State of the Art Safety Standards in RA
THE EUROPEAN SOCIETY OF REGIONAL ANAESTHESIA & PAIN THERAPY

European Society of Regional Anaesthesia & Pain Therapy
ESRA ITALIA

www.esraitalia.it

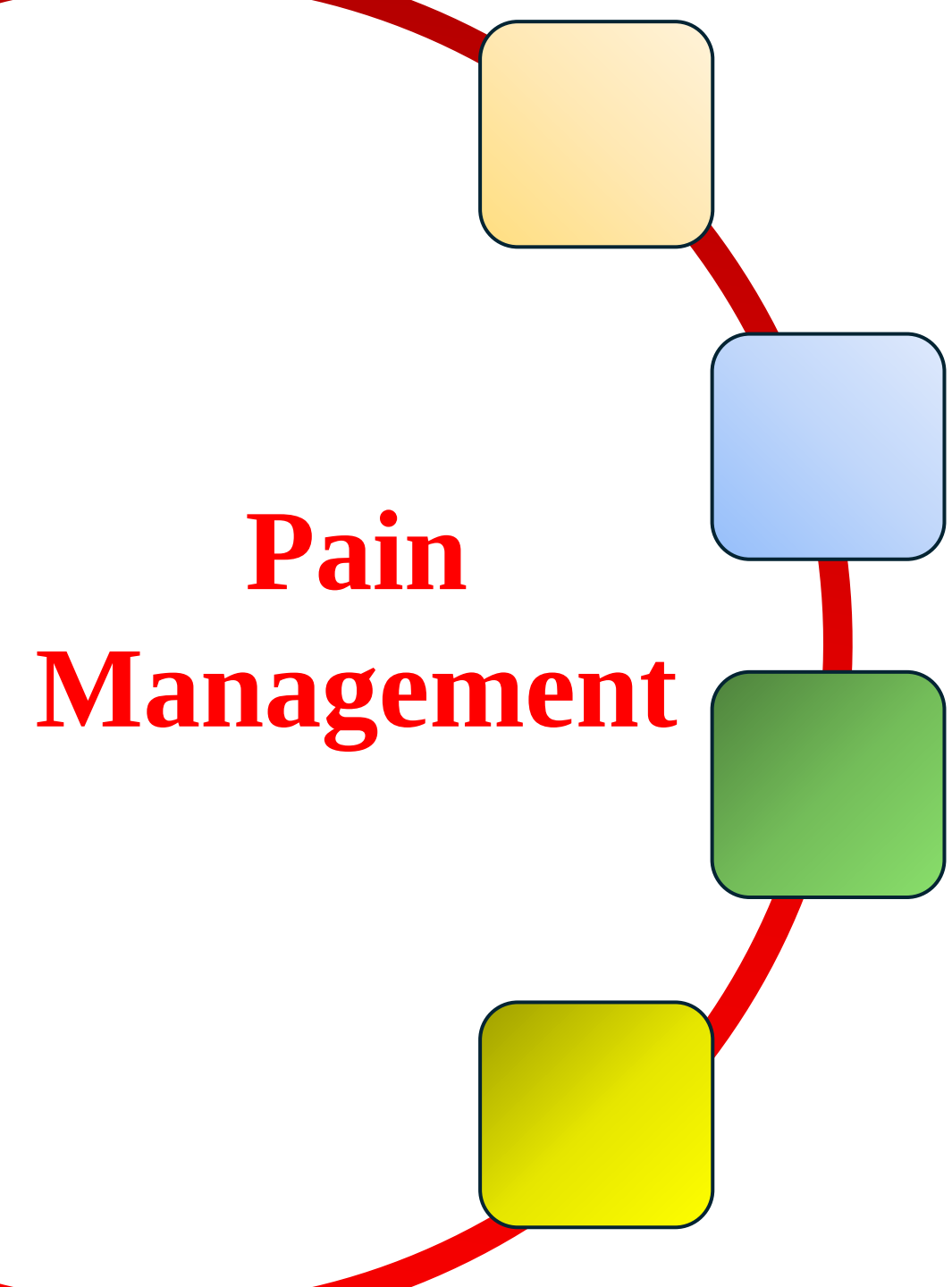
ESRA MEETING - ANNUAL UPDATE

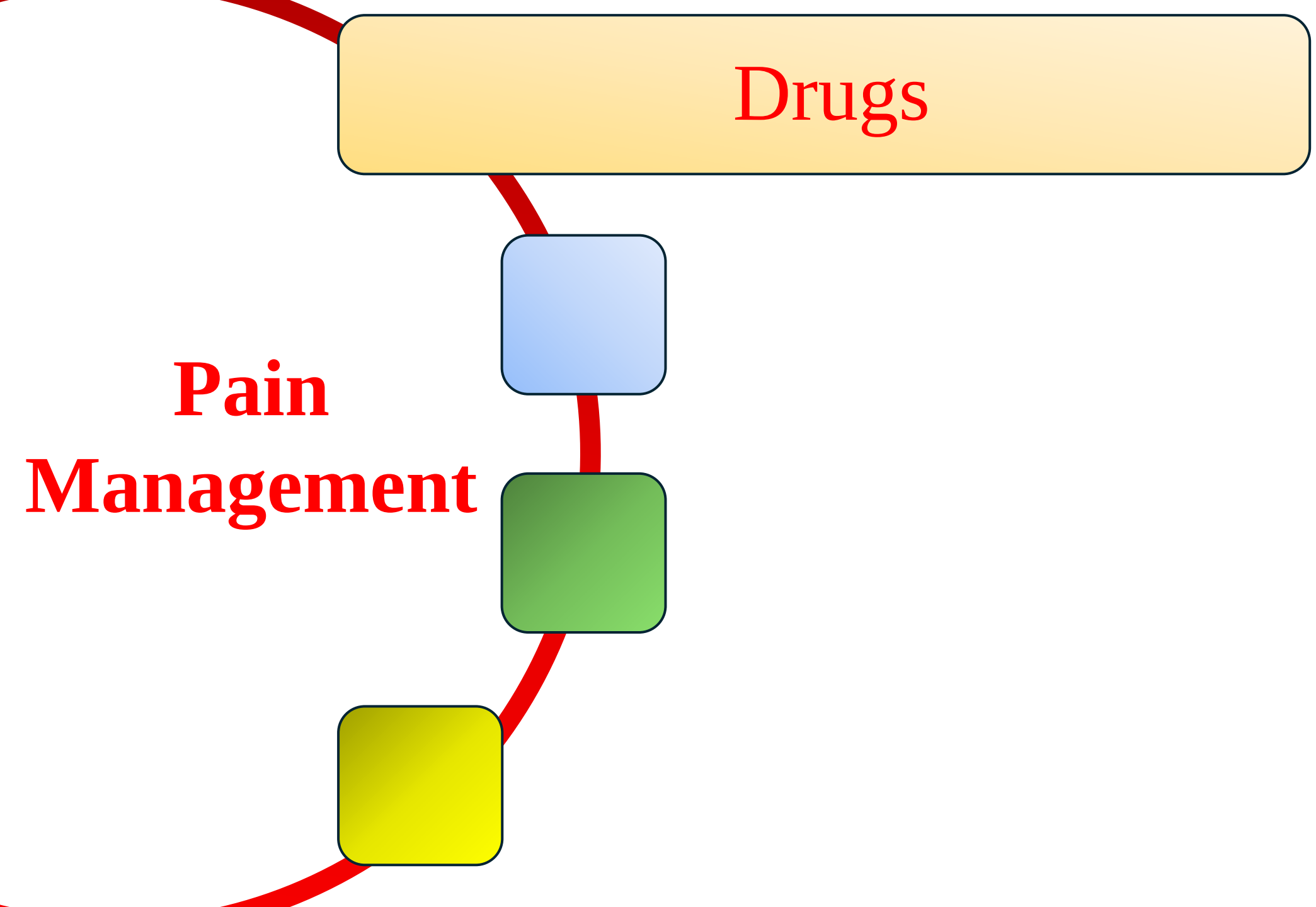
1 day, 1 programme, 3 cities

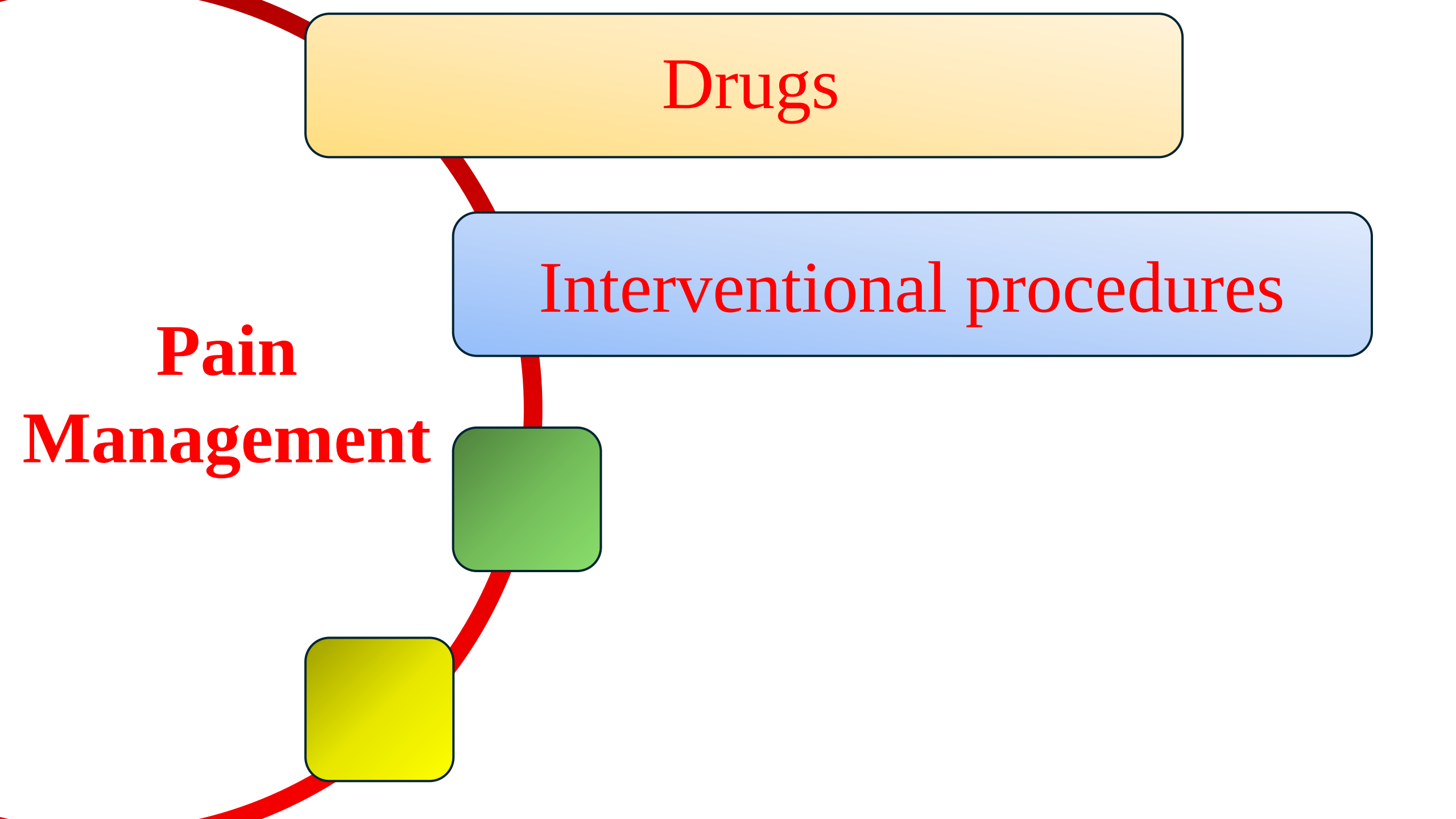
13 APRILE 2024

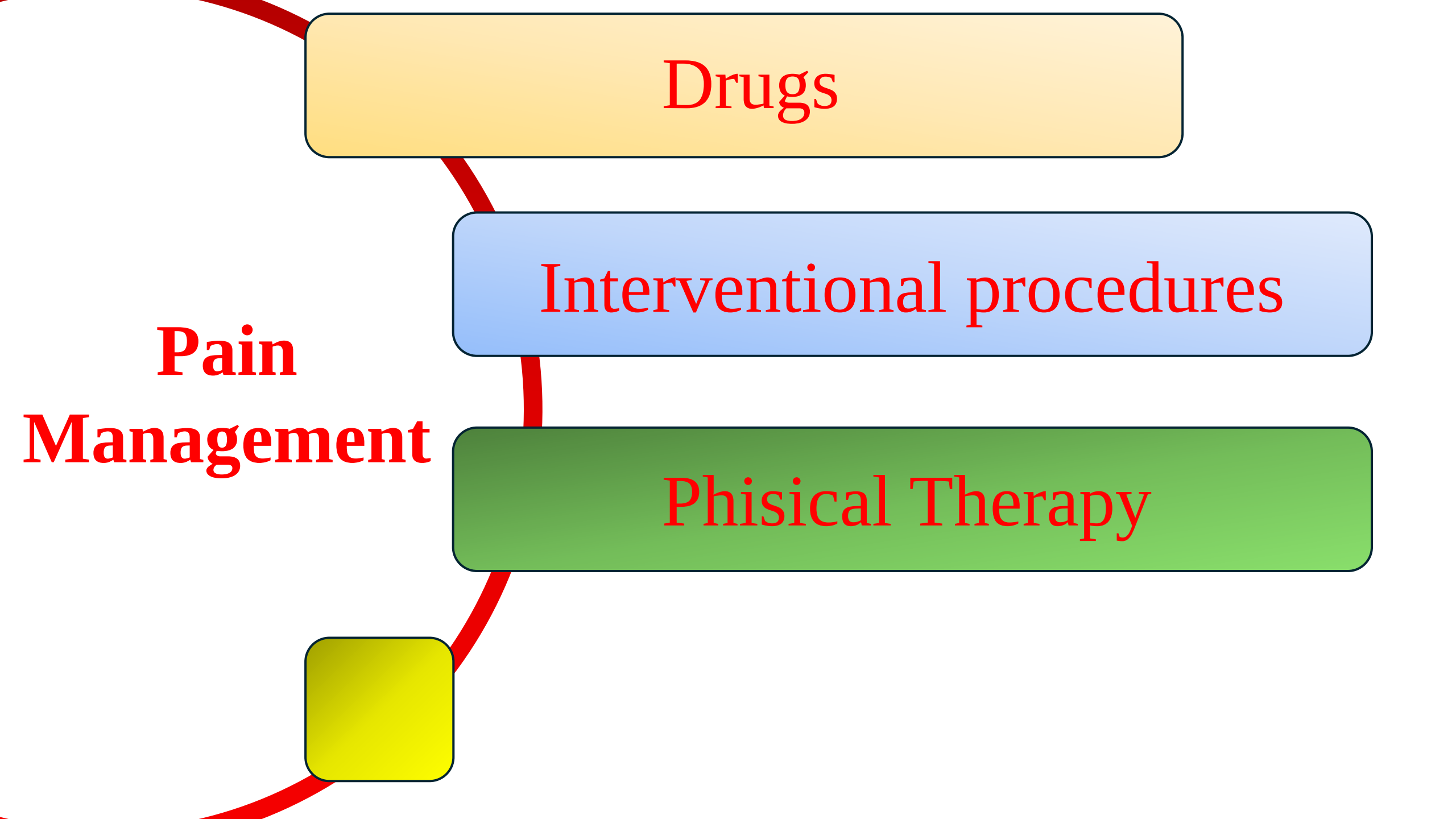
Novità in Terapia del Dolore

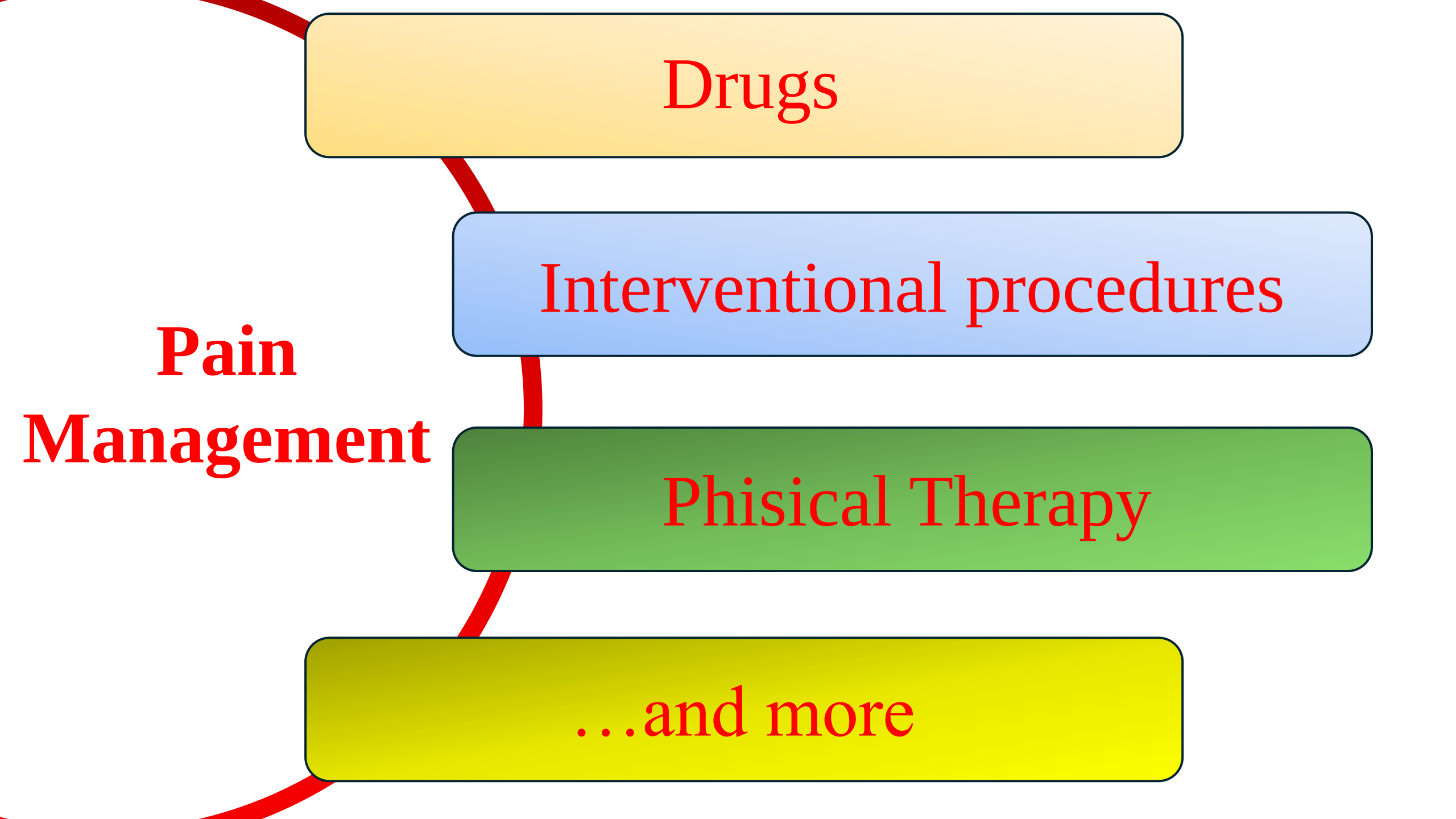
Dott. Pasquale Buonanno
Università degli Studi di Napoli «Federico II»


Pain
Management


Drugs
Pain Management

