GUIÓN

- *Nuevas moléculas*
- *Dolor irruptivo*
- *Abuso de analgésicos*
- *Cambios en vía de administración.*
- *Sistema de liberación novedosos*

Table 1 Clinical bullet points

Tapentadol

- available information is based on studies from non-cancer patients
- reduces gastrointestinal side effects and pruritus
- scarcity of information about analgesic power (reasonable choice for in opioid-rotation?)
- lack of immediate release formulations

Sustained release oxycodone naloxone combinations

- promising approach for the reduction of opioid induced constipation
- 1st RCT in the field of cancer pain now available
- caution in case of liver failure (reversal of opioid analgesia)
- bioavailability of high oral naloxone doses remains unclear: avoid doses beyond the threshold provided by manufacturers!

Rapid onset fentanyl (ROF)

- two guidelines (NICE & EAPC) now available
- Recommendations from these guidelines are in part contradictory
- Take short history of pain episodes and describe ROF to patients who suffer from pain attacks with onset within 10 to 15 minutes

Nabiximols

- 1st RCT from cancer pain reports unfavorable risk / benefit ratio

Ketamine

- practice chancing RCT reports that Ketamine lacks net clinical benefit as an adjunct to opioids as standard coanalgesic

Denosumab (RANK-ligand)

- promising future treatment option for the prevention and treatment of cancer pain[a]
- promising future treatment option for prevention of scelatal related events[a]
- clinical relevance of current findings should be judged critically on an individual basis
- Economic aspects must be considered

Psychosocial interventions and early Palliative Care (ePC)

- new RCTs highlight relevance of psychosocial expertise for cancer pain management
- recommendation of ePC by ASCO may facilitate spread of multimodal and interdisciplinary concepts for cancer pain management

Table 1. New Available Opioid Formulations in Cancer Pain Management

Opioid	Approximate Ratio to Oral Morphine	Mechanism	Toxicity	Notes
Hydrocodone	2:1	μ-receptor agonist	Typical opioid adverse effects	Existing data compared with codeine only
Oxymorphone	1.8:1	μ-receptor agonist	Typical opioid adverse effects	Similar to oxycodone
Tapentadol	1:3.3	Weak μ-receptor agonist; inhibition noradrenaline reuptake	Typical opioid adverse effects	Potential for neuropathic pain; low tendency to increase dose; to be tested in large studies
Oxycodone plus naloxone	1.5:1	μ-receptor agonist; intestinal μ-receptor antagonist	Typical opioid adverse effects with less constipation	Targeted therapy for constipation; to be compared with common laxative regimens
Buprenorphine plus naloxone	Not available	Partial μ-receptor agonist; μ-receptor antagonist	Headache, constipation, insomnia, and withdrawal syndrome, each reported by > 20% of patients	No data on patients with cancer
Rapid-onset opioids (fentanyl)	Buccal tablet, 100:1; sublingual, 100:1; nasal, 200:1; nasal-pectin, 100:1	μ-receptor agonist	Typical opioid adverse effects; local	More rapid than oral morphine for breakthrough pain; cost effectiveness to be established

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HYDROCODONE

Derivado de codeína.

Experiencia previa con paracetamol.

Recientes Especialidades de larga duración sin paracetamol.

Extended-release hydrocodone of 45 or 50 mg per day -> morphine equivalent of 90 or 100 mg per day.

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Toxicidad: Pérdida auditiva

No estudios en pacientes oncológicos

Abuse Deterrent Prolonged Release Erodible Matrix technology

Figure 1. Egalet® ADPREM tablets.

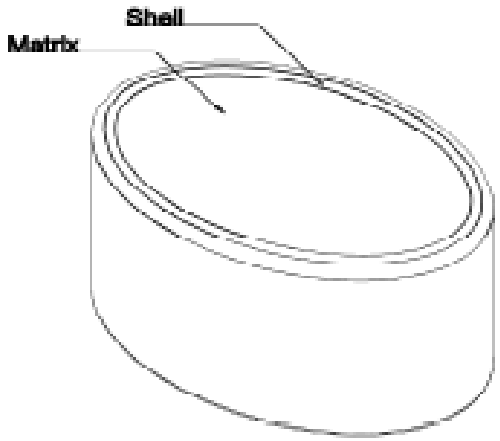
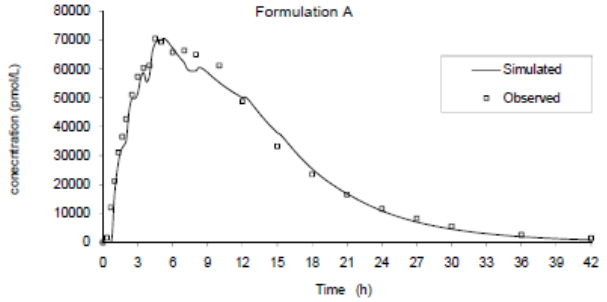


Figure 8. Simulated mean curves obtained based on IVIVC (lines) vs. observed mean values (square = formulation A, diamond = formulation B and triangle = formulation C): internal predictibility.



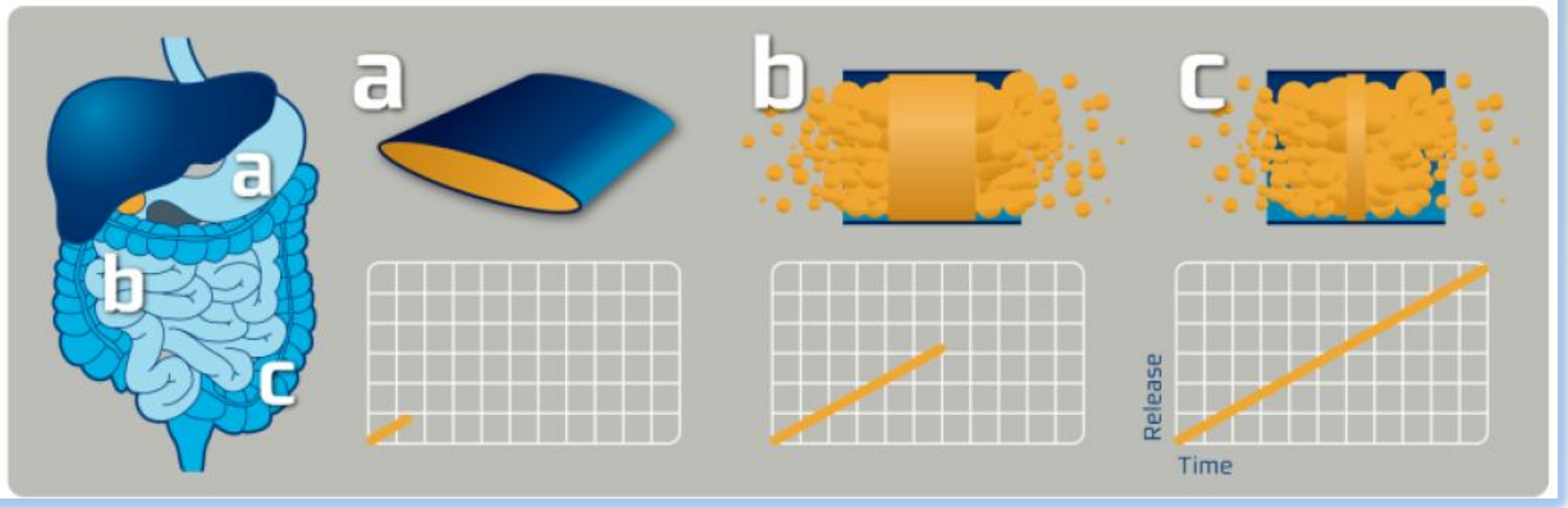
Area de un tamaño definido erosionable por fluido GI.

