Improvements in Pain Management through Appreciation of Nociceptive Pathways and Analgesic Mechanism of Action

Joseph W. Shega, MD

Regional Medical Director

Innovative Hospice Care®

VITAS®

Goals

- Appreciate nociceptive pathways
- Identify analgesic classes by site of action and mechanism of action
- Incorporate a mechanistic approach into pain management

Background

- A plethora of analgesics are available for use
- Analgesics act at unique sites and maintain different mechanisms of action
- Studies suggest pain management can be improved by blocking nociceptive pathways in multiple locations

Improve analgesia and decrease adverse effects

Case 1

- 78 y/o with head/neck cancer progressive disease despite chemo and XRT
- Complains of intermittent severe pain in right face
  - Character: sharp and electric like
  - Radiation: across face
  - Intermittent, lasts seconds, no precipitant

Case 2

- 88 y/o with failure to thrive and multiple chronic medical conditions
- Nurse calls with new onset severely painful rash in dermatomal distribution for last 3 days
  - Character: tingling and numb
  - Radiation from back to around abdomen
  - Anything touches area pain much worse

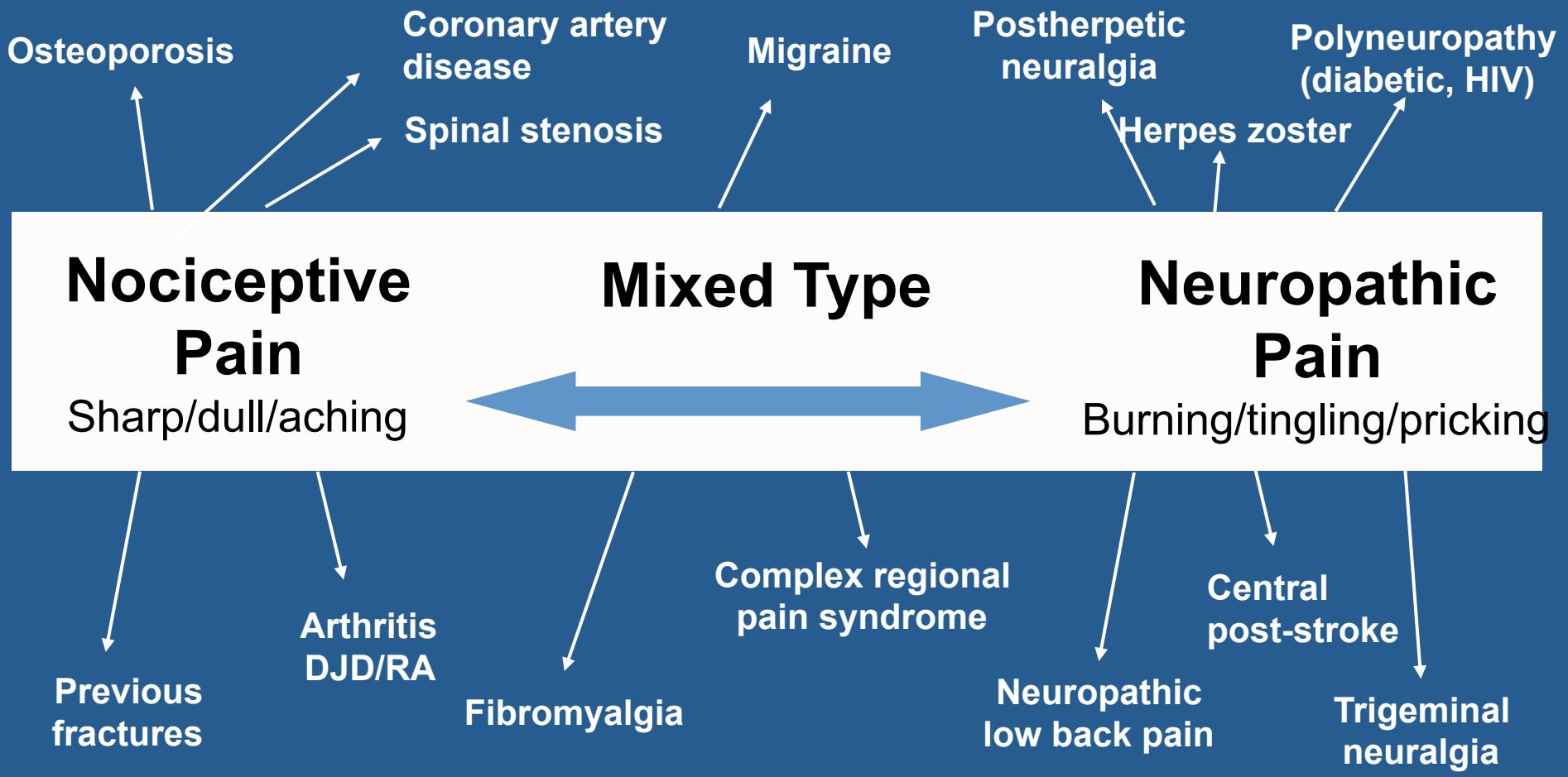
Case3

- 85 y/o hospitalized s/p fall with dislocation many teeth and severe back pain
  - Low back pain 10/10, 3-4/10 best
  - Worse with any movement
  - Ache all times, occasional very sharp
  - Poor appetite, unable sleep, getting a little confused
  - No vertebral fracture

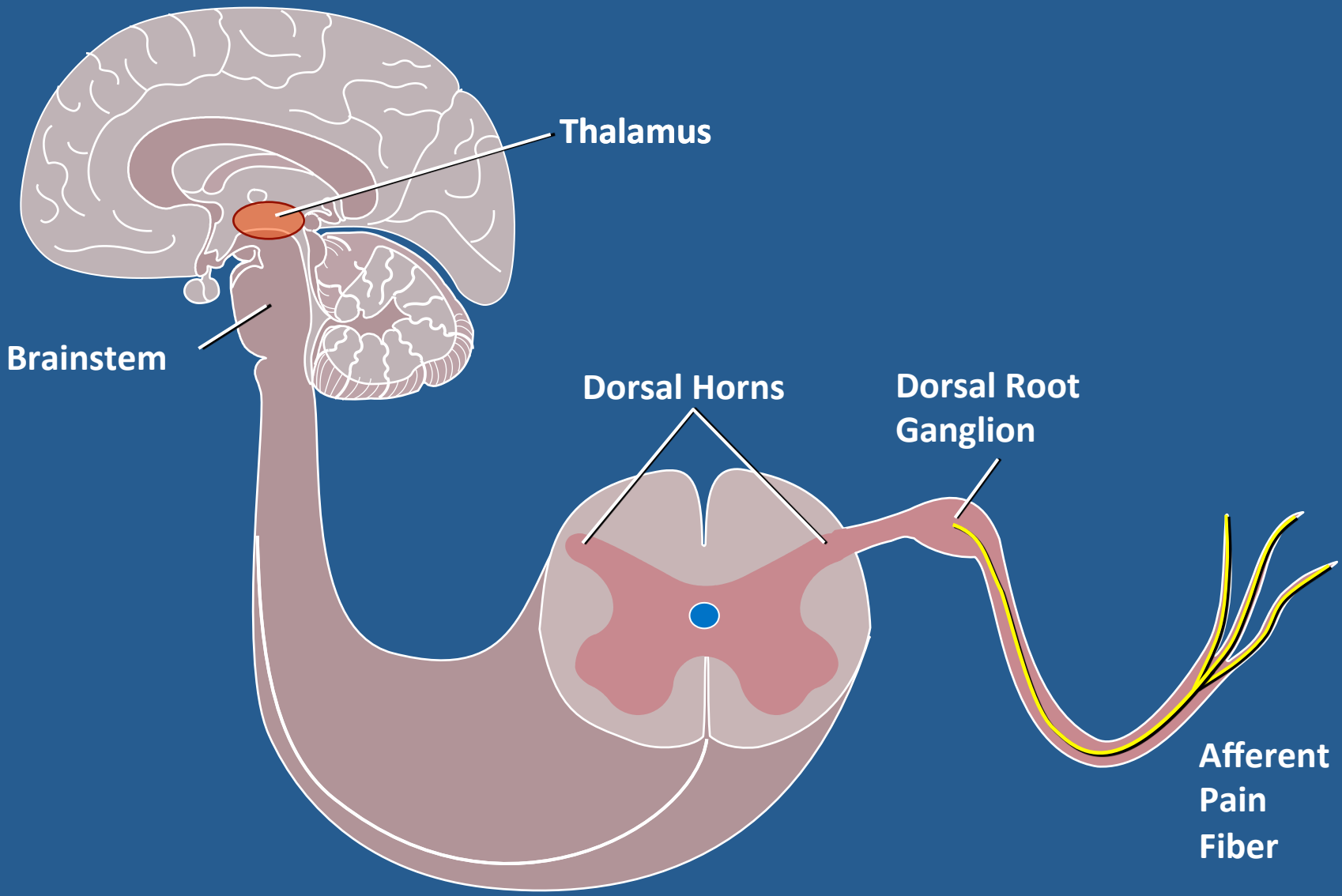
Pain Assessment

- Intensity: e.g., mild, moderate, severe
- Duration: acute, chronic (persistent)
- Pathophysiology: nociceptive, neuropathic
- Etiology if known: e.g., cancer, low back pain, fracture related, arthritis, post-surgical, and fibromyalgia

Common Pain Conditions in Older Adults



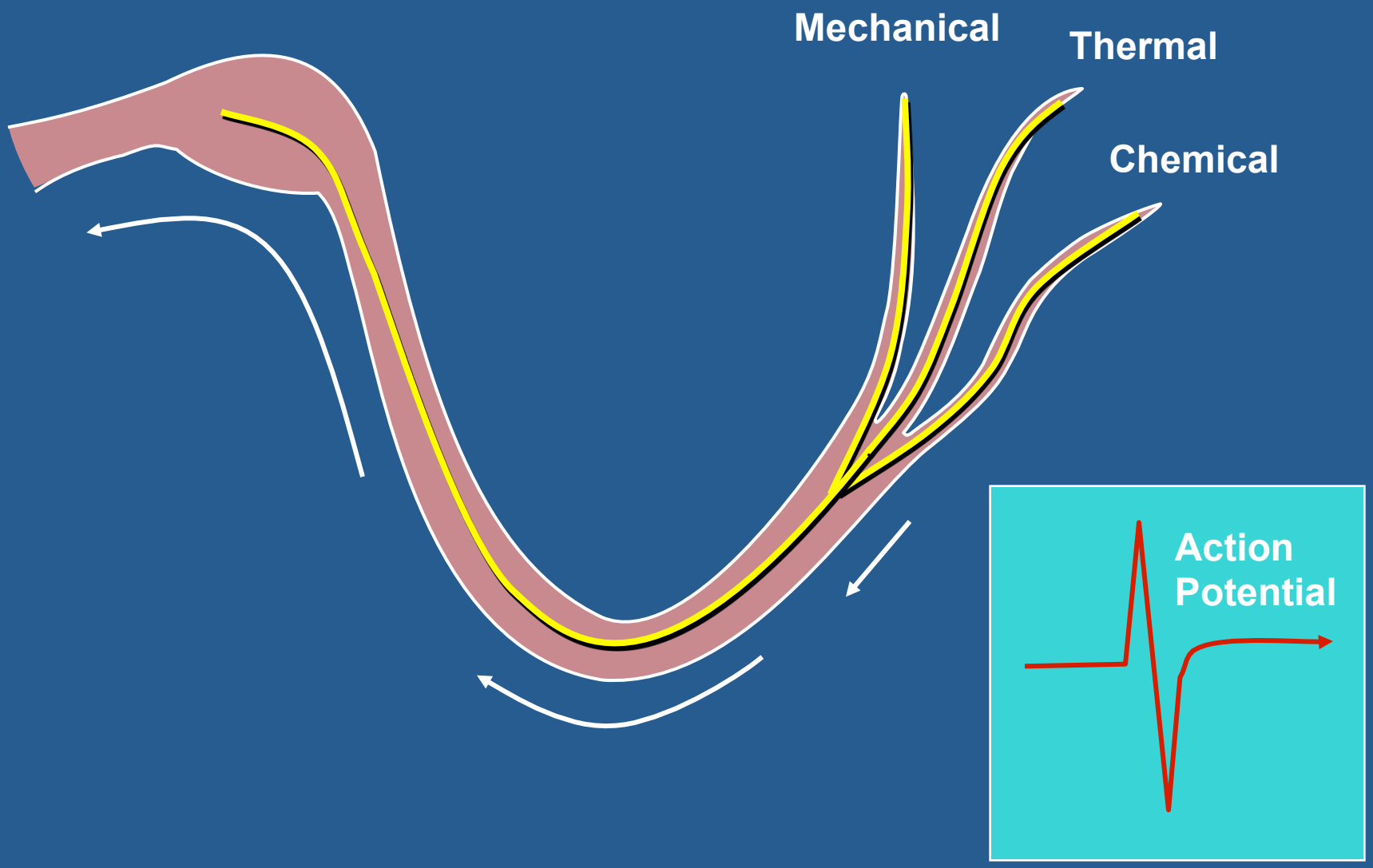
AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc*. 2002;50(6 Suppl):S205-S224.

