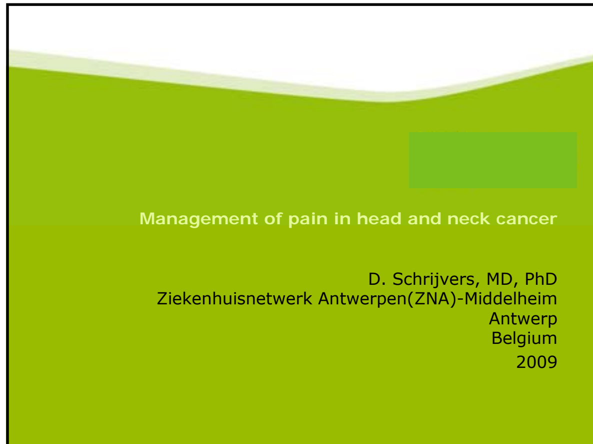
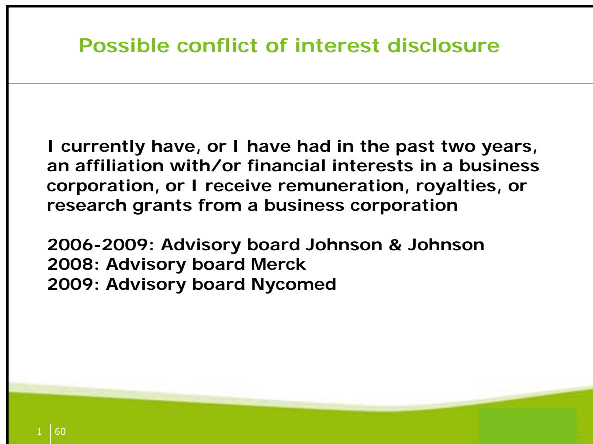

Management of pain in head and neck cancer
D. Schrijvers, MD, PhD
Ziekenhuisnetwerk Antwerpen(ZNA)-Middelheim
Antwerp
Belgium
2009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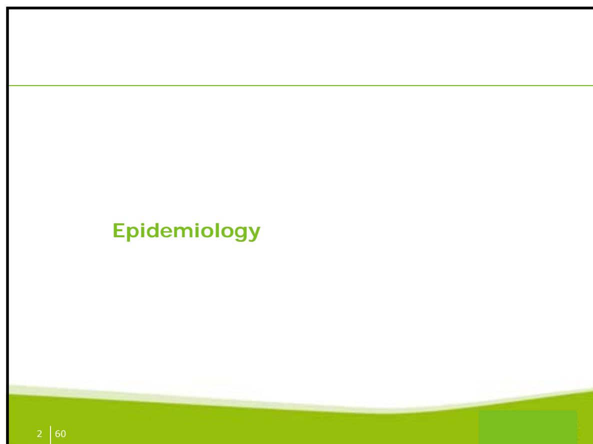
Epidemiology
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Management of cancer pain in head and neck cancer: prevalence

Type of cancer	Pain(%) (95%CI)	N Reports	N Pts
Head/neck	70 (51-88)	3	95
Gastro-intestinal	59 (44-74)	9	564
Lung/bronchus	55 (44-67)	7	1546
Breast	54 (44-64)	7	420
Uro-genital	52 (40-60)	4	336
Gynecological	60 (50-71)	6	372

van den Beuken-van Everdingen MH et al. Ann Oncol 2007

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Management of cancer pain in head and neck cancer: prevalence

Author (year)	Status	Pain(%)	Comment
Foley (87)		80	Tumor-related
Grond (93)		83	Tumor-related
		28	Treatment-related
Agarwal (08)	At diagnosis	99	Advanced head and neck cancer
Logan (08)	5-year survivors	43	Metallic taste predicts pain
Karvonen (08)	Within 2 years after diagnosis		Pain score was significantly associated with survival

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Causes and types

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Management of cancer pain in head and neck cancer: causes

- **Tumor**
  - Bone invasion or metastatic disease
  - Compression of spinal cord/other structures
  - Neural compression, neural damage
  - Obstruction glandular structures
  - (Para-neoplastic syndromes)
- **Cancer treatment**
  - Surgery (resection, reconstruction, acute and late side effects)
  - Chemotherapy (acute and late side effects e.g. stomatitis, neuropathy, inflammation)
  - Radiotherapy (acute and late side effects e.g. mucositis, neuropathy, inflammation)
- **Non-cancer related pain**
- **Pain of unknown origin**

