Clinical Pearls for Medication Use in End of Life Care

MOQC Biannual Meeting

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Disclosures

- No relevant financial disclosures or conflicts of interest

Outline

- Learning Objectives
- Adventures in Symptom Management

Learning Objectives

- Discover the mechanisms of pain and match them with the appropriate medication
- Explore the mechanisms of nausea and match them with the appropriate medication
- Navigate medication options for patients with anxiety/depression, dyspnea, fatigue, and terminal secretions

Pain

- Unpleasant sensory and emotional response associated with actual or potential tissue damage
- Acute – occurs suddenly, short-lived, resolves as acute illness resolves
- Chronic – lasts longer than expected healing process (or > 3mths), affects ADLs

www.iasp-pain.org/terms-p.html
http://www.painfoundation.org/learn/publications/files/PainResourceGuide2009.pdf

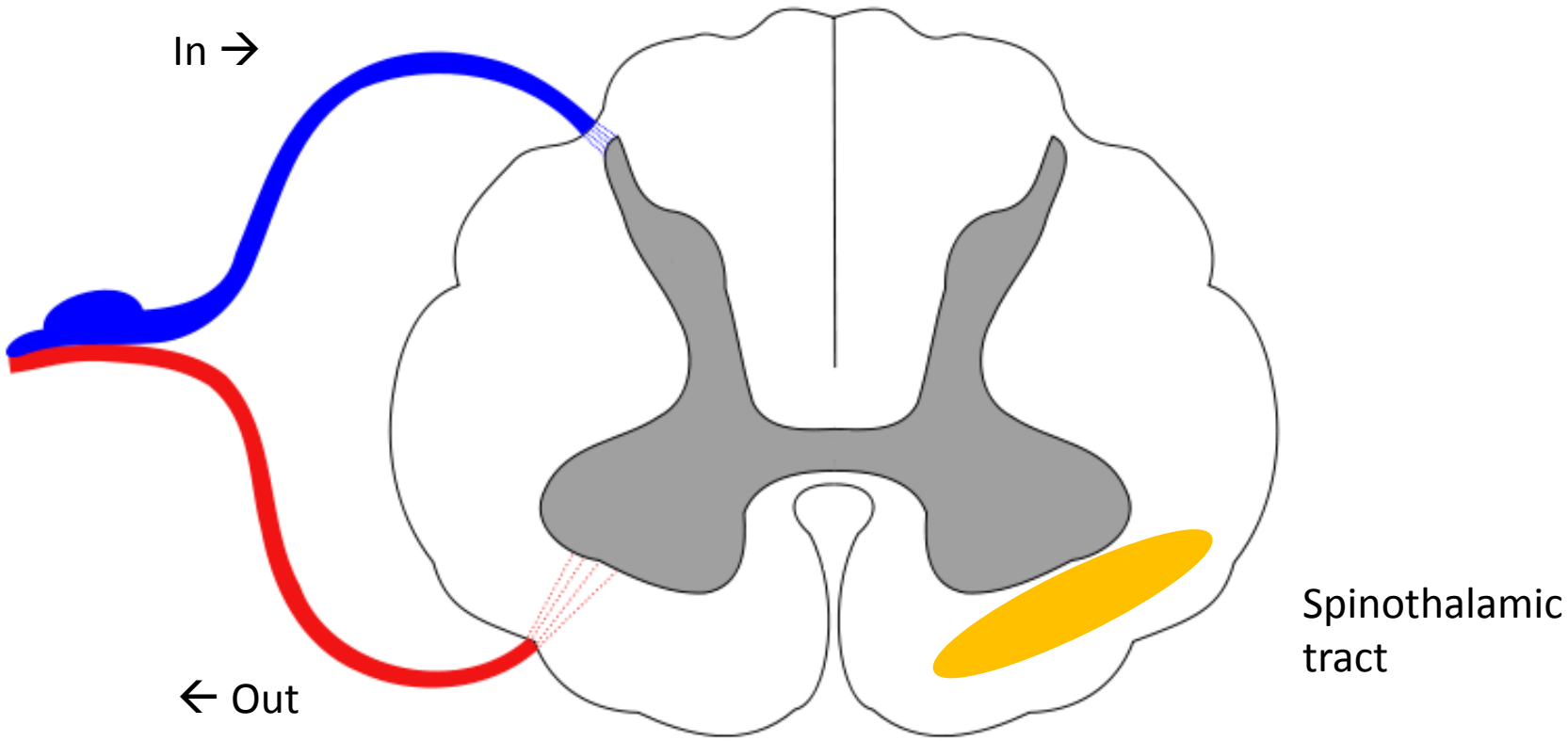
Mechanistic Characterization

Peripheral (Nociceptive)	Neuropathic	Centralized Pain
▪ Inflammation or mechanical damage in tissues ▪ NSAID, opioid responsive ▪ Responds to procedures	▪ Damage or dysfunction of peripheral nerves ▪ Responds to both peripheral (NSAIDs, opioids, Na channel blockers) and central (TCAs, SNRIs) drug therapy	▪ Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia) ▪ Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission
▪ Classic examples ▪ Acute pain 2/2 injury ▪ Osteoarthritis ▪ Rheumatoid arthritis ▪ Cancer pain	▪ Classic examples ▪ Diabetic neuropathic pain ▪ Post-herpetic neuralgia	▪ Classic examples ▪ Fibromyalgia ▪ IBS ▪ TMJD ▪ Tension headache

