



IRCCS

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Sacro Cuore - Don Calabria
Ospedale Classificato e Presidio Ospedaliero Accreditato
Regione Veneto



Cancer Care Center
Negrar di Valpolicella

Incontri di aggiornamento del Dipartimento Oncologico

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SEDE: "Centro Formazione e Solidarietà"

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**Il dolore nel paziente oncologico:
dalla fisiopatologia al trattamento**

Breakthrough pain: quale terapia medica?

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Breakthrough cancer Pain (BTcP)

- **What is it?**

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

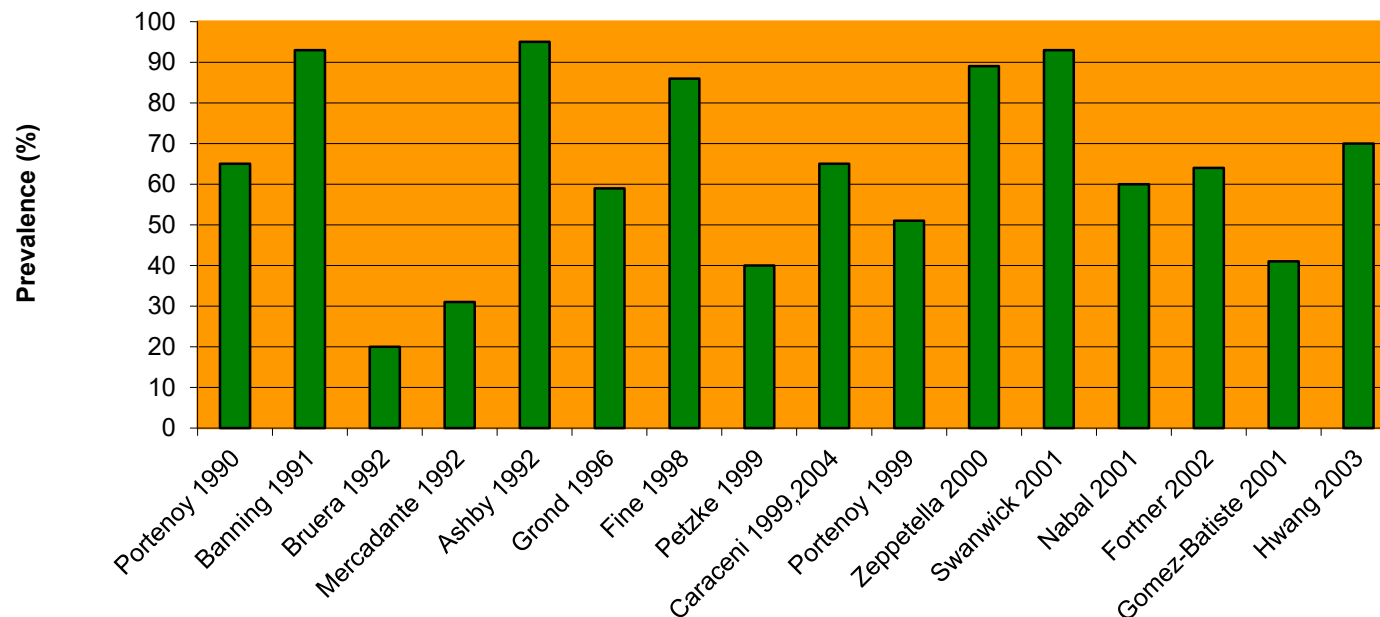
- **Most common definition:**

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

- **Synonyms:**

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

Prevalence of BTcP



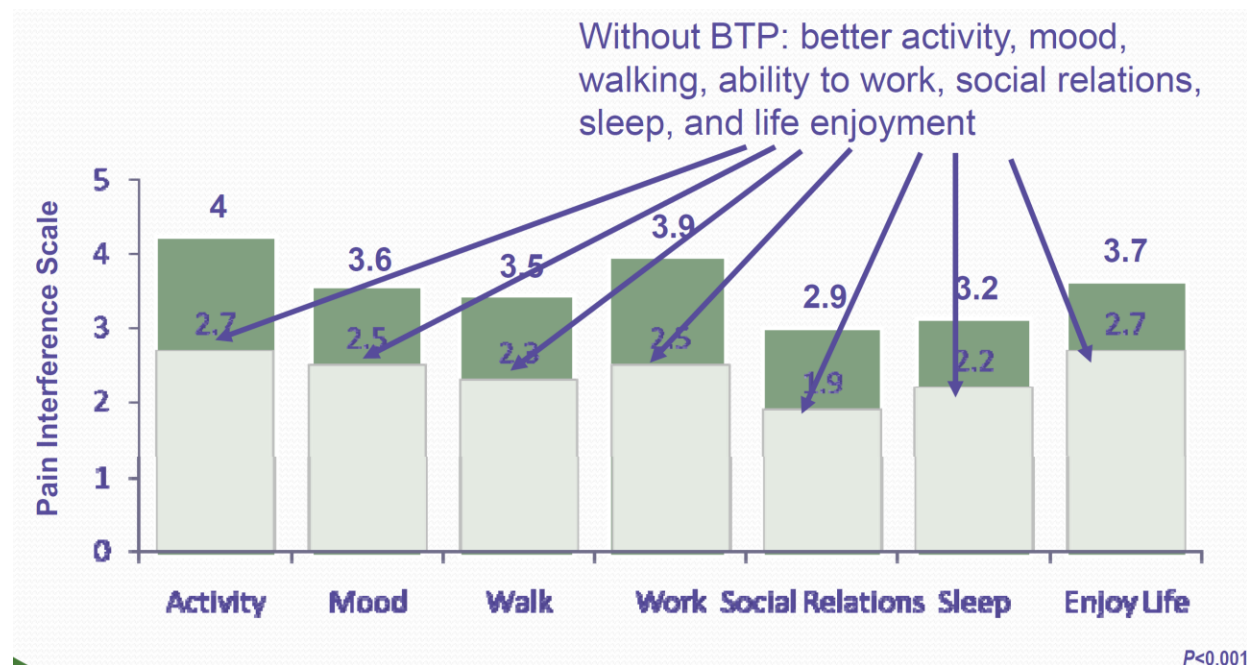
Median Prevalence: 65%

High variability: from 20% up to 95%

Impact of BTcP on QoL

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

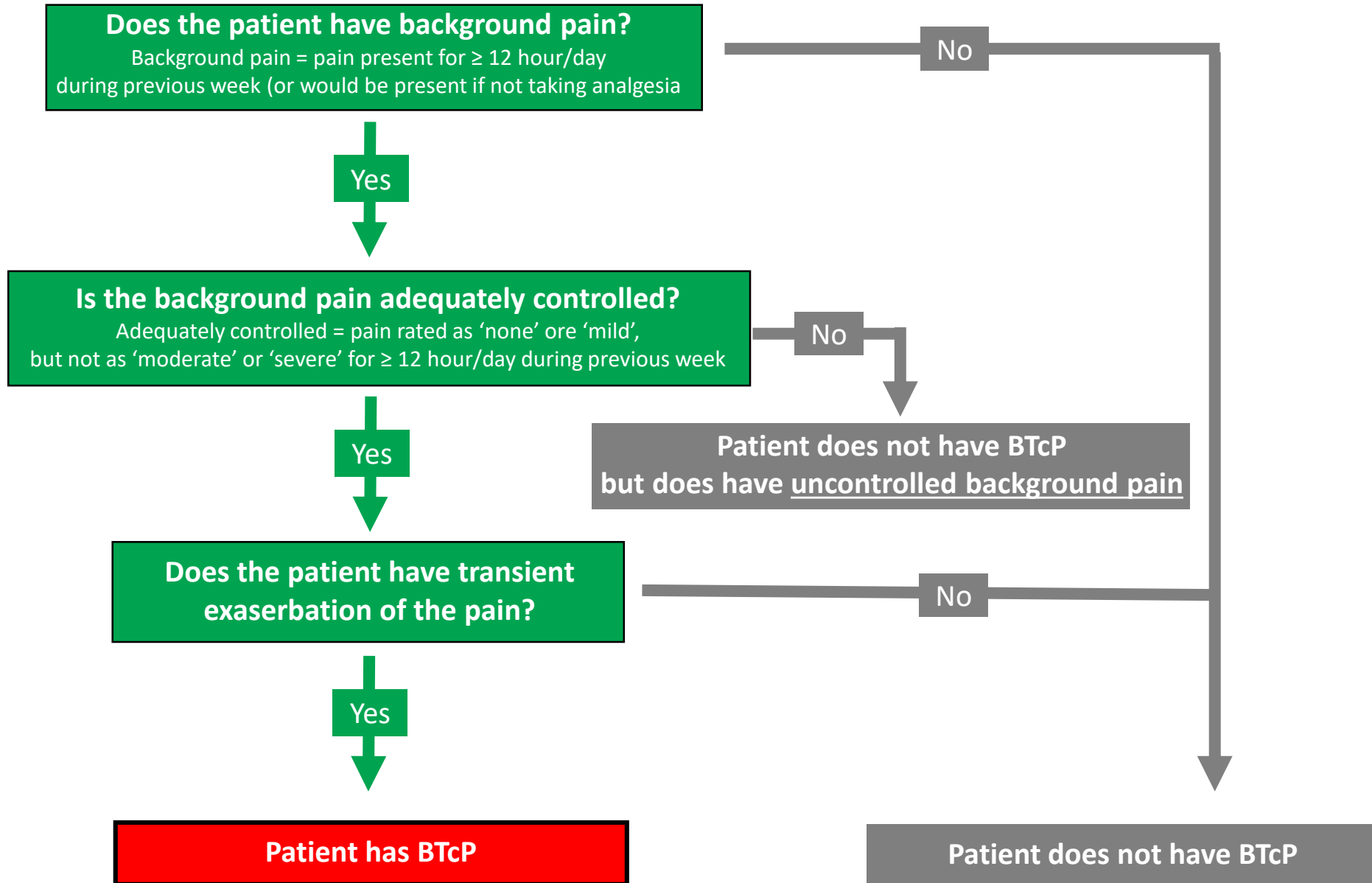
- More severe pain
- Reduced response to opioid therapy
- More problems functioning
- More psychological distress
- Higher cost of care



