OPIOID SWITCHING: WHAT IS THE SCIENTIFIC BASIS?

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Background

- Opioid switching is going to be a popular approach to improve the opioid response.
- According to available data, opioid switching will result in clinical improvement in 50-80% of pts presenting a poor response to one opioid (**Mercadante & Bruera, 2006**).
- The incomplete cross-tolerance among opioids, has contributed to the conclusion that the μ-opioid analgesics differ from one another.
- Several studies in the last decade have suggested that opioids may exert different receptor activities. The knowledge of these receptor aspects can be useful to explain the differences in analgesic or adverse effect responses.

Opioid switching. A systematic and critical review
Mercadante, Cancer 1999
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.

Outline

- Biochemical and molecular mechanisms that can explain the clinical changes, translating in a clinical benefit, occurring with opioid switching.
- Bridging the gap: translating basic research to bedside
- Outcomes

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….

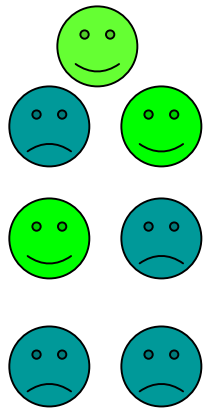
Adverse effects

Analgesia

.. and has strongly reduced the need of alternative procedures

Opioid switching

- Convenience
- Adverse effects
- Uncontrolled pain
- Uncontrolled pain and adverse effects




SCAMBIO MOTO
DA PISTA CON
DONNA DA STRADA

Authors	1° Opioid-dose	2° Opioid-dose	Design	n	Indication	Outcome	Final conversion ratio	Timing (days)
Bruera, 1995	HY sc 276	ME os-rec 444	Pros	37	P	100%	1 .2 (os) 3 (rec)	6.5
Bruera,1996	HY sc 237	ME os-rec 180	Retro	65	AE 12%		1.14	3-6
Ripamonit,1998	HY sc 236	ME os 180	Retro	37	AE P C	100%	1.47	-
Lawlor, 1998	MO os 1165	ME os 100	Retro	14	AE P		11.6	5
Ripamonti,1998	MO os 145	ME os 21	Pros	38	P AE C		7.7	3
Scholes,1999	MO os 240	ME os 24 PRN	Pros	33	P 79% AE	78%	6	3
Mercadante,1999	MO os 125	ME os 25	Pros	24	P AE	79%	5	1-3
Mercadante,2001	MO os 159	ME os 20	Pros	50	P 84% AE 80%	80%	5	3.6
Tse, 2002	MO os 120	ME os 20	Pros	27	AE 88% P		6	3
Santiago-Palma, 2001	FE iv 9	ME iv 36	Pros	19	AE P	88%	4	1-3
Benitez-Rosario 2004	FE TTS 3.6	ME os 72	Pros	17	AE (60%) P (40%)	80%	17	4-7
Mercadante,2003	MO os 317	ME 54	Pros	10	AE P	90%	6.4	1-3
Lawlor,1997	MO sc 55	HY sc 12.6	Retro	34	AE		4.3	3
Lawlor,1997	MO os 150	HY os 31.5	Retro	10	AE		4.7	2
Bruera,1996	MO os sc 145	HY os sc 23	Retro	36	AE 23		5..3	1-2
Bruera, 1996	HY os sc 33	MO os sc 120	Retro	12	AE 9		0.27 (3.6)	1-2
Lawlor,1997	HY sc 24	MO sc 84	Retro	35	AE		0.28 (3.5)	2
Lawlor,1997	HY os 37	MO os 117	Retro	12	AE		0.31 (3.1)	3
Gagnon, 1999	MO-HY sc 114	OX sc 87	Pros	63	AE		1.9	-
	MO sc 91	OX sc 75						
	HY sc 28	OX sc 138						
Donner, 1996	MO os 138	FE TTS 1.4	Pros	98	C		70:1	15
Watanabe,1998	MO-HY os 135	FE sc 2.7-5.2	Retro	17	AE	41%	85:1	2.8

Morphine-fentanyl switching

Common ratio in anesthesia (IV v IV) = 50-80:1

150:1 (Janssen) = underdosing

100:1 (Donner,1996):

25 mcg/h = 0.6 mg/die = 60 mg morfina

50 mcg/h = 1.2 mg/die = 120 mg morfina

75 mcg/h = 1.8 mg/die = 180 mg morfina

100 mcg/h = 2.4 mg /die = 240 mg morfina

- Switching is not adviced in unstable patients……
- Assisted switching: Last dose of the previous opioid and patch, fentanyl induction-infusion and decreasing doses of IV fentanyl, or PCA (TTS-IV ratio 0.9 - 1).

Switching from morphine to methadone

- Equianalgesic ratio depends on the previous dose (Bruera,1996 – Lawlor, 1998, Ripamonti,1998). 4:1 (<90 mg) - 8:1 (90-300 mg) - 12:1 (>300 mg). Progressive decrease of morphine doses and progressive increase of methadone dose to find the same level of analgesia (analgesic valley….)

- An ad libitum schedules for conversion of morphine to methadone has been proposed. An initial 10-12:1 morphine-methadone conversion ratio, up to a maximum of 30-40 mg, given at intervals of 3 hours or more as required, was chosen. When daily methadone requirement was stable, the daily methadone dose was divided twice a day (Morley, 1999). The morphine-methadone-conversion ratio was 6:1, and none trend in dose ratio in relation to the dose of morphine was detected, probably because of the relatively low morphine doses before switching. Using this approach some patients may require several days to achieve pain control (30% required five or more days) (Tse,2002).

- A rapid substitution of morphine with methadone using a fixed ratio 5:1 was used to circumvene these problems in 24 consecutive advanced cancer patients with unacceptable balance between analgesia and adverse effects, which is the most frequent condition requiring opioid switching (Mercadante, 1999).

PHARMAKOKINETICS?
A RULE, NOT AN OPTION

- As observed with the slow onset with fentanyl, methadone requires time to achieve effective plasma concentration, due to its large volume of distribution, and should potentially not be considered as the ideal drug in acute circumstances: poor pain control / adverse effects.

  Methadone requires a “priming” to give an effect, as
  very low plasma concentrations are active only when its large volume of distribution is refilled.

  The risk of methadone accumulation occurs after prolonged administration, rather than in an early phase, during dose finding…..

  … to accellerate this process an initial ratio of 1:5, abruptly stopping morphine to allow rapid metabolite purification, allow to achieve analgesia in 24-48 hrs on average (Mercadante et al, J Clin Oncol 1999, Mercadante et al, J Clin Oncol 2001).

Different approaches, slow or abrupt switch-over, or ad libitum schedules, when switching to methadone may take time, ranging from 3 to 11 days, which is unconvenient in circumstances of uncontrolled symptoms.

As observed with the slow onset with fentanyl, methadone requires time to achieve effective plasma concentration, due to its large volume of distribution, and should potentially not be considered as the ideal drug in acute circumstances.

Switching from morphine to methadone

- Equianalgesic ratio depends on the previous dose

(Bruera,1996 - Ripamonti,1998)

4:1 (<90 mg) - 8:1 (90-300 mg) - 12:1 (>300 mg)

Progressive decrease of morphine doses and progressive increase of methadone dose to find the same level of analgesia (analgesic valley….)

Equianalgesia does not exist in clinical setting. Using this approach the expected effect is reached in 3-4 days, administering about 50% more of methadone dose calculated even in patients who discontinued morphine and started methadone (Mercadante,2001)

Dose finding in opioid switching to methadone

Methadone requires a “priming” to give an effect, as very low plasma concentrations are active only when its large volume of distribution is refilled.
The risk of methadone accumulation occurs after prolonged administration, rather than in an early phase, during dose finding…..

… to accellerate this process a ratio of 1:5 has been proposed for opioid switching, abruptly stopping morphine to allow rapid metabolite purification, and achieve analgesia in 24-48 hrs on average (Mercadante et al, J Clin Oncol 2000, Mercadante et al, J Clin Oncol 2001).

Rapid switching, using a morphine-methadone ratio 5:1

Mercadante et al, JCO 1999

	T0	T1	T2	T3
Pain intensity	5.7	4.4	3.9	3.8
Drowsinss	1.9	1.3	1.2	1.1
Confusion	0.7	0.4	0.4	0.3
Nausea & vomiting	1.1	0.8	0.8	0.7
Dry mounth	1.4	1.4	1.5	1.5
Distress score	5.1	3.9	3.9	3.6
Methadone dose	25.6	27.8	25.7	25.7

	<90 mg	>90mg
Morphine dose	59	224
Methadone at T0	14	45
Methadone dose at T3	20	33

Morphine to methadone switching

Mercadante, J Clin Oncol 1999

Using a conversion ratio of 5:1 and extradoses as needed, discontinuation of morphine:

- rapid elimination of metabolites, possibly contributing to toxicity
- rapid achievement of clinical plasma concentration (high distribution volume requires a priming).

