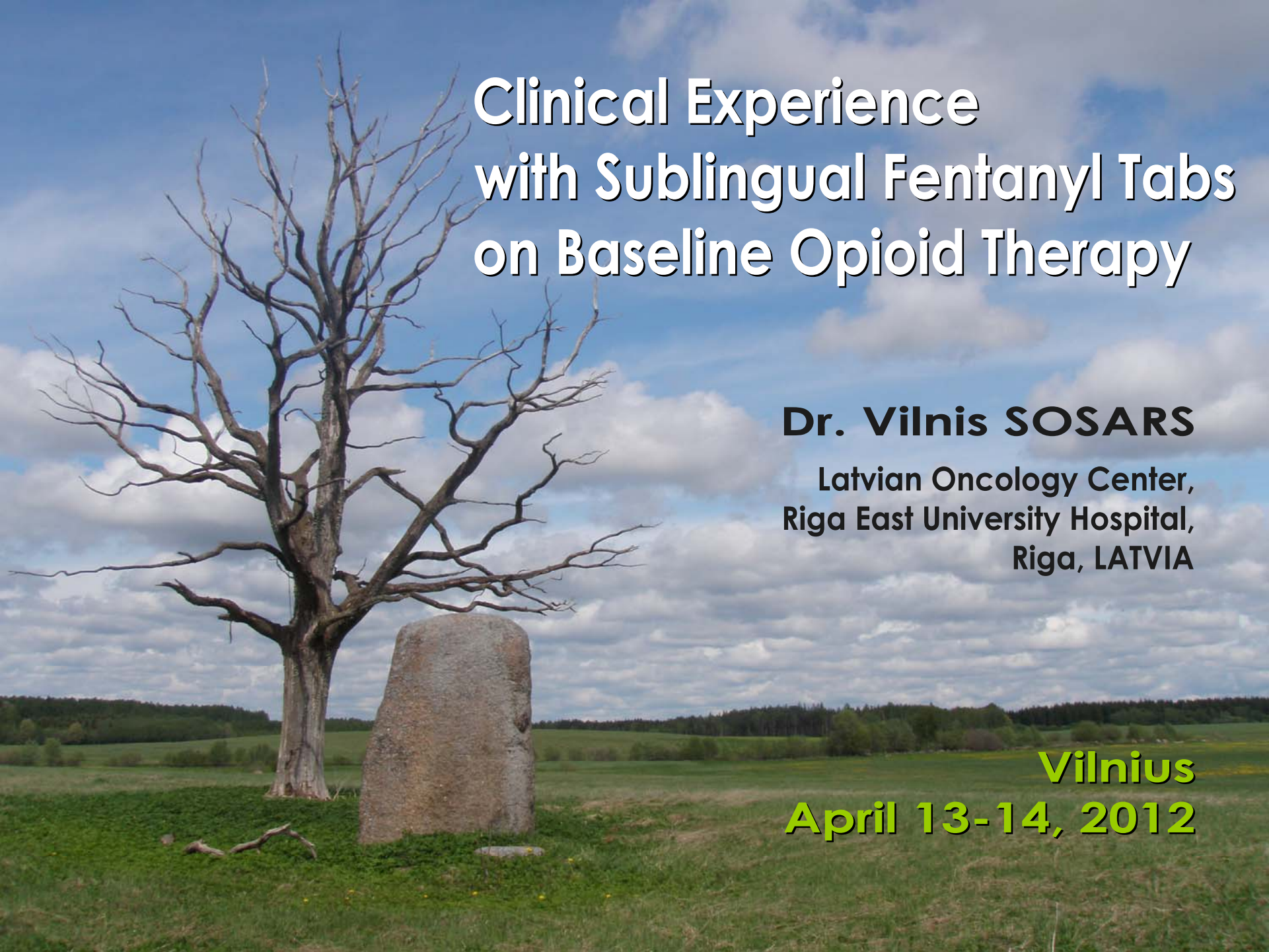

Clinical Experience with Sublingual Fentanyl Tabs on Baseline Opioid Therapy

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Vilnius
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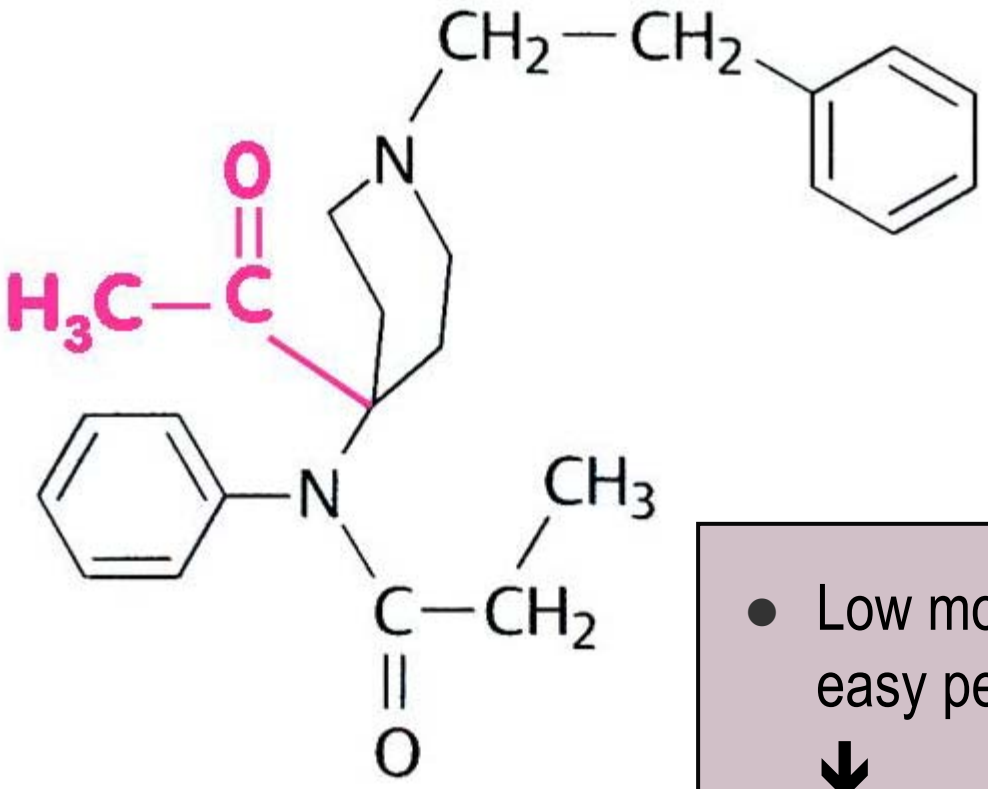
Fentanyl

Carfentanyl



- Low molecular weight,
  easy penetrates skin, mucosa
  ↓
- **TTS, SLF**
  ↓
- Baseline pain therapy, **BTcP** and **BTP**

