Which long lasting drug should be chosen in basic cancer pain treatment

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Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

Augusto Caraceni*, Geoffrey Hanks*, Stein Kaasa*, Michael I Bennett, Cinzia Brunelli, Nathan Cherny, Ola Dale, Franco De Conno, Marie Fallon, Magdi Hanna, Dagny Faksvåg Haugen, Gitte Juhl, Samuel King, Pål Klepstad, Eivor A Laugsand, Marco Maltoni, Sebastiano Mercadante, Maria Nabal, Alessandra Pigni, Lukas Radbruch, Colette Reid, Per Sjogren, Patrick C Stone, Davide Tassinari, Giovambattista Zeppetella, for the European Palliative Care Research Collaborative (EPCRC), on behalf of the European Association for Palliative Care (EAPC)

Here we provide the updated version of the guidelines of the European Association for Palliative Care (EAPC) on the use of opioids for the treatment of cancer pain. The update was undertaken by the European Palliative Care Research Collaborative. Previous EAPC guidelines were reviewed and compared with other currently available guidelines, and consensus recommendations were created by formal international expert panel. The content of the guidelines was defined according to several topics, each of which was assigned to collaborators who developed systematic literature reviews with a common methodology. The recommendations were developed by a writing committee that combined the evidence derived from the systematic reviews with the panellists' evaluations in a co-authored process, and were endorsed by the EAPC Board of Directors. The guidelines are presented as a list of 16 evidence-based recommendations developed according to the Grading of Recommendations Assessment, Development and Evaluation system.

Lancet Oncol 2012; 13: e58–68

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Why recommendations do not work in clinical practice

- Recommendations based on the need to spread out basic information, simple, and reliable, but do not fit many clinical situations
- More complex pain situations (longer survival, more aggressive oncological treatments)
- Improved knowledge about drug use and new available drugs
- Need of flexibility individually-based

OPIOID TITRATION: a critical review. Mercadante S. Eur J Pain 2007

Initiation of opioid therapy is a delicate and challenging phase to obtain the maximum benefit and to gain the patient's compliance, as most adverse effects occur during this phase.
The approach could be different, depending on the clinical situation:

A – pts no longer responsive to non-opioid analgesics
B - pts requiring strong opioids no longer responsive to weaker drugs
C - pts already receiving strong opioids requiring higher doses because of an increase in pain intensity or a new acute pain problem
D - pts who are severely suffering and need an intensive as well as rapid intervention, due to previous lasting undertreatment.

WHO-step 2
Controversies

- What drugs in WHO-step 2 ?
- Fixed combinations of opioid-non opioids?
- Is it morphine ?
- Do we need step 2 ?

IS CODEINE SOME MORPHINE?

- 0-15% of codeine is demethylated to morphine by CYP2D6 (high genetic polymorphism)
- 7-10% are poor metabolizers….

- Poor metabolizers had no analgesia with codeine

  (Sintrup, 1993, Poulsen, 1996)

Original Article

Low Morphine Doses in Opioid-Naive Cancer Patients with Pain

Sebastiano Mercadante, MD, Gianpiero Porzio, MD, Patrizia Ferrera, MD, Fabio Fulfaro, MD, Federica Aielli, MD, Corrado Fiorentini, MD, Lucilla Verna, MD, Walter Tirelli, MD, Patrizia Villari, MD, and Edoardo Arcuri, MD

Anesthesia & Intensive Care Unit and Pain Relief and Palliative Care Unit (S.M., P.F., P.V.), La Maddalena Clinic for Cancer, Palermo; Departments of Anesthesiology and Intensive Care (S.M.) and Medical Oncology (F.F., W.T.), University of Palermo, Palermo; Medical Oncology Department (G.P., F.A., C.F., L.V.), University of L'Aquila, L'Aquila; and Intensive Care and Pain Therapy Unit (E.A.), National Cancer Institute Regina Elena, Rome, Italy

Abstract

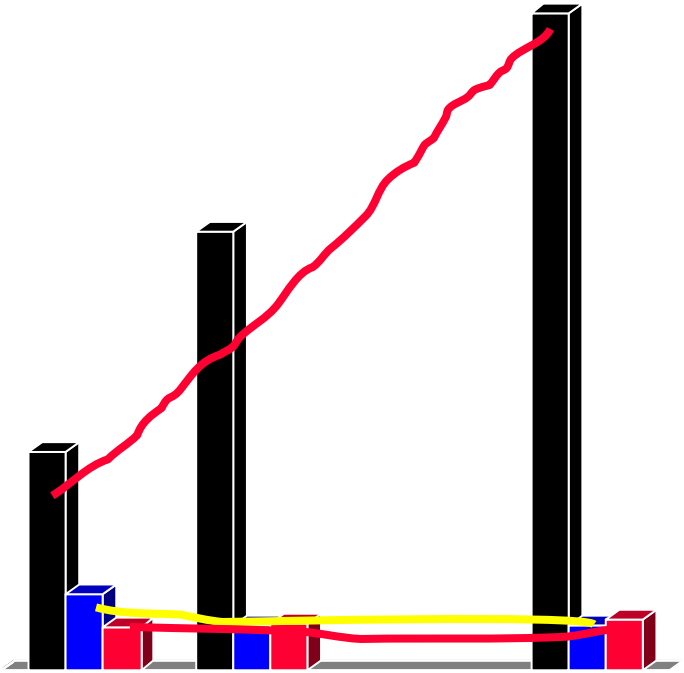
Cancer pain can be managed in most patients through the use of the analgesic ladder proposed by the World Health Organization. Recent studies have proposed to skip the second "rung" of the ladder by using a so-called "strong" opioid for moderate pain. However, usual doses of strong opioids commonly prescribed for the third rung of the analgesic ladder may pose several problems in terms of tolerability in opioid-naive patients. The aim of this multicenter study was to evaluate the efficacy and tolerability of very low doses of morphine in advanced cancer patients no longer responsive to nonopioid analgesics. A sample of 110 consecutive opioid-naive patients with moderate-to-severe pain were given oral morphine at a starting dose of 15 mg/day (10 mg in those older than 70 years). Doses were then titrated according to the clinical situation. Pain intensity, morphine dose, symptom intensity, quality of life, and the requirement for dose escalation were monitored for a period of 4 weeks. The treatment was effective and well tolerated by most patients, who were able to maintain relatively low doses for the subsequent weeks (mean dose 45 mg at Week 4). Only 12 patients dropped out due to poor response or other reasons. The use of very low doses of morphine proved to be a reliable method in titrating opioid-naive advanced cancer patients who were also able to maintain their dose in a 4-week period, below the dose level commonly used when prescribing strong opioids. J Pain Symptom Manage 2006;31:242–247. © *2006 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

A question of dosing…

Very small doses of morphine 12-15 mg/day were administered in a large number of opioid-naive pts with cancer pain (50 and 123 pts), of different origin and with different mechanisms

Low doses of morphine in naive patients Mercadante et al, JPSM 2006

- Morphine was effective
- Unexpectedly, it was extraordinary well tolerated
- OEI was slow



Morphine x 10
Pain
DS

Clinical Therapeutics/Volume 31, Number 10, 2009

Research Letter

Low Doses of Transdermal Buprenorphine in Opioid-Naive Patients With Cancer Pain: A 4-Week, Nonrandomized, Open-Label, Uncontrolled Observational Study

Sebastiano Mercadante, MD[1,2]; Gianpiero Porzio, MD[3]; Patrizia Ferrera, MD[1]; Federica Aielli, MD[3]; Lucilla Verna, MD[3]; Walter Tirelli, MD[4]; Patrizia Villari, MD[1]; and Alessandra Casuccio, BS[5]

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Brief report

Low doses of transdermal fentanyl in opioid-naive patients with cancer pain

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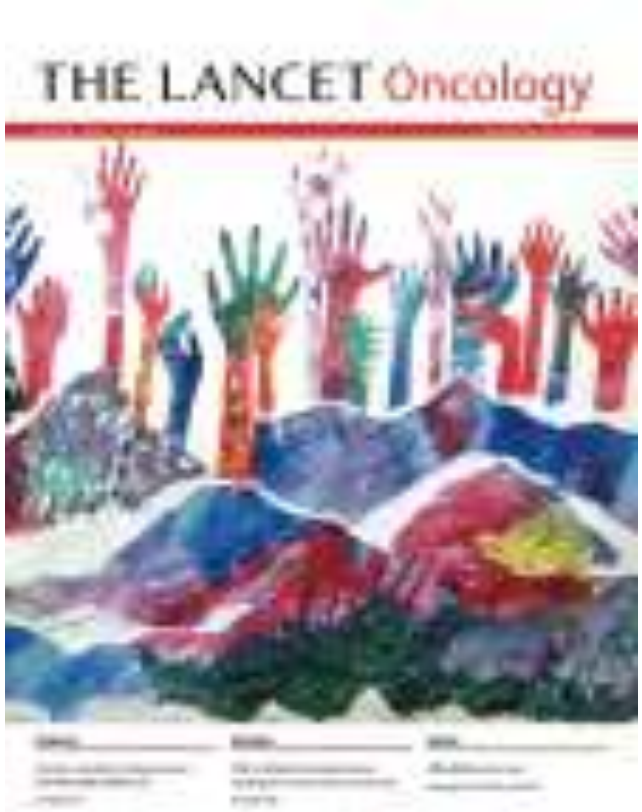
Abstract

Objective:
The aim of this study was to evaluate the effect and tolerability of low doses of transdermal (TD) fentanyl patches in opioid-naive patients with cancer pain.

Methods:
This was a nonrandomized, open-label, uncontrolled study in fifty consecutive opioid-naive patients with advanced cancer and moderate pain. TD fentanyl was initiated at a dose of 12 μg/h. Doses were then adjusted according to the clinical response. Pain intensity, opioid-related adverse effects, TD fentanyl doses, and quality of life were monitored over 4 weeks. The time to dose stabilization and indexes of dose escalation were also calculated.

Results:
Thirty-one patients completed all 4 weeks of the study. Pain control was achieved within a mean of 1.7 days after the start of TS fentanyl therapy. Significant differences in TD fentanyl doses were observed during the study period ($P = 0.03$). Mean doses were doubled 4 weeks after starting the treatment. The level of adverse effects was acceptable in most patients and only a minority of patients discontinued the treatment (13.8%).

Conclusion:
Low doses of TD fentanyl were well tolerated and effective. Observations from this study suggest that randomized, controlled, double-blind studies of TD fentanyl 12 μg/h in opioid-naive patients with cancer pain may be warranted.



EAPC recommendations 2012.

Low doses of strong opioids can replace step 2 drugs

B - Opioid titration in pts no longer responsive to II step opioids

EAPC recommendations: during dose titration it is preferable to use IR morphine that has a rapid onset, a predictable effect, and a short duration of action to allow steady state to be achieved as quickly as possible.

A dose of IR oral morphine is given every 4 hours and the same dose for BP given as often as required.

Pts changing from a weak opioid will usually start with 10 mg every four hours (60 mg/day), while if step two of the analgesic ladder is omitted 5 mg every four hours may suffice.

The total daily dose of morphine should be rewieved daily, based on the assumption that steady state of morphine is reached in about 24 hours. If pain returns before giving the regular dose, the regular dose should be increased (Hanks et al, 2001).

Hanks, De conno, Cherny, Hanna, kalso, McQuay, Mercadante, Meynadier, Poulain, Ripamonti, Radbruck, Roca J Casas, Sawe, Twycross, and Ventafridda:

Morphine and alternative opioids in cancer pain: the EAPC recommendations, Br J Cancer 2001

Point 2

- Patients changing from regular administration of a step 2 opioid will usually start with 10 mg every 4 hours.
- If step 2 of the analgesic ladder is omitted 5 mg every 4 hours may suffice, whereas pts converted from another step 3 opioid will require more.

IR or SR morphine for dose finding during start of morphine to cancer patients: a R-DB trial. Klepstad P et al, Pain 2003

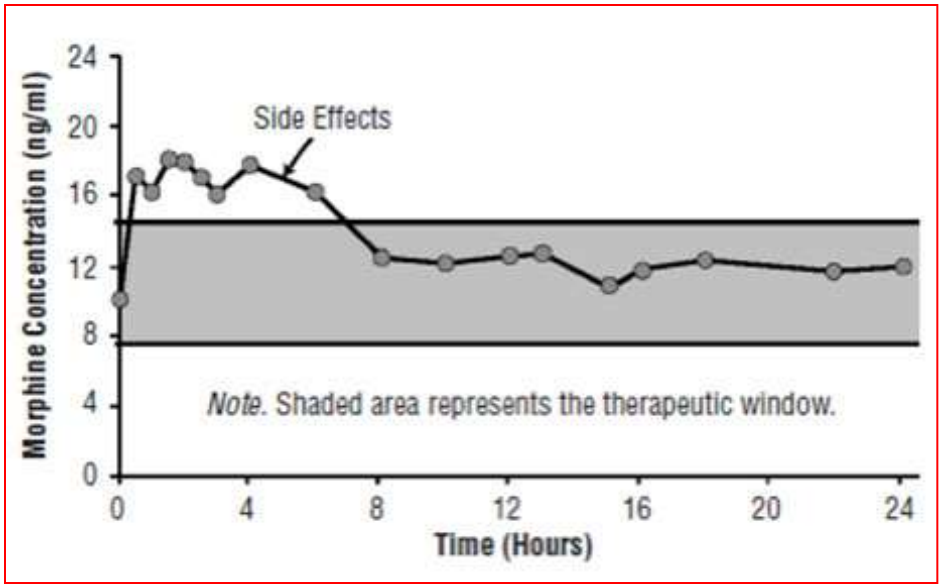
40 pts on 2nd step - R DB DD

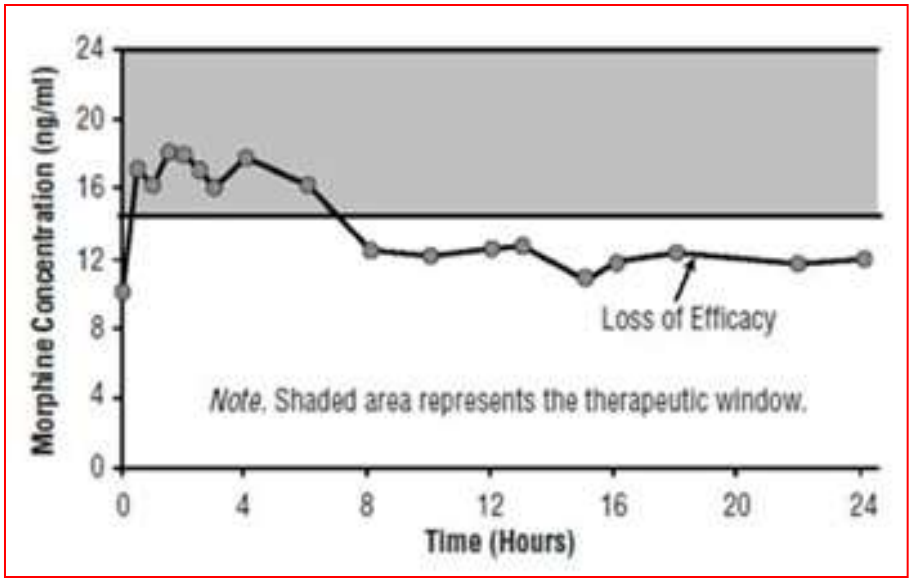
Time needed to titrate:

