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Pharmacotherapy for pain: what to measure, how to measure?

Martini, Christian Hubert

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PHARMACOTHERAPY FOR PAIN

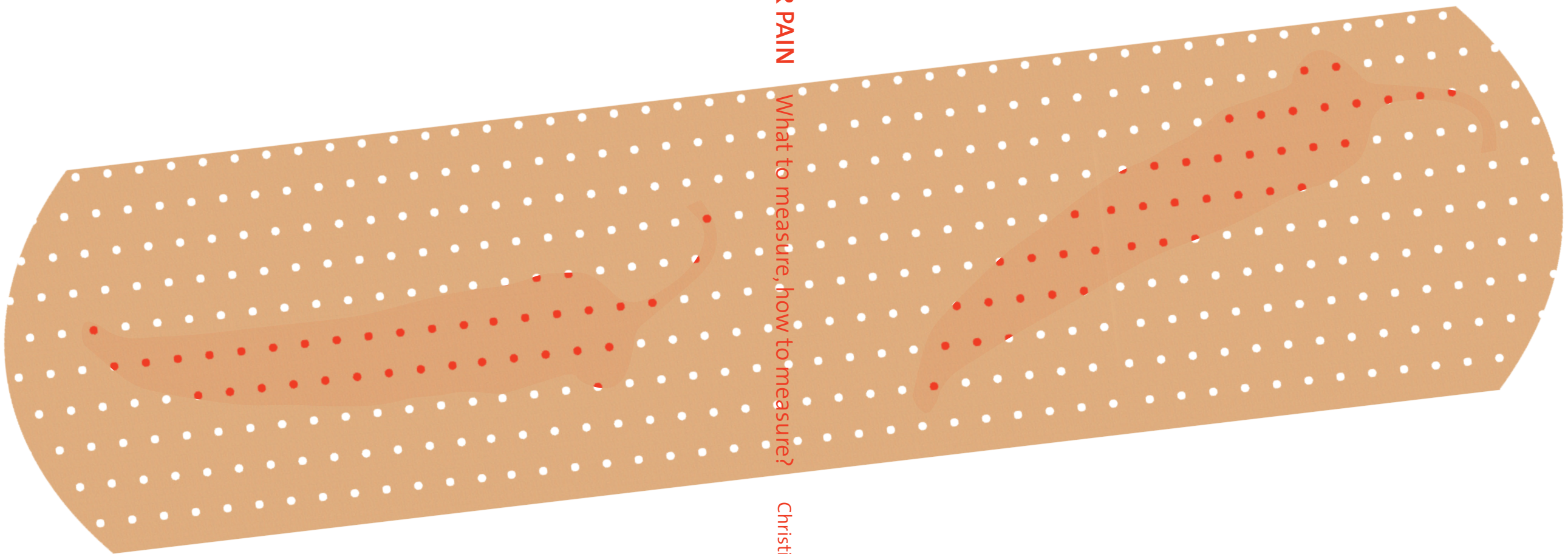
What to measure, how to measure?

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PHARMACOTHERAPY FOR PAIN

What to measure, how to measure?

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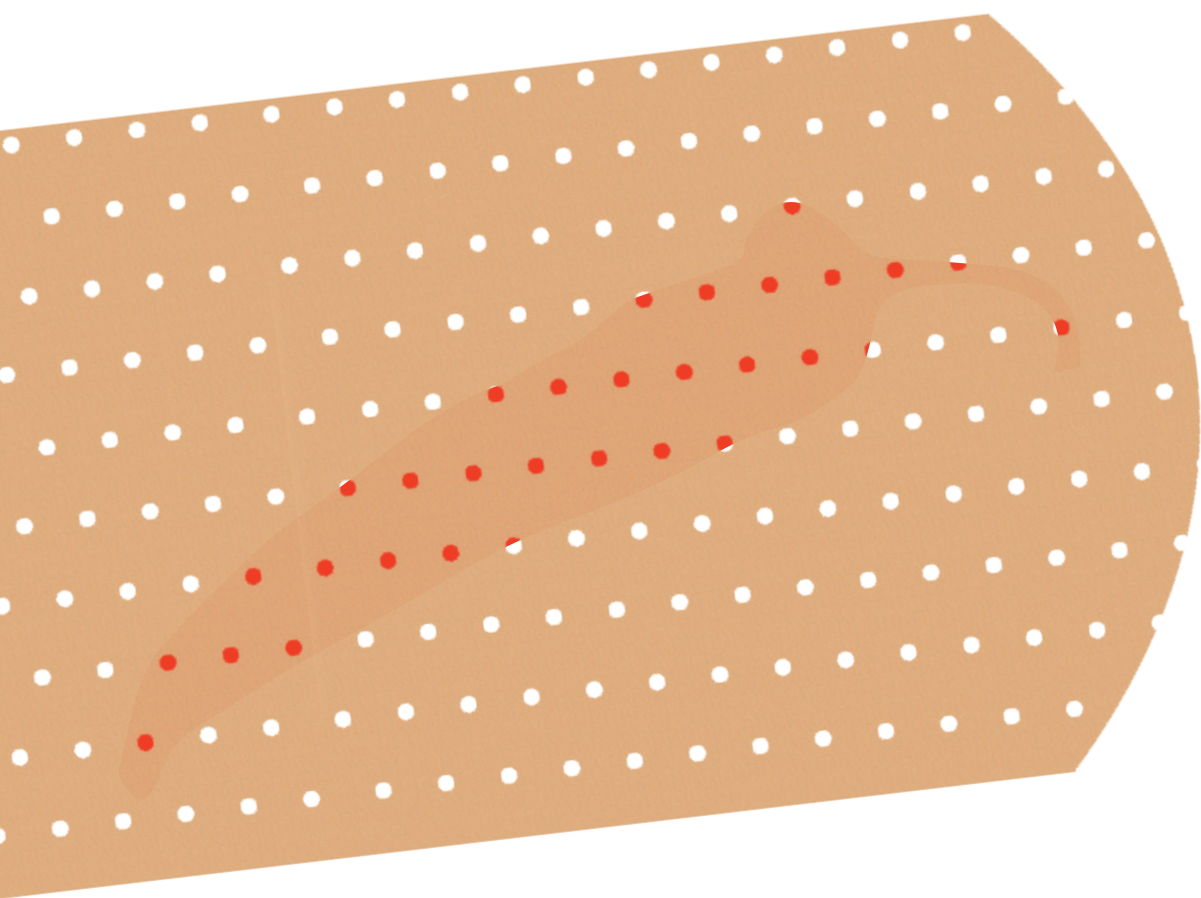
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in 1980

Promotiecommissie

Promotor: Prof. dr. A. Dahan

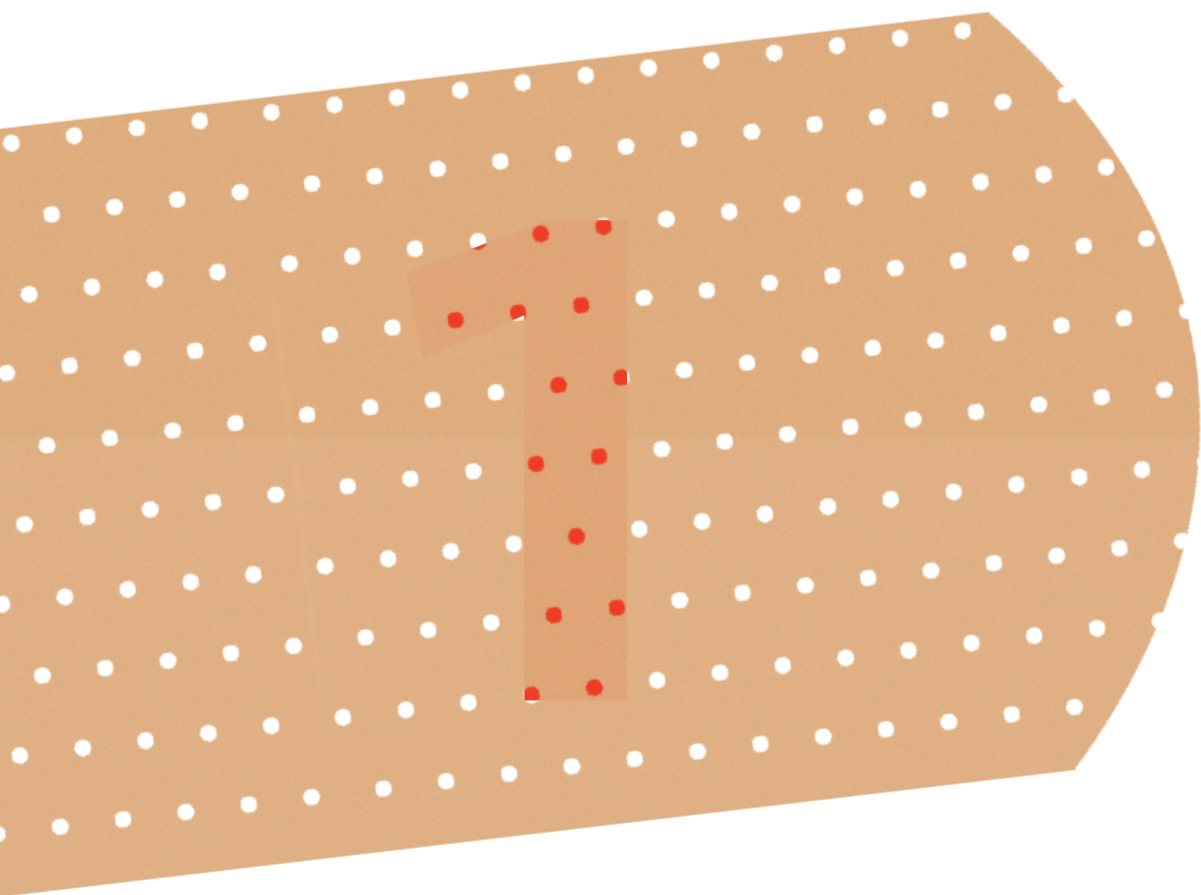
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Chapter 1

Introduction

Throughout human existence a large variety of plants and their extracts are being used for medicinal purposes. Possibly the oldest plant with known strong medicinal powers is the opium poppy, *Papaver somniferum*, with evidence of its use dating back to the prehistoric era.¹ Its powerful analgesic properties and euphoric pleasures were known to many ancient civilizations. Not only the beneficial effects were described but the poisonous natures of the sap from the opium poppy were known as well. In the early 1800s, the German pharmacist and chemist Sertürner took a major step forward towards modern pharmacotherapy with the isolation of the alkaloid morphine from opium sap. Morphine turned out to be a potent analgesic that was used to treat severe pain as well as other ailments such as diarrhea and persistent coughing. Until today, morphine remains the gold standard for treatment of moderate to severe pain.²

Another plant extract with analgesic properties is capsaicin, which is derived from the chili pepper, *Capsicum*, and was first isolated in the early 1800s.³ Capsaicin produces a burning sensation when it comes into contact with the skin (at high concentrations) or mucous membranes (at low concentrations). Paradoxically, capsaicin is used as analgesic ointment in patients with neuropathic pain such as postherpetic neuralgia (PHN) and diabetic polyneuropathy (DPN). When applied as a patch, capsaicin (Qutenza™, Astellas Pharma Inc.) diffuses through the skin (or mucous membrane) and acts at the heat-sensitive transient receptor potential cation-channel subfamily V member 1 (TRPV1), also known as the capsaicin receptor or vanilloid receptor 1 (VR1).⁴ Apart from capsaicin, the TRPV1 receptor is activated by heat ($> 43^{\circ}\text{C}$), acids and the pungent constituents of mustard and wasabi. The TRPV1 receptor is expressed on small afferent nerve C and A δ (nociceptive) fiber endings. While capsaicin initially causes a severe burning sensation, prolonged exposure causes peripheral nerve desensitization, which results in analgesia. Additionally, activation of the TRPV1 receptor causes the inhibition of Piezo proteins (a family of mammalian cation-selective ion channels that respond to mechanical stretch) found in somatosensory neurons of the dorsal root ganglion.⁵ By inhibition of the Piezo proteins, capsaicin might significantly reduce neuropathic pain-related mechanical hypersensitivity.

In the Western world, pain is the most common reason for individuals to seek medical care.² Hence it is not surprising that apart from morphine and capsaicin, in contemporary medicine a large number of drugs are available to treat mild to severe pain with a large variety in mechanisms of action (about half of the currently used pain medication acts at G-protein coupled receptors, which includes the opioid receptor family). A new analgesic being introduced in the early 2000s is tapentadol (Palexia™, Grünenthal GmbH), a

designer drug that targets the μ -opioid receptor (MOR), alike morphine, but additionally interacts with (e.g. inhibits) neuronal noradrenaline reuptake mechanism.⁶ As such it generates two signals:

- (1) at the MOR, albeit at a 50-fold lower affinity compared to morphine; and
- (2) by increasing extraneuronal noradrenaline concentrations at analgesic α_2 -adrenergic receptors in the spinal cord dorsal horn (through noradrenaline reuptake inhibition or NRI).

The two signals produce synergistic analgesia. Activation of the spinal α_2 -adrenergic receptors is a crucial part of the endogenous pain modulatory system.

The ongoing search for new analgesics, new administration techniques (e.g. transcutaneous, transmucosal, intranasal, inhalational, orodispersible) and the regular but sparse introduction of new drugs indicates an apparent dissatisfaction with current pain pharmacotherapies.⁷ The “dissatisfaction” relates to the often-restricted efficacy of analgesic medication frequently combined with the occurrence of side effects that reduces patient compliance. Introduction of new analgesics is a complex, time consuming and costly process. Prior to registration multiple placebo-controlled efficacy trials in large patient populations are performed and similar studies are executed after the drugs have been registered for marketing purposes. Large trials are needed, as the placebo effect in analgesia trials is substantial. In these trials treatment of chronic pain conditions is commonly assessed at preset times during and after treatment by analysis of the total study population (e.g. at 12 weeks of treatment). However, these often high-quality trials are “easily” analyzed by novel approaches.^{7,8} For example, an alternative approach is the identification of specific patient subgroups characterized by differential response patterns in their analgesic response and to determine the presence of significant predictors of effect (Chapters 3 and 4 of this thesis). At the basis of such approach are population (pharmacokinetic and) pharmacodynamic analyses of the data allowing a clear understanding of the temporal profile of treatment in individual patients as well of the within- and between-subject variability (Chapters 2 and 5 of this thesis).

Another relatively new approach is the application of dynamic psychophysical tests as predictor of drug efficacy (Chapter 6 of this thesis). One such test is Conditioned Pain Modulation (CPM), a test designed to engage top-down inhibitory pain pathways. Yarnitsky et al.⁹ and Niesters et al.¹⁰ showed that chronic pain patients who are unable to activate CPM benefit most from medication that interacts with the endogenous pain modulatory system such as duloxetine and tapentadol and *vice versa* patients that have an active CPM have little analgesic benefit from these drugs (Figure 1, which further

highlights the importance of subgroup analysis). New tests and analyses techniques, such as suggested here, will eventually allow optimization of individual pain therapy with specific predictors linked to specific pharmacotherapies. An individual treatment approach based on prediction of effect to specific drugs is needed as some patients (i) respond to certain treatments but are intolerant to others (in fact, this is true for individual opioids as well), (ii) require an adaptation to their dosing scheme, (iii) need a combination of analgesic agents, or (iv) will benefit more from non-pharmacological interventions. Additionally, clinical data are showing that this is true for the analgesic efficacy and the adverse events that pain treatment invariably causes. For example, opioid switching results in improvement of symptoms and side effects in more than 50% of patients.²

Thesis outline

In this thesis novel techniques are described which are developed to analyze or predict the efficacy of pharmacotherapy for pain.

In **Chapter 2** an overview is presented on recent pharmacokinetic pharmacodynamic (PKPD) modeling in acute (in volunteers and postoperative patients) and chronic pain. Novel observations on opioids, NSAIDs, acetaminophen, epidural analgesia, ketamine and GABAergic drugs are described. Additionally, PKPD models of naloxone reversal of opioid-induced respiratory depression are discussed.

Chapter 3 describes the analgesic effect of a capsaicin patch in DPN pain patients. A longitudinal population PD analysis is performed. In addition, a mixture model is applied to match patterns in pain-associated behavior and to identify subgroups that responded differently to treatment.

In **Chapter 4** a subgroup analysis is performed on pooled data from 4 multicenter trials on the effect of capsaicin 8% patch (versus an active control, capsaicin 0.04% patch) in PHN. Apart from longitudinal and mixture analyses, covariates are examined to identify predictors of efficacy.

In **Chapter 5** the analgesic effect of orodispersible oxycodone versus an active comparator (orodispersible paracetamol) for the management of breakthrough pain is quantified. A novel pharmacodynamic model is used that describes the analgesic effect over time with relative sparse data samples and without the need for blood sampling for pharmacokinetic analysis.

Finally, **Chapter 6** describes the effect of tapentadol versus morphine on CPM in healthy volunteers. A difference in CPM engagement between these two “opioids” might proof the difference in mechanisms of action between the classical MOR agonist and the combined MOR-NRI compound.

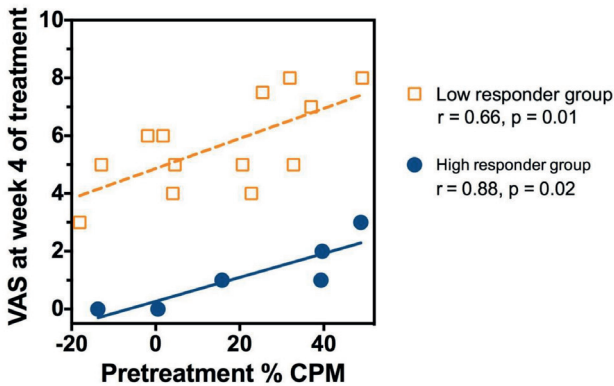
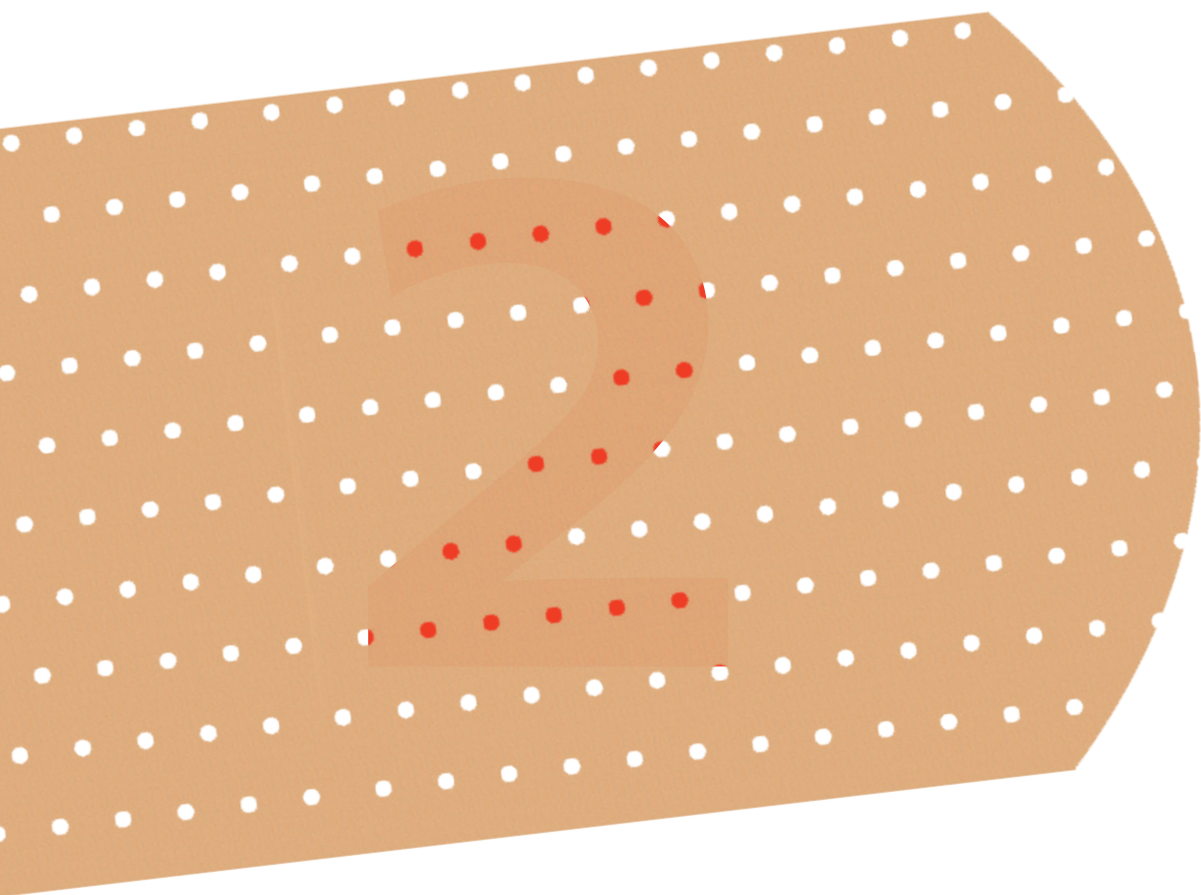


Figure 1 Chronic pain patients with DPN treated with tapentadol or placebo that initially have a diminished ability to engage CPM (negative or small %CPM values) gain the most from treatment with the lowest pain scores after 4 weeks of treatment. This graph further shows the presence of two responder subgroups with an identical relationship between pretreatment CPM and pain relief. In the high responder group 5 of 6 patients received tapentadol; in the low responder group 5 of 13 patients received tapentadol. Data are a reanalysis of Niesters et al.,¹⁰ CPM is conditioned pain modulation, VAS is visual analogue score.

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Chapter 2

Pharmacokinetic–pharmacodynamic modeling in acute and chronic pain: an overview of the recent literature

C.H. Martini, E. Olofsen, A. Yassen, L. Aarts, A. Dahan

Expert Rev Clin Pharmacol 2011; 4(6): 719-28.

INTRODUCTION

The objective of pharmacokinetic–pharmacodynamic (PKPD) modeling is the development and application of mathematical models to describe and/or predict the time course of dose-to-concentration (pharmacokinetics [PK]) and concentration-to-effect (pharmacodynamics [PD]) of pharmacological active agents in health and disease.^{1,2} The PK model part of PKPD models describes the macrodistribution of the drug (drug distribution kinetics). Effect-compartment PKPD models add a hypothetical (infinitely small) effect compartment to describe the delay in effect (i.e., quantification of drug effect in terms of drug concentration at the target or effect site $[C_e]$ vs measured effect). In compartmental models, the concentration–time profiles are described/explained by drug transfer between interconnected hypothetical compartments, mimicking drug absorption, distribution and elimination. Drug distribution towards the target site is described by the plasma effect-site equilibration constant (k_{eo} ; or its half-life $[t_{1/2}k_{eo}] = \ln 2/k_{eo}$), whereas the concentration–effect relationship is often described by a sigmoid maximum effect (E_{max}) model of the form:

$$\text{Effect} = A^\gamma / (1 + A^\gamma)$$

where $A = C_e/C_{50}$ (with C_{50} as the measure of drug potency or the effect-site or steady-state concentration causing 50% of the effect, and γ as the Hill-factor). The first to propose a first-order rate constant between plasma and an effect-compartment was the Italian, Segre, in a pivotal article published in 1968.³ Segre described the transfer function of norepinephrine's effect on the circulatory system and estimated a delay of 15 s between changes in plasma epinephrine concentration and blood pressure in a cat, showing that epinephrine's target site (i.e., the 'biophase') is not in plasma. This concept was later further developed by Hull and Sheiner et al., in two separate studies, both in 1979.^{4,5} Effect-compartment models are empirical models that do not describe the physiological or mechanistic pathway of the drug from its concentration in plasma to effect. Recently, novel mechanism-based biophase distribution models were developed.¹ For example, mechanism-based PKPD models may incorporate concepts from receptor theory describing the drug–receptor interaction (receptor kinetics) in terms of drug-association and -dissociation kinetics and enable the quantification of the rate-limiting factor in drug effect owing to drug distribution versus receptor kinetics.⁶

Rather than analyzing individual PKPD data, population PKPD analyses (i.e., performing a simultaneous analysis on the whole population dataset) has become the acceptable approach in current PKPD modeling studies. A population analysis will lead to an

estimate of the population PK and PD estimates, identify the sources of variability that influence PK and PD, estimate the magnitude of between-subject variability, as well as intrasubject variability, and allow for the estimate of random residual variability (random effects).⁷ To separate random (i.e., variability parameters) from fixed effects (i.e., the PK and PD parameter estimates), nonlinear mixed-effects modeling is required.⁸ Various statistical packages are available to perform nonlinear mixed-effects modeling, of which NONMEM® is considered the most state-of-the-art.⁷⁻¹⁰ NONMEM was developed by Lewis Sheiner and Stuart Beal at the University of California in San Francisco (CA, USA) and was initially developed to analyze PK data but is currently applied to model PK, PD and PKPD datasets.^{9,10} Particularly in studies on the pharmacology of analgesics and anesthetics, drug-drug interactions, population PK, PD and PKPD analyses using NONMEM is currently the gold standard.^{8,10}

In this article, we will discuss population effect-compartment and mechanism-based PKPD and PD modeling studies published in the last 5 years on the effects of various analgesic agents in acute (in volunteers and postoperative patients) and chronic pain patients. End points covered are the relief of experimental and surgery- and disease-induced pain (i.e., antinociception and analgesia). In addition, we will discuss PKPD models of naloxone reversal of opioid-induced respiratory depression, the most life-threatening side effect of potent opioids.

