SACRO CUORE DON CALABRIA

IRCCS
Istituto di Ricovero e Cura a Carattere Scientifico
Sacro Cuore - Don Calabria
Ospedale Classificato e Presidio Ospedaliero Accreditato - Regione Veneto

SACRO CUORE DON CALABRIA
I R C C S
Cancer Care Center

Incontri di aggiornamento del Dipartimento Oncologico

Responsabile Scientifico:
DOTT.SSA STEFANIA GORI

26 ottobre - 9 novembre
23 novembre - 30 novembre
2022

SEDE:
"Centro Formazione e Solidarietà"
Sala Convegni "Fr. Francesco Perez"
IRCCS Sacro Cuore - Don Calabria
Via Don Angelo Sempreboni, 5 - 37024 Negrar di Valpolicella (VR)

Mercoledì 30 novembre
- Sala convegni "Fr. Francesco Perez" -

La gestione del dolore nel paziente oncologico: dalla fisiopatologia al trattamento

Breakthrough pain: quale terapia medica?

Alessandro Inno

SACRO CUORE DON CALABRIA
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Oncologia Medica
IRCCS Ospedale Sacro Cuore Don Calabria
Negrar di Valpolicella (VR)

Breakthrough cancer Pain (BTcP)

- **What is it?**

  A type of pain defined by its **timing** and its **severity**

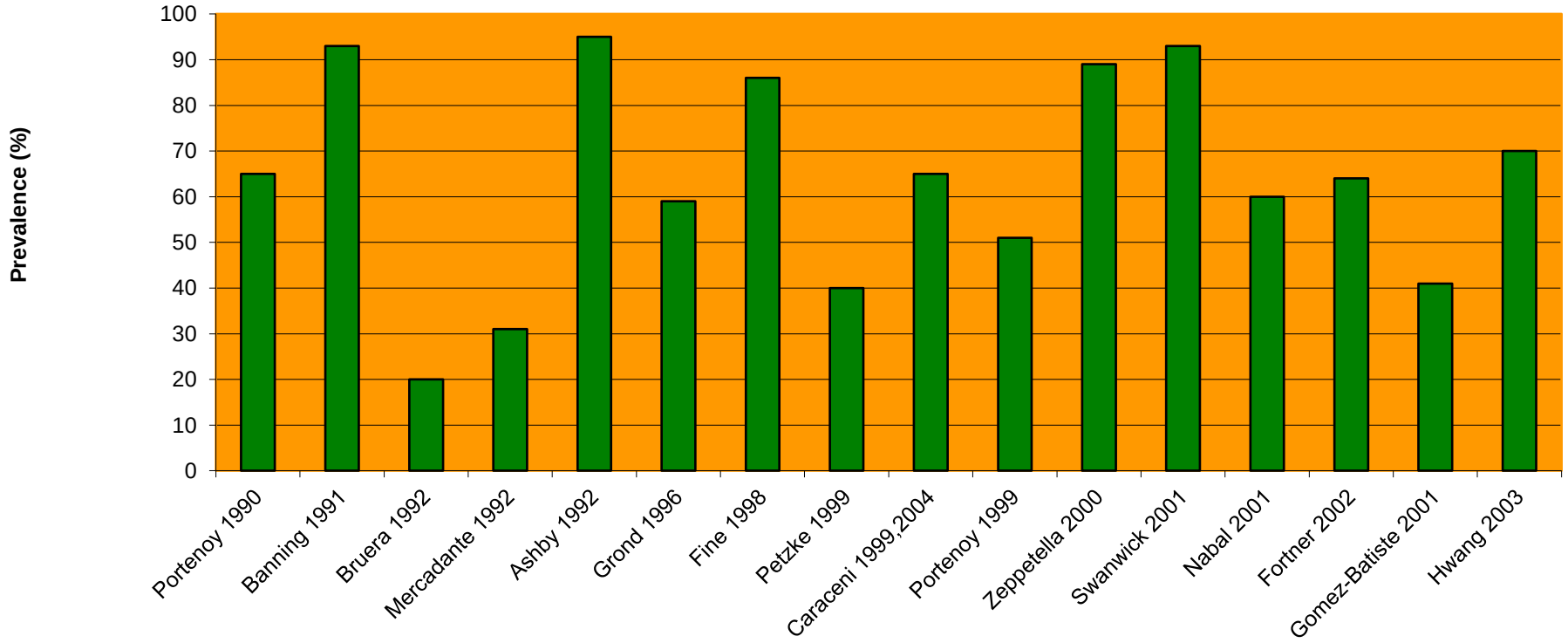
- **Most common definition:**

  A **transitory**, **severe** or **excruciating** pain, which **lasts seconds to hours** and is **superimposed on a background pain** that is controlled using an opioid medication

- **Synonims:**
  - Episodic pain
  - Incident pain
  - Flare-up pain
  - In Italian: **dolore episodico intenso** (DEI)

Portenoy RK, Hagen NA. Pain 1990; 41:273-81.

