Tertulias tecnológicas con los amigos del profesor Ramón Salazar

TRATAMIENTO DEL DOLOR

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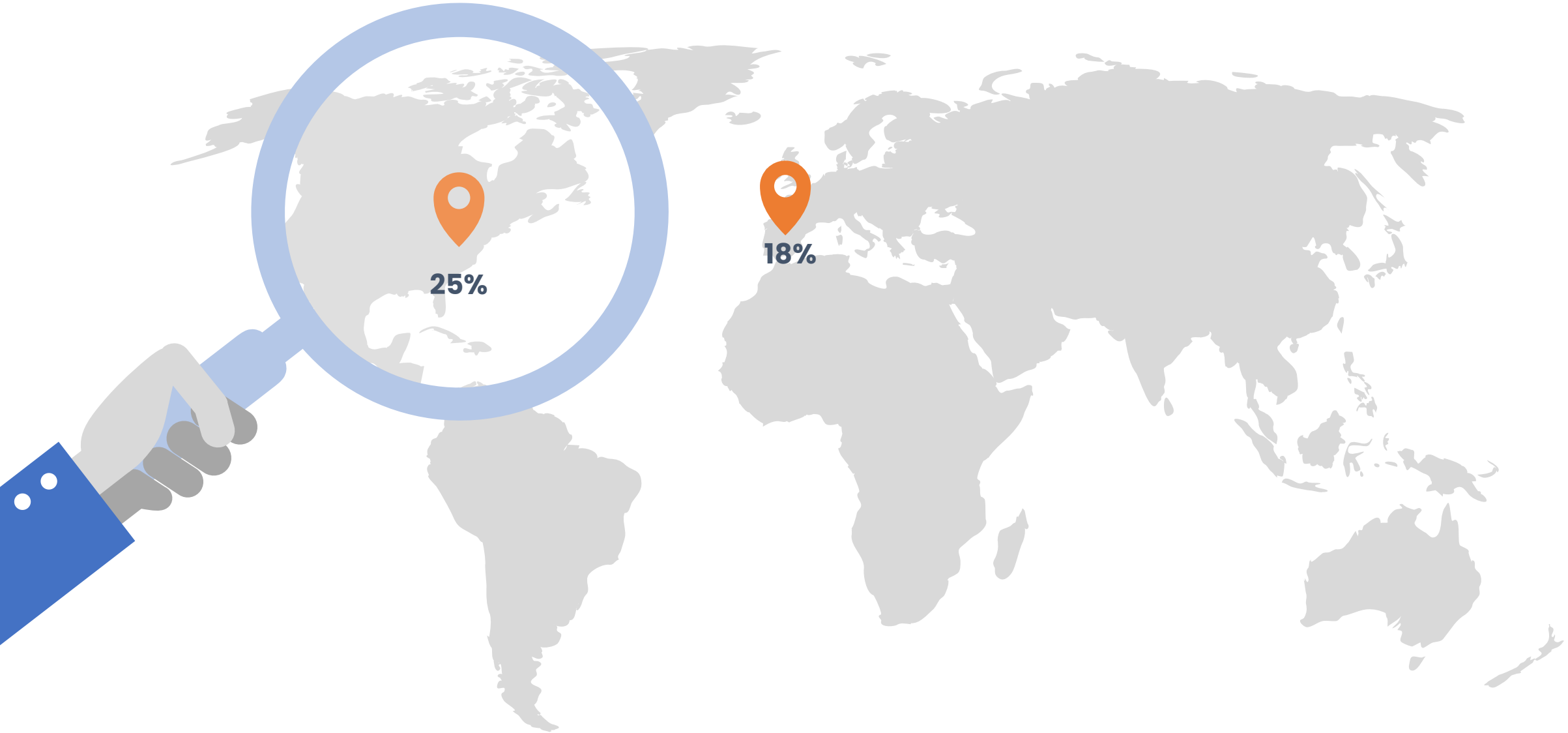
PRIMERO UN MAPA DE LA SITUACIÓN ACTUAL

NUEVA DEFINICIÓN DEL DOLOR - IASP

- **El dolor es una experiencia sensorial y emocional desagradable asociada o similar a la asociada con daño tisular real o potencial**.
  - El dolor es una **experiencia personal influenciada** en diferentes grados por factores biológicos, psicológicos y sociales.
  - **El dolor y la nocicepción son fenómenos diferentes**. El dolor no puede ser inferido solamente por la actividad de las neuronas sensoriales.
  - Las personas aprenden el concepto de dolor a través de las experiencias de vida.
  - Si una persona manifiesta una experiencia dolorosa, ésta debe ser respetada.
  - Aunque el dolor usualmente cumple una función adaptativa, puede tener efectos adversos sobre la funcionalidad y el bienestar social y psicológico.
  - Una de las maneras para expresar dolor es por la descripción verbal; **la incapacidad para comunicarse no niega la posibilidad de que un humano o animal experimente dolor.**

PREVALENCIA DEL DOLOR CRÓNICO



CAUSAS LÍDERES EN AÑOS VIVIDOS CON DISCAPACIDAD – GBD 2016 LANCET

COSTE = 3% PIB

Leading causes 2016	Mean % change in number of YLDs (2006–16)	Mean % change in all-age YLD rate (2006–16)	Mean % change in age-standardised YLD rate (2006–16)
1 Low back pain	18·0	5·0	−2·0
2 Migraine	14·3	1·6	0·1
3 Age-related hearing loss	22·3	8·8	−1·7
4 Iron-deficiency anaemia	7·5	−4·4	−1·8
5 Major depression	11·2	−1·1	−4·9
6 Neck pain	21·9	8·4	0·1
7 Other musculoskeletal disorders	14·4	1·7	−3·5
8 Diabetes	23·6	10·0	−1·2
9 Anxiety disorders	13·1	0·6	−0·7
10 Falls	26·7	12·7	3·4
11 COPD	28·8	14·5	1·4
12 Osteoarthritis	31·5	16·9	2·4
13 Acne vulgaris	5·1	−6·5	2·1
14 Refraction and accommodation	14·9	2·2	−4·9
15 Schizophrenia	16·7	3·8	−0·9
16 Asthma	17·2	4·2	3·6
17 Ischaemic stroke	35·2	20·3	3·7
18 Dermatitis	11·6	−0·7	1·1
19 Opioid use disorders	18·0	4·9	2·7
20 Other mental and substance	17·8	4·8	0·1

Nº 1
DOLOR LUMBAR COMO EJEMPLO DE COMPLEJIDAD EN LA NOCICEPCIÓN

Fuentes de dolor = 22 y puede variar en cada segmento !!

1. Facetas
2. RMP
3. Ramas laterales e intermedias
4. GRD
5. Plexo simpático T-L
6. Disco - Anillo fibroso
7. End-plates
8. Cuerpo vertebral
9. Ligamento iliolumbar
10. Ligamento amarillo
11. Ligamento interespinoso
12. Ligamento supraespinoso
13. Ligamentos intertransversos
14. Fascia tóracolumbar
15. M. Intertransversos
16. M. Interespinosos
17. M. Psoas lumbar
18. M. Cuadrado lumbar
19. M. Multifidos
20. M. Longuísimo
21. M. Iliocostal
22. M. Dorsal ancho

EVOLUCIÓN DEL DOLOR CRÓNICO SEVERO SI NO SE TRATA

Impacto del dolor en la atención y el comportamiento, momento a momento

Relacionado con la sensación

Incapacidad para completar las tareas eficientemente

No son finalizadas o se hacen de una manera inaceptable

Perdida de la autoestima

El Paciente piensa que se ha convertido en una persona inútil e incluso molesta

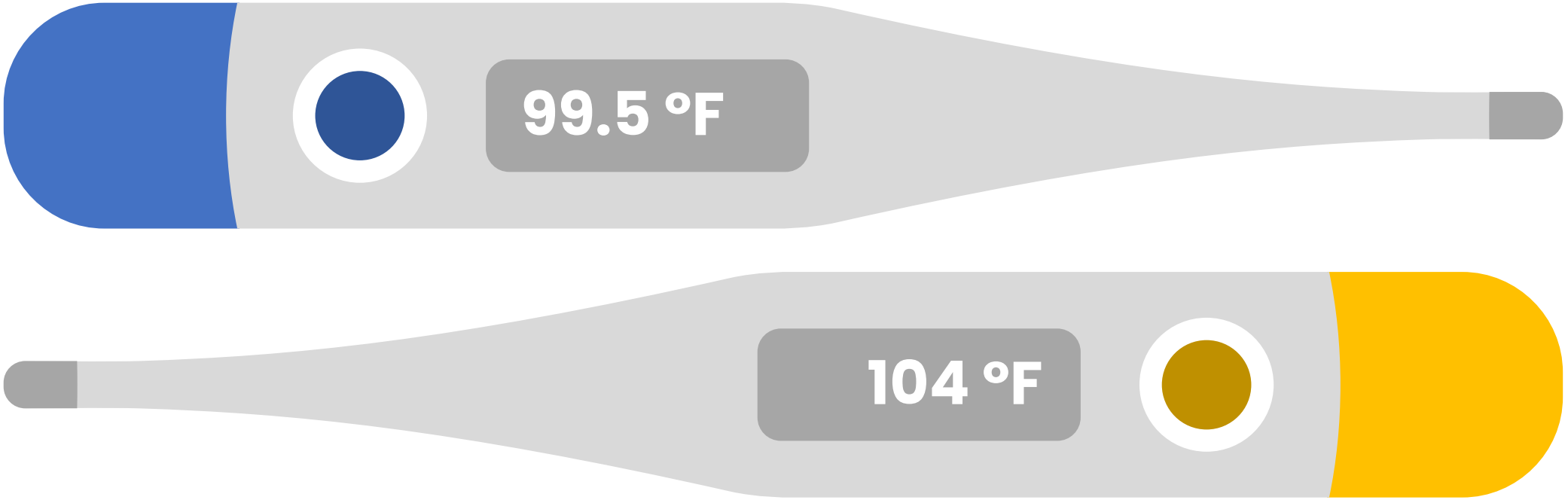
Perdida del soporte económico

Estrategias de compensación

Desmoralización por el proceso legal

Y ES INVISIBLE

NO DISPONEMOS DE UNA HERRAMIENTA OBJETIVA PARA MEDIRLO



NOS BASAMOS EN MEDIDAS SUBJETIVAS

EJ: ESCALA VISUAL ANALÓGICA

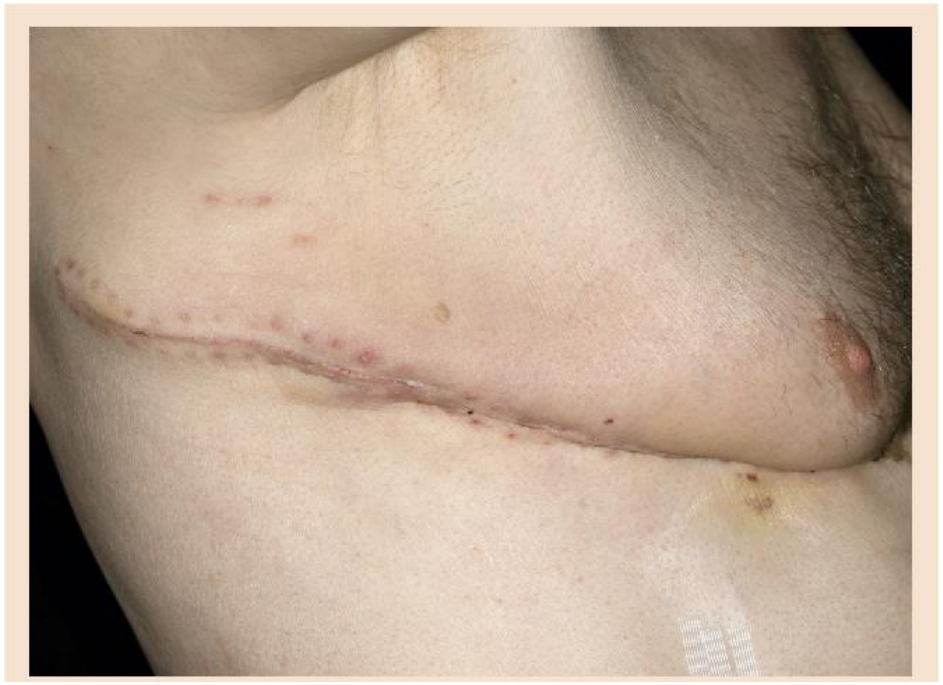
Y EN SU REPERCUSIÓN FUNCIONAL

MÚLTIPLES ESCALAS VALIDADAS

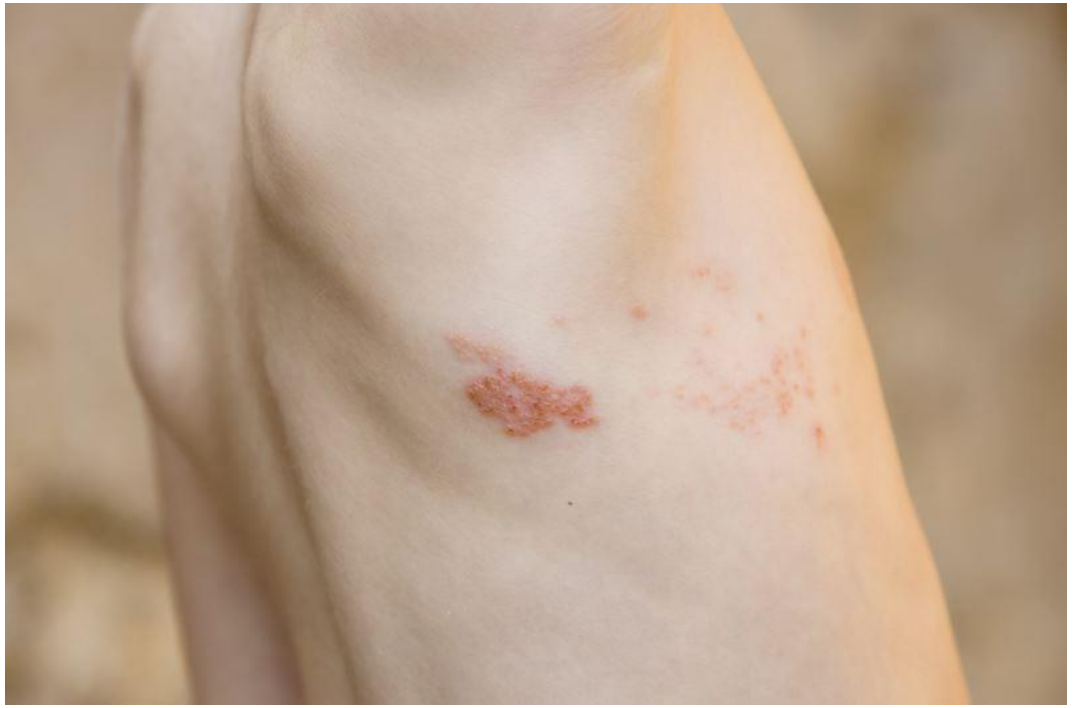
LA RM FUNCIONAL PODRÍA OBJETIVAR PRESENCIA DE DOLOR NEUROPÁTICO

EJEMPLO: ¿CUÁL DUELE MÁS?

NO DOLOR



DOLOR INSOPORTABLE 10/10



LA LEY DEL EMBUDO

FACTORES DE RIESGO DE DOLOR CRÓNICO
CONFLICTIVOS PERO QUE DEBEMOS CONOCER

Las ganancias secundarias (por ejemplo, beneficios de compensación o de asistencia social)

Litigio pendiente

Apoyo familiar insuficiente:

Poco, lo que aumenta las quejas en un intento de ganar la empatía

En exceso, lo que aumenta la dependencia

Los dolores primarios

FACTORES DETERMINANTES DOLOR AGUDO POSTOP SEVERO

MUJER JOVEN

SI

NOCICEPCIÓN EXTENSA

NO SIEMPRE

PERSONALIDAD CATASTRÓFICA E HIPERVIGILANTE

SI

COMPONENTE INCIDENTAL

SI

DOLOR PREOP EXTENSO DIFUSO

SI

DOLOR NEUROPÁTICO

SI

ANALGÉSICOS DISPONIBLES Y LAS DIFICULTADES QUE TENEMOS

MAS DOLOR … MAS PASTILLAS?

