Together against pain

Leiden University Medical Center

Approaches on treatment of chronic pain in the clinic

Albert Dahan MD PhD
Professor of Anesthesiology
Head of the Anesthesia & Pain Research Unit
Leiden University

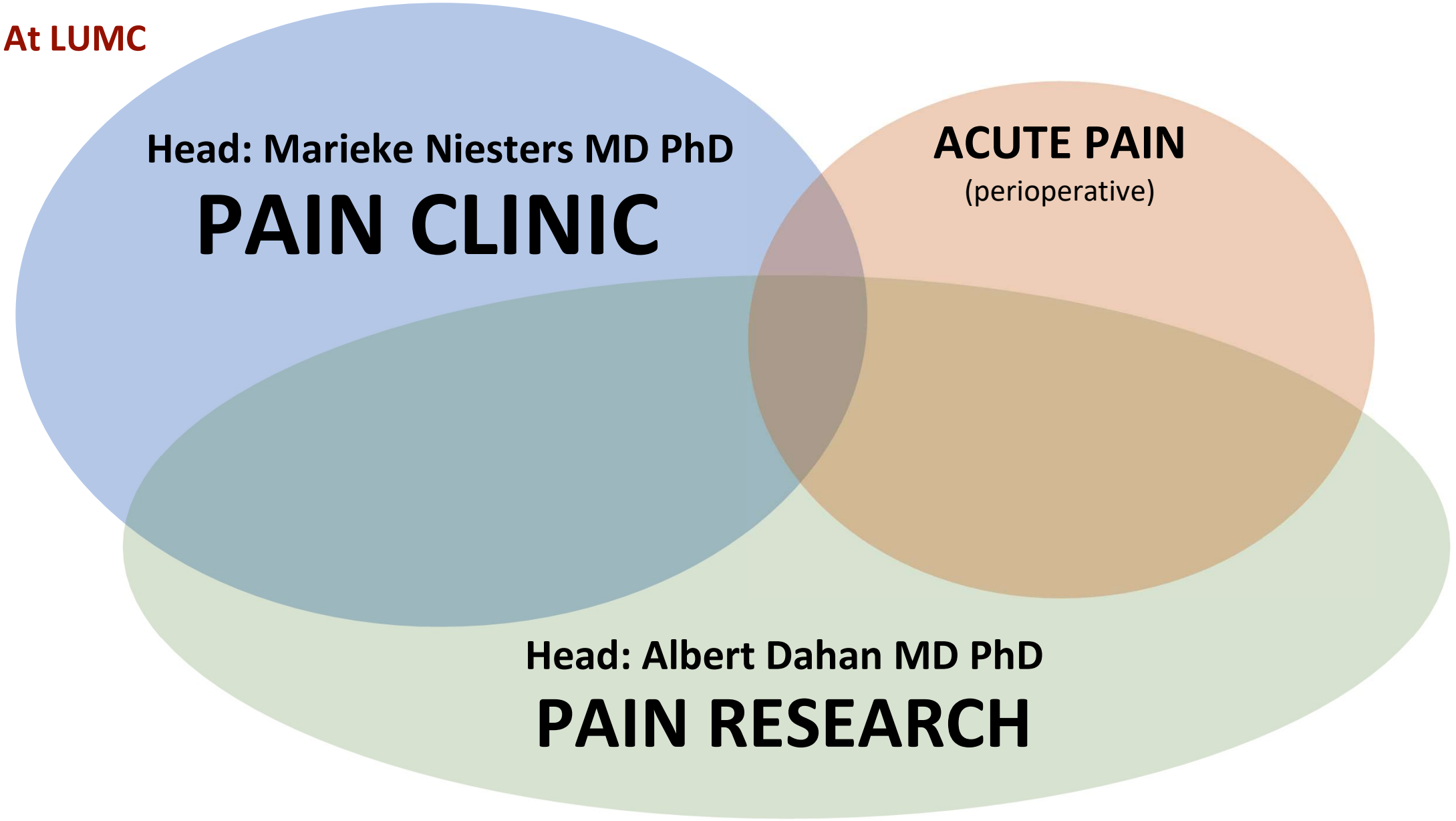
Conflicts of interest

1. ZonMW Grants: TAPTOE, Cannabis project with CHDR

2. Strategic collaboration with the FDA (opioid-interaction with antipsychotics and antidepressants; reversal of opioid induced respiratory depression)

3. Educational grants from MSD/Merck & Co., Medtronic, Grünenthal, Medasense, Trevena, Indivior, Eurocept, Shell

4. Speciality section editor Neuropathic Pain *Frontiers in Pain Research,* Associate editor **Pain**, Associate editor *Anesthesiology*


At LUMC
Head: Marieke Niesters MD PhD
PAIN CLINIC
ACUTE PAIN
(perioperative)
Head: Albert Dahan MD PhD
PAIN RESEARCH

Our current clinical approach (chronic noncancer pain)

- Step 1 Triage
- Step 2 Visit to the clinic (45-60 min)
- Step 3 Multidisciplinary consultation
- Step 4 Shared decision making
- Step 5 Treatment (pharmacological, intervention, wait-and-see)
- Step 6 Review and reconsideration

An example

- 45 yr old patient tumor of the jaw
- 1 yr ago surgery: tumor removal (not completely)
- Neuropathic symptoms, phantom sensations - pain?
- Step 2 and 3 planned
- Step 4: Diagnosis
- Step 5 Treatment
- Step 6 Review

Pharmacological treatment of chronic noncancer pain

- **Nociceptive**
  - Acetaminophen
  - NSAIDs
  - Tramadol
  - **Tapentadol (MOR and NRI)**
- **Neuropathic**
  - Antidepressants (SNRIs, SSRIs, TCA)
  - Antiepileptics (pregabalin, gabapentin)

- Mixed (nociceptive and neuropathic)
- Visceral
- Ischemic

Interventional treatment of chronic noncancer pain

- TENS
- Qutenza (capsaicin patch)
- Corticosteroid injection
- PRF (pulsed radiofrequency) and RF
- Neuromodulation
- Surgery

Cancer pain: neurolytic blocks

Phenotypical dependent treatment

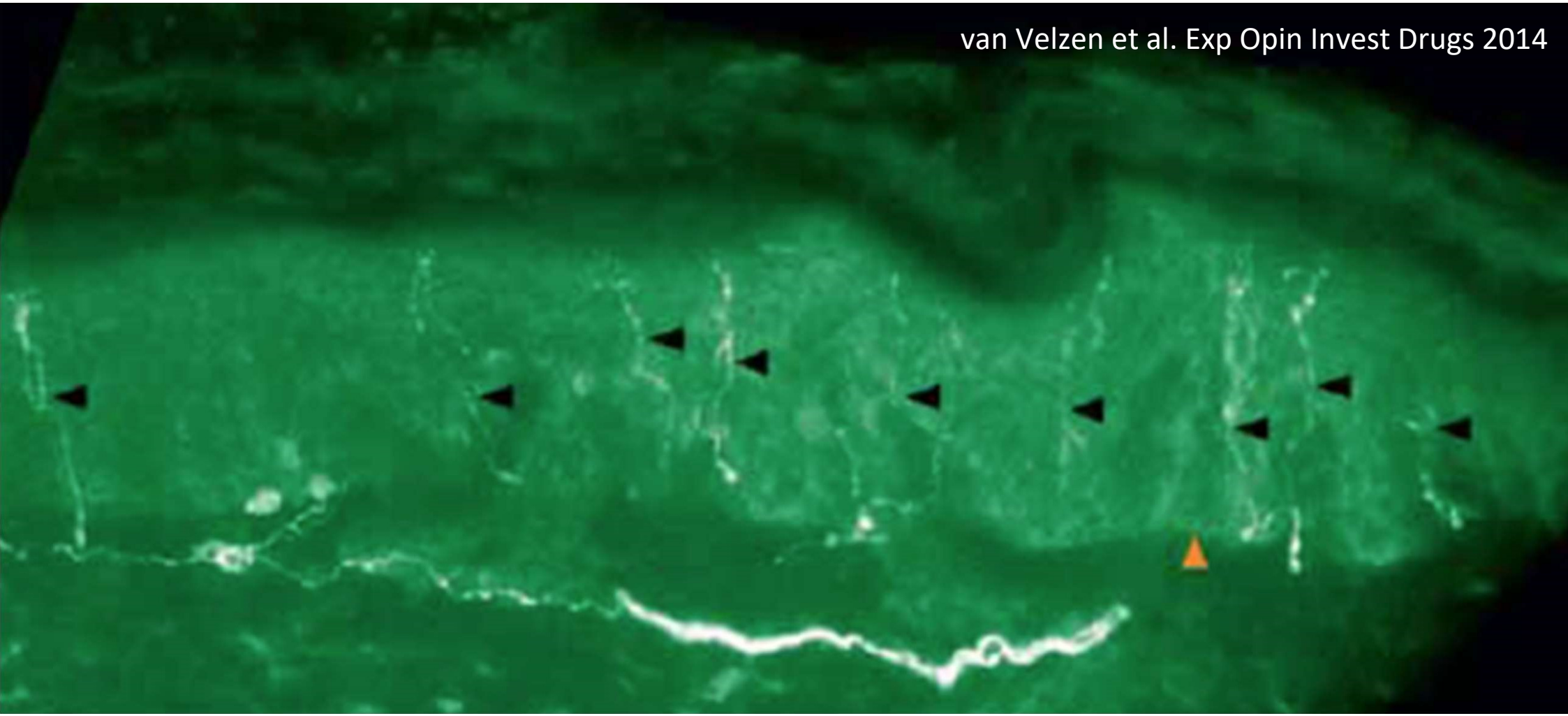
Treatment of groups based on phenotype not on underlying disease

- Quantitative sensory testing (QST)
- Cornea confocal microscopy (CCM)
- Questionnaires
- Endogenous pain modulation testing (CPM and OA)