Prevalence of BTcP



Median Prevalence: 65%

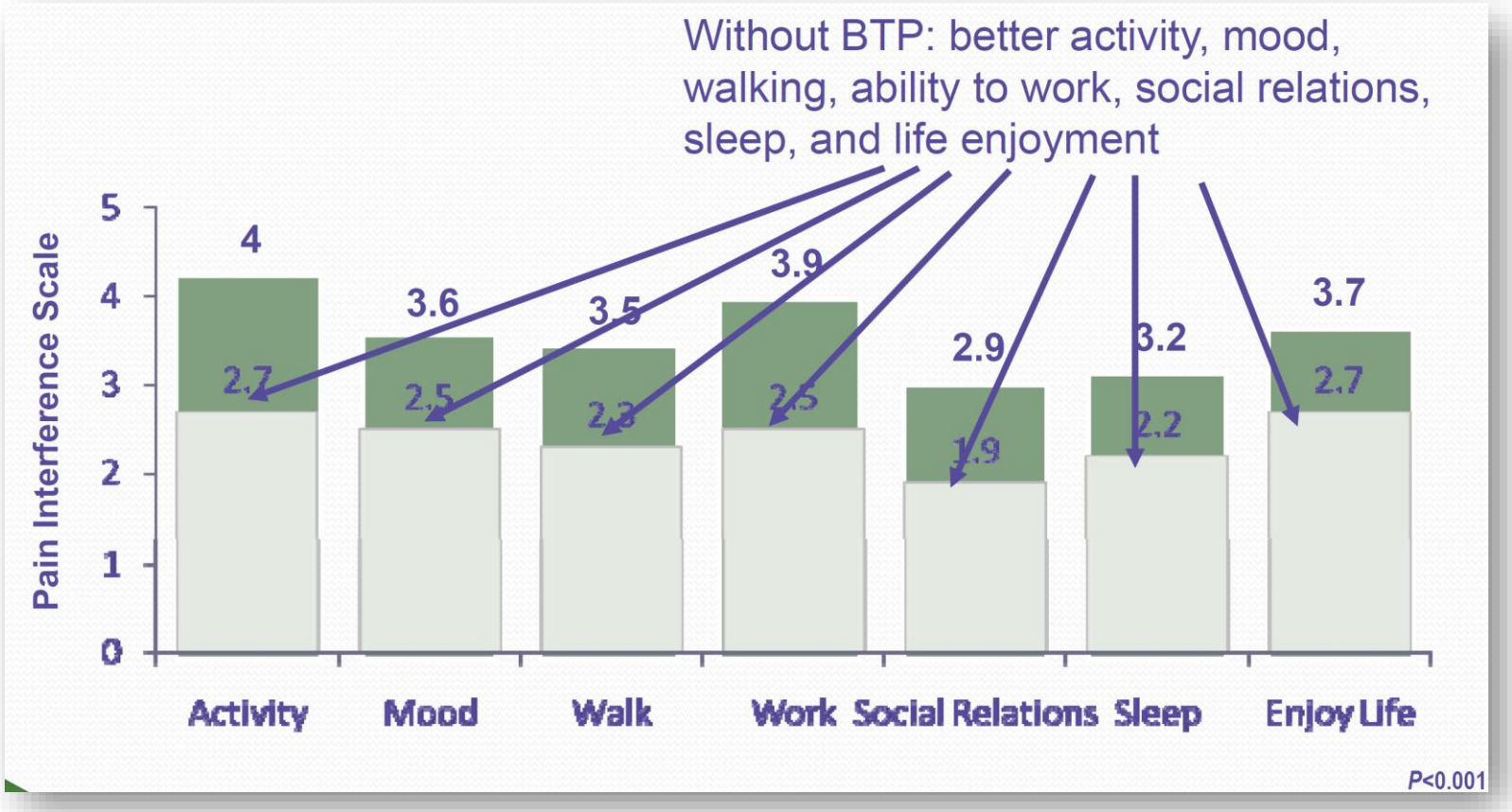
High variability: from 20% **up to 95%**

Zeppetella G et al. Expert Opin Pharmacother 2003; 4(4):493-502.

Impact of BTcP on QoL

Compared with patients without breakthrough pain, patients with breakthrough pain have:

- More severe pain
- Reduced response to opioid therapy
- More problems functioning
- More psychological distress
- Higher cost of care



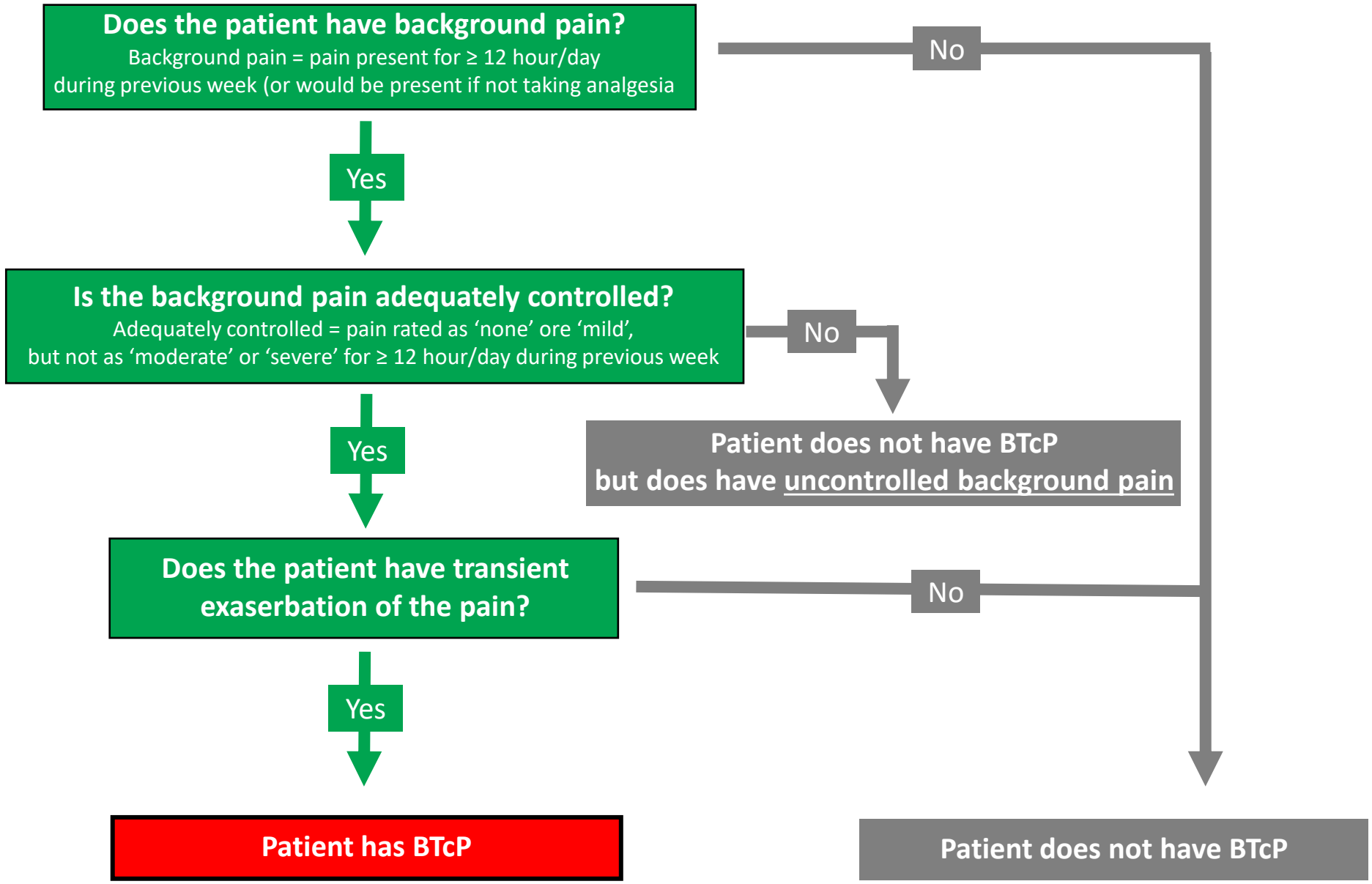
Portenoy RK, Hagen NA. Pain 1990; 41:273-81.