- **OPUESTO MODELO BIOPSICOSOCIAL, QUE ES LO QUE MEJOR FUNCIONA**

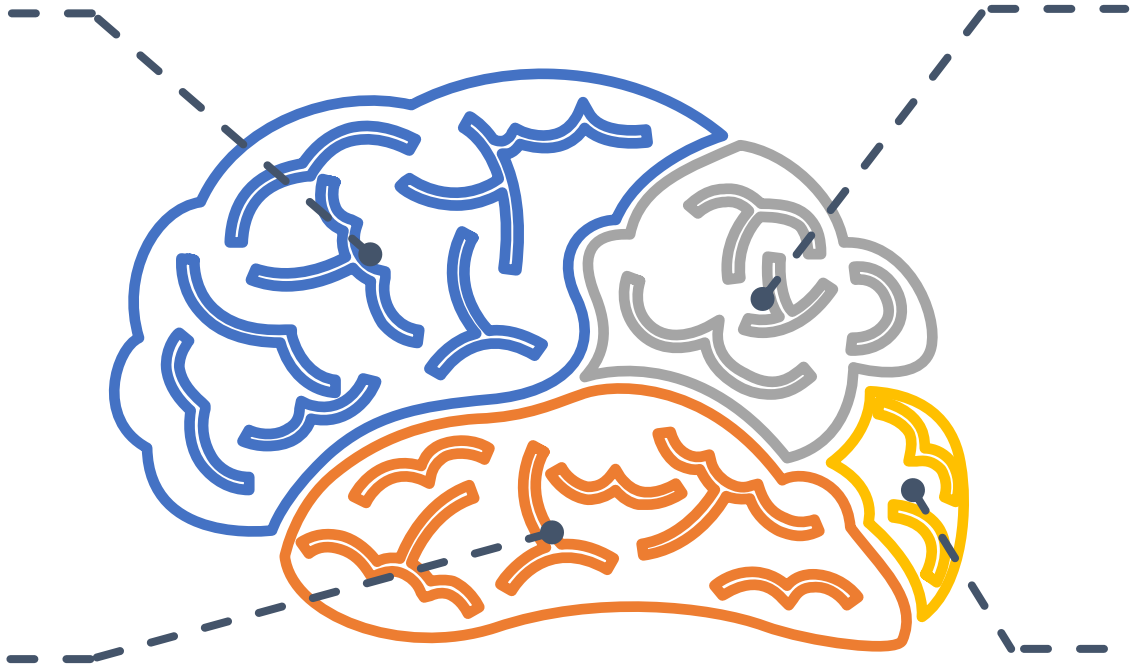
TIPOS DE DOLOR – SU TRATAMIENTO DIFIERE

NOCICEPTIVO SOMÁTICO

ACTIVACIÓN NORMAL DEL SISTEMA SOMATOSENSORIAL DE ÓRGANOS DENSOS (EJ: HUESO, MÚSCULO)

NOCICEPTIVO VISCERAL

ACTIVACIÓN NORMAL DEL SISTEMA SOMATOSENSORIAL DE ÓRGANOS VISCERALES (EJ: VESÍCULA, PÁNCREAS)



NEUROPÁTICO

LESIÓN O ENFERMEDAD DEL SISTEMA SOMATOSENSORIAL. PUEDE SER EL CENTRAL O EL PERIFÉRICO

NOCIPLÁSTICO

FUNCIÓN ALTERADA DEL SISTEMA SS EN LA PERIFERIA Y EL SNC, CAUSANDO SENSIBILIDAD AUMENTADA. EJ: FIBROMIALGIA

ANALGÉSICOS DISPONIBLES

AINES

PARACETAMOL / METAMIZOL

TOXINA BOTULÍNICA

IRSN

ATD

GABAPENTINOIDES Y OTROS ANTIEPILÉTICOS

CAPSAICINA

NMDA ANTAGONISTAS

OPIOIDES

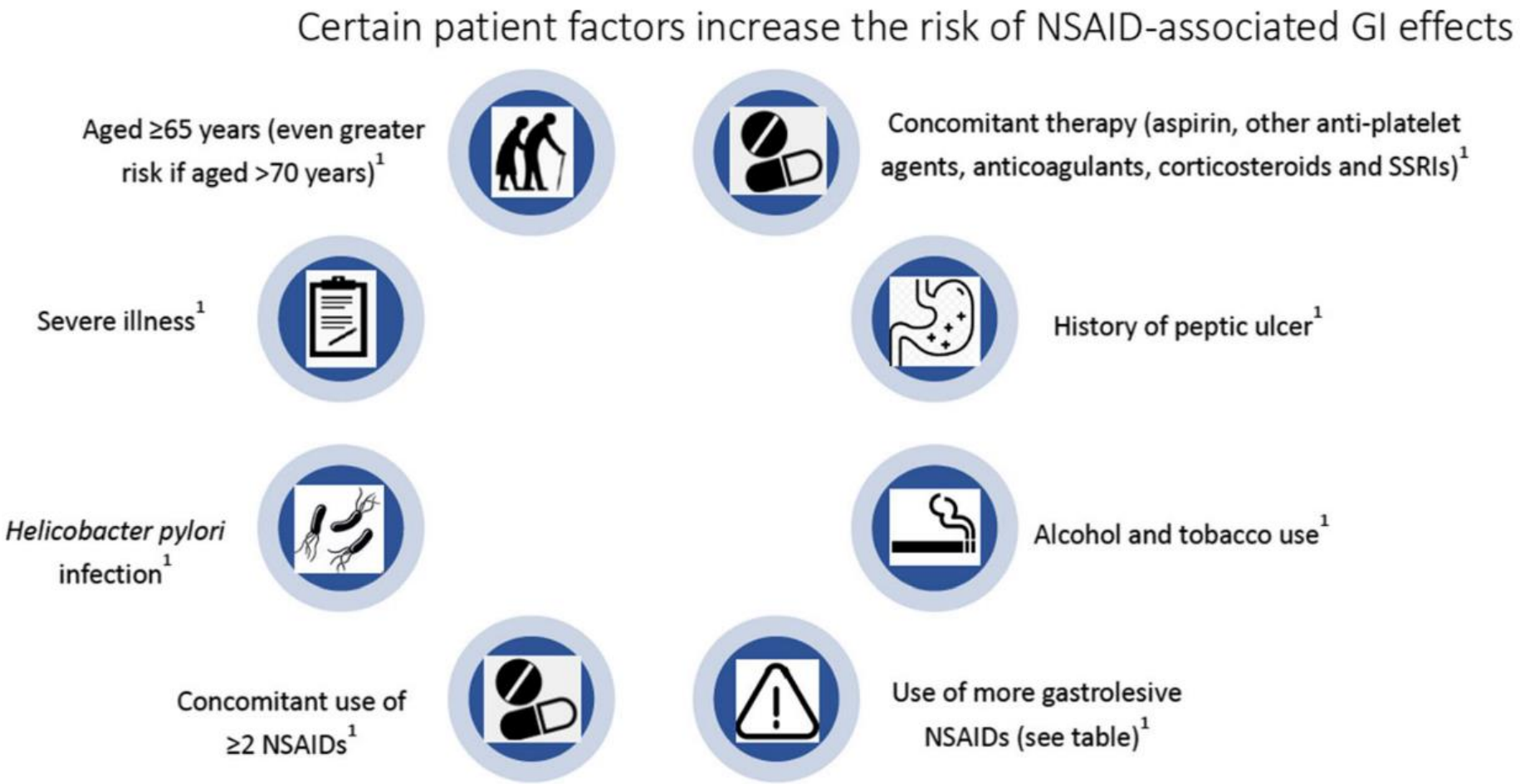
ANTI-TNF

ANTI-NGF

ANESTÉSICOS LOCALES

ESTEROIDES / CANNABINOIDES

RIESGOS GI DE LOS AINES



Adv Ther (2019) 36:2618–2637

Nonaspirin Nonsteroidal Anti-Inflammatory Drugs and Risk of Hemorrhagic Stroke

A Systematic Review and Meta-Analysis of Observational Studies

Patompong Ungprasert, MD; Eric L. Matteson, MD; Charat Thongprayoon, MD

All Nsaids RR 1,09
Meloxicam RR 1,27
Diclofenac RR 1,27
Rofecoxib RR 1,35

Background and Purpose—T stroke and use of nonsteroidal anti-inflammatory drugs (NSAIDs) is not well establ view and meta-analysis of observation studies to further characterize this possible as

Methods—Case–control and c o, relative risk, hazard ratio, or standardized incidence ratio comparing risk of hem rs versus nonusers were systematically searched. Point estimates from each study w) and 95% confidence intervals (CI) for all NSAIDs and individual NSAIDs were ca inverse variance method.

Results—Ten studies were identified and included in our data analysis. As a single group, NSAIDs use was associated with a small but insignificant risk of hemorrhagic stroke with the pooled RR of 1.09 (95% CI, 0.98–1.22). Individual NSAIDs analysis revealed a significantly increased risk among diclofenac and meloxicam users (RR 1.27; 95% CI, 1.02–1.59 and RR 1.27; 95% CI, 1.08–1.50, respectively). The risk estimate for rofecoxib users was higher, but statistically nonsignificant (RR 1.35; 95% CI, 0.88–2.06).

Conclusions—Overall, the use of NSAIDs is not associated with an increased risk of hemorrhagic stroke, although this risk was modestly significantly elevated in diclofenac and meloxicam users.

(*Stroke*. 2016;47:356-364. DOI: 10.1161/STROKEAHA.115.011678.)

Schink T, et al. (2018) Risk of ischemic stroke and the use of individual non-steroidal anti-inflammatory drugs: A multi-country European database study within the SOS Project. PLoS ONE 13(9): e0203362.

ISCHEMIC STROKE

COXIBS RR 1,08
TRADITIONAL RR 1,16
KETOROLAC RR 1,46
YOUNGER AGE
MALES
PRIOR HISTORY OF IS

Background and purpose

A multi-country European study using data fr
tries was performed to evaluate in a large stu
stroke (IS) associated with individual NSAIDs
and co-medication.

Methods

Case-control study nested in a cohort of new
and age-matched controls were selected and
use of individual NSAIDs compared to past u

Results

49,170 cases of IS were observed among 4,593,778 new NSAID users. Use of coxibs (odds ratio 1.08, 95%-confidence interval 1.02–1.15) and use of traditional NSAIDs (1.16, 1.12–1.19) were associated with an increased risk of IS. Among 32 individual NSAIDs evaluated, the highest significant risk of IS was observed for ketorolac (1.46, 1.19–1.78), but significantly increased risks (in decreasing order) were also found for diclofenac, indomethacin, rofecoxib, ibuprofen, nimesulide, diclofenac with misoprostol, and piroxicam. IS risk associated with NSAID use was generally higher in persons of younger age, males, and those with a prior history of IS.

Conclusions

Risk of IS differs between individual NSAIDs and appears to be higher in patients with a prior history of IS or transient ischemic attack (TIA), in younger or male patients. Co-

Arfè A et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. BMJ 2016;354:i4857

ABSTRACT

OBJECTIVES

All Nsaids (USE PRECEDING 14 DAYS, 19% increased RISK) RR 1,19
KETOROLAC RR 1,83
NAPROXEN RR 1,16

European countries (the Netherlands, Italy, Germany, and the United Kingdom).

PARTICIPANTS

Adult individuals (age ≥18 years) who started NSAID treatment in 2000-10. Overall, 92 163 hospital admissions for heart failure were identified and matched with 8 246 403 controls (matched via risk set sampling according to age, sex, year of cohort entry).

MAIN OUTCOME MEASURE

Association between risk of hospital admission for heart failure and use of 27 individual NSAIDs, including 23 traditional NSAIDs and four selective COX 2 inhibitors. Associations were assessed by multivariable conditional logistic regression models. The dose-response relation between NSAID use and heart failure risk was also assessed.

RESULTS

Current use of any NSAID (use in preceding 14 days) was found to be associated with a 19% increase of risk of hospital admission for heart failure (adjusted odds ratio 1.19; 95% confidence interval 1.17 to 1.22), se of any NSAIDs (use >183 days dmission for heart failure aditional NSAIDs (diclofenac, acin, ketorolac, naproxen, icam) and two COX 2 inhibitors xib). Odds ratios ranged from interval 1.07 to 1.27) for naproxen or ketorolac. Risk of heart failure c, etoricoxib, indomethacin, piroxicam, and rofecoxib used at very high doses (≥2 defined daily dose equivalents), although some confidence intervals were wide. Even medium doses (0.9-1.2 defined daily dose equivalents) of indomethacin and etoricoxib were associated with increased risk. There was no evidence that celecoxib increased the risk of admission for heart failure at commonly used doses.

CONCLUSIONS

The risk of hospital admission for heart failure associated with current use of NSAIDs appears to vary between individual NSAIDs, and this effect is dose dependent. This risk is associated with the use of a large number of individual NSAIDs reported by this study, which could help to inform both clinicians and health regulators.

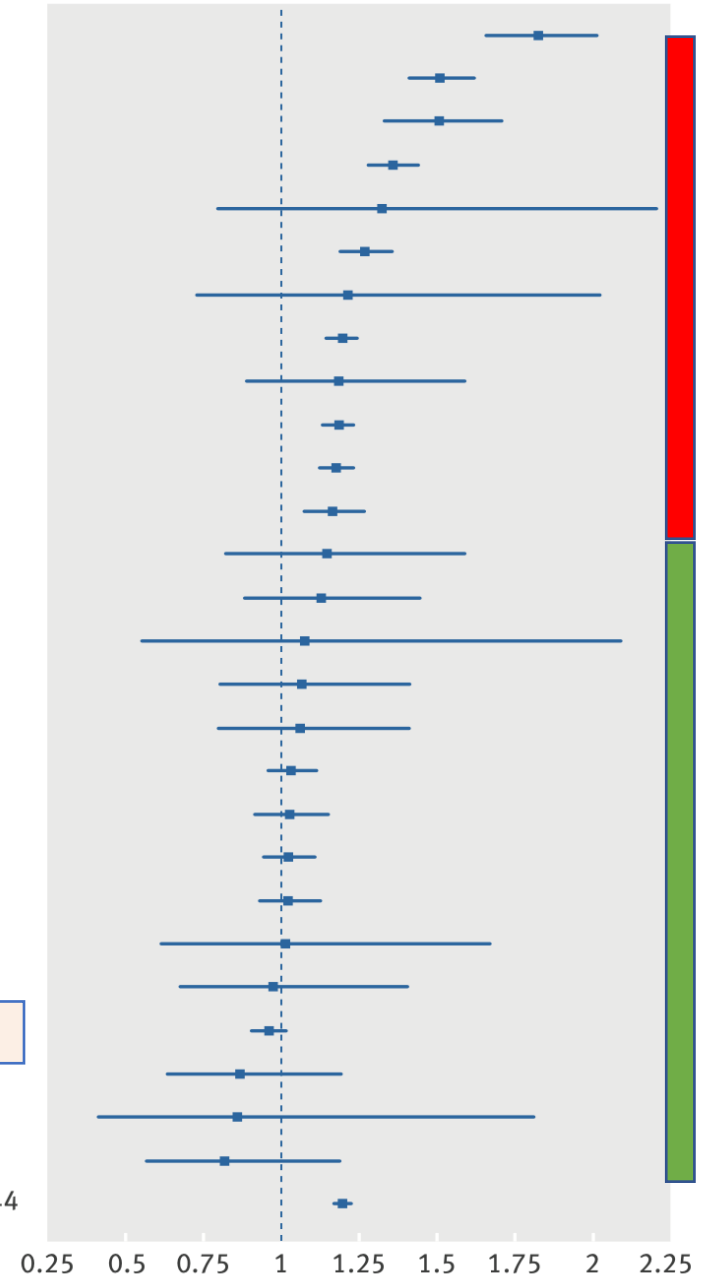
HEART FAILURE

I N) are a

Arfè A et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. BMJ 2016;354:i4857

HEART FAILURE

NSAID	No/percent		Odds ratio (95% CI)
	Case patients	Controls	
Ketorolac	449/0.49	17 459/0.21	1.83 (1.66 to 2.02)
Etoricoxib	835/0.91	50 039/0.61	1.51 (1.41 to 1.62)
Indomethacin	267/0.29	13 556/0.16	1.51 (1.33 to 1.71)
Rofecoxib	1213/1.32	78 930/0.96	1.36 (1.28 to 1.44)
Sulindac	16/0.02	639/0.01	1.32 (0.79 to 2.21)
Piroxicam	974/1.06	74 422/0.90	1.27 (1.19 to 1.35)
Acemethacin	16/0.02	979/0.01	1.21 (0.73 to 2.02)
Diclofenac	3228/3.50	241 792/2.93	1.19 (1.15 to 1.24)
Dexibuprofen	47/0.05	3668/0.04	1.19 (0.89 to 1.59)
Nimesulide	2717/2.95	197 387/2.39	1.18 (1.14 to 1.23)
Ibuprofen	2012/2.18	135 945/1.65	1.18 (1.12 to 1.23)
Naproxen	590/0.64	42 397/0.51	1.16 (1.07 to 1.27)
Valdecoxib	38/0.04	2801/0.03	1.14 (0.82 to 1.59)
Nabumetone	66/0.07	5298/0.06	1.13 (0.88 to 1.45)
Tiaprofenic acid	9/0.01	834/0.01	1.07 (0.55 to 2.09)
Lornoxicam	50/0.05	4324/0.05	1.06 (0.80 to 1.41)
Tenoxicam	51/0.06	4716/0.06	1.06 (0.80 to 1.41)
Ketoprofen	749/0.81	66 950/0.81	1.03 (0.96 to 1.11)
Aceclofenac	296/0.32	28 758/0.35	1.03 (0.91 to 1.15)
Meloxicam	629/0.68	54 491/0.66	1.02 (0.94 to 1.11)
Diclofenac, combination	453/0.49	37 292/0.45	1.02 (0.93 to 1.12)
Proglumethacin	16/0.02	1401/0.02	1.01 (0.61 to 1.67)
Flurbiprofen	30/0.03	2781/0.03	0.97 (0.68 to 1.40)
Celecoxib	1253/1.36	118 925/1.44	0.96 (0.90 to 1.02)
Etodolac	40/0.04	3578/0.04	0.87 (0.63 to 1.19)
Dexketoprofen	8/0.01	528/0.01	0.86 (0.41 to 1.81)
Oxaprozin	29/0.03	3647/0.04	0.82 (0.57 to 1.19)
Current use of any NSAID	16 081/14.45	1 193 537/14.44	1.19 (1.17 to 1.22)



Bally M, et al. Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. BMJ. 2017;357:j1909

ABSTRACT

OBJECTIVE

To characterise the determinants, time course, and risks of acute myocardial infarction associated with use of oral non-steroidal anti-inflammatory drugs (NSAIDs).

DESIGN

Systematic review followed by a one stage bayesian individual patient data meta-analysis.

DATA SOURCES

Studies from Canadian and European healthcare databases.

REVIEW METHODS

Eligible studies were sourced from computerised drug prescription or medical databases, conducted in the general or an elderly population, documented acute myocardial infarction as specific outcome, studied selective cyclo-oxygenase-2 inhibitors (including rofecoxib) and traditional NSAIDs, compared risk of [illegible] users with [illegible] analyses, and [illegible] indicator variable [illegible] cency, duration [illegible] res were the [illegible] acute myocardial [illegible] egory of NSAID [illegible] rdial infarction [illegible] ersus non-use in the preceding year and the posterior probability of acute myocardial infarction.