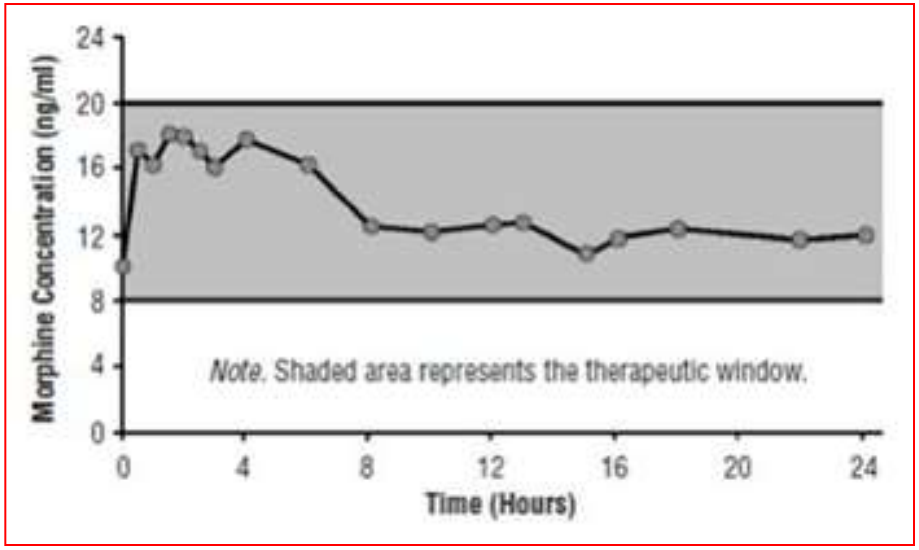
2.3 days IM (94 mg): more tiredness

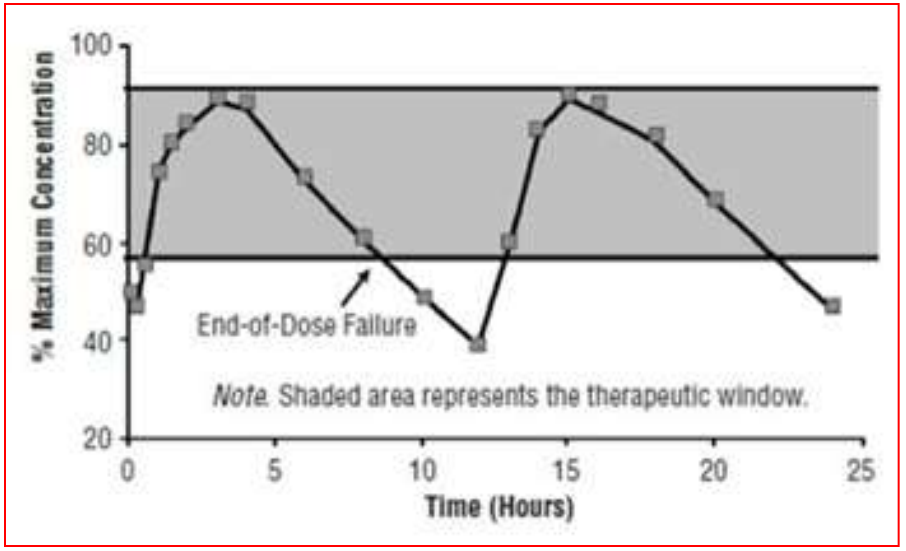
1.7 days SR once (82 mg)

A simplified titration using SR once daily is equally effective as IM given every 4 hours


Morphine Concentration (ng/ml)
24
20
16
12
8
4
0
Side Effects
Note. Shaded area represents the therapeutic window.
0
4
8
12
16
20
24
Time (Hours)


Morphine Concentration (ng/ml)
24
20
16
12
8
4
0
Loss of Efficacy
Note. Shaded area represents the therapeutic window.
0
4
8
12
16
20
24
Time (Hours)

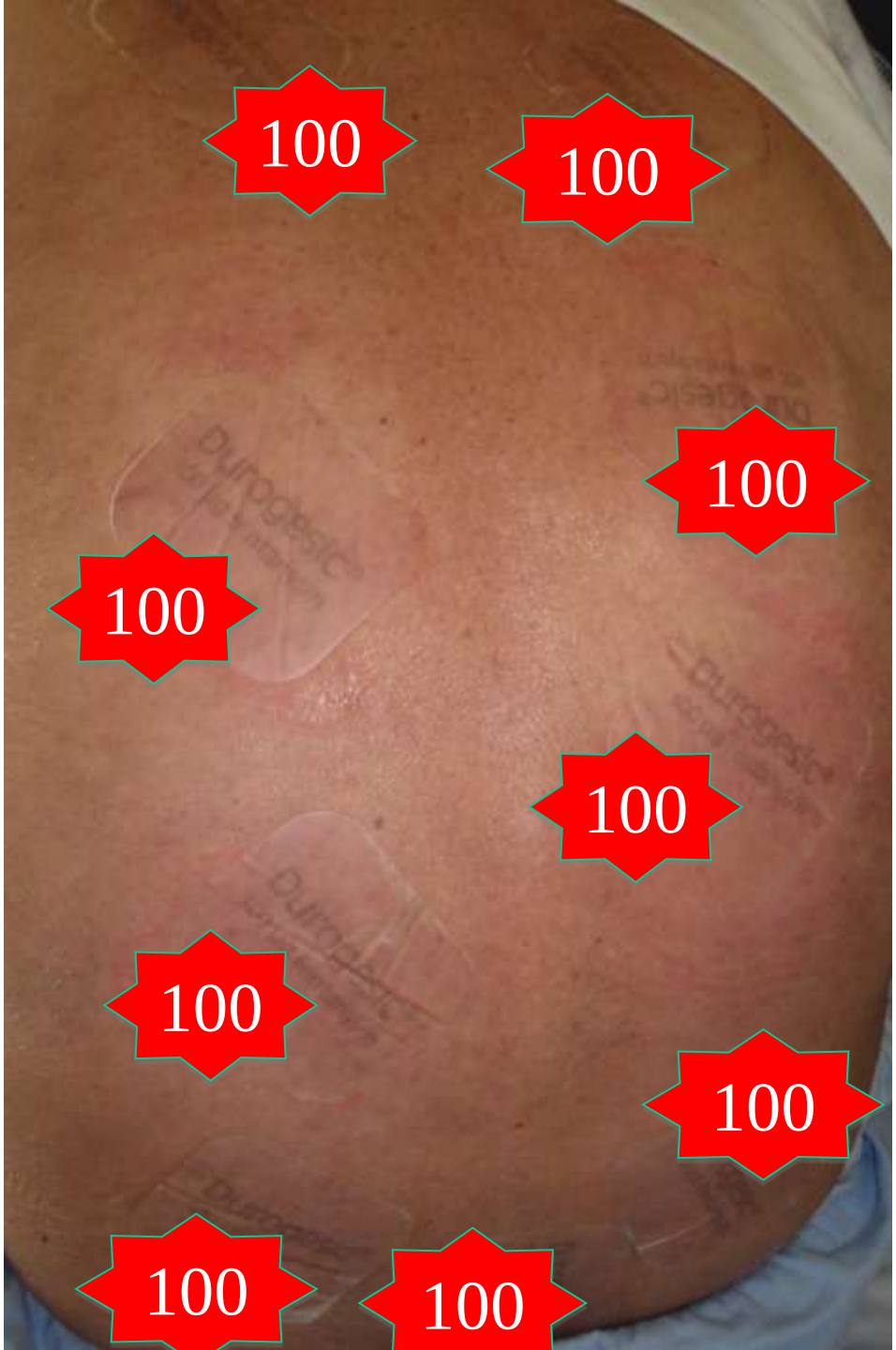

Morphine Concentration (ng/ml)
24
20
16
12
8
4
0
Note. Shaded area represents the therapeutic window.
0
4
8
12
16
20
24
Time (Hours)


% Maximum Concentration
100
80
60
40
20
End-of-Dose Failure
Note. Shaded area represents the therapeutic window.
0
5
10
15
20
25
Time (Hours)

TRANSDERMAL OPIOIDS
No comparative studies with other alternative routes.

Advantages:
No availability of oral route (vomiting, BO, dysphagia)
Easy to use
Less constipation

Disadvantages:
Unstable pain condition (need of rapid titration…)
Possible less analgesia in the last 12-24 hrs
High doses (number of patches)



At admission:

900 mcg/h
Transdermal
fentanyl

Pain **20?/10**

Crying and complaining

confused

CRITERIA FOR SELECTING ANALGESIC FOR CANCER PAIN: DRIVERS IN DECISION

- Overall Efficacy
- Overall AE profile
- Individual clinical situation
- Pretreatment
- Pain intensity
- Pain mechanism
- Onset
- Comorbidity
- Interactions
- Abuse potential
- Cost
- Cultural influence
- Guidelines

The effects of liver impairment on opioids used to relieve pain in cancer patients

Table 1. Recommended use of opioids in patients with liver dysfunction (as adapted by the author)

Opioid	Recommended Usage	Comment	Dosing Recommendations
Morphine	*Use cautiously* and monitor patient for adverse effects	In severe hepatic impairment, oral bioavailability may equal that of intravenous	Increase the dosing interval
Hydromorphone	*Use cautiously* and monitor patient carefully for adverse effects	In severe hepatic impairment oral bioavailability may increase significantly	Increase the dosing interval
Oxycodone	*Avoid use.*	In moderate hepatic impairment efficacy could change	
Codeine	*Avoid use.*	In moderate hepatic impairment, codeine will have unpredictable efficacy and adverse effects	
Methadone	*Not advised*	Not advised in moderate liver failure due to risk of accumulation and fatal adverse effects	
Fentanyl	Appears safe, but patches may be problematic	Hepatic blood flow may be an important factor in its clearance	Dose adjustment may not be necessary, but monitor the use of patches for adverse effects
Tramadol	*Avoid use.*	In moderate hepatic impairment, Tramadol will have unpredictable efficacy and adverse effects	

PALLIATIVE MEDICINE

Review

Palliative Medicine
25(5) 525–552

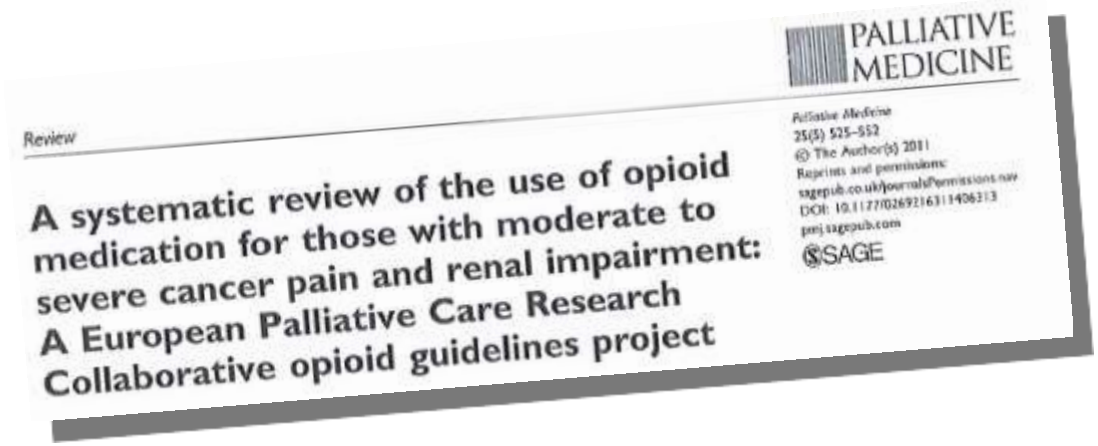
DOI: 10.1177/0269216311406313
pmj.sagepub.com
SAGE

A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: A European Palliative Care Research Collaborative opioid guidelines project

Table 5. Mild to moderate renal impairment

Recommendations for the use of opioids in cancer related pain:
Estimated glomerular filtration rate (GFR)
30–89 ml/min (mild to moderate renal impairment)
The presence of renal failure should not be a reason to delay the use of an opioid for those with cancer pain when needed

- All opioids that are appropriate for cancer pain can be used with consideration of reduced dose or frequency at a lower eGFR
- Monitor for changes in renal function and consider a pre-emptive change of opioid in rapidly deteriorating renal function
- Assess for any reversible factors
- Be aware that estimations of GFR may be less accurate in the presence of cachexia, low protein states, oedema and with acute renal failure. An estimated GFR at the lower end of the moderate renal impairment range should therefore prompt consideration of a change of opioid to one considered safer in renal impairment.



PALLIATIVE MEDICINE

Review

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Table 1. Stratification of glomerular filtration rate (GFR; stage of chronic kidney disease)

Stage	GFR	Notes and description
1	>90 ml/min	Normal renal function
2	60–89 ml/min	Mild renal impairment (if other evidence of chronic kidney damage)
3	30–59 ml/min	Moderate renal impairment
4	15–29 ml/min	Severe renal impairment
5	<15 ml/min	End-stage renal failure

Table 4. Metabolite activity and risk stratification

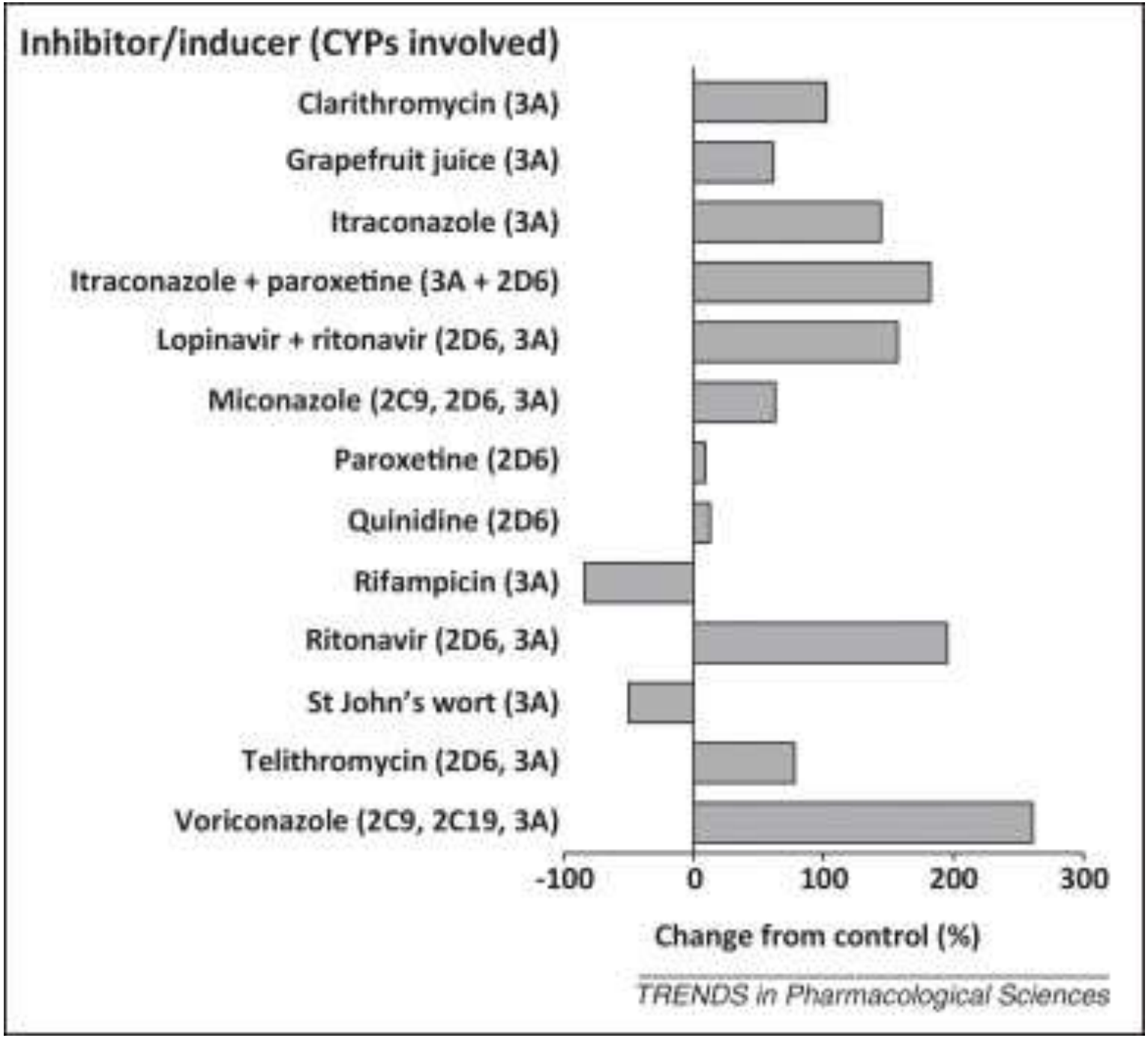
Group 1 (No clinically significant active metabolites)
Fentanyl, alfentanil and methadone
Group 2 (Active or probably active metabolites-stratified according to degree of toxicity or risk of accumulation)
a) Tramadol and hydromorphone (possible reduced risk of toxicity)
b) Morphine, diamorphine, codeine, dihydrocodeine and oxycodone
c) Pethidine and dextropropoxyphene (high risk of toxicity recommend against use)
Group 3 (Insufficient evidence or experience to make a recommendation for chronic use)
Buprenorphine and sufentanil (active metabolites). Remifentanil (inactive metabolites)

Factors influencing the opioid response

- Specific drugs
- Pain type
- Psychological influences
- Disease and humoral factors
- Receptor disposition
- Plastic changes of CNS
- Drug interactions
- Pharmacogenetics: polymorphisms (opiodi receptors, metabolizing enzymes, carriers)
- Epigenetics

PHARMACOGENETICS

- Enzyme polymorphism
- Polymorphism BBB protein transport
- OR variants - subgroups
- OR distribution and unmasking (peripheral)
- OR cross-talk
- Plastic changes of CNS disease-related
- Plastic changes after opioid administration


Inhibitor/inducer (CYPs involved)
Clarithromycin (3A)
Grapefruit juice (3A)
Itraconazole (3A)
Itraconazole + paroxetine (3A + 2D6)
Lopinavir + ritonavir (2D6, 3A)
Miconazole (2C9, 2D6, 3A)
Paroxetine (2D6)
Quinidine (2D6)
Rifampicin (3A)
Ritonavir (2D6, 3A)
St John's wort (3A)
Telithromycin (2D6, 3A)
Voriconazole (2C9, 2C19, 3A)
-100
0
100
200
300
Change from control (%)
TRENDS in Pharmacological Sciences

Davis MP, Lagman R,LeGrand S. Controversies in pharmacotherapy of pin management. Lancet Oncol 2005

Morphine was recommended as the benchmark opioid by EAPC on the basis of expert opinion.

