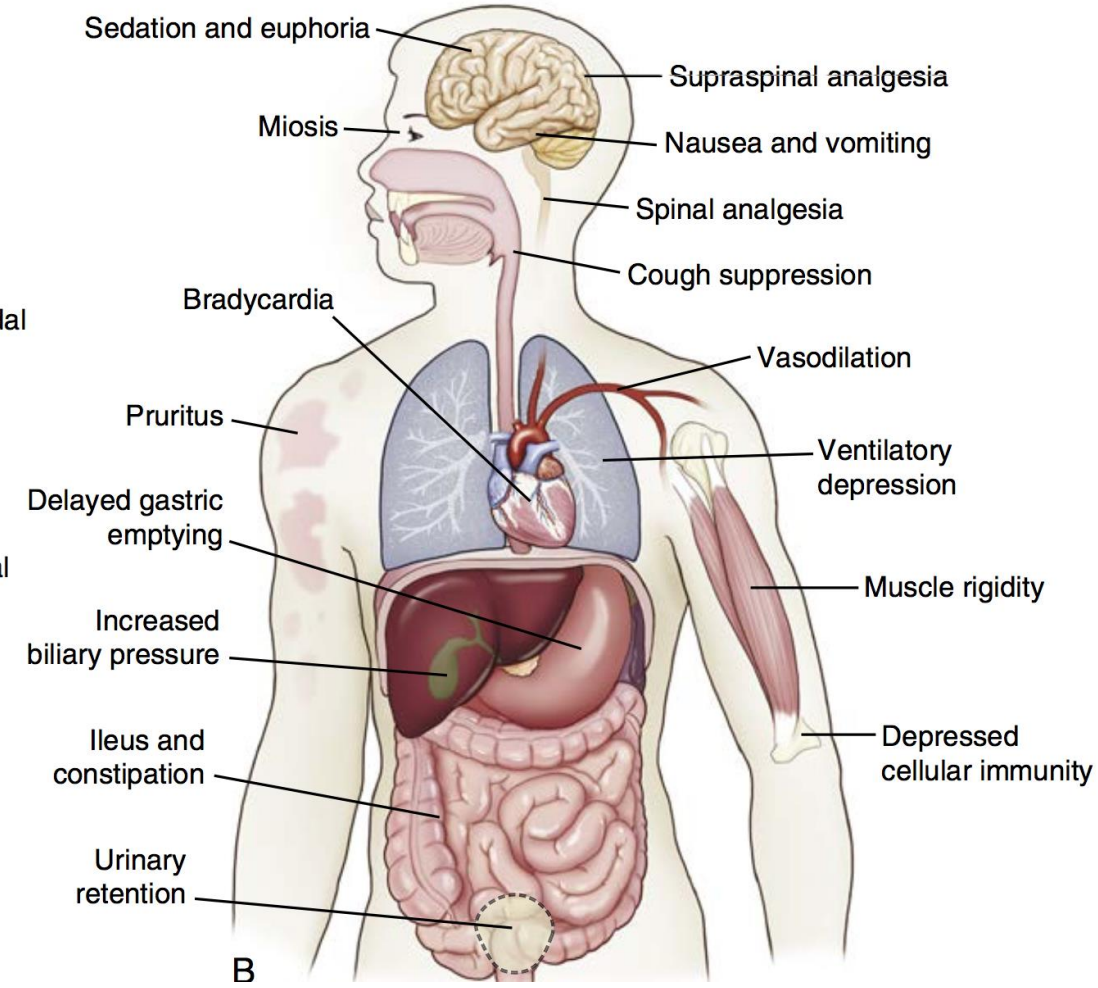
Respiratory depressant effects of the opioids are caused by a dose-dependent depression of the brainstem response to increased CO2 and decreased O2

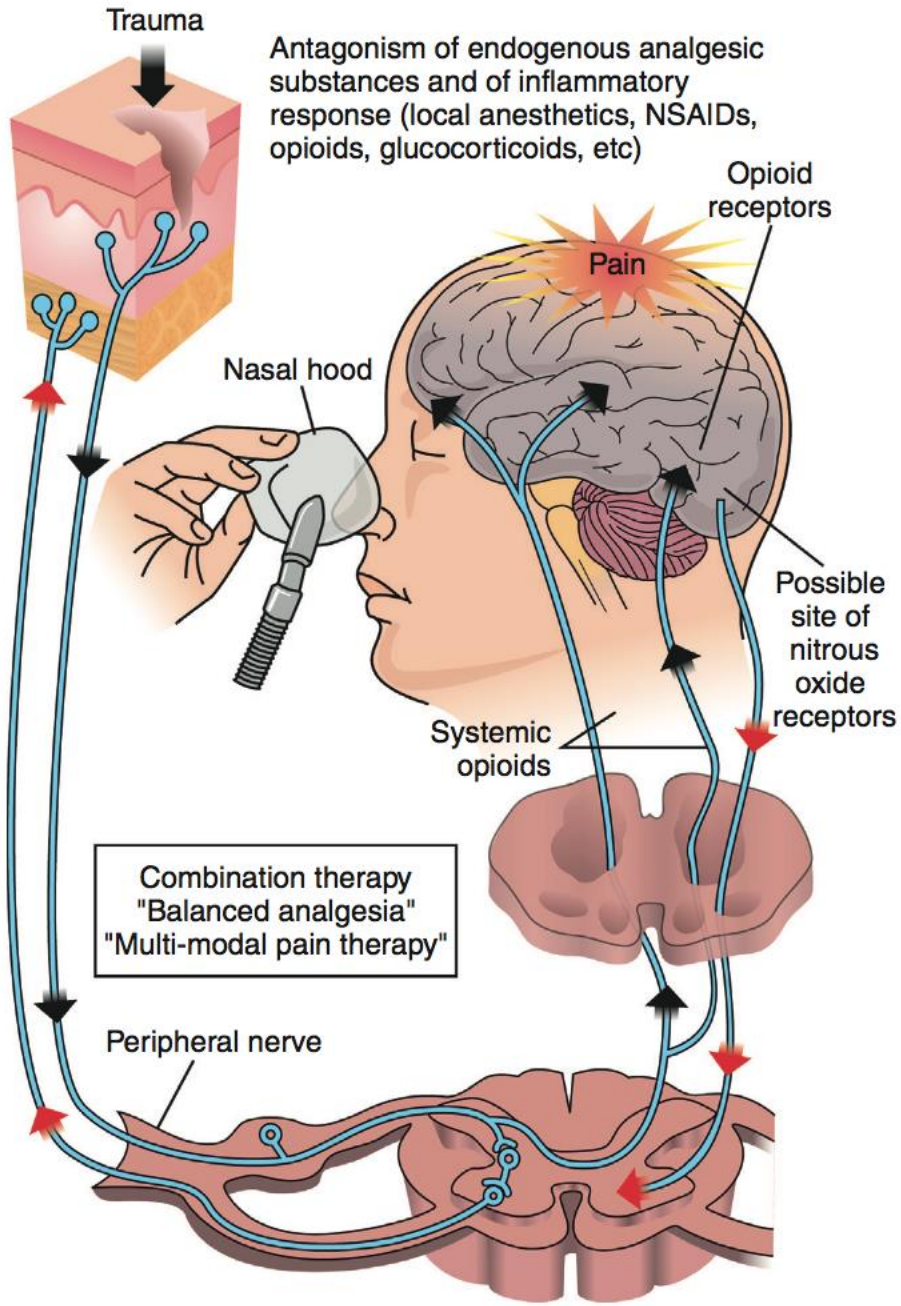
Opioids are known to cause histamine release