RESULTS

A cohort of 446 763 individuals including 61 460 with acute myocardial infarction was acquired. Taking any dose of NSAIDs for one week, one month, or more than a month was associated with an increased risk of myocardial infarction. With use for one to seven days the probability of increased myocardial infarction risk (posterior probability of odds ratio >1.0) was 92% for celecoxib, 97% for ibuprofen, and 99% for diclofenac, naproxen, and rofecoxib. The corresponding odds ratios (95% credible intervals) were 1.24 (0.91 to 1.82) for celecoxib, 1.48 (1.00 to 2.26) for ibuprofen, 1.50 (1.06 to 2.04) for diclofenac, 1.53 (1.07 to 2.33) for naproxen, and 1.58 (1.07 to 2.17) for rofecoxib. Greater risk of myocardial infarction was documented for higher dose of NSAIDs. With use for longer than one month, risks did not appear to exceed those associated with shorter durations.

CONCLUSIONS

All NSAIDs, including naproxen, were found to be associated with an increased risk of acute myocardial infarction. Risk of myocardial infarction with celecoxib was comparable to that of traditional NSAIDS and was lower than for rofecoxib. Risk was greatest during the first month of NSAID use and with higher doses.

Celecoxib 1,24
Ibuprofeno 1,48
Diclofenaco 1,5
Naproxeno 1,53
Rofecoxib 1,58

AMI

trials of NSAIDs have been of limited use for assessing this rare adverse event, as they had small cohorts and poor generalisability.[12] The trials excluded those at

Lo que no te cuentan del paracetamol (y lo que deberías saber, aunque no lo quieras oír)

Durante décadas se ha aceptado su utilidad, al no existir estudios científicos que revisasen sus posibles efectos a largo plazo. La situación ha cambiado recientemente

Cada año, en España se venden 32 millones de envases de **paracetamol**. Es el genérico más consumido, si exceptuamos al omeprazol, con 54,4 millones, pero muy por encima de la simvastatina (un estatina utilizada en el tratamiento de la hipercolesterolemia). Ha ocupado el lugar de la **aspirina** en **nuestros botiquines** (y en nuestros corazones) a la hora de aliviar los dolores de cabeza o la fiebre.

Como cada vez que un medicamento pasa a consumirse de manera frecuente, gran parte de la población tiende a pensar que este sirve para curar cualquier mal. Sin embargo, como pide el profesor honorario de la Universidad de Oxford **Andrew Moore**, experto en dolor, pide que lo pensemos dos veces antes de consumirlo. En parte, porque para determinadas enfermedades es inútil, o al menos **no más útil que un placebo**. También, porque si nos excedemos con la dosis, tenemos serias posibilidades de dañar nuestro hígado. Debemos recordar siempre que no es un antiinflamatorio, como sí es el ibuprofeno.

https://www.elconfidencial.com/alma-corazon-vida/2016-10-31/paracetamol-no-te-cuentan_1280141/

Y PARACETAMOL?

METAMIZOL TAMPOCO ?

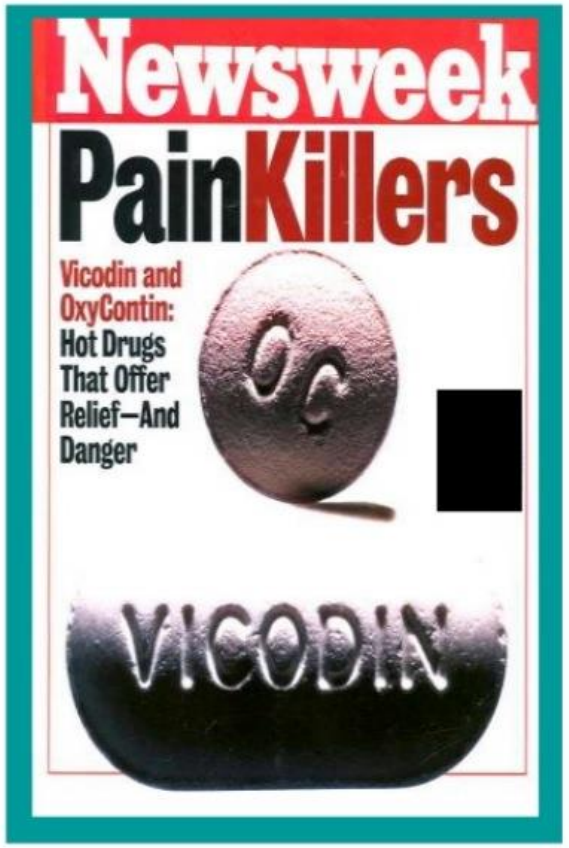
La **Agencia Española de Medicamentos y Productos Sanitarios (Aemps)** ha recordado que los medicamentos que contienen metamizol son medicamentos sujetos a prescripción médica, tras la revisión de los casos de agranulocitosis notificados en el **Sistema Español de Farmacovigilancia** y el consumo de *metamizol* en España.

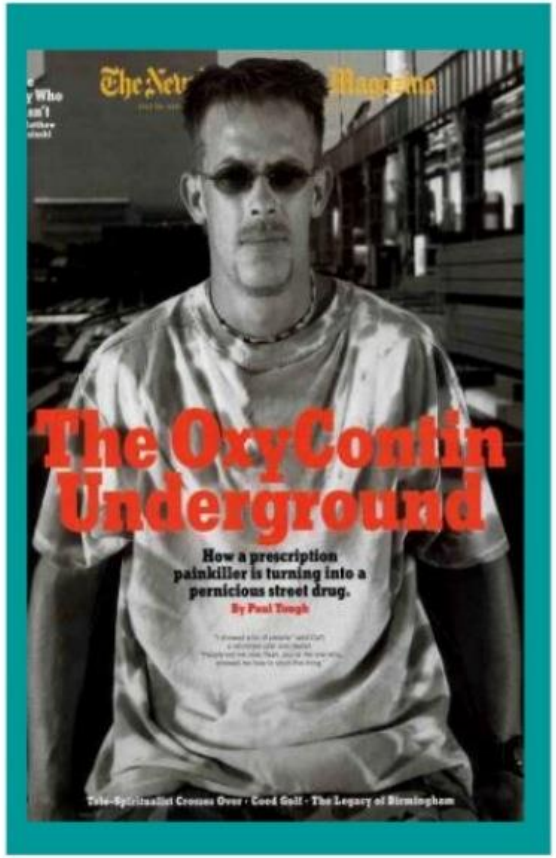
En un comunicado, la Agencia ha recomendado utilizar *metamizol* solo para tratamientos de corta duración a las dosis mínimas eficaces, vigilando la aparición de sintomatología indicativa de agranulocitosis. Y en el caso de que sea necesario un tratamiento prolongado, realizar controles hematológicos periódicos incluyendo fórmula leucocitaria.

> **La Aemps aconseja que antes de prescribir *metamizol* hay que llevar a cabo una anamnesis detallada para evitar su uso en pacientes con factores de riesgo de agranulocitosis**

Asimismo, la Aemps ha aconsejado que antes de prescribir *metamizol* hay que llevar a cabo una anamnesis detallada para evitar su uso en pacientes con factores de riesgo de agranulocitosis e informar al paciente de que interrumpa el tratamiento en casos de aparicición de signos o síntomas sugestivos de agranulocitosis. También, recomienda no utilizar *metamizol* en pacientes en los que no sea posible realizar controles.

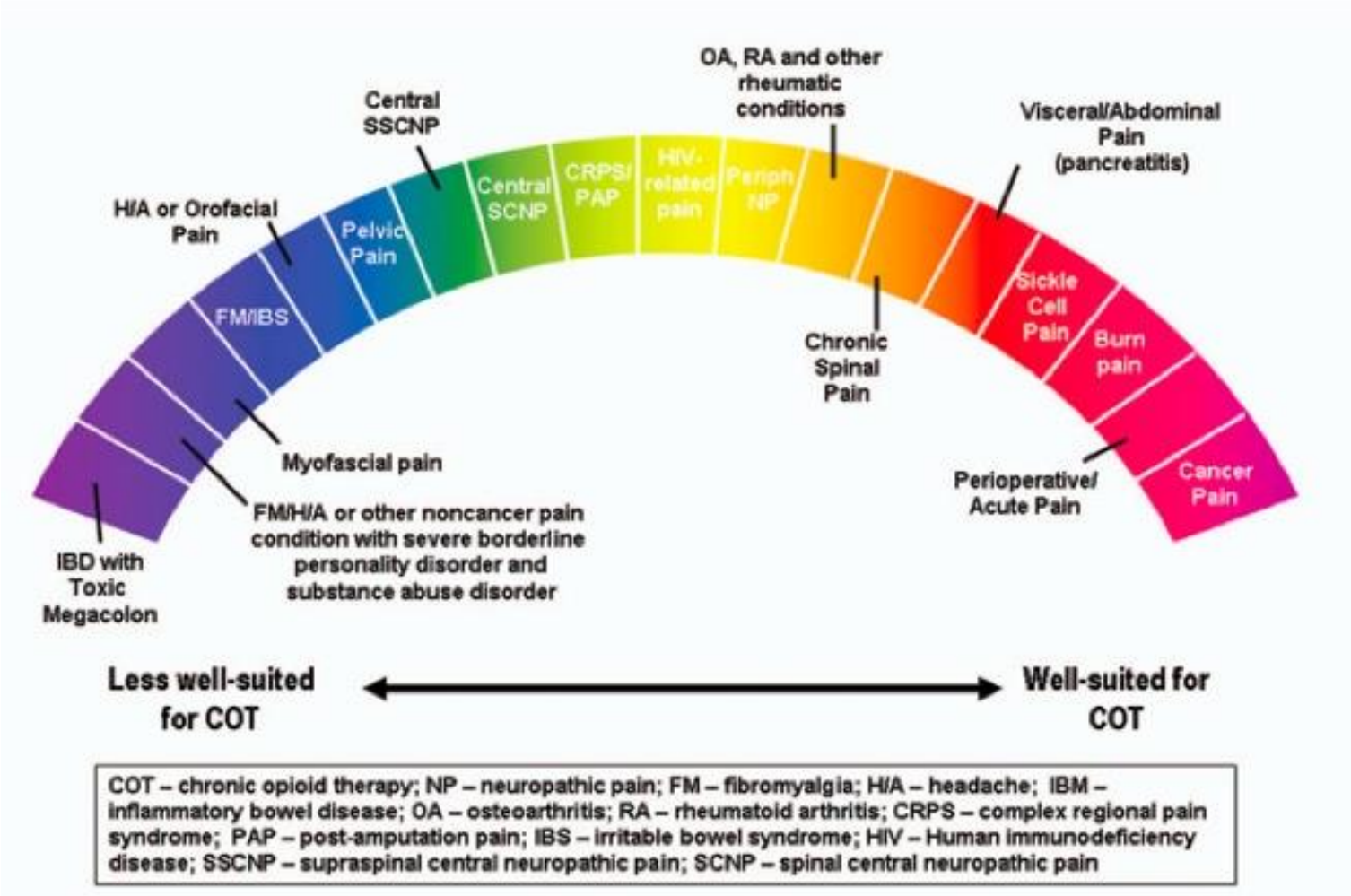
Y LAS POCAS MOLÉCULAS QUE TENEMOS, ADEMÁS HAN SIDO MAL PRESCRITAS EN CIERTOS PAÍSES





Y SABEMOS DESDE HACE MUCHO TIEMPO A QUIEN PODEMOS DAR OPIOIDES Y A QUIEN NO ES CONVENIENTE

Smith HS. Conventional practice for medical conditions for chronic opioid therapy. *Pain Physician*. 2012;15(3 Suppl):ES1–7.



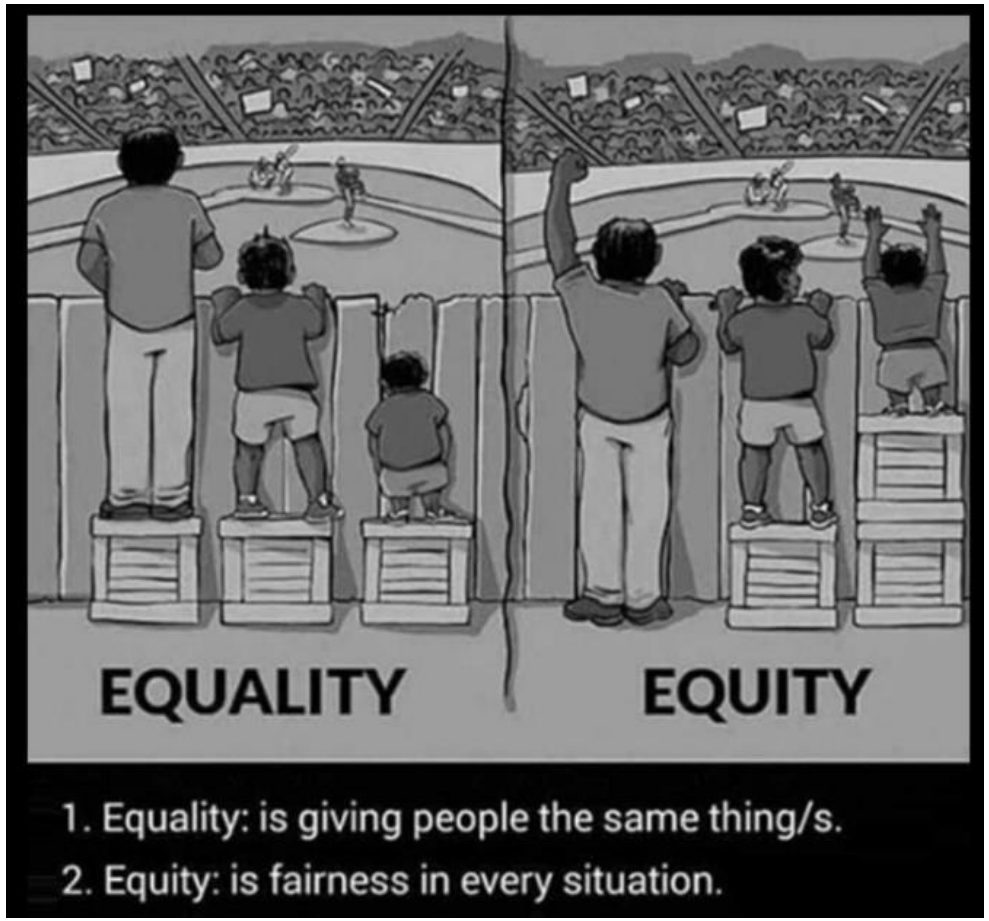
A VER SI VAMOS A TENER QUE ACABAR TRATANDO EL DOLOR CON OTRO DOLOR … MODULACIÓN CONDICIONADA DEL DOLOR