However, state of art does not specify an opioid of choice, as no opioid has never been resulted more effective than another in controlled studies

3rd step
The opioid of choice?

A systematic review of randomized trials on the effectiveness of opioids for cancer pain.

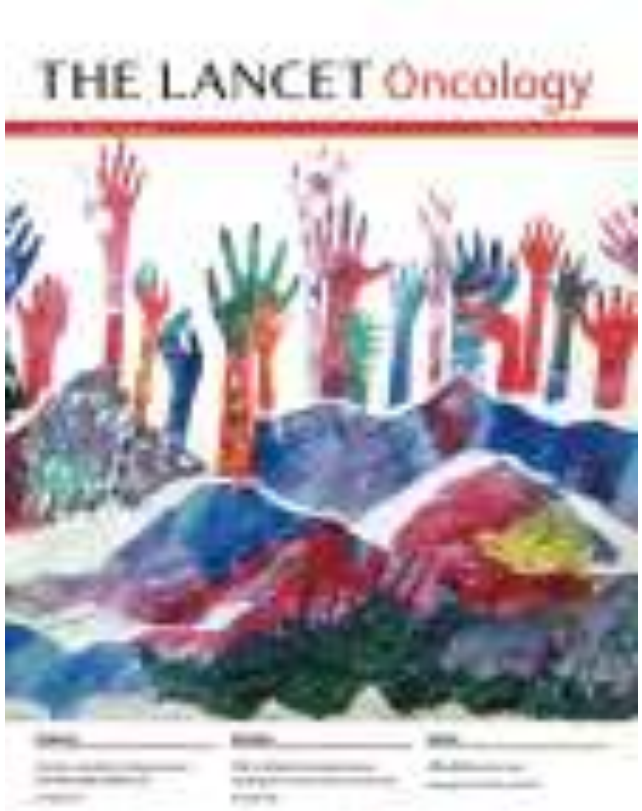
Koyyalagunta et al. Pain Physician 2012

- Poor evidence
- No opioid of choice

RANDOMIZED CONTROLLED STUDY OF SUSTAINED-RELEASE ORAL MORPHINE, TRANSDERMAL FENTANYL AND ORAL METHADONE IN CANCER PAIN MANAGEMENT: A PHARMACOECONOMICAL EVALUATION. Mercadante et al, Eur J Pain 2008

- All the three opioids used as first-line therapy were effective, well tolerated, and required similar amounts of symptomatic drugs or co-analgesics.
- Methadone was significantly less expensive, but required more changes, up and down, of the doses, suggesting the need of more expertise
- Fentanyl produced less AE, but resulted to be more expensive, with the highest OEI

EAPC recommendations
2012



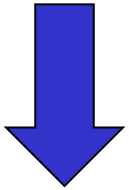
Doses of about 60 mg of oral morphine equivalents of any opioid, are equally effective as starting doses in tolerant pts who had received step 2 drugs unsuccessfully, assisted by PRN opioid doses for eventually assisting titration

- Morphine 60
- TTS fentanyl 0.6 (25 mcg/h)
- Methadone 12
- Oxycodone/naloxone 40/20
- Oxycodone 40
- TTS buprenorphine 0.8 (35 mcg/h)
- Hydromorphone 12
- Tapentadol 200

Assisting opioid titration when using slow preparations: SR morphine, SR oxycodone, methadone, transdermal drugs: fentanyl and buprenorphine

- 1/6 of the daily dose as equivalents of oral morphine (also useful as BP medication)

Whatever the drug you use, success will be depedent on how the drug is used,
based on careful considerations of individual clinical conditions, and appropriate knowledge of pharmacokinetics-dynamics



Physician-based treatment

- D – Severe pain on emercency basis

  With inadequate pain relief, opioid doses have to be increased stepwise, that is with a dose increase of 33-50% every 24 hours (Hanks et al,2001).

  This approach can lead to a time span of several days or even weeks until adequate pain relief is obtained.

  Differently from population previously described, which had moderate pain intensities and required simple titration schedule, allowing to achieve appropriate pain control in 1-2 days, cancer pain emergency is commonly defined in accordance with severity (pain intensity of 8/10 or greater on a numerical scale), duration and progression over time.

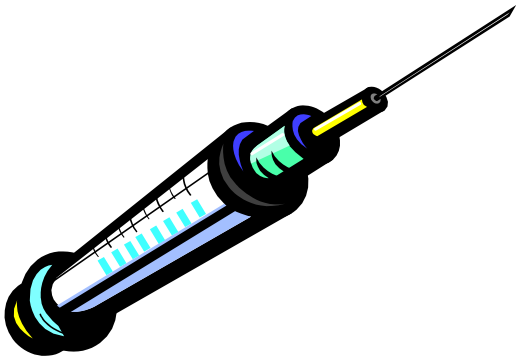
  Acute severe pain requires rapid application of powerful analgesic strategies and aggressive treatment, which are distinct from chronic management techniques.

Parenteral administration may reduce pharmacokinetic limitations of the oral route

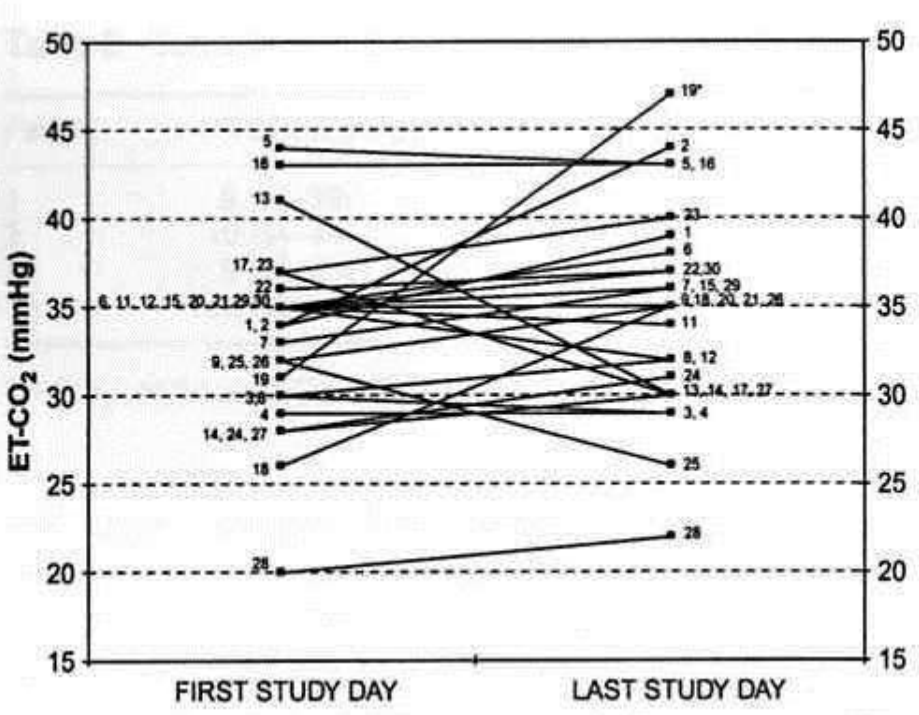
- ABSORPTION

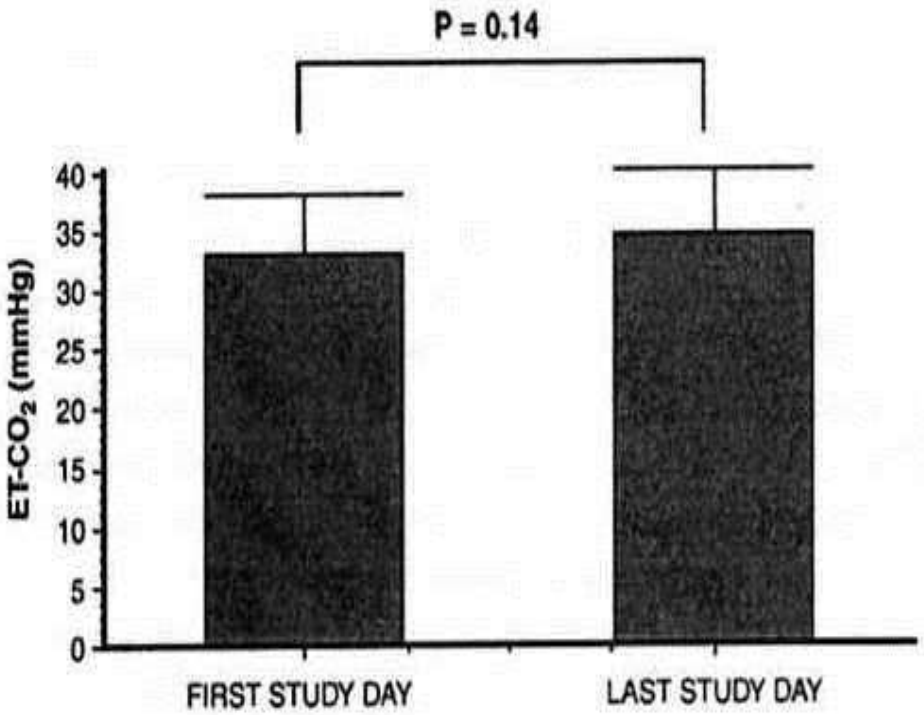
  Independent on mucosal damage and surgery, and swallowing
- AVAILABILITY
- LESS METABOLITE FORMATION

  (less toxicity?)
- RAPIDITY !!!!!



	Before titration	Pain control
Pain score	6.8	1.9
Opioid dose	73	169





Rapid titration with intravenous morphine for severe cancer pain and immediate oral conversion

Mercadante et al, Cancer, 2002,
Mercadante, Lancet Oncol 2010

Cancer pain emergencies presenting with excruciating pain require a rapid application of powerful analgesic strategies. Oral morphine titration requires too long periods to allow immediate pain relief

Rapid Titration with Intravenous Morphine for Severe Cancer Pain and Immediate Oral Conversion

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BACKGROUND. Cancer pain emergencies presenting with severe excruciating pain require a rapid application of powerful analgesic strategies. The aim of the current study was to evaluate a method of rapid titration with intravenous morphine to achieve relief of cancer pain of severe intensity.

METHODS. Forty-nine consecutive patients admitted to a Pain Relief and Palliative Care Unit for severe and prolonged pain were enrolled in the study. Pain was evaluated on a numeric scale of 0–10 (0 indicated no pain and 10 indicated excruciating pain). After the initial assessment (T0), an intravenous line was inserted and boluses of morphine (2 mg every 2 minutes) were given until the initial signs of significant analgesia were detected or severe adverse effects occurred (T1). A continuous reassessment was warranted and the effective total dose administered intravenously was assumed to last approximately 4 hours and was calculated for 24 hours. The dose immediately was converted to oral morphine (a 1:3 ratio for low doses and a 1:2 ratio for high doses).

RESULTS. Data from 45 patients was analyzed. A significant decrease in pain intensity was achieved in a mean of 9.7 minutes (95% confidence interval [95% CI], 7.4–12.1 minutes), using a mean dose of intravenous morphine of 8.5 mg (95% CI, 6.5–10.5 mg). The doses administered rapidly were converted to oral morphine and pain control was maintained until the patient's discharge, which occurred in a mean of 4.8 days (95% CI, 4.1–5.2 days). The incidence of adverse effects was minimal.

CONCLUSIONS. The results of the current study demonstrate that cancer pain emergencies can be treated rapidly in the majority of cancer patients with an acceptable level of adverse effects. Intravenous administration of morphine requires initial close supervision and continuity of medical and nursing care. *Cancer* 2002;95:203–8. © 2002 *American Cancer Society.*

DOI 10.1002/cncr.10636

49 pts with severe pain (NPS 7-10)

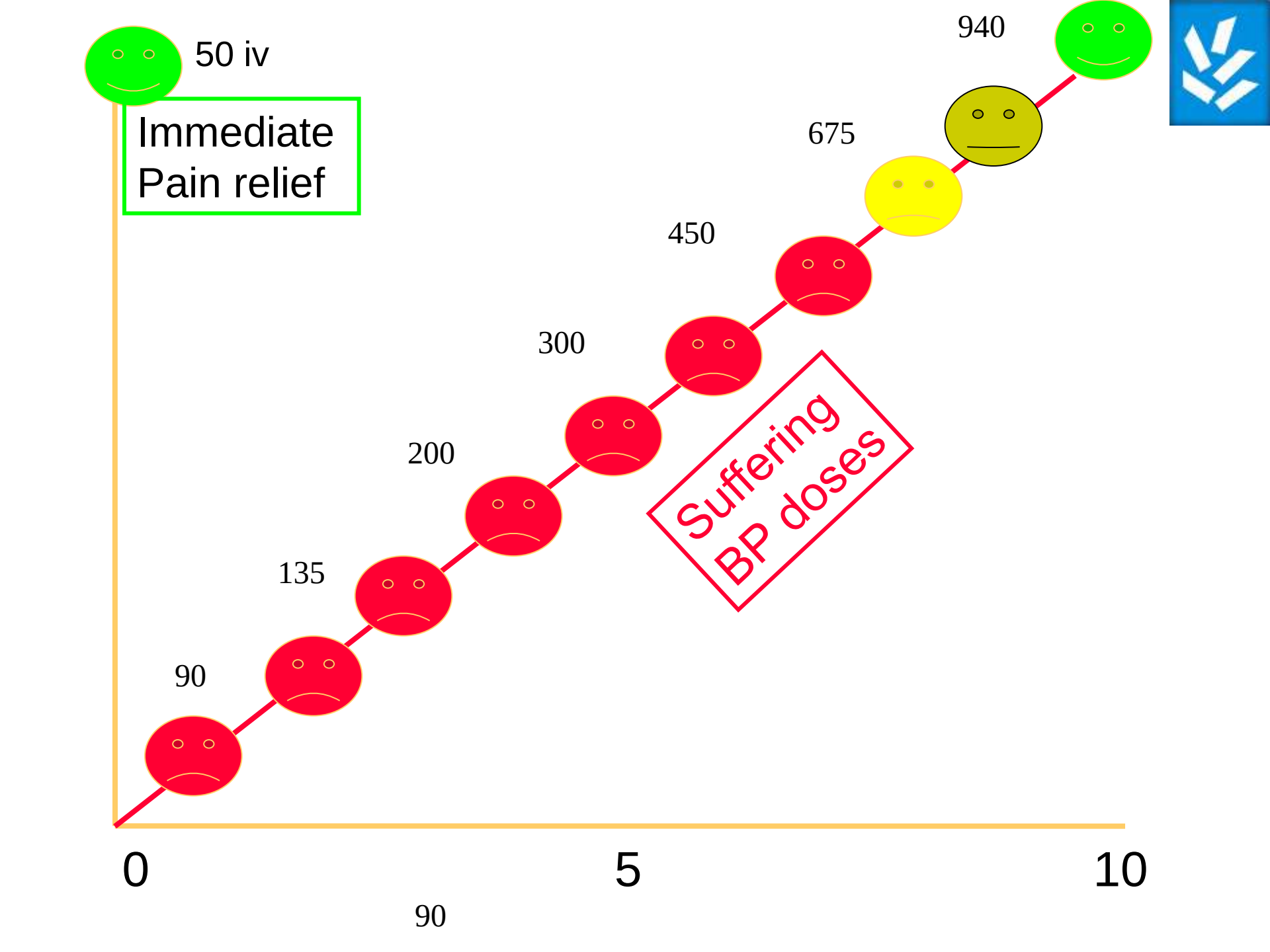
T0: Dose finding: titration with IV morphine 2 mg until signs of significant analgesia occur (T1).

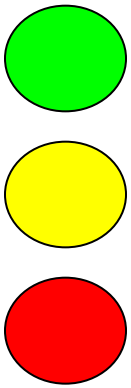
The dose was converted immediately to oral dosing assuming the effect lasting about 4 hours.

Example: Test dose 10 mg of IV morphine are equivalent to 60 mg daily: oral dose will be 120 mg (using a IV:os conversion of 1:2).

The same IV test dose will be available for breakthrough pain in the first 24 hours

Reassessment……


50 iv
Immediate
Pain relief
940
675
450
300
200
135
90
Suffering
BP doses
0
5
10
90



Low escalation index

Increasing escalation index

Prevalence of adverse effects

OPIOID RESPONSE IS A DYNAMIC ISSUE AND MAY CHANGE IN TIME

C - opioid re-titration in patients who are receiving strong opioids unsuccessfully

- Opioid dose should be increased against pain….
- … as no ceiling effect exists
- Sufficient increasing dose (50%)
- Evaluation of OEI….

….risks of intrinsic toxicity….