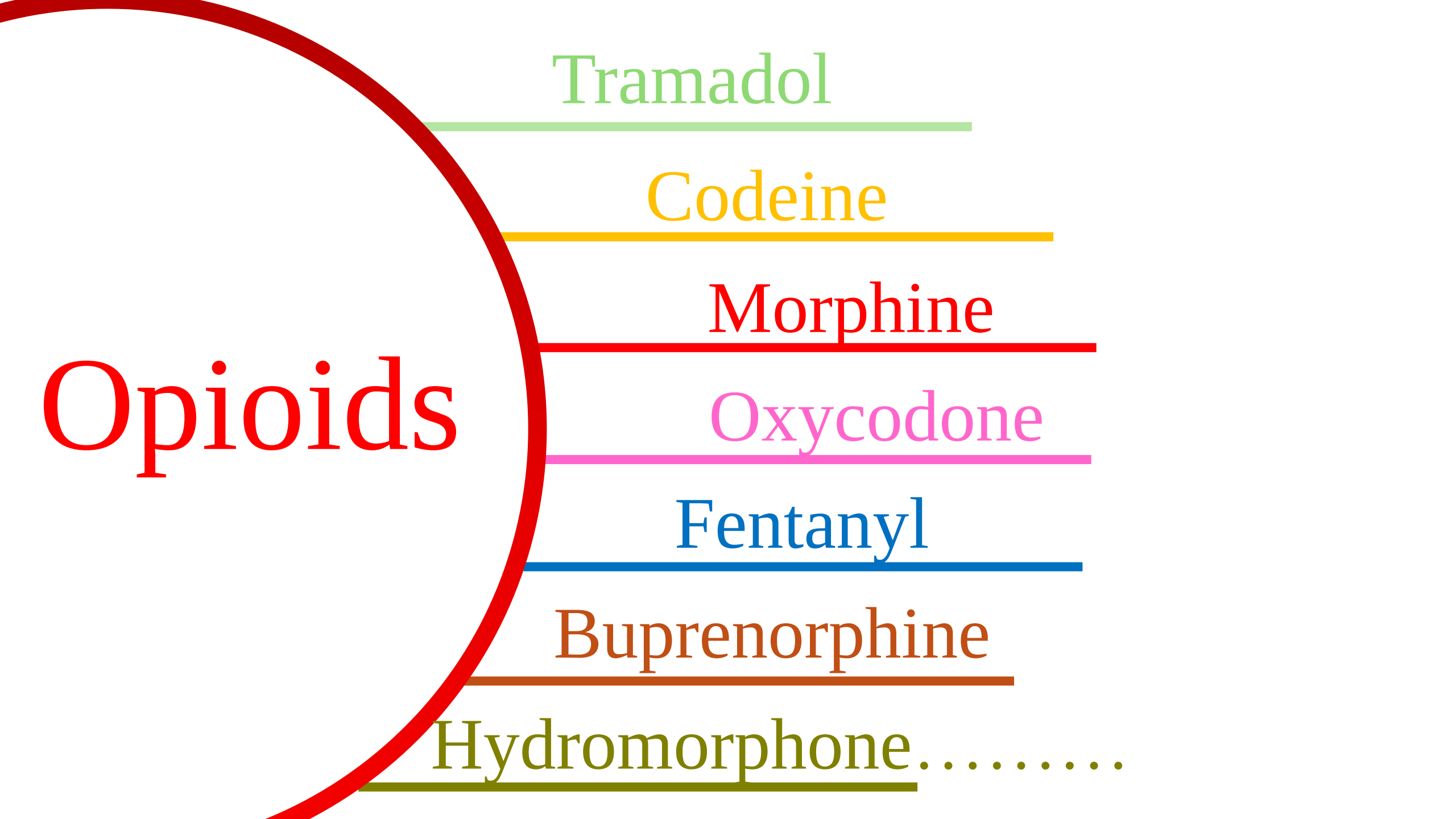

Drugs
Interventional procedures
Pain Management


Drugs
Interventional procedures
Pain Management
Phisical Therapy


Pain Management
Drugs
Interventional procedures
Phisical Therapy
…and more

Drugs

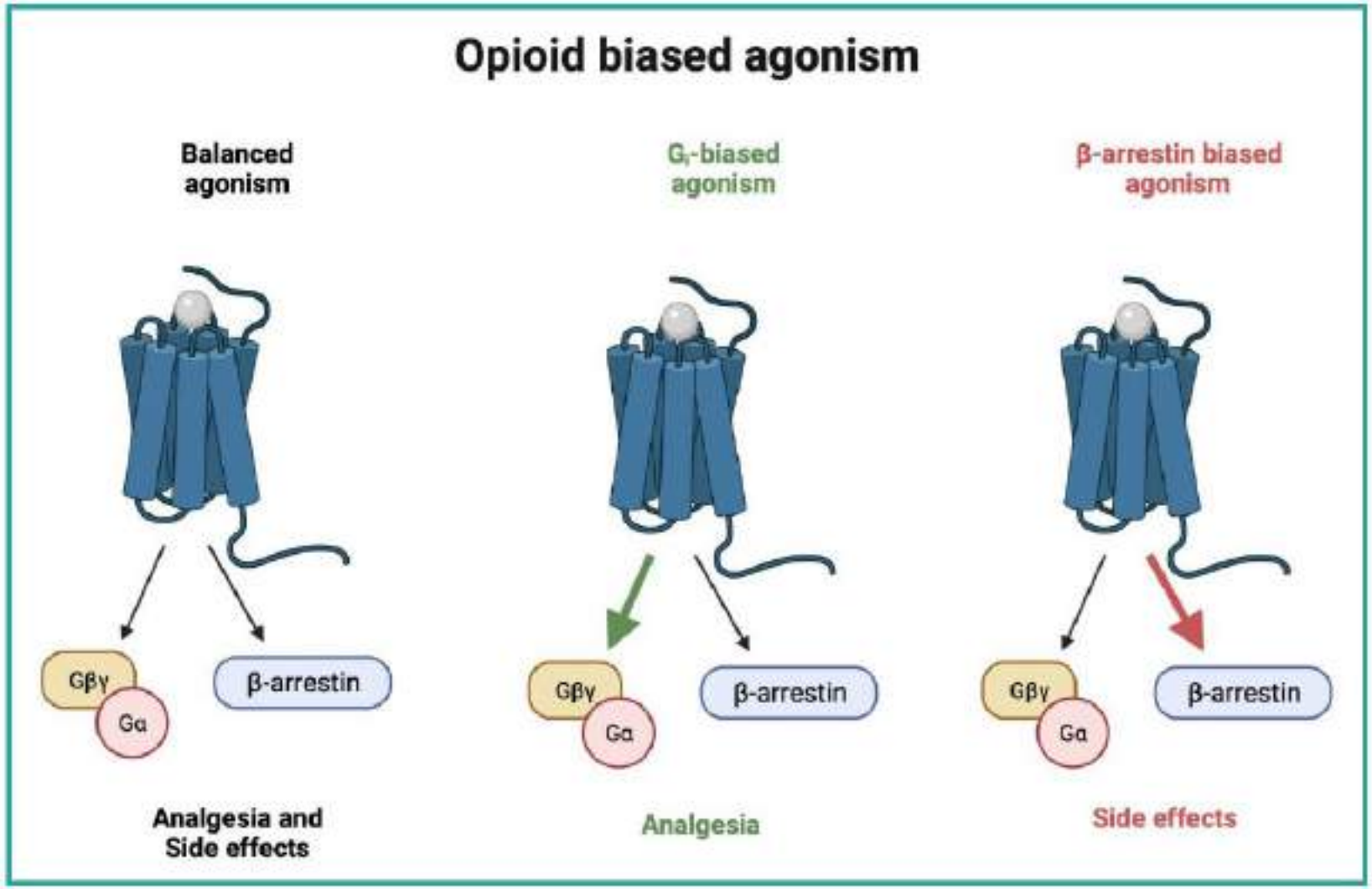
Opioids


Opioids
Tramadol
Codeine
Morphine
Oxycodone
Fentanyl
Buprenorphine
Hydromorphone……

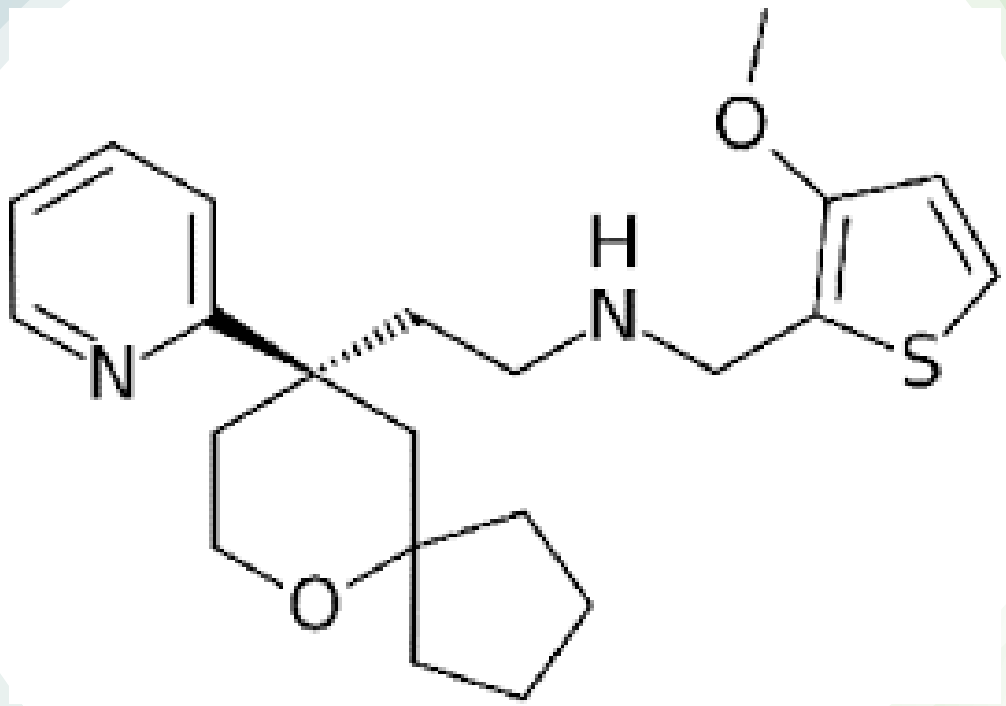
Opioids

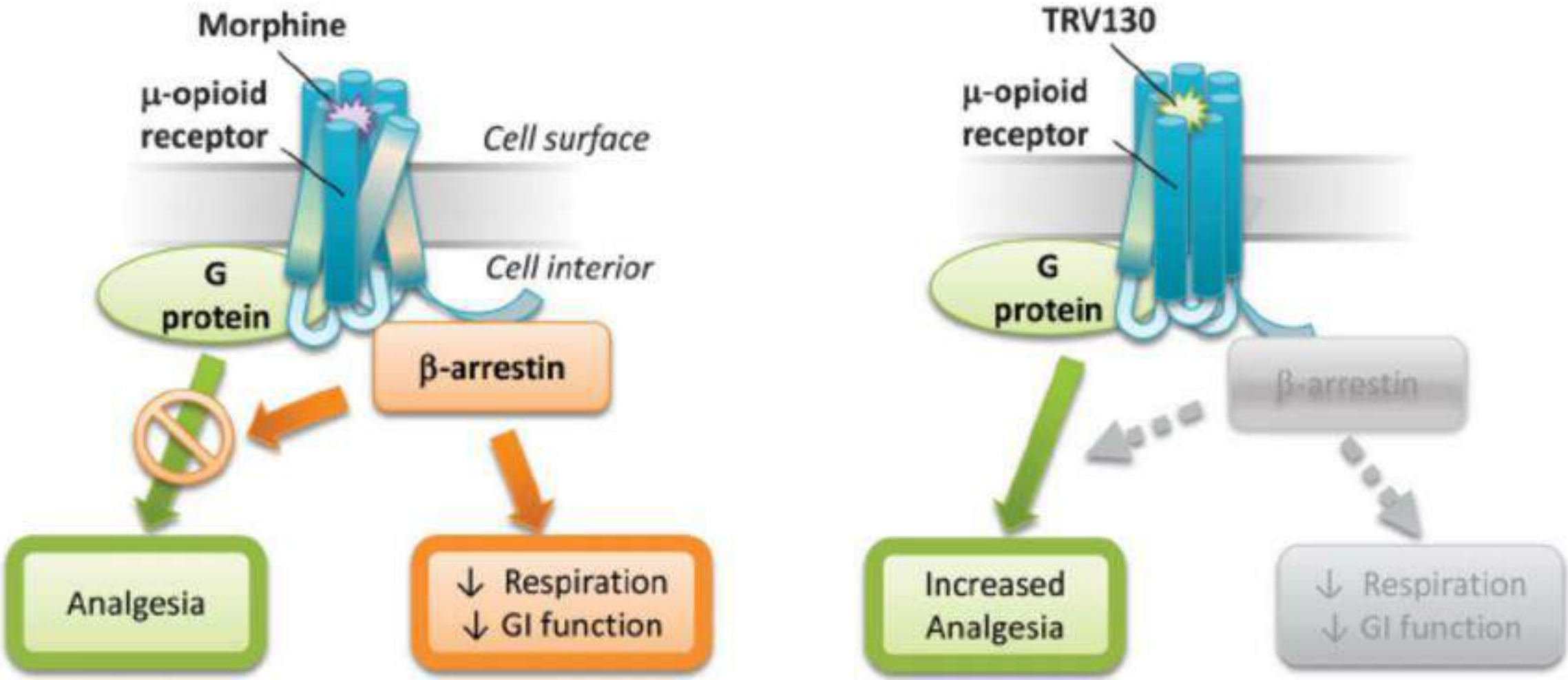
Side effects

- Sedation
- Dizziness
- Nausea
- Vomiting
- Constipation
- Physical dependence
- Tolerance
- Respiratory depression

