The (early) clinical development of new analgesics: the point of view of a pain clinician.

Prof. dr. Bart Morlion

Bart Morlion: disclosure

Over the past 3 years, I received honoraria for:

- Speaker's activities
  - Krka, Grünenthal, Pfizer, GSK, Haleon, Sandoz, Viatris
- Consultancy activities
  - Grünenthal, Pfizer, GSK, GW, Shionogi, Mundipharma, Haleon,
  - Consultancy in due diligence review for investors

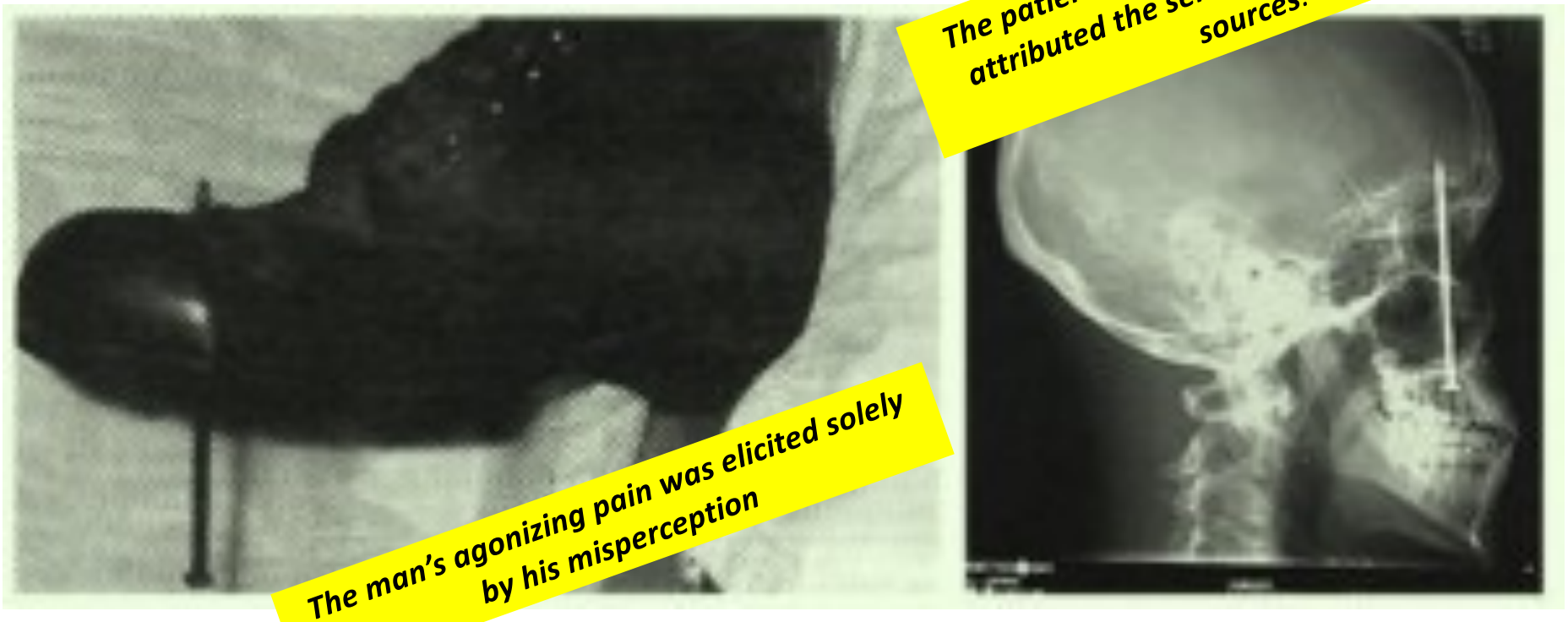
New Analgesics?

- The landscape of pain
- Challenges
- Developments

New Analgesics?

- The landscape of pain
- Challenges
- Developments

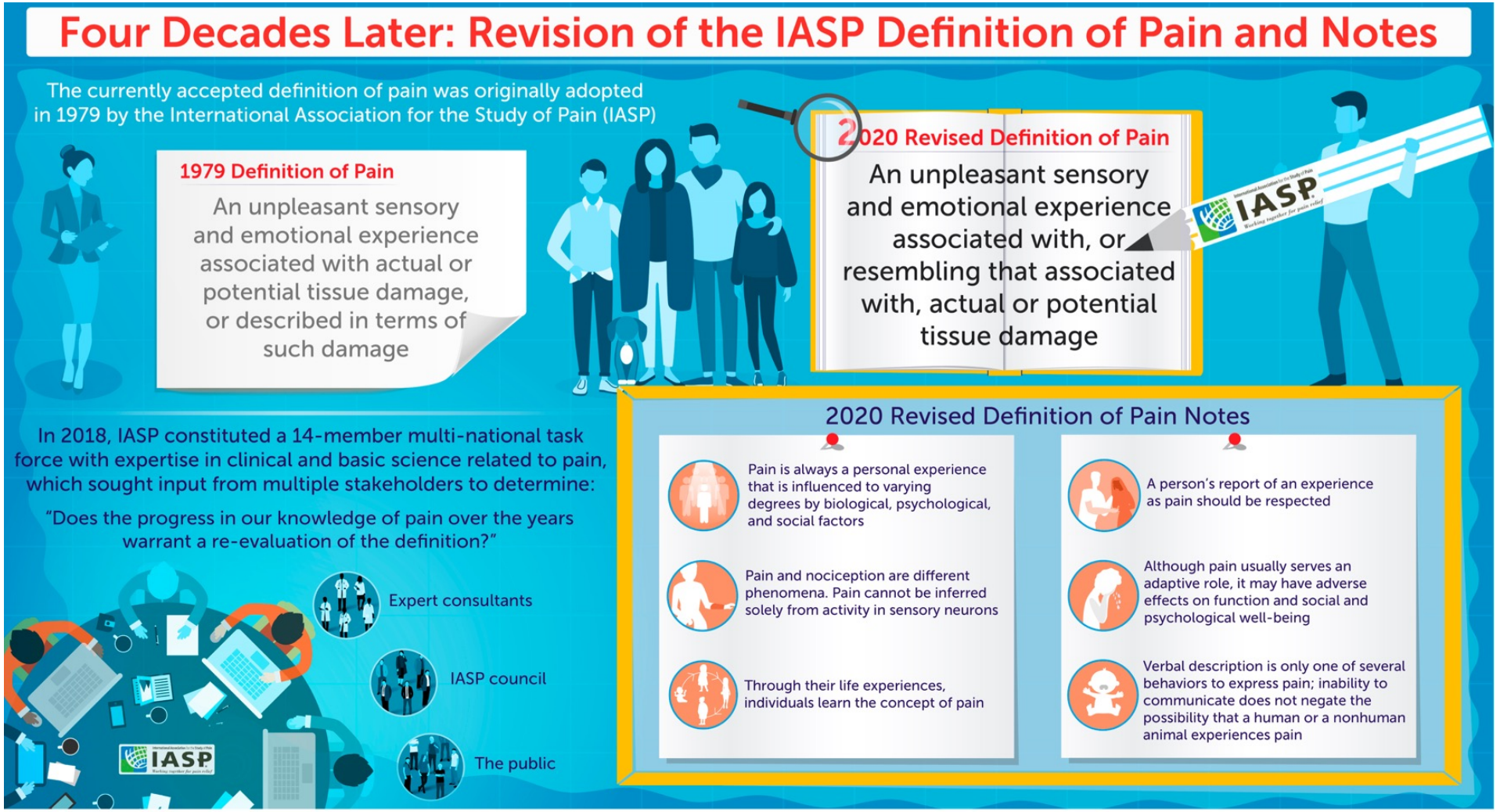
A tale of two nails



The patient was unaware of the injury and attributed the sensation to more familiar sources."

The man's agonizing pain was elicited solely by his misperception

Fisher JP, Hassan DT, O'Connor N. Minerva. Br Med J 1995;310:70; Associated Press, Wide World Photos. 1/16/05.



The revised IASP definition of pain: concepts, challenges, and compromises
Raja *et al*. (2020) | Pain
DOI: 10.1097/j.pain.0000000000001939

PAIN®

Chronic Pain

‘Pain that persists or recurs for longer than 3 months’

World Health Organization Definition ICD-11

Chronic pain is multifactorial

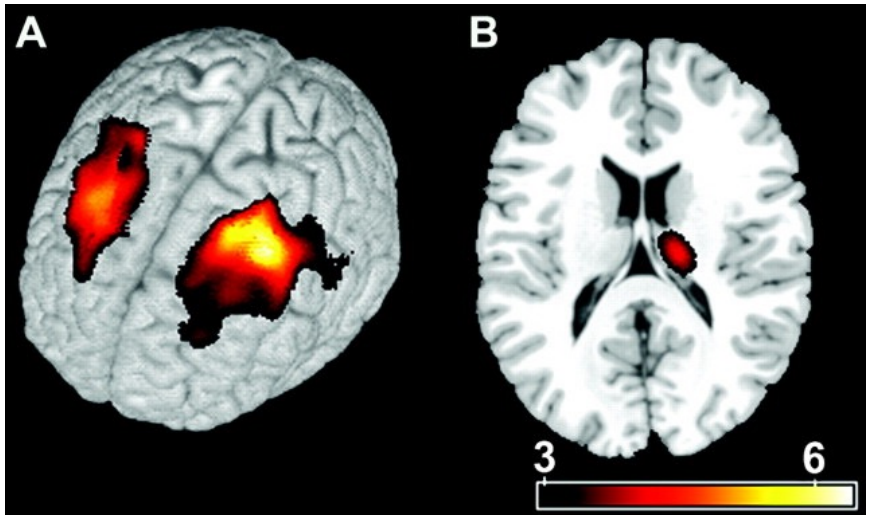
- biological, psychological and social factors contribute to the pain syndrome.
  - Even if an initial injury in an anatomical structure can be identified, the pain experience and disability of an individual will be determined by an array of psychosocial factors
  - Limited effectiveness of biomedical and monomodal treatments
  - Need for multimodal & interdisciplinary approach

https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1581976053 Accessed October 2022; Morlion, B. Nature Rev Neurol. 2013;9:462–73

WHO definition of disease

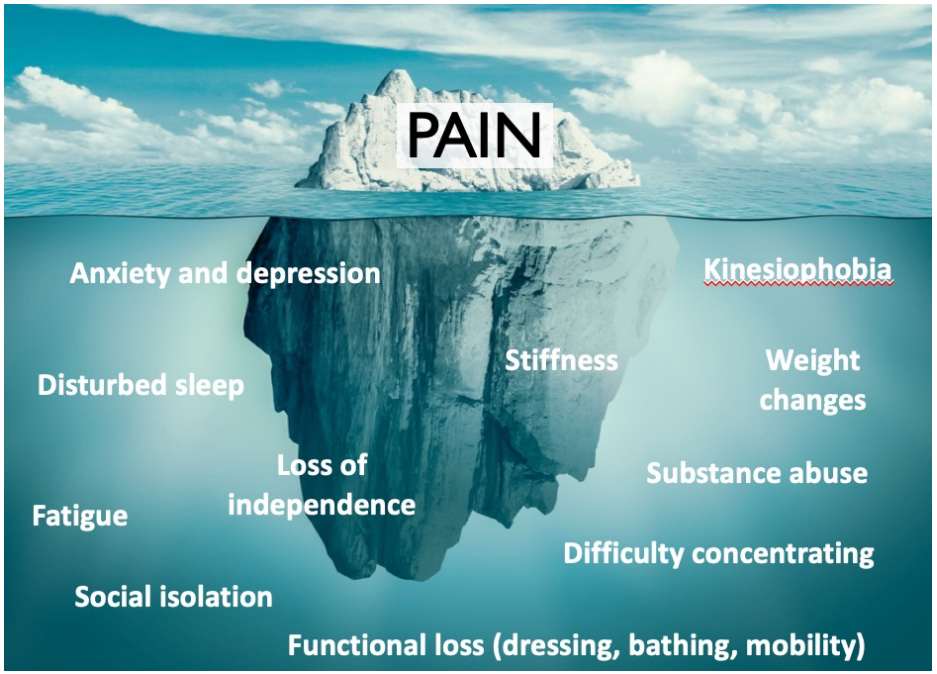
"a particular abnormal condition that negatively affects the structure or function of part or all of an organism"

Advances in neuroimaging have shown altered brain structure in patients with chronic pain



Apkarian AV, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci. 2004;24:10410–5. Ung H, et al. Multivariate classification of structural MRI data detects chronic low back pain. Cereb Cortex. 2014;24:1037–44. Robinson ME, et al. Gray matter volumes of pain-related brain areas are decreased in fibromyalgia syndrome. J Pain. 2011;12:436–43. Barad MJ, et al. Complex regional pain syndrome is associated with structural abnormalities in pain-related regions of the human brain. J Pain. 2014;15(2):197-203.

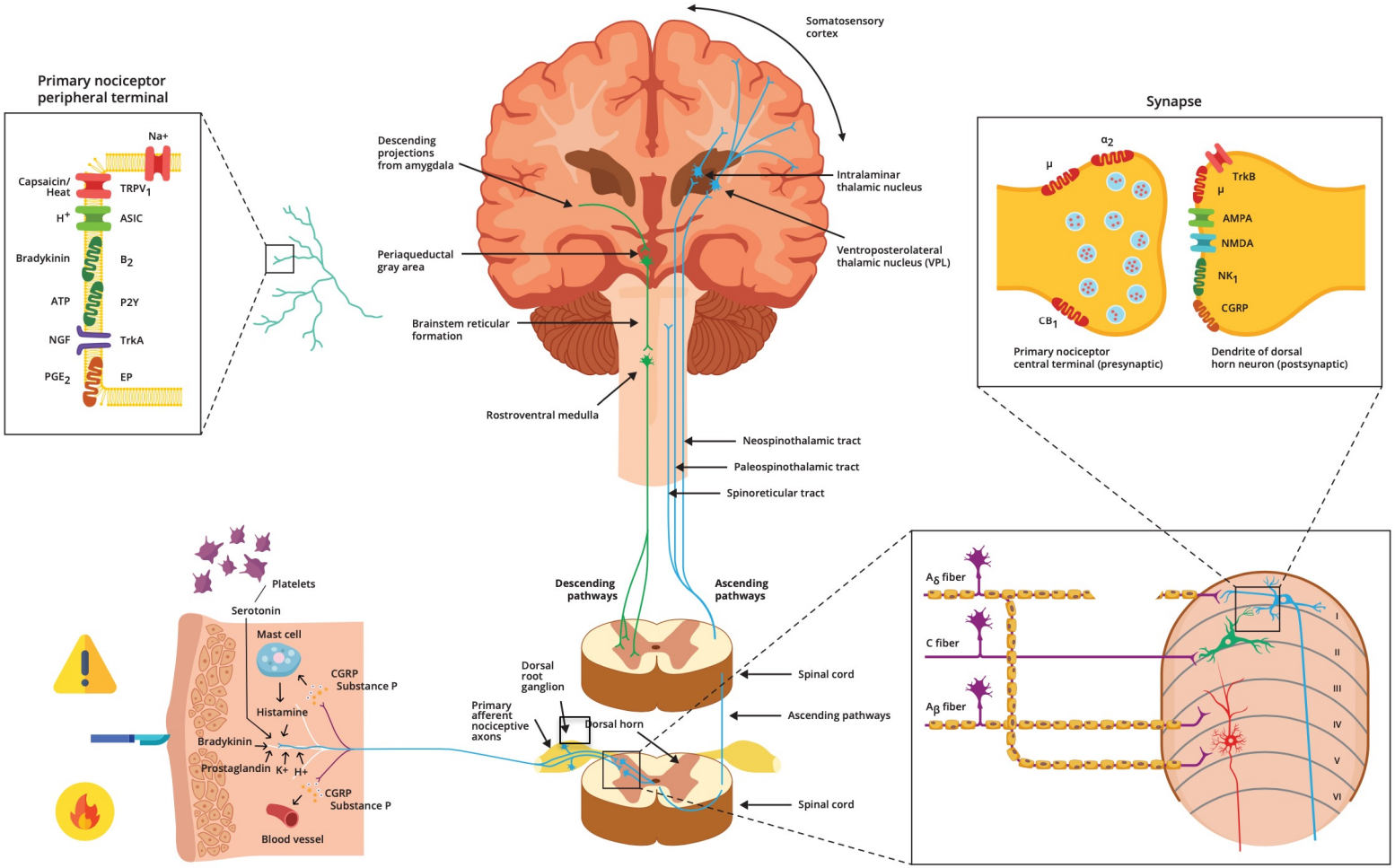
Chronic pain leads to typical co-morbidity, decreased QoL and reduction of ADLs



Duenas M et al. A review of chronic pain impact on patients, their social environment and the health care system. J Pain Res 2016;9:457–67.