Methadone dose is then changed in order to achieve the best balance between analgesia and adverse effects (not necessarily to be reduced, particularly in pts with poor analgesia)

The rationale of this approach was confirmed analizing opioid plasma concentration during switch-over. Using a fixed morphine-methadone ratio of 5:1, “effective” methadone plasma concentration were achieved on the first day to peak on the second day and a significant clinical effect was evident on the first day in terms of pain control and improvement in adverse effect, although plasma concentration do not exactly reflect pharmacodynamics.

Doses were changed according to the clinical situation, requiring an increase initially, and then a decrease in methadone dose in the following days to produce a final morphine-methadone ratio of 6.46 in comparison with the initial 5:1. Of interest, the mean previous dose of morphine was 317 mg/day, which is relatively high (Mercadante,2002).

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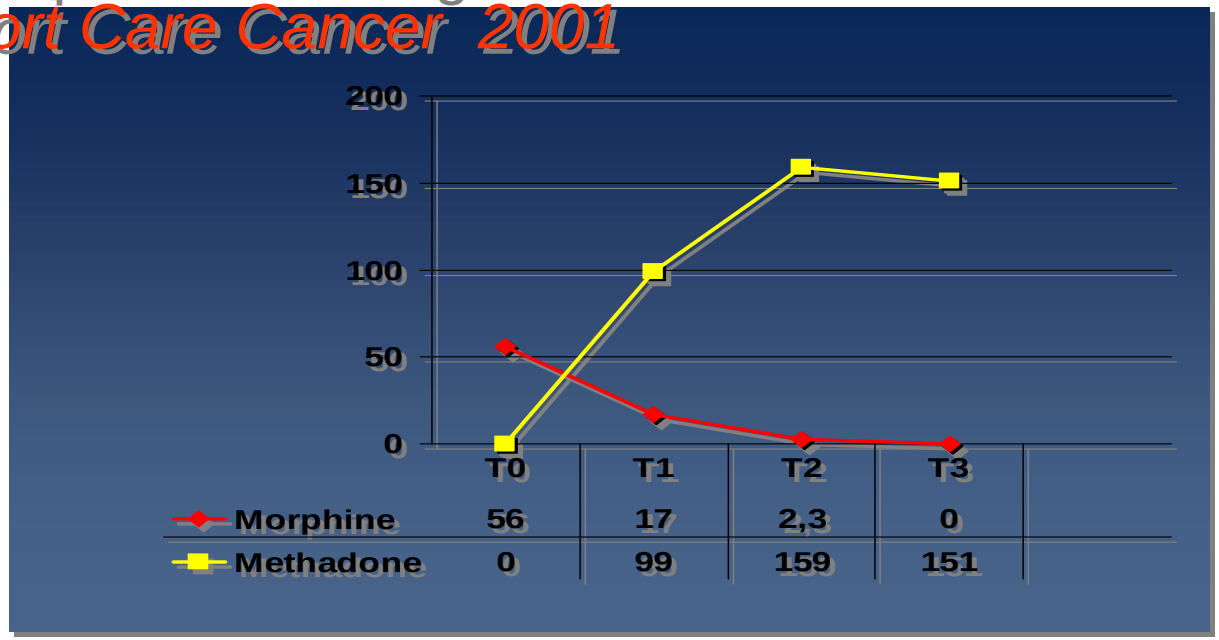
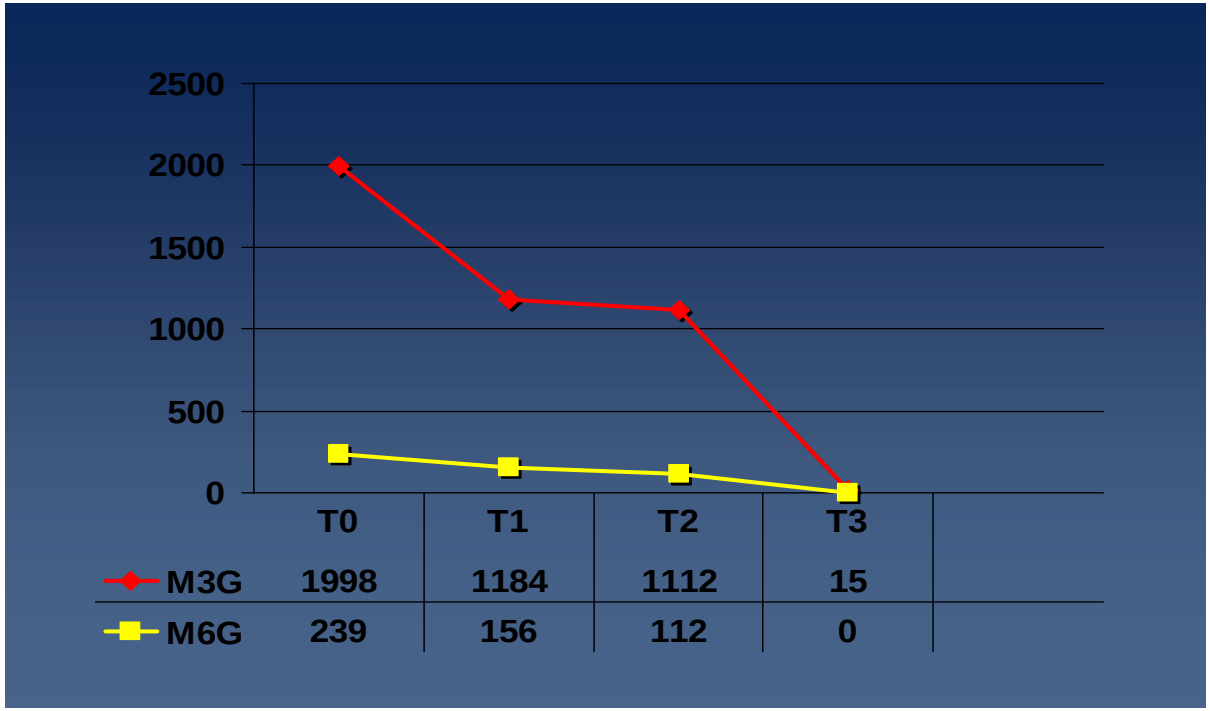
Plasma changes during opioid switching.

Mercadante et al, Support Care Cancer 2001





Santiago-Palma et al, Cancer 2004

Fentanyl-methadone initial ratio 1:20

- Postponing the administration of methadone from 8 to 24 hours after removing the patch, according to the dose of fentanyl.

However, there are no pharmacokinetic data supporting this approach, as elimination curves of fentanyl after removing the patch are similar, independently of the dose.

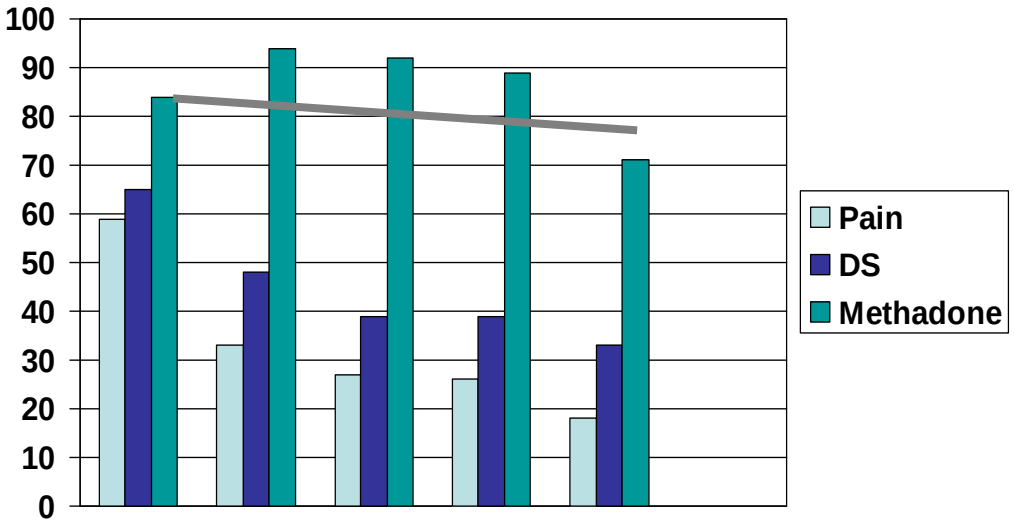
On the other hand, methadone has a high distribution volume and the first doses are unlikely to produce effective plasma concentration, due to its body disposition, so that the risk of overdose is unlikely even though fentanyl concentration slowly decays.

