NOVIDADES NO TRATAMENTO COM OPIOIDES

Novelties in therapeutic with opioids

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Novelties in therapeutic with opioids

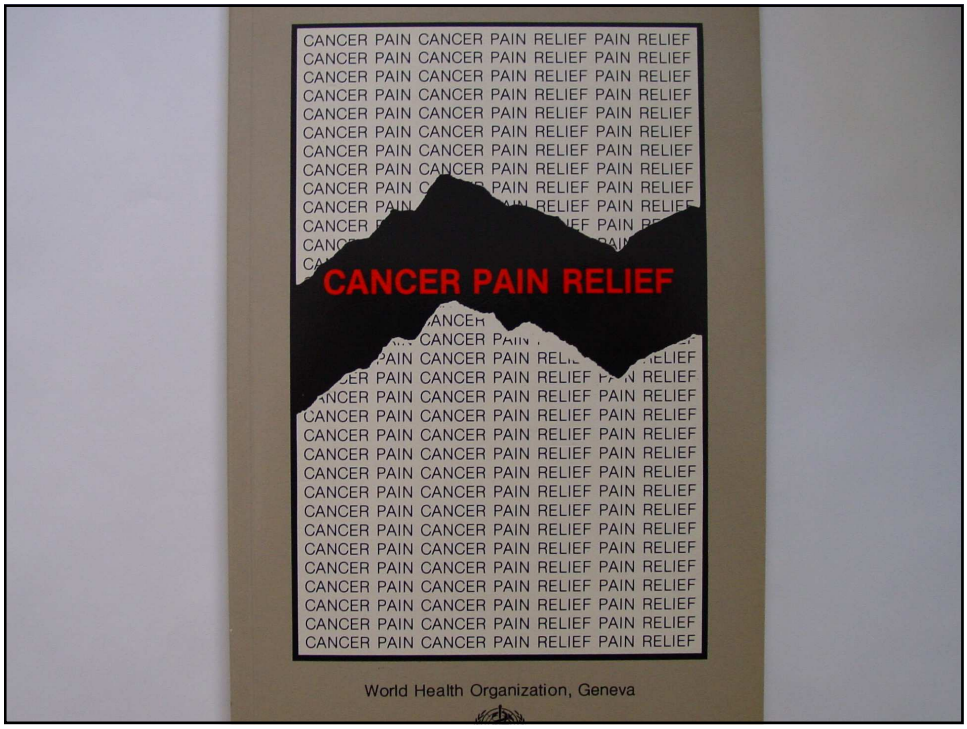
"Total Pain"

St. Christopher Hospice 1967

WHO Expert Meeting 1982

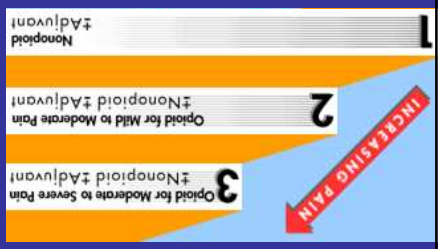
Figure 4: Some of the 1982 WHO group at the Villa D' Este on Lake Como, Italy.
L to R: John Bonica, Mark Swerdlow, Robert Twycross, Kathleen Foley, Vittorio Ventafridda, and Jan Stjernswärd.

J.J Bonica,
K.M. Foley,
A.Rane,
M. Swerdlow,
R. Twycross,
V. Ventafridda,
J. Birkham,
P.B. Desai,
M. Martelete,
F. Takeda,
R. Tiffany



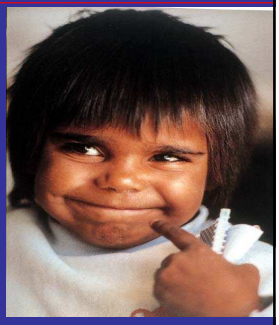
WHO`s Pain Ladder

- Assessment and Examination
- Diagnosis of pain (nociceptive/neuropathic)
- “by the mouth” (keep it simple)
- “by the clock”
- “by the step”
- Choice of drug
- Route of administration
- Dose titration
- Prophylaxis and treatment of side effects



Novelties in therapeutic with opioids

“Pain relief in cancer is largely a solved problem….”



