XXXIII CONGRESSO NAZIONALE AIRO

AIRO2023

BOLOGNA,
27-29 OTTOBRE 2023
PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

DRUGLAB2 Terapia di supporto in corso di radio-chemioterapia radicale per tumori del distretto testa collo

Terapia antalgica

Ida D'Onofrio

UOC Radioterapia – Ospedale del Mare Napoli

Associazione Italiana
Radioterapia e Oncologia clinica

COI DISCLOSURE

No **conflict of interest** to declare

Backgroung

Chemo-radiotherapy-induced **pain** is **frequent (>80%)**

✓ interferes with **daily activities (33**% of pts) and **social activities** (**50–60%** of pts)

→greatly affect the patient's **overall quality of life**

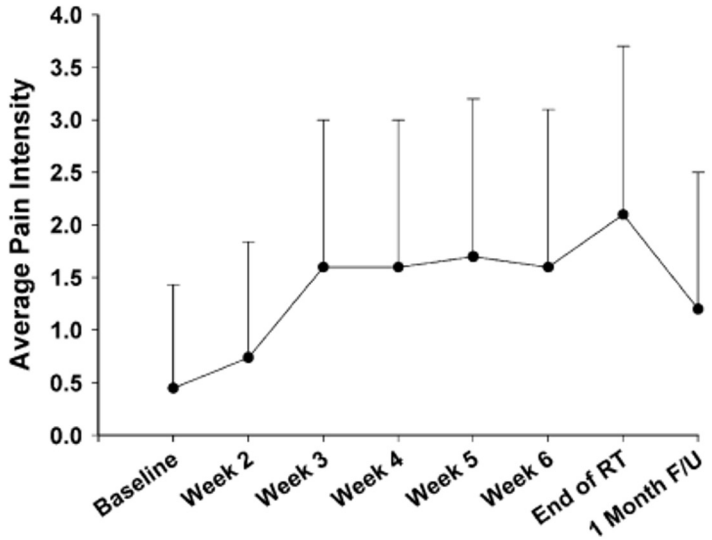
✓ increase the **costs of care** (drugs,tube feeding, hospitalization)

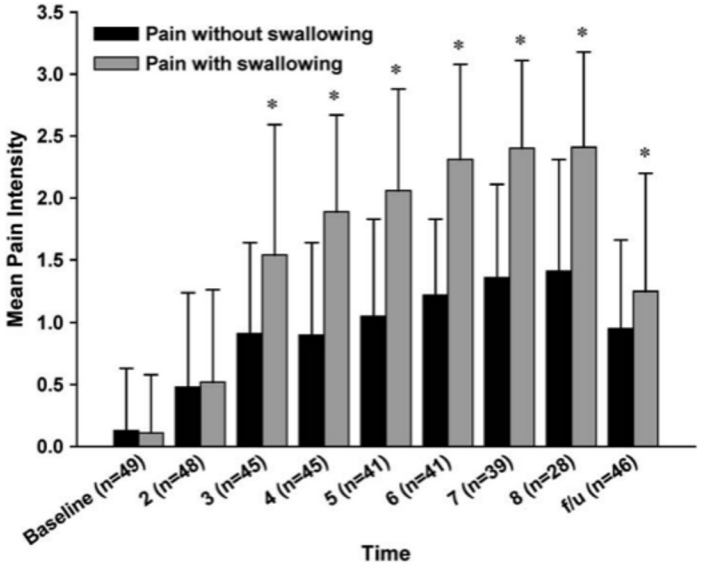
→Reduce treatment compliance with detrimental effect on Tumor Control

Sandler et al. Int J Radiation Oncol Biol Phys 2018

Escalation of pain intensity in CHT-RT HNC

Generally **start at week 3→ peak at week 5 →**persist for **2–4 weeks after** the end of radiotherapy, with a gradual remission

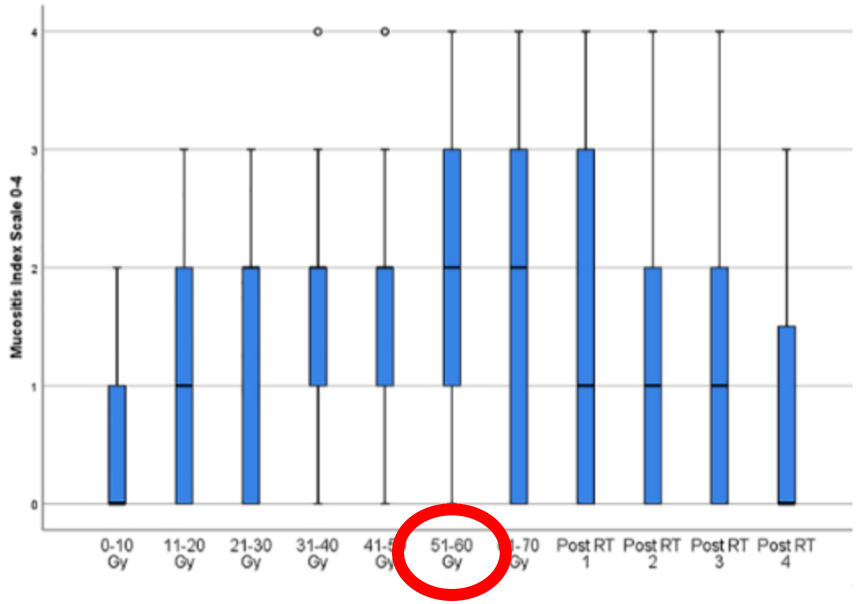




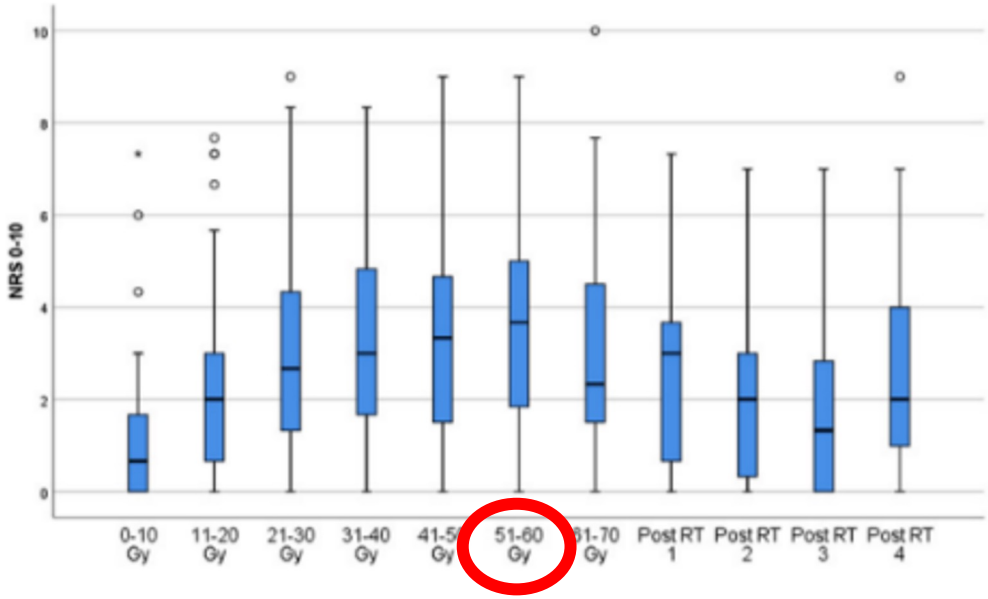
WONG 2006 Journal of Pain and Symptom Management