Liberación prolongada y controlada de una fracción del fármaco.

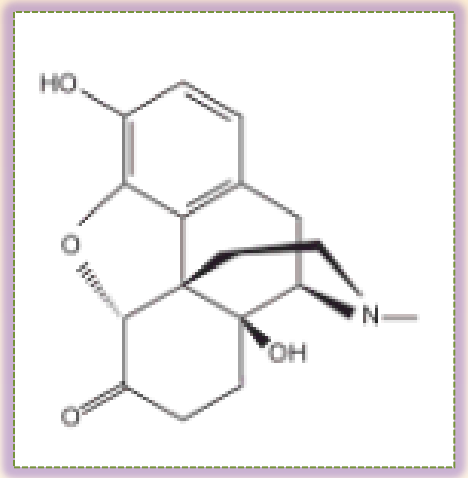
EGALET® ADPREM* - TECHNOLOGY

* Abuse Deterrent Prolonged Release Erodible Matrix

a) Egalet® tablet reaches the stomach, release of drug begins
b) Egalet® tablet during release
c) Egalet® tablet has released almost completely



OXIMORFONA



Matriz hidrofílica agregada con liberación retardada según penetra agua.

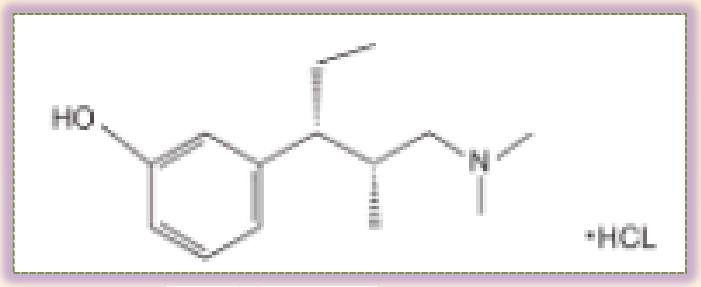
Niveles plasmáticos mantenidos por 12 h.

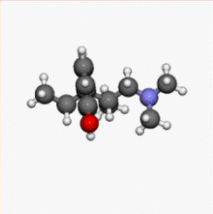
Mayor afinidad por receptor μ que morfina.

Equivalencia 1.8:1

Util en situaciones de dolor estable

TAPENTADOL





Event	Tapentadol ER (n = 894)	Oxycodone CR (n = 223)
Constipation	202 (22.6)	86 (38.6)
Nausea	162 (18.1)	74 (33.2)
Vomiting	63 (7.0)	30 (13.5)
Dry mouth	81 (9.1)	10 (4.5)
Diarrhea	71 (7.9)	12 (5.4)
Dizziness	132 (14.8)	43 (19.3)
Somnolence	133 (14.9)	25 (11.2)
Headache	119 (13.3)	17 (7.6)
Fatigue	87 (9.7)	23 (10.3)
Pruritus	48 (5.4)	23 (10.3)

Mecanismo de acción doble:

- Estimulante receptor μ
- Inhibidor recaptación noradrenalina

Inicialmente como preparado de acción rápida, luego en preparado de acción retardada 2 veces/día.

Dolor moderado-intenso

Fármaco prometedor en dolor neuropático.

Reducción de la tolerancia

Menor incidencia de efectos secundarios gastrointestinales.

TAPENTADOL

Ventajas

Reduccion de efectos secundarios gastrointestinales.

Inconvenientes

No datos de ensayos comparativos en cáncer.

Papel en pacientes ya tratados con opioides.

Precio

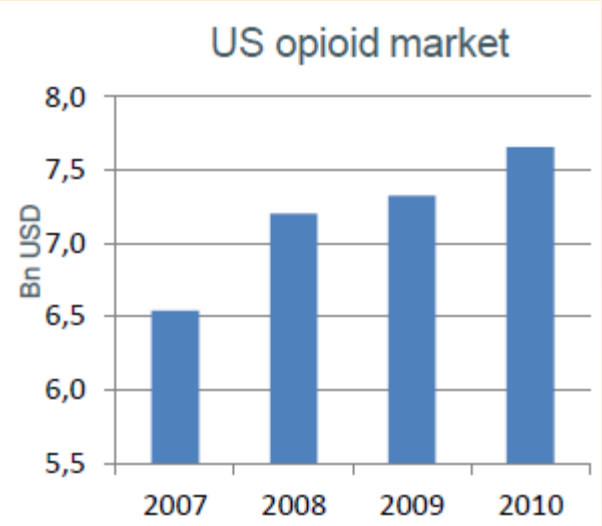
Ausencia de preparados de liberación rápida o inmediata.