BTcP: Characteristics

- **Moderate to severe intensity**
- **Rapid onset (3-5 minutes in 45% of patients)**
- **Relatively short duration: median 30’ (15-240’)**
- **Frequency: median 4 episodes per day (1-60/d)**
- **Often unpredictable**

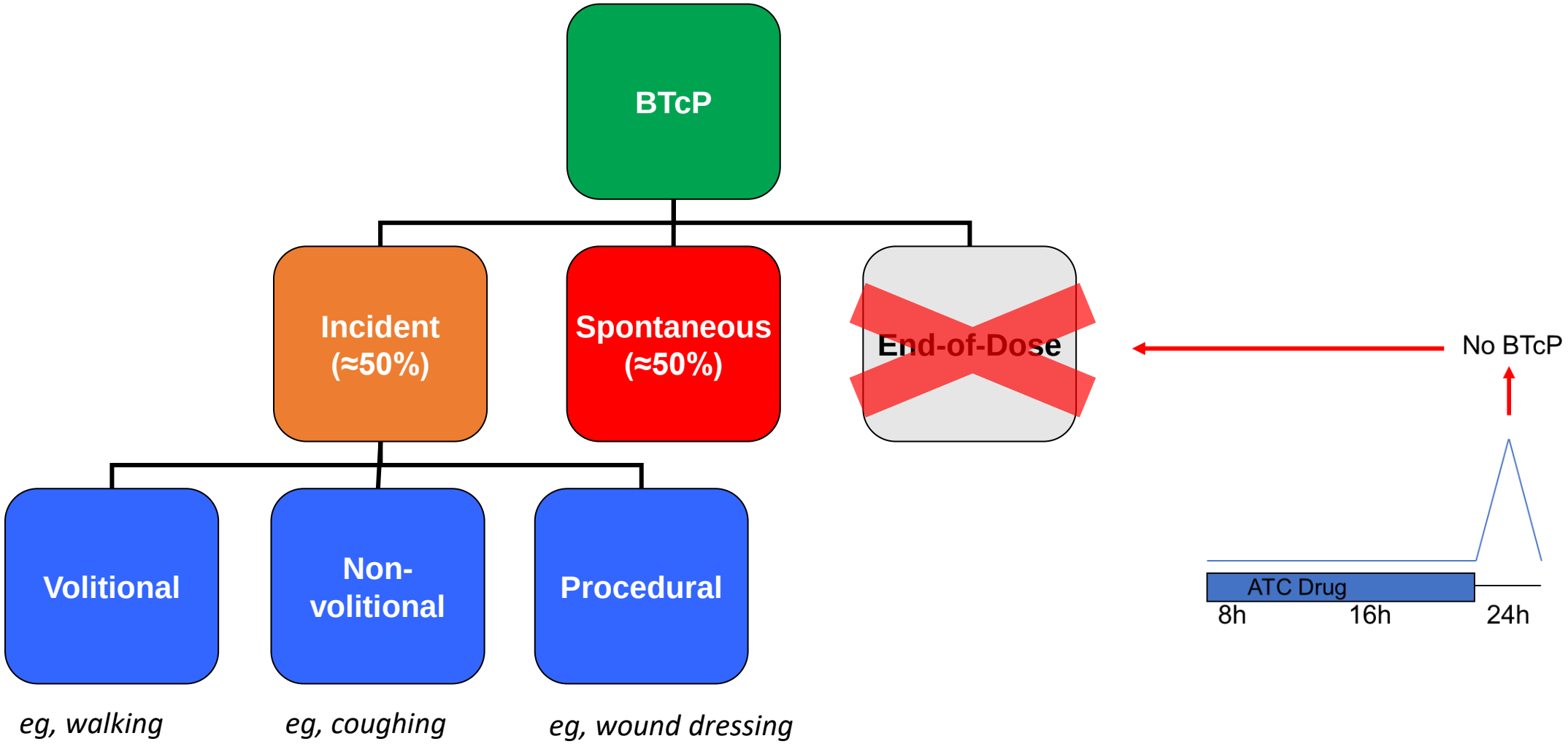
Slatkin NE et al. J Support Oncol 2007; 5(7):327-34.

Diagnosis of BTcP: Davies Algorithm



Fallon M et al. Ann Oncol 2018 1;29(Supplement_4):iv166-iv191; Davies AN et al. Eur J Pain 2009;13:331-8.

Classification of BTcP



Modified from: McCarberg BH. Pain Med 2007;8 (Suppl 1):S8-13.

BTcP: Variability

Intensity

Duration

Typology

Inter-patient variability

Intra-patient variability

Need for

Personalized Treatment

Treatment of BTcP

Treat the underlying cause, if possible

- Cause of the pain
  - *Example: radiotherapy for bone pain*
- Cause of the specific episode
  - *Examples:*
    - *Cough medicine for cough-related pain*
    - *Brace for a limb in case of movement-related pain*