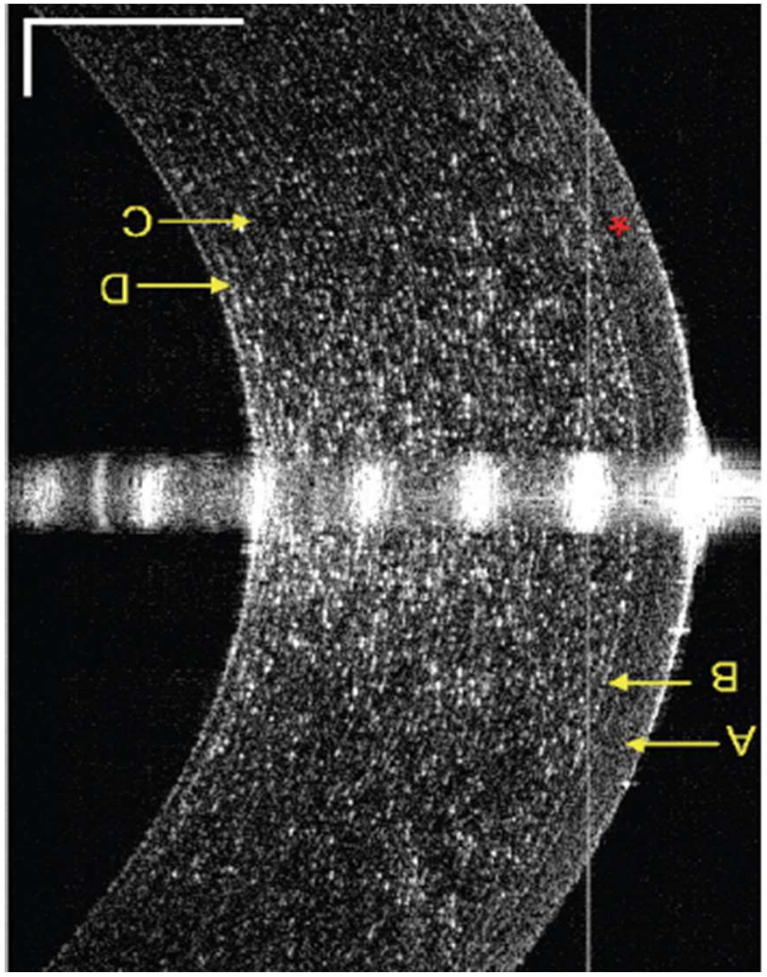
An example of one such strategy

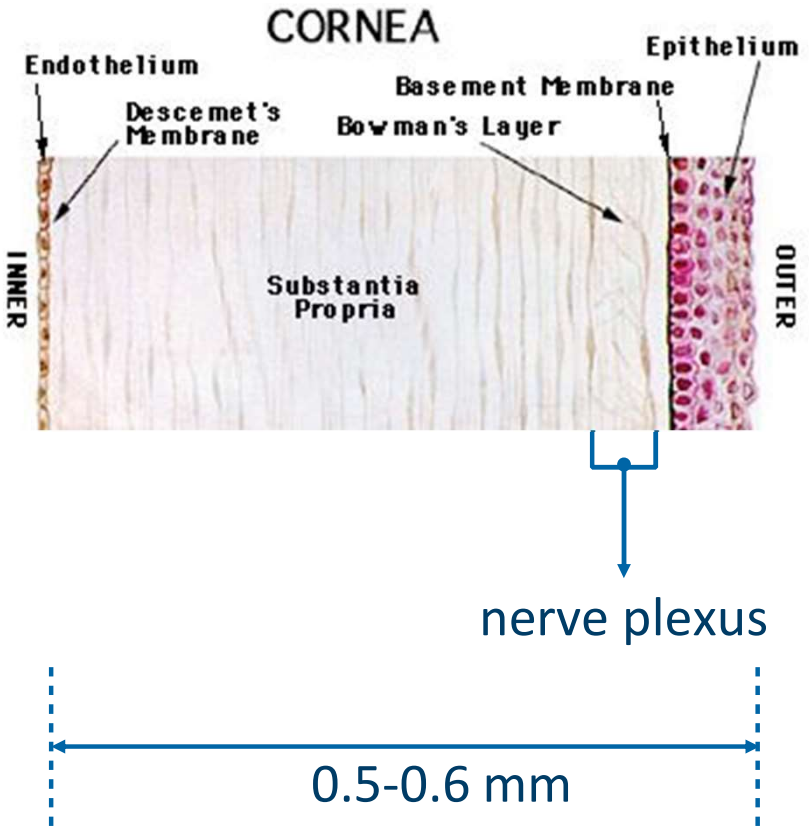
- Allodynia +/- AND
- CPM +/- AND
- OA +/- AND
- Temporal summation: central sensitization +/- AND
- CCM normal/abnormal