It is exactly what happens at induction with TTS fentanyl when the last administration of a long acting opioid, for example slow release morphine, is usually given at the same time of patch application.

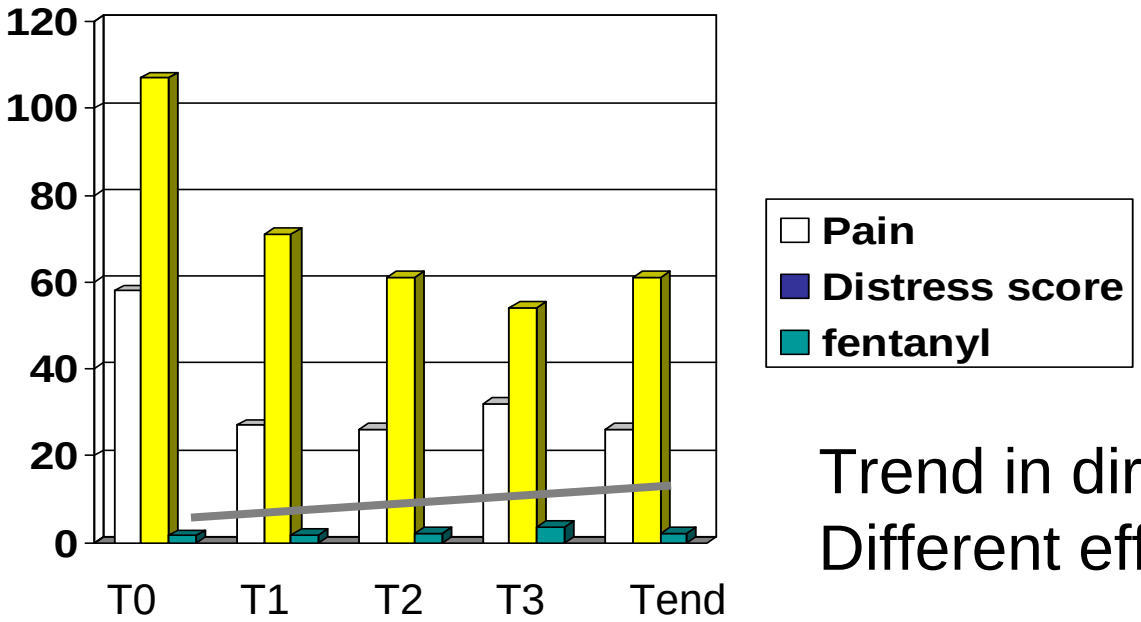
RAPID SWITCHING BETWEEN TTS FENTANYL AND METHADONE IN CANCER PATIENTS
Mercadante et al, J Clin Oncol, 2005

- A prospective study was carried out on 31 consecutive patients who switched from TTD fentanyl to oral methadone, or viceversa, because they had substantial adverse effects limiting further increase in opioid doses, or poor analgesia despite a rapid opioid escalation.
- A fixed conversion ratio of fentanyl-methadone of 1:20 was chosen as a starting dose, assisted by rescue doses of opioids. Subsequently, doses were changed according to the clinical need in an intensive palliative care setting.
- Successful stabilization: improvement >33% in pain intensity and distress score

Mean final ratio fentanyl-methadone1:15



From fentanyl 4.2
to methadone 84 mg (1:20)
Final ratio 1:17



From methadone 30.8
to fentanyl 1.54 (20:1)
Final ratio 13:1

Trend in directional differences….
Different efficacies?

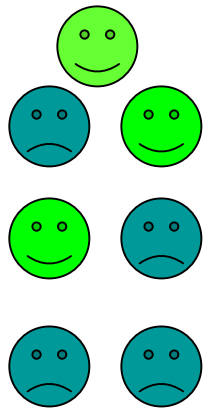
Caution in switching to methadone is particularly necessary for patients who receive opioids for prolonged periods and have reached very high dose of opioids, possibly having a high level of tolerance, and therefore more prone to unexpected effects with methadone, which possesses distinguished properties among opioids.

It should be recognized that doses of hydromorphone or morphine, and level of tolerance, are quite different according to the setting and countries and data from different studies should be carefully interpreted in any particular context.

Studies of patients switched from fentanyl, did not confirm an influence between the previous fentanyl dose and conversion ratio, despite the high doses of fentanyl previously used. It could be due to the lipophilic and selective receptor affinities of these two drugs (?).

Opioid switching

- Convenience
- Adverse effects
- Uncontrolled pain
- Uncontrolled pain and adverse effects



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

Tolerance and hyperalgesia

- It is becoming evident that chronic opioid treatment leads not only to the loss of the analgesic effect, but also causes abnormal opioid-mediated pain. It has been suggested that opioid-induced pain and antinociceptive tolerance may share underlying mechanisms with the abnormal pain occurring after peripheral nerve injury (**Mao, 1995, 2002**).
- Sharing the activation of excitatory glutamate receptors (N-methyl-D-aspartate - NMDA) type in the central nervous system.

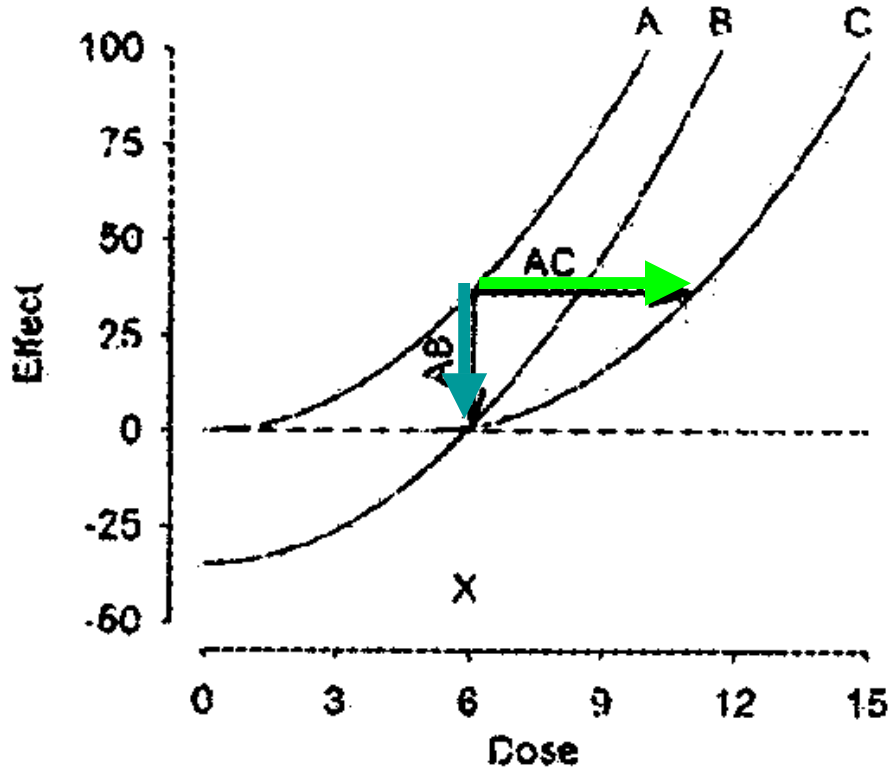
Tolerance and OIH share the same net effect on dose requirement. Either condition necessitates dose escalation for maintaing a certain drug effect