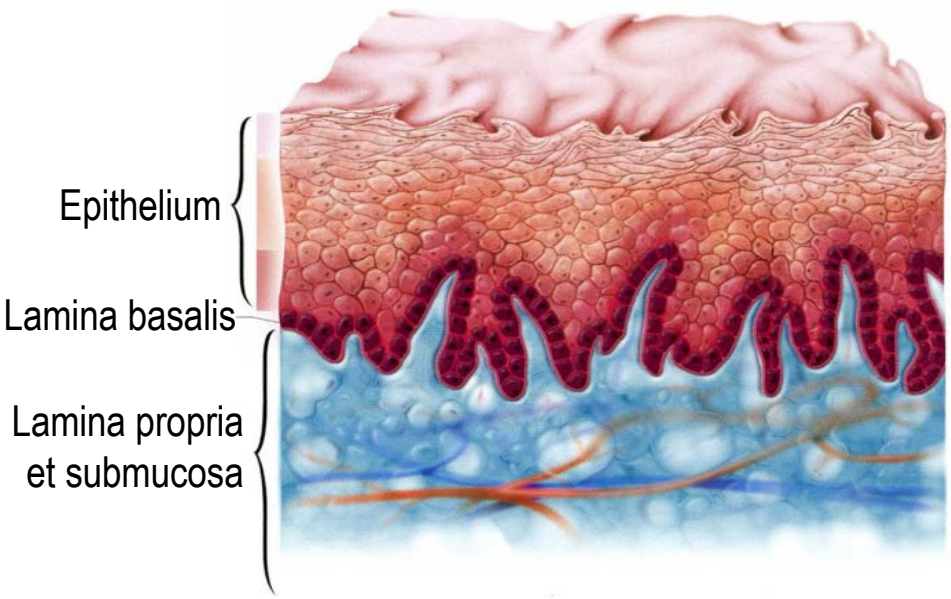
Fentanyl (F) Physiochemical Properties

- High lipid solubility, F from TTS or transdermal therapeutic system/patch easy passes liphophilic epidermis/dermis
- Absorption enhancer (F dissolved in ethanol) increases skin flux up to 500-fold
- Can be dissolved and easy pass through an adhesive silicone (poliacrile)
- High affinity to central μ opioid receptors