A central decrease in sympathetic tone, leading to a tendency toward vagal-dominated bradycardia. As a result of these two effects, direct and indirect vasodilation occurs

Opioid Analgesic Effect






Trauma
Antagonism of endogenous analgesic substances and of inflammatory response (local anesthetics, NSAIDs, opioids, glucocorticoids, etc)
Opioid receptors
Pain
Nasal hood
Possible site of nitrous oxide receptors
Systemic opioids
Combination therapy
"Balanced analgesia"
"Multi-modal pain therapy"
Peripheral nerve
Central neural blockade (epidural/intrathecal local anesthetics, opioids, α-agonists)

Meperidine

Meperidine, the first totally synthetic opioid, is also known by its non-U.S. name “pethidine”.

Its duration of action is anywhere from 3 to 5 hours.

Tachycardia, decreased myocardial contractility, and mydriasis

One of the metabolites, normeperidine, is long acting and pharmacologically active and can cause toxic effects in the CNS that can result in increased EEG activity, myoclonus, and seizures

Of all the opioids, meperidine is the one most likely to cause histamine release.

In addition to the potential to create symptoms similar to anaphylaxis, this histamine release may also be responsible for vasodilation that can lead to clinically significant hypotension

Fentanyl

Fentanyl is 60 to 80 times more potent than morphine, and there is a 2 to 3 times greater affinity for fentanyl at the opiate receptor compared with morphine

After injection, fentanyl is characterized by a rapid onset of action owing to its ease of crossing the blood-brain barrier.

It is rapidly eliminated, with 99% of a single dose cleared from the plasma within 60 minutes

Remifentanil

unique properties by being μ-selective

It also has an ester linkage and is thus metabolized by tissue and plasma esterases

is imparts an extremely short half-life and limits the accumulation of the drug in the tissues

Naloxone

is short-acting antagonist can be used to quickly reverse the effects of opioids

Sudden reversal of an opioid with naloxone has also been associated with rebound sympathetic stimulation that can cause dysrhythmias, hypertension, myocardial infarction, stroke, and pulmonary edema.

INTRAVENOUS SEDATIVE-HYPNOTICS

Barbiturates

Propofol

Ketamine

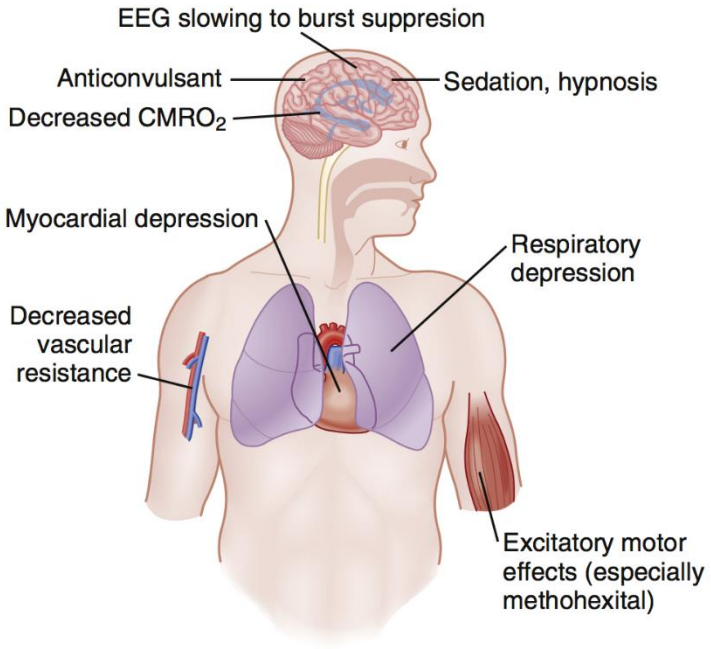
Intravenous Sedative-Hypnotics

Methohexital and propofol are thought to exert their action by interacting with GABA receptors

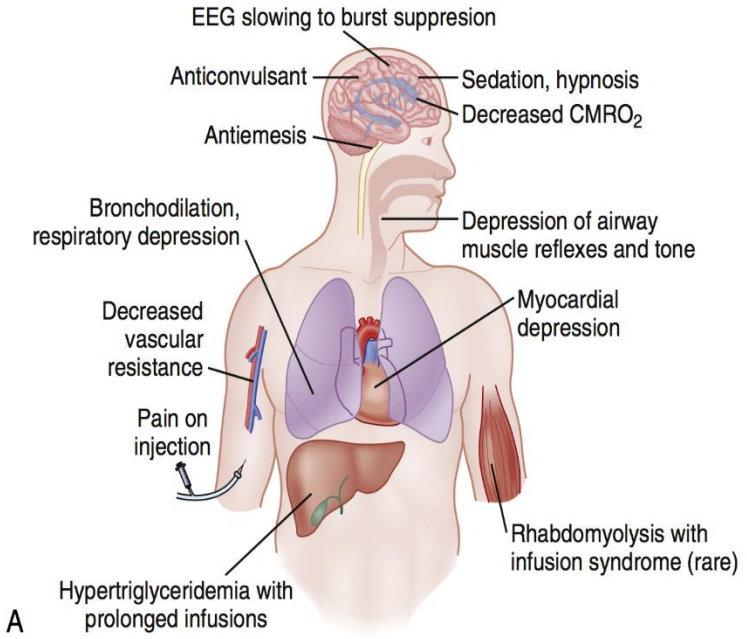
Those sites are different from the sites associated with the BZD.

Intravenous Sedative-Hypnotics

Methohexidal



Propofol



Methohexital

Excitatory effects, such as hiccups and myoclonic movement, have classically been associated with methohexital, occurring as frequently as 90% of the time in patients who receive it

Methohexital causes tachycardia and hypertension because there is cardiac compensation for peripheral vasodilation.

Methohexital and other barbiturates appear to lower the pain threshold and have been credited with antianalgesic properties, but there is still debate whether this is a real phenomenon

Propofol

Propofol tends to provide cardiovascular stability by exerting a central sympatholytic effect that maintains a stable heart rate

there might be a slight—but clinically insignificant—decrease in blood pressure

Both propofol and methohexital can cause apnea following large induction doses.