Abuso de analgésicos y psicotropos

ESCALADA ABUSO DE PSICOTROPOS

Escalada en el abuso de

- Depresores SNC
- Estimulantes SNC
- Opioides

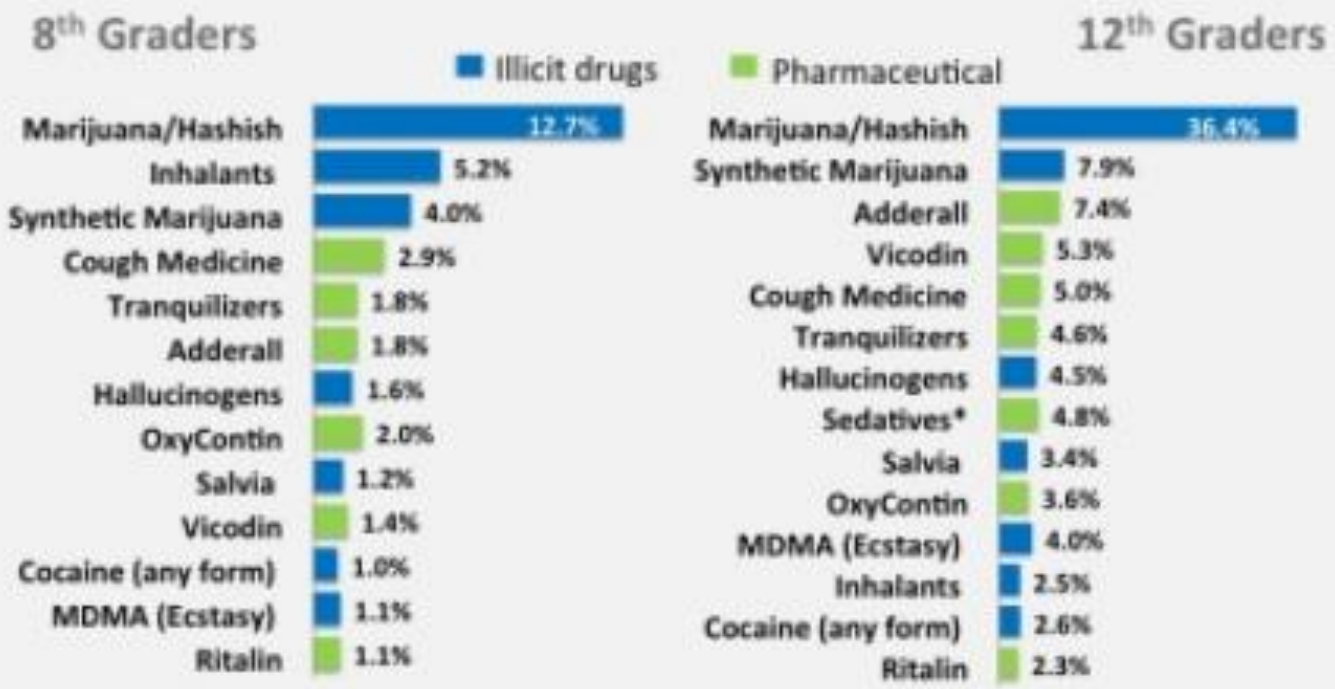


Manipulación de los preparados para su uso por otras vías

Desarrollo de sistemas para evitar el abuso.

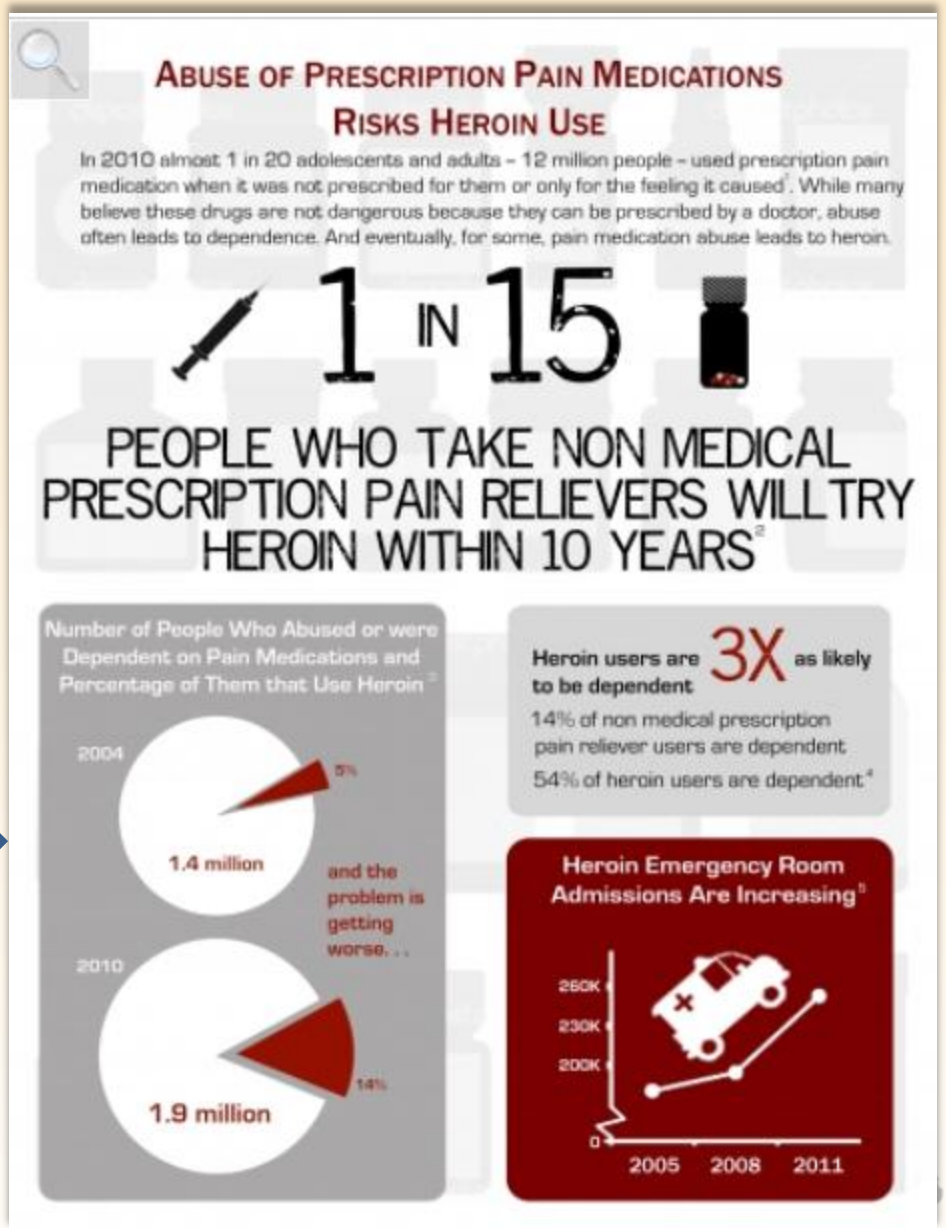
- Estabilidad mecánica: estructura rígida, no soluble
- Gelificación
- Combinación con antagonista