Tolerance: right shift of dose-response curve

desensitization process

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

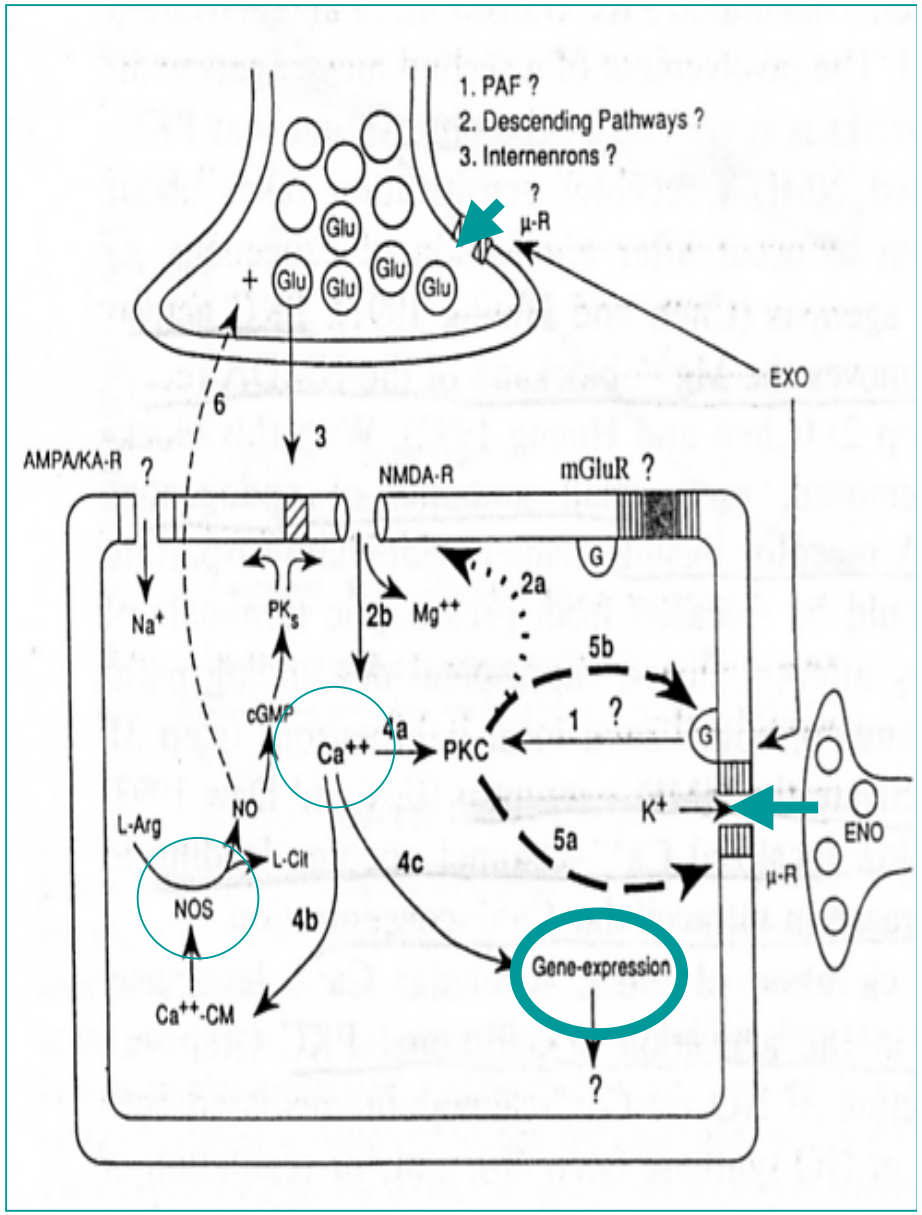
excitatory signalling



Central mechanisms subserving morphine tolerance

Pre-synaptic opioid action has been shown to inhibit neurotransmitter release (SP)
Post-synaptically activation of mu-receptor initiated activation of NMDA-R:

•Morphine may initate a second-messanger (G-protein-mediate PKC activation),
• Removing Mg+ blockade on NMDA-R,
• Opening Ca++ channels and increasing
• Intracellular Ca++ concentration
• Additional PKC activation
• Dissociation between G-protein and OR (desensitization of OR coupling).
• NO can diffuse resulting in a positive feedback
•NO counteract presynaptic inhibitory effects of opioids
•Up-regulation of cAMP (hyperactivity)



Interactions between mechanisms of hyperalgesia and morphine tolerance

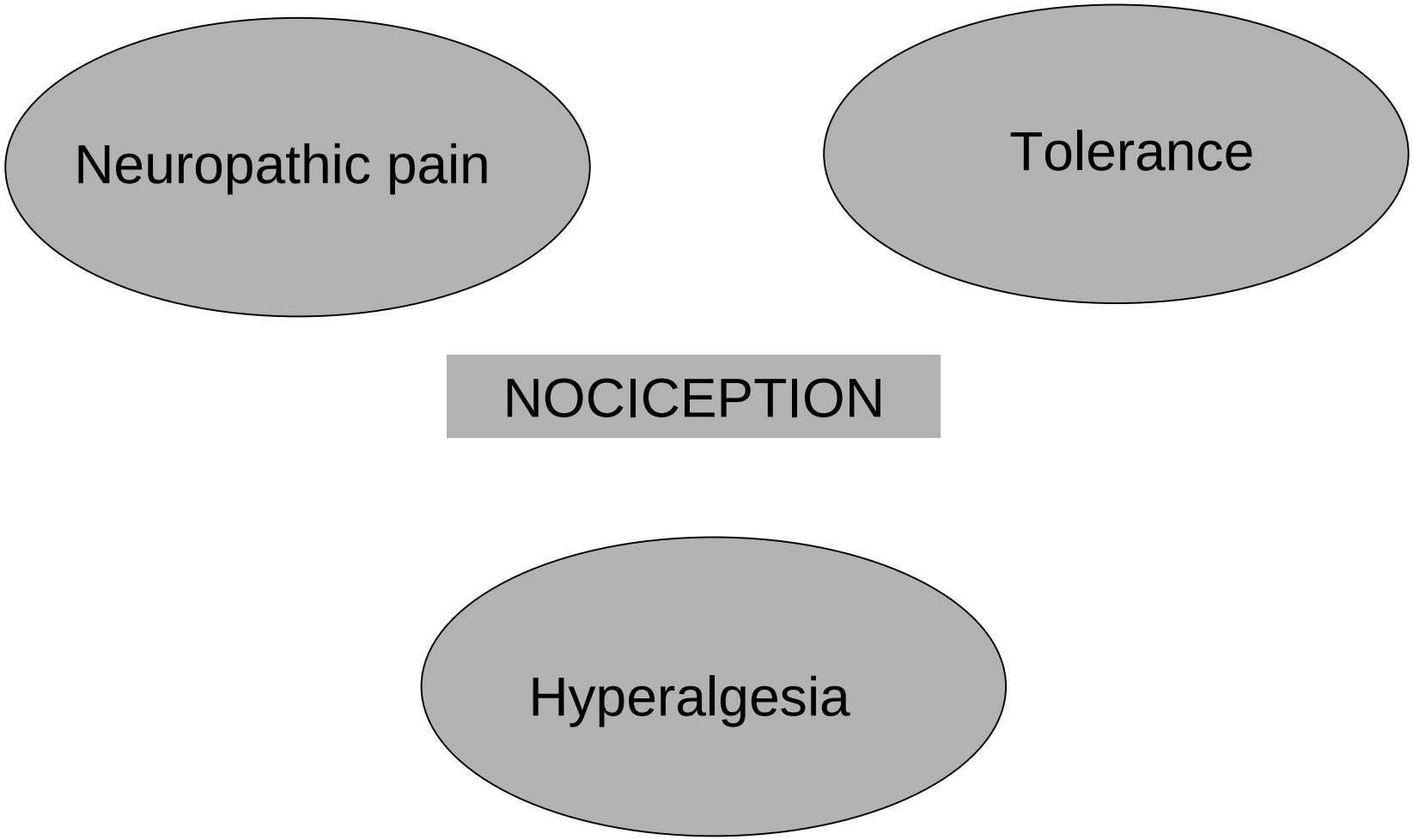
Morphine tolerance is associated with hyperalgesia under circumstances that are not related to nerve injury:

- Addicted-hyperalgesia on methadone maintainance
- Hyperalgesia naloxone-precipitated
- In animals, tolerance and hyperalgesia are prevented by MK-801 or GM1 ganglioside

Activation of NMDA R and PKC are critical in neuropathic pain, morphine tolerance and hyperalgesia

- The increased pain state is phenotypically comparable to the state of tolerance, and tolerance can develop even in the absence of opioid administration (neuropathic pain).
- In neuropathic pain there is constitutionally resistance to opioids

Interaction of factors: the pain connection



Descending system promotes and amplifies the signals: communication of supraspinal and spinal sites