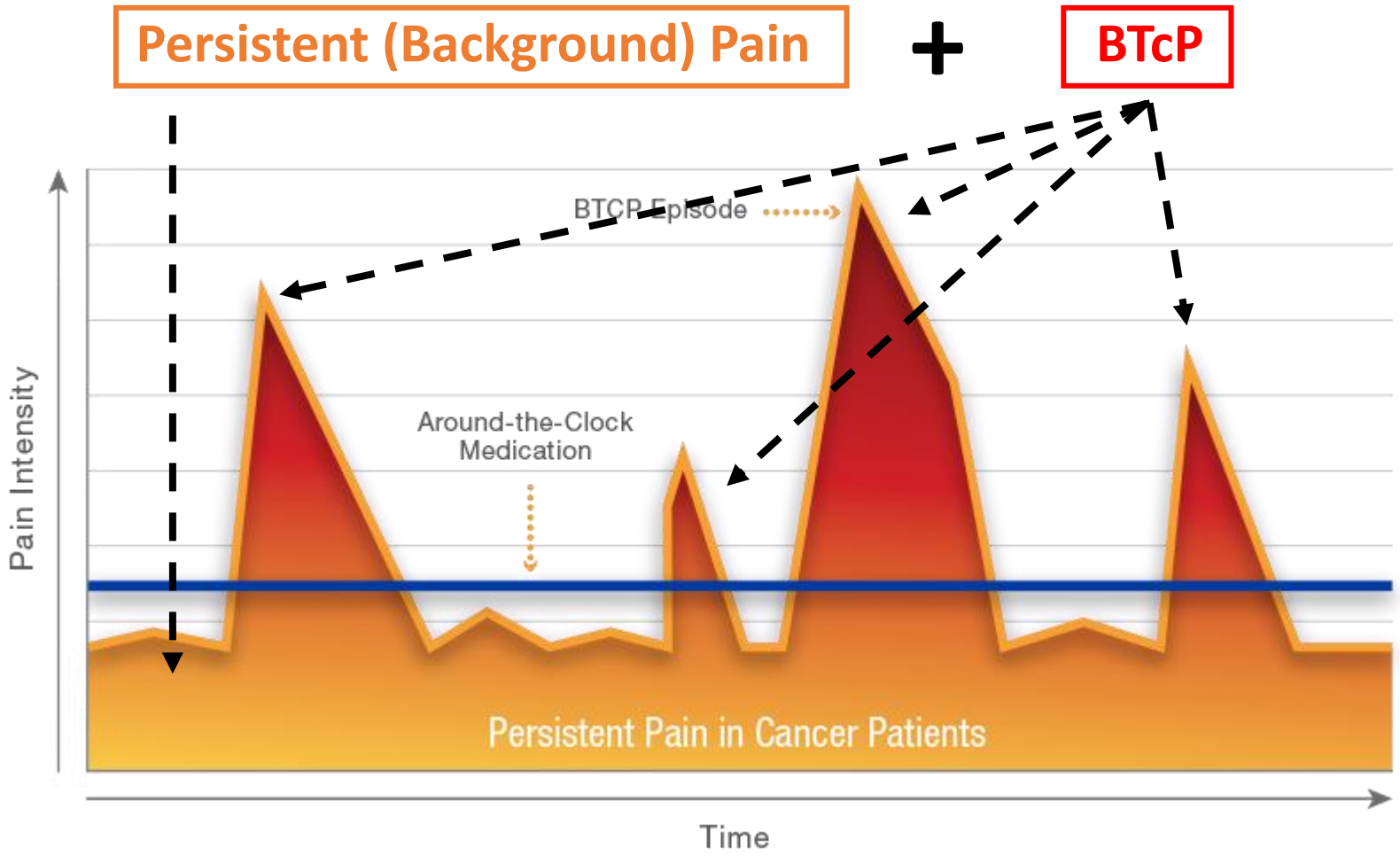
Treatment of BTcP

Non-drug therapies

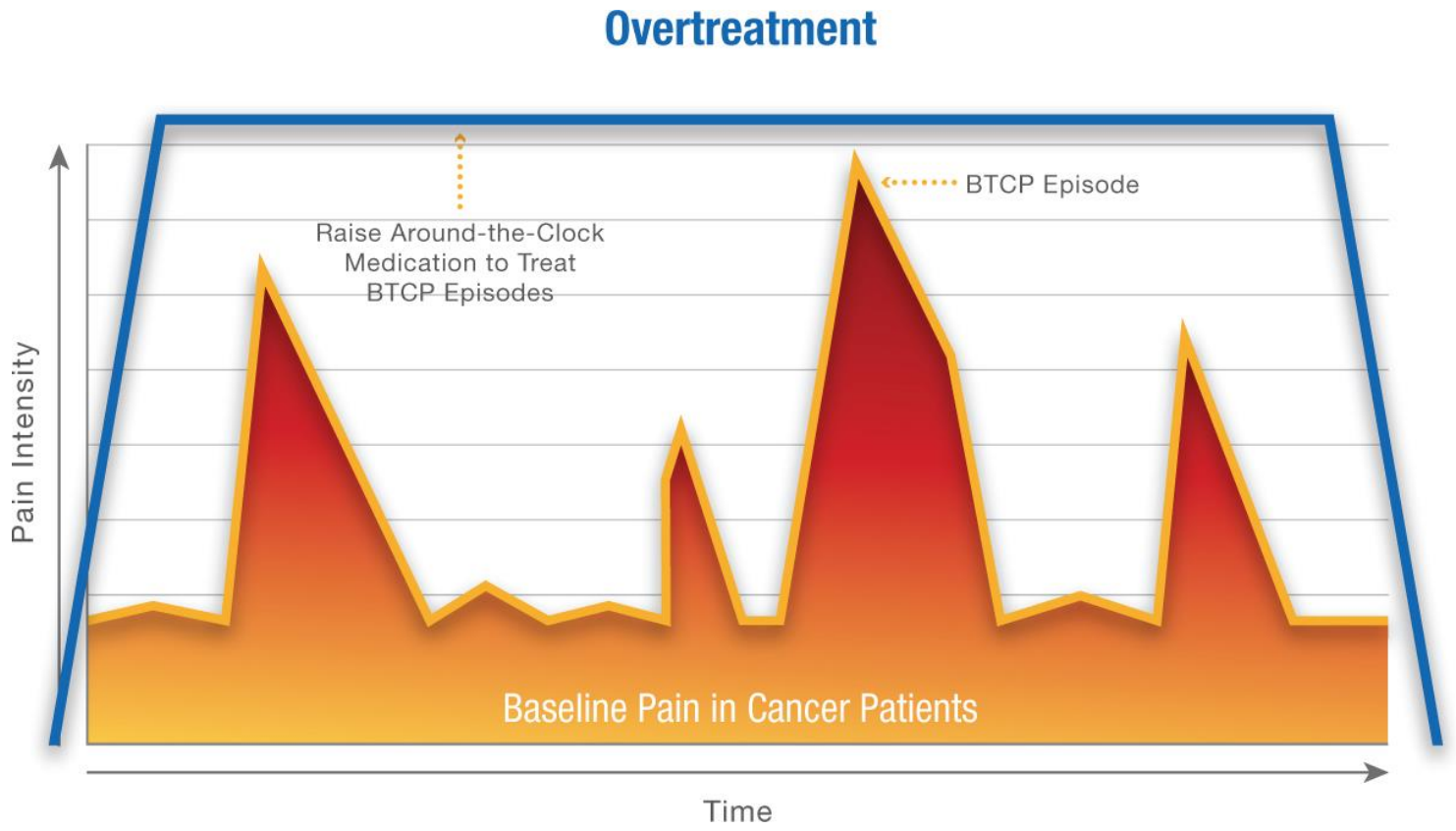
- Application of heat or cold
- Massage or stretching
- Psychotherapy or deep relaxation techniques