Top Drugs among 8th and 12th Graders, Past Year Use

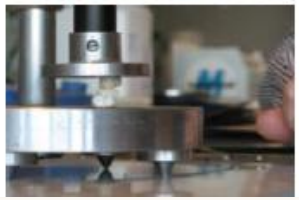


* Only 12th graders surveyed about sedatives use

Source: University of Michigan, 2013 Monitoring the Future Study


ABUSE OF PRESCRIPTION PAIN MEDICATIONS
RISKS HEROIN USE
In 2010 almost 1 in 20 adolescents and adults – 12 million people – used prescription pain medication when it was not prescribed for them or only for the feeling it caused[1]. While many believe these drugs are not dangerous because they can be prescribed by a doctor, abuse often leads to dependence. And eventually, for some, pain medication abuse leads to heroin.
1 IN 15
PEOPLE WHO TAKE NON MEDICAL PRESCRIPTION PAIN RELIEVERS WILL TRY HEROIN WITHIN 10 YEARS[2]
Number of People Who Abused or were Dependent on Pain Medications and Percentage of Them that Use Heroin[3]
2004
5%
1.4 million
and the problem is getting worse. . .
2010
14%
1.9 million
Heroin users are 3X as likely to be dependent
14% of non medical prescription pain reliever users are dependent
54% of heroin users are dependent[4]
Heroin Emergency Room Admissions Are Increasing[5]
260K
230K
200K
0
2005
2008
2011

BEST-IN-CLASS TAMPER RESISTANCE



NO EASY EXTRACTION

NO INJECTION
- Does not dissolve
- Turns into gel

NO SNORTING
- Impossible to crush
- Extremely difficult to grind

NO SMOKING
- Poor combustion
(melts and develops 'plastic-like' odors)

NO CHEWING
- Not possible to chew due to extreme hardness of tablet

Dolor irruptivo/ nuevas vías fentanilo

Identificando dolor irruptivo: Algoritmo diagnóstico

¿Tiene el paciente dolor basal?

↓

¿Está el dolor basal controlado adecuadamente?

↓

¿Presenta el paciente exacerbaciones transitorias de su dolor?

Identificando dolor irruptivo: Algoritmo diagnóstico

Q1.Do you have pain related to your cancer?

Yes / No

If no, do not proceed with remainder of questionnaire

Q2. Is the pain present most of the time*, or would be present if not taking painkillers?

(* pain present for ≥12 hr/day during the last week)

Yes / No

If no, do not proceed with remainder of questionnaire

Q3. Is the pain well controlled for most of the time*?

(* pain rated as 'none' or 'mild' but not as 'moderate' or 'severe', for ≥12 hr/day during the last week)

Yes / No

If no, do not proceed with remainder of questionnaire

Q4.Do you have short - lived exacerbations of the pain ('breakthrough pain')?

Yes / No

If no, do not proceed with remainder of questionnaire

Q5.Are you taking a strong painkiller* for the constant pain ('background pain')?

(* e.g. morphine, fentanyl, hydromorphone, methadone, oxycodone)

Yes / No

If no, do not proceed with remainder of questionnaire

Table 1 The 'gold standard treatment' for breakthrough pain

1.	Rapidly effective (bioavailability)
2.	Easy to use (no injection)
3.	To avoid accumulation and long-lasting side effects: rapid elimination
4.	Well tolerated
5.	Easy to take, even in case of bowel occlusion
6.	Associated with few side effects
7.	Superior to conventional treatments

Management of breakthrough pain Lossignol and Dumitrescu 305

DOSIFICACIÓN

Se asume una relación entre

- dosis de fármacos opioides para el control del dolor basal
- dosis precisa para el control del dolor irruptivo.

Probablemente esta asociación sea apropiada para el dolor irruptivo no incidental

Recomendaciones:

- 5-10% de la dosis total diaria cada 2-3 h ("si precisa")
- la dosis cada 4 h utilizada como dosis de rescate cada 1-2 h
- 25-50% de la dosis cada 4 h administrada cada 4 h.

Una estrategia común:

- Doblar la dosis de rescate si la respuesta analgésica es inferior al 50%
- Incrementar la dosis en un 50% si la respuesta es del 50-100%

*Para **fentanilo** la dosis apropiada requiere titulación de la dosis de rescate en un proceso de tanteo en múltiples pasos*

- *iniciándose a dosis bajas a fin de minimizar efectos secundarios y mejorar tolerancia.*