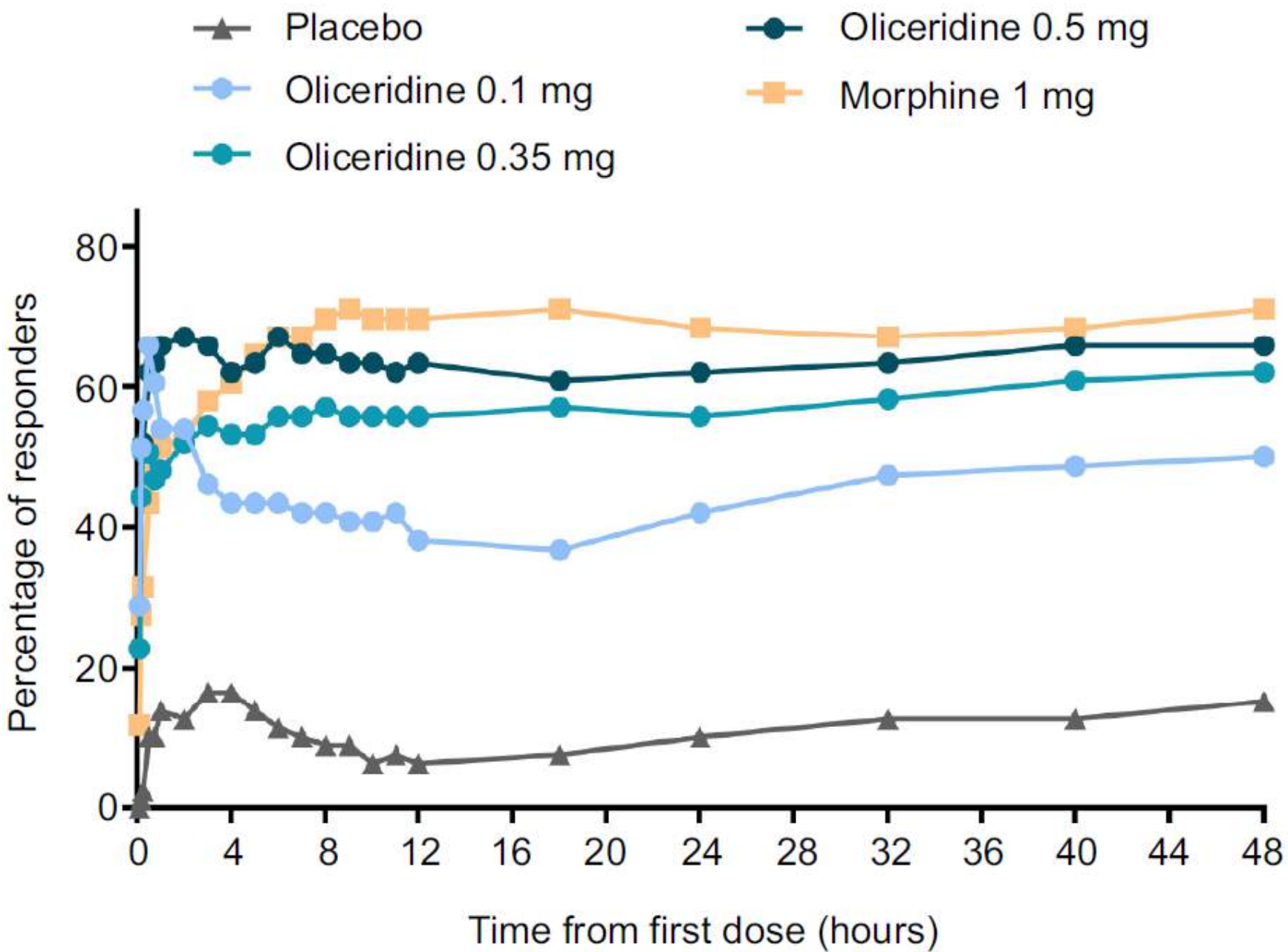

Opioid biased agonism
Balanced agonism
Gi-biased agonism
β-arrestin biased agonism
Gβγ
Gα
β-arrestin
Gβγ
Gα
β-arrestin
Gβγ
Gα
β-arrestin
Analgesia and Side effects
Analgesia
Side effects

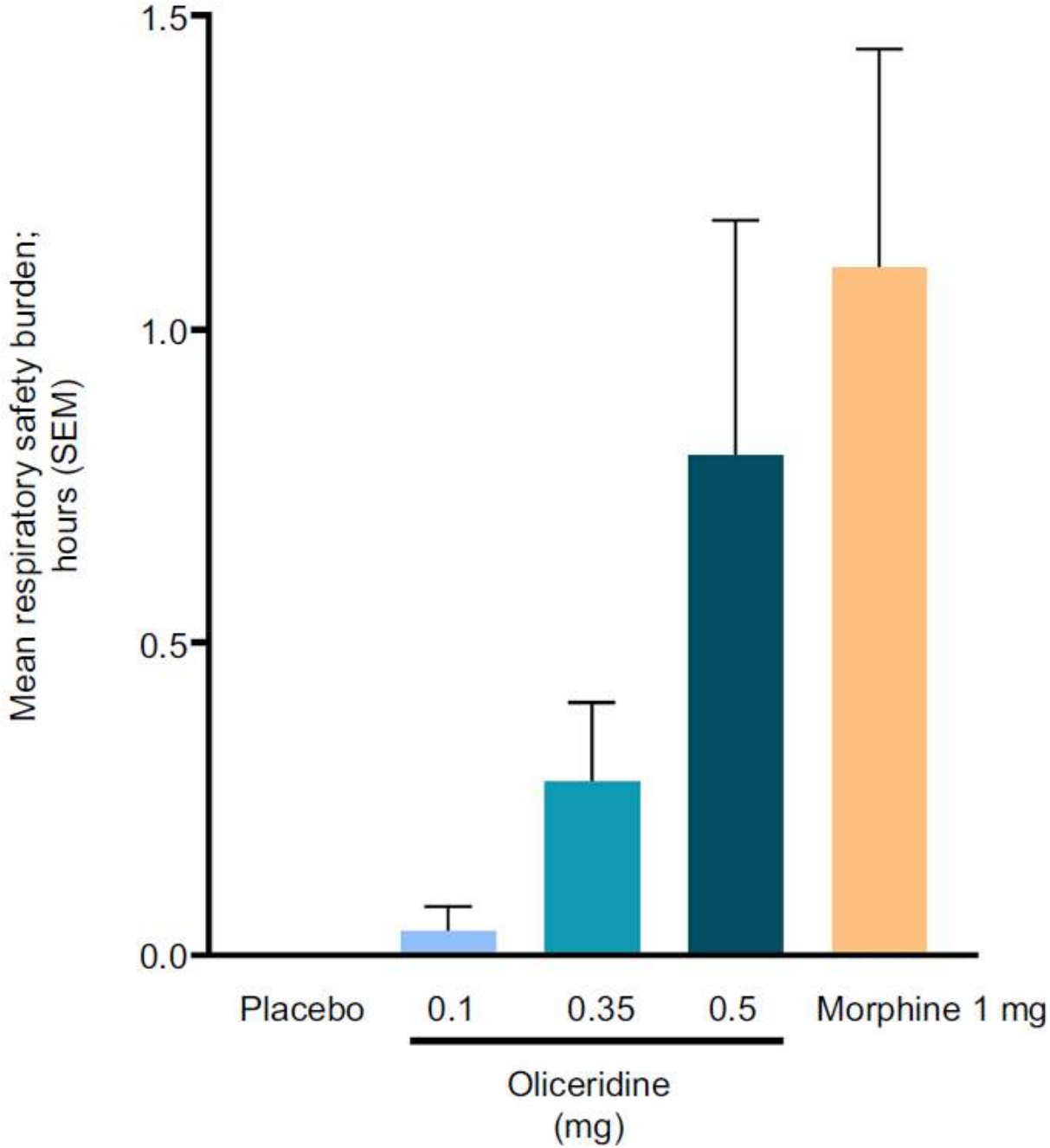
- **Oliceridine**

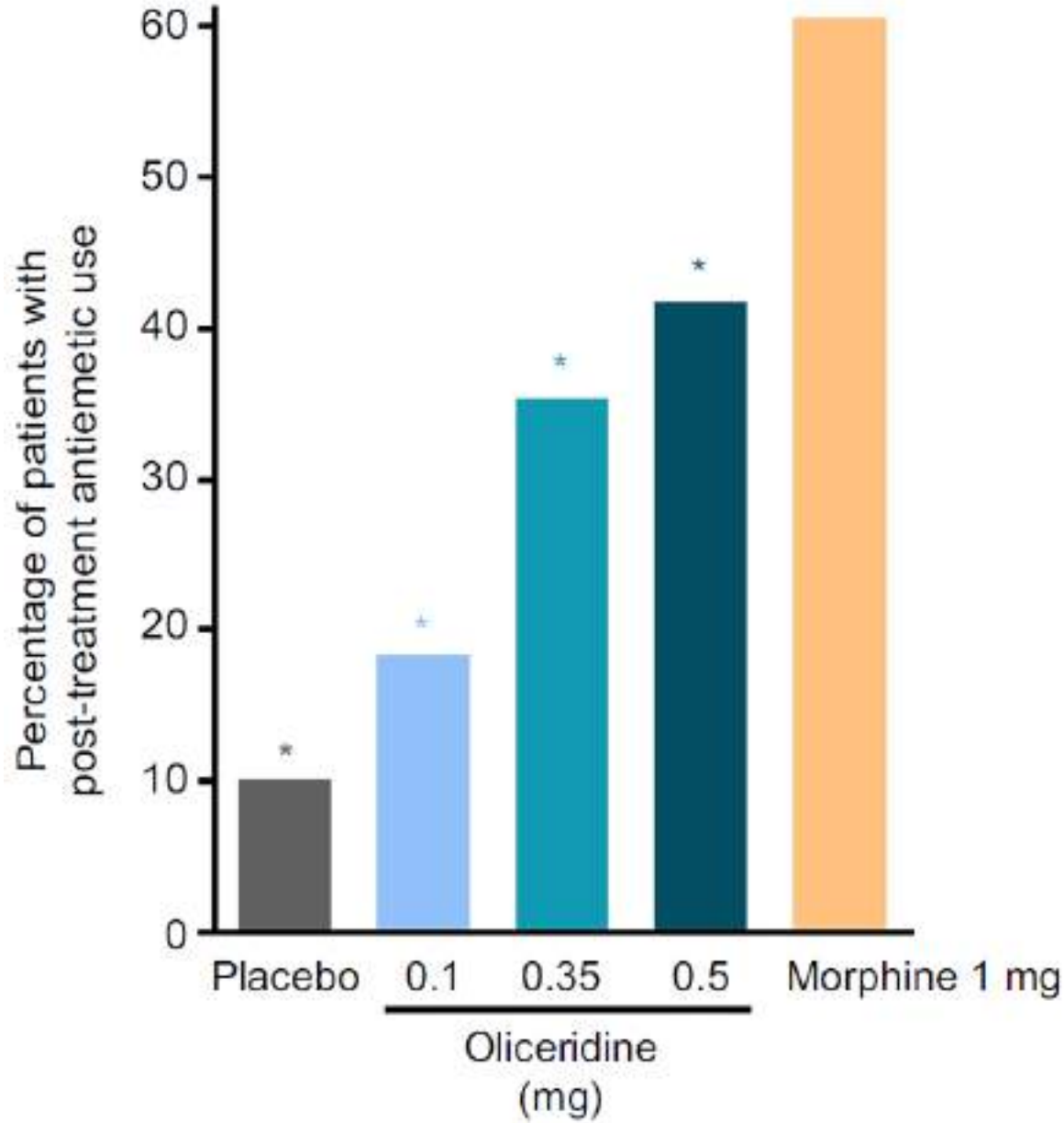



Morphine
μ-opioid receptor
Cell surface
Cell interior
G protein
β-arrestin
Analgesia
↓ Respiration
↓ GI function
TRV130
μ-opioid receptor
G protein
β-arrestin
Increased Analgesia
↓ Respiration
↓ GI function

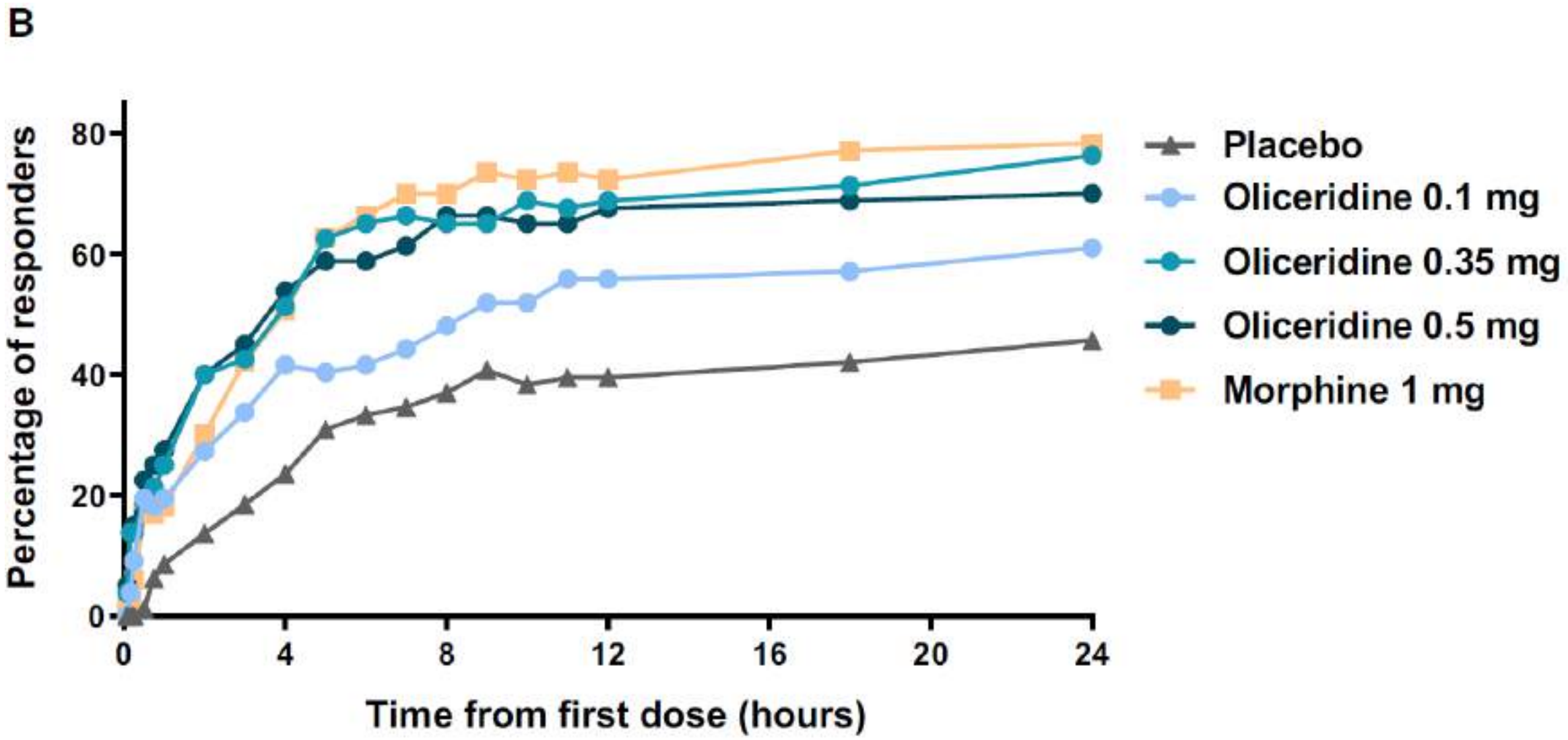
APOLLO-I

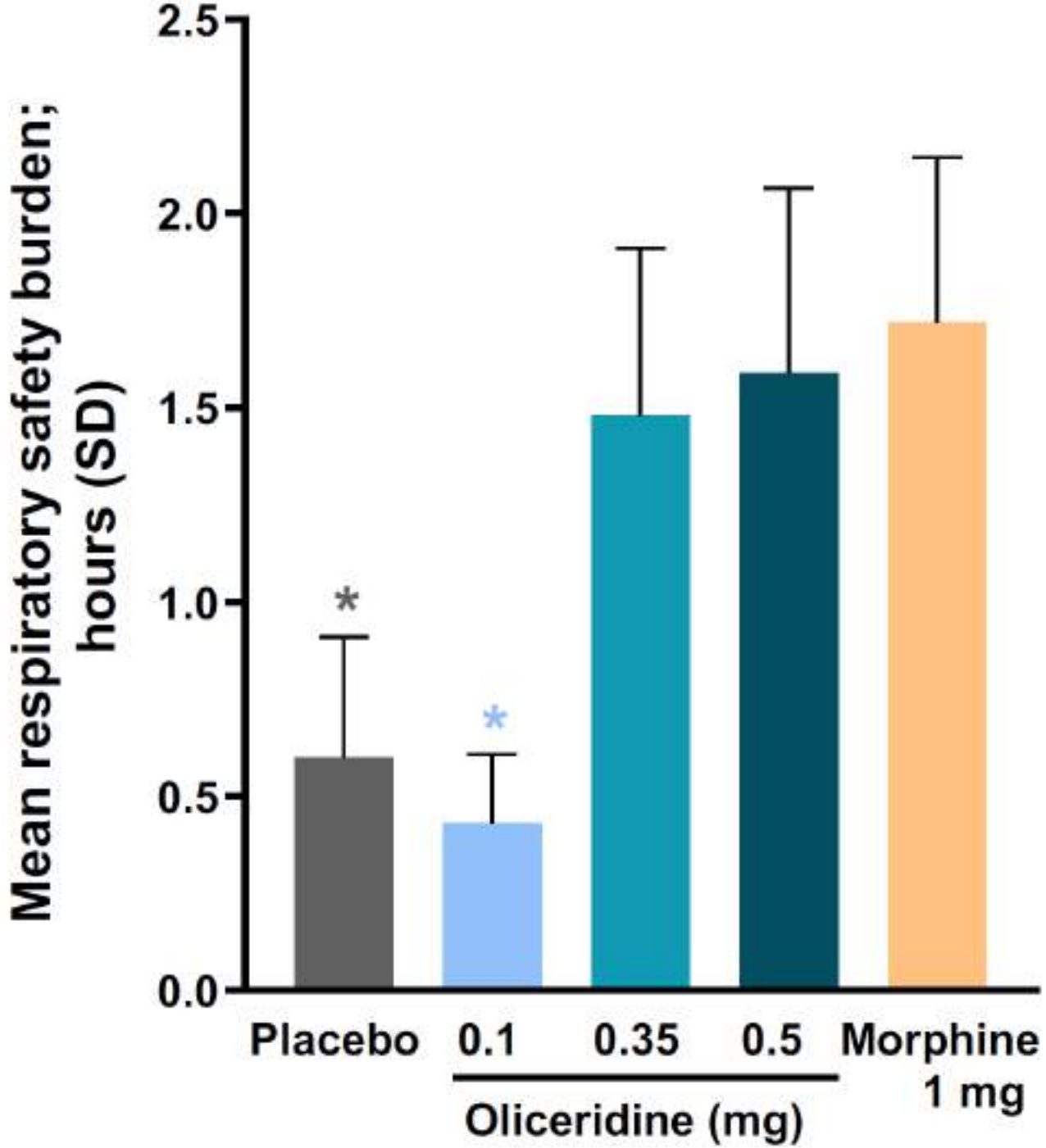

Placebo
Oliceridine 0.5 mg
Oliceridine 0.1 mg
Morphine 1 mg
Oliceridine 0.35 mg
Percentage of responders
0
20
40
60
80
0
4
8
12
16
20
24
28
32
36
40
44
48
Time from first dose (hours)

