HIGH DOSE OPIOID THERAPY: ARE WE STILL TREATING PAIN?

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Opioids produce abnormal pain in animal studies

- Opioids given over time maintain their level of efficacy, but the concurrent development of hyperalgesia serves to counteract the antinociceptive effect of opioids, producing an impression of tolerance
- Opioid-induced hyperalgesia is an umasking of a compensatory neuronal hyperactivity in response to morphine-induced inhibition of neuronal function
- This hyper-responsiveness, or sensitization, become evident after higher doses, when opioid is removed, in undertreated pain, or intermittently in the presence of changes in plasma concentration (miniwithdrawals…).

Causes of declining analgesia and need of opioid escalation

- Disease-related factors:

Progression of disease (increased nociception)

Increased humoral factors

Reversible hyperalgesia (therapy-induced flares)

- Factors related to patient-drug interaction

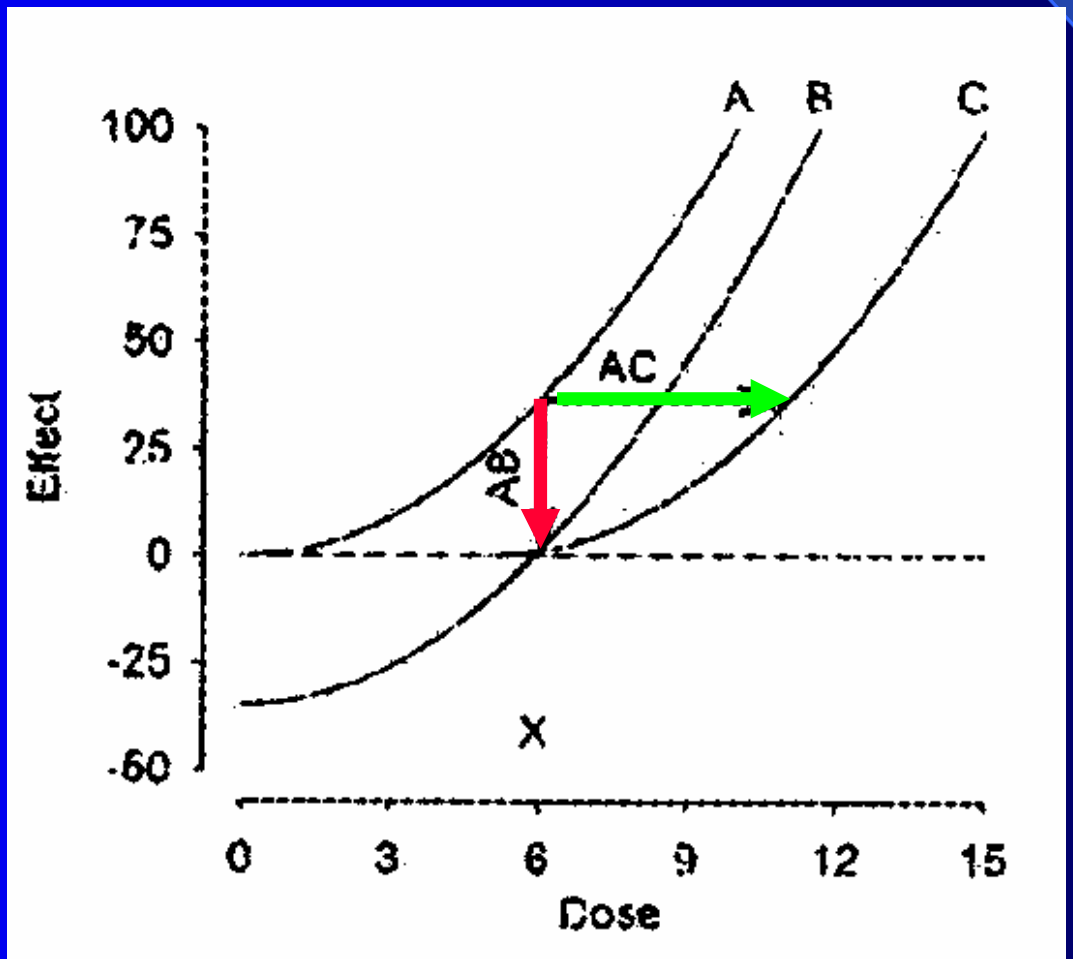
Tolerance

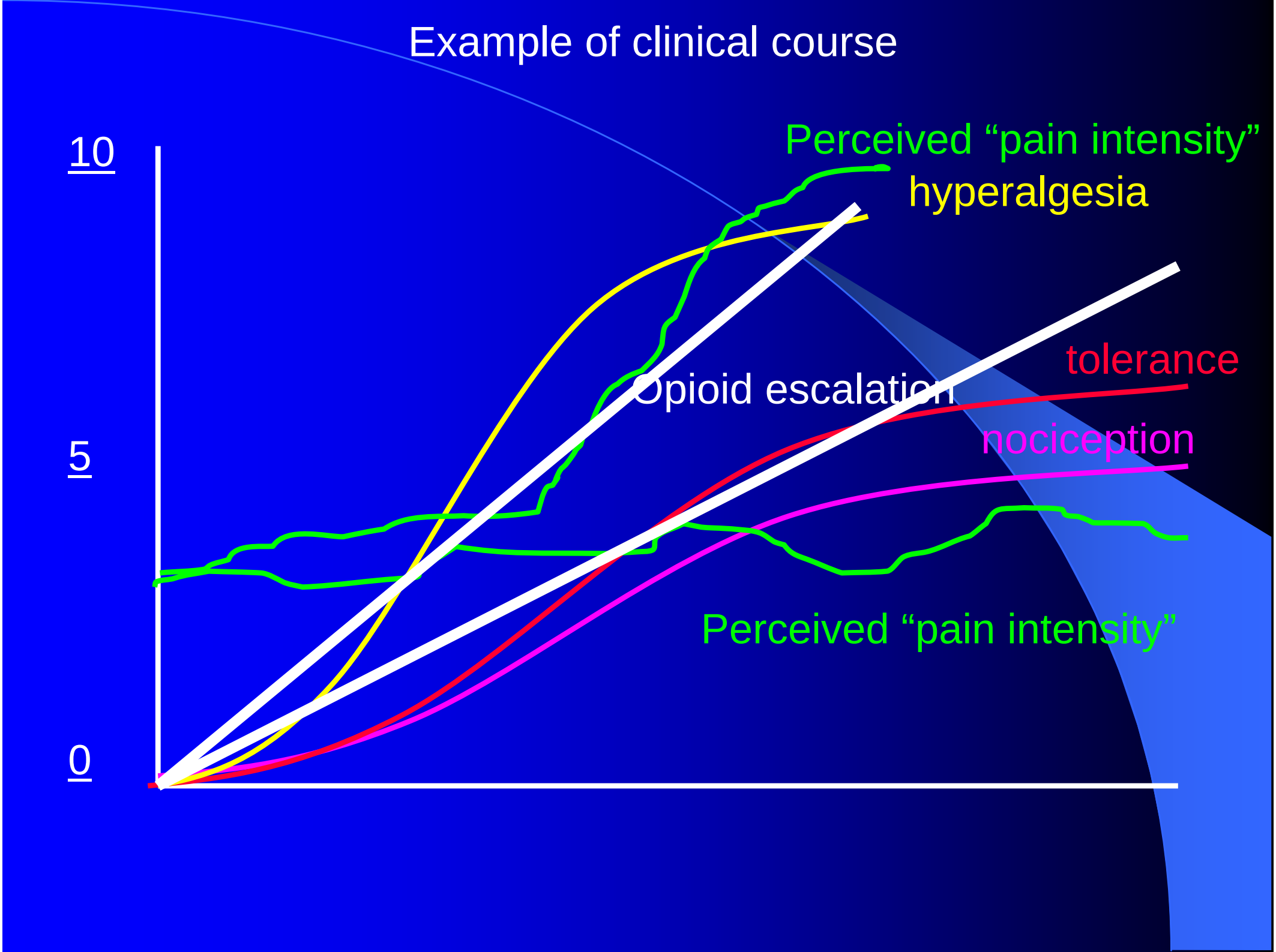
Hyperalgesia

Tolerance and OIH share the same net effect on dose requirement. Either condition necessitates dose escalation for maintaing a certain drug effect