Positive correlation Mucositis Grade-Pain intensity

Mucositis Incidence



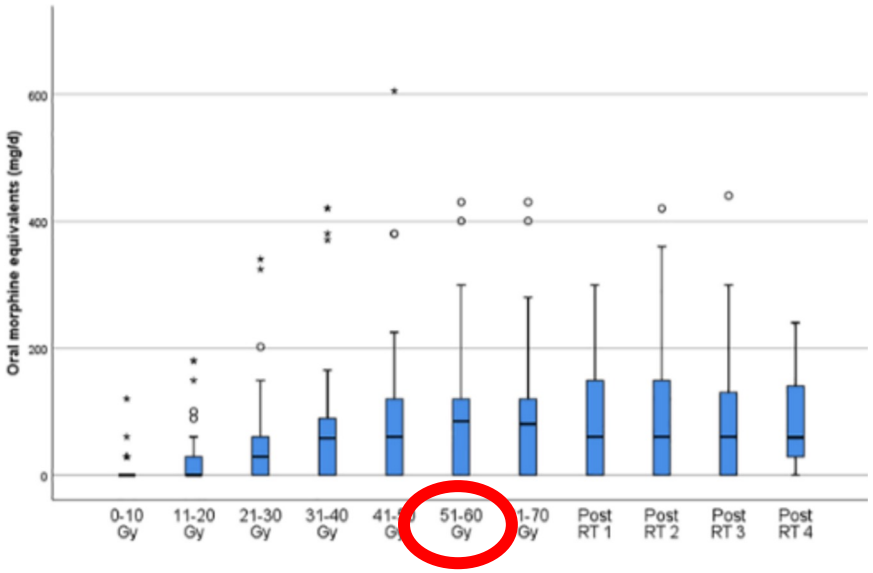
Pain intensity



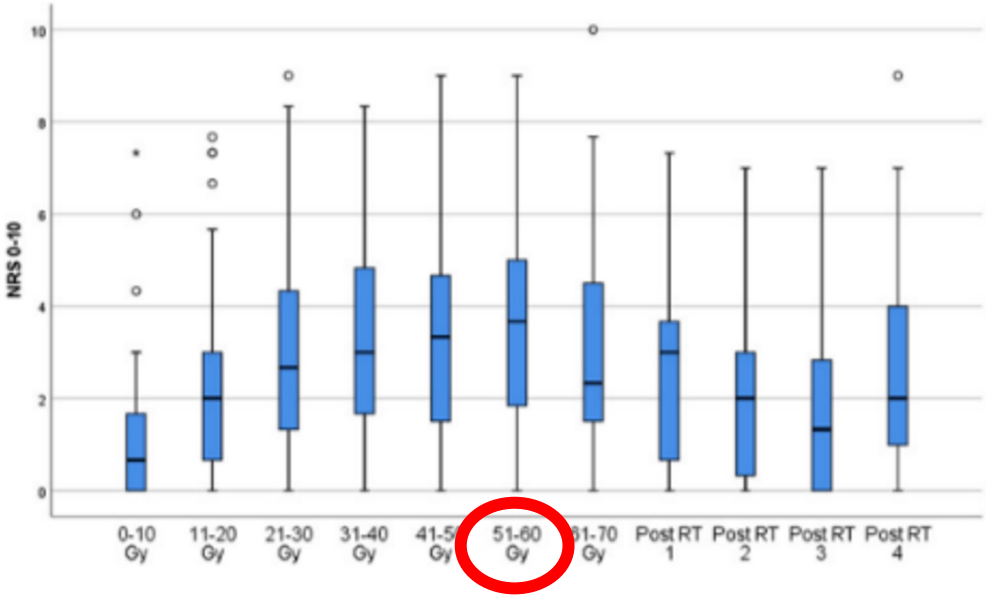
Söderlund Schaller Scand J Pain 2021

Positive correlation Mucositis Grade-Pain intensity

Opioid Dose



Pain intensity



Söderlund Schaller Scand J Pain 2021

Factors Influencing Pain Management

- **PAIN INTENSITY** NRS, VRS, VAS

- **PAIN TIMING (Frequency/duration)**
  - **Back-ground** = pain present for ≥ 12 hour/day during previous week
  - **Breakthrough** = *transitory* pain, which lasts seconds to hours and is superimposed on a background pain that is controlled (*) an opioid medication
  - **Swallow-related pain**

(*) pain rated as 'none' ore 'mild'

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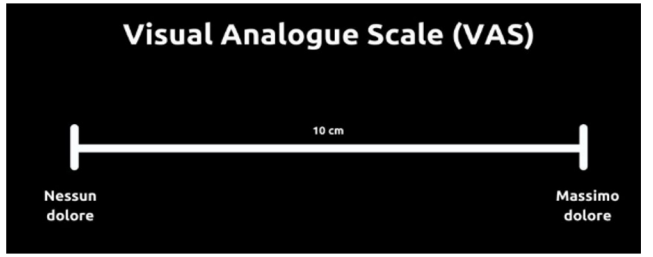
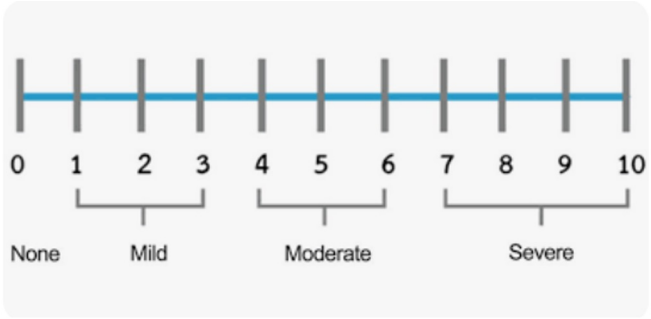
First Level: rapid assessment of pain

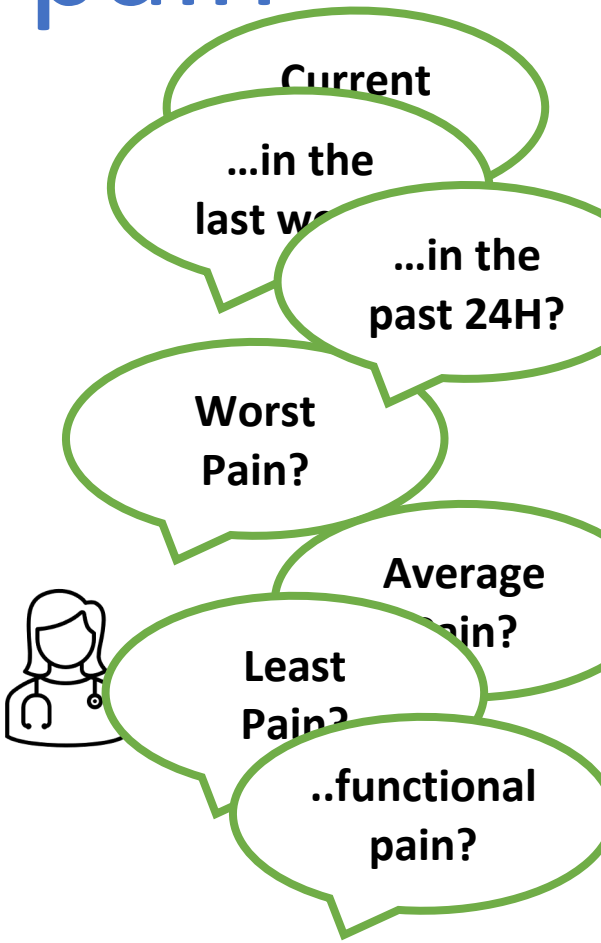
Visual Analogue Scale (VAS)



Numerical Rating Scale (NRS)