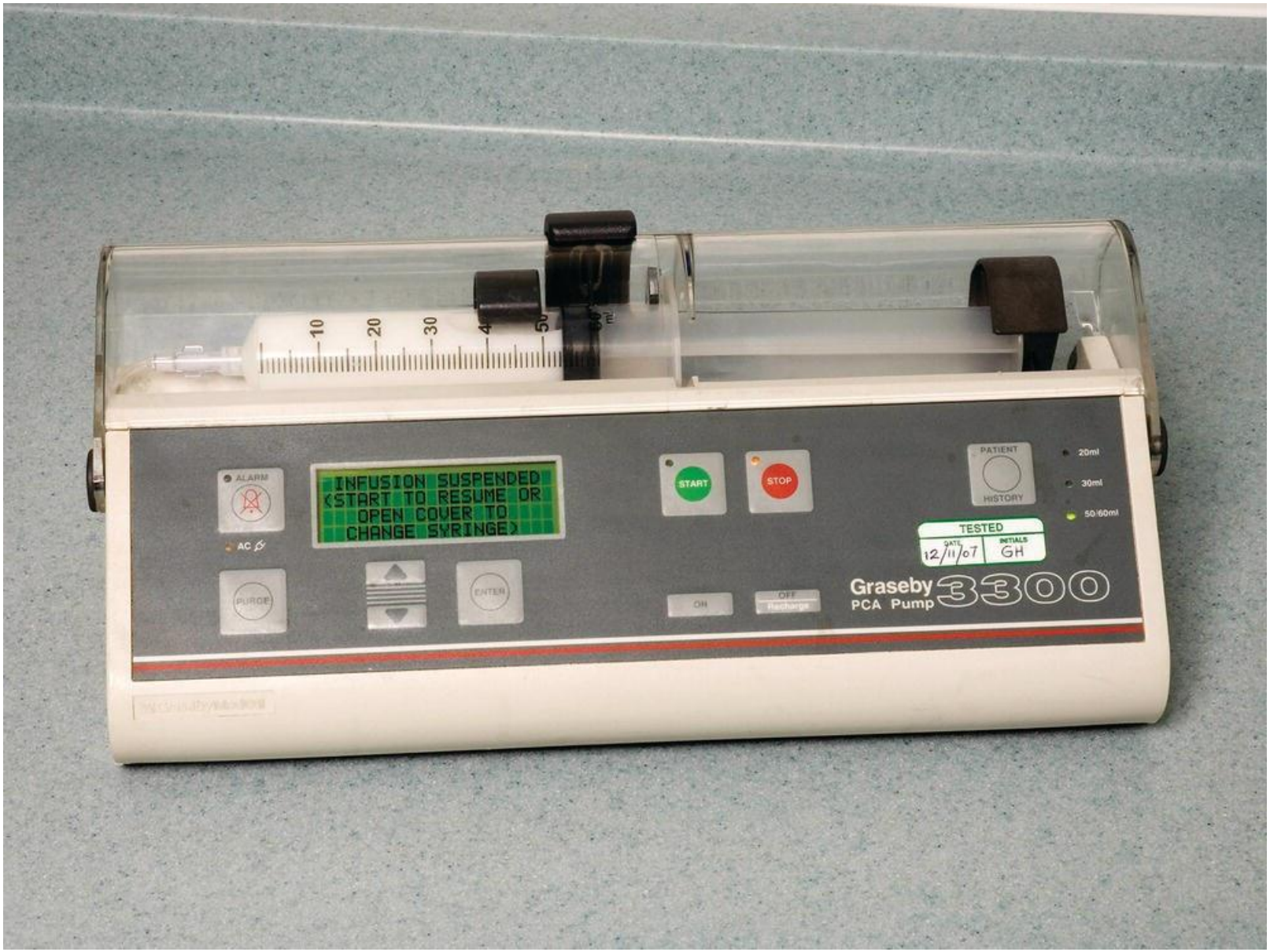
It does not cause nausea and vomiting; to the contrary, it possesses antiemetic properties and has been administered in subhypnotic doses for the treatment of nausea and vomiting.

Propofol causes little or no histamine release and has not been associated with allergic reactions

It has bronchodilating properties that may be due to direct effects on smooth muscle

Propofol (Cont)

- It is associated with pain on injection
- Is rapid metabolism makes propofol an ideal drug for continuous-infusion anesthesia
- propofol infusion syndrome : The syndrome is characterized by the combination of metabolic acidosis, acute bradycardia and/or asystole, and rhabdomyolysis, and it can be fatal
- occur with propofol infusions longer than 48 hours


INFUSION SUSPENDED
(START TO RESUME OR
OPEN COVER TO
CHANGE SYRINGE)
ALARM
AC
START
STOP
PATIENT
HISTORY
20ml
30ml
50/60ml
TESTED
DATE
12/11/07
INITIALS
GH
PURGE
ENTER
ON
OFF
Recharge
Graseby
PCA Pump
3300

Ketamine

Glutamate is an excitatory neurotransmitter in the brain and is important for many higher CNS functions

Glutamate receptors have multiple subtypes, of which the *N*-methyl-d-aspartate (NMDA) receptor is a cationic subtype

Glutamate, particularly in the presence of glycine, binds to the NMDA receptor and causes increased ow of sodium, potassium, and calcium, resulting in neural excitation.

Ketamine is a noncompetitive antagonist of NMDA, thus inhibiting glutamate activity and causing CNS depression

There are other drugs that cause NMDA antagonism as well, including certain opioids (e.g., methadone) and the over-the-counter antitussive dextromethorphan.

Ketamine (cont)

Ketamine is described as causing a functional dissociation of EEG activity between the hippocampus and the thalamoneo- cortical system . Other sedative-hypnotics act more specifcally on discrete locations within the midbrain and brainstem.