Tolerance: right shift of dose-response curve

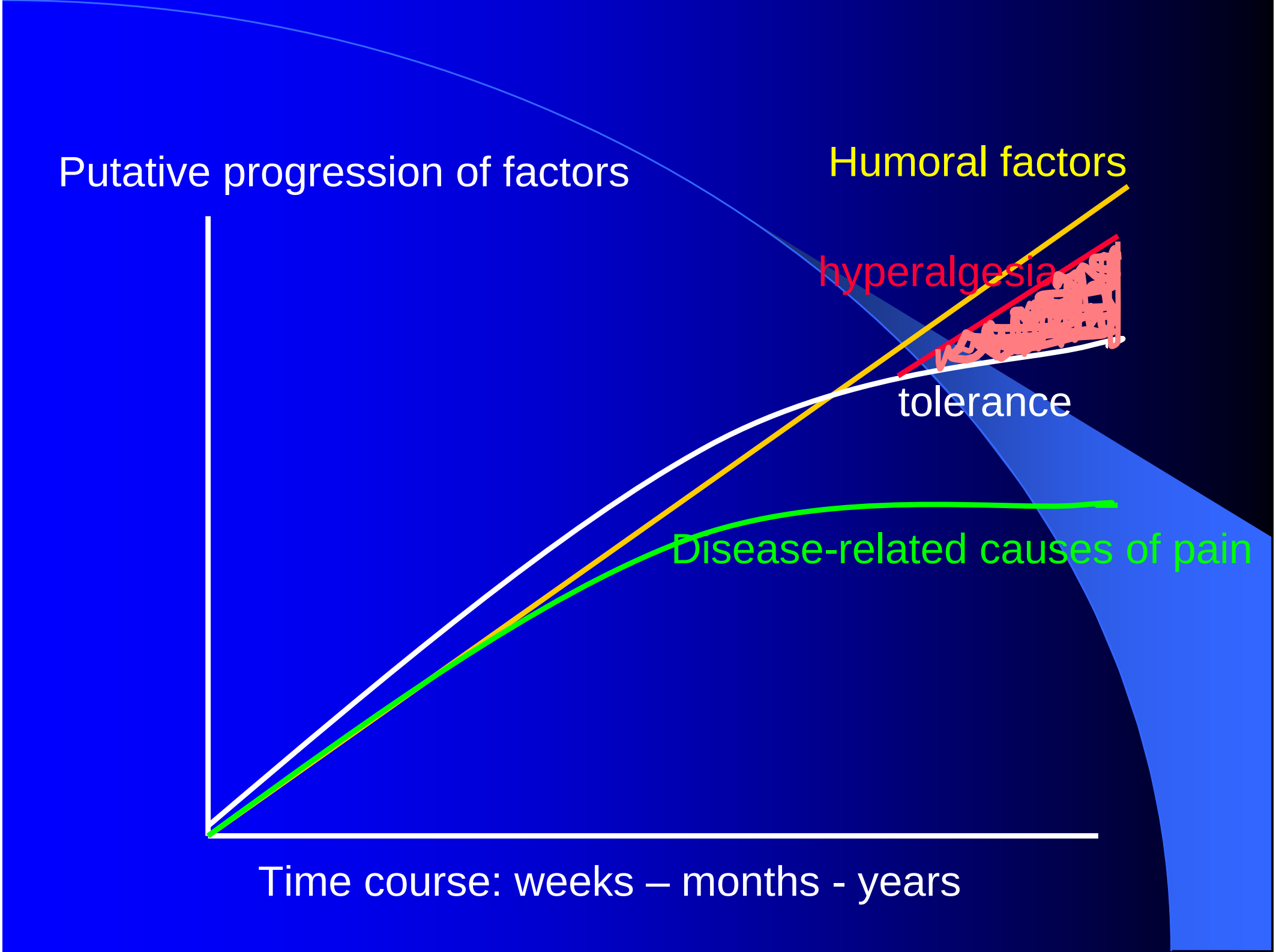
Increased pain sensitivity (OIH): a downward shift of dose-response curve




Example of clinical course
10
5
0
Perceived “pain intensity”
hyperalgesia
Opioid escalation
tolerance
nociception
Perceived “pain intensity”

Factors possibly involved

- Unjustified increased doses
- Mini-withdrawal syndromes
- High level of untreated nociception inducing early hypersensitization
- Genetics?
- Disease-related factors


Putative progression of factors
Humoral factors
hyperalgesia
tolerance
Disease-related causes of pain
Time course: weeks – months - years

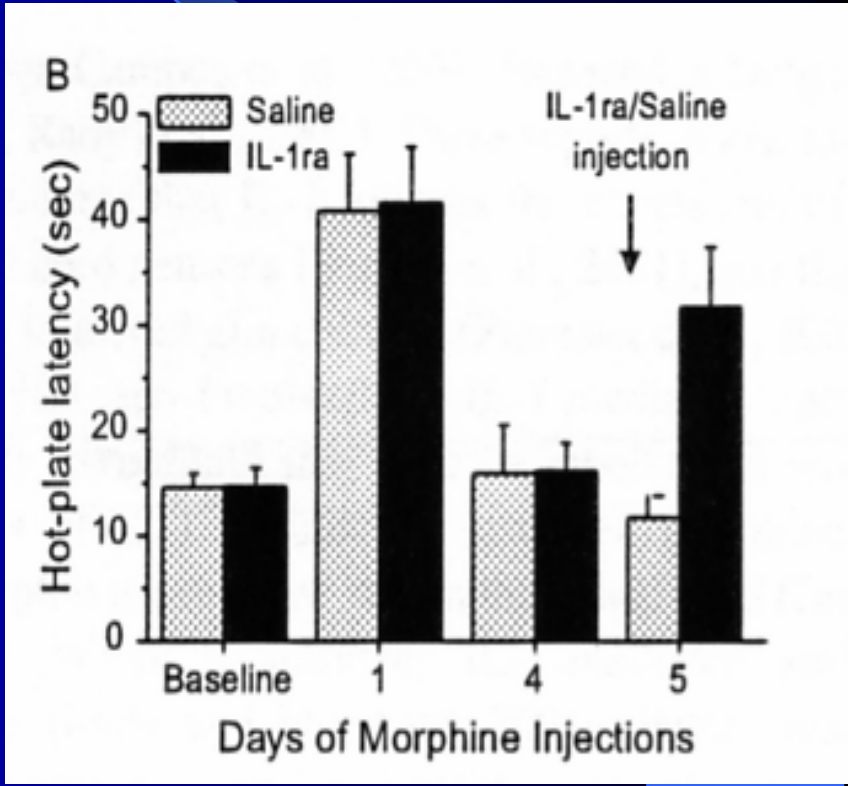
A genetic analysis of opioid-induced hyperalgesia (OIH) in mice
Liang et al, Anesthesiology 2006