LIBERACIÓN DE ENDORFINAS NORADRENALINA …

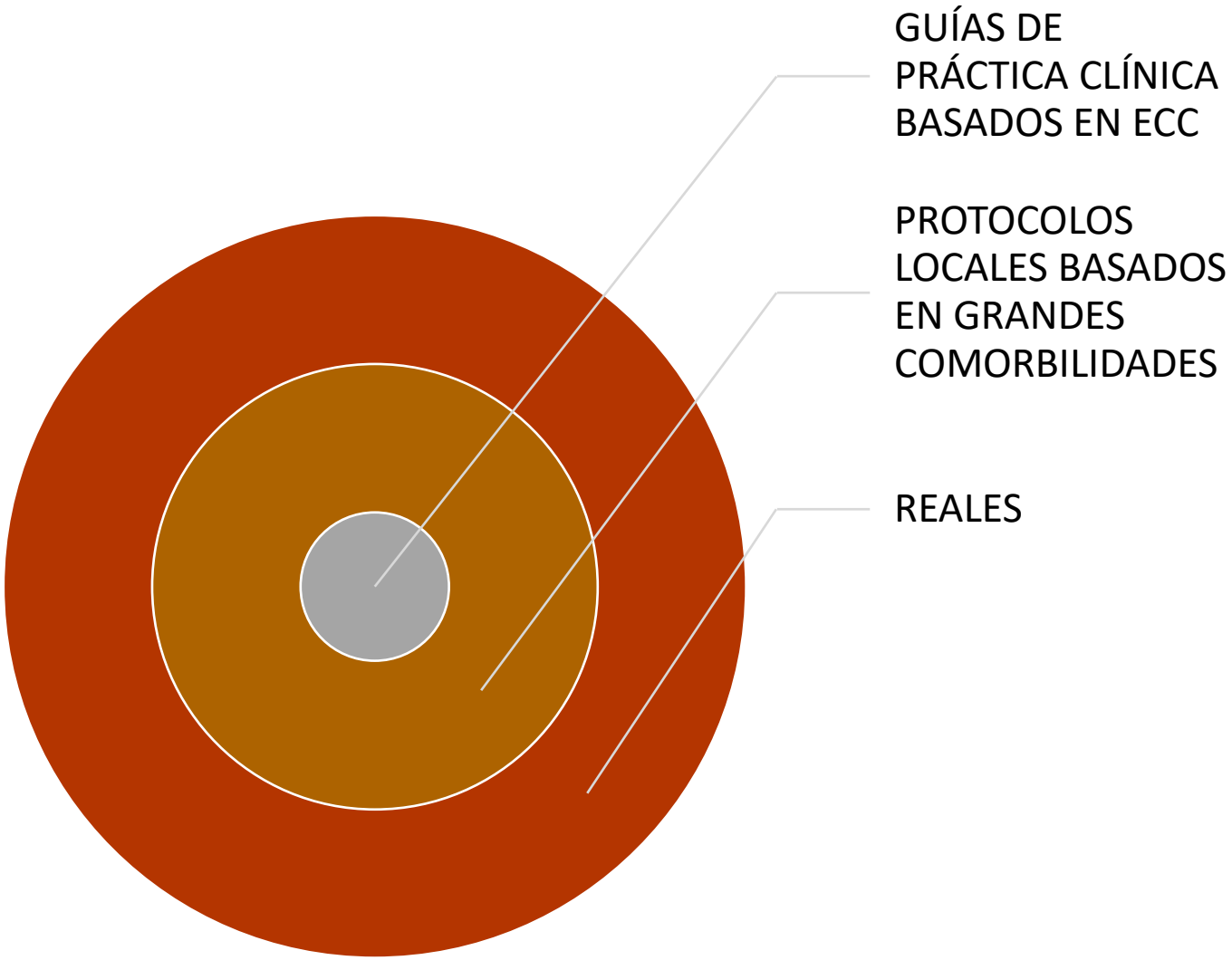
EL SISTEMA INHIBITORIO DESCENDENTE SE PUEDE POTENCIAR EJ CON EJERCICIO

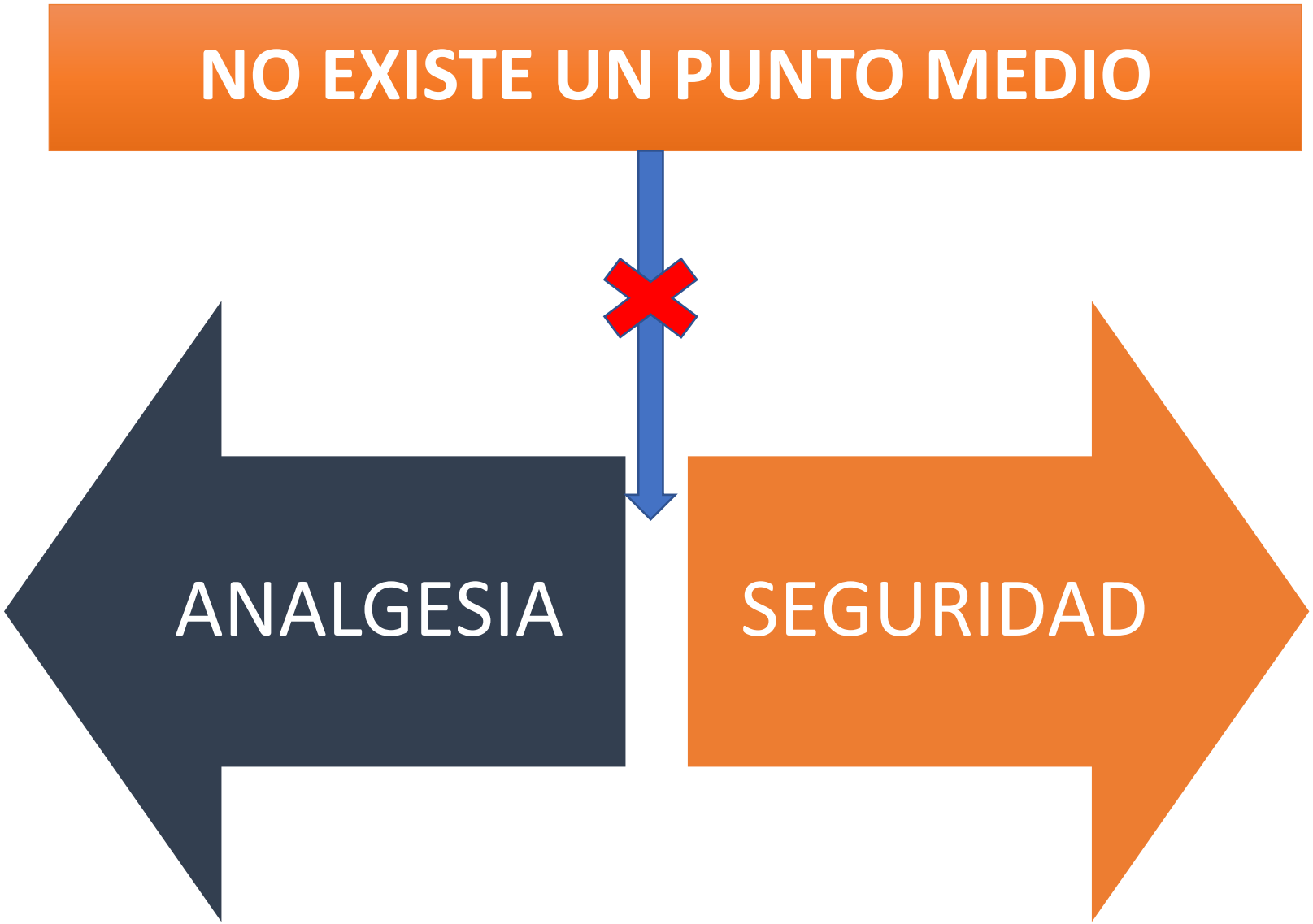
¿QUÉ ES LO QUE HACEMOS REALMENTE?

EL ÉXITO RESIDE EN NO DAR A TODOS LO MISMO SI NO A CADA UNO LO QUE PRECISA SIEMPRE BASADO EN PROTOCOLOS CON EVIDENCIA

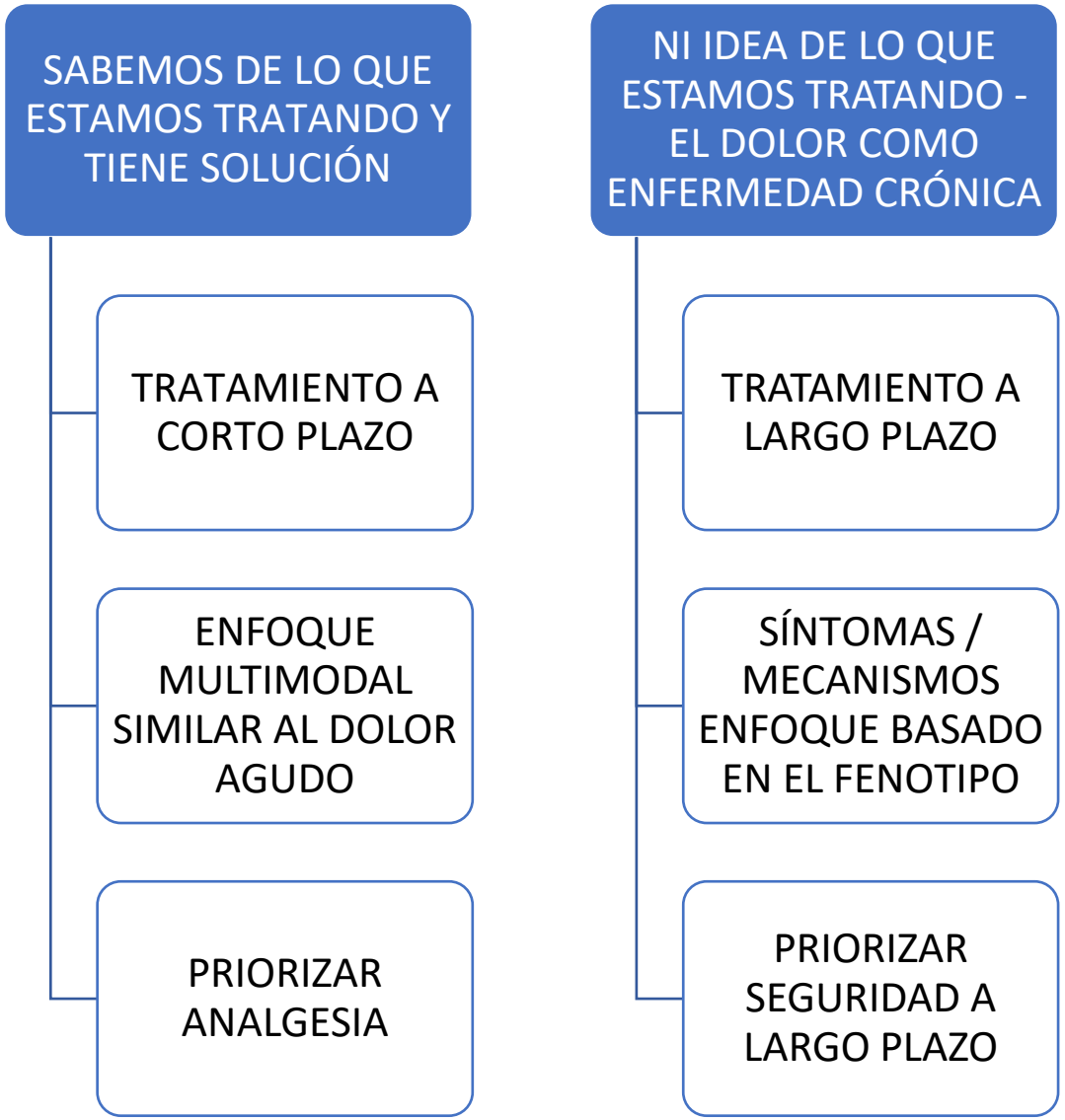


LOS PACIENTES NO SON LOS DE LAS GUÍAS




NO EXISTE UN PUNTO MEDIO
ANALGESIA
SEGURIDAD

LA MENTE DEL PRESCRIPTOR



20 Comorbilidades a tener en cuenta

1. Allergy to drugs
2. Moderate to severe renal and liver impairment
3. Cardiac failure & hypertensi
4. CAD and Stroke
5. Dehy
6. E
7. Ac
8. Ant
9. Bleeding disorders
10. Peptic ulcer and Lower GI disease
11. Pharmacological interactions
12. Lon drome

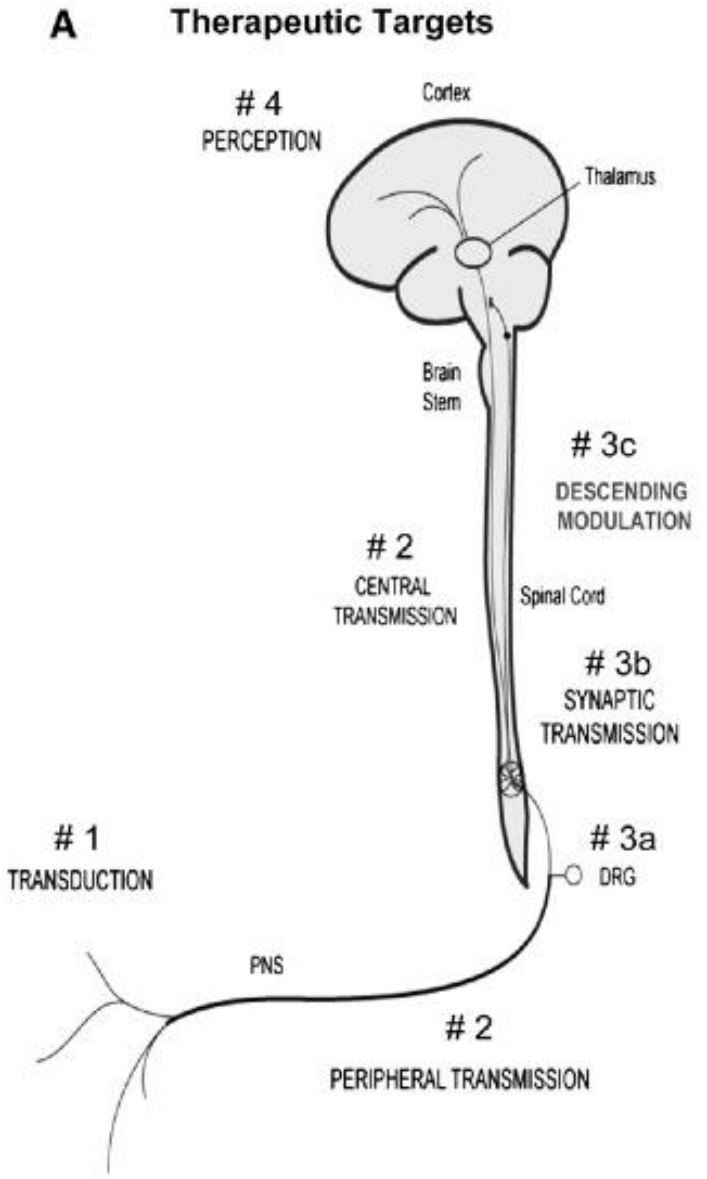
Esto es la vida real y es difícil de conciliar con las guías de práctica clínica disponibles.

ve impairment

17. Conditions with unsteady Gait
18. Driving and risky job
19. Dizziness
20. Non-familiar support

COMO NO SALEN NUEVAS MOLÉCULAS, LLEVAMOS 10 AÑOS OPTANDO POR COMBINACIONES APROVECHANDO SINERGIAS

LA INDUSTRIA TECNOLÓGICA ESTÁ GANANDO LA BATALLA



B Target-directed Drugs

#1: Transduction
Capsaicin, local anesthetic, NSAID, steroid, opioid, anti-TNFα agent

#2: Transmission - action potential propagation
Local anesthetic, TCA

#3a: Plasticity – DRG ectopic activity
Local anesthetic, TCA, anti-TNFα agent, NSAID

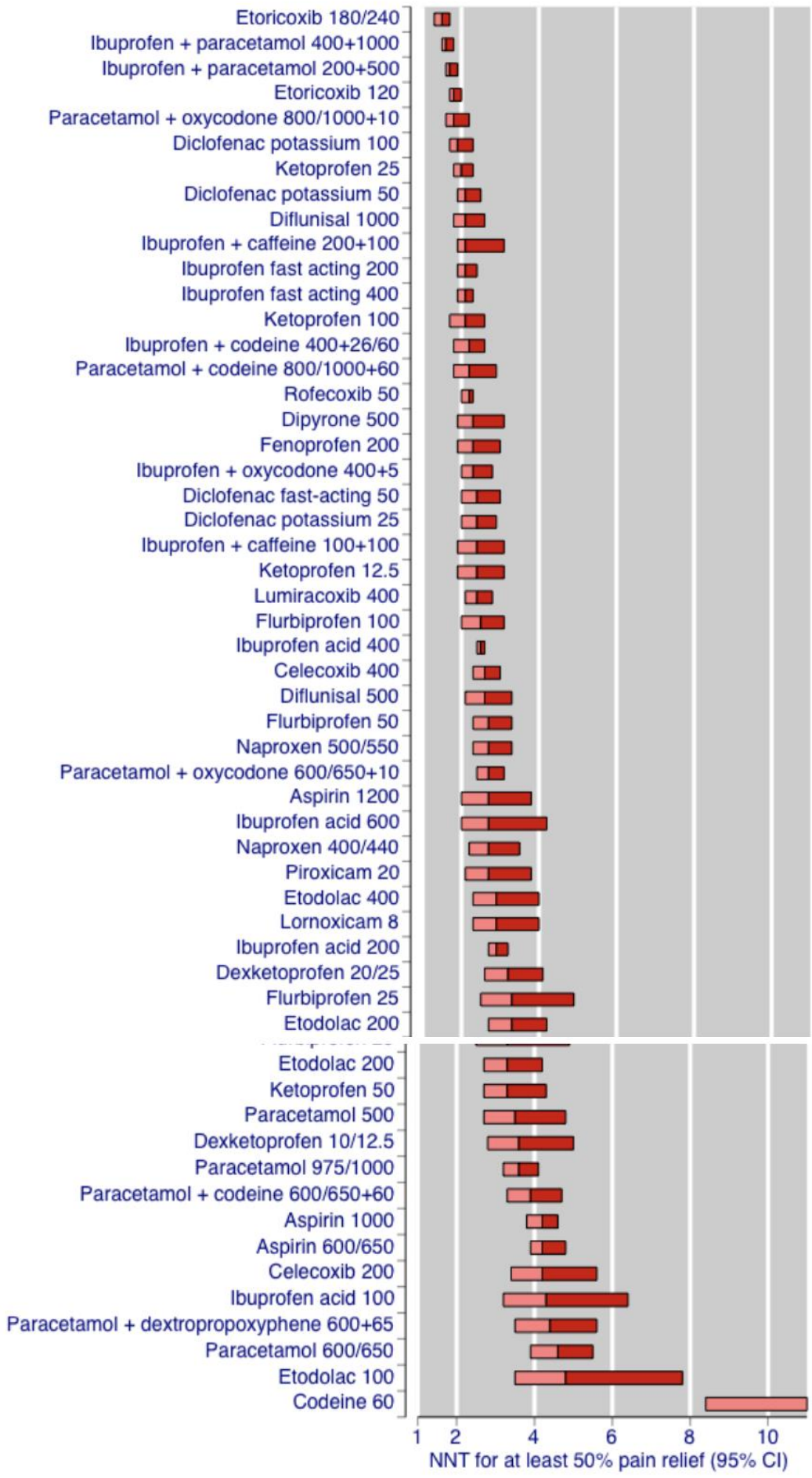
#3b: Plasticity – synaptic transmission
Ion channel blocker, NMDA receptor antagonist, opioid, tramadol, α-adrenergic receptor agonist, COX-2 inhibitor, anti-TNFα agent, ziconotide

#3c: Plasticity - descending modulation
TCA, SNRI, opioid, tramadol

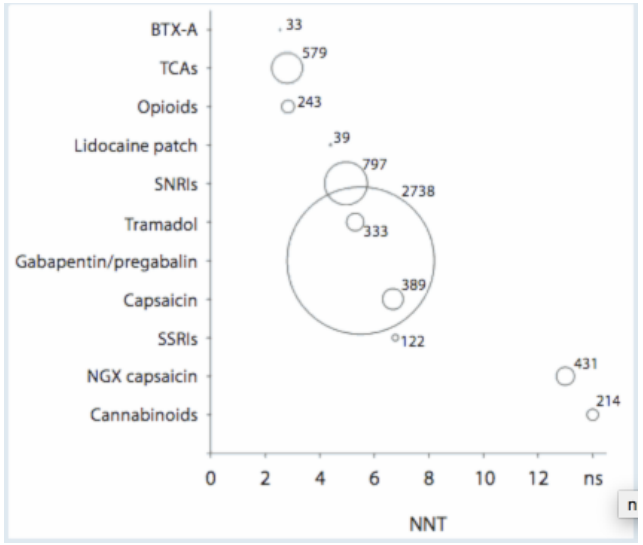
#4: Perception
TCA, SNRI, opioid, tramadol, ion channel blocker

Mao J. Combination Drug Therapy for Chronic Pain: A Call for More Clinical Studies. The Journal of Pain, Vol 12, No 2, 2011

Figure 1. Single dose oral analgesics in moderate or severe pain: NNT for at least 50% maximum pain relief over four to six hours.



