BASIC ASPECTS OF ANALGESIA

Mahmoud Al-Khrasani

al-khrasani.mahmoud@med.semmelweis-univ.hu

20.02.2019

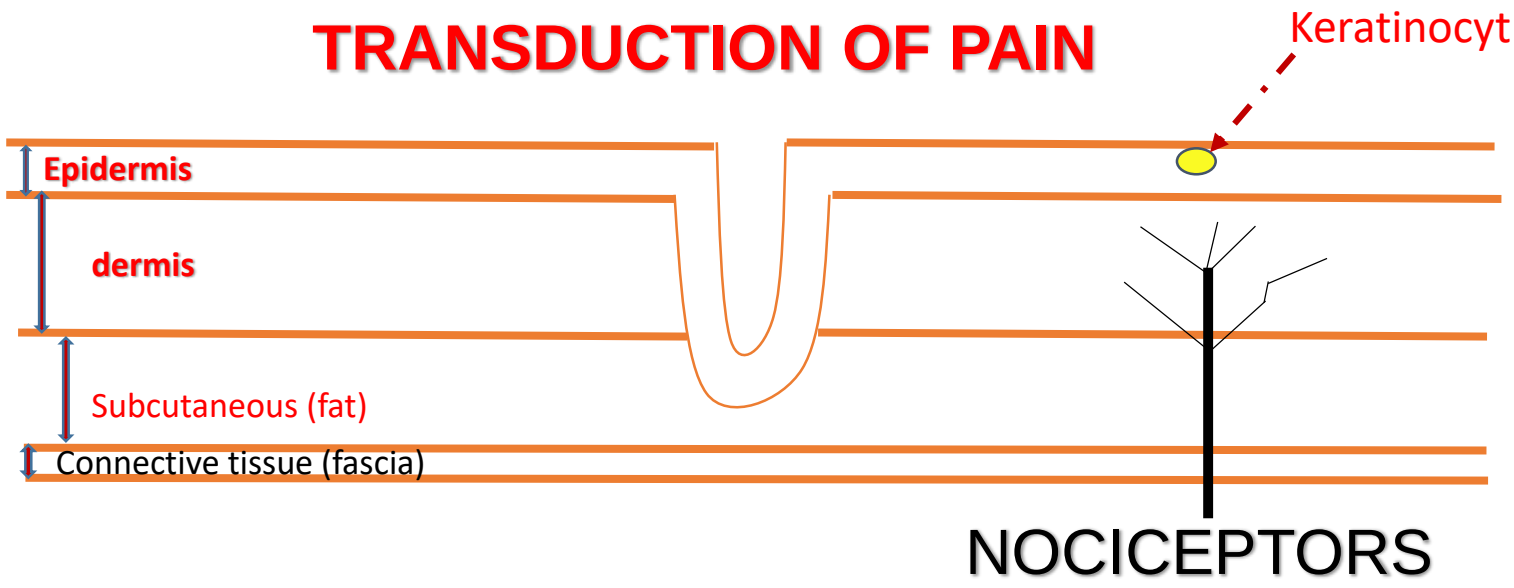
Definition

„An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”

(International Association for the Study of Pain, IASP).

This definition avoids relating pain to the stimulus.

TRANSDUCTION OF PAIN



- Are the receptors of pain evoked by chemical, mechanical and heat stimuli. Distribution: periphery
- Show specific response for pain.
- Their sensitivity is increased upon tissue damage

Nociception

- The neural process of encoding noxious stimuli (IASP).

Nociceptors activation → Perception → transmission of actual information to the brain

PRIMARY AFFERENT FIBRES

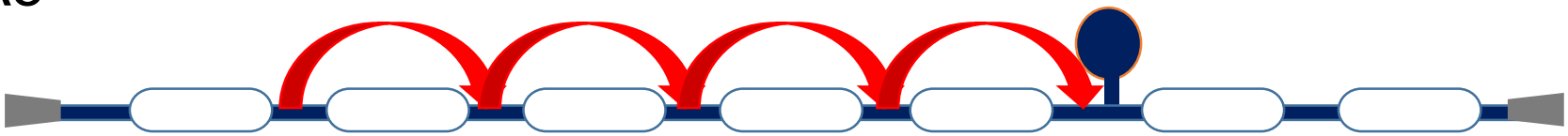
- Noxious sensory information carrier:
  Aδ and C fibers
- Non-noxious stimulus carrier: Aβ fibers

	Aβ	**Aδ**	**C**
Diameter	Large	Small 2-5µm	Smallest <2µm
Myelination	Highly	Thinly	Unmyelinated
Conduction velocity	> 40 ms-1	5-15ms-1	< 2ms-1
Receptor activation thresholds	Low	High and low	High
Sensation on stimulation	Light touch, non-noxious	Rapid, sharp, localised pain	Slow, diffuse, dull Burning pain
		Mechanical and thermal stimuli responsible for the initial reflex response to acute pain	Polymodal

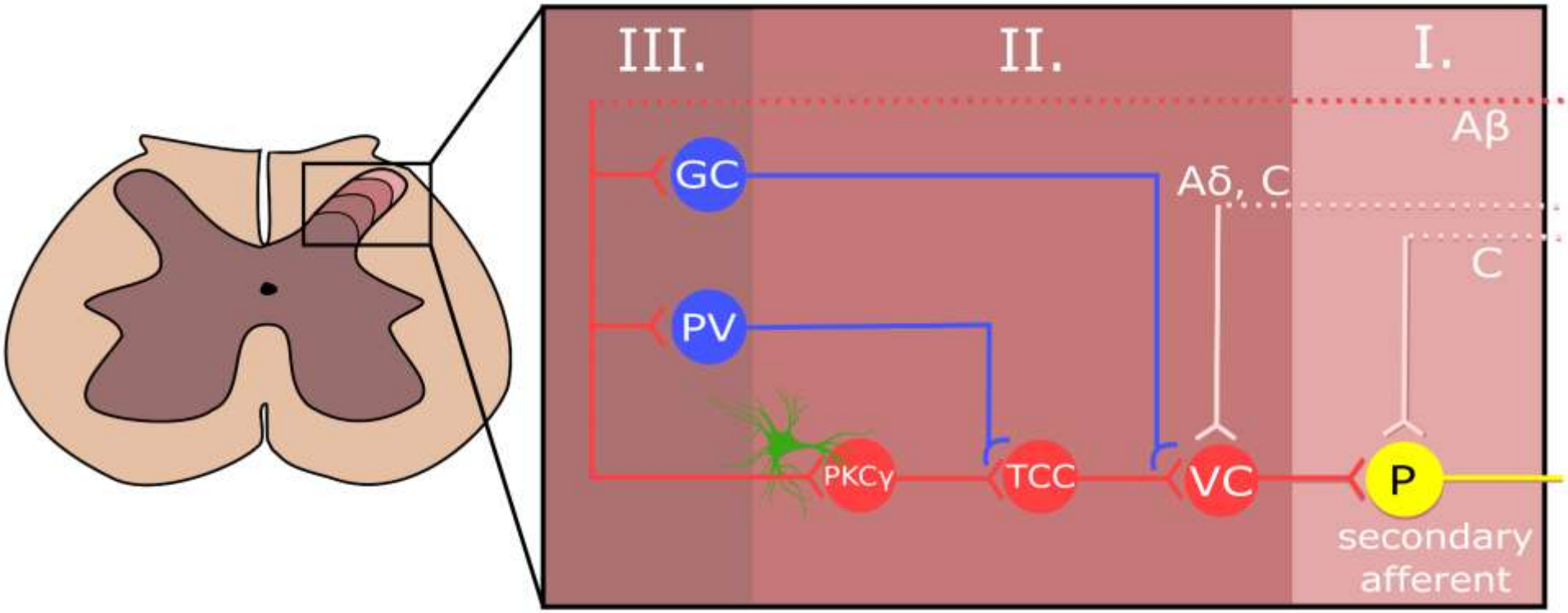
Polymodal: responding to multiple modalities, chemical, mechanical (touch, pressure, stretch) and thermal stimuli

Saltatory conduction

Aδ



C fibers



Excitatory interneurons: protein kinase Cγ (PKCγ); transient central cells (TCC) vertical cells (VC)
Inhibitory interneurons: glycinergic (GC), parvalbumin (PV)