Fentanilos rápidos

Fentanilo para dolor irruptivo

Agonista potente receptor μ

↓

100 x potencia morfina

↓

Lipofílico

↓

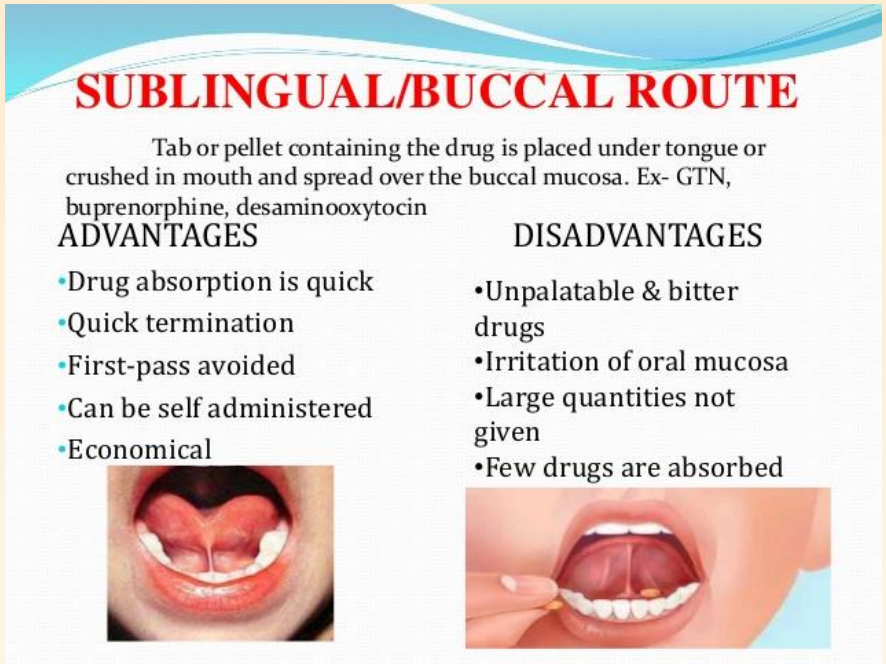
Metabolismo de 1º Paso

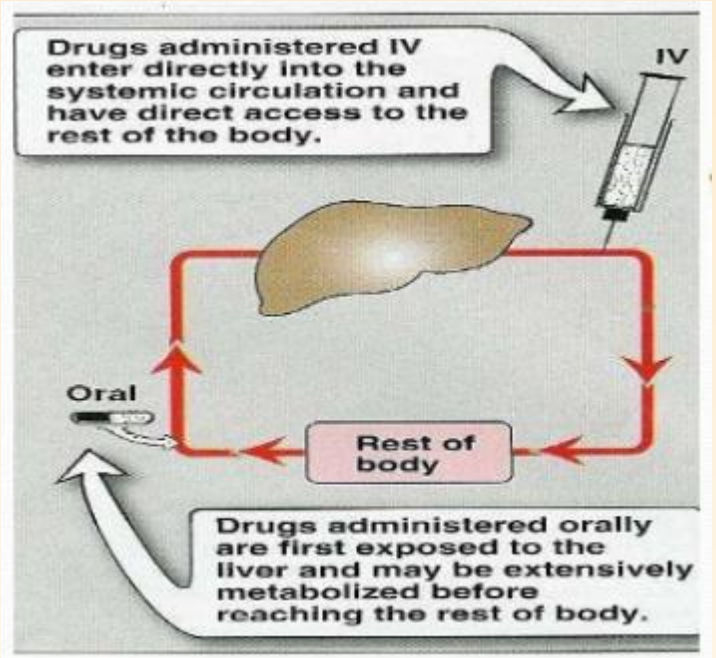
Generación de productos

- Transmucoso
- Bucal efervescente
- Sublingual
- Aerosol sublingual
- Intranasal:
  - *Solucion acuosa*
  - *Solucion gelificada*
- Titulación de dosis
- Coste-efectividad
- Abuso potencial

Acción en un plazo de 10-15 min

Las otras vías de Fentanilo: bucal





Areas de administración oral

- Sublingual
- Bucal
- Gingival
- *Máxima permeabilidad:sublingual*

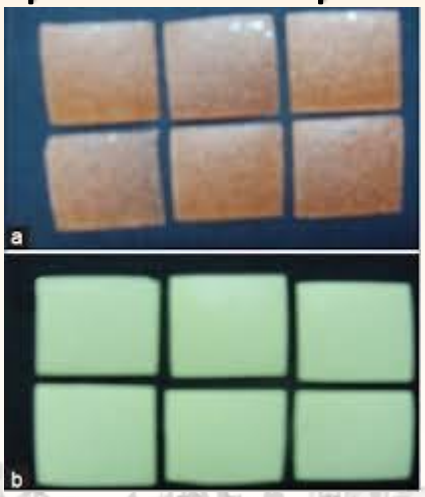
Las otras vías de Fentanilo: bucal

Tabletas

- Rápidamente absorbido
- Analgesia precoz
- Pico plasmático: 35-90 min
- Mayor biodisponibilidad que OTFC

Película soluble

- Capa externa inactiva que reduce la cantidad de fentanilo absorbido
- Absorbido 51% en mucosa oral
- Disponible en pocos países



Fentanilo nasal

Conexión directa entre SNC y atmósfera.

Los fármacos dispersados en mucosa olfativa pueden ser absorbidos por:

- Neuronas olfativas
- Plexo capilar subyacente
- LCR

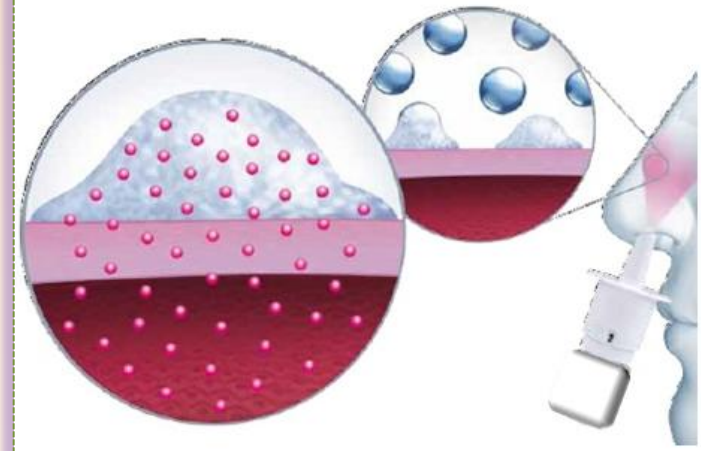
Fentanilo intranasal más eficaz que OTFC

Preferencia de los pacientes

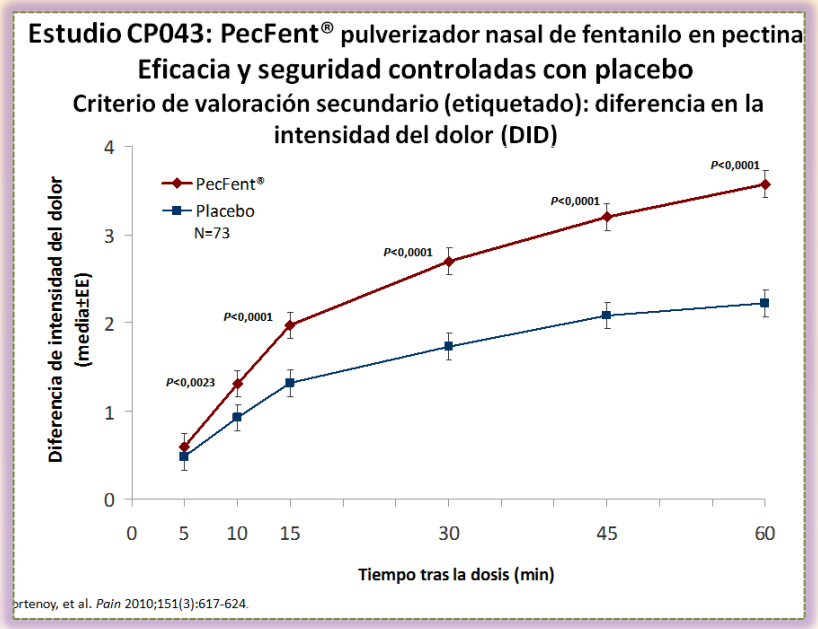
Variantes con pectina

Cuestiones de costo-eficacia

Fentanilo intranasal



Representación gráfica de la formación del gel de PecSys y la difusión del fentanilo



PecFent® está disponible en dos concentraciones:

- Envase amarillo – concentración de 100 µg/pulverización.
- Envase violeta – concentración de 400 µg/pulverización.