Mixed Pain States

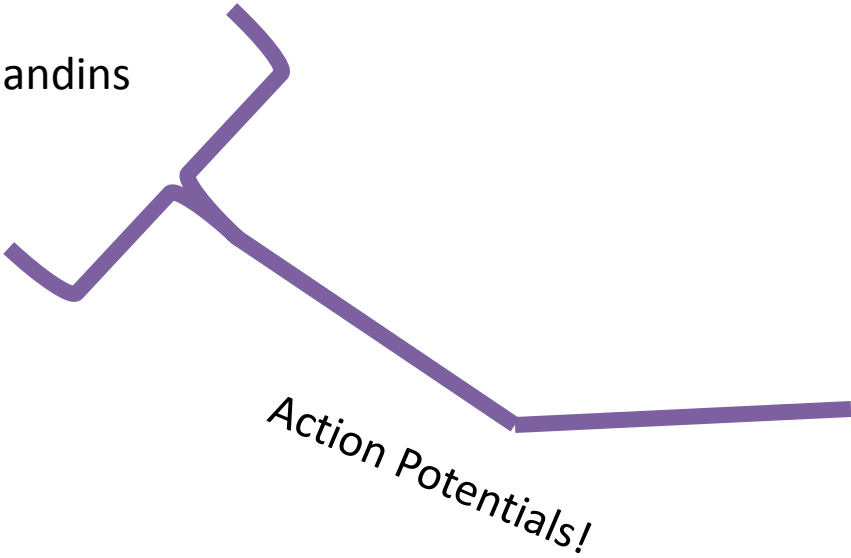
The Brain

Spinal Cord

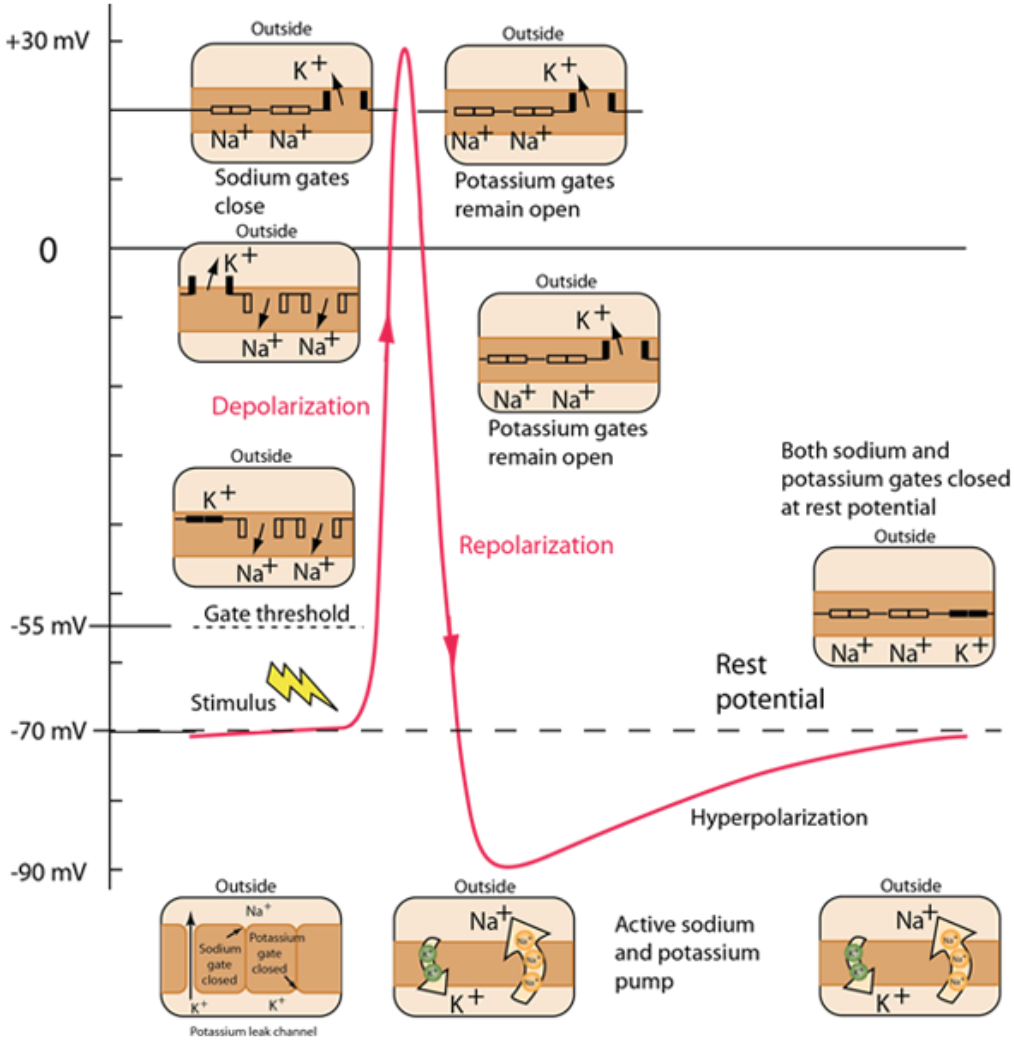


Injury

Prostaglandins

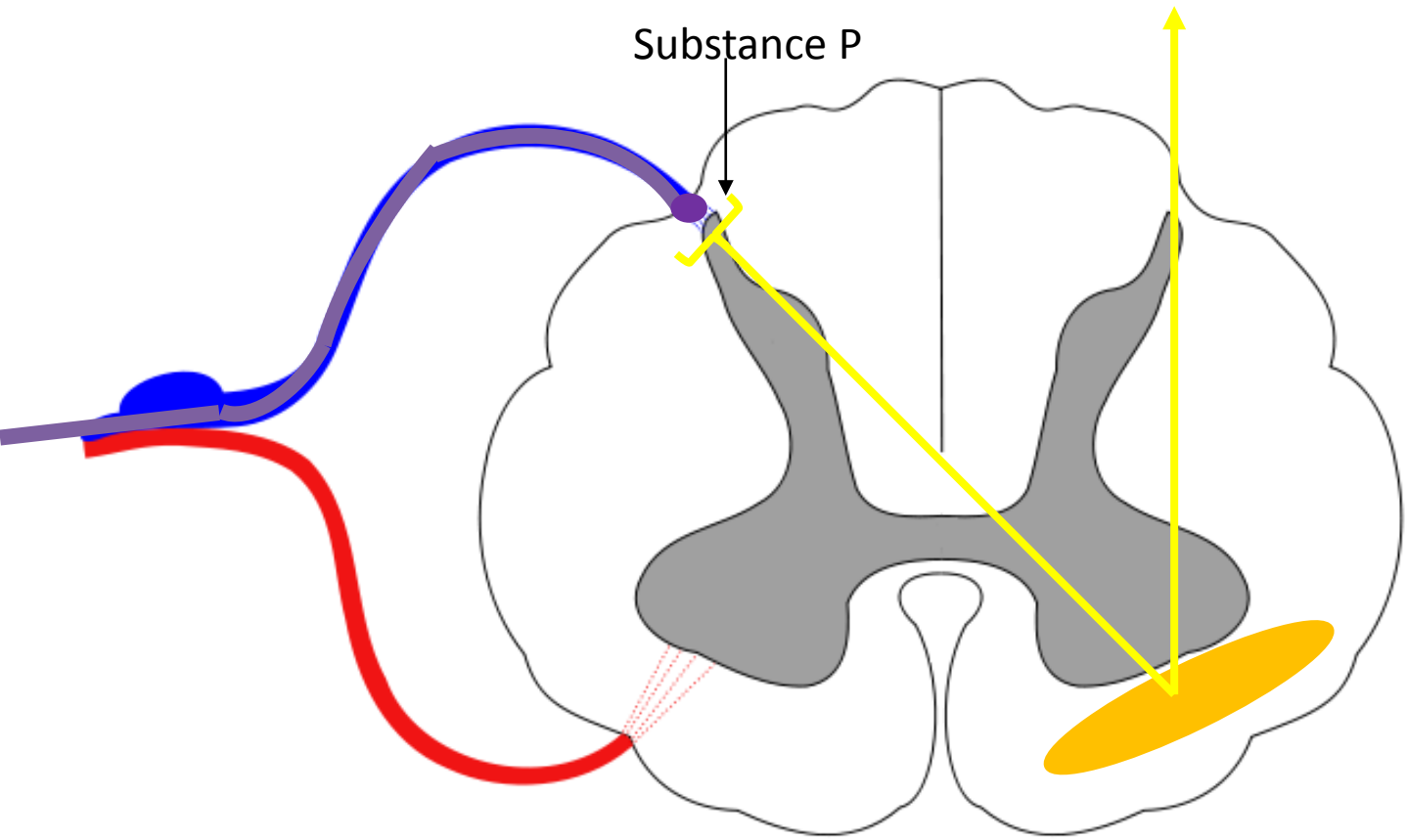


Action Potentials

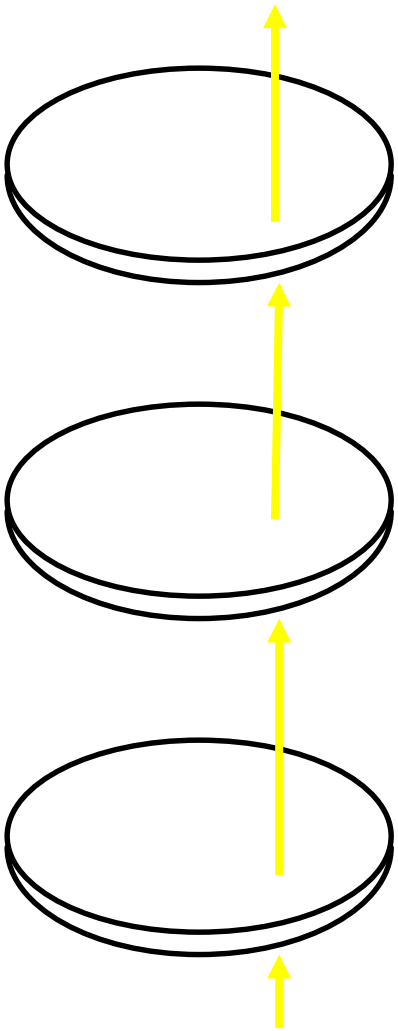


http://hyperphysics.phy-astr.gsu.edu/hbase/Biology/actpot.html

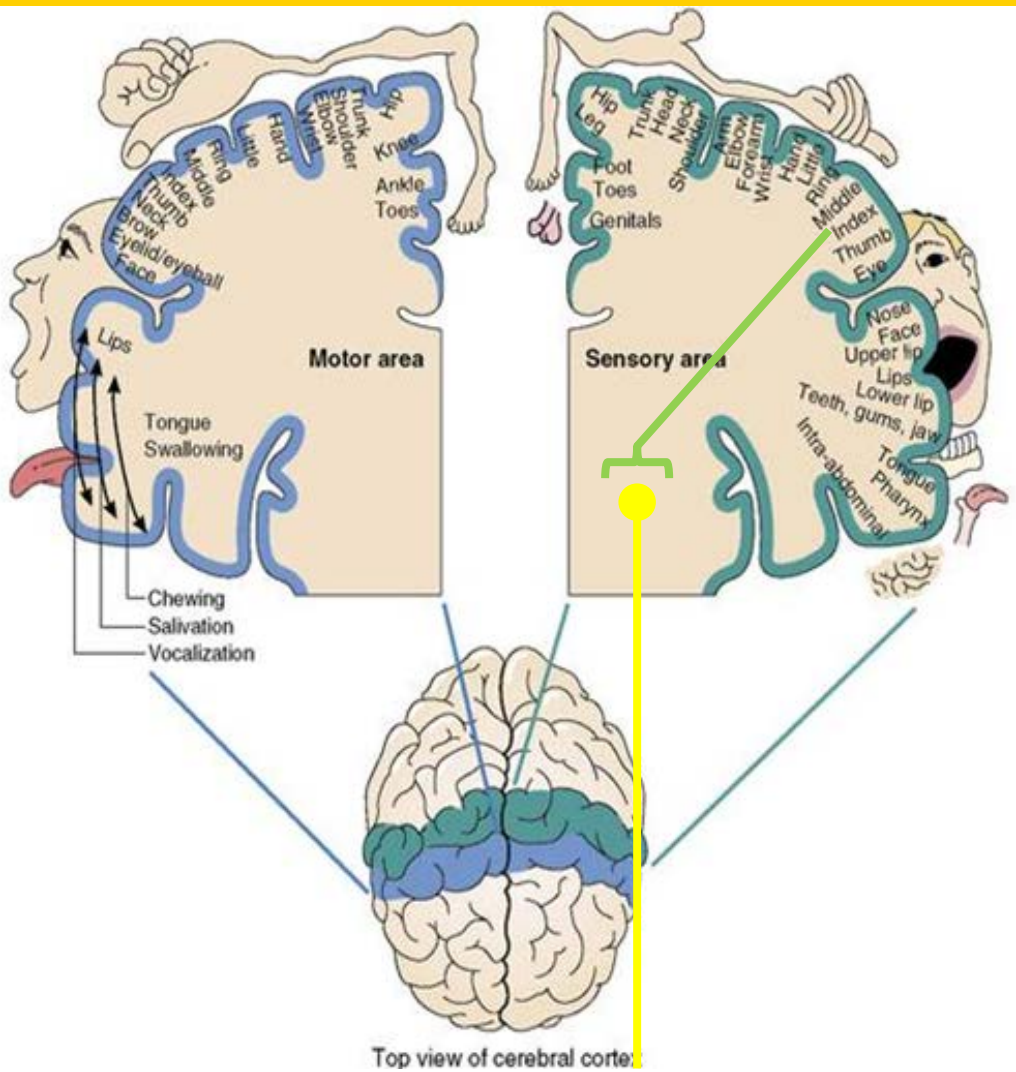
Spinal Cord



Brainstem

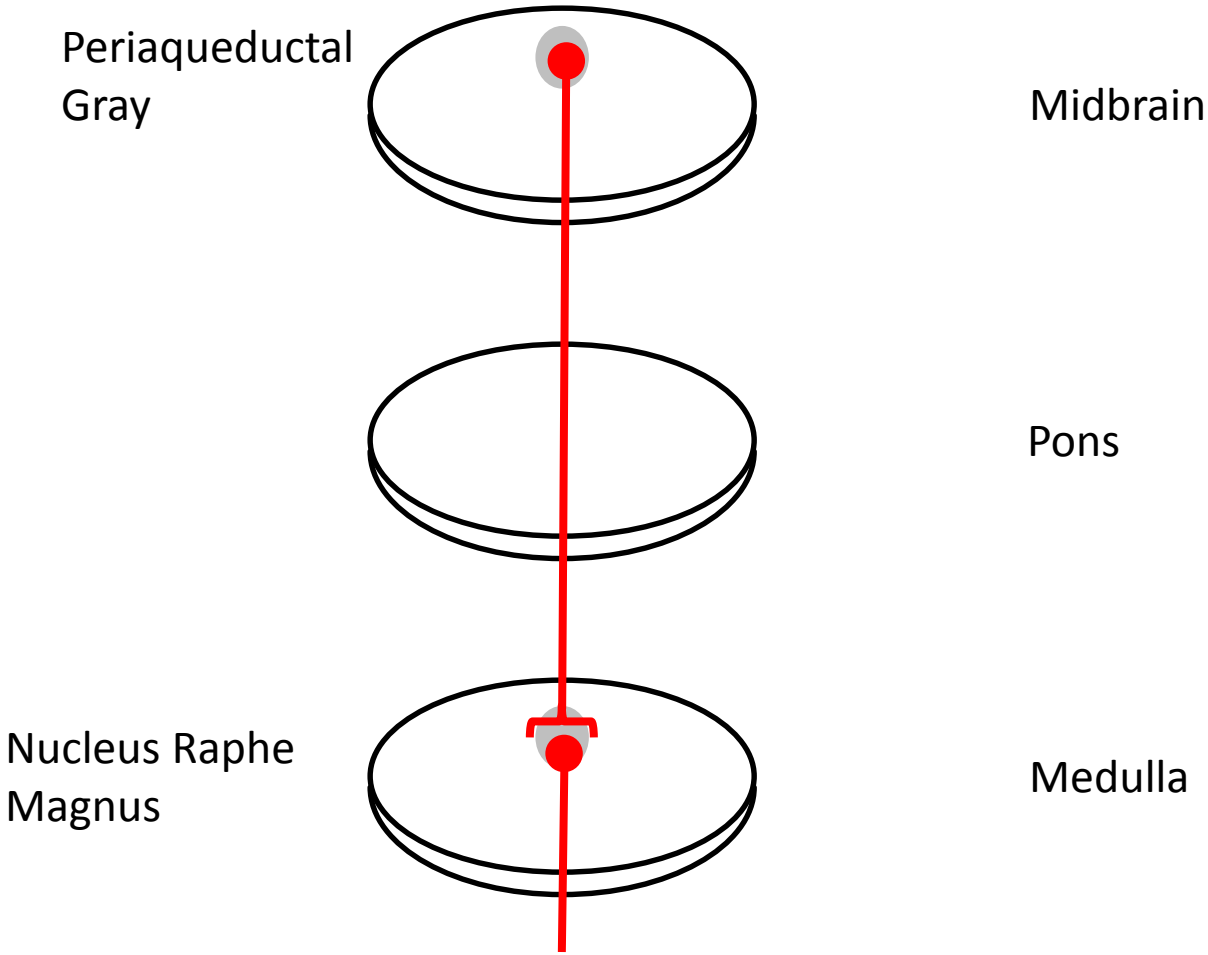


Somatosensory Cortex

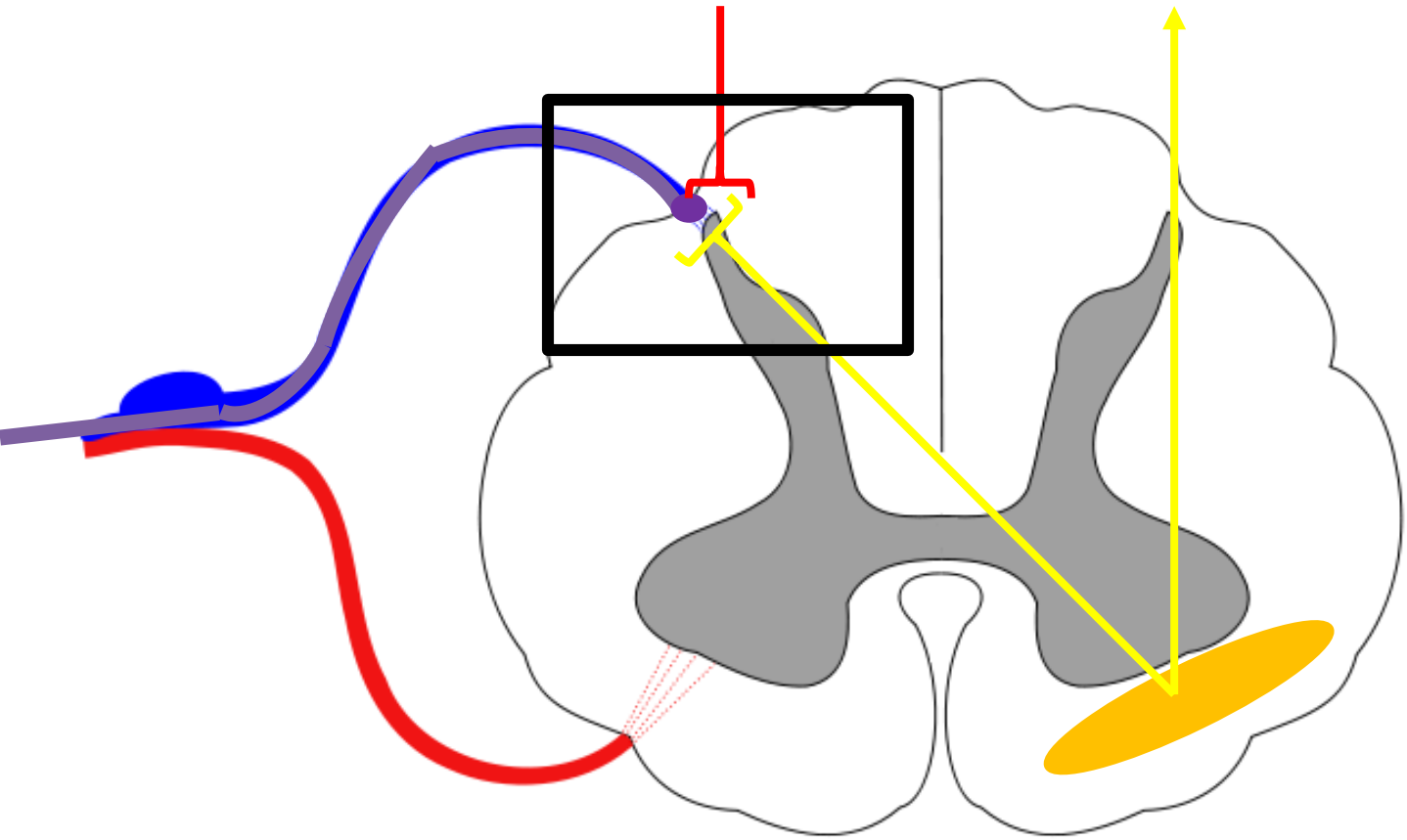


