Palliative Care

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for Medical Education and Research

Palliative care: a global perspective

- Tens of millions of people worldwide are affected by lifethreatening illnesses such as HIV/AIDS and cancer.

- Majority of cases occur in the developping world, where access to prompt and effective treatment is often still difficult.

  Cancer deaths:
  Out of 9 Mo new cases worldwide in 1985, 55% were in the developping world.
  In 2005, they will represent 15 Mo and 66% of cases.

  Ref: Information and communication Unit. WHO regional office for Africa.

- Source of major suffering for patients and families as well as economical hardships

Palliative care: a global perspective

- There are major differences in access to palliative care services between regions and countries,
- .. as well as serious impediments to opioid availability in many countries

Palliative care: WHO's definition (1)

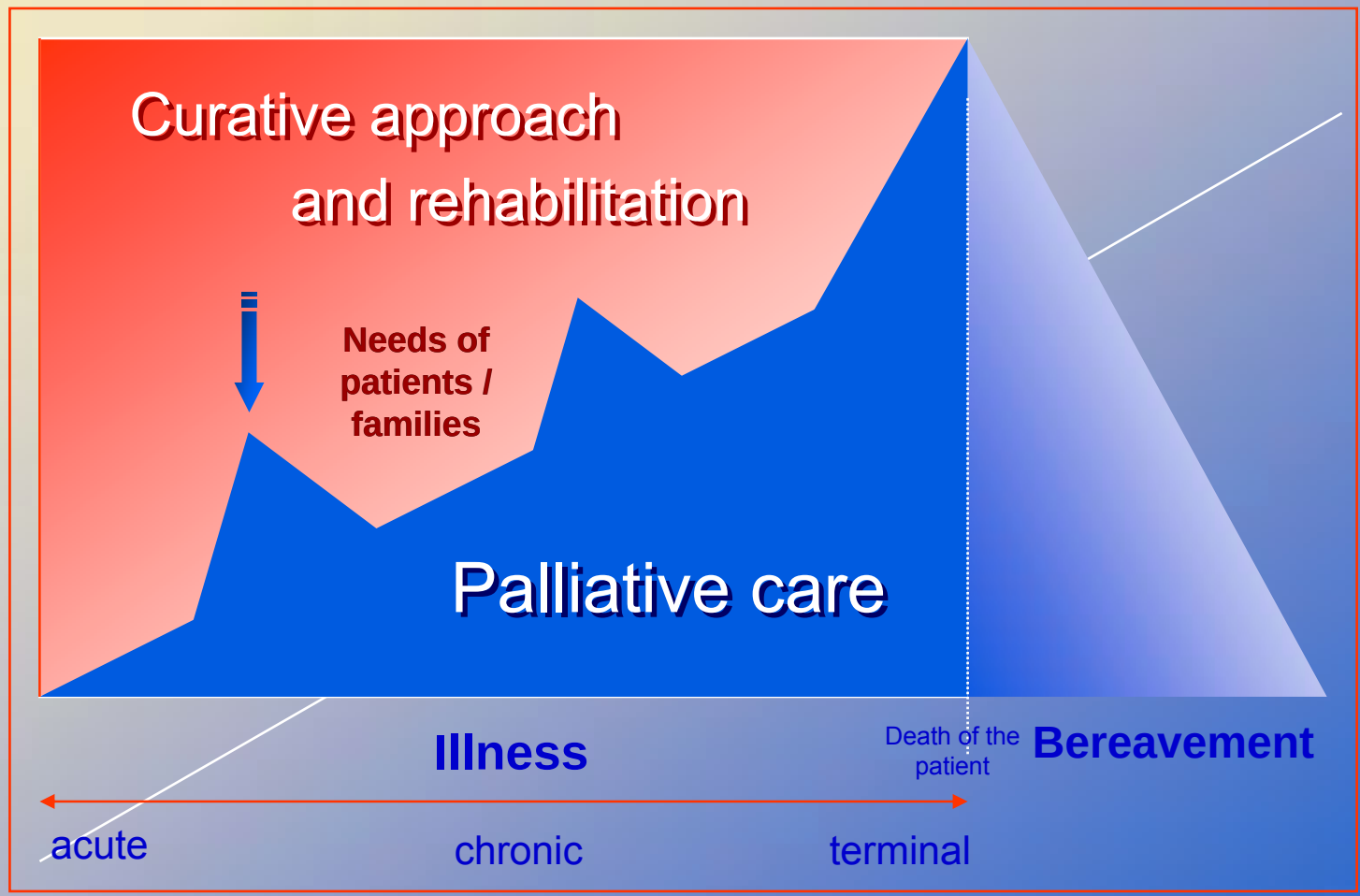
- Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual

Palliative care: WHO's definition (2)

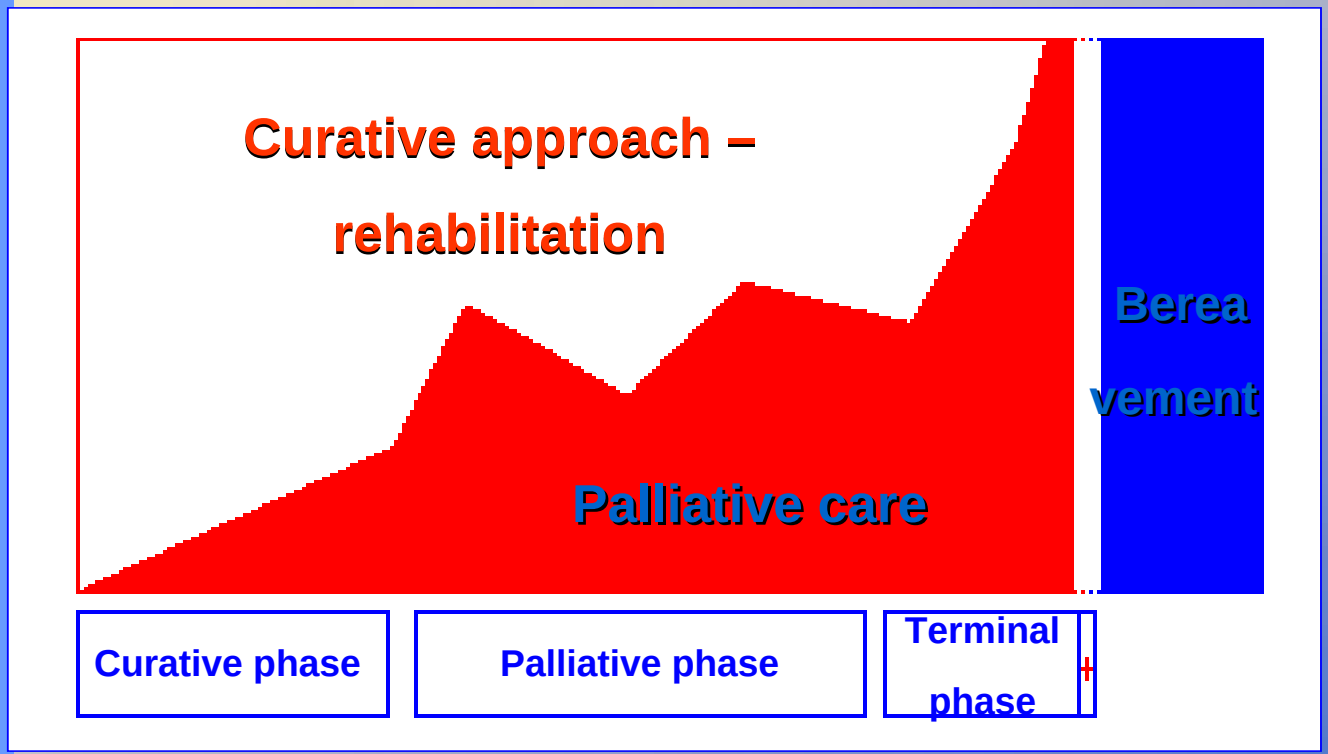
- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten or postpone death
- Integrates the psychosocial and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness

Old vision of palliative care

Complementarity between curative approach and palliative care



Curative treatments and palliative care



Symptom prevalence in cancer patients

- **275 consecutive advanced cancer patients**

Symptom	Prevalence	95% confidence interval
Asthenia	90	81-100
Anorexia	85	78-92
Pain	76	62-85
Nausea	68	61-75
Constipation	65	40-80
Sedation-confusion	60	40-75
Dyspnea	12	8-16

Bruera. Oxford Textbook of Pall Med 1998

Prevalence of symptoms in advanced cancer

- **Prospective study 1840 cancer patients, 7 hospices in Europe, USA, Australia. Vainio A, Auviven A, JMSP 1996;12(1):3-10**

  There are statistically significant differences in symptom prevalence depending on Iary site of cancer and the hospice:

  * Moderate to severe pain: 51%
    (43% in stomach cancer - 80% in gynecological cancer)

  * Nausea: most prevalent in gynecological (42%) and stomach (36%) cancers

  * Dyspnea most prevalent in lung cancer (46%)

Definition of pain

«Pain is an unpleasant sensory and emotional experience associated with actual and potential tissue damage or described in terms of such damage ».

Pain is always subjective.

IASP (International Association for the Study of Pain)

Patient suffering from pain: what should we do?

1. Assess his(her)/pain(s):

- ☺ history
  (ask patients, relatives and professional caregivers)
- ☺ validated assessment tools
- ☺ physical examination, including neurological
- ☺ complementary tests, if/when appropriate, in order to answer specific questions

Patient suffering from pain: what should we do?

2. *Diagnose the pain(s)*:

- ☺ Origin(s):
  primary disease, treatments, other
- ☺ Type of pain:
  nociceptive, neuropathic
- ☺ Mecanism of pain
- ☺ Different dimensions of the pain experience and other symptoms

Origin of pain in cancer patients

- Underlying disease (78%)
- Treatments (19%)

  Chemotherapy: eg, mucositis, post-chemotherapy neuropathies
  Radiotherapy: eg, post-radiation plexopathies
  Surgery: eg, post-thoracotomy pain

- No direct relationship with one or the other (3%)

  Ex: postherpetic neuralgias,
  inflammatory or degenerative arthropathies,
  diabetic neuropathies,...

Types of pain

Nociceptive pain

Activation of nociceptors in the different tissues/organs

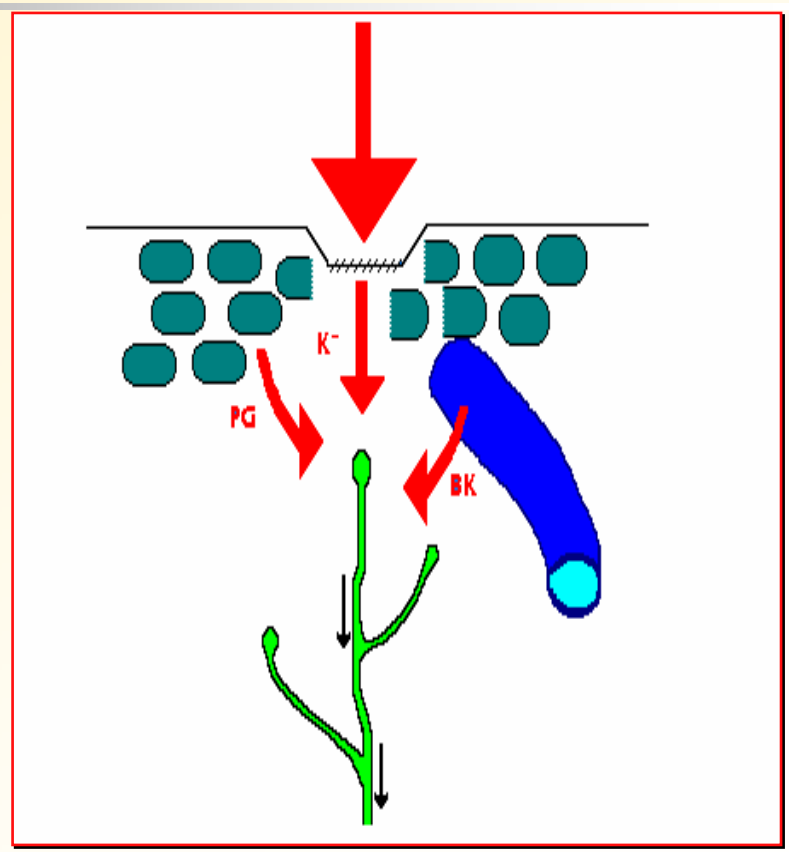
by tissue damage

Somatic pain

Well localised

Visceral pain

Poorly localised, deep, dull, cramping, referred



Modified from Mazzocato, Sylvana 02

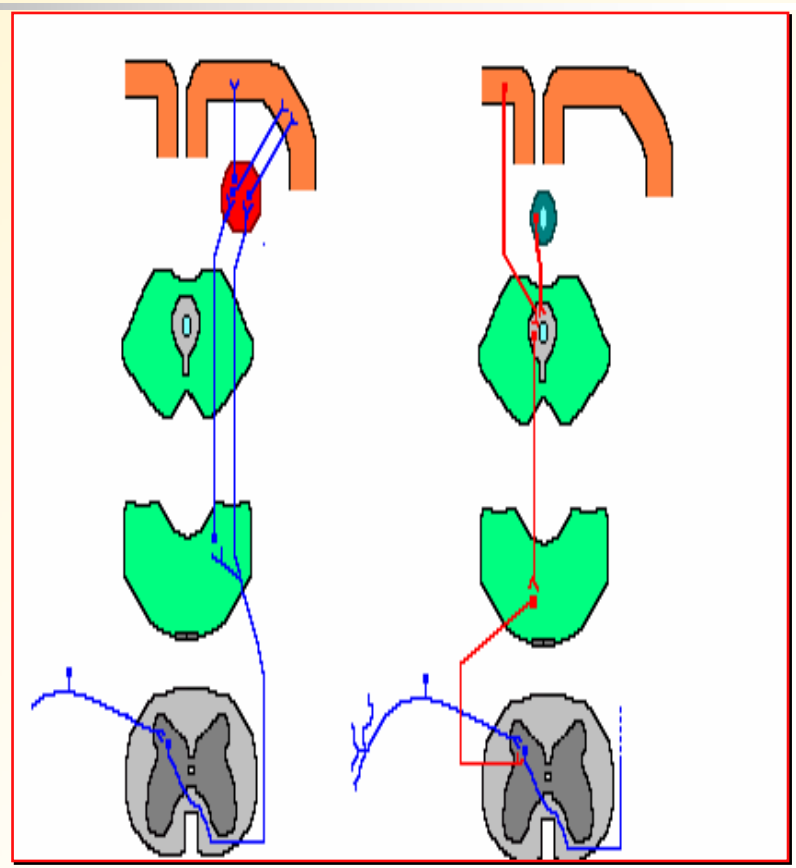
Types of pain

Neuropathic pain

Peripheal or central alteration of nerve conduction

Dysesthesias: burning sensation,numbness, tingling, as well as sharp and shooting, paroxystic exacerbations

Associated with a sensory deficit, hyperesthesia, allodynia; in the region innervated by the affected nerve structure (dermatoma, radicular distribution, etc.)