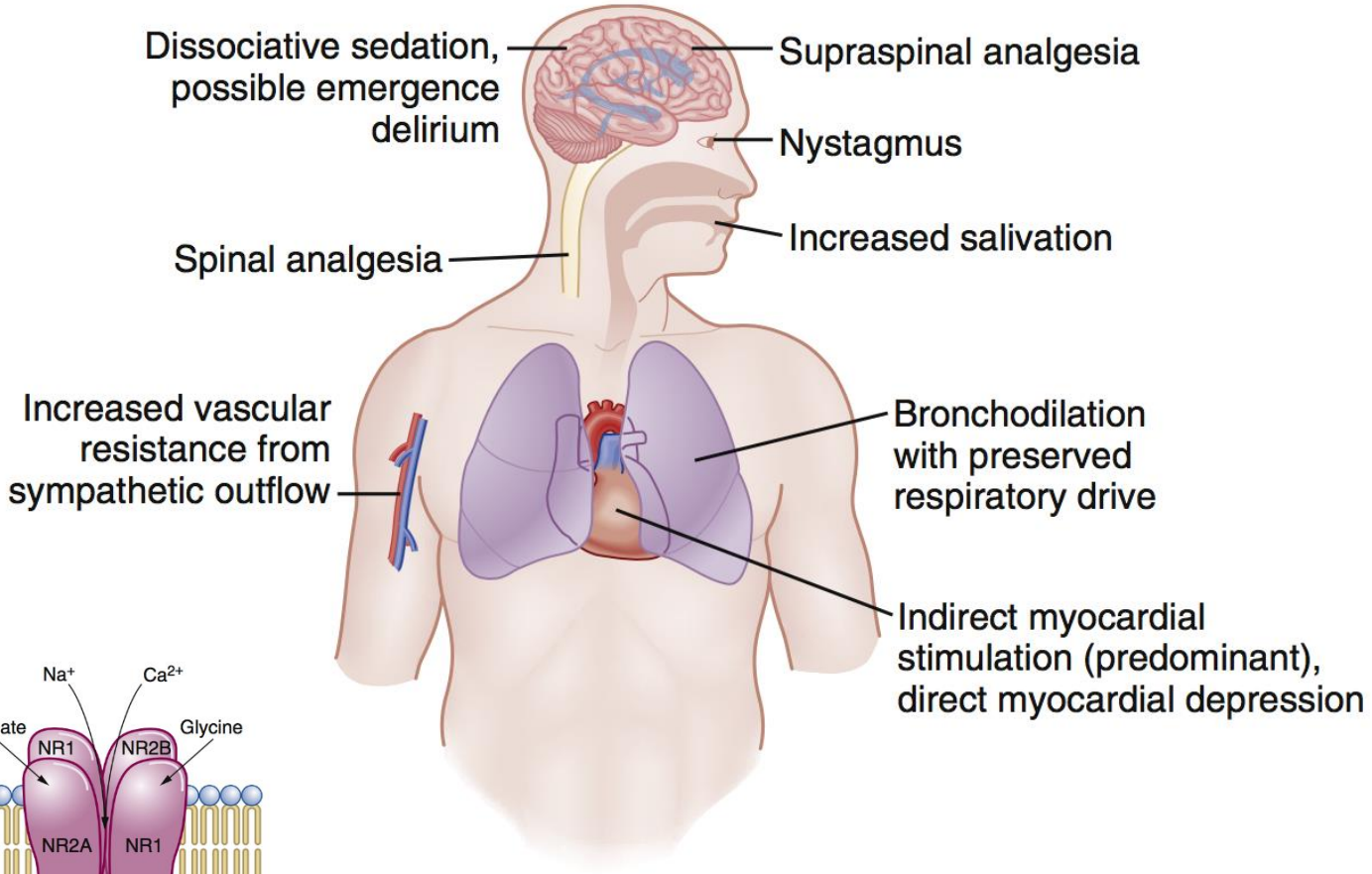
Ketamine causes a profound dose-dependent analgesia.

Useful adjunct for patients where it is not possible to achieve absolute local anesthesia (e.g., maxillofacial infections

Ketamine is sympathomimetic through direct CNS stimulation, thus causing an increase in heart rate, cardiac contractility, and rate pressure product and mild respiratory depression

The brainstem response to hypercarbia is maintained, as is the functional residual capacity. Ketamine is a bronchodilator by relaxing smooth muscle as a result of its sympathomimetic e ects.

Ketamine


Dissociative sedation, possible emergence delirium
Supraspinal analgesia
Nystagmus
Increased salivation
Spinal analgesia
Increased vascular resistance from sympathetic outflow
Bronchodilation with preserved respiratory drive
Indirect myocardial stimulation (predominant), direct myocardial depression
Na+
Ca2+
Glutamate
Glycine
NR1
NR2B
NR2A
NR1
Mg2+
Intracellular
Ketamine
NMDA
A

Ketamine

Absolute Contraindications	Relative Contraindications	Relative Contraindications continued
Hypersensitivity to ketamine	Moderate to severe hypertension	Intracerebral mass or hemorrhage, Increased ICP
Open eye procedures	Ischemic heart disease	Eye injury, increased intraocular pressure, glaucoma
Acute porphyria	Congestive heart disease	Psychiatric disorders: schizophrenia, acute psychoses
Liver failure	Pre-eclampsia	Non-controlled hyperthyroidism
	History of CVA	Patients taking thyroxin
	Acute or Chronic Alcohol Intoxication	Cerebral trauma

Pharmacokinetics of Intravenous Agents

	Distribution Half-Life (min)	Elimination Half-Life (hr)	Clearance (mL/min)
Midazolam	7-15	2-4	300-550
Diazepam	3-10	20-40	15-35
Methohexital	5-6	2-5	700-900
Propofol	2-4	1-3	1400-2800
Ketamine	11-17	2-3	1250-1400

INHALATIONAL AGENTS

Inhalational Agents

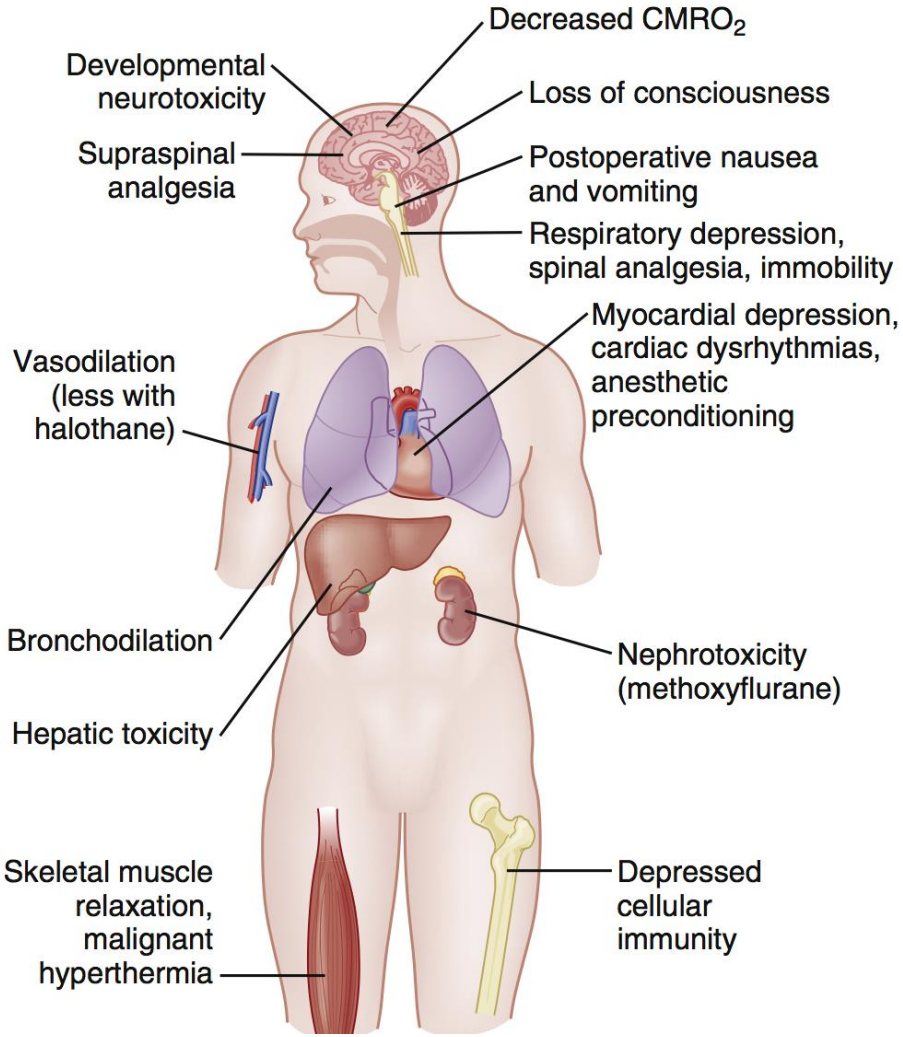
Of all the gases, nitrous oxide is the least soluble, providing a very rapid onset of action and recovery