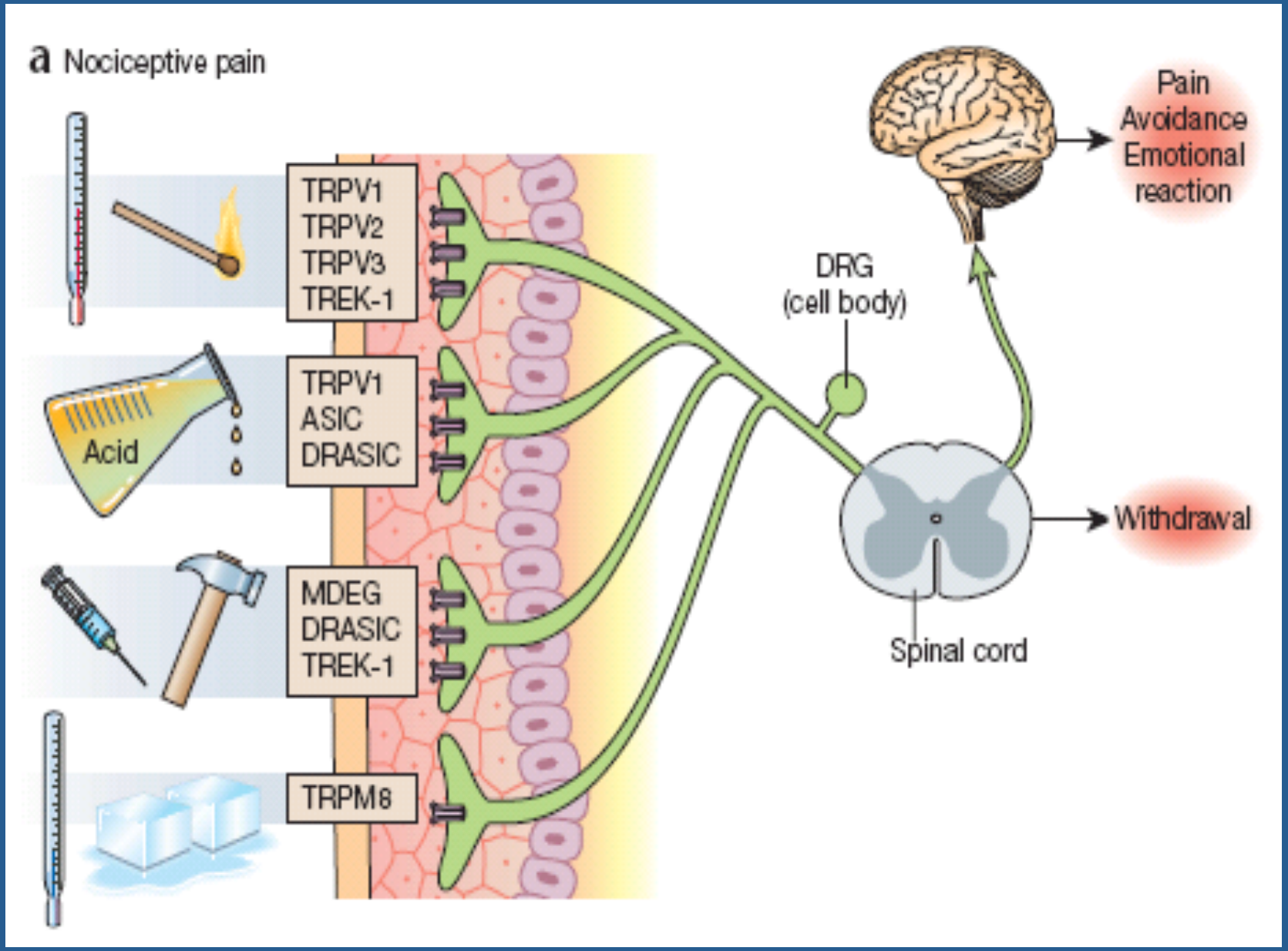

Thalamus
Brainstem
Dorsal Horns
Dorsal Root Ganglion
Afferent Pain Fiber

Peripheral Neurons

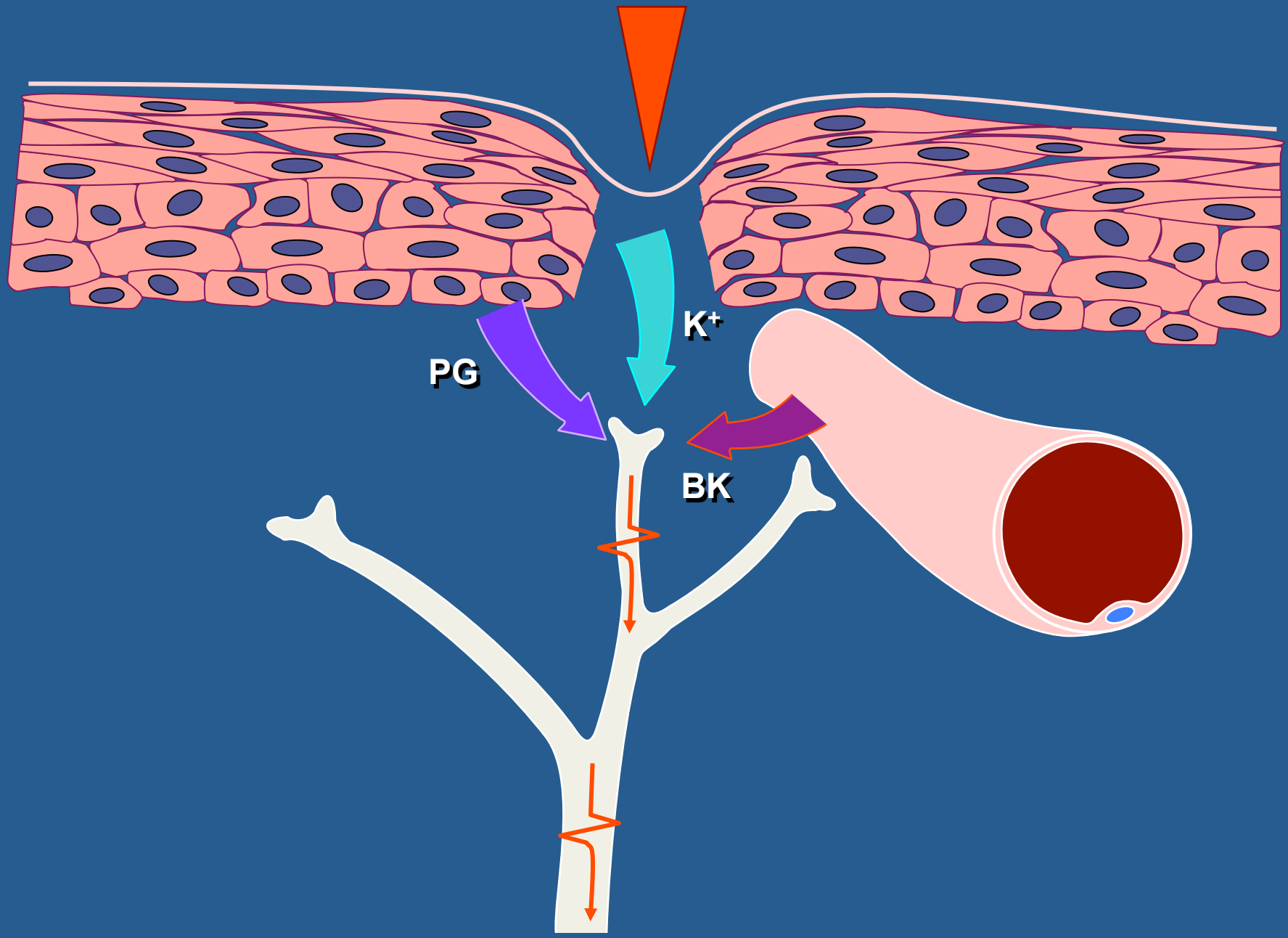
- Aβ - Low threshold mechanoreceptors
  - Pressure & vibration
- Aδ – High and low threshold mechanoreceptors (myelinated)
  - Pressure and pain
- C – High threshold mechanoreceptor and thermoceptor (unmyelinated)

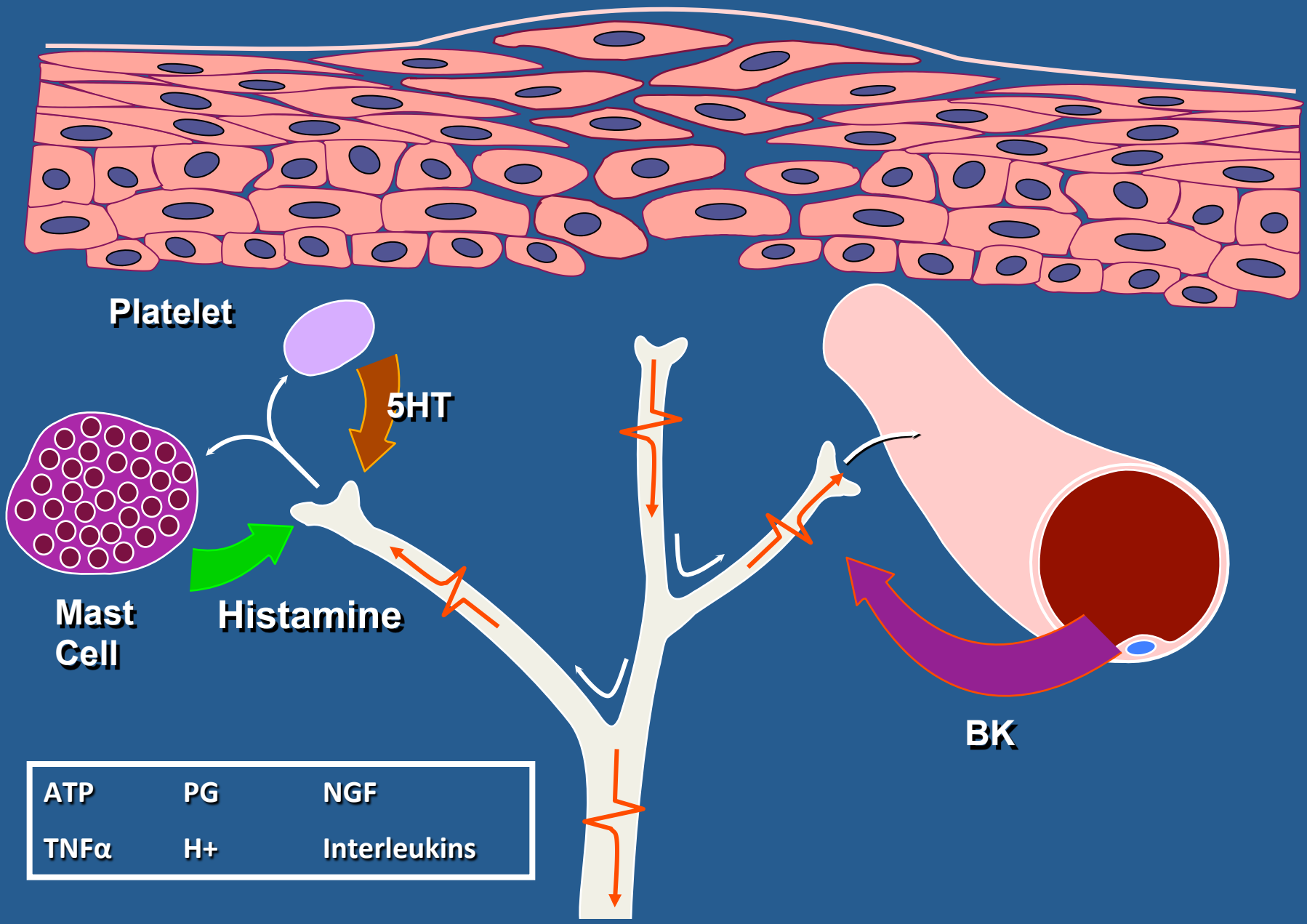
Transduction





Scholz and Woolf. Nature Neuroscience, 2002


K+
PG
BK


Platelet
5HT
Mast Cell
Histamine
BK
ATP
PG
NGF
TNFα
H+
Interleukins

Steroids (Lipocortin)

Phospholipase A_2

Arachidonic Acid

NSAIDS

Cyclooxygenase

Prostaglandins

Corticosteroids

- Dexamethasone has least mineralocorticoid effect
- All can produce glucocorticoid effects
- Can be given orally, IV, SQ, epidurally
- May produce psychosis
- Long-term use can cause proximal muscle wasting and bone loss

Non-Opioids

- Acetaminophen
  - Analgesic, antipyretic
  - Liver toxicity
- Nonsteroidal Antiinflammatory Drugs (NSAIDS)
  - Analgesic, antipyretic, antiinflammatory
  - GI bleeding, bleeding, renal dysfunction

Non-Opioids: COX-2

- COX-2 Inhibitors
  - No difference in analgesic efficacy
  - Questionable long-term GI benefit
  - No difference in renal effects
  - Cardiovascular complications