Skin biopsy: Aδ and C-fibres

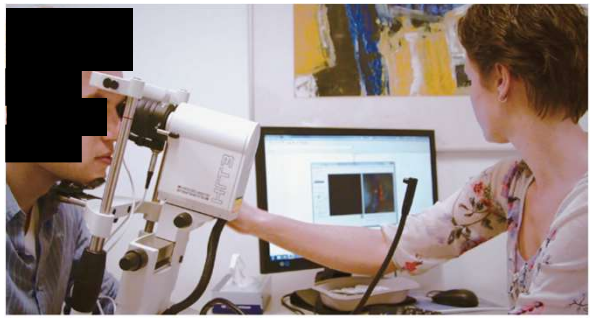


Cornea Confocal Microscopy

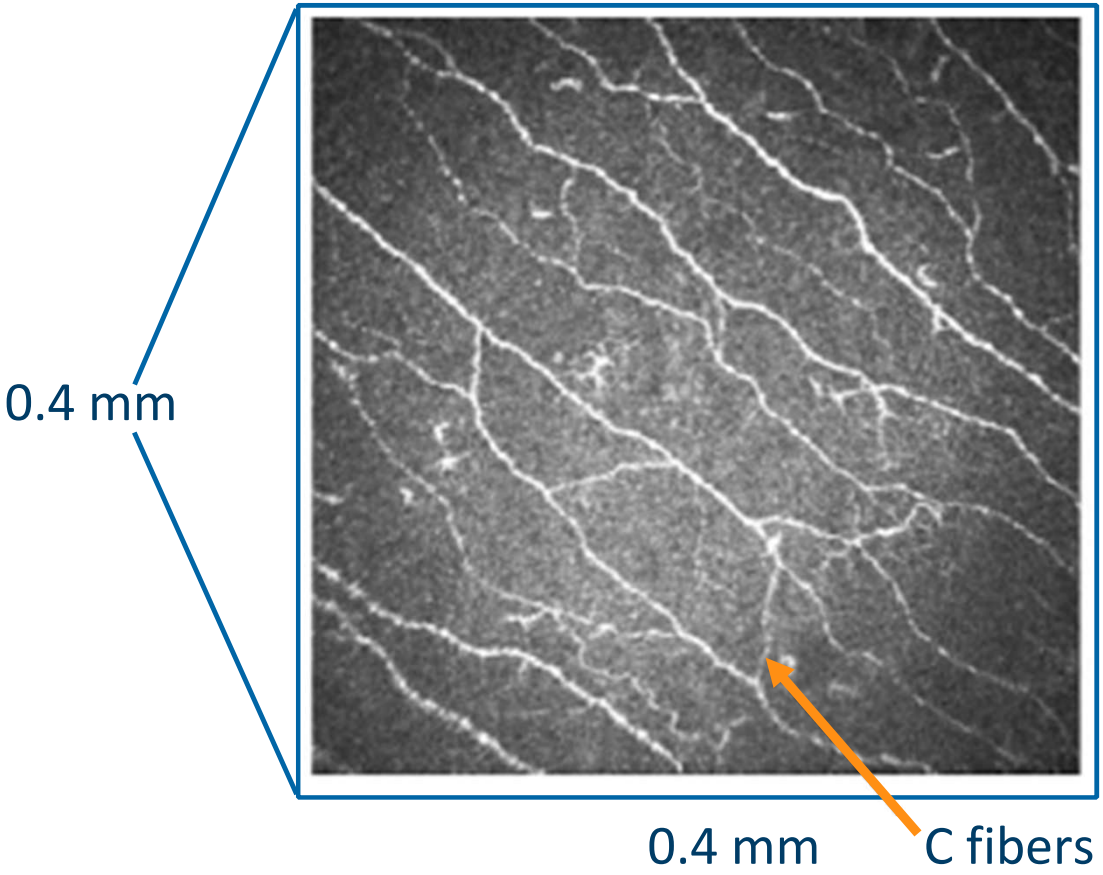


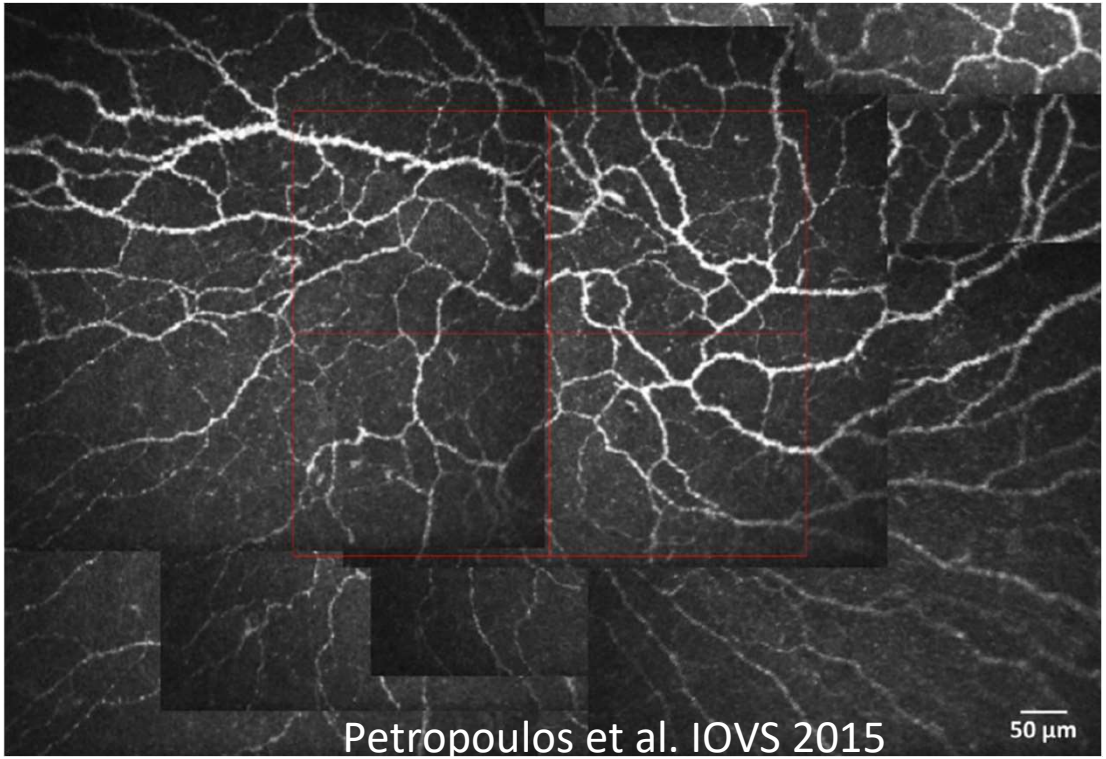


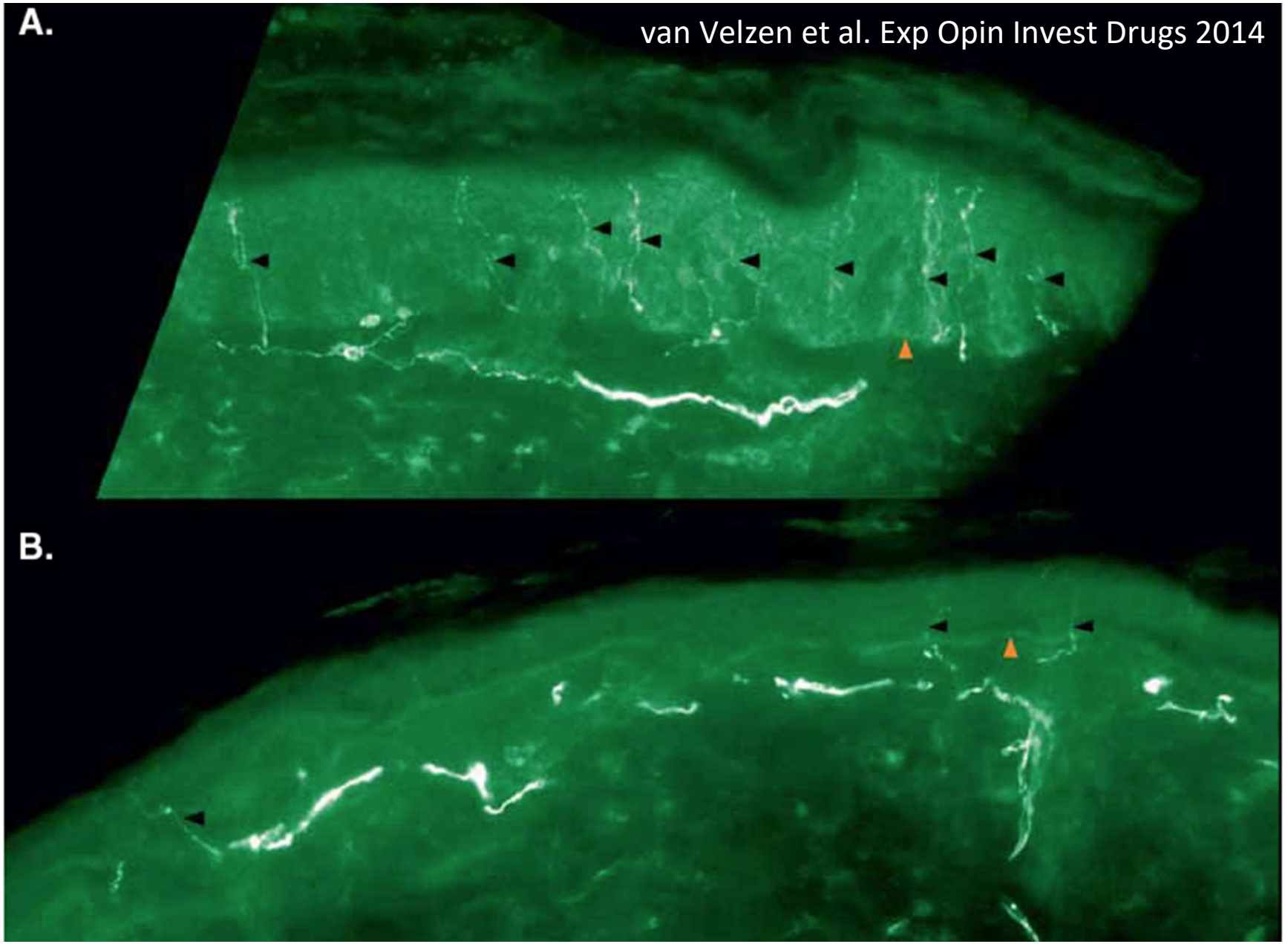
- Density n/mm^2
- Length mm/mm^2
- Branching n/mm^2



