

Clinical Uses of Dexmedetomidine

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September 25, 2005
Ophthalmic Anesthesia
Society

Problems with Sedatives

- Inconvenient
- Costly
- Side effects
 - Nausea
 - Respiratory depression
 - Disorientation
 - Dysphoria
- Prolonged sedation
- Allergic reactions

An Ideal Drug



- Hugh Anthony Craig III
 - Born in 1950
 - Scored 800 on Math SAT
 - Quit Cornell Engineering
 - Formed Huey Lewis and the News

I Want a New Drug

- I want a new drug. One that won't make me sick
- One that won't make me crash my car. Or make me feel three feet thick.

- I want a new drug. One that won't spill.
- One that don't cost too much. Or come in a pill.

- I want a new drug. One that won't go away.
- One that won't keep me up all night. One that won't make me sleep all day

- I want a new drug. One that does what it should.
- One that won't make me feel too bad. One that won't make me feel too good

- I want a new drug. One with no doubt
- One that won't make me talk too much. Or make my face break out

Pharmacologic Agents Used for Sedation and Analgesia*

- Opioids¹
 - Morphine sulfate
 - Fentanyl
- Benzodiazepines¹
 - Midazolam
- Sedative/hypnotics¹
 - Propofol
- α_2 Agonists²
 - Dexmedetomidine

*Many of these agents are not labeled for all discussed clinical applications. Please refer to full prescribing information for each agent.

1. Shapiro et al. *Crit Care Med*. 1995;23:1596-1600. 2. Bhana et al. *Drugs*. 2000;59:263-268.

Benzodiazepines: Pharmacodynamics

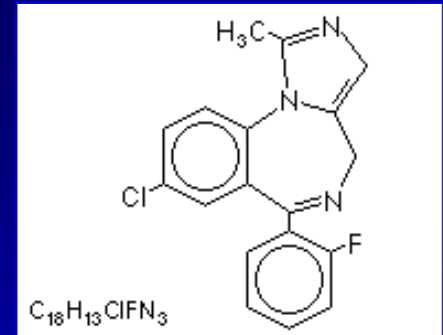
- Amnesia
- Sedation/anxiolysis
- Anticonvulsant
- Relief of muscle spasm

Benzodiazepines: Mechanisms of Action

- Benzodiazepines
 - GABA_A receptor modulation in CNS
 - Facilitate binding of GABA
 - Hyperpolarize cells, more resistant to excitation
 - Receptors postsynaptic

Midazolam: Clinical Effects

- Sedation, anxiolysis, and amnesia¹
- Rapid onset of action intravenously¹
- Possible accumulation in liver failure²
- Anterograde amnesia³
- Prolonged recovery after long-term use⁴
- Combination with opioids increases hypotensive effects⁵



1. Wagner, O'Hara. *Clin Pharmacokinet.* 1997;33:426-453. 2. Lerch, Park. *Br Med Bull.* 1999;55:76-95. 3. Harvey. *Am J Crit Care.* 1996;5:7-16. 4. Shafer. *Crit Care Med.* 1998;26:947-956. 5. Heikkilä et al. *Acta Anaesthesiol Scand.* 1984;28:683-689.

Benzodiazepines: Reversal Agents

- Flumazenil
 - Transiently antagonizes the benzodiazepine component of ventilatory depression and sedation during use with opioids
 - Reverses CNS and circulatory side effects of benzodiazepines within 2 minutes
 - Useful for diagnostic evaluation
 - Caution: may cause seizures (withdrawal syndrome)

Benzodiazepines

Advantages

- Amnesia¹
- Anxiolysis¹
- Sedation¹

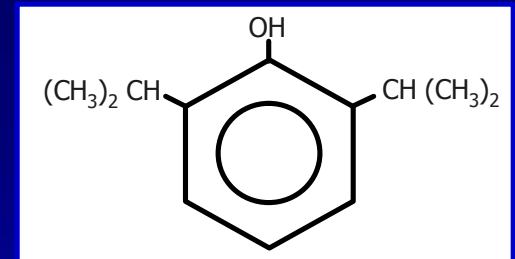
Limitations

- Respiratory depression^{2,4}
- Hypotension²
- Lack of analgesia⁴
- Oversedation/deep sedation²
- Paradoxical agitation²

1. Pepperman. *Care of the Critically Ill*. 1989;5:195-199. 2. Harvey. *Am J Crit Care*. 1996;5:7-16.
3. Lerch, Park. *Br Med Bull*. 1999;55:76-95. 4. Crippen. *Crit Care Clin*. 1990;6:369-392.

Propofol: Pharmacodynamics and Pharmacokinetics

- Mechanism of action not well understood
 - GABA_A receptor modulation is most likely
- Metabolized rapidly; very short half-life
- Metabolites are inactive



Propofol: Pharmacodynamics

- Anesthesia and sedation¹
- Rapid onset of and short duration of action^{1,2}
- Time to extubation faster than with midazolam^{3,4}
- Decrease in BP and HR from sympathetic effects¹

1. Lerch, Park. *Br Med Bull.* 1999;55:76-95. 2. Harvey. *Am J Crit Care.* 1996;5:7-16.
3. Wagner, O'Hara. *Clin Pharmacokinet.* 1997;33:434. 4. Ostermann et al. *JAMA.*
2000;283:1451-1459.

Propofol: Clinical Effects

- Decreases IOP and ICP^{1,2}
- Decreases SNS activity^{1,2}
- Cardiovascular depression^{1,3}
- Bronchodilation and relief of bronchospasm

Propofol

Advantages

- Sedation¹
- Hypnosis¹
- Anxiolysis¹
- ↓ ICP¹
- ↓ Cerebral metabolic rate¹
- Relief of bronchospasm¹

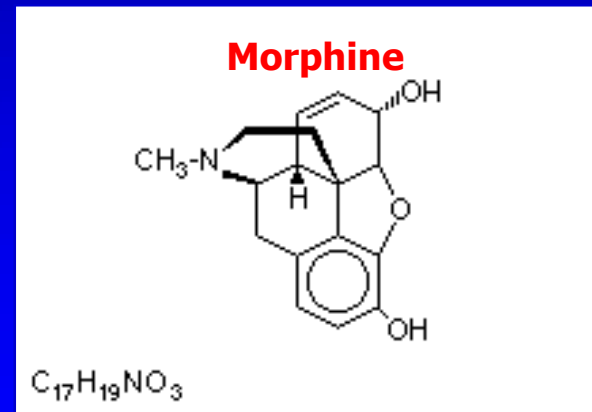
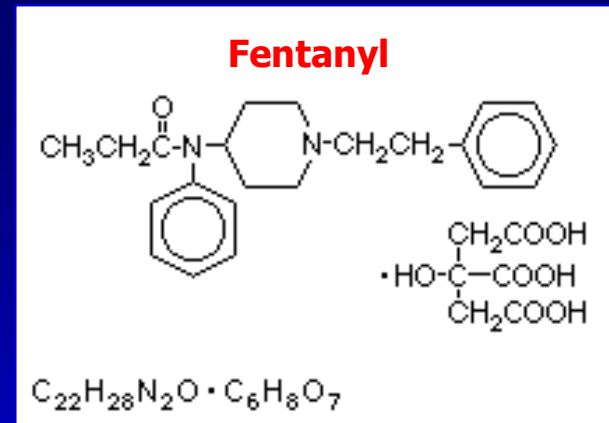
Limitations

- Respiratory depression (enhanced by opioids)¹
- Hypotension¹
- Decreased contractility²
- Lack of analgesia³
- Hypertriglyceridemia¹
- Preservative issues⁴
- Potential for infection⁵

1. Harvey. *Am J Crit Care*. 1996;5:7-16. 2. Lerch, Park. *Br Med Bull*. 1999;55:76-95. 3. Wagner, O'Hara. *Clin Pharmacokinet*. 1997;33:426-453. 4. Diprivan® [package insert]. 5. Prielipp et al. *Crit Care Clin*. 1995;11:983-1003.