http://www.esd-training.org.uk/MotorcontrolAdvanced5.html

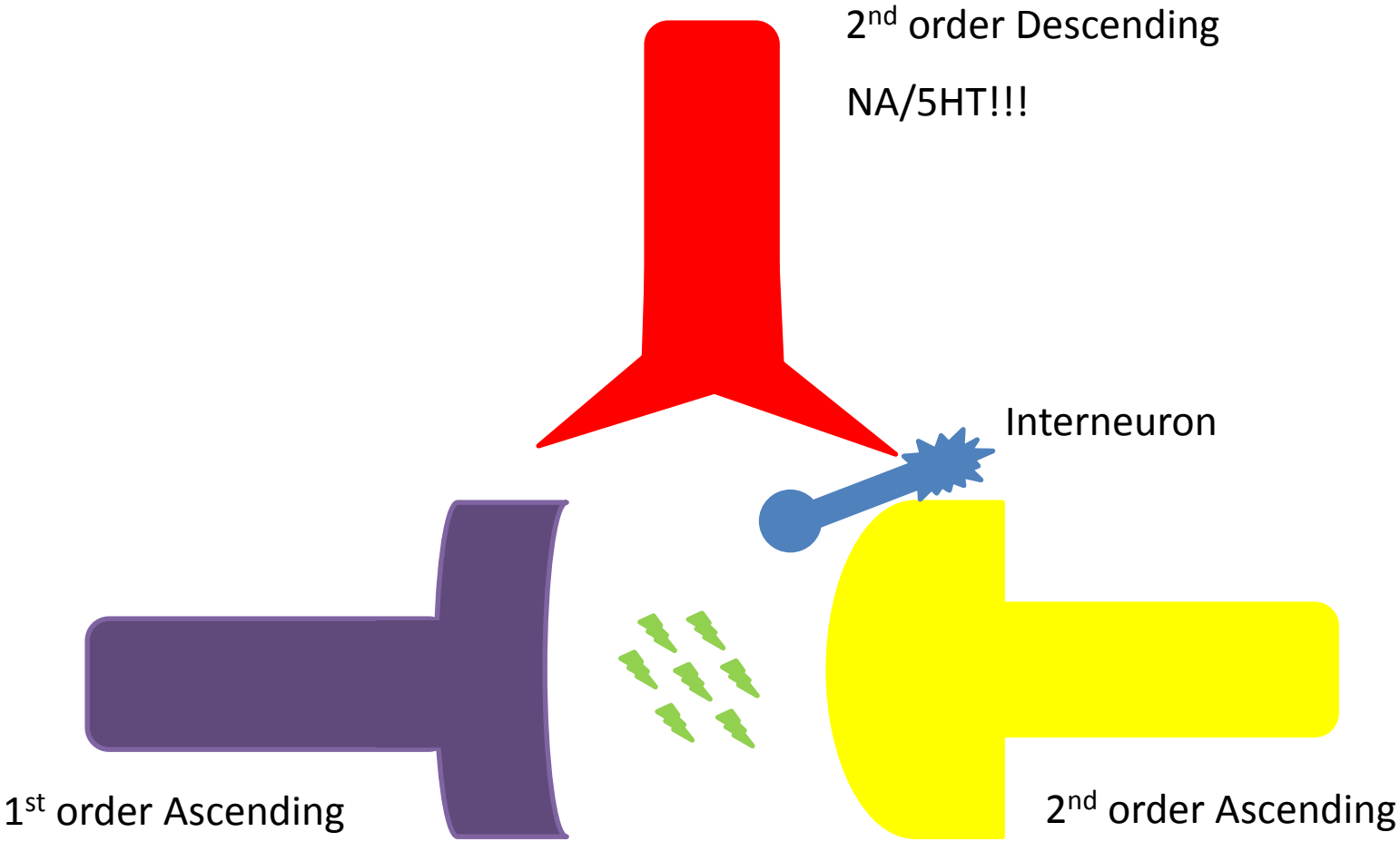
Brainstem


Periaqueductal Gray
Midbrain
Pons
Nucleus Raphe Magnus
Medulla

Spinal Cord

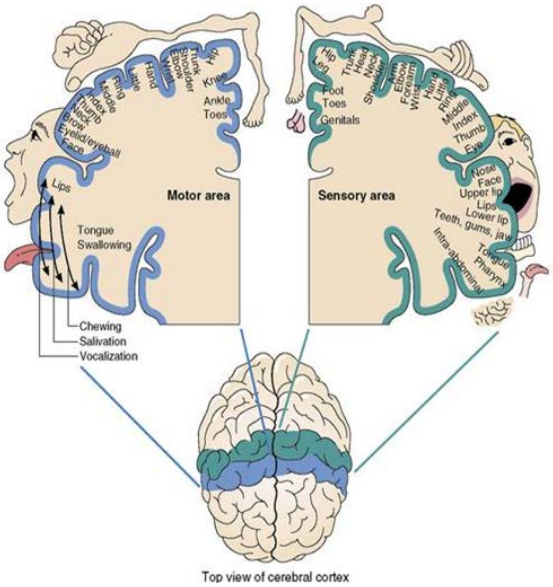


Gate Theory


2nd order Descending
NA/5HT!!!
Interneuron
1st order Ascending
2nd order Ascending

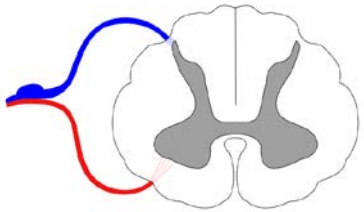
Pathophysiology-Pharmacology

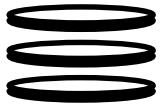
Opioids
Alpha2 Agonists



Local anesthetics
NSAIDs

Local anesthetics
Opioids