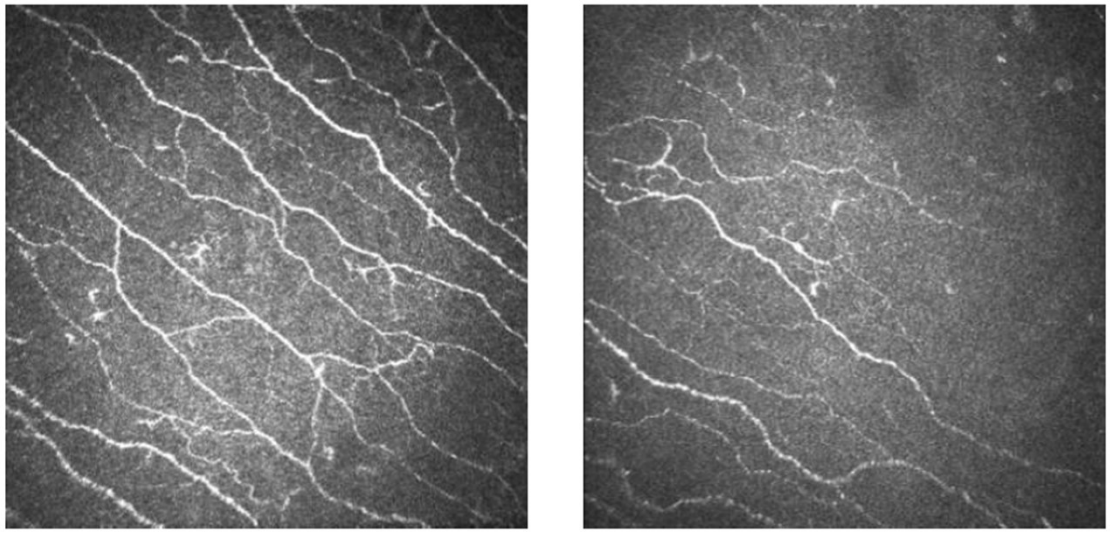
Normal Cornea



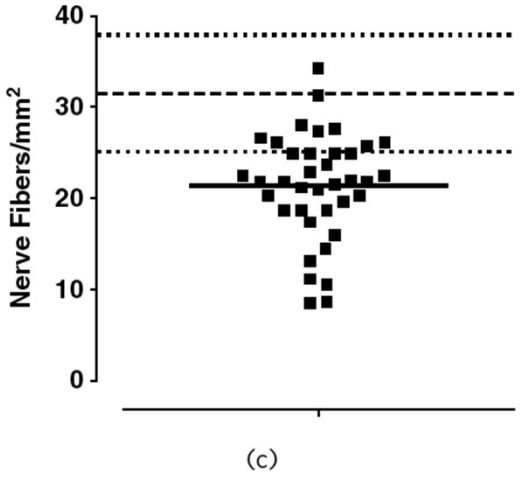


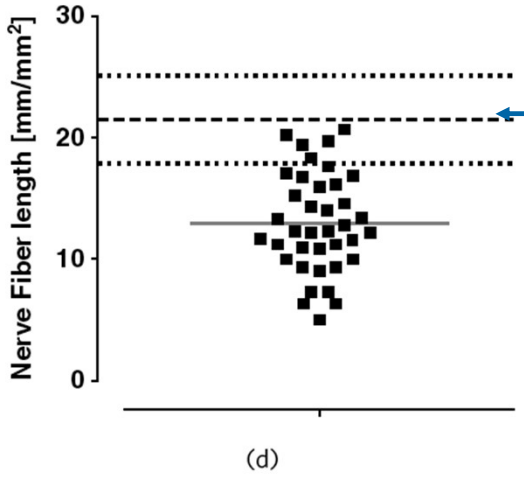

A.
van Velzen et al. Exp Opin Invest Drugs 2014
B.

NORMAL **SFN**



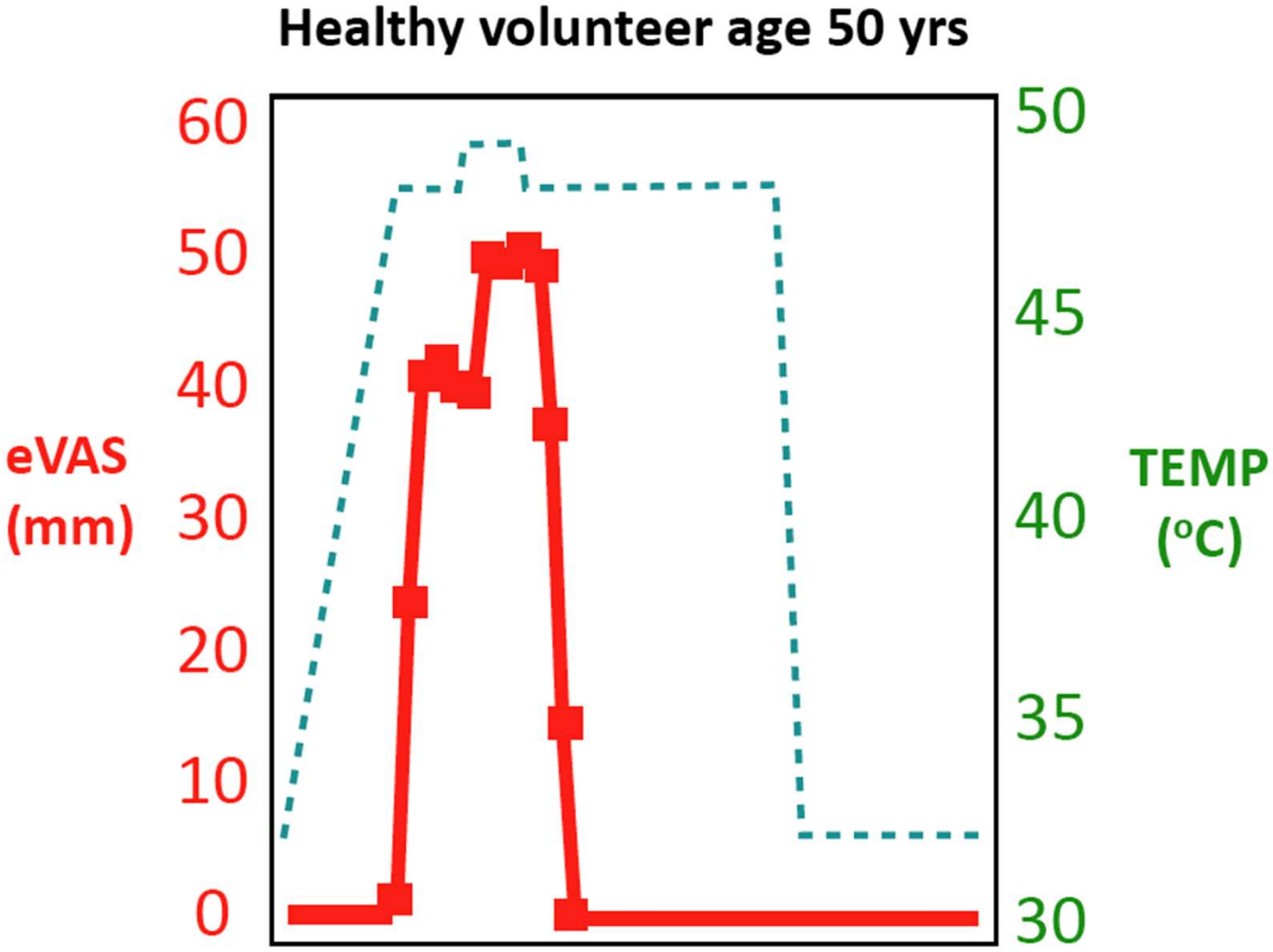
Cornea Nerve Density **Cornea Nerve Length**