Opioids: Clinical Effects

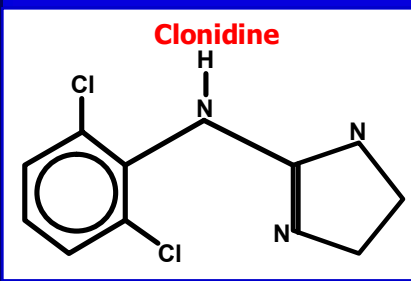
- Analgesia¹
- Sedation¹
- Tolerance¹
- Respiratory depression¹
- Withdrawal symptoms¹
- Hypotension¹
- Bradycardia²
- Constipation¹



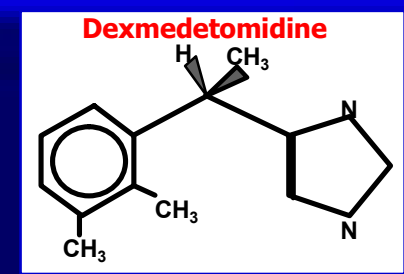
Opioids: Mechanisms of Action

- Analgesia by μ and κ receptors¹
- Sedation by κ receptor¹
- Inhibit adenylate cyclase, hyperpolarize neurons, suppress discharge
- Endorphins are endogenous ligands
- Antagonist available²

1. Wagner, O'Hara. *Clin Pharmacokinet.* 1997;33:426-453. 2. Stoelting. *Pharmacology and Physiology in Anesthetic Practice.* 3rd ed. 1999.



α_2 Agonists



Clonidine

- Selectivity: $\alpha_2:\alpha_1$ 200:1¹
- $t_{1/2}$ β 8 hrs¹
- PO, patch, epidural²
- Antihypertensive¹
- Analgesic adjunct¹
- IV formulation not available in US

Dexmedetomidine

- Selectivity: $\alpha_2:\alpha_1$ 1620:1³
- $t_{1/2}$ β 2 hrs³
- Intravenous³
- Sedative-analgesic³
- Primary sedative
- Only IV α_2 available for use in the US

1. Maze. White paper; 2000. 2. Khan et al. *Anaesthesia*. 1999;54:146-155. 3. Kamibayashi, Maze. *Anesthesiology*. 2000;93:1345-1349.

α_2 Agonists: Mechanisms for the Hypnotic Effect

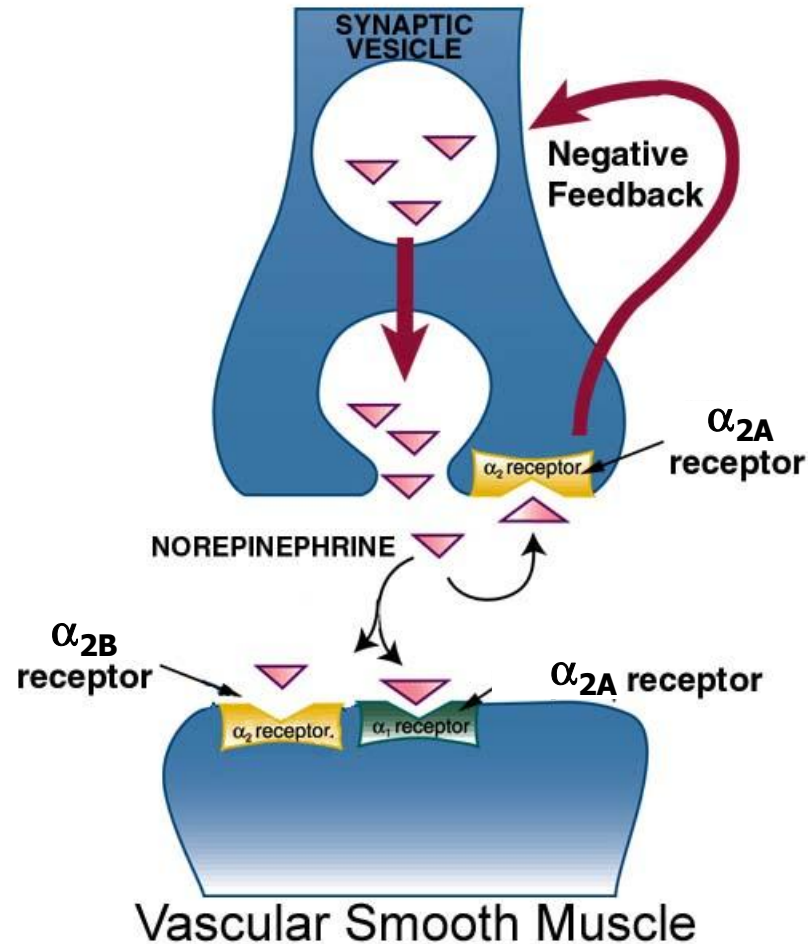
- Hyperpolarization of locus ceruleus neurons¹
 - α_{2A} -Adrenoreceptor subtype
 - Activation of K⁺ channels
 - Inhibition of Ca⁺⁺ channels
 - Inhibition of adenylyl cyclase
- ↓ Firing rate of locus caeruleus neurons²
- ↓ Activity in ascending noradrenergic pathway¹

α_2 Agonists: Pharmacodynamics

- Sedation/hypnosis¹
- Anxiolysis¹
- Analgesia¹
- Sympatholysis (BP/HR, NE)¹
- Reduces shivering²
- No effect on ICP³
- No respiratory depression¹