Modified from Mazzocato, Sylvana 02

History of pain

- How/when did the pain begin?
- Localisation(s)
- Intensity
- Temporal characteristics
  Does it have a periodicity? How long?
- How is the pain described:
  words used by the patient (gives clue to the underlying etiology/sensation and emotional component)
- What improves the pain?
  Types of therapies tried and what benefit they had
- What makes the pain worse?
- How does the pain impact the patient's life? (home, friends, work)
- Patient's understanding of pain
- Important elements in past medical and psychological history

Assessment of pain intensity

- Visual analog scale:

No pain _____ Worst possible pain

- Numerical scale:

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst possible pain

- Categorical scale:

No pain | Week pain | Moderate pain | Severe pain | Very severe pain | Extreme pain

Benefits of a systematic pain assessement

- Identification of patients in pain, even if they don't complain
- Active role for the patient, and an attentive ear
- Prescription of effective treatments
- Monitoring of treatment effects and pain evolution
- Facilitation of communication between doctors, nurses and other healthcare professionals

Pain management

- **Systematic multidimensional assessment, regular reassessments**
- **Treat the cause:**

  - when possible and reasonable (benefits > disadvantages)

- **Treat symptoms:**

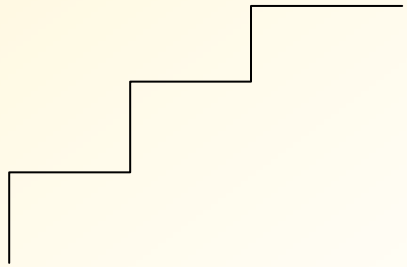
  - systemic analgesics (WHO guidelines)
  - local measures: eg; cold, heat, position, local application of anaesthetics or opioids in painful ulcerations
  - invasive treatments: injection of trigger zones, blocks (eg coeliac plexus in painful pancreatic cancer), spinal analgesia, if specialist available and simple analgesics fail

- **Treat the patient as a whole human being** (body, mind, spirit)
  Interdisciplinary communication, patient and family education
- **Consider the patient and his family as the unit of care**

Symptomatic pain medications

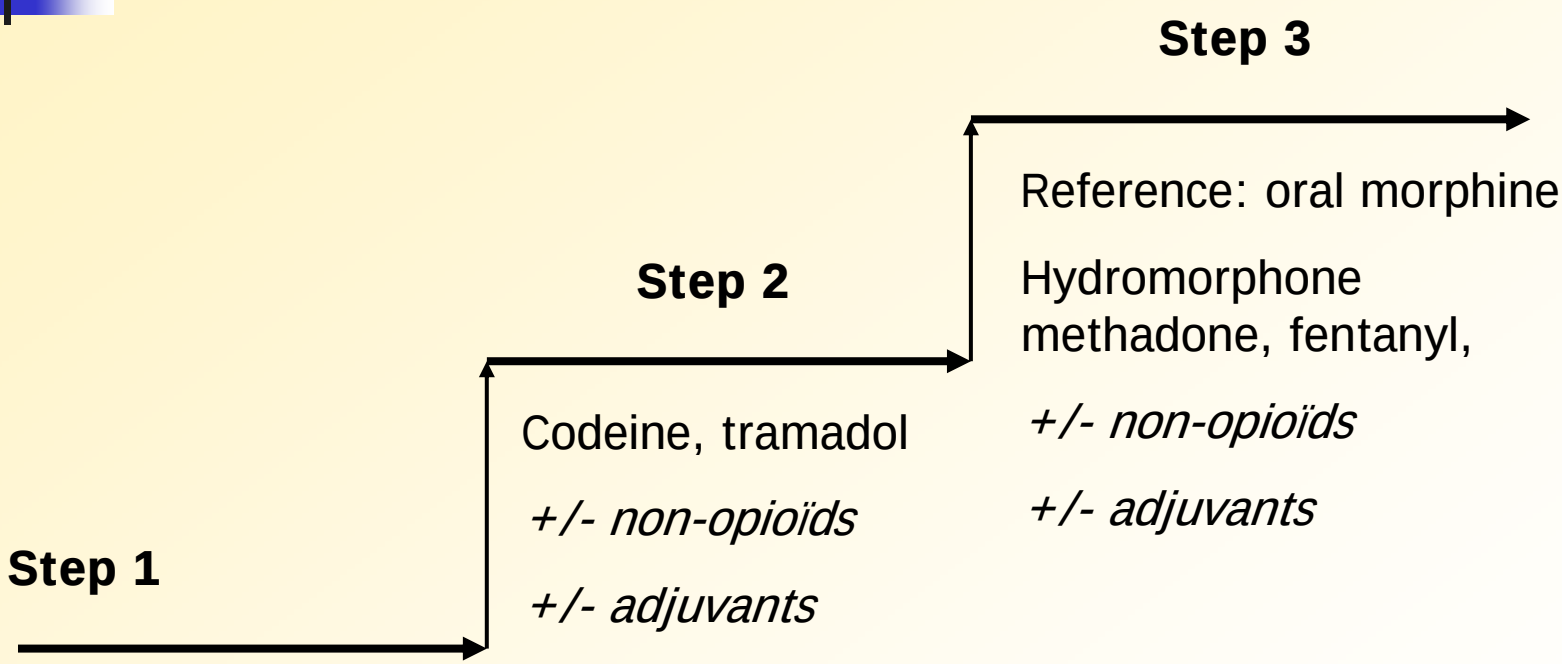
By the mouth

By the ladder



By the clock

WHO analgesic ladder



WHO, in collaboration with IASP 1999

Step 2: Codein

- Biotransformation into morphine by Cyt. P450.

  Iso-enzyme absent in 7-10% caucasians. In those cases, codein will probably be poorly effective

  Dose: 30-60 mg/4h

Step 2: tramadol

- Opioïd (week affinity for the μ recept) + noradrenergic effect (noradrenaline and serotonin)
- Peak plasma concentration: approx. 70 min, prolonged in the elderly
  T1/2 env 6 h, prolonged in liver failure
- Kidney elimination of tramadol and its metabolites
- Doses:
  initially: 50 mg/6-8h and 15-20 mg breakthrough
  (analgesic effect: 3-7h with chronic administration)
  maximal studied dose: 400 mg/d. In the elderly > 75 yrs: 300 mg

Step 2: tramadol

- **Side effects:**

  frequent nausea/vomiting
  dizziness
  sweating
  dry mouth
  constipation
  convulsions

Step 2: tramadol

- Potentially dangerous drug interactions, particularly with antidepressants: SSRIs, tricyclics, IMAO:

  serotoninergic syndrome

Schaad, Med et Hyg 2001;2346

Serotoninergic syndrome

Gastro-intestinal	Cramps Diarrhea
Neurological	Headaches Dysarthria Incoordination Myoclonia
Cardiovascular	Tachycardia Hypo/hypertension Cardiovascular collapsus
Psychiatric	Confusion Dysorientation
Other	Sweats Hyperthermia Hyperreflexia

Step 3: initiation of treatment

- **Morphine is the narcotic of first choice, since it is the most cost-effective**

Give explanations to the patient, patient and family education

- Start with a short acting substance; oral morphine

  A. Opioid naive patient:
  5 mg/4h
  Breakthrough, if pain in between regular dosis: 4-hourly dose, to be repeated if needed up to every hour. Monitor treatment response (analgesic as well as possible adverse effects)

  B. Patient previously treated with another opioid (ex.: step 2):
  Start at least by the equianalgesic dose!

Step 3: dose titration

A/ Increases by approx. 30%

B/ $$\frac{\text{Regular doses + breakthroughs taken in 24h}}{6} = \text{new 4 hourly dose}$$

☺ Adjust breakthrough doses (4 hourly dose)

☺ Reassess if need for more than 3 breakthroughs/day

Step 3:
when stable and well controlled pain

- Switch to a slow-release form if necessary: for eg MST
  24h dose in slow-release form= 24h dose in short acting form
  Slow release morphine tablets: q 12h

- Prescribe breakthrough doses (in short acting form):
  Equivalent to the 4 hourly dose, q 1h

- Reassess at regular intervals
  Adapt doses by approx. 30%

Transdermal fentanyl

- Not a first choice!