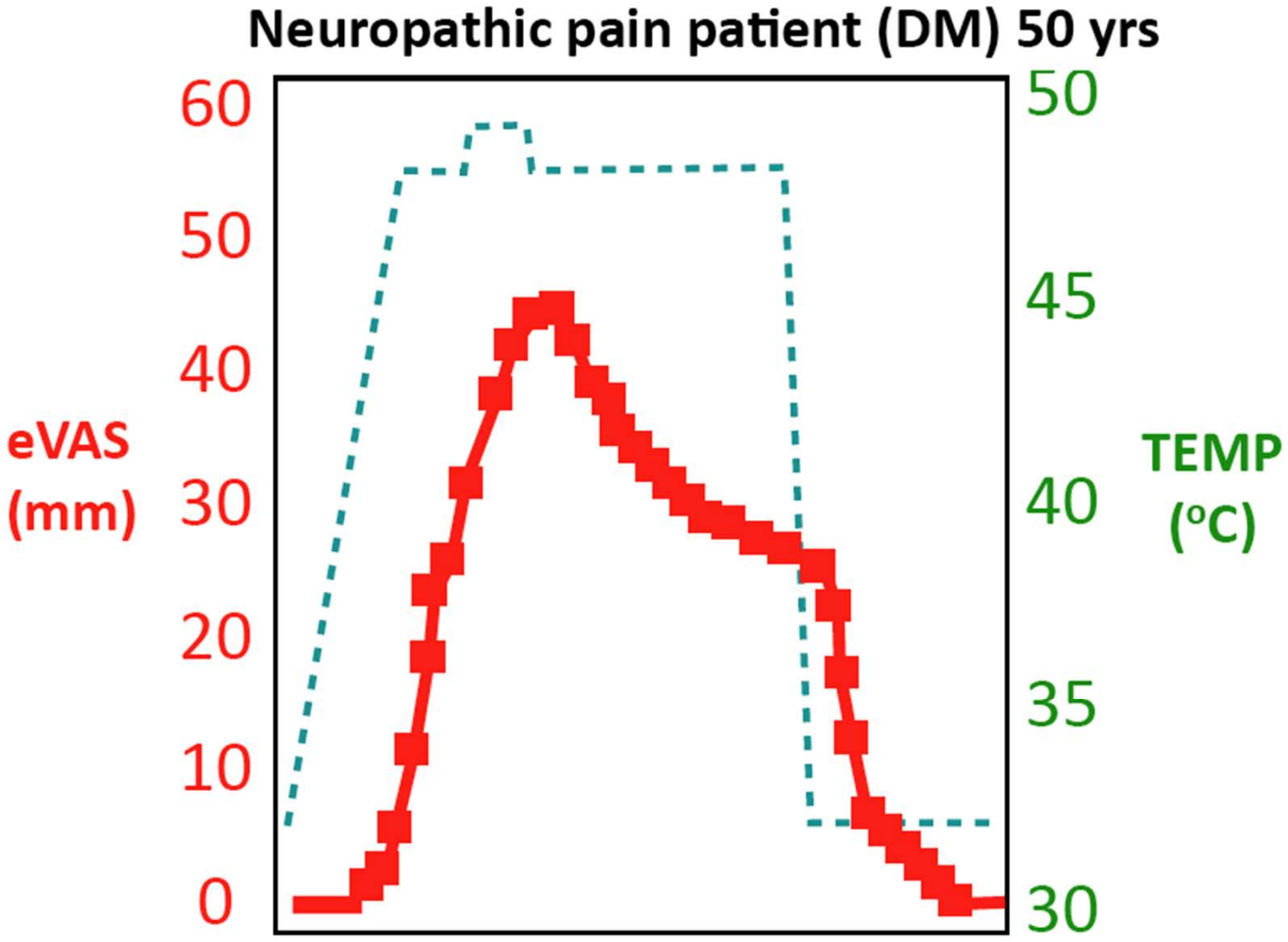
normal

Offset Analgesia



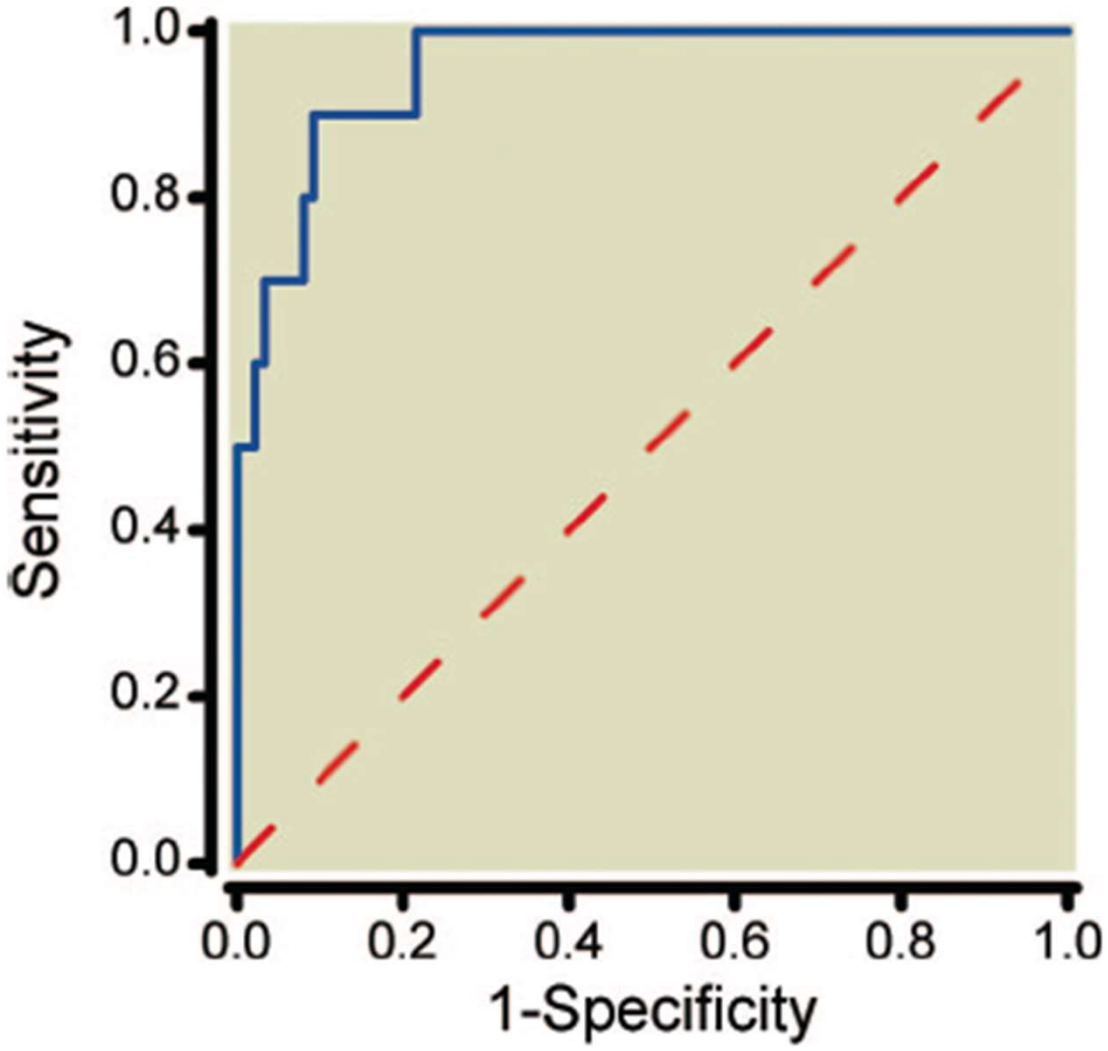
Niesters et al. 2016

Offset Analgesia



Niesters et al. 2016

Offset Analgesia



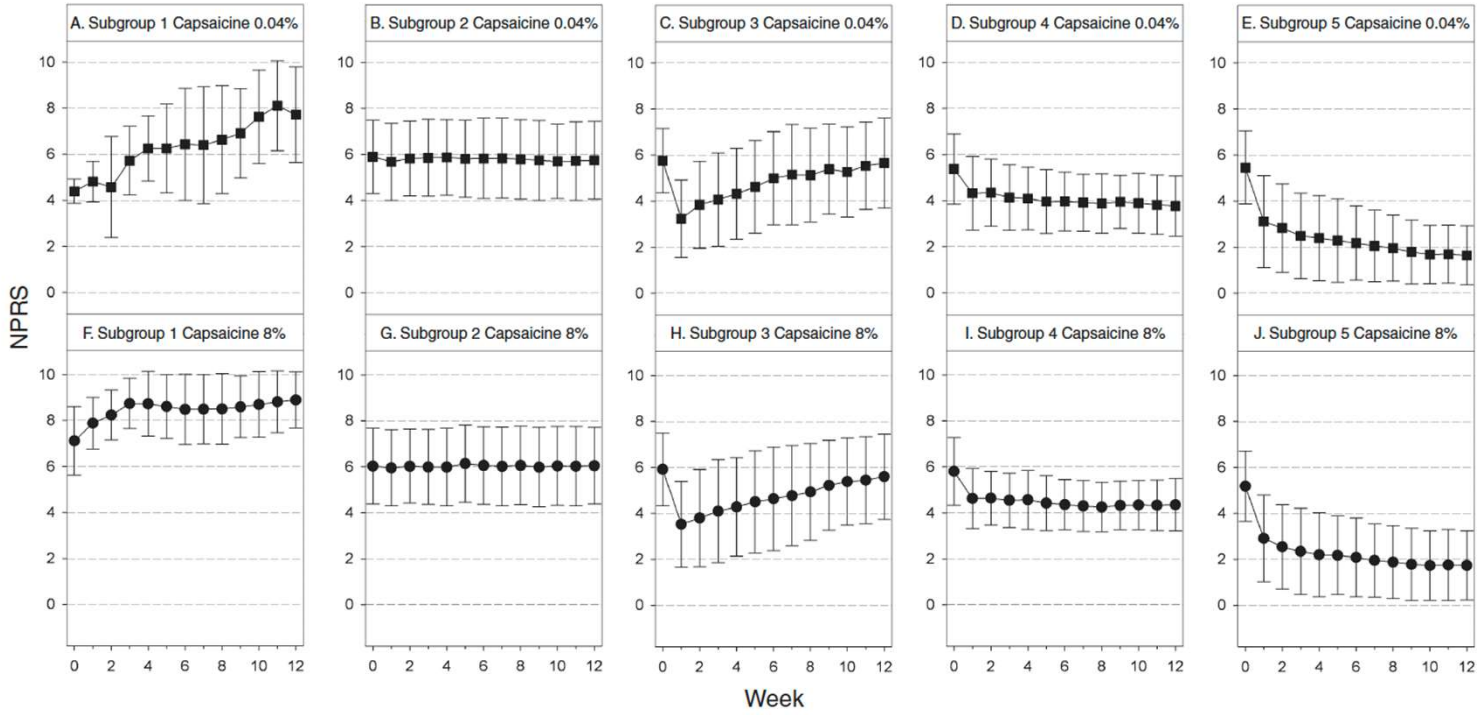
		T2DM	Sarcoidosis	Fibromyalgia	**All**
CCM normal	*No signs of Central Sensitization*	10%	19%	31%	**20%**
	Yes signs of Central Sensitization	35%	36%	18%	**30%**
CCM not normal	*No signs of Central Sensitization*	16%	29%	21%	**22%**
	Yes signs of Central Sensitization	39%	16%	31%	**29%**

European Journal of Pain
2013

ORIGINAL ARTICLE

A novel approach to identify responder subgroups and predictors of response to low- and high-dose capsaicin patches in postherpetic neuralgia

C.H. Martini[1]*, A. Yassen[2]*, A. Krebs-Brown[3], P. Passier[2], M. Stoker[4], E. Olofsen[1], A. Dahan[1]

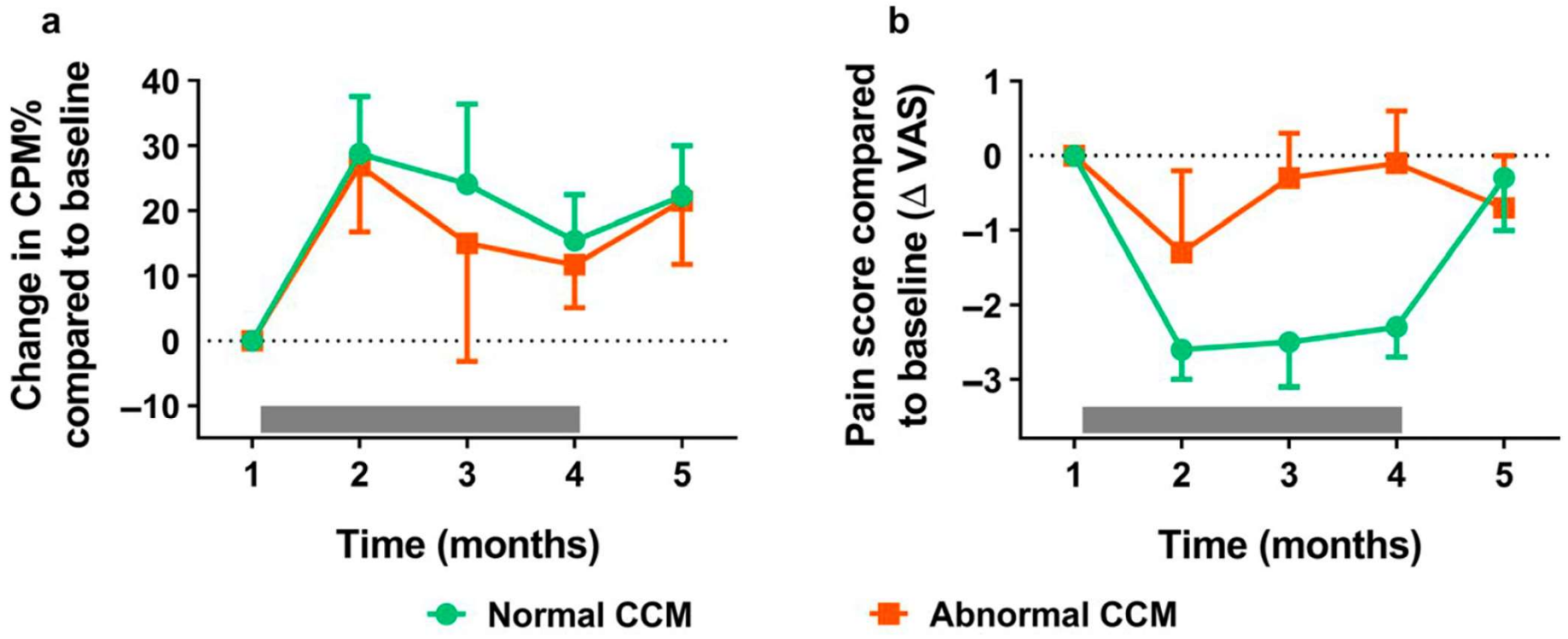


ORIGINAL ARTICLE

EJP European Journal of Pain WILEY 2019

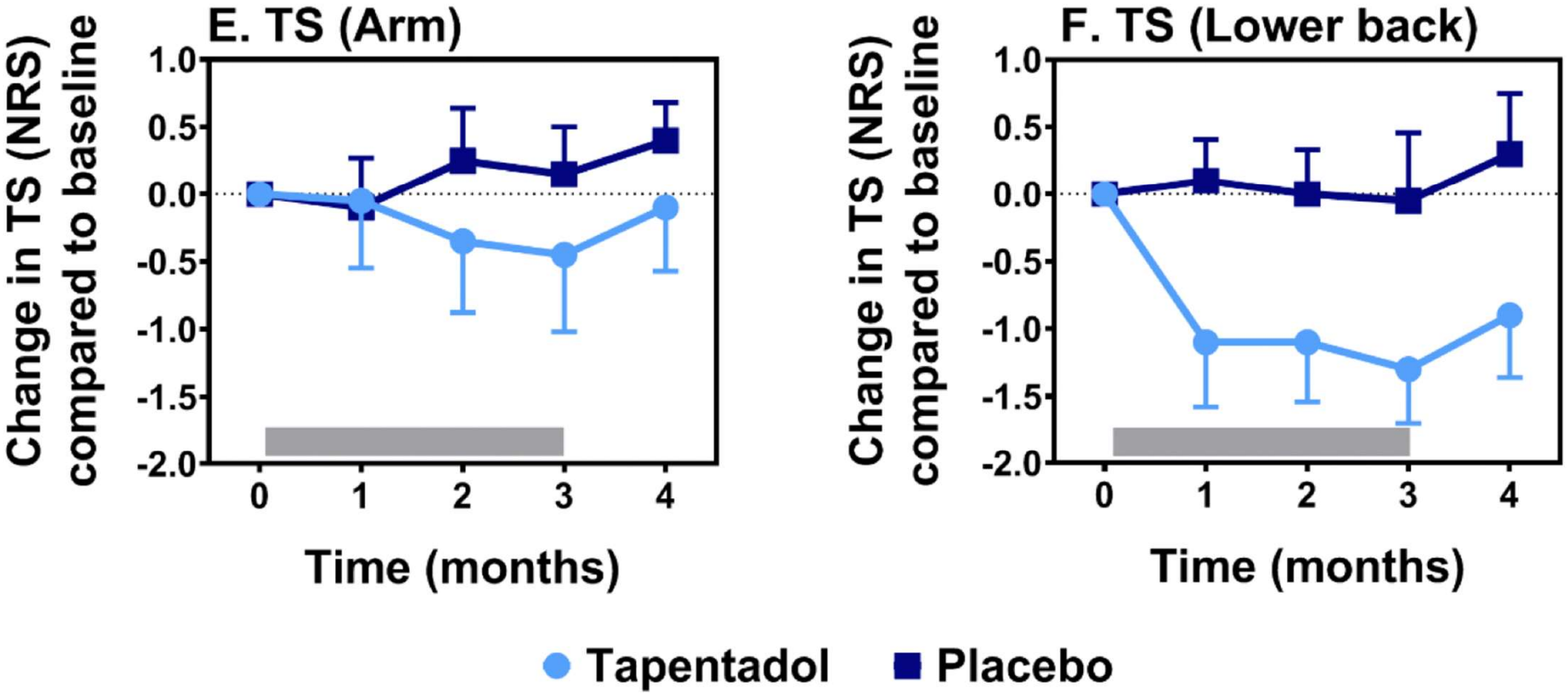
Cornea nerve fibre state determines analgesic response to tapentadol in fibromyalgia patients without effective endogenous pain modulation