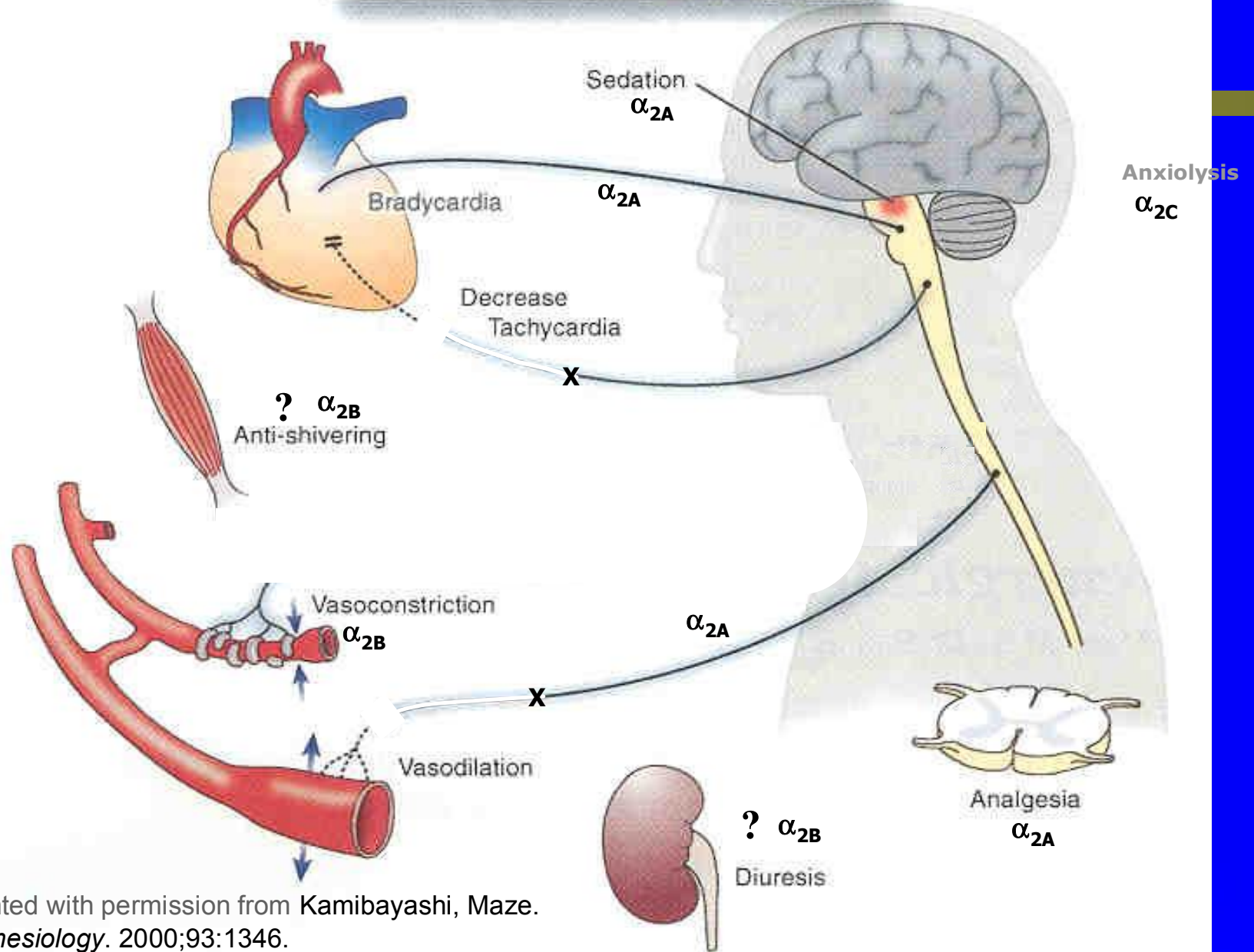
1. Aantaa et al. *Drugs of the Future*. 1993;18:49-56. 2. Kamibayashi, Maze. *Anesthesiology*. 2000;93:1345-1349. 3. Maze. White paper; 2000.