Juni P, Rutjes AWS, Dieppe PA. BMJ 2002;324:1287-1288

Capsaicin Cream

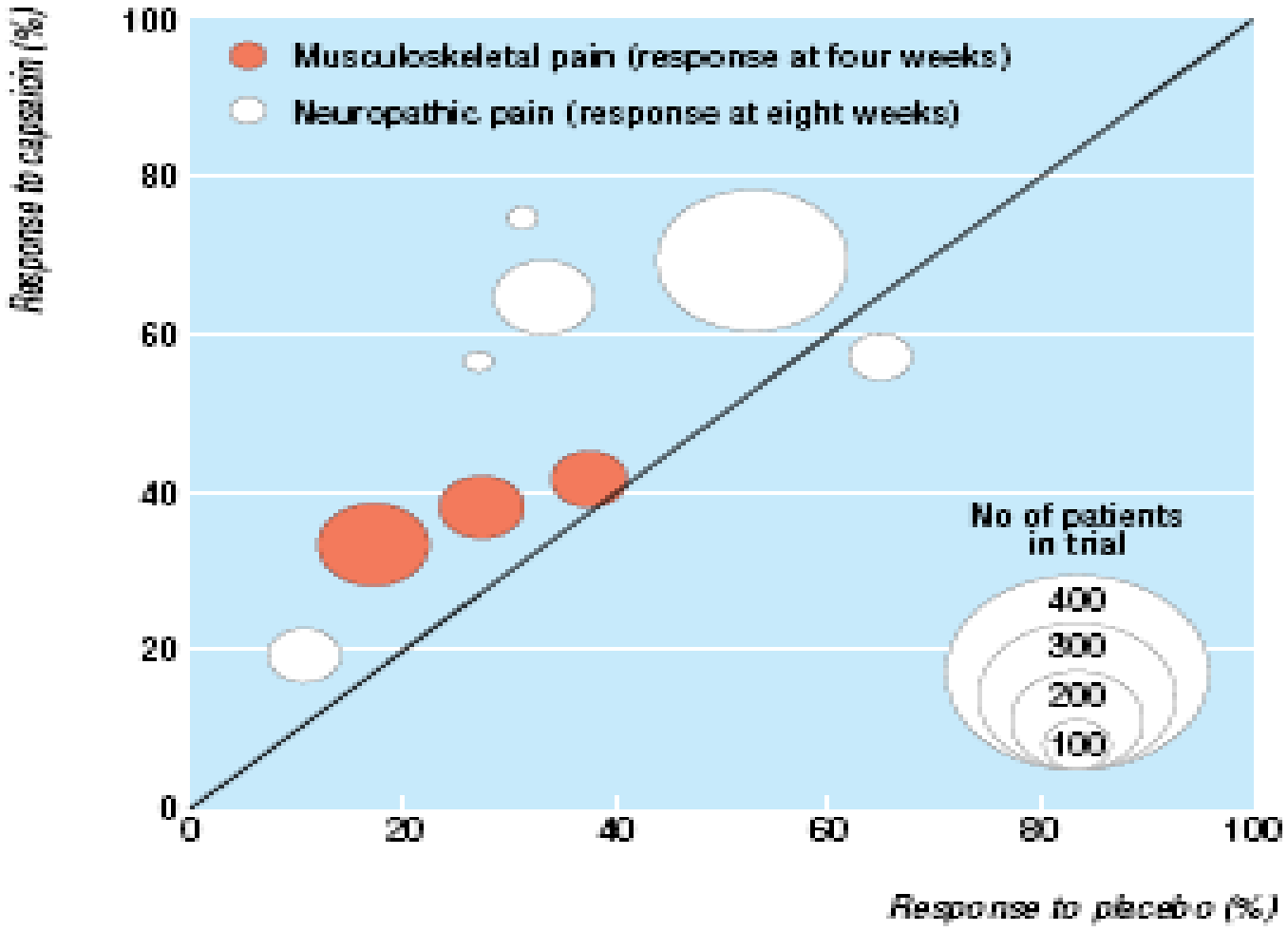
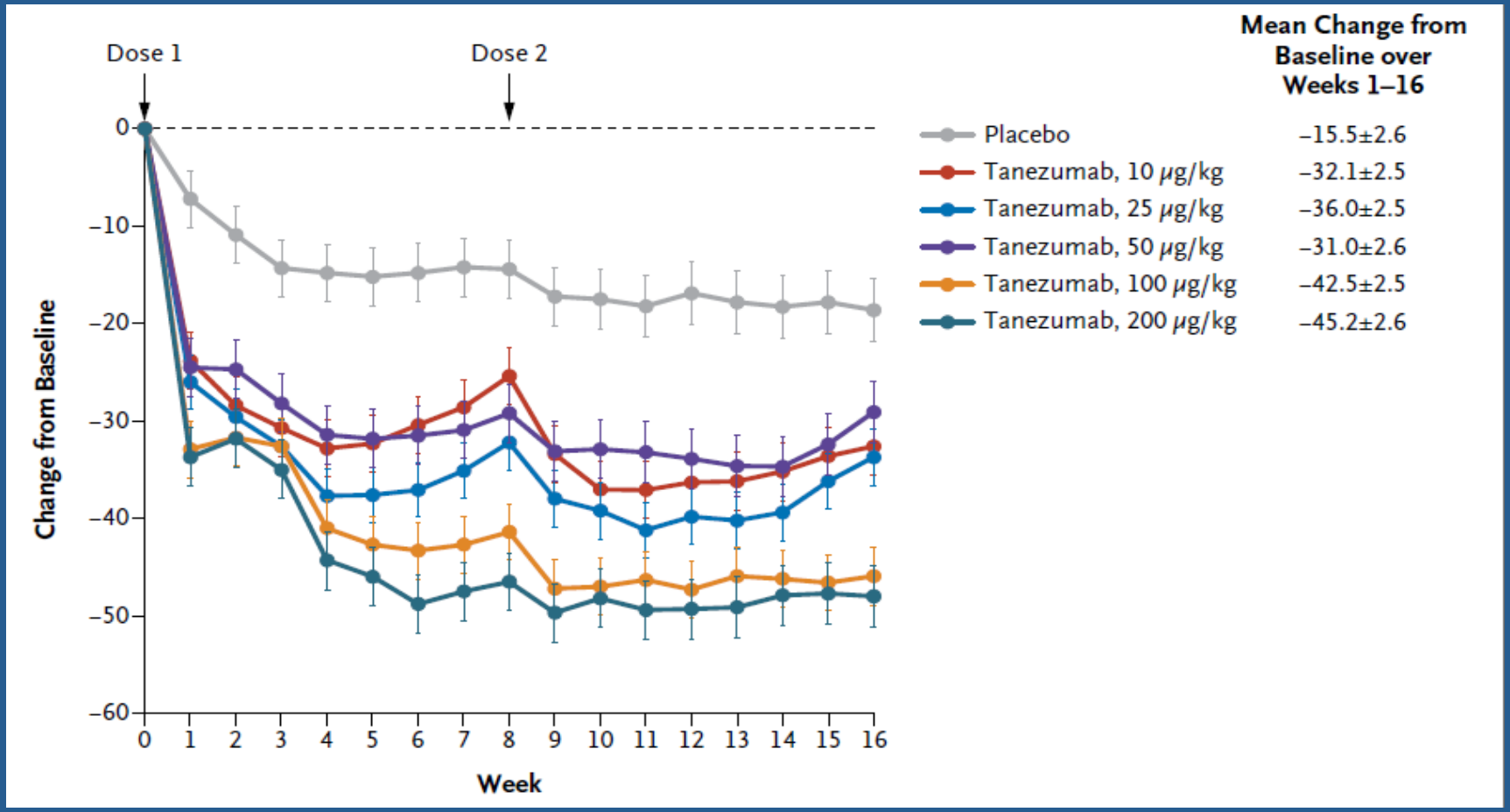


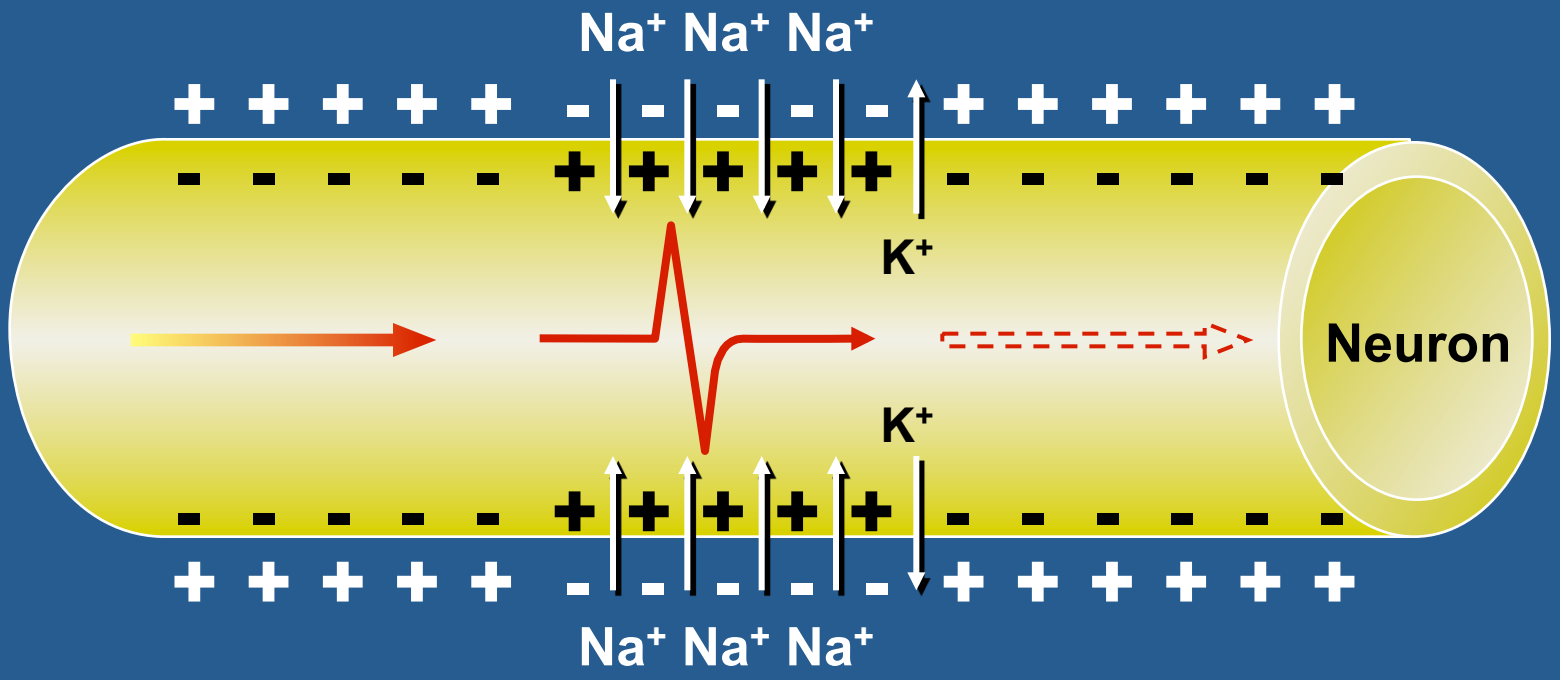
Fig 2 L'Abbé plot showing response to capsaicin and placebo in individual randomised controlled trials

Tanezumab (Nerve Growth Factor Ab)

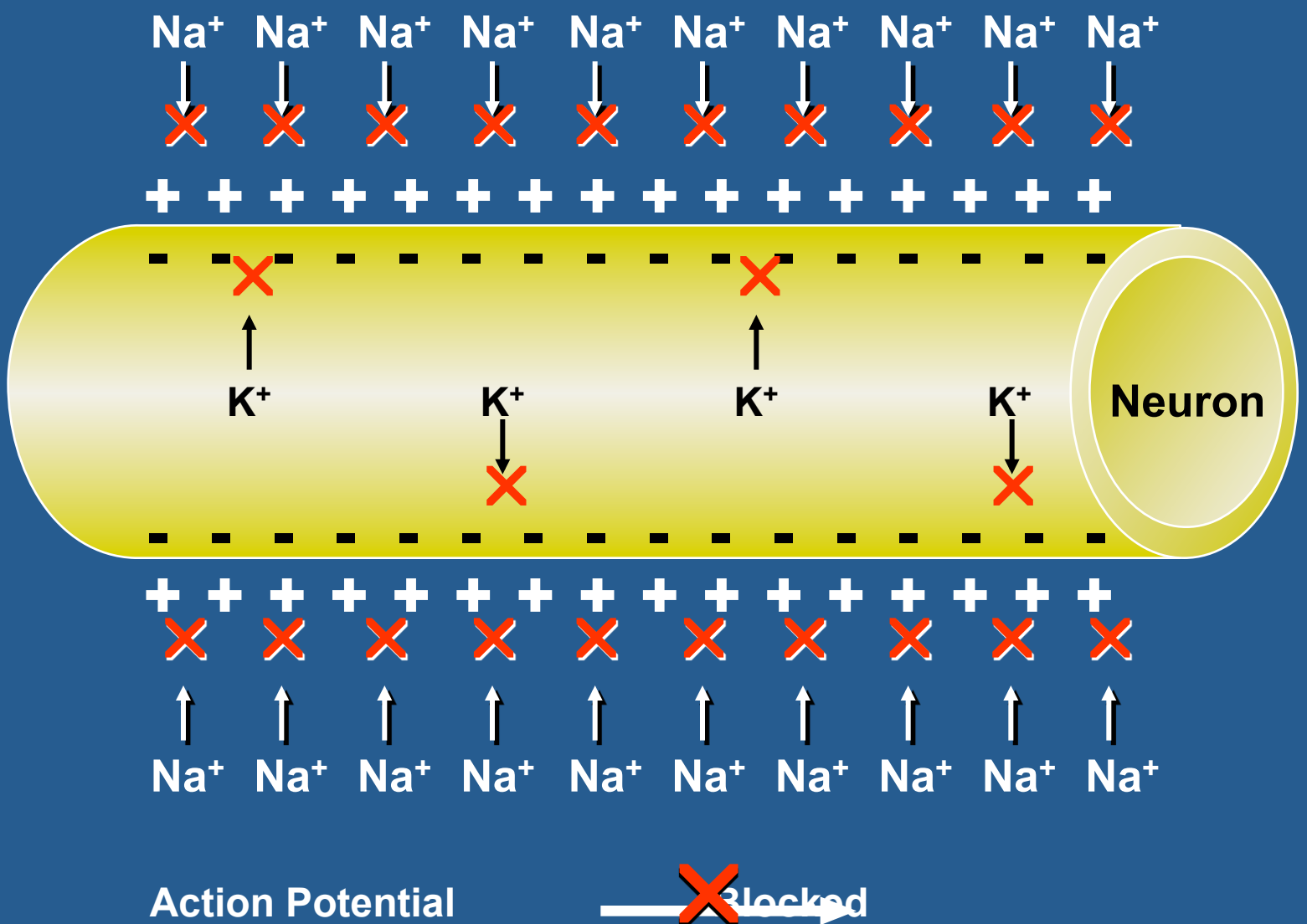


NEJM 2012

Conduction



Anticonvulsants / Anesthetics



Sodium Channel Isoforms

Isoform (standard nomenclature)	Other names in literature	Gene name	Typical distribution
$Na_v1.1$	Type I	*SCN1A*	Dendrites
$Na_v1.2$	Type II/IIA	*SCN2A*	Unmyelin. initial segments
$Na_v1.3$	Type III	*SCN3A*	Early neuronal development
$Na_v1.4$	SkM1, μ1	*SCN4A*	Skeletal muscle (mature)
$Na_v1.5$	H1, SkM2, μ2	*SCN5A*	Heart, Immature Skel. musc.
$Na_v1.6$	Cer3, PN4	*SCN8A*	Nodes, synapses, dendrites
$Na_v1.7$	PN1, hNE-Na, Nas	*SCN9A*	Unmyelinated PNS (pain)
$Na_v1.8$	SNS, PN3	*SCN10A*	Unmyelinated PNS (pain)
$Na_v1.9$	NaN, SNS2	*SCN11A*	PNS – free nerve endings
$Na_v2.x$	ret1, NaG, *atypical*	*SCN7A*	Nonmyelinating Schwann c.