- The degree of mechanical allodynia acquired during morphine administration varies for the different strains
- B2-AR genes associated with the development of OIH
- B-blocking substances reversed OIH
- B2-AR null mutant did not develop OIH

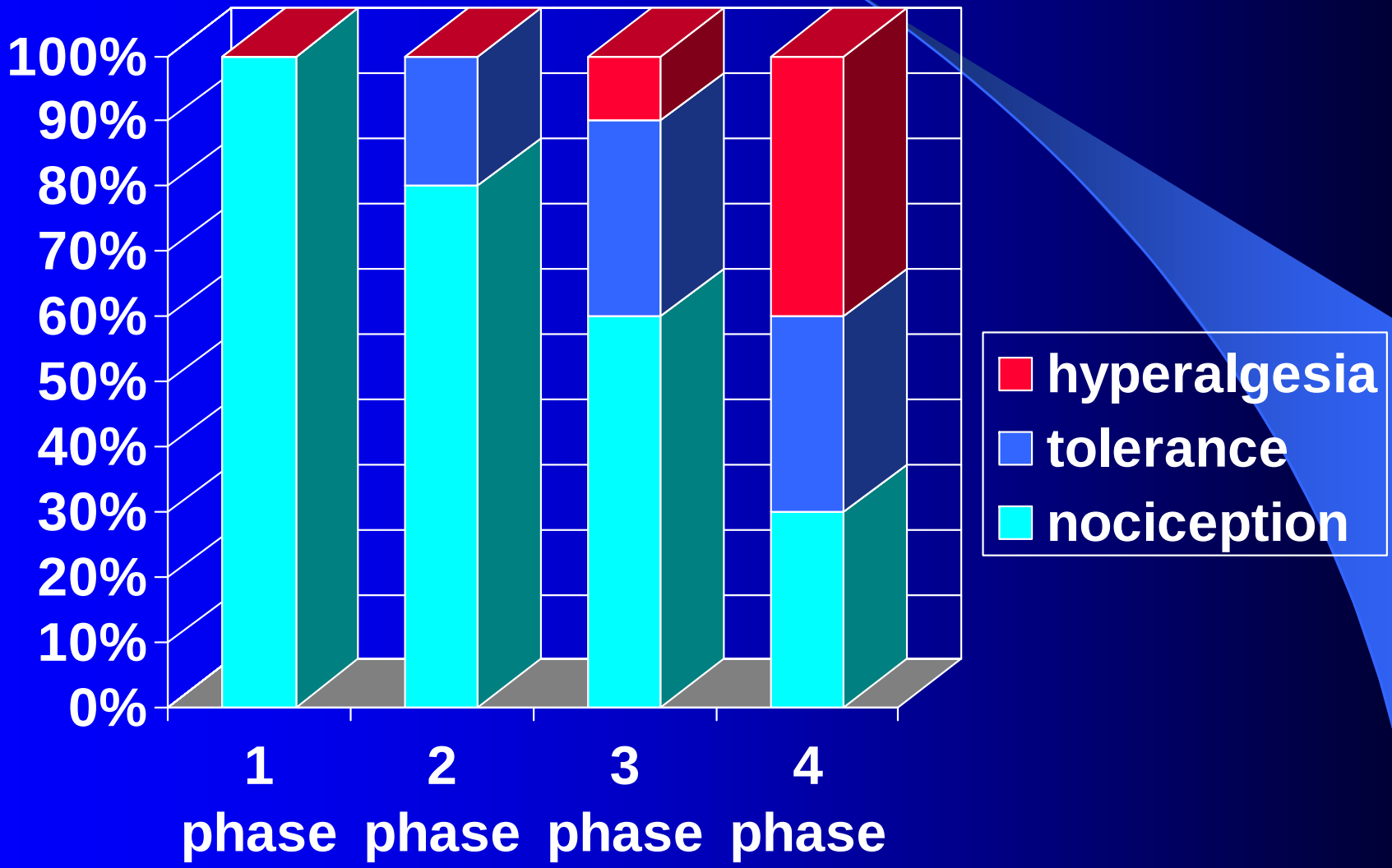
The antianalgesic effect of cytokines

Chronic opioid administration induces:

- glia activation (Watkins, 2002)
- an IL-1 mediated homeostatic response, which serves to limit the duration and extent of morphine analgesia and which underlies the development of tolerance (Shavit, 2005)
- Morphine tolerance is attenuated by genetic or pharmacological blockade of IL-signaling



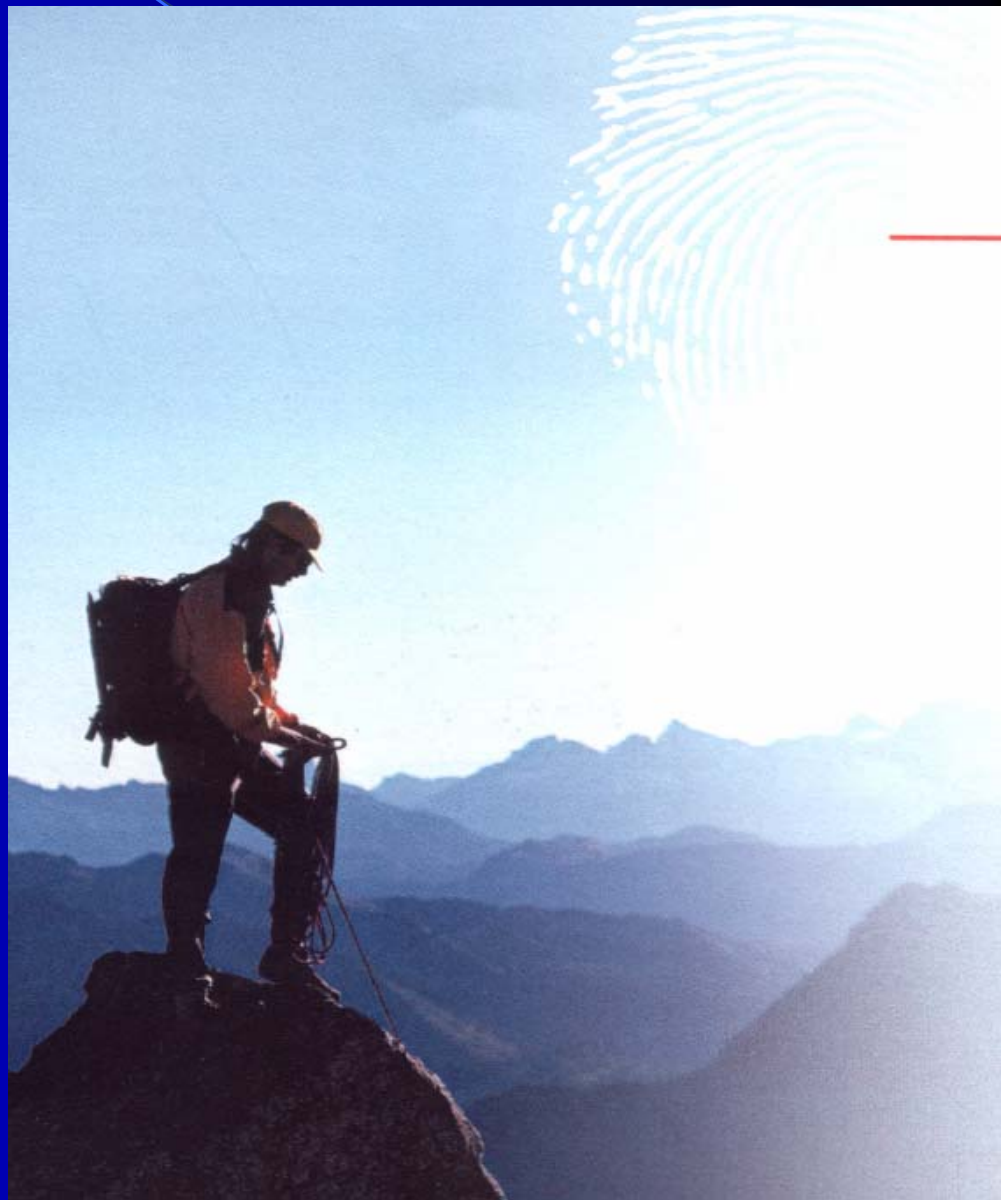
Consequences of opioid escalation: components of pain perception change in time