PecFent® puede liberar dosis de 100, 200, 400 y 800 µg, tal como sigue:

Color del envase	Dosis necesaria (microgramos)	Concentración del producto (microgramos)	Cantidad
Amarillo	100	100	Una pulverización administrada en **un solo** orificio nasal
Amarillo	200	100	Dos pulverizaciones administradas **una en cada** orificio nasal
Violeta	400	400	Una pulverización administrada en **un** solo orificio nasal
Violeta	800	400	Dos pulverizaciones administradas **una en cada** orificio nasal

LIMITACIONES CON LOS FENTANILOS RÁPIDOS

Inconsistencia Guías EAPC vs. NICE

- ¿Debe ser fentanilo "rápido" el fármaco de elección en dolor irruptivo?

Planteamiento pragmático:

- Usar un fármaco eficaz con los menores costos.
- En muchos casos la morfina de liberación rápida será suficiente.
- Ante episodios de muy rápida instauración plantear fentanilo.
- Y preguntar al paciente cuál prefiere: bucal/nasal

Table 2. Criteria for opioid choice in 'moderate to severe pain' (7 - 10 NRS) in current guidelines: comparison of WHO, ESMO, NCCN and EAPC.

	Recommended opioids	Route of administration	Comments
Patients able to take oral therapy	Morphine Oxycodone Hydromorphone Methadone	Oral	Morphine is considered the drug of first choice by WHO, ESMO NCCN considers it 'one of the most commonly used opioids, like oxycodone, hydromorphone and fentanyl'. EAPC provides weak recommendation that morphine, oxycodone and hydromorphone may be used indifferently as first choice. The use of methadone can be complicated because of inter-individual differences in plasma half-life, analgesic potency and duration of action. It is recommended for use only by experienced physicians (ESMO, EAPC, NCCN)
Patients unable to take oral therapy Stable pain	Fentanyl TTS Buprenorphine TDS Morphine s.c.	Transdermal or subcutaneous	WHO does not consider Fentanyl and Buprenorphine, not yet marketed in the transdermal formulation. NCCN, EAPC and ESMO agree that TTS Fentanyl is a valid alternative to oral opioids; EAPC and ESMO also indicate buprenorphine TDS. NCCN does not recommend its use All guidelines agree on the use of subcutaneous morphine
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Patients With renal failure	Fentanyl TTS Buprenorphine TDS	Transdermal	Buprenorphine TDS is mentioned as the safest opioid in severe renal failure (ESMO, EAPC)
Patiens with controlled background pain and breakthrough pain (BTP)	Immediate release opioids (morphine, oxycodone, hydromorphone) Fentanyl buccal nasal preparations	Oral Subcutaneous Buccal, sublingual, intranasal	WHO and NCCN does not specifically consider BTP. ESMO recommend to assess and treat BTP: does not provide specific guidance, but asks to 'tailor' drug, rescue dose and route of administration. EAPC provides 'strong recommendation' to deal with additional doses of oral immediate release opioids or buccal or nasal fentanyl

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Patiens with controlled background pain and breakthrough pain (BTP)	Immediate release opioids (morphine, oxycodone, hydromorphone) Fentanyl buccal nasal preparations	Oral Subcutaneous Buccal, sublingual, intranasal	WHO and NCCN does not specifically consider BTP. ESMO recommend to assess and treat BTP: does not provide specific guidance, but asks to 'tailor' drug, rescue dose and route of administration. EAPC provides 'strong recommendation' to deal with additional doses of oral immediate release opioids or buccal or nasal fentanyl

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CONTROVERSIAS CON SEGUNDO ESCALÓN

Probada la eficacia de los opioides débiles?	• No está probada la diferencia con fármacos de primer escalón
Duración limitada	• 30-40 días
Efecto techo	
Falta un ensayo comparativo definitivo	

Controversias con segundo escalón

Treatment of cancer pain

Strong recommendation

Mild Pain → Step 1 NRS 1 – 3 → NSAIDs-paracetamol → Periodical reassessment of cancer pain. Use rescue medications. If pain not controlled go on the next step

Weak recommendation

Mild-moderate Pain → Step 2 NRS 4 – 6 → Weak opioids +/- NSAIDs-paracetamol → Periodical reassessment of cancer pain. Use rescue medications. If pain not controlled do not change opioid but go on the next step

Strong recommendation

Moderate-severe pain → Step 3 NRS 7 – 10 → STRONG OPIOIDS +/- NSAIDs-paracetamol

Increase the dose of opioid every day, considering the number of opioid rescue doses used, till pain control or side effects

Side effects

Go on or, if necessary,opioid or route of opioid administration switching, using an equianalgesic dose of the same or different opioid:
- ✓Oral or transdermal Long acting opioid
- ✓Symptomatic treatment

Persisting Pain

- ✓Reasses the pain intensity and its causes
- ✓Consider the type and/or doses of adjuvants
- ✓Consider opioid or route of opioid administration switching
- ✓Consider invasive interventions
- ✓Team decision

Use always rescue doses to treat breakthrough pain

Adjuvant drugs such as corticosteroids, anticonvulsants, antidepressants, should be considered at any step when necessary

Table 1. Criteria for opioid choice in 'mild to moderate pain' (4 - 6 NRS) in current guidelines: comparison of WHO, ESMO, NCCN and European Association Palliative Care (EAPC).

	Recommended opioid	Route of administration	Comments
Patients with pain mild to moderate (4 - 6 NRS) or Pain patients not adequately controlled by paracetamol/ NSAIDs	II WHO step: Codeine Tramadol Hydrocodone or III WHO step: Morphine Oxycodone Hydromorphone low dose	Orally or eventually i.v. for morphine (titration in NCCN)	Already WHO pointed as arbitrary and for practical purposes the division between II and III step, mainly based on the ceiling effect of opioid partial agonists ESMO and EAPC indicate the option of using low doses of III step opioids as an alternative to codeine and tramadol, associated or less with non-opioid