Causes of declining analgesia and need of opioid escalation

- Disease-related factors

Progression of disease (increased nociception)

Pain mechanism

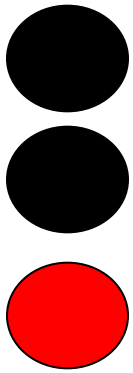
Increased humoral factors

Reversible hyperalgesia (therapy-induced flares)

- Factors related to patient-drug interaction

Tolerance

Hyperalgesia



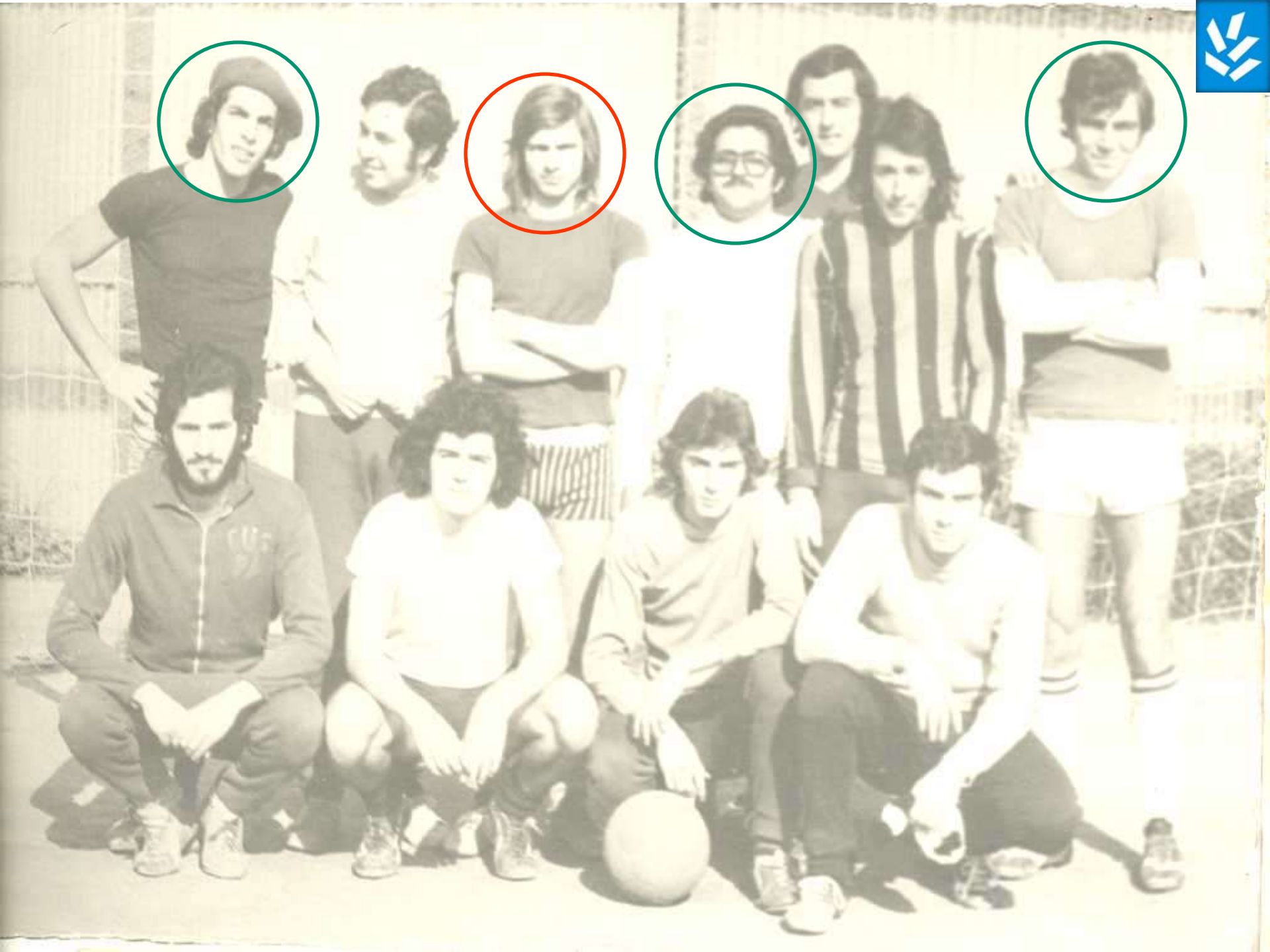
Prevalence of adverse effects
and/or ineffective opioid dose escalation

Rationale for opioid switching, Mercadante, Cancer 1999

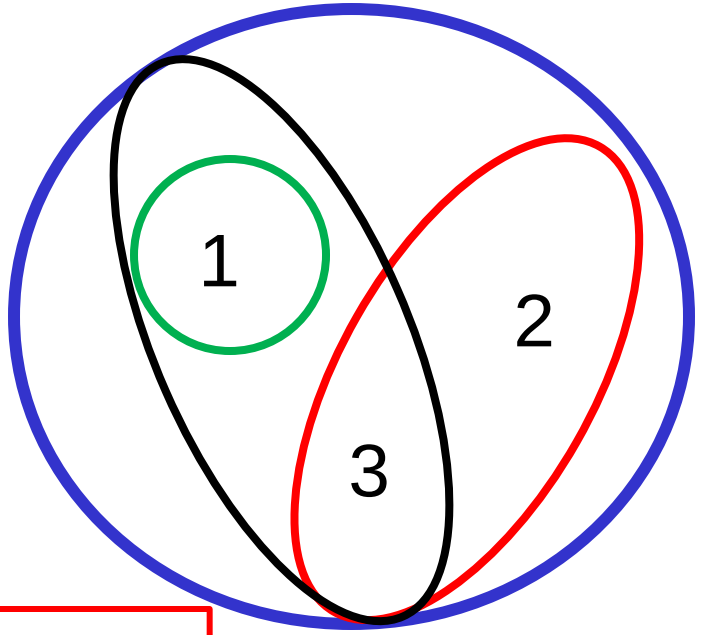
Different clinical response produced by a new opioid due to:

- different receptor activity produced by different opioids.
- different receptor opioid-pattern
- individual variance
- asymmetric tolerance
- dynamic plastic changes of receptors.

So similar, so different



Drug	Receptor selectivity
▲	1,3
▲	2,3
▲	1
▲	1,2,3



Cross-tolerance

	▲	▲	▲	▲
▲	-	Partial	Partial	Complete
▲	Partial	-	No	Complete
▲	Complete	No	-	Complete
▲	Partial	Partial	Partial	-

Pasternak,TRENDS IN Pharmacol Sci 2001

Opioid switching: from the beginning to nowadays. Mercadante & Bruera, submitted

- Opioid selectivity
- Genetics – metabolism
- Genetics – receptor
- Plastic changes
- Changes in drug-disease-individual relationships

Original Article

Opioid Rotation for Toxicity Reduction in Terminal Cancer Patients

Noémi D. de Stoutz, MD, Eduardo Bruera, MD, and Maria Suarez-Almazor, MD, PhD

Palliative Care Program (N.D.D.), Medizinische Klinik C, Kantonsspital, St. Gallen, Switzerland; Palliative Care Program (E.B.), Edmonton General Hospital, and Healthcare Quality and Outcome Research Center (M.S-A.), University of Alberta, Edmonton, Alberta, Canada

Abstract

Accumulation of active (toxic) metabolites of opioids might explain cases of opioid toxicity when high doses are used for long periods of time. Other mechanisms of late toxicity of opioids may be found at the receptor level. Whatever the cause, a change of opioids using equianalgesic doses can be expected to improve symptoms of toxicity in some patients, while

Pain, 59 (1994) 313–316

PAIN 02636

Clinical Notes

Disappearance of morphine-induced hyperalgesia after discontinuing or substituting morphine with other opioid agonists

Per Sjøgren [a,*], Niels-Henrik Jensen [a] and Troels Stachelin Jensen [b]

[a] *Multidisciplinary Pain Center, Department of Anesthesiology, Herlev University Hospital, DK-2730 Herlev (Denmark) and* [b] *Department of Neurology, Aarhus University Hospital, DK-8000 Aarhus C (Denmark)*

(Received 25 October 1993, accepted 25 March 1994)

Pain, 53 (1993) 353–355

PAIN 02333

Clinical Note

Opioid hyperexcitability: the application of alternate opioid therapy

Neil MacDonald [a], Linda Der, Sharon Allan [b], and Phillip Champion [c]

[a] *Alberta Cancer Foundation, University of Alberta, Edmonton, Alb. T6G 2J3 (Canada),* [b] *British Columbia Cancer Agency, Victoria, BC V8R 1J8 (Canada) and* [c] *Queen Elizabeth Hospital, Charlottetown, PEI C1A 8T5 (Canada)*

(Received 4 January 1993, revision received 1 March 1993, accepted 12 March 1993)

Pain Reviews 1998; **5** 51–58

The use of methadone in cancer pain poorly responsive to other opioids

JS Morley[a] and MK Makin[b]

[a]Pain Research Institute, University Department of Neurological Science, Walton Hospital and [b]Marie Curie Centre, Liverpool, UK

Pain, 49 (1992) 87–91

PAIN 02057

Clinical Note

Individual variability in the response to different opioids: report of five cases *

Bradley S. Galer, Nessa Coyle, Gavril W. Pasternak and Russell K. Portenoy

Pain Service, Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021 (USA)

(Received 9 September 1991, revision received 26 December 1991, accepted 30 December 1991)

TEMPORAL VARIABILITY OF CLINICAL RESPONSE TO OPIOIDS: EXPRESSION OF CSN PLASTICITY?

Sebastiano Mercadante

Servizio di Anestesia, Ospedale Buccheri La Ferla FBF, & SAMOT, Palermo, Italy

Correspondence to Dr.Sebastiano Mercadante
Chief of pain relief and palliative care
SAMOT,v.Villafranca 99,90141 Palermo,Italy.

Opioid switching. A systematic and critical review. Mercadante & Bruera, Cancer Treat Rev 2006

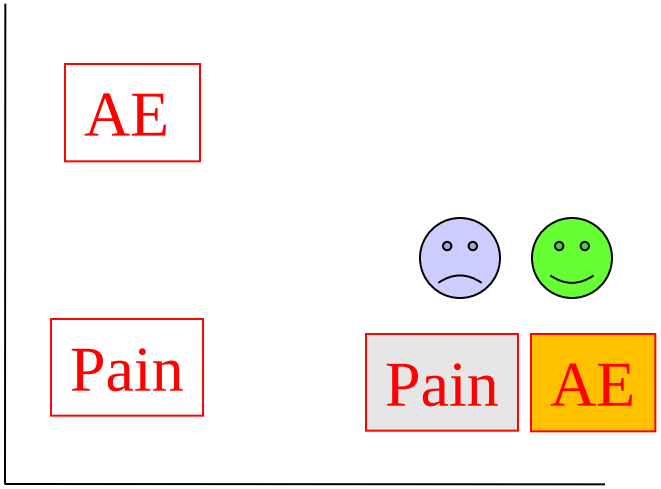
Opioid switching: from the beginning to nowadays, 2015

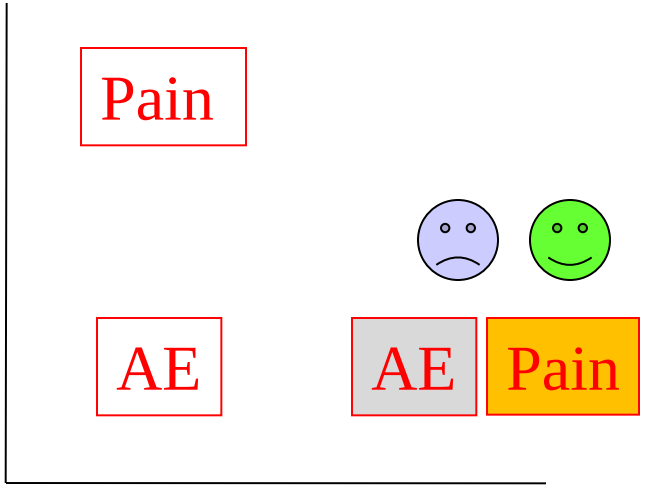
Opioid switching has a chance to improve the clinical opioid response in 50-80% of cases of patients with unconvenient balance between analgesia and adverse effects….

Adverse effects

Analgesia

…. and has strongly reduced the need of interventional procedures


AE
Pain
Pain
AE


Pain
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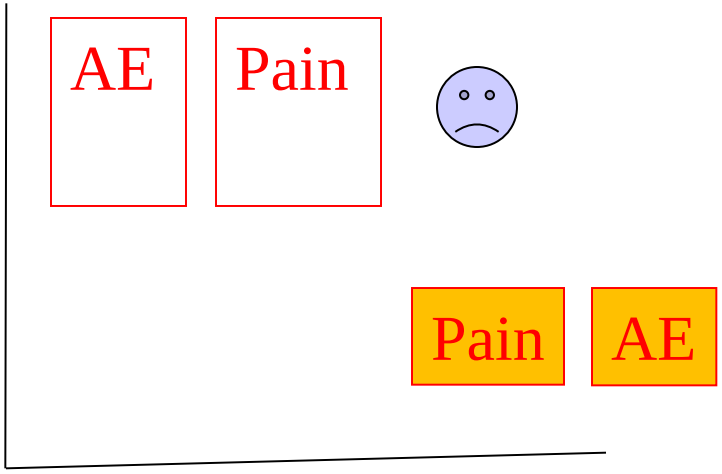
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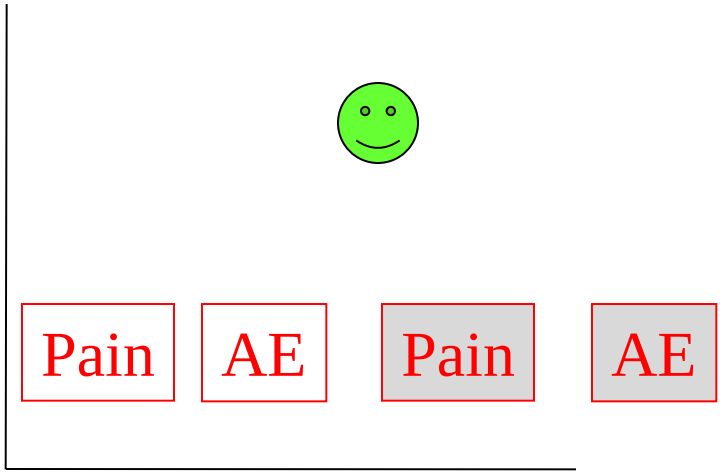
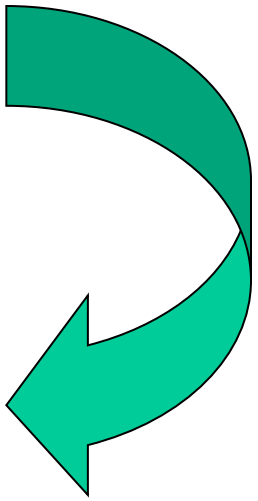

Pain
AE
Pain
AE

Canadian experiences… Hagen et al, JPSM 2003

- 16 gr of Iv morphine



- Oxycodone 60 mg

Palliative Care Rounds

Hyperalgesia: An Emerging Iatrogenic Syndrome

Sebastiano Mercadante, MD, Patrizia Ferrera, MD, Patrizia Villari, MD, and Edoardo Arcuri, MD

Anesthesia and Intensive Care Unit & Pain Relief and Palliative Care Unit (S.M., P.F., P.V.), La Maddalena Cancer Center, Palermo; and Pain Relief & Intensive Care Unit (E.A.), National Cancer Institute, Regina Elena, Rome, Italy