F flow through the skin is 1000-fold times greater than in M

- F molecular weight is 285 g/mol
  (transdermal permeability <1000 g/mol + lipid solubility)
- M molecular weight is 337 g/mol
- Surface of the corresponding M patch to F
  could be 6.25 m^2
- Octanol/water coefficient if pH 7.4:
  for F is 717 and M 0.7

Mouth Mucosa



- Surface 200 cm^2 (large area)
- Blood supply:
  link with the circulation system
  (well vascularized)
- Blood flow speed 2,4 $ml/min/cm^2$
- Well penetrable for lipophilic molecules
- Covered by saliva,
  uniform temperature

F for Transmucosal Administration

- Rapid pass through oral mucosal membranes
- Absorption of F is transcellular
  because of lipophilicity and non-ionized state
- M is absorbed via paracellular route
  because it is hydrophilic and ionized (salts)
- In mouth:
  - 51% of F absorbed and
    60% absorbed in 2,5 minutes
  - M absorbed 20%

Pharmacodynamic of Sublingual F (I)

- Rapid absorption
- Rapid redistribution, to cross blood-brain barrier, because of non-ionized fraction, targetting central μ receptors
- Rapid onset of analgesia: 43% within 3 minutes
- Short duration of effect (about an hour)

Pharmacodynamic of Sublingual F (II)

- Hepatic metabolism → absence of active metabolites: norfentanyl, phenylacetic acid and small quantity of active p-OH or phenethyl fentanyl
- Rapid renal excretion of metabolites
- Non-invasive and convenient, easy to use
- Easy to overcome "dry mouth" syndrome – before rinse mouth with water

Portenoy RK & Hagen NA, 1990: First Talk about Breakthrough Pain (BTP)

Essential Terminology:

1. Background, *baseline pain*...

   ATC – around the clock (analgesia), SR medication, prolonged... **TTS**

2. Transient, transitory pain, pain flare, episodic pain, end-of-dose (tail) pain, incident pain, BTcP (cancer), BTP...

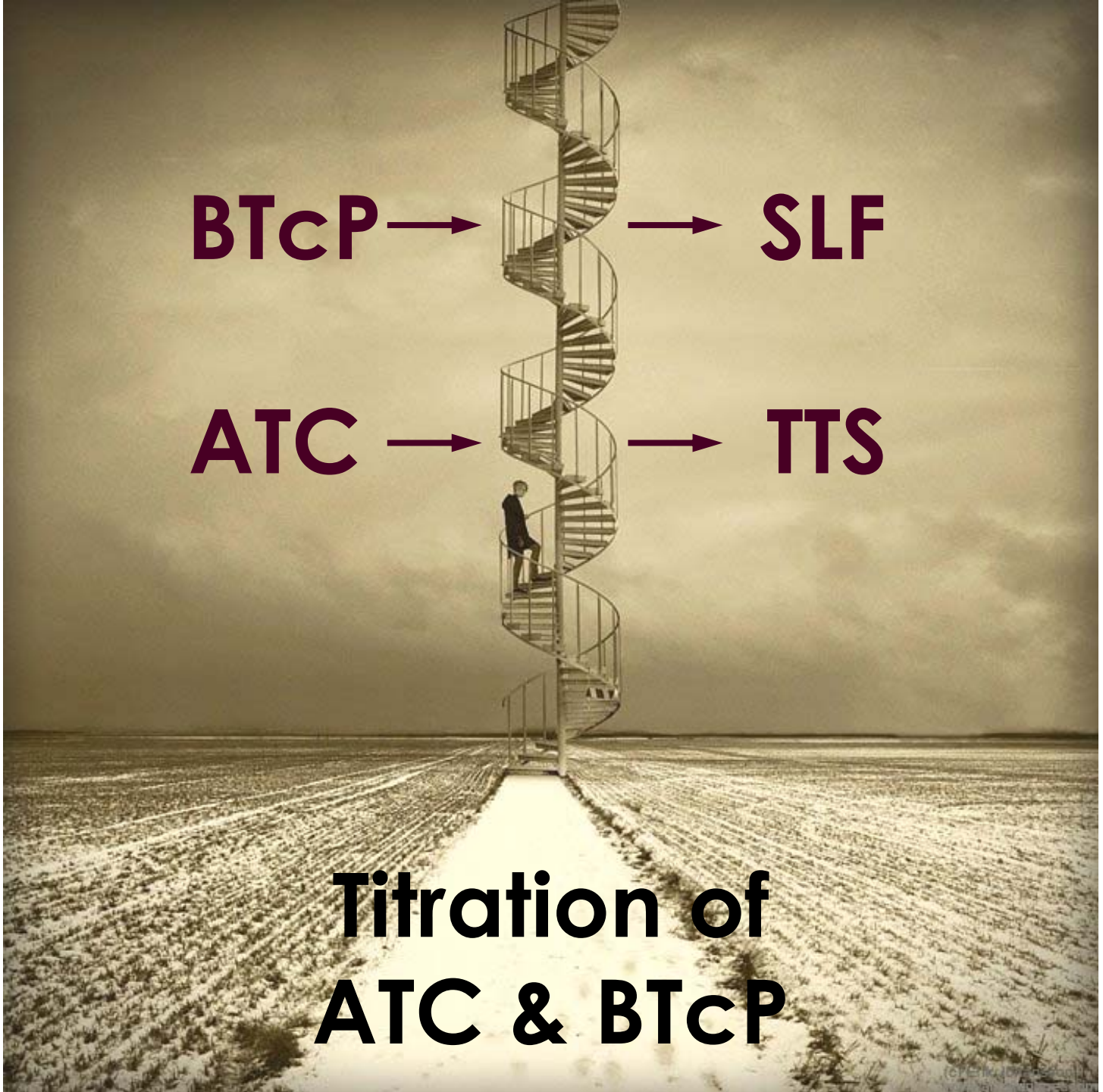
   Rescue medication, as needed, as required, normal release, short acting... **SLF**