Neurobiology of Pain in a Nutshell

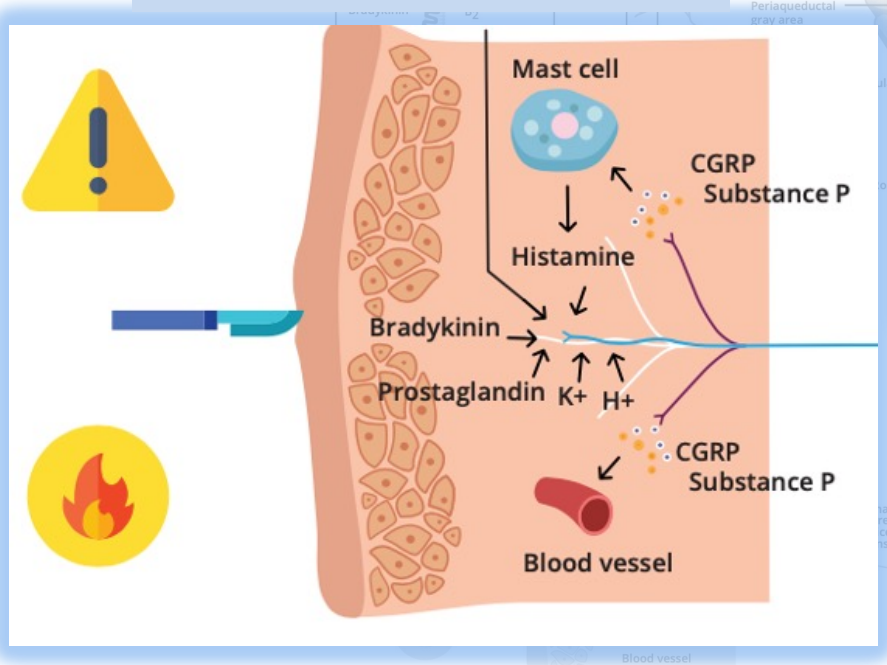
- Transduction
- Transmission
- Modulation
- Perception



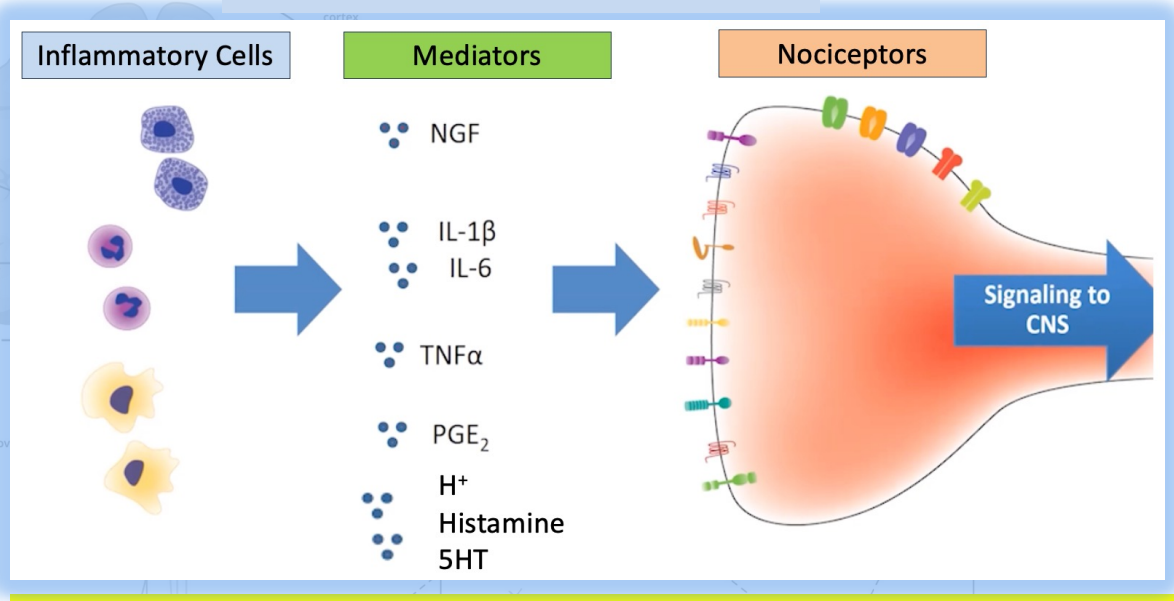
Graphic composed by the author

Chronification: Amplified Ascending Signalling

Cutaneous Nociceptors



Neuroinflammation



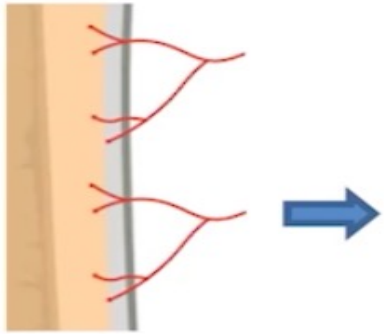
Hyperexcitability

- Increased sensitivity to chemical, thermal and mechanical stimuli
- Hyperexcitable axons generate spontaneous activity of the neuron

Morlion B et al Curr Med Res Opin. 2018 Jul;34(7):1169-1178. Gilron I, et al. Lancet Neurol. 2013;12:1084–1095. *Graphic composed by the author*

Summation: more excitation of nociceptors by a stimulus

- Sensitization triggers hyperexcitability: more excitation of more nociceptors by a stimulus (also non noxious stimuli)

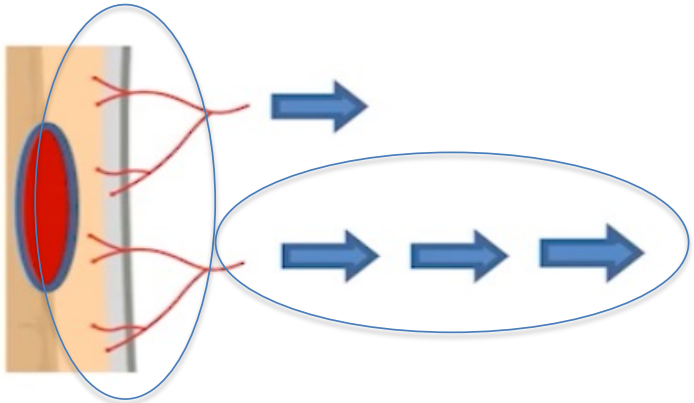


Healthy

- Enhanced nociceptor output by

‘Spatial summation’

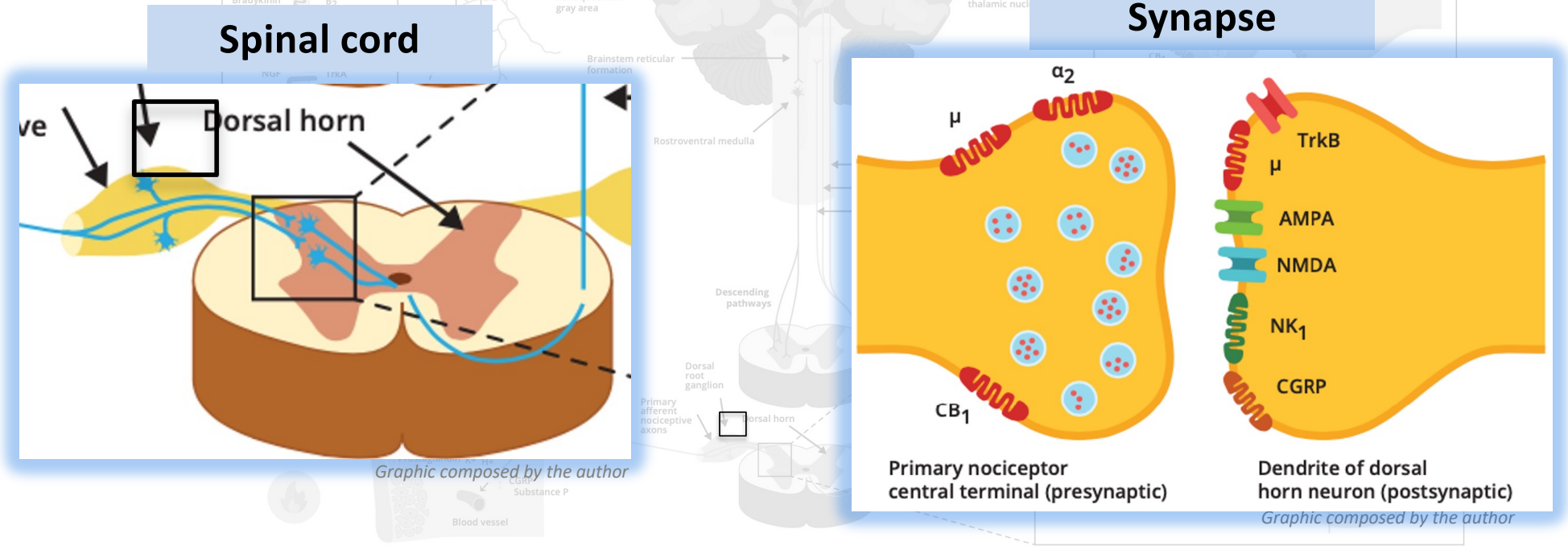
‘Temporal summation’



Inflamed

Chronification: Amplified Ascending Signalling

- Changes in the protein expression and trafficking in cell bodies in the Dorsal Root Ganglia
- Changes at the Dorsal Horn Synapse Drive Central Pain Perception

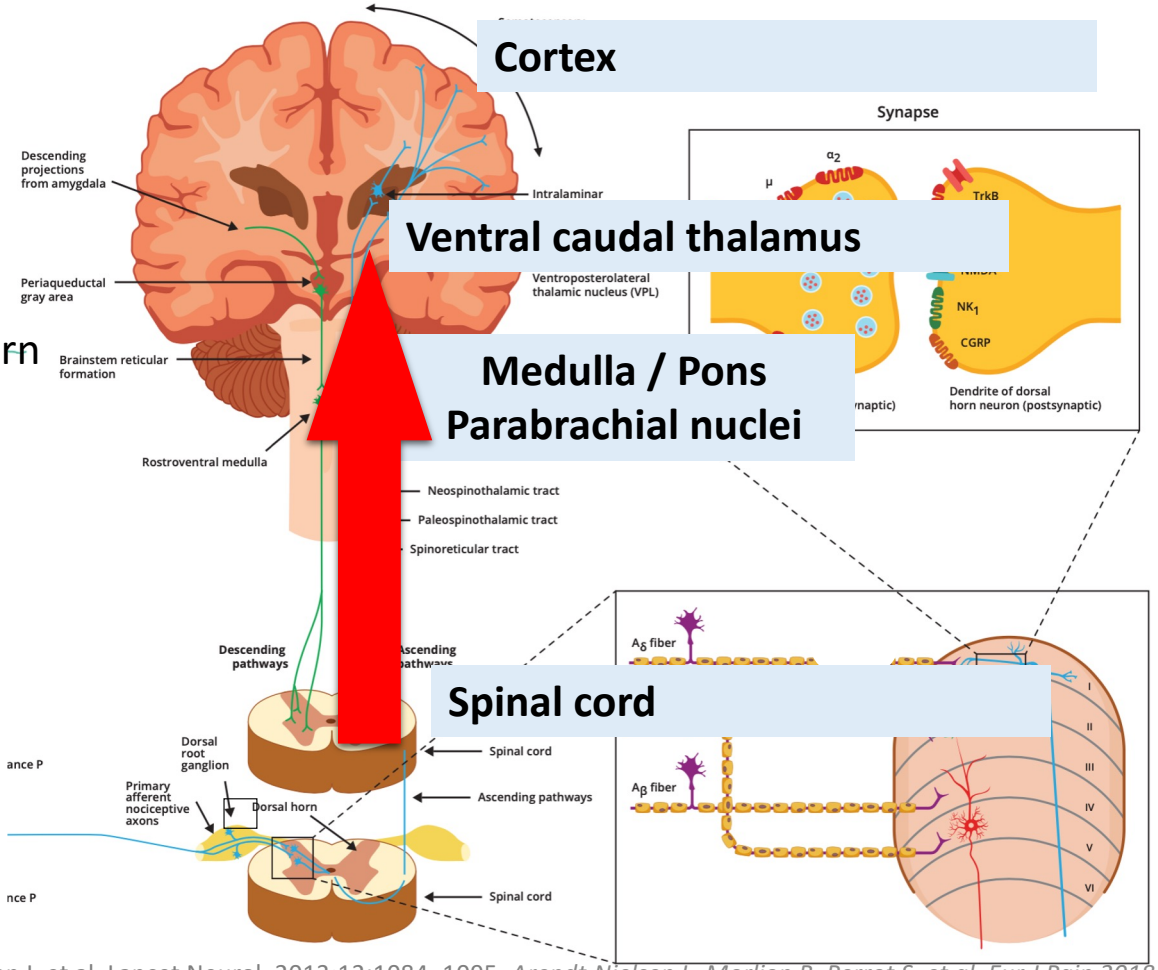


Morlion B et al Curr Med Res Opin. 2018 Jul;34(7):1169-1178. Gilron I, et al. Lancet Neurol. 2013;12:1084–1095. *Graphic composed by the author*

Chronification: Amplified Ascending Signalling

Possible mechanisms

- NMDA receptor activation
- Microglial activation
- Altered gene expression in dorsal horn neurons
- Synaptic plasticity, reorganization
- Further leading to thalamic and somatosensory cortex changes
- Decreased inhibition



Morlion B et al Curr Med Res Opin. 2018 Jul;34(7):1169-1178. Gilron I, et al. Lancet Neurol. 2013;12:1084–1095. *Arendt-Nielsen L, Morlion B, Perrot S, et al. Eur J Pain 2018;22:216–41 Graphic composed by the author*