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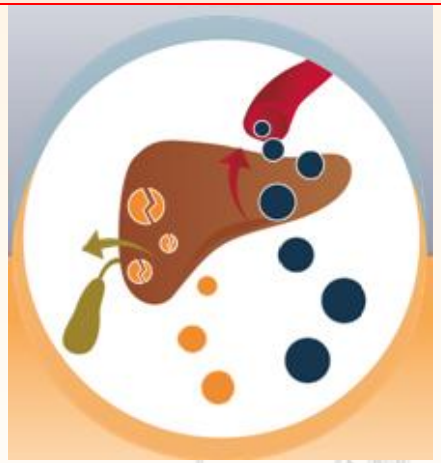
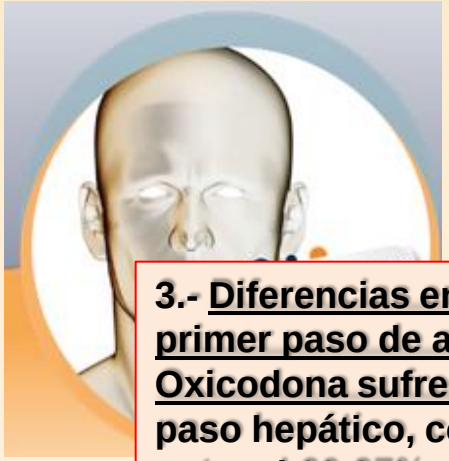
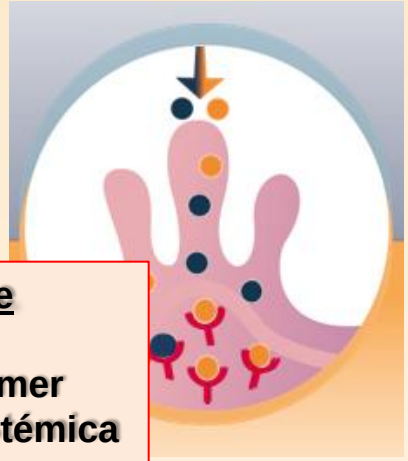
¿Opioide a dosis bajas?

Combinación oxicodona/naloxona

2.- **La afinidad diferencial de oxicodona y naloxona por los receptores opioides.**
Naloxona tiene una afinidad por los receptores opioides muy superior a la oxicodona: bloqueará los receptores, y/o desplazará a oxicodona
Resultado de este bloqueo de los receptores por la naloxona: función intestinal “normalizada”.



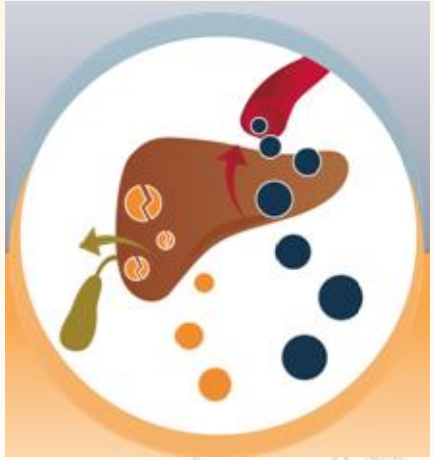




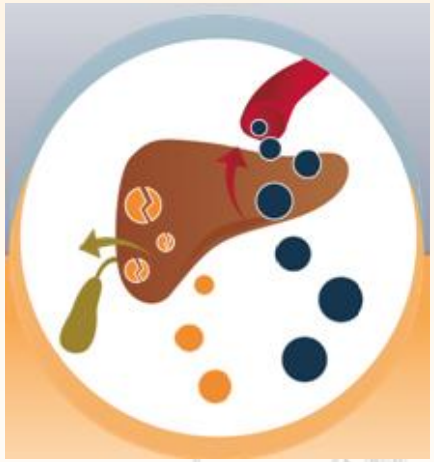
3.- <u>Diferencias en el metabolismo hepático de primer paso de ambos fármacos</u>

<u>Oxicodona sufre un bajo metabolismo</u> de primer paso hepático, con una biodisponibilidad sistémica entre el 60-87%, alcanzando SNC (efecto analgésico)

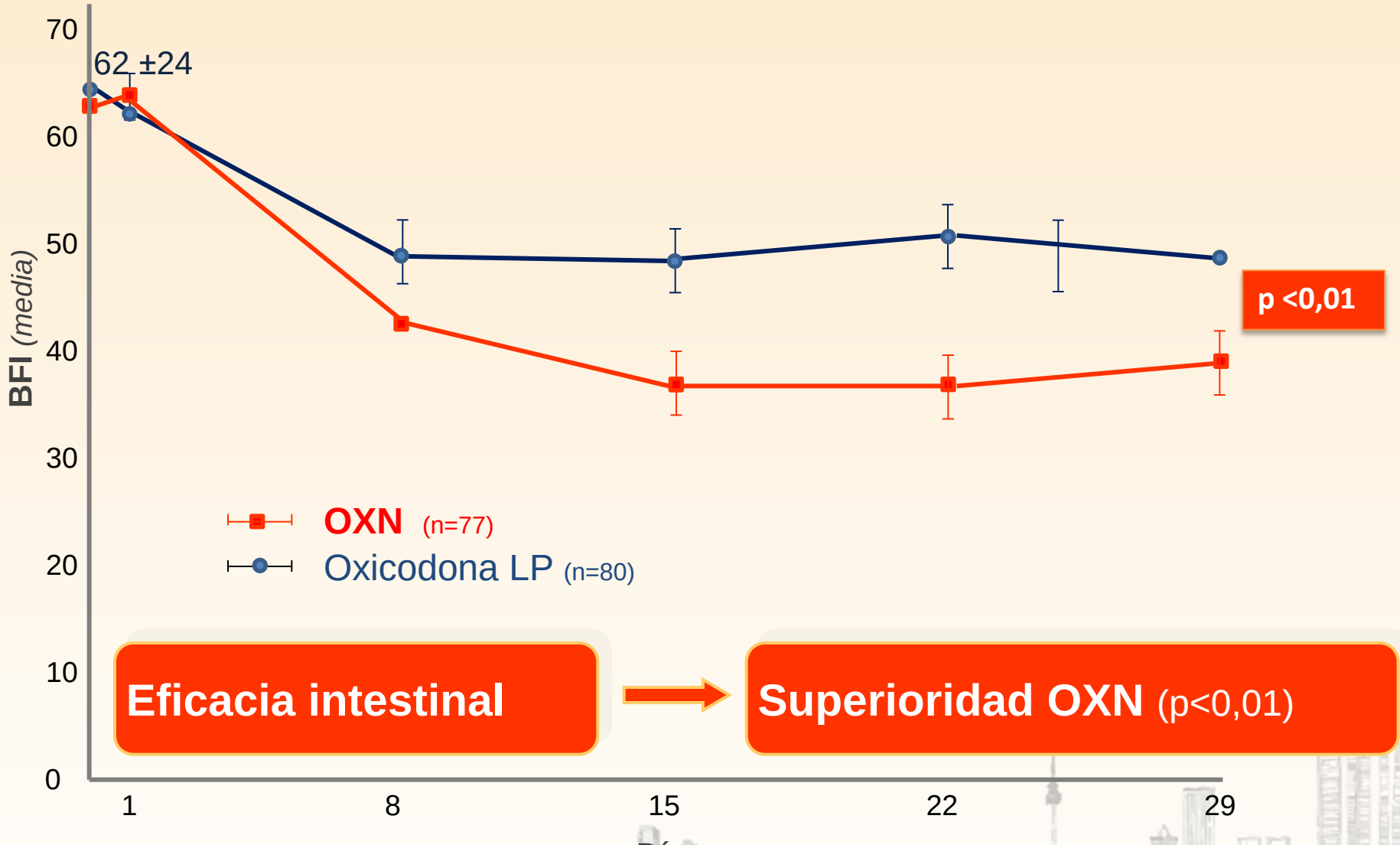
<u>Naxolona se metaboliza de forma prácticamente íntegra en el hígado</u>, un 98% del fármaco es degradado y no puede contrarrestar la analgesia del agonista en el SNC