NNT DOLOR NOCICEPTIVO



Neuropathic pain syndrome	Drug	NNT (95% CI)	Recommended daily dose
Peripheral neuropathic pain*	TCAs	2.2 (1.9–2.6)	Up to 150 mg (titrate over 6 weeks)
	Gabapentin	4.4 (3.4–6.2)	1800–3600 mg (titrate over 2–4 weeks)
	Pregabalin	5.0 (3.5–8.6)	600 mg (titrate over 1 week)
	Tramadol	3.9 (2.7–6.7)	200–400 mg (titrate from 100 mg)
	CR-oxycodone	2.6 (1.9–4.1)	60–120 mg (titrate from 20 mg)
	Topical lidocaine	4.4 (2.5–17.5)	5% patch or gel (12 h on, 12 h off)
Trigeminal neuralgia	Carbamazepine	1.8 (1.4–2.7)	Up to 1000 mg (titrate from 200 mg)

NNT: the number of patients needed to be treated for one patient to achieve a pain reduction of more than 50%. *Except for HIV-associated polyneuropathy

NNT EN DOLOR NEUROPÁTICO

NNT DE DIFERENTES TRATAMIENTOS EN OTRAS PATOLOGÍAS

- ESTATINAS EN ENFERMEDAD CV. El NNT para prevenir un episodio cardiovascular (muerte coronaria o infarto no fatal) tras 5 años de tratamiento es de 10 (con infarto previo) y 16 (con angina previa).
- DENOSUMAB EN PREVENCIÓN DE FRACTURAS EN PACIENTES CON OSTEOPOROSIS ESTABLECIDA ES DE 9 A 71 DEPENDIENDO DEL RIESGO
- FARMACOS ANTI-HTA. NNT = 24. Esto significa que aproximadamente 24 personas con hipertensión moderada o grave deben tratarse durante 5 años con fármacos para que una persona evite un efecto adverso cardiovascular.

BUENAS COMBINACIONES (SINERGIA)

TRAMADOL/OPIOID + NSAID/PARACETAMOL

Table 1. Representative Studies of CDT for Chronic Pain

Pain Condition	Drug Combination	Study Type	Study Outcome	Reference
Spinal cord injury	Morphine, clonidine, or combination [intrathecal]	Single-drug vs multidrug comparison	Positive: Better pain relief with combination	91
Post-herpetic neuralgia, painful diabetic neuropathy	Morphine, gabapentin, combination, or placebo [oral]	Single-drug vs multidrug comparison	Positive: Better pain relief with combination; a few more adverse events with combination	33
Painful diabetic neuropathy	Oxycodone, gabapentin, combination, or placebo [oral]	Single-drug vs multidrug comparison	Positive: Better pain relief and fewer adverse events with combination	40
Mixed neuropathic pain	Oxycodone, pregabalin, or combination [oral]	Single-drug vs multidrug comparison	Positive: Better pain relief and fewer adverse events with combination	30
Post-herpetic neuralgia, painful diabetic neuropathy	Nortriptyline, gabapentin, or combination [oral]	Single-drug vs multidrug comparison	Positive: Better pain relief and less frequent side effect (dry mouth) with combination	32
Lumbar radiculopathy	Morphine, nortriptyline, combination, or placebo [oral]	Single-drug vs multidrug comparison	Negative: No better pain relief with combination	51

MALAS COMBINACIONES (INSEGURAS)

Serotonin Syndrome

tramadol+TCA or SNRI

Sedation/Confusion

opioid+TCA or SNRI

Constipation

opioid+TCA or SNRI

Liver Toxicity

duloxitine+acetaminophen

Electrolyte Change

gabapentin+topiramate

Hematological Change

carbamezapine+mexiletine

Bleeding
Antidepressants an NSAIDs
Opioid analgesic

Arrhythmias
Ion channel Blockers combinations

Arrhythmias
Methadone + Drugs to increase Qtc interval

UN EJEMPLO DE INTENTO DE ABORDAJE BIOPSICOSOCIAL.

MÉTODO EXPLAIN PAIN (EXPLICAR EL DOLOR)

Enseñar los procesos biológicos

Enseñar a las personas que su sistema de transmisión de peligro puede volverse muy sensible, lo que puede llevar a más mensajes de peligro, pero siempre es el cerebro el que decide si debe o no producir dolor

Asegurar a las personas que su dolor es completamente real aunque el tejido no esté en peligro

Hipervigilar vs Ignorar la zona de dolor
Hipervigilancia del entorno

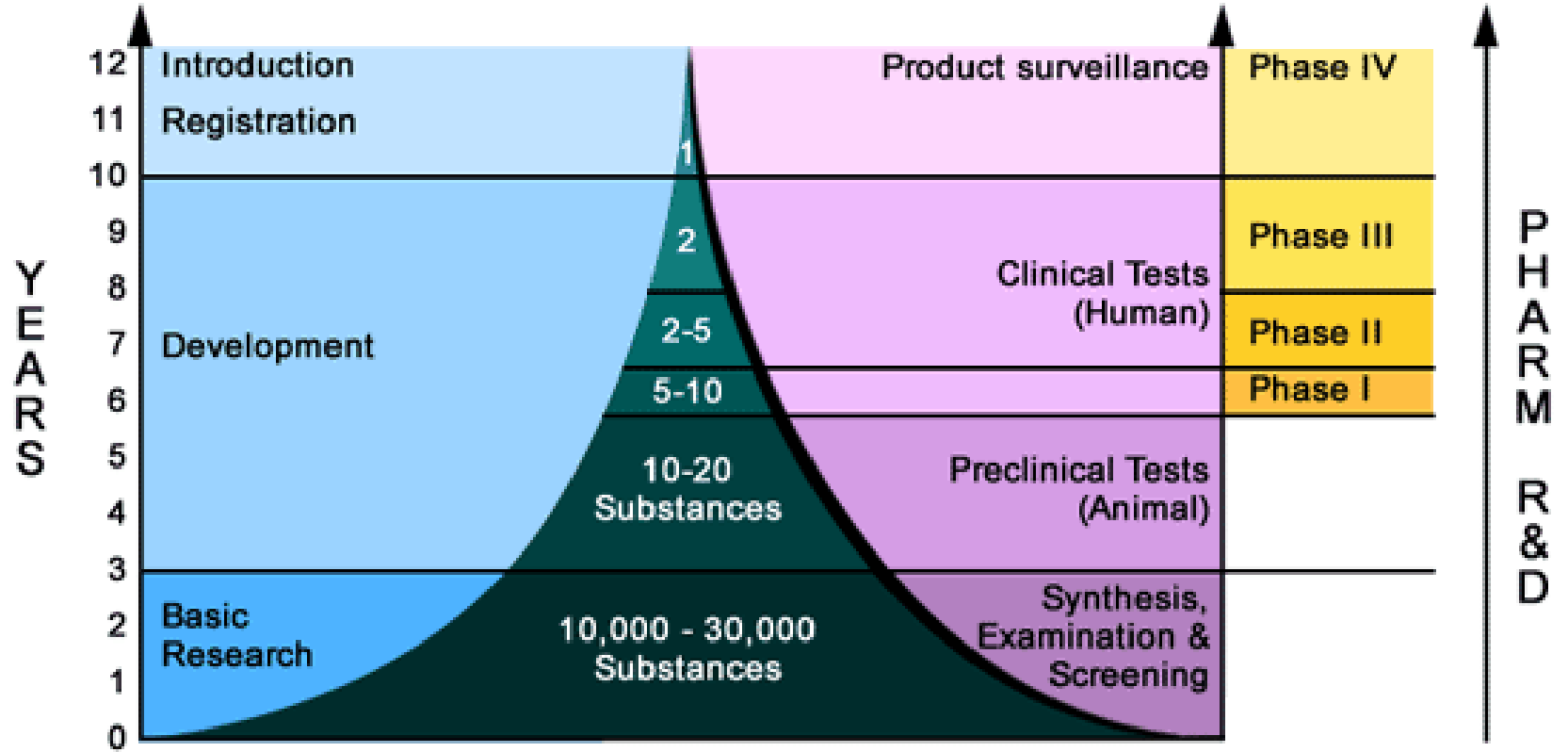
El cerebro puede rechazar el mensaje de peligro que le llega de la médula espinal

Enseñar a las personas que el dolor puede ser sobreprotector

Muchas veces podemos tratar los desencadenantes nociceptivos periféricos y centrales. Tanto el propio paciente como nosotros.

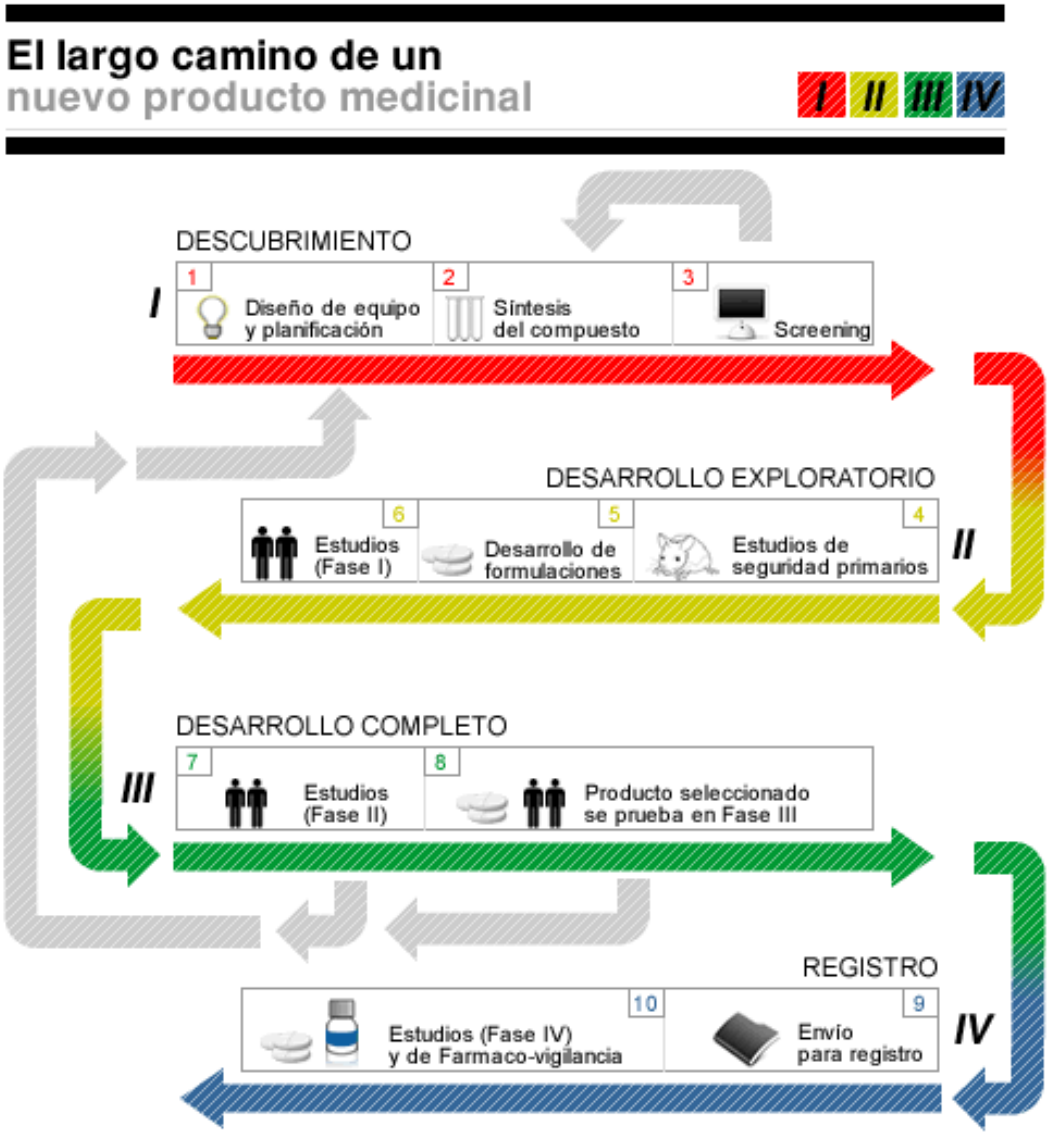
Y ¿POR QUÉ NO SALEN ANALGÉSICOS NUEVOS?

30.000 : 1

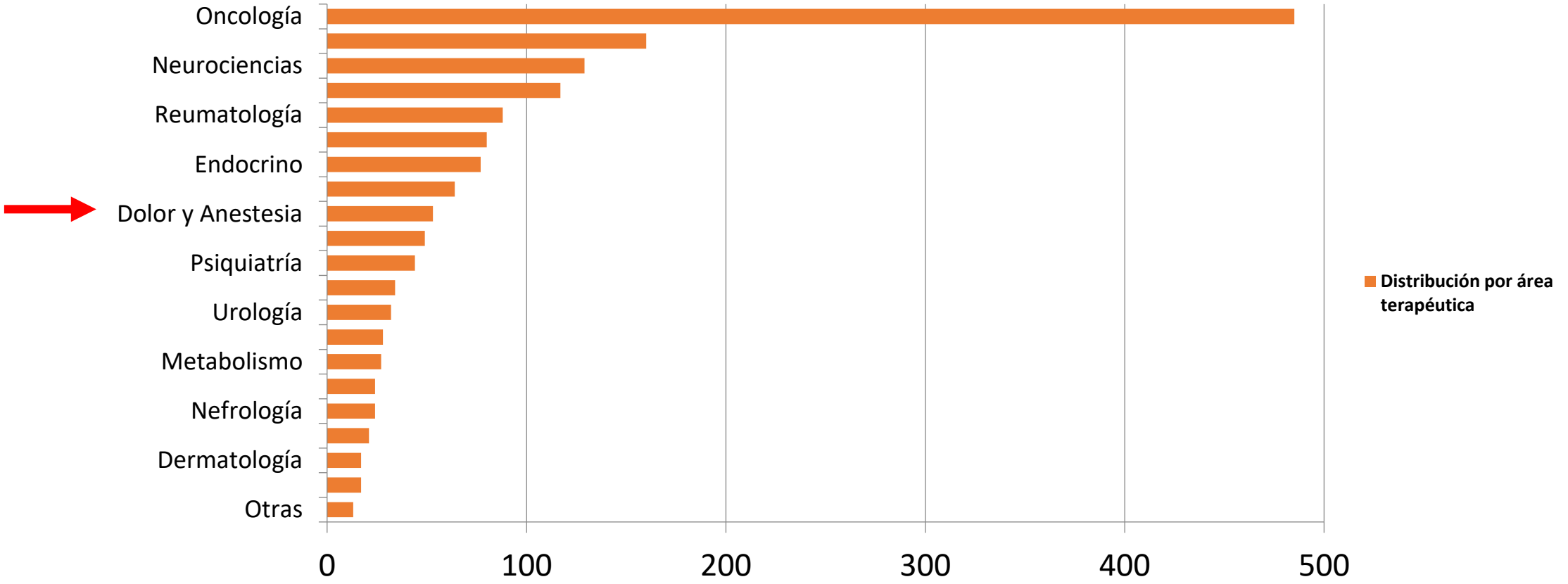

YEARS
12
11
10
9
8
7
6
5
4
3
2
1
0
Introduction
Registration
Development
Basic
Research
1
2
2-5
5-10
10-20
Substances
10,000 - 30,000
Substances
Product surveillance
Clinical Tests
(Human)
Preclinical Tests
(Animal)
Synthesis,
Examination &
Screening
Phase IV
Phase III
Phase II
Phase I
PHARM R&D

Desarrollo del Medicamento

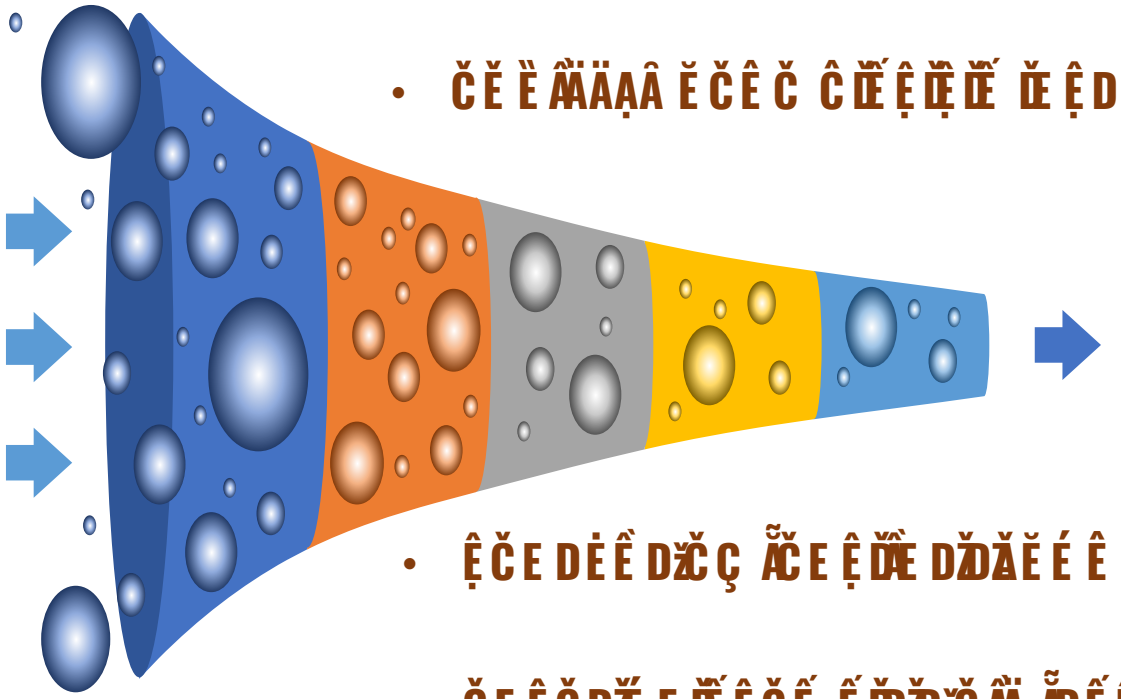
10-12 AÑOS



Distribución de los EC por área terapéutica (2012)