- **Indications:**

  * Stable pain
  * Effective dose previously determined by a short acting opioid
  * Swallowing difficulties, alteration of drug absorption or other intolerances to the oral route

Transdermal fentanyl

- **Contraindications:**

  * Economical considerations: expensive +++++
  * Acute pain
  * Unstable pain
  * Skin problems
  * Generalised edema

Morphine and other opioids: feared effects

- **Addiction**
  Almost *never* in a well managed pain treatment

- **Physical dependance**
  Means withdrawal when medication abruptly stopped of in the case of administration of an antagonist

- **Tolerance**
  Need to increase doses in order to maintain the same effect
  Very rarely a problem in clinical practice

Morphine: side effects

- **Classical:**
  nausea, vomiting (prevent)
  constipation (systematically prescribe laxatives)
  drowsiness

  Sometimes also:
  Sweating, itching, urinary retention

Morphine: side effects

- **Nausea/vomiting: prevent**
  for eg metoclopramide
  10 mg po if occasional episodes (breakthrough only)
  if necessary, 10 mg/4h + 10 mg breakthrough

  alternative: haloperidol
  1 mg po if occasional episodes
  if necessary, 1 mg/12h + 1 mg breakthrough

  NB: both metoclopramide and haloperidol can be given sc

Morphine: side effects

- **Constipation: to be systematically prevented:**

  <u>stimulant laxative:</u>
  eg: Na picosulfate 10 drops morning + evening,to be adjusted
  alternatives: bisacodyl, senne derivatives

  +

  <u>osmotic:</u>
  eg. lactilol: 10 mg tds

  reassess min. twice a week and adjust

Morphine: adverse effects

- **Neurotoxicities:**

  myoclonias,
  delirium,
  hyperalgesie/allodynia,
  hallucinations

  mainly in the case of renal failure (accumulation of active metabolites)

Opioid toxicities

- **Hydrate**
  If oral route not possible/sufficient, prefer sc route:
  NaCl 0.9% or min 1/3 NaCl, eg 80-100cc/h

- **If possible, change opioid**
  eg: switch from morphine to hydromorphone

- **Rule out other aggravating factors**
  eg: renal failure, hypercalcemia, etc.

- **Treat symptoms**
  haloperidol for hallucinations/agitation

Buprenorphine

- Not a first choice
- Partial mu receptor agonist, week instrinsic activity and efficacy, ceiling effect
- Maximal effective dose unknown in humans

  30-70 times more potent than morphine

  Duration of action: 6-9h
- Metabolised by the liver. No modification of pharmacoconetics in renal
- Possible indications: severe renal failure, need for relatively low doses of opioids.
- Do not associate it with a pure agonist!

meperidine / pethidine

- **Contraindicated for chronic administration:**

  - neurotoxicities (normeperidine) with risks of myoclonus /seizures
  - short duration action

Co-analgesics

- **NSAIDS:**

  Particularly in bone metastasis

  Beware of adverse effects, and of the increased risks of opioid toxicity through renal failure

Co-analgesics

- **Corticosteroïds:**

  Examples of indications:
  - Intracranial hypertension
  - Tumor compressions, eg epidural spinal cord compression
  - Nerve infiltrations
  - Distension of the liver capsule

  Eg: dexamethasone 12-16 mg/d
  Decrease gradually to determine minimal effective dose

  Beware of side effects!

Co-analgesics

- **Antidepressants:** (tricyclics or SSRIs)

  Neuropathic pain

  Beware of side effects as well as drug interactions

Co-analgesics

- **Anticonvulsants:**

  gabapentine (Neurontin®)
  Initial doses: 100 mg/8h
  Increase progressively and monitor clinical effects

  clonazepam (Rivotril ®)
  Initial doses: 0.5 mg nocte
  Increase carefully. Risks of drowsiness, confusion, falls

Co-analgesics

- **NMDA antagonists, eg:**

  *** methadone**

  Very useful and cheep opioid, could be more effective than others in neuropathic pain.

  Needs to be used by experienced professionals, because of its particular pharmacological characteristics (long half-life, 1 to over 60 hrs, important interindividual variability)

  * dextrometorphan

  * ketamine (not a 1st choice, indicated in neuropathic pain if other treatments fail, and in resistant pain. To be used by experienced professsionals)

Co-analgesics

- **Bisphosphonates:**

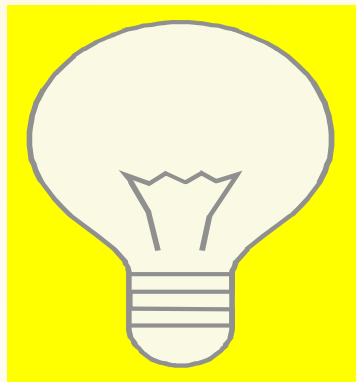
  Decreased « bone events » due to bone mets.

  Demonstrated particularly for breast carcinomas, myelomas, prostate cancer.
  Also indicated in bone metastases from other origins.

  Injection every 4 weeks

  Eg: zoledronate: 4 mg iv 15 min every 3-4 weeks
  pamidronate: 60-90 mg iv
  (if 0 iv line, clodronate can be given sc; less effective)

Crescendo pain: look for…



- Complications of the underlying disease
  (eg: pathological fracture, epidural spinal cord compression, intestinal obstruction)
- Accumulation of opioid toxic metabolites
- Delirium (impaired capacity to express pain)
- Urinary retention/fecal impaction in a patient with cognitive failure or impaired capacity to communicate
- Somatisation; expression of a global suffering as pain
- Opioid tolerance (usually develops slowly)