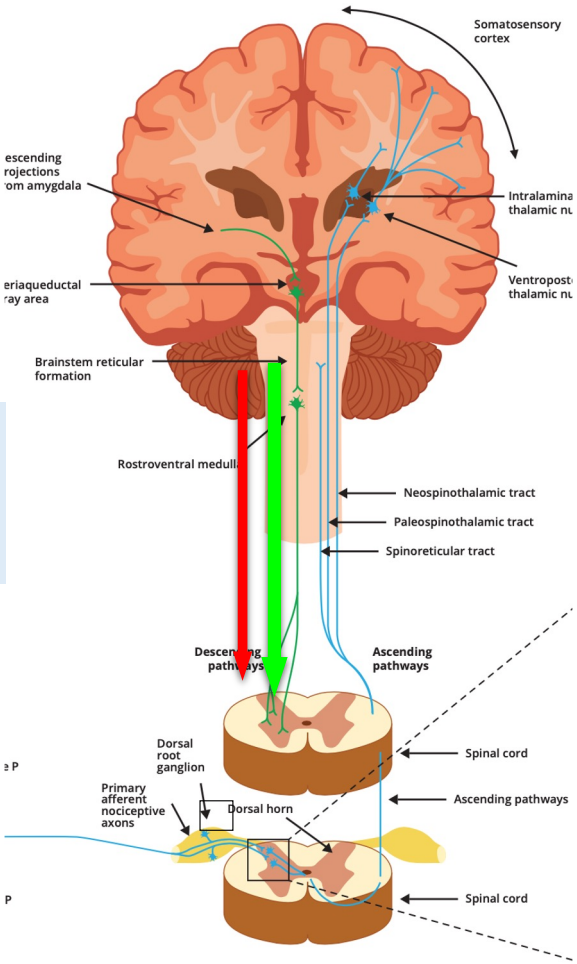
Chronification: decreased inhibition

Cortex

Midbrain
Periaquaductal gray: PAG

Medulla / Pons
Locus ceruleus (LC)
Rostral Ventral Medulla (RVM)

Spinal cord

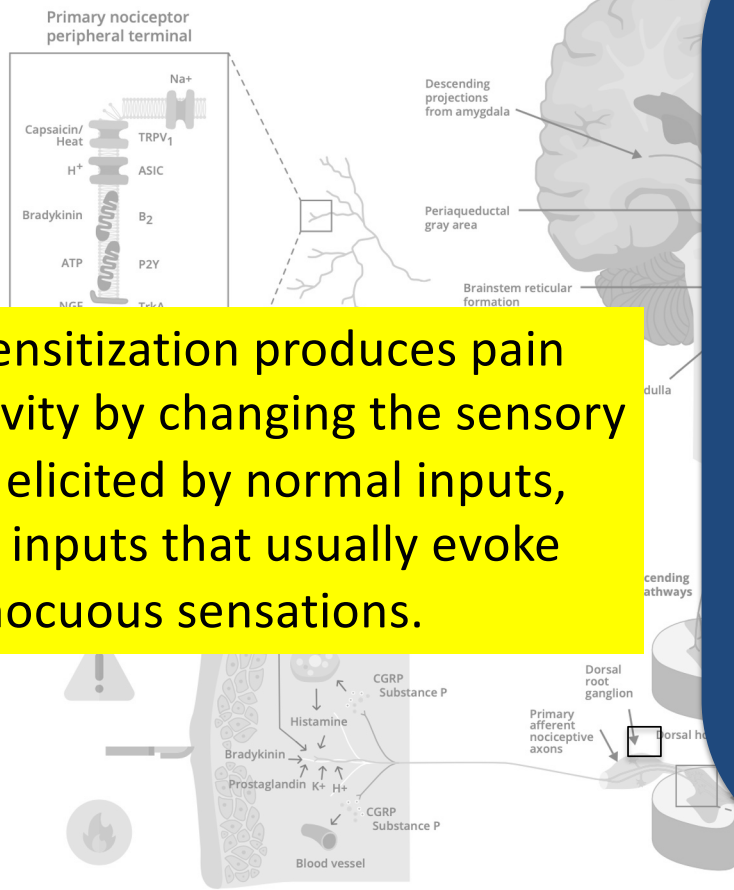


Opioid pathways from hypothalamus and PAG

Monaminergic pathways from
LC: NA
Raphe nuclei: 5-HT
Be aware 5-HT facilitatory pathway

Graphic composed by the author

Neurobiological processes of chronification



Central sensitization produces pain hypersensitivity by changing the sensory response elicited by normal inputs, including inputs that usually evoke innocuous sensations.

Peripheral sensitization

- Reduction threshold for nociceptor activation
- Increase in membrane excitability
- Primary allodynia and hyperalgesia

Central sensitization

- Amplification of synaptic strenghts in nociceptive circuits
- Secondary hyperalgesia

Failing descending inhibition

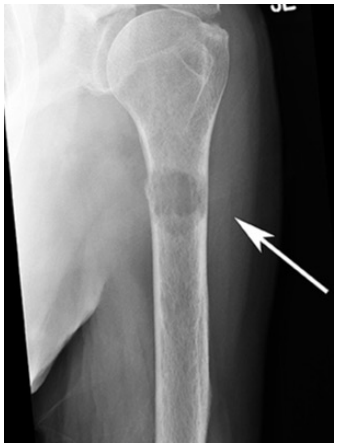
Signs of central sensitization

- Spreading of signs: more widespread referred pain
- Higher pain intensity
- Pain hypersensitivity
- Spontaneous pain
- Sleep disturbance
- Cognitive disturbance

Morlion B et al Curr Med Res Opin. 2018 Jul;34(7):1169-1178. Gilron I, et al. Lancet Neurol. 2013;12:1084–1095. *Arendt-Nielsen L, Morlion B, Perrot S, et al. Eur J Pain 2018;22:216–41 Graphic composed by the author*

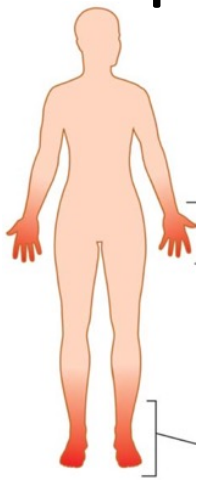
Mechanistic Descriptors of Pain

Nociceptive[1]



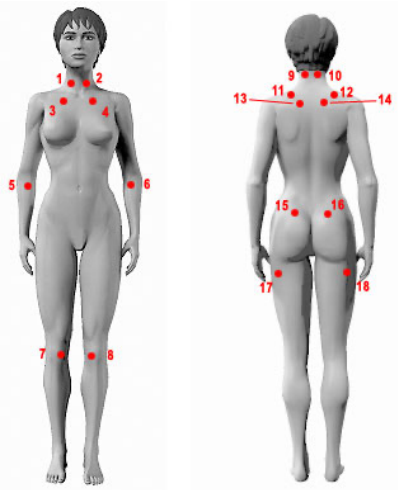
Pain that arises from actual or threatened damage to non-neural tissue and is due to the **activation of nociceptors.**[3]

Neuropathic[1]



Pain caused by a **lesion or disease of the somatosensory nervous system**. [3]

Nociplastic[1,2]

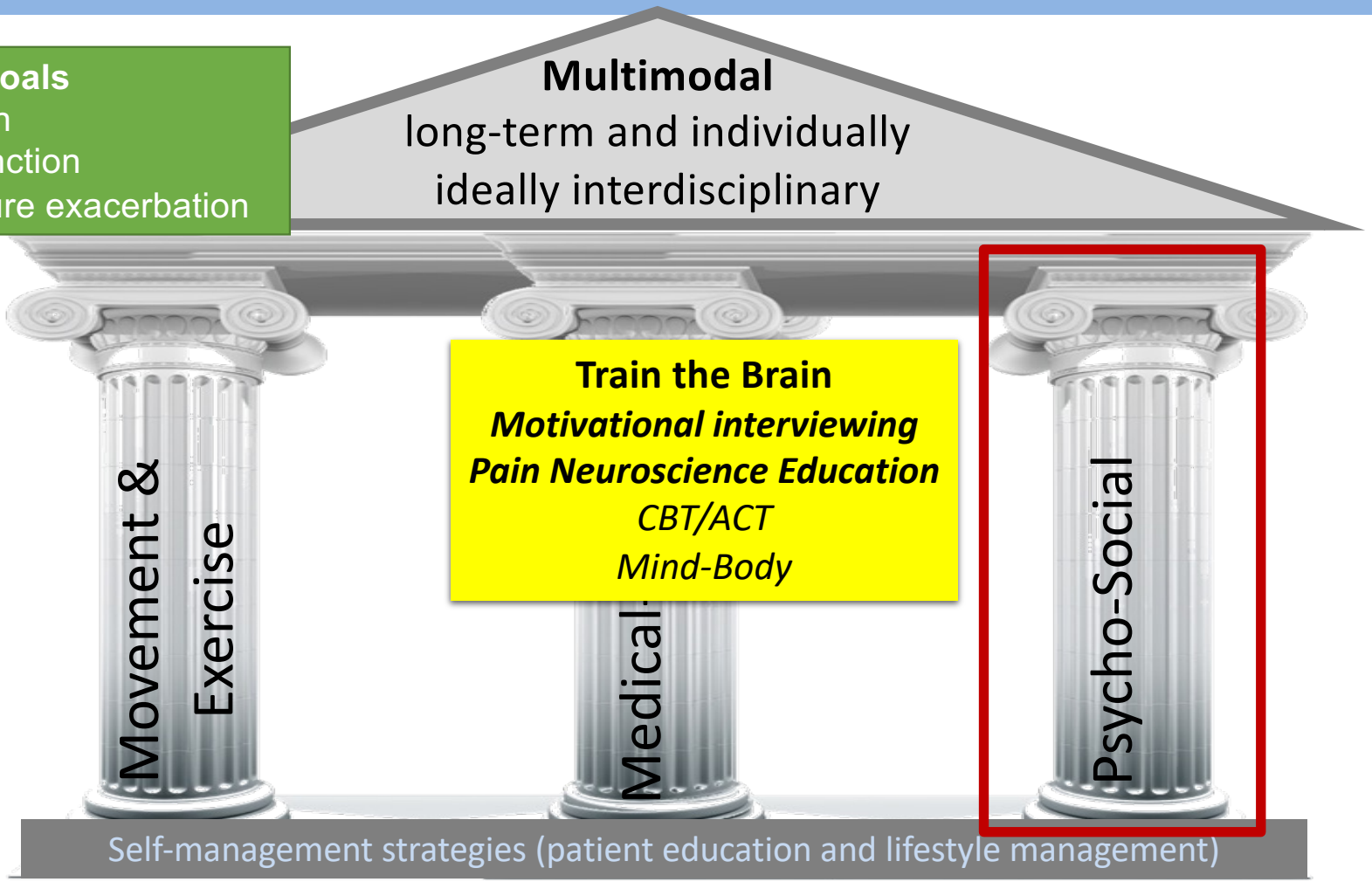


Pain that arises from **altered nociception** despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.[3]

Adapted from 1. Woolf C. Ann Intern Med. 2004;140:441–51. 2. Kosek E, et al. Pain 2016;157:1382–6; 3 https://www.iasp-pain.org/resources/terminology/

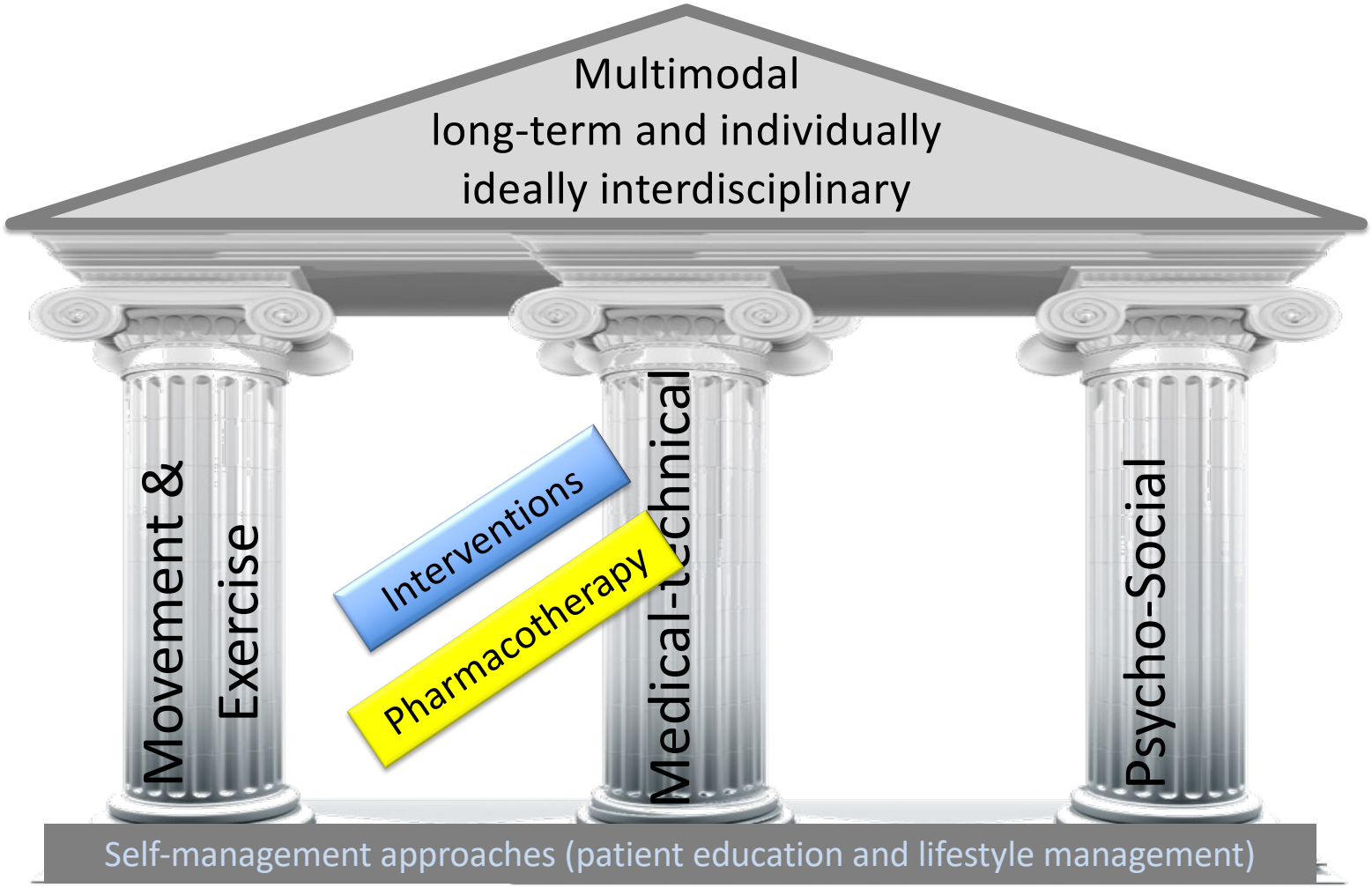
Mostly need for behavorial change

Goals
- Reduce pain
- Maintain function
- Prevent future exacerbation



Graphic composed by the author. Adapted from Morlion B. . Nat. Rev. Neurol. 462-473 (2013)

Management of Pain



Adapted from Morlion B. . Nat. Rev. Neurol. 462-473 (2013)

New Analgesics?