Peripheral α_2 Receptors



α_2 -Receptor Subtypes

Physiology of α_2 Adrenoceptors

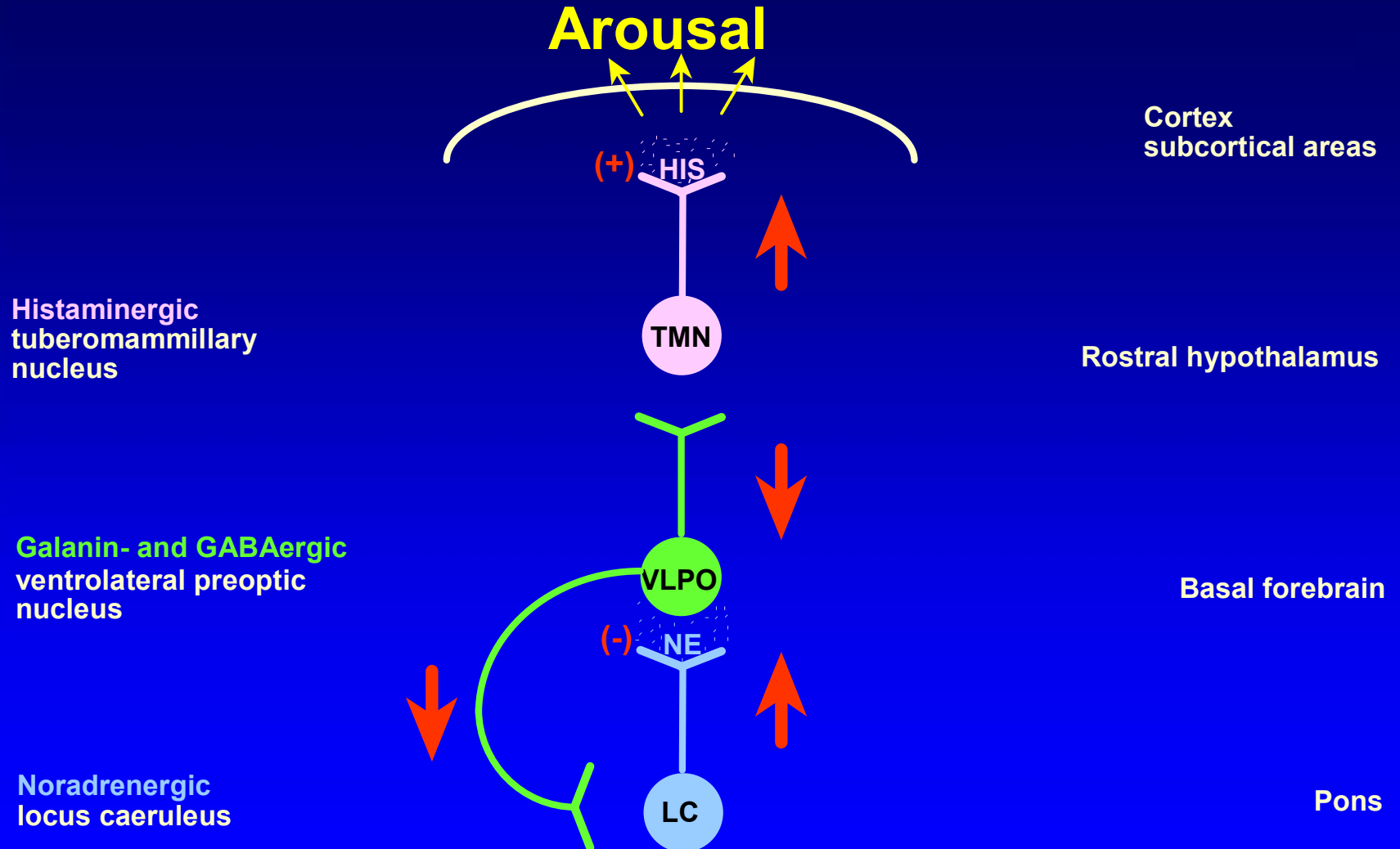


Causes of Unconsciousness

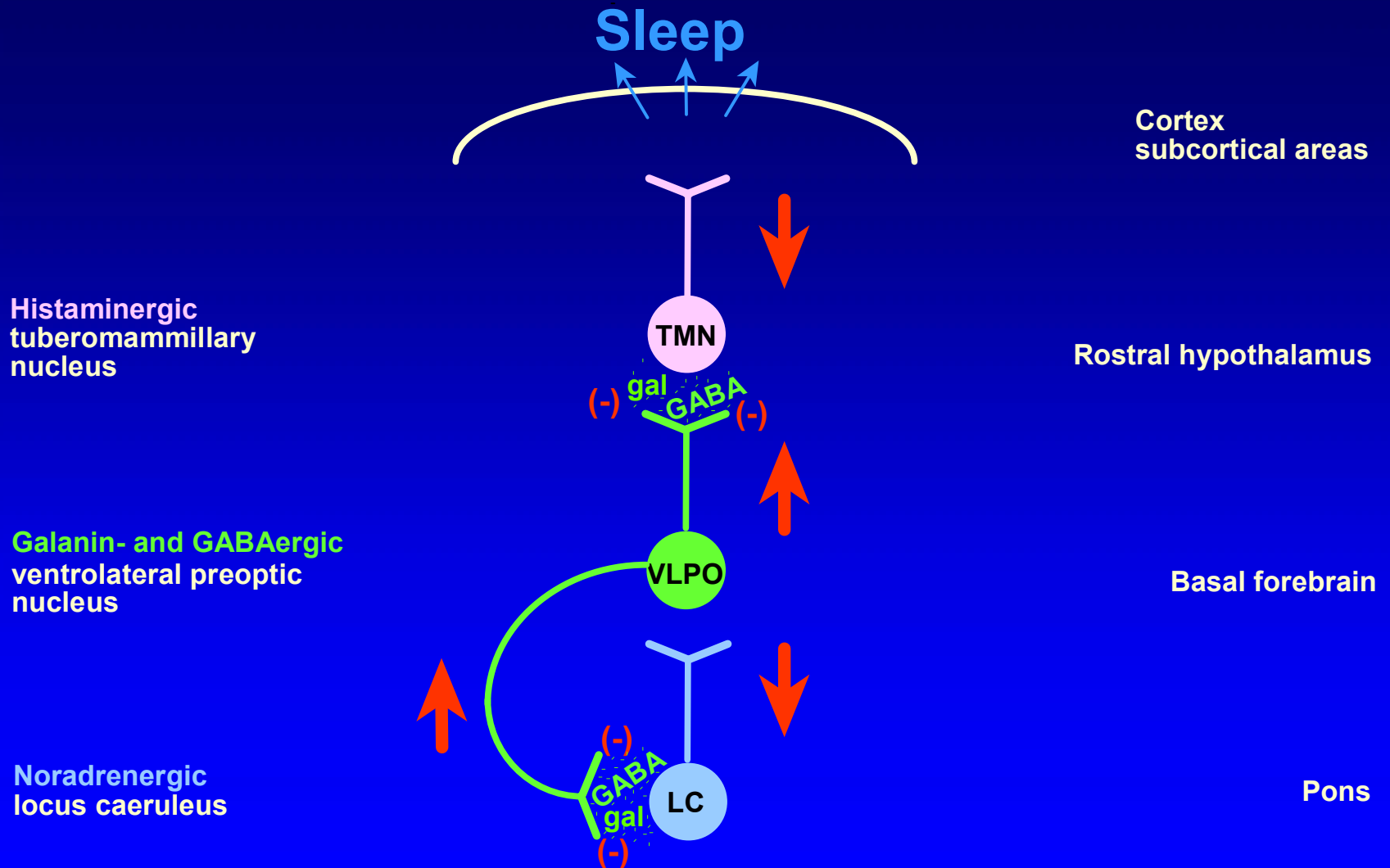
- Natural sleep
- Head injury
- Seizure/Post-ictal
- Sedative
- General anesthetic
- Exposure to Dr. Feldman's Lecture on Physics of Closed Circuit Anesthesia