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Management of cancer pain in head and neck cancer: types

- **Temporal relationship**
  - Acute pain
  - Chronic pain
  - Incident pain/break through pain
- **Physiopathological mechanism**
  - Nociceptive pain
    - Somatic pain
      - Deep
      - Superficial
    - Visceral pain
  - Neuropathic pain

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Management of cancer pain in head and neck cancer: multi-dimensional process

- **Physical aspects**
  - Cancer pain
  - Other somatic symptoms (e.g. cough, nausea, dysphagia)
- **Psychological aspects**
  - Frustrations, depression, anxiety
- **Social aspects**
  - Financial, place in family, job loss
- **Spiritual aspect**
  - Meaning of disease, life

→ Multidisciplinary team approach

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Nociceptive pain

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Management of cancer pain in head and neck cancer: nociceptive pain

- **Nociceptive pain**
  - > Transduction
  - > Transmission
  - > Perception

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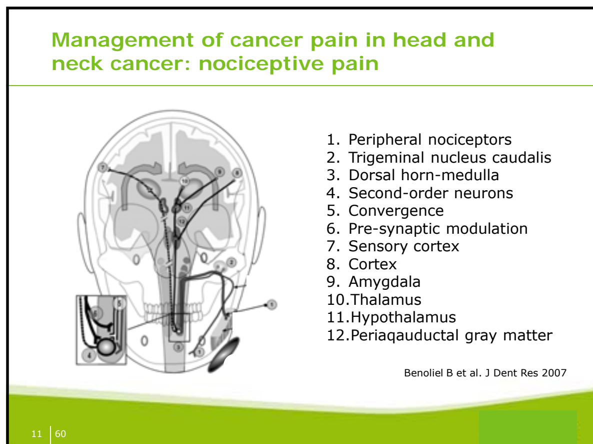
Management of cancer pain in head and neck cancer: nociceptive pain



1. Peripheral nociceptors
2. Trigeminal nucleus caudalis
3. Dorsal horn-medulla
4. Second-order neurons
5. Convergence
6. Pre-synaptic modulation
7. Sensory cortex
8. Cortex
9. Amygdala
10. Thalamus
11. Hypothalamus
12. Periaqauductal gray matter

Benoliel B et al. J Dent Res 2007

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Management of cancer pain in head and neck cancer: nociceptive pain

1. Secretion various agents
   1. Prostaglandins
   2. Cytokines
   3. RANK ligand
   4. Growth factors
2. Inflammation- recruitment of inflammatory cells
   1. Prostaglandins
   2. Cytokines
3. Reduced pH
4. Activation of osteoclasts with bone destruction
5. Sequestration osteoblast-derived osteoprotegerin
6. Invasion of adjacent structures

(Interleukin, PG = prostaglandin, ET-1 = endothelin-1, RANK = receptor activator for nuclear factor-B, COX-2 = cyclo-oxygenase 2, TNF- = tumor necrosis factor)

Benoliel B et al. J Dent Res 2007

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Management of cancer pain in head and neck cancer: nociceptive pain-receptors

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Management of cancer pain in head and neck cancer: nociceptive pain-inflammation

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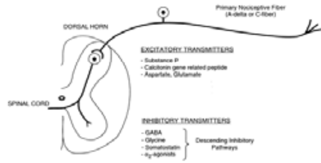
Management of cancer pain in head and neck cancer: nociceptive pain-transmission



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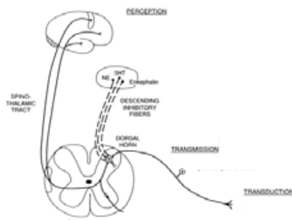
Management of cancer pain in head and neck cancer: nociceptive pain-perception



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Management of cancer pain in head and neck cancer: nociceptive pain-modulation

- **Interference with pain transduction**
  - Redrawal of traumatic factors
  - Interference with mediators
- **Interference with pain transmission**
- **Interference with pain perception**