- The landscape of pain
- Challenges
- Developments

The ideal analgesic from a clinical perspective

1. Rapid onset of action.
2. Prolonged duration of action.
3. Minimisation of interruption by pain.
4. Production of analgesia over a wide range of pain types.
5. Effectiveness in different patient populations.
6. Good tolerability profile.

Moore ND. Acute Pain, 2009; 11(3–4): 129-137.

Tremendous steps in the basic research of pain

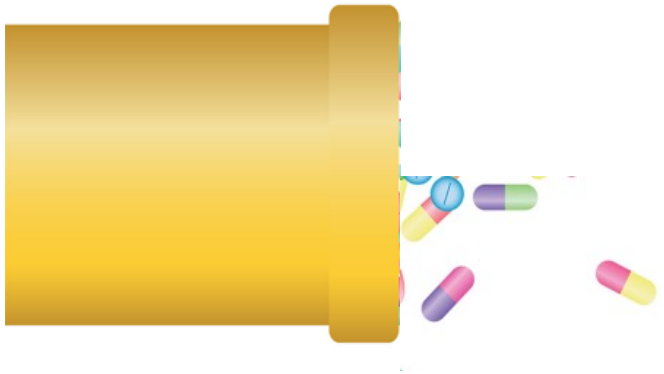
Identification of many new targets

Many strategies are very promising in rodent models

Run for non-addictive analgesics

The vast majority of new pharmacotherapies have failed in clinical trials

Only very few reach the market !

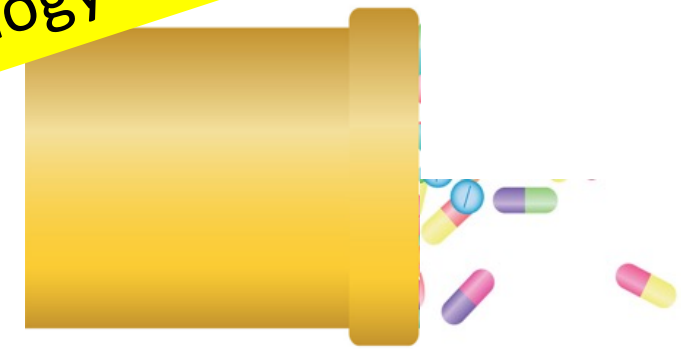


Failed Clinical Trials in Inflammatory and Neuropathic Pain

- NK-1 antagonist
- Cannabinoid agonist
- NMDA antagonist
- TRPV1 antagonist
- Anti-NGF antibodies
- 5-HT-3 antagonist
- Chemokine antagonist
- Glia modulators
- Glycine antagonist
- Na^{+} channel blocker
- NMDA antagonist and morphine (MorphiDex)
- COX-2 inhibitor
- Renin angiotensin aldosterone system
- Ca^{++} channel blocker

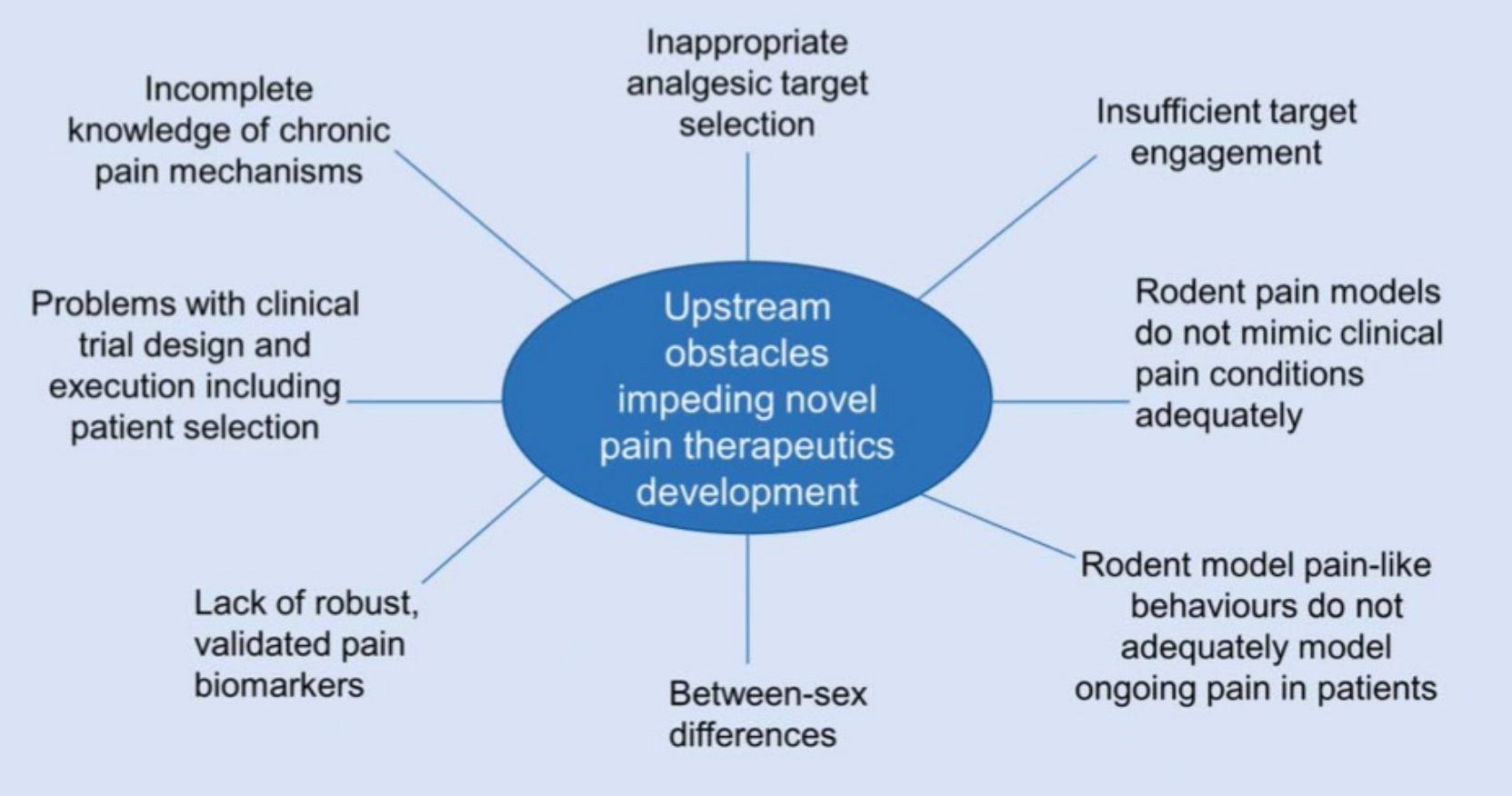
Yezierski RP, Hansson P. The Journal of Pain, Vol 19, No 6 (June), 2018: pp 571-588

Challenge in the pain space for drug development: complex biology



- Investments in the research of biomarkers
- Biomarker target engagement in humans for early proof of concept studies
- Early fail is cheap fail.

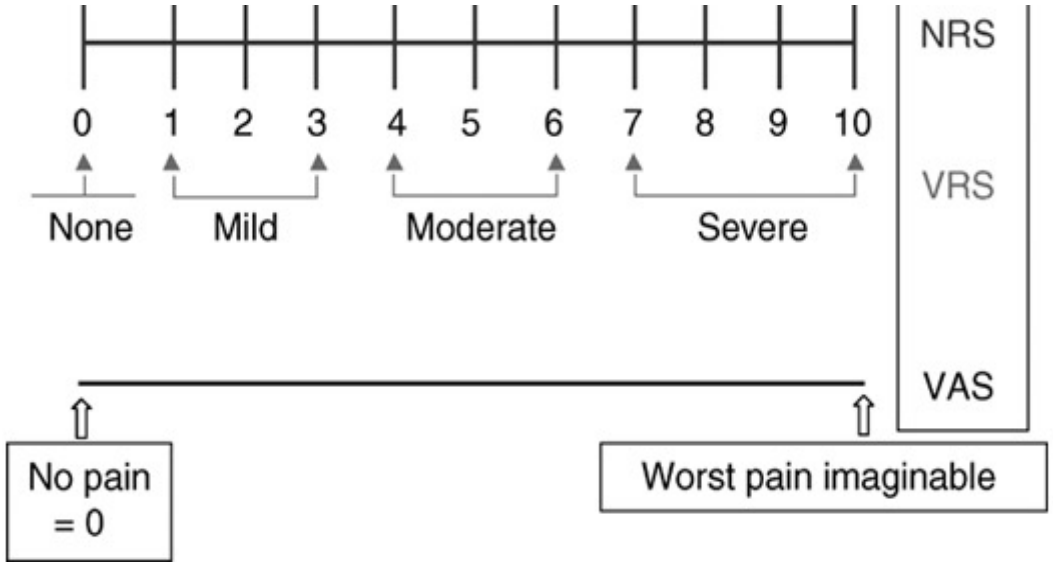
Lack of efficacy in early phase clinical trials: why?



Smith MT . Pain. 2022 Nov 1;163(Suppl 1):S15-S28: Kingwell K. Nature Reviews Drug Disc, Vol 21 Nov. 2022

Measuring Pain: ‘self-report’ remains the gold standard remains

- **Unidimensional**: selfreporting
  - Numeric rating scale (NRS)
  - Verbal rating scale (VRS)
  - Visual analogue scale (VAS)



- **Multidimensional:** Assesses not only pain intensity, but also the potential negative impacts of pain on such areas as sleep, mood, activity, appetite, energy, and functioning, including social functioning and relationships
  - Brief Pain Inventory
  - McGill Pain Questionnaire

Cleeland, C. S. et al. Annals, Academy of Medicine, Singapore, 2004, 23(2), 129–138; Melzack R. Pain. 1975; 1: 277-299.

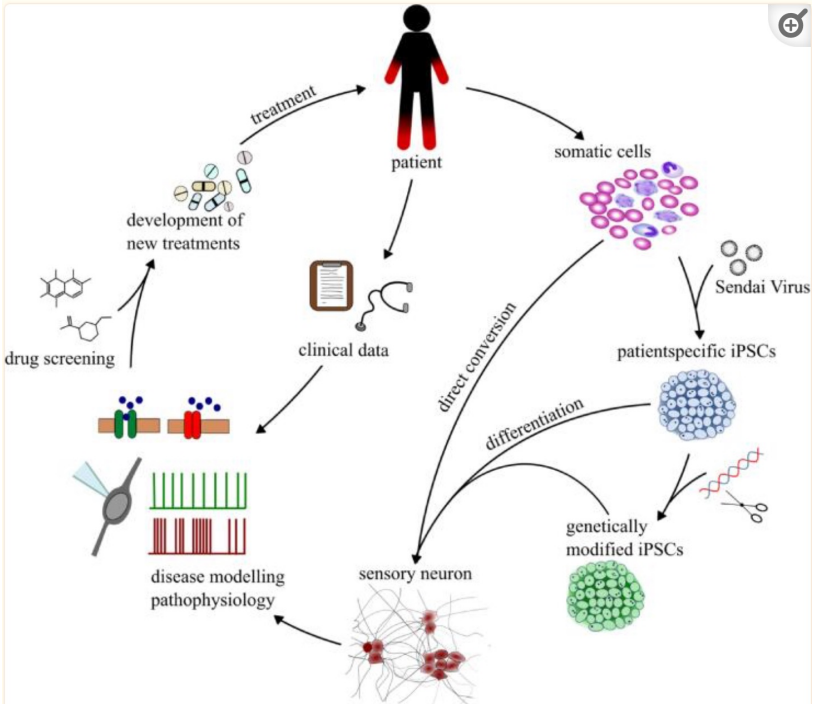
Categories for Measurement of Pain

- Self-report
- Observation of behaviour
  - Animals
  - Neonates
  - Cognitive impaired
- Indirect physiology
  - Quantitative sensory testing (QST), EEG , EMG

Tracey I et al. Neuron. 2019 Mar 6;101(5):783-800

Pain Biomarkers and Analgesic Discovery

- Large computational screens of large virtual libraries to find potential non-opioid analgesics
- Neuroimaging
- Target agnostic approach
  - Using human induced pluripotent stem cells (iPSC) derived neurons to screen for nociceptor-selective compounds



- Phase I: not only focus on safety and tolerability but should also explore
  - Proof-of-mechanism
  - Proof-of-concept
  - Early fail is cheap fail

Lampert A et al. Neurobiol Pain. 2020 Nov 18;8

Pharmacotherapy of pain: mostly ‘Old Wine in New Bottles’

Antinociceptive herbs and spices

Pharmacotherapy of Pain

Acute Pain

- Mostly inflammatory & nociceptive mechanisms
- Paracetamol/NSAIDs/COX-2 inhibitors/opioids
- NNT: 1.5-2.5

Chronic Pain

- More neuropathic and nociplastic mechanisms
- Only 40-[illegible] patients reach 30% pain relief
- [illegible]ments ranging from <10 to 20 mm
- [illegible]o
- [illegible]ypical analgesics
  - Antidepressants, anticonvulsants, NMDA antagonists, opioids, alpha 2 agonists etc., capsaicin etc...
- NNT: 4->10

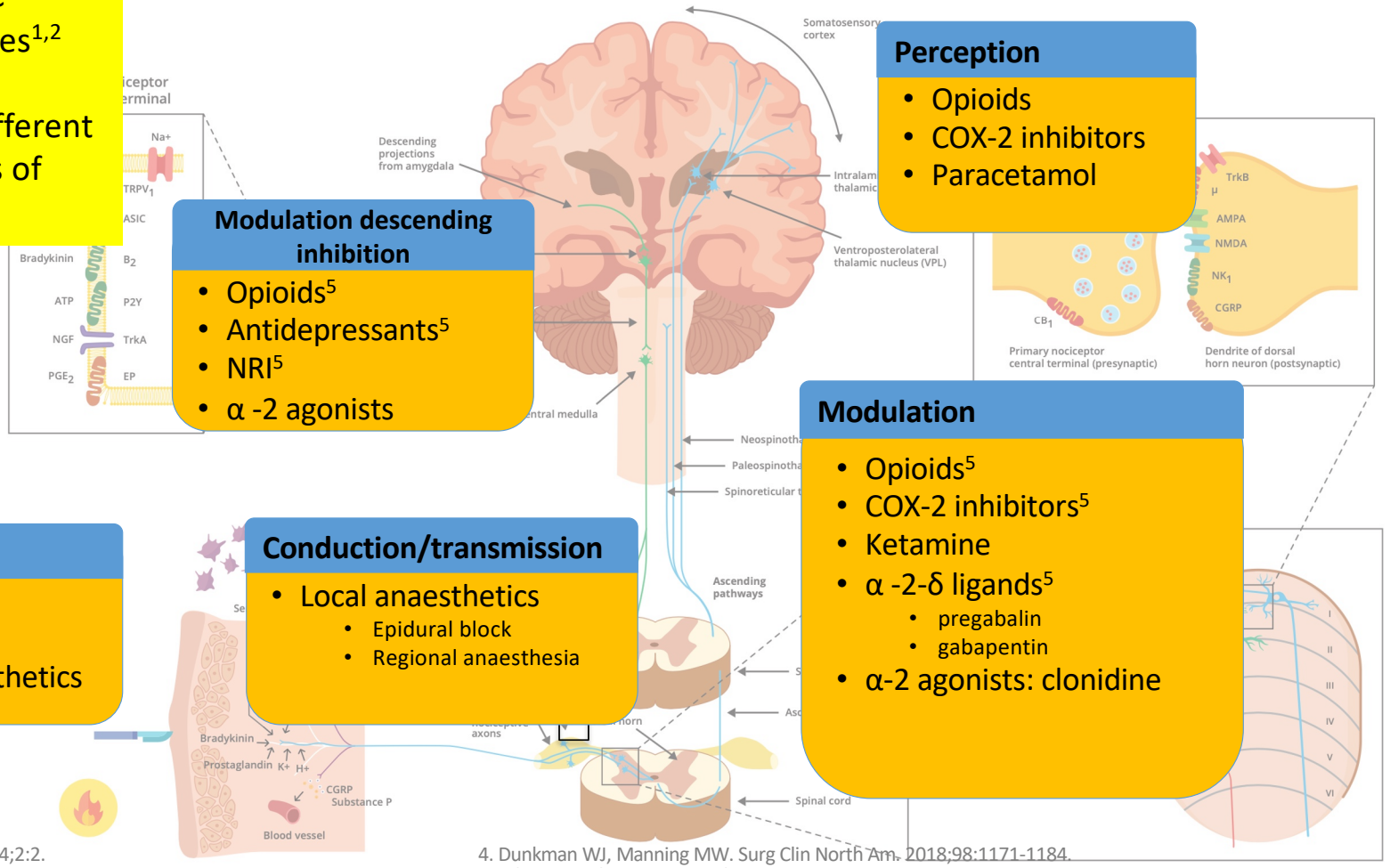
+ Important Placebo Effects
=Cognitive Modulation of Pain

a. Moore RA, et al. Cochrane Database Syst Rev. 2015:CD010794; b. Dworkin RH, et al. Pain. 2011;152:S107-15; c. Dworkin RH, et al. Pain. 2007;132:237-251; d. Attal N, Bouhassira D. Pain. 2015;156 (Suppl 1):S104-14.