PKPD MODELING OF ACUTE ANTINOCICEPTION & PAIN

Morphine & its metabolites

Morphine, first extracted from opium in 1806, is still considered the gold standard in the treatment of severe acute and chronic pain, although it has no clear superiority in efficacy or tolerability over other opioids.¹¹ In 2005, Lötsch listed six PKPD studies on morphine.¹² Studies were performed either on a surrogate measure of opioid effect, pupil size, or on electrical noxious cutaneous stimulation. One of the studies discussed demonstrated that sex was a significant covariate on pain relief responses, with greater morphine potency in women ($C_{50} = 250$ nM in men vs 150 nM in women) (Table 1) but with a slower onset/offset time (blood effect-site equilibration $t_{1/2}k_{eo}$ for pain relief response [pain tolerance] was 1.6 h in men vs 4.8 h in women), without any sex differences in morphine's PK.¹³ These data were later confirmed in a systematic review and meta-analysis and account for the difference in opioid consumption between men and women in postoperative patient-controlled analgesia morphine studies.¹⁴ Interestingly, while studies on pupil size had similar estimates for $t_{1/2}k_{eo}$ as observed in pain studies, the potency of morphine

Table 1 Population pharmacodynamic model estimates for various analgesic agents and naloxone using pain relief or respiration as effect parameter; studies performed in healthy volunteers or patients

	$t_{1/2}$, k_{eo}	k_{on} (ml/ ng/min)	k_{off}^a (min^{-1})	K_D (k_{off}/k_{on})	C_{50}	Effect parameter	Population
Morphine men ¹³	1.6 h				250 nM	antinocicep- tion	V
Morphine women ¹³	4.8 h				125 nM	antinocicep- tion	V
M6G ^{12,16}	6-8 h				750 nM	antinocicep- tion	V
Morphine ¹⁷	1.2 h	0.85	0.14	160 nM		respiration	V
M6G ¹⁷	2.7 h	0.04	0.03	880 nM		respiration	V
Naloxone ¹⁷	5-8 min				0.5-2 nM	respiration	V
Morphine ²⁰	1.7 h				124 nM	postop. analgesia	P
M6G ²⁰	3 h				13 nM	postop. analgesia	P
Buprenorphine ²²	75 min	0.25	0.01	0.09 nM		respiration	V
Fentanyl ²²	16.4 min	>100	>100	-	1140 ng/ml	respiration	V
Buprenorphine ²⁵	155 min	0.06	0.08	2.66 nM		antinocicep- tion	V
S-Ketamine ²⁹	^b				373- 2200 ng/ml ^c	antinocicep- tion	V

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	$t_{1/2}, k_{eo}$	k_{on} (ml/ ng/min)	k_{off}^a (min^{-1})	K_D (k_{off}/k_{on})	C_{50}	Effect parameter	Population
S-Ketamine ³⁵	11 days ^d				10.5 ng/ml	chronic CRPS pain relief	P
Pregabalin ³⁶	11-h				1.54 $\mu\text{g/ml}$	chronic fibromyalgia pain relief	P
SC-75416 ³⁰					5500 ng/ml	post oral surgery pain relief	P
Rofecoxib ³⁰					284 ng/ml	post oral surgery pain relief	P
Valdecoxib ³⁰					68 ng/ml	post oral surgery pain relief	P
Ibuprofen ³⁰					6840 ng/ml	post oral surgery pain relief	P
Ibuprofen ³¹	28 min				10,200 ng/ml	post oral surgery pain relief	P
Acetaminophen ^{32,33}	53 min				10 mg/L	posttonsil- lectomy pain relief	P

a: $t_{1/2}, k_{off}$ is calculated as $\ln 2/k_{off}$;

b: no hysteresis observed between plasma concentration and effect;

c: C_{50} varied depending on the nociceptive assay employed (see text);

d: The values of 11-days represent a rate-constant from disease modulation ($t_{1/2}, k$) unrelated to the blood-effect-site equilibration half-life.

C_{50} = Steady-state concentration causing 50% of the effect; CRPS = Complex regional pain syndrome; K_d = Equilibrium dissociation constant; k_{eo} = Effect-site equilibration constant;

K_{off} = Receptor dissociation constant; K_{on} = Receptor-association constant; P = Patients; $t_{1/2}$ = Half-life; V = Volunteers.

	$t_{1/2}, k_{eo}$	k_{on} (ml/ ng/min)	k_{off}^a (min^{-1})	K_D (k_{off}/k_{on})	C_{50}	Effect parameter	Population
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was much greater for miosis (C_{50} ranging from 17 to 24 nM, without occurrence of any sex differences). Collectively, these data indicate that morphine has an onset time that is much smaller than observed in any of the other opioids currently in clinical use.^{12–14} In comparison, $t_{1/2}k_{eo}$ (derived from yet another surrogate end point of opioid effect: changes in EEG power spectrum) is 5–6 min for fentanyl and sufentanil, 1–2 min for alfentanil and remifentanyl, 8–19 min for methadone and 17 min for piritramide.¹² This makes morphine a relatively slow and consequently difficult to control opioid analgesic. Note, however, that currently no comparable data on morphine's effect on EEG-related parameters are available.

Morphine is rapidly metabolized in the liver into the (presumably) inactive morphine-3-glucuronide (M3G) and the active morphine-6-glucuronide (M6G). Animal studies indicate that M6G is a μ -opioid receptor agonist with greater potency than morphine and rapidly crosses the blood–brain barrier (BBB).¹⁵ By contrast, PKPD studies in humans revealed a three- to five-fold lower potency than observed in animals after intravenous M6G administration coupled with a slow transfer of the drug across the BBB ($C_{50} = 750$ nM and $t_{1/2}k_{eo}$ 6–8 h).¹² Using data obtained from healthy volunteers that were injected with either intravenous morphine or intravenous M6G, we were able to construct a population PKPD model of morphine's metabolism into M6G and determine M6G's contribution to morphine analgesia.¹⁶ The fraction of morphine metabolized into M6G was $6.0 \pm 0.2\%$ (median value $\pm$ standard error); M6G formation was sex independent. Simulation studies demonstrated that repetitive morphine infusions (0.1 mg/kg at 8-h intervals) resulted in stable M6G effect-site ('brain') concentrations of 10–20 nM that contributed approximately 8 (women) and 15% (men) to the analgesic response. Under conditions of renal impairment, the effect-site M6G concentration rose by a factor of ten and its estimated contribution to effect increased by a factor of two. These findings derived from modeling studies and simulations are important as they tempered the initial aspirations of M6G as the replacement of morphine in the treatment of severe acute pain and exemplify the strength of population PKPD modeling studies in the development of new (analgesic) drugs.^{12,15,16} The aspirations were based on early observations in animals and later in humans that M6G causes less respiratory depression and possibly less nausea and vomiting compared with the parent compound.¹⁵ However, its low potency but especially its slow passage across the BBB and accumulation in renal impairment make it an analgesic that is even more difficult to control than morphine in perioperative patients and should be avoided in patients with reduced renal function. Previously discussed studies used effect-site PKPD modeling and consequently remained uninformed on receptor kinetics. Using a mechanism-based PKPD approach, Olofsen et al. described naloxone reversal of morphine- and M6G-induced respiratory depression.¹⁷

They estimated the following pharmacokinetic parameters: k_{eo} or the biophase distribution constant, k_{on} or the receptor association constant, k_{off} or the receptor dissociation constant of morphine and M6G, and k_{eo} of naloxone. Naloxone is a μ -opioid receptor antagonist used both in clinical practice to reverse opioid-induced respiratory depression and in the treatment of opioid addiction. Since it was first synthesized in 1960 by Jack Fishman and further developed through the early 1970s by Harold Blumberg,¹⁸ little progress has been made on the policies required to administer appropriate doses of naloxone that cause rapid reversal with a limited chance of renarcotization. The study by Olofsen et al.¹⁷ and especially the additional model simulations are insightful and enable the development of specific guidelines on the reversal of the toxic effects of morphine and its active metabolite M6G in clinical practice. The parameter estimates of the study are given in Table 1. Morphine and M6G both display slow receptor association/dissociation kinetics with an apparent potency ($K_d = k_{off}/k_{on}$) similar to C_{50} values obtained in previous studies (see earlier). Naloxone had rapid receptor kinetics with $t_{1/2}k_{eo}$ of approximately 5 min on average, while its apparent estimated potency was greater for M6G reversal than for morphine reversal. The latter observation is hard to explain as naloxone is a competitive antagonist at the opioid receptors (i.e., its effect is described by a single equilibrium dissociation constant). Possibly, the differences in potency may be related to the ability of M6G to increase the affinity of naloxone for the μ -receptor.¹⁷ Since the elimination $t_{1/2}$ of naloxone is between 15 and 30 min, naloxone is a limiting factor in the reversal of (long-acting) opioids. However, in addition, the slow receptor kinetics of morphine (and M6G) limits naloxone's ability to disperse the opioid agonist from the receptor rapidly. This has clinical consequences as increasing the naloxone dose will not increase the speed of morphine reversal (i.e., the increase in ventilation over time), although the magnitude and duration of reversal will increase (Figure 1). Taken together, a sufficient high dose of naloxone is required, preferably administered as continuous infusion, to reverse morphine-induced respiratory depression with a reduced chance of renarcotization; the speed of reversal is not affected by the naloxone dose. Note that these observations regard only opioid agonists that have slow receptor association/dissociation kinetics (such as morphine, M6G and buprenorphine, see later) but are not valid for opioids with rapid kinetics such as fentanyl or any of the other fenyliopiperidines (with the exception of remifentanyl; if the remifentanyl infusion is stopped, breathing resumes within minutes).¹⁹ A more rapid reversal of fentanyl just requires a greater dose of naloxone, as naloxone reversal is not dictated by receptor kinetics of the agonist (fentanyl).

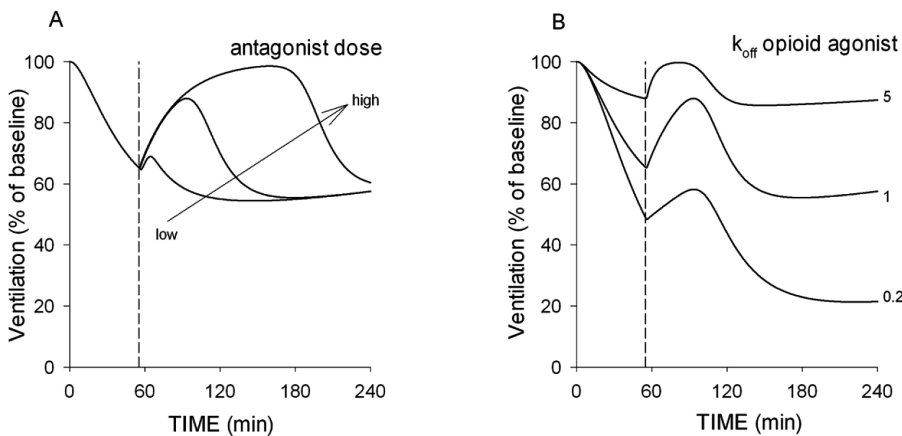


Figure 1 Effect of naloxone on opioid-induced respiratory depression. A. Mechanism-based PKPD modeling of the ability of different doses of an opioid antagonist (naloxone, given at $t = 55$ min, low dose = 0.1 mg, high dose 0.4 mg) to reverse the opioid-induced respiratory depression from an opioid agonist with relatively low k_{off} -value (opioid agonist injected at $t = 0$ min). The speed of reversal is independent of the antagonist dose and is determined by the agonist opioid receptor k_{off} -value. B. Effect of variations in the k_{off} -value of an opioid agonist (injected at $t = 0$ min over 90 s) on the effect of a fixed dose of an opioid receptor antagonist (naloxone, given at $t = 55$ min over 90 s) on reversal of opioid-induced respiratory depression. K_{off} -values are relative with 0.2 min⁻¹ = 0.2 × typical value, 1 = typical value, 5 = 5 × typical value. Here the typical value = 0.03 min⁻¹. K_{off} : Receptor dissociation constant. Data adapted from Olofsen et al.¹⁷

Two recent studies analyzed the effect of morphine on acute postoperative pain using a population PKPD analysis in NONMEM. Mazoit et al. modeled morphine's effect taking the potential effects of M3G and M6G into account in patients in acute pain following a variety of surgical interventions with a mean age of 51 years.²⁰ They assumed additive agonistic effects from morphine and M6G and an antagonistic effect from M3G. Using a sigmoid E_{max} model with pain (as determined from a visual analogue scale [VAS] scoring system) as effect variable, they estimated a tenfold greater potency of M6G compared with morphine ($C_{50} = 124$ [morphine] vs 13 nM [M6G]) and an inhibitory effect from M3G with C_{50} of 880 nM. The analgesic effect of M6G was delayed significantly relative to morphine ($t_{1/2k_{\text{eo}}}$: 1.7 [morphine], 3 [M6G] and 3 h [M3G]). Age, sex and weight did not improve the PD model. The M6G potency is much greater than observed in earlier studies in volunteers^{12,16,17} and, although one may argue that in the Mazoit study measurements were made for 24–48 h (compared with 6–10 h in previous studies), the M6G potency is an indirect estimate derived from a study where morphine, but not M6G, was administered.

Consequently, the true potency of M6G remains unknown, in comparison with previous studies where only M6G was administered. Of further interest is the observation of an antagonistic or hyperalgesic effect of M3G with a relatively slow distribution into the biophase. This suggests that reduced morphine efficacy may coincide with M3G's hyperalgesic effect, requiring the switch to other opioid analgesics in some patients.

Abbou Hammoud et al. modeled the effect of morphine titration in the first postoperative hours on pain relief (using VAS) in patients (mean age of 62 years) following orthopedic surgery.²¹ They used an indirect response $E_{\max}$ model with variations in pain expressed by the equilibrium of K_{in} (a zero-order rate constant of the appearance of pain) and K_{out} (a first-order rate constant of the disappearance of pain) with morphine inhibiting K_{in} . They added a virtual kinetic compartment, as no PK data were available. They estimated a value for ED_{50} (dose of morphine causing 50% pain relief) of 10.2 ± 0.8 mg with significant covariates including initial VAS (direct postoperative VAS just before dosing), and the use of additional pain medication (but not age, sex or weight). The model is of interest as it predicts that greater titration doses are associated with a significant reduction in time to achieve analgesia (especially in patients with a greater initial VAS), albeit at the expense of increased toxicity (sedation in their study).

Buprenorphine

There is a renewed and increasing interest in this 30-year-old semisynthetic opiate derived from the morphine precursor, thebaine. Currently, buprenorphine is applied in the treatment of chronic pain using a relatively novel patch formulation and in the treatment of addiction (SubutexTM or in combination with naloxone Subutex [Reckitt Benckiser, Slough, UK]). Buprenorphine is a partial agonist at the μ -opioid receptor and displays typical opioid behavior (analgesia, sedation, nausea, delayed gastric emptying and respiratory depression). Yassen et al. performed a series of experiments in men using a mechanism-based population PKPD approach.^{6,22-24} The most important observations from these studies are:

- In the clinically relevant intravenous dose range of 0.05–0.6 mg/kg, buprenorphine displayed a lack of ceiling effect for antinociception (related to the absence of saturation of receptor occupancy);²⁴
- Rate-limiting factors in the onset and offset of antinociceptive effect are biophase distribution and slow receptor association–dissociation (Table 1);²⁴
- In contrast to antinociception, ceiling was observed for respiratory depression at high buprenorphine concentrations (the intrinsic activity of buprenorphine is 56%);²³
- Reversal of buprenorphine-induced respiratory depression with naloxone is possible,

however, owing to the slow receptor kinetics of buprenorphine, in combination with the fast elimination kinetics of naloxone, naloxone is best administered as a continuous infusion rather than a single bolus injection (optimal dosage is 2–4 mg naloxone per h).⁶

Naloxone reversal is slow, however, and cannot be accelerated by giving higher naloxone doses (see earlier). The findings from these modeling studies indicate that buprenorphine is an opioid analgesic that provides long-term analgesia without ceiling over the clinical dose-range and has a limited effect on the respiratory systems. In case life-threatening respiratory depression does occur, it can be antagonized but requires high doses and continuous infusions of naloxone. These data demystify some of the old beliefs around buprenorphine that can still be found in older textbooks, including the existence of a ceiling in analgesic effect and inability to reverse buprenorphine-induced respiratory depression.

Ketamine

The third ‘senior’ analgesic that we discuss is the 50-year-old N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine. Initially developed as an anesthetic, multiple studies show that at low (subanesthetic) doses, ketamine is a potent analgesic in the treatment of both acute and chronic pain.²⁵ In the last few years, a series of investigations on population PKPD modeling in children and adults has been published. The studies in children were aimed at the anesthetic properties of ketamine and will not be discussed here.^{26,27} In healthy volunteers, Sigtermans et al. tested the effect of increasing doses of the S(+)-enantiomer of ketamine (S-ketamine) on antinociception using two different nociceptive assays: heat pain (a fixed-heat stimulus was applied to the arm giving a baseline [i.e., predrug] VAS of 6 cm or greater) and tolerance to electrical pain (a 10-Hz stimulus train increasing at 0.5 mA/s).²⁸ Using an effect-compartment population PKPD analysis yielded a significant difference in ketamine’s potency in the two assays (Table 1) with a sixfold greater potency for pain relief of heat pain. Of further interest is the observation of hyperalgesic responses following S-ketamine withdrawal that was modeled with a linear trend term. This phenomenon has recently been described in experimental and clinical studies. A delay between concentration and effect (that is hysteresis) was not observed for any of the antinociceptive end points. This indicates an almost immediate passage of S-ketamine across the BBB and rapid receptor kinetics. Similar observations were made previously on the effect of ketamine racemic mixture on EEG slowing in adults and on estimates of arousal and recall memory during anesthesia in children.²⁶

COX inhibitors

Kowalski et al. constructed PKPD models to describe the effect of the experimental COX-2 inhibitor SC-75416 (Pfizer, MI, USA) and performed trial simulations to enhance the further development of this analgesic.²⁹ SC-75416 is a selective COX-2 inhibitor that has anti-inflammatory and analgesic activity. They studied postoral surgery patients and performed comparisons with placebo, ibuprofen, rofecoxib and valdecoxib. In an initial study, an oral solution of SC-75416 was followed by a capsule formulation. They constructed logistic effects models in NONMEM with three main components: placebo effect (modeled by an exponential function) and drug effect (modeled by a sigmoid E_{max} function); random effect; and investigating pain relief. The estimated EC₅₀ values for SC-7541, rofecoxib, valdecoxib and ibuprofen were 5.5, 0.3, 0.07 and 6.8 µg/ml, respectively. The most important results of the study were: the study and trial simulations prompted further study developments (pursuing a high-dose strategy) that otherwise might not have been considered; the approach resulted in time and cost savings by not having to repeat the postoral surgery study and formulation rework was carried out to optimize drug delivery.

Li et al. performed a PKPD analysis of dental pain relief by ibuprofen.³⁰ Their aim was to assess the efficacy of a novel effervescent formulation in comparison with the standard tablets of NSAIDs. In a group of patients following third-molar extraction surgery, the effect of the two formulations and placebo were modeled using an E_{max} pain relief model and hazard models to analyze time to pain relief and remedication. The data show differences in PK parameters between the two formulations with a greater oral absorption rate for the effervescent ibuprofen and greater effect-site concentrations between $t = 0$ and 2.5 h following dosing. This caused more rapid pain relief and less remedication for the effervescent formulation compared with standard ibuprofen. The authors constructed nomograms to correlate time to pain relief with PK profiles. Overall, these data indicate the usefulness of PKPD modeling in the development of new formulations of analgesic drugs (see later).

Acetaminophen

Another example where model-based analysis was used to aid the development of a new formulation is the study by Green et al.³¹ They performed PKPD analysis on pain relief data following administration of four different acetaminophen (paracetamol) formulations (Tylenol®, Panadol® Rapid and two that used new formulation technologies from Imaginot Pty, Ltd., Brisbane, Australia) to explore possible differences in PD outcomes. The authors used the PKPD data from Anderson et al. to do a simulation on the effects of the new formulation.³² PK data were obtained from volunteers that received a single dose of 1 g of

the four formulations; PD data were obtained from simulations on an earlier published PD model that quantified pain relief following tonsillectomy. Interestingly, their data indicate that the placebo effect was appreciable and there was a potential difference between acetaminophen and placebo at $t = 0$ and 30 min post dosing only. With respect to the comparison between formulations, the authors conclude that their analysis suggests a significant reduction in time to onset of effect with the newer formulations. The current approach of learning drug behavior from already published datasets was used ‘because running a confirmatory clinical trial was prohibitively expensive’.³¹

Epidural anesthesia/analgesia

Epidural anesthesia and analgesia is obtained by an injection of a local anesthetic, an opioid or their combination into the epidural space. The injected drugs spread over the epidural space, diffuse towards the intrathecal space (where the drugs diffuse into and bind to neuronal tissue) and into blood vessels of the epidural space. Depending on the concentration used and type of drug injected, motor and sensory blockade develops and dissipates. Onset/offset times and spread of the effect across the spinal segments vary and depend on the kinetic and dynamic properties of the injected anesthetic/opioid. Olofsen et al. are the first to develop a population PKPD model of epidural anesthesia and analgesia.³³ Their analysis enables the development of predictive epidural anesthesia, in this case, analgesia models that may improve therapeutic outcome. An indirect assessment of the epidural drug concentration was made by estimation of the time course of systemic drug absorption from the epidural space (by measurement of the drug concentration after an epidural injection). Simultaneously, they assessed the level of sensory blockade over time. Tested drugs were the local anesthetics levobupivacaine and ropivacaine. The epidural segments were modeled by central and peripheral absorption compartment- and effect-sites. Differences were observed in the onset/offset half-lives between the two drugs (15 min for levobupivacaine and 25 min for ropivacaine). Age was a significant modifier with respect to onset/offset half-lives (increasing age reduced $t_{1/2}$ for levobupivacaine at all segments) and anesthetic potency (increasing age increased the potency at segments Th12 and higher for ropivacaine). The model enables individualized dosing depending on age, sex and drug, and gives a predictive indication of the time course of the sensory blockade (Figure 2).

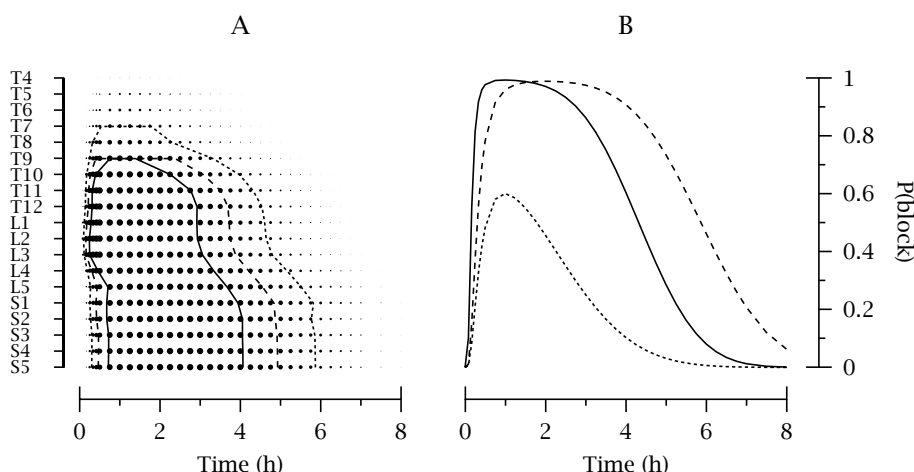


Figure 2 Population PKPD modeling of epidural analgesia. A. Blockade probabilities after an epidural injection of 125 mg ropivacaine in a 50 year old patient. The size of the dots is proportional to the probability of blockade with 90% (solid line), 75% (broken line), and 50% (dotted line) isoeffect lines. Time is expressed on the x-axis and the dermatome level on the y-axis. B. Probability of blockade, $P(\text{block})$, for dermatomes S5 (broken line), Th11 (solid line) and Th7 (dotted line) versus time. Data adapted from Olofsen et al.³³

PKPD MODELING IN CHRONIC PAIN

Ketamine

In a reanalysis of a study on the long-term (12 week) effects of a 100-h S-ketamine infusion on pain relief in chronic pain patients owing to complex regional pain syndrome type 1, Dahan et al. used an inhibitory sigmoid effect-compartment model of the form: $\text{PAIN score} = \text{BASELINE PAIN} / (1 + [C_e / C_{50}]^\gamma)$, and onset/offset rate constant k .³⁴ This very simple model satisfactorily described the 12-week pain relief data with a value for C_{50} of 10 ng/ml and $t_{1/2}k$ of 10.9 days (95% CI: 5–21 days). The C_{50} for relief of chronic (neuropathic) pain is approximately 50-times lower than that observed for the relief of acute nociceptive pain (in volunteers) and suggests a different mode of action of S-ketamine in these two distinct pain states. This is an example derived from chronic pain data of the power of PKPD modeling in understanding the complex behavior of analgesic agents. The parameter $t_{1/2}k$ is not synonymous to the blood effect-site equilibration parameter $t_{1/2}k_{eo}$. While the later parameter described the passage of the drug to the postulated receptor site, parameter k reflects the dynamics of disease modulation by S-ketamine. The plasma concentration of S-ketamine drops rapidly below detection values (within

hours) following the withdrawal from ketamine, while its analgesic effect persists for weeks, probably owing to the initiation of a complex cascade of events of which NMDAR desensitization is the first step of this disease-modulatory process.