Alpha2 Agonists





SNRIs/TCAs

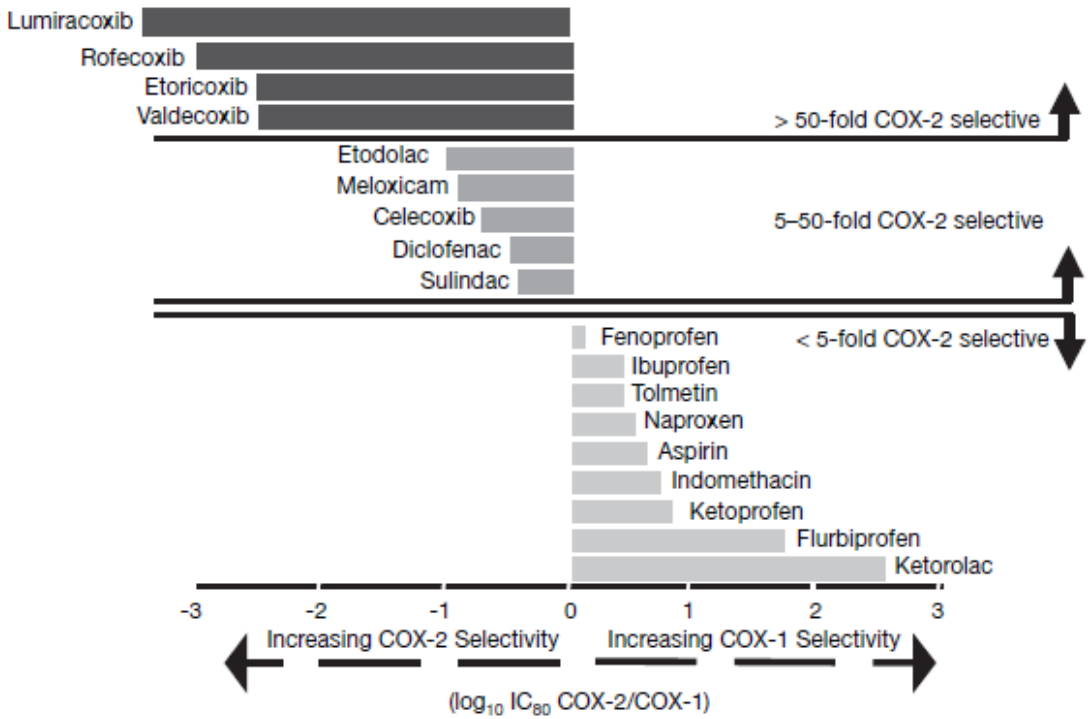
Name Those Drugs!

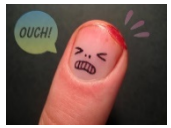
- Name at least 50 drugs to treat pain

Acetaminophen	Oxycodone	Desipramine	Carbamazepine
Diclofenac	Hydromorphone	Imipramine	Oxcarbazepine
Etodolac	Oxymorphone	Amitriptyline	Naltrexone
Fenoprofen	Buprenorphine	Doxepin	Mexilitene
Ibuprofen	Methadone	Gabapentin	Corticosteroids
Indomethacin	Fentanyl	Pregabalin	Cannabinoids
Ketorolac	Remifentanil	Duloxetine	Tizanidine
Meloxicam	Sufentanil	Venlafaxine	Carisoprodol
Naproxen	Levorphanol	Milnacipran	Chlorzoxazone
Sulindac	Butorphanol	Lidocaine	Baclofen
Celecoxib	Nalbuphine	Triptans	Cyclobenzaprine
Codeine	Tramadol	Corticosteroids	Methocarbamol
Morphine	Tapentadol	Ketamine	Dexmedetomidine
Hydrocodone	Nortriptyline	Topiramate	Clonidine

NSAIDs

- Inhibit cyclo-oxygenase enzymes
  - Decreases the formation of prostaglandin precursors

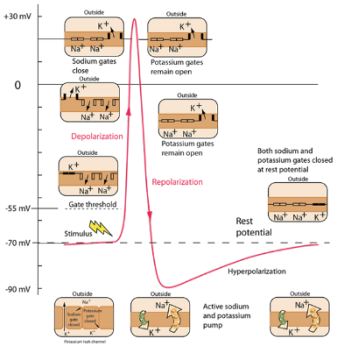




Herndon. Pharmacother. 2008; 28(6):788-805.