Inhalation agents exert their analgesic effect: supraspinal opiate receptors in the brainstem and adrenergic receptors in the spinal cord

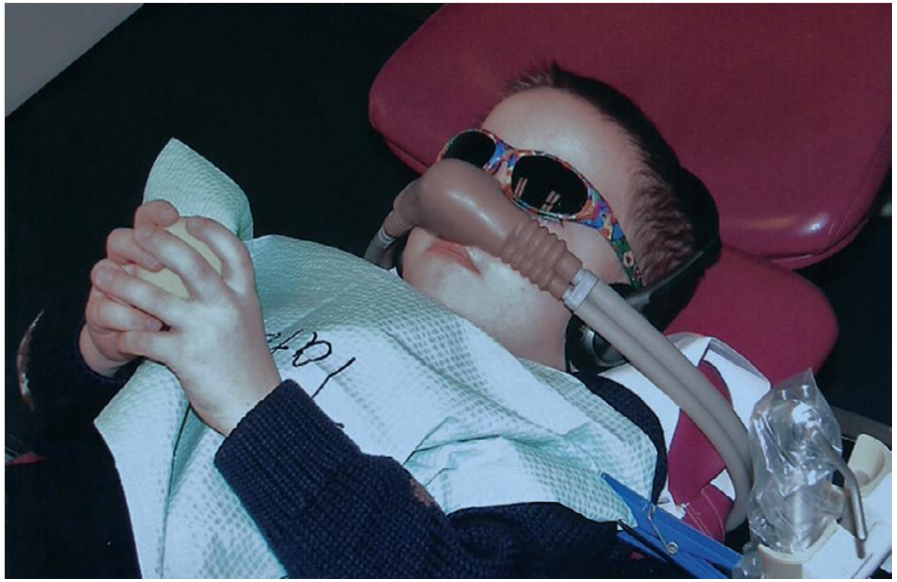
The precise location at which inhalation agents produce unconsciousness and amnesia has not been identified, although proposed sites of action include the hippocampus and the thalamus

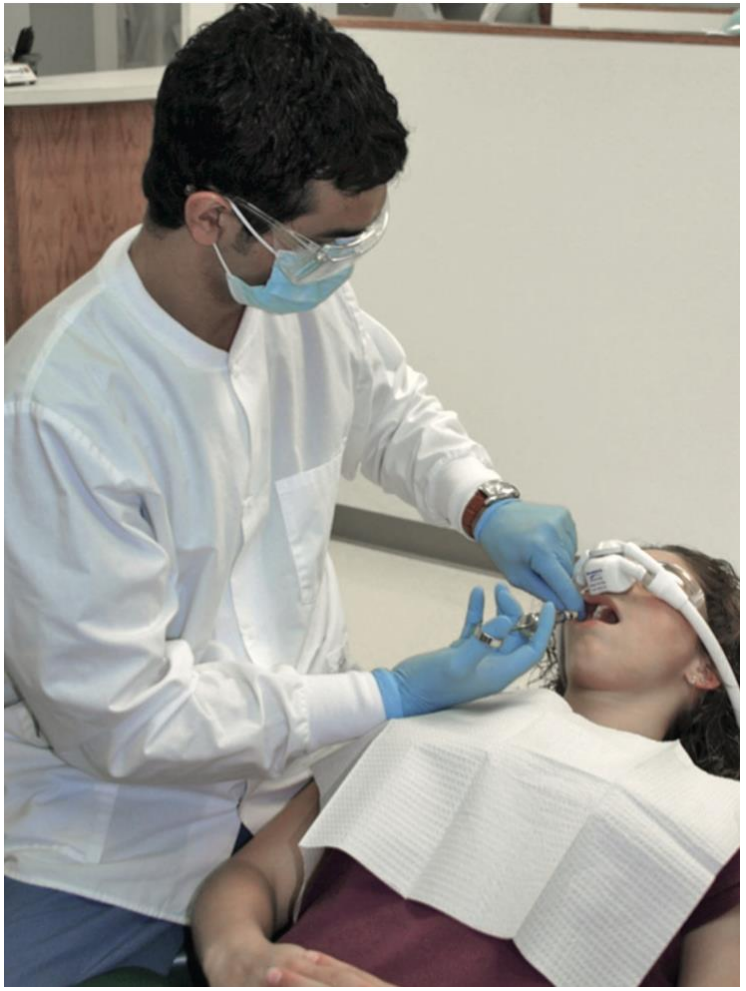
There is sufficient evidence, however, to indicate that the potent inhalation agents (not including nitrous oxide) increase inhibitory transmissions via the GABA pathway by interaction with the GABA receptor. Nitrous oxide, it appears, interacts with and blocks NMDA receptors and does not have any activity at the GABA receptor