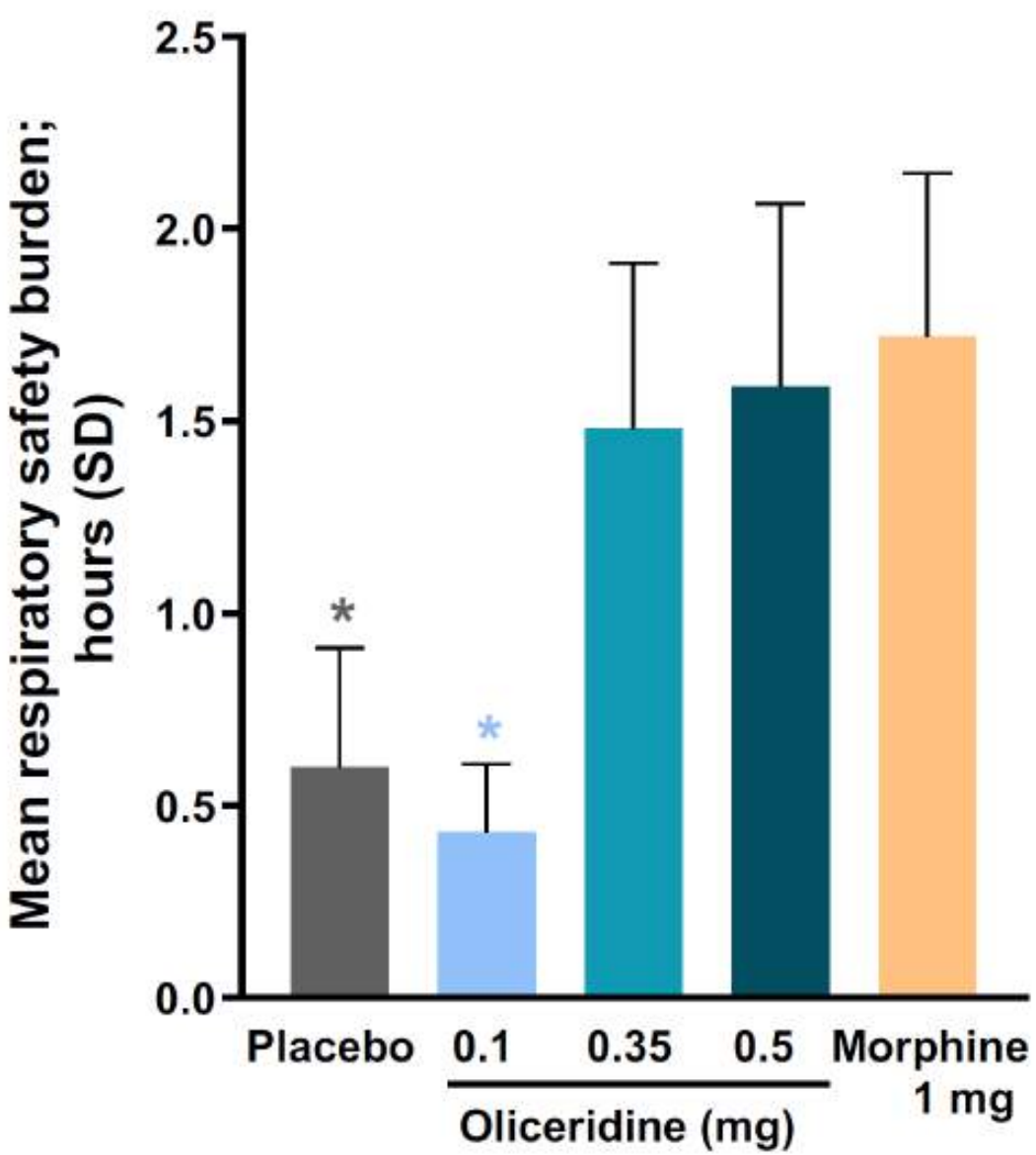

Mean respiratory safety burden; hours (SEM)
1.5
1.0
0.5
0.0
Placebo
0.1
0.35
0.5
Morphine 1 mg
Oliceridine (mg)

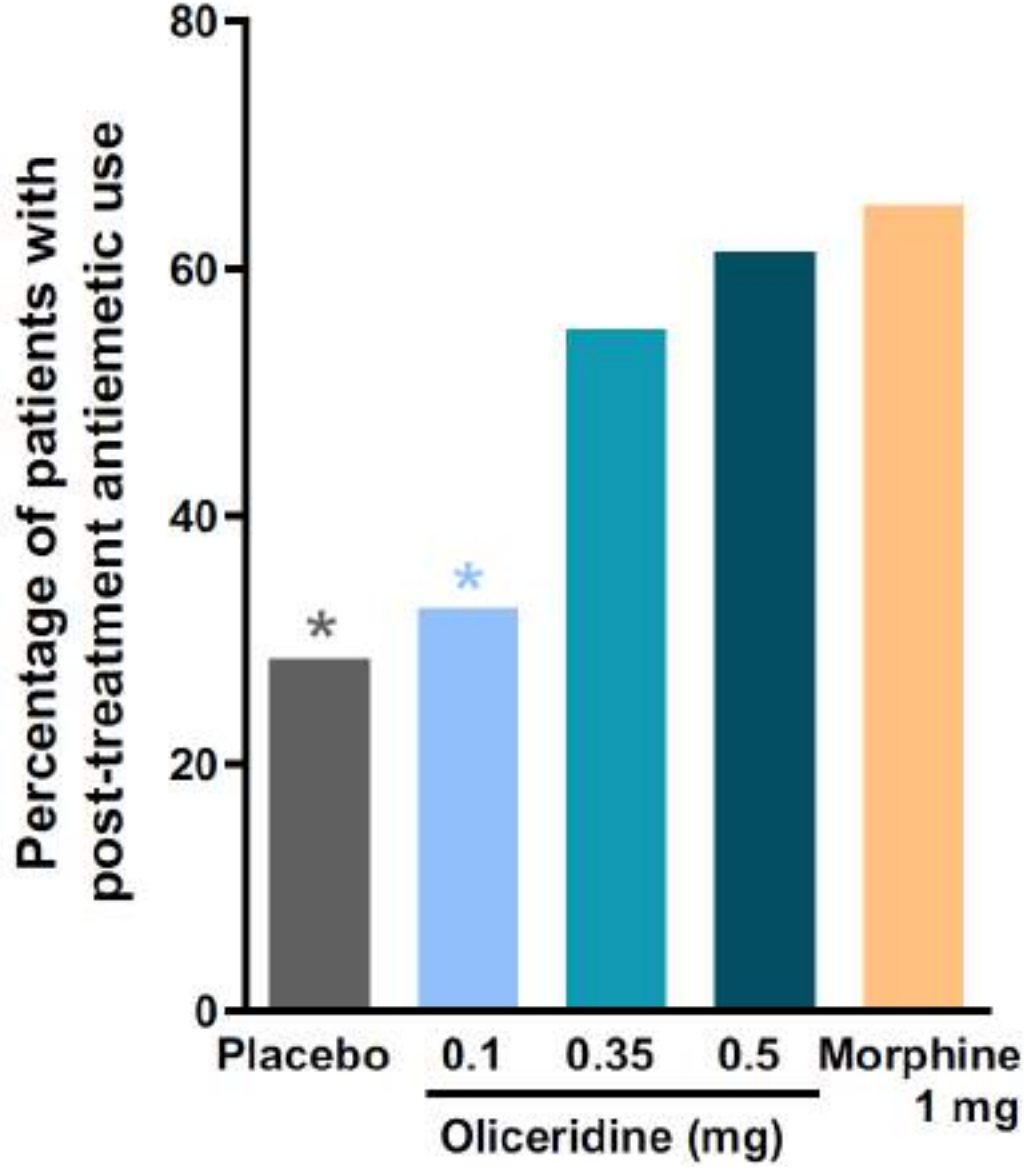

Percentage of patients with post-treatment antiemetic use
60
50
40
30
20
10
0
*
*
*
*
Placebo
0.1
0.35
0.5
Morphine 1 mg
Oliceridine (mg)

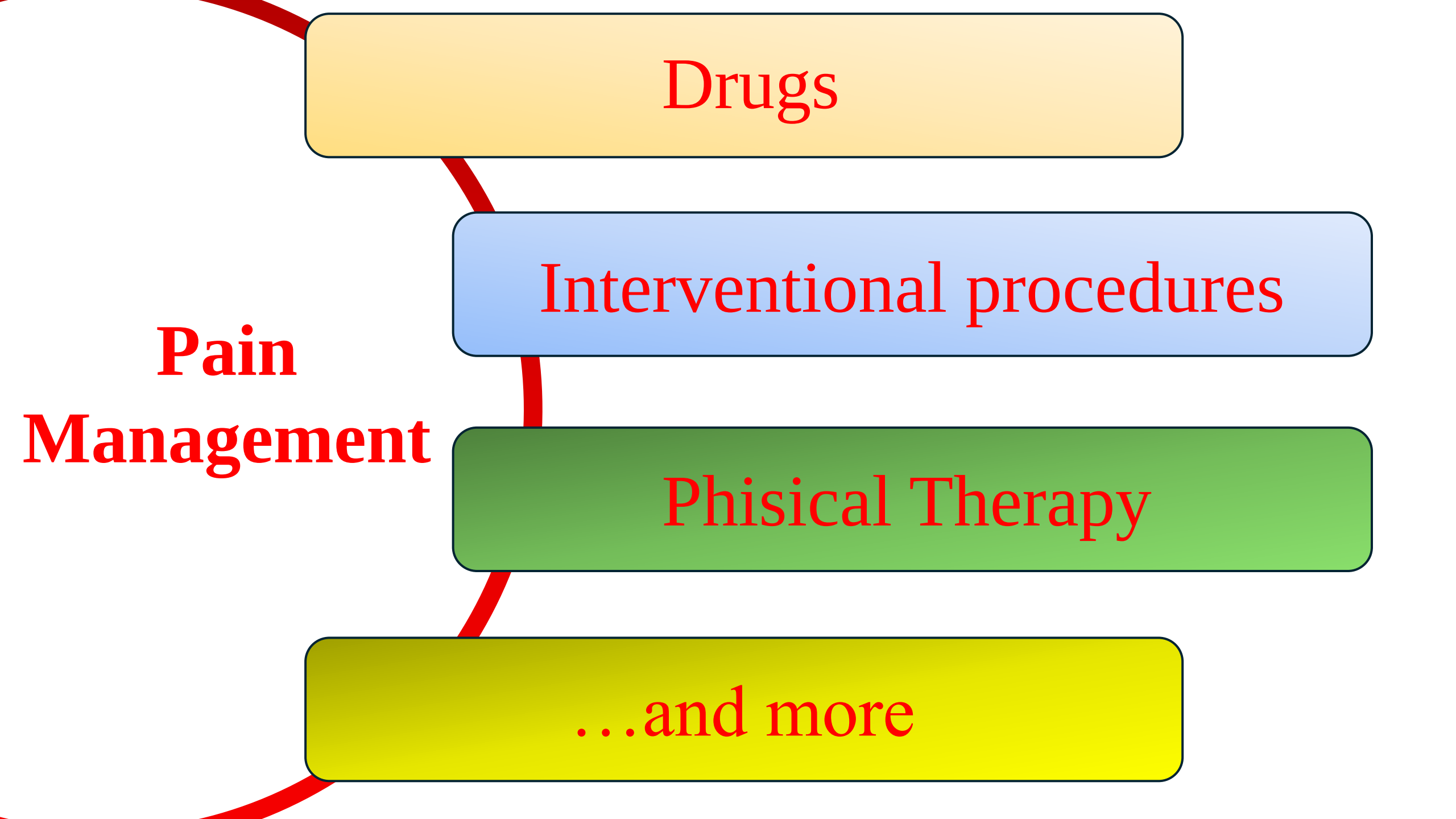
APOLLO-2


B
Percentage of responders
80
60
40
20
0
0
4
8
12
16
20
24
Time from first dose (hours)
Placebo
Oliceridine 0.1 mg
Oliceridine 0.35 mg
Oliceridine 0.5 mg
Morphine 1 mg


Mean respiratory safety burden; hours (SD)
2.5
2.0
1.5
1.0
0.5
0.0
*
*
Placebo
0.1
0.35
0.5
Morphine 1 mg
Oliceridine (mg)

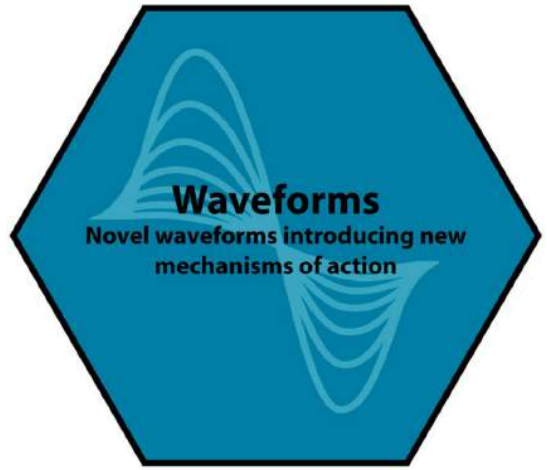

Mean respiratory safety burden; hours (SD)
2.5
2.0
1.5
1.0
0.5
0.0
*
*
Placebo
0.1
0.35
0.5
Morphine 1 mg
Oliceridine (mg)