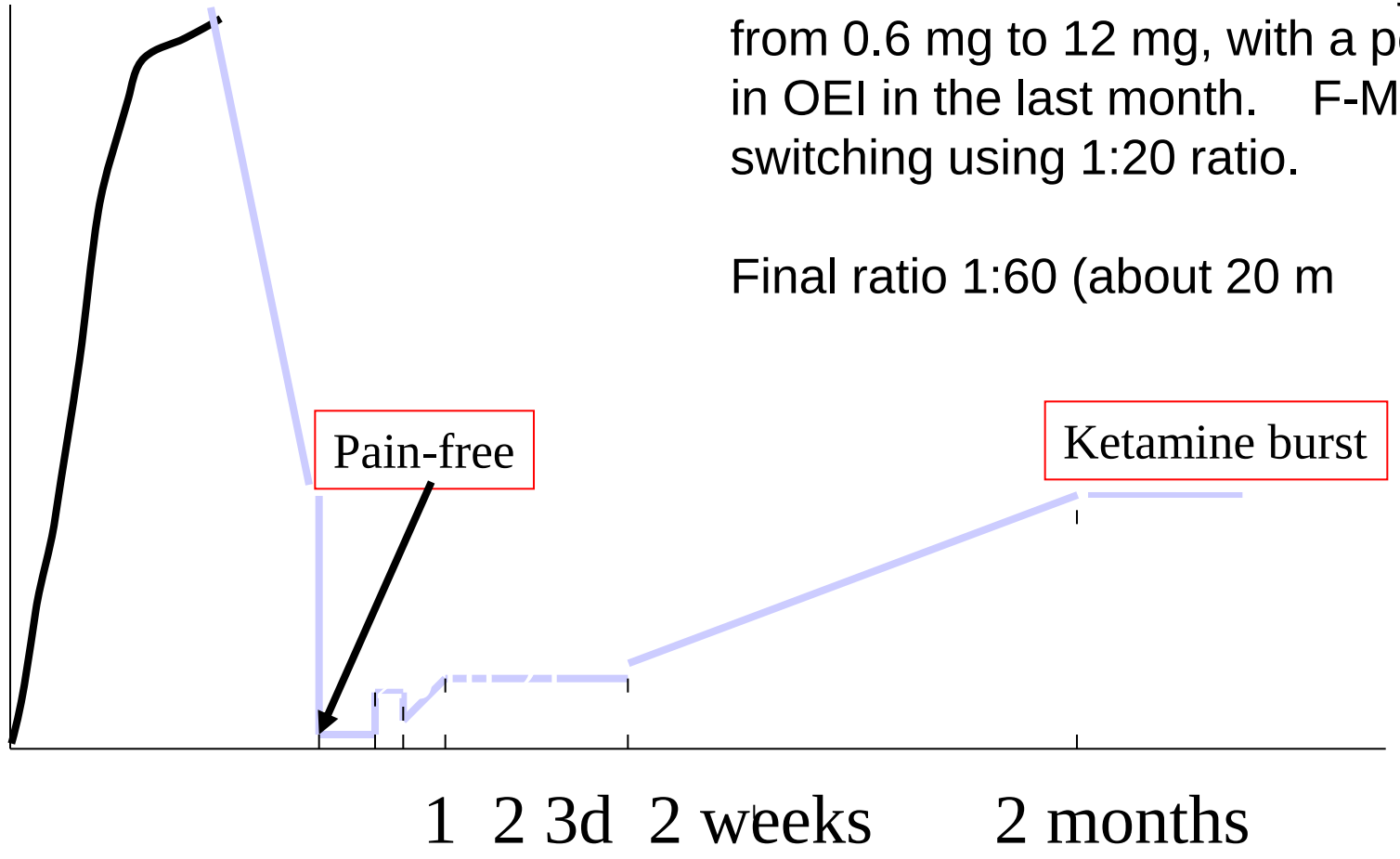
Abstract

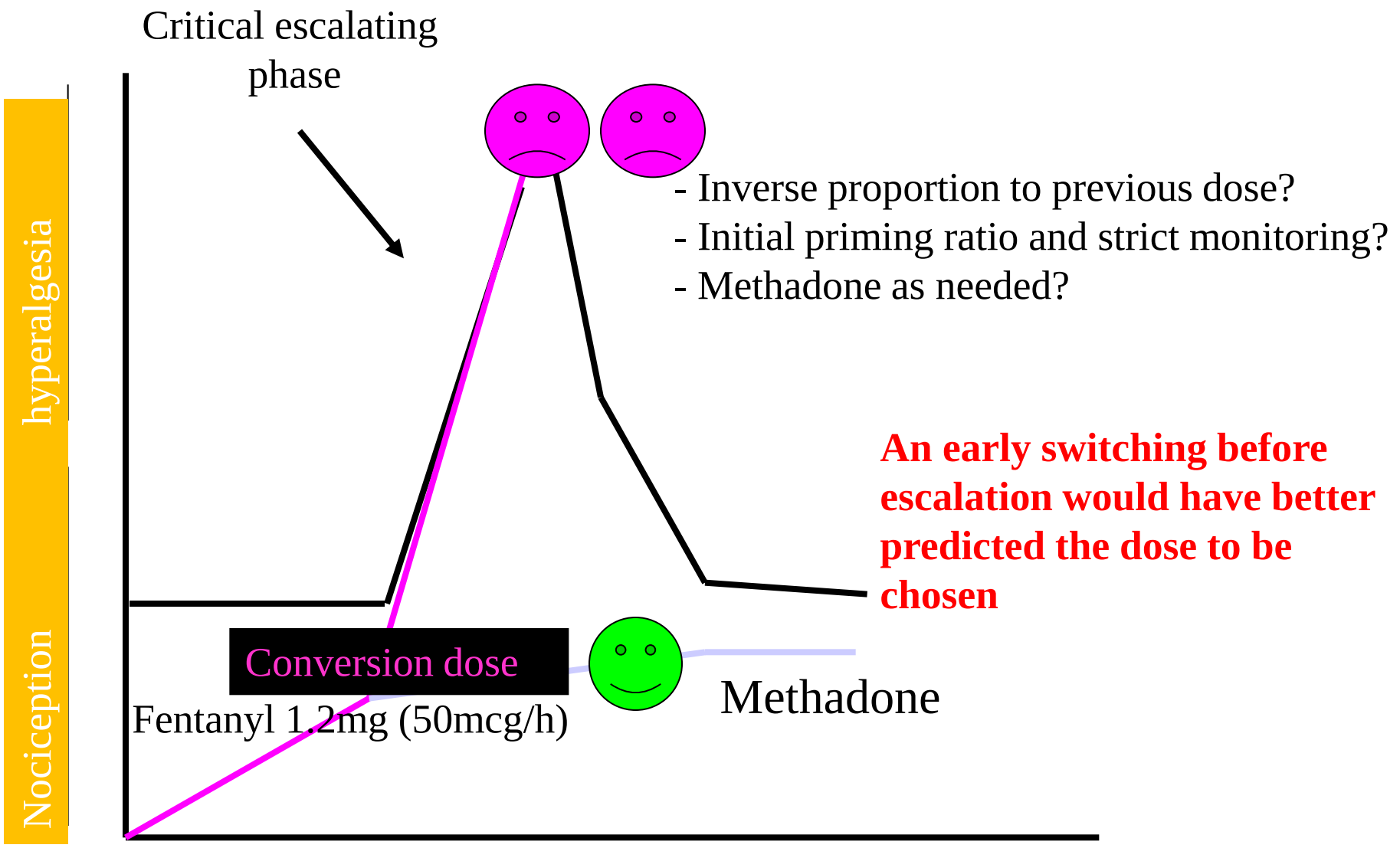
Clinical reports suggest that opioids, intended to abolish pain, can unexpectedly produce hyperalgesia. This paradoxical effect may be mechanistically related to tolerance induced by increasing doses of opioids. Two case reports illustrate a syndrome characterized by increasing pain pursued by escalating opioid doses, which results in a worsening of the clinical picture. Several experimental data may help explain the course of this challenging clinical condition. In escalating opioid doses rapidly, a risk of opioid-induced hyperalgesia should be recognized, as higher doses of opioids may stimulate rather than inhibit the central nervous system by different mechanisms. Alternative procedures should be taken into consideration to break this cycle, should it occur. More data are needed to detect this condition, as currently no diagnostic information on specific markers, clinical or biochemical, exists. J Pain Symptom Manage 2003;26:769–775.

Case report U.F. m, 55 yr, sarcoma chest wall,
Tolerant patient receiving opioids for 3 years, with progressive increase in transdermal fentanyl from 0.6 mg to 12 mg, with a peak in OEI in the last month. F-M switching using 1:20 ratio.

Final ratio 1:60 (about 20 m

Fentanyl TTS Methadone
500 mcg/h (12 mg) 80 mg …x 3



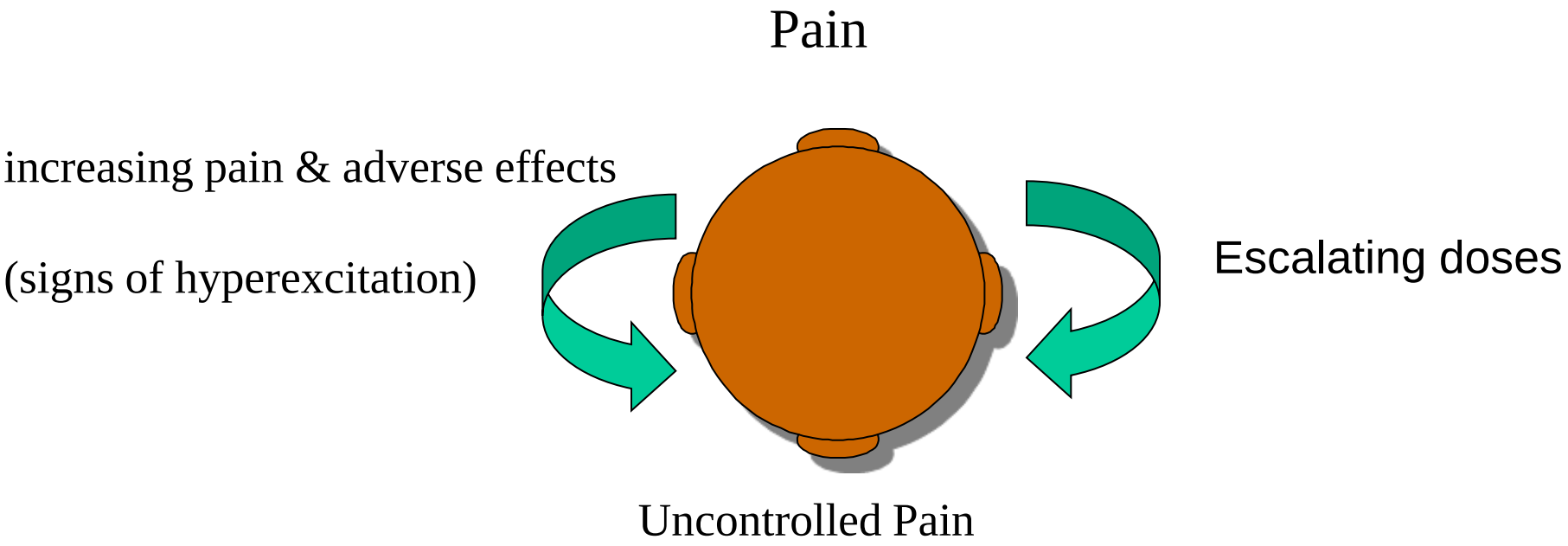

Critical escalating phase
hyperalgesia
Nociception
- Inverse proportion to previous dose?
- Initial priming ratio and strict monitoring?
- Methadone as needed?
An early switching before escalation would have better predicted the dose to be chosen
Conversion dose
Fentanyl 1.2mg (50mcg/h)
Methadone

Dose ratio in opioid switching

Choice of conversion ratios in opioid switching and hyperalgesia

The need for dynamic calculation

The ratio to choose is likely to depend on recent high escalation index rather than the dosage itself



Factors influencing conversion ratios when switching to methadone

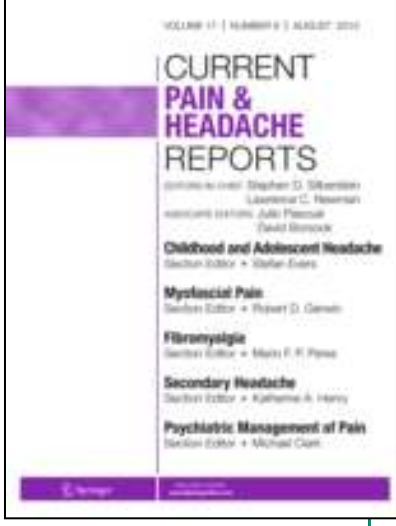
• Adverse effects	↓ dose	(↑ ratio)
• Uncontrolled pain	↑ dose	(↓ ratio)
• Escalation doses	↓↓ dose	(↑ ratio)
• Both	↓ dose	(↑ ratio)
• Convenience	=	

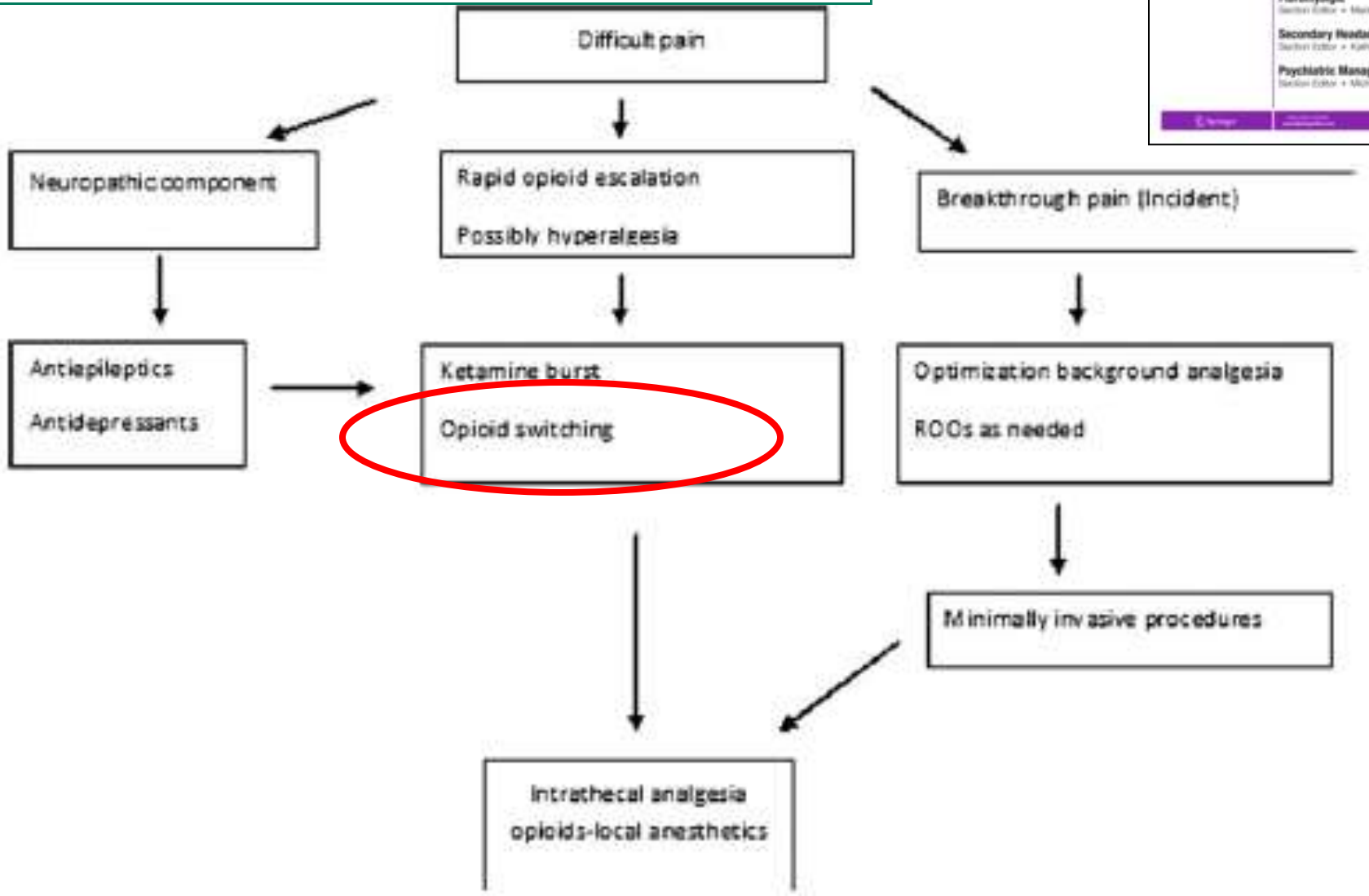
Curr Pain Headache Rep (2014) 18:395
DOI 10.1007/s11916-013-0395-y

CANCER PAIN (D MARCUS, SECTION EDITOR)

Managing Difficult Pain Conditions in the Cancer Patient

Sebastiano Mercadante





Champions Palliative Care
Palermo, 16-18th april 2015

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Recenti

2014

Mercadante's band

127 "Mi piace" · 3 ne parlano

✓ Ti piace | ✓ Segui già | Messaggio

Comunità

Luogo di informazione, condivisione e consulenza per terapia del dolore e cure di supporto, La Maddalena Cancer Center, Palermo

Informazioni · Suggerisci una modifica

Foto

127

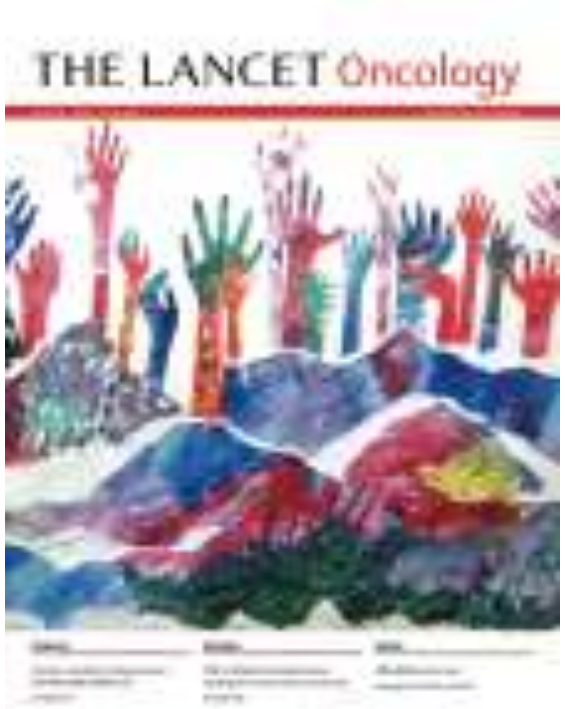
Persone a cui piace

Eventi

In evidenza

Equianalgesic ratios

In adult patients with pain directly due to cancer, which is the evidence of the optimal equianalgesic ratios between different opioids and strategies for switching therapy from one opioid to another one?