From Al-Khrasani et al., 2019

Pain generation, localization, intensity

Cortex

TERCIER AFFERENS

Thalamus

SECONDAR AFFERENS

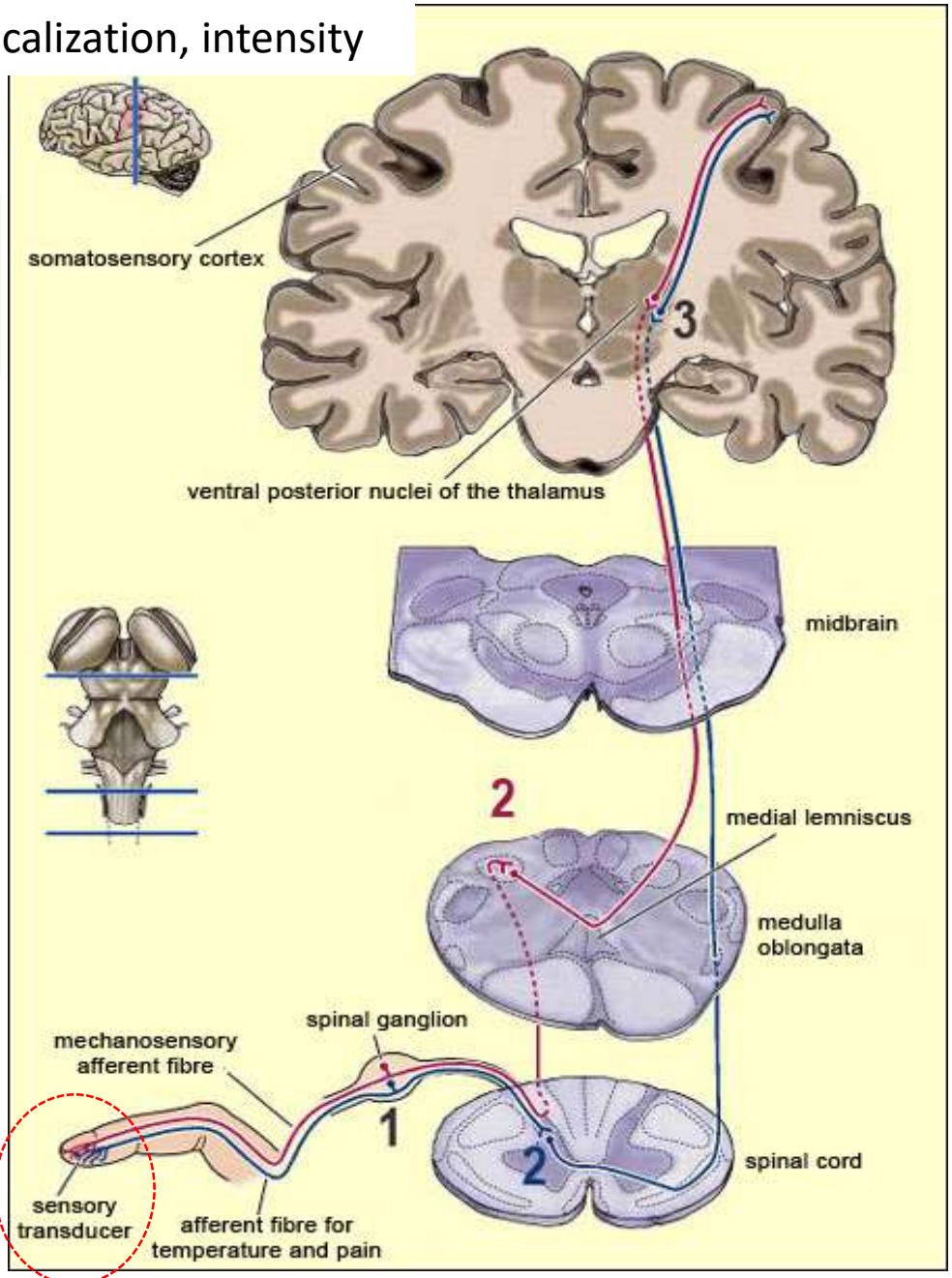
Gerinc velő

PRIMER AFFERENS

Nociceptorok

free nerve endings

Pain components
Sensory
Affective



Ascending pain pathway (Purves et al., 2003).

Descending pathway

Hypothalamus

PAG

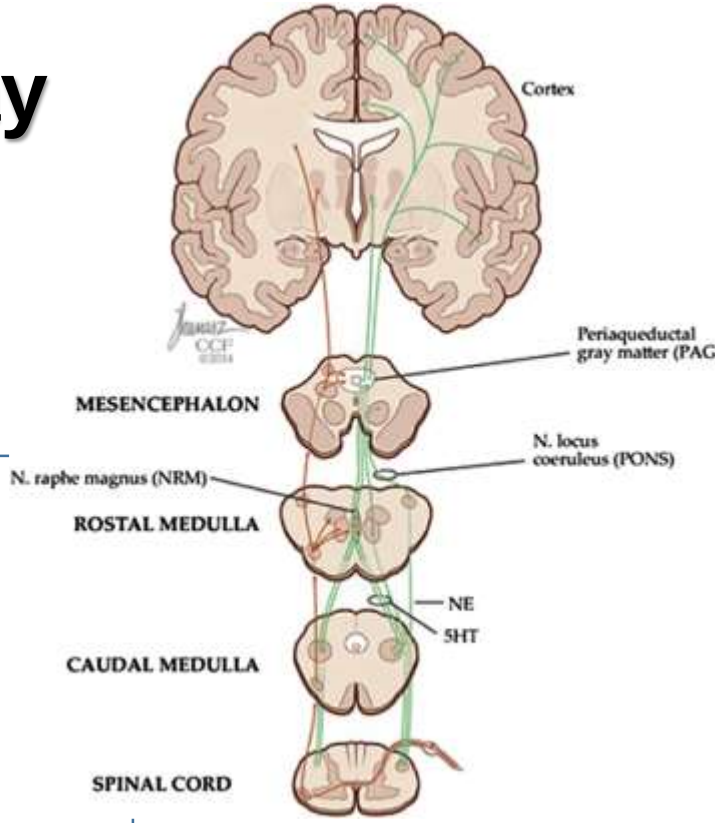
Nucleus coerleus

NE

RVM includes RM

Nucleus raphe

5HT



(Bourne et al., 2014).

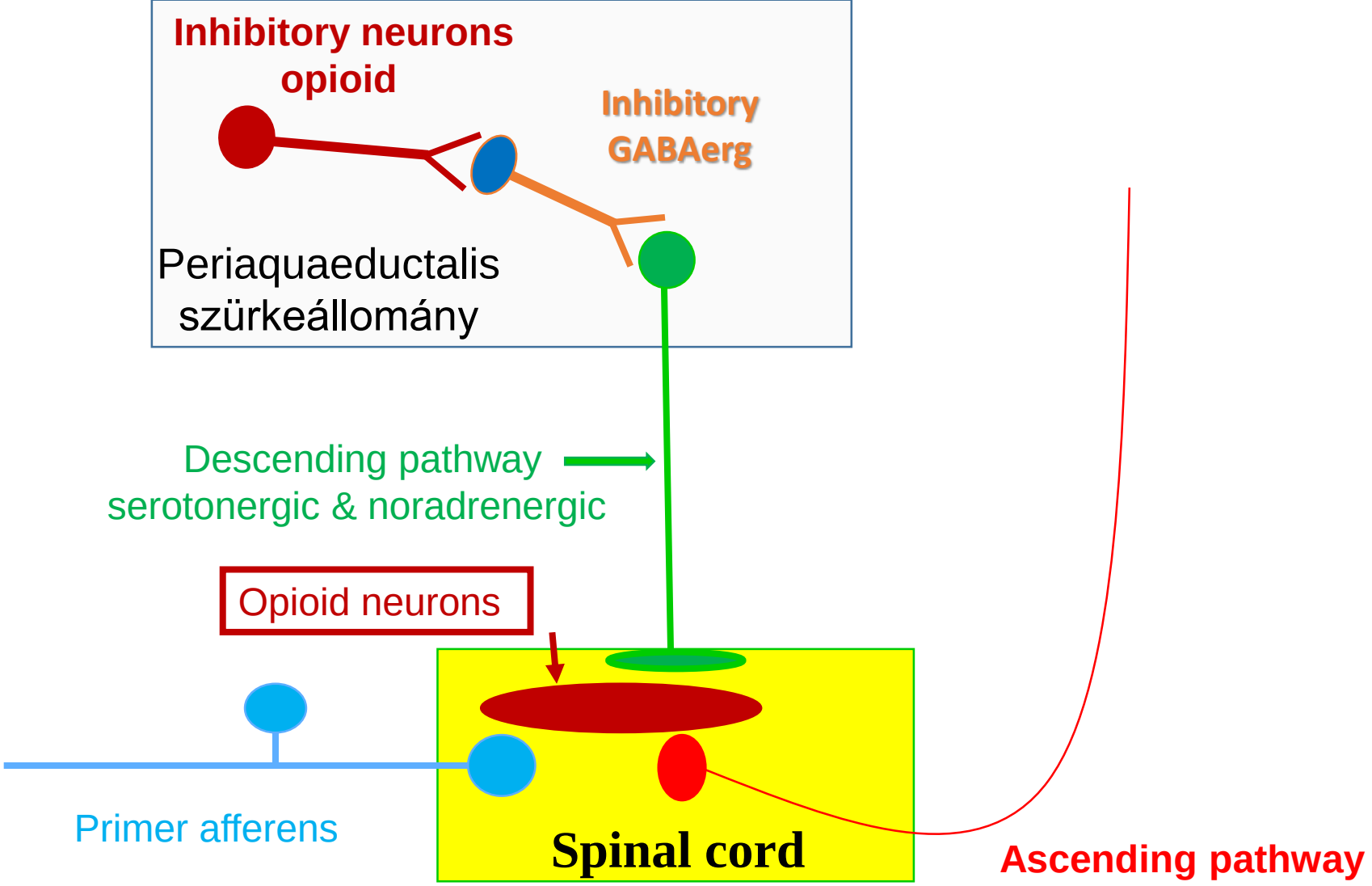
α2-contribution
α1-on inhibitory interneurons
(GAGA-ergic, Glycinergic)
In NP dysfunction in NA-ergic system
(restoration by NET inhibitors)

5-HT2, 5-HT3

Nefopam inhibits NET, SERT and DET

spinal dorsal horn

RVM: rostral ventromedial medulla


Inhibitory neurons
opioid
Inhibitory
GABAerg
Periaquaeductalis
szürkeállomány
Descending pathway
serotonergic & noradrenergic
Opioid neurons
Primer afferens
Spinal cord
Ascending pathway

CLASSIFICATION OF PAIN

many ways to classify pain

Nociceptive
Somatic
Visceral

Inflammatory
evoked by proinflammatory m.
acid
activation & sensitization of
nociceptive pain pathway
Hyperalgesia

Neuropathic
disease or lesion in the somatosensory n.
- hyperalgesia or allodynia
- paresthesias (tingling)
(spinal cord injury, diabetic neuropathy,
postherpetic neuralgia, post-stroke pain, phantom pain)

Types	Source	Innervation	Character.
Visceral	internal organs	C fibres	diffuse and poorly localised, (deep, dull or dragging)

Nociception

- The neural process of encoding noxious stimuli (IASP).