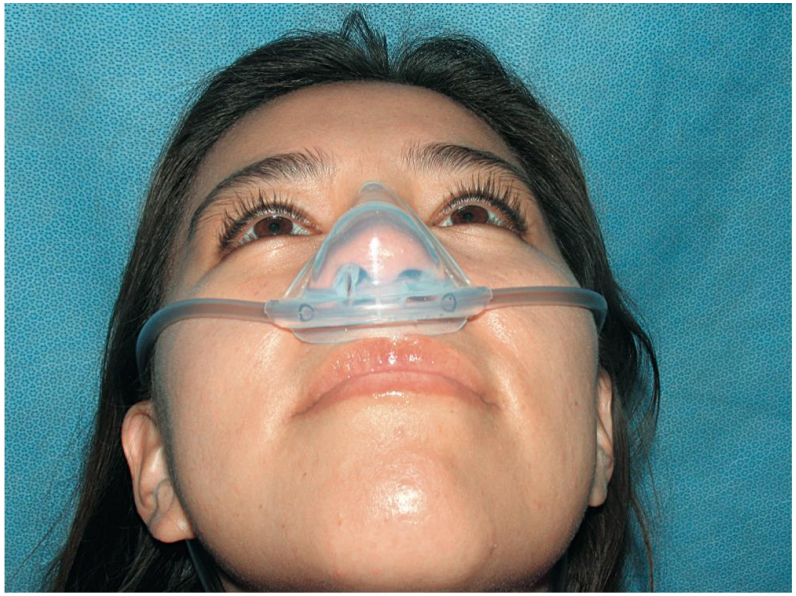
Inhalational

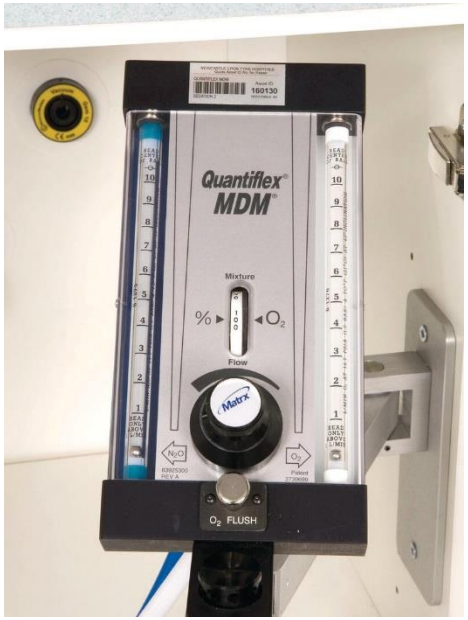


N2O








Quantiflex
MDM
Mixture
Flow
O2 FLUSH

N20

- Nitrous oxide is the only inhalational agent in routine use for conscious sedation
- It was discovered by Joseph Priestly in 1772 as an anesthetic agent for exodontia

Nitrous Oxide

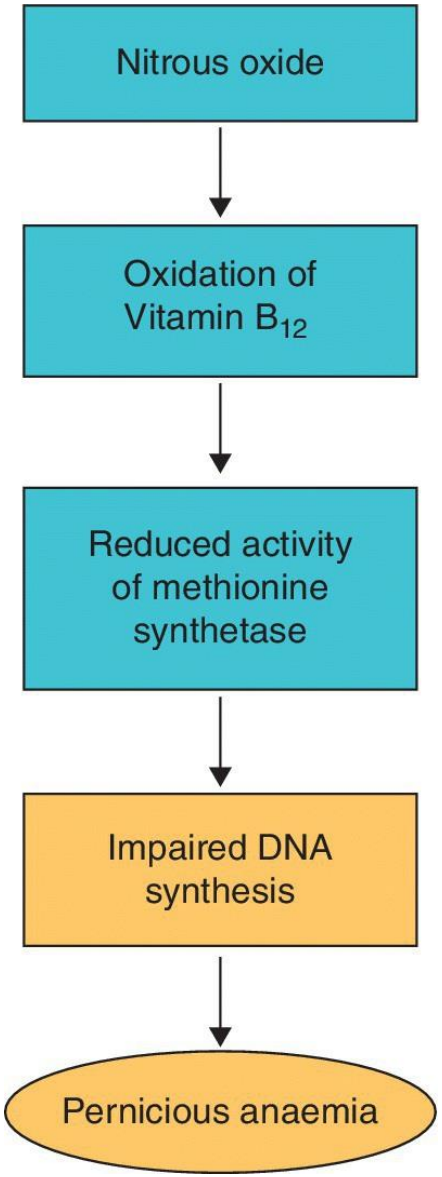
Nitrous oxide is a weak general anesthetic but a powerful analgesic

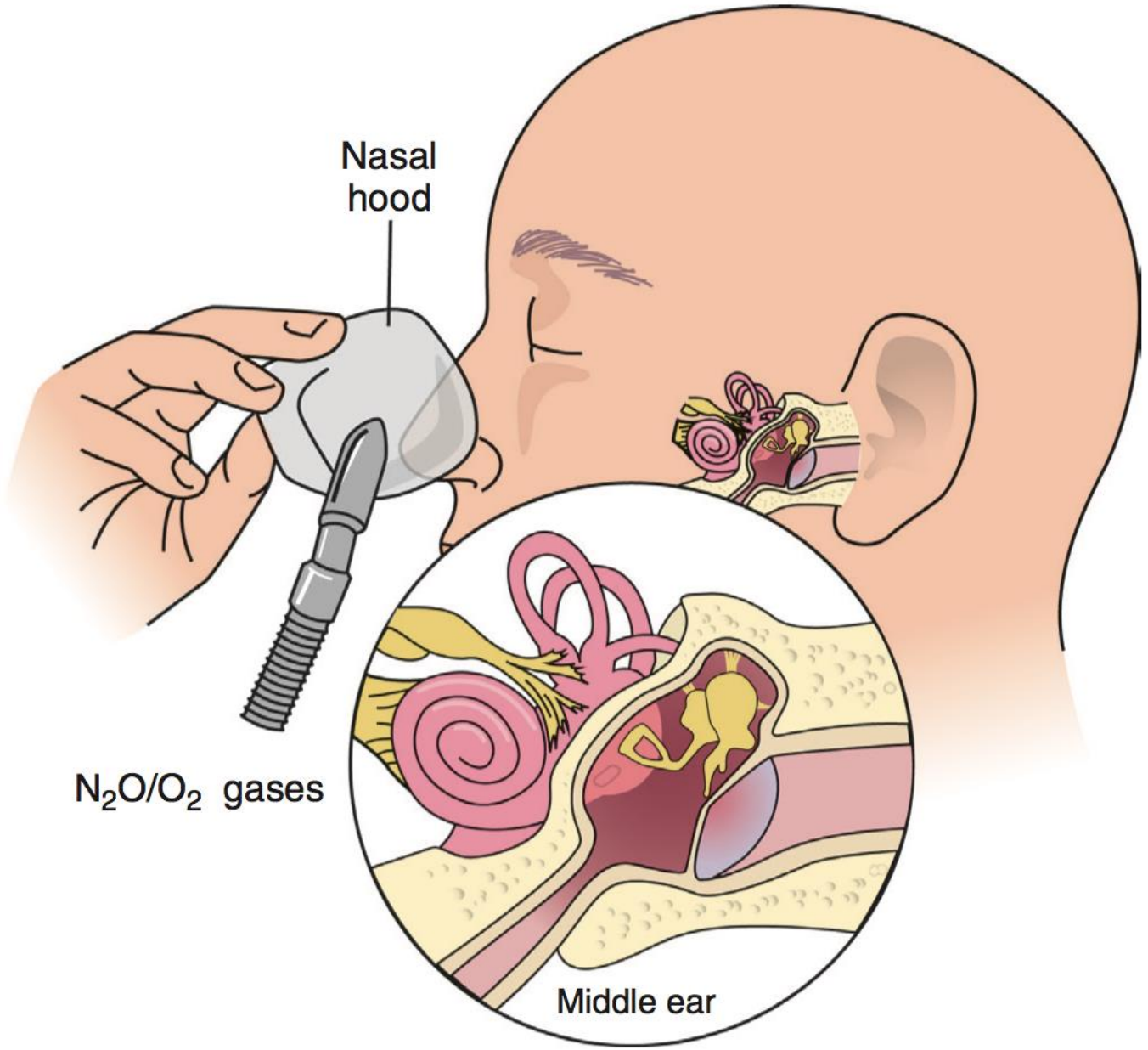
It has been estimated that a 20% concentration of nitrous oxide affords the same degree of analgesia as a dose of 15 mg of morphine

Nitrous oxide causes a decrease in myocardial contractility, peripheral vascular resistance, cardiac output, and blood pressure. It causes a decrease in respiratory rate but an increase in minute ventilation because of increased tidal volume.