Multimodal pharmacotherapy of pain

- Targeting the basic nociceptive processes[1,2]

- Combination of different drugs and/or routes of administration[3,4]



Perception
- Opioids
- COX-2 inhibitors
- Paracetamol

Modulation descending inhibition
- Opioids[5]
- Antidepressants[5]
- NRI[5]
- α -2 agonists

Modulation
- Opioids[5]
- COX-2 inhibitors[5]
- Ketamine
- α -2-δ ligands[5]
  - pregabalin
  - gabapentin
- α-2 agonists: clonidine

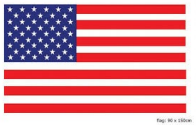
Transduction[5]
- NSAIDs
- COX-2 inhibitors
- Topical local anaesthetics

Conduction/transmission
- Local anaesthetics
  - Epidural block
  - Regional anaesthesia

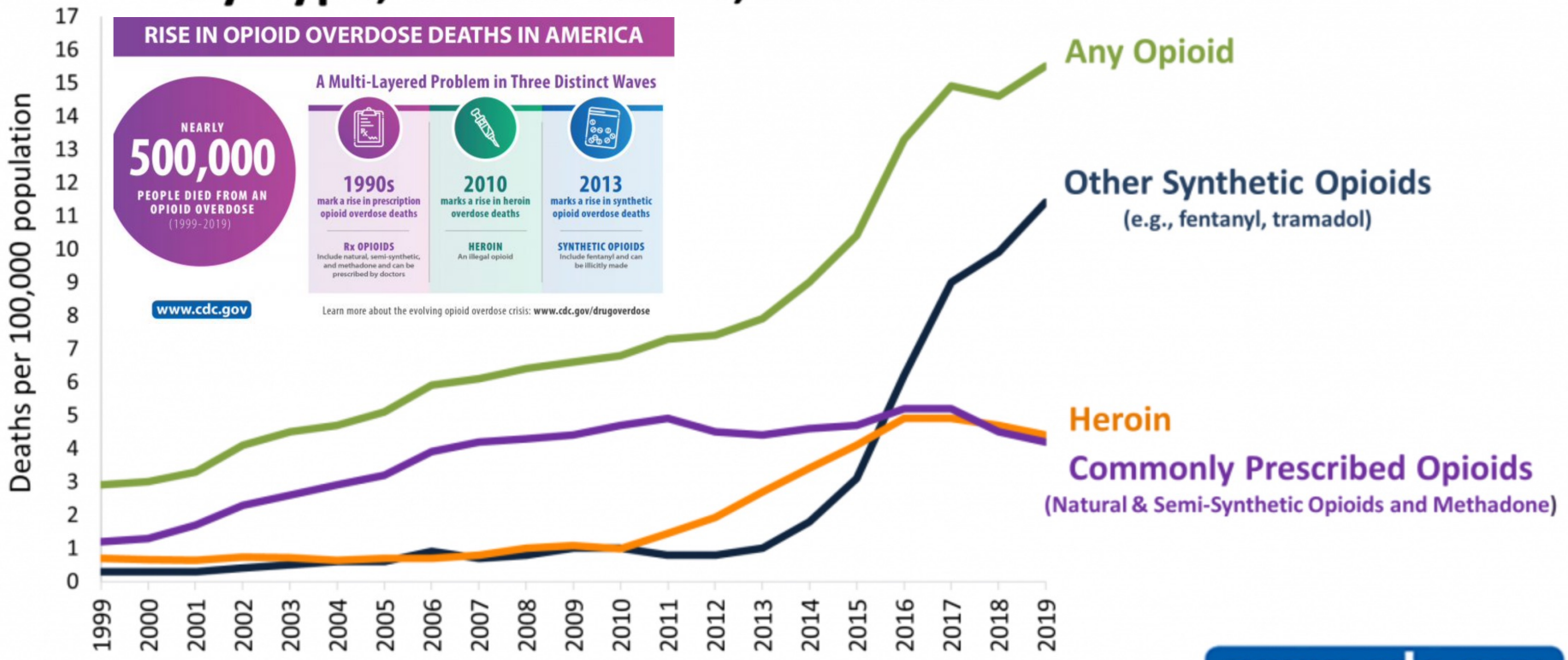
1. Kumar S, et al. OA Anaesthetics. 2014;2:2.
2. Julius D, Basbaum AI. Nature. 2001;413:203-210.
3. Lee B, et al. Best Pract Res Clin Anaesthesiol. 2018;32:101-111.
4. Dunkman WJ, Manning MW. Surg Clin North Am. 2018;98:1171-1184.
5. Gilron I, et al. Lancet Neurol. 2013;12:1084–1095.

Graphic composed by the author

Opioid crisis US



Overdose Death Rates Involving Opioids, by Type, United States, 1999-2019



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/.

www.cdc.gov
Your Source for Credible Health Information

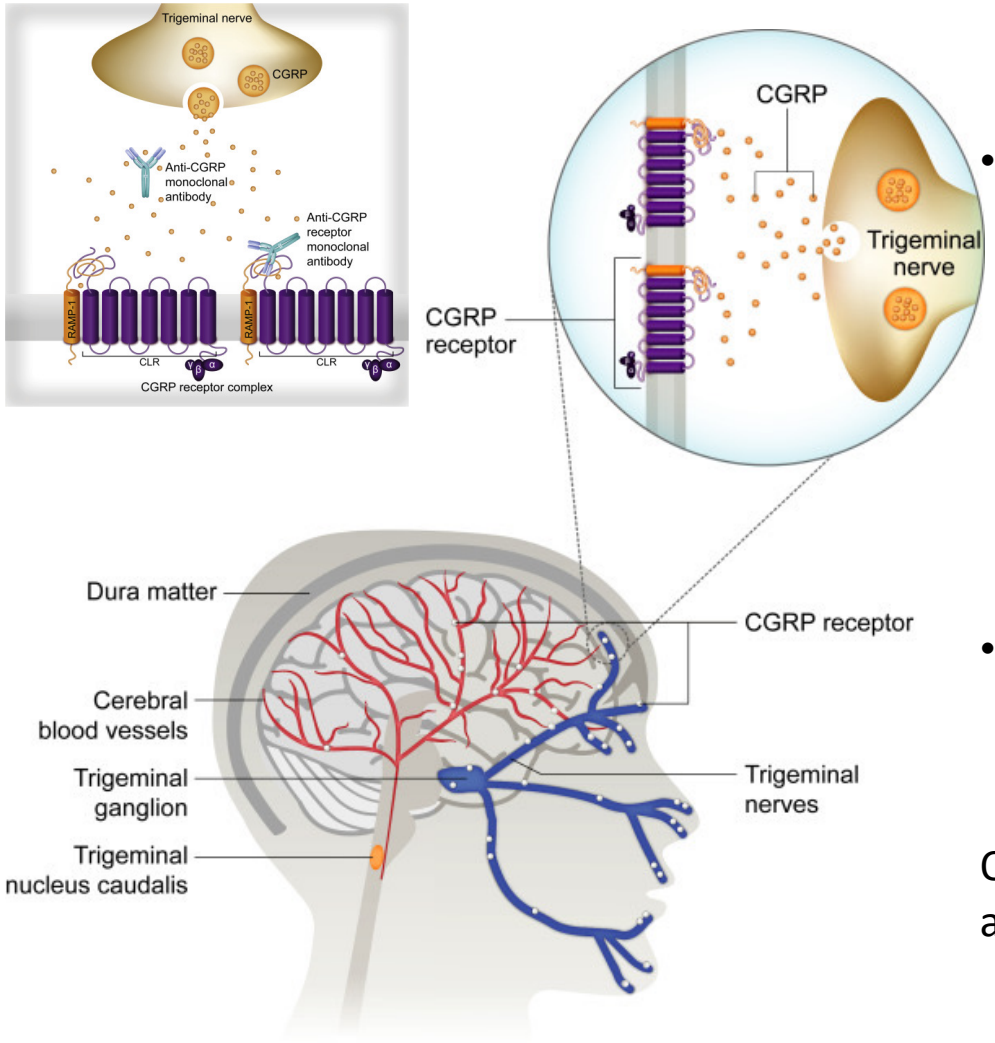
BJ Morlion 2021

Enormous need for more efficacious and safer analgesics with no abuse liability

- NIH funds $945 million in research to tackle the national opioid crisis through NIH HEAL Initiative

https://heal.nih.gov/files/2022-08/heal-initiative-annual-report-2022.pdf *Accessed Dec 5th 2022*

CGRP: example of successful target identification leading to market introduction.



CGRP = calcitonin gene-related peptide

- Anti-CGRP monoclonal antibodies (mAbs) in the preventive treatment of episodic and chronic migraine
  - Erenumab
    - a fully human mAb, targets the CGRP-R.
  - Fremanezumab
    Galcanezumab
    Eptinezumab
    - humanized mAbs that bind to the CGRP ligand

- Gepants: small molecule CGRP receptor antagonists.
  - Recently introduced: remigepant orally for treatment of acute migraine and prevention

Other novelty: dipants: target the 5-HT1F receptor to provide acute treatment without vasoconstrictive effects.

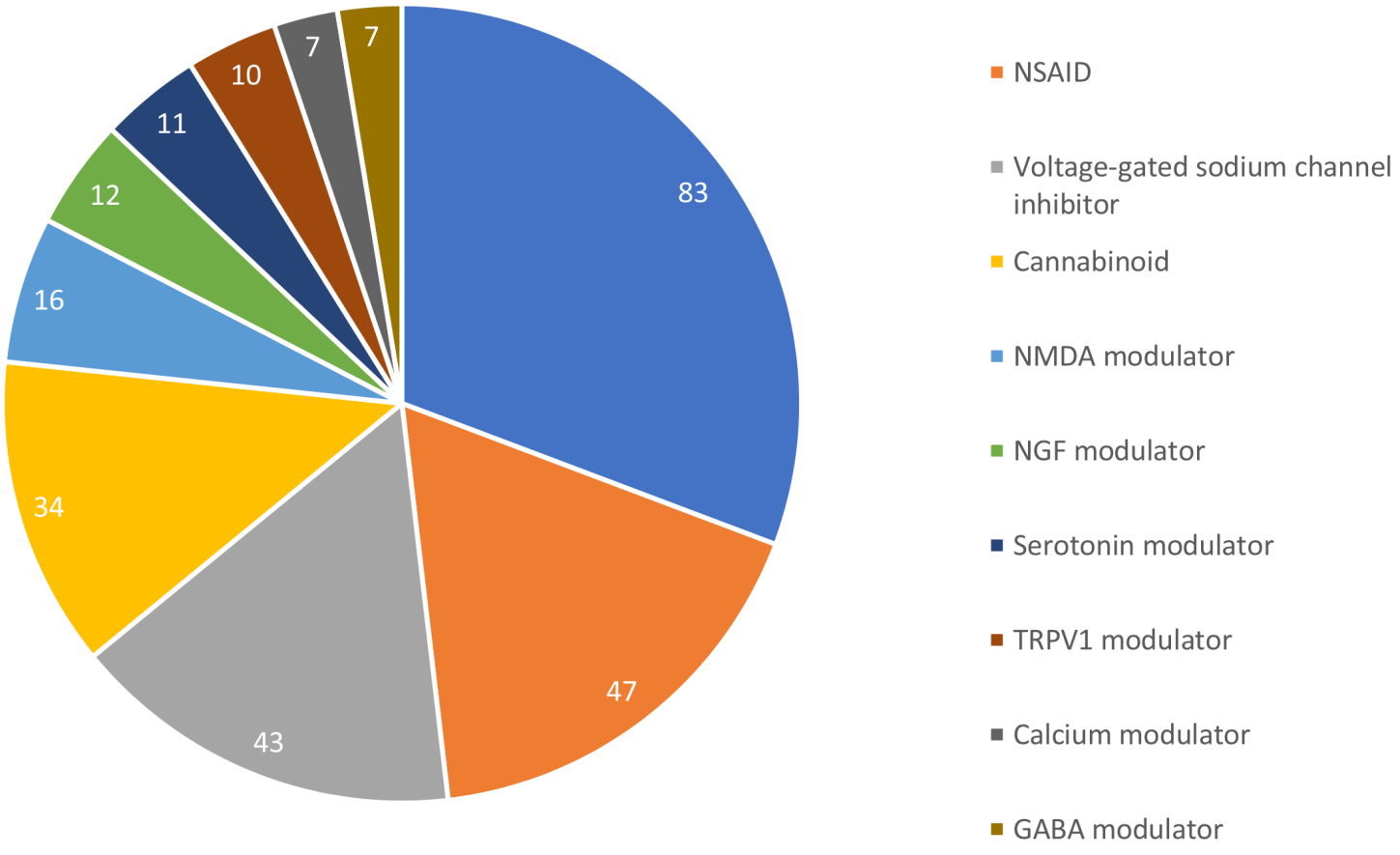
Ceriani CEJ et al. Headache. 2019 Oct;59(9):1597-1608.

New Analgesics?