Assuming that PK of S-ketamine is irrelevant in describing its prolonged analgesic effect in chronic pain, in addition a (population-based) time-series analysis was performed using a mixture model and autoregressive (Kalman) filter constructed in NONMEM. The model assumes an exponential return of pain values towards baseline pain with autoregressive factor F , which is comparable to parameter k . Indeed, the observed value of $t_{1/2}F$ corresponded well with the range observed for k : 15–41 days. The mixture model allows the estimation of the chance of an analgesic effect to ketamine (or placebo) by objectively subdividing the patient population into four subgroups: two types of nonresponders and two types of responders (Figure 3). This type of analysis is attractive as it rapidly allows a subdivision of analgesic responses into various subgroups that may be defined a priori without the need for PK data. Mixture models using time-series analysis may be especially advantageous when quantifying the analgesic efficacy of drugs in terms of onset/offset time, division into subgroups, magnitude of variability and placebo effect, or when quantifying the effect of drugs that act locally, such as local applications of lidocaine or capsaicine.

Pregabalin

Pregabalin is an analog of GABA and acts at the $\alpha 2\delta$ protein associated with voltage-gated calcium channels. It has anxiolytic, antiepileptic and analgesic properties. Byon et al. performed a pregabalin exposure-response analysis in fibromyalgia chronic pain patients.³⁵ They modeled the probability of an observed specific daily pain score (on an 11-point categorical scale) using a proportional odds logistic regression model in NONMEM with additive components: baseline pain, placebo response (exponential function) and drug effect ($E_{\max}$ and linear models were tested). The logistic regression approach is used when pain or pain relief is scored with an ordered categorical scale and was first introduced by Sheiner in 1994.³⁶ Byon et al. incorporated data from four separate randomized, placebo-controlled studies including 2758 patients with daily dosing for 8–14 weeks in the dose range of 150–600 mg two- to three-times per day.³⁵ The average drug concentration was estimated from the pregabalin dose and renal function. The $E_{\max}$ drug effect model gave the best results and they estimated an EC_{50} of 1.4 $\mu\text{g/ml}$ (equivalent to 174 mg/day in a patient with creatinine clearance of 100 ml/min), the delay in drug effect had a $t_{1/2}$ of 11 h. Sex and age were significant covariates, with increasing values for $E_{\max}$ with increasing age and in men compared with women.

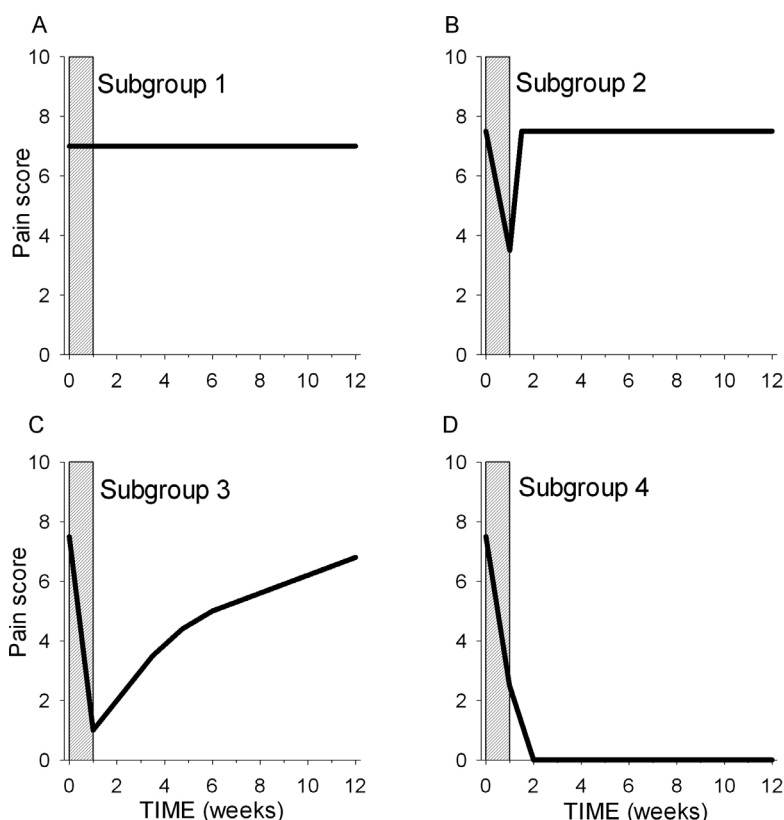


Figure 3 Mixture analyses of the effect of a 1-week ketamine treatment (dashed box) on pain scored in patients with chronic pain. The analysis objectively divided the total population response into 4 categories, with A = no response to treatment, B = a response in the treatment week only, C = a long-term response with a slow return towards pre-treatment baseline, and D = full recovery. Data adapted from Dahan et al.³⁴

Expert commentary & five-year view

In the last 5–6 years, only a limited number of studies have been published on population PKPD modeling of analgesic agents used in acute and/or chronic pain. The majority of studies focused on older analgesics, including morphine, buprenorphine and ketamine, while studies on newer agents were scarce and limited to morphine's metabolite M6G, the experimental NSAID SC-75416 and pregabalin. We believe that population PKPD modeling is an important tool, not only in the description of the time course of drug effect (which enables the appropriate use of the drug), but equally important

to understand the interaction of a specific pharmacological agent within the often complex disease processes and possibly even understand the complexities of the disease itself. Furthermore, model-based analysis using a population PKPD approach is useful in the development of new formulations of older drugs such as was shown for ibuprofen^{29,30} and acetaminophen.³¹ Simulation-based PKPD modeling may be a cheap but valid alternative to expensive large clinical trials.³¹

In the upcoming 5 years, we foresee various advances in the use of population PKPD models in acute and chronic pain, most importantly in the development of new analgesic agents, in the development of new formulations or the switch towards new indications of already registered analgesics. Particularly in the development of new analgesic agents, population PKPD modeling enables simultaneous assessment of the various properties of analgesics by calculation of utility or safety functions. There are various possible calculations of the therapeutic utility functions possible such as the probability of analgesic effect minus the probability of side effect. In an animal study, Yassen et al. performed a logistic regression analysis to characterize the relationship between drug exposure and two effects of buprenorphine and fentanyl: antinociception and respiratory depression.³⁷ Odds ratios for both end points were calculated and were, for buprenorphine, 29 and 2 for antinociception and respiratory depression, respectively, while for fentanyl these values were 3 and 2.5. The safety index, calculated as the odds ratio for analgesia divided by the odds ratio for a side effect of 1.2 for fentanyl and 14 for buprenorphine, suggests a distinct margin of safety for these two opioids, with greater safety for buprenorphine compared with fentanyl. Respiratory depression, as a complication of potent opioid analgesics, is seldom studied, while respiratory events are potentially life-threatening side effects of these agents.³⁸ Hence, we encourage the industry to determine the safety index in the development of new analgesic agents. Particularly when developing potent analgesic agents or new formulations (such as for fentanyl and sufentanil), PKPD studies on opioid side effects (including respiratory depression, nausea/vomiting, delayed gastric emptying and sedation) should be part of the preregistration study process.

Another advancement would be the use of PD mixture models in NONMEM to predefine response groups into responders and nonresponders. Both responders and nonresponders require further a priori descriptions with patients that experience at least 50% pain relief throughout the treatment period as most clinically relevant. Apart from drug effect per se, the variability within the different groups is an important marker of drug efficacy. Moreover, patients in the different response groups may be further examined to link specific patient characteristics (such as parameters derived from quantitative sensory testing, duration of disease, severity of pain symptoms and variability in pain symptoms)

to drug efficacy, eventually allowing prediction of drug response based entirely on these pretreatment assessments.³⁹ We predict an important place for mixture modeling in NONMEM in the development of new drugs or new indications of already registered drugs.

The chronification of pain is complex and poorly understood. Both peripheral and central processes play important roles, although the specifics vary per disease. To fully understand the effect of analgesics on these processes, disease-modulatory PKPD models are required that describe the effects of specific analgesics within the various pain pathways.³¹ These models need to be dynamic as processes vary over time. For example, it may well be that chronic pain in its initial phase has predominant peripheral inflammatory components, while over time structural plastic changes within the spinal cord or at supraspinal sites develop. Abandanes et al. use PET to predict brain target occupancy of duloxetine, a serotonin-reuptake inhibitor with analgesic properties, with various dosing regimens, using a mechanism-based PK brain target occupancy models.⁴⁰ They define 50% receptor occupation (OC_{50}) as the drug plasma concentration that achieves 50% receptor occupation with $OC_{50} = k_{off}/k_{on}$. Applying these techniques to specific pharmacological targets of chronic pain within the different timeframes of the lifecycle of the disease and linking receptor occupation to pain relief is an example of the building of disease-modulatory PKPD models. Such models will increase our insight into the disease process (such as the process of chronification of pain) and will improve treatment development.

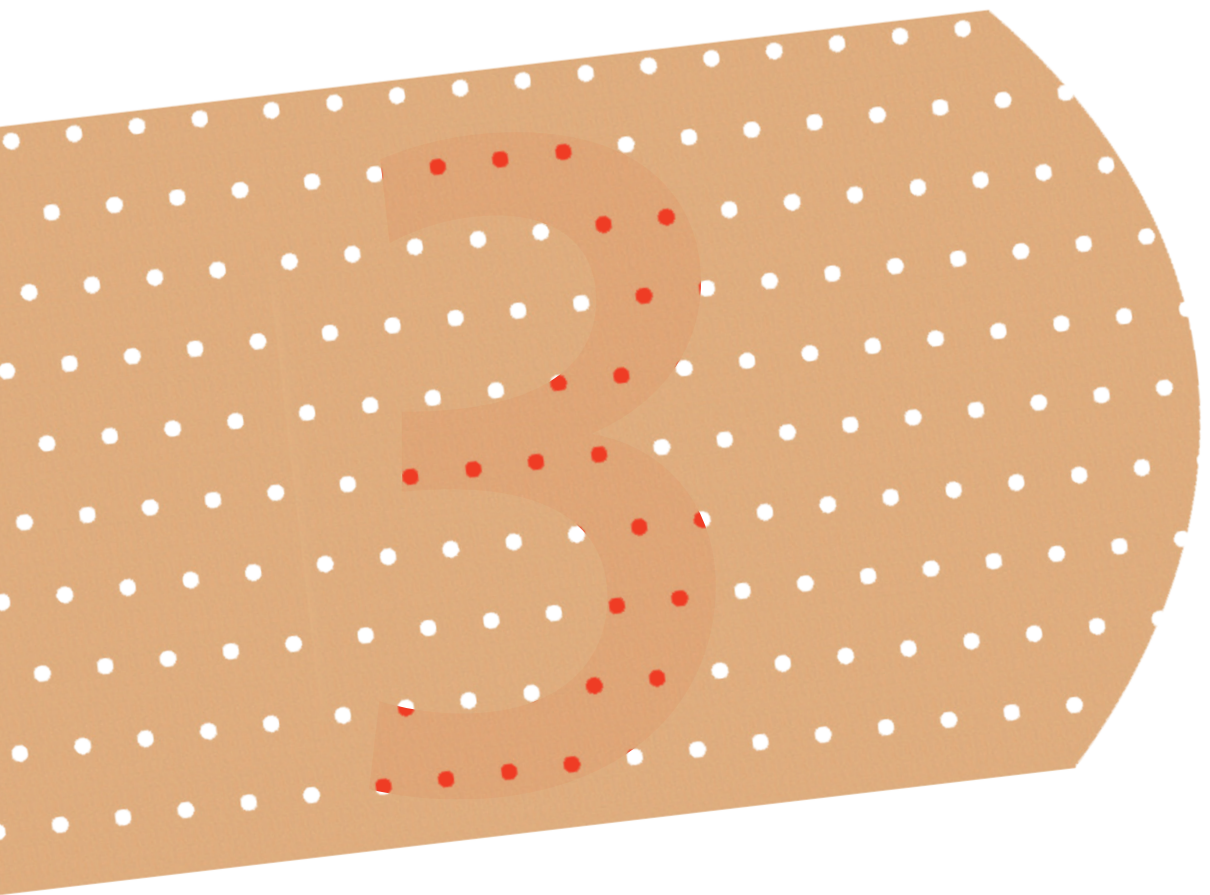
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Section 1 | CAPSAICIN



Chapter 3

Pharmacodynamic analysis of the analgesic effect of capsaicin 8% patch (Qutenza™) in diabetic neuropathic pain patients: detection of distinct response groups

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INTRODUCTION

The development of painful diabetic peripheral neuropathy (DPN) is a common longterm complication in diabetic patients. It is relatively more common in older patients and patients with suboptimal glycemic control.¹ Although the exact pathophysiologic mechanism is unknown, several contributing factors have been proposed, such as microvascular insufficiency, oxidative stress, nitrosative stress, defective neurotrophism, and autoimmune-mediated nerve destruction.^{2,3} Patients with DPN exhibit a variety of pain symptoms and sensory qualities. Approximately 20%–24% of patients experience onset of insidious pain (or dysesthesias) and present with varying degrees of numbness, tingling, burning pain, loss of sensations, paresthesias and loss of balance or coordination. Of the 60% of diabetics who develop neuropathy, about 30%–40% have no symptoms.⁴ Attempts to treat DPN can be divided into those directed at modification of the underlying disease process and those directed toward symptom suppression.⁵ No consensus on the optimal management of neuropathic pain exists and consequently the treatment of pain is largely empirical and diverse, relying primarily on antidepressants, anticonvulsants and narcotic analgesics.⁶ This study focuses on the local application of a high concentration (8%) capsaicin patch, NGX-4010 (Qutenza™) for treatment of painful DPN. Capsaicin is the pungent ingredient in chili peppers and it is believed that exaggerated activity of capsaicin-sensitive nerve fibers is involved in the pain of peripheral neuropathies like DPN and postherpetic neuralgia.⁷ Capsaicin is a highly selective activating ligand for transient receptor potential vanilloid 1 (TRPV1), which is a ligand-gated nonselective cation channel highly expressed in small diameter primary afferent neurons (C- and A δ -fibers), especially those nerve fibers that specialize in the detection of painful or noxious sensations.^{8–10} Activation of this receptor by capsaicin results in a burning sensation, hyperalgesia, allodynia, and erythema (due to release of vasoactive neuropeptides from small-diameter sensory axons).⁹ After prolonged exposure to capsaicin, the small diameter sensory axons become less sensitive to a variety of stimuli, including capsaicin itself or thermal stimuli, resulting in a reduced pain response.⁸ These later stage effects of capsaicin are frequently referred to as “dysfunctionalization” and serve as the rationale for the development of capsaicin formulations for the treatment of various neuropathic pain syndromes.⁷ Studies have shown that such alterations from prolonged low-concentration capsaicin exposure are reversible, at which point normal function (the detection of noxious sensations) returns.^{11,12}

In this study, patients received a single treatment with the high concentration capsaicin patch (NGX-4010). While a (limited) descriptive analysis of the data has been published previously,²⁰ an independent re-analysis was performed, using nonlinear mixed effect

modeling in NONMEM considering the whole time course of effect (0–12 weeks).¹⁴ The aims of the study were (i) to get an indication of the variability in responses and attempt to identify subgroups in response to capsaicin treatment using a pharmacodynamic mixture model; (ii) to describe the magnitude of effect and time courses of onset and offset of effect of 8% capsaicin patch in the observed subgroups.

METHODS

The study was registered in the Clinical Trial register (www.clinicaltrials.gov) under number NCT00082316.

Patient population and study design

After approval of the protocol by the local ethics committee patients with moderate to severe pain (numerical pain rating score [NPRS] of 3 or greater on a scale from 0 [no pain] to 10 [worst possible pain]), secondary to DPN were enrolled in the study. DPN was defined as neuropathic pain (related to type I or II diabetes mellitus) in both feet for at least 3 months prior to the study.

Inclusion criteria were: men and women aged at least 18 years, absence of pain from other causes (eg, from fibromyalgia, arthritis, mononeuritis multiplex, hereditary neuropathy), intact skin around the treatment area, absence of significant medical problems of the heart, kidneys, liver, or lungs. Chronic pain medication was allowed with the exception of any topical medication in the affected areas of the body, including nonsteroidal anti-inflammatory drugs, menthol, methyl salicylate, local anesthetics, steroids, or capsaicin. After the screening visit, no pain medication changes were allowed. Exclusion criteria included a history of substance abuse, pregnancy or lactation, the presence of cancer, opioid medication use, unless orally or transdermally administered and not exceeding a total daily dose of morphine 60 mg/day, chronic alcohol abuse, uncorrected vitamin B12 deficiency, or treatment with any drugs that may have contributed to the neuropathy during the 90 days prior to the study, hypersensitivity to capsaicin (ie, chili peppers or over-the-counter capsaicin products), local anesthetics or adhesives.

This multicenter study had a randomized, open-label design and was aimed at the evaluation of the tolerability and efficacy of the application of 1–4 high-concentration capsaicin (640 g/cm²) patches, preceded by the topical application of lidocaine 4%. Prior to treatment with NGX-4010, the lidocaine cream was applied over and extending 1–2 cm beyond the perimeter of the marked painful area(s) for 60 minutes. After removal of the topical anesthetic, up to four 20 x 14 cm capsaicin patches were applied for 60–

90 minutes. The patch(es) were then removed and a cleansing gel was used to remove excess capsaicin from the skin, after which the treated area was gently washed with soap followed by water. The patients were monitored for at least 2 hours following treatment before being discharged. For discomfort, the patients were permitted to use analgesic medications during (oxycodone oral solution 1 mg/mL) and after treatment (hydrocodone/acetaminophen tablets, 5/500 mg, two tablets every 8 hours, for a maximum of 5 days).

The primary study parameter was the average NPRS for the past 24 hours obtained at 24-hour intervals at 0900 PM. Average weekly NPRSs were used in the analysis, without imputation for missing scores. Pain scores were obtained for 12 weeks following the application of the capsaicin patch.

Pharmacodynamic data analysis

Model fitting was performed using a nonlinear mixed effects modeling approach using nonlinear mixed effect modeling software (NONMEM version VII level 1; ICON Development Solutions, Ellicott City, MD).¹⁴ The first-order conditional estimation (FOCE) with interaction algorithm was used for model development. The performance of the analysis was evaluated by various selection criteria, including visual inspection of the goodness-of-fit plot, changes in the objective function value and parameter estimates and their respective standard errors. Using the likelihood ratio test, the significance level was set at $\alpha = 0.01$, which corresponds to a reduction of 6.6 units in objective function value (χ^2 distribution) to discriminate between two nested structural models after inclusion of one additional parameter. Model diagnostic checks of the final model were conducted using R (R-project, version 2.12.0).

Pharmacodynamic model

The effect of capsaicin 8% on NPRS was characterized using a Bateman function with the following structure:

$$\text{Effect} = \frac{k_{\text{onset}}}{k_{\text{onset}} - k_{\text{offset}}} \cdot (e^{-k_{\text{offset}} \cdot \text{time}} - e^{-k_{\text{onset}} \cdot \text{time}}) \quad (1)$$

The Bateman function characterizes the time course of NPRS pain score from week 0 (baseline) to week 12 in terms of two first-order rate constants describing the onset (k_{onset}) and offset (k_{offset}) of the effect following the application of capsaicin 8%. The change in NPRS from week 0 to week 12 was computed as follows:

$$\text{NPRS}(t) = \text{NPRS}_o \cdot (1 - \alpha \cdot \text{Effect}) \quad (2)$$

where NPRS_o is the NPRS pain score at baseline and α is the magnitude of effect. Random effects were included in the pharmacodynamic model provided that the parameters are either normally or log-normally distributed. For example, the pharmacodynamic parameter α was modeled assuming a normal distribution allowing for the estimation of negative values of the parameter α (increase in NPRS pain score):

$$\alpha_j = \theta_\alpha + \eta_j \quad (3)$$

where α_j is the estimate of α for the j th individual and θ_α represents the population estimate for the pharmacodynamic parameter α . η_j describes the inter-individual variability on α , which is assumed to be a normally distributed random effect variable with mean zero and variance ω^2 . Similarly, the inter-individual random effect variables for NPRS_o and k_{onset} were assumed to be normally distributed. The inter-individual variability random effect variable for k_{offset} was assumed to be log-normally distributed.

Residual variability, which is a measure of the unexplained variability (including error associated with reporting of chronic pain outcome), was described using an additive error model:

$$\text{NPRS}_{\text{obs},ij} = \text{NPRS}_{\text{pred},ij} + \varepsilon_{ij} \quad (4)$$

where the residual variability, ε_{ij} , at time point i for individual j , is a normally distributed random effect variable with mean zero and variance σ^2 .

Mixture model

Aside from the advantage of the use of the population approach in simultaneously analyzing individual data, the nonlinear mixed effects modeling approach also enables the definition of a mixture model, in which the existence of subgroup of patients that may respond differently to capsaicin 8% patch treatment can be explored. For this analysis, it is assumed that the structural model is the same for subgroups, but that patients may differ in their onset and offset of response and also may respond differently to capsaicin 8% patch in terms of magnitude of response. To this end, the pharmacodynamic parameters, k_{onset} , k_{offset} and α are assumed to be distributed multimodally and therefore the mixture feature in NONMEM is used to differentiate between subgroups of patients on the basis of the distribution of the pharmacodynamic parameter estimates. Initially, based on visual inspection of the individual data, the mixture model was defined to

separate four sub-groups of patients, including patients that show (1) worsening of response, (2) no response, (3) maximum response with trend to return to baseline after 12 weeks and (4) maximum response which is maintained during 12 weeks.

RESULTS

The data from 91 patients were included in the analysis. Data of patients with early termination from the study were included in the analysis ($n = 13$). Early termination was most often related to unsatisfactory therapeutic response and occurred most often in week 6 of the study. An overview of the demographic patient data (of patients included in the analysis) is provided in Table 1. The mean time course profiles of the numerical pain rating score for the total population are shown in Figure 1A. The mean percentage of pain reduction from baseline at week 12 for the total population was 30.5% (95% confidence interval [CI]: 21.1%–39.9%). The proportion of patients that show at least 30% reduction in NPRS from baseline at week 12 was 46.8%; the 50% responder rate at week 12 was 33.8%.

Description of the four subgroups

The mixture model analysis clearly showed that the dataset can be separated into subgroups (Tables 2–4). These subgroups have different shapes of the time versus response profile, indicating that patients differ in their response to capsaicin 8% treatment. The mean time course profiles of NPRS pain score for the different subgroups are shown in Figure 1B–E. The standard errors shown serve to illustrate that the average NPRS score in each subgroup (except for subgroup 1) is estimated with a high degree of precision as indicated by the relative low standard errors.

Table 1 Demographics of patients involved in the analysis

Characteristic	% of population
Number of patients	91
Sex distribution (n)	
Men	52 (57.1%)
Women	39 (42.9%)
Age $\pm$ SD (years)	58.7 $\pm$ 11.21
Age distribution (n)	
< 65 years	63 (69.2%)
$\geq$ 65 years	28 (30.8%)
Weight $\pm$ SD (kg)	97.7 $\pm$ 22.86
Height $\pm$ SD (cm)	172.5 $\pm$ 9.81
Race distribution (n)	
White	69 (75.8%)
African American	10 (11.0%)
Hispanic	9 (9.9%)
Other	3 (3.3%)

SD = standard deviation

Patients in subgroup 1 ($n = 3$) displayed a worsening of response (increase in NPRS score) following capsaicin 8% treatment that was maintained during the 12 weeks of the study (Figure 1B). The mean increase in NPRS from baseline at week 12 was 28.0%. Note, however, that this subgroup contains just three subjects.