Antieptileptics

- Carbamazepine/oxcarbazepine efficacy in trigeminal neuralgia→NNT 1.7/NNH 22
- Lamotrigine, topiramate, valproic acid, and phenytoin positive and negative trials, more negative than positive
- All considered third line agents except carbamazepine and trigeminal neuralgia

Local Anesthetics

- Topical
  - EMLA® Cream
  - Lidoderm® patch
- Intravenous
- Epidural/intrathecal

Fast Fact #148 www.eperc.mcw.edu
Mao J, Chen LL. *Pain* 2000; 87:7-17

Lidocaine Patch 5%

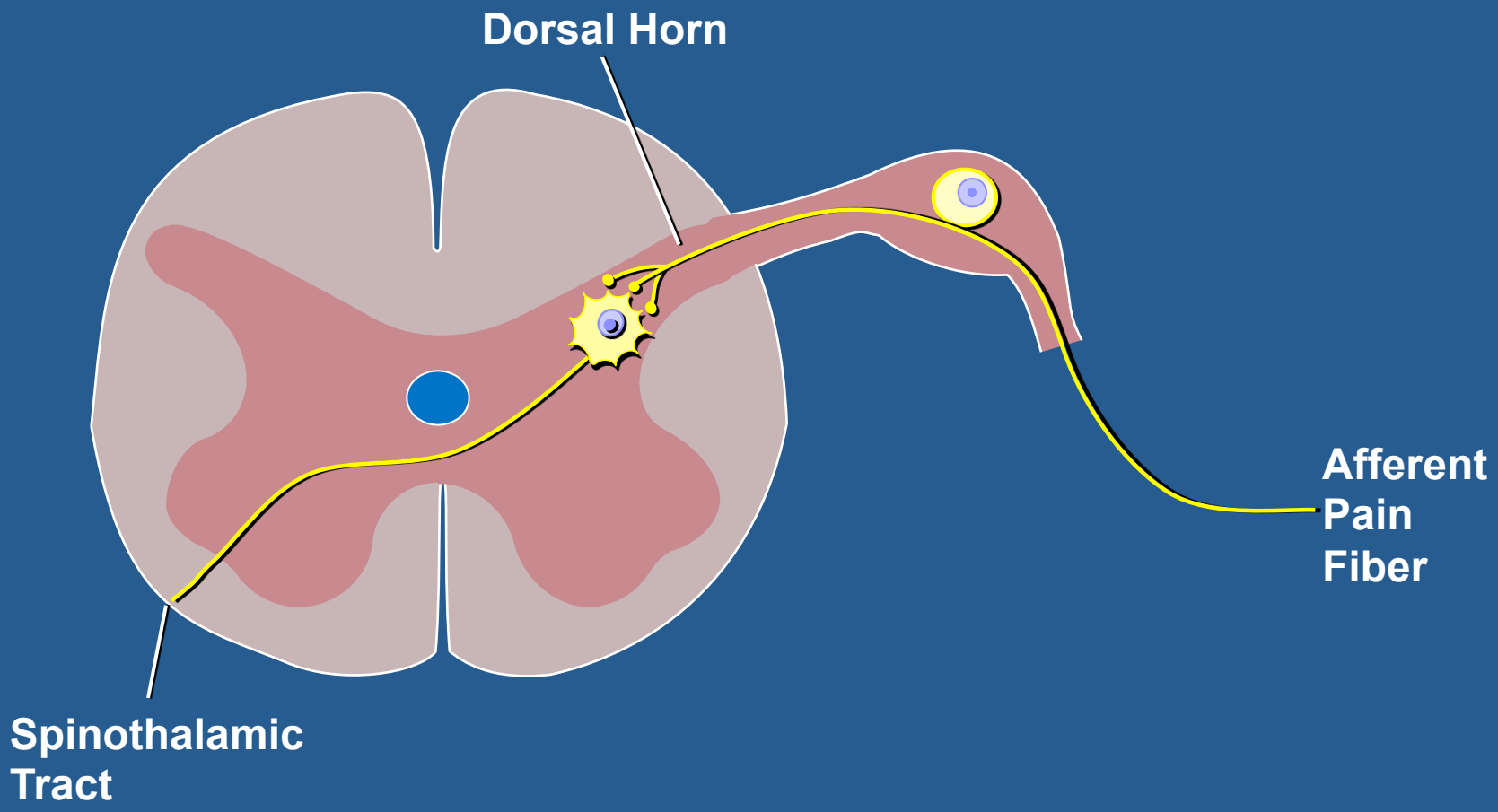
- PHN and diverse group peripheral NP conditions→ NNT 4.4
- Mild skin reactions- rash and erythema
- Blood level minimal up to 4 patches/day
- Caution in hepatic failure and other class I antiarrythmics
- 12 hours on and 12 hours off

Meier T et al. Efficacy of lidoderm patch in the treatment of focal peripheral neuropathic pain syndrome: a randomized double blind controlled study. Pain 2003;106:151-158.

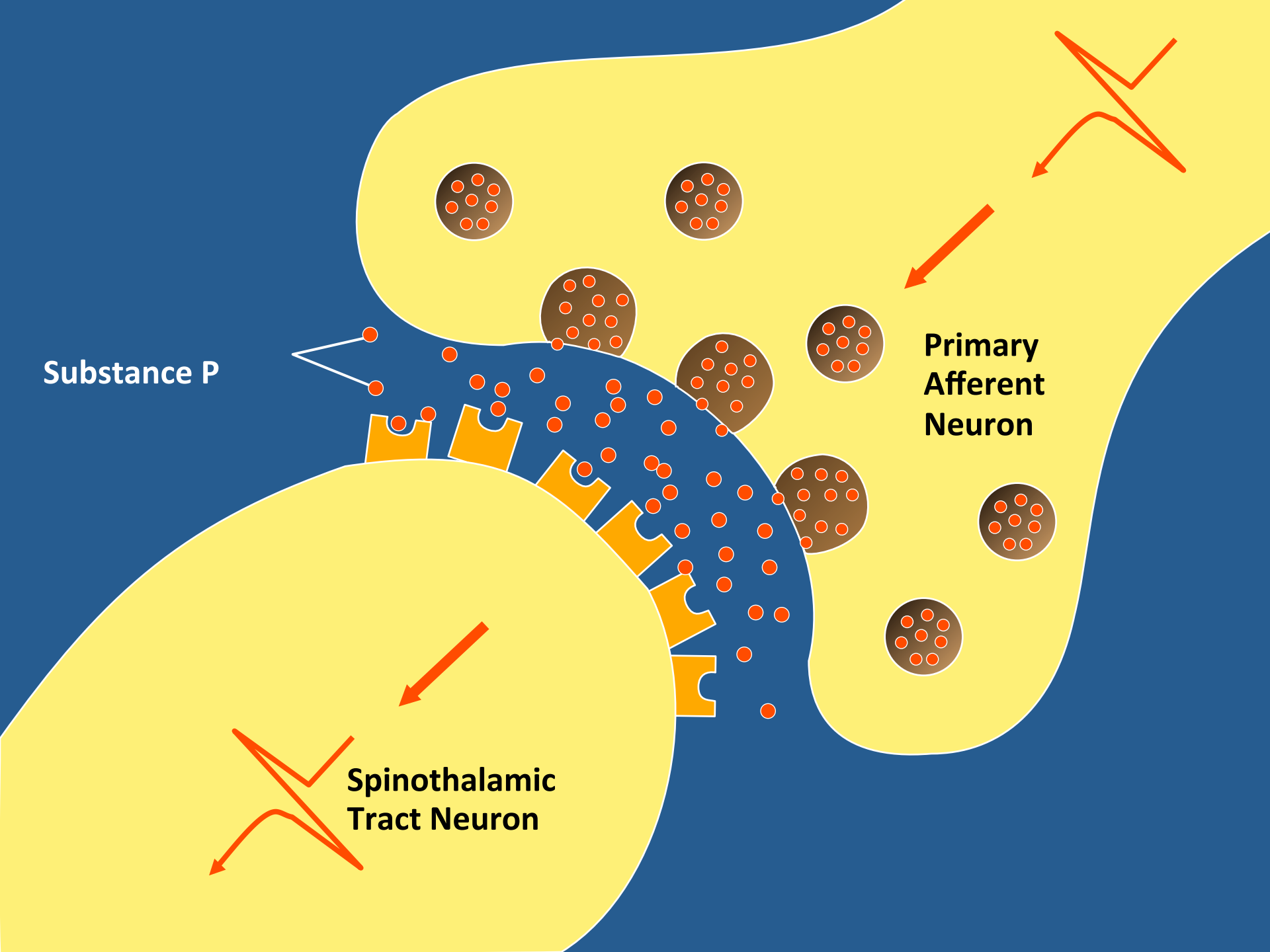
Intractable Neuropathic Pain: Parenteral Lidocaine

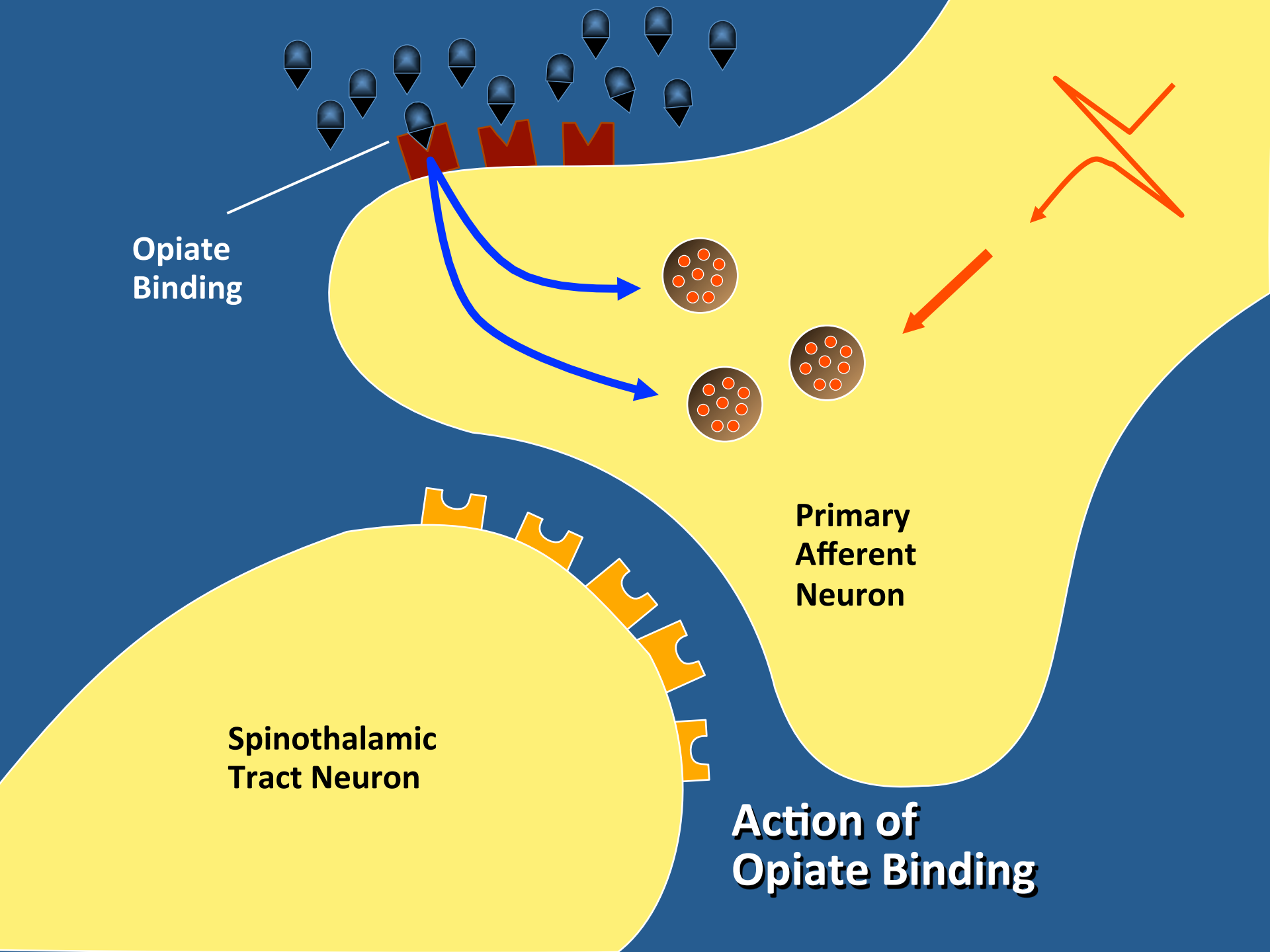
- Test dose of 1-2 mg/kg lidocaine IV or SQ over 30-60 minutes
- Perioral numbness suggests toxicity; stop infusion and restart at slower rate once numbness resolved
- If effective, begin continuous infusion of 1-2 mg/kg/hour