- The landscape of pain
- Challenges
- Developments

Top 10 analgesic drug classes currently in early phases of drug development

until the therapeutic exploratory phase (phase I/II)



Hijma JH , Groeneveld GJ. Medicine in Drug Discovery 10 (2021)

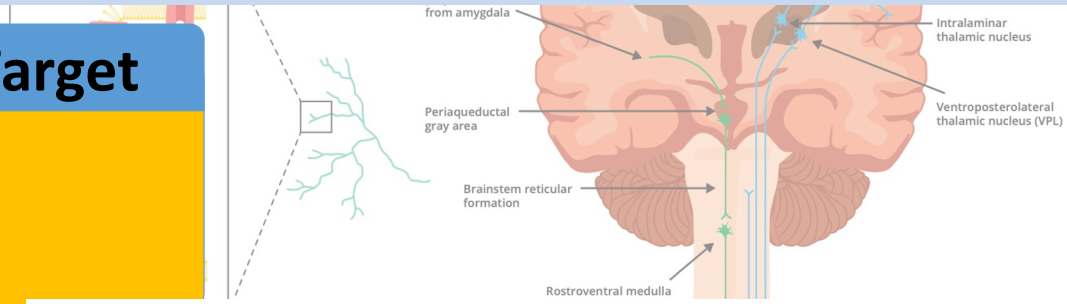
Block transduction / Counter-irritation transduction

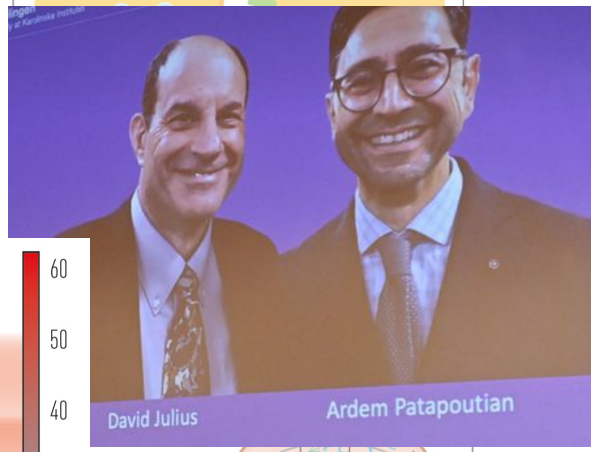
Examples

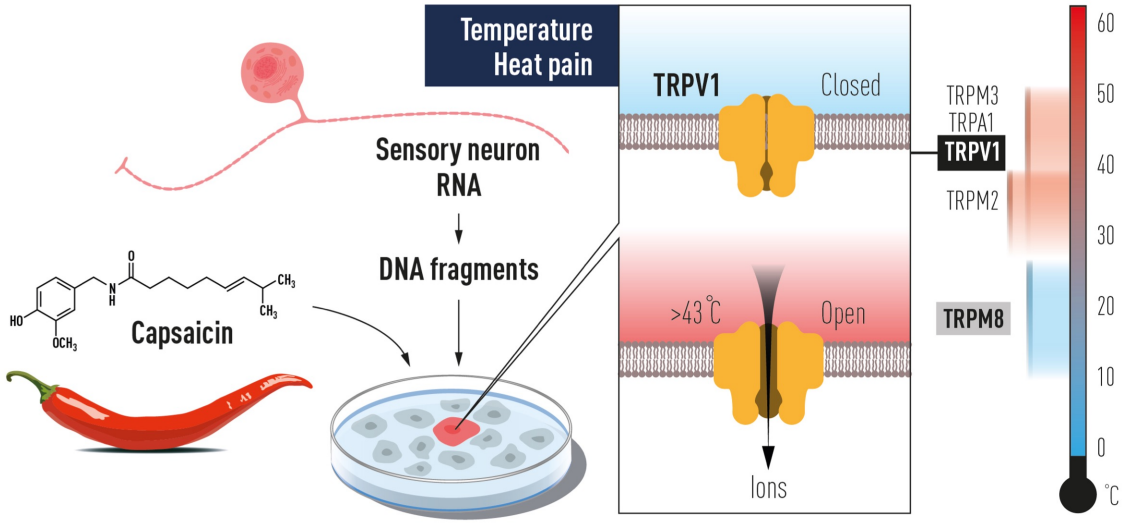
• Resiniferatoxin	Grünenthal	NME	TRPV1 agonist	OA knee	III
• LY3526318	Eli Lilly	Small molecule	TRPA1 antagonist	Pain	II

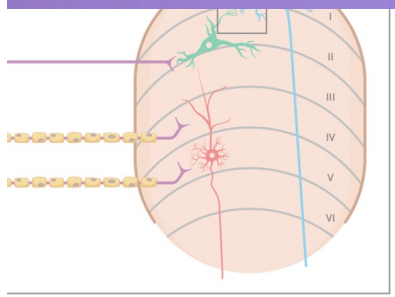
Analgesic Target

- **TRPV1**
- **TRPA1**





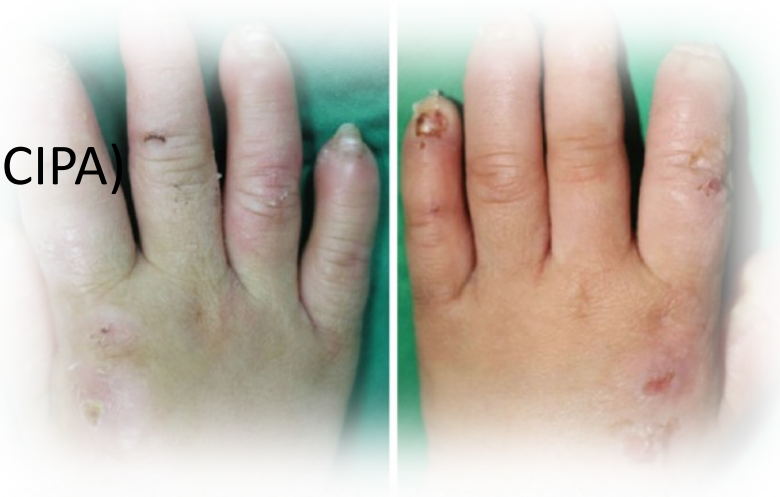




Graphic composed by the author

Genetics in analgesic development: learning from monogenic pain disorders

- **Loss of function**
  - Congenital Insensitivity to Pain with Anhidrosis (CIPA)
  - loss-of-function recessive mutations in Nav1.7

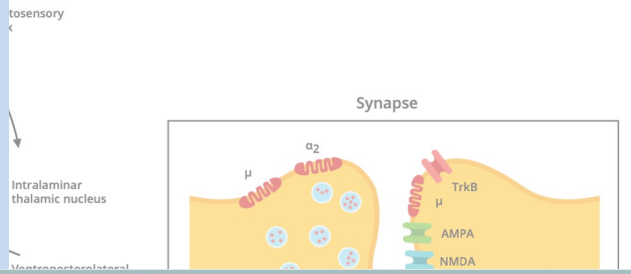


- **Gain of function**
  - Point mutations in SCN9A gene encoding Nav1.7
  - inherited erythromelalgia (IEM)
  - paroxysmal extreme pain disorder (PEPD) formerly known as familial rectal pain (FRP)
  - increased excitability of Nav1.7

Emery E. et al. Exp Op Ther Targets, 2016 VOL. 20, NO. 8, 975–983;
Alsaloum M, Higerd GP, Effraim PR, Waxman SG. Nat Rev Neurol. 2020 Oct 27

Block **transmission** by blocking sodium channels expressed by nociceptors

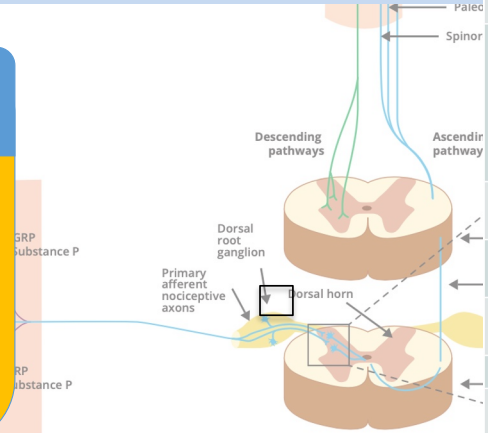
- Family of 9 channels, but Nav1.7, 1.8 and 1.9 predominantly expressed on nociceptor neurons
- Strong genetic validation (loss and gain of function): initial focus on Nav 1.7 as target : but not very “druggable”
- High-selectivity needed: now focus on voltage sensing domain 4 (VSD4)
- Probably 100% target engagement needed to achieve a clinical effect
- BBB crossing? Benefit or just adding side effects?
- New Focus on Nav1.8
  - E.g. VX-548 VERTEX
    Small molecule Nav1.8. inhibitor POP/DPN Phase II/III



Drug candidate	Sponsor	Modality	Development status
PF-05089771	Pfizer	Small-molecule inhibitor	Discontinued in 2015 after failed phase II trial in painful diabetic peripheral neuropathy
TV-45070	Teva/Xenon	Small-molecule inhibitor	Discontinued in 2017 after failed phase II trial in post-herpetic neuralgia
RG-6029/GDC-0310	Roche/ Genentech/Xenon	Small-molecule inhibitor	Discontinued in 2018 prior to phase II initiation
Vixotrigine	Biogen	Small-molecule inhibitor	Discontinued in painful lumbosacral radiculopathy after phase II failure in 2018; phase III trial planned in trigeminal neuralgia; phase II trial ongoing in small fibre neuropathy
BIIB-095	Biogen	Small-molecule inhibitor	Phase I trial for neuropathic pain ongoing
ST-2427	SiteOne	Small-molecule inhibitor	IND for post-operative pain
AM-6120, AM-8145 and AM-0422	Amgen	Peptide derived from tarantula venom	Discovery
Nav1.7-targeted mAb	Shionogi	mAb	Discovery
VY-NAV-01	Voyager Therapeutics	Gene therapy Nav1.7 knockdown	Discovery

Analgesic Target

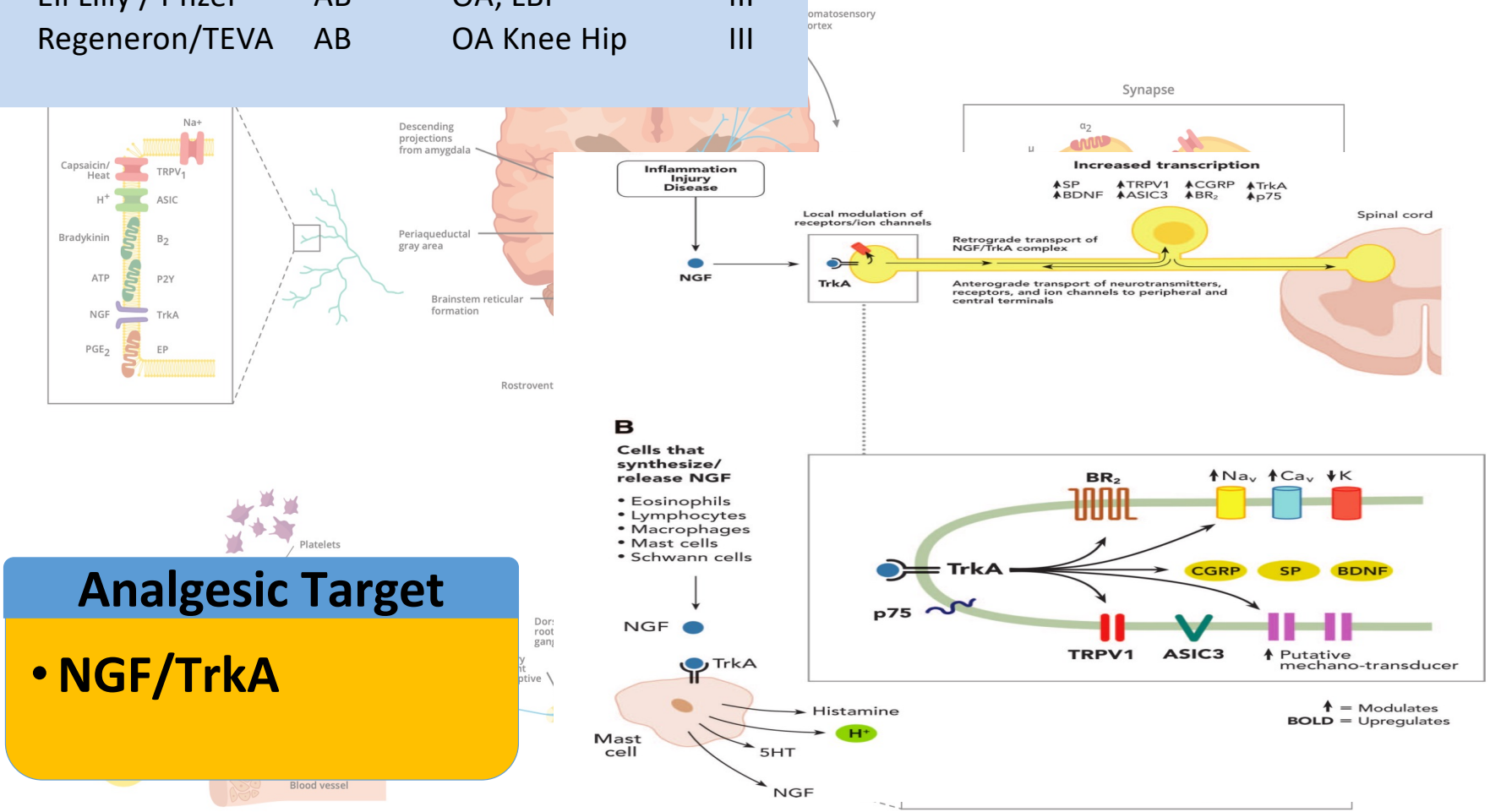
- **NaV inhibitors**
  - **Nav1.7**
  - **Nav1.8**



Kingwell K Nature Reviews Drug Discovery 2019, 2022

Reduce NGF or its action on the receptor

Tanezumab	Eli Lilly / Pfizer	AB	OA, LBP	III
Fasinumab	Regeneron/TEVA	AB	OA Knee Hip	III