Epidural spinal cord compression

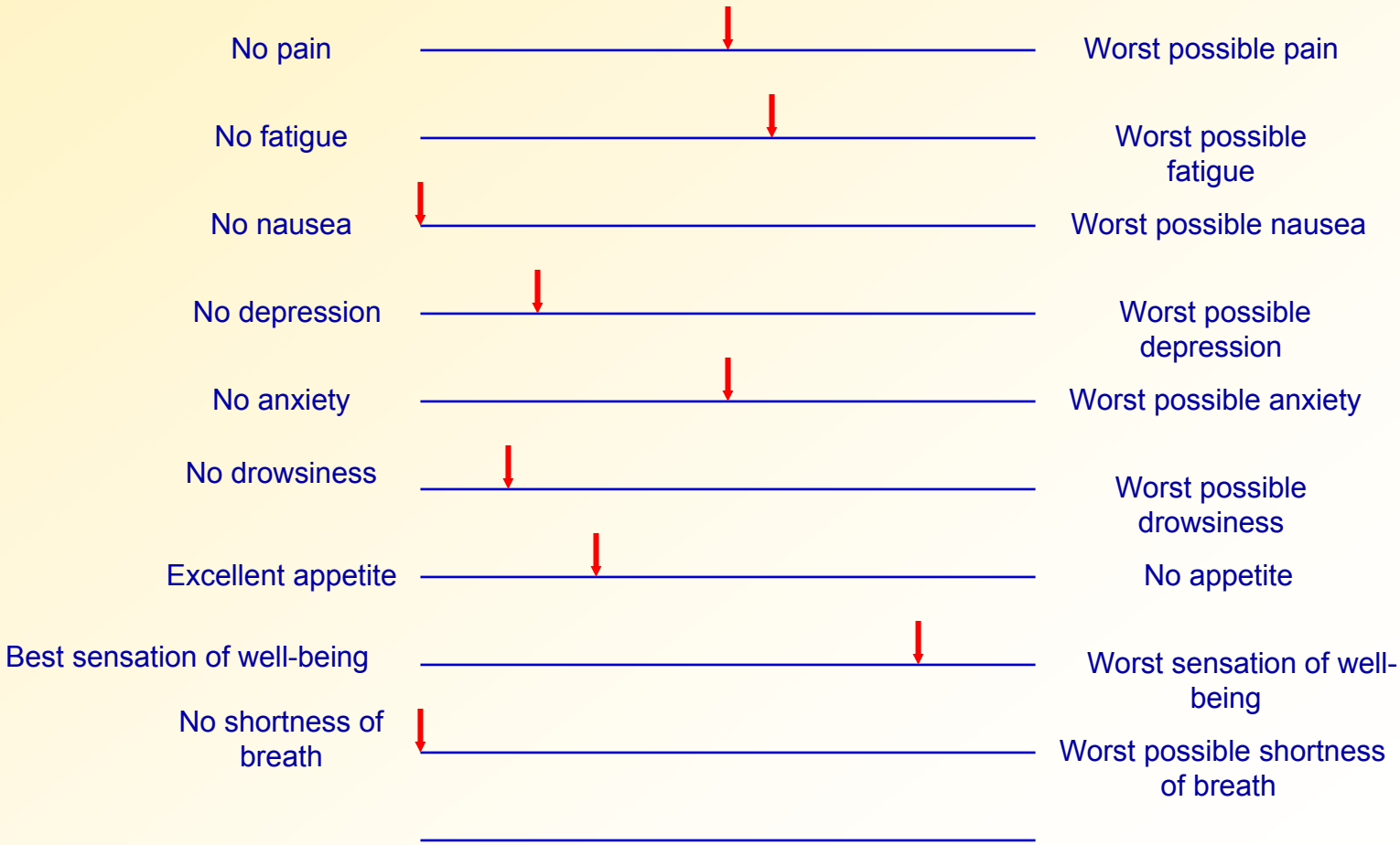
- **Emergency:** functional prognosis depends on neurological deficits at the time of initiation of treatment

- High suspicion if:
  * Vertebral pain that:
    changes, increases, worsens in recumbent position,
    Lhermitte's sign
  * Radiculopathy
  * Muscle weakness +/- sensory deficits, incontinence

- Dexamethasone 12-16 mg/d, emergency MRI if possible (CT Scan as 2nd choice)

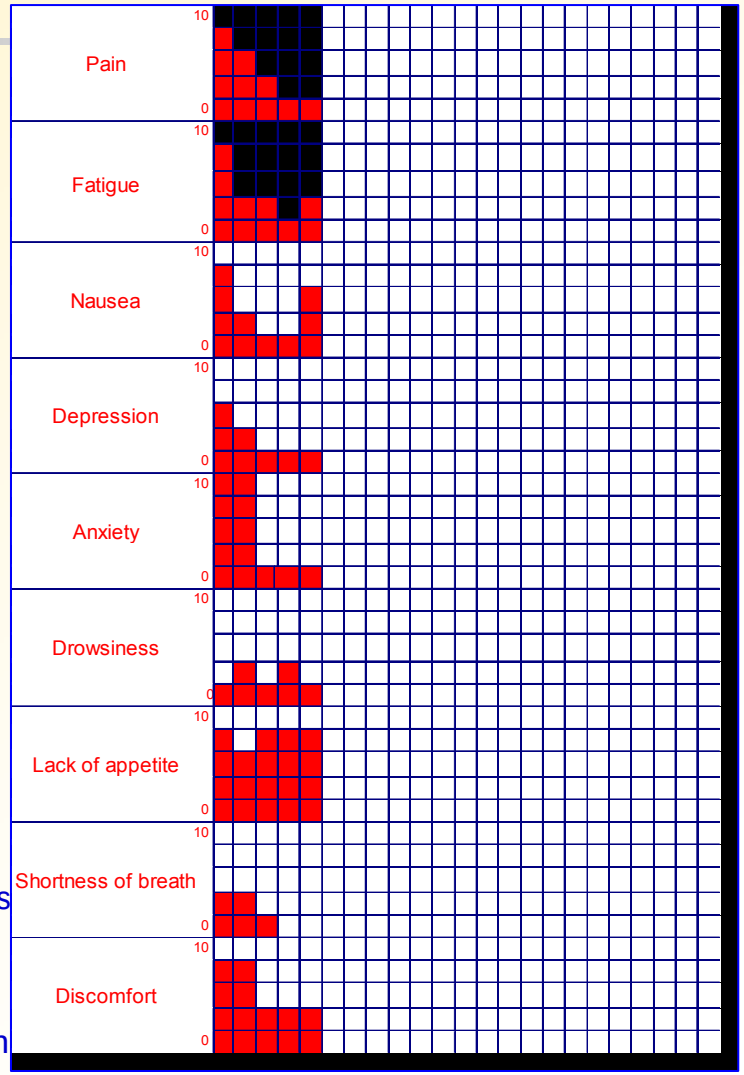
- Radiotherapy +/- vertebroplasty +/- laminectomy

Edmonton symptom assessment



Edmonton Symptom Assessment System

No pain		Worst possible pain
No fatigue		Worst possible fatigue
No nausea		Worst possible nausea
No depression		Worst possible depression
No anxiety		Worst possible anxiety
No drowsiness		Worst possible drowsiness
Excellent appetite		No appetite
No shortness of breath		Worst possible shortness of breath
Best sensation of well-being		Worst possible sensation of well-being