Membrane Stabilizers

- Sodium-channel blockers
  - Carbamazepine
  - Oxcarbazepine
  - Lamotrigine
  - Phenytoin
  - Topiramate
- Calcium-channel blockers
  - Gabapentin
  - Pregabalin
- Anesthetics
  - Lidocaine
  - Mexiletine



Mechanistic-Pharmacology

	Peripheral (Nociceptive)	Neuropathic	Centralized
NSAIDs	√	X	X
Opioids	√	√	X
Surgery/Injections	√	√	X
TCAs	√	√	√
SNRIs	√	√	√
Gabapentinoids	X	√	√
Cannabinoid	X	√	√

Agitation and Delirium

- Drugs are not like cowbells
- Identify and treat underlying and reversible causes first
- Opioid rotation and de-prescribe
  - Anticholinergics, opioids, anxiolytics, hypnotics, anticonvulsants, antidepressants, steroids
  - NSAIDs, omeprazole, ranitidine, anti-infectives

Bush. Ann Oncol. 2018; 29 (S4): iv143-65.
Inouye. Lancet. 2014; 383 (9920): 911-22.
Caraceni. EJC Suppl. 2013; 11 (2): 233-40.

Neurotransmitters

Delirium Source	ACH	DA	GLU	GABA	5HT	NE	Trp	Mel	Phe	His	Cytok	HPA axis	Cort	NMDA activity	RBF Δ	Inflam	EEG
Anoxia/hypoxia	↓	↑	↑	↑	↓	↓	⇔	↓	↑	↑,↓	⇊↑	⇊	↑	↑	⇊	↑	↓
Aging	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	⇊↑	⇊	↑	↓	⇊	↑	↓
TBI	↑	↑	↑	↑	↑	↑	↑	↓	↑	↓	↑⇊	↑	↑	↑	↑	↑⇊	↓
CVA	↓	↑	↑	↑	↑	↑	↑	↓	↑	↓	↑⇊	↑	↑	↑	⇊	↑⇊	↓
Hepatic Encephalopathy	⇔	↓	↑	↑↑	↑	↓	↑	↓	↑	↑	↑⇊	⇊	↑	↑	⇊	↑	↓
Sleep deprivation	↓	↓	⇊	↑	↑	↑	↓	↓⇊	↑	↑	↑	⇊	↑	↑	↑	↑⇊	↓
Trauma, Sx, & Post-op	↓	↑	↑	↑	↓	↑	↓	↓	↑	↑	↑	↑	↑	↑	⇊	↑	↓
ETOH & CNS-Dep Withdrawal	↑	↑	↑	↓	↑	↑	↓	↓	↑	↑	↑	↑⇊	↑	↑	↓	↑	↑
Infection/Sepsis	↓	↓	↑	↑	↓	↓	↓	↓	↓	↓	↑	↑⇊	↑	↑⇊	⇊	↑	↓
Dehydration & Electrolyte Imbalance	⇔	↑	↑	↑	↓	↑	?	↓	?	↑	↑	⇊	↑	↑	↓	⇊↑	⇊
Medical Illness	↓	↑	↑	⇊	↓	↑	↓	↓	↑	↑	↑	↓	↑	↑	⇊	⇊	⇊

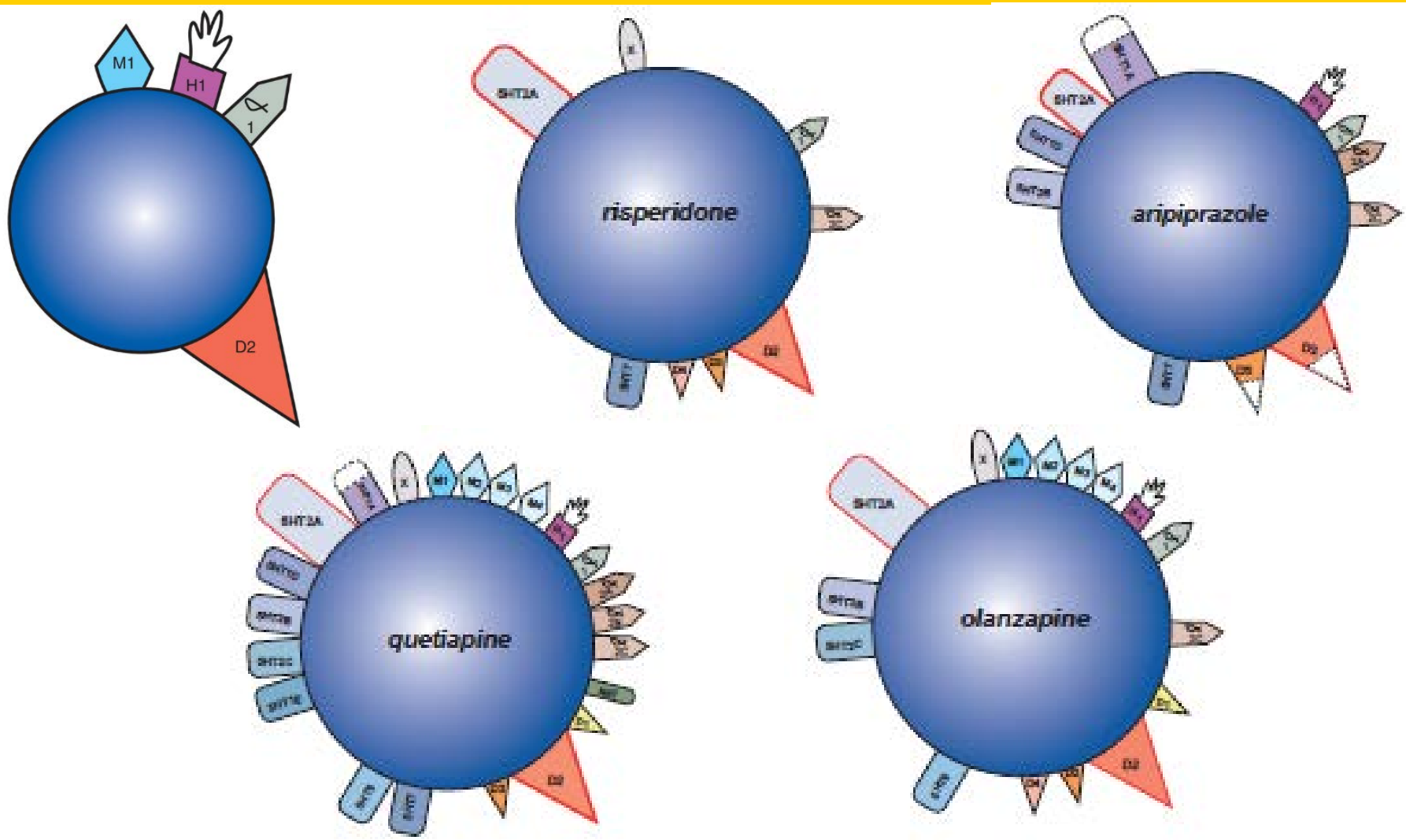
Maldonado. Int J Geriatr Psychiatry. 2018; 33: 1428-57.