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Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Ligand	System	Receptor
Dynorphin	Intraspinal	κ-opioid receptor
Enkephalin	Intraspinal Midbrain	μ- and δ-opioid receptor
Endorphin	Midbrain	μ-opioid receptor
Orphanin	Midbrain	δ-opioid receptor
GABA	Intraspinal	GABA receptors
Glycine	Intraspinal	Glycine receptors
Anandamide	Intraspinal	CB1 receptors
5-hydroxytryptamine (HT)	Bulbospinal	5-HT1b receptor 5-hHT 3 receptor
Nor-epinephrine	Bulbospinal	alpha2 receptors

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Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor

Taylor et al. J Pharmacol Exp Ther 2001

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Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor

Taylor et al. J Pharmacol Exp Ther 2001

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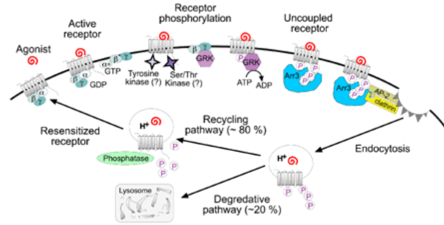
Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor



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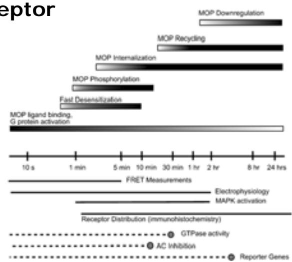
Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor



Kumar et al. Cochrane Database Syst Rev 2006

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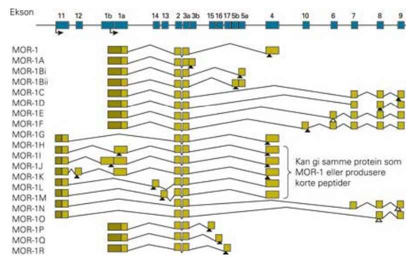
Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor



Klepstad P et al. Tidsskr Nor Laegeforen 2005

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Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor

	μ-1	μ-2	κ	δ
Supraspinal analgesia	x		x	(x)
Spinal analgesia	x	x	x	x
Respiratory depression		x		
Cardiovascular depression	x			
Hypothermia	x			
Diuresis			x	
Anti-diuresis	x	(x)		
Nausea and vomiting	x	(x)		
Constipation		x	(x)	(x)
↓ Gastric emptying/acid secretion				x
Euphoria	x			
Dysphoria			x	
Tolerance/dependency		x		(x)
Convulsions/stress/shock				x

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Management of cancer pain in head and neck cancer: nociceptive pain-modulation

Opioid receptor

Machelska H. et al. Anesth Analg 2002

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Neuropathic pain

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Management of cancer pain in head and neck cancer: neuropathic pain

A. Transcription and axonal trafficking of sodium channels to the site of injury and concomitant attenuation of potassium → channels hyperexcitable and ectopic activity
B. At the cell body of primary afferent neurons → sympathetic neuronal sprouting
C. Changes in gene transcription and activation of various kinases and proteins. Following activation, microglia release various pro-nociceptive cytokines (IL-1, TNF, neurotrophins)

Gilron I. et al. CMAJ 2006

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Evaluation of pain

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Management of cancer pain in head and neck cancer: evaluation

- Anamnesis
- Pain evaluation scales
  - Numerical
  - VAS
- Clinical examination
- Imaging

BRIEF PAIN INVENTORY

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Management of cancer pain in head and neck cancer: evaluation

- Pain evaluation instruments
  - > Neuropathic pain (DN4) questionnaire

INTERVIEW OF THE PATIENT

Question 1: Does the pain have one or more of the following characteristics?

	yes	no
1 - Burning		
2 - Painful cold		
3 - Electric Shocks		

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	yes	no
4 - Tingling		
5 - Pins and Needles		
6 - Numbness		
7 - Itching		

EXAMINATION OF THE PATIENT

Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

	yes	no
8 - Hypoesthesia to touch		
9 - Hypoesthesia to prick		

Question 4: In the painful area, can the pain be caused or increased by

	yes	no
10 - Brushing		

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Treatment

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Etiologic treatment

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Management of cancer pain in head and neck cancer: anti-cancer treatment

- **Anti-cancer treatment**
  - Surgery: lack of data of effect on pain control
  - Radiotherapy: data of beneficial effect in bone metastases
  - Chemotherapy: lack of data of effect on pain control
- **Prevent and treat side effects of treatment**
  - Treatment-induced mucositis
    - Radiotherapy: 85% (Grade 3–4: 59%)
    - Chemo-radiation: 98% (Grade 3–4: 75%)
    - Chemotherapy: 40%