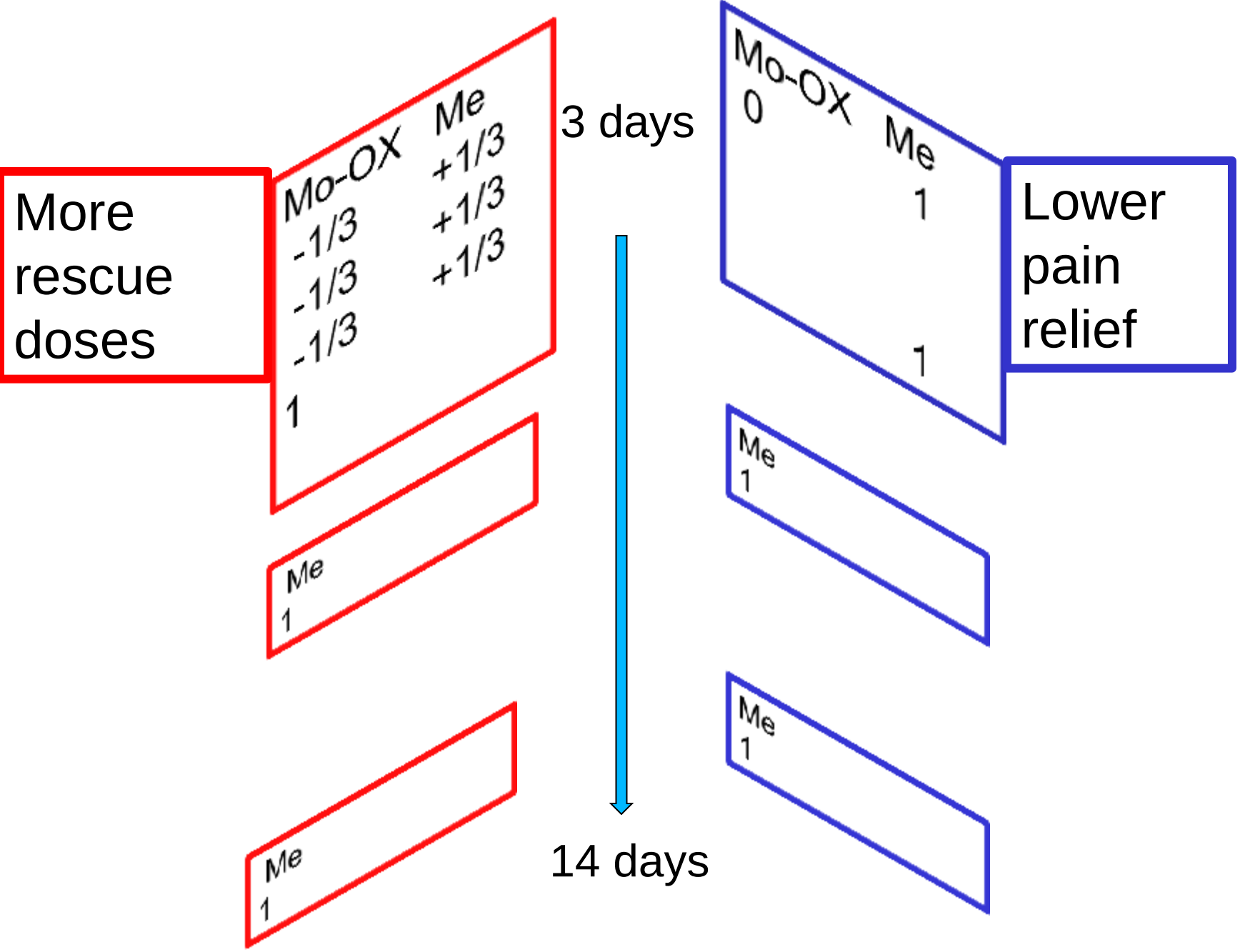
Conversion ratios suggested with methadone:

- inversely proportional to previous opioid doses (Edmonton)
- as needed & variants (Liverpool)
- fixed priming and then clinical flexibility (Palermo)

Norvegian wood

Moksnes K, et al. How to switch from morphine or oxycodone to methadone in cancer patients? A randomized clinical phase II trial Eur J Cancer, 2011

Stop and go strategy (SAG) for switching from oxycodone or morphine to methadone produced more pain, more drop-out and adverse effects, suggesting that a switch performed in three days (3DS) works better than SAG.


More rescue doses
Mo-OX
-1/3
-1/3
-1/3
Me
+1/3
+1/3
+1/3
1
Me
1
Me
1
3 days
14 days
Mo-OX
0
Me
1
1
Me
1
Me
1
Lower pain relief

Nociception - opioid escalation – tolerance – hyperalgesia early switching?

- Opioid dose escalation may have an intrinsic risk, particularly when it is accelerated unsuccessfully, as increasing doses of opioids may worsen the clinical picture in some circumstances, and an appropriate diagnosis is of paramount importance to avoid unfavourable clinical consequences.

- The clinical implications of this observation are relevant. Rapid escalating opioid doses, possibly due to the development of opioid-induced tolerance-hyperalgesia, should be considered a sort of impeding adverse effect requiring a refined assessment and possibly an earlier indication for opioid switching.

- These considerations should indicate a meaningful approach during opioid escalation, possibly anticipating opioid switching or other alternative measures to avoid clinical disasters in patients with poor pain control.

HOW LONG A PT, INTESIVELY TREATED, SHOULD SUFFER?

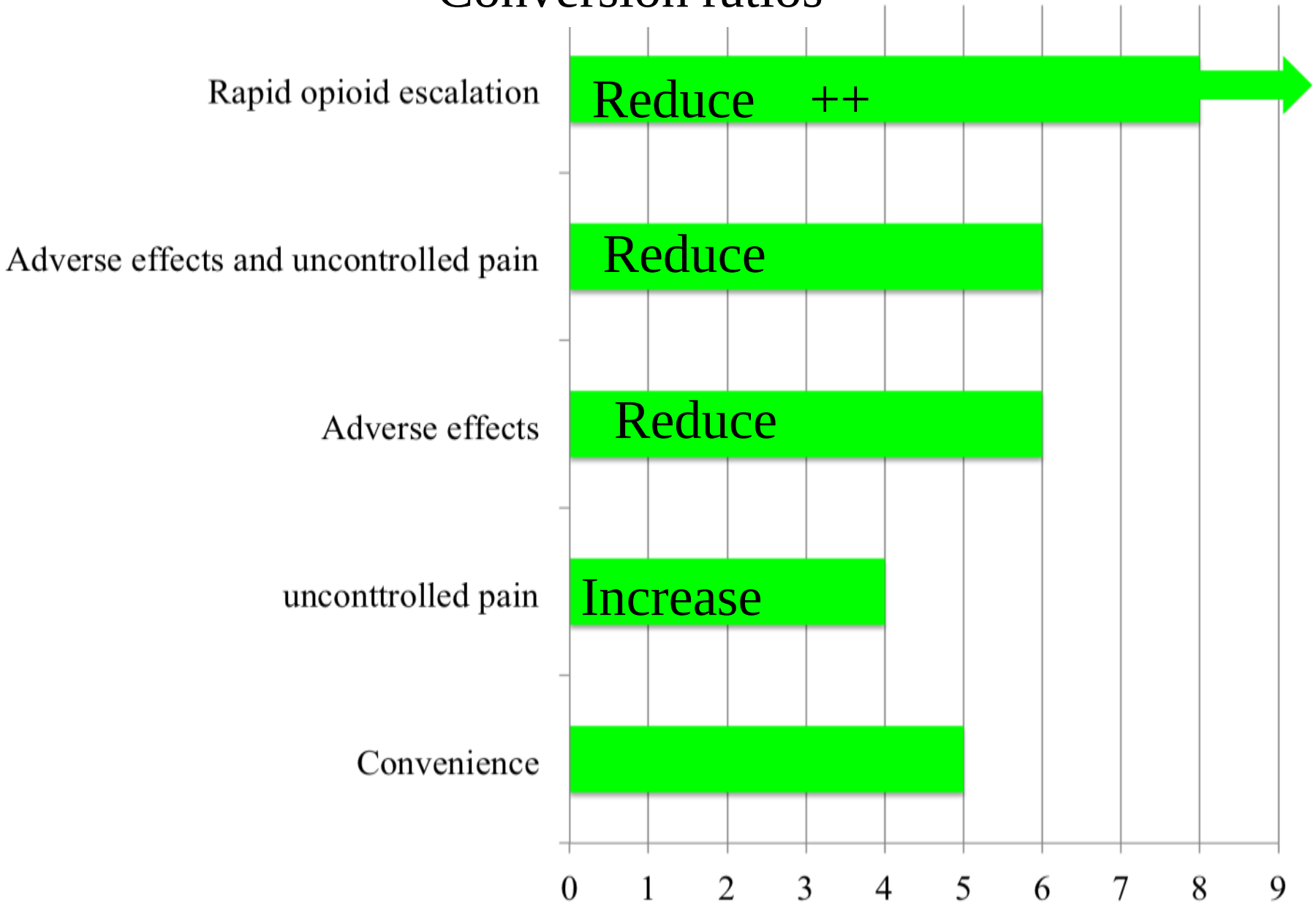
Kumar 2000
From this series, the maximum bolus of morphine was 34.5 mg. This means that these pts received 23 boluses of 1.5 mg every 10’ in 215’.

In the meantime most of the initial amount of morphine boluses are largely eliminated, so that the real effective dose is difficult to determine.

This can explain the IV-oral ratio of 1:1 used by authors for oral conversion.

20min

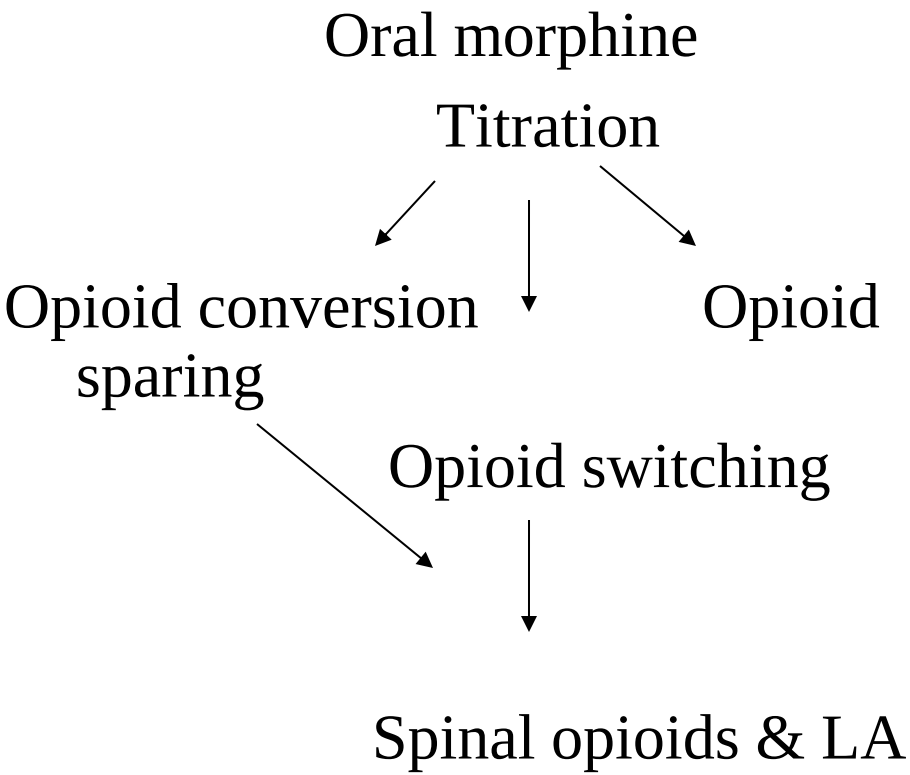
Conversion ratios



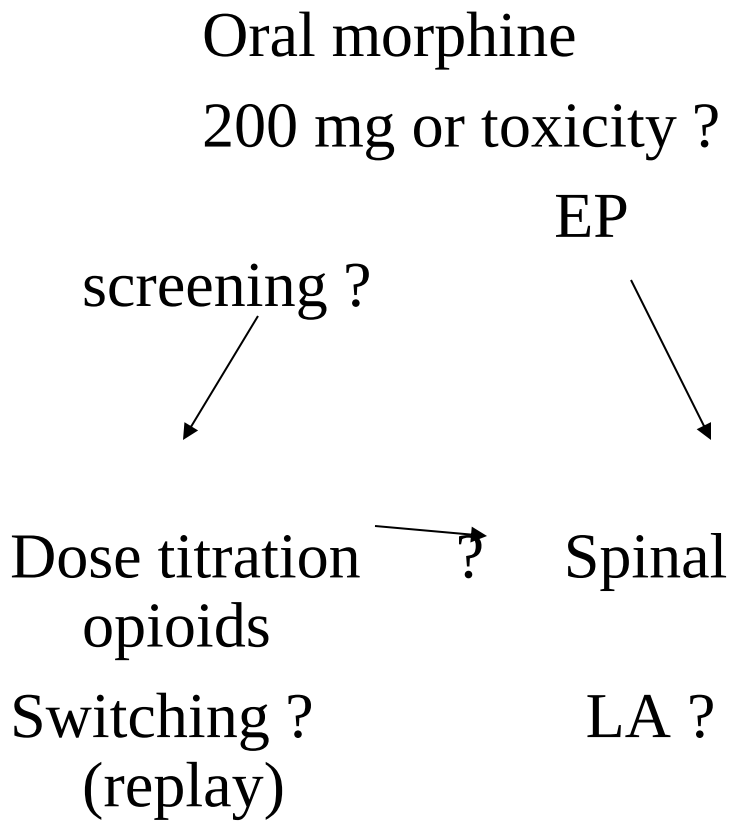
Indications and need of use of spinal analgesia
Mercadante S, et al. Crit Rev Ematol Oncol 2011

In pioneer studies of spinal analgesia in cancer pain no clear indications were provided to start this complex treatment.
It seems that patients should optimize their treatment by using multiple trials of opioids administered by different routes and administering other indicated non-opioid analgesics and symptomatic drugs, before being defined as refractory.
After an appropriate selection, neuraxial analgesia is used in a selected number of patients with cancer pain, accounting for approximately 2% of those seen for pain consultation.

Concerns



Expert current practice



Smith's study

Intrathecal Treatment in Cancer Patients Unresponsive to Multiple Trials of Systemic Opioids

Sebastiano Mercadante, MD,† Giuseppe Intravaia, RN,* Patrizia Villari, MD,* Patrizia Ferrera, MD,* Salvatore Riina, BS,* Fabrizio David,* and Salvatore Mangione, MD†*

least three opioids
least two routes !!!

Hi, Dad, what's … app?

Review Article

Opioid combination: rationale and possible clinical applications

Sebastiano Mercadante

Anesthesia and Intensive Care and Pain Relief and Palliative Care, Via san Lorenzo 312, 90146 Palermo, Italy

Corresponding to: Sebastiano Mercadante, MD. Anesthesia and Intensive Care and Pain Relief and Palliative Care, Via San Lorenzo 312, 90146 Palermo, Italy. Email: terapideldolore@lamaddalenanet.it or 03sebelle@gmail.com.

Abstraot: The aim of this review is to provide a potential benefit of an opioid combination at receptor sites, based on experimental data and preliminary clinical studies where a combination of opioids with different characteristics yielded greater analgesic activity with lesser adverse effects. The receptor activity, including intrinsic activity, endocytosis, and oligomerization, and the interaction on opioid receptors and between different opioid receptors or different sites are described. Finally, Clinical observations of opioid combinations reported in literature regarding the possible benefits of such an approach are presented.