EJEMPLOS DE FÁRMACOS QUE HAN CAÍDO EN FASES 1, 2 Y 3 RECIENTEMENTE

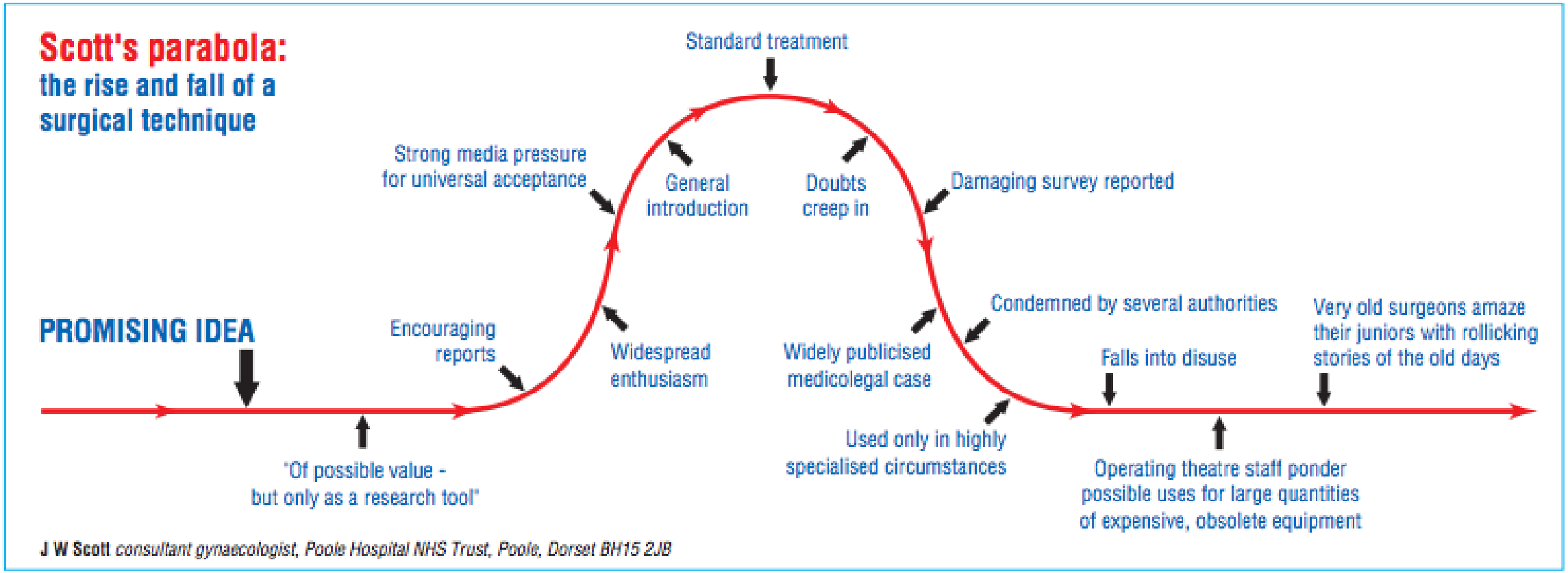


- DDžČÅÀÄ ÃČE ĘČDŽÉ E ĚĚĘČ Ê DĈDĚĘÉÊ ĊD ČE DžŽÉ ĘDE ÉĚE Č ĚĚĘĚÉ Ą ÉDDĐĈĘĚĚÉ ÄÈ ĐDĚČĘ
- ČĚ È ÃÀÄĄÂ ĚČÊČ ĈĚĚÉĘĚĚ ĚĘDÊÉĘĚĈĚDžÉÉÊ ĚE DDžĈČĈĚĈ

- ĘČE DĖÈ DžČÇ ÃČE ĘĚÈ DŽĐÄĚÉÊ ČÊĘÊÉÉĚĚ ÊÜĚĚĈČDžDE ĘD ĚÊÉ DŽÉ DÉĚĚČ
- ČE ĘČDŽÉ E ĚĚĘČÉ ÉĚDŽDžČÃÄ ÃDÉĘDĚ DÃDŽÉ E ĊĚÉ Đ Č Ê DžČĂ
- ĚĚÉ Ę Ê ĚDŽÉ Č DE ĈĚŲĘĚĈČ ÃÇĠHHĬ ĖĒFHI FĖ ŽĒHĒĠĖIJ FĖ IJHFĞH ŽHHÍIHĠĒFH ĬHI ÎHĠÍĒĠĖ FĖ ĒG

EL EFECTO PLACEBO ES REALMENTE IMPORTANTE

INCLUSO PARA LOS MÉDICOS … LA PARÁBOLA DE SCOTT



Placebo

- Opioides endógenos
- Dopamina…

Three arms:

1) a no-treatment arm that controlled for regression to the mean and normal fluctuations in illness (‘‘waitlist’’)

2) a placebo treatment arm which used a validated placebo acupuncture device administered in a business- like no frills clinical context (‘‘limited placebo’’)

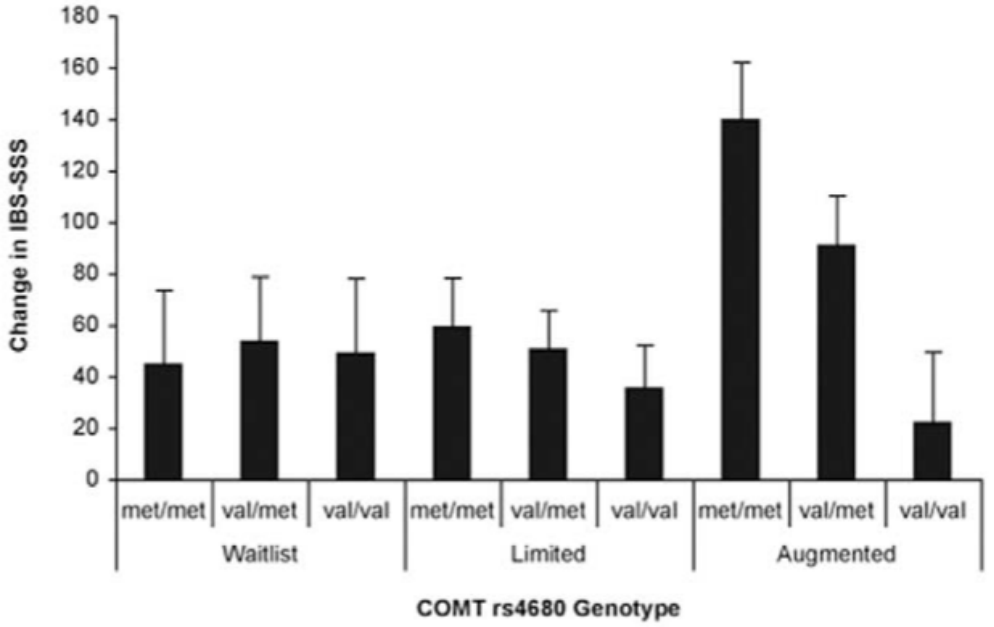
3) a limited placebo arm augmented with a supportive warm provider who expressed confidence in the effectiveness of the treatment (‘‘augmented placebo’’).

OPEN ACCESS Freely available online

PLOS ONE

Catechol-O-Methyltransferase val158met Polymorphism Predicts Placebo Effect in Irritable Bowel Syndrome

Kathryn T. Hall[1,2]*, Anthony J. Lembo[2,3], Irving Kirsch[2,4], Dimitrios C. Ziogas[5], Jeffrey Douaiher[6], Karin B. Jensen[2,7], Lisa A. Conboy[2], John M. Kelley[2,7,8], Efi Kokkotou[2,3], Ted J. Kaptchuk[1,2]



Rakvåg TT, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain. 2005 Jul;116(1-2):73-8

Table 5
COMT genotype and allele frequencies in the total of 207 cancer patients

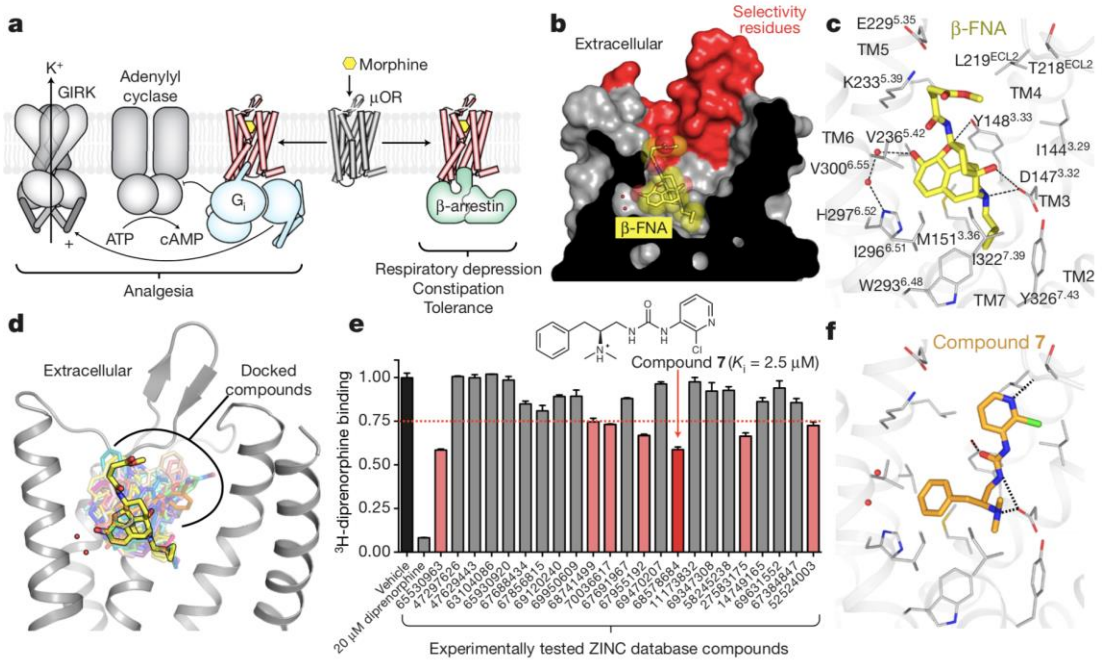
	Genotype frequencies			Allele frequencies	
	Val/Val	Val/Met	Met/Met	Val	Met
N	44	96	67	184	230
Relative frequencies	0.21	0.47	0.32	0.44	0.56

Table 6
Pharmacological observations for Val158Met genotype groups

	Val/Val ($n=44$)	Val/Met ($n=96$)	Met/Met ($n=67$)
Morphine dose (mg/24 h)[a,b]	155 (160)	117 (100)	95 (99)
Morphine serum (nmol/l)	119 (199)	86 (88)	78 (72)
M6G serum (nmol/l)	711 (992)	506 (493)	410 (484)
M3G serum (nmol/l)	3809 (4436)	2812 (2209)	2536 (2707)

Y ¿ QUÉ HAY DE NUEVO EN ANALGESIA FARMACOLÓGICA?

- Opioides sesgados
- Opioides bifuncionales
- Opioides moduladores alostéricos
- Moduladores del receptor opioide patológico
- Methoxyflurano
- Sevoflurano en úlceras
- Bupivacaína liposomal
- Celecoxib / Tramadol
- Desinferatoxina (TPRV1)
- Optogenética
- Opioides foto-enjaulados



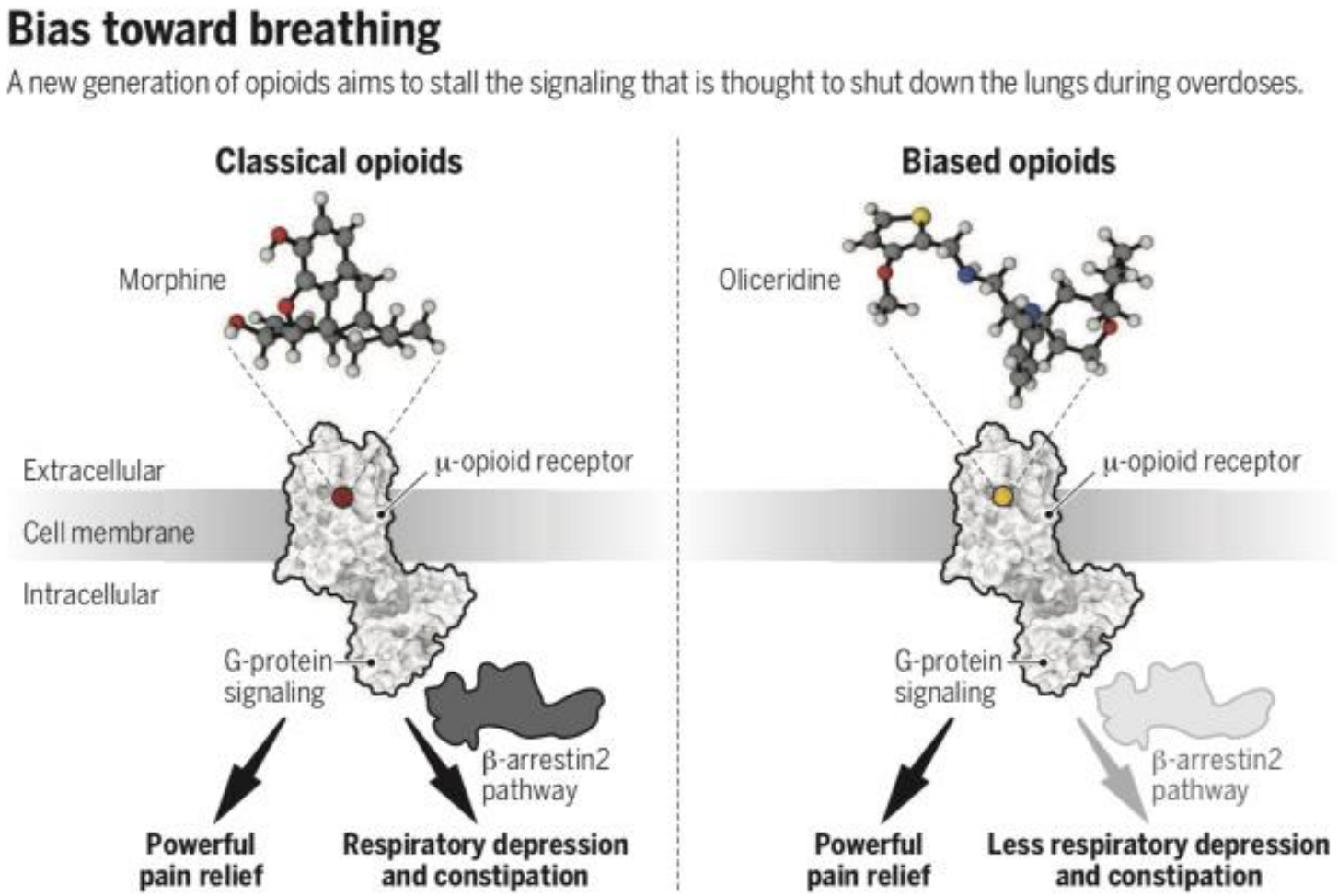
Structure–based discovery of opioid analgesics with reduced side effects

Aashish Manglik[1]*, Henry Lin[2]*, Dipendra K. Aryal[3]*, John D. McCorvy[3], Daniela Dengler[4], Gregory Corder[5], Anat Levit[2], Ralf C. Kling[4,6], Viachaslau Bernat[4], Harald Hübner[4], Xi-Ping Huang[3], Maria F. Sassano[3], Patrick M. Giguère[3], Stefan Löber[4], Da Duan[2], Grégory Scherrer[1,5], Brian K. Kobilka[1], Peter Gmeiner[4], Bryan L. Roth[3] & Brian K. Shoichet[2]

APROBADO POR LA FDA AGOSTO 2020

OPIOIDES SESGADOS - OLICERIDINA

OPIOIDES SESGADOS - OLICERIDINA



Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

A randomized, Phase IIb study investigating oliceridine (TRV130), a novel μ-receptor G-protein pathway selective (μ-GPS) modulator, for the management of moderate to severe acute pain following abdominoplasty

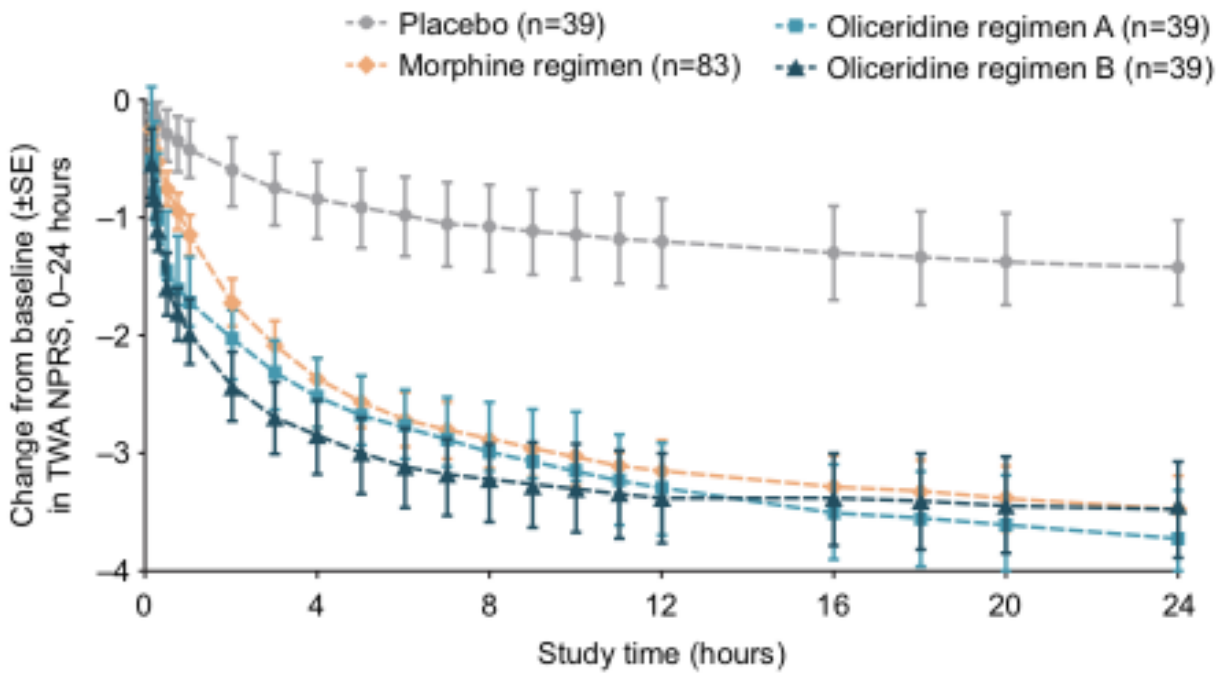
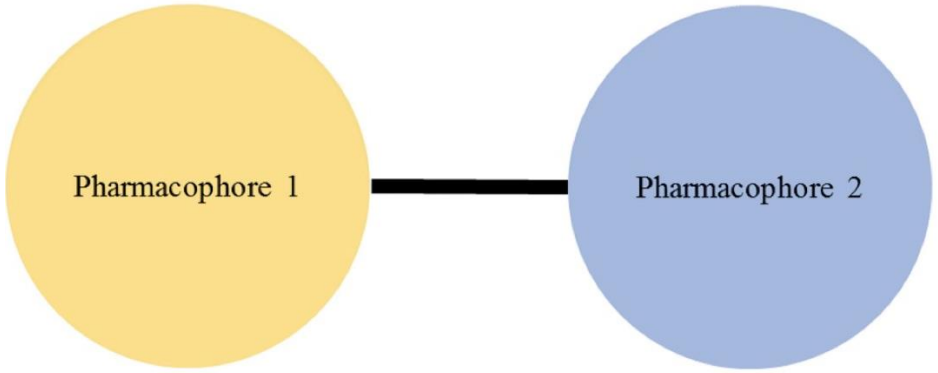