Incidence of bowel obstruction

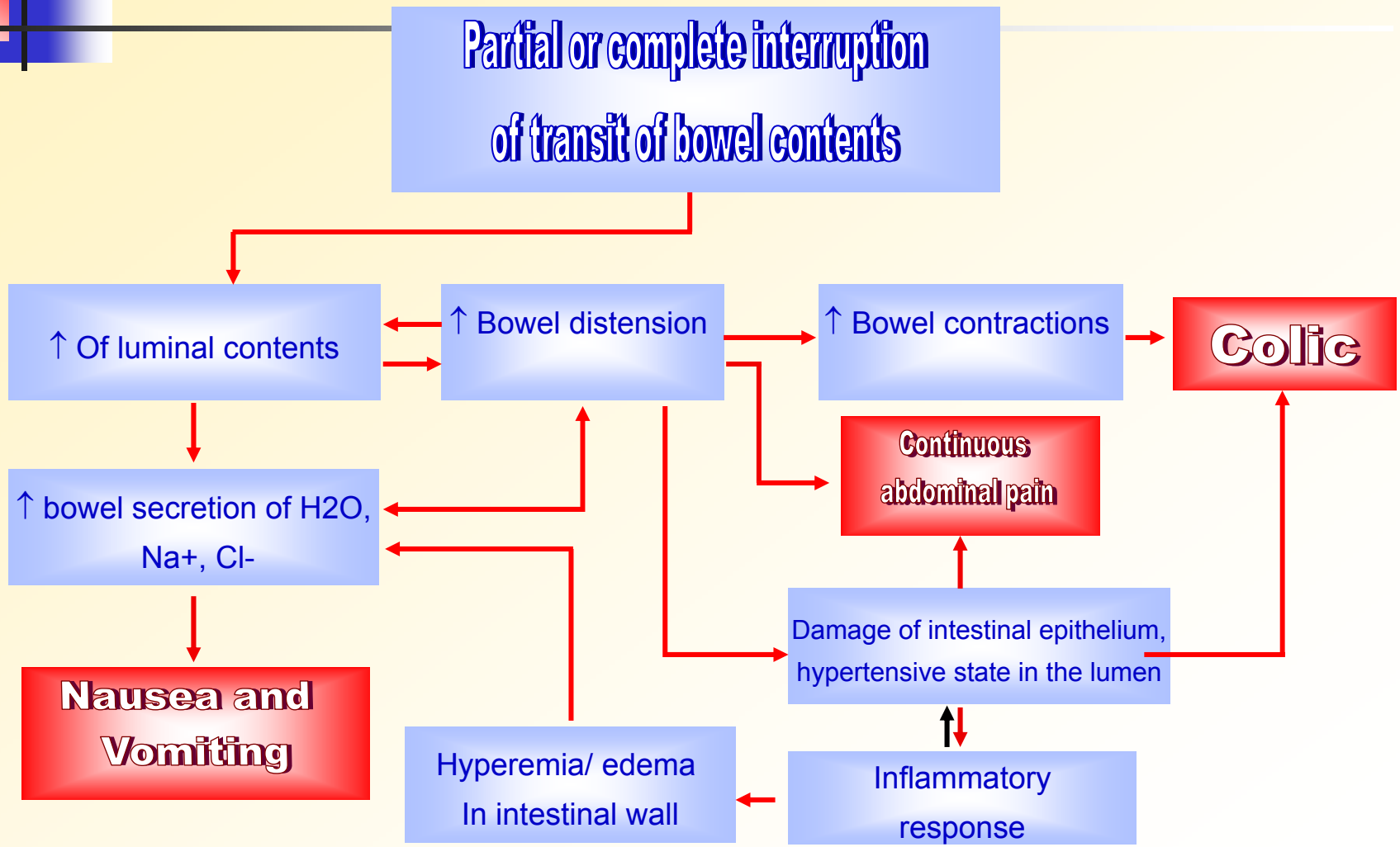
Authors	Primary cancer	% patients with intestinal obstruction
Castaldo et al, 1981	Ovary	5.5
Lund et al, 1989	Ovary	14
Solomon, 1983	Ovary	14.7
Tunca et al, 1988	Ovary	25
Beattie et al, 1989	Ovary	42
Soo et al, 1988	Gynecological Ca	5
Kyllonen, 1987	Rectum	4.4
Baines et al, 1985	Colorectal	10
Philipps et al, 1985	Colon	16
Kyllonen, 1987	Colon	24
Baines et al, 1985	Miscellaneous	3
Steiner, 1991	Miscellaneous	6

Pathophysiology

- **Mechanical obstruction**
  - Extraluminal tumor (78 %)
  - Intraluminal tumor

- **Functional obstruction**
  - Tumor extension in the retroperitoneum, with coeliac plexus infiltration
  - Dysfunction of autonomous nervous sytem
  - Tumor extension in the serous membranes or digestif wall muscle layers
  - Lung infection, M infarction, pancreatitis, electrolyte abnormalities
  - Drugs

Pathophysiology



Symptoms

Symptpms	Frequency
Nausea / vomiting	68 - 100 %
Colicky pain	72 - 76 %
Continuous abdominal pain	92 %
Diarrhea	34 %
Constipation	13 %

Surgery

Auteurs	Tumeur primaire	Mortalité opératoire (%)	Autres complications (%)	Survie (mois)
Lund et al, 1989	Ovaires	32	32	2 (médiane)
Soo et al, 1988	Ca gynécologique	11	15.5	2.5 (médiane)
Pictus et al, 1988	Ovaires	16.5	31	2.5 (médiane)
Krebs et al, 1983	Ovaires	12	12	3.1 (médiane)
Clarke-Pearson et al, 1987	Ovaires	14	49	4.5 (médiane)
Rubin et al, 1989	Ovaires	9	11.5	6.8 (moyenne)
Tunca et al, 1981	Ovaires	14	NR	7 (moyenne)
Beattie et al, 1989	Ovaires	9	9	7 (moyenne)
Castaldo et al, 1981	Ovaires	13	43	12 (médiane)

Ripamonti C. *Curr Opin Oncol* 1994; 9: 193-200.

Surgery

Authors	lary Tumor	Operative mortality (%)	Other complications (%)	Survival (mo)
Chan et al, 1992	Miscellaneous	40	80	2 (median)
Osteen et al, 1980	Miscellaneous	NR	NR	3 (median)
Annest et al, 1979	Miscellaneous	18	44	4 (mean)
Aranha, 1981	Miscellaneous	46	15	4.5 (mean)
Turnbull et al, 1989	Abdominal	13	44	4.5 (mean)
Aabo et al, 1984	Miscellaneous	24.4	NR	4.5 (median)
Lau et al, 1993	Colorectal	37	27	6.1 (median)
Aranha et al, 1981	Miscellaneous	27.5	22.5	7 (mean)
Walsh et al, 1984	Miscellaneous	19	NR	11 (median)

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Walsh et al, 1984	Miscellaneous	19	NR	11 (median)

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Contraindications to surgery

Absolute

- Recent laparotomy demonstrating that further corrective surgery was not possible
- Previous abdominal surgery which showed diffuse metastatic cancer
- Involvement of proximal stomach
- Intra-abdominal carcinomatosis demonstrated radiologically with a contrast study revealing a severe motility problem
- Diffuse palpable intra-abdominal masses
- Massive ascites which rapidly recur after drainage

Ripamonti C et al. *Support Care Cancer* 2001; 9: 223-233.

Contraindications to surgery

Relative

- Extra-abdominal metastases producing symptoms which are difficult to control
- Nonsymptomatic extensive extra-abdominal malignant disease
- Poor general performance status
- Poor nutritional status (marked weight loss/cachexia, marked hypoalbuminemia, low lymphocyte count
- Advanced age in association with cachexia
- Previous radiotherapy of the abdomen or pelvis

Ripamonti C et al. *Support Care Cancer* 2001; 9: 223-233.

Medical symptomatic treatment

Authors	Primary Tumor	Mean survival
Ventafridda et al, 1990	Miscellaneous	13.4 days (2 - 50)
Fainsinger et al, 1994	Miscellaneous	18 days (2 - 41)
Isbister et al, 1990	Miscellaneous	29 days
Steiner et al, 1991	Miscellaneous	1.6 months (1 - 4)
Baines et al, 1985	Miscellaneous	3.7 months (1 - 12)

Treatment of nausea

Anti secretory drugs

Antisecretory drugs
Hyoscine butylbromide: 40-120 mg/day sc,iv
or hyoscine hydrobromide: 0.8-2.0 mg/day sc
or Glycopyrrolate: 0.1- 0.2 mg tid sc or iv