How to Define Breakthrough Cancer Pain (BTcP)

- **BTcP** is a transient increase in pain intensity over background pain

- **BTcP** is a transitory exacerbation of pain experienced by the patient who has *relatively stable* or *adequately controlled background pain* as a result of *an opioid treatment regimen* (if strong, severe pain, cancer pain)

- **BTcP** → transitory exacerbation of pain, more severe, *greater cost of care*...



Eric Johansson, Sweden

Clinical Experience with SLF (I): PC Patients and BTcP Episodes

- Received 63 patients, all with cancer in advanced stage of the disease, in PC setting
- 562 pain episodes
- **SLF:**
  - 20 pts (31.7%) 100 µg, 130 episodes
  - 26 pts (41.2%) 200 µg, 140 episodes
  - 5 pts (7,9%) 300 µg, 80 episodes
  - 10 pts (15.8%) 400 µg, 160 episodes
  - 2 pts (3.1%) 600 µg, 52 episodes

Clinical Experience with SLF (II): Percentage of Dosage

- 100 mg 23.1%
- 200 mg 24.9%
- 300 mg 14.2%
- 400 mg 28.4%
- 600 mg 9.2%

Clinical Experience with SLF (III): Pain Characteristics

- **ATC:**
  - Tramadol SR 200 mg/daily
  - Doltard SR 60 → 240 mg/daily
  - TTS 25 → 300 µg/h
- ATC ranging 2–3 (4) (numeric scale 10)
- BTcP strength ranging (6)–7–8–9 (10)
- Time of significant pain relief in 3–4 (5–10) minutes
- Strength of BTcP relieved by SLF in 1–3 (4–5) minutes

Clinical Experience with SLF (IV): Side Effects

- Side effects are rare, several cases:
  - palpitation
  - slight fever
  - (heart disease as concurrent disease)
- Background:
  - fatigue
  - slight nausea
- One case – F intolerance with TTS:
  - skin rash
  - rapid desquamation

In 98% SLF well-tolerated, used immediately when BTcP started

Clinical Case No.1

Eric Johansson, Sweden

Male, 54 yrs old

- **Diagnosis:**
  - Left small cell lung cancer
  - Metastases in mediastinum
  - Left pleural effusion
- **Received therapy:**
  - chemotherapy, 5 courses – Cisplatin, Etoposid
  - + radiotherapy 36 Gy on tumour site and mediastinal lymphnodes