Key Words: Opioid combination; cancer pain; chronic pain; tolerance; opioid receptor

Rapid escalation…

….plain

uncontrolled pain
despite ripid
escalation

Controlled pain
Flat dosing

Morphine
720

360

7 days
1.99

methadone 30 mg

0.19

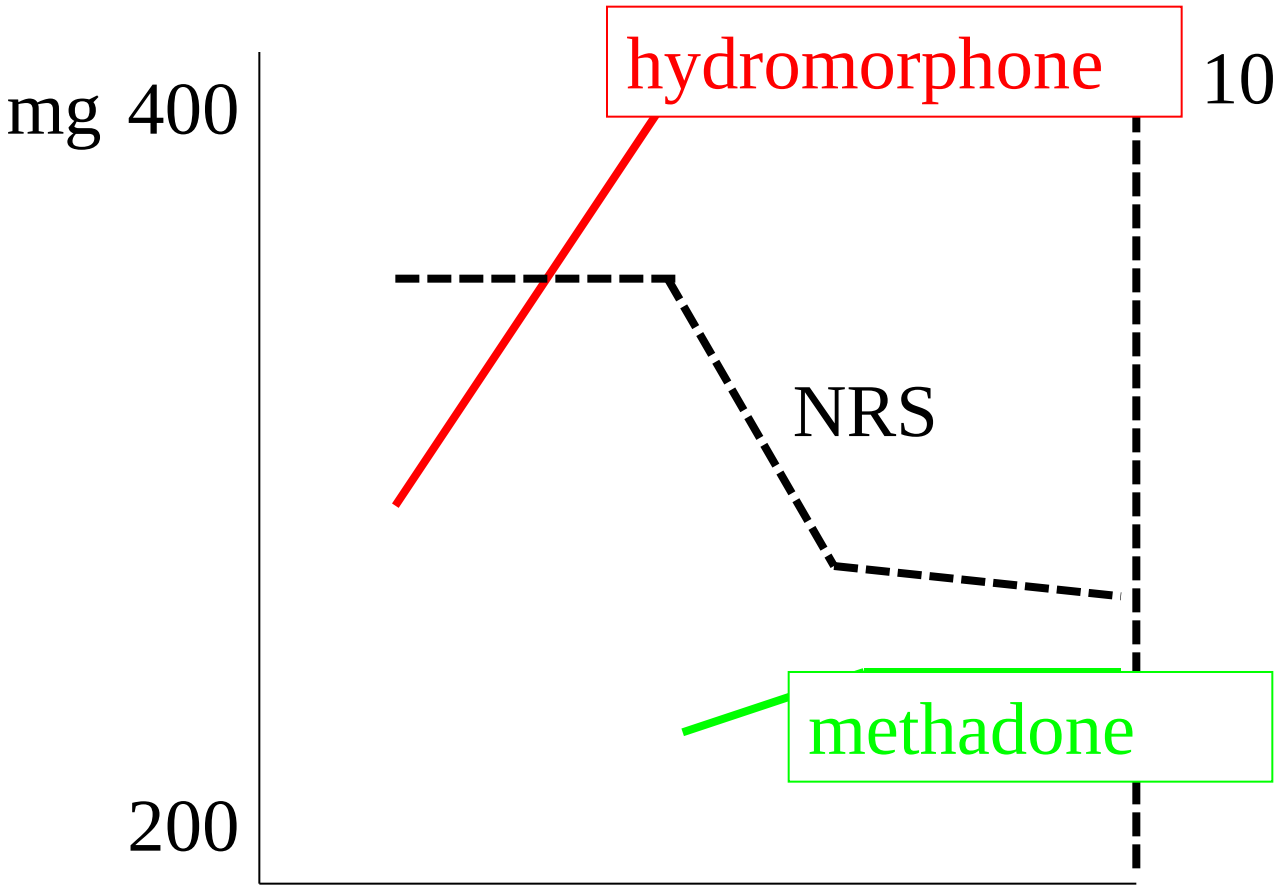
0.27

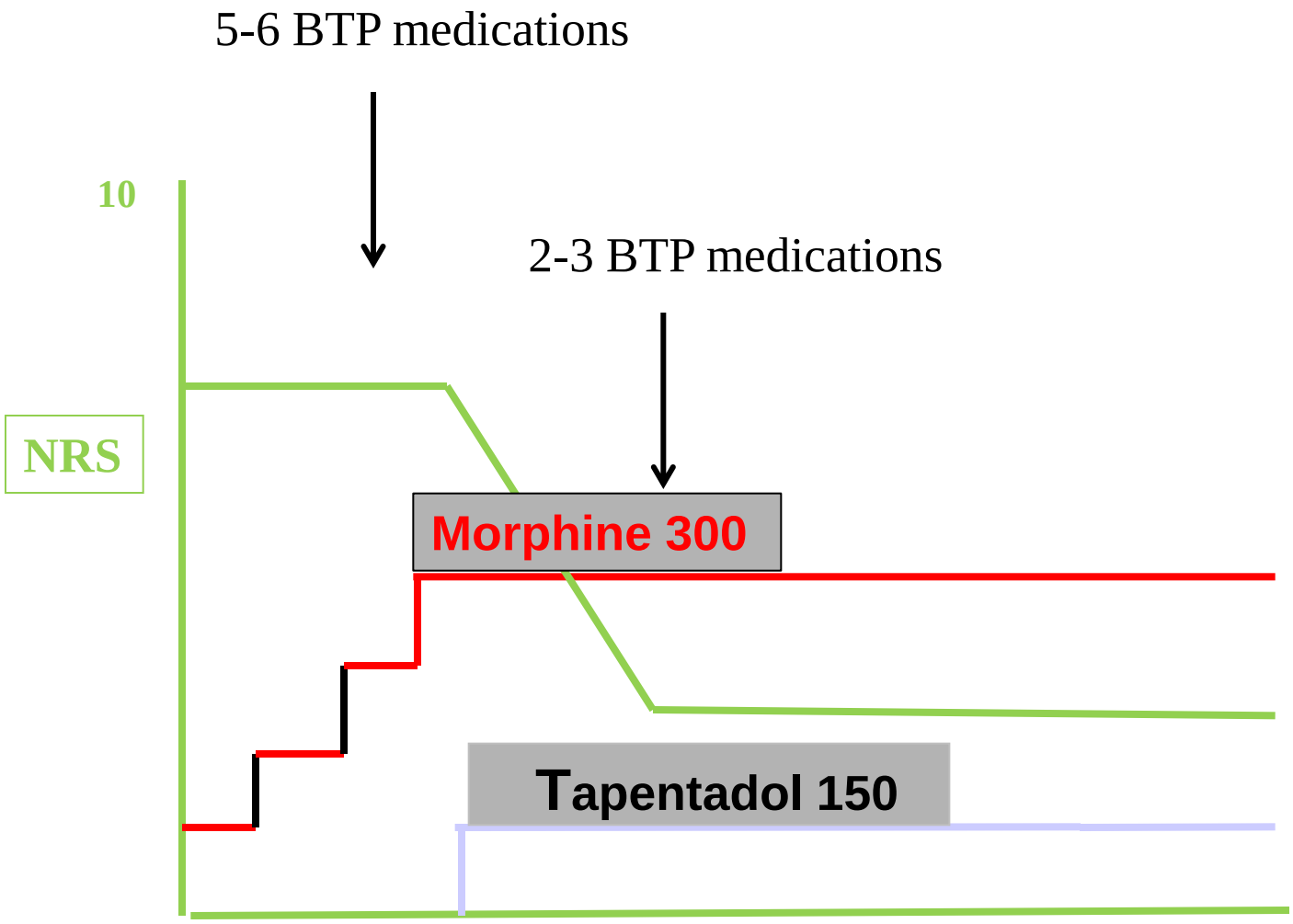
methadone 60 mg

0.18

0.09

67 yrs. Lung cancer, apex syndrome




5-6 BTP medications
10
2-3 BTP medications
NRS
Morphine 300
Tapentadol 150

Cognome e Nome [redacted] Nato il ______ Età ______

Residente a ______ Via ______ Tel. ______

Anamnesi - Esame obiettivo

Port 14·6·2011 catetere peridurale INAVIA-PORT (portatile 4000)

pompa deltec dd 5800, infus. continua

formula ziconotide - ropivacaina

17/09/2011 Dolore T dx nella sede chirurgica Altro sfintere, ingresso ...

l'ambito ... dx ora è pure ottenuto

Diagnosi MPM EPITELIOCELLULARE T1 4 linee kg 61 VINORELBINA extrapleurale

dolore toracico dx

Terapia

POMPA

Co Efferalgan 1

~~Morfina fl. ogni 8 = 1 puntura S.C. - 4-5 fiale~~

PALEXIA 150 mg x 2

MEGACE 160 x 1

DELTACORTENE 25 x 1

TRANSTEC 52 ogni 3 giorni

EFFENTORA 600 ...

ORAMORPH gocce 25 gocce

DEPALGOS 20 1 al mattino ... 1 ... 1 la sera

Comunicazioni particolari:

Da conservare per le visite successive

Per il Dott.

Lo Specialista

TLM mod 46/03

What are we going to have?

- Mox-duo (morphine-oxycodone 3:2)
- Peripheral mu agonism (frakefamide)
- Peripheral Mu antagonism
- Central K antagonism
- Peripheral K activity
- Opioid-agonist – tachynin antagonist
- Opioid agonist – orphanin agonist
- Cannabinoids
- Palmitoiletanolamide

- Anti-hypertensive ca-antagonists
- Octreotide
- IT ziconotide
- ?

All patients gave their consent

Cannabinoids

- Cannabinoids act primarily through specific receptors: CB1 receptors are predominantly distributed in the central nervous system including the immune system).

- Aspirin of the 21 century
- Cannabis use is prevalent among chronic non cancer pain population for a wide range of symptoms, prevalently inhaled, younger more frequently (Ware, 2003)
- Pain & spasticity in multiple sclerosis (Rog 2005)
- Poor additive effects, mild AE ++ (Buggy, 2003, Bernan, 2004, Naef 2003)

Clinical Therapeutics/Volume 31, Number 10, 2009

Research Letter

Low Doses of Transdermal Buprenorphine in Opioid-Naive Patients With Cancer Pain: A 4-Week, Nonrandomized, Open-Label, Uncontrolled Observational Study

Sebastiano Mercadante, MD[1,2]; Gianpiero Porzio, MD[3]; Patrizia Ferrera, MD[1]; Federica Aielli, MD[3]; Lucilla Verna, MD[3]; Walter Tirelli, MD[4]; Patrizia Villari, MD[1]; and Alessandra Casuccio, BS[5]

[1]Anesthesia & Intensive Care Unit, and Pain Relief & Palliative Care Unit, La Maddalena Cancer Center, Palermo, Italy; [2]Anesthesiology and Intensive Care, University of Palermo, Palermo, Italy; [3]L'Aquila per la Vita Home Care Service, Department of Experimental Medicine, University ... [4]Intensive Care and Pain Therapy Unit, National Cancer Institute "Regina ... [5]Department of Clinical Neuroscience, University of Palermo, Palermo, Italy

Brief report

Low doses of transdermal fentanyl in opioid-naive patients with cancer pain

Sebastiano Mercadante
Anaesthesia & Intensive Care Unit, and Pain Relief & Palliative Care Unit, La Maddalena Cancer Centre, Palermo, Italy
Anaesthesiology and Intensive Care, Master of Palliative Medicine, University of Palermo, Palermo, Italy

Gianpiero Porzio
L'Aquila per la Vita – Home Care Service, L'Aquila, Italy

Patrizia Ferrera
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Federica Aielli
L'Aquila per la Vita – Home Care Service, L'Aquila, Italy

Claudio Adile
Anaesthesia & Intensive Care Unit, and Pain Relief & Palliative Care Unit, La Maddalena Cancer Centre, Palermo, Italy

Corrado Ficorella
Department of Oncology – University of L'Aquila

Abstract

Objective:
The aim of this study was to evaluate the effect and tolerability of low doses of transdermal (TD) fentanyl patches in opioid-naive patients with cancer pain.

Methods:
This was a nonrandomized, open-label, uncontrolled study in fifty consecutive opioid-naive patients with advanced cancer and moderate pain. TD fentanyl was initiated at a dose of 12 µg/h. Doses were then adjusted according to the clinical response. Pain intensity, opioid-related adverse effects, TD fentanyl doses, and quality of life were monitored over 4 weeks. The time to dose stabilization and indexes of dose escalation were also calculated.

Results:
Thirty-one patients completed all 4 weeks of the study. Pain control was achieved within a mean of 1.7 days after the start of TS fentanyl therapy. Significant differences in TD fentanyl doses were observed during the study period ($P = 0.03$). Mean doses were doubled 4 weeks after starting the treatment. The level of adverse effects was acceptable in most patients and only a minority of patients discontinued the treatment (13.8%).

Conclusion:
Low doses of TD fentanyl were well tolerated and effective. Observations from this study suggest that randomized, controlled, double-blind studies of TD fentanyl 12 µg/h in opioid-naive patients with cancer pain may be warranted.

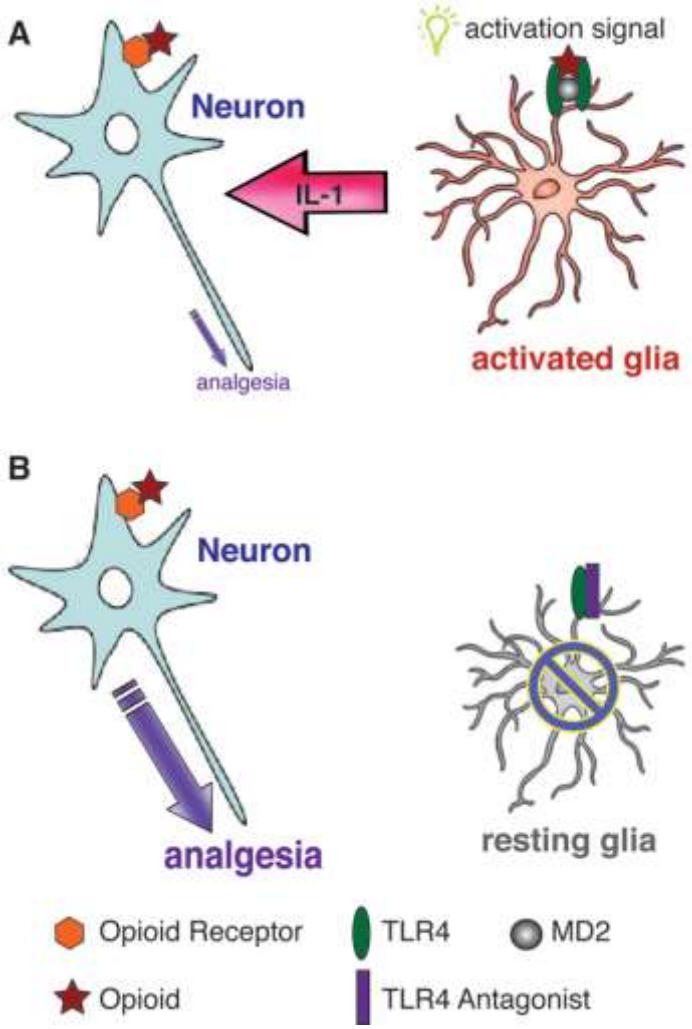
Efficacy and tolerability of cancer pain management with controlled-release oxycodone tablets in opioid-naïve cancer pain patients, starting with 5 mg tablets. Koizumi et al. Jpn J Clin Oncol 2004.

- A starting dose of SR oxycodone 5 mg every 12 h.
- 18 out of 20 (90%) attained stable, adequate pain control. Two-thirds of the patients attained stable, adequate pain control without any dose titration.
- The mean length of time was 1.2 days.

These opioid effects on glia are caused by the activation of a non-classical, non-stereoselective opioid receptor that is distinct from the receptor expressed by neurons that suppresses pain. Opioid administration leads to an opposing process: glial release of proinflammatory cytokines that oppose the analgesic actions of opioids. The glial opposition of analgesia occurs in response to opioid administration. Both pain suppression and proinflammatory cytokine-induced pain enhancement simultaneously occur as opponent processes. Blocking proinflammatory cytokine actions markedly enhances the magnitude and duration of opioid analgesia. Indeed, morphine dose-response functions performed in the absence versus presence of cytokine inhibitors reveal a marked leftward shift in the dose-response function when proinflammatory cytokine actions are blocked, demonstrating that these endogenous proinflammatory mediators naturally compromise the analgesic efficacy of both intrathecally and systemically delivered opioid analgesics. Glial proinflammatory cytokines upregulate in response to chronic opioids, contributing to the development of opioid tolerance, opioid dependence/withdrawal, and opioid reward, measured both neurochemically (via *in vivo* microdialysis) and behaviorally (via conditioned place preference). Of fundamental importance is our discovery that opioids activate glia via a non-stereoselective receptor separate from the classical opioid receptor: toll-like receptor 4 (TLR4). Given that neuronally inactive (+)-naloxone blocks this glial receptor, but not neuronal opioid receptors, this finding predicts that (+)-opioids such as (+)-naloxone should potentiate opioid analgesia by not blocking morphine effects on neurons, yet removing glial activation that opposes analgesia. This is true.