Nociceptors activation → Perception → transmission of actual information to the brain.

Neurotransmitters involved in the nociception:

- Substance P
- Glutamate
- Neuropeptides
- Tachykinins
- Calcitonin gene-related peptide
- Somatostatin
- Neurotrophins (NGF, BDNF)
- Aspartate

TISSUE DAMAGE

↓

RELEASE INFLAMMATORY MEDIATORS

Bradykinin (nociceptor activator)
Serotonin (nociceptor activator)
Prostaglandins (Nociceptor sensitizer)
Histamine (Nociceptor sensitizer)
Cytokines (Nociceptor sensitizer)
H+ (hyperalgesia)

↓ threshold

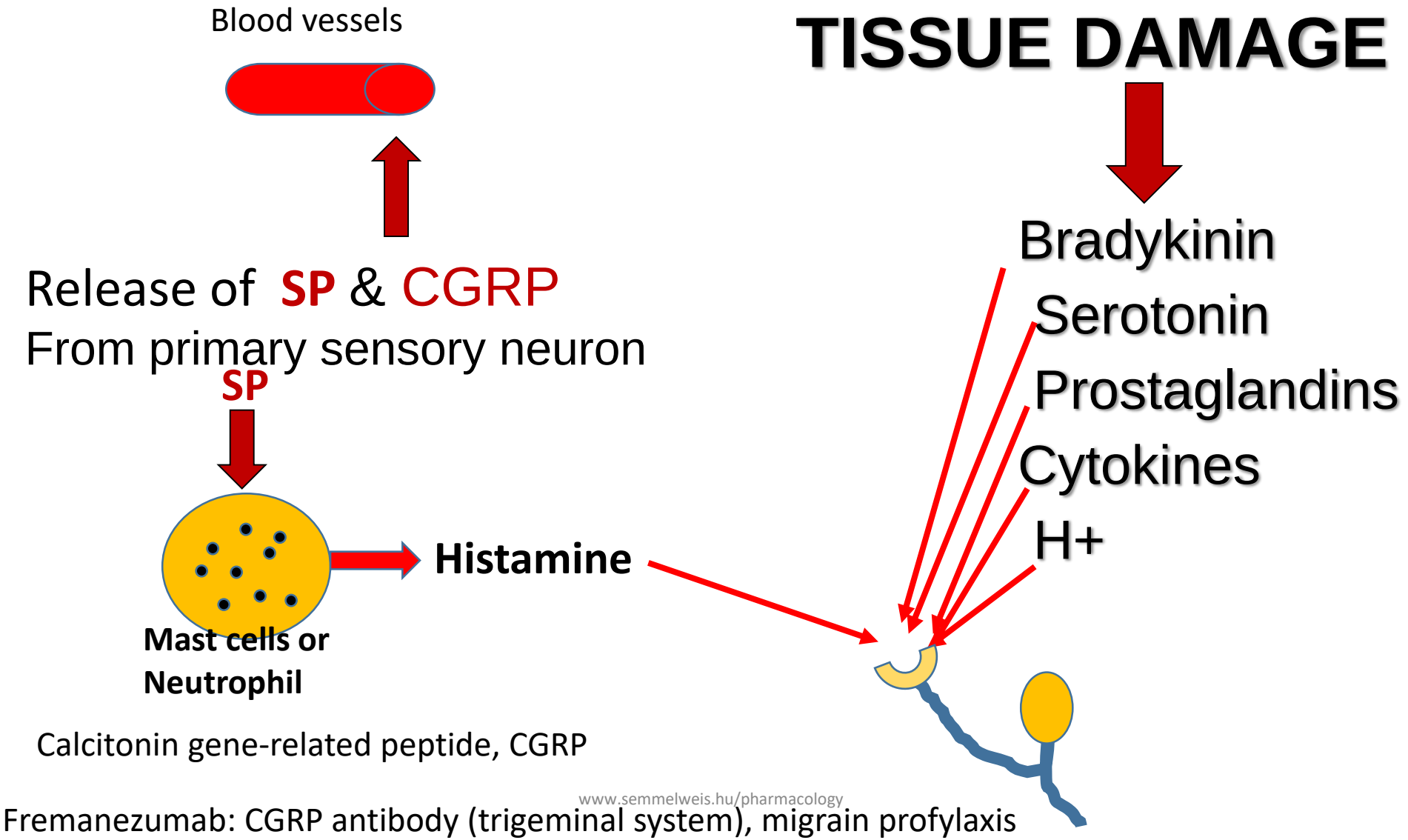
↓

less stimuli

primary sensitisation

nociceptors stimulation

Peripheral Sensitization



Calcitonin gene-related peptide, CGRP

Fremanezumab: CGRP antibody (trigeminal system), migrain profylaxis

Ischemic pain:

Angina

Intermittent claudication

Sickle cell anemia

Lactic acid (anaerobic metabolism) when the O2 supply is insufficient.

Acid-sensing ion channel number 3 (ASIC3)

Local tissue acidosis & painful states

In peripheral tissues, acidic pH can directly excite nociceptive neurons by activating:

- Acid-sensing ion (Na) channels (ASICs), are considered as one of key ion channels to excite nociceptive neurons.

- Other channels regulated by acidic pH:

voltage-gated Na^+, K^+ and Ca^{2+} channels

transient receptor potential vanilloid 1 (TRPV1)

(Wemmie et al., 2006 and Holzer, 2009),

-Tetrodotoxin-resistant (TTX-R) Na^+ channels

expressed on small- and medium-sized sensory neurons (DRG and trigeminal ganglia)

have role in inflammatory, NP and cold pain.

(Zimmermann et al., 2007, Eijkelkamp et al., 2012 and Waxman and Zamponi, 2014).

- TTX-R Na+ inhibited by KOR agonists via an opioid receptor-independent mechanism.

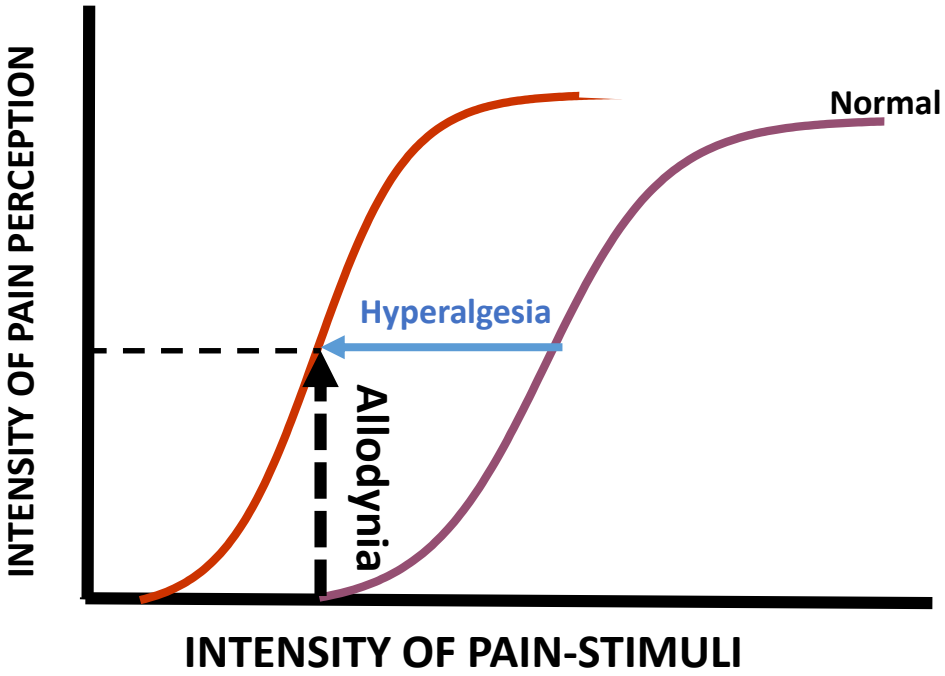
Classification of pain III.

- **Nociceptive pain**

  Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.

- **Neuropathic pain**

  Pain caused by a lesion or disease of the somatosensory nervous system.