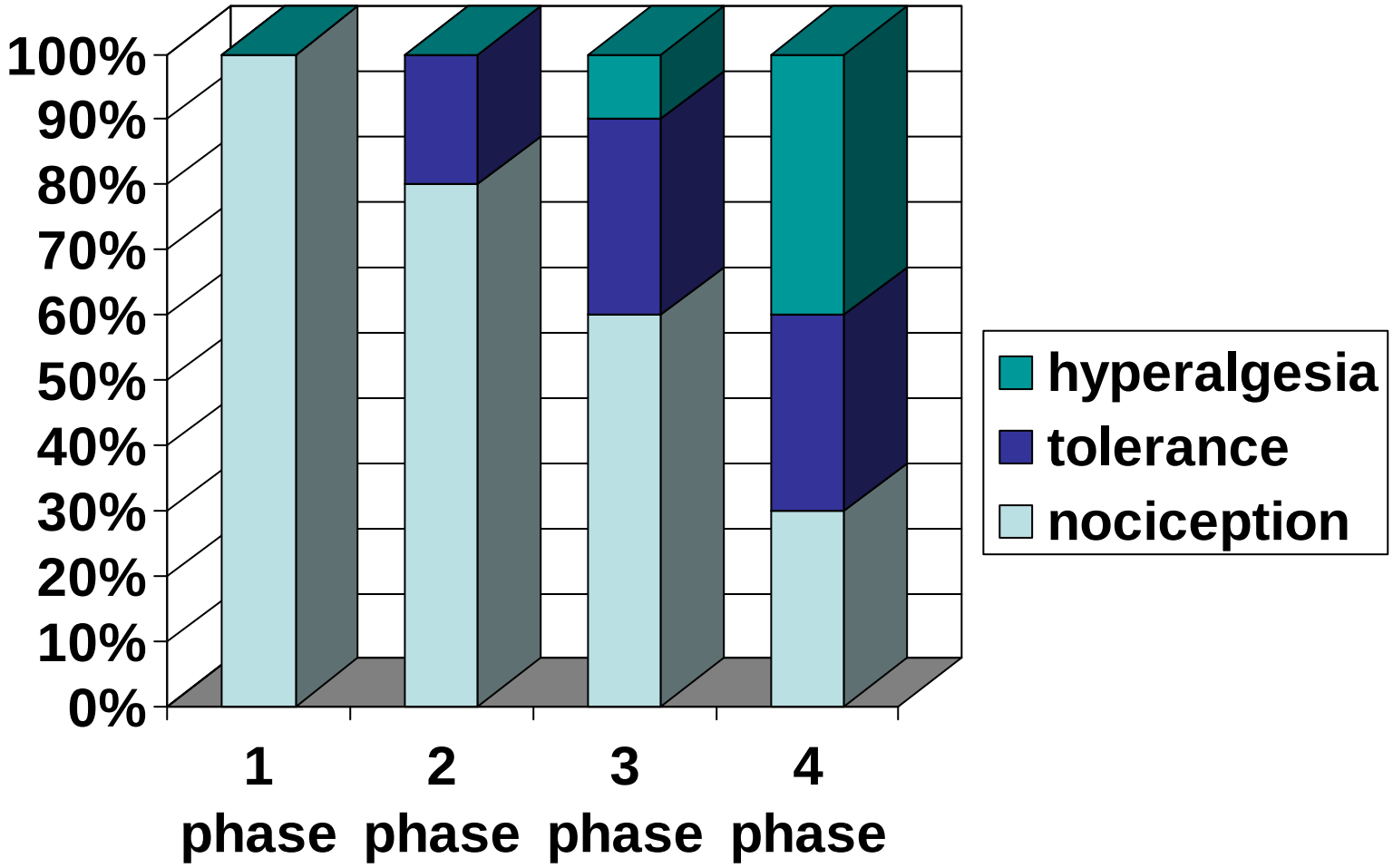
- Opioid-induced pain sensitivity also depend from a descending regulatory system arising from supraspinal sites, resulting in enhanced ability of CCK to excite facilitatory pathways (**Ueda, 2003**).
- Activation of descending facilitation produces a cascade of events in the spinal cord: up-regulation of spinal dynorphine levels and the release of excitatory transmitters from primary afferents.
- Spinal dynorphin is an expression of marker of apparent opioid tolerance that is likely reflected in part by increased pain sensitivity (**Vanderah, 2001**).
- As genetic variations in μ-receptor exist, propensity to develop opioid-induced tolerance and hyperalgesia could be determined genetically (**Ross, 2005**).

Vanderah, Pain 2001

Mechanisms of opioid-induced pain and antinociceptive tolerance: descending facilitation and spinal dynorphin

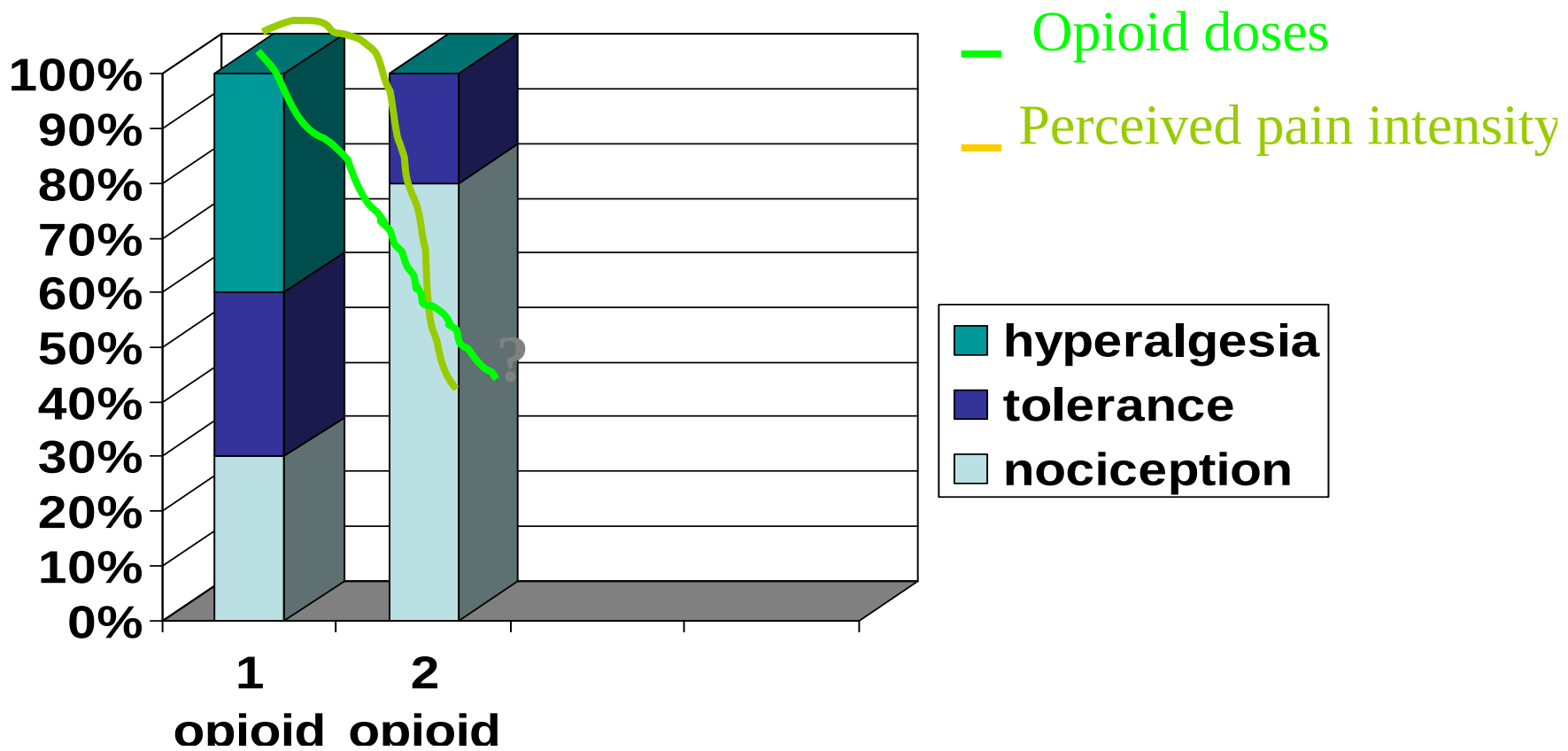
Overexpression of dynorphine, marker of a status of hyperexcitaion (NMDA hyperactivity), able to decrease the analgesic effects of morphine (apparent tolerance or hyperalgesia)