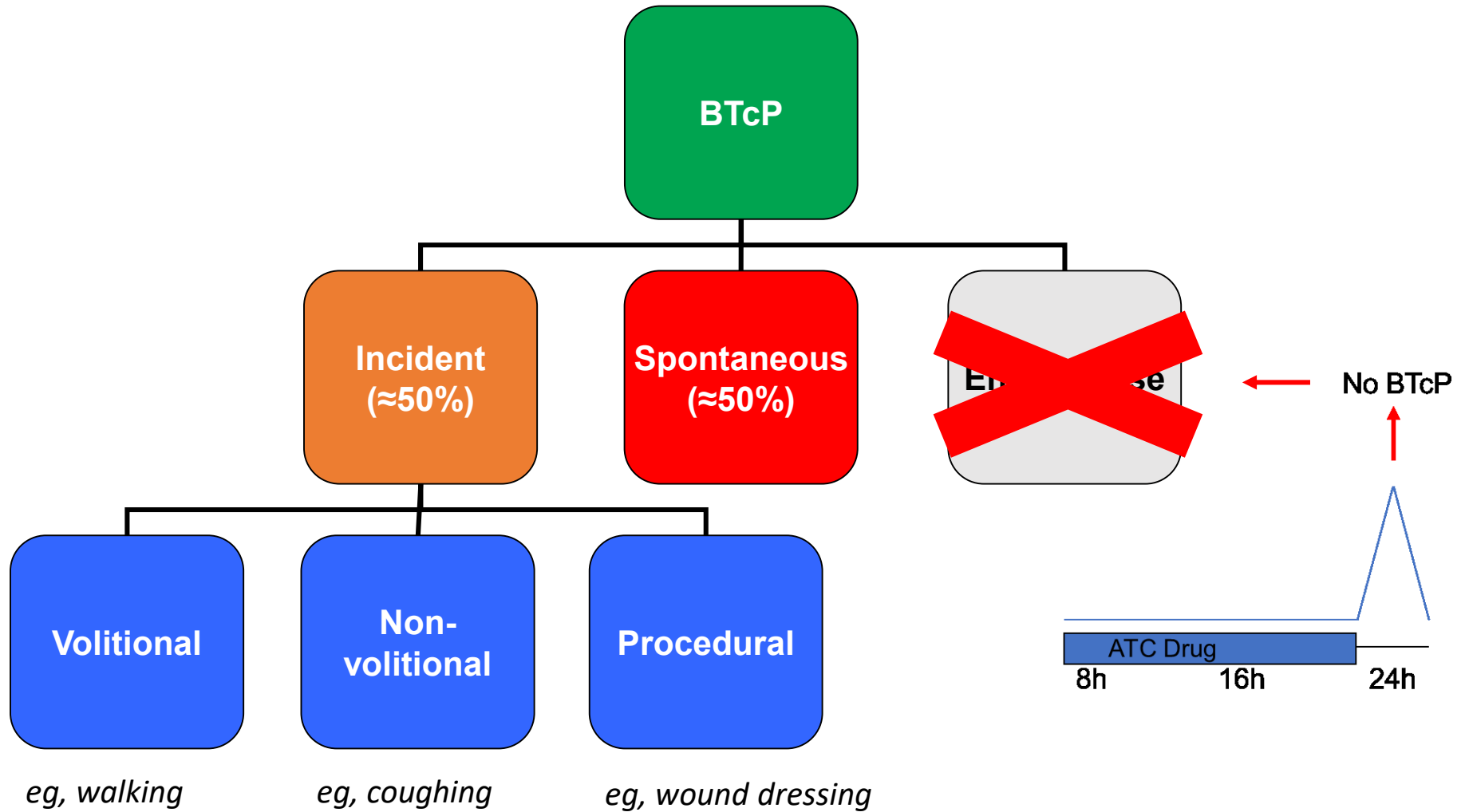
BTcP: Characteristics

- **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**

Diagnosis of BTcP: Davies Algorithm



Classification of BTcP



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*

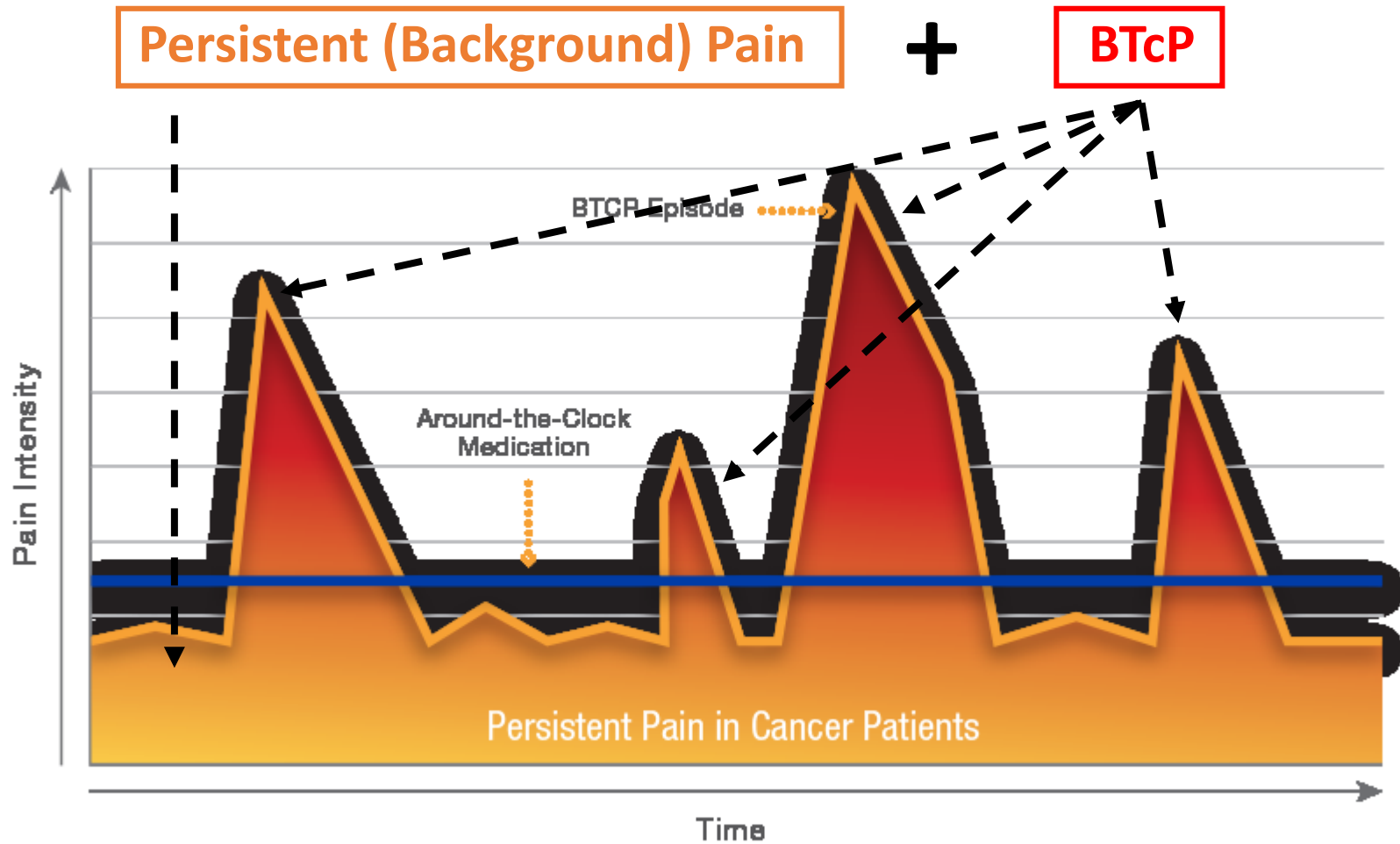
Treatment of BTcP