Disease trajectory after special therapy

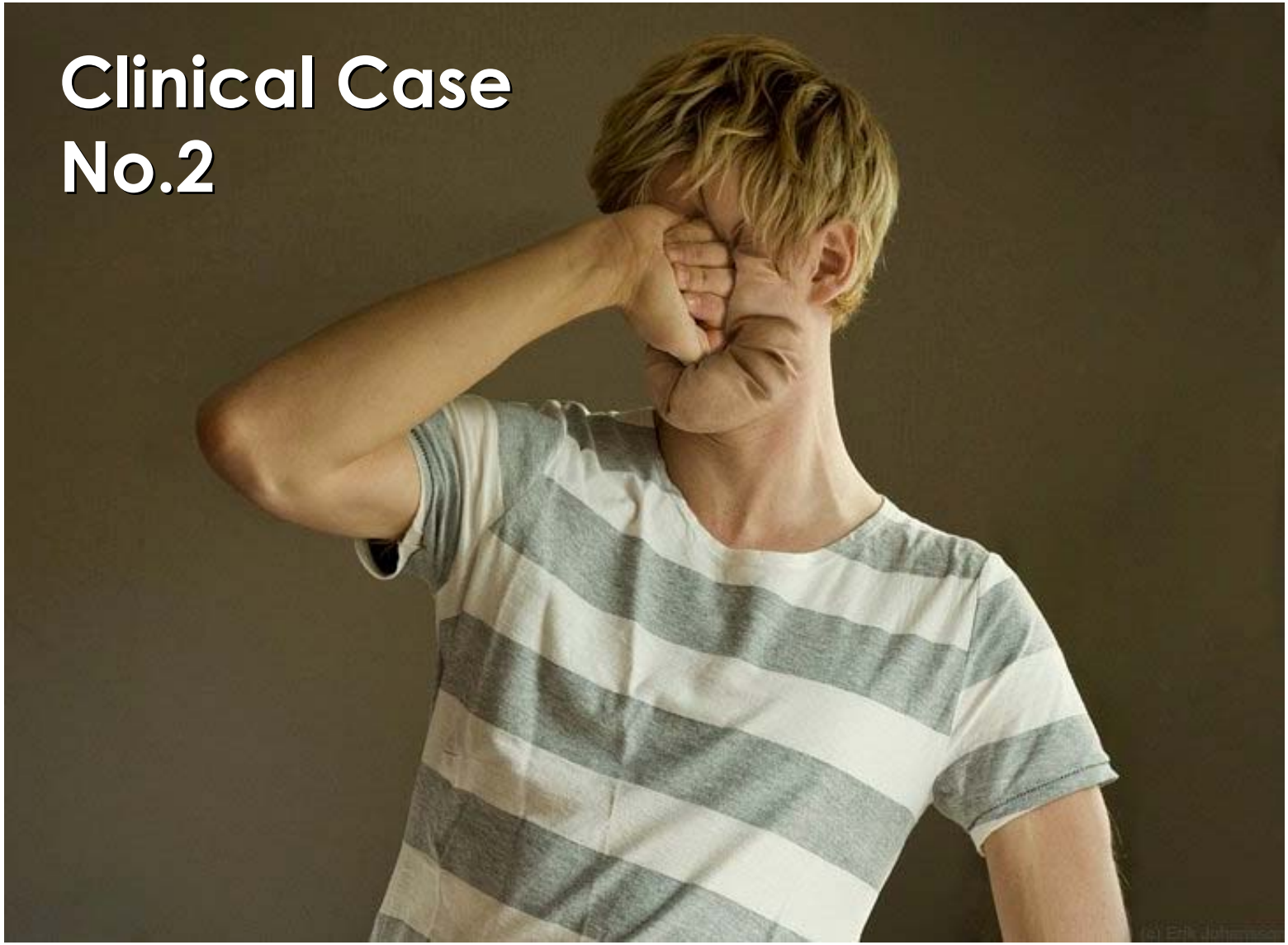
- Progression:
  - mts in the bones
  - fracture of Th12
- Mixed pain – nociceptive + neuropathic:
  - irradiation to arms and legs
  - leg paresis
- Admitted at the PC unit:
  - TTS 75 μg/h
  - tab. DHC 60 mg b.d.
- Baseline pain: 5–6, worse at night
- Sharp BTcP, 2–6 episodes daily

ATC with TTS Patch

- During 5 weeks titrated from **75 µg/h**
  to **100 µg/h** (**19** days) **+ SLF** 100-200 µg – 300-400 µg
  (titrated, 1–3 episodes daily)
- **150 µg/h** (3 days) + **SLF** 400 µg
  (2–5 sharp episodes daily, numeric scale 8–9)
- **200 µg/h** + **SLF** 600 µg
  (2–4 episodes a day, numeric scale 6–7, after SLF 2–3)

- **Adjuvants:** Mannitol, Pregabalin (Lyrica), Dexamethason
  - died a month later with a good pain control

Clinical Case No.2



Eric Johansson, Sweden

Male, 52 yrs old, with right trigeminal neuropathy for 25 years!