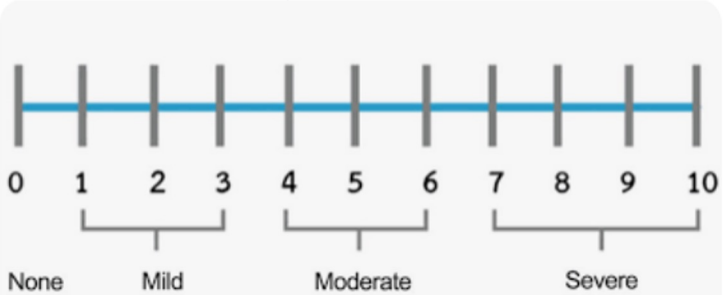
Verbal Rating Scales (VRS)



Second Level: clearer assessment of pain

BPI Pain Items	BPI Interference Items
Worst pain in last 24 hours	General activity
Least pain in last 24 hours	Mood
Pain on average	Walking ability
Pain right now	Normal work (including housework)
	Relations with other people
	Sleep
	Enjoyment of life

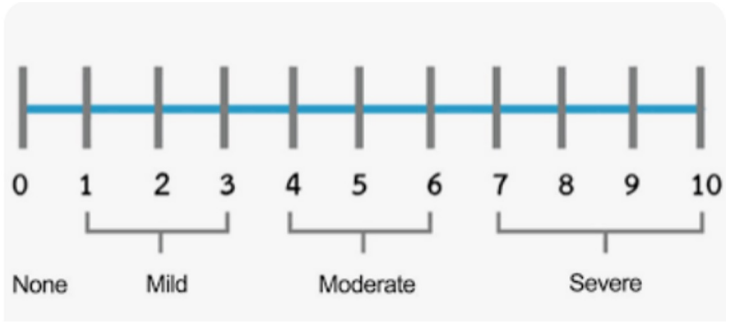
The **Brief Pain Inventory - Short Form (BPI-SF)**
9 item self-administered questionnaire
severity impact on **daily functioning**



No interference

Complete interference

Second Level: clearer assessment of pain



Short Form McGill Pain Questionnaire (MPQ-SF)

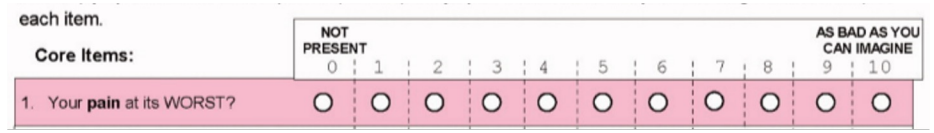
	None	Mild	Moderate	Severe
Throbbing				
Shooting				
Stabbing				
Cramping				
Gnawing				
Hot-Burning				
Aching				
Heavy				
Tender				
Splitting				
Tiring-Exhausting				
Sickening				
Fearful				
Punishing-Cruel				

Sensory Dimension

Affective D.

Third Level : multidimensional tools

MDASI Symptom Items	MDASI Interference Items
Pain Fatigue Nausea Disturbed sleep Distress/feeling upset Shortness of breath Difficulty remembering Lack of appetite Drowsiness Dry mouth Sadness Vomiting Numbness/tingling	Walking Activity Working (including housework) Relations with other people Enjoyment of life Mood

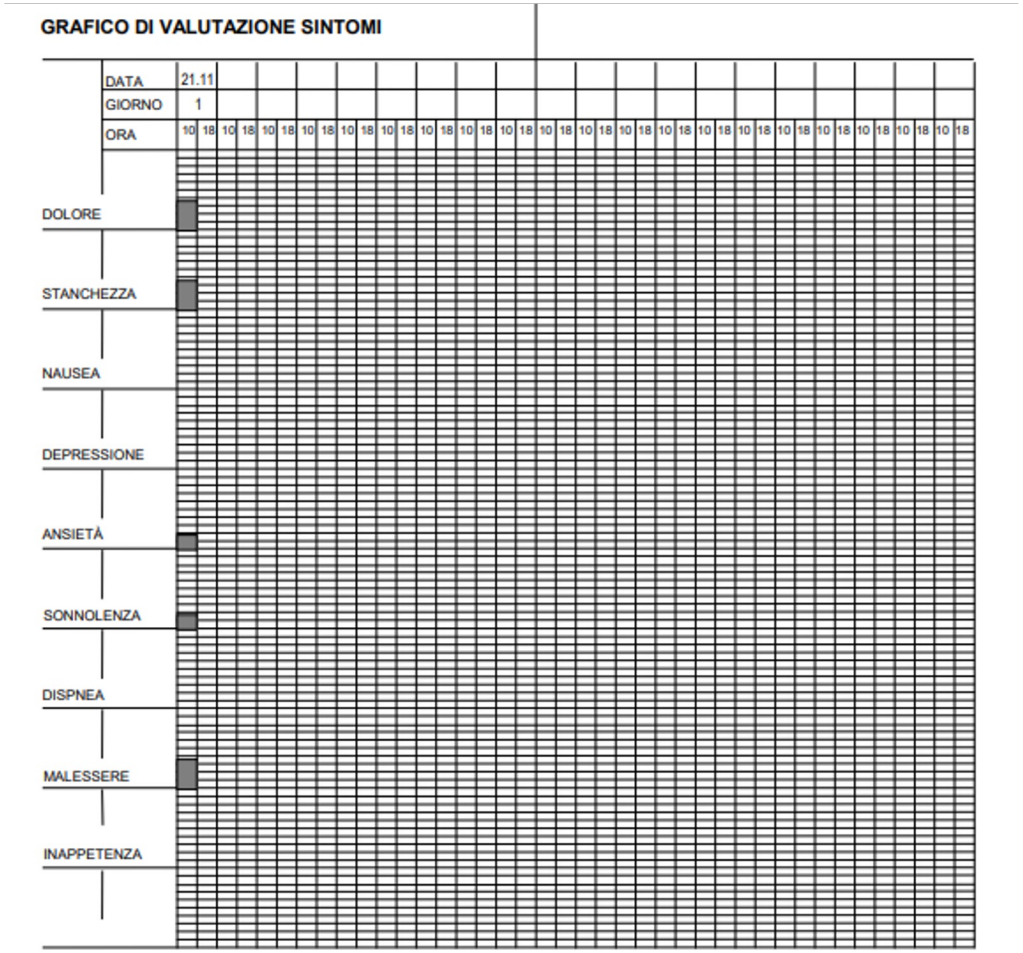


MDASI

MD Anderson Symptom Inventory: an instrument for measuring *multiple cancer-related symptoms*

Third Level : multidimensional tools ESAS

non ho dolore	il peggior dolore possibile
non sono stanco	la peggior stanchezza possibile
non ho nausea	la peggior nausea possibile
non sono depresso	la peggior depressione possibile
non sono ansioso	la peggior ansia possibile
non sono sonnolente	la peggior sonnolenza possibile
non mi manca il respiro	la peggior mancanza di respiro possibile
mi sento bene	nessun senso di benessere
ho appetito	nessun appetito