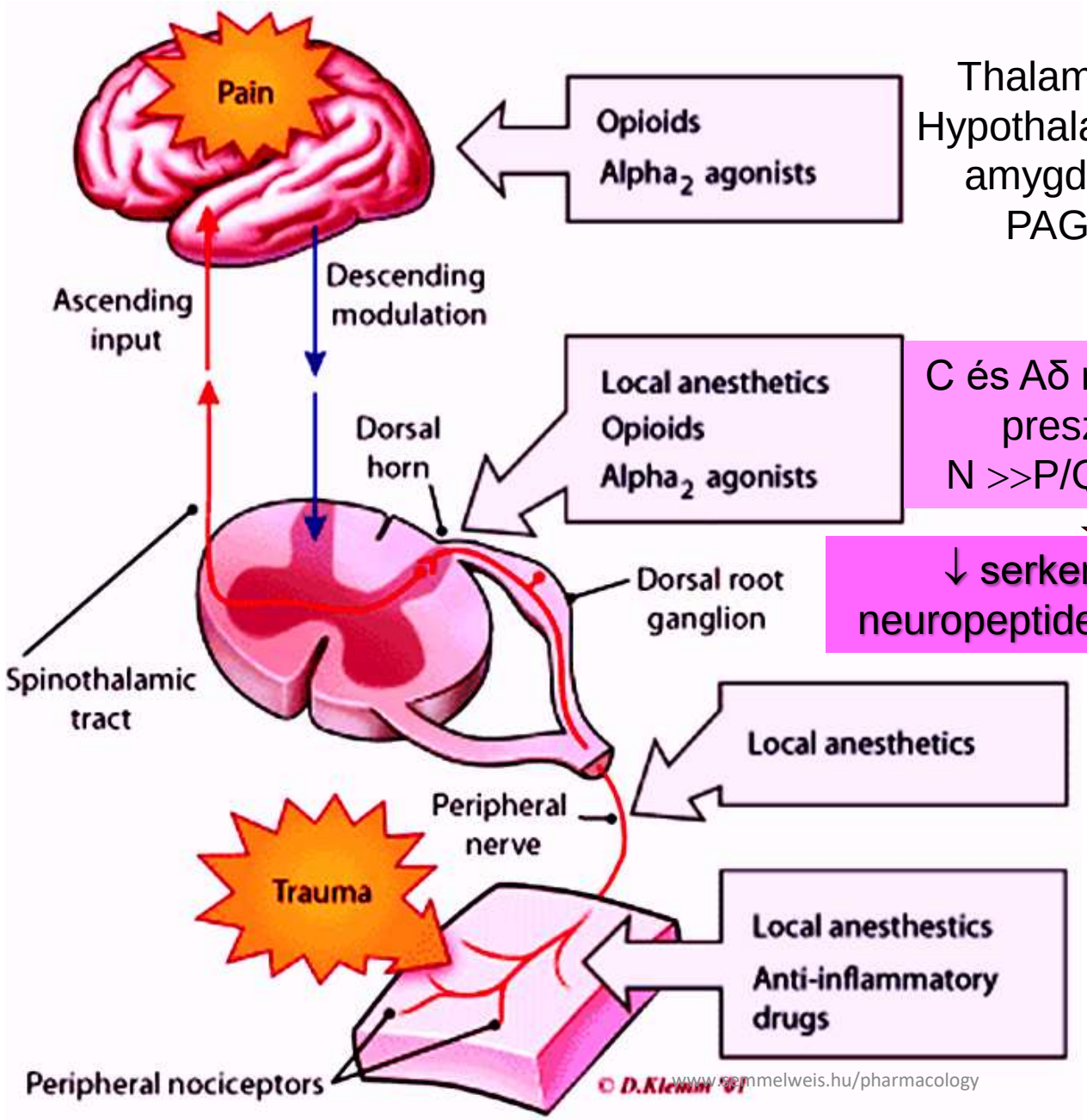
Hyperalgesia

Increased pain from a stimulus that normally provokes pain.
(reflects increased pain on suprathreshold stimulation)

Allodynia

Pain due to a stimulus that does not normally provoke pain.
(The stimulus leads to an unexpectedly painful response)

THE TARGETS OF ANALGESIC AGENTS



Thalamus
Hypothalamus
amygdala
PAG

C és Aδ rostok (MOR)
preszinaptikus
N >>P/Q Ca^{2+} gátlás

↓ serkentő neurohormonok
neuropeptidek (glutamát & P-anyag)

MOLECULAR MECHANISMS

Damage of peripheral sensory fibers results in:

↑expression of the following:

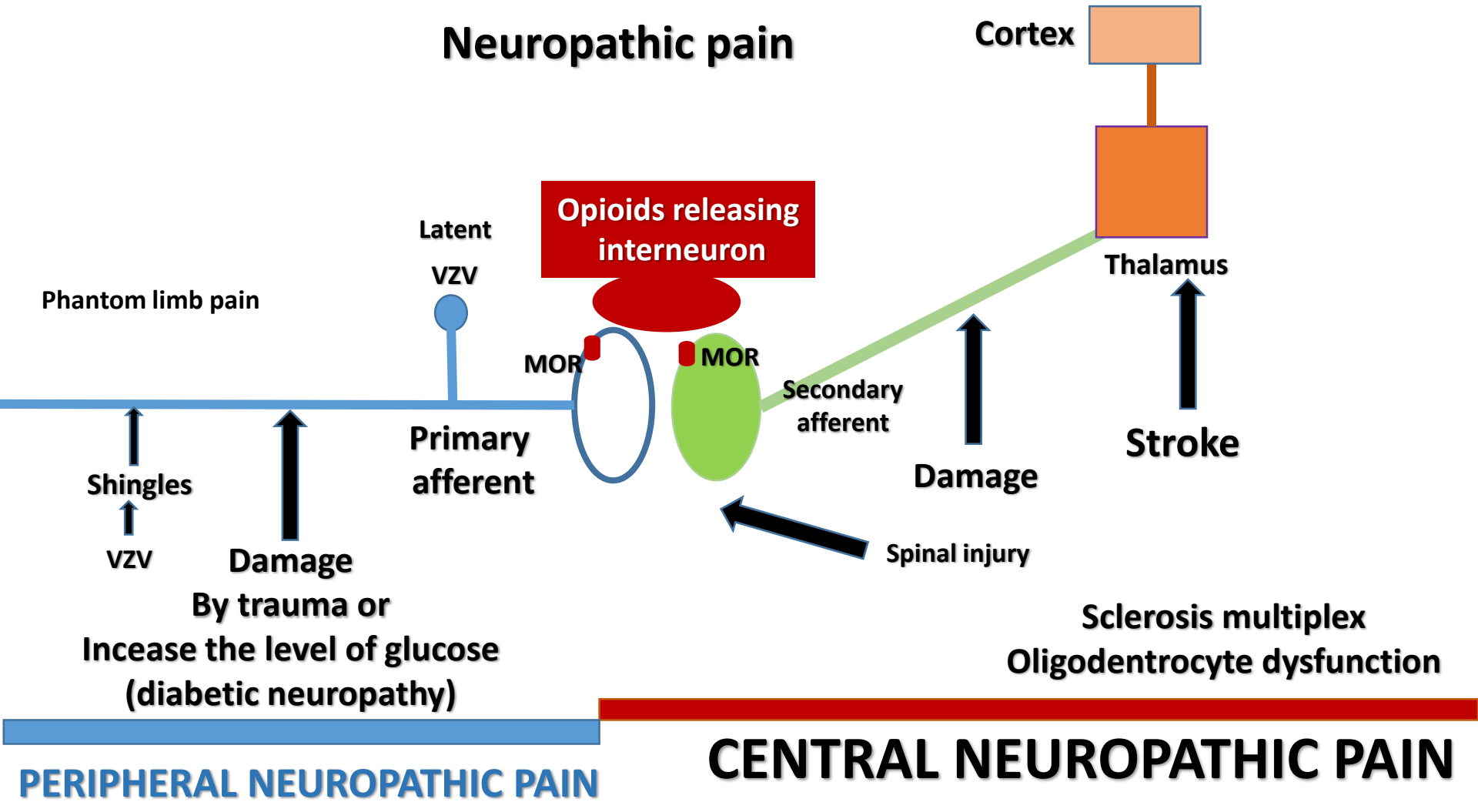
(in myelinated neurons contribute to hyperalgesia)

- $Ca_v\alpha2\delta$-1 channel subunit
- $Na_v1.3$ sodium channel (1nM TTX)
- Bradykinin (BK) B1 and capsaicin TRPV1 receptors

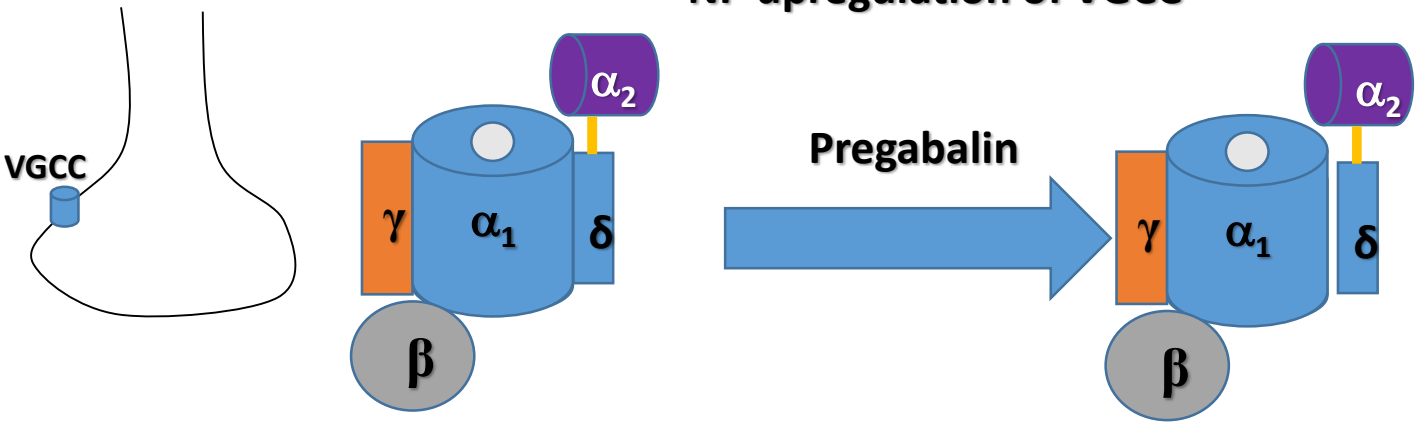
Down regulation of the following:

- $Na_v1.8$ Na channel (100μM TTX)
- B2 receptor, substance P (SP), MORs in unmyelinated

ns.