or

Somatostatin analogue
Octreotide
0.2-0.9 mg/day sc

Anti-emetics

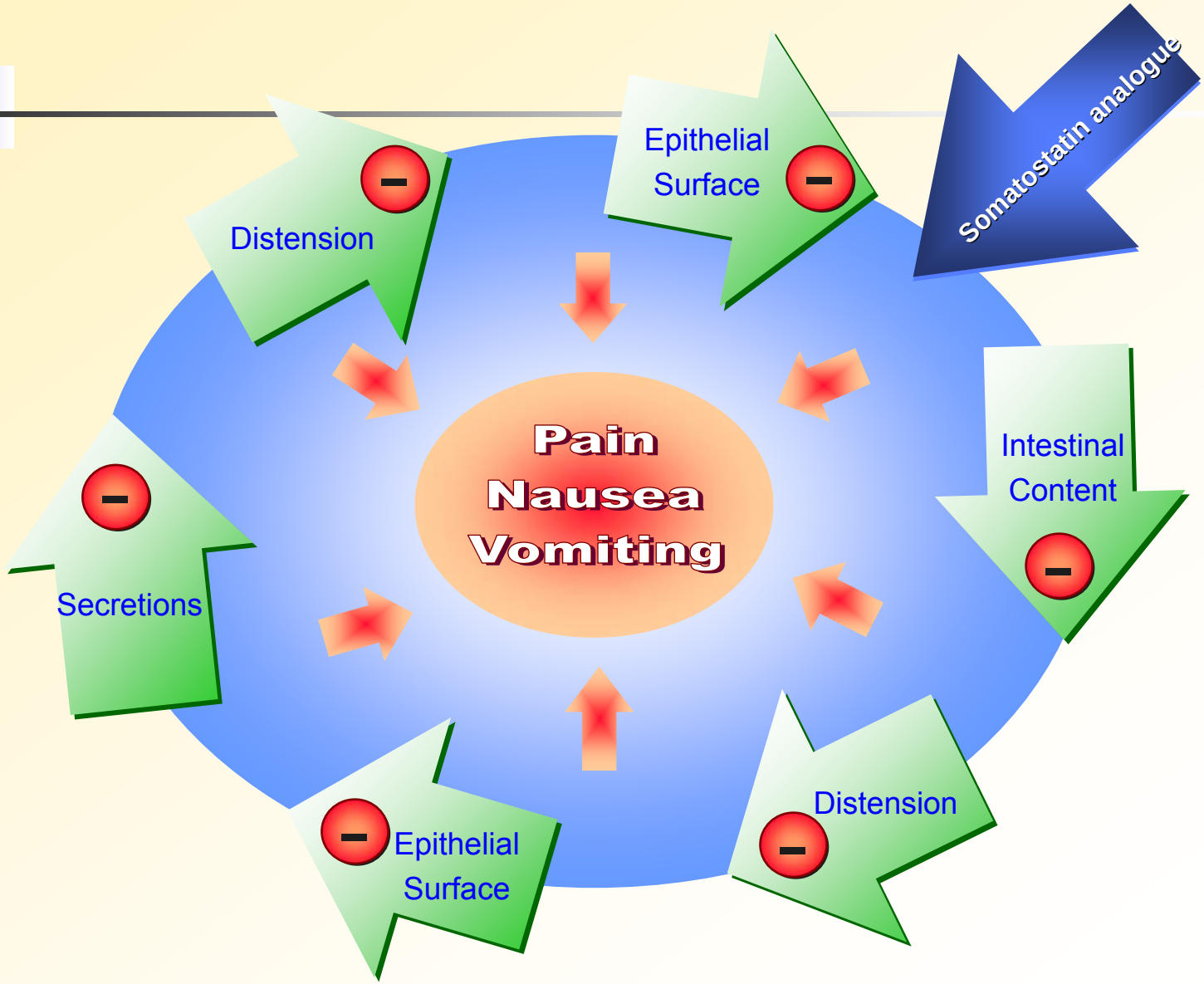
Prokinetic drug
- Metoclopramide
  60 - 240 mg/day sc, if partial obstruction and no colic

Neuroleptic drugs
- Haloperidol 5 - 15 mg/day sc
  or methotrimeprazine 6.12-50 mg/d sc
  or prochlorperazine 25 mg 8 hourly pr
  or chlorpromazine 50-100 mg 8 hourly pr or im

or

Antihistamine drug
cyclizine 100-150 mg/day sc or 50 mg 8 hourly PR
or dimenhydrinate 50-100 mg sc prn

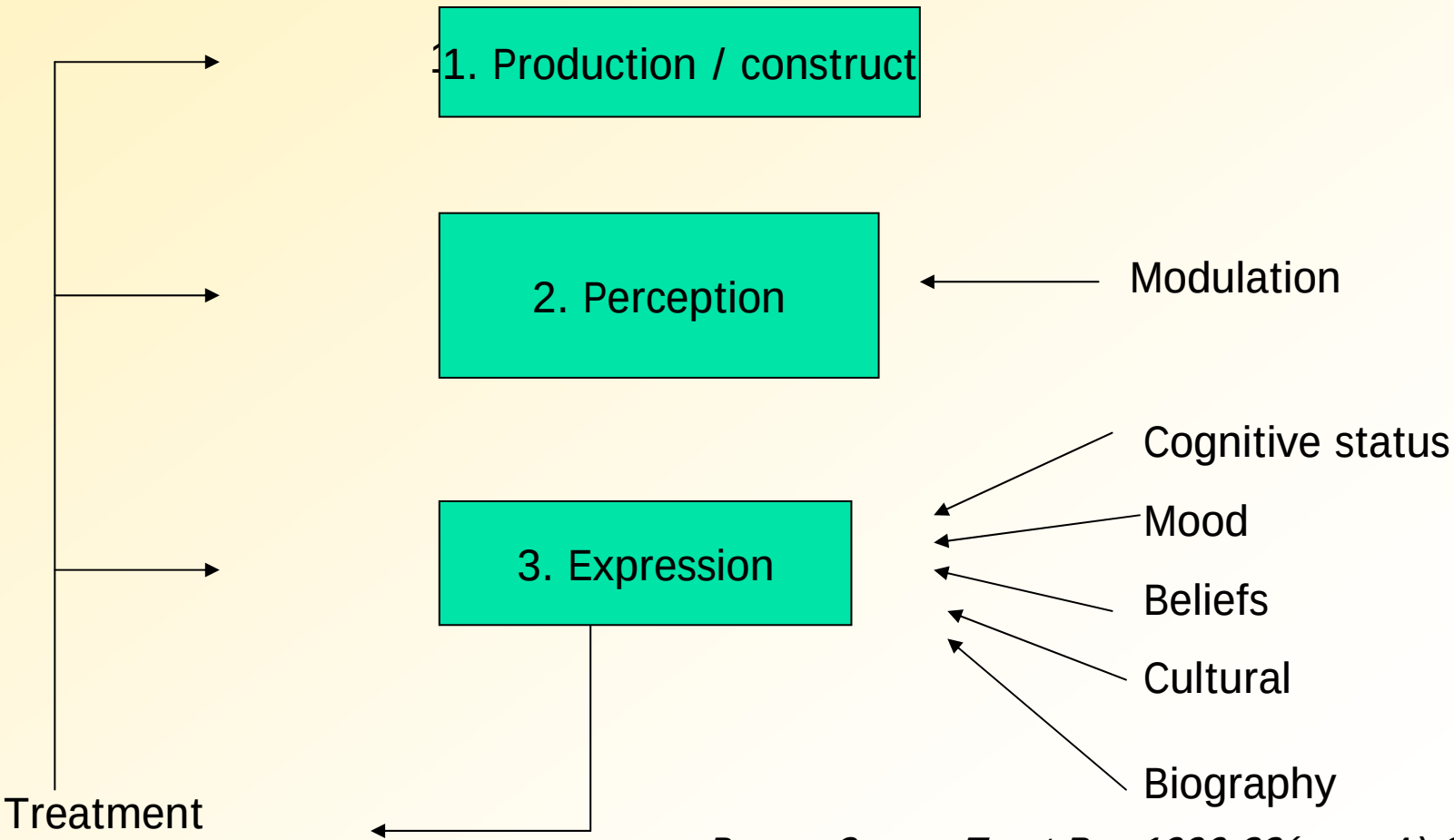
Somatostatin analogue: mechanism of action