Ferrini RL & Paice JA. *J Supportive Onc* 2004; 2:90-94



Transmission


Substance P
Primary
Afferent
Neuron
Spinothalamic
Tract Neuron


Opiate
Binding
Primary
Afferent
Neuron
Spinothalamic
Tract Neuron
Action of
Opiate Binding

Opioids

- Morphine
- Oxycodone
- Hydromorphone (Dilaudid®)
- Fentanyl
- Oxymorphone
- Hydrocodone
- Codeine

- Oral
- Rectal
- Intravenous - PCA
- Subcutaneous
- Epidural - PCEA
- Intrathecal
- Transdermal
- Buccal
- Intramuscular

Tramadol (Ultram ®)

- A synthetic non-opioid analog of codeine with complex pharmacology: among other actions, it is a *mu*-opioid-receptor agonist
- Analgesic effect roughly equivalent to Tylenol #3 ®
- Side effects similar to opioids--nausea, confusion, dizziness, constipation
- Caution in those on SSRIs (serontonin crisis)
- Contraindicated if seizure history
- Maximum dose 400mg daily

Opioid Efficacy

- Peripheral and central NP conditions→NNT 2.5/NNH 9.0
- First line treatment
  - Cancer pain
  - Severe pain
  - Acute neuropathic pain
- Long term studies lacking

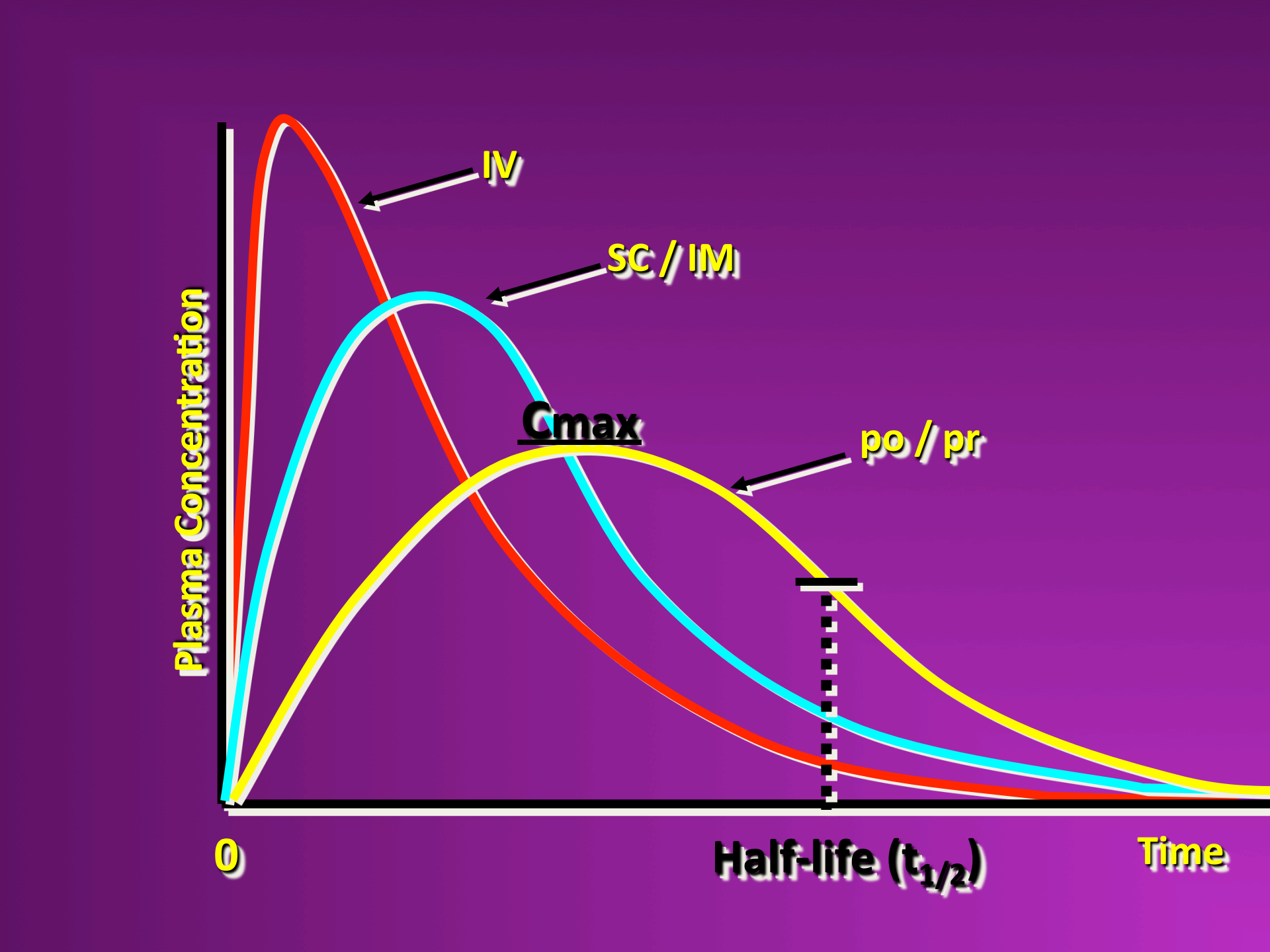
  Immunologic changes and hypogonadism

Initiation of Opioids

Opioid	Normal Starting Dose in Younger Adults (mg)	Suggested Starting Dose in Older Adults (mg)
Codeine	30-100	15-50
Oral morphine	5-15	2.5-7.5
Oxycodone	5-10	2.5-5
Oral hydromorphone	2-4	1-2

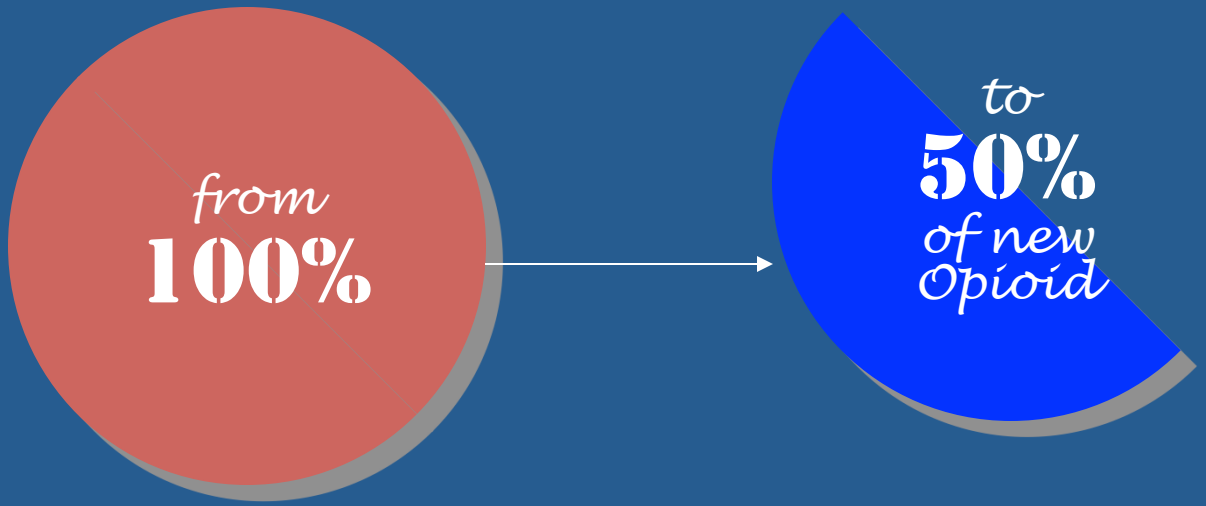
Equianalgesic Dosing

Drug	Oral (mg)	IV (mg)	Duration (h)
morphine	30	10	3 - 4
hydromorphone	8	2	3 - 4
oxymorphone	10	1	> 4
codeine	200	130	3 - 4
oxycodone	20-30	-	3 - 4
hydrocodone	30	-	3 - 4
meperidine	300	100	2 - 3


IV
SC / IM
Cmax
po / pr
Plasma Concentration
0
Half-life ($t_{1/2}$)
Time

Incomplete cross-tolerance

- If a switch is being made from one opioid to another it is recommended to **start the new opioid at ~50%** of the equianalgesic dose.
- This is because the ***tolerance*** a patient has towards one opioid, may not completely transfer ("incomplete cross-tolerance") to the new opioid.



Opioid Use in Renal Failure

- Not rec'd: meperidine, codeine, dextropropoxyphene, morphine
- Use with caution: oxycodone, hydromorphone
- Safest: fentanyl, methadone
- Opioid dosing