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



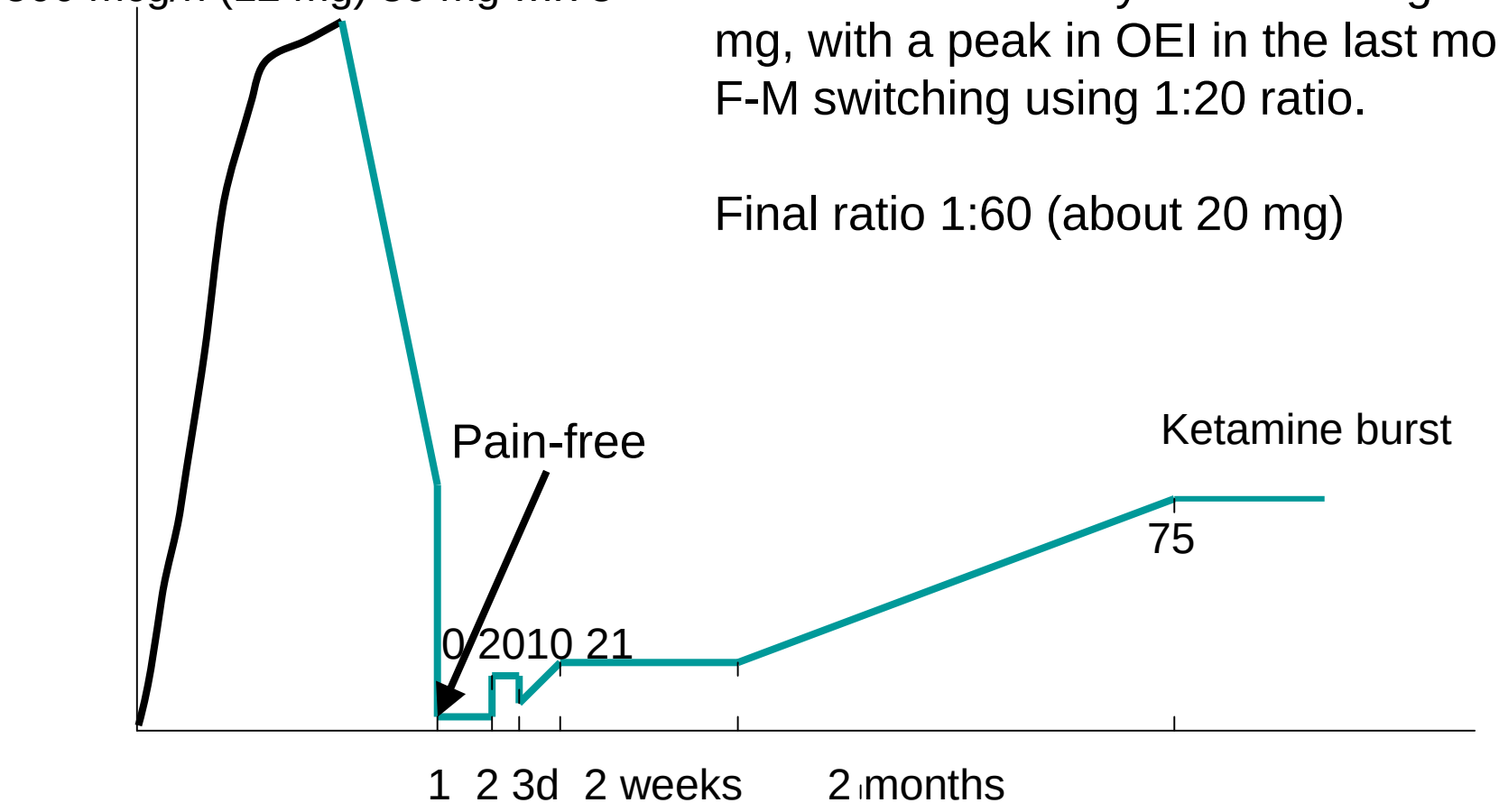
Hyperalgesic states and opioid switching

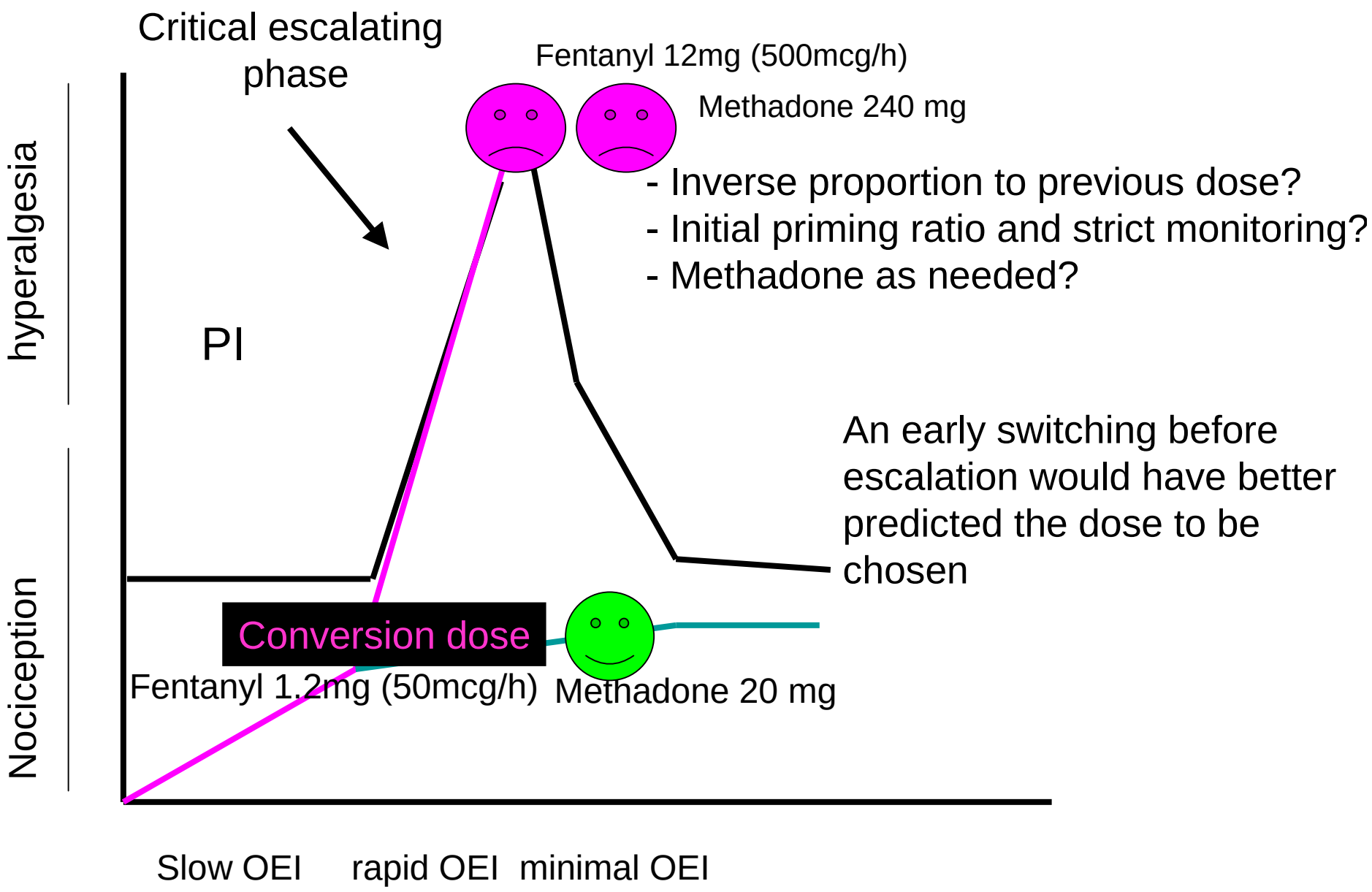
Discontinuation of the offending drug and reduced doses of the second opioid may change the clinical picture dramatically.
How much…. it is impossible to predict..