Treating hyperalgesia due to rapid-ripid opioid escalation

- Switching
- Anti-hyperalgesic drugs
- Intrathecal analgesia

including local anesthetics



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

The rationale is based on the 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.

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

Adverse effects

Analgesia

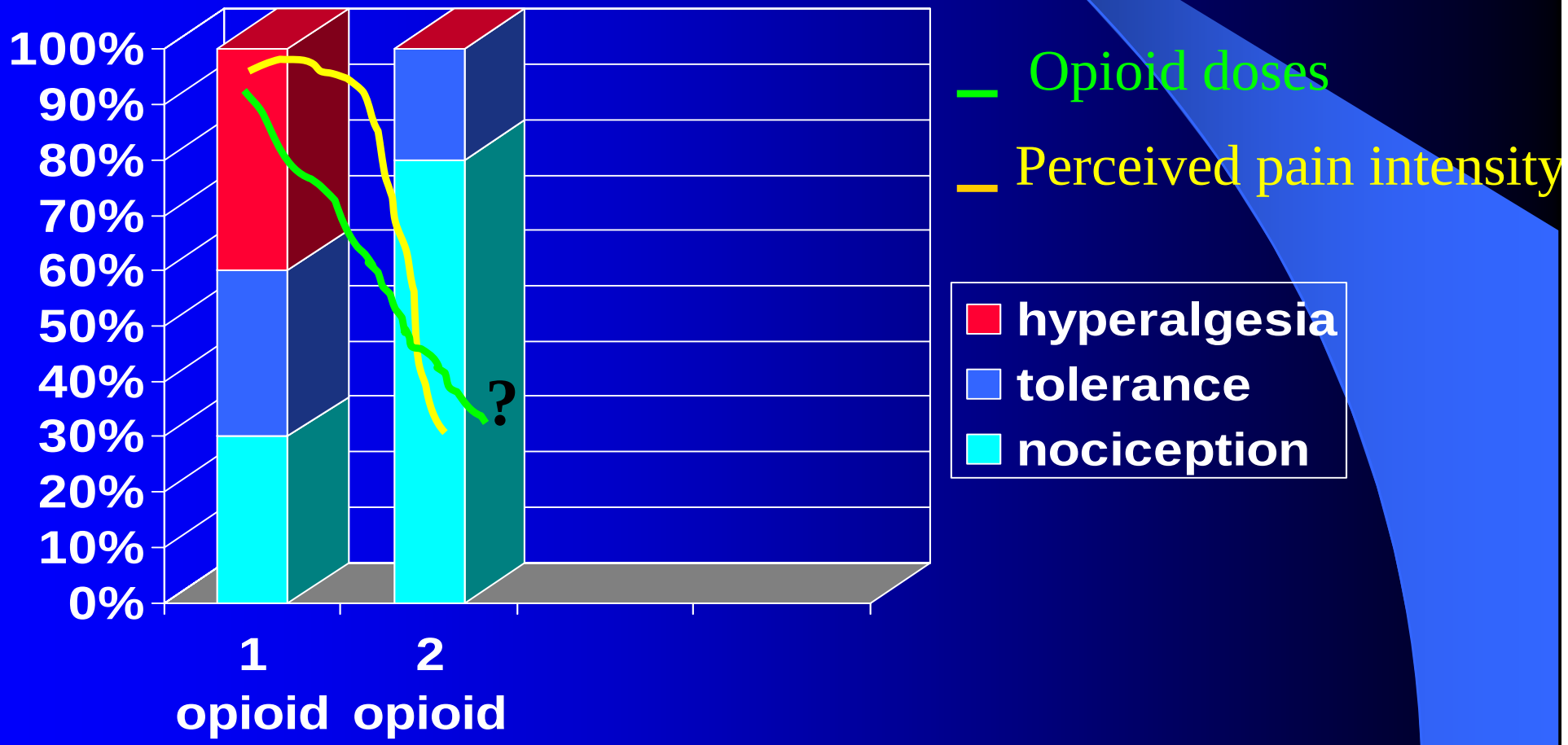
.. and has strongly reduced the need of alternative procedures

Globally, opioid switching may reasonably allow a clinical improvement at least in more than 50% of patients presenting a poor response to one opioid.

Unfortunately the setting of uncontrolled pain in the presence of adverse effects is quite difficult to fit controlled study designs.

Pts switched for convenience (looking for equianalgesia) are different from patients switched for uncontrolled pain
…. who are different from patients with adverse effects and controlled pain
… who are different from patients with uncontrolled pain and adverse effects

Discontinuation of the offending drug and reduced doses of the second opioid may change the clinical picture dramatically.
How much is impossible to predict..



Opioid switching and hyperalgesia
Mercadante et al, Am J Hosp Care 2005

Conversion ratios suggested with methadone:

- inversely proportional to previous opioid doses
- as needed & variants
- fixed priming and then clinical flexibility

In pts receiving high doses of opioids the ratio is likely to depend on recent high escalation index rather than the dosage itself