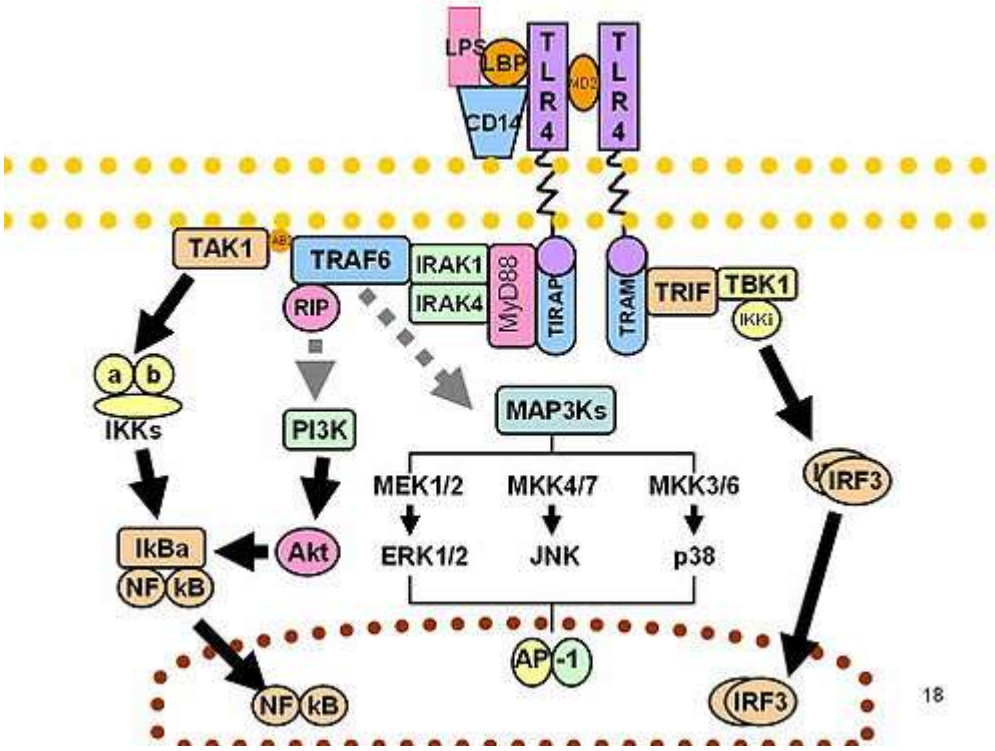
Suppressing glial activation will suppress the pathological pain of various etiologies, improve opioid analgesia, suppress opioid tolerance, suppress opioid dependence, and suppress opioid reward linked to drug craving/drug seeking.

Opioid activation of glia is fundamentally different than for neurons: glial receptors are not stereoselective, opioid effects on glia must be via different receptors (TLR4) than for neurons, effects of glia and neurons should be separable, and to increase the efficacy of opioids, one should either modify opioids so they do not bind glia and/or create long-lasting, orally available versions of [+]-naloxone.



More recently it was discovered that several opioid ligands (e.g., morphine and the opioid receptor antagonist naloxone) affect glia by binding to the glial receptor toll-like receptor 4 (TLR4) (Hutchinson et al. 2010). Unlike classical neuronal opioid receptors, which only bind the (-)-enantiomer of opioids, TLR4 binds opioids in a non-stereoselective fashion with both (-)- and (+)-ligands affecting the signaling cascade. Our recent data demonstrate that antagonism of PAG TLR4 using the prototypical TLR4 antagonist LPS-RS, or (+)-naloxone prevents the development of tolerance to systemic (-)-morphine. Similarly, activation of PAG TLR4 using (+)-morphine is sufficient to induce tolerance to subsequent systemic administration of (-)-morphine. These results indicate that PAG TLR4 mediates glial cell facilitation of morphine tolerance development.

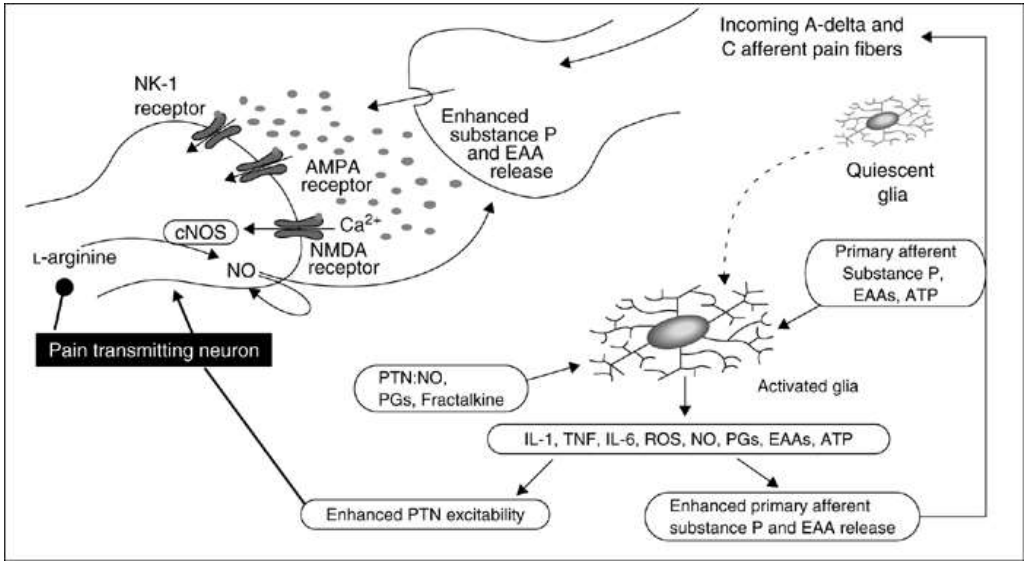
Collectively, this research could provide novel and crucial information about the mechanisms by which central nervous system glia regulate morphine tolerance generally, and could provide a potential therapeutic target for the enhancement of analgesic efficacy in the clinical treatment of chronic pain specifically.



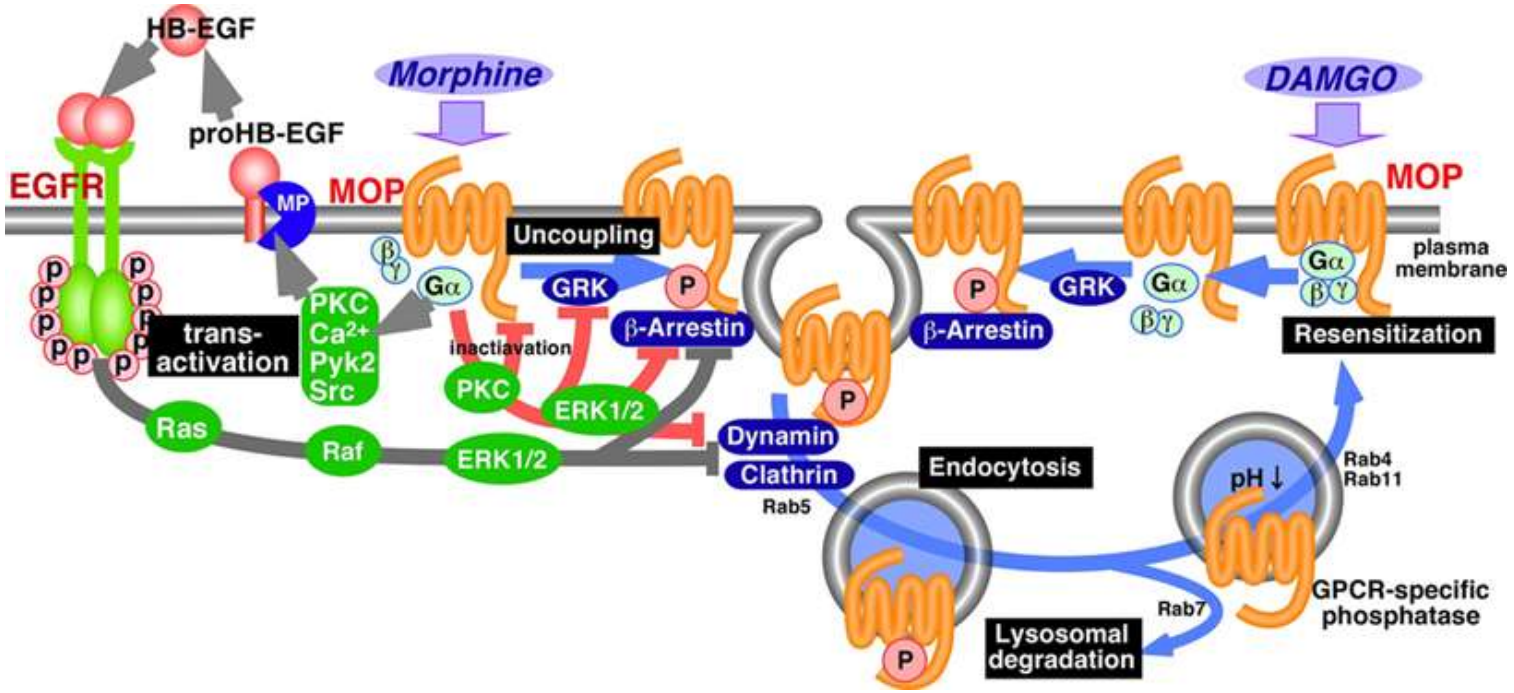
In neuropathic pain, damage to the peripheral nerves shifts the glia to an activated state within the spinal cord. This occurs as a consequence of signals released by stressed and damaged neurons, including factors that activate the “endogenous danger signal” receptor, toll-like receptor 4 (TLR4). Once activated, the microglia release proinflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF); later, anti-inflammatory cytokines are generated to help dampen the injury response.

The use of opioids in chronic pain is often limited by hyperalgesia and tolerance. Glia play a key role in the formation and maintenance of morphine tolerance, as chronic morphine treatment has been shown to increase microglial reactivity.

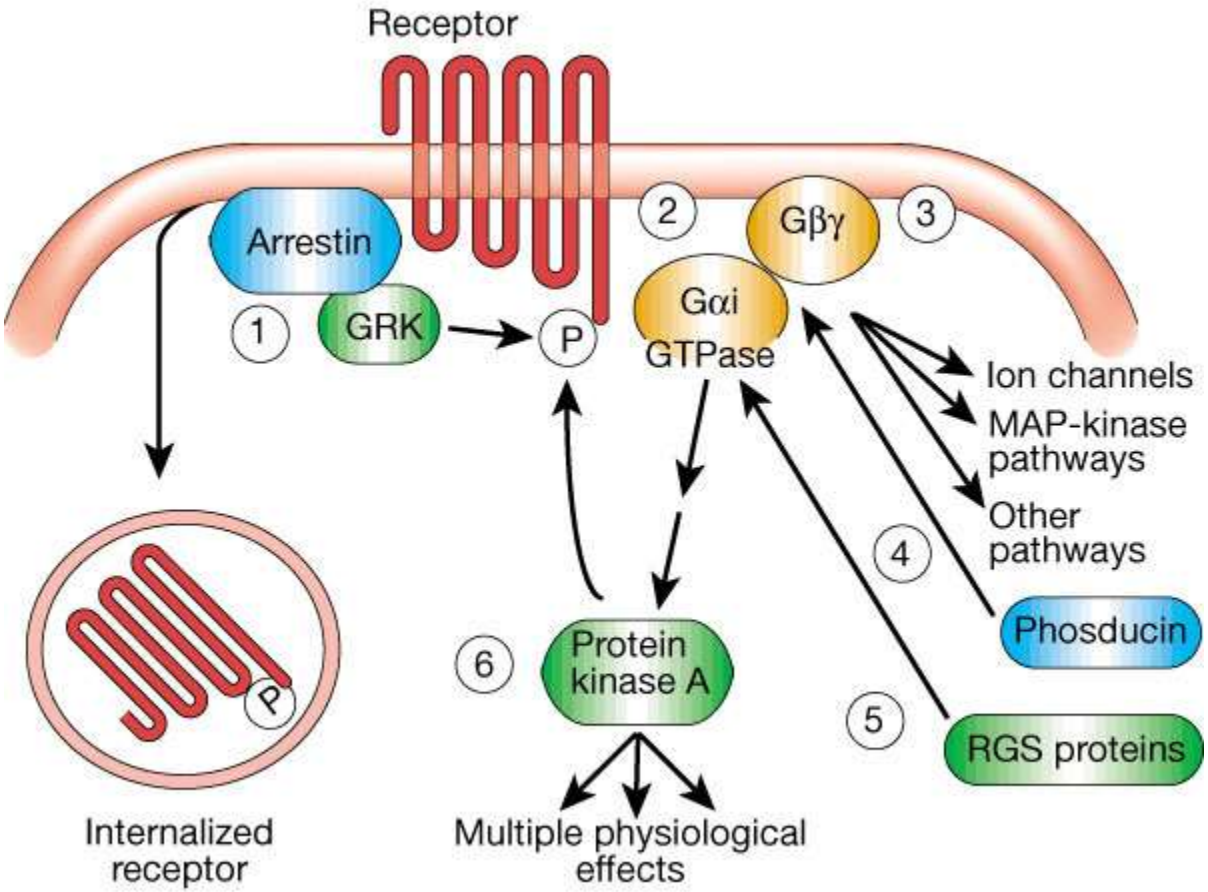
Minocycline, an antibiotic in the tetracycline class, and propentofylline, a glial modulator that decreases mechanical allodynia (an enhanced pain response to touch), can inhibit spinal microglial reactivity and attenuate the development of morphine tolerance. It has been hypothesized that morphine enhances microglial reactivity by inducing the release of proinflammatory cytokines and chemokines, as well as through direct signaling between microglia and nociceptive neurons.



Differential mu-Opioid receptor trafficking upon the stimulation by different agonists. When mu-Opioid receptor (MOP) is stimulated by DAMGO, the signal is coupled to an activation of G protein (G_i or G_o), followed by G protein-coupled receptor kinase (GRK)-catalyzed phosphorylation of MOP and association with beta-arrestin. Clathrin and dynamin are then associated to the membrane containing beta-arrestin-associated MOP to form receptor-containing endosome. Thus endocytosed MOP in the endosome has two fates, lysosomal degradation and resensitization via dephosphorylation. When MOP is stimulated by morphine, on the other hand, the MOP endocytosis does not occur. However, morphine stimulation causes more potent desensitization (acute tolerance) of MOP than DAMGO stimulation, as seen in so-called RAVE hypothesis (see details in the text). As morphine-induced MOP endocytosis is facilitated in the presence of protein kinase C (PKC) inhibitor, morphine-induced PKC phosphorylation of MOP may precede GRK-mediated one and prevent the endocytosis. PKC-phosphorylated MOP seems to be a major mechanism underlying desensitization of MOP in the membrane. The DAMGO-induced PKC activation seems to be simply slower than GRK activation, since similar PKC-mediated desensitization (acute tolerance) occurs when the endocytosis is prevented in the presence of dominant negative mutant of dynamin. MOP : mu-opioid receptor, GRK : G protein coupled receptor kinase, PKC : protein kinase C, ERK1/2 : extracellular signal-regulated kinase1/2, GPCR : G-protein coupled receptor, MP : Metalloprotease, EGF : epidermal growth factor, EGFR : epidermal growth factor receptor, Pyk2 : proline-rich tyrosine kinase 2



Anti-opioid NMDA receptor hypothesis underlying morphine tolerance. As morphine action (analgesia) is enhanced to some extent in NR2A$^{-/-}$ mice, compared with wild-type (WT) mice, without changes in basal nociceptive threshold, morphine stimulation may also cause a glutamate-NMDA (NR2A) receptor activation (possibly mediated by a dis-inhibition of GABA neuronal activity), which in turn limits the morphine inhibitory action. Following chronic morphine treatments, NR2A proteins are up-regulated and cancel the morphine analgesic activity (tolerance).



Drug-induced adaptations in the efficacy of receptor–G_i coupling could contribute to drug tolerance or sensitization. A possible mechanism is altered phosphorylation of the receptor by GRKs or its subsequent association with arrestins (1). Other possibilities include alterations in G-protein - (2) or -subunits (3) or in other proteins (for example, phosducin (4) or RGS proteins (5)) that modulate G protein function. Phosphorylation of the receptor by protein kinase A (6) or other kinases represents another potential mechanism. Also shown is agonist-induced receptor internalization, which may be mediated by receptor phosphorylation

Mice treated with demethylating drugs showed increased expression of mu-opioid receptor relative to control.

May opioids may hasten death in advanced cancer patients?

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The Use of Opioids in the Last Week of Life in an Acute Palliative Care Unit

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Abstract

In 77 patients who died, oral morphine equivalents were 170 and 262 mg/d at −7 and Tend, respectively. Almost all patients were receiving transdermal drugs or intravenous morphine at Tend. Intravenous morphine was more frequently used in sedated patients ($P = .015$). No differences in age, gender, opioid doses, and opioid escalation index (OEI) were found among patients who used opioids. In patients who were sedated, doses of opioids were significantly higher ($P = .012$). In the last week of life, intravenous morphine is the preferred modality to deliver opioids. Doses increased prevalently in sedated patients before starting sedation with the purpose to treat dispnoea.

Keywords

opioids, end of life, intravenous morphine