CrCl	>50 mL/min	normal
	10 - 50 mL/min	75% of Nl
	<10 mL/min	50% of Nl

Opioid adverse effects

Common

Constipation

Dry mouth

Nausea / vomiting

Sedation

Sweats

Uncommon

Bad dreams / hallucinations

Dysphoria / delirium

Myoclonus / seizures

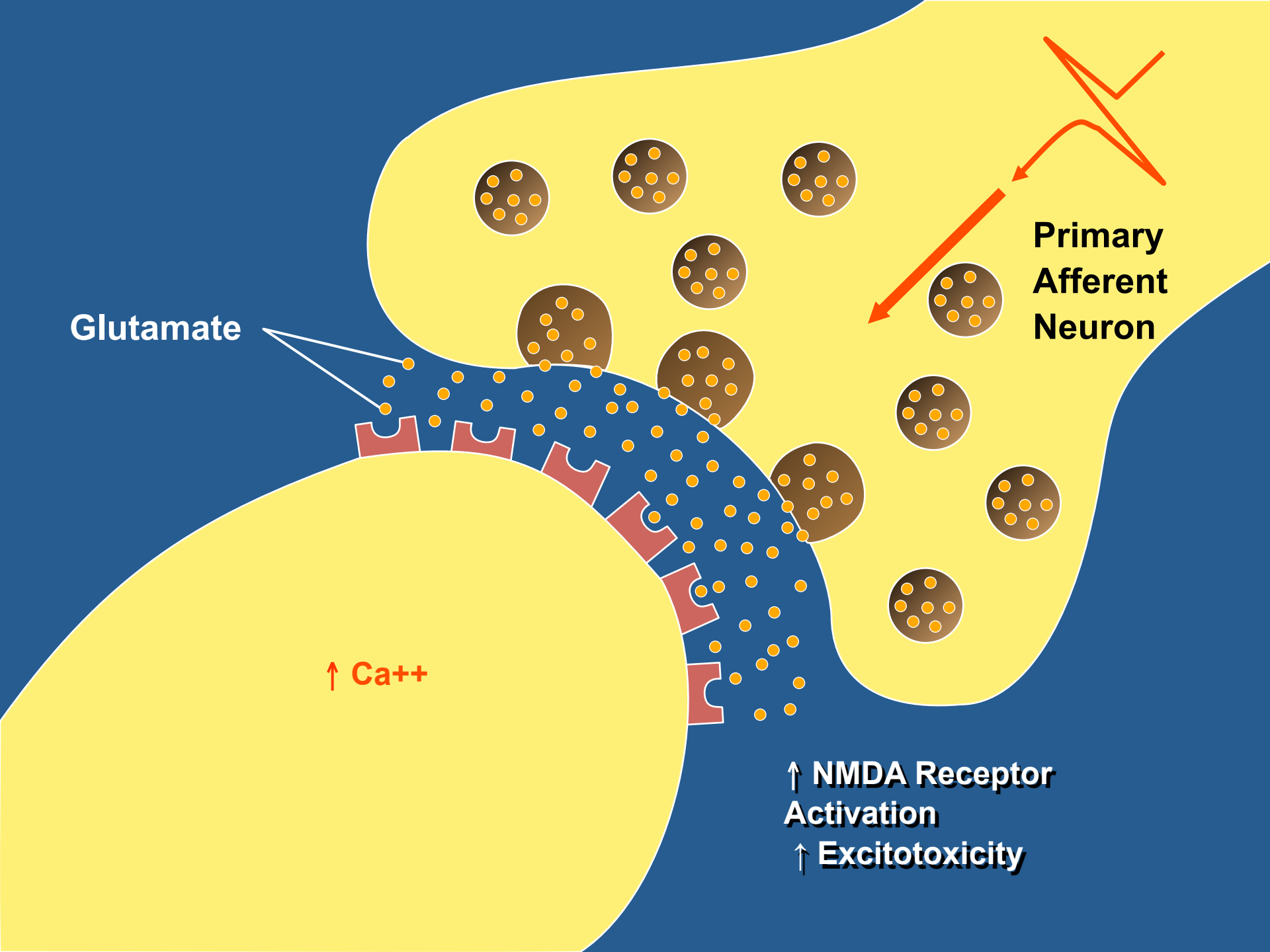
Pruritus / urticaria

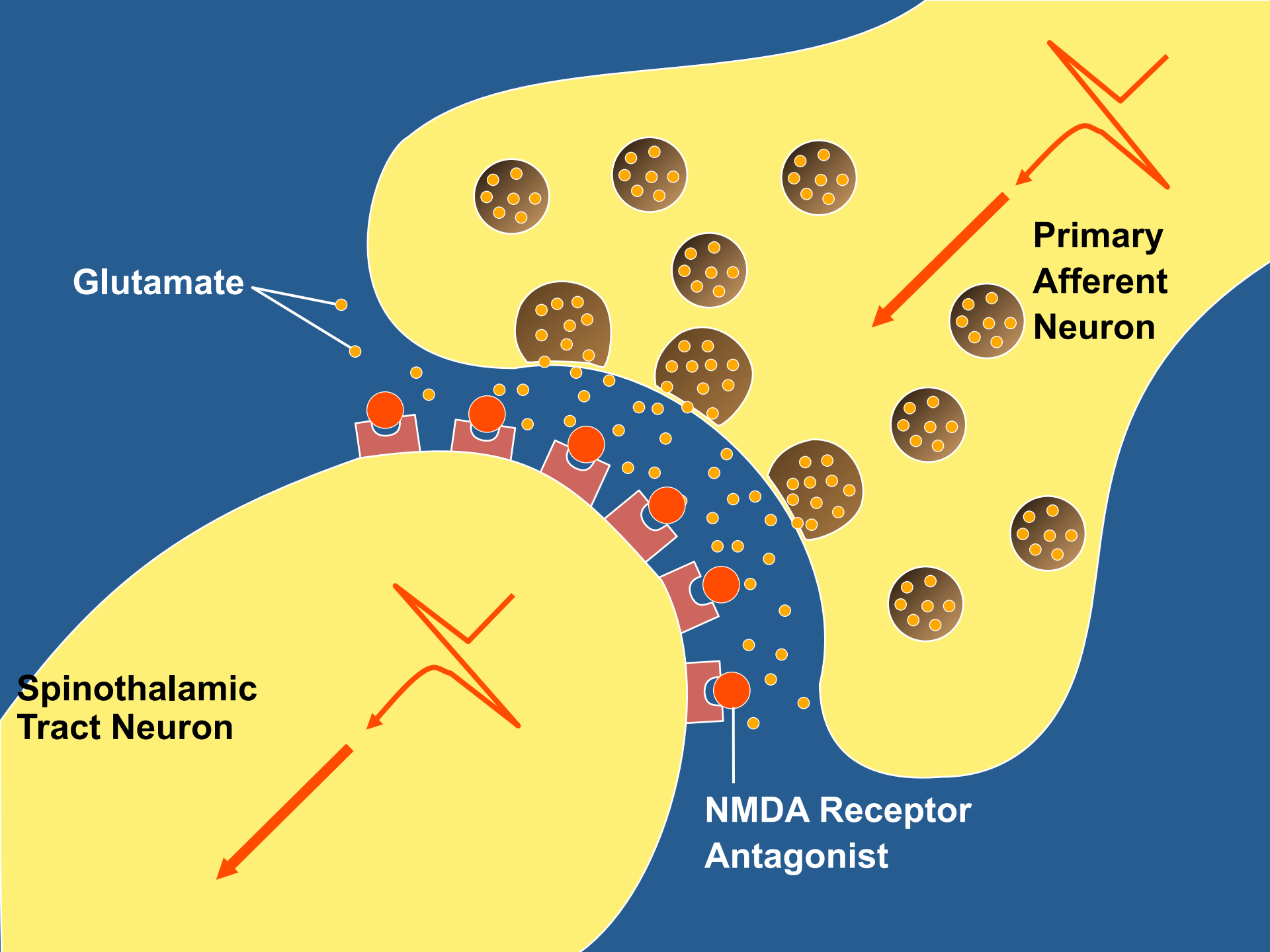
Respiratory depression

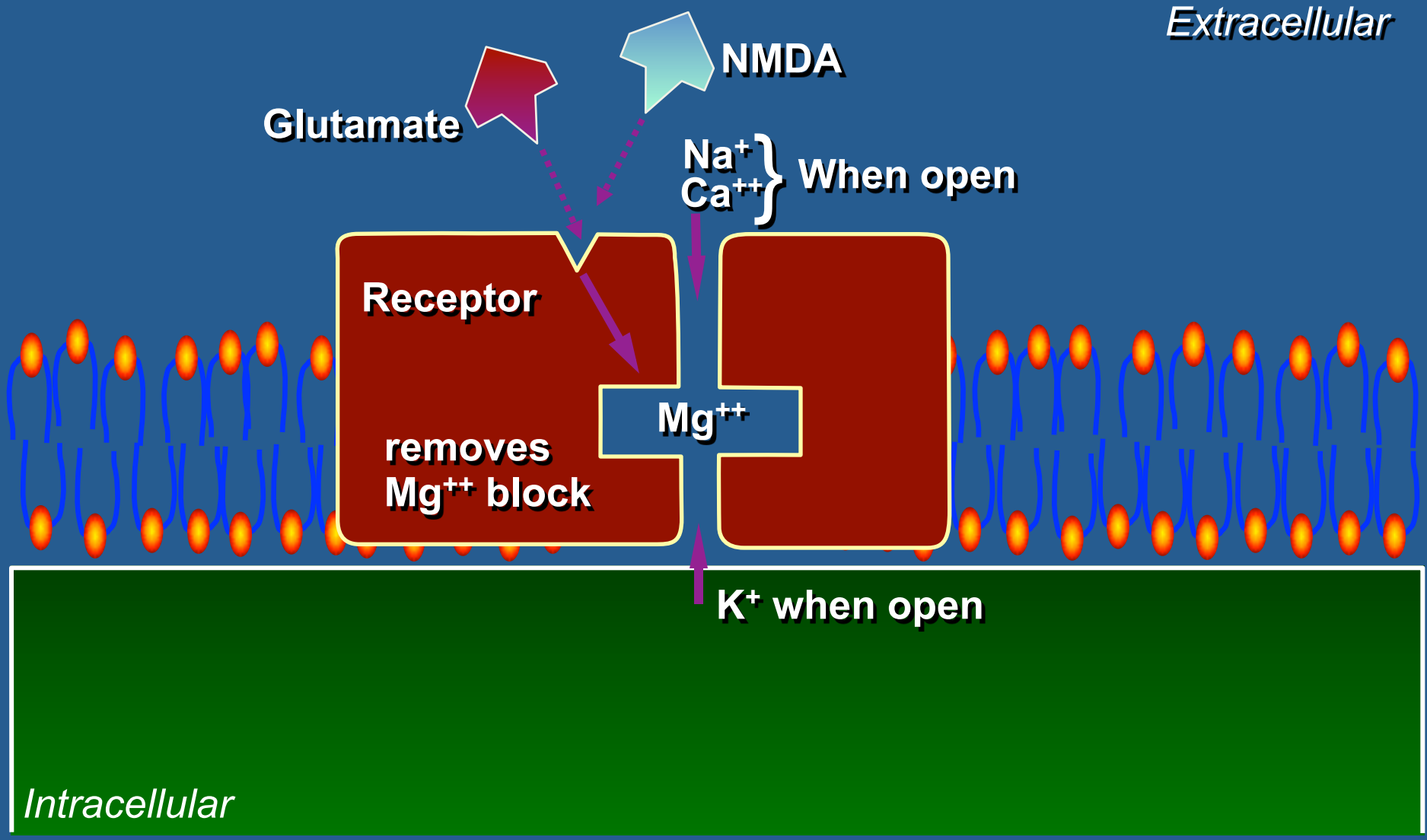
Urinary retention

Hypogonadism

SIADH


Primary
Afferent
Neuron
Glutamate
↑ Ca++
↑ NMDA Receptor
Activation
↑ Excitotoxicity


Glutamate
Primary
Afferent
Neuron
Spinothalamic
Tract Neuron
NMDA Receptor
Antagonist


Extracellular
NMDA
Glutamate
Na+
Ca++
When open
Receptor
Mg++
removes
Mg++ block
K+ when open
Intracellular

NMDA Receptor Antagonists

- Methadone
- Ketamine→NNT 3.9/NNH 9.0
  - Opioid sparing and deceases pain intensity
  - Oral test dose (20mg po)
  - frequency every 6 to 8 hours
  - Usually administer 100mg over course of day and can increase 100mg daily to 500mg

Fast Fact #132

Bell, Eccleston, Kalso. J Pain Symptom Manage 26:867-75, 2003

Ketamine: Adverse effects

- Doses Related- lower dose fewer effects
  - Psychotomimetic: cognition and psychiatric
  - Increased heart rate and blood pressure
  - Nausea, vomiting, anorexia
  - Hyperslavation
  - Ulcerative cystitis
- Extra caution in patients with
  - Increased ICP
  - Seizures
- No known drug interactions

Prommer E J Palliat Med 2012

Calcium Channel α2-δ

- Gabapentin and pregabalin
- Voltage-gated calcium channel binder, decreases glutamate, norepinephrine, and substance p
- Efficacy in a variety of peripheral nerve conditions and fibromyalgia
- generally well tolerated – dizziness, sedation, and peripheral edema
- Renal dosing