Table 2 TEAEs in ≥10% of patients

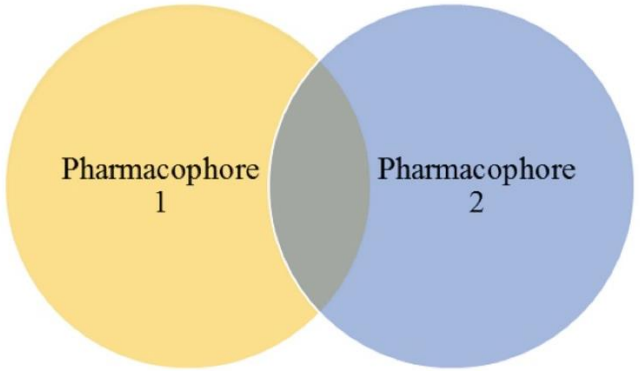
	Placebo (n=39)	Oliceridine		Morphine regimen (n=83)
		Regimen A (n=39)	Regimen B (n=39)	
TEAEs in ≥10% of patients				
Patients with ≥1 TEAE	24 (62%) [48]	26 (67%) [54]	32 (82%) [67]	78 (94%) [238]
Gastrointestinal disorders				
Nausea	7 (18%) [7]	16 (41%) [17]	18 (46%) [18]	60 (72%) [63]
Vomiting	3 (8%) [3]	6 (15%) [6]	6 (15%) [6]	35 (42%) [35]
Nervous system disorders				
Headache	5 (13%) [5]	6 (15%) [6]	6 (15%) [6]	14 (17%) [14]
Dizziness	1 (3%) [1]	1 (3%) [1]	4 (10%) [4]	7 (8%) [7]
Somnolence	0	0	2 (5%) [2]	10 (12%) [10]
Vascular disorders				
Hypotension	1 (3%) [1]	6 (15%) [6]	3 (8%) [3]	7 (8%) [7]
Phlebitis	4 (10%) [4]	0	2 (5%) [2]	1 (1%) [2]
Respiratory, thoracic, and mediastinal disorders				
Hypoventilation	4 (10%) [5]	4 (10%) [4]	12 (31%) [12]	34 (41%) [34]
Respiratory depression	0 (0) [0]	3 (8%) [3]	0 (0) [0]	9 (11%) [10]

Notes: Data are number of patients (%) [number of events]. Loading/demand doses (mg/mg): oliceridine regimen A, 1.5/0.10; oliceridine regimen B, 1.5/0.35; morphine, 4.0/1.0.
Abbreviation: TEAE, treatment-emergent adverse event.



FARMACOFORO BIVALENTE

FARMACOFORO BIFUNCIONAL



Bifunctional opioid receptor ligands as novel analgesics

Christopher W. Cunningham*, Waleed M. Elballa, Stephanie U. Vold

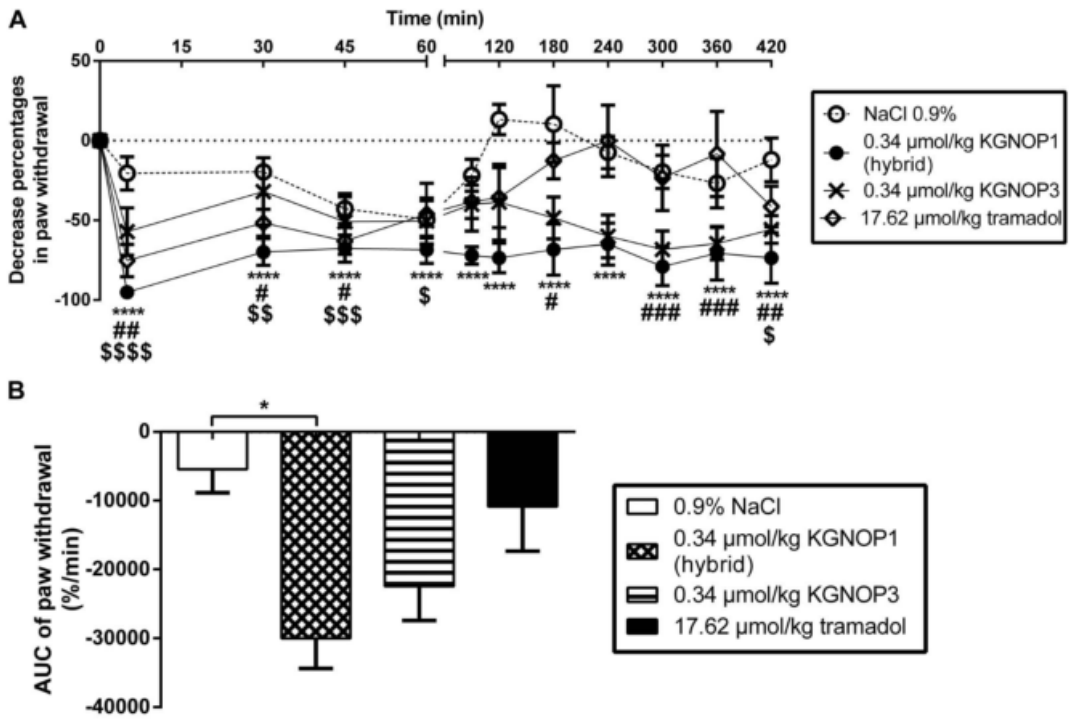
Department of Pharmaceutical Sciences, Concordia University Wisconsin, Mequon, WI, USA

Neuropharmacology 151 (2019) 195–207

Highlights

- Bifunctional opioid analgesics have therapeutic advantages over μOP receptor agonists.
- μOP/δOP receptor ligands produce antinociception with minimal tolerance.
- μOP/κOP receptor ligands may lead to non-addicting analgesics.
- μOP/κOP receptor ligands are being studied in alcohol use disorders.
- μOP/NOP receptor ligands have an improved safety profile in animal models of pain.

OPIOIDES BIFUNCIONALES



Research Paper

PAIN

OPEN

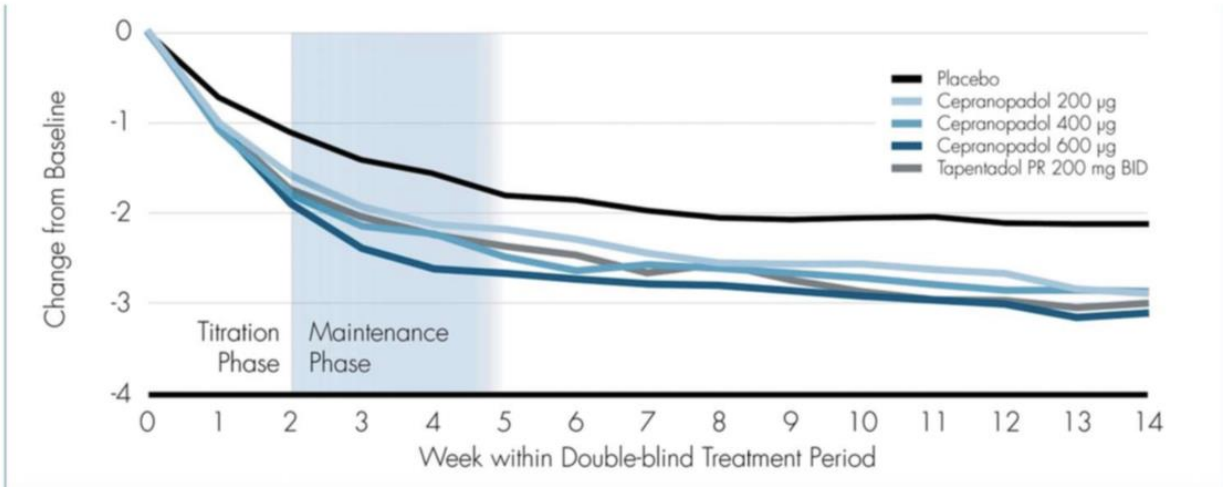
Bifunctional peptide-based opioid agonist/ nociceptin antagonist ligand for dual treatment of nociceptive and neuropathic pain

Camille Lagard[a,b,c], Lucie Chevillard[a,b,c], Karel Guillemyn[d], Patricia Risède[a,b,c], Jean-Louis Laplanche[a,b,c,e], Mariana Spetea[f], Steven Ballet[d], Bruno Mégarbane[a,b,c,g,*]

KGNOP1

- **Agonista mu, delta y kappa**
- **Antagonista NOP**

OPIOIDES BIFUNCIONALES - KGNOP1



Research Paper
PAIN
OPEN

Cebranopadol, a novel first-in-class analgesic drug candidate: first experience in patients with chronic low back pain in a randomized clinical trial

Annette Christoph[a,*], Marie-Henriette Eerdekens[a], Maurits Kok[a], Gisela Volkers[a], Rainer Freynhagen[b,c]

CEBRANOPADOL

- **Agonista mu, delta y kappa**
- **Agonista NOP**

OPIOIDES BIFUNCIONALES - CEBRANOPADOL

OPIOIDES MODULADORES ALOSTÉRICOS

REVIEW ARTICLE THEMED ISSUE

Allostery at opioid receptors: modulation with small molecule ligands

Discovery of positive allosteric modulators and silent allosteric modulators of the μ-opioid receptor

Neil T. Burford[a], Mary J. Clark[b], Tom S. Wehrman[c], Samuel W. Gerritz[a], Martyn Banks[a], Jonathan O'Connell[a], John R. Traynor[b,1], and Andrew Alt[a,1]

1521-0111/93/2/157–167$25.00
MOLECULAR PHARMACOLOGY

https://doi.org/10.1124/mol.117.108561
Mol Pharmacol 93:157–167, February 2018

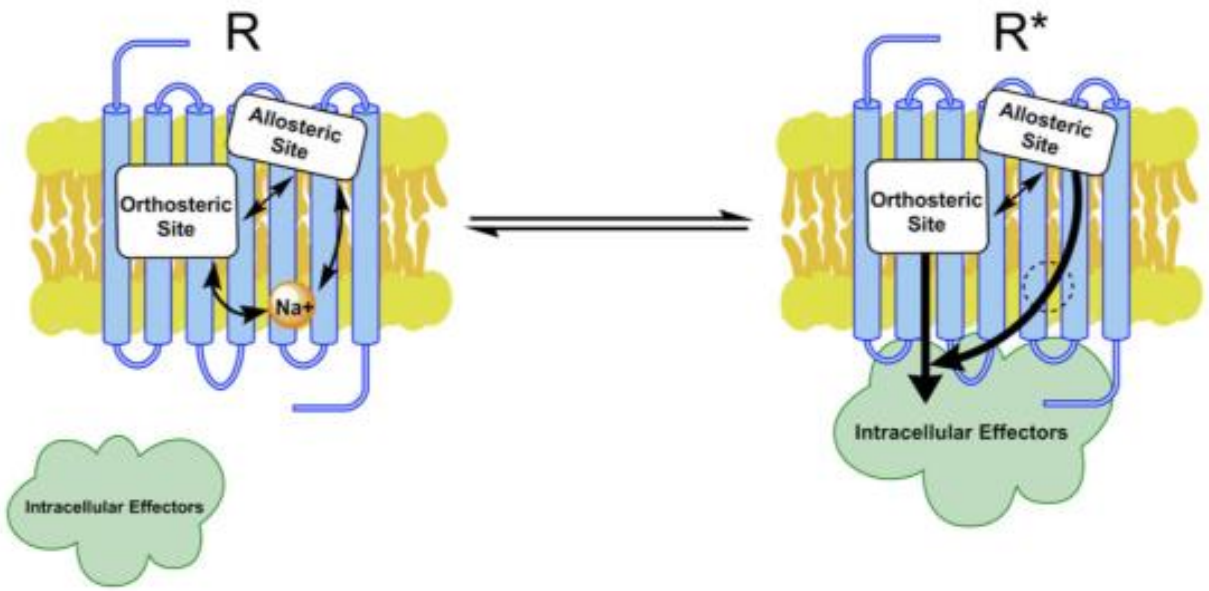
Pharmacologic Evidence for a Putative Conserved Allosteric Site on Opioid Receptors

Review

Development of allosteric modulators of GPCRs for treatment of CNS disorders

Hilary Highfield Nickols [a], P. Jeffrey Conn [b,*]

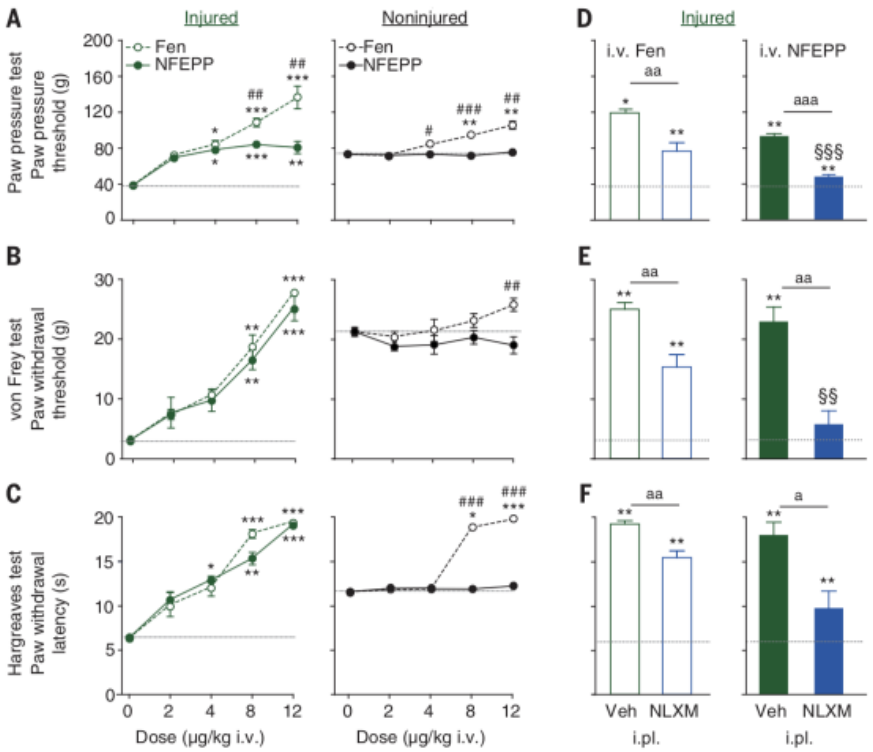
[a] Division of Neuropathology, Department of Pathology, Microbiology and Immunology, Vanderbilt University, USA
[b] Department of Pharmacology, Vanderbilt University, Nashville, TN 37232, USA



	μ-OR	δ-OR	κ-OR
Salvinorin A	x	–	–
Cannabidiol	x	x	–
THC	x	x	–
BMS-986122	x	–	–
BMS-986121	x	–	–
BMS-986124	–	–	–
BMS-986187	x	x	–
MS1	x	–	–
Ignavine	x	–	–
SCH-202676	x	x	x

[a]To date, no modulators have been identified for NOP receptors.