Eric Wilkes, 1985

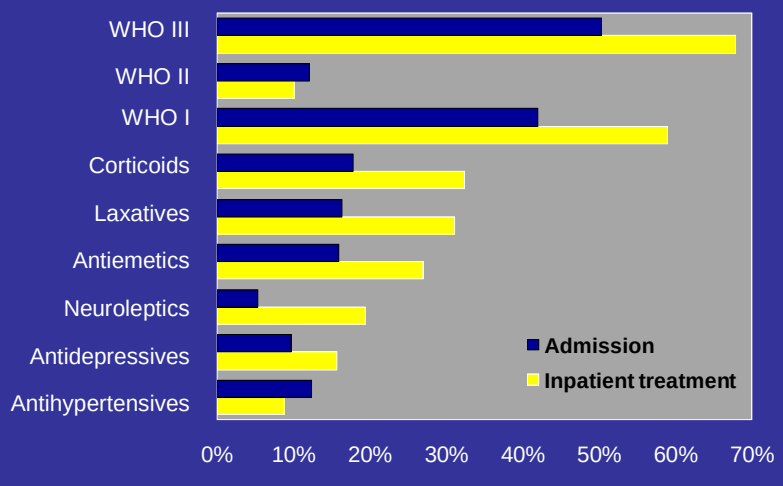
Critical Symptoms in Palliative Care*

Symptom	Frequency
Pain	82%
Anxiety	28%
Dyspnoea, breathlessness	20%
Depression	20%
Vomiting	12%
Disorientation, confusion	11%
Constipation	9%

*n = 1,304

Radbruch L, Nauck F et al. Support Care Cancer. 2003;11:442-451.

Core Documentation Germany HOPE
Drugs used most frequently*



*(n=1304)

Nauck F, Ostgathe C et al. Pall Med 18 (2004) 100-7

EAPC Survey: Morphine Use by Country*

Country	Oral NR No (%) pts	Oral SR No (%) pts	Parenteral No (%) pts
Austria	3 (5)	6 (10)	20 (34)
Belgium	8 (7)	8 (7)	14 (13)
Finland	7 (5)	21 (15)	4 (3)
France	36 (23)	34 (21)	39 (24)
Germany	25 (25)	26 (26)	20 (20)
UK	172 (22)	132 (17)	4 (0.5)
Italy	4 (2)	45 (17)	33 (12)
Spain	21 (11)	32 (16)	25 (13)
Sweden	18 (11)	33 (20)	25 (15)
Total	**520 (17)**	**561 (19)**	**302 (10)**

*Selected countries
NR = Normal release; SR = Sustained release

Klepstad P, et al. *Palliat Med.* 2005;19:477-484.

EAPC Survey: Conclusions

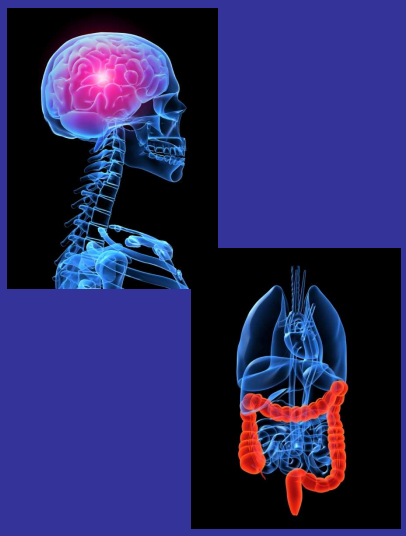
EAPC EUROPEAN ASSOCIATION FOR PALLIATIVE CARE

- One-third of the patients had clinically significant pain
- Large variation exist across countries in the use of both opioids and non-opioids
- The intensity of pain was distributed relatively evenly across participating countries
- For patients using morphine, only a minority needed high doses

Klepstad P, et al. *Palliat Med.* 2005;19:477-484.

Opioids and Opioid Receptors

- Opioids function by binding and activating their receptors
- These receptors are present in both the CNS and in the peripheral nervous system



Sternini C, et al. *Neurogastroenterol Motil.* 2004;16 (Suppl 2):3-16.

„side effects of opioids are usually minimal“

S. M. Tempest, Meyler´s side effects of drugs

Chronic Opioids and Their Effects

- The chronic use of opioids is justified if the balance between analgesia and side effects favors analgesia
- It is essential that side effects are acceptable to the patient and that they do not alter the patient's quality of life
- Sedation, nausea, and constipation can limit opioid use

Coluzzi F, et al. *Minerva Anestesiol.* 2005;71:425-433.