Pain → increasing dose → increasing pain →

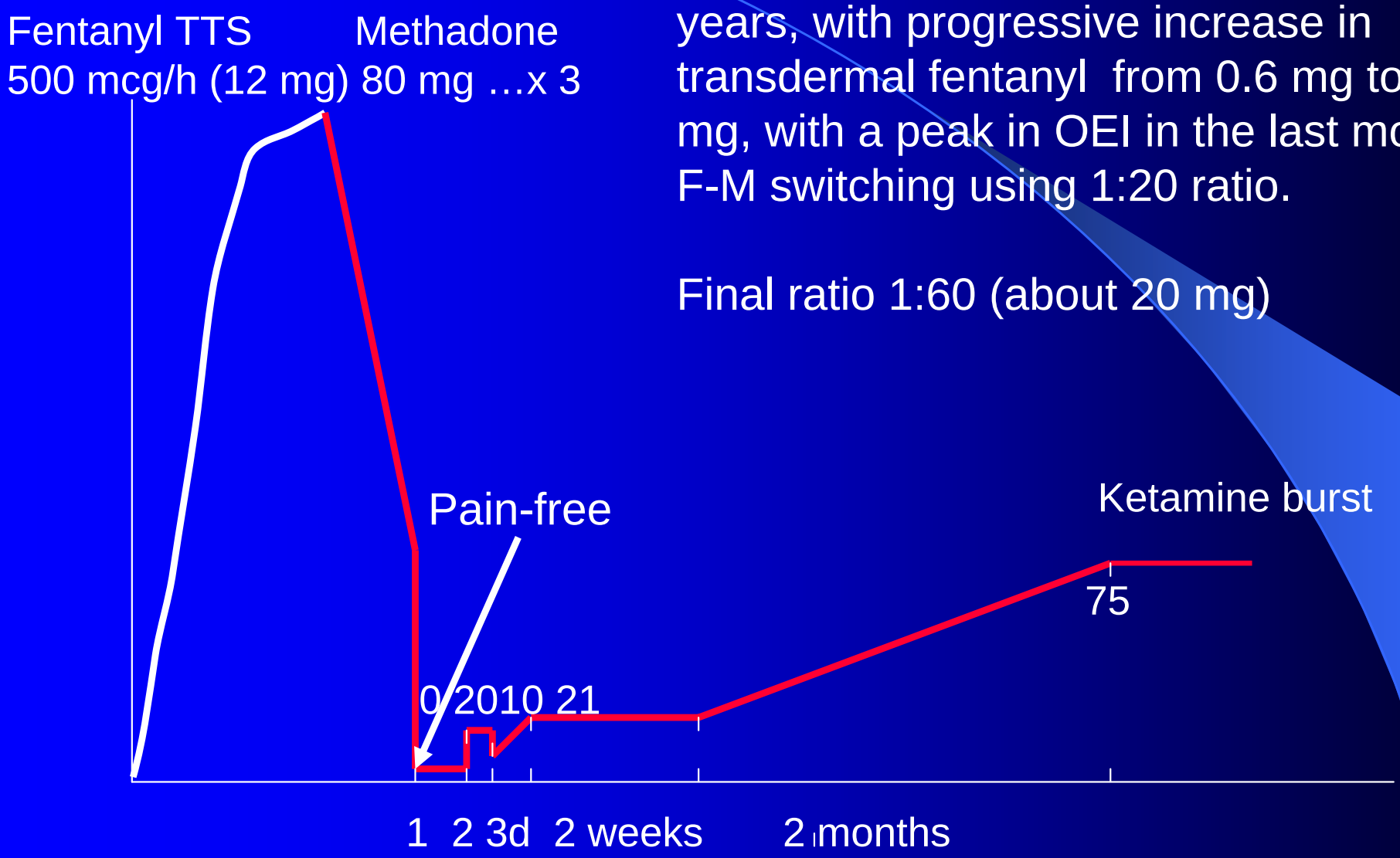
→Increasing dose → Increasing pain →

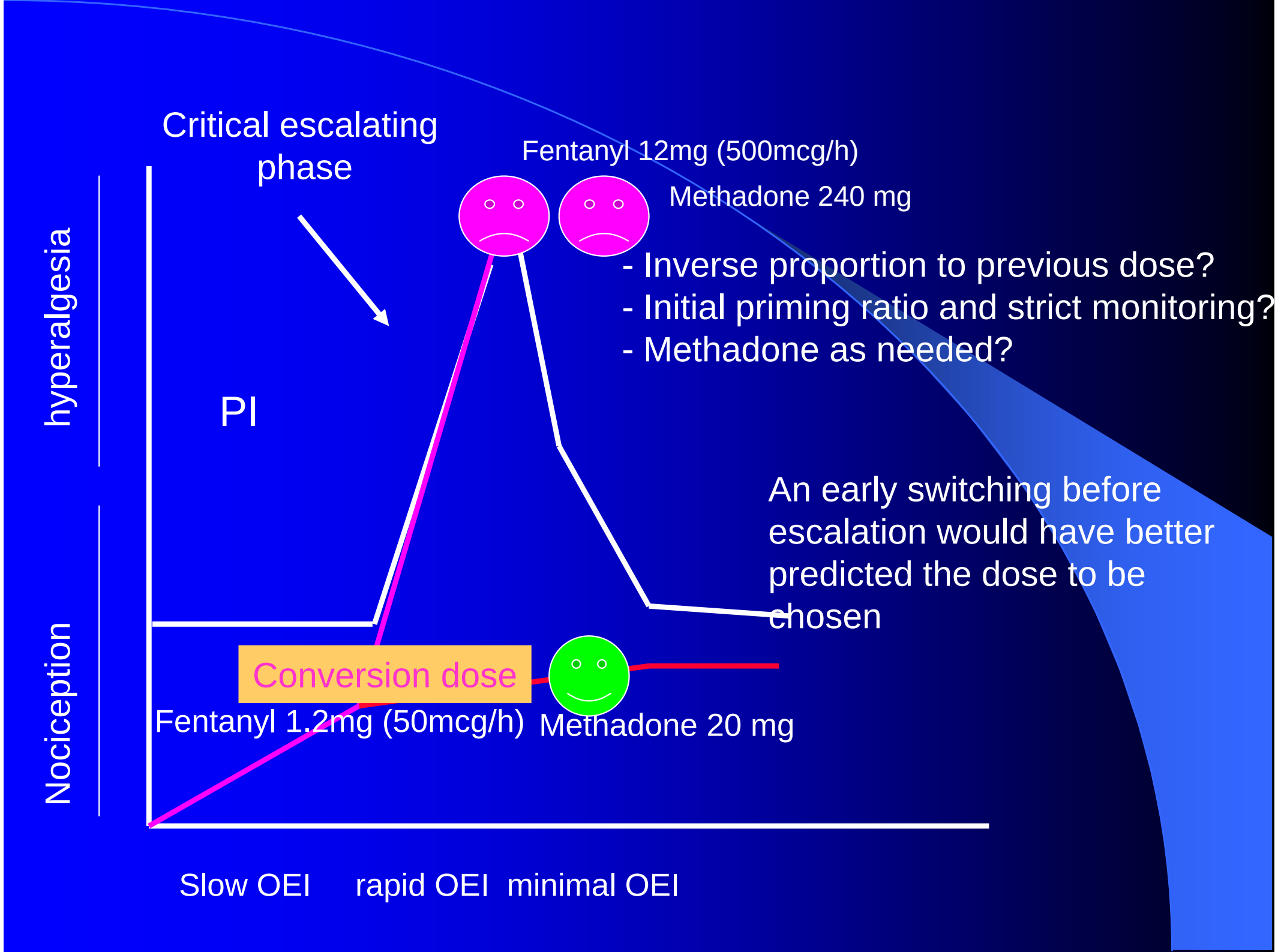
- → Increasing dose →
- → increasing pain & adverse effects (signs of hyperexcitation)

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 mg)