Naidu MU et al. Neoplasia 2004; Elting LS et al. Int. J. Radiation Oncology Biol Phys 2007

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Management of cancer pain in head and neck cancer: treatment-induced mucositis

Chemotherapy
Radiotherapy
Initiation
production of reactive oxygen species (ROS)
DNA and non-DNA damage
Message Generation
activation of transcription factors (NF-κB)
production of pro-inflammatory cytokines (TNF-α, IL-6)
production of effector proteins
Signaling and Amplification
production of pro-inflammatory cytokines (TNF-α)
Ulceration
bacterial colonization
stimulation of cytokines release
Healing
mesenchymal cells and extracellular matrix signals
Amifostine
GM-CSF/G-CSF
TGF-β3
rHuKGF
Pentoxifylline
PTA
Sucralfate
Oral cooling
Azelastine
Vitamin E
Zinc sulfate
Benzydamine
Prostaglandin E1&E2
Corticosteroids
Chlorhexidine
Povidone-Iodine
Iseganan
Low-energy helium neon laser

Stokman MA et al. J Dent Res 2006

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Management of cancer pain in head and neck cancer: treatment-induced mucositis

Clarkson JE et al.Cochrane Database Syst Rev2007

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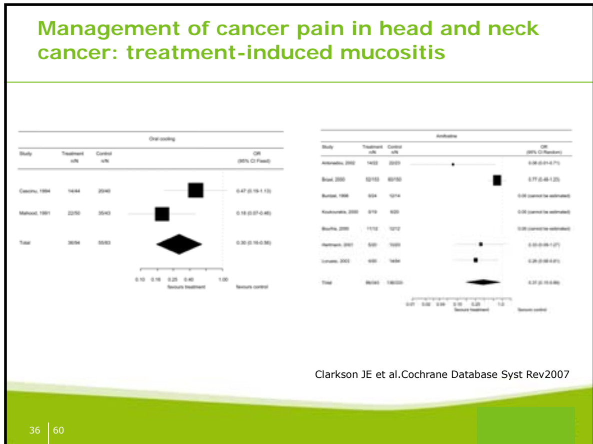
Management of cancer pain in head and neck cancer: treatment-induced mucositis



Clarkson JE et al.Cochrane Database Syst Rev2007

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Management of cancer pain in head and neck cancer: treatment-induced mucositis

- Several of the interventions have some benefit at preventing or reducing the severity of treatment-related mucositis
- The strength of the evidence is variable
- There is a need for well designed and conducted trials with sufficient numbers of participants

Clarkson JE et al.Cochrane Database Syst Rev2007

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Symptomatic treatment

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Management of cancer pain in head and neck cancer: fundamental treatment principles

- According to the pain characteristics

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Management of cancer pain in head and neck cancer: symptomatic treatment

- **Medication**
  - Analgesics
  - Adjuvant analgesics
- **Interventional techniques**
  - Physiotherapy
  - Neurolytic/neurostimulatory interventions
  - Acupuncture
  - Other
- **Psychological support**
- **Social support**
- **Spiritual support**

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Management of cancer pain in head and neck cancer: analgesics

- **By the clock**
  - Medication is given *regularly*
  - Appropriate medication for *breakthrough pain*
  - *Readily access* to medication
- **By the easiest way**
  - Medication is given by the mouth/transdermal
- **By the ladder**
  - Medication according to pain intensity
  - Medication potency sequentially escalated
- **For the individual patient**
  - Adapted to the organ function/co-morbidity/age
  - Careful and regular *monitoring* essential
  - Additional medication for *side effects*

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Management of cancer pain in head and neck cancer: analgesics

- Pain ladder by the World Health Organization

Severe pain — **Step 3:** Strong opioids (e.g. morphine), with or without non-opioids

Moderate to severe pain — **Step 2:** Mild opioids (e.g. codeine), with or without non-opioids

Mild to moderate pain — **Step 1:** Non-opioids – aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol

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Management of cancer pain in head and neck cancer: analgesics level I

- **Paracetamol**
  - > Simplest and safest analgesic
  - > Mechanism of action not fully understand
    - Central effect
    - Cox inhibitor
  - > Indication
    - Nociceptive pain
    - (Chemotherapy-induced) Neuropathy
  - > Side effects
    - Sweating
    - Hepatotoxicity