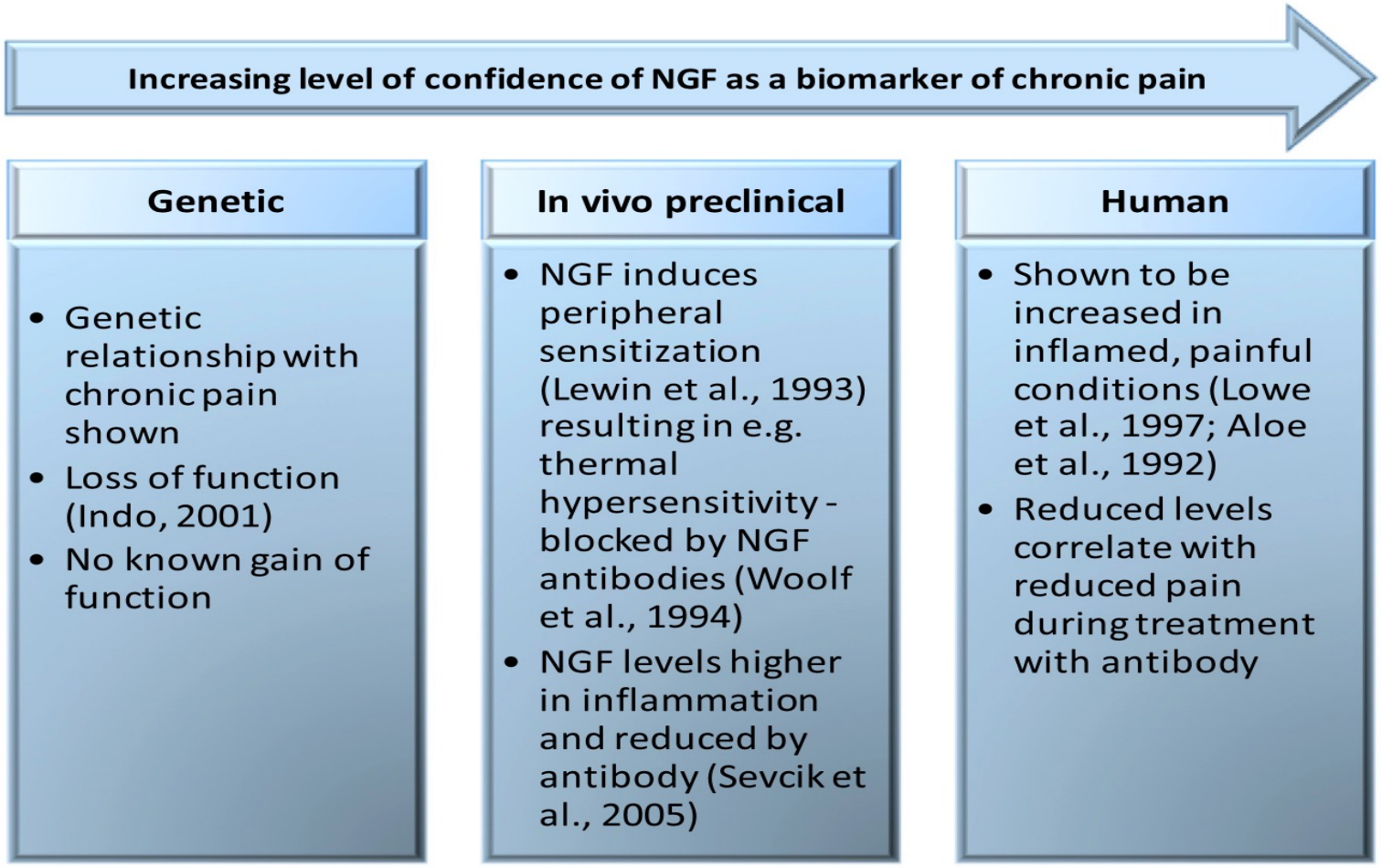


Analgesic Target

- **NGF/TrkA**

Aloe et al, J Transl Med 2012; Mantyh et al, Anesthesiology 2011

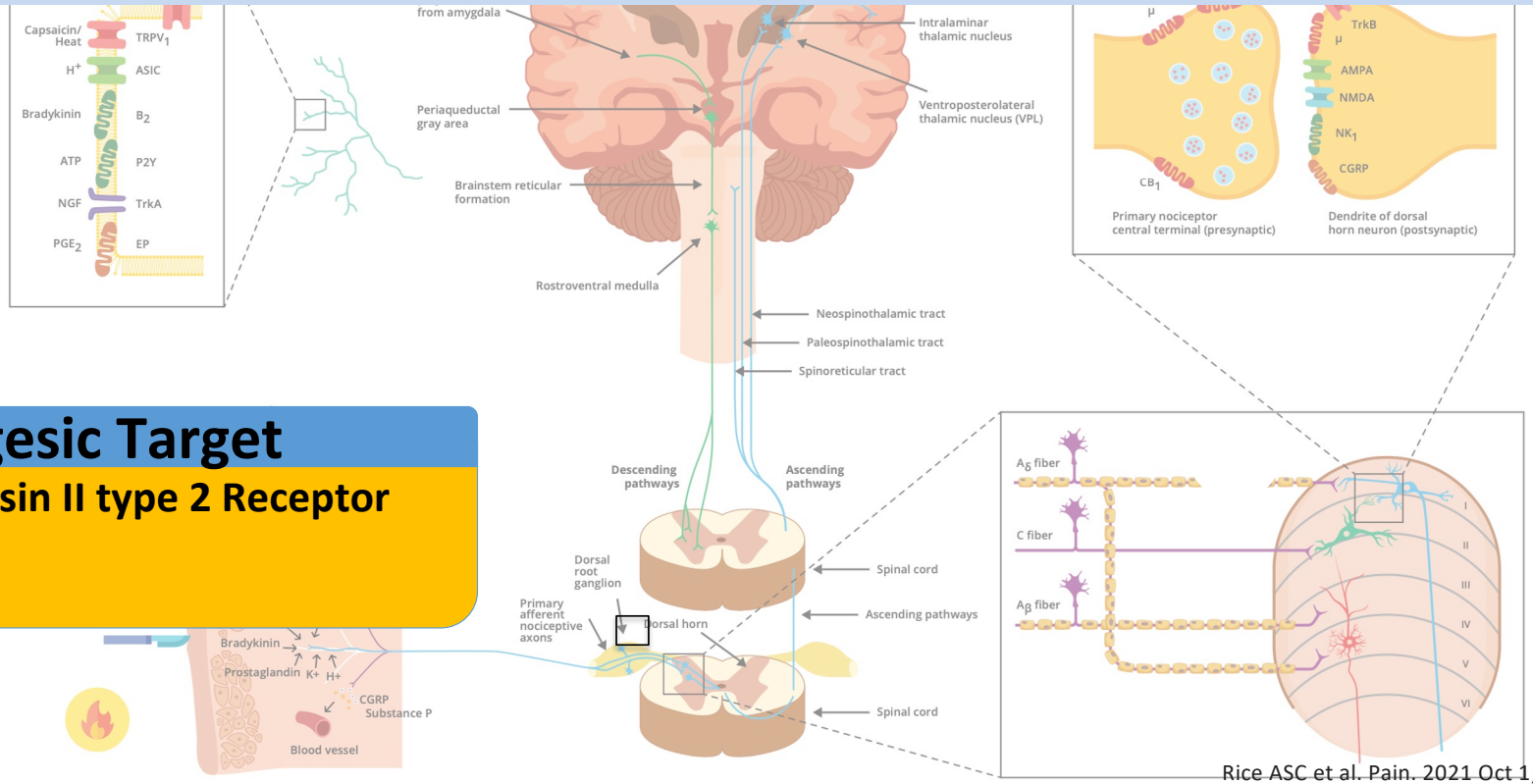
Cross-Species Validation of Biomarker Evaluation



Tracey I et al. Neuron. 2019 Mar 6;101(5):783-800

Contribute to immune activation of nociceptors; expressed in macrophages

EMA-401 (olodanrigan)	Novartis	AT2R Antagonist	DPN / PHN	II
CFTX-1554	Confo Therapeutics	AT2R Antagonist	NeP	Preclin



Analgesic Target

- **AT2R Angiotensin II type 2 Receptor**

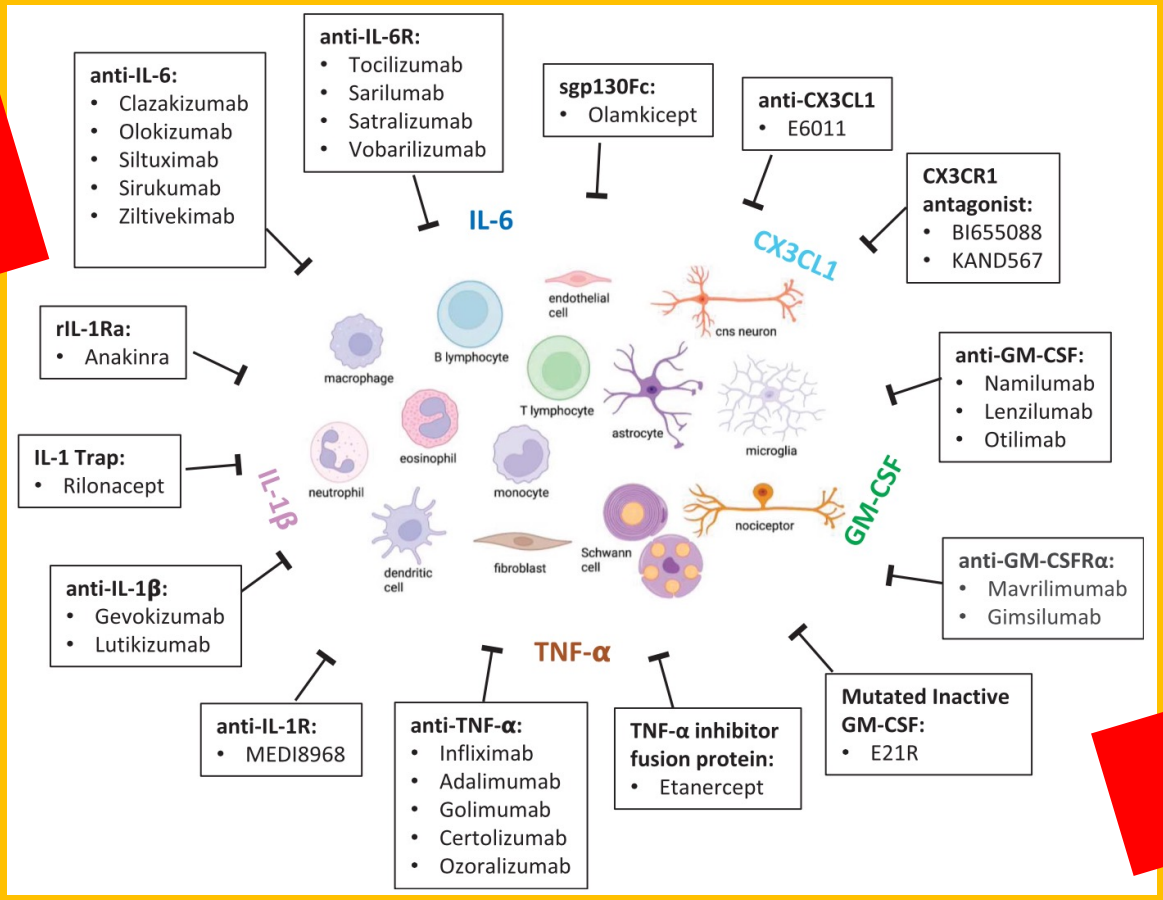
Rice ASC et al. Pain. 2021 Oct 1;162(10):2578-2589.

https://www.confotherapeutics.com/2020/10/15/confo-therapeutics-announces-selection-of-first-product-candidate-and-initiation-of-pre-clinical-development/

Reduce pro-inflammatory cytokines and their receptors

Analgesic Target

Repurposing
But RA differs from chronic pain



Immunogenic
ADA formation

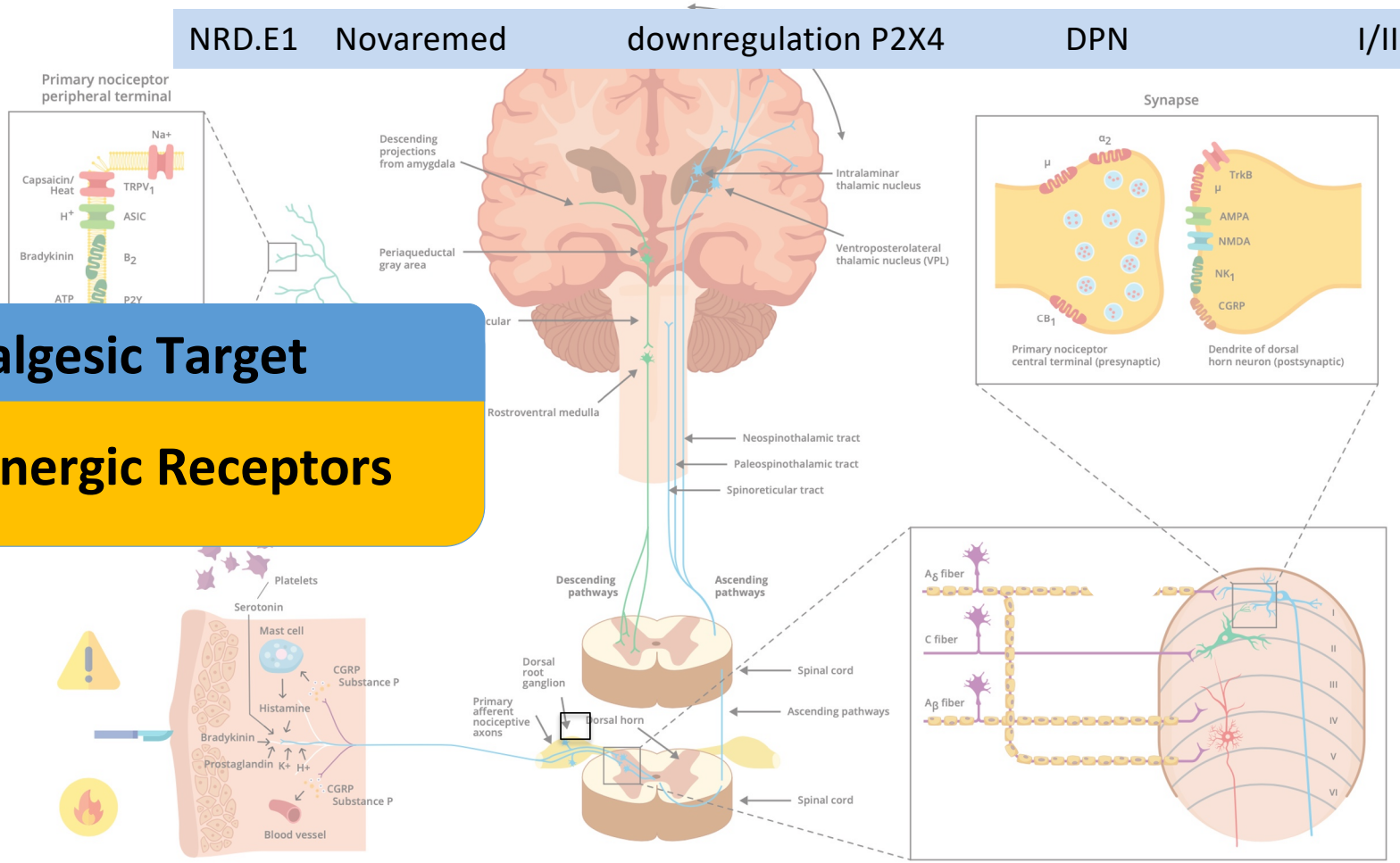
Kalpachidou, T et al. PAIN: November 2022 - Volume 163 - Issue S1 - p S79-S98