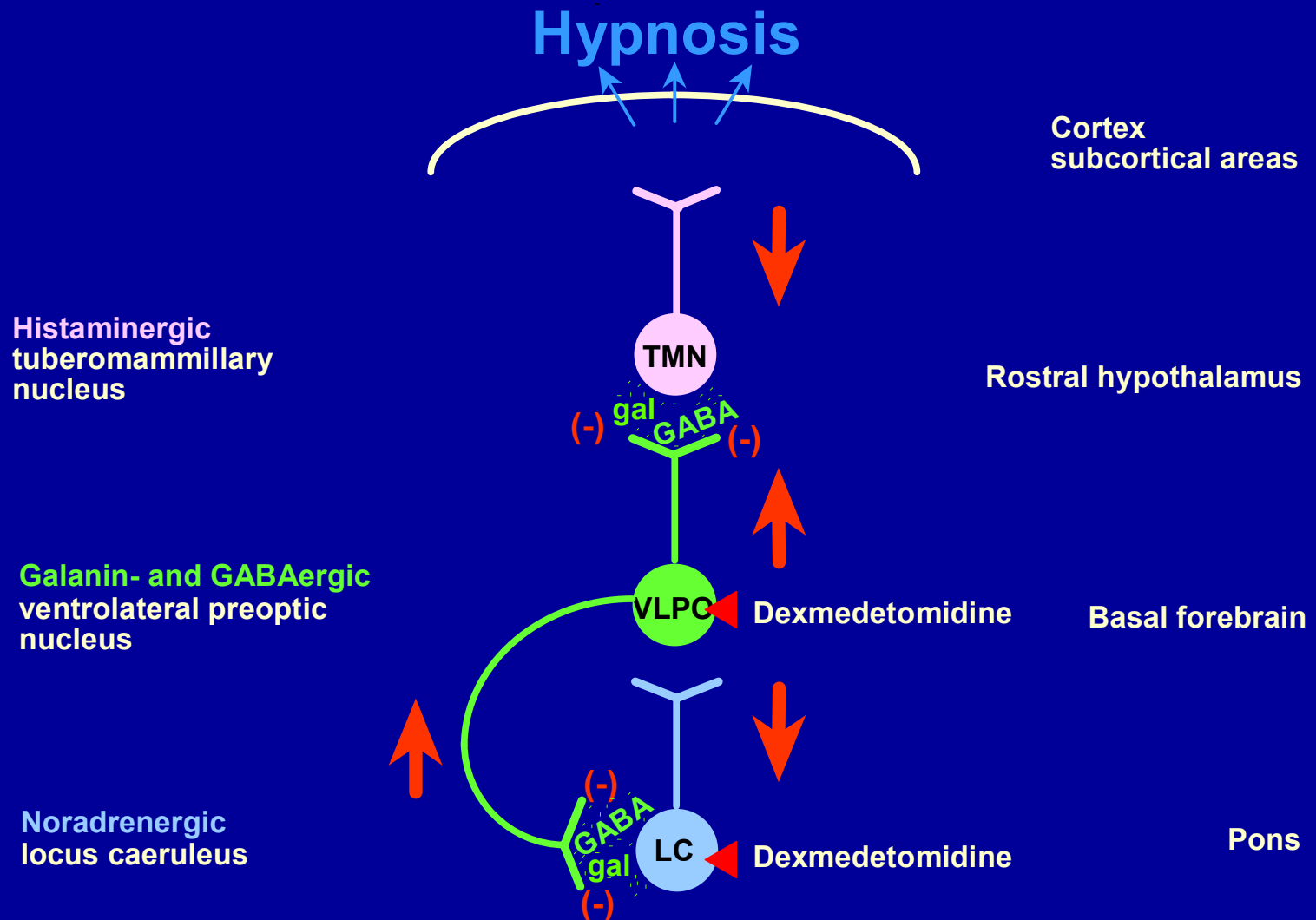
Natural Sleep Pathway



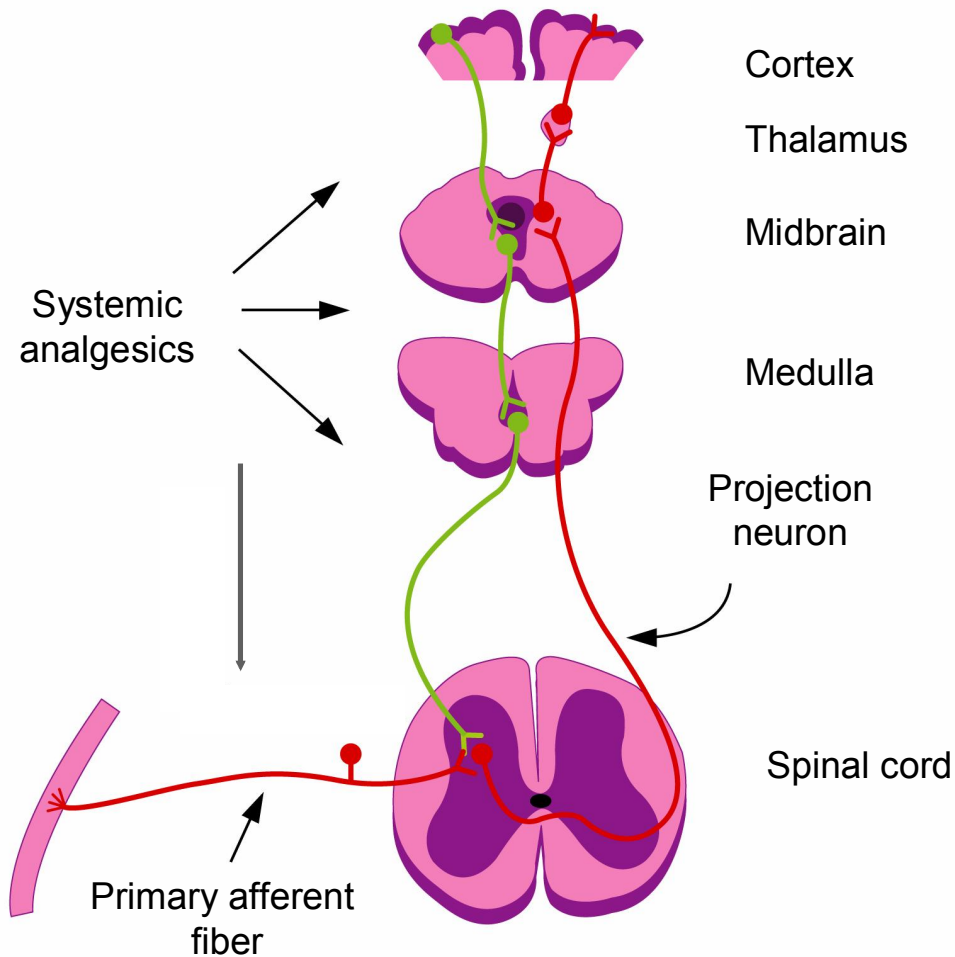
Natural Sleep Pathway



Dexmedetomidine Activates Natural Sleep Pathways



Ascending and Descending Pathways Affecting Nociception

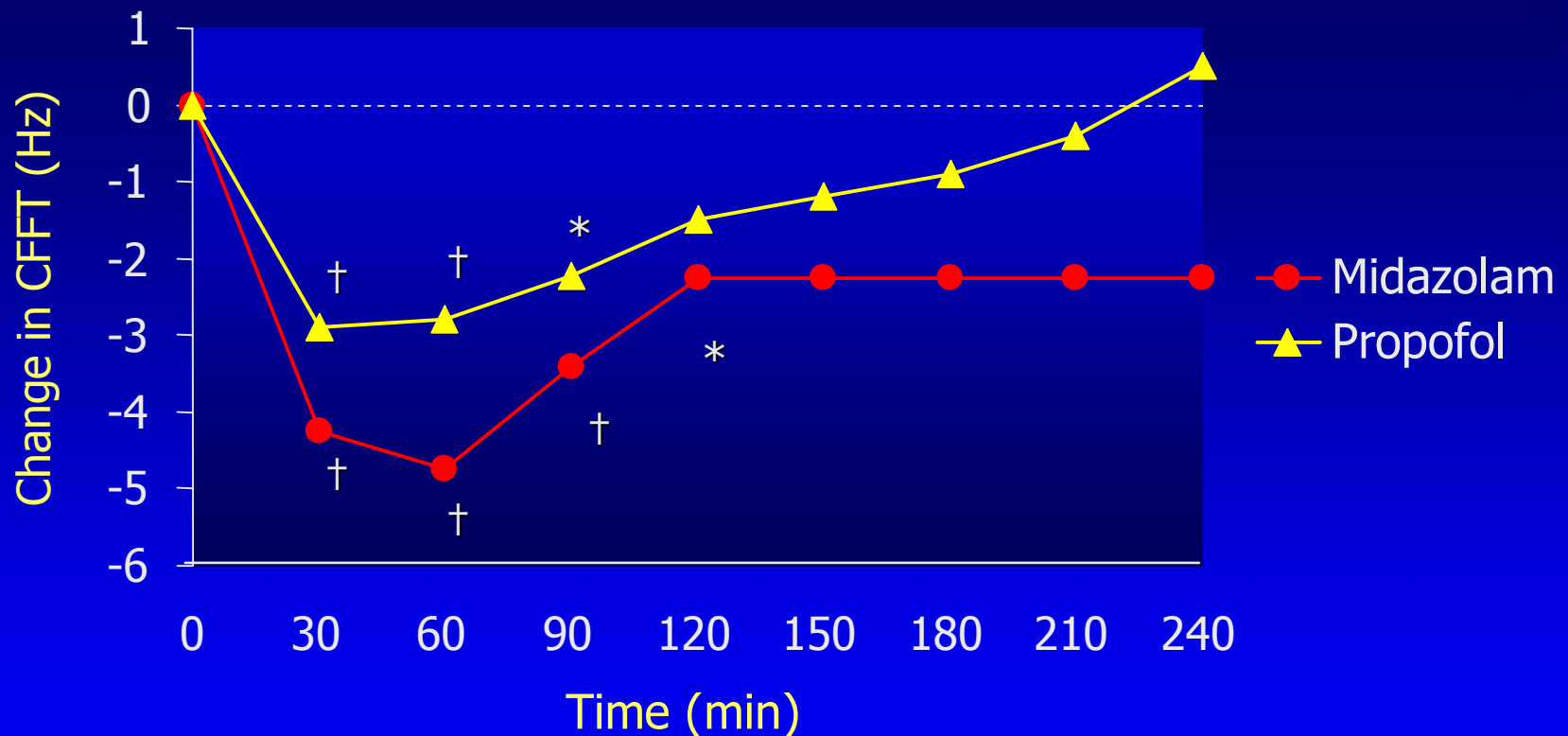


Mechanisms for Analgesic Effect

| | Opioids | α_2 Agonists |
|--------------------------------|---|---|
| Peripheral nociceptors | Inhibit inflammation | Inhibit sympathetic-mediated pain |
| Primary afferent neurons | Inhibit release of SP and glutamate | Inhibit release of SP and glutamate |
| Second order neurons | Inhibit firing | Inhibit firing |
| Subcortical | Decrease emotive aspects | Decrease emotive aspects |
| Descending inhibitory pathways | Activate PAG; activate noradrenergic pathways | Disinhibit A5/A7 noradrenergic pathways |

SP=substance P; PAG=periaqueductal gray.