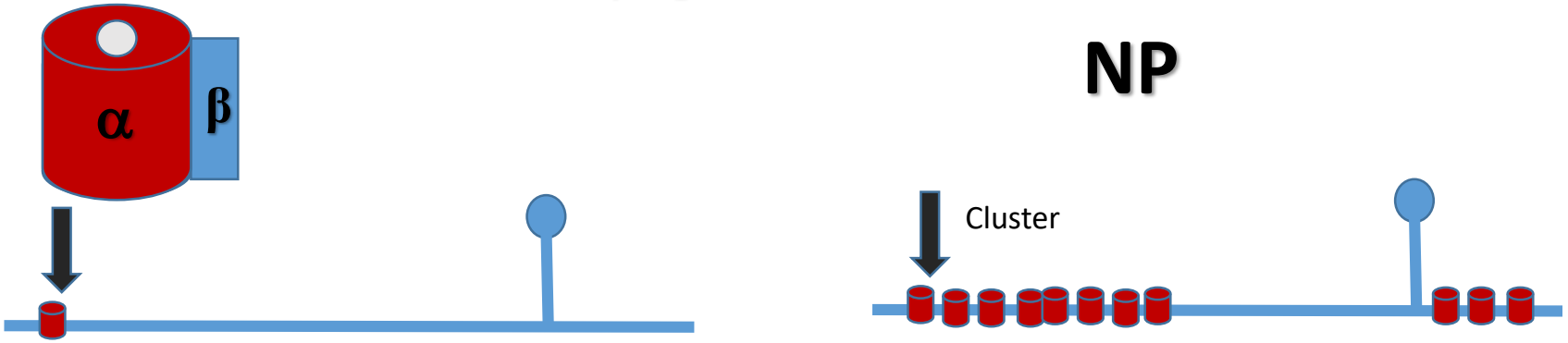

Neuropathic pain
Cortex
Thalamus
Opioids releasing interneuron
Latent
VZV
Phantom limb pain
MOR
MOR
Secondary afferent
Primary afferent
Shingles
VZV
Damage
By trauma or
Incease the level of glucose
(diabetic neuropathy)
Damage
Stroke
Spinal injury
Sclerosis multiplex
Oligodentrocyte dysfunction
PERIPHERAL NEUROPATHIC PAIN
CENTRAL NEUROPATHIC PAIN

NP upregulation of VGCC



Pregabalin: binds to $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits

NP upregulation of Nav 1.3



Target of pain killers I.

- **Receptors**

  - Opioid receptors

  - NMDA receptors

  - α2 Adrenoceptor: tizanidin

  - Serotonin receptors

  - Imidazoline receptors

  - Tyrosinkinase receptors

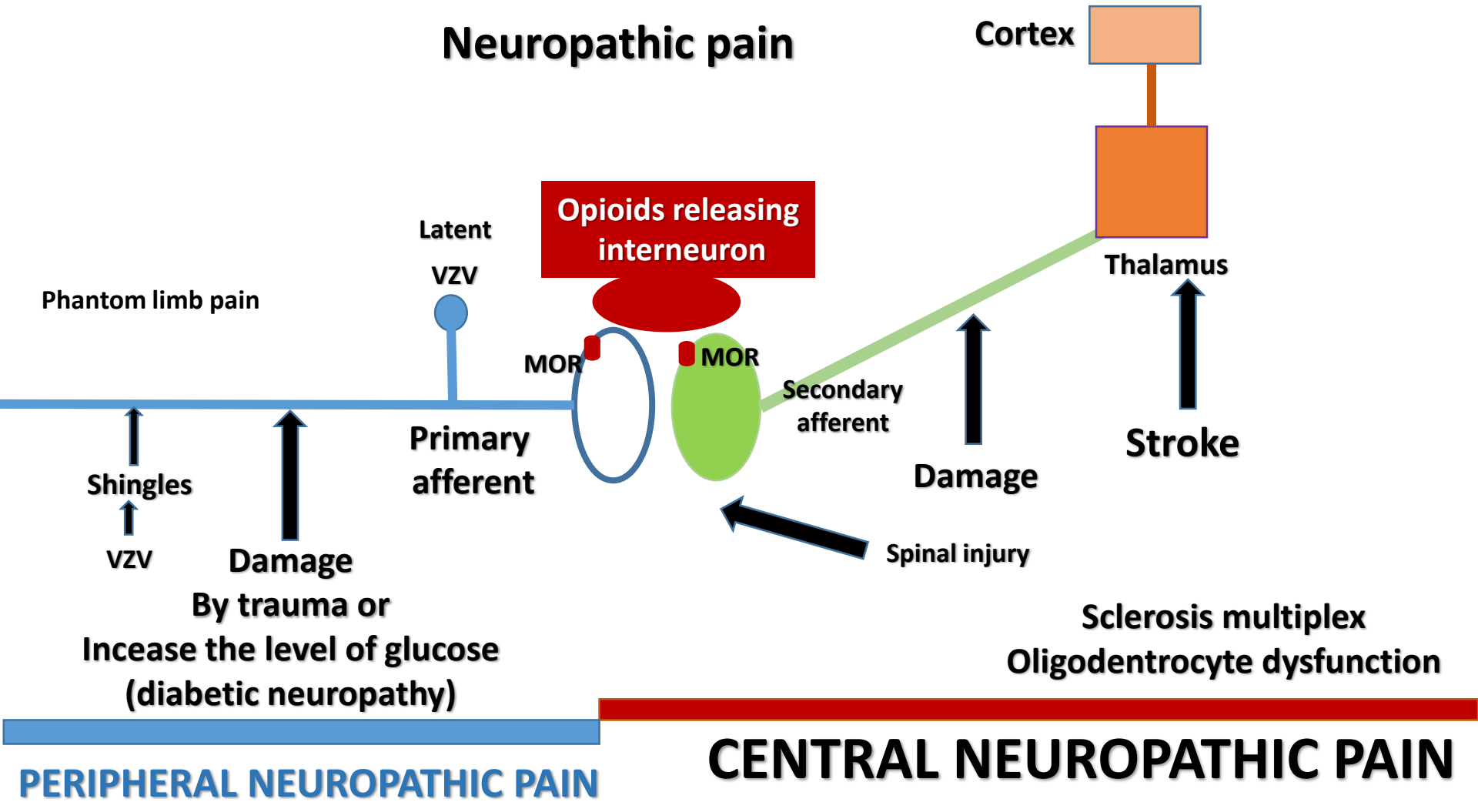
Target of pain killers II.

- **Channels**

  - Calcium channels:

Gabapentinoids or $\alpha_2\delta$ ligands: inhibit α2δ subunit-containing VDCCs: pregabalin, gabapentin

Use: DPN also central NP (150-600mg/day)


Neuropathic pain
Cortex
Thalamus
Opioids releasing interneuron
Latent
VZV
Phantom limb pain
MOR
MOR
Secondary afferent
Primary afferent
Shingles
VZV
Damage
By trauma or
Incease the level of glucose
(diabetic neuropathy)
Damage
Stroke
Spinal injury
Sclerosis multiplex
Oligodentrocyte dysfunction
PERIPHERAL NEUROPATHIC PAIN
CENTRAL NEUROPATHIC PAIN

Target of pain killers II.

- **Channels**

  - Sodium channels

NP: Nav1.3, Nav1.7 és Nav1.8

Na^+ channel blockers: Carbamazepin és oxcarbazepin az első választandó szer a Trigeminus neuralgia kezelésében.

Target of pain killers II.

- **Transporters**

- Serotonin transporter (SERT), norepinephrine transporter (NET), dopamine transporter (DAT).

Non selective

Amitriptyline and it's active metabolite Nortriptyline:

neuropathic pain, migraine, Fibromyalgia.

SERT & NET inhbitors

Duloxetine & venlafaxine: DPN (Diabetic peripheral neuropathy), chronic musculoskeletal pain, fibromyalgia.

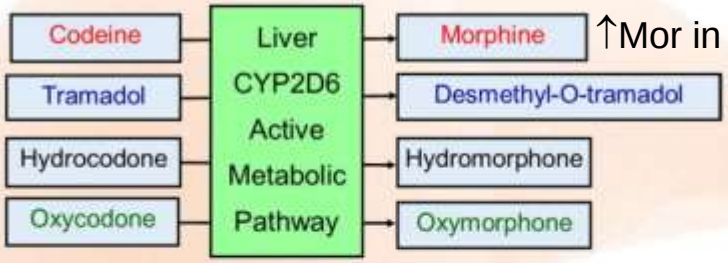
Target of pain killers III.