Subgroup 2 contains 28 patients that showed no or minimal response to capsaicin 8% treatment (Figure 1C). On average, a slight increase in NPRS pain score from baseline of 5.62% was observed (Table 2), while none of the patients in that subgroup showed at least 30% reduction in NPRS from baseline at week 12.

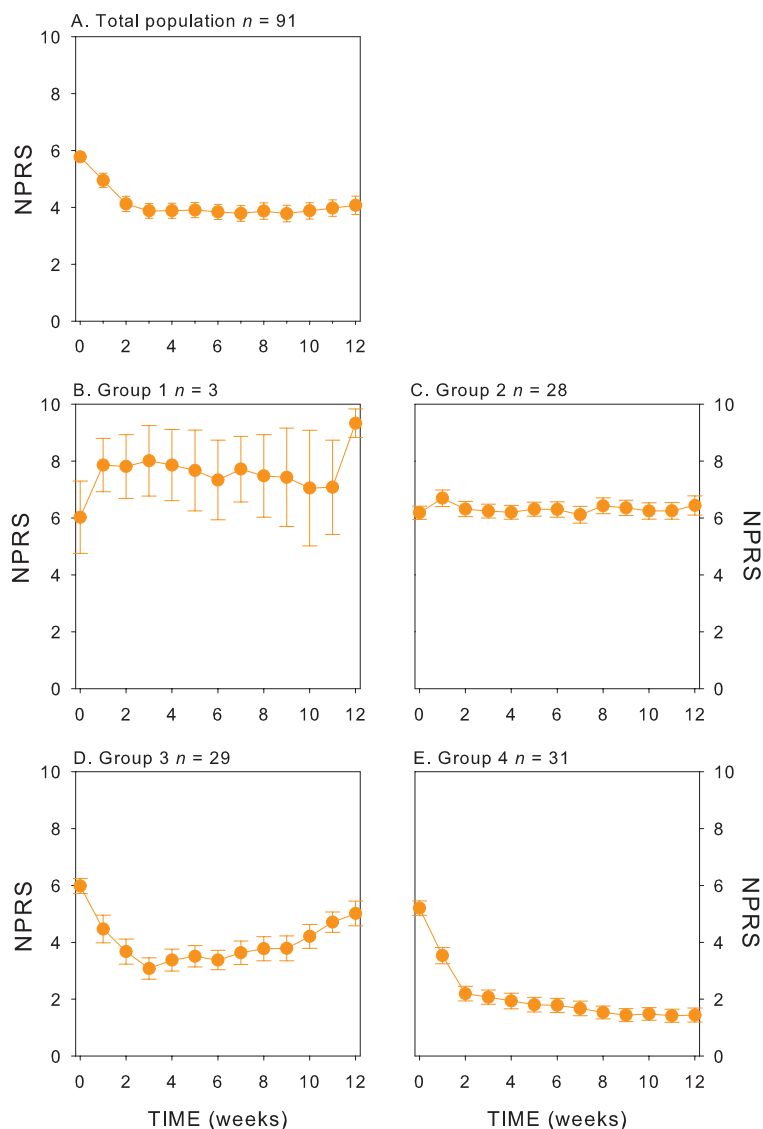


Figure 1 (A) Mean response of the total population ($n = 91$). (B) Mean response of patients belonging to group 1 (patients with a deterioration of their pain) as determined from the mixture model analysis. (C) Mean response of patients belonging to group 2 (patients with no response to treatment). (D) Mean response of patients belonging to group 3 (patients with an initial drop in NPRS followed by a slow decline towards baseline NPRS). (E) Mean response of patients belonging to group 4 (patients with a reduction in NPRS which is maintained throughout the study period). Values are mean $\pm$ SEM. NPRS = numerical pain rating score; SEM = standard error of the mean.

Table 2 Pharmacodynamic parameter estimates

Subgroup	Typical estimate ± SE			
	1	2	3	4
Fixed effect parameters (θ)				
NPRS _o	6.0 ± 0.1	6.0 ± 0.2	6.0 ± 0.2	6.0 ± 0.2
k _{onset} (week ⁻¹)	0.76 ± 0.12	0 ± NE	0.76 ± 0.12	0.76 ± 0.12
k _{offset} (week ⁻¹)	0 ± NE	0 ± NE	0.09 ± 0.04	0 ± NE
α	-0.2 ± 0.08	0 ± NE	0.79 ± 0.06	0.79 ± 0.06
Inter-individual random effect parameters				
NPRS _o (%CV)	2.04 ± 0.323 (24%)			
k _{onset} (%CV)	0.20 ± 0.08 (58%)			
k _{offset} (%CV)	1.30 ± 0.75 (114%)			
α (%CV)	0.20 ± 0.08 (subgroup 1: 232%; 2-4: 57%)			
Residual random effect parameter				
Additive residual error	0.51 ± 0.082			

NPRS_0 = numerical pain rating score at baseline;

k_{onset} = the response-onset rate constant;

k_{offset} = the response-offset rate constant;

α = magnitude of effect.

Subgroup 3 and 4 do show a clear analgesic response to capsaicin 8% treatment. On average, the 29 patients in subgroup 3 had a quick reduction in NPRS with a nadir of 42.6% reduction in NPRS occurring between weeks 3 and 4, followed by a slow increase NPRS towards baseline (Figure 1D). At the end of the study the mean NPRS reduction was 15.6%, while the proportion of patients that showed at least 30% reduction in NPRS pain score was 34.8%; the 50% responder rate was 13.0%.

Patients in subgroup 4 show a sharp reduction in NPRS that was maintained during the 12 weeks of the study (Figure 1E). The mean percentage reduction in NPRS from baseline is 69.7% at week 12 and 90.3% of the patients showed at least 30% reduction in NPRS pain score from baseline at week 12, while 74.2% of the patients showed at least 50% reduction in NPRS pain score from baseline.

To get an indication of the adequacy of the model, best, median and worst data fits of NPRS obtained in groups 3 and 4 are given in Figure 2. The goodness-of-fit plots given in Figure 3 do not show any systemic deviation of the model predicted versus observed NPRS.

Table 3 Percentage reduction in numerical pain rating score from baseline at week 4 and 12

	% of total population	Week 4 % (mean ± SE)	Week 12 % (mean ± SE)
Total population	100	33.7 ± 3.99	30.5 ± 4.84
Subgroups			
Worsening of response (Group 1)	3.3	-34.7 ± 10.3	-28.0 ± 1.84
No response (Group 2)	30.8	0.01 ± 2.12	-5.62 ± 3.7
Maximum response with trend to return to baseline (Group 3)	31.9	42.5 ± 5.94	15.6 ± 6.30
Maximum response which is maintained during 12 weeks (Group 4)	34.1	61.7 ± 5.24	69.7 ± 5.11

SE = standard error

Pharmacodynamic parameter values

Speed of onset

These distinct profiles are translated into quantitative estimates of pharmacodynamic parameters, which may differ across the different subgroups. For subgroups 1, 3, and 4, the rate of onset was estimated at 0.76 week⁻¹ (Table 2), corresponding to a half-life ($t_{1/2, \text{onset}}$) of 0.91 weeks, indicating that every 0.91 weeks the NPRS is reduced or increased (in case of subgroup 1) by 50% relative to the NPRS obtained in the previous week. Differences in onset of effect between the subgroups has been formally tested for during the analysis, but did not result in a further improvement of the model fit at the level of $\alpha = 0.01$, indicating that the rate of onset of response is similar for the subgroups. For subgroup 2, the patients that showed no or minimal response to capsaicin 8% treatment, the rate constant for onset of effect was assumed to be 0 and was based on the reasonable assumption that this subgroup has no kinetics of action. In total 28 patients of 91 patients (30.8%) showed no effect to capsaicin 8% treatment.

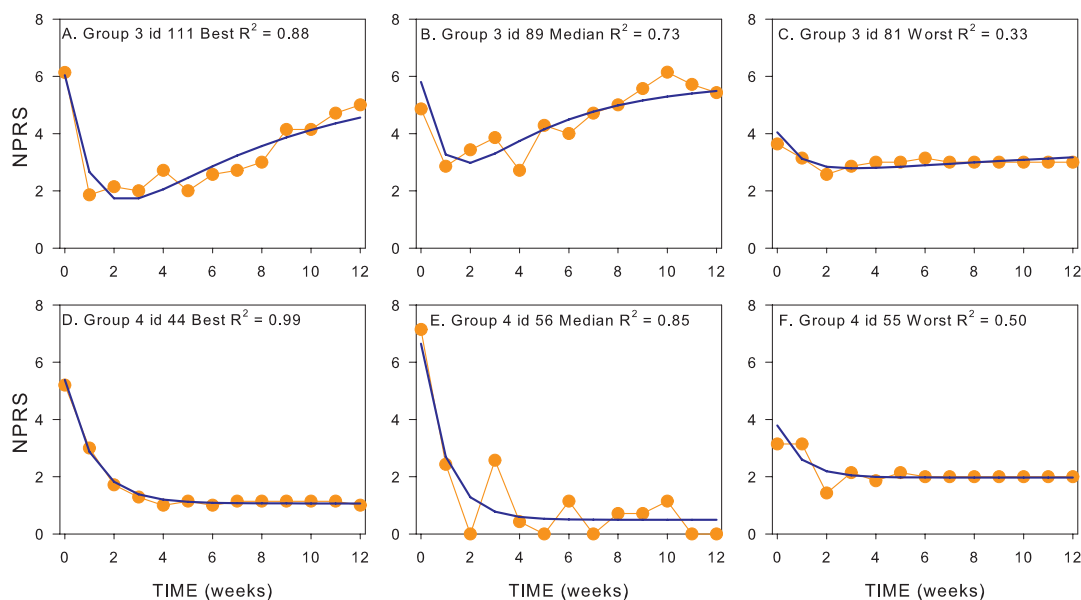


Figure 2 Examples of the data fits of Groups 3 and 4. Best, median and worst fits of NPRS responses belonging to Groups 3 (A, B, and C) and 4 (D, E, and F) are given. NPRS = numerical pain rating score.

Speed of offset

The offset of effect was quite different between the subgroups. Patients in subgroup 3 ($n = 29, 31.9\%$) showed a response to capsaicin 8% patch treatment, which gradually returned toward baseline. The estimate of the rate constant of offset for subgroup 3 was 0.09 week^{-1} (Table 2), corresponding to a half-life ($t_{1/2, \text{offset}}$) of 7.8 weeks (based on the 12-week treatment period). This indicates that every 7.8 weeks the NPRS is increased by 50% relative to the NPRS of the previous week. Subgroups 1, 2 and 4 did not have an offset of effect. For subgroup 4 ($n = 31, 34.1\%$ of patients) this is shown in Figure 1E by a well-preserved maintenance of the maximum response during the 12 study weeks, showing no offset of effect. For subgroup 1 ($n = 3, 3.3\%$ of patients), NPRS pain scores go up and remain at higher scores after treatment with capsaicin 8%.

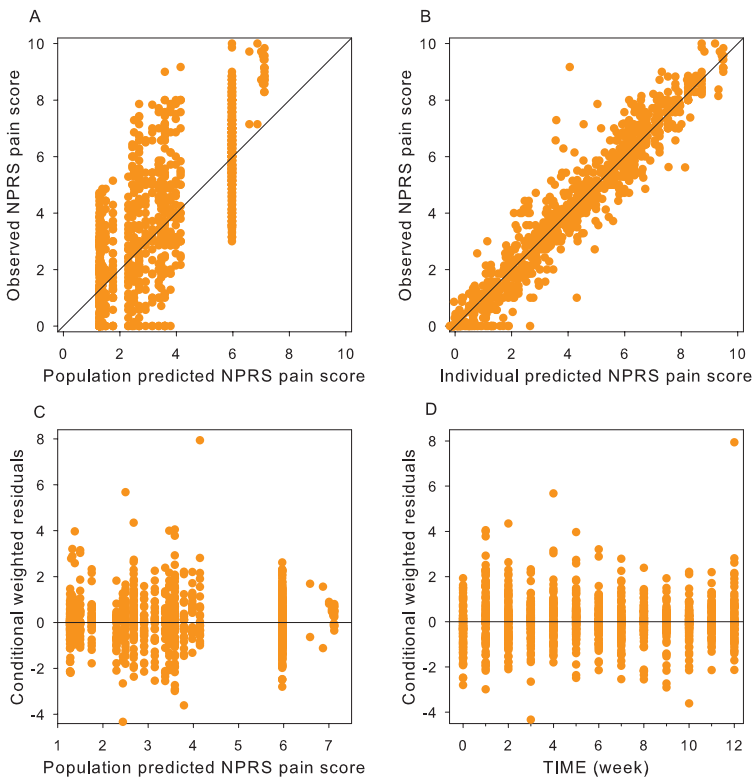


Figure 3 Goodness-of-fit plots of the final pharmacodynamic model. Observed versus population predicted (A) and individual predicted NPRS pain score (B). The black lines are the lines of identity. In the lower panel the conditional weighted residuals versus population predicted NPRS score (C) and time (D) are plotted. NPRS = numerical pain rating score.

DISCUSSION

The development of effective and safe treatments for chronic neuropathic pain indications remains challenging. The heterogeneity (eg, ethnicity, age, sex) and complexity (eg, disease processes, underlying mechanisms) of the chronic pain population, including DPN patients, is well recognized and may partly explain the large variability in the response to pharmacological treatment.^{15,16} In the current study a mathematical pharmacodynamic model was developed, considering the time course of response, to quantify the magnitude and onset/offset times of the effect of capsaicin 8% patch in the treatment of DPN. In addition, a mixture model was applied to objectively match patterns in pain-associated behavior (NPRS). The main findings of the study are: (i) on average, a single application of capsaicin 8% patch produced a variable analgesic response with an average 30.5% pain reduction (95% CI: 21.1%–39.9%) from baseline NPRS at week 12 in DPN patients; and (ii) using the pharmacodynamic mixture model, four distinct subgroups could be identified that respond differently to capsaicin 8% treatment. Subjects allocated to group 1 (3.3% of patients) showed worsening of pain; group 2 (31%) showed no change in NPRS from baseline pain; group 3 (32%) had a quick drop in NPRS with a nadir between weeks 3 and 4, followed by a slow return towards baseline; group 4 (34%) had a quick reduction in NPRS that was maintained throughout the 12 weeks of the study (Figure 1; Table 2). With the exclusion of group 1, each of the groups displayed a significant reduction in response variability separating a heterogeneous population into homogenous subgroups in terms of response to treatment. This further underlines the relevance of collecting time course data during and after the treatment period and provides confidence that the developed pharmacodynamic model adequately described the time course of response in individual patients.

The division into the four subgroups was based on characterization of the time course of the response in terms of onset/offset times and magnitude of response. The onset of response had a half-life of about 1 week that was similar for groups 3 and 4 and also group 1. In the latter group the response was algescic rather than analgesic. This indicates that the onset of efficacy is relatively fast and within 3–4 weeks maximum reduction in NPRS was achieved ($3-4 \times t_{1/2, \text{onset}}$). Group 1 includes just three patients and cannot be considered a robust response group compared to groups 2, 3, and 4. It is not possible to understand the algescic behavior in this small group. Possible causes include the presence of unpredictable and varying pain in these patients with spontaneous worsening of symptoms irrespective of treatment, or the presence of mood-related disorders with a poor or erratic response to any medication.

In group 3, NPRS was reduced by 42.6% from baseline at week 4 after treatment (30% and

50% responder rates were 60.7% and 42.9%, respectively, Table 3). In group 4, reduction in NPRS from baseline was 61.7% at week 4 after treatment (30% and 50% responder rate were 83.9% and 64.5%, respectively, Table 4). The response to capsaicin 8% patch treatment was further maintained or even increased from week 5 to at least week 12 in this subgroup, indicating long-lasting pain relief from a single patch application. Only in group 3 a response–offset rate constant could be estimated with a half-life of 7.8 weeks. This indicates that in group 3 the NPRS increased slowly ($\approx 50\%$ increase every 7.8 weeks from week 4 on), suggesting that patients in group 3 would need retreatment after 10 to 12 weeks (at that time the reduction in NPRS is less than 20%). Furthermore, a design in which retreatment is applied would enable assessment of stable treatment reactions. We previously assessed the effect of a 1-week ketamine intravenous treatment on neuropathic pain in patients with complex regional pain syndrome type 1 (CRPS1).^{17,18} At the end of the 12-week follow-up, about 20% of the subjects had significant pain relief (ie, relief 30% of baseline pain score versus 47% in the current study, Table 4). While this suggests a rather poor efficacy of ketamine in the treatment of CRPS1 pain a subsequent subgroup analysis using a pharmacodynamic mixture model showed that 37% (11/30) of patients were unresponsive to ketamine treatment following the treatment week (cf, our groups 1 and 2), 56% (17/30) of patients had an initial analgesic response ($>50\%$ of baseline pain) that slowly returned towards baseline levels (cf, our current group 3) and just 7% (2/30) patients had persistent pain relief (cf, group 4).⁷ Evidently, patients that were unresponsive to ketamine are not suitable for retreatment. In contrast, patients in the ketamine group 3 were given the opportunity for retreatment with ketamine. Similarly, in our current study, patients in group 3 would be well served by retreatment. The current and previous analyses indicate that subdividing patients into specific subgroups provides additional information of the effect of pharmacological treatment on pain responses over time by identifying homogenous subgroups with two classes of responders (ie, group 3 and 4 responders). This approach is superior to the dichotomous classification of patients into responders versus nonresponders made at a specific time-point following treatment (eg, at an arbitrary week following treatment). Also in our study, conclusions drawn from a dichotomous study outcome at week 12 would significantly differ from those obtained using the current approach and would have missed the earlier but transient robust analgesic effects and would have suggested the need for retreatment at week 12 in most patients. Retreatment of patients in subgroups 1 and 2 is not warranted, as discomfort will predominate without any therapeutic benefit. Retreatment in subgroup 4 is not needed since the analgesic response to the patch application was maintained during the observation period. We restricted the mathematical modeling of the treatment responses to analgesia.

We did not take side effects into account, as serious adverse events did not occur (side effects were transient capsaicin-application related, and included local erythema, pain, and itching).¹³ Still, for other types of systemic medication that show similar large variability in response efficacy (eg, NMDA receptor antagonists, GABAergic, antiepileptic and antidepressant medications) nontransient central side effects (sedation/nausea/dysphoria/hallucinations) may occur in patients that experience analgesia as well as those that do not.^{17,18} Especially for these medications with a narrow therapeutic index the characterization of subgroups is important as it allows a more accurate description of the efficacy–safety balance. Concomitant modeling of analgesia and side effects will allow the development of so-called utility functions in which the balance between safety and efficacy is quantified over time.^{19,20} For example patients that do not respond to medication (cf, our groups 1 and 2) are especially vulnerable to a potential imbalance between efficacy and safety as they lack any treatment advantage.

A limitation to our analysis is that in case of small response groups (subgroup 1 with just three patients), changes observed in effect could easily be due to random variation without any relationship to treatment. Furthermore, while our classification into four response groups is an important enrichment tool (eg, for assessment of treatment efficacy or an indicator for the need for treatment switch) it remains a post-hoc analysis. A useful addition to our analysis would be to incorporate a priori functional or neurosensory testing allowing response prediction. To the best of our knowledge, so far, no useful link has been made between any functional testing and drug response outcome. A first approach could be the use of quantitative sensory testing (QST) or brain-evoked potentials using electrical (SEP) or laser stimulation (LEP) of the skin prior to treatment. For example, specific QST, SEP, or LEP patterns detected may be linked to specific response groups. Our model-based approach can be seen as a complementary tool to functional tests like QST, combining mechanistic insights in chronic pain conditions with patient outcome measures. An additional approach could be to link response groups to patient covariates (including patient characteristics, genetic factors (e.g., variations in the *TRPV1* gene), disease severity/state. While this initially requires post-hoc testing, subsequent studies may be designed to address the prognostic value of these covariates in predicting the response to treatment. The developed pharmacodynamic model can be used as a basis for identification of covariates that have potential prognostic value for prediction of treatment outcome, our patient population, however, was too small to allow for such covariate analysis.

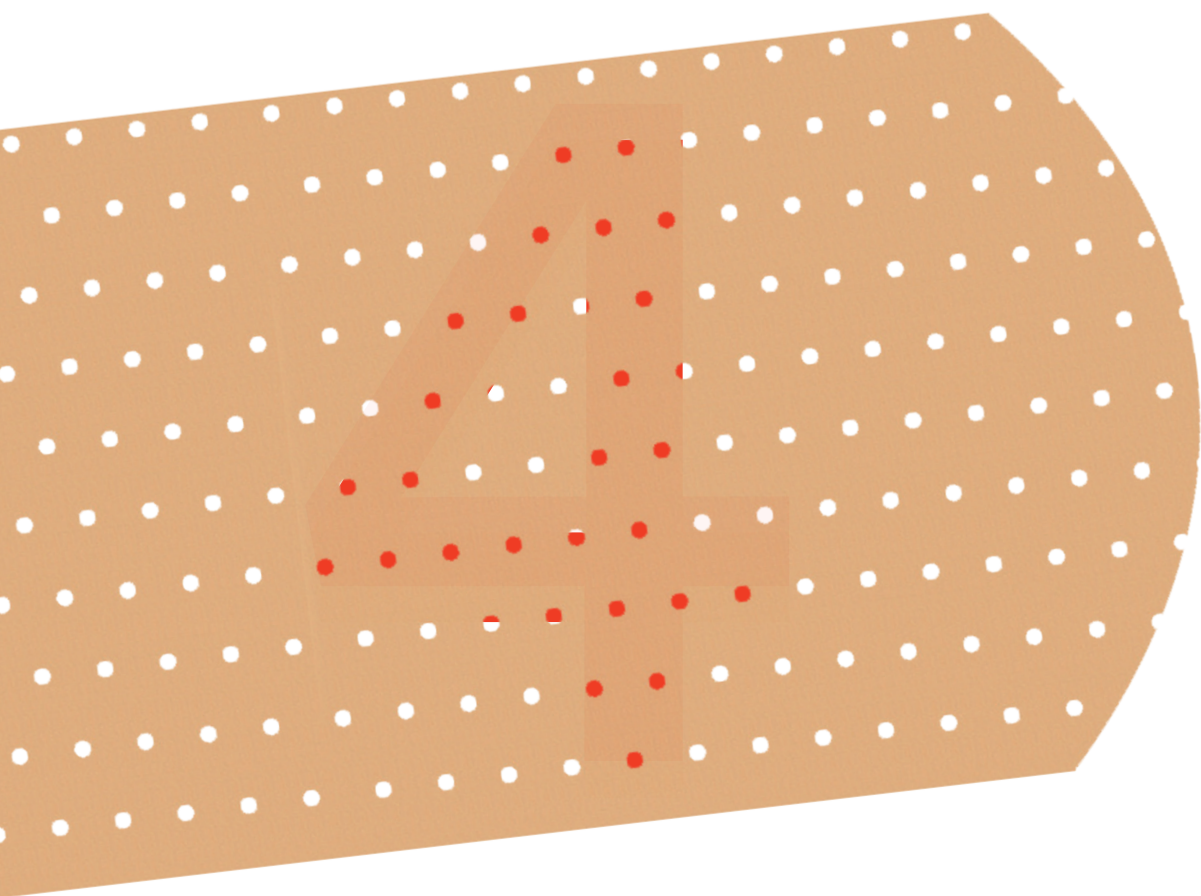
In conclusion, we showed that characterization of the time course of the analgesic response is essential to further understand the heterogeneity in treatment effect (and study population). In the current study in a relatively small population of neuropathic

pain patients, about two-thirds of the patients showed significant reduction in pain following a single application of capsaicin 8% patch. In one subpopulation (34%) the 30% and 50% responder rate was around 90% and 70% at week 12. These results indicate that the single topical application of capsaicin 8% patch provides an effective and long-lasting treatment in DPN pain, although the efficacy should be viewed in light of the open-label study design. Finally, we and others,^{17,18} have shown that the model-based approach may have added value in analyzing longitudinal data from chronic pain trials and may provide insights into the nature of drug response and allows the optimization of treatment algorithms for patients suffering from chronic pain conditions. We applied the mixture model analysis to a small population of DPN patients treated with a single capsaicin 8% patch, but it may be a valuable tool for all therapies with similar large response variability in a variety of chronic pain syndromes, including ketamine, pregabalin, duloxetine, and gabapentin.^{17,21–23}

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Chapter 4

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

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INTRODUCTION

Postherpetic neuralgia (PHN) is a chronic neuropathic pain condition caused by the varicella zoster virus.^{1,2} The virus is usually contracted in childhood (causing chicken pox) but remains dormant in the nervous system. Reactivation in later life (causing acute herpes zoster) may be complicated with longterm neuropathic pain confined to the affected dermatomes. PHN develops in 8–19% of patients following acute herpes zoster, although prevalence increases with age.² Recent trials on the efficacy of topical treatment with capsaicin 8% versus an active control patch (capsaicin 0.04%) in PHN patients^{3–6} reported favourably on the safety and efficacy of capsaicin 8% with significant pain relief at week 12 after patch application. However, an appreciable effect from the active control patch was observed, although responses were smaller compared to the test treatment (difference in effect <10%).