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Management of cancer pain in head and neck cancer: analgesics level I

Non-steroidal anti-inflammatory drugs

- > Diverse groups
- > Main mechanism of action = reduction PG synthesis
- > Ceiling analgesic effect
- > Opioid dose-sparing effect
- > Indications
  - Bone pain
  - Inflammatory pain
- > Side effects
  - Gastrointestinal side effects
  - Renal failure
  - Bleeding disorders

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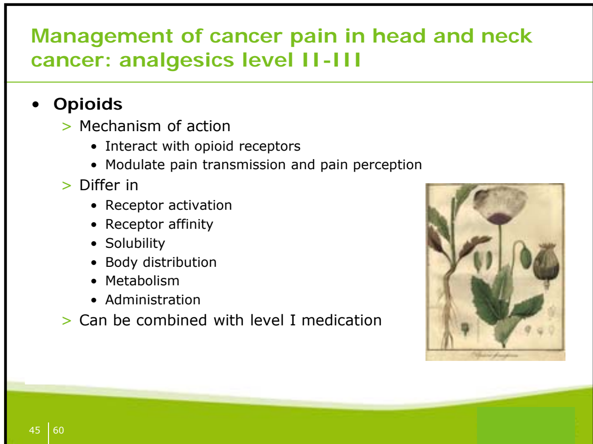
Management of cancer pain in head and neck cancer: analgesics level II-III

- **Opioids**
  - Mechanism of action
    - Interact with opioid receptors
    - Modulate pain transmission and pain perception
  - Differ in
    - Receptor activation
    - Receptor affinity
    - Solubility
    - Body distribution
    - Metabolism
    - Administration
  - Can be combined with level I medication



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Management of cancer pain in head and neck cancer: analgesics level II-III

- **Receptor activation**

Drug	Opioid receptor activation		
	μ	κ	δ
Morphine	A(1+2)	a	a
Oxycodone	A	A	
Fentanyl	A(1)	a	
Methadone	A		A
Hydromorphone	A		a
Buprenorphine	a		
Tramadol	a		

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Management of cancer pain in head and neck cancer: analgesics level II-III

- **Receptor affinity**

Drug	Affinity	
	Low	High
Morphine		+
Fentanyl		+
Methadone		+
Buprenophine	+	
Tramadol	+	

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Management of cancer pain in head and neck cancer: analgesics level II-III

- **Solubility**

Drug	Solubility Low	Intermediate	High
Morphine		+	
Oxycodone		+	
Fentanyl (L)	+		
Methadone (L)	+		
Hydromorphone (H)			+

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Management of cancer pain in head and neck cancer: analgesics level II-III

- **Metabolism**

Drug	Metabolisation	Metabolite
Codeine	CYP2D6	Morphine
Oxycodone	CYP2D6	
Morphine	UGT3B7	M3G-M6G
Hydromorphone	UGT3B7	
Fentanyl	CYP3A4	
Methadone	CYP3A4	
Tramadol	CYP2D6 (poor/rapid)	

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Management of cancer pain in head and neck cancer: analgesics level II

- **Codeine**
  - Weak opioid activity
- **Tramadol**
  - Weak opioid activity
  - Noradrenaline + Serotonin uptake
- **Tilidine**
  - Weak opioid-like activity
- **Buprenorphine**
  - No ceiling effect for analgesia
  - Ceiling effects for side-effects
  - No restriction for future opioid use
  - Additive effect when co-administered with morphine

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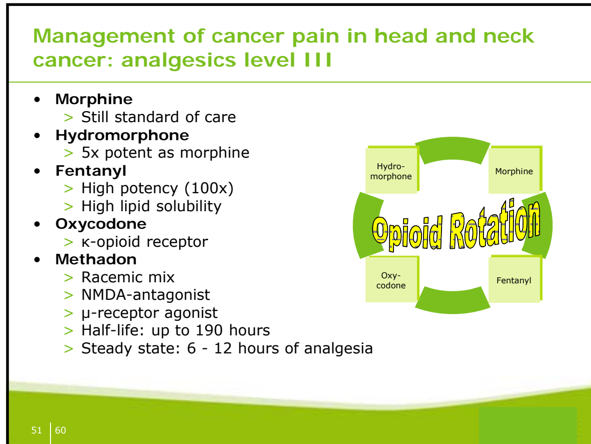
Management of cancer pain in head and neck cancer: analgesics level III