Strategies to treat side effects of opioids

- Dose reduction
- Adding an adjuvant analgesic
- Treating side effects
- Use non-pharmacological treatments
- Complementary and alternatively medicine
- Opioid rotation
- Antagonists

“Persistent pain is a major public health problem, accounting for untold suffering and lost productivity around the world…”

WHO. *The World Health Report (*2001)

Novelties in therapeutic with opioids
Too many choices?

How many opioids do we need?

- **MORPHINE**
- **OXYCODONE**
- **HYDROMORPHONE**
- FENTANYL
- OXYMORPHONE
- METHADONE

Which Opioids...?

- Although various types of opioid are in clinical use
  - Mixed μ-agonist/antagonists (*e.g.,* butorphanol)
  - Partial μ-agonists (*e.g.,* buprenorphine)
  - Weak μ-agonists (*e.g.,* codeine, hydrocodone, propoxyphene)
  - Potent μ-agonists (*e.g.,* morphine, methadone, oxycodone, hydromorphone, fentanyl, sufentanil)

  …only the latter are widely used in palliative care in situations where unmet clinical need calls for the investigation of new routes of delivery

Alternative Routes of Opioid Administration

- Many routes of administration for potent opioids have been in use for a long time, and are widely accepted as 'established'[1]
  - Oral
  - Intravenous
  - Subcutaneous
  - Intramuscular
  - Rectal
  - Intraspinal / epidural
  - Transdermal patch

Novelties in therapeutic with opioids?

1 Alexander-Williams JM & Rowbotham DJ. *Br J Anaesth* 1998; **81:** 3 – 7

Novel Routes of Opioid Administration

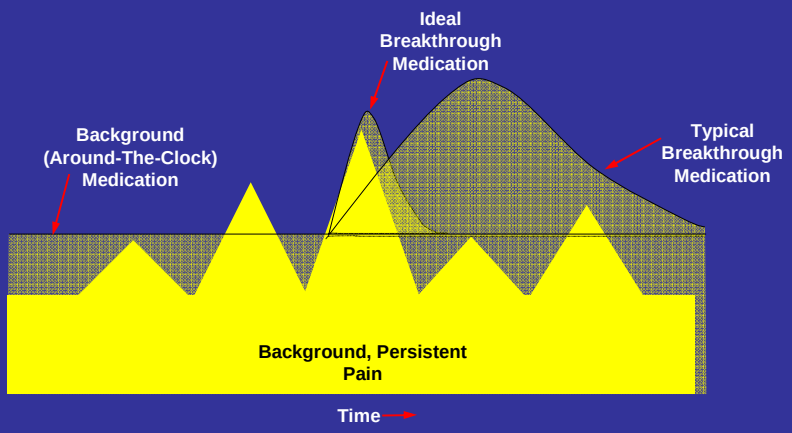
- Novel routes of administration that have been explored include
  - Oral Transmucosal
  - Sublingual
  - Intranasal
  - Inhaled
  - Iontophoretic Transdermal
  - Metered Dose Transdermal Spray
- But what are they trying to achieve…?

Modifying Formulations Offer Great Potential

- The idea of using delivery-modifying formulations to optimise intranasal opioids is not new
- For a rapidly absorbed drug such as fentanyl, modulating absorption may better match the time course of the ‘typical’ breakthrough pain episode
- Conversely, for a poorly absorbed drug like morphine, improving absorption may make it more useful for the control of more predictable, but more chronic pain

Breakthrough Cancer Pain

Transient exacerbation or recurrence of pain in someone who has mainly stable or adequately relieved background pain[1]



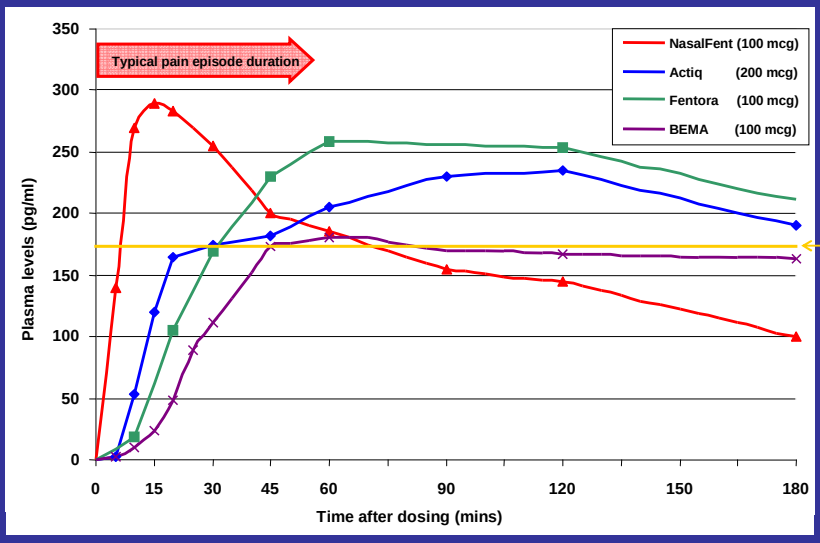
1 Portenoy RK & Hagen NA, 1990; *Pain* **41**: 273 – 281

Which Novel Route and Which Opioid...?