Capsaicin is a highly selective ligand of the vanilloid 1 receptor (TRPV1) or capsaicin receptor.^{7,8} This ligand-gated receptor is expressed on small primary afferent peripheral nerve endings, particularly of those fibres that detect painful and noxious sensations (C and Ad-fibres).^{9,10} Acute activation of the receptor causes burning pain, allodynia, hyperalgesia and erythema, while more prolonged exposure causes desensitization of the afferent fibres, resulting in a reduced response to noxious and thermal stimuli.¹¹ These later effects are at the basis of the use of capsaicin topical formulations in the treatment of various neuropathic pain syndromes, including PHN, diabetic neuropathic pain and HIV-related neuropathy.¹²

In this study, we pooled data from four double-blind, randomized controlled trials on the efficacy of capsaicin 8% versus 0.04% patches in patients with PHN.^{3–6} Our analysis has three parts: (1) we characterized the longitudinal responses of each patient; (2) collected them in one of five specific response groups; and (3) performed a covariate analysis. Our methodology is distinct from more common and traditional approaches, in which the responder rate at fixed time points during or following treatment are quantified. Our approach allows for a more descriptive examination of specific patient populations with links to a variety of effect predictors. We argue that application of this analytical approach improves insight in the cause of treatment success or failure in individual chronic pain patients.

The study aims were as follows: description of the time course of effect of a topical application of capsaicin 8% and 0.04% in patients with PHN; identification of subpopulations in analgesic response patterns; and determination of covariates that improve prediction of treatment effect.

METHODS

Patients

Data from four double-blind, randomized controlled trials on the efficacy of the capsaicin 8% patch versus capsaicin 0.04% patch in patients suffering from PHN were pooled and analysed.³⁻⁶ In all four trials, PHN patients were included when they had a pain score of 3–9 on a numerical pain rating scale (NPRS) ranging from 0 (no pain) to 10 (worst imaginable pain). PHN was defined as persistent or recurrent neuropathic pain for at least 3–6 months after vesicle crusting due to acute herpes zoster infection. As spontaneous improvement of PHN during the first 6 months may occur, only subjects with at least 6 months of pain since vesicle crusting were included. All subjects were at least 18 years old, of both sexes, did not have significant pain due to other causes, had intact skin at the treatment area, had no history or current problem with substance abuse, were not pregnant during screening and follow-up period, and had no significant internal medical problems. Subjects could be on stable chronic oral pain medication regimens, but could not use any topical pain medications on the affected areas, such as non-steroidal anti-inflammatory drugs, menthol, methyl salicylate, local anaesthetics including 5% lidocaine patch, steroids or capsaicin. After inclusion, no pain medication changes were allowed.

Exclusion criteria were (1) concomitant opioid medication use, unless orally or transdermally administered and not exceeding a total daily dose of morphine 60 mg/day, or equivalent; (2) evidence of another contributing or immunologic cause for the sensory neuropathy, such as chronic alcohol abuse, hereditary neuropathy, uncorrected vitamin B12 deficiency, or treatment with any drug(s) that may have contributed to the neuropathy during the 90 days prior to the first treatment visit; (3) significant ongoing or recurrent pain of another aetiology, including fibromyalgia, arthritis and mononeuritis multiplex; (4) any implanted medical device (spinal cord stimulator, intrathecal pump or peripheral nerve stimulator) for the treatment of neuropathic pain; (5) hypersensitivity to capsaicin (i.e., chilli peppers or over-the-counter capsaicin products), local anaesthetics or their components, oxycodone hydrochloride, hydrocodone bitartrate or adhesives; (6) painful PHN areas located on the face, above the hairline of the scalp and/or in proximity to mucous membranes; and (7) evidence of cognitive impairment, which may interfere with subject's ability to complete daily pain diaries (which requires the subject's recall of average PHN pain level in the past 24 h).

The studies were approved by the Institutional Review Boards/Human Ethics Committees at the participating sites, and conducted according to regulatory requirements (e.g., Good Clinical Practice guidelines) and the ethical principles as written down in the Declaration of Helsinki. Written consent was obtained from all patients before inclusion in the study.

Study design

All studies were randomized, double-blind, controlled, multicentre evaluations of the efficacy of the high-concentration capsaicin patch (640 mg/cm², Qutenza®, NeurogesX, San Mateo, CA, USA), for the treatment of PHN compared to an identically formulated control patch (0.04% capsaicin, 3.2 mg/cm²). After a 14-day period of baseline pain assessment, patients were treated with a capsaicin patch. First, they received a local anaesthetic cream (lidocaine 4%) on the affected areas prior to placement of one or more patches containing study drug. This local anaesthetic was used for the prevention of pain associated with the placement of the capsaicin patch. After removal of the local anaesthetic, subjects received a single 30-, 60- or 90-min treatment with the 8% or 0.04% capsaicin patches (maximum area treated 1000 cm²) over the affected skin area. After treatment, the patch(es) were removed and the treatment area(s) were cleaned with a cleansing gel to remove residual capsaicin. Subjects were monitored for at least 2 h following treatment before being discharged. In case of discomfort during application and the first hour thereafter, cooling could be applied or oxycodone (oral solution 1 mg/mL) could be taken. Furthermore, rescue medication was available to the patients for the 3–5 day period following patch placement: two tablets of Vicodin® (5 mg hydrocodone/500 mg acetaminophen) (Abbott Labs, Abbott Park, IL, USA) every 8 h. The primary efficacy parameter was the average NPRS over the past 24 h obtained at 9 a.m. at 24-h intervals. Average weekly NPRS scores obtained were used in the current analysis, without imputation of missing scores. Pain scores were obtained for the 12-week period following patch application.

Analysis of longitudinal efficacy data and mixture analysis (Figure 1)

A longitudinal model using a Bateman function was developed using a non-linear mixed effect model to describe the time course of NPRS scores following application of the low- or high-concentration capsaicin patch [see Appendix 1 and Figure 1 (longitudinal model)].¹³ Next, subgroups in the data were objectively identified using the identical structural model but allowing differences in magnitude of response and in onset/offset response times [see Appendix 1 and Figure 1 (mixture analysis)]. The procedure resulted in five distinct response populations: (1) a population showing worsening of response (i.e., pain increases during treatment); (2) a population showing no analgesic response; (3)

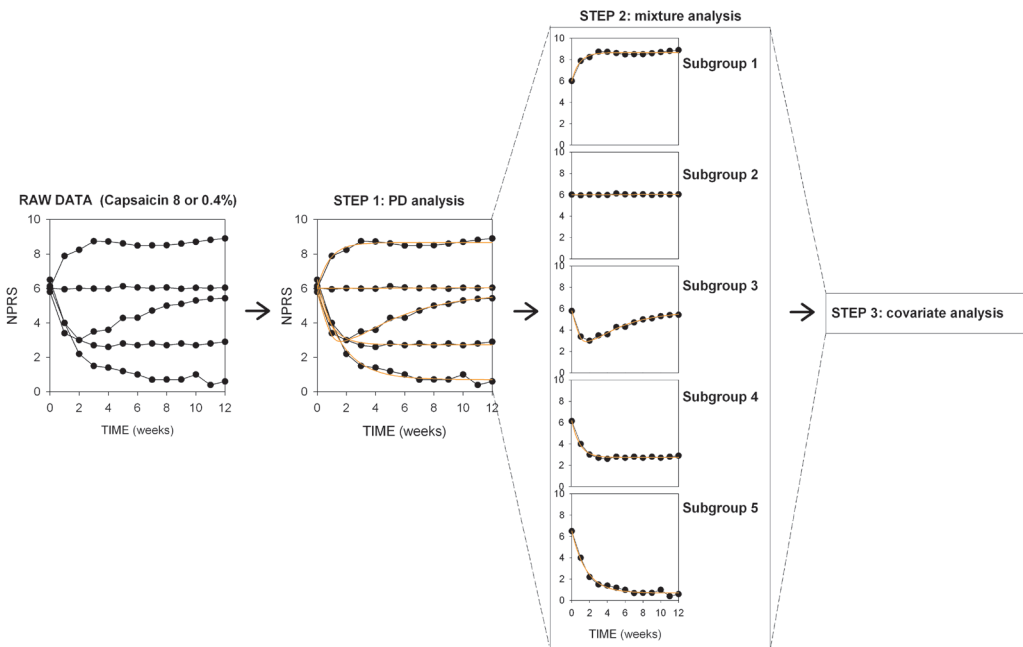


Figure 1 Outline of the data analyses. The raw data are analysed using a pharmacodynamic (PD) model (step 1: longitudinal pharmacodynamic analysis) characterized by two first-order rate constants describing the onset (k_{ONSET}) and offset (k_{OFFSET}) and a parameter that describes the magnitude of effect (a). See also equations (A1) and (A2) of Appendix 1. Next (step 2: mixture analysis), the data are grouped into 1 of 5 possible responder groups on the basis of the parameter (k_{ONSET} , k_{OFFSET} and a) distributions. Finally, (step 3: covariate analysis) the relationships that exist between a set of covariates and the five patient responder profiles following treatment with low- or high-concentration capsaicin patches was explored.

a population showing a (partial or full) analgesic response with return to pretreatment pain levels within 12 weeks; (4) a population showing a partial analgesic response at week 1 that remained constant during the study period; and (5) a population that showed an ongoing decline in pain rating during the 12 weeks of the study.

Covariate analysis

For the covariate analysis, multinomial logit models were used to investigate the relationships that exist between covariates and the five patient responder profiles following treatment with low- or high-concentration capsaicin patches. To this end, the

response variable is the subgroup classification number (1–5) for each patient obtained from the mixture analysis. The independent (predictor) variables that were collected in the four clinical studies and included in the covariate analysis were seven categorical and seven continuous variables, as shown in Table 1. The multinomial logit models were implemented in R (version 2.12.0; [http:// www.r-project.org](http://www.r-project.org)) using the multinom function in the nnet package. The stepAIC function in the MASS package was used to perform the stepwise backward elimination covariate model selection based on the Akaike information criterion (AIC).

Table 1 List of covariates

Categorical variables	
1	Concomitant use of opioids: yes/no
2	Concomitant use of antidepressants: yes/no
3	Concomitant use of anticonvulsants: yes/no
4	Concomitant use of any other pain medication: yes/no
5	Use of pain co-medication (opioids/antidepressants/anticonvulsants): yes/no
6	Sex: male/female
7	Race: Caucasian, African American, Asian American, other
Continuous variables	
8	NPRS at week 0 (baseline)
9	NPRS after lidocaine pre-treatment and before capsaicin patch application
10	NPRS after capsaicin patch removal
11	Variance in NRPS during run-in (pre-treatment) period
12	Age
13	Weight
14	Duration of disease

NRPS = numerical pain rating score

RESULTS

Data from 1248 patients who had participated in one of four trials were pooled, yielding a total of 15,547 numerical pain rating scores. Further, 526 patients were treated with the low concentration capsaicin patch (i.e., the active control 0.04% capsaicin) and 722 patients were treated with Qutenza (8% capsaicin). An overview of the population characteristics is provided in Table 2. The mean time course of NPRS scores of all patients treated with the active control and high-concentration capsaicin patches are shown in Figure 2. The mean pain reduction in NPRS from baseline at week 12 for the patients treated with control or 8% capsaicin were 23.9% and 29.0%, respectively.

Table 2 Patient characteristics

	0.04 % capsaicin patch	8 % capsaicin patch (Qutenza)
Number of patients	526	722
Sex distribution (<i>n</i>)		
Men	277 (47.3 %)	340 (47.1 %)
Women	249 (52.7 %)	382 (52.9 %)
Age ± SD (years)	70.8 ± 11.9	70.8 ± 11.4
Age distribution (<i>n</i>)		
< 65 years	134 (25.5 %)	184 (25.5 %)
≥ 65 years	392 (74.5 %)	538 (74.5 %)
Weight ± SD (kg)	78.8 ± 17.7	78.0 ± 18.2
Race distribution (<i>n</i>)		
Caucasian	480 (91.2 %)	664 (92.0 %)
African American	19 (3.6 %)	19 (2.6 %)
Asian American	6 (1.1%)	19 (2.6 %)
Other	21 (4.0%)	27 (3.7 %)

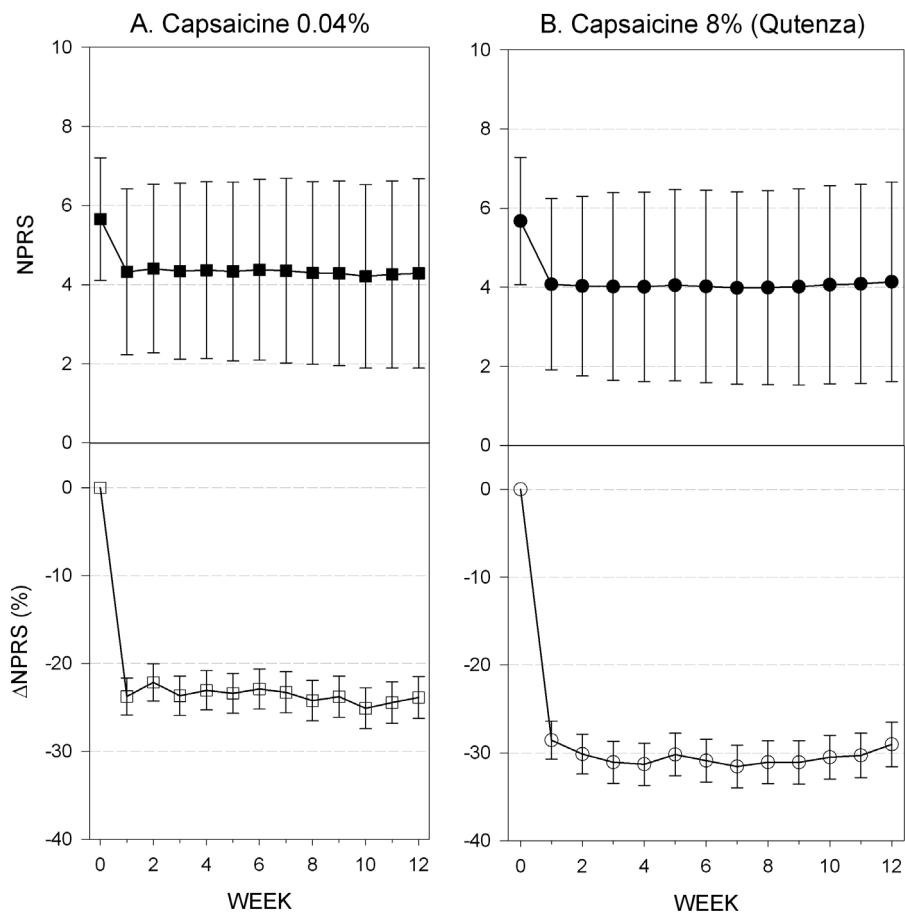


Figure 2 Time course of effect of the low-dose capsaicin patch (A, capsaicin 0.04%) and Qutenza (B, capsaicin 8%) on the numerical pain rating score (NRPS). Values are mean $\pm$ SD.

Description of the five subgroups

Longitudinal and mixture model analysis of the NRPS scores resulted in five well-defined subgroups with differences in magnitude of effect and onset/offset times (Appendix 1). The mean time-course profiles are given in Figure 3. The graphs indicate that the subgroup analysis yielded similar profiles in patients treated with high-dose capsaicin patch and those treated with the active control patch. Apart from subgroup 1, the standard deviations of the subgroup data points were all smaller compared to those of the NRPS scores of the total population (cf. Figure 2A and B with Figure 3), an indication that the

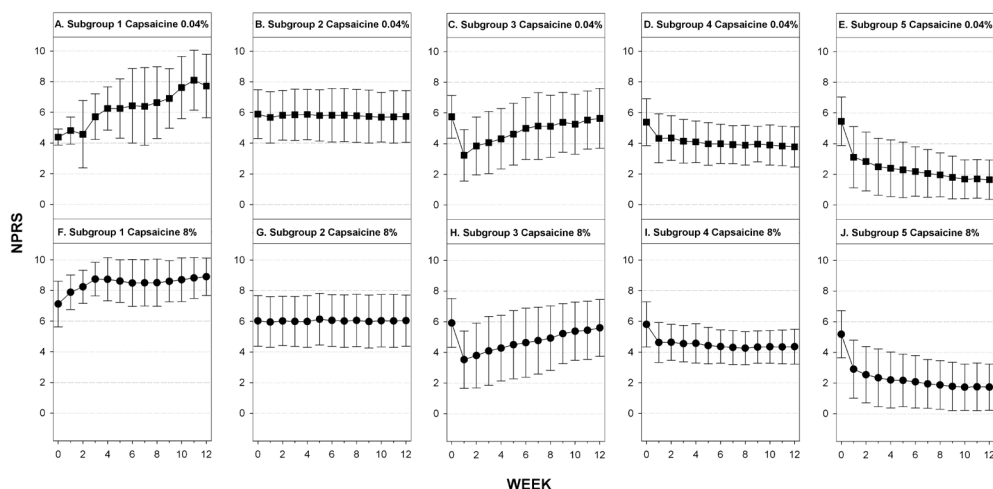


Figure 3 Time course of effect separated by subgroup. Top panels (A–E): treatment with active control (capsaicin 0.04% patch); bottom panels (F–J): treatment with capsaicin 8% patch. Values are mean $\pm$ SD.

subgroups constitute a more homogenous set of patients (i.e., patients responding to treatment with similar time profiles were correctly lumped together).

Subgroup 1

Only a small fraction of patients displayed worsening of pain during treatment (1.5% and 0.8% of patients treated with the high-dose capsaicin and active control patch, respectively; Table 3). Despite its small size, incorporation of this subgroup was an important addition to the mixture analysis, yielding a significant improvement in the goodness of fit over a four-subgroup mixture model as judged by the objective function value.

Subgroup 2

Subgroup 2 contained all patients that showed no response to treatment (i.e., non-responders). The number of non-responders differed between treatments: 22.7% of patients treated with capsaicin 8% versus 39.1% of patient treated with the active control patch. The percentage change in NPRS from baseline at week 12 was comparable between the two treatment arms with an observed 8% reduction in NPRS (active control) versus an observed increase in NPRS of 8% (capsaicin 8%; Table 3).

Table 3 Subgroup distribution

Subgroup	population (%)	% reduction in NRPS at week 12*	30% reduction in NPRS at week 12 (%) [‡]	50% reduction in NPRS at week 12 (%) [‡]
Treatment with capsaicin 8% (n = 722)				
1	11 (1.5)	-27.1	0	0
2	164 (22.7)	-0.8	0	0
3	178 (24.7)	4.5	27 (3.8)	6 (0.9)
4	105 (14.5)	24.4	31 (4.3)	2 (0.3)
5	264 (36.6)	67.4	252 (35)	198 (27.4)
Treatment with capsaicin 0.04% (n = 526)				
1	4 (0.8)	-84.6	0	0
2	206 (39.1)	0.8	3 (0.6)	0
3	93 (17.6)	-0.3	10 (1.9)	5 (0.9)
4	75 (14.3)	30.2	40 (7.6)	2 (0.4)
5	148 (28.2)	69.6	144 (27.3)	125 (23.8)

* Negative values indicate an increase in NPRS.
‡ Presented are the number of patients and percentage of total population.
NPRS = numerical pain rating score.

Subgroup 3

The patient fraction that showed an initial reduction in NRPS at week 1 followed by a slow return towards baseline was 17.6% (active control) versus 24.7% (capsaicin 8%; Table 3). The effect at week 1 was similar between treatments: a reduction in NRPS of 43.6% and 40.4% in patients treated with the active control and high-dose patch, respectively. Return to baseline occurred faster in patients treated with the active control with NRPS values at week 6 within 10% of baseline. In contrast, patients treated with the high-dose patch showed a return to 10% of baseline at week 9.

Subgroup 4

In contrast to patients in subgroup 3, patients classified into subgroup 4 showed a reduction in NRPS at week 1 that was maintained throughout the time course of study.

Patients treated with the active control patch (14.3%) showed a 30.2% reduction in NRPS from baseline at week 12. Patients treated with the 8% capsaicin patch (14.5%) showed a mean 24.7% reduction in NRPS from baseline at week 12.

Subgroup 5

This subgroup included all patients that showed a large reduction in NRPS scores in week 1, with a further progressive decrease in NRPS scores during the time course of the study. For patients treated with the high-dose patch, subgroup 5 was the largest subgroup including 36.6% of the patients. Their mean reduction in NRPS scores from baseline at week 12 was 67.4% (Table 3). A similar treatment effect at week 12 was observed for patients treated with the active control assigned to subgroup 5 (28.2% of the study population): a 69.6% reduction in NRPS. Differences between treatment groups were the different proportion of patients responding with 30% and 50% reduction in NRPS (Table 3) and the proportion of patients allocated to this subgroup.

Covariate analysis

Significant covariates detected in the analysis of the NRPS data of patients treated with the high-dose capsaicin patch were age, duration of disease, concomitant opioid use, variability in the NRPS observed in the 14-day pre-study run-in phase, baseline NPRS and NPR scores after lidocaine pretreatment (before capsaicin patch application). There was some overlap in significant covariates between treatment groups (age, baseline NPRS and run-in pain score variability were significant predictors in both treatment groups). For the low-concentration capsaicin treatment, the following covariates were further identified: age, concomitant use of anticonvulsants, sex, NPRS after capsaicin patch removal and baseline NPRS.

Our analysis allowed a separate quantification of covariate behaviour among the five subgroups. As expected, covariate effects differed between subgroups. Figure 4 shows the probabilities of belonging to subgroups 2, 4 and 5 as a function of the significant predictor variables upon treatment with capsaicin 8% and active control. The covariates showed limited predictive effect on the other subgroups (data not shown).

Capsaicin 8% treated patients (Figure 4A–F)

In patients treated with capsaicin 8%, age affected the probabilities of belonging to subgroups 2 and 5 (Figure 4A): the probability of belonging to subgroup 5 decreased with increasing age (45% at age 50 years, 33% at 80 years); the reverse was true for belonging to subgroup 2, where the probability of belonging to that response profile increased with the patient age at the time of treatment. Duration of disease most importantly affected

the probability of belonging to subgroup 5, with a sharp reduction in efficacy of treatment with an increase in the duration of disease (in Figure 4B the disease duration range is 0.5–25 years). A striking observation was the effect of the local anaesthetic pretreatment on NRPS scores as predictor of the efficacy of the capsaicin 8% patch (Figure 4C). When pain was completely relieved by lidocaine, the cumulative probability of falling in subgroups 4 and 5 was 70% (subgroup 4 = 32%, subgroup 5 = 38%) and in subgroup 2, 15%. In contrast, when pain scores were elevated after lidocaine pretreatment (NRPS = 10), the probability of capsaicin 8% treatment success decreased to 5% (subgroup 4) and 20% (subgroup 5), and the probability of falling in subgroup 2 increased to 51%. Concomitant opioid use had a negative effect on treatment outcome (Figure 4D), as did high baseline pain scores (the probability of belonging to subgroup 5 decreased from 50% at baseline NRPS 3 to 20% at baseline NRPS 9; Figure 4E). Finally, the variability of pain reporting in the 14 days prior to treatment also had a significant impact on treatment efficacy. When variability was high, the probability of being in subgroup 5 was almost 80% and in subgroup 2 0%. In contrast,

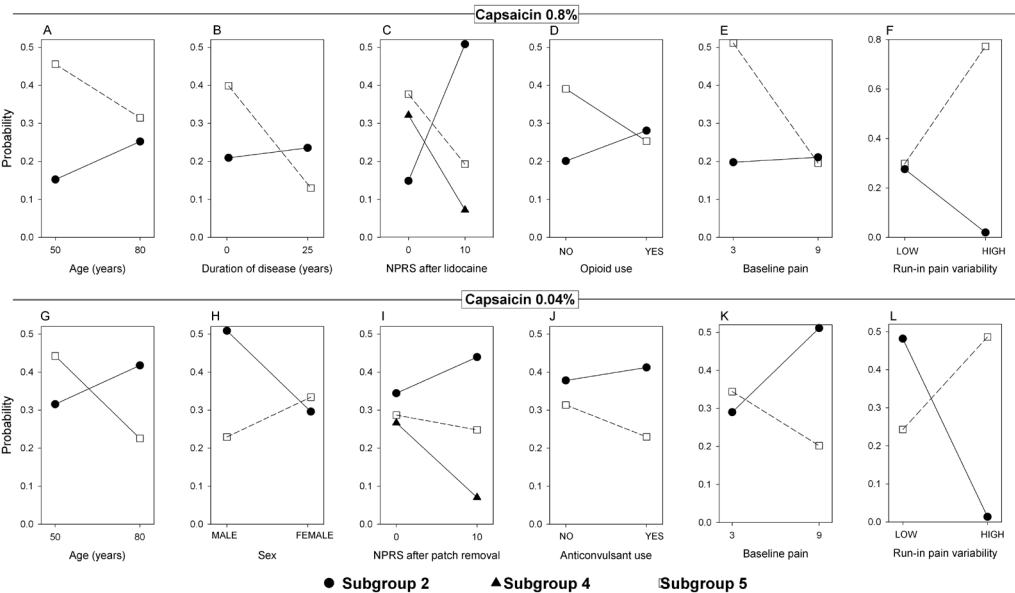


Figure 4 Influence of significant covariates on the probability of belonging to specific subgroups. (A–F) Patients treated with capsaicin 8%; (G–L) patients treated with active control. Note that panel F has a different y-axis. Values are median probabilities. The covariates showed little predictive effect on the subgroups not depicted here.

at low variability (i.e., pain scores were constant over time), the probability was 28% for belonging to either subgroup 2 and 5 or 28% (Figure 4F).