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)

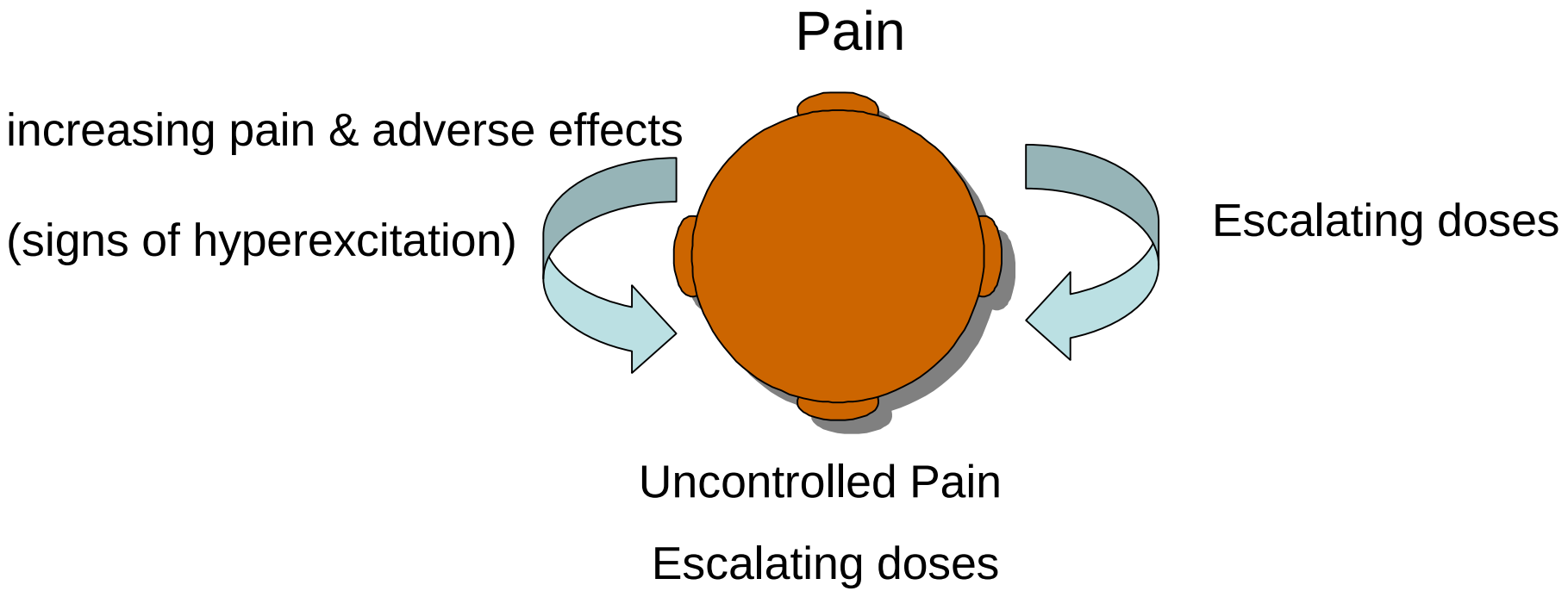



Critical escalating phase
Fentanyl 12mg (500mcg/h)
Methadone 240 mg
- Inverse proportion to previous dose?
- Initial priming ratio and strict monitoring?
- Methadone as needed?
hyperalgesia
PI
An early switching before escalation would have better predicted the dose to be chosen
Nociception
Conversion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

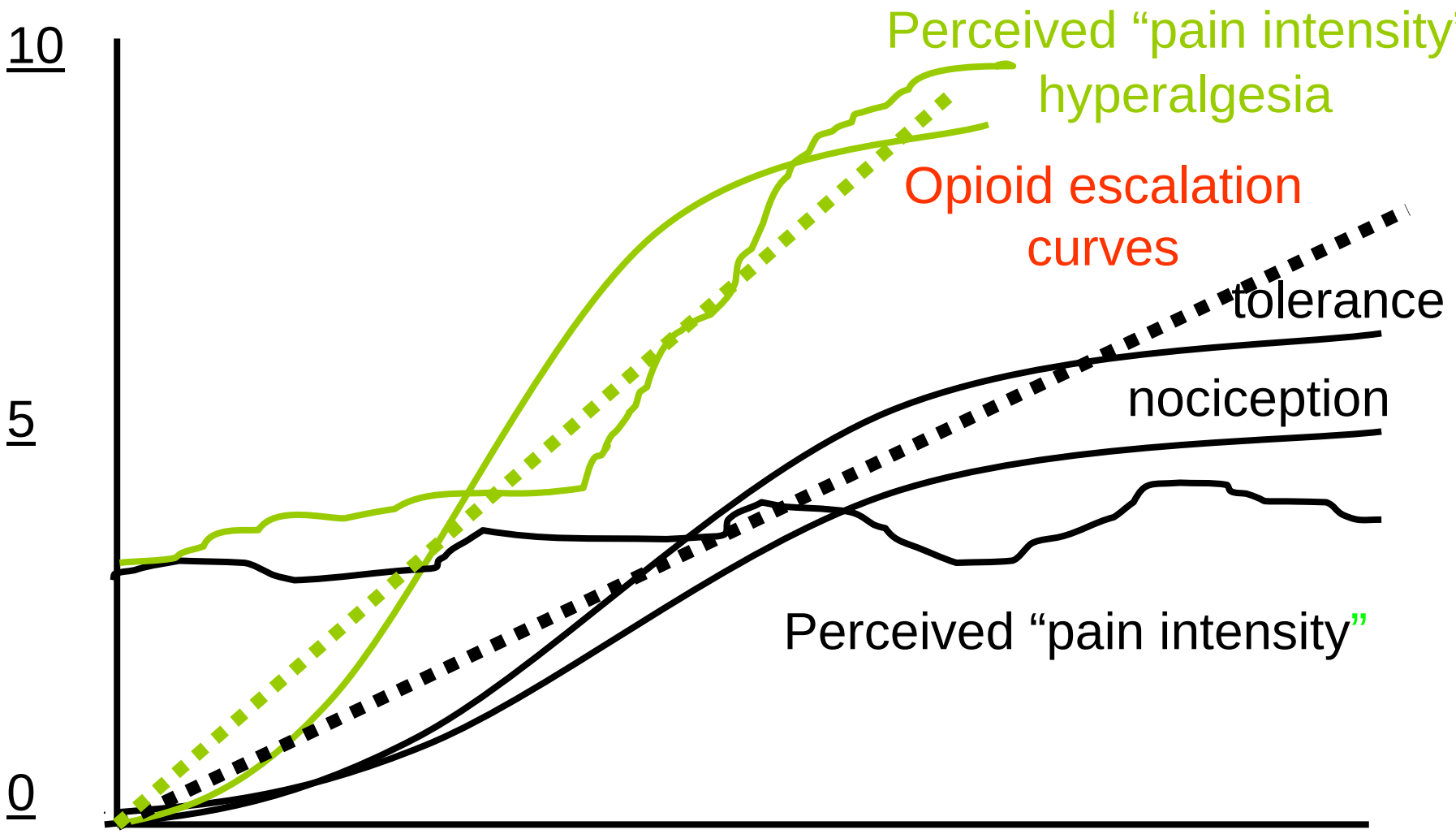
Dose ratio in opioid switching

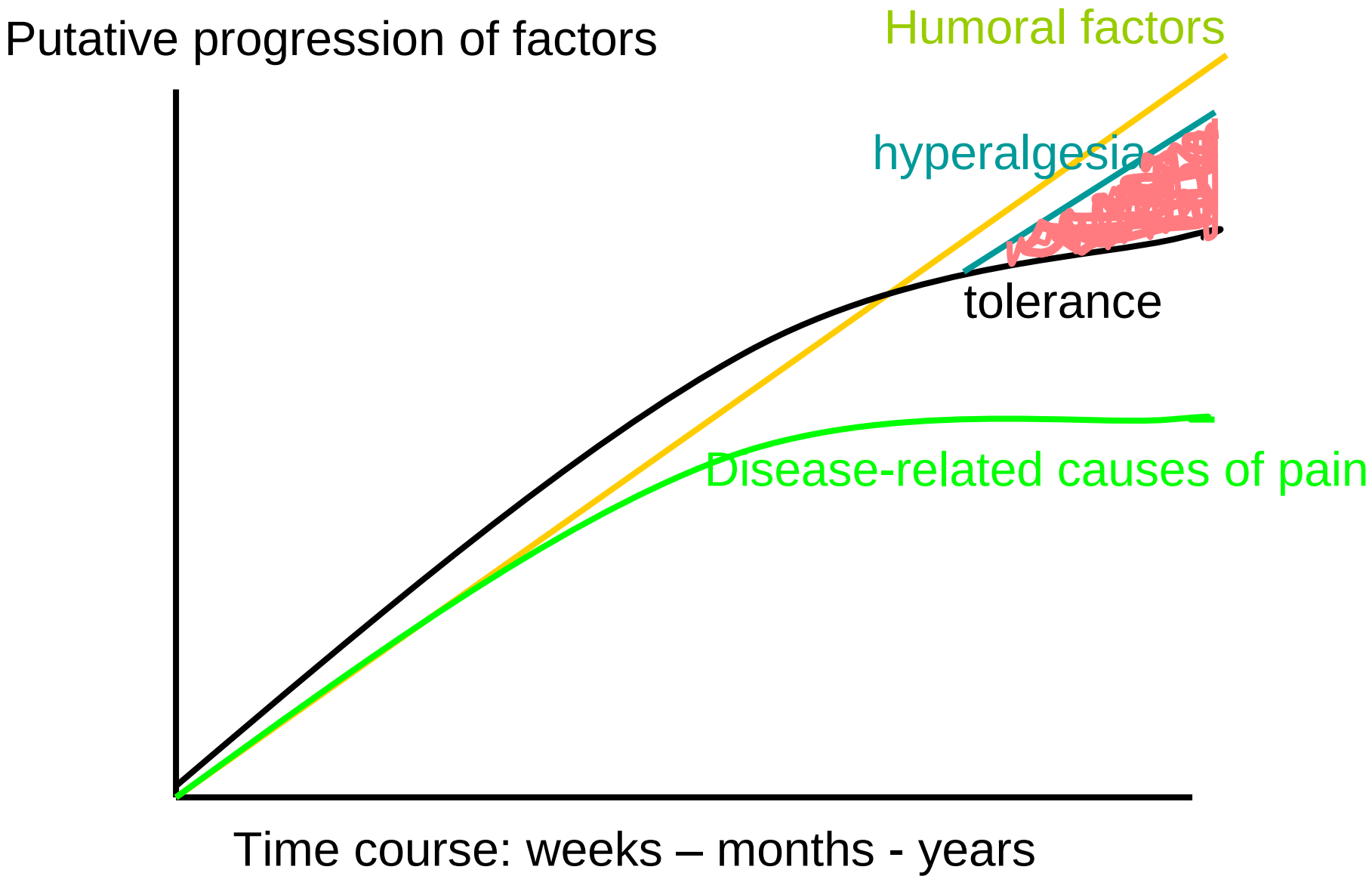
Choice of conversion ratios in opioid switching and hyperalgesia
The need for dynamic calculation