Drug therapies

Components of cancer pain



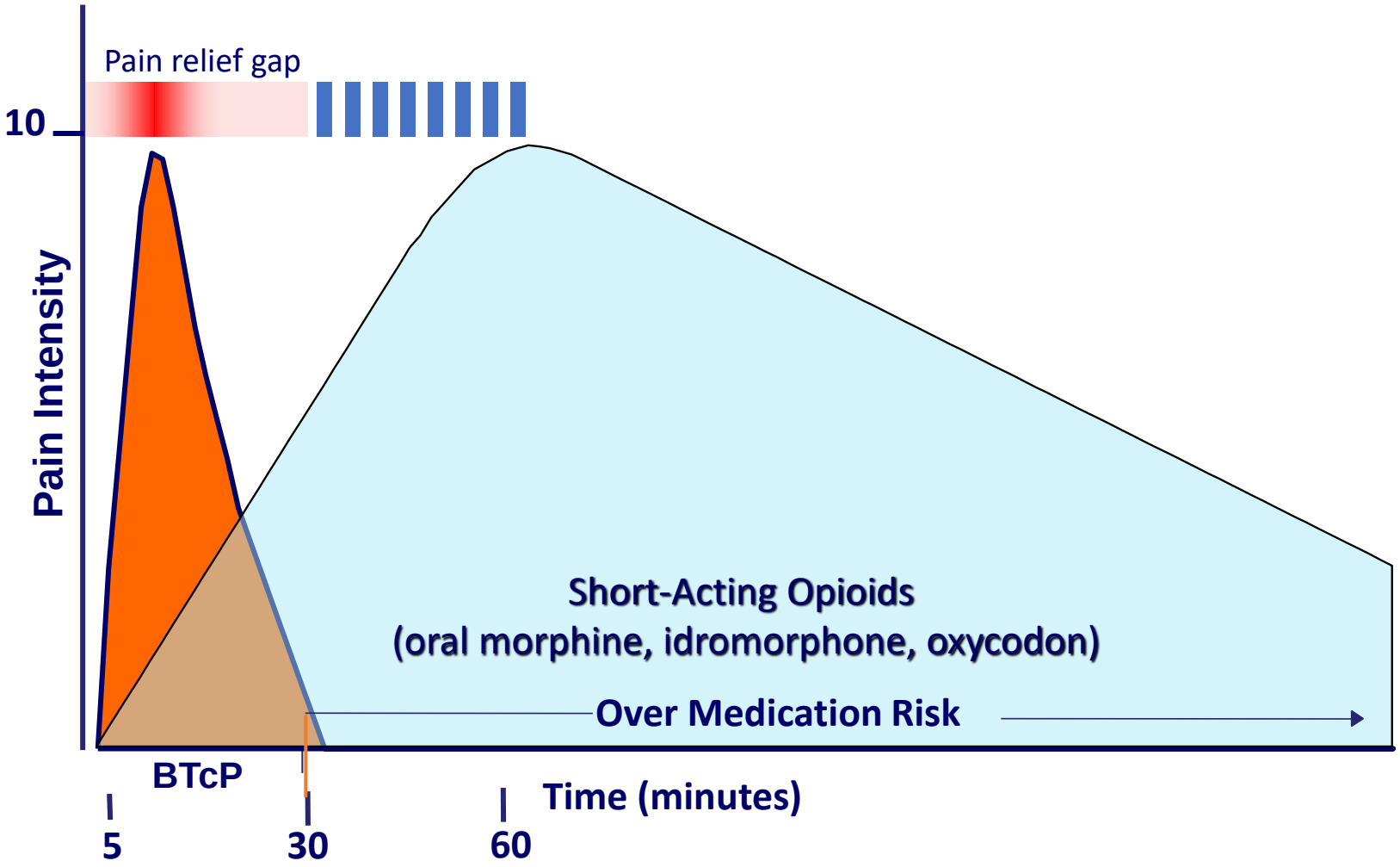
Raising ATC for BTcP



Overtreatment = ↑ **Side effects**

- Constipation
- Sleepiness
- Confusion

Oral SAO for BTcP:
Pain relief Gap / Overtreatment



There is still a role for Oral SAO in the management of BTcP?

May be still a reasonable choice for:

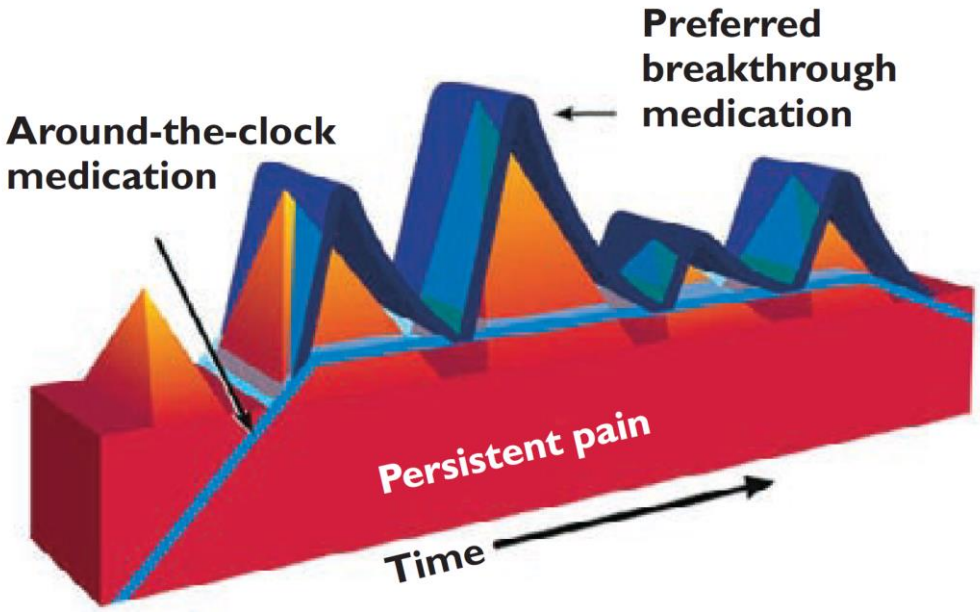
- **Predictable BTcP (Incident, volitional or procedural)**

  Anticipated before starting activity (30' before)

- **Slow on-set BTcP**

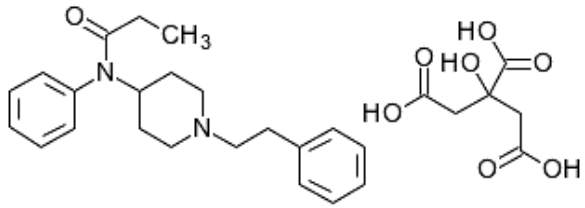
Ideal BTcP medication

- Rapid onset
- Short duration of effect
- Minimal side effects
- Non-invasive, easy-to-use
- Cost-effective



Rapid Onset Opioids (ROOs)