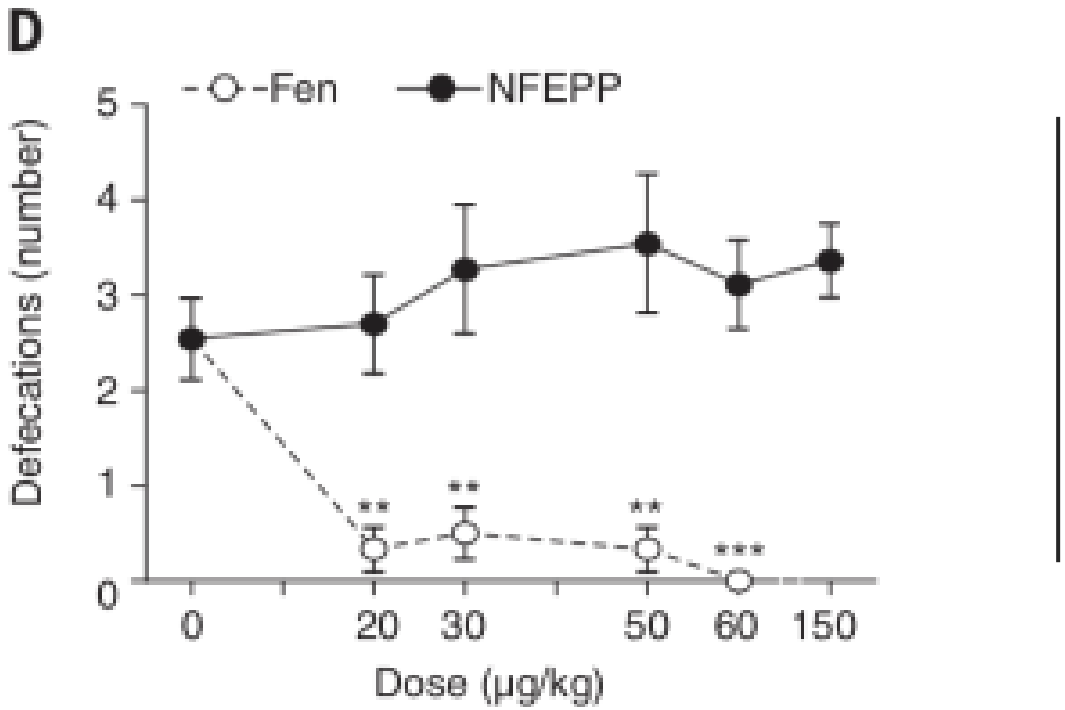
OPIOIDES MODULADORES ALOSTÉRICOS

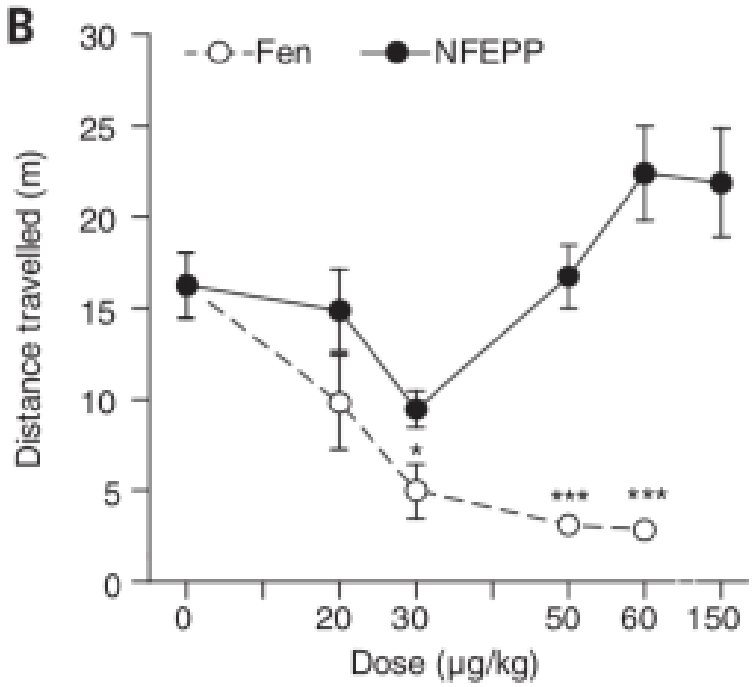


PAIN RESEARCH

A nontoxic pain killer designed by modeling of pathological receptor conformations

MODULADOR DEL RECEPTOR OPIOIDE PATOLÓGICO



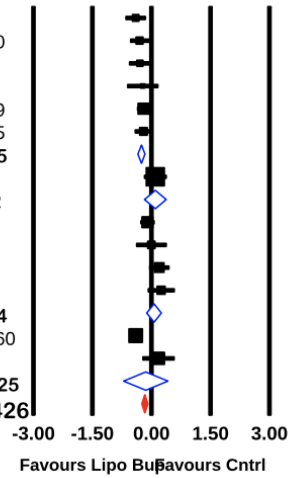


MODULADOR DEL RECEPTOR OPIOIDE PATOLÓGICO

Role of Periarticular Liposomal Bupivacaine Infiltration in Patients Undergoing Total Knee Arthroplasty—A Meta-analysis of Comparative Trials

Preet Mohinder Singh, MD, DNB [a, *], Anuradha Borle, MD [a], Anjan Trikha, MD [a], Lia Michos, BS [b], Ashish Sinha, MD, MBA [c], Basavana Goudra, MD, FRCA, FCARCSI [d]

Group by Subgroup	Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value	Liposomal Bup	Control	Relative weight
Femoral	Cien et al 2015	-0.40	0.13	-0.65	-0.15	0.00	57	65	13.43
Femoral	Broome et al 2014	-0.30	0.12	-0.53	-0.07	0.01	100	100	15.69
Femoral	Surdam et al 2016	-0.29	0.14	-0.56	-0.02	0.03	40	40	11.80
Femoral	Emerson JR et al 2016	-0.22	0.20	-0.60	0.16	0.26	36	36	5.65
Femoral	Barrington et al (B) 2016	-0.20	0.08	-0.35	-0.05	0.01	316	349	35.23
Femoral	Sporer et al 2016	-0.20	0.11	-0.41	0.01	0.07	272	325	18.20
Femoral		**-0.25**	**0.05**	**-0.35**	**-0.16**	**0.00**	**821**	**915**	
In-Art	Jain et al 2016 (I)	0.10	0.14	-0.18	0.38	0.48	63	82	100.00
In-Art		**0.10**	**0.14**	**-0.18**	**0.38**	**0.48**	**63**	**82**	
Infil	Schroer et al 2016	-0.10	0.09	-0.27	0.07	0.24	58	53	36.63
Infil	Barrington et al 2016	0.00	0.19	-0.38	0.38	1.00	40	38	16.49
Infil	Jain et al 2016 (P)	0.20	0.12	-0.04	0.44	0.11	63	62	27.35
Infil	Collis et al 2016	0.25	0.17	-0.08	0.58	0.14	54	51	19.52
Infil		**0.07**	**0.09**	**-0.12**	**0.25**	**0.48**	**215**	**204**	
Multi	Chughtai et al 2016	-0.40	0.01	-0.41	-0.39	0.00	14668	80160	56.05
Multi	White et al 2016	0.18	0.20	-0.22	0.58	0.37	55	65	43.95
Multi		**-0.15**	**0.29**	**-0.71**	**0.42**	**0.61**	**14723**	**80225**	
Overall		**-0.17**	**0.04**	**-0.25**	**-0.09**	**0.00**	**15822**	**81426**	



Pooled mean difference in length of stay (Liposomal Bupivacaine - Control)

- Bupivacaína liposomal permite un mejor control del dolor perioperatorio solo marginalmente (solo 1 punto) en pacientes sometidos a PTR.
- El uso de la infiltración de bupivacaína liposomal también contribuye a la estancia hospitalaria pero solo mínimamente (1/4 de día).

PENTHROX ® - Methoxyflurane

Eager et al. Systematic Reviews (2021) 10:47
https://doi.org/10.1186/s13643-021-01600-0

Systematic Reviews

PROTOCOL Open Access

Inhaled methoxyflurane (Penthrox) for analgesia in trauma: a systematic review protocol

Michael M. Eager[1,2], Grant S. Nolan[3,4], Kathryn Tonks[2], Anoopama Ramjeeawon[3*] and Natalie Taylor[1]

J Anesth Hist. 2020 Jun;6(2):79-83. doi: 10.1016/j.janh.2019.07.001. Epub 2019 Oct 15.

The Reincarnation of Methoxyflurane

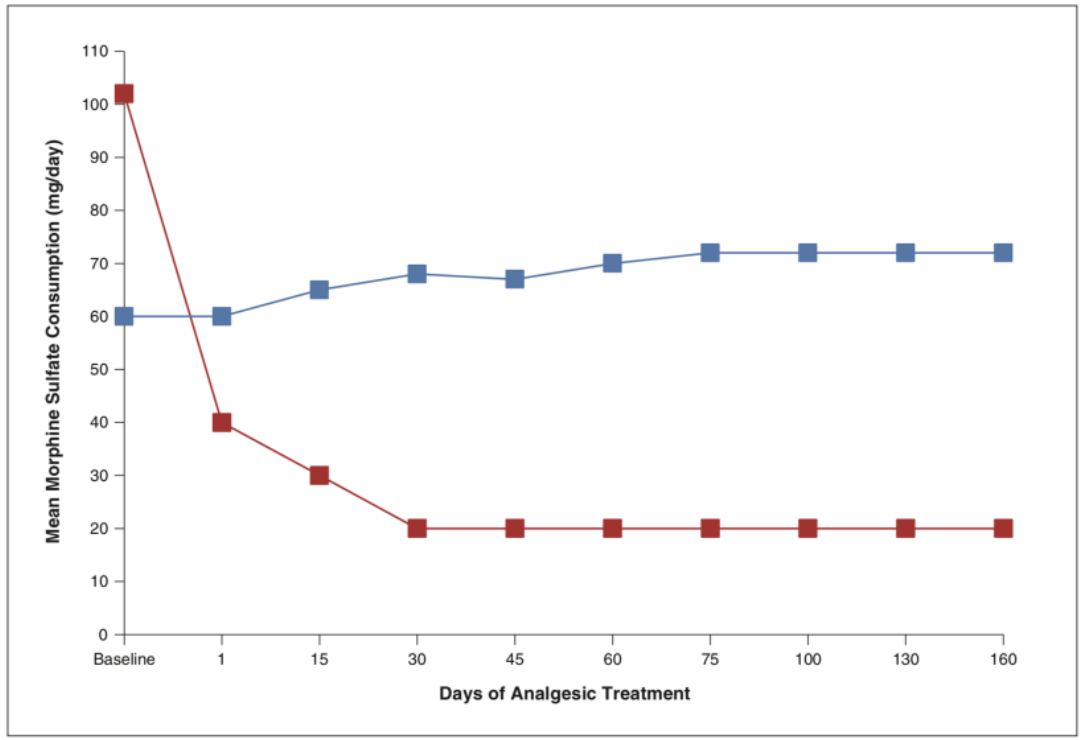
Methoxyflurane-induced nephrotoxicity continues to be a major concern, but with cautious administration of recommended doses methoxyflurane has been established as a remarkably safe analgesic agent with minimal side effects for patients in need of rapid and potent pain relief.

Efficacy and safety of topical sevoflurane in the treatment of chronic skin ulcers

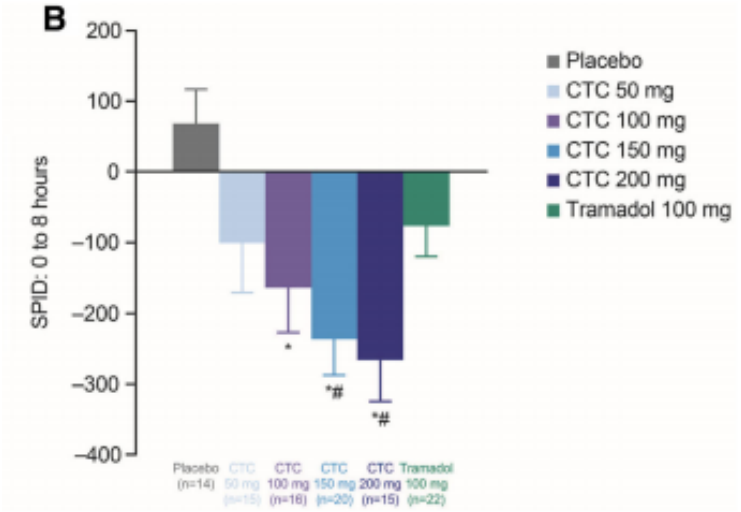
F. Dámaso Fernández-Ginés, M.Pharm., Pharmacy Department, Torrecárdenas Hospital, Almería, Spain.

Purpose. Results of efficacy and safety assessments of topical sevoflurane use in patients with long-term treatment-refractory vascular

Figure 1. Mean daily consumption of morphine sulfate during study by patients treated with sevoflurane (red line) or without sevoflurane (blue line).

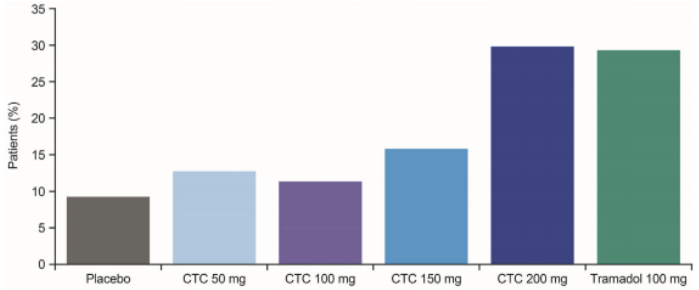


Sevoflurano tópico en úlceras



Co-crystal of Tramadol–Celecoxib in Patients with Moderate to Severe Acute Post-surgical Oral Pain: A Dose-Finding, Randomised, Double-Blind, Placebo- and Active-Controlled, Multicentre, Phase II Trial

José López-Cedrún[1] · Sebastián Videla[2,11] · Miguel Burgueño[3] · Inma Juárez[4] ·



CO-CRISTAL CELECOXIB/TRAMADOL

DESINFERATOXINA

Published in final edited form as:
Pain. 2018 October ; 159(10): 2105–2114. doi:10.1097/j.pain.0000000000001314.

Long-term pain relief in canine osteoarthritis by a single intra-articular injection of resiniferatoxin, a potent TRPV1 agonist

M. J. Iadarola[#1,*], **M. R. Sapio**[#1], **S. J. Raithel**[1], **A.J. Mannes**[1], **D. C. Brown**[2]

[1]Department of Perioperative Medicine, Clinical Center, National Institutes of Health.

[2]Translational and Comparative Medical Research, Elanco Animal Health.

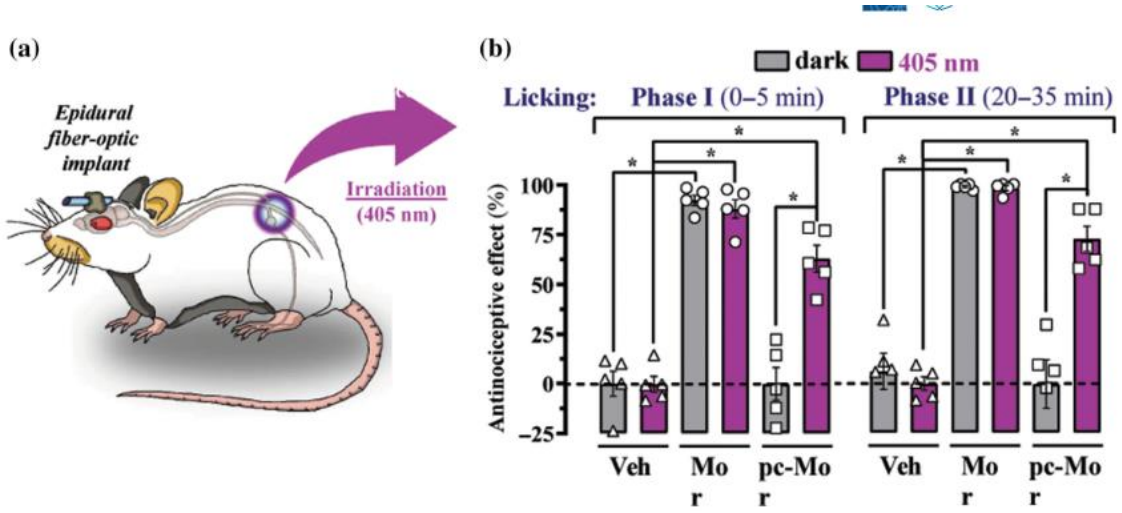
[#] These authors contributed equally to this work.

4/12/2021

Grünenthal acquires Mestex AG and its Phase-III-ready investigational medicine MTX-071 for the treatment of pain associated with osteoarthritis of the knee

- With the acquisition of Mestex AG, Grünenthal secures global rights for an attractive late-stage asset that could offer an innovative therapy option for millions of patients affected by pain related to osteoarthritis of the knee.
- MTX-071 is a highly potent Transient Receptor Potential Vanilloid 1 (TRPV1) agonist. Its administration can reversibly defunctionalise TRPV1-expressing nociceptors. This can result in long lasting pain relief.

MORFINA FOTO-ENJAULADA



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DOI: 10.1111/bph.15645

THEMED ISSUE ARTICLE

Remote local photoactivation of morphine produces analgesia without opioid-related adverse effects

Marc López-Cano[1,2] | Joan Font[3,4] | Ester Aso[1,2] | Kristoffer Sahlholm[1,2,5,6] | Gisela Cabré[7] | Jesús Giraldo[8,9,10] | Yves De Koninck[11,12] | Jordi Hernando[7] | Amadeu Llebaria[3] | Víctor Fernández-Dueñas[1,2] | Francisco Ciruela[1,2]

OPTOGENETICS

SCIENTIFIC REPORTS

OPEN

Optogenetic silencing of nociceptive primary afferents reduces evoked and ongoing bladder pain

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Vijay K. Samineni[1,2], Aaron D. Mickle[1,2], JangyeolYoon[3], Jose G. Grajales-Reyes[1], Melanie Y. Pullen[1], Kaitlyn E. Crawford[3], Kyung Nim Noh[3], Graydon B. Gereau[1,2], Sherri K. Vogt[1,2], H. Henry Lai[2,4], John A. Rogers[3,5,6] & Robert W. Gereau IV[1,2]

- SCientifiC **RePORtS** | 7: *15865* | DOI:10.1038/s41598-017-16129-3

CONCLUSIONES

- ✓PRECISAMOS DE NUEVOS ANALGÉSICOS SEGUROS Y ESPECIALMENTE PARA DOLOR NEUROPÁTICO Y NOCIPLÁSTICO
- ✓EL PACIENTE DEBE SER INFORMADO SOBRE LO QUE LE PASA – EXPLICAR EL DOLOR Y QUE SEA PARTE ACTIVA EN EL TRATAMIENTO
- ✓ABORDAR FACTORES MODIFICADORES
- ✓AJUSTAR EXPECTATIVAS
- ✓PRIMAR LA SEGURIDAD A LARGO PLAZO EN EL DOLOR CRÓNICO
- ✓TENEMOS QUE SEGUIR INFORMANDO DEL MODELO BIOPSICOSOCIAL A TODOS LOS COMPAÑEROS Y GESTORES
- ✓SIEMPRE ALIVIAR Y ACOMPAÑAR

MUCHAS GRACIAS POR SU ATENCIÓN

¿PREGUNTAS?