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



Example of clinical course




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

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

Conclusion

- Clinical observations on opioid combination are based on a consistent body of experimental data
- However, it remains to be seen whether:

  a) opioid synergy and/or specific drug combination can be demonstrated

  b) study designs are complex in the context of the individual response to opioid escalation

  c) complex treatment could be detrimental

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

Conversion ratios suggested with methadone:

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

No pain relief from morphine? Individual variation in sensitivity to morphine and the need to switch to an alternative opioid in cancer patients. Ross et al, SCC 2006

- In this prospective study 74% (138/186) had a good response to morphine (responders). One patient was lost
- 25% (47/186) did not respond to morphine. These non-responders were switched to alternative opioids (switchers).
- 37 achieved a successful outcome when switched to oxycodone and an additional 4 were well controlled when switched to more than one alternative opioid.
- Overall successful pain control with minimal side effects was achieved in 96% (179/186) of pts.
- No significant differences in the need to switch between the two hospital sites.

A retrospective study of the association between haematological and biochemical parameters and morphine intolerance in patients with cancer pain. Riley et al, Palliat Med 2004

- Data were analysed from 100 controls who tolerated morphine and 77 patients who were switched to an alternative opioid.
- Patients > 78 yrs (P = 0.03), or with a high white cell (P = 0.002) or high platelet count (P = 0.003), were more likely to switch. Although our numbers were small, patients with severe organ impairment were more likely to switch. However, a model including white cell count, platelet count, age, serum albumin and alkaline phosphatase, accurately separated switchers and controls in only 68% of cases.
- There was no significant difference between the two groups in terms of the numbers of patients having cytotoxic drugs in the two weeks prior to the haematological and biochemical analysis.
- Similarly, there were no significant differences in histological diagnoses between groups.
- The white cell count was the strongest single effect observed and, as such, warrants further investigation. Further studies are needed in order to accurately define a model that will predict those patients likely to be intolerant of morphine.

PHARMACOGENETICS

- Enzyme polymorphism
- OR variants
- OR distribution and unmasking (peripheral)
- OR subgroups
- OR cross-talk
- Plastic changes after nerve injury
- Plastic changes after opioid administration

Genetic predictors

- UGT2B7
- OPRM1
- COMPT
- MDR1,ABCB1
- Inteleukin-1B, IL-1 receptor antagonist
- Melanocortin-1-receptor
- Haplotypes…

Switchers form morphine to oxycodone: Genetic variation and reponse to morphine in cancer patients. Ross et al, Cancer 2008

- COMPT and MDR-1 genotypes were correlated with morphine-related central side effects.
- Genotype data did not correlate with morphine dose or serum concentration of morphine and metabolites.

Other factors influencing the opioid response

- Pain type
- Psychological influences
- Disease and humoral factors
- Receptor disposition
- Plastic changes of CNS
- Drug interactions

Mercadante & Portenoy, JPSM 2001

FREQUENCY, INDICATIONS, OUTCOMES, AND PREDICTIVE FACTORS OF OPIOID SWITCHING IN AN ACUTE PALLIATIVE CARE UNIT

Mercadante et al, J Pain Symptom Manage 2008, in press

- Oral morphine 100 = intravenous morphine 33 = TTS Fentanyl 1 = Intravenous fentanyl 1 = oral methadone 20 = intravenous methadone 16 = oral oxycodone 70 = transdermal buprenorphine 1.3.

- The treatment was assisted by opioids used as needed, and doses were changed according to the clinical response in an intensive acute setting

- 118 pts underwent opioid substitutions.
- 96 substitutions were successful after the first switching,
- 7 further substitutions were successful in pts who failed after the first
- 103 substitutions effective.
- The mean time to achieve a daily dose stabilization was 3.2 days.
- 22 substitutions failed at first instance. A second switch was successful in 7 pts and failed in another 4.
- The indications for opioid switching were uncontrolled pain and adverse effects (50.8%), adverse effects (28.8%), uncontrolled pain (15.2%), convenience (4.2%).
- The majority of pts were switched from fentanyl (53) or morphine (44) and the majority of pts were switched to methadone (60). No differences among the different opioid sequences in determining a successful switching were observed ($p=0.243$; Pearson's chi-square test).
- Globally, switching to transdermal drugs, including fentanyl and buprenorphine, required a shorter time for achieving dose stabilization in comparison with the other sequences ($p=0.0015$).
- Changes in doses were more frequently observed in pts switched to methadone, while were less frequently reported in pts switched to transdermal drugs ($p=0.005$). Switching to buprenorphine was more frequently performed for adverse effects ($p<0.0005$), mainly gastrointestinal.
- No relationship between the starting opioid dose and dose at stabilization after switching ($p=0.810$), or time to achieve stabilization ($p=0.064$) has been found. Hospital discharge was proportional to the time needed to achieve dose stabilization ($p<0.0005$).
- The presence of both poor pain control and adverse effects was related to unsuccessful switching ($p<0.004$). No relationship between the opioid dose, opioid sequence, pain mechanism, adjuvants, and unsuccessful switching was found.
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Unsuccessful switching

- 22 pts opioid switching failed.
- A second-line substitution was performed in 11 pts. 4 pts did not benefit from a second-line switching
- 3 were subsequently treated IT.
- The presence of both poor pain control and adverse effects was more often found as the reason for substitution in pts who were unsuccessfully switched (p=0.004).
- Other factors, including gender and age, opioid dose, type of opioid, pain type did not influence the switching outcome**.**
- Renal failure was present in 16% of pts, but this finding was not significantly related to the failed switching, as creatinin values did not influence negatively the outcome (p>0.05).
- Finally, no differences in the previous use of adjuvants were found in the different opioid sequences and no relation with the use of a particular adjuvant and failed switching was observed
- Globally, 8 pts subsequently underwent an IT treatment, which was effective in most cases.
- One of these patients was not able to tolerate even minimal doses of IT opioids (0.5 mg of IT morphine), and received just a local anesthetic infusion for his pain. Of the 22 pts who were considered as a failure, 8 pts (36%) were particularly advanced and had a short survival, requiring in some cases terminal sedation.

- Although an initial conversion ratio was the option of choice, opioid conversion should not be a mere mathematical calculation, but just a part of a more comprehensive patients' assessment of the actual opioid therapy, evaluating the underlying clinical situation, pain and adverse effect intensity, comorbidity, concomitant drugs, and excluding any possible pharmacokinetic factor limiting the effectiveness of a certain drug

MORE ALTERNATIVES….

….MORE SATISFACTION….

About the opioid response?

The answer, my friend…….
…..is blowing in the wind

As it is….

Just like a woman….

Unpredictable…..

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