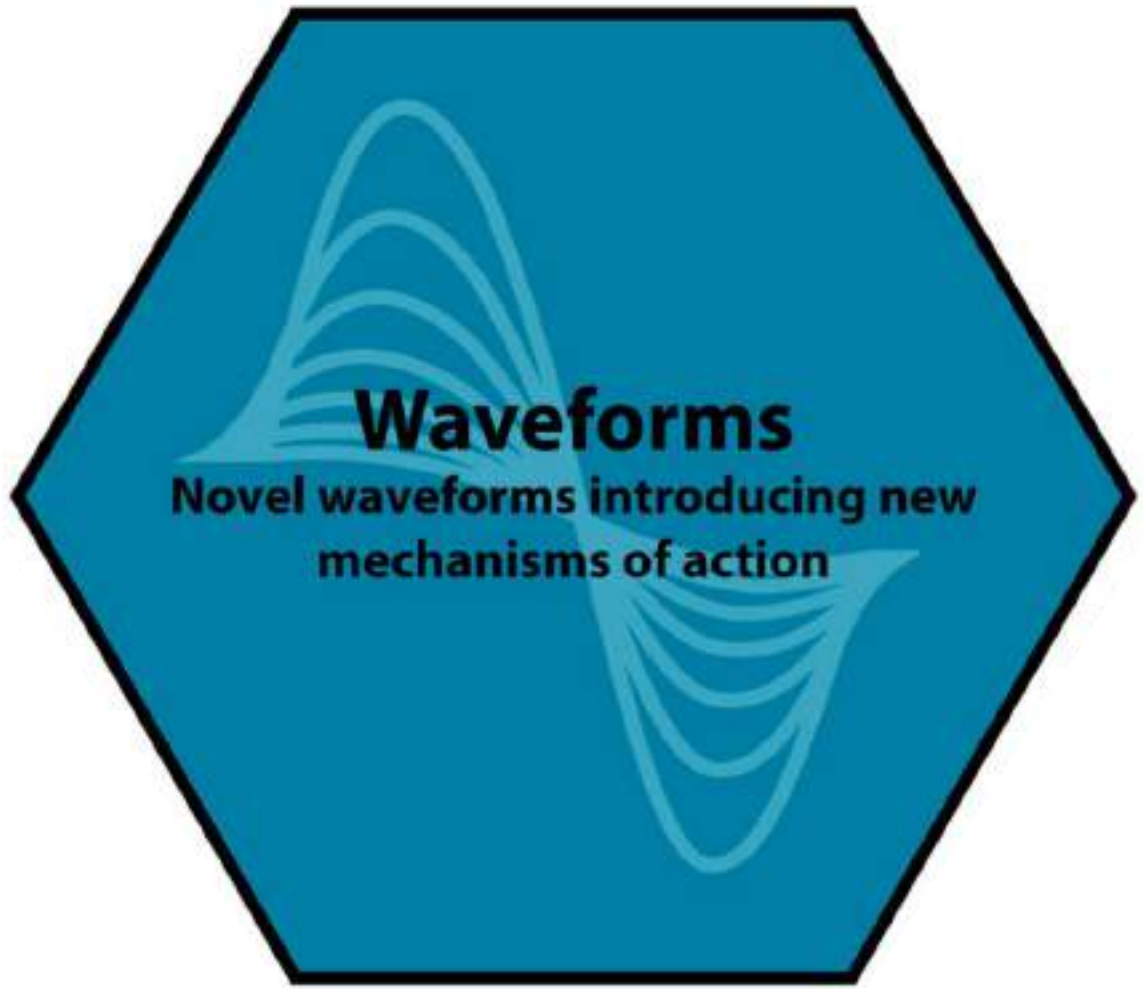

Percentage of patients with post-treatment antiemetic use
80
60
40
20
0
*
*
Placebo
0.1
0.35
0.5
Morphine 1 mg
Oliceridine (mg)


Pain Management
Drugs
Interventional procedures
Phisical Therapy
…and more

Interventional procedures

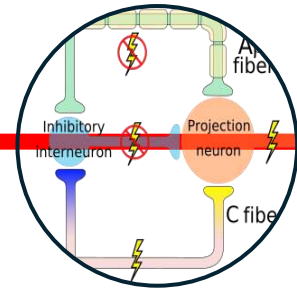

Waveforms
Novel waveforms introducing new mechanisms of action
Neurorestorative Devices
Functional electrical stimulation (FES) to improve function after spinal cord injury
Artificial Skins
Advancements in polymer and circuit technology towards the development of wearable electrodes
Advances in Spinal Cord Stimulation
Closed Loop Systems
Integration of evoked compound actional potentials (ECAP) to effectively modulation neurostimulation
Implantable Electrodes
Advancements in material science leading to safe and inert implanted electrodes
Injectable Electrodes
Development of novel injectable electrodes to reach more anatomical targets


Waveforms
Novel waveforms introducing new mechanisms of action


Waveforms
Novel waveforms introducing new mechanisms of action

Timeline of advances in spinal cord stimulation

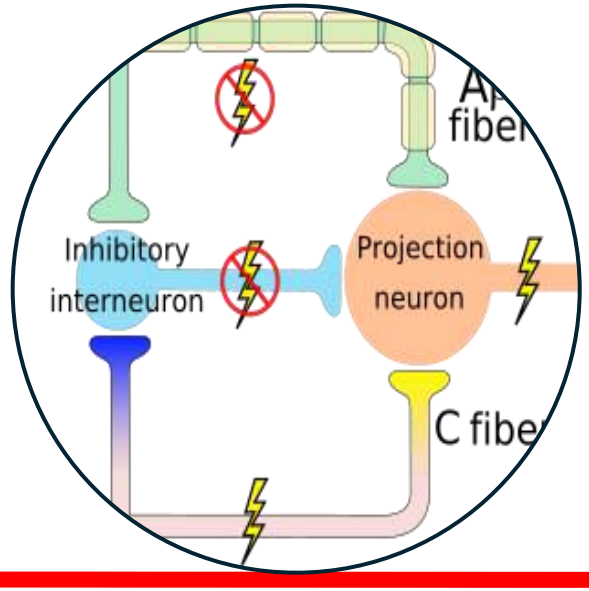
46 A.D.

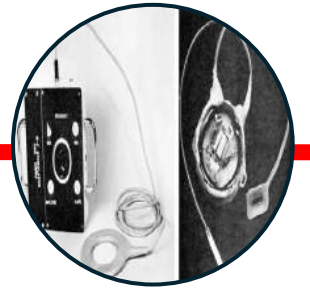


Roman use of torpedo fish for gout.

Timeline of advances in spinal cord stimulation

1965

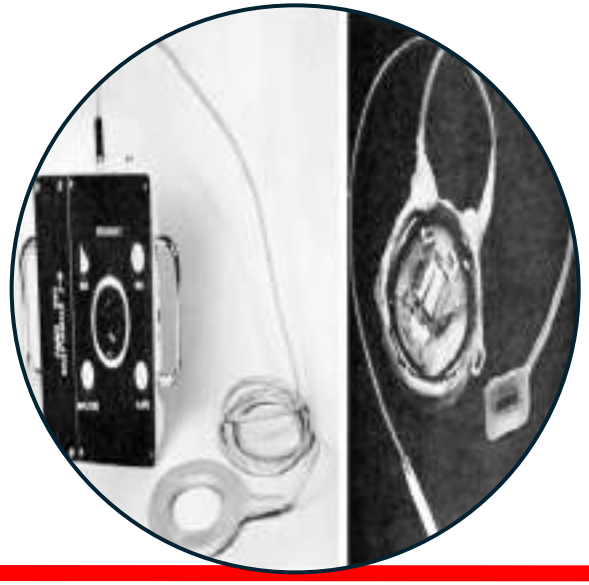


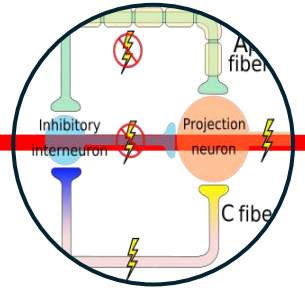


Gate Control Theory.

Timeline of advances in spinal cord stimulation

1967

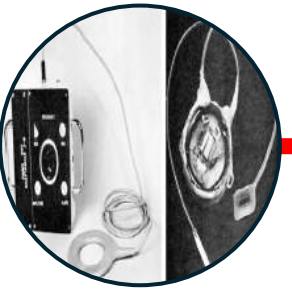




Dr. Norman Shealy: first spinal cord stimulator in human

Timeline of advances in spinal cord stimulation

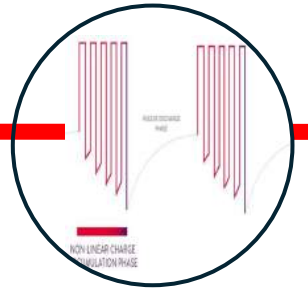
1968



First spinal cord stimulator
commercially available

Timeline of advances in spinal cord stimulation

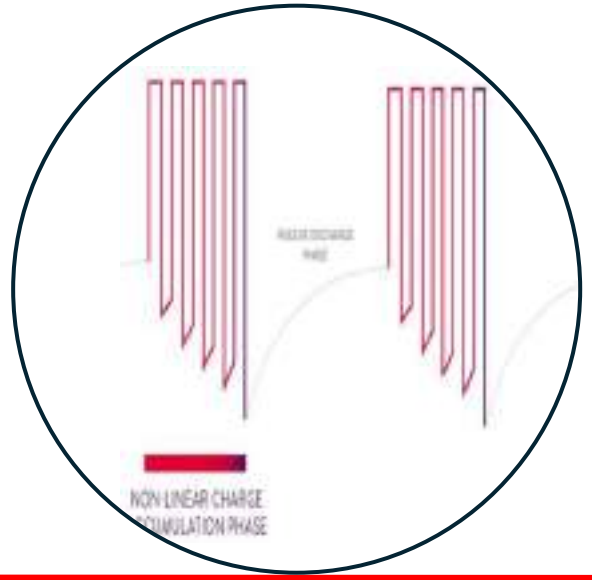
1981

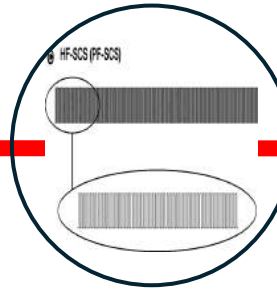


First fully implantable
spinal cord stimulator

Timeline of advances in spinal cord stimulation

2004

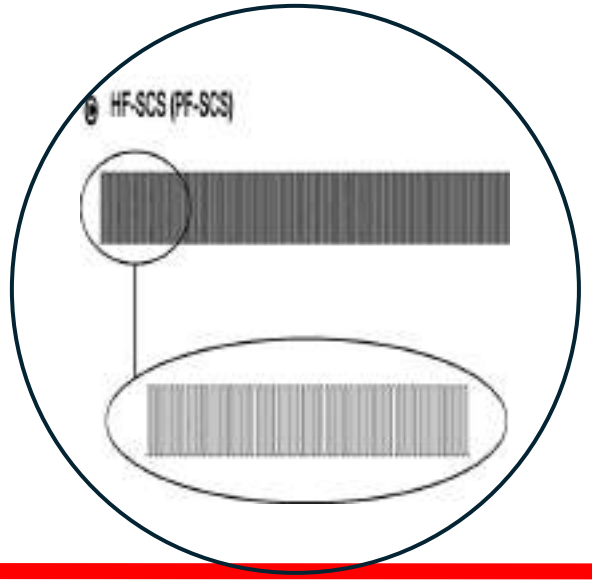


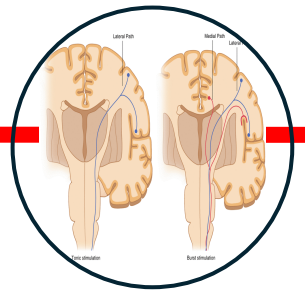


Burst spinal cord stimulation pioneered by Dr De Ridder

Timeline of advances in spinal cord stimulation

2015

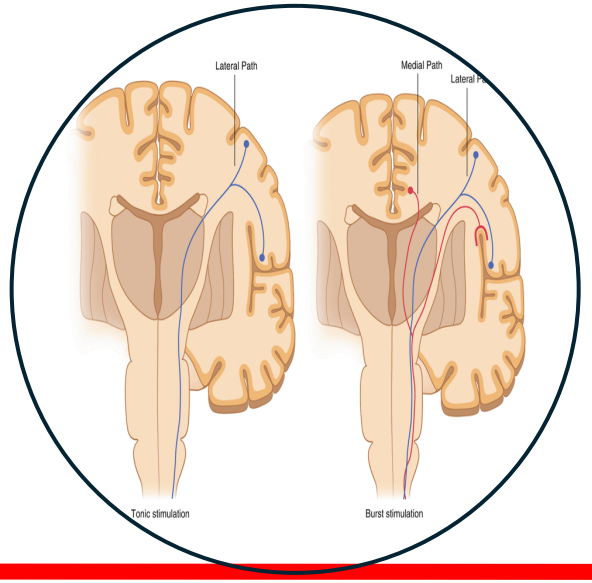


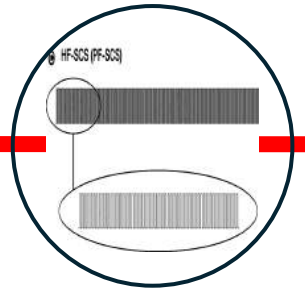


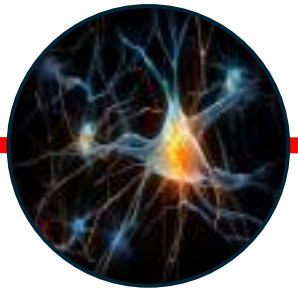
High frequency approved
by FDA

Timeline of advances in spinal cord stimulation

2015



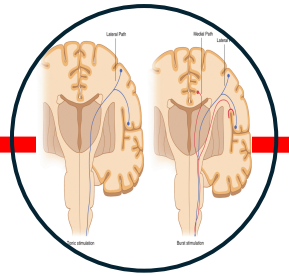




Burst approved by FDA

Timeline of advances in spinal cord stimulation

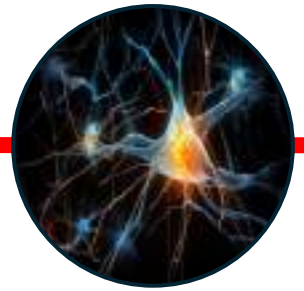
2020



Differential target multiplexed available in US

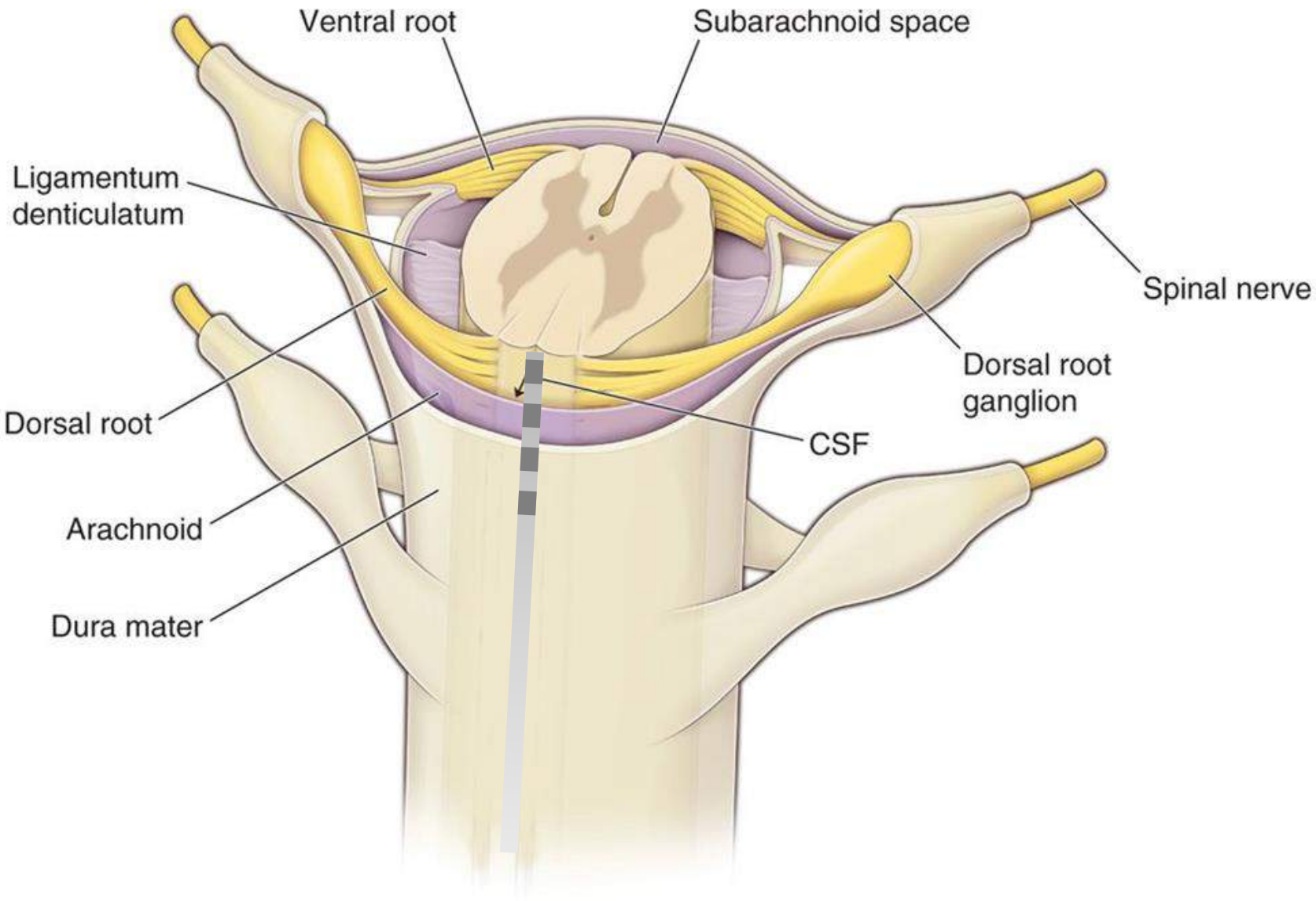
Timeline of advances in spinal cord stimulation