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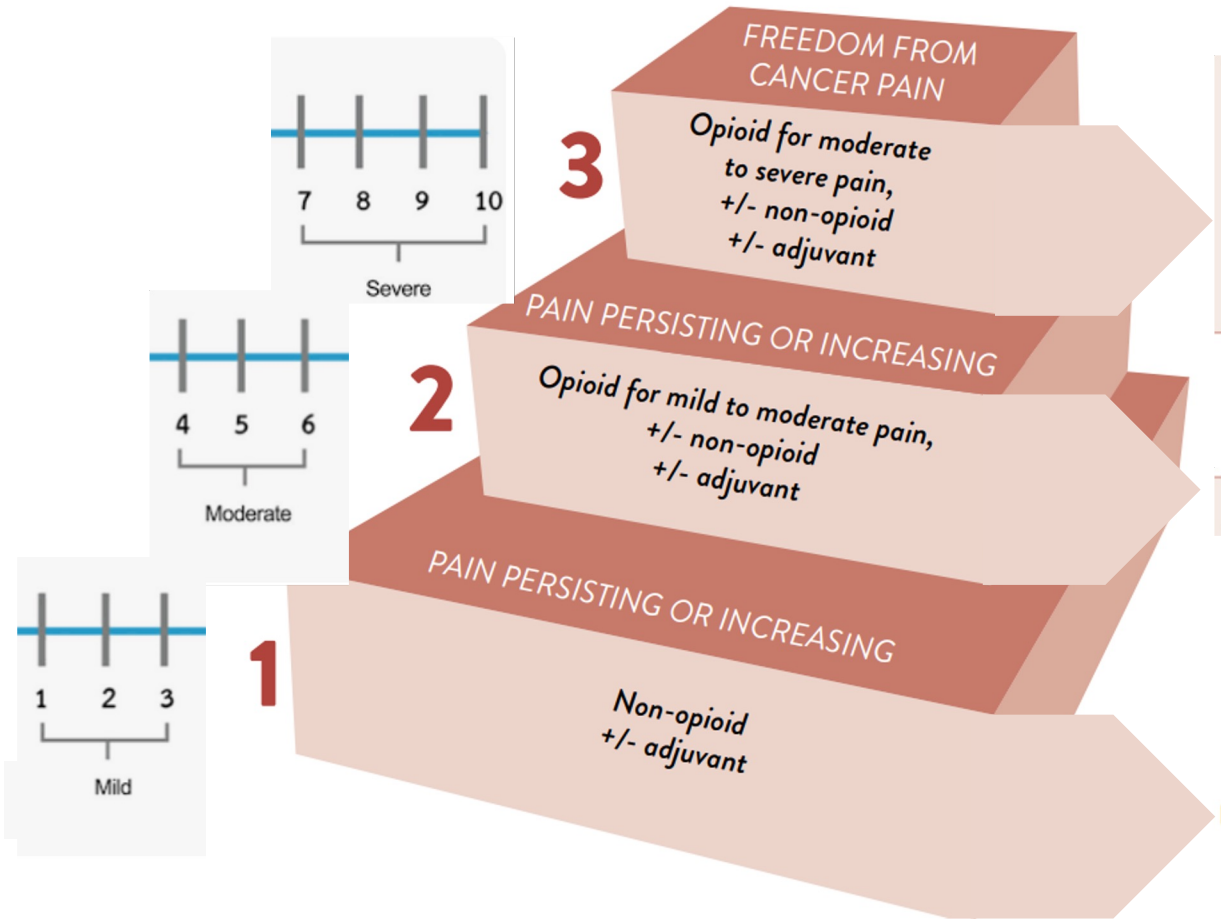
- **PAIN INTENSITY** NRS, VRS, VAS

- **PAIN TIMING (Frequency/duration)**
  - **Back-ground** = pain present for ≥ 12 hour/day — Fixed Dose (Long-acting opioid)
  - **Breakthrough** = *transitory* pain — Rescue Dose (Short-acting opioid)
  - **Predictable pain (Swallow-related,…)**

- **PATIENT CHARATERISTIC** (age, organ dysfunctions, compliance)

- **PAIN ETIOLOGY**



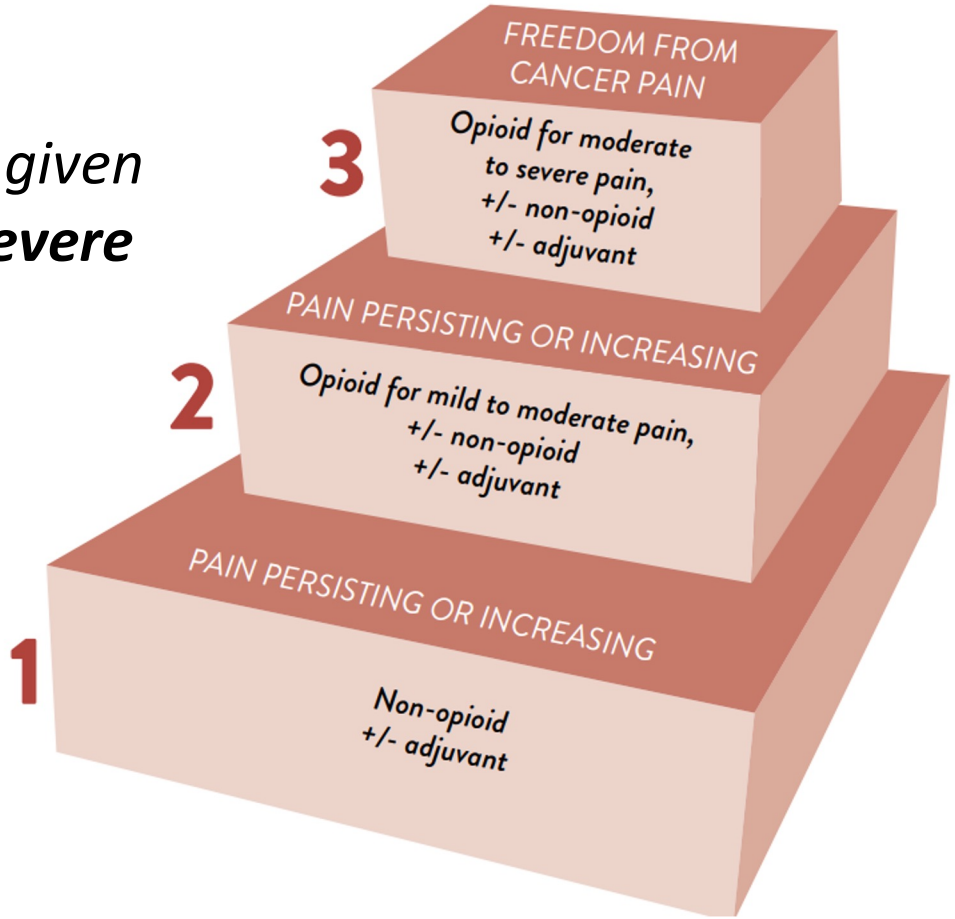
Strong opioids	Morphine oral tablet and liquid and injectable	
	Hydromorphone oral tablets and liquid and injectable	
	Oxycodone oral tablets and liquid	
	Fentanyl injectable, transdermal patch, transmucosal lozenge	
	Methadone oral tablet, liquid, injectable	
Weak opioids	Codeine oral tablets and liquid and injectable	
Non-opioids	Paracetamol	Paracetamol oral tablets and liquid. Rectal suppositories, injectable
	NSAIDs	Ibuprofen oral tablets and liquid
		Ketorolac oral tablets and injectable
		Acetylsalicylic acid oral tablets and rectal suppositories

Adjuvants	Steroids
	Antidepressants
	Anticonvulsants
	Bisphosphonates

WHO GUIDELINES 2018

WHO PAIN Ladder

Mild analgesics (paracetamol, NSAIDs) should ***not*** *be given* ***alone*** *for initiation of management of* ***moderate or severe pain.*** *Patients may be started on a combination of* ***paracetamol and/or NSAIDs with an opioid…***



WHO GUIDELINES 2018

Key Considerations in Opioid Therapy

1. Which opioid should be prescribed and at what dosage?
2. When/How to increase the dosage?
3. How to perform opioid equianalgesia?
4. How to limit the therapy's side effects?
5. How to discontinue the therapy?

Which opioid should be prescribed and at what dosage?