- Atypical, dull, stabbing, sharp pain, on scale 8–9
- During the last 2 years daily 2–5 episodes per hour caused by talking, brushing teeth, eating.

  Sensitization of pain!

Previous treatment – no malformation on MR or other investigations

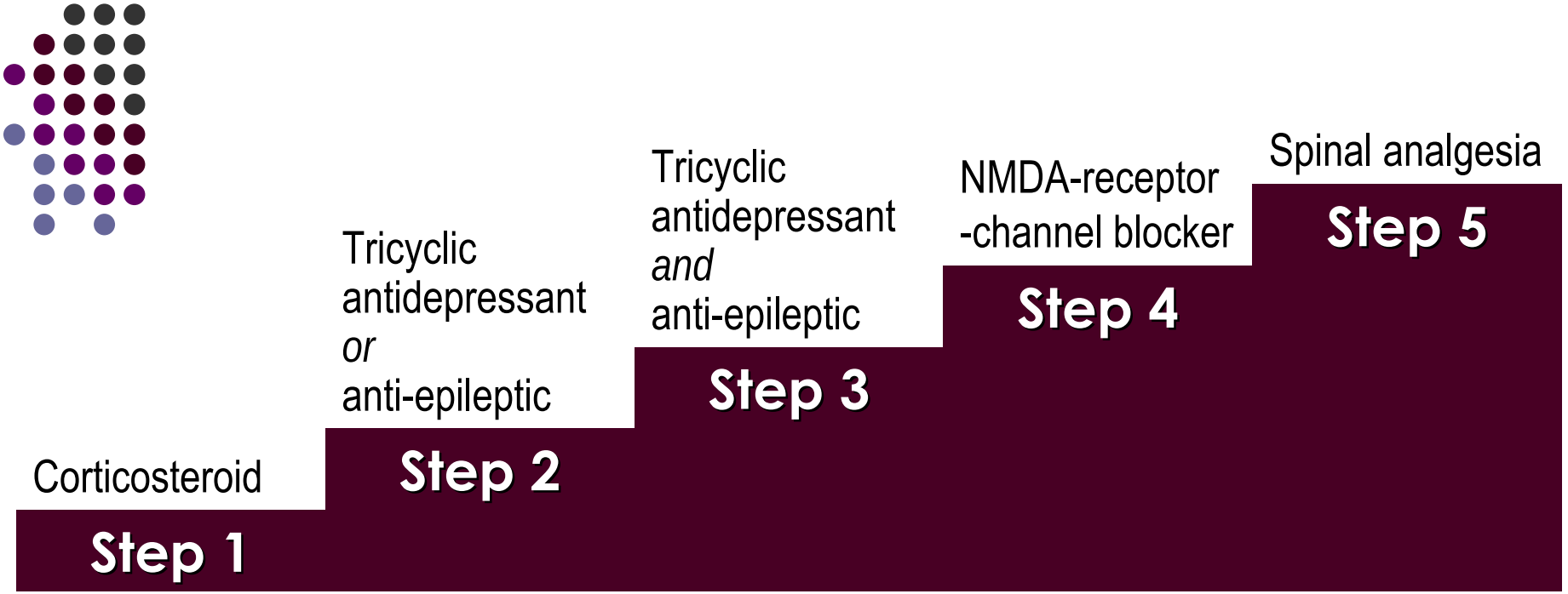
- **In 2010 decompression surgery of the right trigeminal nerve root:**

  Teflon septum inserted between the blood vessel and the nerve root not to compromise the nerve

  ↓

  No clinical effect

- Received **Carbamazepin** (**2000 mg daily**), **Amitryptilin**, **Tramadol**, **DHC** – without effect
- **Alternative therapy** 6 weeks in India with **leeches** put on the painful areas to suck the blood – relative, short-term improvement



Adjuvant analgesics for neuropathic pain (NP).
In cancer pain use only if the pain does not respond to the combined use of a **NSAID** and a **strong opioid**.

Corticosteroids used if NP is associated with limb weakness.

Robert Twycross and Andrew Wilcock.
Symptom Management in Advanced Cancer.
Third edition. 2001.