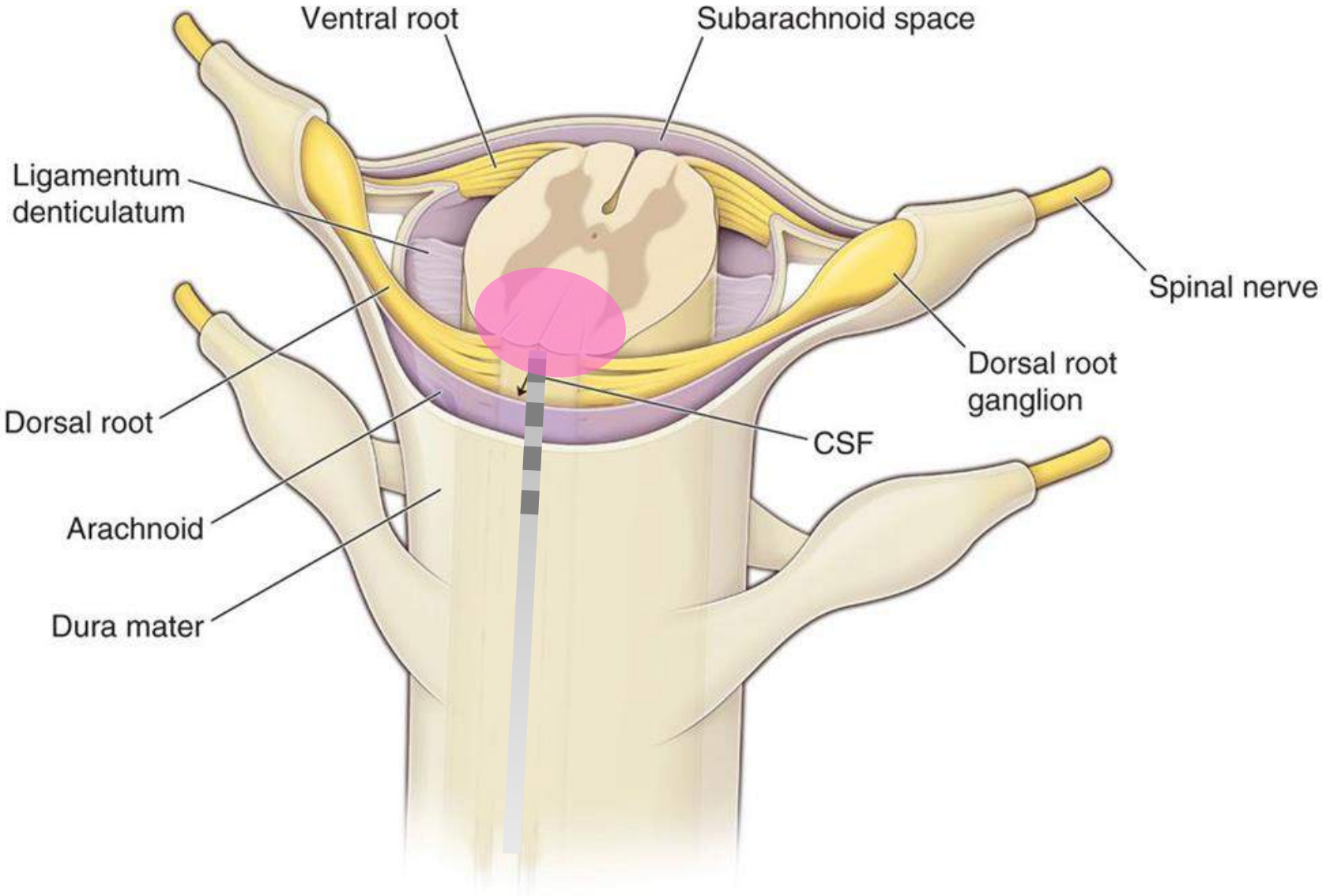
2022

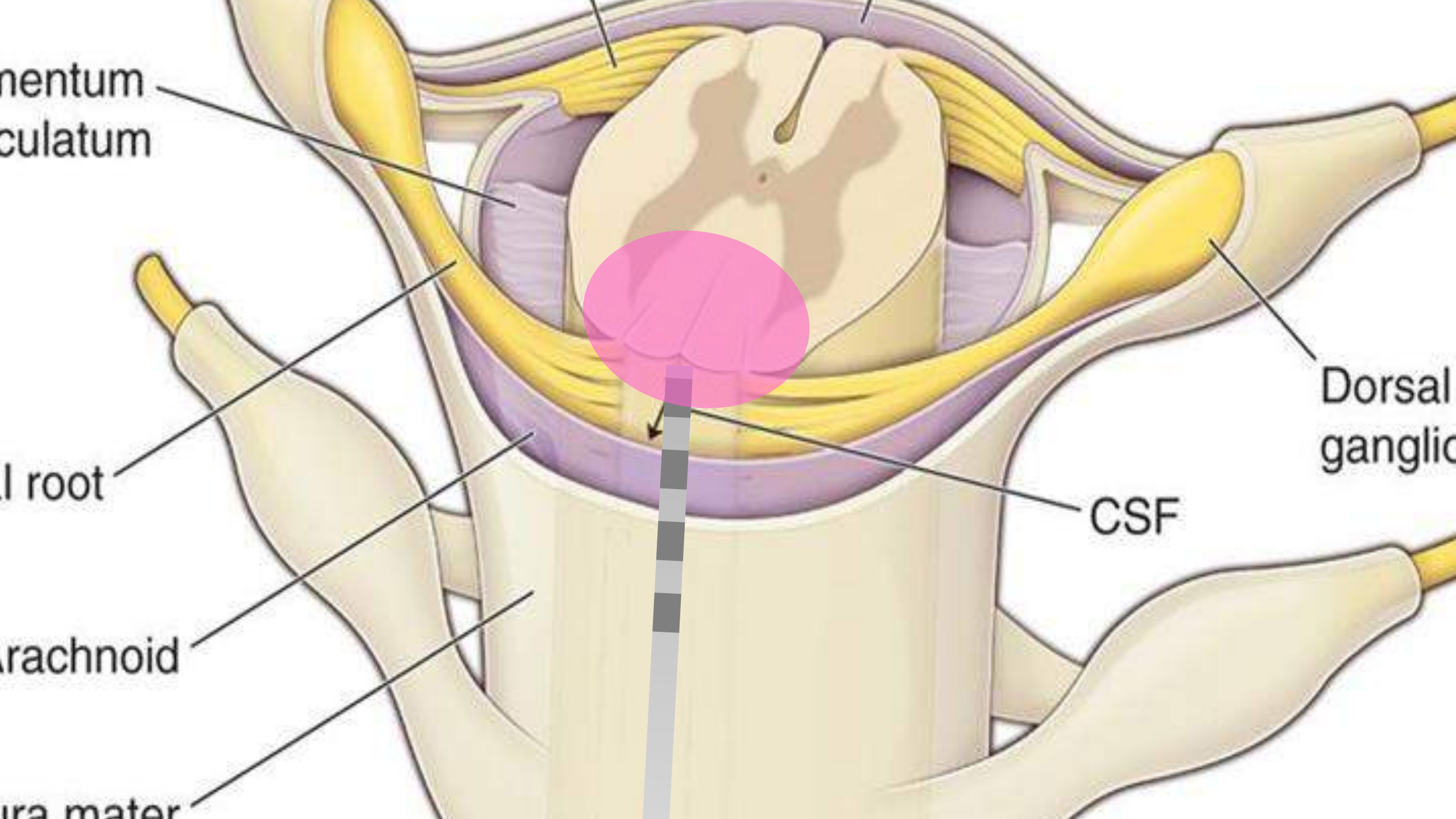


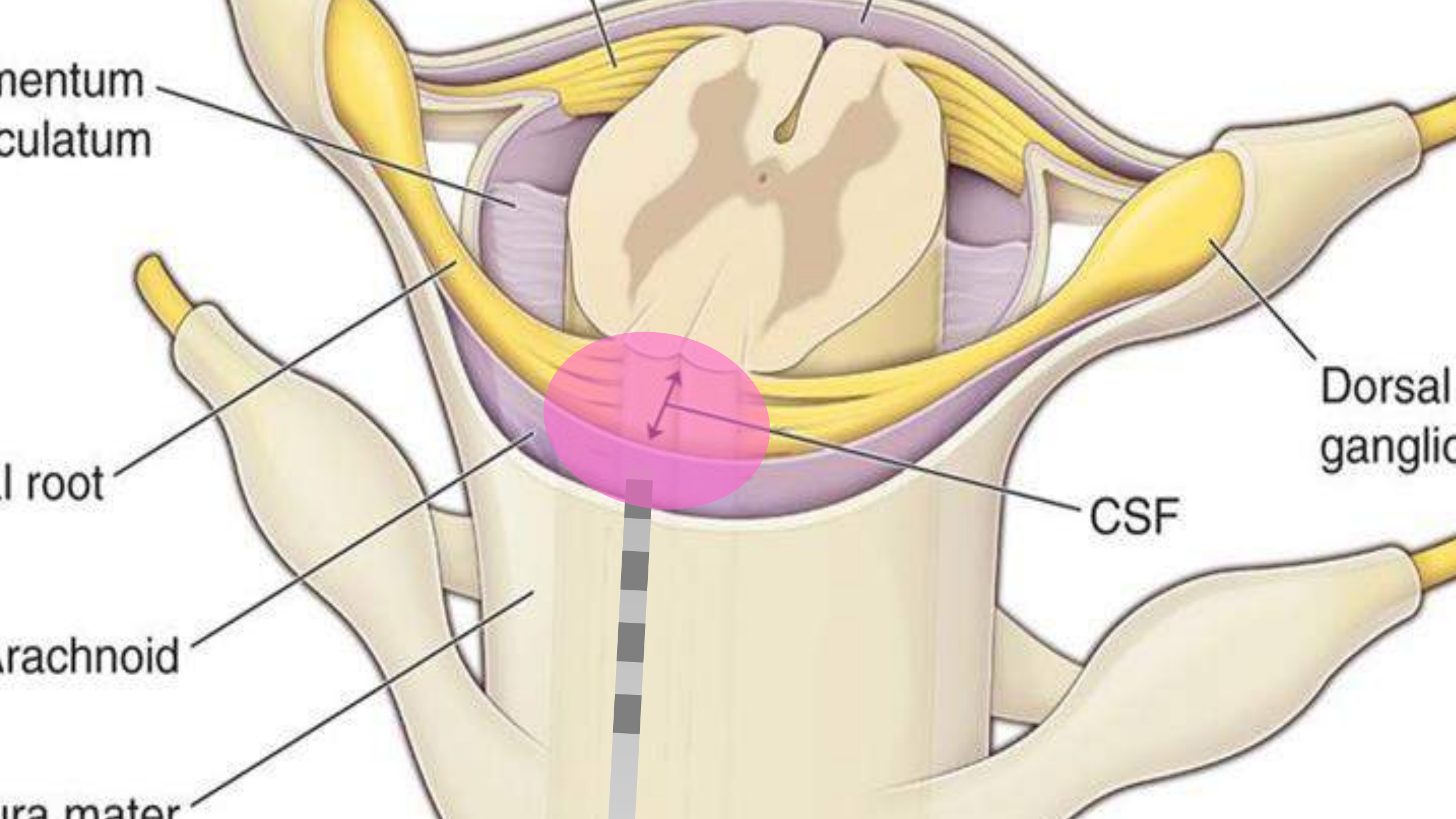
Closed loop approved
by FDA

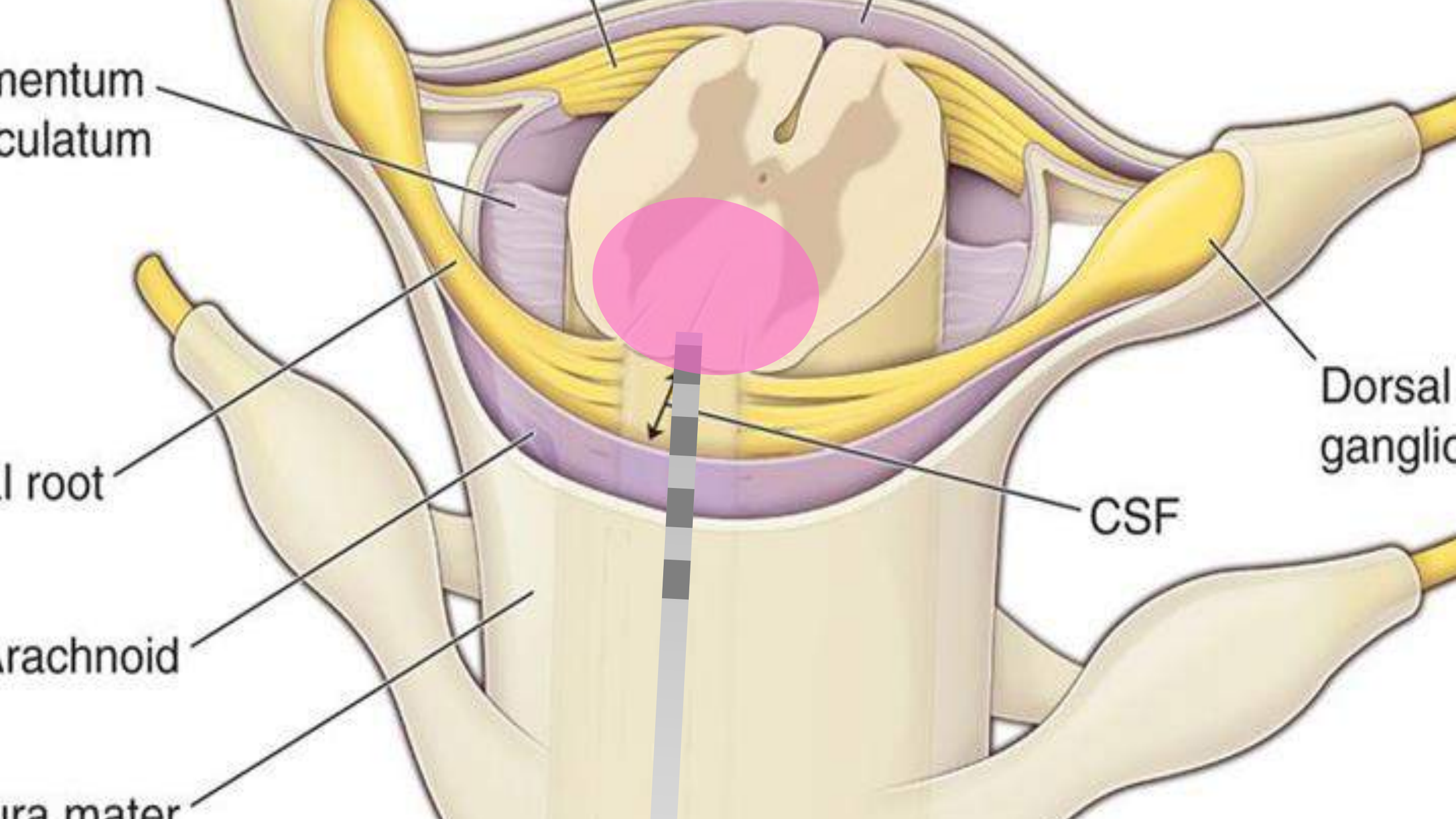
Stimulation

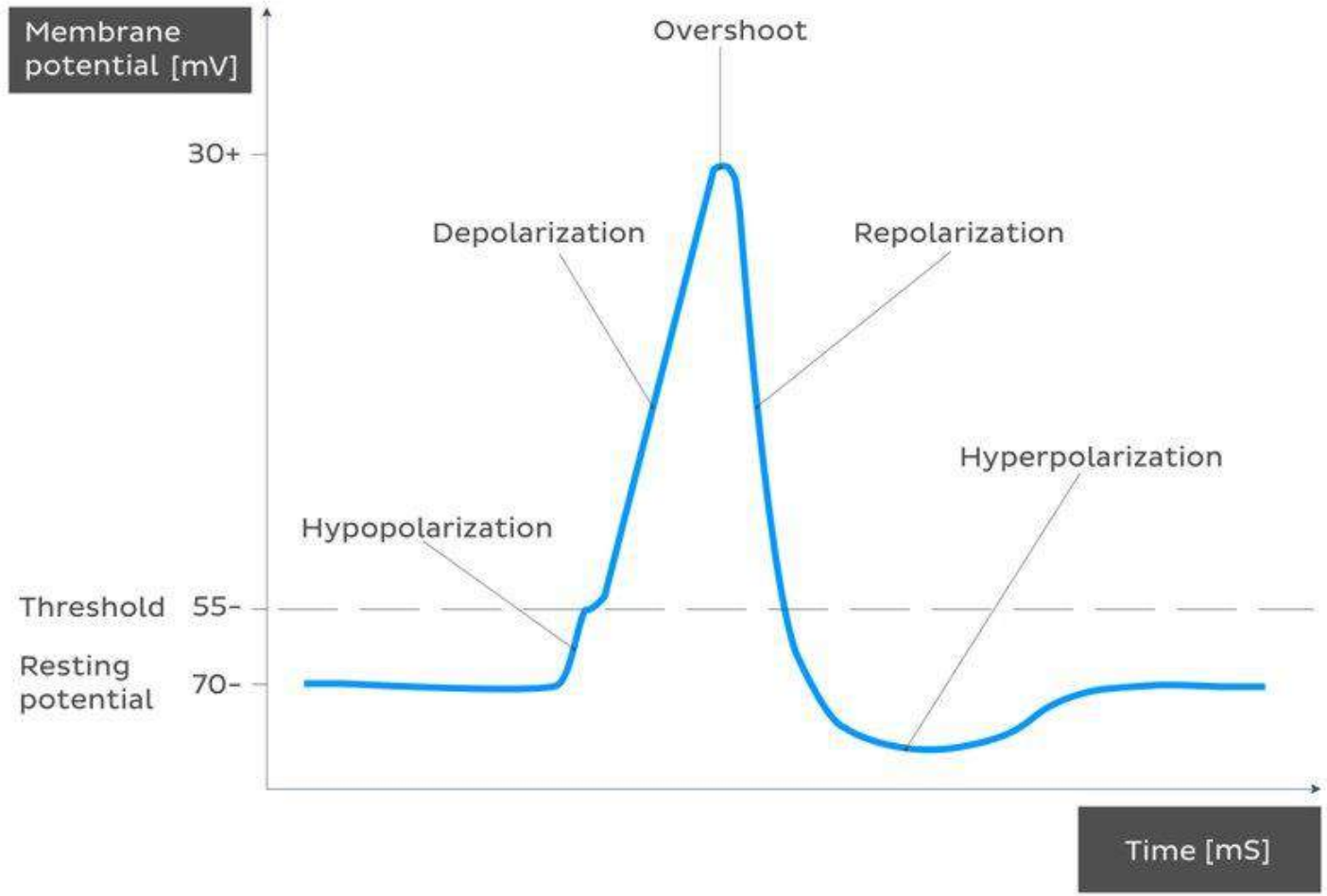



Ventral root
Subarachnoid space
Ligamentum denticulatum
Spinal nerve
Dorsal root ganglion
Dorsal root
CSF
Arachnoid
Dura mater