Non-drug therapies

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

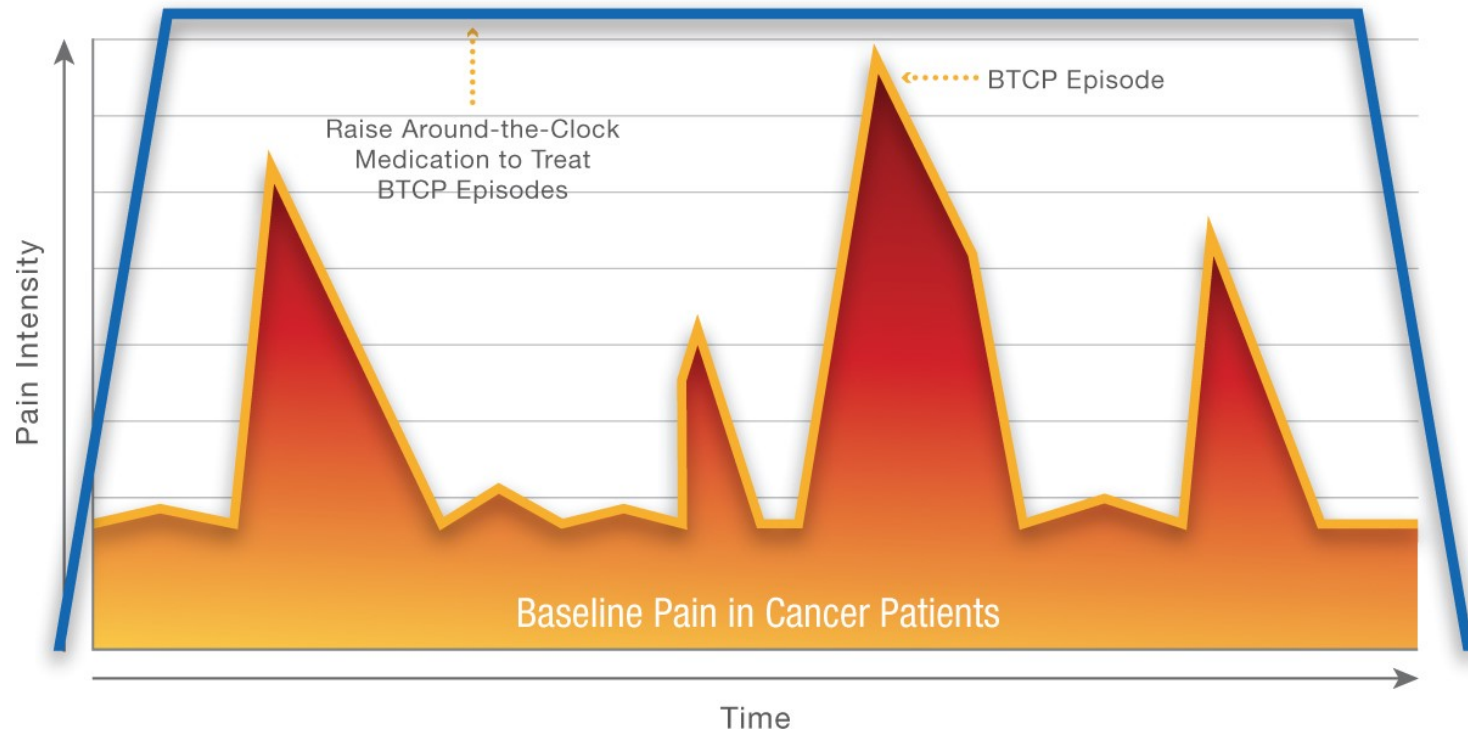
Drug therapies

Components of chronic pain



Raising ATC for BTcP

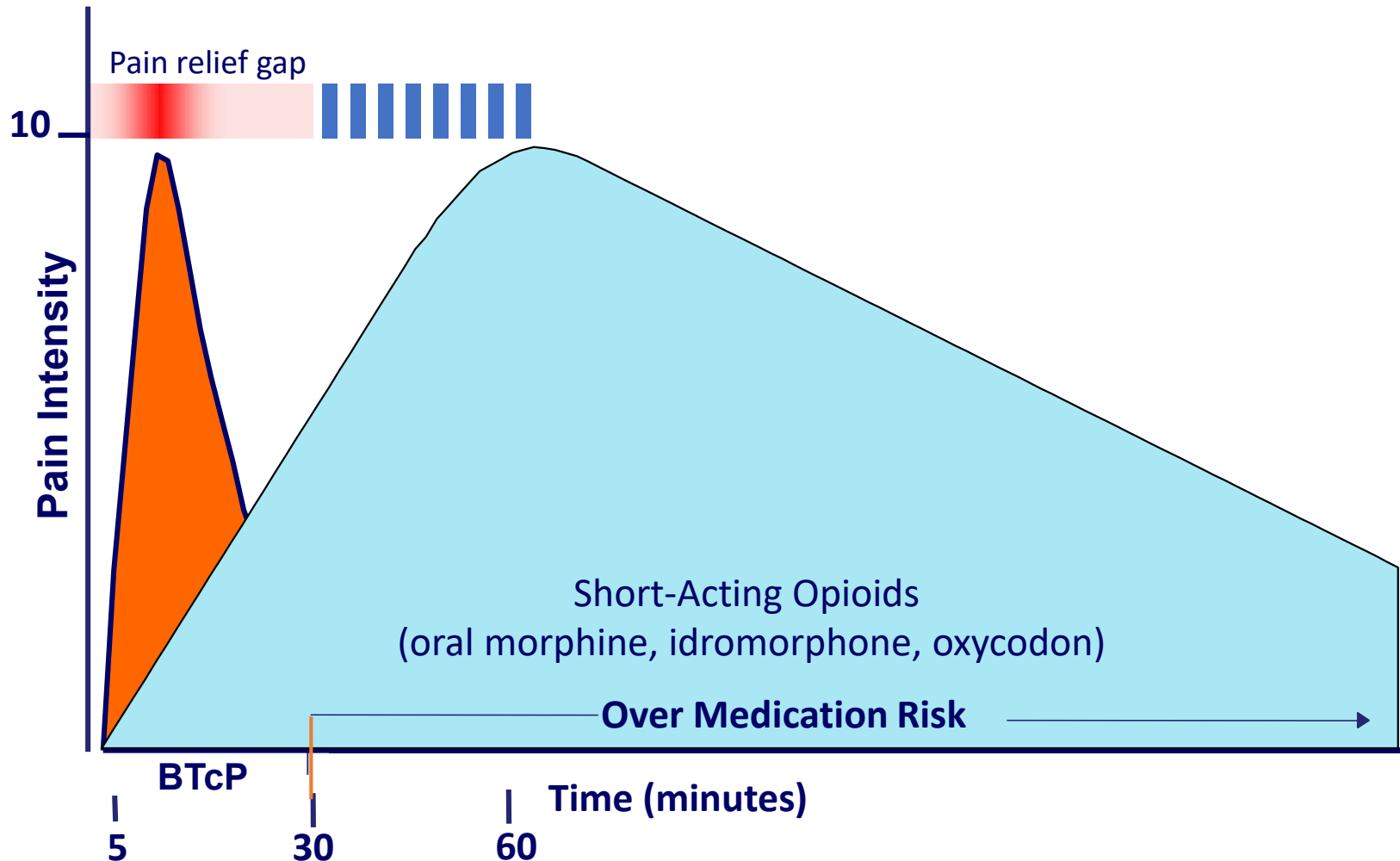
Overtreatment



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:

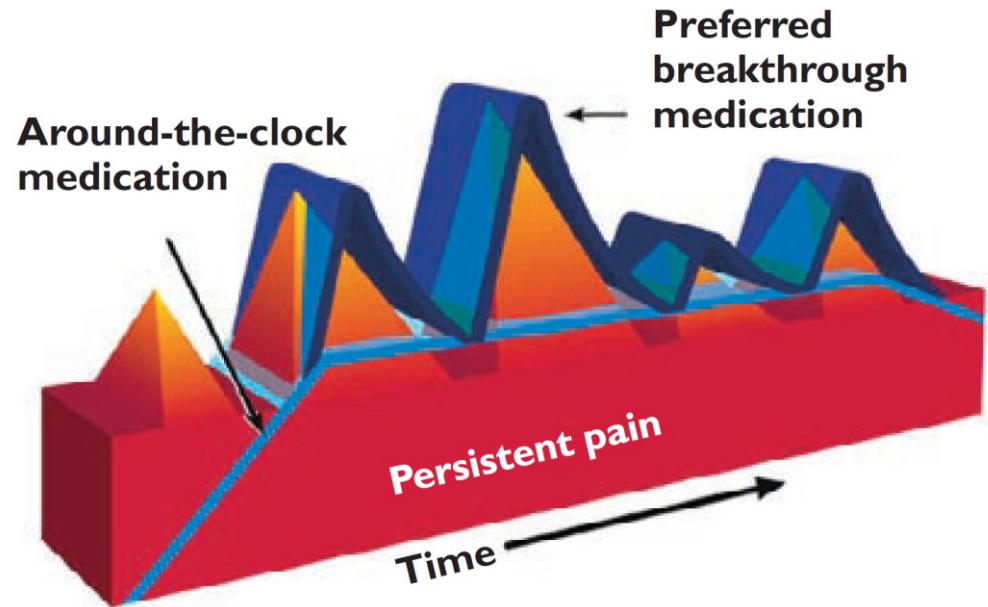
- **Predictable BTcP (Incident, volitional or procedural)**

Anticipated before starting activity (30' before)

- **Slow on-set BTcP**

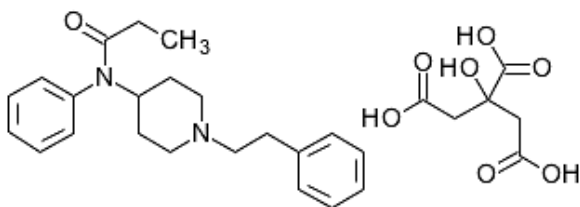
Ideal BTcP medication

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



Rapid Onset Opioids (ROOs)