lock activation of nociceptors by ATP

NRD.E1	Novaremed	downregulation P2X4	DPN	I/II

Analgesic Target

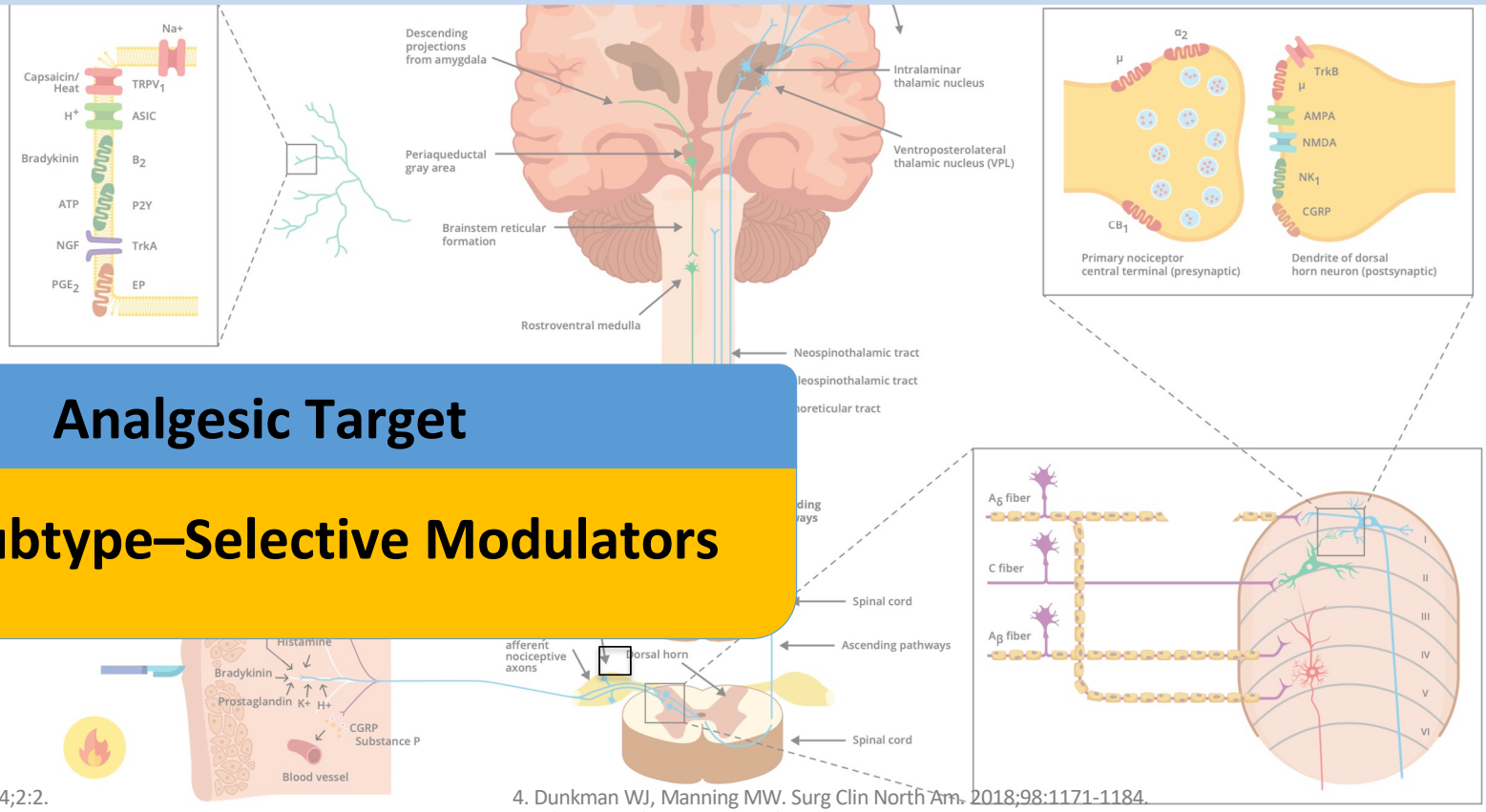
- **P2X Purinergic Receptors**



Graphic composed by the author

Target GABA receptors in nociceptive circuits

PF-06372865: a novel α2/α3/α5 gamma-aminobutyric acid A (GABAA) subunit selective partial positive allosteric modulator (PAM)



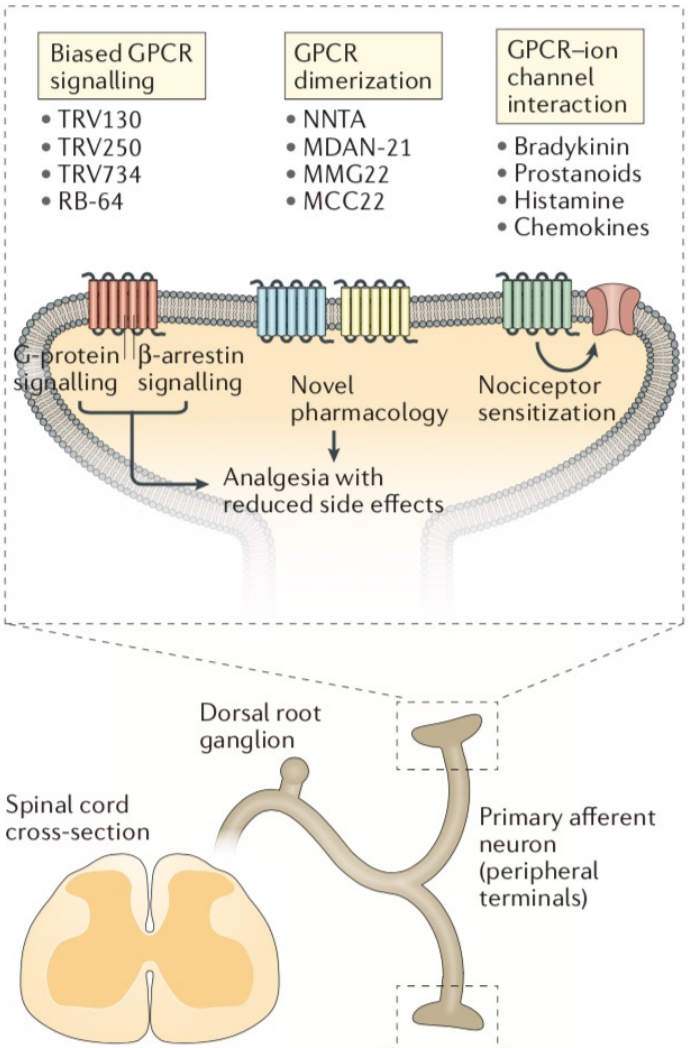
Analgesic Target

- **GABA Subtype–Selective Modulators**

1. Kumar S, et al. OA Anaesthetics. 2014;2:2.
2. Julius D, Basbaum AI. Nature. 2001;413:203-210.
3. Lee B, et al. Best Pract Res Clin Anaesthesiol. 2018;32:101-111.
4. Dunkman WJ, Manning MW. Surg Clin North Am. 2018;98:1171-1184.
5. Gilron I, et al. Lancet Neurol. 2013;12:1084–1095.

Graphic composed by the author

Targeting opioid receptors G-protein coupled receptors (GPCRs)



Strategies to mitigate adverse effects of opioids

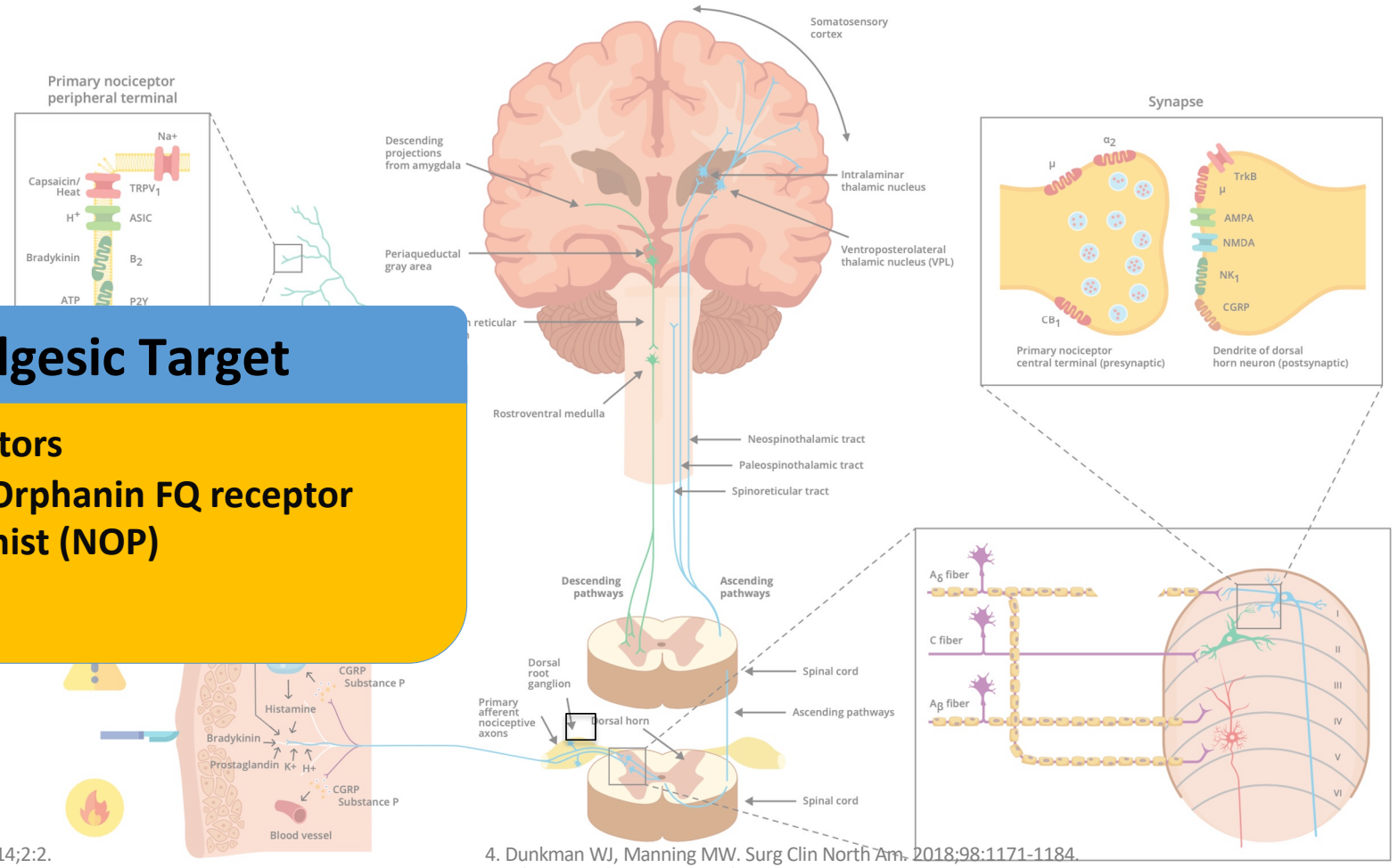
- Mechanistic approach to side effects
- Abuse-deterrent opioids
- Peripherally restricted receptor ligands
- Heteromers, bivalent ligands and isoforms
- Biased ligands

Yekkirala et al. Nature Reviews: Drug Discovery Aug. 2017

Mitigating the central dysphoria of opioids; peripheralized agonist

Analgesic Target

- **Kappa receptors**
- **Nociceptin/Orphanin FQ receptor Peptide agonist (NOP)**



1. Kumar S, et al. OA Anaesthetics. 2014;2:2.
2. Julius D, Basbaum AI. Nature. 2001;413:203-210.
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4. Dunkman WJ, Manning MW. Surg Clin North Am. 2018;98:1171-1184.
5. Gilron I, et al. Lancet Neurol. 2013;12:1084–1095.

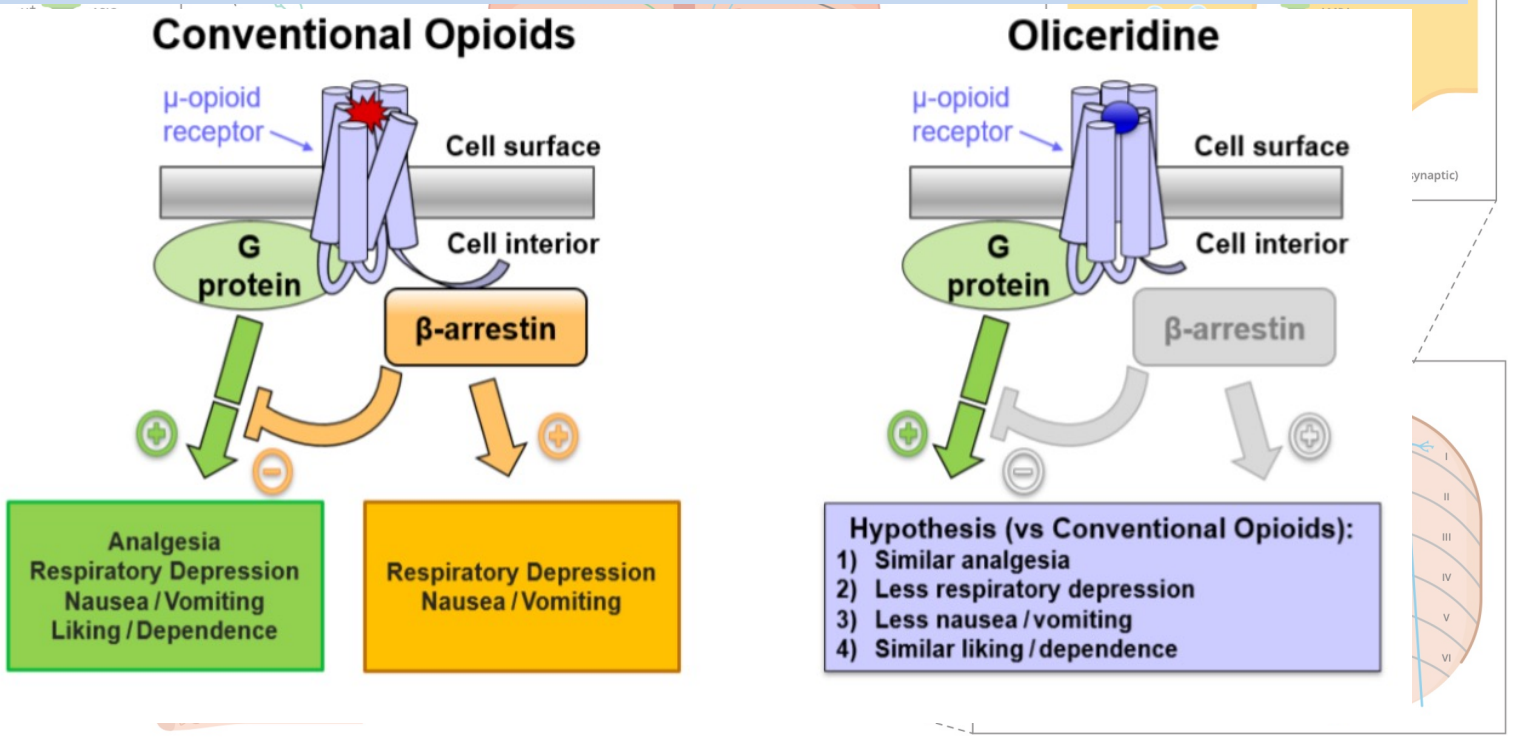
Graphic composed by the author

Opioids

Try to differentiate analgesic and adverse effects of mu opioid receptor activation

“Biased” ligands

selectively engage some signalling pathways while avoiding, or even inactivating, other signalling pathways mediated by the same receptor



https://www.fda.gov/media/121230/download *Last accessed 28 Oct 2020; Graphic composed by the author*


?
A fresh look at old remedies
Cinnamon
Cloves
Turmeric
Capsaicin
Menthol
Turmeric
Lemon Verbena
Cannabis sativa
…

New Analgesics?

- Pain is complex and extremely prone to cognitive modulation
- Acute and chronic pain: distinct pathophysiological mechanisms
- Golden bullet for all pain: utopy
- High placebo response in clinical trials
- Lack of standardized pain measures: ‘self reporting’
- Need for more human biomarkers and target engagement
- Pain subtype-targeted pharmacotherapy: more realistic