Tine van de Donk | Monique van Velzen | Albert Dahan | Marieke Niesters



Tapentadol treatment results in long-term pain relief in chronic low back pain patients and associates with reduced segmental sensitization

Tine van de Donk et al. Pain Reports 2020



New pharmacological options

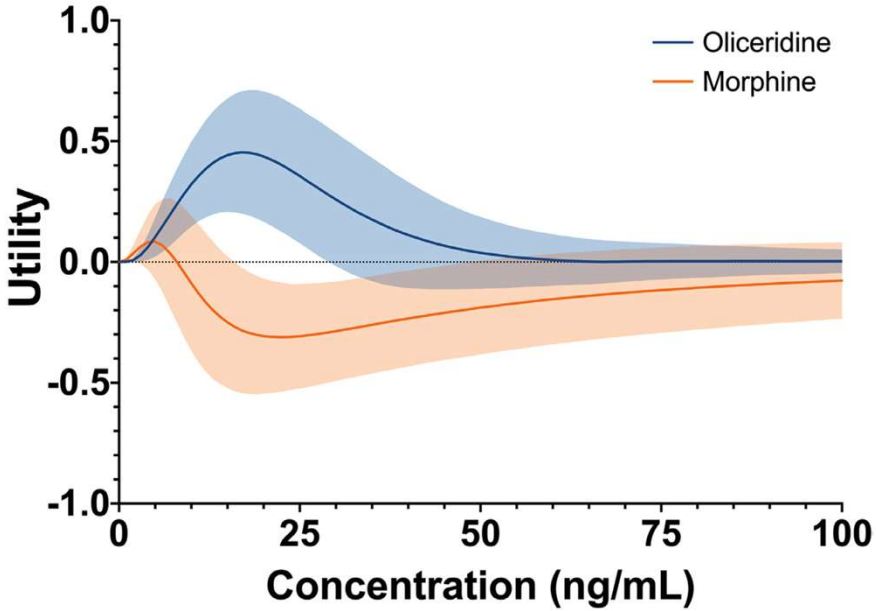
- Cannabis/cannabinoids
- Biased ligands (opioids)
- Enhancement of endogenous pain modulation
- Anti-inflammatory agents (biologicals)
- **Benefit – harm assessment**
- Stimulants/antagonistst to increase dosing

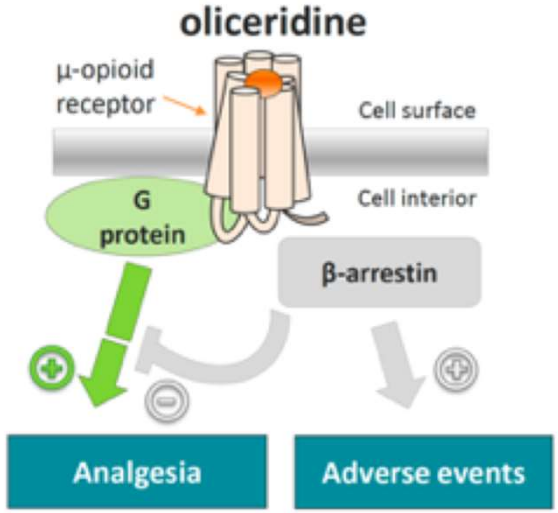
ANESTHESIOLOGY

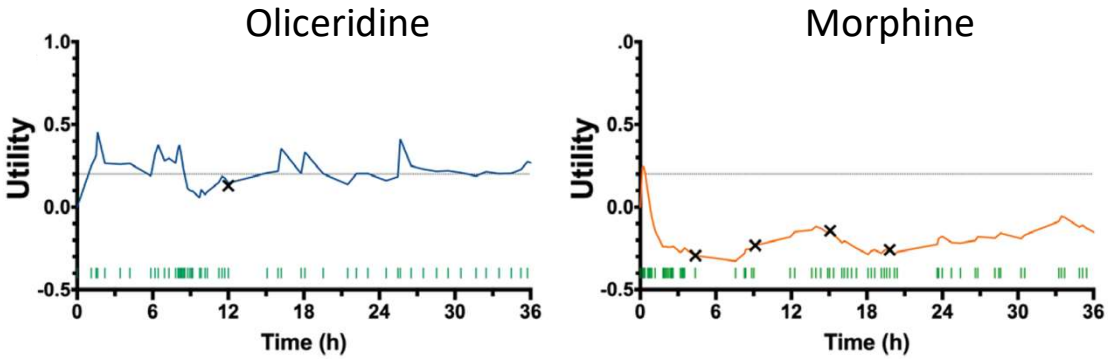
Benefit and Risk Evaluation of Biased μ-Receptor Agonist Oliceridine *versus* Morphine

Albert Dahan, M.D., Ph.D., C. Jan van Dam, M.D., Marieke Niesters, M.D., Ph.D., Monique van Velzen, Ph.D., Michael J. Fossler, Pharm.D., Ph.D., Mark A. Demitrack, M.D., Erik Olofsen, Ph.D.

ANESTHESIOLOGY 2020; 133:559–68







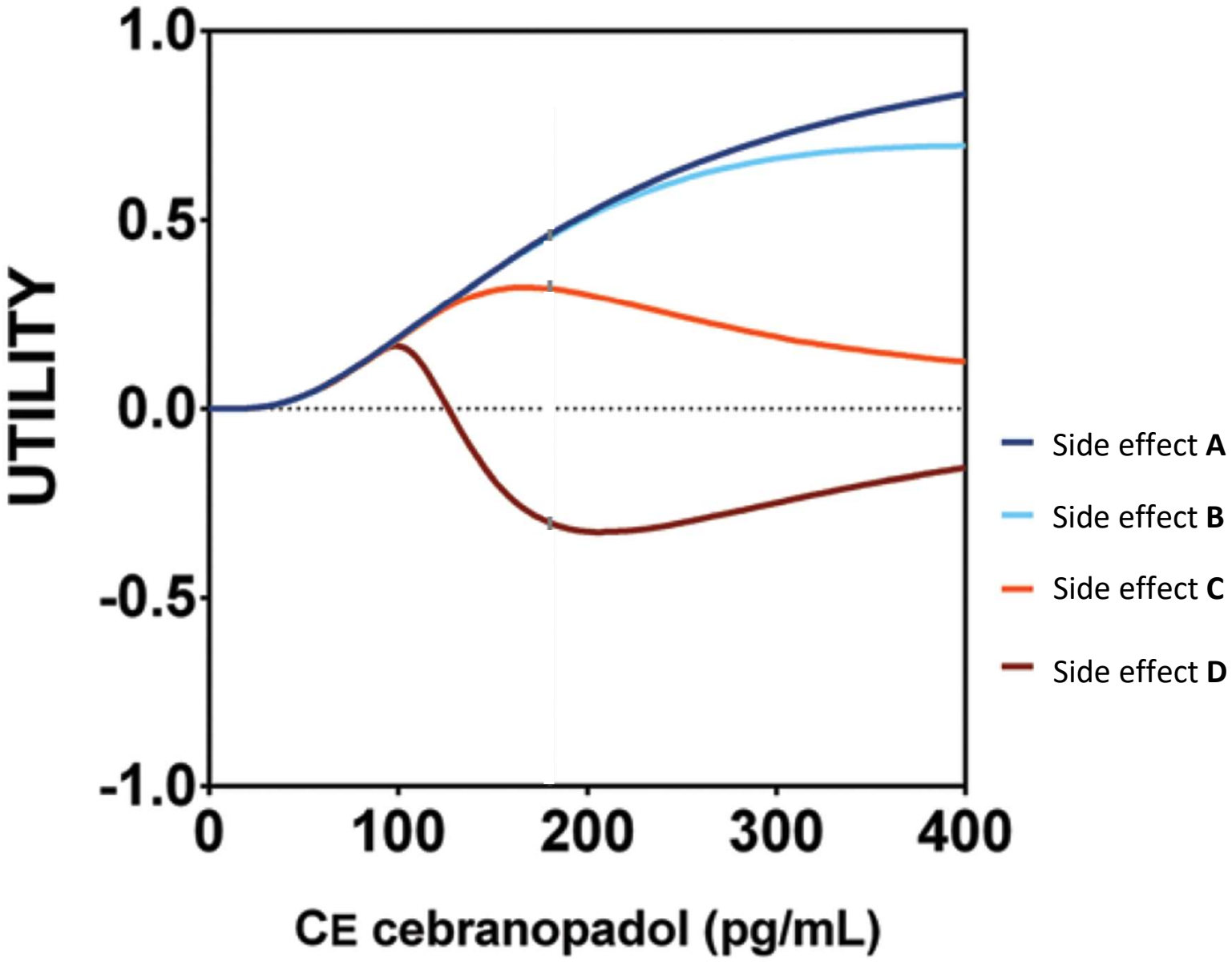
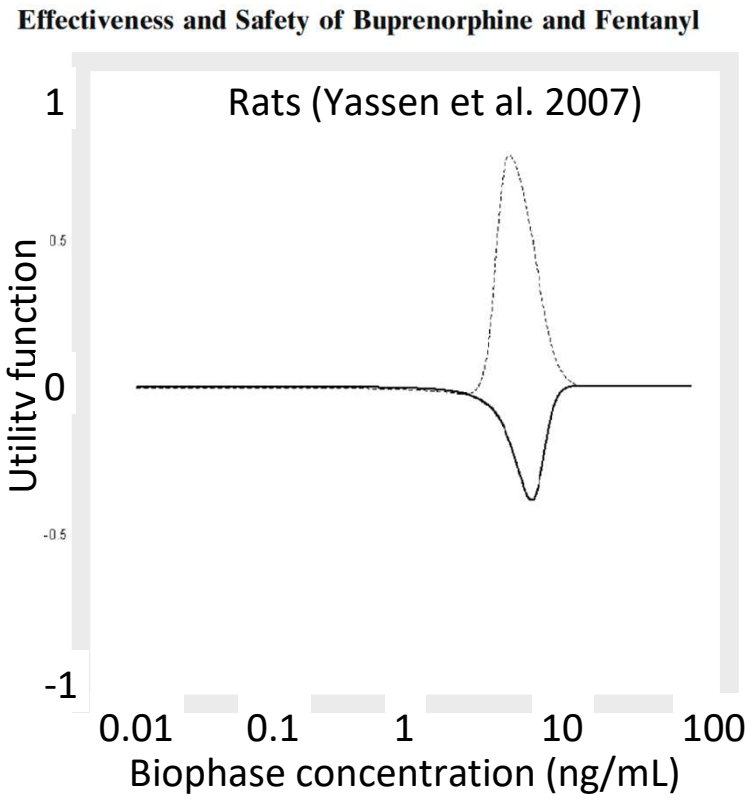
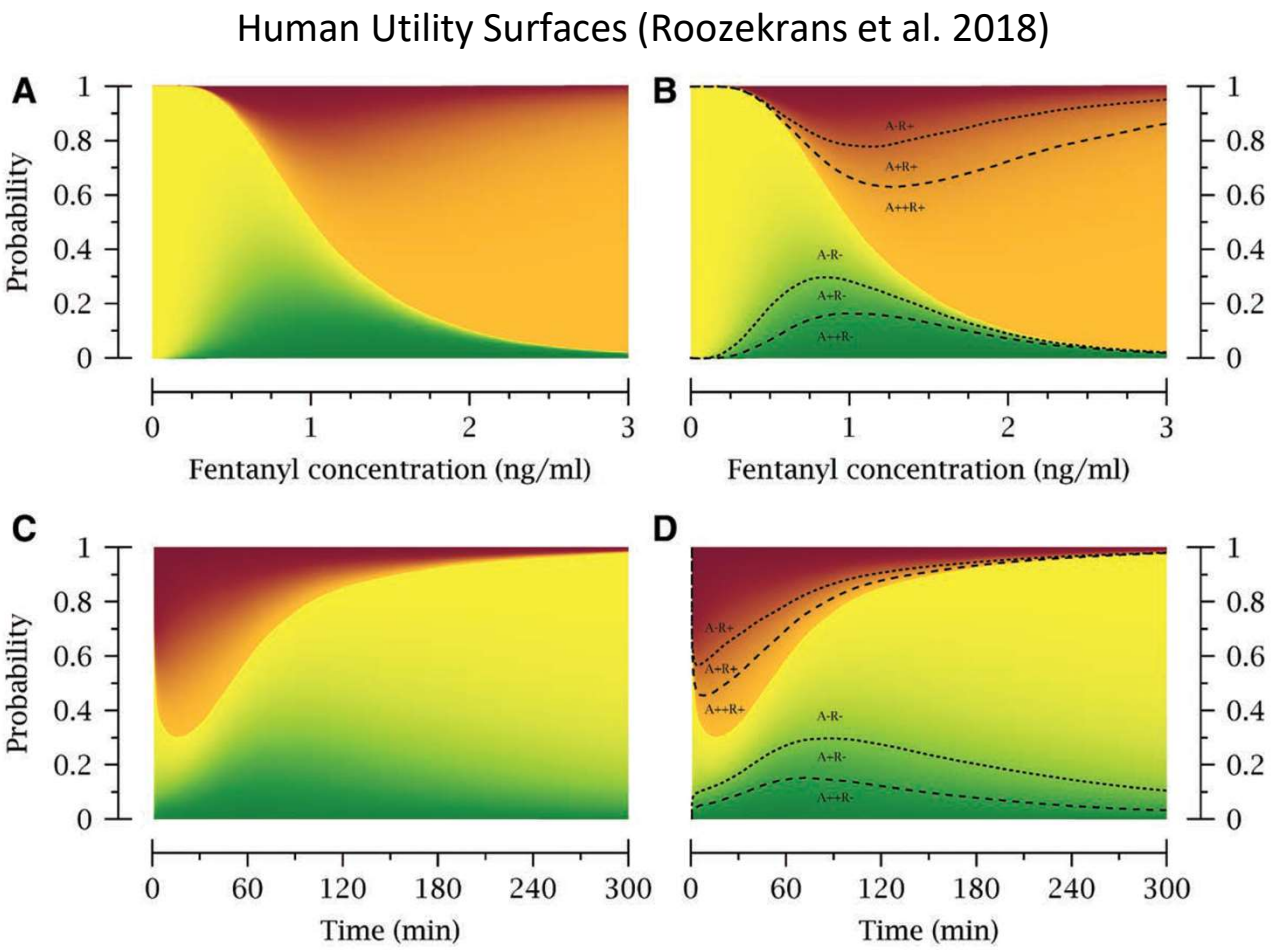