Strong Opioids

- Morphine
- Oxycodone
- Fentanyl
- Hydromorphone
- Methadone
- Buprenorphine

Different formulations and routes of administration

Oral Route:
- Tablets
- Capsules
- Oral solution

Injectable Route:
- Intramuscular injections
- Subcutaneous injections
- Intravenous injections

Transdermal Route:
- Skin patches (e.g., fentanyl patches)

Which opioid should be prescribed and at what dosage?

- **Fixed and rescue medication** with an appropriate dose and schedule for each.
- **Lowest effective dose** for the shortest duration to limit AE-opioid&dependence
- Favoring **less invasive administration routes** (Oral-Transdermal administration)
- No consistent advantage has been attributed to a specific choice of opioid= **Individualized choice** ba s.

ESMO

Recommendation:

- Fentanyl and buprenorphine (via the t.d. or i.v. route) are the safest opioids in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate < 30 mL/min)

Which opioid should be prescribed and at what dosage?

TYPICAL STARTING DOSES

- Morfina Orale 5 mg per os ogni 4H
- Fentanyl 12-25 mcg cerotto transdermico ogni 72H
- Ossicodone + Paracetamolo = 5-10 mg ogni 8H
- Ossicodone = 5-10 mg ogni 12 H
- ….

MEDICINE	TYPICAL STARTING DOSE
Paracematol	500–1000 mg orally every 6 hours
Ibuprofen	400–800 mg orally every 8 hours
Morphine	5 mg orally every 4 hours 2 mg IV/SC every 4 hours
Fentanyl	12–25 mcg/hr transdermal patch every 72 hours

WHO Guideline 2018

When/How to increase the dosage?

- Early and **continuous follow-up contacts according to the patient's symptoms**

RESCUE DOSE>4 →INCREASE FIXES DOSE

Rescue < 3 - **BTcP NRS >4**→INCREASE ROO

- The interval between dose escalations should be long enough to allow a **steady state** to be approached (and to avoid side effects):
  - **2–3 days** for the **modified-release oral formulations**
  - **3–6 days** for the **transdermal patch**

- increase in the scheduled dose by 30–100%, or by an amount equal to the *average daily consumption of supplemental doses for BCTP*

K Portenoy, Lancet 2011

How to perform opioid equianalgesia?

TABELLA DI EQUIANALGESIA (dosaggi in mg/die)													
OSSICODONE CR	10	20	30	40	50	60	70	80	90	100	120	140	160
MORFINA (OS)	20	40	60	80	100	120	140	160	180	200	240	280	320
MORFINA (Sottocute)	10	20	30	40	50	60	70	80	90	100	120	140	160
MORFINA (E.V.)	10	20	30	40	50	60	70	80	90	100	120	140	160
MORFINA (Epidurale)	2	4	6	8	10	12	14	16	18	20	24	28	32
MORFINA (Intratecale)	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2	2.4	2.8	3.2
FENTANYL (TTS)			25			50			75		100		125
BUPRENORFINA (TTS)			35	52.5		70			105		140		
IDROMORFONE	4	8	12	16	20	24	28	32	36	40	48	56	64
TRAMADOLO SR	100	200	300	400	500	600							
CODEINA (+Paracetamolo)	120	240											

ESMO

Recommendation:

- A different opioid should be considered in the absence of adequate analgesia (despite opioid dose escalation) or in the presence of unacceptable opioid side effects [III, C].

How to limit the therapy's side effects?

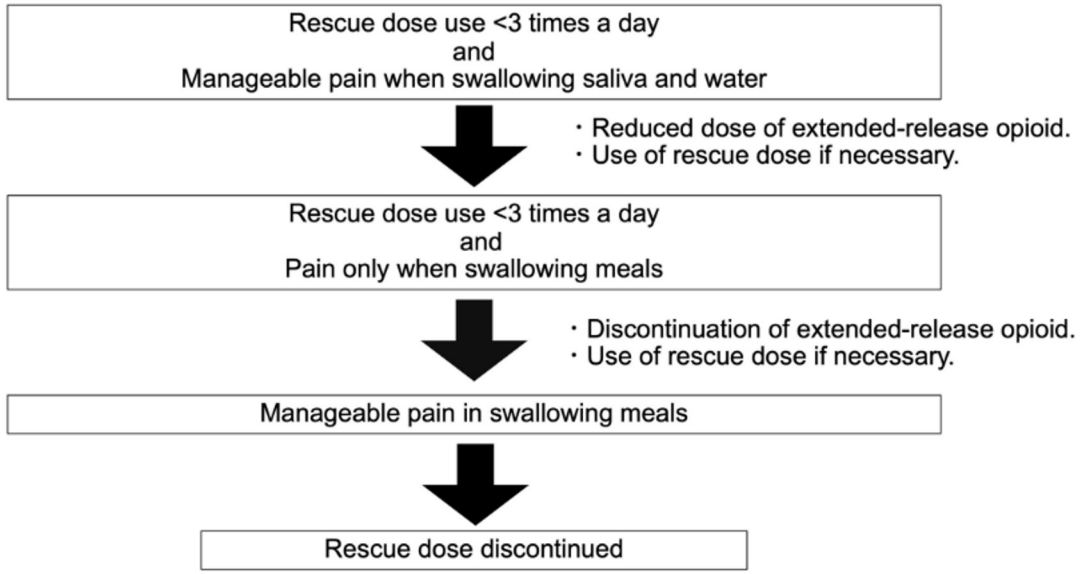
Symptomatic drugs for side effects:

- CONSTIPATION = Increased hydration and laxatives

- NAUSEA/VOMITING = Use of antiemetics (Metoclopramide, Haloperidol, Scopolamine, Ondansetron)

- RESPIRATORY DEPRESSION – CLOUDED STATE= Opioid Agonist Drugs (Naloxone)"

How to discontinue the therapy?
Descalation Program (PLODE)



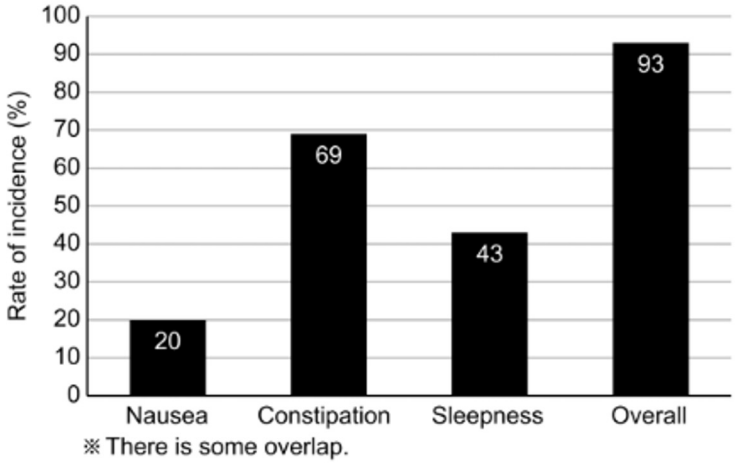


FIGURE 2
Opioid-induced side effects (All Grade) observed at the initiation of PLODE program.