Opioid receptors and NE/5HT „uptake” inhibitors

- Tramadol:

Tramadol —CYP2D6→ O-desmethyltramadol (M1), shows higher affinity for opioid receptors than the parent molecule, tramadol

Tramadol —CYP3A4→ **Inactive metabolite (M2)**



↑Mor in ultrarapid metabolizer phenotype

Vidya Chidambaran et al., 2017

Opioids: up to 41 % of postoperative respiratory depression in children

CYP2D6 metabolizes 5-10% of codeine to morphine

A TREATMENT STRATEGY OF PAIN (CP)

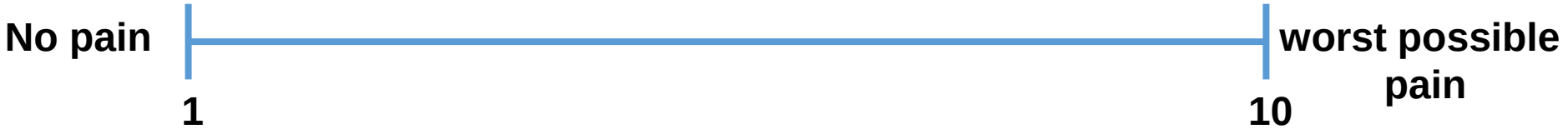
"Pain is whatever the experiencing person says it is, existing whenever he says it does".)

ASSESSMENT OF PAIN

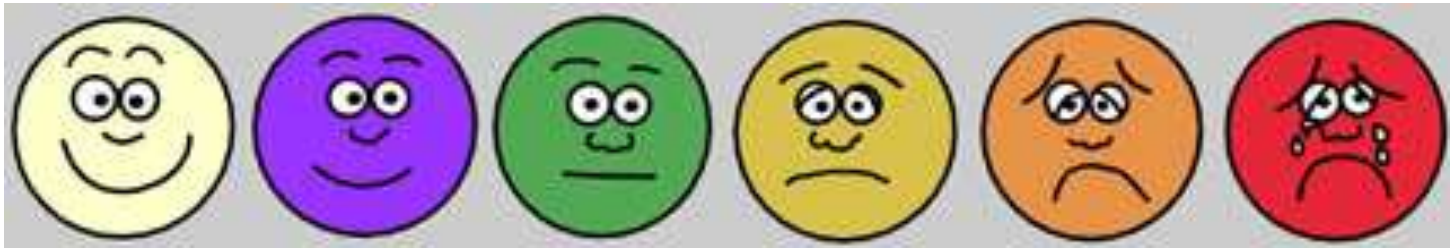
- There is no absolute scale - the sensation of pain is individual.
- What is the pain, is a sign, symptom or both?
- The pain scales are based on patient self-assessment before and after drug administration (pain is reported by the patients in agreement with Margo McCaffery's pain definition (believe what the patients say).
- Consider the patient's' positions (rest or moving etc.).

ASSESSMENT OF PAIN

- NRS (Numeric Rating Scale):points from 0 to 10



- VAS (visual analogue scale): continuous variable from 0 to 10



McGill Pain Questionnaire

What Does Your Pain Feel Like?
How Does Your Pain Change with Time?
How Strong is Your Pain?
(**quality and intensity of subjective pain**)

Group	Words
1	Flickering, Pulsing, Quivering, Throbbing, Beating, Pounding
2	Jumping, Flashing, Shooting
3	Pricking, Boring, Drilling, Stabbing
4	Sharp, Cutting, Lacerating
5	Pinching, Pressing, Gnawing, Cramping, Crushing
6	Tugging, Pulling, Wrenching
7	Hot, Burning, Scalding, Searing
8	Tingling, Itchy, Smarting, Stinging
9	Dull, Sore, Hurting, Aching, Heavy
10	Tender, Taut (tight), Rasping, Splitting
11	Tiring, Exhausting
12	Sickening, Suffocating
13	Fearful, Frightful, Terrifying
14	Punishing, Grueling, Cruel, Vicious, Killing
15	Wretched, Blinding
16	Annoying, Troublesome, Miserable, Intense, Unbearable
17	Spreading, Radiating, Penetrating, Piercing
18	Tight, Numb, Squeezing, Drawing, Tearing
19	Cool, Cold, Freezing
20	Nagging, Nauseating, Agonizing, Dreadful, Torturing

10 words from the all categories which best fits the nature of the pain they feel.
Next: 3words from 1-10 categories that best fit the nature of the pain that they feel.
2words from11-15 categories.
1 word from 16. and 1 word from 17-20 categories. then select the most appropriate seven terms.

1-10 Sensory

11-15 Affective

16 Evaluative

17-20 Miscellaneous

ASSESSMENT OF PAIN

- Non-verbal patients: behavioral judgment (facial movements, vocalization, decreased appetite, limited movements, increasing confusion, agitation)
- Neuropathic Pain Scale
- Neuropathic Pain Symptom Inventory

CLASSIFICATION OF PAIN I.

- **Non-pathological pain** (mostly caused by tissue damage)
  - Acute or chronic
    - Acute: e.g. cut (postoprative pain), bruise, fracture, crush, burn, MI, breakthrough pain
    - Chronic: e.g. osteoarthritis, muscle spasm, chronic inflammatory pain (RA)
  - Somatic or visceral
  - Inflammatory or non-inflammatory
  - Cancer pain (may have psychological and pathological components as well)

CLASSIFICATION OF PAIN II.

- **Pathological pain** (caused by nerve injury or abnormal neuronal function) – may be associated with **hyperalgesia** and/or **allodynia**
  - Neuralgia (e.g. trigeminal) – feels like needle punch series or lightning
  - Neuropathy (e.g. diabetic, postherpetic) – feels like burning
  - Phantom pain
  - Pain syndromes
    - Central pain syndrome (caused by stroke, tumors, multiple sclerosis)
    - Complex regional pain syndrome – large area feels constant burning sensation
  - Fybromyalgia
  - Irritable bowel syndrome
  - Headache syndromes – migraine, cluster, tension headache

CLASSIFICATION OF PAIN III.

- **According to IASP**
  - Region of the body involved
  - System whose dysfunction may be causing the pain
  - Duration and pattern of occurence
  - Intensity and time since onset
  - Etiology
- **According to Woolf** et al. (Woolf et al: Towards a mechanism-based classification of pain?. Pain. 1998;77(3):227–9):
  - Nociceptive pain
  - Inflammatory pain
  - Neuropathic pain

TYPES OF ANALGESICS

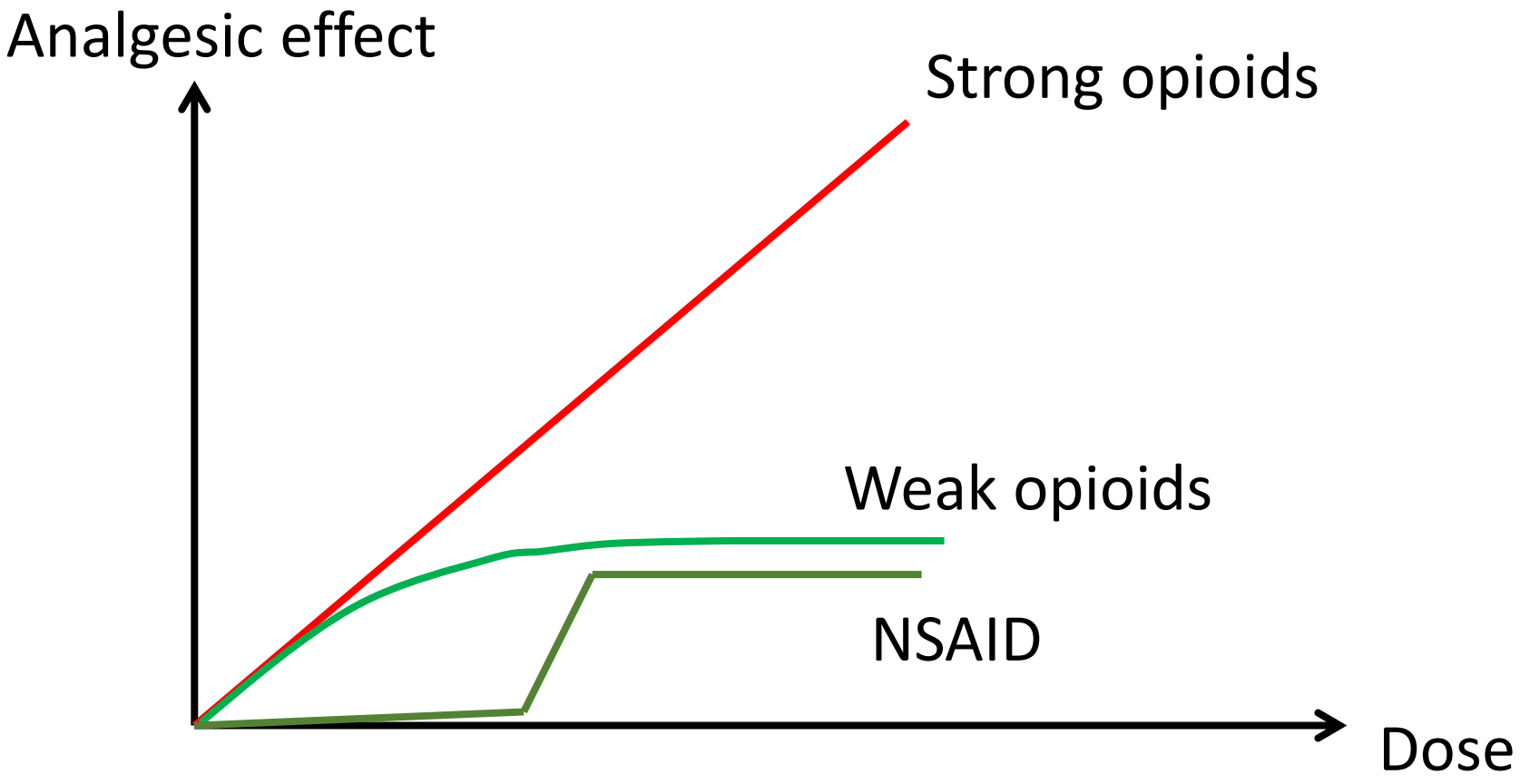
- **Non-steroidal antiinflammatory drugs (NSAIDs):**
  - acetylsalycilic acid, ibuprofen, diclofenac, ”coxibs”
- **Minor analgesics:**
  - Acetaminophen (paracetamol)
- **Opioids**
  - Weak: tramadol, tapentadol, codein
  - Strong: morphine, hydromorphone, oxymorphone, oxycodone, fentanyl, buprenorphine
- **Altenative analgesics:**
  - Tricycliclic antidepressants (e.g. amitryptiline)
  - Antiepileptics (carbamazepine, gabapentin, pregabalin)
  - Capsaicin (given locally)