Propofol and Midazolam: Critical Flicker Fusion Scores

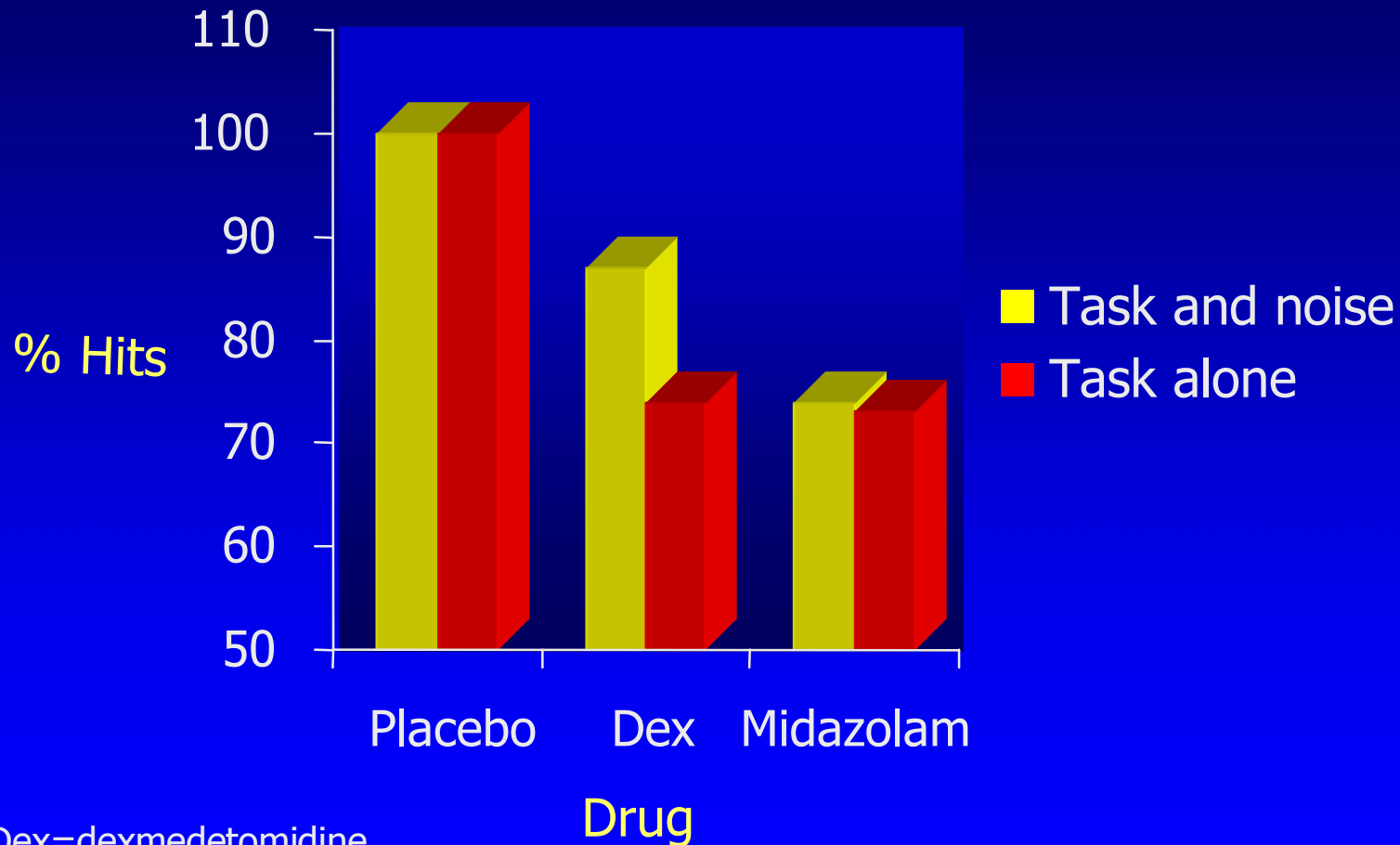


* $P < 0.05$; † $P < 0.005$.

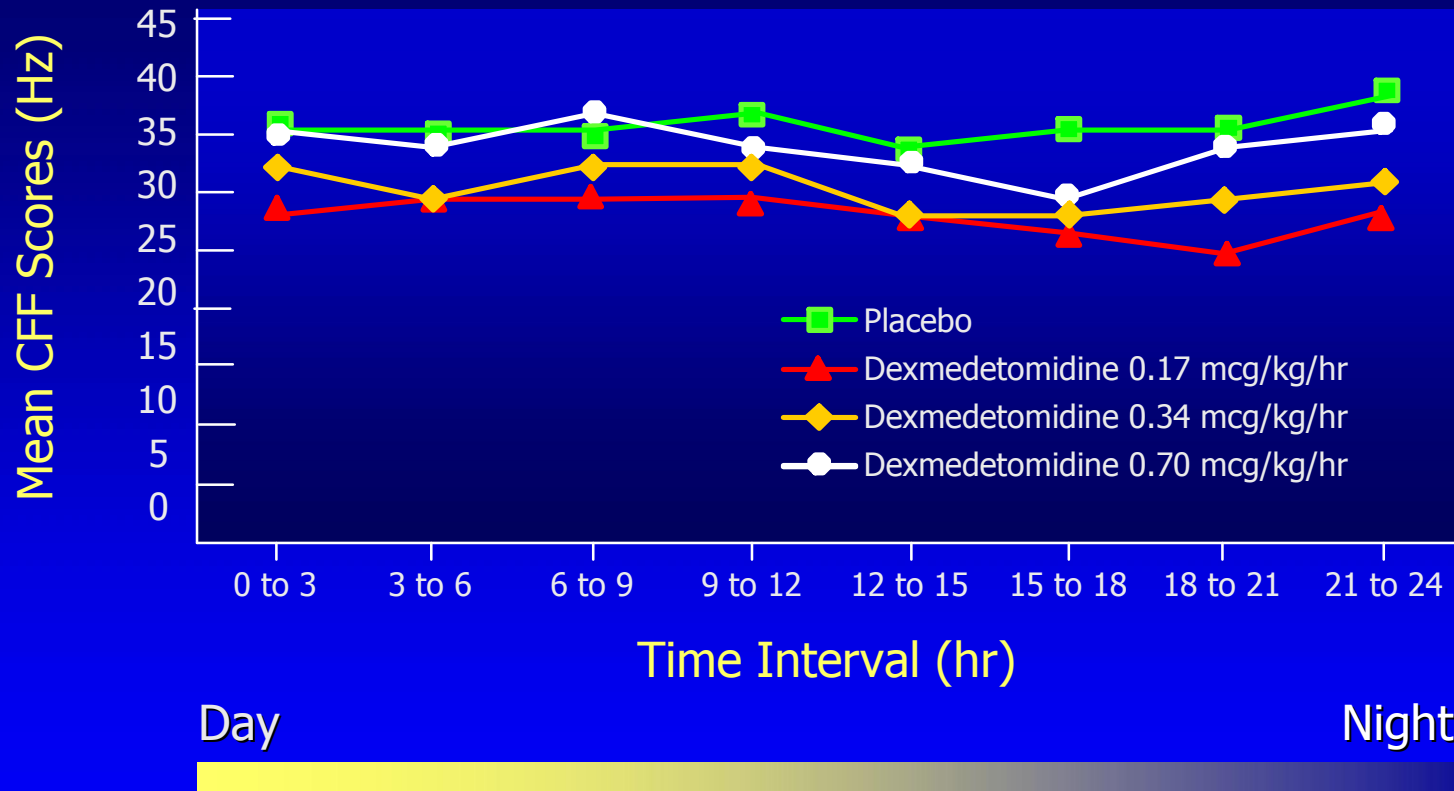
CFFT=critical flicker fusion threshold.