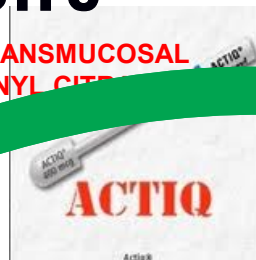
Fentanyl citrate



- Strong analgesia
- Rapid transmucosal absorption (highly lipophilic)

OTFC

ORAL TRANSMUCOSAL
FENTANYL CITRATE



FBT

FENTANYL
BUCCAL TABLET



SLF

SUBLINGUAL
FENTANYL



INFS

INTRANASAL
FENTANYL
SPRAY

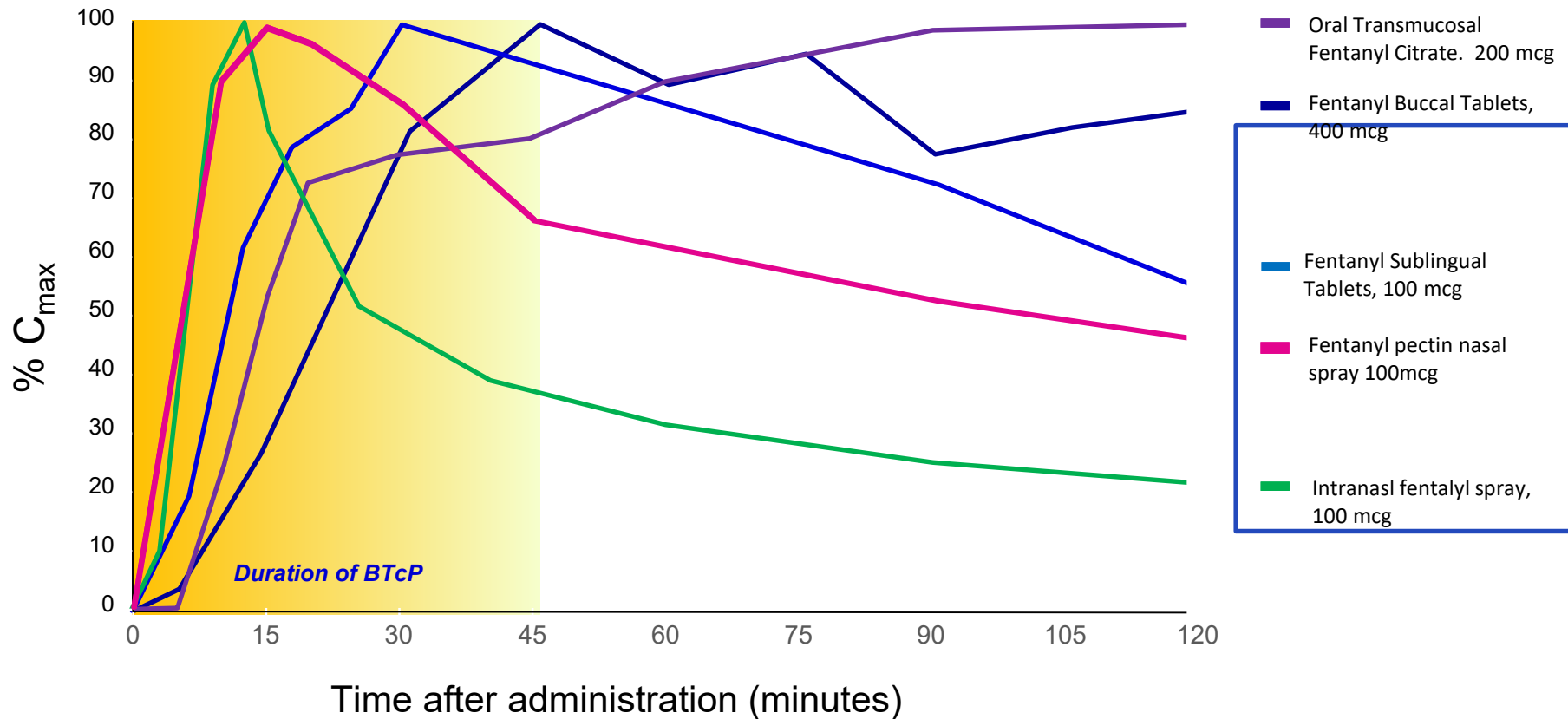


FPNS

FENTANYL
PECTINE
NASAL SPRAY

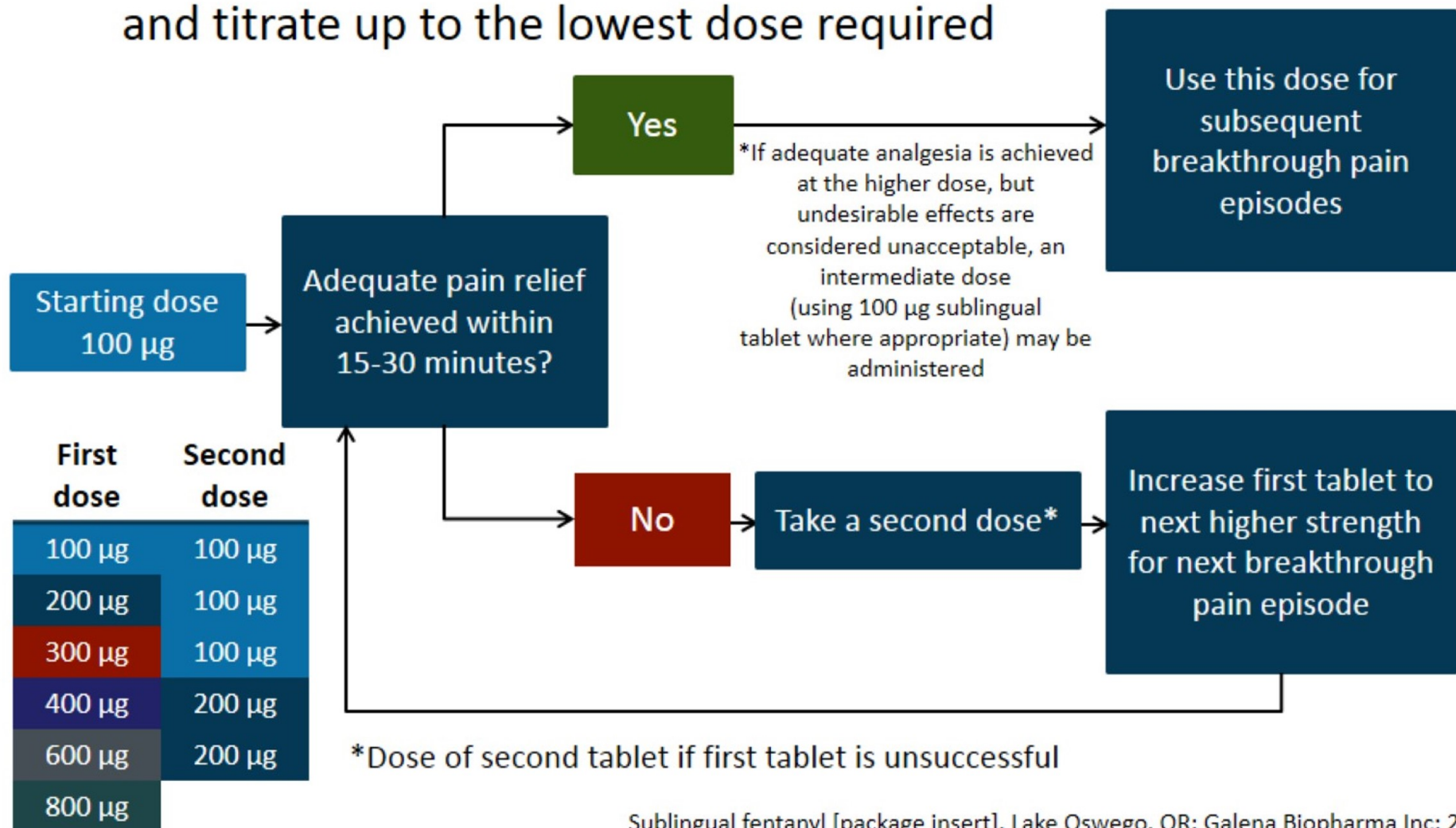


Pharmacokinetics of different fentanyl formulations

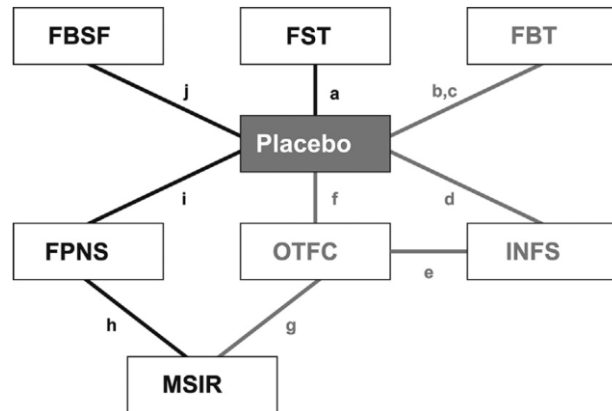


Titration

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

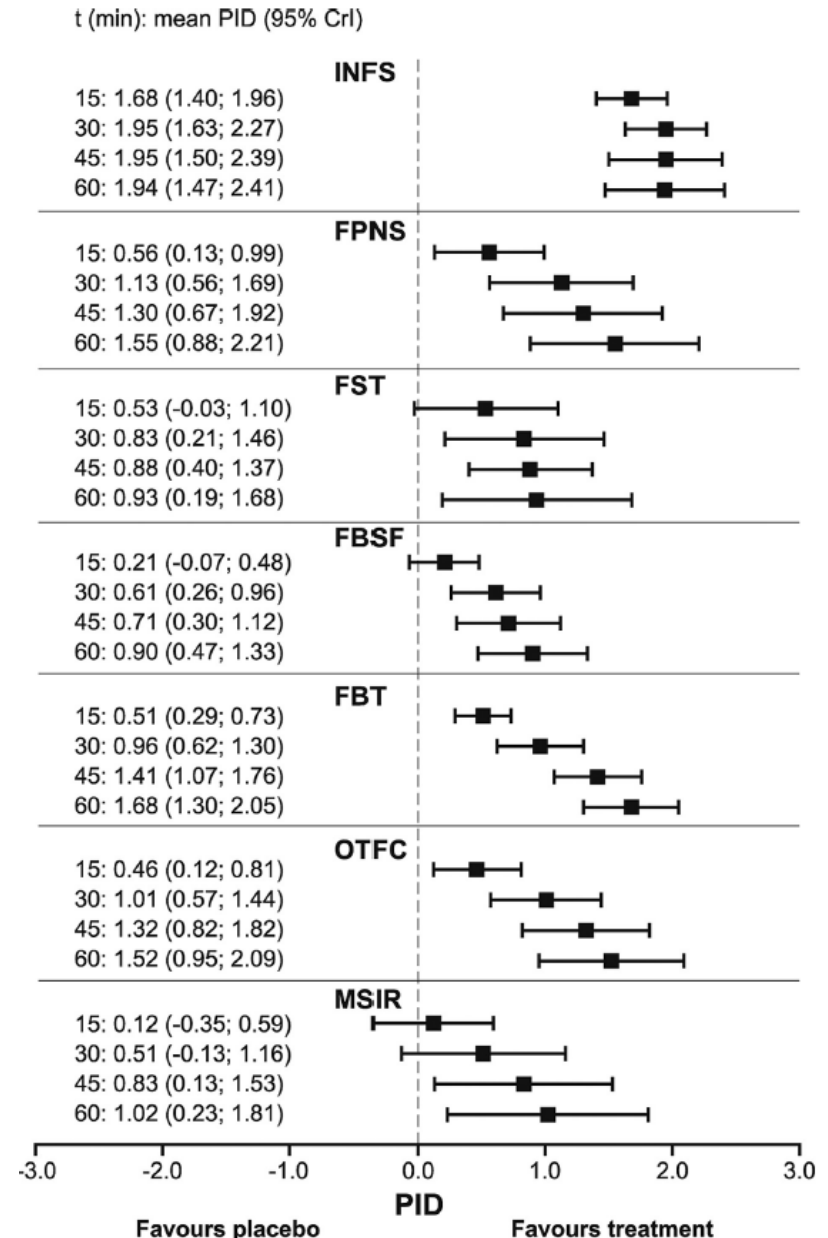
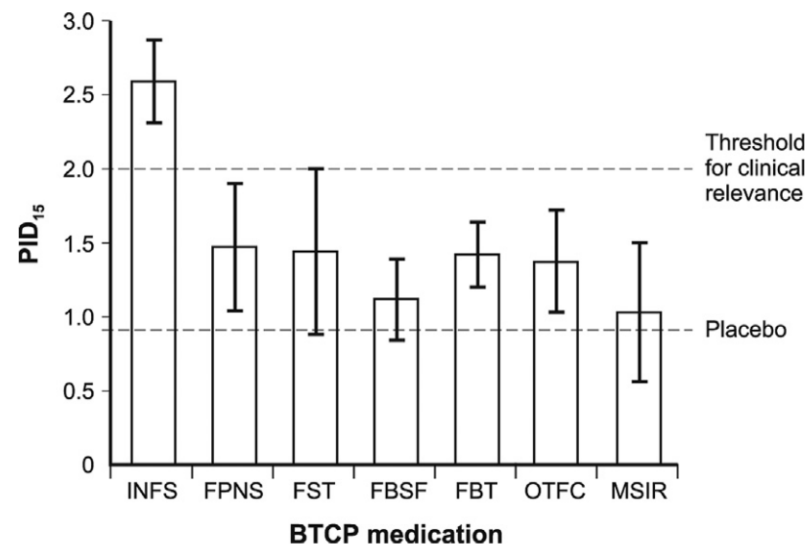


Network Meta-Analysis on the efficacy of opioids for BTcP



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.

PID₁₅ = Pain intensity difference at 15'



E' raccomandabile l'utilizzo del fentanyl trans mucosale per il controllo del dolore episodico intenso?

Qualità Globale delle evidenze GRADE	Raccomandazione clinica R28	Forza della raccomandazione clinica
Moderata	<p><i>L'utilizzo del fentanyl trans mucosale nel controllo del dolore episodico intenso <u>rispetto alla morfina</u> dovrebbe essere preso in considerazione. Non vi sono al momento evidenze di letteratura sufficienti ad orientare nella scelta della formulazione di fentanyl.