Antipsychotic Mechanism

- Remember your antipsychotic pharmacology?
  - Typical – block D2 receptors
    - Chlorpromazine, haloperidol
  - Atypicals – block D2 receptors + something else
    - Usually 5HT2a antagonism
- D2 Occupancy of 60-80%
  - Haloperidol – 8 mg per day
  - Risperidone – 4 mg per day
  - Olanzapine – 15 mg per day
  - Aripiprazole – 10 mg per day
  - Quetiapine – 500 mg per day

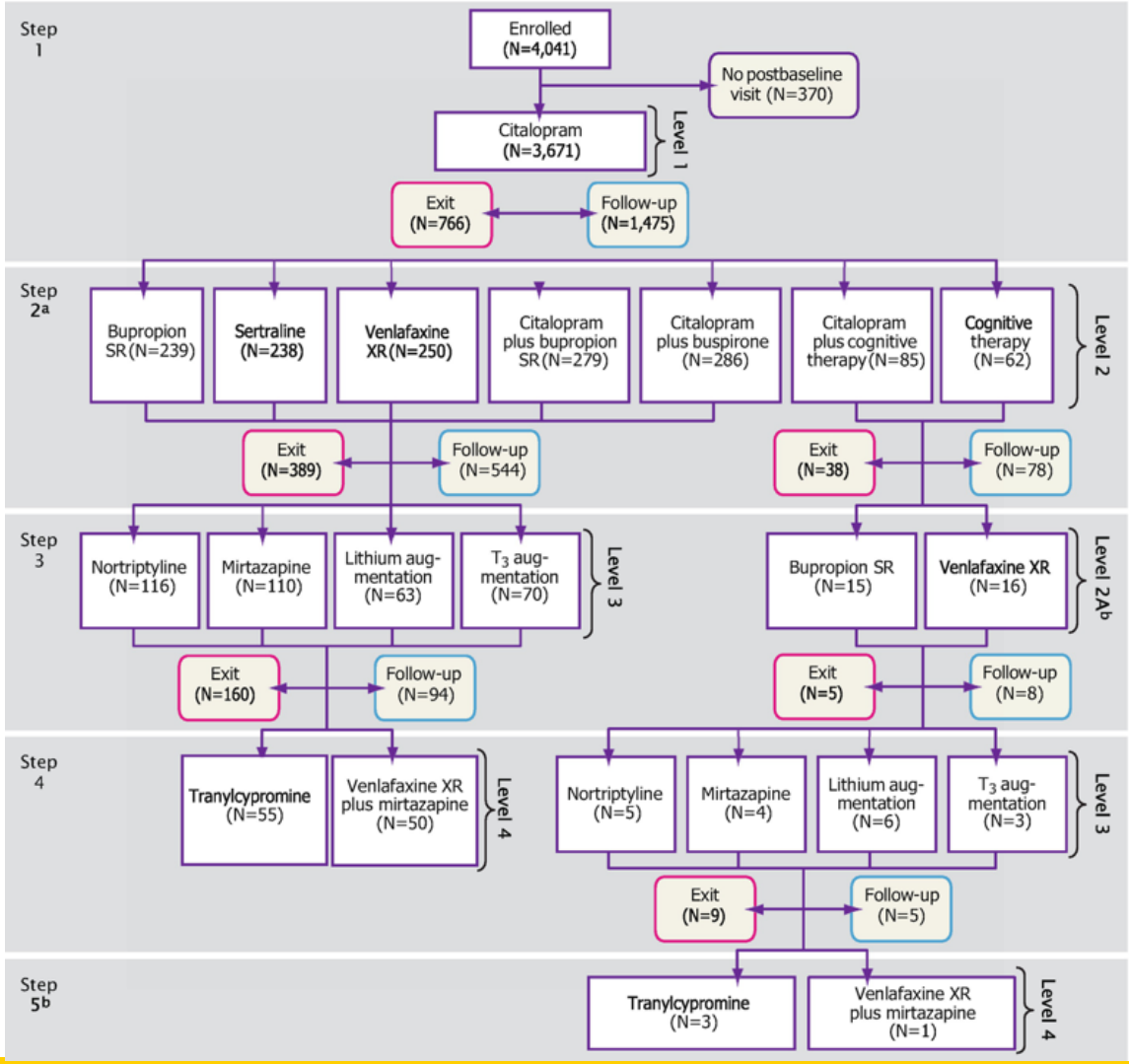
Agar. JAMA IM. 2017; 177: 34-42.
Bush. Ann Oncol. 2018; 29 (S4): iv143-65.

Which Antipsychotic?



Stahl's Essential Pschyopharmacology. 3rd Ed. 2008.

Anxiety and Depression



Rush. Antidepressants. pp51-99. (Handbook of Experimental Pharmacology)

Depression/Anxiety

Class	Drug	Dose	Metabolism	Notes
SSRI's	Fluoxetine	Usual: 20 mg QD Max: 80 mg QD Effective: 20 mg QD	2D6	Most Activating; Weight loss; Long t½
	Sertraline	Usual: 25-50mg QD Max: 200 mg QD Effective: 50 mg QD	2D6	GI Upset
	Citalopram	Usual: 10-20mg QD Max: 40 mg QD Effective: 20 mg QD	2C19 major 2D6 minor	Dose-related QTc, mild sedation, weans off easily (mod t ½)
	Escitalopram	Usual: 10mg QD Max: 20 mg QD Effective: 10 mg QD	2C19; 3A4	
	Fluvoxamine	Usual: 50 mg QD Max: 300 mg QD Effective: 100 mg QD	Hepatic	GI Upset
	Paroxetine	Usual: 20 mg QD Max: 50 mg QD Effective: 20 mg QD	2D6	Most Sedating; ACh effects; Short t½ (can precipitate withdrawal)

Depression/Anxiety

Class	Drug	Dose	Metabolism	Notes
SNRI's	Venlafaxine	Usual: 75mg/day Max: 375 mg Effective: 75 mg	2D6	GI upset; Insomnia; Dose dependent BP↑; SSRI at low doses
	Desvenlafaxine	Usual: 50 mg QD Max: 100 mg QD Effective: 50 mg QD	3A4	Not much benefit seen above 100 mg; same as venlafaxine plus lipid ↑
	Duloxetine	Usual: 20 mg QD Max: 120 mg QD Effective: 90 mg QD	1A2, 2D6	GI upset; insomnia; anticholinergic

Depression/Anxiety

Class	Drug	Dose	Metabolism	Notes
TCA's	Amitriptyline	Usual: 25 mg QHS Max: 300 mg QHS Effective: 100 mg QHS	Hepatic	Sedating; QTc
	Imipramine	Usual: 75 mg QD Max: 200 mg QD Effective: 75 mg QD	2D6	Sedating; QTc
	Nortriptyline	Usual: 25 mg TID Max: 150 mg QD Effective: 75 mg QD	2D6	Orthostasis; QTc; can give full dose at once
	Desipramine	Usual: 25-50mg QD Max: 300 mg QD Effective: 25 mg QD	Hepatic	Orthostasis; QTc

Depression/Anxiety

Class	Drug	Usual Dose	Metabolism	Notes
Atypicals	Mirtazapine	Usual: 15mg QHS Max: 45 mg Effective: 15 mg	1A2, 2D6, 3A4	Sedating at low doses (<15 mg); Weight gain (~10 lbs); Noradrenergic at higher doses (not ideal for cards)
	Bupropion	Usual: 100mg BID Max: 450 mg Effective: 200-250 mg	2B6, 2D6	Lowers seizure threshold; Most activating antidepressant
	Trazodone	Usual: 150mg/day Max: 400 mg Effective: 150 mg	3A4	Nausea; Dry Mouth; Sedating
	Buspar	Usual: 5mg TID Max: 60 mg Effective: 10 mg	3A4	GI Upset; Cardiovascular effects

Depression/Anxiety

Class	Drug	Usual Dose	Metabolism	Notes	
Stimulant	Methylphenidate	Usual: 2.5-5mg 8a, 12p Max: 60 mg Effective: 5 mg	De-esterification	Arrhythmia, insomnia	CA related-fatigue. OK to use w/pacer
Steroid	Dexamethasone	Usual: 4-8mg BID Max: - Effective: 4 mg BID	Hepatic	Used when also have other needs (bone pain, loss of appetite)	Shorter prognosis (max 2-4 wks)
GABA	Gabapentin	Usual: 300mg/day Max: 3600 mg Effective: 300 mg	None	Sedation & neuropathic pain	