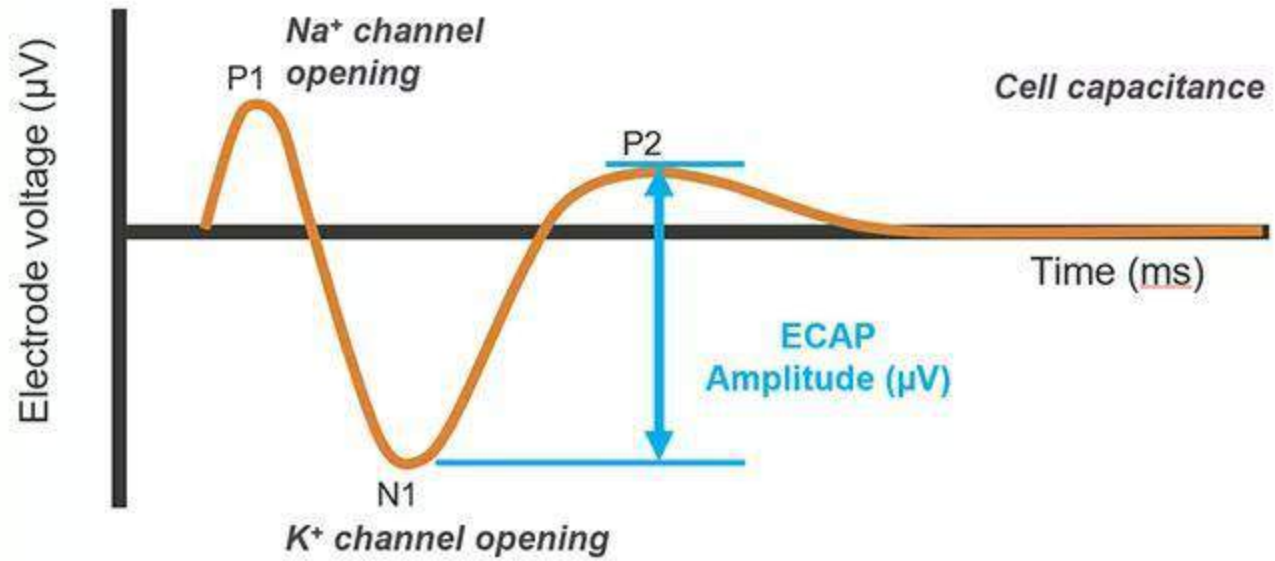

mentum
culatum
l root
rachnoid
ura mater
CSF
Dorsal
ganglio

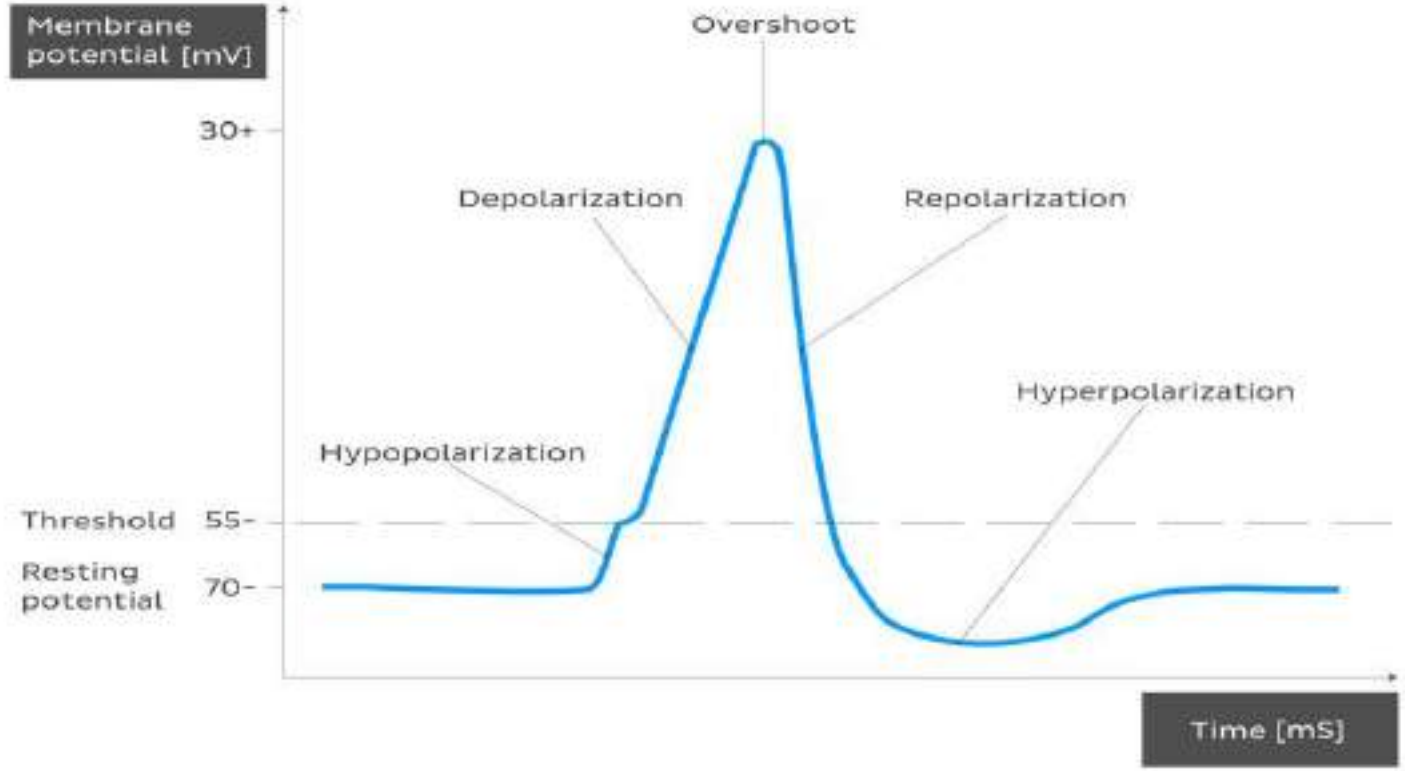

mentum
culatum
l root
Arachnoid
ura mater
CSF
Dorsal
ganglio

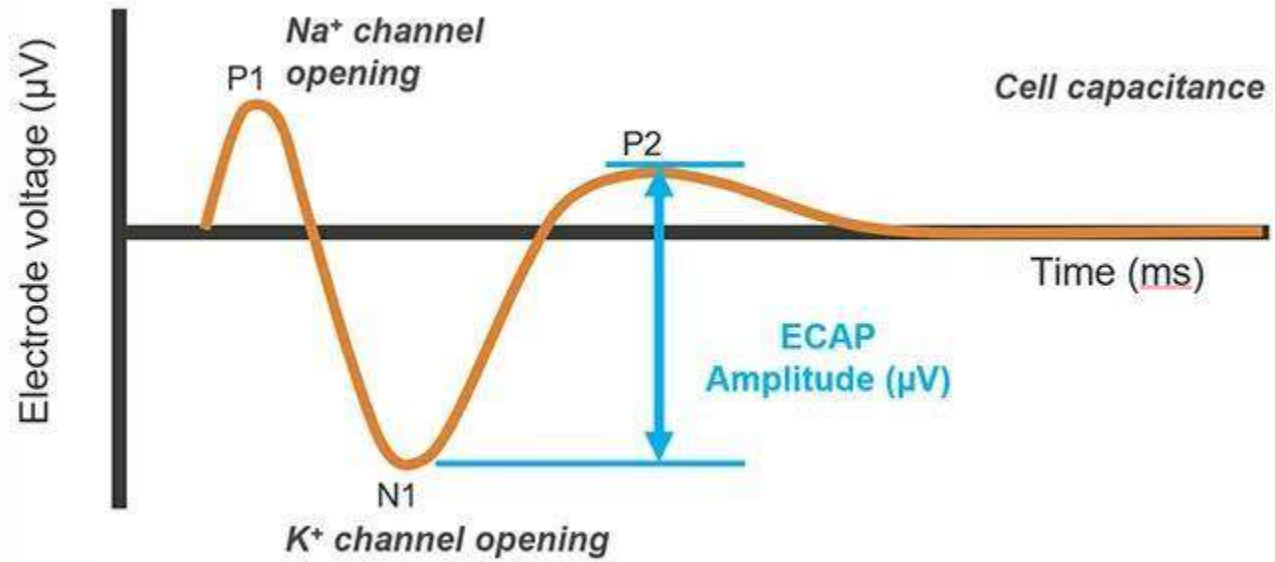

mentum
culatum
l root
Arachnoid
ura mater
CSF
Dorsal
ganglio

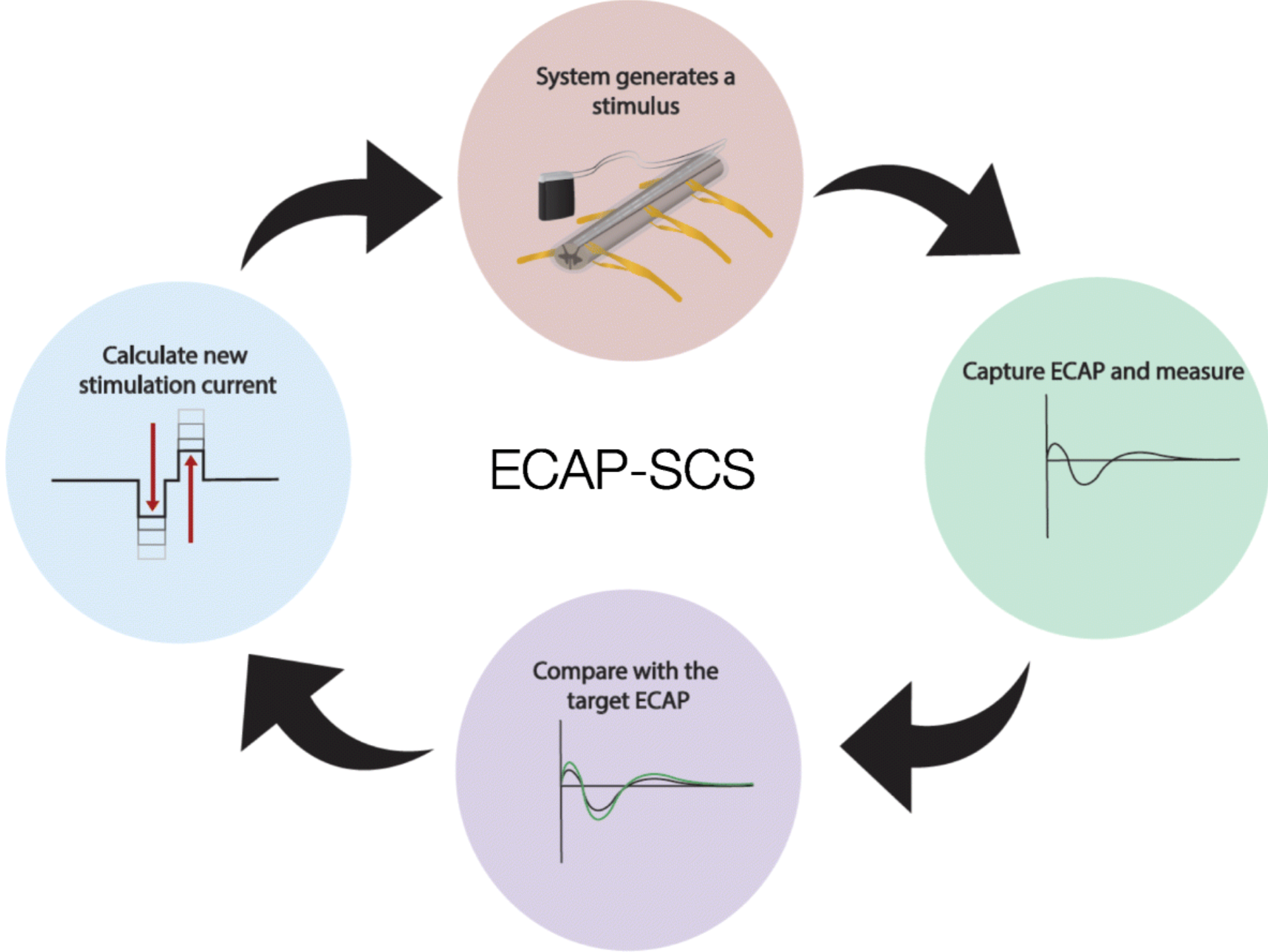

Membrane potential [mV]
30+
Overshoot
Depolarization
Repolarization
Hyperpolarization
Hypopolarization
Threshold
55-
Resting potential
70-
Time [mS]