Fentanyl citrate



- **Strong analgesia**
- **Rapid transmucosal absoprtion (highly lipophylic)**

OTFC

ORAL TRANSMUCOSAL FENTANYL CITRATE

FBT

FENTANYL BUCCAL TABLET

SLF

SUBLINGUAL FENTANYL

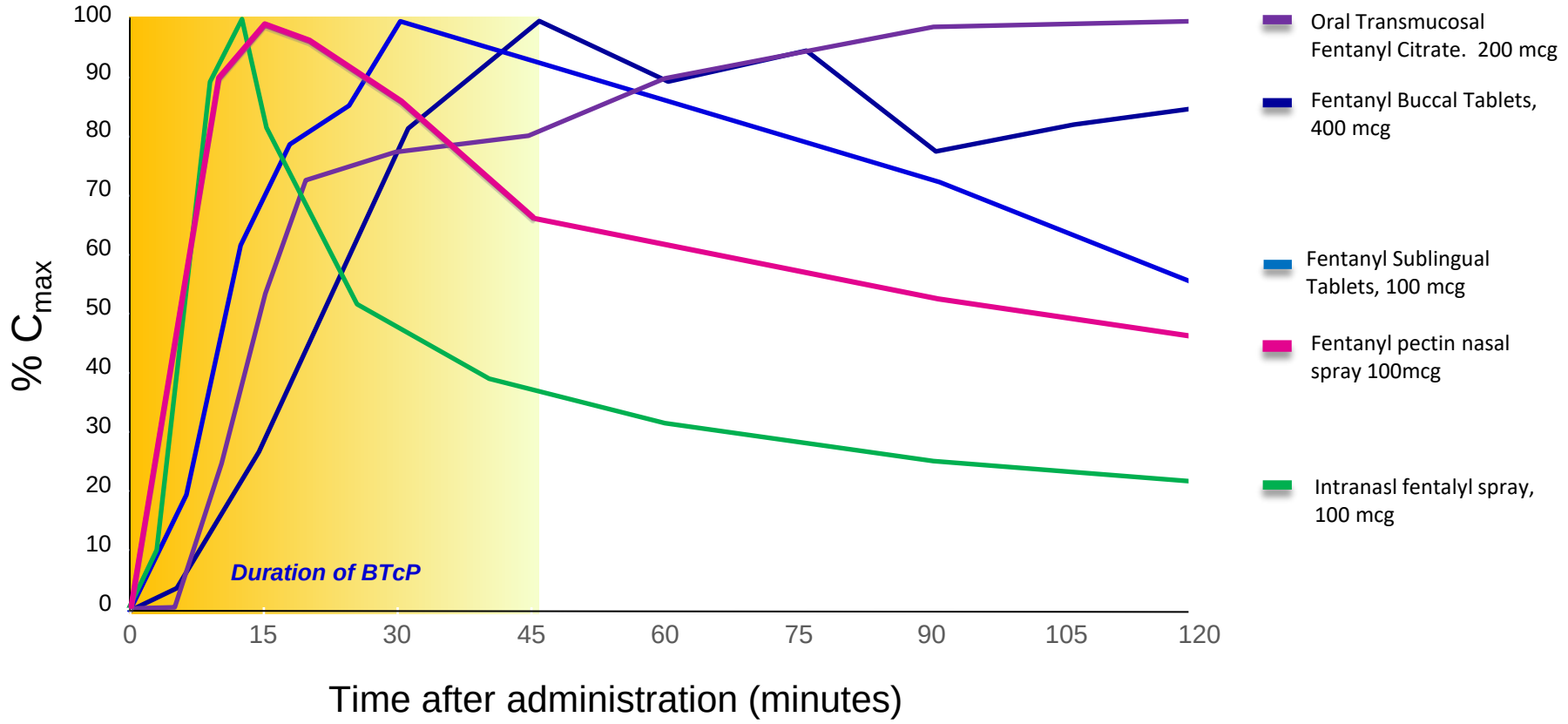
INFS

INTRANASAL FENTANYL SPRAY

FPNS

FENTANYL PECTINE NASAL SPRAY

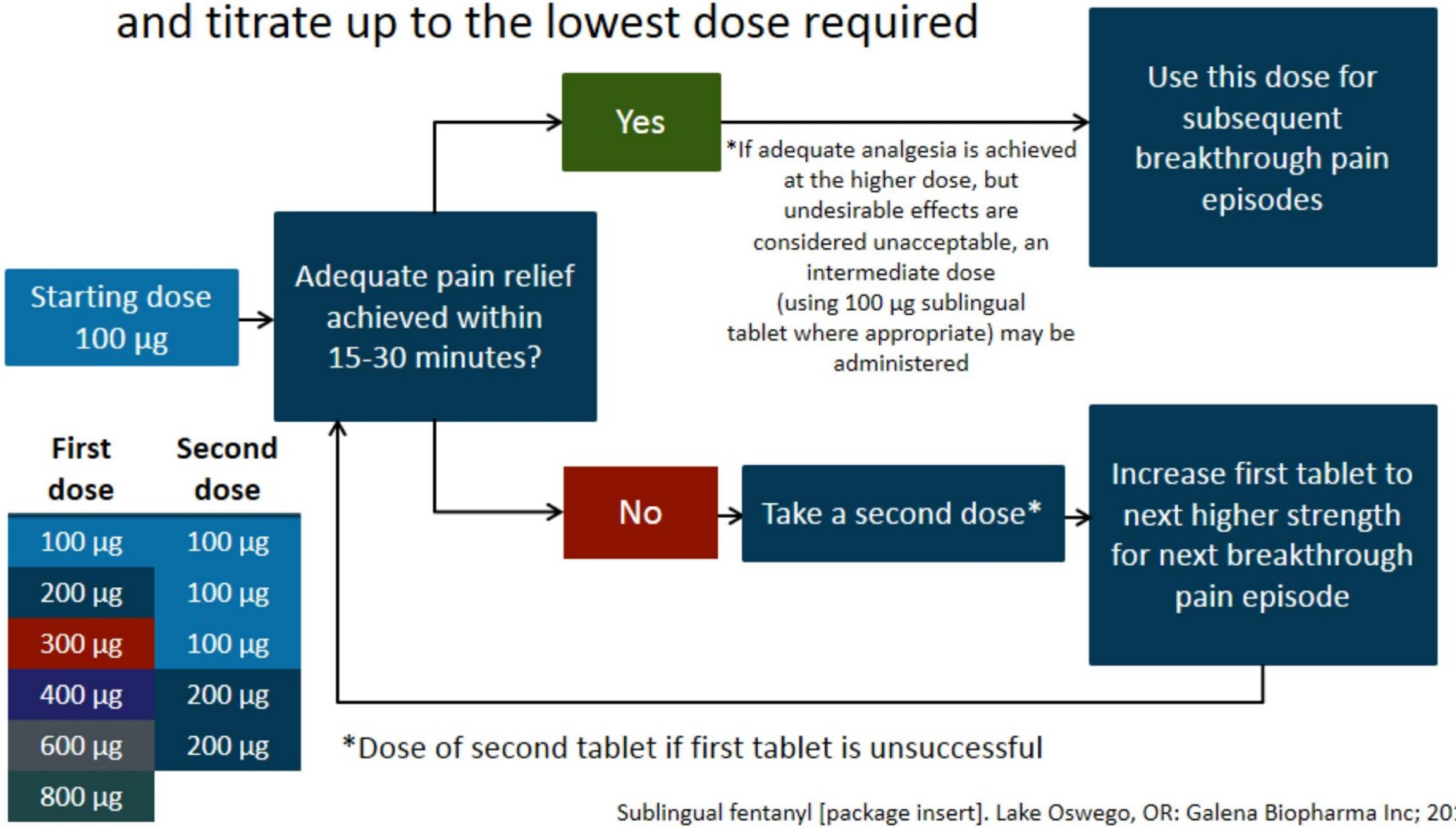
Pharmacokinetics of different fentanyl formulations



Gatti A et al. Adv Ther 2012; 29:464-72.