Active control treatment (Figure 4G–L)

Covariates age, baseline pain scores and variability in the NRPS observed in the 14-day pre-study run-in phase affected probabilities of subgroup 2 and 5 participation similar to those observed following capsaicin 8% treatment (Figure 4G,K,L). Further, gender effects (Figure 4H: men have a higher probability of falling in subgroup 2 compared to 5, while for women, the probabilities are similar), NRPS after control patch removal (Figure 4I) and the use of anticonvulsants (Figure 4J) were significant predictors of effect.

Model parameters

The parameter estimates are given in Table 4 and discussed in Appendix 1.

DISCUSSION

In the current analysis, we pooled data from four double-blind, randomized controlled trials of the efficacy of the capsaicin 8% transdermal patch (Qutenza) versus an active control (capsaicin 0.04% transdermal patch) in PHN. The current novel analysis of the pooled dataset consisted of three distinct parts (1): (1) a longitudinal analysis of the NPRS scores, followed by (2) a mixture analysis enabling the division of the data set into five distinct response groups; and (3) a covariate analysis aimed at the quantification of the covariate-related probability of falling into one of the five subgroups. The more common and traditional approach of analysing pain data is by assessing the magnitude of change in NPRS from baseline at a predefined time following treatment (e.g., 12 weeks following treatment) in terms of responder rate (e.g., number of patients having 30% or 50% reduction in NPRS). This approach neglects the information inherently present in the temporal profile of the response data and the possibility of the presence of subgroups with real mechanistic between-group differences. This is important as therapeutic strategies may differ among different response groups. For example, patients in the subgroup that show no treatment response (subgroups 1 and 2 in our analysis) are probably better off with a different therapeutic option, while patients that show a transient effect (subgroup 3) may benefit from a repeated patch application. We recently developed two longitudinal models to characterize the time course of NPRS scores in patients with complex regional pain syndrome (treated with ketamine) and patients with diabetic polyneuropathy (treated with the capsaicin 8% patch).^{13,14} Based

on the time-course analyses, we detected four response profiles. A drawback of these studies was the small number of subjects included and, consequently, the inability to link specific predictors to effect profiles.

Response groups

The current analysis yielded five homogenous response groups. Two subgroups showed either an increase in pain response or no treatment effect (subgroups 1 and 2). The cumulative proportion of patients in these subgroups was 39.9% after treatment with capsaicin 0.04% and 24.3% after treatment with Qutenza. The group that showed the greatest analgesic efficacy (subgroup 5) contained 36.6% of the population after Qutenza and 28.2% after active control. These data indicate that while active control response profiles may be similar to those observed from treatment with the test drug, the proportional distribution of patients among the five response groups is in favour of Qutenza with, compared to the active control, 40% less patients showing no response and 25% more patients showing a full analgesic effect. Just reviewing the analgesic data of the total population would have concluded that both active control and test drug cause effective analgesia, albeit with a small advantage of the test drug (Figure 2). The different subgroup treatment efficacies may be related to the differences in pain mechanisms and a strategy to identify these subgroups will allow mechanism rather than disease-based pain treatment.

Predictors of effect

The covariate analysis enabled us to identify factors that may explain why patients respond differently to therapy. There was overlap in covariates between treatments (age, baseline pain and run-in pain variability). This suggests a similar mechanism of action of the test drug and the control. Indeed, the small amount of capsaicin present in the control patch may have an analgesic effect. However, six covariates differed between treatment groups. This would suggest a difference in the mechanism of action of the two treatments. Possibly, the active control patch served as a true placebo treatment, engaging opioidergic and non-opioidergic placebo analgesic mechanisms, with the presence of active compound in the control patch causing some burning pain on application enhancing the placebo response.¹⁵ It may be argued that both mechanisms were activated upon treatment with the active control patch. An important observation in patients treated with the active control is that men had a greater probability of being a non-responder compared to women (probability of falling in subgroup 2: men 51% vs. women 29%; Figure 4H). Previous studies on placebo responses were unable to detect a sex difference in acute pain models.^{16,17} However, placebo may behave differently in different pain models and is

strongly dependent on the study set-up and patient expectations.

Covariate analysis yielded a set of important predictors that in part may explain the efficacy of capsaicin 8% treatment. Increasing age and a longer duration of disease reduced the probability of falling into subgroup 5 (Figure 4A and B). These factors are possibly interdependent (i.e., an older patient may have a more prolonged disease process than a younger patient) but confirm the notion of the complexity of treating chronic pain in the elderly. Opioid use and high baseline pain scores reduce the probability of a full analgesic response (Figure 4D and E). It may possibly be that the lack of opioid efficacy is a symptom of (general) therapy resistance, although further study is required to understand this important issue. The finding that run-in pain score variability influences the efficacy of treatment (for test drug and active control) is an interesting and novel observation. Patients that show high variability in their run-in pain scores have an almost 80% probability of a full analgesic response and almost 0% probability of falling into the non-responder group (Figure 4F). In contrast, low variability (a constant NPRS value for 14 days) results in a probability for subgroups 2 and 5 of about 30%. Possibly the low variability NPRSs are an indication of a rigid and fully manifested chronic pain process with severe central plastic changes unresponsive to therapy. The reverse may be the case in patients that experience variable pain scores over time. We believe that this is an important first observation that needs further confirmation. Finally, pain scores following lidocaine pretreatment over the skin where the capsaicin 8% patch will be applied predicted treatment efficacy. The probability of being a non-responder increases from 14% at a pain score of zero to 51% at a pain score of 10. The reverse was observed for subgroups 4 and 5 (Figure 4C). While lidocaine and capsaicin have distinct mechanisms of action, the current finding indicates a common target, i.e., the peripheral nerves, and suggests that synergistic treatment effects are possible when combining the two treatments.

We restricted our covariate analysis to a set of 14 variables (Table 1). It may well be that other factors alone or in combination with the current set may enhance our ability to predict therapy efficacy; e.g., by adding functional or neurosensory testing [such as quantitative sensory testing (QST), responses to electrical or laser stimulation of the skin, conditioned pain modulation (CPM)]. Specific patterns in the QST profile may represent specific disease modalities with a greater or lesser probability of therapy efficacy. There are various examples in the literature that concur with our suggestion. Eisenberg et al. showed that the magnitude of heat pain thresholds predicts the magnitude of reduction of pain intensity in response to oxycodone treatment (the greater the heat pain threshold the greater the opioid effect; $R^2 = 0.17$) in healthy volunteers.¹⁸ Yarnitsky et al. showed that patients with less efficient CPM have greater analgesic responses to duloxetine ($R^2 = 0.39$) in patients with painful diabetic neuropathy.¹⁹ We recently showed a significant

correlation between the magnitude of CMP and pain relief in patients with chronic neuropathic pain and treated with placebo, morphine and ketamine.²⁰ Finally, also genetic factors, such as variations in the TRPV1 gene, may be used in predictive analyses of treatment effect.

Conclusions and final remarks

Pain data from 1248 patients with PHN and treated with a capsaicin 8% patch or an active control were successfully divided into five response groups using time-course and mixture analyses. Covariate analysis identified factors that enhanced prediction of treatment responses. The most important variables identified include age, disease duration, pain score following local anaesthetic pretreatment of the affected skin area, baseline pain and pretreatment pain score variability. Further studies should address whether incorporation of additional variables (TRPV1 gene-related, sensory testing-related, symptom-related) may enhance prediction of treatment effect. Our current and previous analytical approach provides strong indications of the existence of specific subgroups and predicting variables related to treatment of chronic pain patients. This indicates not only that our approach may be applied across different chronic pain syndromes, but suggests also that our approach is a step towards individually tailored treatment. An example could be to treat patients with Qutenza who display a large variability in their pain scores at baseline or those patients that respond favourably to a baseline trial with topical lidocaine. This latter approach is similar to the approach of Campbell et al. who determined the effect of capsaicin as a predictor of topical clonidine treatment in painful diabetic neuropathy.²¹ As discussed by Sindrup and Finnerup and shown here, drugs have different efficacies in subgroups of patients, possibly related to different pain mechanisms despite a presumed common underlying disease.²²

APPENDIX 1: THE LONGITUDINAL MODEL AND MIXTURE ANALYSIS

The longitudinal model was developed within the non-linear mixed effect modelling software (NONMEM version VII level 1, ICON Development Solutions, Ellicott City, MD) to describe the time course of NPRS following application of the low- (0.04%) and high-concentration capsaicin path.²³ The first-order conditional estimation (FOCE) was used for model development. The performance of the analysis was evaluated by various selection criteria, including visual inspection of the goodness of fit plot, changes in the objective function value and parameter estimates and their respective standard errors. Using the likelihood ratio test, the significance level was set at $\alpha = 0.01$, which corresponds

to a reduction of 6.6 units in objective function value (χ^2 distribution) to discriminate between two nested structural models after inclusion of one additional parameter. Model diagnostic checks of the final model were conducted using R (R-project, version 2.12.0).

Longitudinal model

The effect of low- or high-concentration capsaicin patches on NPRS was characterized using a Bateman function with the following structure:¹³

$$\text{Effect} = [k_{\text{ONSET}} / (k_{\text{ONSET}} - k_{\text{OFFSET}})] \cdot [e^{-(\text{time}-k_{\text{OFFSET}})} - e^{-(\text{time}-k_{\text{ONSET}})}] \quad (\text{A1})$$

The Bateman function characterizes the time course of NPRS pain score from week 0 (baseline) to week 12 in terms of two first-order rate constants describing the onset (k_{ONSET}) and offset (k_{OFFSET}) of the effect following the application of capsaicin 8%. The change in NPRS from week 0 to week 12 was computed as follows:

$$\text{NPRS}(t) = \text{NPRS}_0 \cdot (1 - \alpha \cdot \text{Effect}) \quad (\text{A2})$$

where NPRS_0 is the NPRS pain score at baseline and α is the magnitude of effect. Random effects were included in the longitudinal model provided that the parameters are either normally or log-normally distributed. For example, the parameter α was modelled assuming a normal distribution allowing for the estimation of negative values of the parameter α (increase in NPRS pain score):

$$\alpha_j = \theta_\alpha + \eta_j \quad (\text{A3})$$

where α_j is the estimate of α for the j -th individual and θ_α represents the population estimate for the parameter α . η_j describes the interindividual variability on α , which is assumed to be a normally distributed random effect variable with mean zero and variance ω^2 . Similarly, the interindividual random effect variables for NPRS_0 and k_{ONSET} were assumed to be normally distributed. The interindividual variability random effect variable for k_{OFFSET} was assumed to be log-normally distributed.

Residual variability, which is a measure of the unexplained variability (including error associated with reporting of chronic pain outcome), was described using an additive error model:

$$\text{NPRS}_{\text{obs},ij} = \text{NPRS}_{\text{pred},ij} + \epsilon_{ij} \quad (\text{A4})$$

where the residual variability, ϵ_{ij} , at time point i for individual j , is a normally distributed random effect variable with mean zero and variance σ^2 .

Mixture analysis

Aside from the advantage of analysing the longitudinal data within a mixed effect model framework, the NONMEM software allows for the definition of a mixture model, in which the existence of subgroups of patients that respond differently to the assigned treatment can be explored. For this analysis, it is assumed that the structural model is the same for subgroups, but that patients may differ in their onset and offset of response and also may respond differently to treatment in terms of magnitude of response. To this end, the parameters, k_{ONSET} , k_{OFFSET} and α are assumed to be distributed multi-modally and the mixture feature in NONMEM is used to differentiate between subgroups of patients on the basis of the parameter distributions. Based on visual inspection of the individual data, the mixture model was defined to separate five distinct subgroups of patients.

Results

The data were adequately fitted to the model and a clear separation among the five subgroups was achieved. Among treatments, the most important differences occurred in the proportion of patients falling in a specific subgroup (Table 3): almost twice as many patients on active control were in subgroup 2 (i.e., non-responders) compared to patients treated with capsaicin 8% (39% vs. 22%), while more subjects on capsaicin 8% fell into subgroup 5 (37% vs. 28%). Table 4 gives the parameter estimates including measures of between-subject (ω^2) and residual variability (σ^2). Parameter α showed little difference among treatment groups, indicating that both treatments were equally effective in terms of magnitude of effect of the five subgroups. Values of α ranged from -0.18 (subgroup 1) to 0.6 (subgroups 3 and 5) for patients treated with capsaicin 8% and from -1.4 (subgroup 1) to 0.7 (subgroups 3 and 5) for patients treated with active control. A negative value for α indicates that pain scores increased with treatment. Since pain scores did not change in subgroup 2, a value for k_{ONSET} could not be estimated for this subgroup. No offset in effect (return towards baseline) in subgroups 1, 2, 4 and 5 was presents (i.e., their $k_{\text{OFFSET}} = 0$). Only for subgroup 3, a k_{OFFSET} was detected: 0.48/week versus 0.27/week for active control and 8% capsaicin treatments, respectively. These rate constants are equivalent to half-life of 1.4 weeks (active control) and 2.6 weeks (capsaicin 8%) and indicate that every 1.4 and 2.6 weeks the NPRS increases by 50%. The difference in values is due to the faster return towards baseline in patients on active control compared to those on the capsaicin 8% patch.

Table 4 Model parameter estimates

	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4	Subgroup 5
Treatment with capsaicin 8% (n = 722)					
<i>Parameter estimates</i>					
NPRS ₀	5.70 ± 0.06	5.70 ± 0.06	5.70 ± 0.06	5.70 ± 0.06	5.70 ± 0.06
K _{ONSET} (week ⁻¹)	1.31 ± 0.09	-	1.31 ± 0.09	1.31 ± 0.09	1.31 ± 0.09
K _{OFFSET} (week ⁻¹)	0	0	0.27 ± 0.04	0	0
α	-0.18 ± 0.05	0	0.61 ± 0.04	0.24 ± 0.04	0.61 ± 0.04
<i>Between patient variability (ω²)</i>					
NPRS ₀	2.43 ± 0.12	2.43 ± 0.12	2.43 ± 0.12	2.43 ± 0.12	2.43 ± 0.12
α	-	-	0.15 ± 0.03	-	0.15 ± 0.03
K _{ONSET} (week ⁻¹)	0.70 ± 0.10	-	0.70 ± 0.10	0.70 ± 0.10	0.70 ± 0.10
K _{OFFSET} (week ⁻¹)	-	-	1.25 ± 0.17	-	-
<i>Residual variability (σ²)</i>					
	0.370 ± 0.0241				
Treatment with capsaicin 0.04% (n = 526)					
<i>Parameter estimates</i>					
NPRS ₀	5.68 ± 0.07	5.68 ± 0.07	5.68 ± 0.07	5.68 ± 0.07	5.68 ± 0.07
K _{ONSET} (week ⁻¹)	1.06 ± 0.09	-	1.06 ± 0.09	1.06 ± 0.09	1.06 ± 0.09
K _{OFFSET} (week ⁻¹)	0	0	0.48 ± 0.08	0	0
α	-1.40 ± 0.82	0	0.71 ± 0.03	0.27 ± 0.01	0.71 ± 0.03
<i>Between patient variability (ω²)</i>					
NPRS ₀	2.50 ± 0.14	2.50 ± 0.14	2.50 ± 0.14	2.50 ± 0.14	2.50 ± 0.14
α	-	-	0.17 ± 0.04	-	0.17 ± 0.04
K _{ONSET} (week ⁻¹)	0.52 ± 0.09	-	0.52 ± 0.09	0.52 ± 0.09	0.52 ± 0.09
K _{OFFSET} (week ⁻¹)	-	-	1.12 ± 0.21	-	-
<i>Residual variability (σ²)</i>					
	0.40 ± 0.03	0.40 ± 0.03	0.40 ± 0.03	0.40 ± 0.03	0.40 ± 0.03

NPRS₀ = numerical pain rating score at baseline;

K_{ONSET} = first-order rate constants describing the onset of effect;

K_{OFFSET} = first-order rate constants describing the offset of effect;

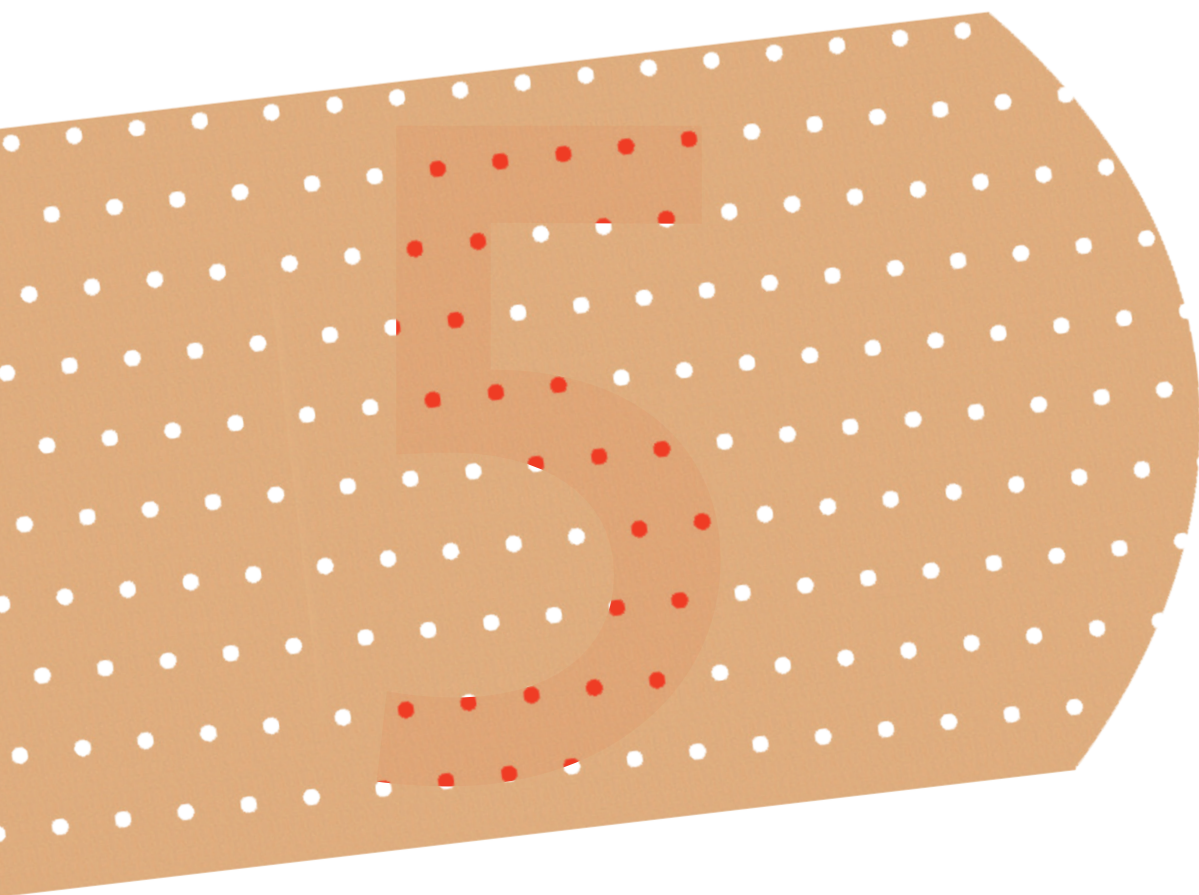
α = magnitude of analgesic effect.

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Section 2 | OPIOIDS



Chapter 5

A randomized controlled trial and novel mathematical analysis of the analgesic effect of oxycodone versus paracetamol orodispersible tablets

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INTRODUCTION

Many patients with chronic cancer and non-cancer pain experience episodes of breakthrough pain, which is defined as “a transitory exacerbation of pain that occurs on a background of otherwise stable pain while using long-term, around-the-clock analgesics to control chronic pain”.^{1,2} Breakthrough pain is usually treated with rapid onset opioid analgesics and a number of formulations using different administration routes are available, including intranasal, sublingual, oral transmucosal and transbuccal routes.^{2,3} For effective treatment of breakthrough pain, or any other form of severe acute pain, a rapid onset of action is important. Most studies that assess the efficacy of rapidly acting opioids in immediate-release formulations use a fixed time-point at which superiority of one treatment over another is assessed (*eg.* 15 or 30 min following drug intake) without taking into account the full temporal profile of analgesic effect.^{2,4,5}

A relatively new treatment option for breakthrough pain is the use of orodispersible (*ie.* disintegrating or melt) tablets (OT) of lipophilic opioids that are applied on or under the tongue and that give a rapid onset of analgesia. The OT melts in the mouth but is predominantly absorbed in the gut. Few studies have characterized the onset of analgesia of orodispersible tablets. Rauck *et al.*⁶ showed a significant reduction in pain intensity at 10 min following administration of sublingual orodispersible fentanyl. In the current study we quantified the antinociceptive effect of a 20 mg orodispersible oxycodone tablet (OOT) in a population of healthy volunteers. We recently showed that a longitudinal pharmacodynamic analysis provides important information on the onset and offset of action of analgesic treatment and argued that this approach is superior to analysis of effect at fixed time points during the course of treatment.⁷⁻⁹ In the current study we applied a modified pharmacodynamic analysis to overcome some of the problems of the previous analysis using two experimental pain models (electrical and pressure pain) over a 5-hour test period. The effect of OOT was assessed relative to an active placebo comparator, a 500 mg paracetamol orodispersible tablet (POT), using a randomized, double blind and crossover design.

The main aim of the study was to quantify the temporal antinociceptive profile of administration of OOT *versus* POT. We hypothesize that oxycodone produces greater analgesia than the active comparator and meaningful analgesia, as defined by a 30% increase in response thresholds within 20 min.^{10,11}

METHODS

Subjects

Healthy female volunteers were recruited to participate in the study performed at Leiden University Medical Center after approval of the protocol by the local Medical Ethics Committee. Female volunteers were chosen for reasons of availability and the fact that most drug trials systematically exclude females. The trial was registered (ISRCTN59463510) at controlled-trials.com and recruitment lasted from 1 January, 2013 - 1 March 2013. All participants gave written informed consent and underwent a physical examination before enrollment in the study. Inclusion criteria were: age 18 - 65 years, body mass index 18 - 35 kg/m² and body weight 50 - 100 kg. Exclusion criteria included: (a) a history of mental health problems; (b) a history of alcohol or substance abuse; (c) two or more of alcohol units/day; (d) positive pregnancy test; (e) not using oral contraceptives, not surgically sterilized, or not post-menopausal; (f) a history of allergic or anaphylactic reaction or significant intolerance to prescription or non-prescription drugs or food, and (g) any other condition that in the opinion of the investigator would complicate or compromise the study, or the well-being of the subject.

Study design

In this randomized, double blind, active-comparator, crossover study, subjects were randomized to receive one orodispersible oxycodone 20 mg tablet (OxyNorm Instant, Mundipharma Pharmaceuticals BV, Hoevelaken, The Netherlands) on one occasion and placebo (one paracetamol 500 mg orodispersible tablet; Roter, Hilversum, The Netherlands) on another occasion. One week was allowed for washout. The subjects were requested to fast for at least 6-hours prior to the intake of study medication. The tablets were placed under the tongue; the subject was not allowed to swallow until the drug had completely disintegrated. To assess the analgesic treatment efficacy, electrical and pressure nociceptive assays were applied. Prior to the study the subjects were familiarized with both pain tests.