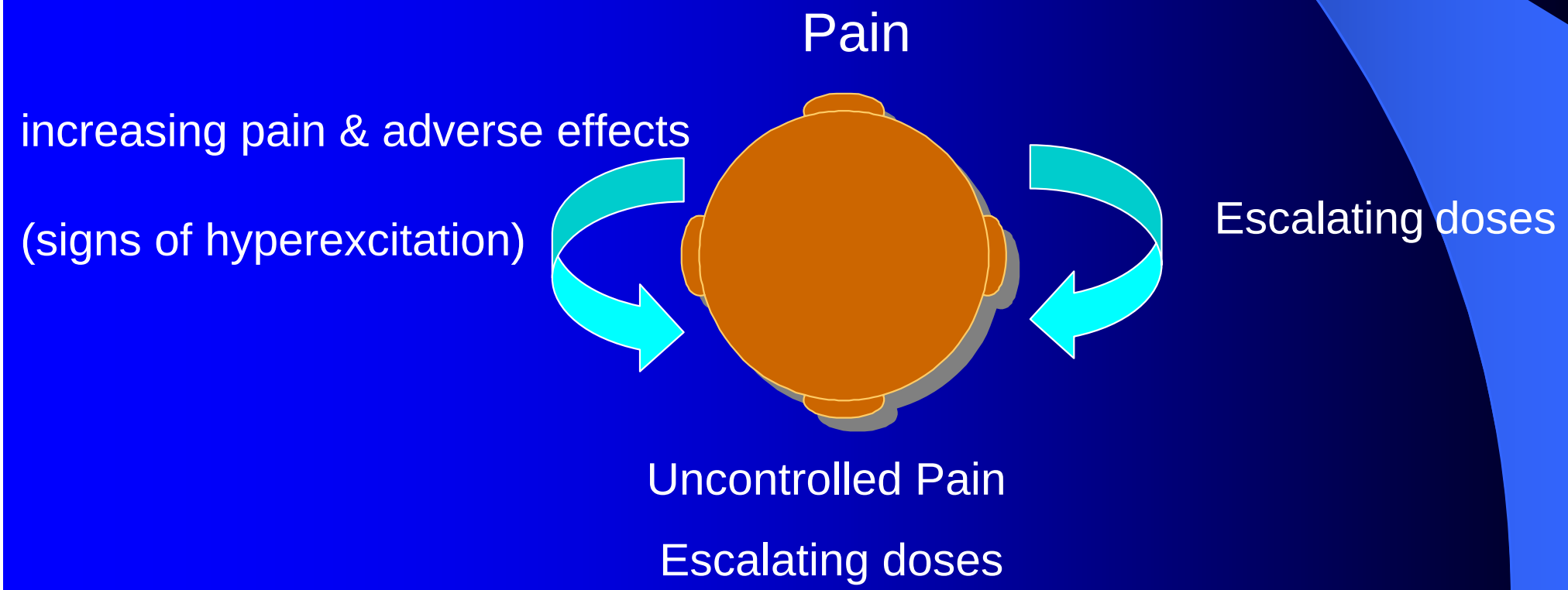



Critical escalating phase
Fentanyl 12mg (500mcg/h)
Methadone 240 mg
- Inverse proportion to previous dose?
- Initial priming ratio and strict monitoring?
- Methadone as needed?
hyperalgesia
PI
Nociception
An early switching before escalation would have better predicted the dose to be chosen
Conversion dose
Fentanyl 1.2mg (50mcg/h)
Methadone 20 mg
Slow OEI
rapid OEI
minimal OEI

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



- This can explain way conversion ratios could be different in patients with adverse effects and adequate pain control in comparison with patients with adverse effects and/or uncontrolled pain

INDICATIONS FOR OPIOID SWITCHING

1. Adverse effects – acceptable analgesia
2. Adverse effects – poor analgesia
3. Poor analgesia?
4. High level of tolerance?

Escalating doses may still produce analgesia …however,

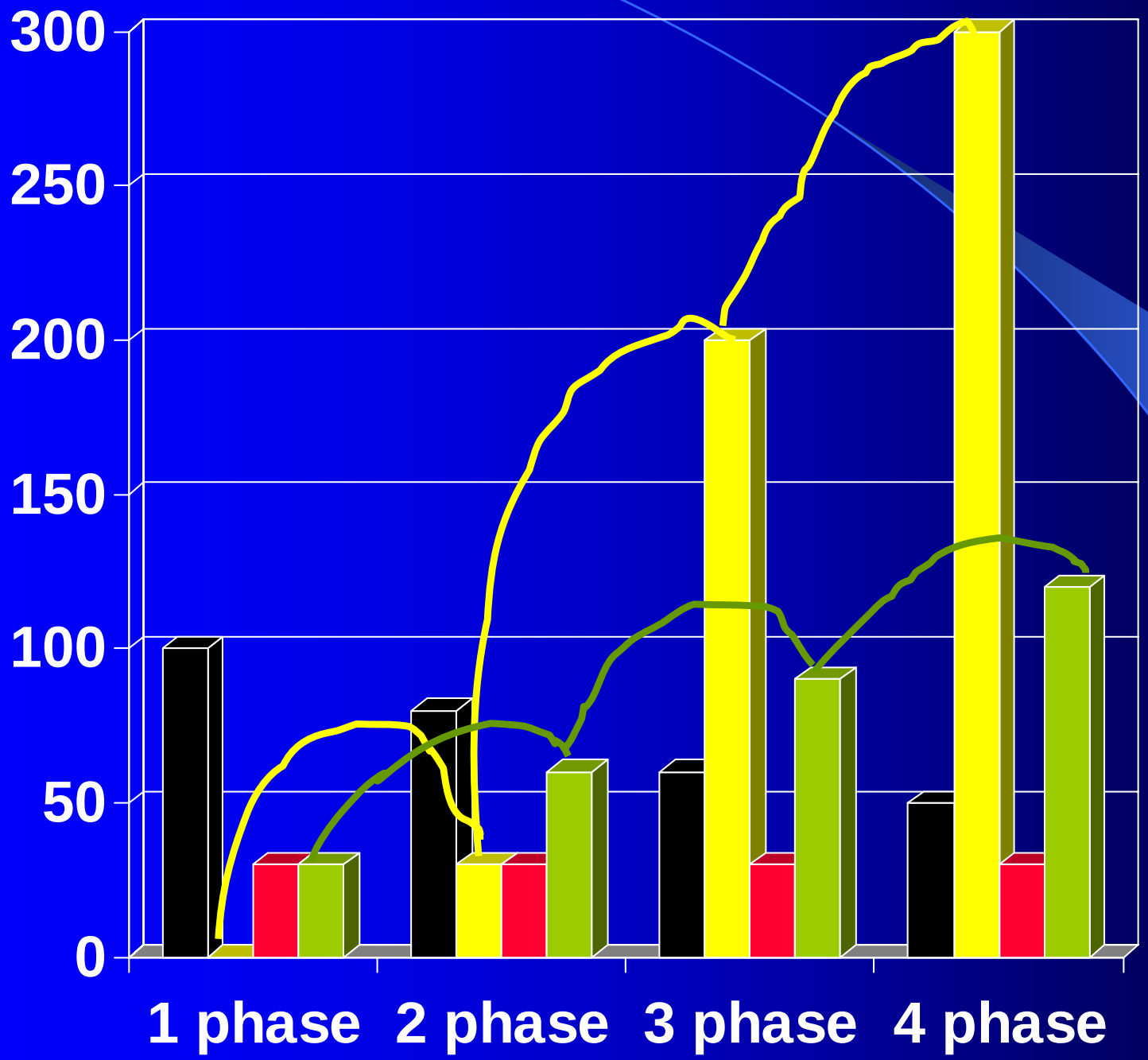
Risks for developing adverse effects (case 3)

Risks for developing hyperalgesia (case 4)