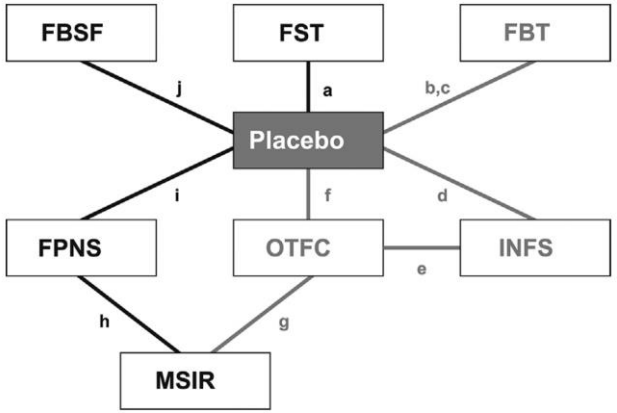
Titration

- When using ROOs, start at the lowest dose and titrate up to the lowest dose required



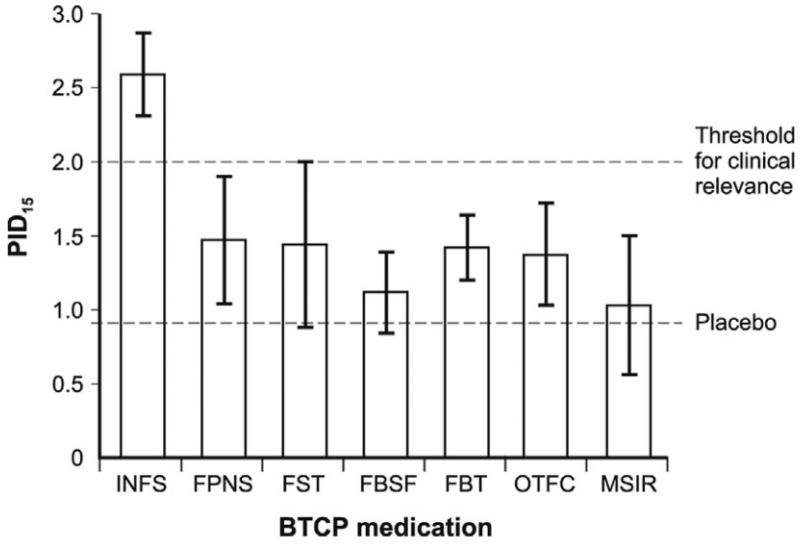
Sublingual fentanyl [package insert]. Lake Oswego, OR: Galena Biopharma Inc; 2013.

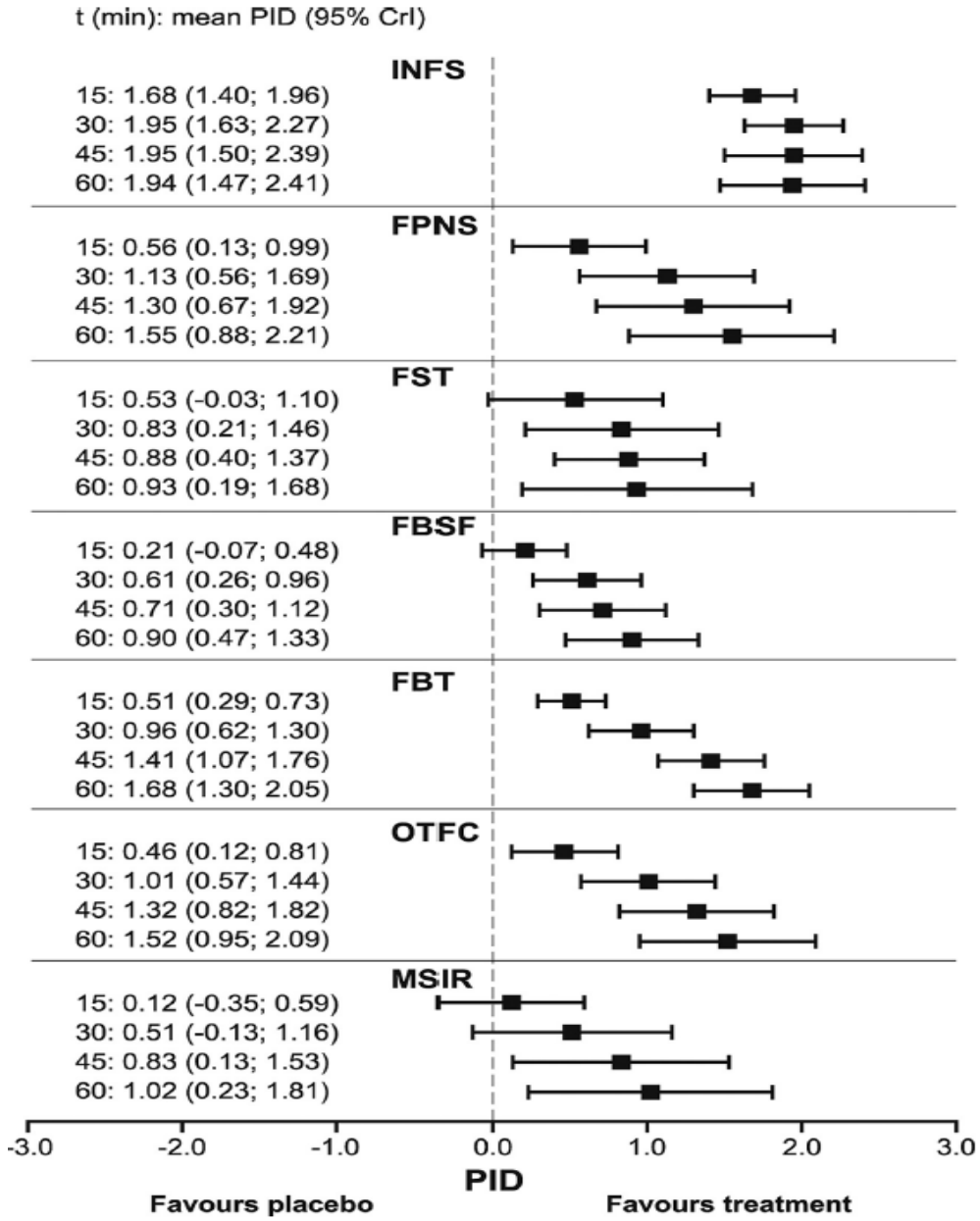
Network Meta-Analysis on the efficacy of opioids for BTcP



FBSF = fentanyl buccal soluble film; FST = fentanyl sublingual tablets; FBT = fentanyl buccal tablets; FPNS = fentanyl pectin nasal spray; OTFC = oral transmucosal fentanyl citrate; INFS = intranasal fentanyl spray; MSIR = morphine sulfate immediate release.