Depression/Anxiety

Class	Drug	Usual Dose	Duration (hrs)	Onset (min)	Metabolism	Notes
BZDs	Alprazolam	Usual: 0.25-0.5 TID Max: 4 mg	3-4	30	3A4	Don't prolong QT, could be used short term as a bridge
	Clonazepam	Usual: 0.25mg BID Max: 4 mg	6-8	60	Hepatic conjugation	
	Diazepam	Usual: 2-10mg BID-QID Max: 40 mg	4-6	30	3A4, 2C19	
	Lorazepam	Usual: 1mg BID to TID Max: 10 mg	4-6	30	Hepatic conjugation	
	Oxazepam	Usual: 10mg TID Max: 120 mg	-	120-240	Hepatic conjugation	
	Temazepam	Usual: 7.5-15mg QHS Max 30 mg	4-6	30	Hepatic	
	Triazolam	Usual: 0.125-0.5mg QHS Max: 0.5 mg	-	30	3A4	

Alprazolam 0.5 mg = Clonazepam 0.25 -0.5 mg = Diazepam 10 mg = Lorazepam 1 mg = Oxazepam 20mg = Temazepam 20 mg = Triazolam 0.5 mg = Midazolam 2mg

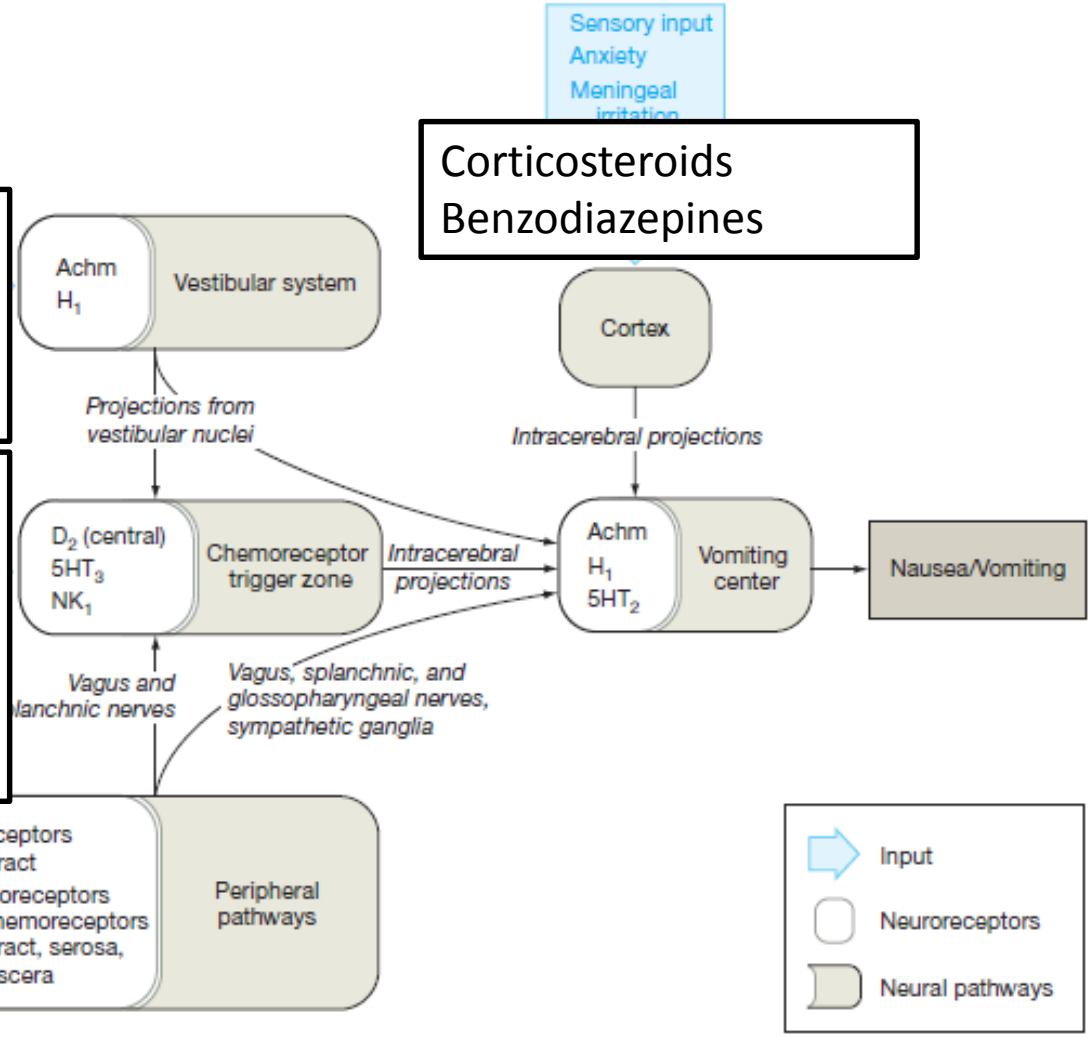
Nausea and Vomiting

Corticosteroids
Benzodiazepines

Promethazine
Diphenhydramine
Scopolamine
Olanzapine

Metoclopramide Aprepitant
Antipsychotics
Prochlorperazine
Promethazine
Ondansetron
Olanzapine

Metoclopramide
Ondansetron
Olanzapine



Wood. JAMA 2007; 298 (10): 1196-1207.

Dyspnea

Kako. JPSM. 2018; 56 (4): 493-500.

Fatigue

Medication	Dosing	Notes
Methylphenidate	• 2.5-5mg QAM • Titrate to effect or BID dosing • 60 mg max per day	• ADEs: nervousness, agitation • Caution: CV disease, anxiety
Modafinil	• 100mg QAM • Titrate to effect or 200 mg QAM • 400 mg max per day	• ADEs: headache, anxiety • Caution: liver disease, uncontrolled anxiety
Dexamethasone	• 2-4 mg BID • Second dose no later than 2pm	• ADEs: insomnia, hyperglycemia • Caution: short term use only
Donepezil	• 5 mg QAM • Titrate to effect or 10 mg QAM • Max 10 mg	• ADEs: nausea • Caution: CV disease
Amantadine	• 100 mg BID • Titrate to effect • Max 400 mg per day	• ADEs: GI/CNS effects • Caution: ESRD

Corticosteroid Tips

Corticosteroid Conversion Chart				
Glucocorticoid	Approximate Equivalent Dose (mg)	Relative Anti-Inflammatory (Glucocorticoid) Potency	Relative Mineralocorticoid (Salt Retaining) Potency	Biological Half-Life (Hours)
Short-Acting				
Cortisone	25	0.8	0.8	8 - 12
Hydrocortisone	20	1.0	1.0	8 - 12
Intermediate-Acting				
Methylprednisolone	4	5	0.5	18 - 36
Prednisolone	5	4	0.8	18 - 36
Prednisone	5	4	0.8	18 - 36
Long-Acting				
Dexamethasone	0.75	25	0.0	36 - 54

Meikle. Am J Med .1977; 63(1): 200-207.
Jaward. Am J Hosp Palliat Care. 2019; 36 (2): 158-68.

Secretions

- Stop using drugs!
- If you must use drugs to palliate a family member or caregiver:
  - Atropine or glycopyrrolate

Wee. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD005177.

Clinical Pearls for Medication Use in End of Life Care

MOQC Biannual Meeting

June 2019

Michael A. Smith, PharmD, BCPS