1.- El hecho de que tanto <u>oxicodona como naloxona sean de liberación prolongada</u>, lo que garantiza una liberación continuada durante 12 h de ambos fármacos, y por lo tanto una absorción también simultánea a través de la pared intestinal



Mejoría de la función intestinal con OXN



Eficacia intestinal → **Superioridad OXN** (p<0,01)

Ahmedzai et al. *Palliat.Med. 26 (1):50-60, 2012.*

3.2.3. Oxicodona

La **oxicodona** es un congénere semisintético de la morfina del que existen nuevas formulaciones orales (de liberación normal y modificada). Dada su mejor disponibilidad sistémica (entre el 60-90%), la dosis equianalgésica de oxicodona oral es entre la 1/2 - 2/3 partes de la dosis de morfina oral.

Liberación retardada: Oxicodona (Oxycontin®)

Dosis inicial: Ajustar dosis en insuficiencia renal o hepática grave (50% dosis)

Escalonamiento:

Dosis diaria de oxicodona LR+ 1/2 de la dosis total diaria de rescates = nueva dosis de oxicodona

Oxicodona y naloxona (Targin®)

Dosis inicial: 5 mg/2,5 mg
10 mg/5 mg
20 mg/10 mg
40 mg/20 mg

Escalonamiento:

- Dosis inicial habitual para un paciente no tratado previamente con opioides: 10 mg/5 mg oxicodona/naloxona cada 12 horas.
- Pacientes que estén recibiendo tratamiento con opioides podrán recibir dosis mayores de Targin
- Dosis diaria *máxima* de Targin®: 80 mg oxicodona/40 mg naloxona.
- En lugar de /12 h valorar dosificación asimétrica en algunos casos (según el patrón de dolor).

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Combinación oxicodona/naloxona

Precauciones

- Función hepática.
- Dosis de rescate con opioides “rápidos”

Nabiximoles

¿Cannabinoides como posibles fármacos adyuvantes a los opioides?

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
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Available online at www.jpain.org and www.sciencedirect.com

Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial

Russell K. Portenoy,* Elena Doina Ganae-Motan,† Silvia Allende,‡ Ronald Yanagihara,§ Lauren Shaiova,¶ Sharon Weinstein,# Robert McQuade,** Stephen Wright,†† and Marie T. Fallon‡‡

Delta-9-tetrahidrocannabinol

- Efectos psicoactivos
- Analgesia
- Relajación muscular
- Aumento de apetito

Anabidiol

- Analgesia
- Efecto antiinflamatorio
- Reduce efecto psicoativo de THC

- Frente a placebo resultado negativo.
- No aportan beneficio analgésico.

Ketamina

A dosis subanestésicas para dolor oncológico.

Uso empírico

Efectos adversos psiquiátricos: alucinaciones

Ensayo de Hardy 2012

Comparación frente a placebo de ketamina subcutánea.

Resultados negativos

Incluyendo dolor neuropático

Table 2 Ten basic rules for management of cancer pain

1. Rule out non-cancer related causes of pain!

   eg, gastritis, urinary tract infection, pathologic fractures, myocardial infarction

2. Consider potential benefit of radiotherapy in addition to pharmacologic therapy

3. Opioid therapy:

   - If pain is moderate to severe: initiate opioid therapy according to WHO step III
   - Start with potent μ agonist (eg, morphine, hydromorphone, fentanyl, oxycodone)
   - Provide both a baseline ("regular"- or "scheduled"-) opioid, eg, sustained release (SR) morphine or sustained release hydromorphone on demand (rescue) opioid medication, eg, immediate release (IR) morphine

   Dosing of IR opioids:

   1/6th or less than the daily dose of the SR opioid

   Beware of strict dose "calculation" in case of high doses of SR opioid and if baseline opioid is provided as transdermal opioid

   - Adjust dose of SR according to temporal pattern of pain, eg, If pain is higher during day, provide double morning dose of SR opioid
   - Identify breakthrough cancer pain (pain episodes, pain attacks, BcP)

   Identify triggers (eg, physical activity)

   Educate patient to take IR opioid in advance

   (eg, 30 minutes before taking a walk)

   If BcP requires fast onset of analgesia (within 15 min): rapid onset fentanyl (nasal/buccal)

   - In case of dose escalation (>300 mg oral morphine equivalent/d):

   consider opioid rotation

   careful dose calculation,

   start with rather lower doses but provide sufficient on-demand opioid medication

4. Identify concomitant neuropathic pain: initiate and titrate co-analgesics (eg, pregabalin)

5. Identify other factors that contribute to total pain

   Other symptoms (eg, dyspnoea, anxiety, depression etc)

   Psychosocial domain (feeling left alone, no communication about disease, feeling urged to "fight")

   Spiritual burden (eg, feeling of guilt, perceived loss of dignity)

   Existential suffering (wish for hastening death, perceived meaningless of life)

6. Advanced disease stages: consider potential benefit of glucocorticoids
7. Provide non-opioid on a fixed, regular basis (NSAIDS, dipyrone)
8. Consider potential benefit of bisphosphonate or radionuclide therapy
9. Integrate specialized palliative care services
10. Invasive procedures (eg, neuroaxial anesthesia): rarely necessary but important option

Comillas.
Cantabria

¡Gracias!

Como Oncólogos:

Mantengámonos en todo momento sensibles hacia el dolor ajeno