DIFFERENCES BETWEEN THE NSAIDS AND OPIOIDS

- **NSAIDs**
  - Peripheral mechanism (COX inhibition)
  - Excellent effect against inflammatory pain
  - Limited efficacy – ceiling effect, over a certain level the action is insufficient
  - Very steep dose-response curve – narrow dose window (e.g. ibuprofen 400mg-800mg/dose)
  - GI ulceration is a common side effect
  - Coxibs may cause cardiovascular events

- **Opioids**
  - Central mechanism (inhibition of pain transmission)
  - The best pain killers ever (they even act in neuropathic pain though in higher doses)
  - Unlimited analgesic effect
  - Theoretically unlimited dose (e.g. hydromorphone 4mg-2000mg)
  - Most severe side effect: respiratory depression – the only limit before dose escalation
  - Other severe side effects: constipation!!! (no tolerance), epileptiform sizures

Dose-response comparison of opioids and NSAIDs



Ten universal precautions in pain medicine

Make an appropriate differential diagnosis: look for a source of pain that can be cured, thereby solving the pain problem as well as identifying any comorbid conditions.

Perform a psychological assessment, including risk of addictive disorders: if a patient refuses this type of assessment, he or she should be considered unsuitable for pain management using controlled substances.

Document informed consent: this should include a discussion with the patient about the risks and benefits of any course of therapy.

Use a treatment agreement: this helps to reinforce expectations and obligations for both the clinician and the patient before therapy is initiated.

Assess pain level and function before and during therapy: essential to help determine the success of the medication trial as well as indicating where changes may be appropriate.

Individualize therapy with or without adjunctive medication: opioid medications should neither be a routine first choice for pain treatment nor the treatment of last resort. Apply the principles of rational pharmacotherapy based on the needs of the patient.

Reassess pain score and functionality: helps document a rationale for therapy continuation or modification.

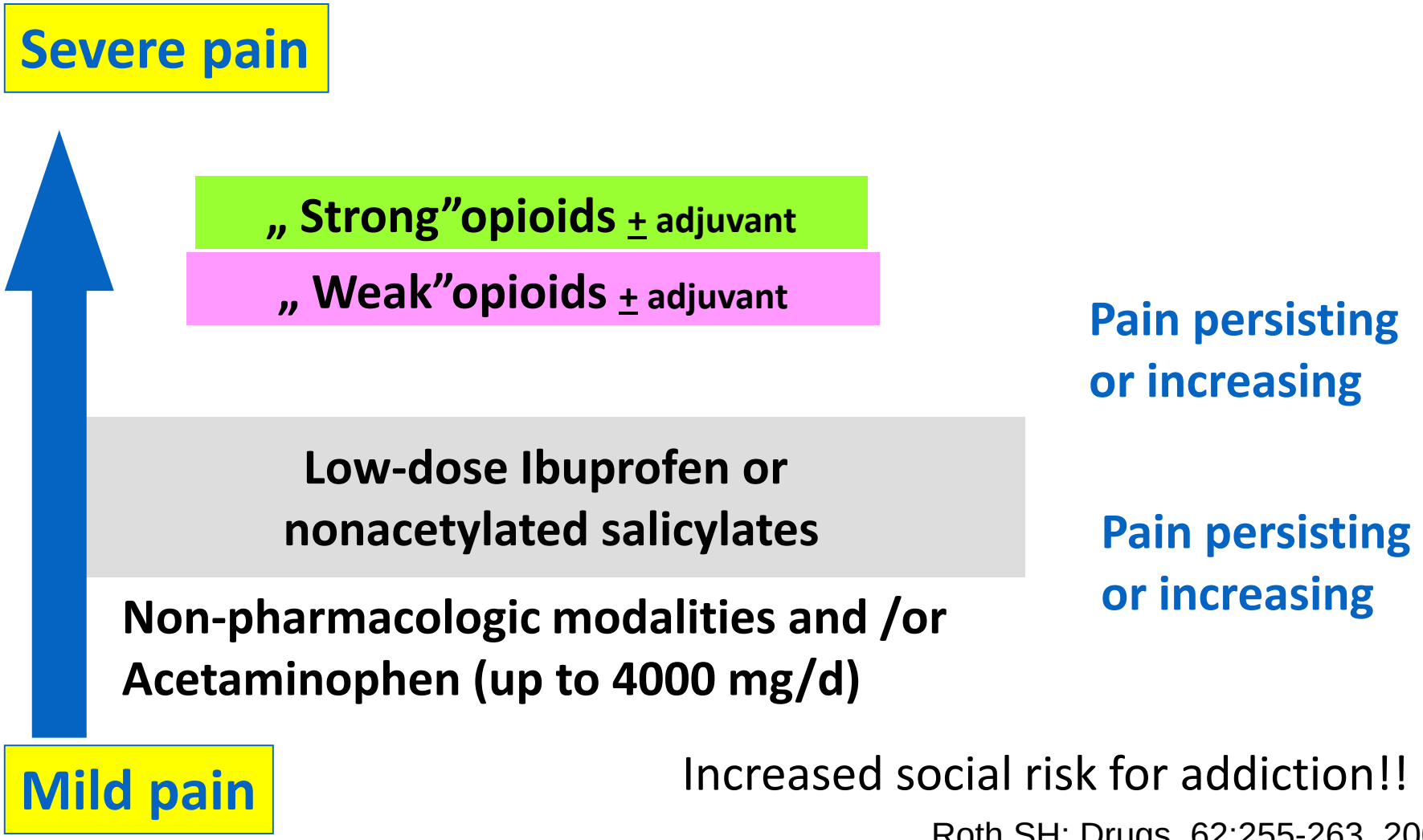
Regularly assess the 4 "As": frequently revisit the patient's analgesia, activity, adverse effects of therapy, and aberrant drug-taking behaviors.

Periodically review pain diagnosis and comorbid conditions, including addictive disorders: a patient's condition may evolve over time and require a redirection of therapy.

Document all assessments and care plans: this helps reduce medico-legal exposure and risk of regulatory sanctions.

Source: B. McCarberg and S. Stanos: Key patient assessment tools and treatment strategies for pain management. Pain Practice, Volume 8, Issue 6, 2008 423–432

Analgesic ladder for non-cancer pain



Increased social risk for addiction!!

Roth SH: Drugs, 62:255-263, 2002

FIRST LINE TREATMENT FOR NEUROPATHIC PAIN (NP)

Tricyclic Antidepressants. (20–30% of antidepres. dose)	p. neuropathy post-herpetic neuralgia neuropathic pain post–spinal cord injury	supported by multiple guidelines **Side effects:** cardiac arrhythmias orthostasis, urinary retention, dry mouth.
	limited effect: radiculopathy, HIV and chemotherapy-induced p.neuropathy	
Serotonin & NE Reuptake Inhibitors (duloxetine, venlafaxine)	p. diabetic neuropathy painful p.neuropathy NP secondary to MS	supported by multiple international guidelines
	osteoarthritis chronic low back pain fibromyalgia	
Gabapentinoids: gabapentin and pregabalin	NP	supported by multiple international societies
	postherpetic neuralgia p. diabetic neuropathy spinal cord injury (pregabalin)	
Topical lidocaine	Np (post-herpetic neuralgia)	5% lidocaine patch

Second line treatment for neuropathic pain (NP)

Tramadol	firstline in acute NP cancer-related NP Intermittent exacerbations of NP	in most guidelines
Opioids	NP: but long-term efficacy? and significant side effects to 2nd-4th-line in most guidelines.	- Second* - Third** - Fourth-line***

Third line treatment for neuropathic pain (NP)

SSRIs **Anticonvulsants:** lamotrigine, carbamazepine, topiramate and sodium valproate **NMDA antagonists**	For patients do not tolerate or no adequate pain relief from first- or second-line therapy. a referral to a specialist pain clinic is recommended. level of evidence: inconclusive
Capsaicin (8%)	