</i></p> <p>Nei confronti con la morfina la rapidità d'azione pare significativamente migliore, a fronte di un non aumentato rischio di effetti collaterali. <u>Non vi sono al momento evidenze in letteratura sufficienti a orientare la scelta della formulazione di Fentanyl.</u> (Vedi paragrafo 21).</p>	Positiva debole
Bassa	<p><i>L'utilizzo del fentanyl trans mucosale nel controllo del dolore episodico intenso <u>rispetto al placebo</u> deve essere preso in considerazione. Non vi sono al momento evidenze di letteratura sufficienti ad orientare nella scelta della formulazione di fentanyl</i></p> <p>Nel confronto con il placebo l'efficacia del farmaco è significativamente migliore, senza una presenza di effetti collaterali maggiori. Non vi sono al momento evidenze in letteratura sufficienti a orientare la scelta della formulazione di Fentanyl. (vedi paragrafo 21)</p>	Positiva forte

PROs and CONs of different formulations

Formulation	Advantages	Disadvantages
Oral transmucosal fentanyl citrate	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • <u>Takes time to dissolve</u> • Relatively low surface area for absorption • Absorption may be variable • May be <u>difficult for patients with dry mouth/mucositis</u> • Potential <u>dental decay with prolonged use</u> • Patients may require training on correct use
Fentanyl buccal tablet Fentanyl buccal soluble film	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Smaller surface area for absorption • Lower permeability via buccal membrane vs sublingual membrane • May be <u>difficult for patients with dry mouth/mucositis</u>
Sublingual fentanyl tablet Sublingual fentanyl spray	<ul style="list-style-type: none"> • Rapid onset of action • Mucosally absorbed dose bypasses hepatic first-pass metabolism • Can be used by patients who cannot swallow or have difficulty swallowing 	<ul style="list-style-type: none"> • May be limited to lower doses • <u>Drug and delivery system maybe ingested in the saliva</u> • <u>May be difficult for patients with dry mouth/mucositis</u>
Intranasal fentanyl spray Fentanyl pectin nasal spray	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Patients may need training on correct administration technique • Potential for application site AEs • <u>May be unsuitable for patients with illnesses that affect the nasal mucosa</u> • Quantity of drug may be variable • <u>Nasal drip or swallowing can affect absorption</u> • May be difficult for patients lacking manual dexterity • Dose limited to <0.2 mL

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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