Alfentanil	Inhaled
Sufentanil	Inhaled
Fentanyl	Inhaled; Simple Intranasal; Sublingual; Novel Transdermals; Modified Intranasal; Oral Transmucosal
Morphine	Inhaled; Simple Intranasal; Modified Intranasal

Brief pain ⟷ **Sustained pain**

Nasal Fentanyl: Delivering a Promising Pharmacokinetic Profile



Note: Data not taken from a direct head-to-head comparison

BTcP Therapies: Delivery Systems

1998	2006/2008	2009	2008	2009	2009
Oral trans -mucosal fentanyl citrate OTFC	FENTORA®(US)/ EFFENTORA™(EU)	ONSOLIS™ (US) FBSF	Rapinyl™/ Abstral (EU) SLF	Instanyl™ (EU) INFS	NasalFent® (EU) FPNS

Oral Transmucosal Lozenge

Effervescent Buccal Tablet

Fentanyl Buccal Soluble Film

Sublingual Fentanyl

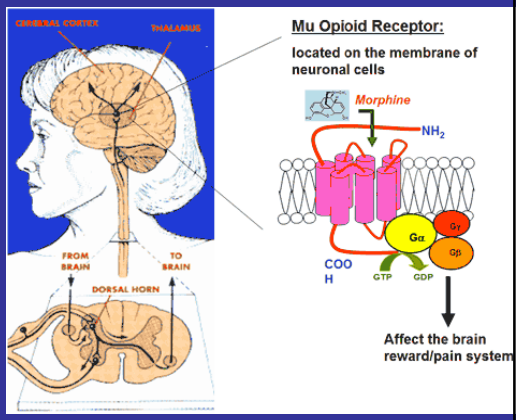
Intranasal Fentanyl Spray

Fentayl Pectin Nasal Spray

Fentanyl: Overview

A Nearly 40-Year History of Analgesic Efficacy

- Mu-opioid receptor agonist [1]
  - Brain, spinal cord, smooth muscle
  - Analgesia, sedation, respiratory depression, euphoria
- Estimated potency of 80 to 100 times that of morphine [2]



1. Anderson R et al. J Pain Symptom Manage. 2001;21:397-400.
2. Pereira J et al. J Pain Symptom Manage. 2001;22:672-687.

BTcP Therapies: Early Absorption parameters

	Actiq	Effentora	Onsolis	Abstral	Instanyl	Nasalfent
Dose (mcg)	400 100-1600	400 100-800	400 100-1200	400 100-800	400 50-200	400 100-800
Dwell Time (min)	15	15-20			N/A	N/A
Cmax (ng/mL)	0.6	0.9	0.7	0.7	2.5	1.5
Tmax (min)	120 (30–240)	45 (20–240)	60 -	- (23–240)	15 (6-90)	20 (5-90)

Factors Influencing Choice of Opioid and Route

- The patient's pain
  - Severity
  - Duration
  - Speed of onset
  - Opioid responsiveness
- The patient's circumstances
  - Side effect experience / prior opioid exposure
  - Ease of administration / Level of clinical support
  - Patient preference

Novelties in therapeutic with opioids

original article

Annals of Oncology 21: 615–626, 2010
doi:10.1093/annonc/mdp581

Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Europe: a report from the ESMO/EAPC Opioid Policy Initiative

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[1]Cancer Pain and Palliative Medicine Unit, Department of Oncology, Shaare Zedek Medical Center, Jerusalem, Israel; [2]European Society for Medical Oncology; [3]Palliative Care Working Group; [4]Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain; [5]European Society for Medical Oncology; [6]European Association for Palliative Care and [7]Palliative Medicine, Aachen University, Aachen, Germany