PID_{15} = Pain intensity difference at 15'





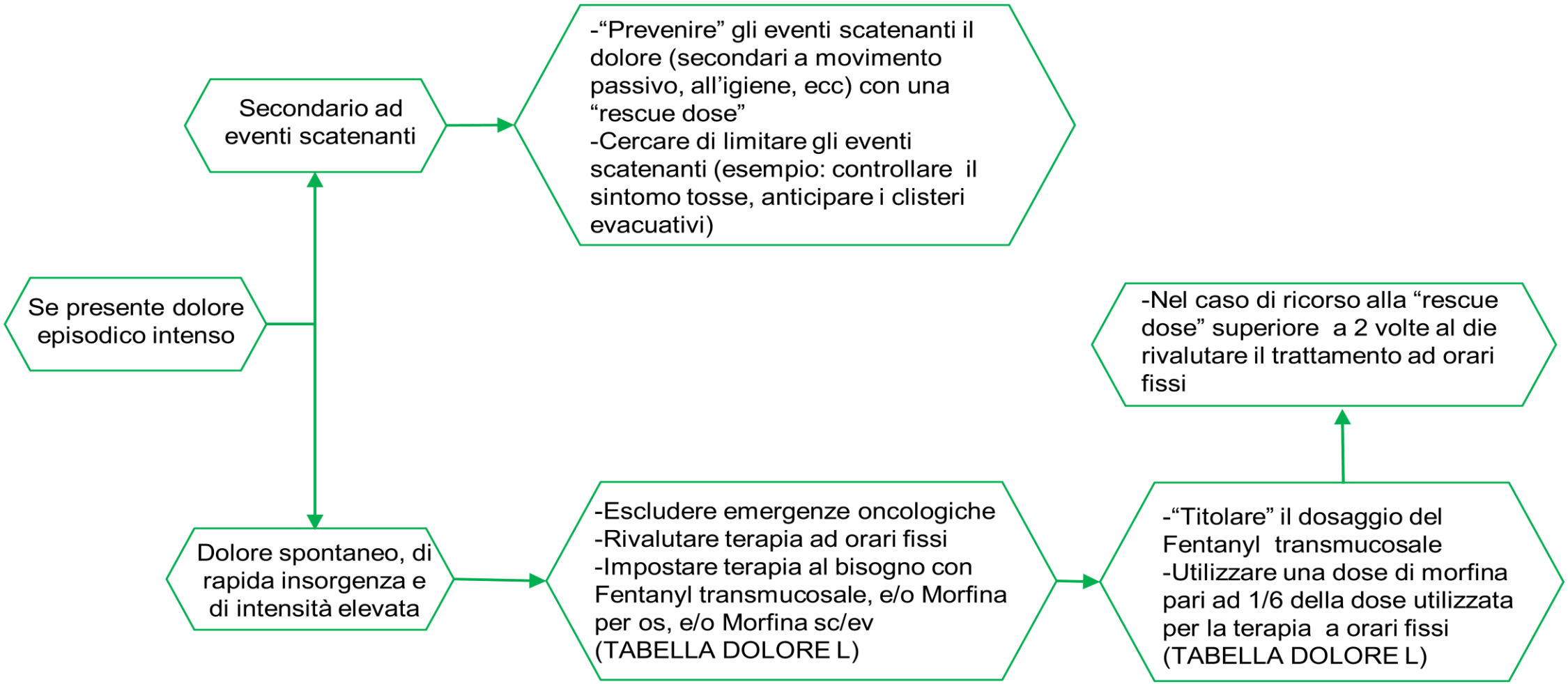
Zeppetella G et al. J Pain Symptom Manage 2014; 47:772-785.

PROs and CONs of different formulations

Formulation	Advantages	Disadvantages
Oral transmucosal fentanyl citrate	• Rapid onset of action • Mucosally absorbed dose (25%) bypasses hepatic first-pass metabolism • Can be stopped if toxicity develops • Can be used by patients who cannot swallow or have difficulty swallowing	• Takes time to dissolve • Relatively low surface area for absorption • Absorption may be variable • May be difficult for patients with dry mouth/mucositis • Potential dental decay with prolonged use • Patients may require training on correct use
Fentanyl buccal tablet Fentanyl buccal soluble film	• Rapid onset of action • Mucosally absorbed dose (48-51%) bypasses hepatic first-pass metabolism • Greater bioavailability than oral transmucosal products • Can be used by patients who cannot swallow or have difficulty swallowing	• Smaller surface area for absorption • Lower permeability via buccal membrane vs sublingual membrane • May be difficult for patients with dry mouth/mucositis
Sublingual fentanyl tablet Sublingual fentanyl spray	• Rapid onset of action • Mucosally absorbed dose bypasses hepatic first-pass metabolism • Can be used by patients who cannot swallow or have difficulty swallowing	• May be limited to lower doses • Drug and delivery system maybe ingested in the saliva • May be difficult for patients with dry mouth/mucositis
Intranasal fentanyl spray Fentanyl pectin nasal spray	• Rapid onset of action • Systematically absorbed dose bypasses hepatic first-pass metabolism • Can be given by caregivers • Convenient • Can be used by patients who cannot swallow or have difficulty swallowing	• Patients may need training on correct administration technique • Potential for application site AEs • May be unsuitable for patients with illnesses that affect the nasal mucosa • Quantity of drug may be variable • Nasal drip or swallowing can affect absorption • May be difficult for patients lacking manual dexterity • Dose limited to <0.2 mL

Smith HS. J Pain Res 2013;6:189-200.

Figura 4: Dolore episodico intenso



GRADE QUESITO 19: ***Nei pazienti affetti da tumore è raccomandabile l'utilizzo del fentanyl vs morfina nel controllo del dolore episodico intenso o Breakthrough cancer pain (BtcP)?***
RACCOMANDAZIONE: L'utilizzo del fentanyl transmucosale nel controllo del dolore episodico intenso rispetto alla morfina può essere preso in considerazione.
Forza della raccomandazione**: CONDIZIONATA A FAVORE**
Motivazioni/Commenti al bilancio Beneficio/Danno: Sono stati identificat i 4 RCT (5-8) ed è stata eseguita una metanalisi. I 4 studi in questione hanno confrontato il fentanyl rispetto alla somministrazione di morfina (con diverse modalità di somministrazione). I risultati orientano verso una riduzione moderata del dolore episodico intenso con il fentanyl rispetto alla morfina (SMD -0.47 95% IC -1.16-0-22) anche se non raggiungono una significatività statistica. Questo a fronte di effetti collaterali sovrapponibili tra i due farmaci (RR 0.83, 95% IC 0.63-1.13) Non vi sono al momento evidenze in letteratura sufficienti a orientare la scelta della formulazione di Fentanyl.
Implicazioni per le ricerche future: Sono auspicabili trial di fase III vs morfina ad IR con analisi per ITT, formale calcolo del sample size e allocazione adeguata nel paziente con dolore episodico intenso da cancro
Qualità delle Evidenze La qualità globale delle evidenze è stata giudicata **MODERATA** in quanto tali evidenze derivano da studi affetti da limitazioni metodologiche prevalentemente dovute a rischio di bias: studi crossover, sostanziali perdite al follow-up.
Qualità globale delle evidenze: MODERATA
COI: Nessun conflitto dichiarato

Conclusions

- BTcP is a **significant problem**
- It should be adequately **recognized and diagnosed**
- **Personalized treatment** is needed
- **ROOs** represent **drugs of choice**
- Choose **the right formulation for the right patient**

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INSIEME
NELLA RICERCA
Più forti nella cura

Grazie per l'attenzione

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