Ai Horinouchi Frontiers in Oncology 2023

Breakthroug Cancer Pain (BTcP)

Most common definition:

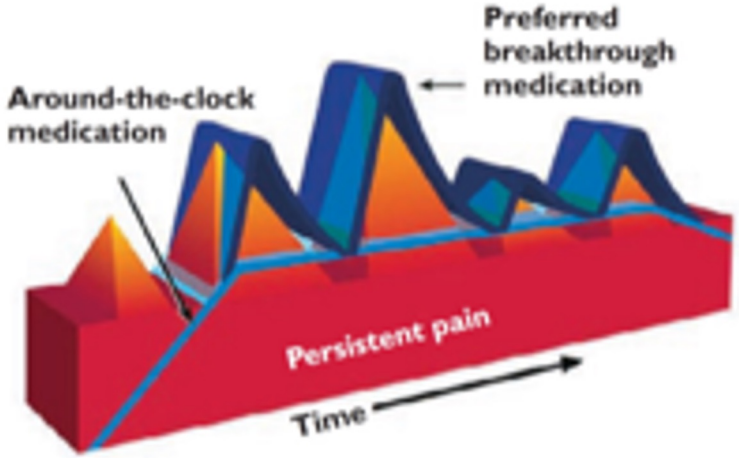
Paroxysmal, intense, and transitory flare of pain, lasting seconds to hours. It occurs in the context of **background pain controlled** by opioid therapy in cancer patients

Characteristics and triggers:

- **Incident Pain**: This type occurs predictably and is associated with specific activities or events, such swallowing.
- **Spontaneous Pain**: no clear trigger and can occur unexpectedly at any time.
- **End-of-Dose Failure**: This type happens when the prescribed around-the-clock opioid medication loses its effectiveness before the next scheduled dose is due

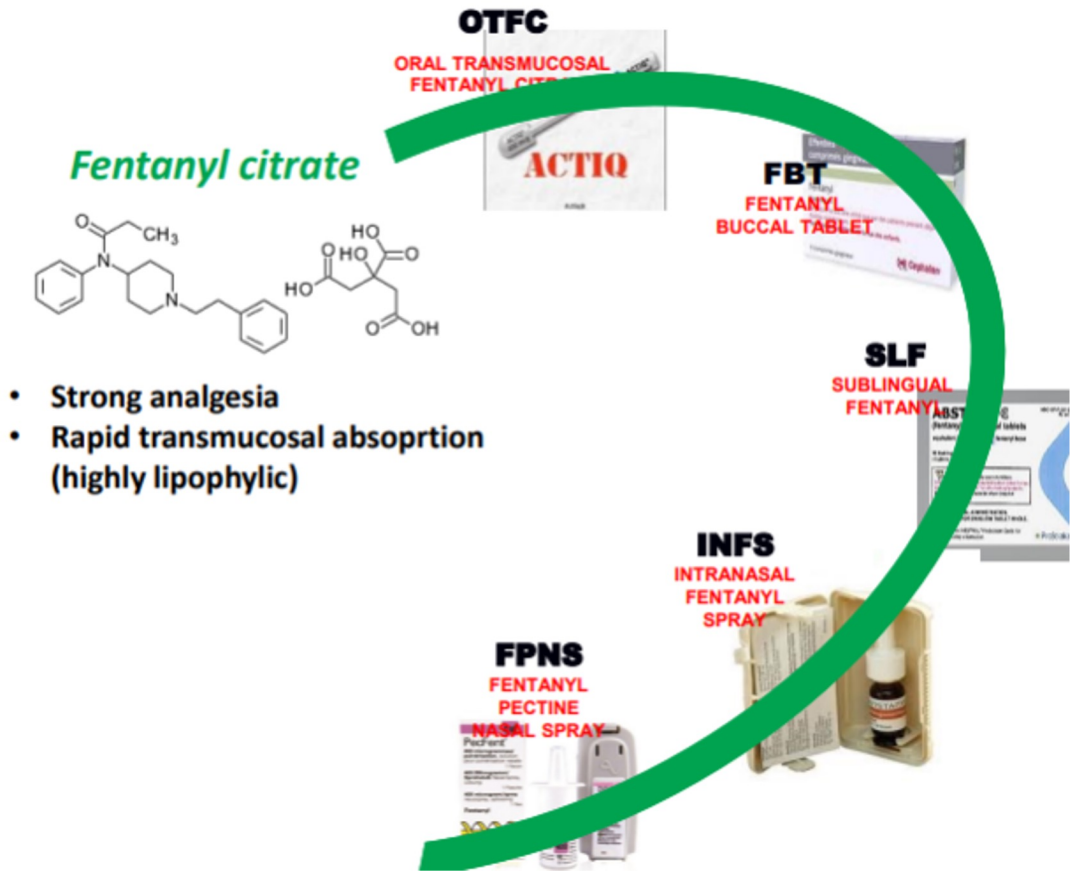
Ideal BTcP Medication

- Rapid onset opioid (ROO)
- Short duration of effect
- Minimal side effects
- Non invasive- easy to use

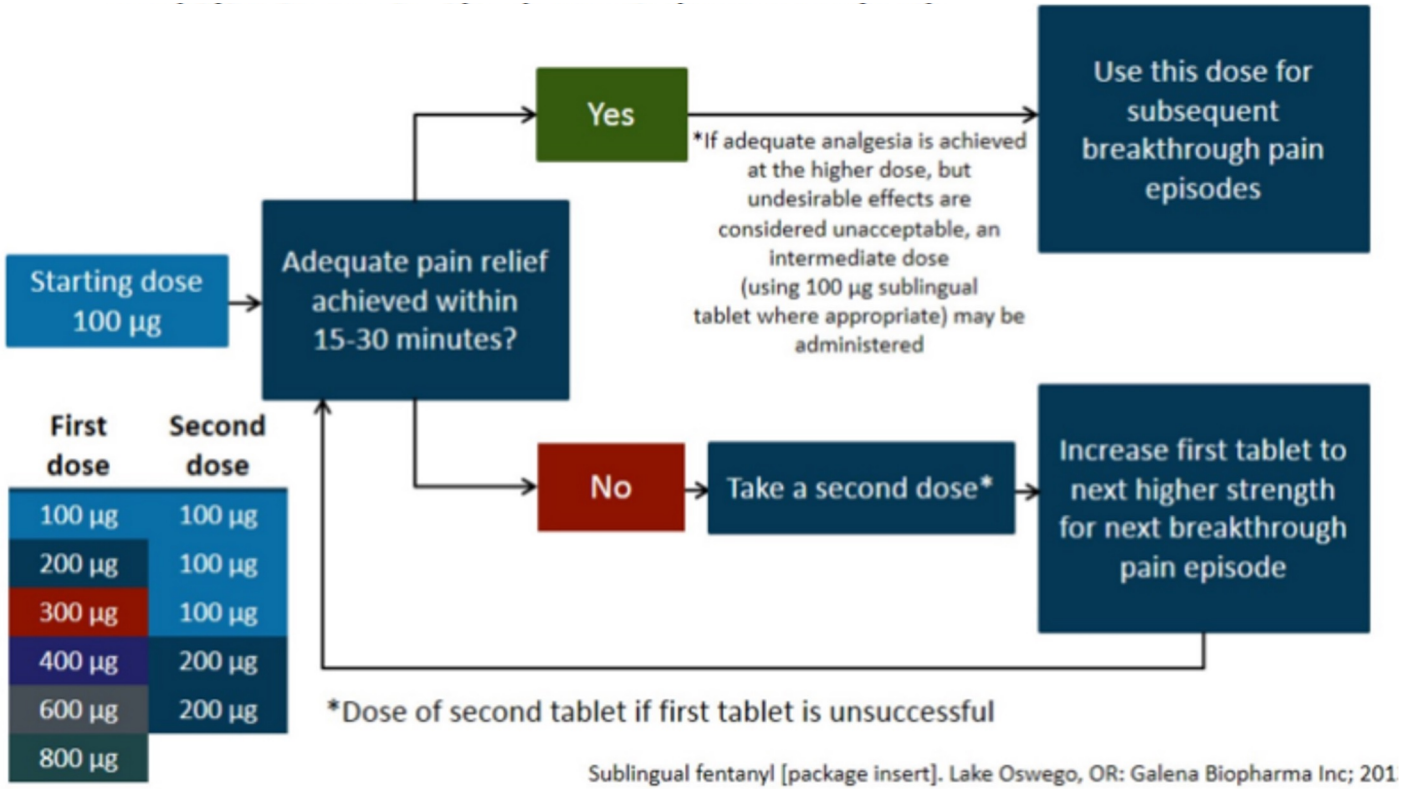


Approved only for cancer patients considered to be *opioid tolerant.*
Background opioid doses = at least 60 mg of oral morphine, 25 µg/H transdermal fentanyl, 30 mg of oral oxycodone daily