1.0
0.5
0.0
-0.5
-1.0
UTILITY
0
100
200
300
400
CE cebranopadol (pg/mL)
Side effect A
Side effect B
Side effect C
Side effect D

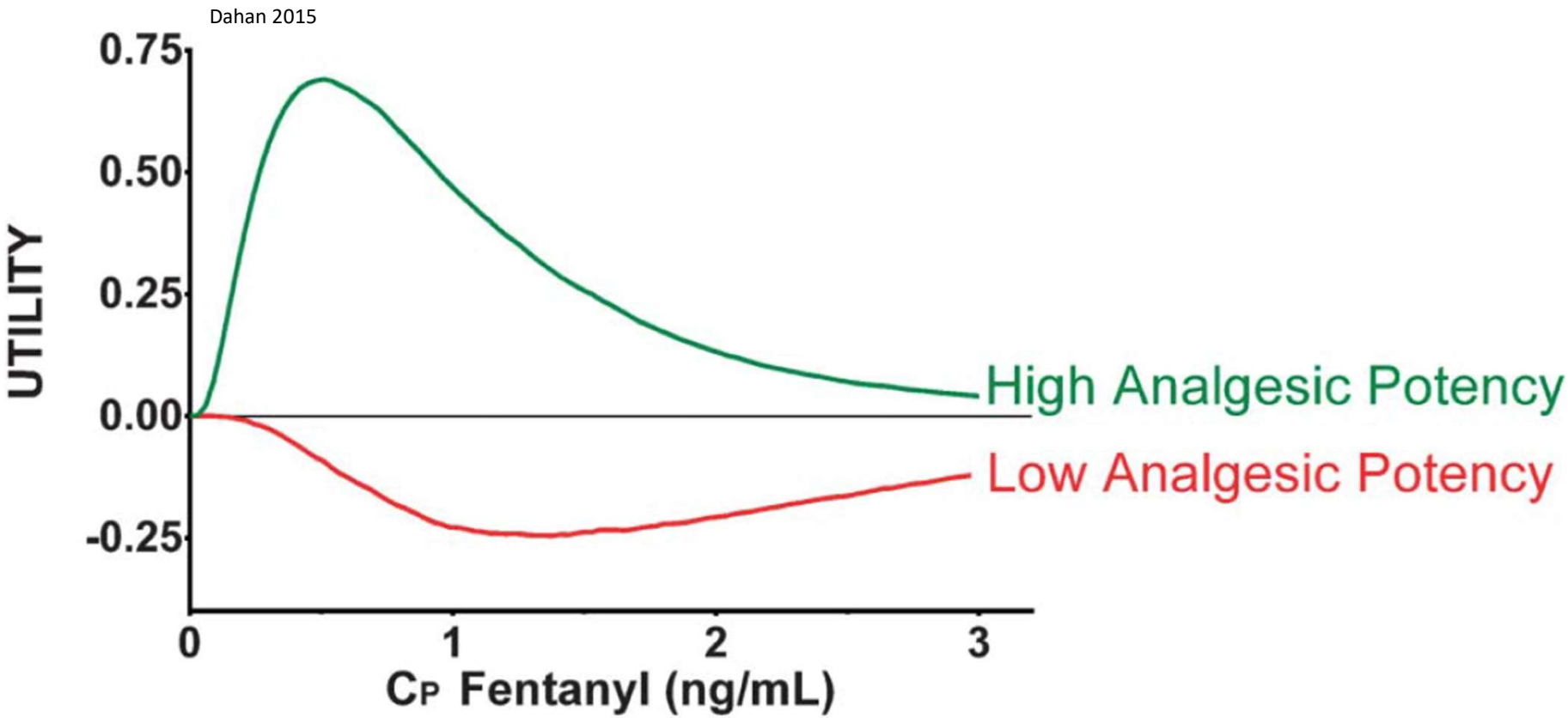
Table 1 Construction of the utility functions and surfaces based on pharmacokinetic-pharmacokinetic modeling studies