Chronic exposure can lead to peripheral neuropathies and bone marrow suppression through inactivation of the methionine synthetase pathway

Increased incidence of spontaneous abortion and decreased fertility in health care providers exposed to nitrous oxide on a regular basis.


Nitrous oxide
Oxidation of Vitamin B_{12}
Reduced activity of methionine synthetase
Impaired DNA synthesis
Pernicious anaemia

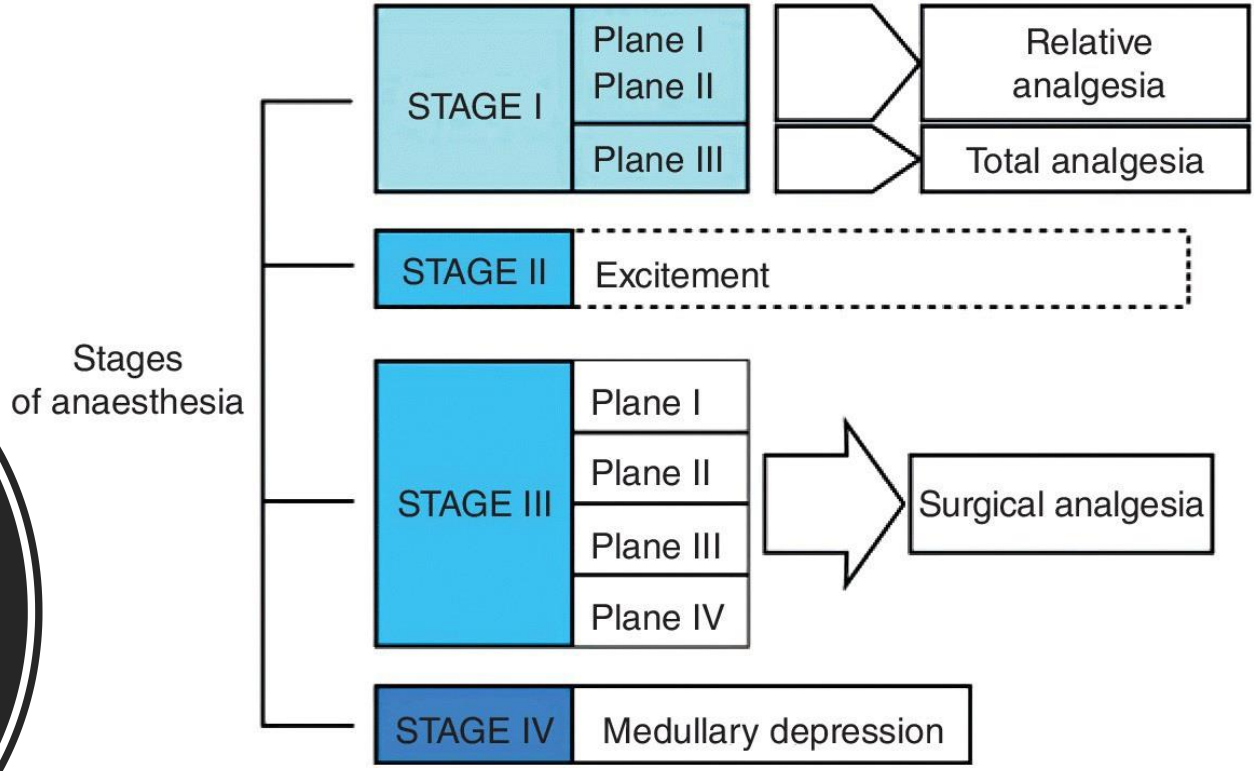

Nasal
hood
N_2O/O_2 gases
Middle ear

Inhalational agents

	Nitrous Oxide	Halothane	Isoflurane	Desflurane	Sevoflurane
Boiling pt (°C)	50.2	48.5	22.8	58.5	
Vapor pressure (mm Hg)	Gas	244	240	669	170
Odor	Sweet	Organic	Ethereal	Ethereal	Ethereal
Stability in soda lime	Yes	No	Yes	Yes	No
Blood: gas partition coefficient	0.46	2.54	1.46	0.42	0.69
MAC (37° C)	104	0.75	1.17	6.6	1.80
% Metabolized	0.004	15-20	0.2	0.02	5

Modified from Stoelting RK: *Pharmacology and physiology in anesthetic practice*, ed 3, Philadelphia, Lippincott-Raven, 1999, pp 36, 67.

Guedel's Stages of Anaesthesia



Plane I	Moderate sedation and analgesia, obtained at concentrations of 5–25% nitrous oxide.
Plane II	Dissociation sedation and analgesia, occurring at concentrations of 20–55% nitrous oxide.
Plane III	Total analgesia, obtained with concentrations of nitrous oxide usually well above 50%.

ORAL AND INTRANASAL

Oral Sedation

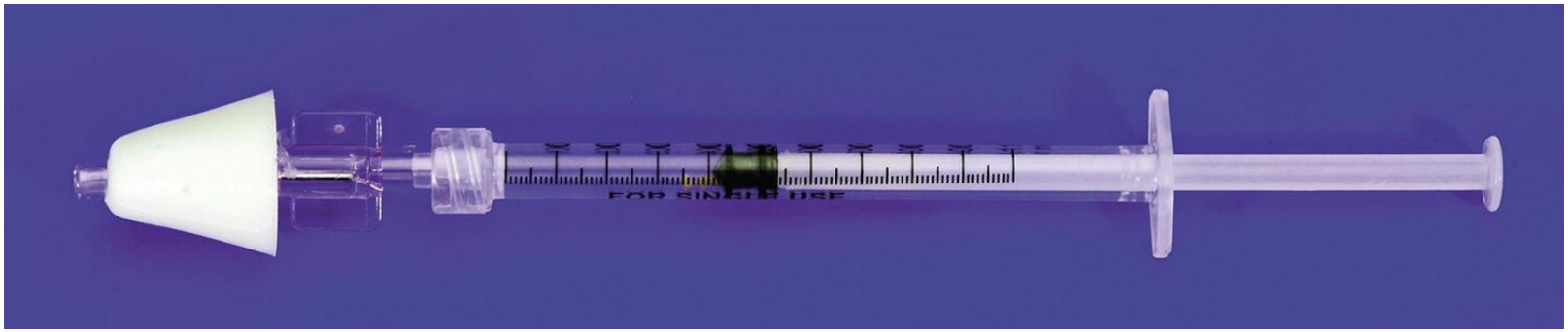
- Mostly used as the premedication
- BZD (Diazepam, Oxazepam, Midazolam)