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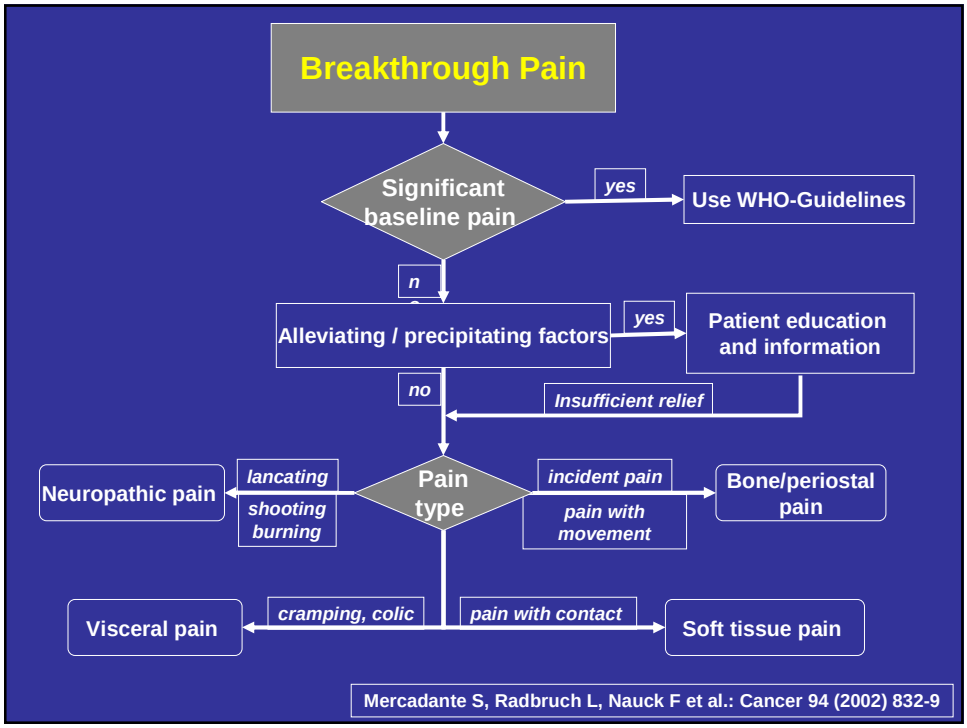
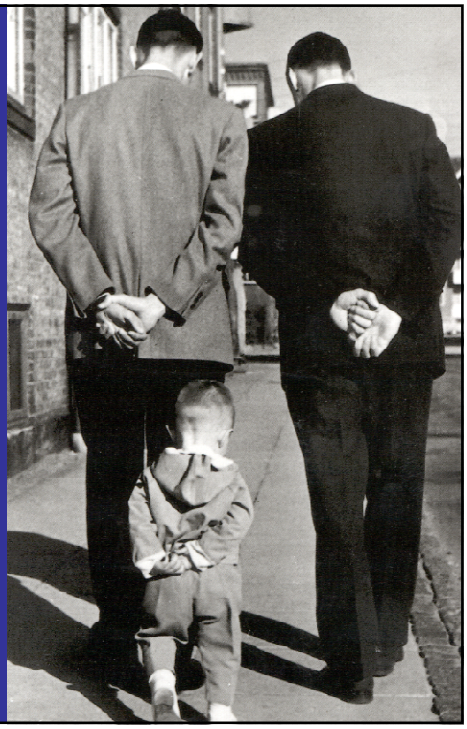
Exceptions included the exclusion of oral immediate release morphine in Turkey; exclusion of immediate release oxycodone in Portugal, Greece, Belgium and Turkey and exclusion of oral methadone in Portugal, Cyprus, Greece and Turkey.



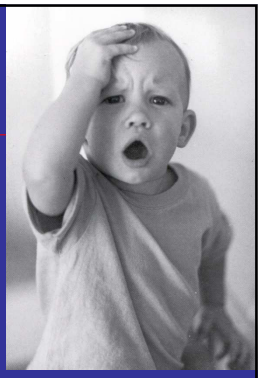
We do not see things as they are

We see things as we are

Talmudic Teachings



Take home message



- End-of-life care has become an issue of great clinical and public health importance, with a growing population of the elderly, and the increasingly chronic nature of death[1]
- Therapeutic priorities will change towards the end of life, focusing on a patient's expectations and wishes, as death is an expected and accepted outcome[2]

1. Van den Block L, et al. Arch Intern Med. 2008;168:1747-1754.
2. Nauck F, et al. *Lancet Oncol.* 2008;9:1086-1091.