Electrical noxious stimulation

A locally designed and manufactured transcutaneous electrical stimulation device (TES) was used to create a constant current electrical stimulus train (stimulation at 20 Hz, pulse duration 0.2 ms).¹² The device was attached to 2 surface electrodes that were applied on the skin over the tibial bone of the non-dominant side. The location of the electrodes was chosen such that the electrical stimulation did not cause any muscle contraction. The current over the electrodes was increased from 0 mA at a rate of 1 mA/s,

with a cutoff of 128 mA. The subjects were instructed to indicate when the stimulation became painful (electrical pain threshold, EPT_h) by pressing a button on a control box. By pressing a second button the subjects could end the stimulus train when the pain was perceived as intolerable (electrical pain tolerance, EPT_{ol}). Prior to drug administration baseline values were obtained. To that end, three tests were performed at 5 min intervals. The three currents obtained for pain threshold and tolerance were averaged and served as baseline values. Following treatment, TES was applied at $t = 5, 10, 15, 20, 25, 35, 45, 55, 65, 75, 85, 95, 110, 125, 140, 170, 200, 230, 260$ and 290 min.

Pressure pain

An FPN 100 N Algometer (FDN 100, Wagner Instruments Inc., Greenwich, CT) was used to deliver pressure pain on an area of 1 cm² between thumb and index finger.¹³ The FDN 100 has a force capacity ($\pm$ accuracy) of 100 ± 2 N (10 ± 0.2 kgf) and graduation of 1N (100 gf), respectively. A gradually increasing pressure was manually applied and the subjects were asked to indicate when the procedure became painful (pressure pain threshold, PPT_h). The pressure was then released. Following treatment, the pressure test was applied at $t = 30, 60, 90, 120, 180, 240$ and 300 min.

Randomization and blinding

Randomization was performed by the local pharmacy using a computer-generated randomization list. The pharmacy repackaged the tablets into unmarked and identical containers. The repackaged tablets were allocated 1:1 on the morning of the study ensuring blinding of volunteers and investigators.

Conventional statistical analysis

The study was powered to detect a 25% difference in treatment effect on EPT_{ol} (SD 25%, power 0.9). To determine the effect of treatment, a two-way analysis of variance was performed (factors treatment, time and treatment $\times$ time). Comparisons of time-effects^{5,14} and the area-under-the time-response curves (AUC), determined from the linear trapezoid rule, were compared using t-tests. The statistical analysis was performed with the R statistical package (version 2.8, R-project; www.r-project.org); the comparisons were 2-sided with p-values < 0.05 considered significant.

Pharmacodynamic analysis

A longitudinal pharmacodynamic model was developed to describe the time course of the pain responses of primary end-points EPT_{ol}, EPT_h and PPT, following administration of oxycodone and paracetamol. The model was constructed with the non-linear mixed

effect modeling software NONMEM version VII (ICON Development Solutions, Elliott City, MD). The pharmacodynamic model consisted of a modified Bateman function that describes the time course of the response in terms of two first-order rate constants describing the waxing (with rate constant k_{ON}) and waning (with rate constant k_{OFF}) of the response. The model is of the form:

$$\text{Effect}(t) = \text{BLN} \cdot [1 + \text{EFF} \cdot \text{BF}(t)] + \text{TRD}/300 \cdot t \quad (\text{A1})$$

where t is time, BLN is the baseline value of the measured variables (EPTh, EPTol and PPTh), EFF the maximum observed drug effect (effect at T_{MAX} where $\text{BF}(t = T_{\text{MAX}})$ has a maximum possible value of 1), TRD a trend term and BF the modified Bateman Function with (cf. Martini et al.⁸):

$$\text{BF} = [e^{-k_{\text{OFF}} \cdot t} - e^{-k_{\text{ON}} \cdot t}] / [(k_{\text{ON}}/k_{\text{OFF}})^{-k_{\text{OFF}}/(k_{\text{ON}} - k_{\text{OFF}})} - (k_{\text{ON}}/k_{\text{OFF}})^{-k_{\text{ON}}/(k_{\text{ON}} - k_{\text{OFF}})}] \quad (\text{A2})$$

In case $k_{\text{ON}} = k_{\text{OFF}} = k$, the modified Bateman Function, $\text{BF}(t)$, equals $k \cdot t \cdot e^{(-k \cdot t + 1)}$. The time to maximum effect, T_{MAX} , was calculated as follows:

$$T_{\text{MAX}} = \log(k_{\text{ON}}/k_{\text{OFF}})/(k_{\text{ON}} - k_{\text{OFF}}), \text{ when } k_{\text{ON}} \neq k_{\text{OFF}} \quad (\text{A3})$$

and

$$T_{\text{MAX}} = 1/k, \text{ when } k_{\text{ON}} = k_{\text{OFF}} \quad (\text{A4})$$

Random effects were included in the model allowing for assessment of between-subject variability (ω^2) and within-subject or residual variability (σ). Analysis was performed simultaneously on the complete data set allowing discrimination of drug effect on EFF, k_{ON} and k_{OFF} . p-values < 0.01 were considered significant. In the analysis the responses to oxycodone and paracetamol were assumed to be independent, as inter-occasion variability of the measured pharmacodynamic responses is large, no pharmacokinetic data were obtained and the two drugs have different mechanisms of action.

Bootstrap Analysis and Area-Under-The-Curve (AUC) Calculation

A bootstrap validation procedure was performed to obtain the probability distributions of model parameters and derived parameters, such as T_{MAX} and AUC. One-thousand bootstrap data sets were simulated by including 12 random subjects to the oxycodone group and 12 random subjects to the paracetamol group. Model parameters and derived

parameters were estimated from each bootstrap data set. Quantiles of the parameter distributions were calculated using the statistical program R, and yielded 95% confidence intervals, and medians for internal validation.

As a measure of effect, AUCs were calculated as follows:

$$\text{for } k_{\text{ON}} = k_{\text{OFF}}: \text{AUC} = \text{EFF} \cdot e/[k_{\text{ON}} \cdot (1 - (1 + k_{\text{ON}} \cdot T_{\text{END}}) \cdot e^{(-k_{\text{ON}} \cdot T_{\text{END}})})], \quad (\text{A5})$$

$$\text{for } k_{\text{ON}} \neq k_{\text{OFF}}: \text{AUC} = \text{EFF} \cdot [(1 - e^{(-k_{\text{OFF}} \cdot T_{\text{END}})})/k_{\text{OFF}} - (1 - e^{(-k_{\text{ON}} \cdot T_{\text{END}})})/k_{\text{ON}}] / [(k_{\text{ON}}/k_{\text{OFF}})^{(-k_{\text{OFF}}/(k_{\text{ON}} - k_{\text{OFF}}))} - (k_{\text{ON}}/k_{\text{OFF}})^{(-k_{\text{ON}}/(k_{\text{ON}} - k_{\text{OFF}}))}] \quad (\text{A6})$$

where T_{END} is the end of study time (300 min). All AUC's given are divided by the 300 (the duration in min of the study) to give an average end-point value over time.

Side effects

Heart rate and oxygen saturation (using a finger pulse oximeter) were monitored throughout the studies. In case of oxygen saturation levels below 94%, oxygen could be administered through a facemask. All incidences of nausea, vomiting and dizziness/ lightheadedness were scored; all none expected side effects were noted as well.

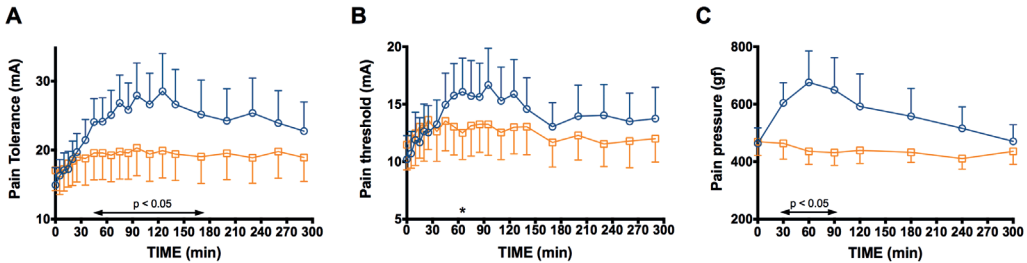


Figure 1 Mean treatment responses ($\pm$ standard error of the mean) for pain tolerance (A), pain threshold (B) and pain pressure pain (C). * $p = 0.02$. At $t = 0$, the treatment was administered.

RESULTS

Twelve volunteers were enrolled and completed the study with mean age 22 (range 18-31) years, weight 68 (53-94) kg and height 174 (160-199) cm. In none of the subjects respiratory issues were clinically observed.

Conventional analysis

In Figure 1 the mean responses are given for all three pain indices. Significant treatment and treatment $\times$ time effects were observed for EPTol ($p < 0.001$), EPTh ($p < 0.01$) and PPTTh ($p < 0.01$). For EPTol a significant difference between OOT and POT responses was observed from $t = 45$ to $t = 170$ min (from $t = 45$ to 55 min, $p < 0.05$; from $t = 65$ to 170 min, $p < 0.01$). In contrast, for EPTh a difference in effect between treatments was observed at $t = 65$ only ($p = 0.02$). For PPTTh treatments differed at $t = 30$ ($p < 0.001$), 60 ($p = 0.01$) and 90 min ($p = 0.02$). The AUC differed only for EPTol between treatments: OOT 9.2 ± 2.2 vs. POT 2.1 ± 1.0 ($p < 0.05$). Variability in the responses was large with the greatest variability observed for EPTh (coefficient of variation of the AUC of the measured pain response data = 61-87%), followed by EPTol (60-64%) and PPT (32-51%) (Figure S1).

Pharmacodynamic analysis

As judged by the eye, the data were adequately fitted by the pharmacodynamic model, irrespective of end-point or treatment. For both treatments, best, median and worst data fits for electrical pain tolerances are given in Figures 2 (OOT) and S2 (POT) with the corresponding data fits for electrical pain threshold and pressure pain threshold. The model parameter estimates are given in Table 1.

Transcutaneous electrical stimulation

20 mg OOT produced an increase in EPTol and EPTh response currents but its effect on pain tolerance was more potent (parameter EFF is 2.2 greater for tolerance than threshold, Table 1). For both indices, the 500 mg paracetamol orodispersible tablet produced about 14% of the analgesic efficacy of oxycodone. The response profile over time was similar for paracetamol and oxycodone and for threshold and tolerance with identical values for k_{ON} and k_{OFF} (paracetamol vs. oxycodone and tolerance vs. threshold, χ^2 -test: $p > 0.05$). The onset and offset of the response differed significantly ($p < 0.01$) with a more rapid onset ($t_{1/2}k_{ON} = 45$ min) than offset ($t_{1/2}k_{OFF} = 154$ min).

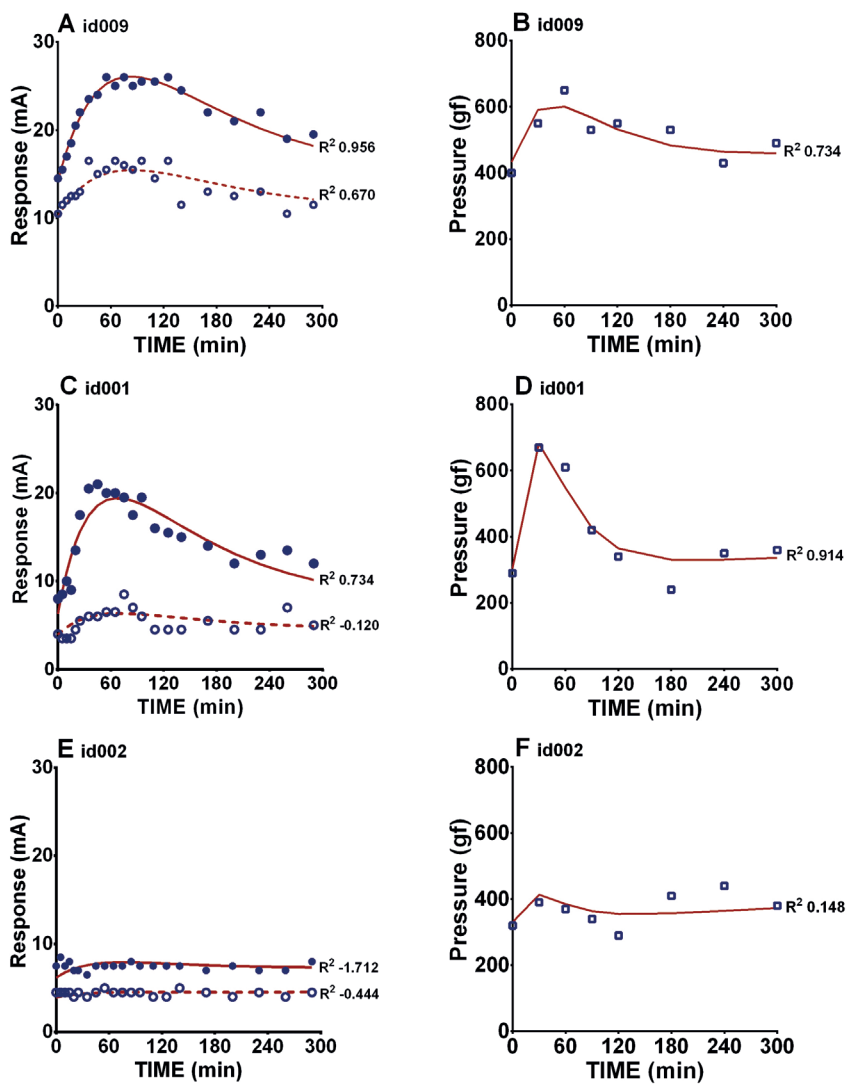


Figure 2 Examples of oxycodone data fits. Best (A), median (C) and worst (E) data fits of electrical pain tolerance data (as determined by the coefficient of determination, R^2) are shown, with corresponding fits for electrical pain threshold (A, C and E) and pain pressure threshold (B, D, F). Closed circles denote the measured electrical pain tolerance data, open circles the measured electrical pain threshold data, open squares the measured pressure pain threshold data. The lines are the data fits.

Pressure Pain Assay

The effect of OOT on pressure pain threshold was comparable to that on the electrical pain threshold in terms of potency (parameter EFF for both indices ≈ 0.4), Table 1). Paracetamol's analgesic effect relative to that of oxycodone was not different from that observed in the electrical pain assay. In contrast to the observations in the electrical pain model, the rate constants for onset and offset did not differ ($t_{1/2}k = t_{1/2}k_{ON} = t_{1/2}k_{OFF} = 30$ min, $p > 0.05$). The k-value was similar in paracetamol and oxycodone treatment groups.

Population responses

Population pharmacodynamic responses are given in Figures 3A and B, showing the difference in effect of treatment on the magnitude and the temporal profile between (and within) electrical and pressure pain models. In panels C and D of Figure 3, the percentage change relative to baseline of the oxycodone responses are plotted. The time to an increase in baseline responses of 30% are given as an index of clinical relevant effect.^{10,11} For electrical pain, a 30% increase was observed at $t = 15$ and 41 min for EPTol and EPT_h respectively; for pressure pain at $t = 18$ min.

Bootstrap analysis

The results of the bootstrap validation process are given in Table S1, showing good correspondence with the pharmacodynamic parameter estimates (Table 1). Additional values were computed including T_{MAX} (time of peak analgesic effect; 111 and 43 min in the electrical and pressure pain models, respectively, for both treatments) and the various AUCs.

Side effects

Following oxycodone administration, five subjects experienced nausea, two of which vomited. Three subjects experienced dizziness/lightheadedness. In none of the subjects saturation levels dropped below 94%. Following paracetamol administration, one subject became nauseated.

Table 1 Parameter estimates of the longitudinal pharmacodynamic model

	Estimate ± SE	$\omega^2 \pm SE$
Electrical pain threshold and tolerance		
Baseline threshold (mA)	8.9 ± 1.3	0.46 ± 0.10
Baseline tolerance (mA)	12.6 ± 1.5	0.40 ± 0.09
$K_{ON} \text{ (Electrical Pain) } (\text{min}^{-1})$	0.015 ± 0.003	0.48 ± 0.30
$k_{ON} \text{ (Electrical Pain) } / k_{OFF} \text{ (Electrical Pain)}$	2.44 ± 1.90	3.60 ± 2.63
EFF threshold*	0.43 ± 0.15	1.20 ± 0.54
EFF tolerance*	0.96 ± 0.32	0.42 ± 0.21
σ	1.88 ± 0.31	-
Pressure pain threshold		
Baseline value (gf)	422 ± 29	0.19 ± 0.05
$k_{(\text{Pressure Pain})} / k_{ON(\text{Electrical pain})} \#$	1.50 ± 0.20	-
EFF*	0.40 ± 0.09	0.49 ± 0.24
σ	57.5 ± 8.4	-
Trend term		
TRD (mA/min)	0 (FIX)	0.04 ± 0.04
Paracetamol versus Oxycodone		
* Relative paracetamol effect (%)	14.1 ± 4.8	-

Values are median ± SE. k_{ON} is the rate constant of the waxing response, k_{OFF} is the rate constant of the waning response. # for pressure pain $k = k_{ON}(\text{Pressure Pain}) = k_{OFF}(\text{Pressure Pain})$. * EFF is the oxycodone effect with the relative paracetamol effect as % of the oxycodone EFF. ω^2 is the between-subject variability (in the log-domain), σ is the variance of the residual error. TRD is a trend term.

DISCUSSION

The analgesic effect of orodispersible oxycodone was quantified with a mathematical model of analgesia evolution based on a modified Bateman function. The oxycodone formulation displayed analgesia greater than placebo with a faster onset than offset for electrical pain ($t_{1/2}k_{ON} = 45$ min, $t_{1/2}k_{OFF} = 154$ min) but similar onset and offset values for pressure pain (both 30 min). The analgesia efficacy parameter showed that oxycodone produced greater analgesia as determined from EPTol (EFF = 2.2) than either EPTh or PPTh (EFF = 0.4). Paracetamol had little effect on any of the three end-points (analgesic effect 14% of that of oxycodone).

Conventional statistical analysis versus longitudinal analysis

Most clinical studies on the efficacy of acute pain medication test pain relief at fixed time points following the intake of study medication by comparing the effect to placebo using t- or comparable tests at predefined time points. For example, Schachtel et al.⁵ used an onset-of-action model to assess the onset of analgesia by the flurbiprofen lozenge in patients with a sore throat by performing pain intensity assessments at 2-min intervals (30 measurements per hour). They observed first significant pain relief by conventional analysis (*ie.* pain relief from treatment > placebo) at $t = 26$ min, while patients perceived reduction of throat pain already after 12 min. Our analysis allows assessment of the temporal profile using a sparse data sampling approach (for example, just 7 measurements in 5 hours were obtained using the pain pressure method). Despite the relatively restricted number of assessments, a reliable estimation of onset and offset (in terms of rate constants) of oxycodone effect could be made. Furthermore, the analysis allows estimation of times to a specific predefined response effects, such as a 30 or 50% increase in response thresholds. We present the 30% change in response thresholds (Figure 3) that, although somewhat arbitrary, is considered by us equivalent to a clinical significant effect in clinical trials, defined by a 30% reduction in pain indices.^{10,11} The 30% increase in response thresholds was observed after 15 (EPTol), 41 (EPTh) and 18 min (PPTh) (Figure 3). Using conventional statistics, significant differences relative to placebo were first observed after 45 (EPTol), 65 (EPTh) and 30 min (PPTh). Finally, our pharmacodynamic analysis, in contrast to conventional statistical analysis, gives a parameter for magnitude of effect (EFF), which allows comparison to other compounds (such as the comparison to the active placebo comparator in our current study or comparison among other strong opioids).

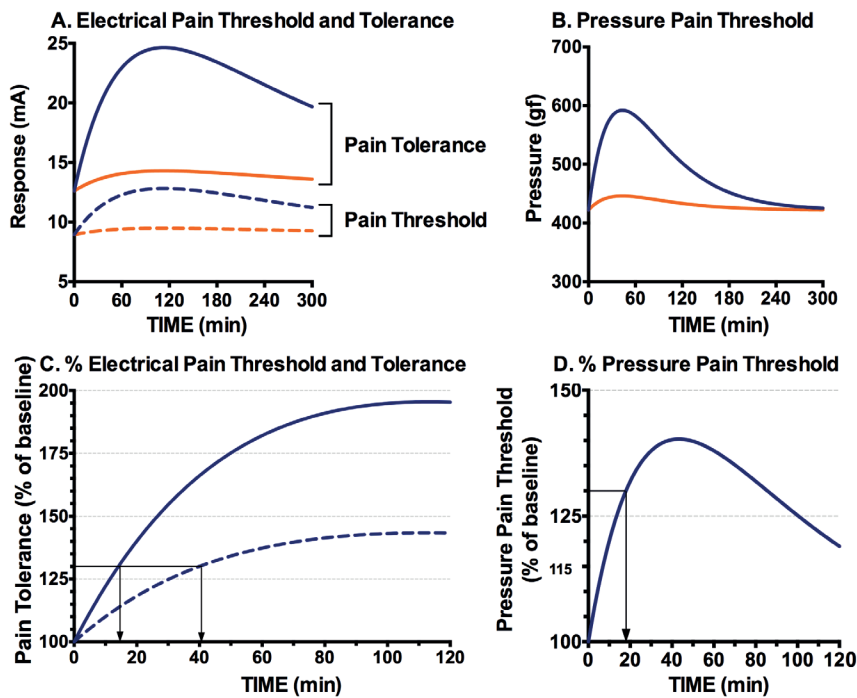


Figure 3 The simulated typical pharmacodynamic response to 20 mg oxycodone (blue lines) and 500 mg paracetamol (orange lines) orodispersible tablets. (A) Electrical pain tolerance (continuous lines) and electrical pain threshold (broken lines). (B) Pain pressure threshold. (C) Electrical pain tolerance (continuous lines) and electrical pain threshold (broken lines) as percentage of the baseline value. The times to an increase of 15% in tolerance and threshold responses are 6.5 and 14.5 min, respectively. (D) Pain pressure threshold as percentage of baseline value. The time to 15% increase in response pressure is 7 min. At $t = 0$ the treatment was administered.

Experimental versus patient studies

In contrast to others (e.g. Rauck et al.⁶; Schachtel et al.⁵), we did not assess pain relief in pain patients but performed our studies in healthy volunteers. Our approach is not only more practical but it yields data not contaminated by various patient-related factors. One such factor is the presence of large variability in pain over time within and among pain patients.⁸ Other factors include co-medication, underlying disease (for example, repetitive hypoxic events due to sleep-related breathing disorders may enhance opioid sensitivity)¹⁵ and past experiences with pain medication. Since the pain stimuli we applied are different from pathophysiological pain, the question remains whether our analysis also applies to patients. We argue that the temporal profile we observed may be applicable to patients as well, albeit with some caution. We previously assessed the

temporal profile of the morphine analgesia in healthy volunteers using an electrical pain assay and observed an effect half-life for pain threshold of 1.6 h.¹⁴ Mazoit et al. observed a similar value (1.7 h) in patients being treated with morphine for postoperative pain.¹⁶ These data suggest similarities in the temporal profile of drug-induced pain relief using experimental and clinical pain as study end-points. Still, caution in blind extrapolation of our results is warranted and we will perform a patient study to validate our current results.

The modified pharmacodynamic model

We previously performed a longitudinal analysis of the effect of capsaicin 8% topical treatment in patients with postherpetic neuralgia.⁸ The current analysis is a modification to the previous one. This was deemed necessary since in the previous analysis both the AUC of the response and the maximal effect of the Bateman function (BF) depend on k_{ON} and k_{OFF} . Consequently, this implies that parameter EFF, a measure of potency, is confounded by the onset and offset characteristics causing difficulty in its interpretation. The modified Bateman function is normalized in such a way that its minimum value is 0 and its maximum value is 1, independent of k_{ON} and k_{OFF} , so that parameter EFF indicates the maximum effect possible (at the dose administered).

Comparing oxycodone to paracetamol

Pain trials are commonly performed with either a placebo or active comparator. In the current study we applied an active comparator, the paracetamol orodispersible tablet. As expected, paracetamol at this low dose produced a relatively small analgesic effect in any of the end-points with 14% efficacy compared to oxycodone. Just 8/12 subjects in the electrical pain model and 3/12 in the pressure pain model showed modest analgesic responses following POT. Similar observations were reported previously by Moore et al. on paracetamol.¹⁷ Hence, taken the lack of a significant “placebo” effect, the use of the weak POT served as an effective method to blind the study. In future studies comparators such as intranasal fentanyl or orodispersible buprenorphine may be used which allows the same blinding but with a greater analgesic effect.