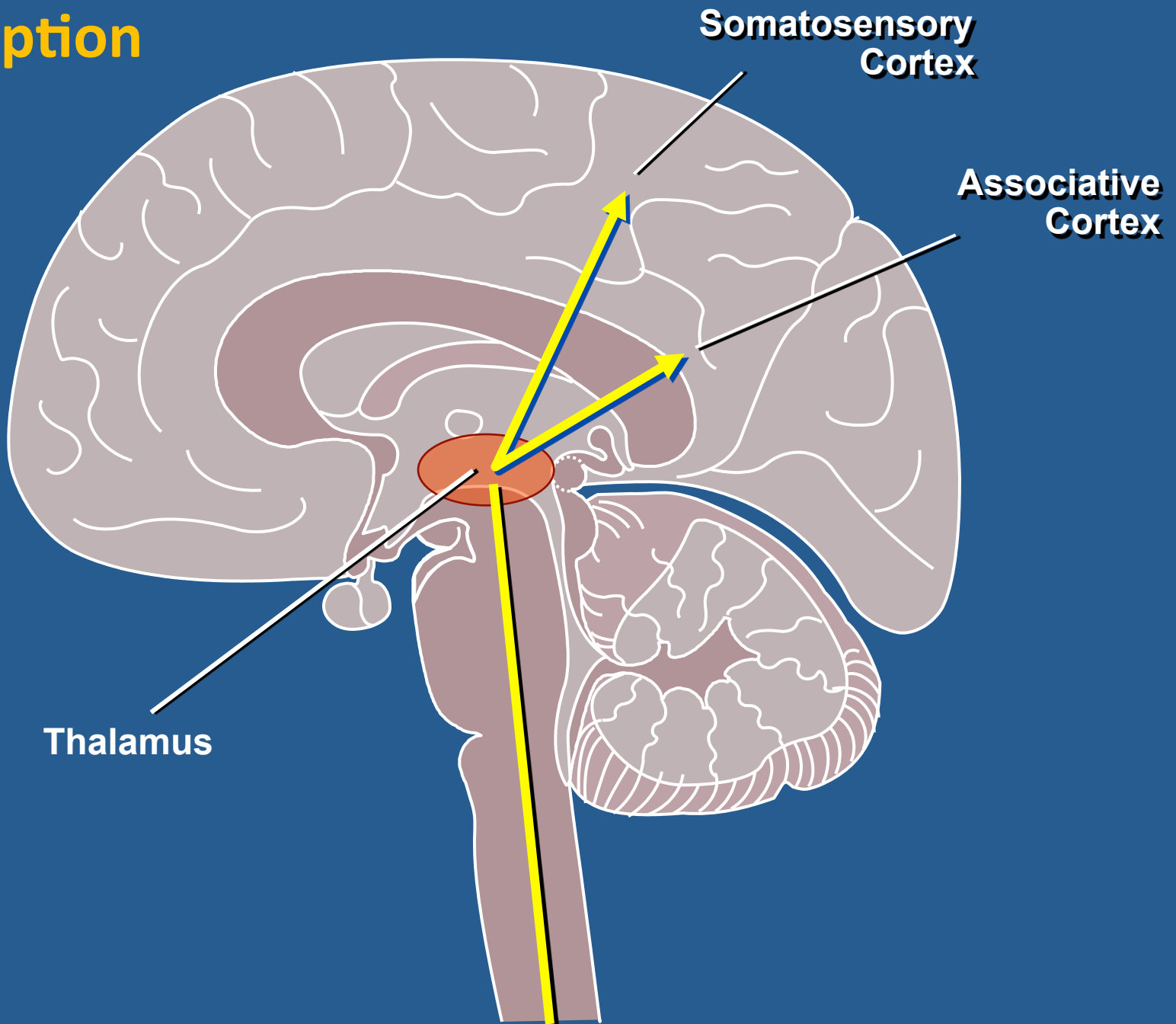
Calcium Channel α2-δ, cont…

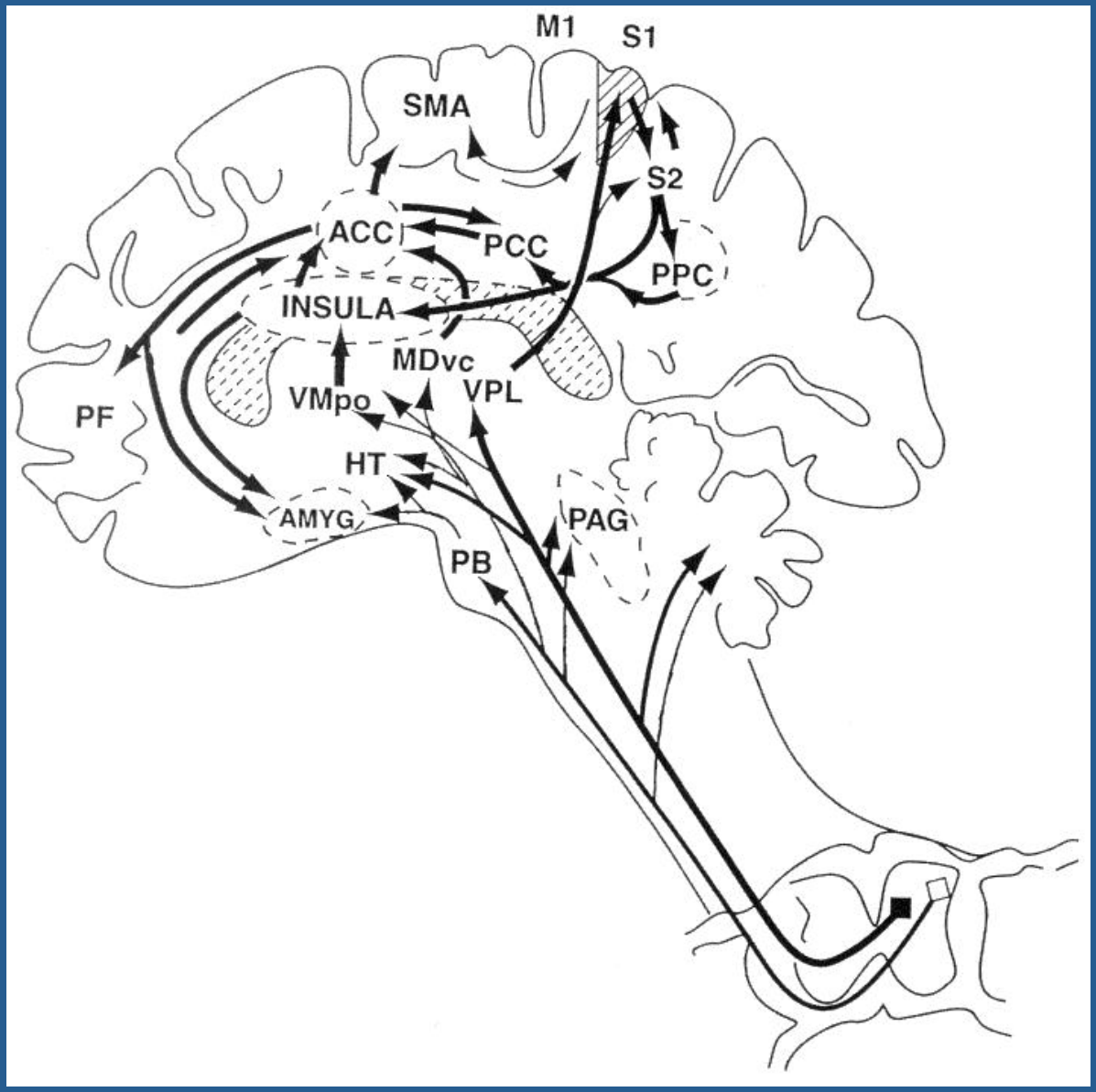
- Gabapentin→NNT 3.8-5.1/NNH 26.1
  - dose – 100 TID or q HS and titrate up to 3600 mg/day
  - Poor bioavailability at high doses
- Pregabalin→ NNT 4.7/NNH 11.7
  - Improved bioavailability at high doses
  - 50 mg bid/tid, increase to 100 mg tid; max 600 mg/day
  - Onset of action sooner/easier to titrate

Antispasm Drugs

- Baclofen
  - 5-20 mg po TID
  - Drowsiness, dizziness, hallucinations
- Tizanidine
  - 2 mg po TID
  - Drowsiness
- Clonazepam
  - 0.5 mg po BID – QID
  - Sedating

Perception





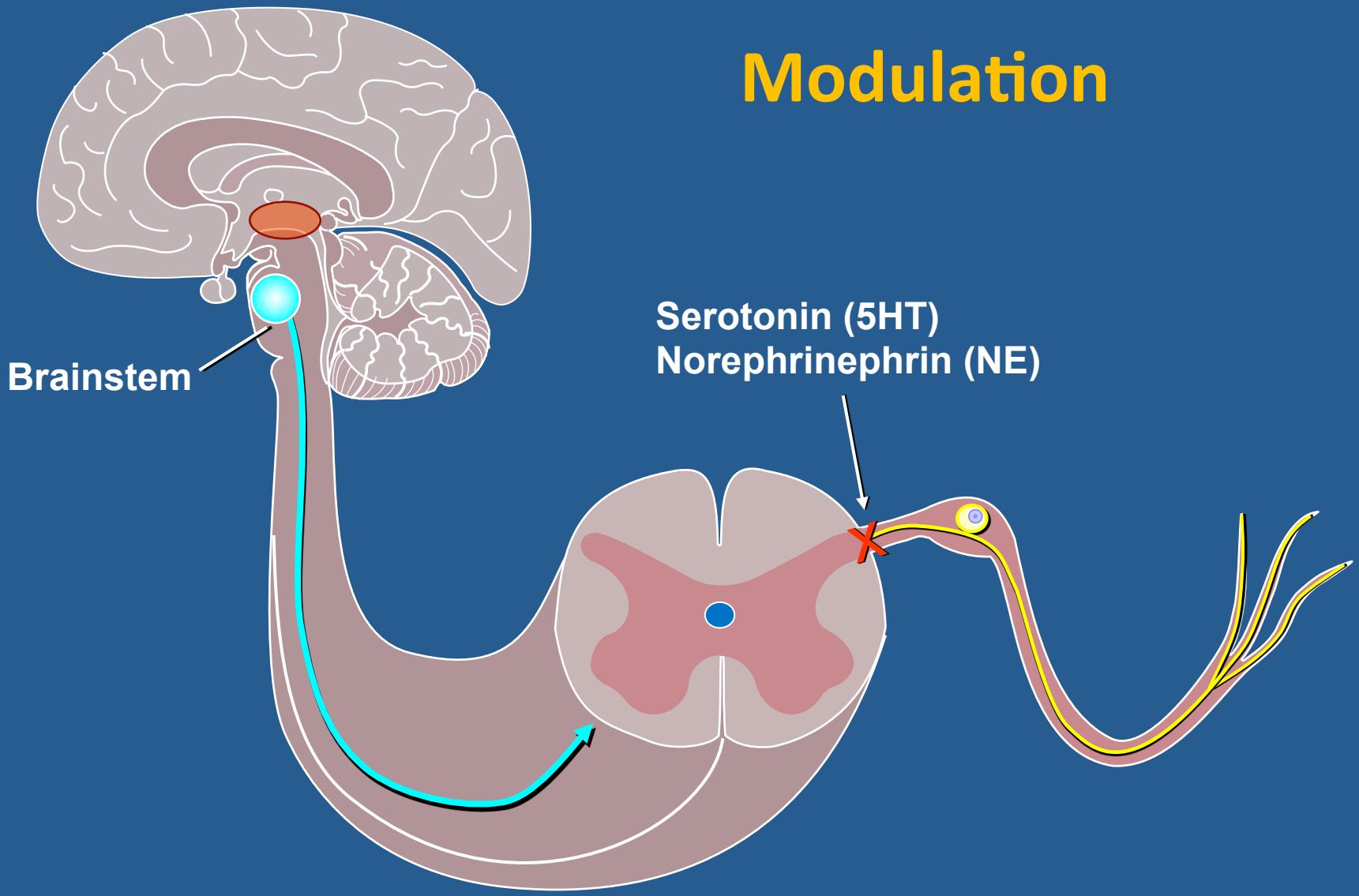
Price: Science, Volume 288(5472).June 9, 2000.1769-1772

Cognitive/behavior Modification

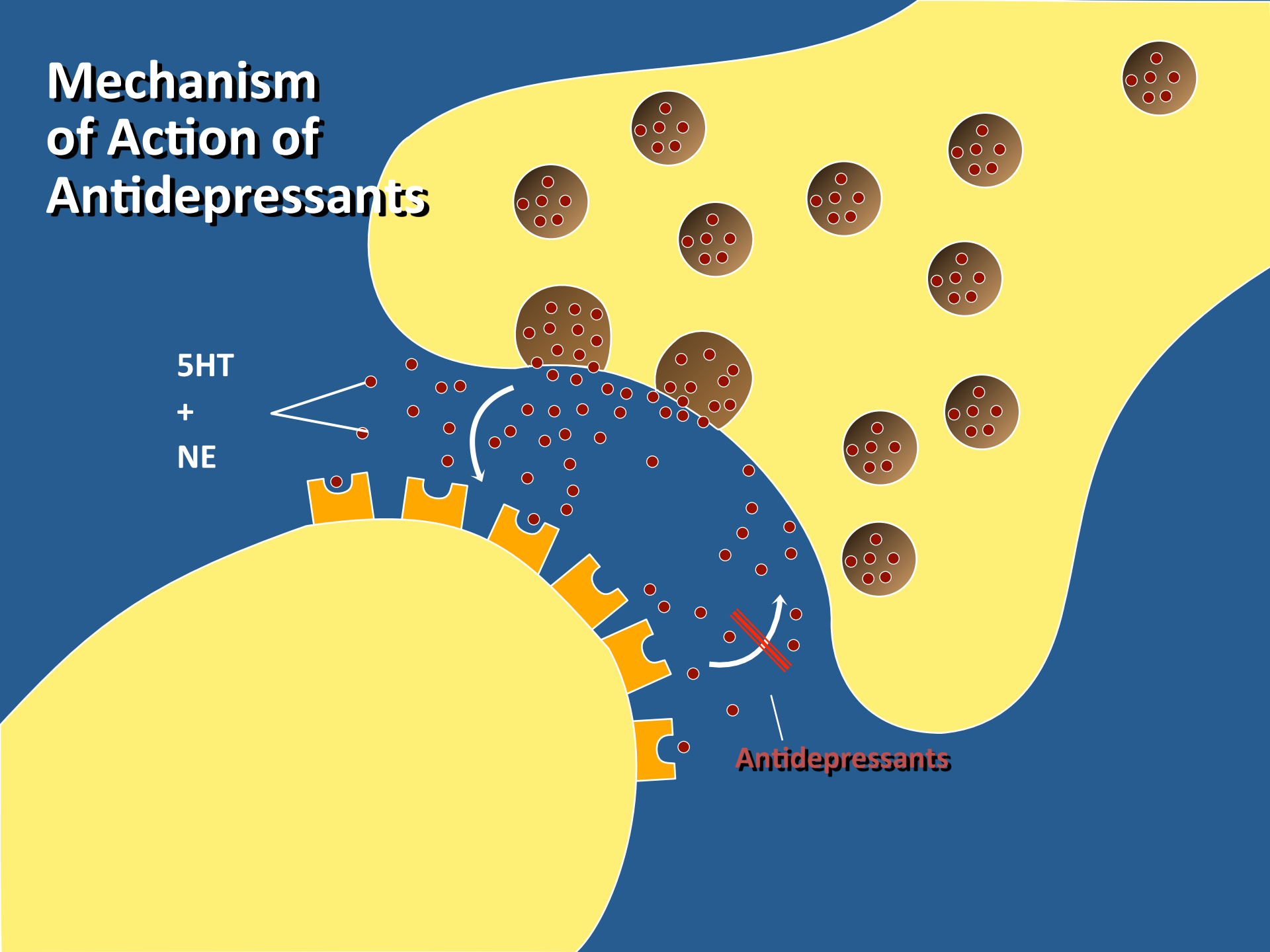
- Relaxation
- Guided imagery
- Distraction
- Cognitive reframing
- Support groups
- Pastoral counseling/prayer

Syrjala et al. Pain 1995;63:189-198

Modulation



Mechanism of Action of Antidepressants



Antidepressants: TCA

- Central and peripheral neuropathic pain→NNT 2-3/NNH 14.7
- Most studied agent, amitriptyline, has most anticholinergic effects
- Alternate agents: nortriptyline, desipramine
- Usually sedating, administer at night
- Start low, 10mg at night titrate gradually every 2 or 3 days, max dose 150mg (cardiac)
- Cardiac toxicity (sinus tach and vent ectopy)