Adapted with permission from Wilson et al. *Br J Anaesth*. 1990;64:52.

Comparison of Equisedative Doses of Midazolam and Dexmedetomidine on Task Performance in Humans



Dexmedetomidine: Critical Flicker Fusion Scores

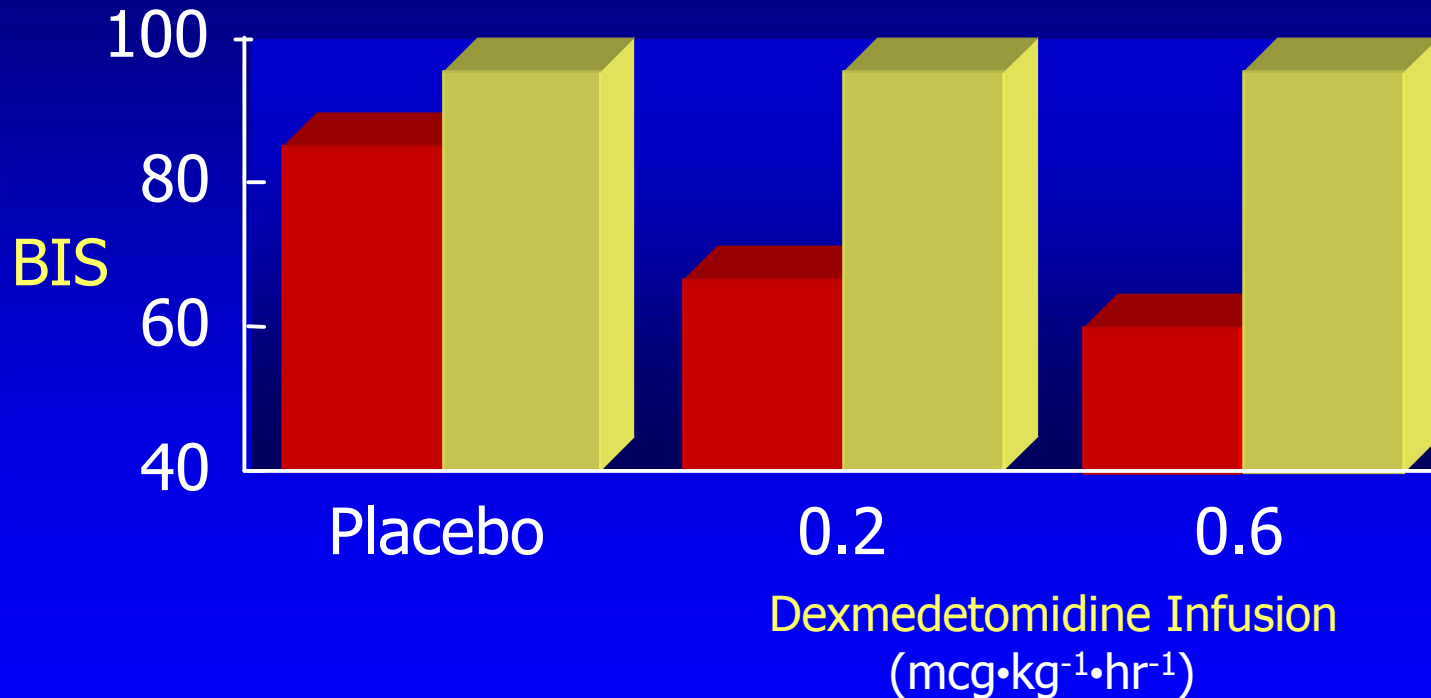


Arousal and Task Performance During Equisedative Doses of Benzodiazepine or α_2 Agonist in Humans

| | Benzodiazepine | α_2 Agonist |
|------------------------------|----------------|--------------------|
| Focused attention | ↓↓ | ↔ |
| Learning | ↓↓ | ↔ |
| Working memory | ↓ | ↔ |
| Task performance | ↓↓ | ↔ |
| Critical flicker fusion test | ↓ | ↔ |

Arousability From Sedation During Dexmedetomidine Infusion

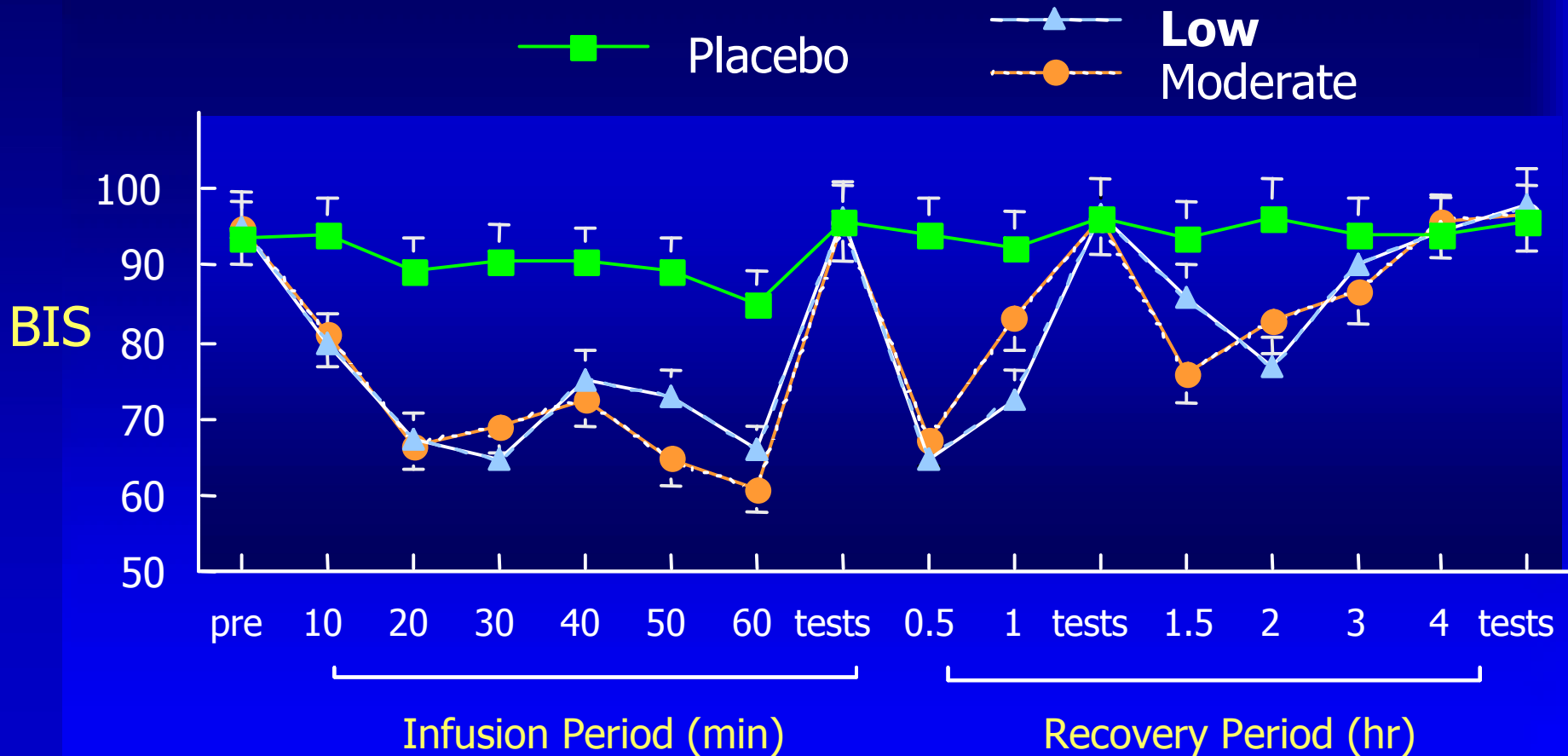
- Just prior to cognitive and cold pressor testing
- During cognitive and cold pressor testing



BIS=Bispectral Index System.