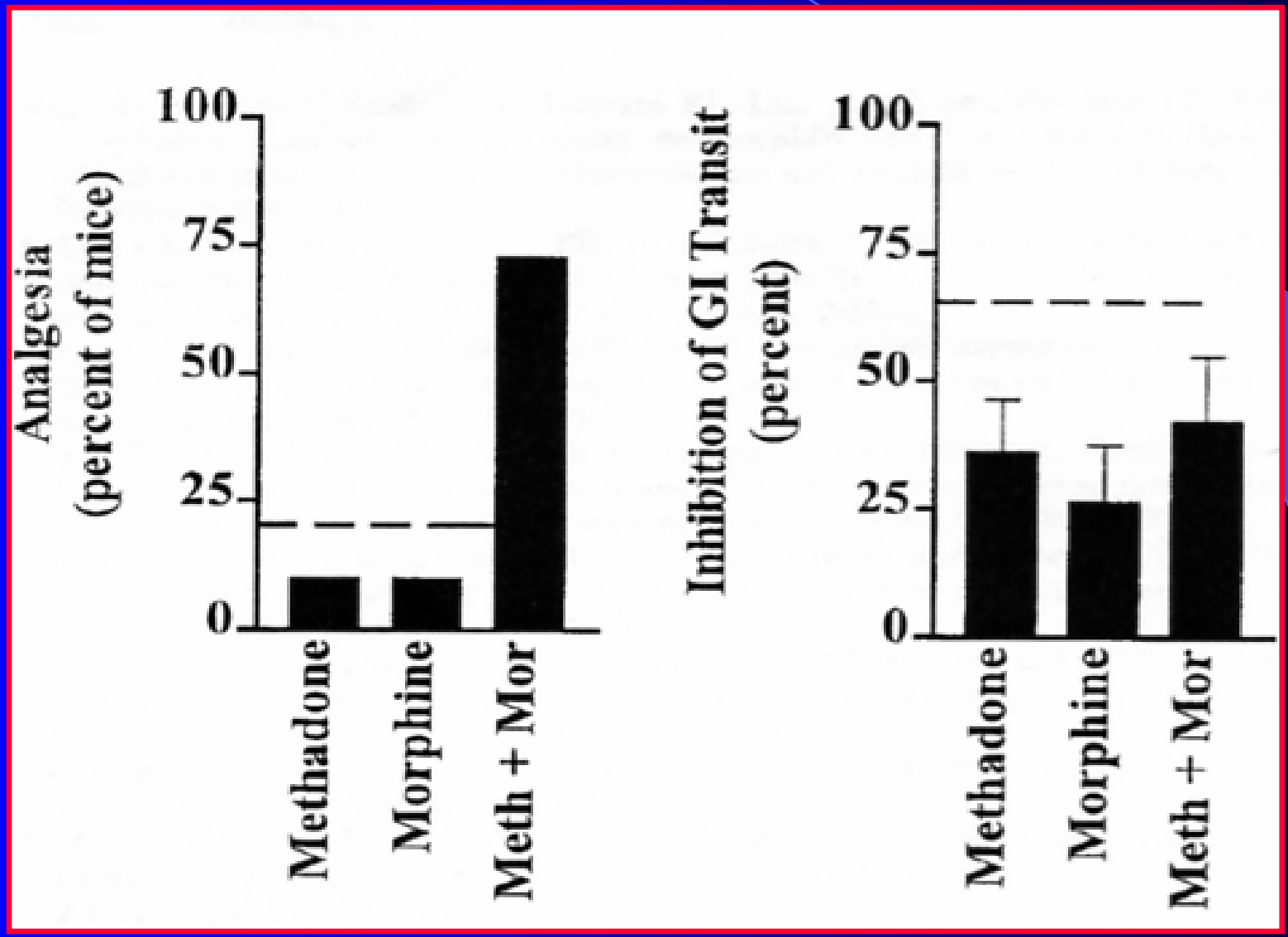
Time to prevent?

- Continuous care – no therapeutic holes
- Early switching
- Opioid semi-switching?
- Pulsatile ketamine?
- Anti-hyperalgesic opioids?

Undertreatment may have consequnces in the development of hyperalgesia

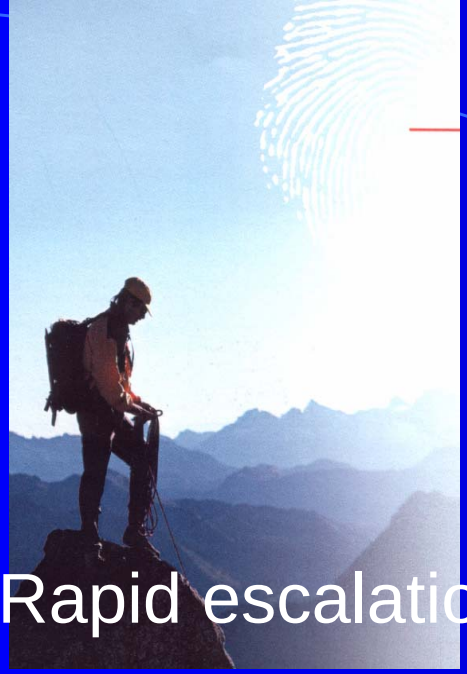


Sinergy between mu opioids: evidence for functional interactions among mu-receptor subtypes (Bolan et al, 2002)



OPIOID COMBINATION IN CANCER PAIN
Mercadante et al J Support Care Cancer, 2005

There are experimental data in favour of a possible opioid combination to reduce tolerance analgesia (He, 2002). Particularly, methadone may reduce also tolerance-hyperalgesia associate with previous morphine doses, probably improving the receptor performance to morphine



Rapid escalation…

….plain

uncontrolled pain with ripid escalation

Controlled pain

Morphine

720

360

7 days

1.99

methadone 30 mg

0.19

0.27

methadone 60 mg

0.18

0.09

Opioid semiswitching

- In the presence of increasing pain despite increasing doses of opioids...
- If no adverse effects are present...
- to avoid the risk of abnormal responses (particulalry with methadone) due to a complete switching, stop & go……

... it could be useful to avoid an abrupt discontinuation of the first opioid, but just to add minimal doses of the second one