Patient was admitted to the PC unit on January, 2012

- Pain episodes according the scale 8–9
- Ineffective
  - Pregabalin, Amitryptilin, Morphine (inj),
  - Doltard up to 90 mg x 2 p/o
- To stop the frequent 10–12 pain episodes per hour (ex iuvantibus) **SLF 200 µg** was given and pain was controlled... for 40 minutes!

Treatment Trajectory

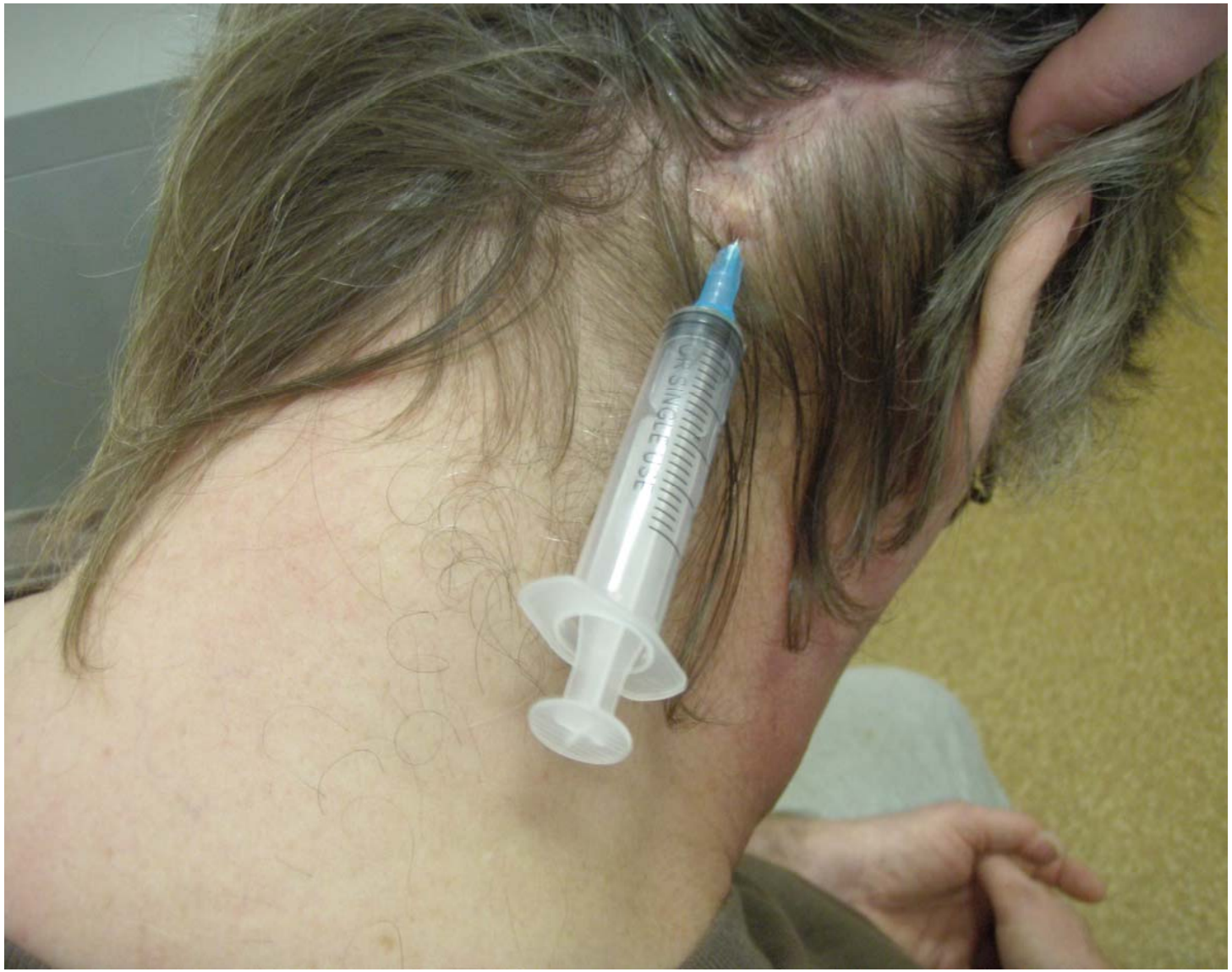
ATC with TTS 25 µg/h ⋯⋯⋯⋯► 300 µg/h

BTP with SLF 200 µg ⋯⋯⋯⋯⋯► 600 µg

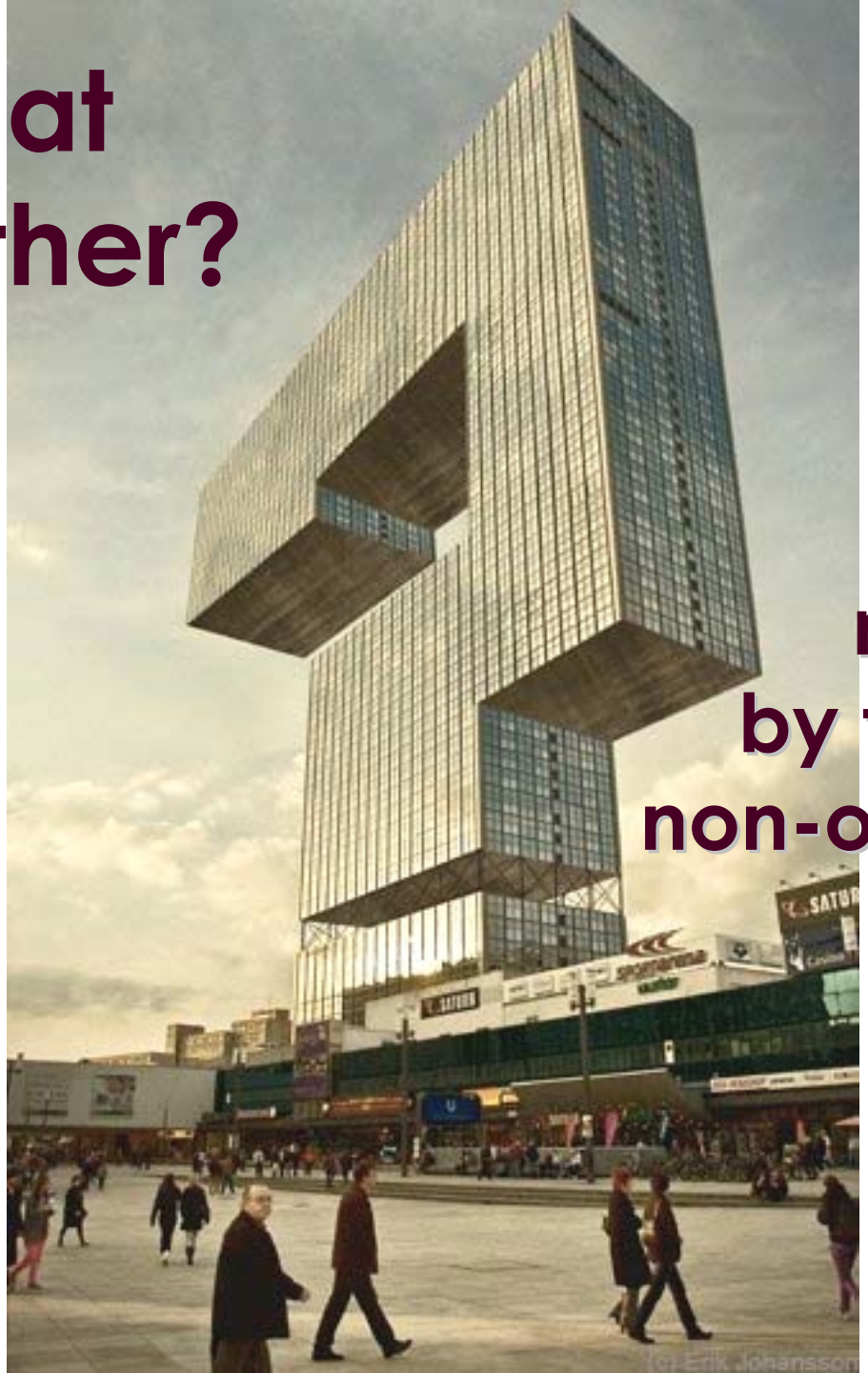
→1–3 pain episodes per day, intensity 5–6

→for 12–14 hours helpful **root neural blocks** beneath the scar with **Lidocain 2% – 5 ml + Dexamethason 8 mg**

(trigger point injections had weak effect)



What further?



Opioids are not reimbursed by the State in non-oncological diseases...

Eric Johansson, Sweden

BTcP

- BTcP in oncology 19–95%
- In 75% not properly treated
- Rapid onset (in 3–4 minutes)
- BTcP episode
  in 64% of case is up to 30 minutes,
  in 2% up to 2 hrs
- In non-oncology BTP is 63–74%

Titration of the Dose

Adjust, titrate ATC + BTP + adjuvants!

Balanced ATC + adjuvants → reduce BTP!

Eric Johansson, Sweden