Ideal BTcP Medication= Rapid Onset Opioids



ROO titration



Sublingual fentanyl [package insert]. Lake Oswego, OR: Galena Biopharma Inc; 201

Iatrogenic predictable pain: Painful swallowing due to mucositis

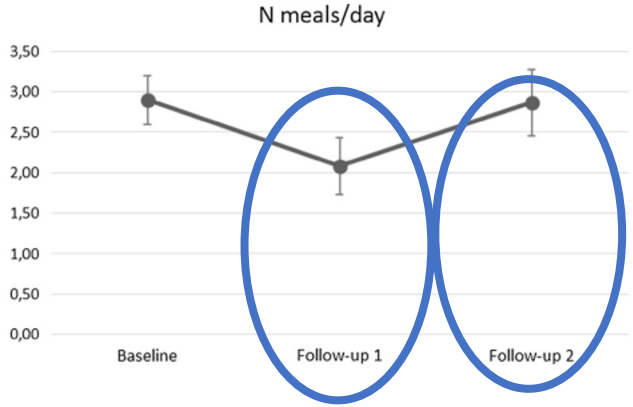
FPNS (Fentanyl pectin Nasal Spray) treatment started at the first follow-up after the appearance of BTP due to painful mucositis (approximately after 3 weeks)

FPNS 30 min before main meals (precipitating factors)

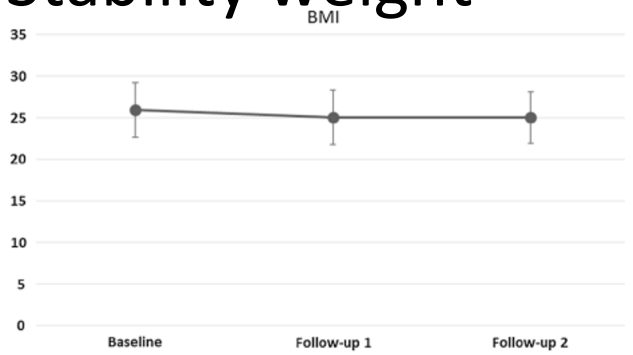
- acceptable safety activity profile.
- FPNS was also effective in reducing the mucositis sequelae
- allowing the completion

R. Mazzola et al Clin Transl Oncol (2017)

Improvement in feeding



Stability weight



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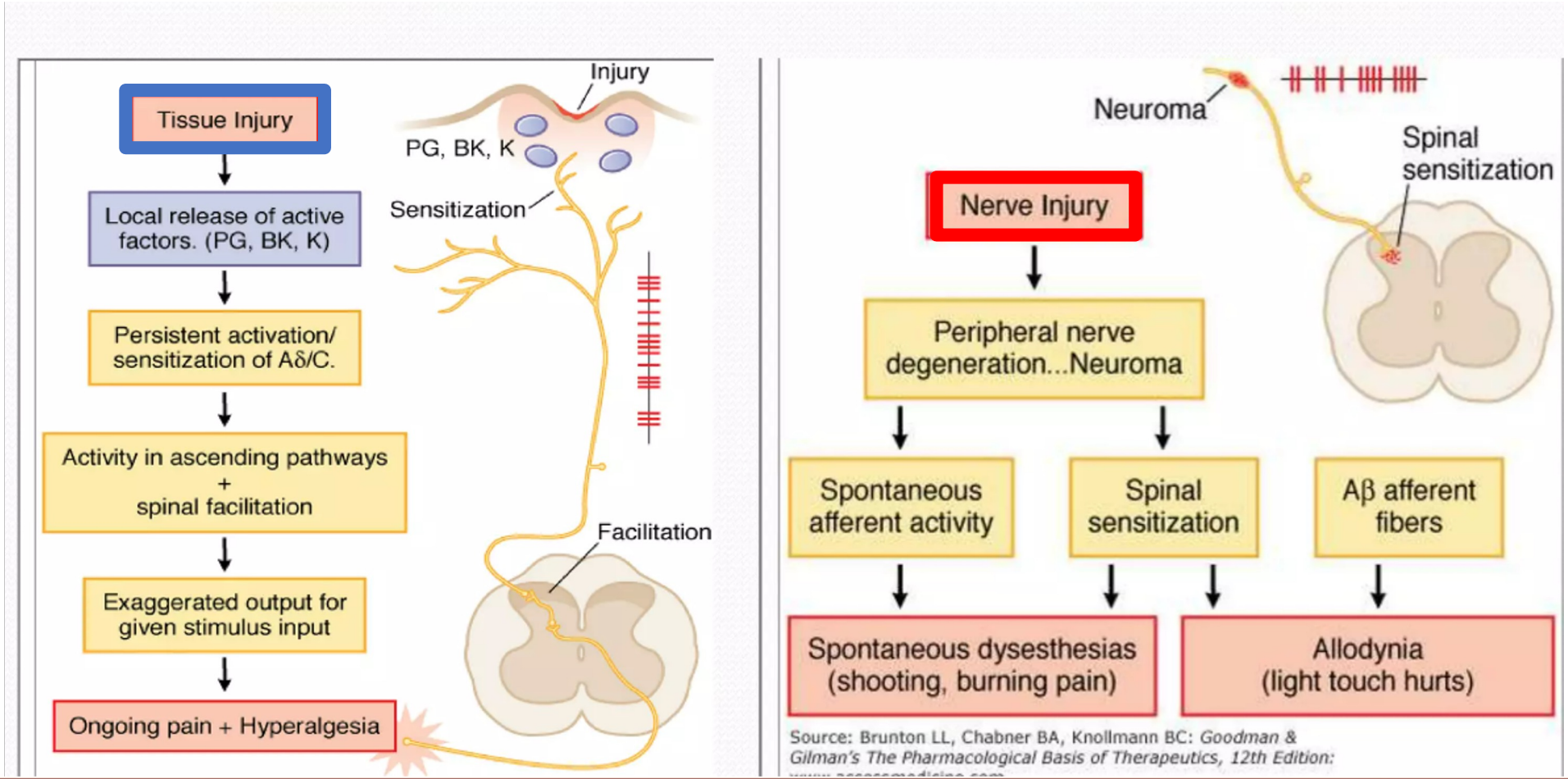
Nociceptive pain vs Neuropatic pain



Neuropatic Pain Assessment

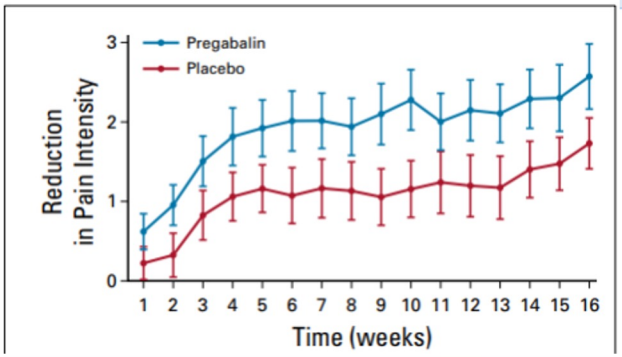
- **Clinical** history, symptoms, physical signs
- **Pain locations** in accordance with radiated innervated areas
- Neuropathic Pain **Questionnaires** [LANSS, NPQ and ID Pain] by trained specialist