*Canadian Pain Society consensus statement2017

**European Federation of Neurological Societies

*** Australian Clinical Practice Guidelines 2018

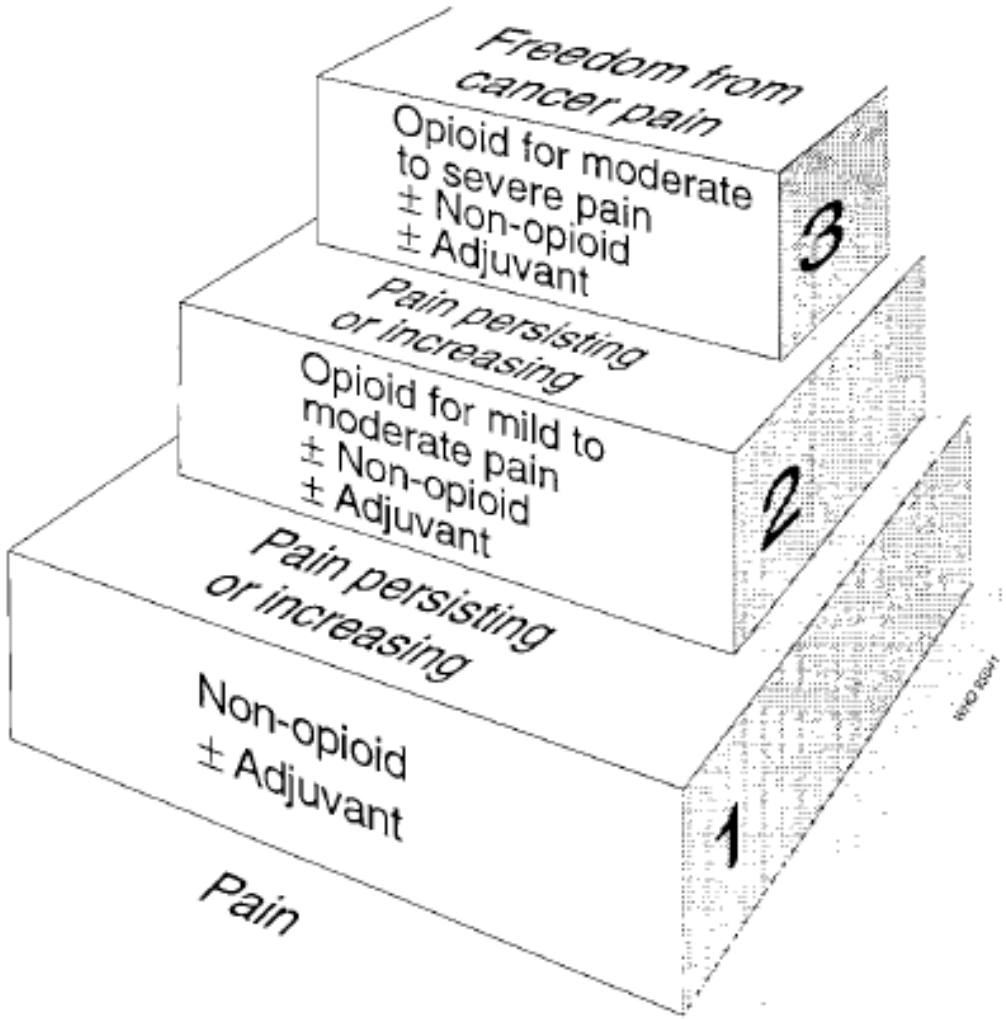
Daniel Bates et al., 2019,.A Comprehensive Algorithm for Management of Neuropathic Pain

Fourth-Line Treatment: Neurostimulation		
Capsaicin (8%)		
Fifth-Line Treatment :		
Low-Dose Opioid		
Sixth-Line Treatment: Targeted Drug Delivery (TDD)		
morphine and ziconotide	directly injection to dorsal horn of the spinal cord For patients with with refractory pain	**By FDA**

Daniel Bates et al., 2019,.A Comprehensive Algorithm for Management of Neuropathic Pain

Three step analgesic ladder for cancer pain

WHO Technical Report Series, No. 804, 1996 (2nd edition)



ADMINISTRATION OF STRONG OPIOIDS

- Enteral
  - Oral
  - Transmucosal
  - Nasal spray
  - Sublingual/buccal
  - Rectal
- Skin
  - Topical (e.g. joints)
  - Transdermal
- Inhalation
- Parenteral
  - Iv
  - Sc
  - Im
  - Epidural
  - Intrathecal

THE ROUTES OF ADMINISTRATION OF OPIOIDS

- Oral:
  - Morphine (sulfate salt) from 30mg 2x a day
  - Hydromorphone (retard capsule) from 8mg once a day
  - Oxycodone (retard) from 10mg once a day
  - Tramadol 50-100mg 4x a day
- Transdermal:
  - 25-100μg/hour fentanyl every third day
  - 5-70μg/hour buprenorphine every fourth day
- Iv:
  - Morphine (hydrochloride) 1mg-10mg per injection
- PCA (patient controlled analgesia)
  - 1-2mg morphine iv. or epidural
  - 15μg sufentanil per os (from a device with sufentanil pill cartridge)

Side effects of treatment with strong opioids

	Frequency %	Dose dependence	Tolerance
Constipation	100	yes	no
Nausea/ vomiting	20	no	yes (5-7 days)
Sedation	At start 20	yes	yes (3-4 days)
Confusion	2	yes	no
Hallucination	1	no	no
Respiratory depression	Practically never seen by patients with tumor (pain is a strong stimulant of respiration)		
Dependence	Practically never seen by patients with tumor		

Opioid bowel syndrome[1,2]

- Symptoms: severe constipation, chronic or recurrent abdominal pain (cramping, spasm), decreased gastric emptying, bloating, delayed GI transit, formation of hard dry stools
- Reasons:
  - activation of excitatory anti-analgesic pathways
  - descending facilitation of pain
  - pain facilitation via dynorphin and CCK activation
  - glial cell activation that produces morphine tolerance and enhances opioid induced pain

1 David M.S. Grunkemeier, MD, Joseph E. Cassara, MD, Christine B. Dalton, PA-C, and Douglas A. Drossman, MD, FACP: The Narcotic Bowel Syndrome: Clinical Features, Pathophysiology and Management, Clin Gastroenterol Hepatol. 2007 Oct; 5(10): 1126–1122.

2 S J Panchal, P Müller-Schwefe, and J I Wurzelmann: Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. Int J Clin Pract. 2007 Jul; 61(7): 1181–1187.

Opioid bowel syndrome

- Treatment:
  - Laxatives against constipation (stool softeners, salt laxatives)
  - H2-blockers or PPIs against reflux
  - New: N-methyl-naltrexone sc., naloxone per os (quaternary N-containing opioids do not enter the brain, naloxone has 100% first pass hepatic metabolism)

Breakthrough pain

- Definition: strong acute pain despite the regular administration of a strong opioid in cancer patients
- Treatment: ultra-rapid opioid add-on therapy for a short time (sublingual/buccal fentanyl)
- Nasal spray (100-800µgfentanyl) max. daily 4x

Development of analgesics

- European Medicines Agency (EMA) regulation:
  - EMA/CHMP/970057/2011 Guideline on the clinical development of medicinal products intended for the treatment of pain
- General rules of drug development must be followed

General rules of analgesic drug development

- Appropriate preclinical studies must be conducted
- **Clinical development:**
  - **Pharmacokinetic studies** – depending on the route of administration relevant guidelines must be considered
  - **Pharmacodynamic studies** – mechanism of action must be understood
  - **Interaction studies** – implications of concomitant use of drugs likely to be co-administered in clinical practice should be evaluated
  - **Exploratory studies** – in the early developmental stage on healthy volunteers with controlled pain stimulus
  - **Dose-response studies**
  - **Pivotal efficacy studies** – randomised, controlled, parallel group trials
    - Superiority to placebo must be proven (with some exceptions)
    - If exists an active comparator must be used too

General rules of analgesic drug development

- Clinical development (continued):
  - Pain assessment methods: NRS, VAS, McGill Ques., Clinical Global Impression (CGI) etc.
  - Confirmatory Efficacy Studies (see next slide)
  - Clinical safety evaluation

CONFIRMATORY EFFICACY STUDIES

Type of pain	Intensity	Model studies examples
Acute	Mild – moderate	Tooth extraction, minor surgery (*e.g.* cutaneous surgery, hernia), headache (other than migraine), primary dysmenorrhoea
Acute	Moderate-severe	- Surgical removal of impacted teeth - Renal and biliary colic (visceral pain) - Well-defined major orthopaedic surgery - Well-defined major abdominal/thoracic surgery (mixed somatic / visceral pain) - Major skeletal trauma - Breakthrough pain - Burns pain (*e.g.* dressing changes)
Chronic	Mild – moderate	Osteoarthritis, rheumatoid arthritis (somatic) Chronic pelvic pain (visceral)
Chronic	Moderate-severe	Advanced cancer: skeletal metastases with movement related pain (somatic), abdominal metastases (visceral)

ADDITIONAL PAIN RELIEF IN CLINICAL STUDIES

- Rescue medication
  - In case of the ineffectiveness of the test drug the patient is allowed to use a know analgesic
- Supplemental medication
  - In case of decreased efficacy of the test drug (for example moving, ambulation, walking may enhance pain) a know analgesic is allowed to add

EXAMPLES TO EFFICACY ENDPOINTS

- SPID: sum of pain intensity difference
- PID: pain intensity difference
- Total Pain Relief
- Clinical Global Impression