Pioneer studies of opioid switching. Bruera et al, 1996-1998

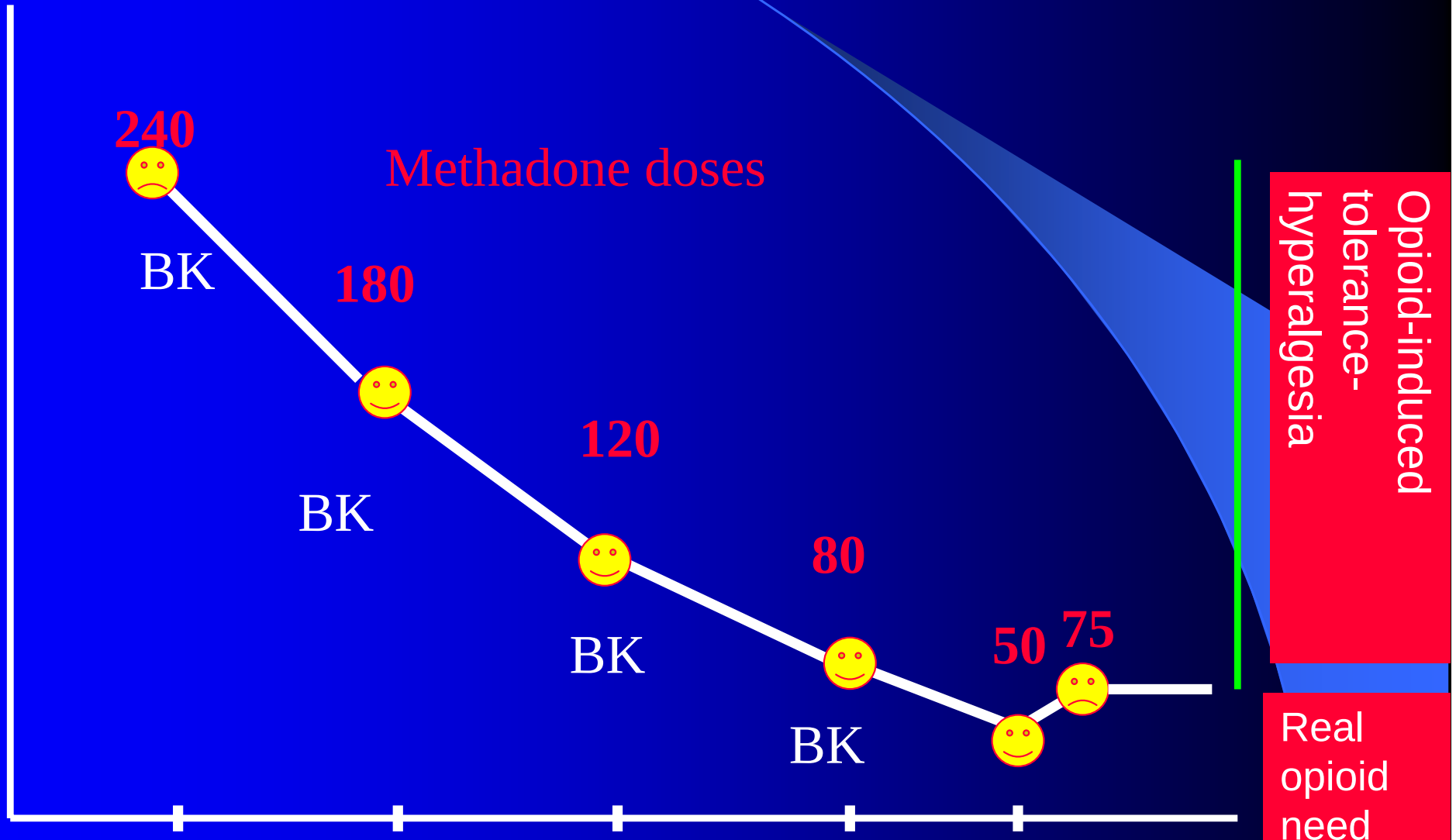
Opioid semiswitching have been already proposed… the right unawarenesss…

… Doses of the first opioid had progressively reduced and methadone had progressively increased….

A sort of primordial opioid semi-switching or opioid combination

BURST KETAMINE TO REVERSE OPIOID TOLERANCE IN CANCER PAIN

Mercadante et al, J Pain Symptom Manage, 2003



Different profiles of opioid-induced anti-hyperalgesia and analgesia. Koppert et al, Pain 2005

- More anti-hyperalgesic than analgesic effects have been found with buprenorphine

Different receptor activity?

K-antagonist effect (dynorphine)?

TOLERANCE AND HYPERALGESIA: TWO MASKS OF THE SAME FACE? AN EMERGING IATROGENIC SYNDROME - IT switching

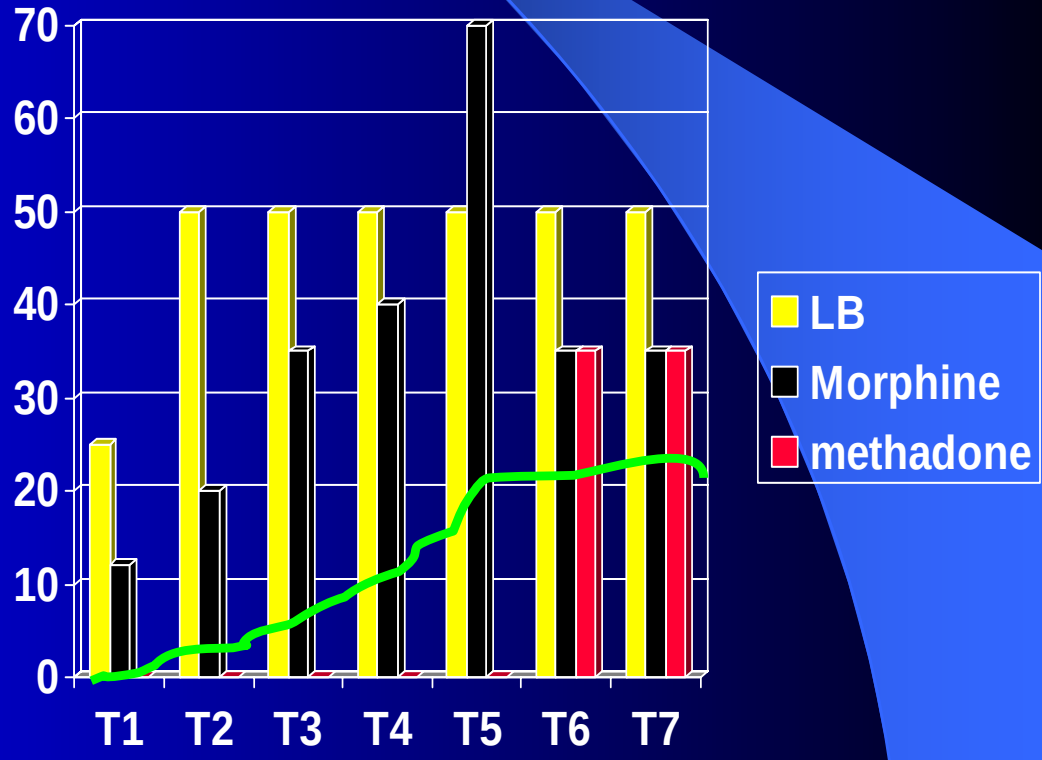
Mercadante et al, JPSM, 2003, Anesth Analg 2004

- IT local anesthetic-opioid combination:

  Blocking transmission pathways of hyperexcitatory state dramatically reduces states of hyperalgesia induced by opioids

- IT opioid switching of semi-switching

  Equivalent doses of IT methadone may improve the response to increasing doses of IT morphine



Conclusion

- Increasing pain with opioid escalation should be assessed carefully.
- Physicians are treating a iatrogenic pain, composed of multiple components.
- It should be considered as an adverse effect to be prevented and treated.
- More complex strategies are required
- Due to the paucity of data and difficulties in developing trials in this field to provide guidelines, and the need to individualize the treatment, only experience and knowledge may help in resolving such difficult clinical situations

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He et al, Cell 2002. Endocytosis serves a protective role in reducing the development of tolerance. Opioids have different tendency to produce endocytosis, regardless of their efficacy.

Morphine has poor ability to promote receptor desensitization and endocytosis.

It has been experimentally demonstrated that endocytosis-promoting agonists (DAMGO, methadone, fentanyl) may facilitate morphine-induced receptor endocytosis, reducing the compensatory adaptive cellular changes that lead to upregulation of the cAMP pathway. Thus a combination of smaller doses of opioids with different characteristics may “brake” the development of tolerance