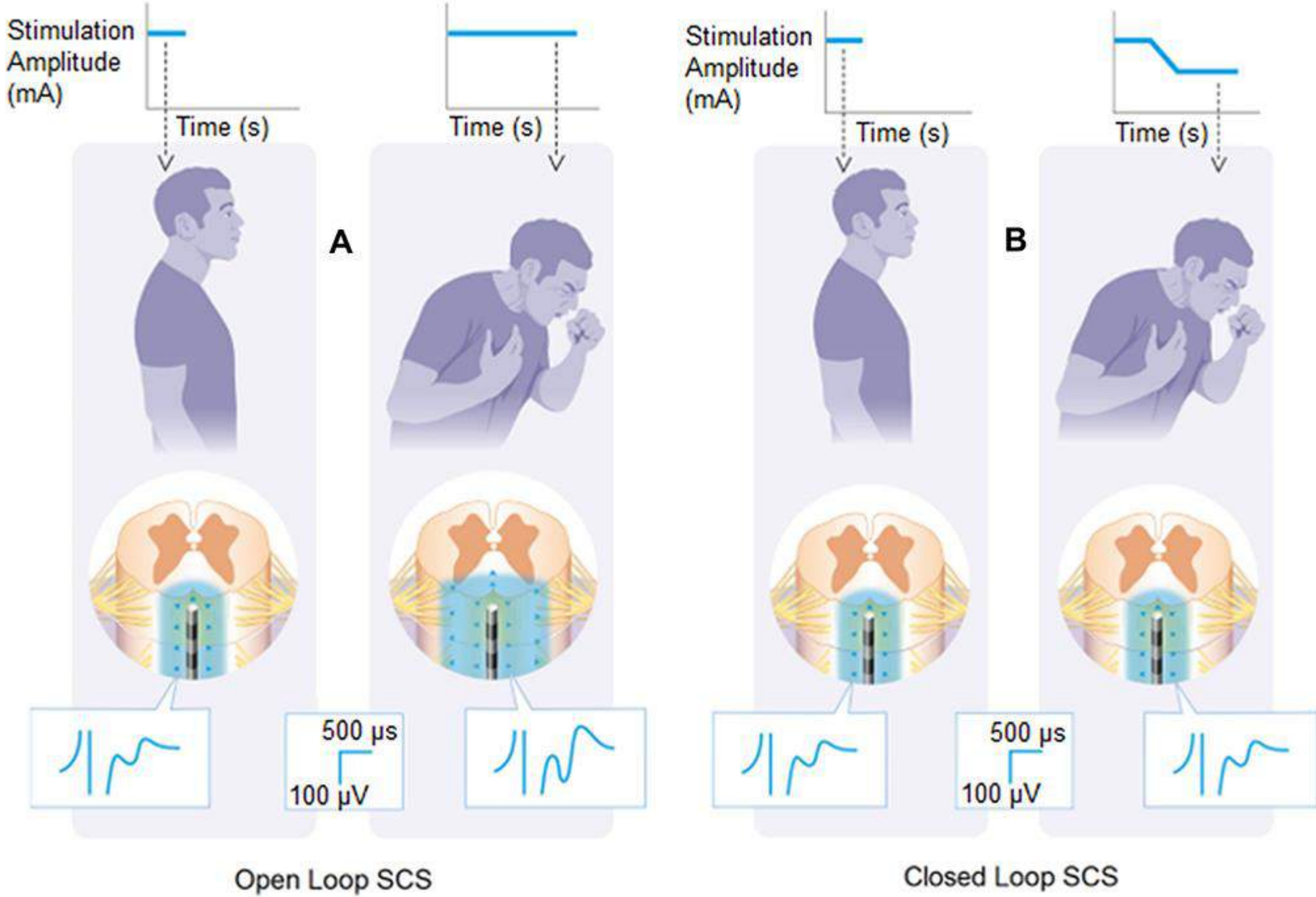
Measuring the ECAP in the Dorsal Column

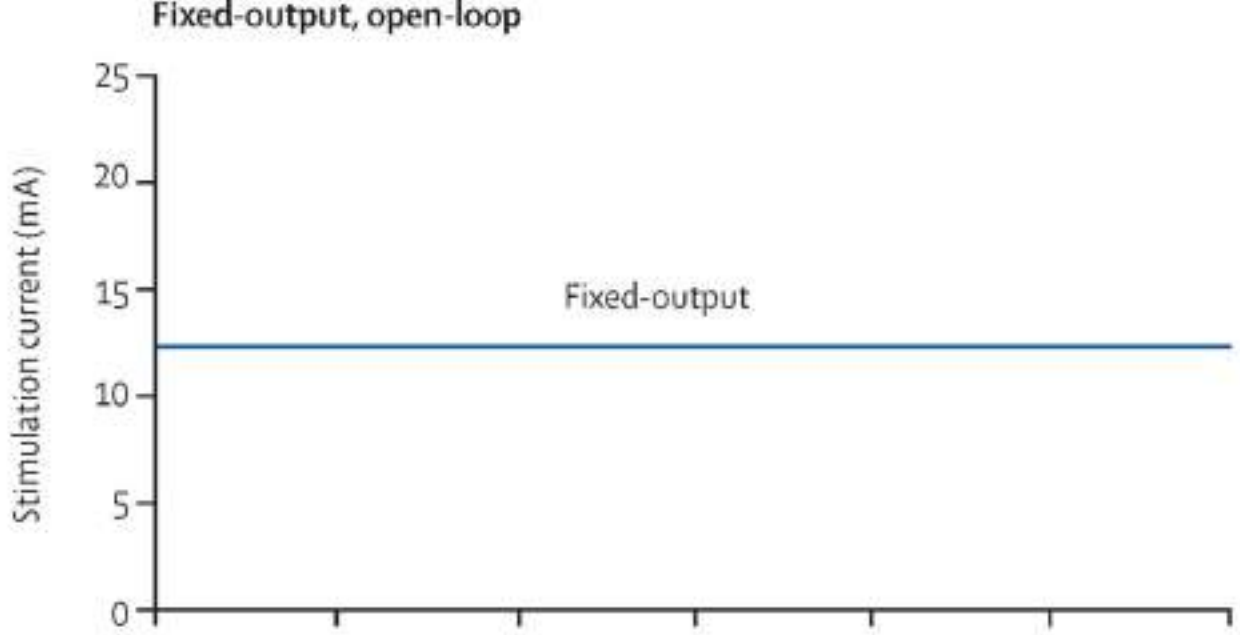


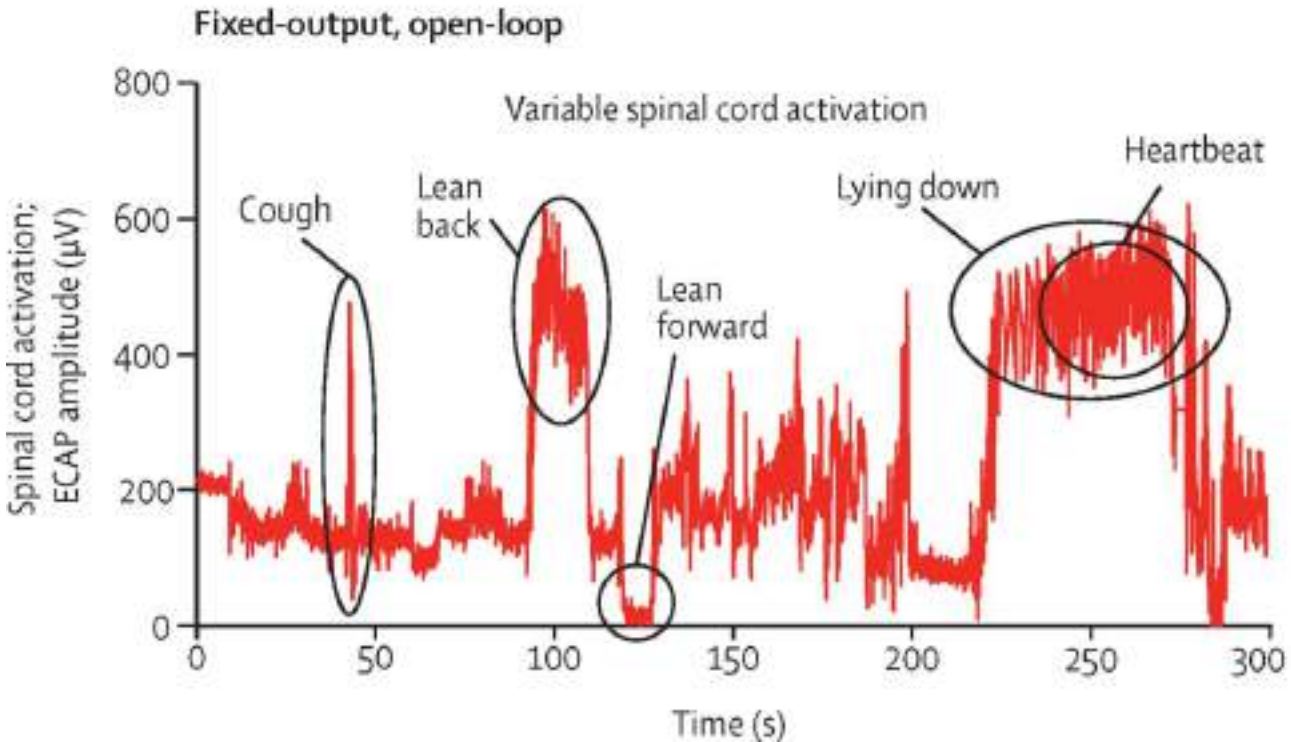

Membrane potential [mV]
30+
Overshoot
Depolarization
Repolarization
Hyperpolarization
Hypopolarization
Threshold
55-
Resting potential
70-
Time [mS]


Electrode voltage (µV)
Na⁺ channel opening
P1
Cell capacitance
P2
Time (ms)
ECAP Amplitude (µV)
N1
K⁺ channel opening


System generates a stimulus
Capture ECAP and measure
Compare with the target ECAP
Calculate new stimulation current
ECAP-SCS


Stimulation Amplitude (mA)
Time (s)
A
Stimulation Amplitude (mA)
Time (s)
B
500 µs
100 µV
500 µs
100 µV
Open Loop SCS
Closed Loop SCS


Fixed-output, open-loop
Stimulation current (mA)
25
20
15
10
5
0
Fixed-output


Fixed-output, open-loop
Spinal cord activation; ECAP amplitude (μV)
800
600
400
200
0
Variable spinal cord activation
Cough
Lean back
Lean forward
Lying down
Heartbeat
0
50
100
150
200
250
300
Time (s)

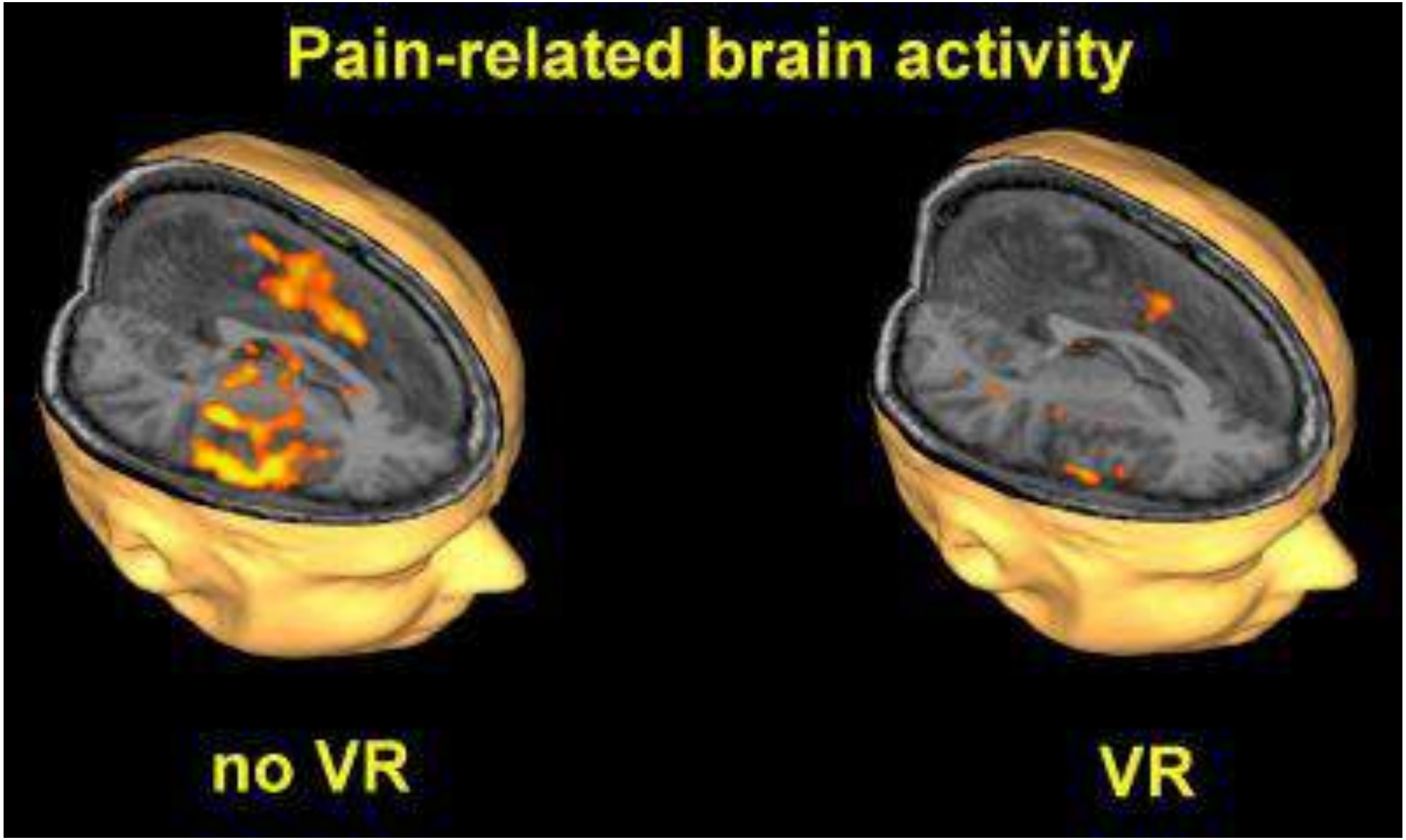

Waveforms
Novel waveforms introducing new mechanisms of action
Neurorestorative Devices
Functional electrical stimulation (FES) to improve function after spinal cord injury
Artificial Skins
Advancements in polymer and circuit technology towards the development of wearable electrodes
Advances in Spinal Cord Stimulation
Closed Loop Systems
Integration of evoked compound actional potentials (ECAP) to effectively modulation neurostimulation
Implantable Electrodes
Advancements in material science leading to safe and inert implanted electrodes
Injectable Electrodes
Development of novel injectable electrodes to reach more anatomical targets


Neurorestorative Devices
Functional electrical stimulation (FES) to
improve function after spinal cord injury


Neurorestorative Devices
Functional electrical stimulation (FES) to
improve function after spinal cord injury

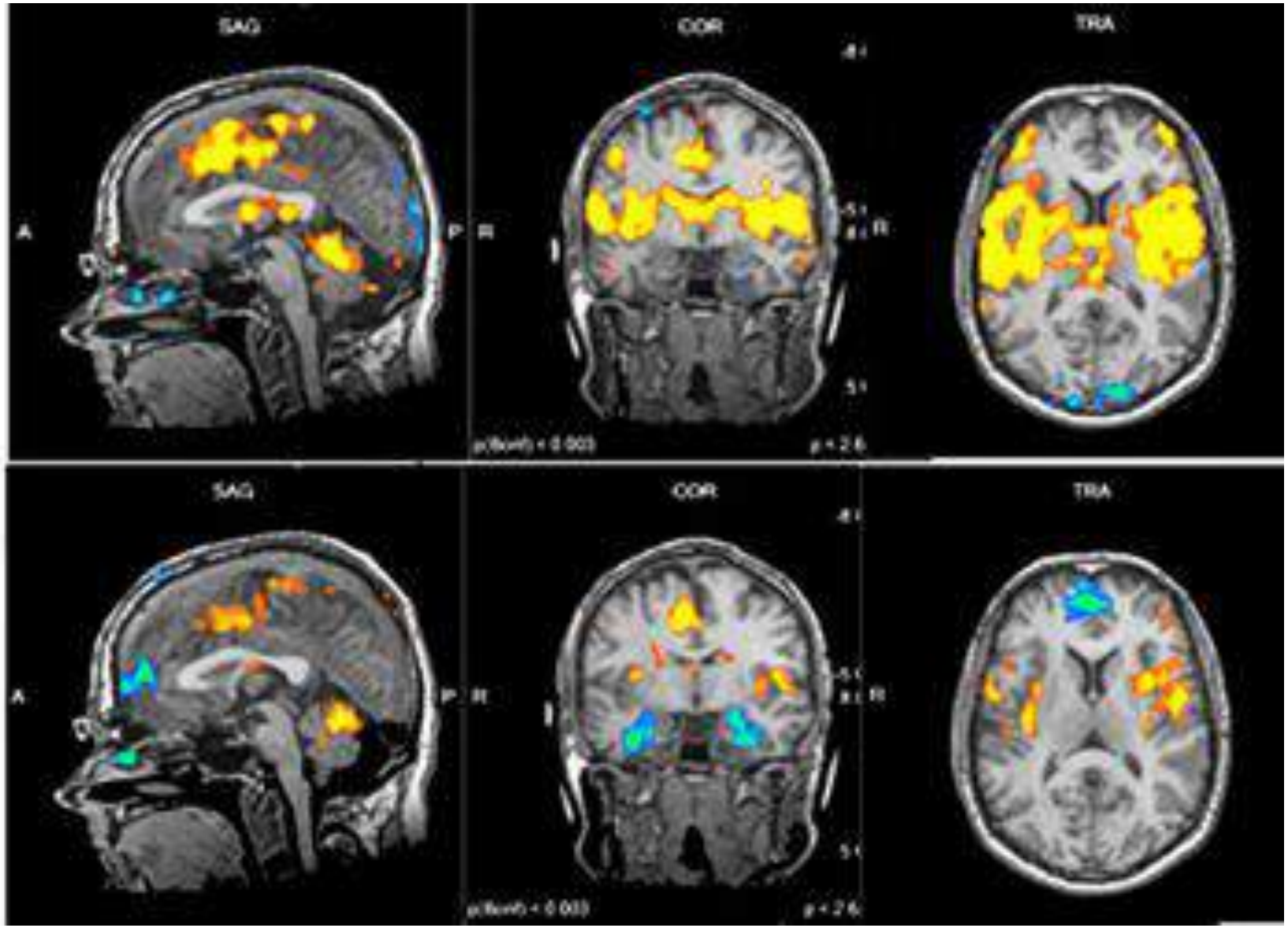
Multifidus fat infiltration

Virtual reality


Pain-related brain activity
no VR
VR

No VR

Yes VR



Virtual Reality and Brain Activity

Less active areas

- Insula (Less Sensory Pain)
- Thalamus (Fewer Pain Signals)
- Anterior Cingulate Cortex (Less Emotional Pain)

More active Areas

- ✓ Perigenual Anterior Cingulate Cortex (positive coping and resilience)
- ✓ Frontal Cortex (Cognitive Processing)


Grazie