- **Morphine**
  - Still standard of care
- **Hydromorphone**
  - 5x potent as morphine
- **Fentanyl**
  - High potency (100x)
  - High lipid solubility
- **Oxycodone**
  - κ-opioid receptor
- **Methadon**
  - Racemic mix
  - NMDA-antagonist
  - μ-receptor agonist
  - Half-life: up to 190 hours
  - Steady state: 6 - 12 hours of analgesia



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Management of cancer pain in head and neck cancer: analgesics II-III

- **Side effects opioids**
  - General: physical dependence, tolerance, hyperalgesia, itching
  - Gastrointestinal: delayed gastric emptying, nausea, vomiting, constipation
  - Neurological: sedation, dizziness, confusion, respiratory depression, muscle rigidity, myoclonus
  - Immunologic and hormonal dysfunction

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Management of cancer pain in head and neck cancer: adjuvant analgesics for neuropathic pain

Medication	Dosing schedule	Side effects
Local anesthetics		
Topical lidocaine	5% patch q 12 h	Erythema, rash
Tricyclic antidepressants		
Amitriptyline	10-25 mg q 8h	Conduction disturbances, orthostatic hypotension, sedation, confusion, urinary retention, dry mouth, constipation
SNRI		
Duloxetine	60 mg q 12-24h	Sedation, ataxia, nausea, dry mouth, constipation, hyperhidrosis, anorexia
Venlafaxine	37.5 mg q 24h	Hypertension, ataxia, sedation, insomnia, nausea, hyperhidrosis, dry mouth, constipation, anxiety, anorexia

mg: milligram; q: every

Gilron I et al. CMAJ 2006

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Management of cancer pain in head and neck cancer: adjuvant analgesics for neuropathic pain

Medication	Dosing schedule	Side effects
Anticonvulsants		
Carbamazepine	100-200 mg/d	Sedation, ataxia, rash, diplopia, hyponatremia, agranulocytosis, nausea, diarrhea, hepatotoxicity, aplastic anemia
Gabapentin	300-900 mg/d	Sedation, ataxia, edema, weight gain, diplopia, nystagmus
Pregabalin	50-150 mg/d	Sedation, ataxia, edema, diplopia, weight gain, dry mouth

mg: milligram; d: day

Gilron I et al. CMAJ 2006

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Management of cancer pain in head and neck cancer: adjuvant analgesics

Medication	Indication	Oral dosing schedule
Neuroleptics		
Haloperidol	Nausea, delirium, pychosis, agitation	2-5 mg q 8h
Benzodiazepines		
Diazepam	Anxiety, muscle spasm myoclonus	2-10 mg q 6-8h
Midazolam	Invasive procedures	0.3-0.5 mg/kg (SC)
Anti-histaminics		
Diphenhydramine	Pruritus, nausea	25-50 mg q 4-6h
Psychostimulants		
Methylphenidate	Somnolence	5-15 mg q 8-12h

Kg: kilogram; mg: milligram; q: every; h: hours; SC: subcutaneously

55 | 60

Management of cancer pain in head and neck cancer: multi-combination treatment

- **Pain treatment**
  - According to pathogenesis
    - Nociceptive
      - Superficial somatic
      - Deep somatic
      - Visceral
    - Pure neuropathic
    - Mixed
  - Dominant mechanism of pain rather than intensity to determine sequence of analgesic therapy

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Management of cancer pain in head and neck cancer: mechanism-based treatment strategy

Tumor Insult Dysfunction → Pathological mechanisms → Clinical symptoms

Disease State | Measurement | Clinical Syndrome

Based on the fact that various pathophysiologic types of pain have different sensitivities to distinct classes of analgesics

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Management of cancer pain in head and neck cancer: mechanism-based treatment strategy

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Management of cancer pain in head and neck cancer: conclusion

- **Pain is prevalent in patients with head and neck cancer**
- **Pain evaluation is of crucial importance**
- **Pain treatment should be directed at**
  - Causes
  - Symptoms
  - Pathophysiological mechanism
- **Studies on pain in patients with head and neck cancer are needed**

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