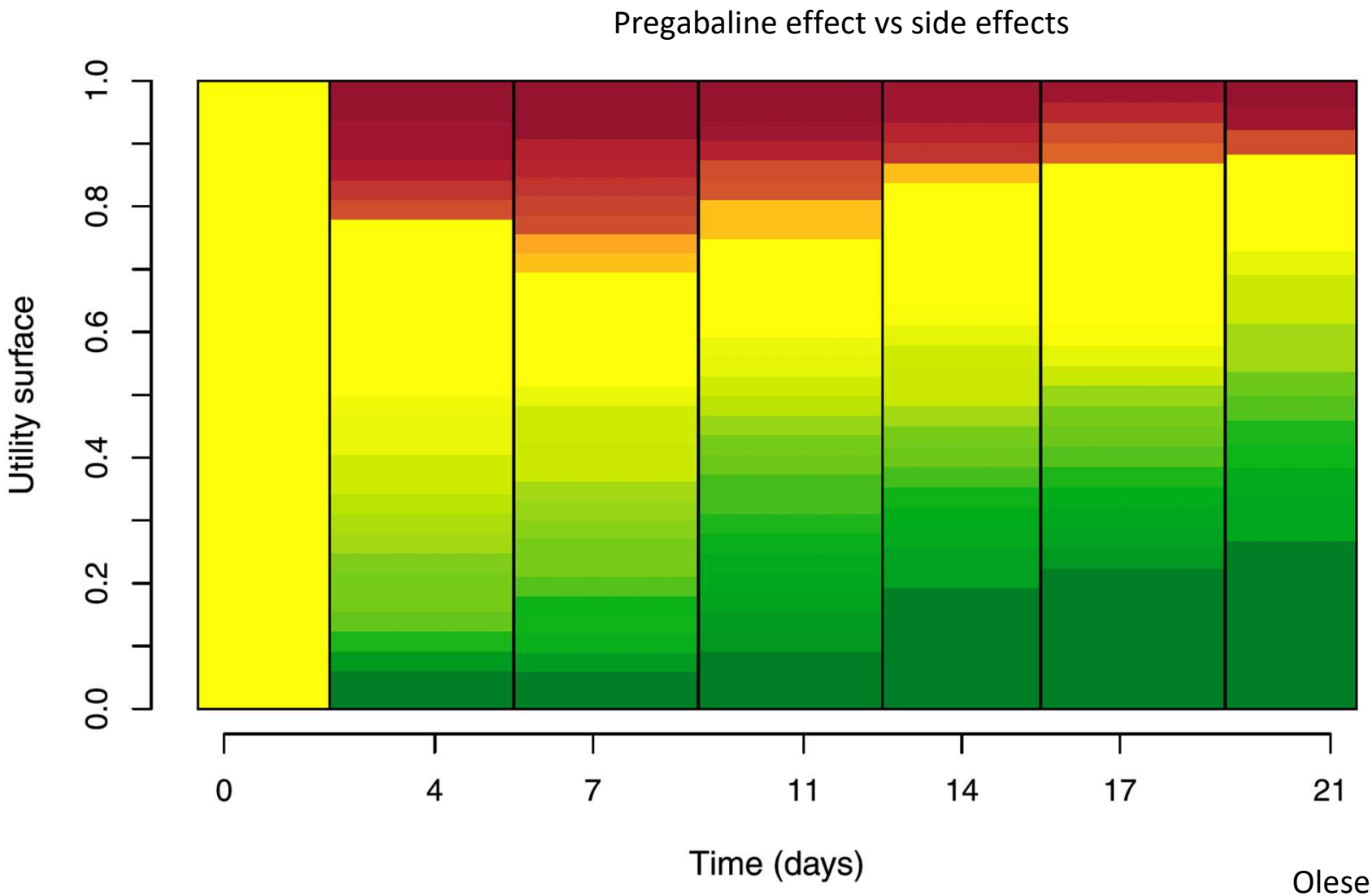
Steps	Action
Step 1	Administer an analgesic to patients or volunteers followed by measurement of analgesic efficacy, toxic (e.g., respiratory depression) responses and plasma drug concentration over time
Step 2	Perform pharmacokinetic-pharmacokinetic analysis of the concentration-effect data to obtain model parameter estimates including inter-individual variances
Step 3	Perform 10,000 simulations for analgesia and toxic effects (in total 20,000 simulations) using parameter estimates and their variability
Step 4	Determine the probability of the occurrence of analgesia (A) and of respiratory depression (RD), based on predefined thresholds, such as: threshold(A) = at least 50% increase in pain tolerance, and threshold(RD) = at least a 50% reduction of isohypercapnic minute ventilation
Step 5	Define your utility and calculate the utility as function of time or as function of biophase concentration. Examples are: $utility_1$ = P(A >50%) – P(RD >50%), cf. *Figure 1*; $utility_2$ = P(A AND NOT RD) = P(A >50% AND RD <50%), cf. *Figure 2A*; $utility_3$ = P(RD AND NOT A) = P(A <50% AND RD >50%), cf. *Figure 2B*
Step 6	Determine the continuum of probabilities of presence or absence of analgesia in combination with the presence of absence of respiratory depression by varying the threshold values and plot these in 2D, cf. *Figure 3*


Effectiveness and Safety of Buprenorphine and Fentanyl
Rats (Yassen et al. 2007)
Utility function
1
0.5
0
-0.5
-1
0.01
0.1
1
10
100
Biophase concentration (ng/mL)


Human Utility Surfaces (Roozekrans et al. 2018)
A
B
C
D
Probability
Fentanyl concentration (ng/ml)
Time (min)
A-R+
A+R+
A++R+
A-R-
A+R-
A++R-

Dahan 2015


0.75
0.50
0.25
0.00
-0.25
UTILITY
0
1
2
3
CP Fentanyl (ng/mL)
High Analgesic Potency
Low Analgesic Potency



Olesen et al. JPET 2019

Analgesic Treatment → Dosing → Effect → Adverse Effect → Dose reduction → Effect ↓

Analgesic Treatment → Dosing → Effect → Adverse Effect → Dose reduction → Effect ↓

Analgesic Treatment → Dosing → Effect → Adverse Effect ↓ → Dose increase → Effect ↑

ANESTHESIOLOGY

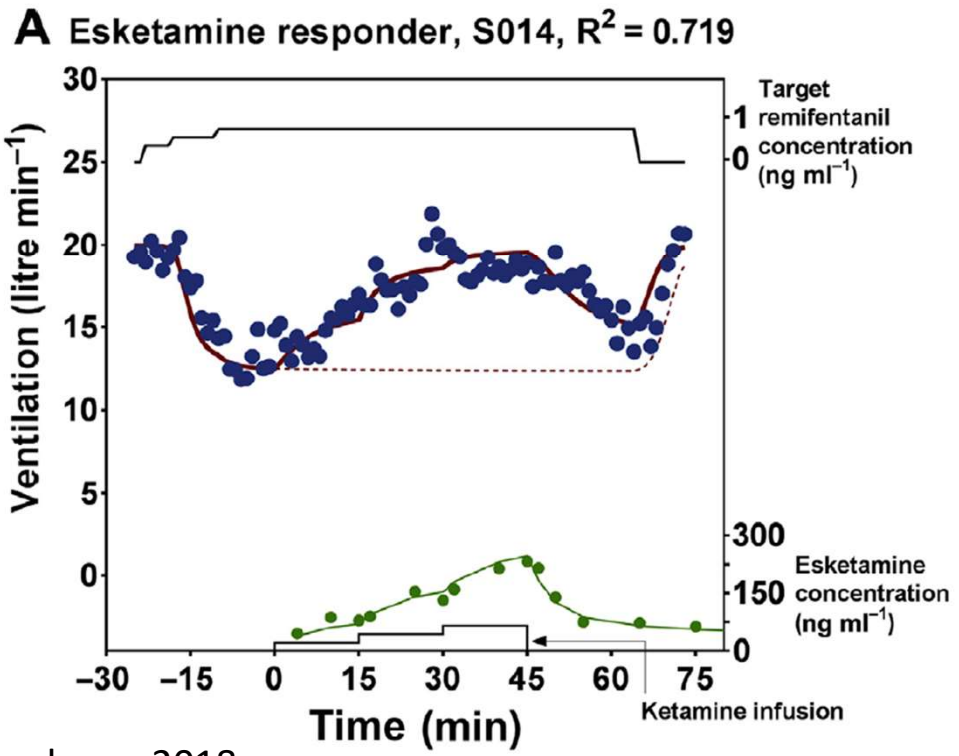
The Journal of

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Volume 6 NOVEMBER, 1945 Number 6

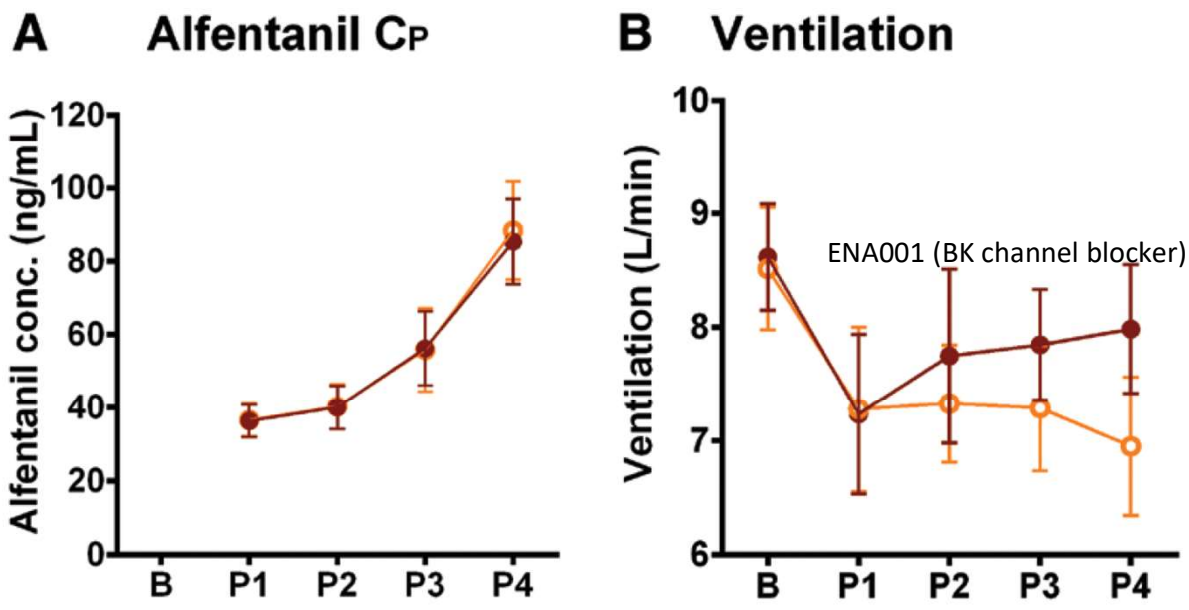
A COMPARISON OF AMPHETAMINE SULFATE WITH OTHER STIMULANTS OF THE CENTRAL NERVOUS SYSTEM IN MORPHINE RESPIRATORY DEPRESSION •

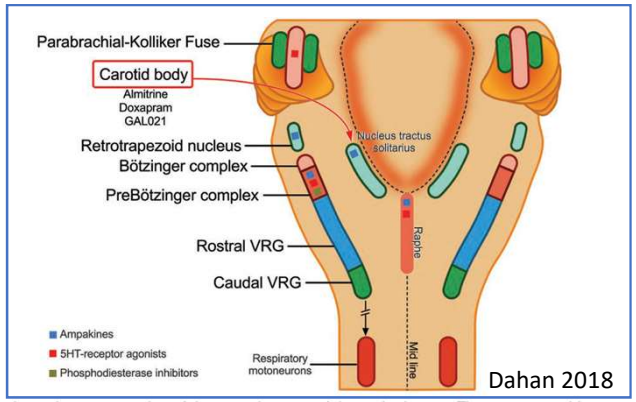
CARROLL A. HANDLEY, PH.D.



Jonkman 2018

Roozekrans 2014 → BK-channel blocker





Dahan 2018

Thank you for listening