Pain quality descriptors attributed to head and neck pain site	
NEUROPATIC	**NOCICEPTIVE**
Aching (25%)	Hurting (27%)
Burning (33%)	Dull (16%)
Stabbing (10%) Lancinante	Throbbling (29%) martellante
Flickering (9%) Tremolio	Sore (40%) dolente
Hot (8%)	Tender (40%) sensibile

J B Epstein, Head & Neck Oncology 2009

Neuropatic Pain – RCT trials

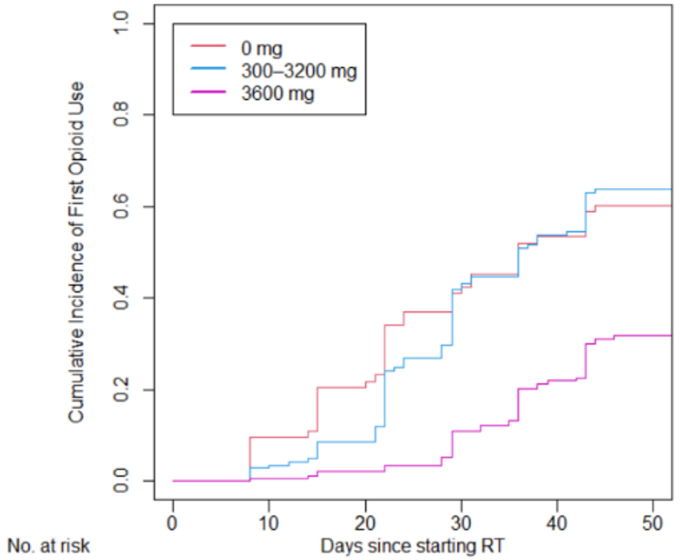
Author	Drug/Comparison	Sample Size (Drug/Comparison)	Indication	Drug Dose	Outcome	Adverse Effects	Timing	Outcome
Herman et al., 2020 [26]	Gabapentin (2700 mg/d) + hydrocodone and/or paracetamol progressing to fentanyl/Gabapentin (900 mg/d) + methadone	60 (31/29)	Pain during therapy	2700 mg/d (p.o.)	No significant difference $p = 0.87$	3% of pts discontinued treatment due to intolerance to gabapentin	Day 1	More patients did **not** require **opioid** administration
Smith et al., 2020 [27]	Gabapentin + NSAIDs and opioids/NSAIDs and opioids	79 (41/38)	Pain during therapy	2700 mg/d (max, p.o.)	Pain reduction $p = 0.004$	Fatigue and sedation	Day 1	**Lower pain** levels
Kataoka et al., 2016 [28]	Gabapentin + paracetamol + opioids/Paracetamol + opioids	22 (11/11)	Pain during therapy	900 mg/d (p.o.)	No significant difference $p = 0.552$	Somnolence, allergic skin reaction	Day 1	No significan difference n VAS maximum median score
Jiang et al., 2018 [29]	Pregabalin/Placebo	128 (64/64)	Neuropathic pain	600 mg/d (max, p.o.)	Pain reduction $p = 0.003$	Dizziness, somnolence, headache, diarrhea, peripheral edema	After RT	Reduction of the mean Brief Pain Inventory interference total score



HERMAN et al 2020
Smith et al 2020
Kataoka et al 2016
Jiang et al 2018

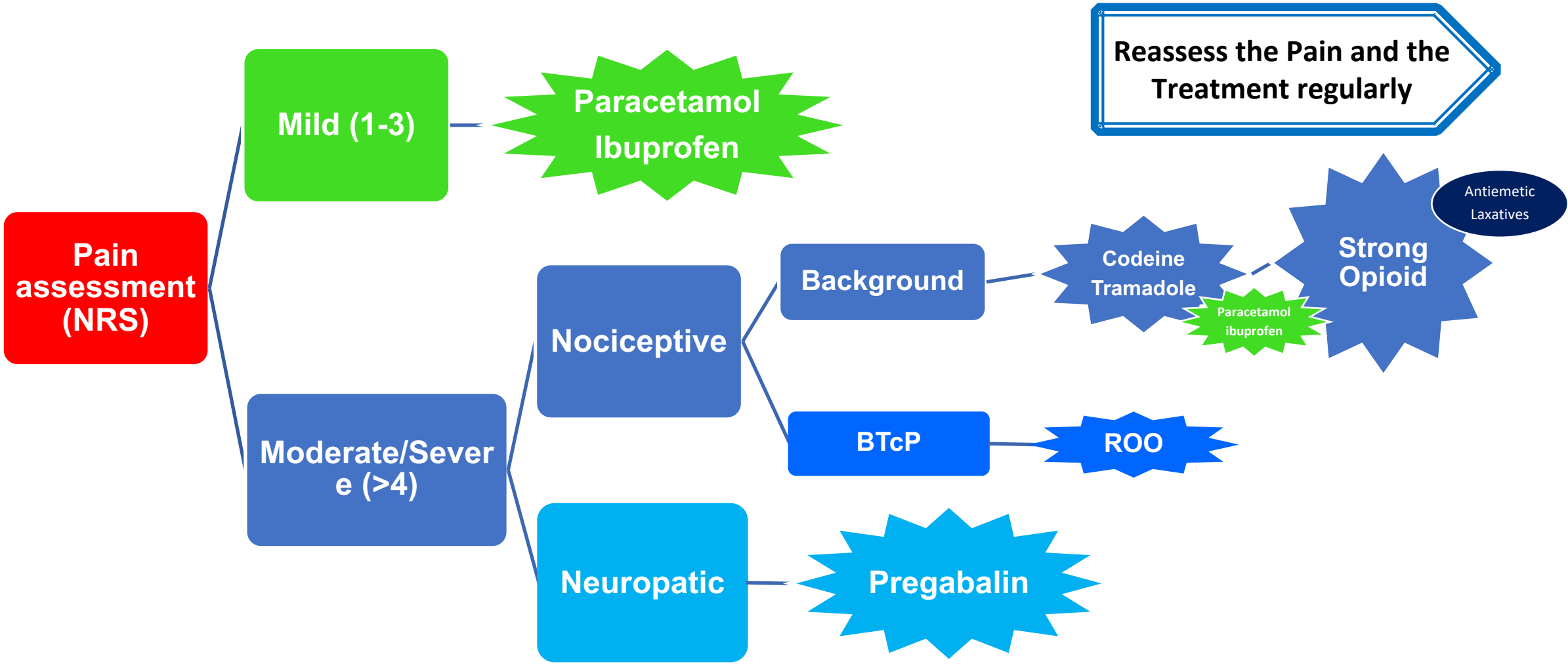
Prophylactic High-Dose Gabapentin

480 pts
HNC RT between 2015 and 2022



- Large observational cohort
- Prophylactic use of **3600 mg gabapentin**
  - Well tolerated
  - halved overall opioid use
  - delayed the time to first opioid use

ML QIU Cancers 2023


Reassess the Pain and the Treatment regularly
Pain assessment (NRS)
Mild (1-3)
Paracetamol
Ibuprofen
Moderate/Severe (>4)
Nociceptive
Background
Codeine
Tramadole
Paracetamol
ibuprofen
Strong Opioid
Antiemetic
Laxatives
BTcP
ROO
Neuropatic
Pregabalin

Severe RT-related pain in HNCp is not a fatality…

- **Accurate assessment** of pain intensity, timing, and characteristics is essential..
- **Early Analgesic Treatment**: Early intervention can mitigate severe pain and reduce the risk of chronic pain development.
- **Personalized pain management** enhances patients' quality of life