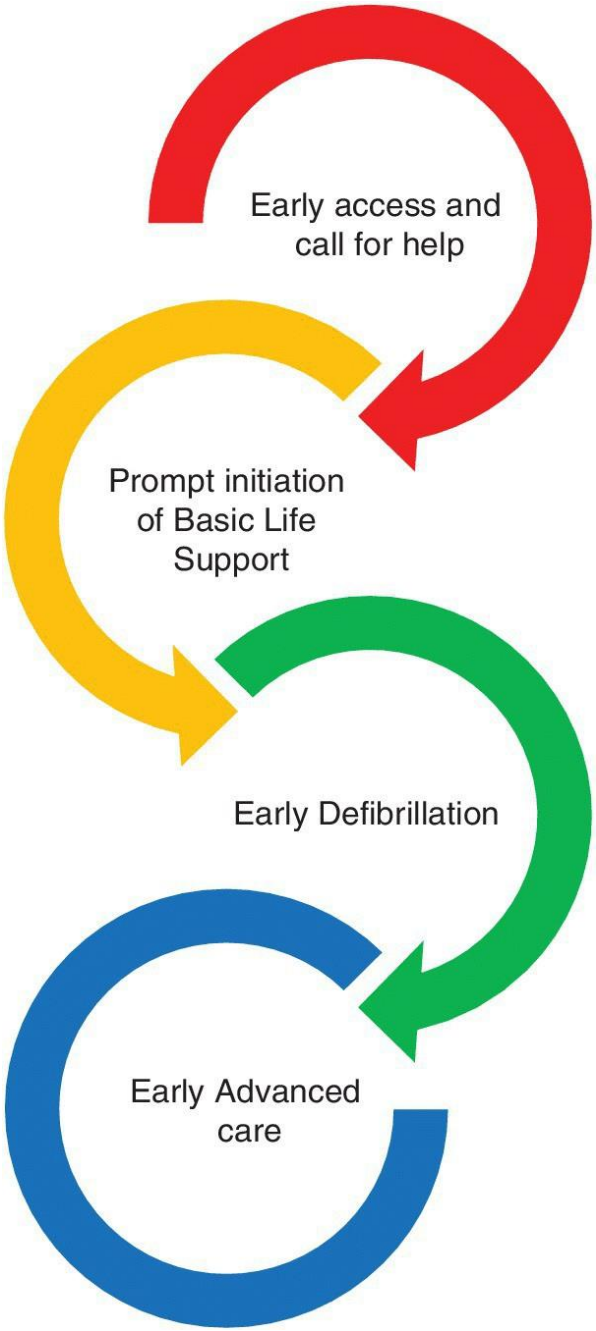
Oral Sedation

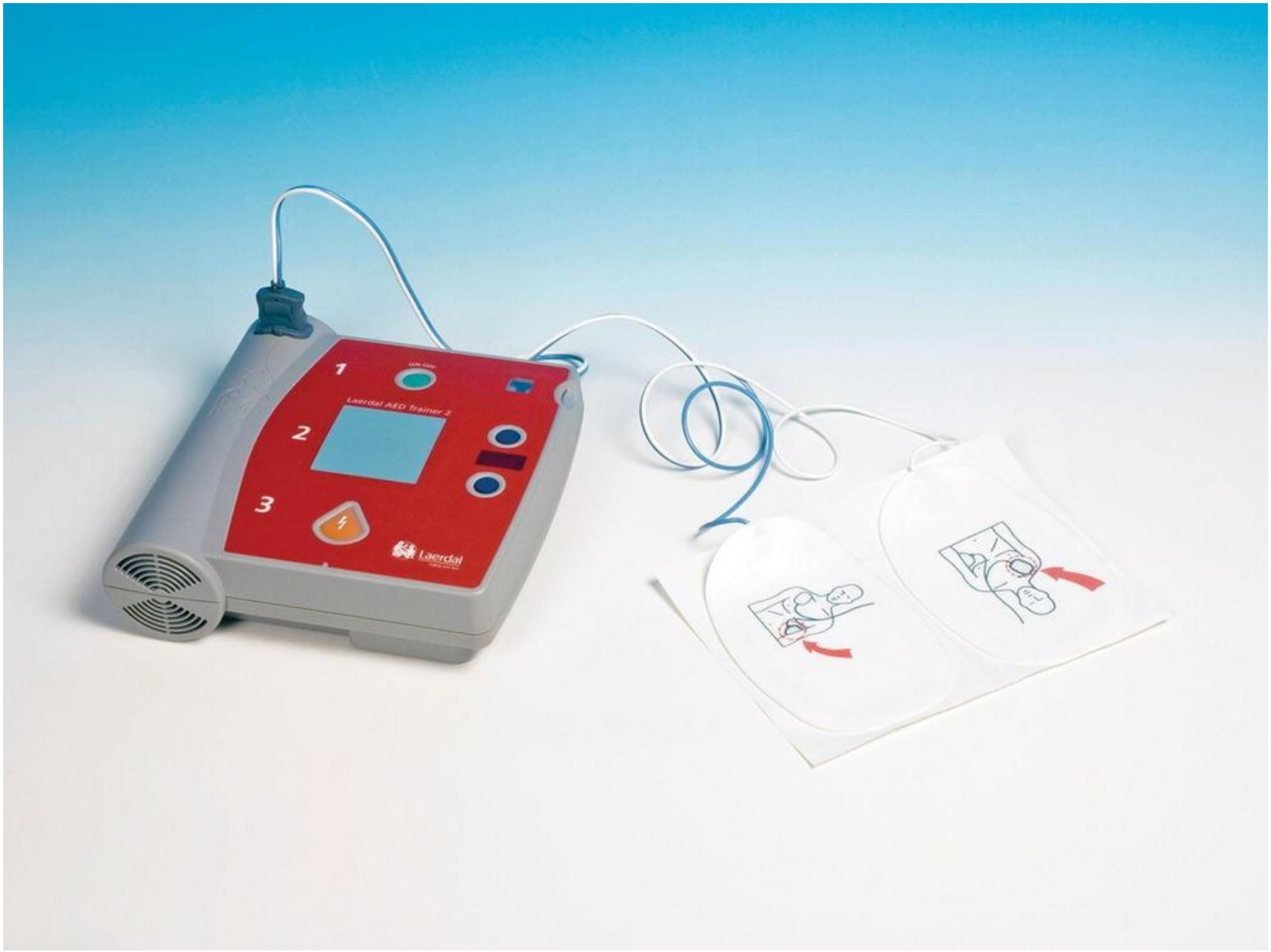
1. Alleviate fear and anxiety
2. Not suppress protective reflexes
3. Be easy to administer
4. Be free to side effect

Nasal Sedation

- Midazolam




Early access and call for help
Prompt initiation of Basic Life Support
Early Defibrillation
Early Advanced care


1
2
3
Laerdal AED Trainer 2
Laerdal