Other measures

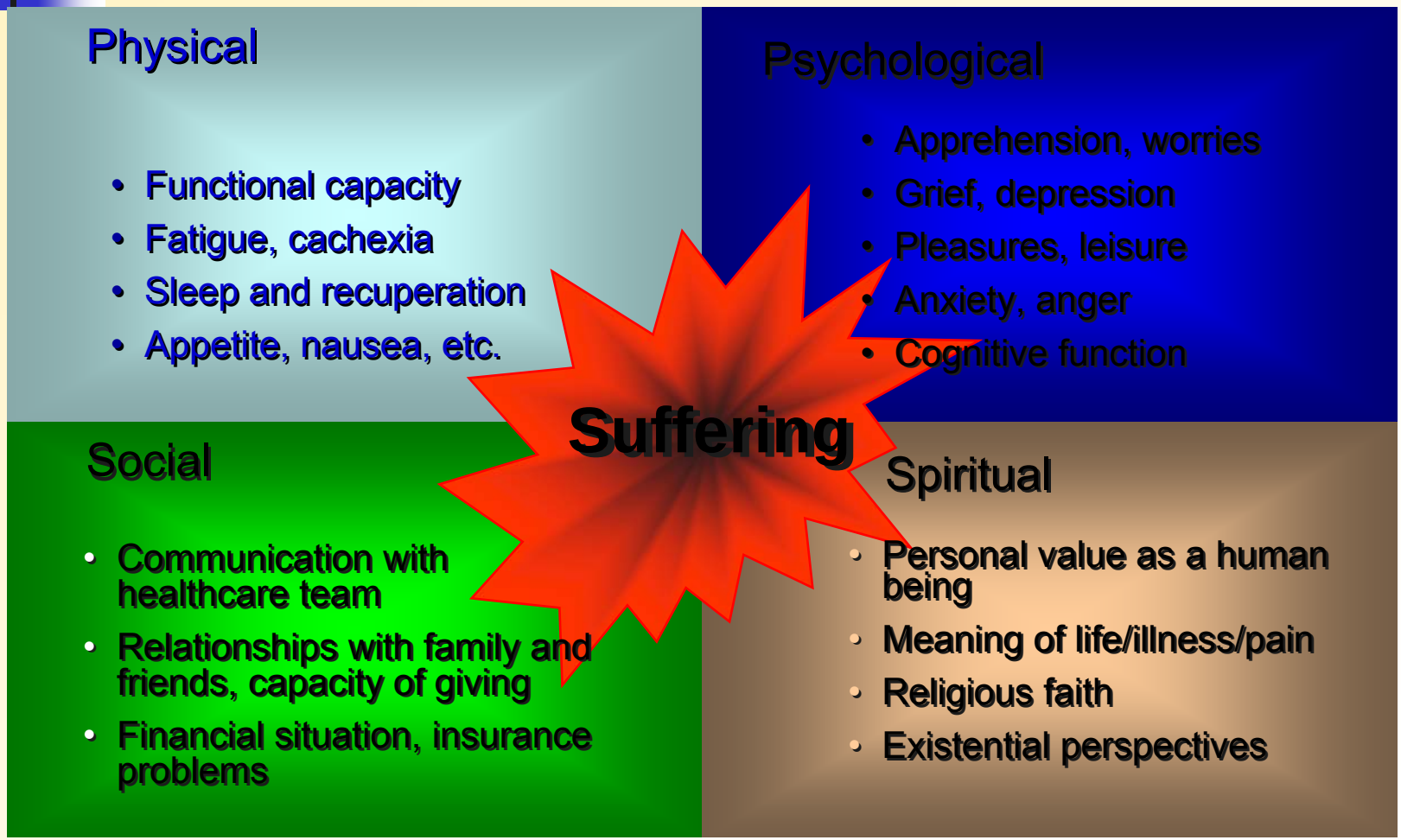
- **Hydratation**
  - 1000-1500 ml/24h sc or iv : ↓ nausea
  - Preoperative iv hydratation IV
- Nasogastric tube
  - Emergency treatment of intestinal obstruction before surgery
  - In case of failure of medical symptomatic treatment (upper intestinal obstruction), prefer gastrostomy (PEG), except if patient very near death
- Parenteral Nutrition
  - Only indicated in patients with slowly growing tumor, with Karnofsky Preformance Status > 50
- Stents
  - Ex:Pyloric obstruction, obstruction of small intestine or colon

Schema of symptom construct



Bruera Cancer Treat Rev 1996;22(supp A):3-12

Total pain


Physical
• Functional capacity
• Fatigue, cachexia
• Sleep and recuperation
• Appetite, nausea, etc.
Psychological
• Apprehension, worries
• Grief, depression
• Pleasures, leisure
• Anxiety, anger
• Cognitive function
Suffering
Social
• Communication with healthcare team
• Relationships with family and friends, capacity of giving
• Financial situation, insurance problems
Spiritual
• Personal value as a human being
• Meaning of life/illness/pain
• Religious faith
• Existential perspectives

Palliative care: a global perspective

- The development of palliative care through effective and low cost approaches represents a priority in order to respond to the urgent needs of the sick and improve their quality of life.

Palliative care: a global perspective

- There is a need to promote a public health approach in which comprehensive palliative care programs are integrated into existing healthcare systems and tailored to the specific cultural and social context of the target populations.

Foundation measures:

little cost, big effect

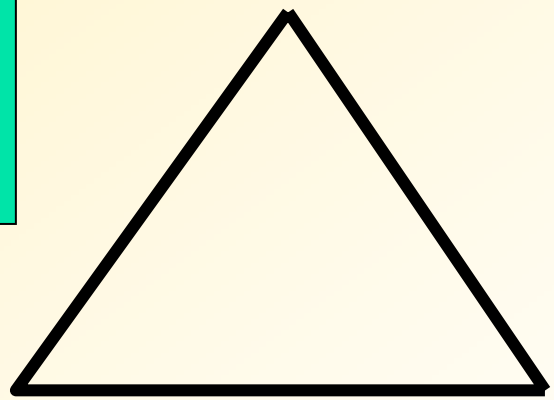
(Stjernswärd J. JPSM 2002;24(2)259)

Education

-Public, professionals
- Undergraduate education for doctors and nurses
- Postgraduate training
- Advocacy (policy makers, administrators, drug regulators)

Drug availability

- Changes in legislation to improve availability especially of cost effective opioids such as morphine sulfate tablets
- Prescribing made easier and distribution, dispensing and administration improved



Governmental policy

- National policy emphasizing the need to alleviate unnecessary pain and suffering of the chronically and terminally ill
- Governmental policy integrating PC into the healthcare system
- Separate systems of care are neither necessary nor desirable

Palliative care: useful international organisations

- WHO Programme on Cancer Control
- EAPC (European Association for Palliative Care) www.eapcnet.org and www.eapcare.org
- International Association for Hospice and Palliative Care www.hospicecare.com
- Hospice Information Service St Christopher's Hospice London www.hospiceinformation.co.uk

Palliative care: some references

- Oxford Textbook of Palliative Medicine 2003
- Hanks GW et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. British Journal of Cancer 2001;84(5):587-593
- WHO guidelines on Cancer pain, opioid availability, symptom control and palliative care:
  - Cancer pain relief (1996)
  - Cancer pain relief and palliative care. Report of a WHO expert committee (1999)
  - Symptom relief in terminal illness 1998
  - Cancer pain relief and palliative care in children 1998
  - National cancer control programmes: Policies and Managerial Guidelines 2002
- Ripamonti et al. Clinical-practice recommendations for the management of bowel obstruction in patients with end-stage cancer. Support Care Cancer 2001;9:223-233
- Journal of Pain and Symptom Management 42(2) august 2002
- Edmonton Regional Pallative Care Program: www.palliative.org
  (useful contents about: clinical work, educational opportunities, informations for general public, links, research and literature)