Adapted from Hall et al. *Anesth Analg*. 2000;90:701.

Arousability From Sedation During Dexmedetomidine Infusion



BIS=Bispectral Index System.

Adapted with permission from Hall et al. *Anesth Analg.* 2000;90:701.

Clinical Effects of α_2 Agonists

- Sedation/hypnosis¹
- Anxiolysis¹
- Analgesia¹
- Decreased sympathetic activity¹
- Decreased BP and HR²
- Vasoconstriction at high doses¹

Dexmedetomidine

Advantages

- Has sedative, analgesic, and anxiolytic effects¹
- Respiratory stability²
- Activates natural sleep pathways
- Arousable, oriented patient³
- No need to discontinue before extubation⁴
- Antishivering⁵

Limitations

- May reduce HR and BP (caution in hypovolemia, shock, and heart block)^{4,6}
- Potentiates effects of opioids, sedatives, and anesthetics⁴
- Dry mouth⁴
- Diuresis
- Vasoconstriction at high dose⁴

1. Aantaa et al. *Drugs of the Future*. 1993;18:49-56. 2. Frangoulidou et al. In: *Redefining Sedation*. 1998:40-50. 3. Mantz, Singer. In: *Redefining Sedation*. 1998:23-29. 4. Precedex[®] [package insert]. 5. Kamibayashi, Maze. *Anesthesiology*. 2000;93:1345-1349. 6. Hassan E. *Drugs*. 2000;59:270.

Pharmacologic Agent Overview

Cardiorespiratory Effects

| Agent | BP | HR | Respiration |
|----------------------------------|----|----|-------------|
| Opioids ¹ | ↓ | ↓ | ↓↓ |
| Benzodiazepines ¹ | ↓ | — | ↓ |
| Propofol ¹ | ↓↓ | ↓ | ↓↓ |
| Dexmedetomidine ^{2,4-5} | ↓↓ | ↓ | — |

—=no effect; ↓=reduced; ↓↓=further reduced.
BP=blood pressure; HR=heart rate.

1. Wagner, O'Hara. *Clin Pharmacokinet.* 1997;33:426-453.
2. Bhana N et al. *Drugs.* 2000; 59:263.
3. Harvey. *Am J Crit Care.* 1996;5:7-16.
4. Dahmani S et al. *Anesthesiology.* 2002;96:A750.
5. Eberspacher E et al. *Anesthesiology.* 2002;96:A802.

CNS Effects

| Agent | Analgesia | <i>Sedation</i> | | | Neuroprotection |
|------------------------------|-----------|-----------------|------------|---------|-----------------|
| | | Hypnosis | Anxiolysis | Amnesia | |
| Opioids ¹ | +++ | + | — | — | — |
| Benzodiazepines ² | — | +++ | ++ | +++ | ++ |
| Propofol ¹ | — | +++ | — | ++ | +++ |
| Dexmedetomidine ³ | ++ | ++ | ++ | + | + |

—=no effect

+ =some effect; ++=more effect; +++=most effect

1. Harvey MA. *Am J Crit Care*. 1996;5:7-16. 2. Pepperman. *Care of the Critically Ill*. 1989;5:195-199. 3. Kamibayashi T, Maze M. *Anesthesiology*. 2000;93:1345.

Adverse Effects

| | Midaz | Propofol | Opioids | Dex |
|--|-------|----------|---------|-----|
| Prolonged weaning ¹ | X | X | X | |
| Respiratory depression ¹ | X | X | X | |
| Hypotension ¹⁻³ | X | X | X | X |
| Constipation ¹ | | | X | |
| Lack of orientation and cooperation (high doses) | X | X | X | |
| Arrhythmias ¹ | | | | X* |

*Bradycardia;

Midaz=midazolam; Dex=dexmedetomidine.

1. Harvey MA. *Am J Crit Care*. 1996;5:7-16. 2. Aantaa R et al. *Drugs of the Future*. 1993;18:49-56. 3. Maze M. *Crit Care Clin*. 2001;4:881.

Clinical Effects

| | Midaz | Propofol | Opioids | Dex |
|---|-------|----------|---------|-----|
| Alleviate anxiety ^{1,2} | X | X | | X |
| Relieve pain ¹⁻⁴ | | | X | X |
| Simulates natural sleep | | | | X |
| Promote arousability during sedation ²⁻⁴ | | | | X |
| Promote respiratory stability ¹⁻⁴ | | | | X |
| | | | | |
| | | | | |

Midaz=midazolam; Dex=dexmedetomidine.

1. Harvey MA. *Am J Crit Care*. 1996;5:7-16. 2. Aantaa R et al. *Drugs of the Future*. 1993;18:49-56. 3. Maze M. White paper; 2000. 4. Maze M. *Crit Care Clin*. 2001;4:881.

Cost of Sedatives

| Product Name | Vial Size | Average Wholesale Price |
|--|------------------------|-------------------------|
| Propofol (Diprivan tm) | 10 mg/ml 50 ml vial | \$34 |
| Midazolam (Versed tm) | 5 mg/ml 1 ml vial | \$9.59 |
| Dexmedetomidine (Precedex tm) | 100 mg/ml 2 ml vial | \$55 |

Clinical Uses for Dexmedetomidine

- Approved by FDA
 - Sedation of mechanically ventilated patients in ICU setting
- Off-Label Uses
 - Sedation for fiberoptic endoscopy and intubation
 - Sedation for MRI
 - Potential role in sedation for ophthalmic surgery



Potential Clinical Use for Ophthalmic Surgery (Off-Label)

- Vitreoretinal
 - Control of hypertension and tachycardia
 - Somnolent – arousable to clear consciousness
- Cornea Transplant
 - Decrease in IOP
 - Control of heart rate
- Oculoplastics
 - Arousable for examination of eyelid function
- Caution:
 - Bradycardia and hypotension
 - Hypertension on loading
 - Dry mouth and thirst
 - Diuresis

How I Have Done It

- Dexmedetomidine (Precedextm)
 - 200mg/2cc vial
 - 1cc (100 mg) / 50 cc syringe Saline
 - Loading dose of 1 mcg/kg (lean body weight)
 - Administer via infusion pump over 10 – 20 minutes
 - Turn down infusion rate to 0.2 mcg/kg/hr
- Wait 3-5 minutes.
- Administer block
- Continue infusion rate in OR if indicated.
- Add small dose of propofol or fentanyl if needed.
- Stop infusion 15-30 minutes before the end of the procedure for outpatients.

My Experience

| Anesthesia Technique | Number of Patients | Number of Life or Sight Threatening Complications |
|----------------------|--------------------|---|
| Retrobulbar | 24,000 | 5 |
| Dexmedetomidine | 16 | 0 |

Summary

- **Dexmedetomidine is a new sedative**
 - Alpha-2 agonist
 - Minimal respiratory depression
 - Hypnosis, anxiolysis, amnesia, and analgesia
 - Patients are arousable with clear consciousness
- **Approved by FDA for ICU sedation**
- **Potential for serious bradycardia and hypotension.**
- **Promising role in ophthalmic surgery.**