Hammack JE, et al. *Pain* 2002; 98:195-203

Antidepressants:SNRI

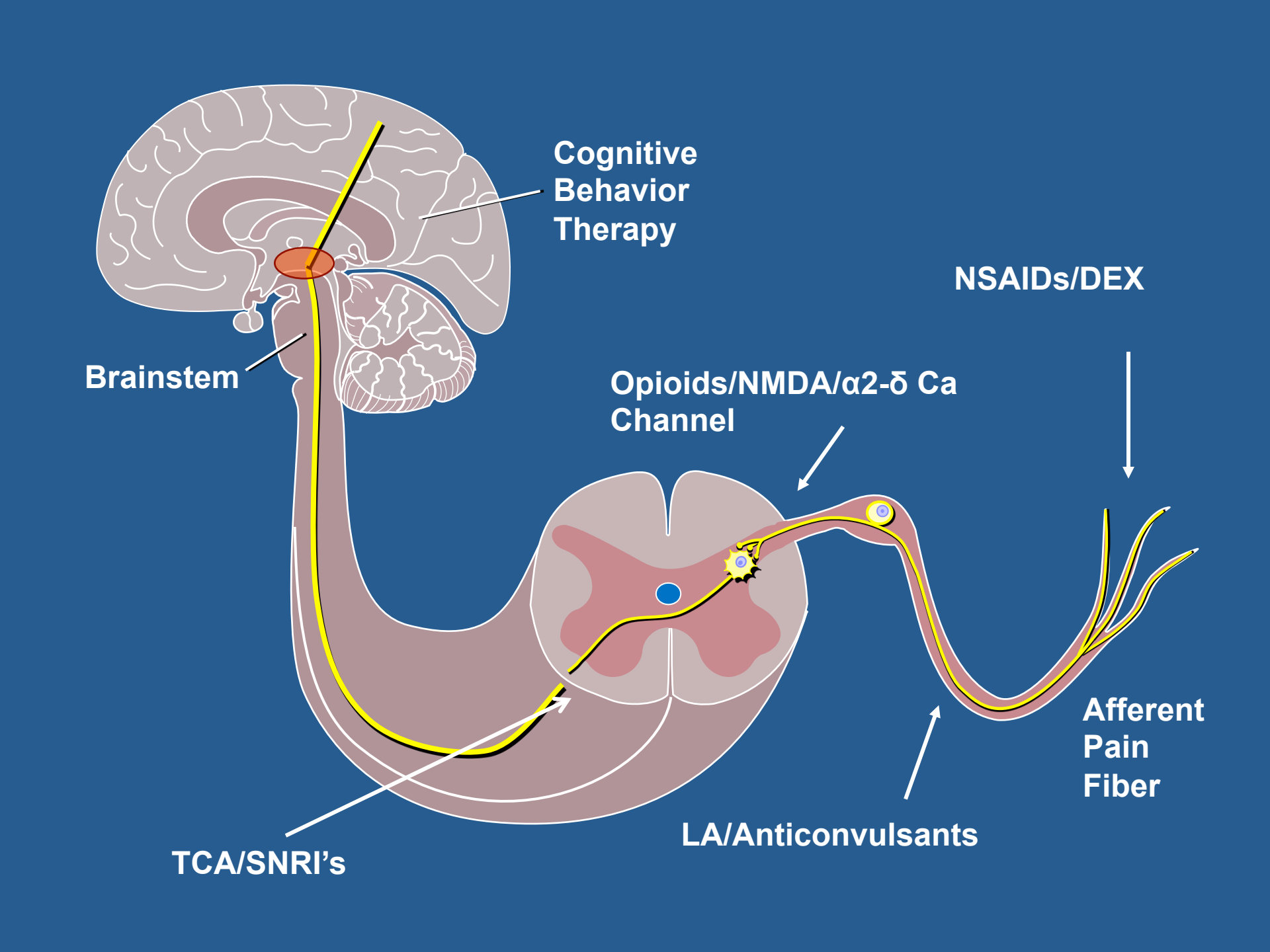
- Venlafaxine (Effexor)
- Peripheral neuropathic pain→NNT 4
- Mechanism: inhibits NE, 5HT, Dopamine reuptake
- Start low 37.5 – 75 po qd; titrate gradually every 3 -4 days; 150-225 mg/day
- Nausea (take with food)
- Cardiac disease (EKG changes) and HTN

Durand et al. *Anti-Cancer Drugs* 2002;13:777-780

Antidepressants: SNRI

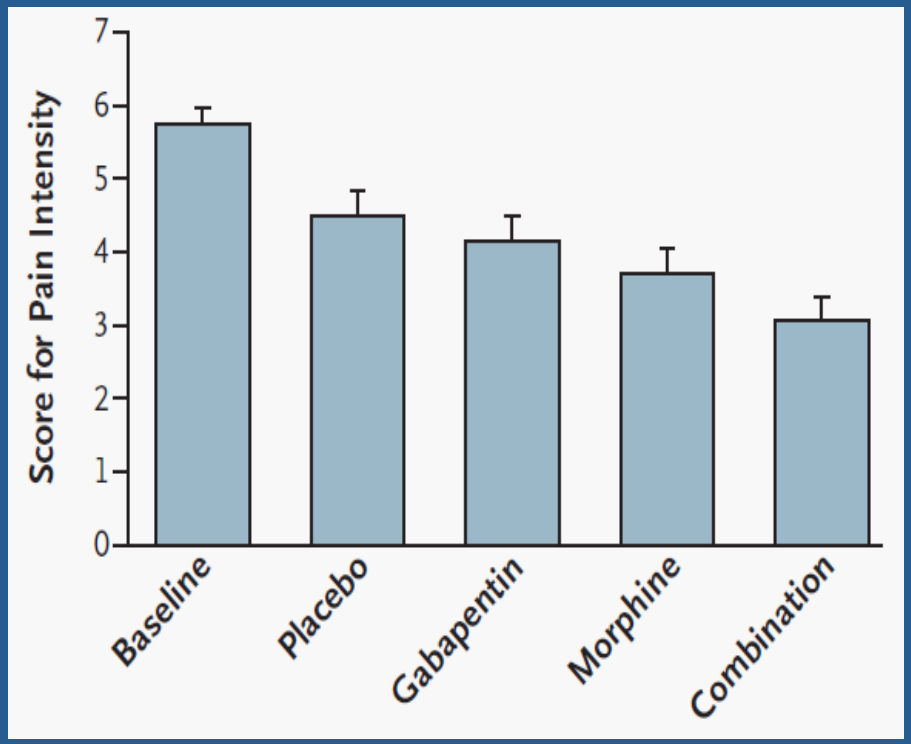
- Duloxetine (Cymbalta)
- Peripheral neuropathic pain→NNT 4
- FDA Approval fibromyalgia and chronic musculoskeletal pain (arthritis and low back pain)
- Mechanism: inhibits NE, 5HT, Dopamine reuptake
- 60 mg po daily
- Don't crush/cut/chew
- Reduce dose with renal disorder, may be contraindicated with hepatic impairment
- Nausea, dry mouth, drowsiness, and dizziness

Durand et al. *Anti-Cancer Drugs* 2002;13:777-780

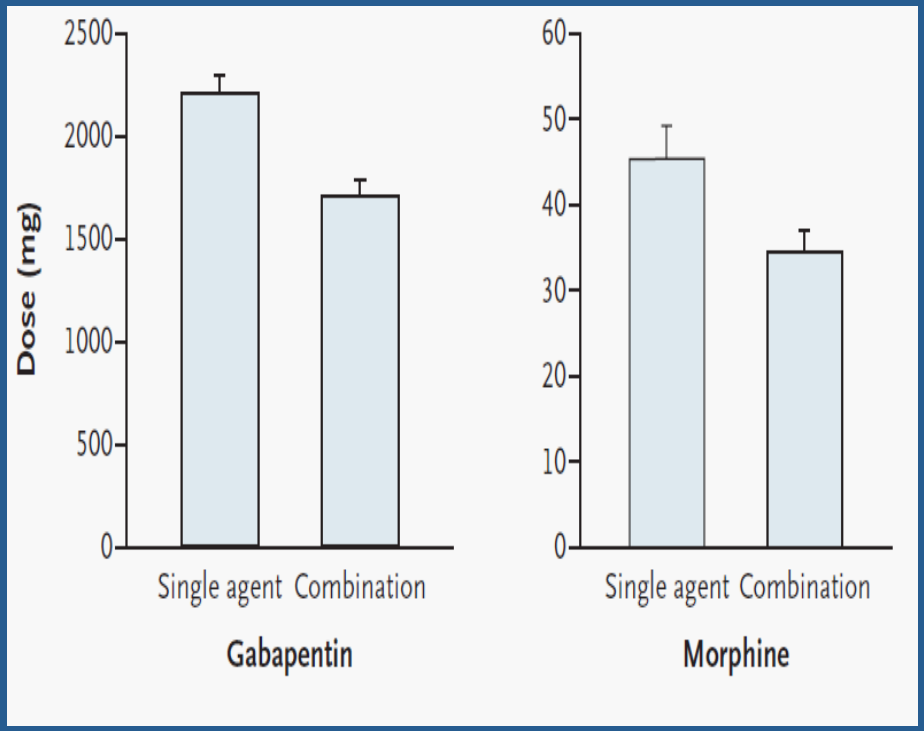

Cognitive
Behavior
Therapy
NSAIDs/DEX
Brainstem
Opioids/NMDA/α2-δ Ca
Channel
Afferent
Pain
Fiber
TCA/SNRI's
LA/Anticonvulsants

Morphine, Gabapentin, or combination for neuropathic pain

Mean Daily Pain



Maximum Tolerated Daily Dose



NEJM 2005

Anticonvulsant or Antidepressant and opioid for neuropathic cancer pain

- About 1 point decrease on 0-10 scale with combination therapy
- Effect of adding second agent generally seen within one week
- Side effects greater if opioid dose not decreased
- Significant for opioid sparing effect

Bennett 2011 Palliative Medicine

Case 1

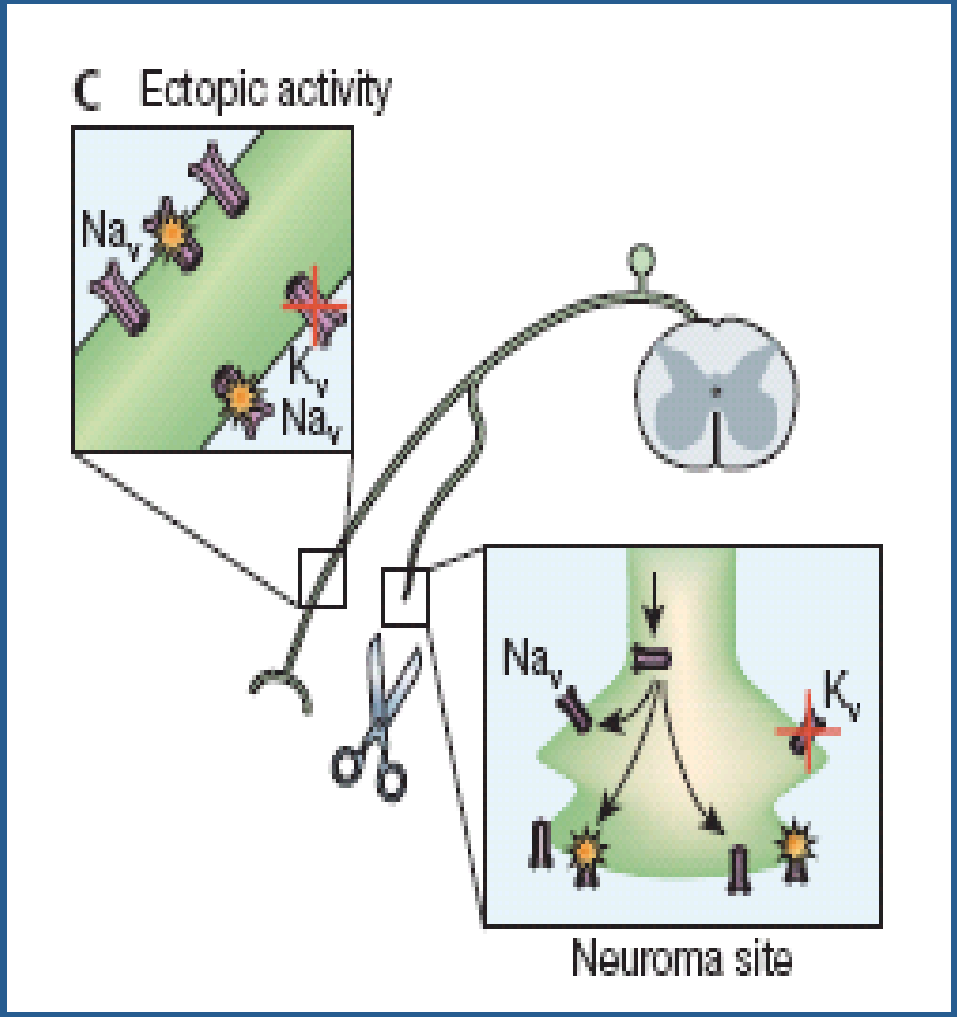
- 78 y/o with head/neck cancer progressive disease despite chemo and XRT
- Complains of intermittent severe pain in right face, sharp and electric like, radiation across face

Case 1cont…

- Neuropathic pain from tumor infiltrating into V2 distribution of facial nerve
- Started carbamazepine twice daily (conduction)
- Morphine 2.5 mg every 6 hours (transmission)
- Pain decreased from 10/10 to 0-1/10
- Died with minimal pain 4 months later
- Never needed opioid

Case 2

- 88 y/o with failure to thrive
- Neuropathic pain-hyperalgesia and allodynia
- Postherpetic neuralgia



Scholz and Woolf. Nature Neuroscience, 2002

Case 2 Cont…

- Opioid (transmission)
  - Oxycodone 2.5mg every 6 hours rtc
- Tricyclic (descending inhibition)
  - Nortriptylline 10mg at night

Case3

- 85 y/o hospitalized s/p fall with dislocation many teeth and severe pain in back from strain
- No vertebral fracture
- Acute on chronic back pain
- Moderate to severe muscle spasm on exam
- High risk delirium (cognitive impairment, dehydration, sensory impairment, urinary catheter)

Case 3 Cont…

- Mixed nociceptive and neuropathic pain
- Muscle relaxant(transmission)
  - Baclofen 2.5mg every 8 hours
- Analgesic (conduction)
  - APAP 650mg every 6 hours RTC
- Opioid (transmission)
  - Oxycodone 2.5mg every 6 hours prn

Thank You