Interestingly, we observed that two subjects did not respond to oxycodone treatment in both nociceptive models. We relate this to genetic factors, probably reduced activity of the CYP2D6 enzyme, which causes less production of oxycodone's active metabolite oxymorphone (the data from both subjects were included in the analyses). Zwisler et al. showed in healthy volunteers that reduced CYP2D6 activity is associated with reduced antinociceptive responses.¹⁸

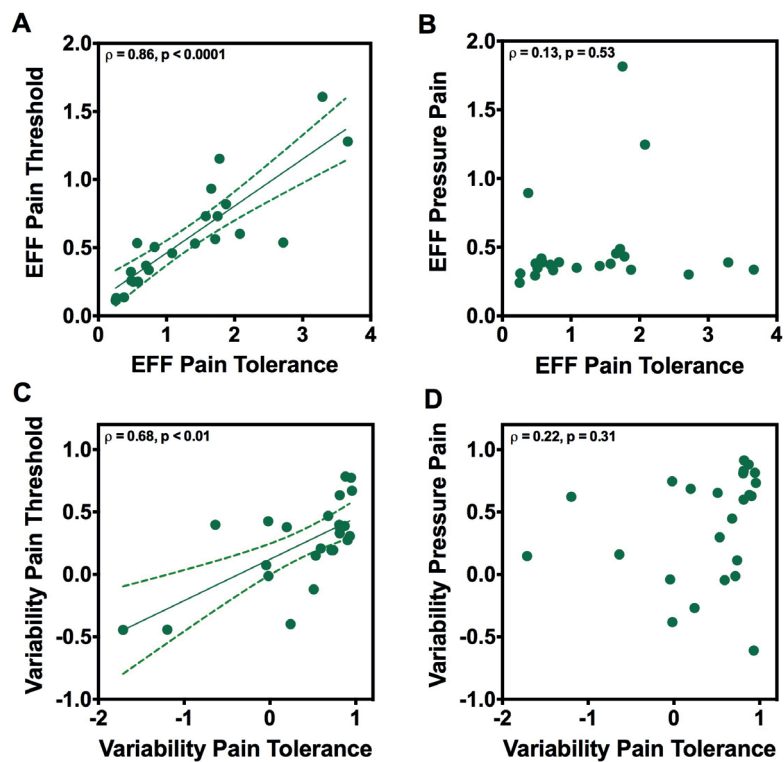


Figure 4 (A) EFF parameter values (see eq. (A1)) from the electrical pain tolerance data analysis (x-axis) plotted against EFF values from the electrical pain threshold data analysis (y-axis). Pearson's correlation coefficient (ρ) = 0.86, $p < 0.0001$. (B) EFF parameter values from the electrical pain tolerance data analysis (x-axis) plotted against EFF values from the pressure pain threshold data analysis (y-axis). $\rho = 0.13, p = 0.53$. (C) The coefficient of determination from electrical pain tolerance data fits (x-axis) plotted against the coefficient of determination derived from electrical pain threshold data fits. $\rho = 0.68, p < 0.01$. (D) The coefficient of determination from electrical pain tolerance data fits (x-axis) plotted against the coefficient of determination from pressure pain threshold data fits. $\rho = 0.22, p = 0.31$. (A-D) Each dot represents data from one individual. (A and C) The continuous line is the linear regression curve $\pm$ 95% confidence interval.

Electrical pain versus pressure pain models

The effect of OOT on the electrical and pressure pain models differed in temporal profile with a more rapid analgesic onset/offset observed in the pressure pain model (Tables 1 and S1, Figures 3A and B). To further explore possible differences among these nociceptive models we compared the individual potency (EFF) and residual variability (R^2) estimates

of the three indices that were measured (Figure 4). As expected we observed a close correlation between EPTol and EPth values for potency (Figure 4A) and variability (Figure 4C). No correlation was present between PPT and EPTol potency and variability estimates (Figures 4B, 4D), a clear indication of the neurophysiological differences between the electrical and pressure pain assays. While skin pressure pain elicits activation of A δ and C-fibers, electrical pain stimulation of the skin bypasses the nerve endings and direct stimulation of the sensory and non-sensory nerves occurs, with also differentiation in central processing and modulation.¹⁹ It is therefore within expectation that oxycodone interacts differently between the two pain models. While pressure pain has the advantage of being more physiological, the electrical stimuli are easily controlled and consequently the electrical nociceptive model is widely used, especially in pharmacological trials.¹⁹

CONCLUSIONS

Orodispersible oxycodone 20 mg produced analgesic effects in two experimental pain models that was well described by a novel mathematical pharmacodynamic model in terms of onset and offset of effect and analgesic efficacy, despite sparse data sampling. This analytical approach has advantages over conventional statistical analyses as it, for example, allows the accurate estimation of the response times to specific events such as the time to a 30% (a measure of clinical importance) increase in response thresholds. For OOT, the response to a 30% increase in response threshold was rather variable and ranged from 15 to 41 min, depending on the end-point chosen. Future studies should incorporate patients and potent opioid comparators.

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Supporting Information

Additional Supporting Information was published in the online version of this article:

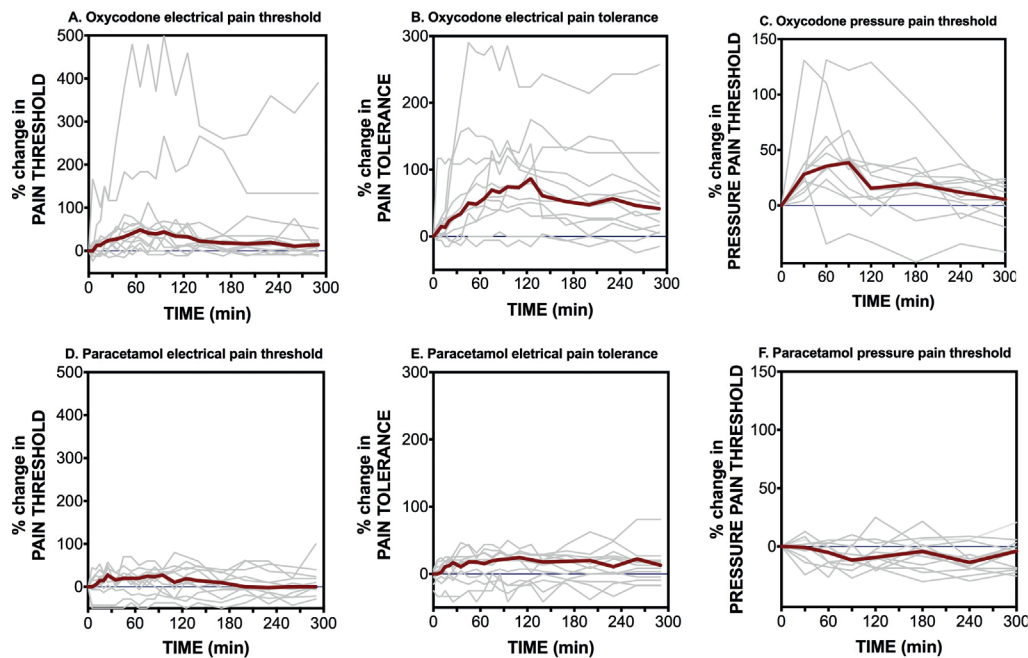


Figure S1 Influence of 20 mg oxycodone and 500 mg paracetamol orodispersible tablets on electrical pain threshold (A and D), electrical pain tolerance (B and E) and pressure pain threshold (C and F). Grey and red lines are the individual and median responses, respectively. At $t = 0$, the treatment was administered.

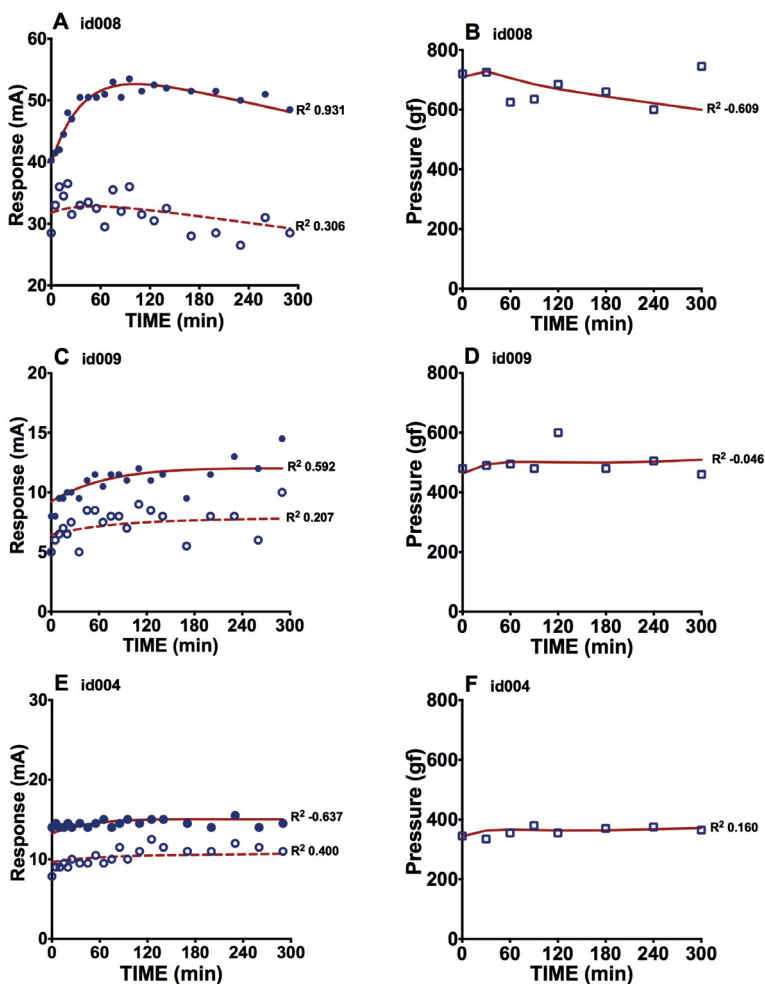
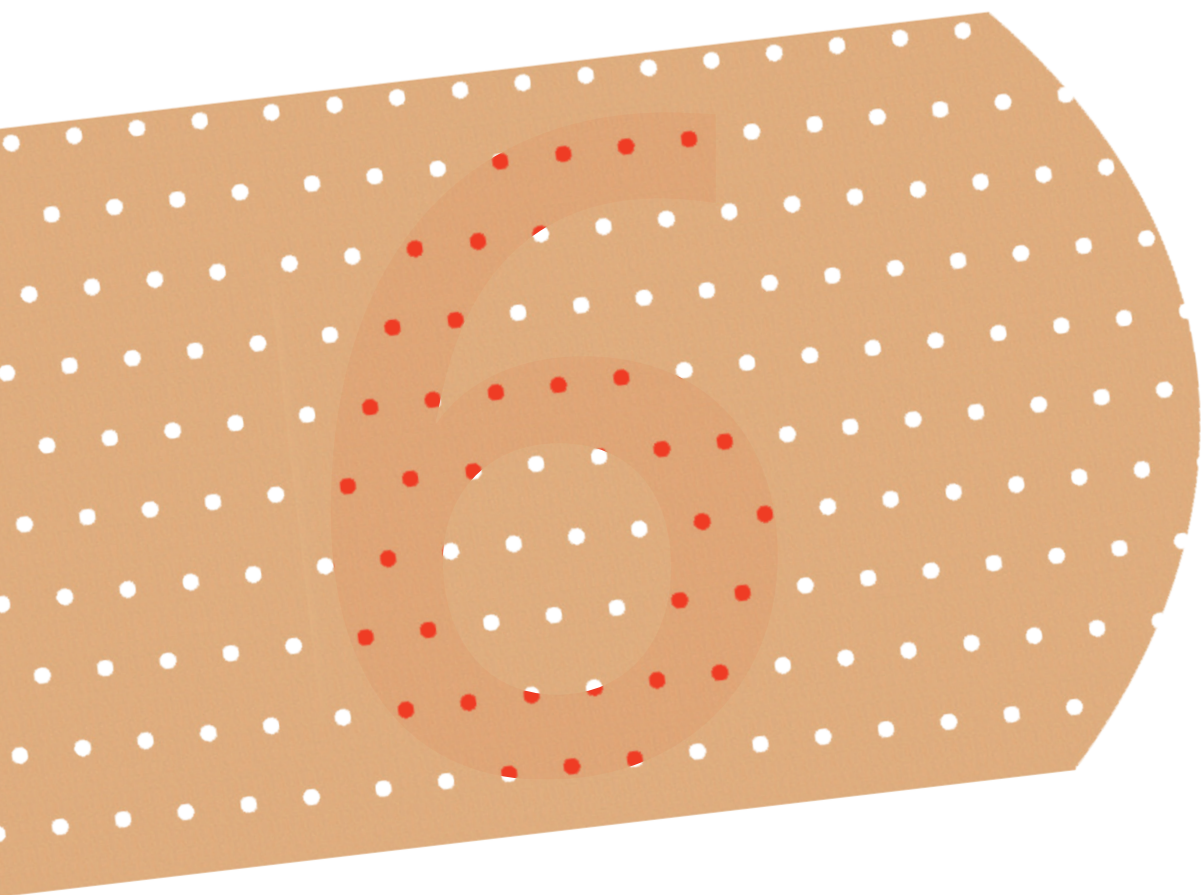


Figure S2 Examples of paracetamol data fits. Best (A), median (C) and worst (E) data fits of electrical pain tolerance data (as determined by the coefficient of determination, R^2) are shown, with corresponding fits for electrical pain threshold (A, C and E) and pain pressure threshold (B, D, F). Closed circles denote the measured electrical pain tolerance data, open circles the measured electrical pain threshold data, open squares the measured pressure pain threshold data. The lines are the data fits.

Supplemental Table 1 Results of the bootstrap analysis

	2.5% quantile	50% quantile	97.5% quantile
Electrical Pain			
Baseline threshold (mA)	6.3	9.0	11.5
Baseline tolerance (mA)	9.5	12.7	15.7
$t_{1/2}k_{ON}$ (min)	25	44	67
$t_{1/2}k_{OFF}$ (min)	63	156	552
EFF threshold oxycodone	0.19	0.43	0.87
EFF tolerance oxycodone	0.39	0.95	1.71
EFF threshold paracetamol	0.02	0.07	0.12
EFF tolerance paracetamol	0.06	0.14	0.26
T_{MAX} (min)	75	111	170
AUC/300 threshold oxycodone (mA/min)	0.147	0.337	0.706
AUC/300 tolerance oxycodone (mA/min)	0.322	0.732	1.400
AUC/300 threshold paracetamol (mA/min)	0.019	0.051	0.090
AUC/300 tolerance paracetamol (mA/min)	0.040	0.112	0.201
Pressure Pain Threshold			
Baseline (gf)	364	421	487
$t_{1/2}k$ (min) *	16	30	48
EFF oxycodone	0.21	0.40	0.67
EFF paracetamol	0.03	0.06	0.10
T_{MAX} (min)	24	43	70
AUC/300 oxycodone (gf/min)	0.093	0.218	0.408
AUC/300 paracetamol (gf/min)	0.012	0.031	0.061
Overall relative paracetamol effect			
Effect (%)	7.0	14.8	30.1

* for pressure pain: $k = k_{ON} = k_{OFF}$



Chapter 6

A randomized controlled trial on the effect of tapentadol and morphine on conditioned pain modulation (CPM) in healthy volunteers

C.H. Martini, M. van Velzen, A. Drewes, L. Aarts, A. Dahan, M. Niesters

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INTRODUCTION

Pain perception is dependent on several modulatory mechanisms that transform afferent nociceptive input into the sensation of pain.¹ Such endogenous pain modulatory mechanisms may be inhibitory or facilitatory and determine the intensity of the painful sensation (ranging from no pain to extremely painful) following a noxious event. An inhibitory mechanism that may be activated under experimental conditions is conditioned pain modulation or CPM; CPM is a surrogate biomarker of endogenous modulation of pain²⁻⁵ and is the human equivalent of diffuse noxious inhibitory controls or DNIC in animals. In the case of DNIC, a spinal-medullary-spinal feedback loop (without the involvement of higher brain centers) is engaged, causing the inhibition of a primary noxious stimulus by a spatially separated secondary noxious event due to inhibition of sensory spinal dorsal horn neurons.⁶ In contrast to DNIC (in animals), CPM (in humans) requires activation of supraspinal pathways. For example, in a recent study, Nahman-Averbuch et al.⁷ show in an fMRI study that CPM is associated with reduced activity in nociceptive brain regions such as the thalamus, insula and secondary somatosensory cortex and brainstem. Alike DNIC, CPM is tested by applying a primary (test) nociceptive stimulus on one part of the body simultaneously with a secondary (conditioning) tonic nociceptive stimulus on a body part remote from the primary site.¹⁻⁵ Data from healthy young volunteers invariably show that the conditioning stimulus inhibits the pain perceived from the test stimulus.^{4,8,9} The current notion is that CPM engages top-down inhibitory pathways that originate at higher sites and converge at dorsal horn neurons to suppress incoming afferent nociceptive information.^{10,11}

Apart from CPM, offset analgesia (OA) is another psychophysical paradigm, which enables testing of endogenous modulation of pain.^{7,8,12} In contrast to CPM, OA reflects temporal filtering of nociceptive information, and causes robust analgesia upon a slight decrease (offset) in noxious stimulus intensity. OA and CPM differ significantly: (1) fMRI studies show that OA is associated with an *increase* in activity in certain brain areas such as the anterior insula, dorsolateral prefrontal cortex and brainstem.⁷ (2) There is no correlation between OA and CPM responses;^{7,8} (3). When affected in chronic pain states, CPM but not OA is improved by pharmacotherapy.^{13,14} These findings indicate that OA and CPM engage two distinct endogenous modulatory mechanisms.

The inability to recruit CPM-related descending inhibitory pain pathways is thought to play an important role in the development of chronic pain. For example, patients with a less efficient or absent CPM have a higher probability of chronic pain following thoracic, abdominal or obstetric surgery.¹⁵⁻¹⁷ Similarly, rodents with the genetic predisposition to effectively engage descending inhibition are better protected against the development of

chronic pain following peripheral nerve damage compared to animals with a lesser ability to do so.¹⁸ Furthermore, in a variety of painful conditions (including complex regional pain syndrome; diabetic-, sarcoidosis- and chemotherapy-induced polyneuropathy; fibromyalgia; chronic pancreatitis) impaired CPM responses have been observed.^{13,19-24} The observation of a link between defects in descending pain control, as tested by CPM, and development and chronification of pain suggests that restoration of descending pain control may be a valuable analgesic tool. Several analgesics have the potential to activate or reinforce descending inhibition as they interact favorably with the neurotransmitter systems involved in descending pain pathways. Most important neurotransmitters include endogenous opioid peptides, noradrenaline (NA) and serotonin and it is thought that their release can produce pain inhibition.^{10,11} Tapentadol is a relatively new analgesic agent that is believed to activate descending inhibitory pain pathways.²⁵ Tapentadol is a combined μ -opioid receptor (MOR) agonist and inhibitor of the neuronal reuptake of the α_2 -adrenergic receptor agonist NA.²⁶ Compared to morphine it displays weak agonist activity at the μ -opioid receptor (MOR), however, due to synergy between the two mechanisms of action, tapentadol has strong antinociceptive and antihypersensitive effects, possibly via enhancement of descending inhibitory pathways.²⁷

We performed a randomized, double blind, placebo-controlled crossover study in healthy (pain free) volunteers to quantify the effect of tapentadol and morphine on CPM. Morphine, in contrast to tapentadol, is a full MOR agonist without significant effect on NA reuptake. Previous data suggest that morphine reduces CPM responses in volunteers.²⁸ We hypothesize that taken the differences in mechanisms of action of morphine and tapentadol and the earlier observation with morphine, these two analgesics behave differently in their effect on CPM with a reduction in CPM by morphine and an increase in CPM by tapentadol.

MATERIALS AND METHODS

Ethics statement and trial registration

Adult volunteers were recruited to participate in this double blind, randomized, placebo-controlled, crossover study that was performed at Leiden University Medical Center. All participants gave written informed consent to participate in the trial. Approval of the protocol and consent procedure was obtained from the LUMC Medical Ethics Committee and the Central Committee on Research Involving Human Subjects (CCMO, The Hague, The Netherlands). Trial registration was at www.trialregister.nl under number NTR2716 (Feb 2011). The protocol and consort checklist are available for review.

Participants

Twelve healthy Dutch-speaking (non-smoking) volunteers of either sex, aged ≥ 18 years with a body mass index $< 30 \text{ kg/m}^2$, were enrolled in the study. Exclusion criteria included: known drug allergies; current use of legally prescribed medication; present or past illicit substance use; present or past alcohol abuse; history of mental illness; pregnancy and/or lactation; any other condition that in the opinion of the investigators would compromise the well-being of the subject when participating in this trial. All volunteers were instructed to abstain from solids and liquids during the 8 hours before dosing.

Study Design

After arrival in the laboratory and an initial practice session, the temperatures of the test and conditioning stimulus were determined. Next the study medication was ingested. CPM responses were obtained 60-90 and 120-150 min after drug intake.

Treatment

The subjects received placebo (cellulose; fabricated by the local pharmacy), morphine immediate release 40 mg (Sandoz BV, Almere, The Netherlands), and tapentadol immediate release 100 mg (Grünenthal BV, Breukelen, The Netherlands) tablets on separate occasions. The order of administration was random. At least two weeks was allowed between treatments for washout. The dose of tapentadol IR was based on the observation that in postsurgical dental pain an oral dose of 100 mg IR caused pain relief for 4 hours (peak effect after 1-1.5 h).²⁹ The dose of morphine is based upon a 2.5-fold greater potency of morphine compared to tapentadol (data provided by the manufacturer and Kress et al.³⁰).

Test stimulus

The test stimulus was a noxious heat stimulus, administered via a calibrated 3x3 cm thermal probe connected to the Pathway Neurosensory Analyzer (Medoc Ltd., Ramat Yishai, Israel). The thermode was placed on the volar side of the lower part of the (non-dominant) upper extremity. During noxious testing the subjects scored their pain intensity rating on an electronic slider, which ranged from 0 (no pain) to 100 (worst pain imaginable). These data on the electronic visual analogue scale (eVAS) were collected at 1 Hz for further analysis. To prevent sensitization of the skin, the thermal probe was repositioned between different zones on the forearm and ample time was allowed between testing.

The temperature of the test stimulus was determined by applying a series of heat stimuli. First the temperature was increased from 32 °C (baseline temperature) by 1.5 °C/s

to a target temperature of 42 °C and kept constant for 10 seconds. If the eVAS was less than 50 mm a next test was performed increasing the target temperature in steps of 1 °C. The cut-off temperature for these series was 49 °C. The lowest temperature evoking an eVAS of at least 50 mm was used during the remainder of the study. This procedure was performed, once on each experiment day, before drug administration. Consequently, small deviations in test stimulus intensity (but not test target temperature) due to the presence of the analgesic were allowed.

Conditioning stimulus (CS)

The CS was applied to the foot and lower leg of the subject (ipsilateral to the site of the test stimulus) and consisted of a thermal (cold water) stimulus. To generate the stimulus the subject's lower extremity was immersed into an 84 L water reservoir. The water was produced by a rapid counter-current water-cooling system (IcyDip, IcySolutions BV, Delft, The Netherlands). Water temperatures in the range of 6°C to 18°C (in steps of 0.5 °C) were offered to the subject and the highest temperature that produced an eVAS of at least 30 mm was used in the remainder of the study. After the exposure to cold water, the subject's extremity was warmed to normal temperature using warm water collected from the counter-current outlet of the IcyDip system. There was at least 1 hour between obtaining the optimal test and conditioning stimuli.

Conditioned pain modulation

We applied the method of King et al.^{19,31} to measure CPM, which was used successfully in previous studies from our laboratory.^{8,14,22} In short, the thermal probe was applied to the volar side of the (non-dominant) underarm and its temperature was increased from baseline 32 °C (temperature close to skin temperature) to the test temperature (at 1.5 °C/s) and was kept constant for 30 s. Next, the temperature was rapidly lowered (at 6 °C/s) to baseline. Each heat test was applied 3 times (with a 3-min rest between tests) after which this same sequence was repeated but now combined with the conditioning stimulus (immersion of foot and leg in cold water). The conditioning stimulus was applied 25 s before the test stimulus and continued until the end of the test stimulus. During all tests the subjects were instructed to rate the pain intensity of the test stimulus (and not the conditioning stimulus) using the eVAS slider. The whole procedure lasted no longer than 30 min. See Figure 1 for an overview of the setup used to induce CPM.

Randomization and blinding

Non-restricted randomization and allocation (1:1:1) was performed by the local pharmacy using a computer-generated randomization list. To ensure blinding of both investigators

and participants, all tablets were recapsulated into identical capsules in form and taste. The capsules were dispensed to the research team on the morning of the study in containers marked by subject number and visit number. The investigators remained blinded to treatment until all data were analyzed.

Data analysis

The study was powered to detect a difference in CPM of $20 \pm 15\%$ (mean $\pm$ SD, with $\alpha = 0.05$ and $1-\beta > 0.95$) between active treatment (morphine or tapentadol) and placebo (SigmaPlot v12.0, Systat Software Inc., San Jose, CA) [8,22]. To quantify the magnitude of CPM, the average peak eVAS without (from 3 tests) and with CS (from 3 tests) were calculated. Next, CPM responses were calculated to correct for variations in peak response between sessions and subjects using the formula:^{8,14,22}

$$\frac{[\text{Peak eVAS (without CS)} - \text{Peak eVAS (with CS)}]}{[\text{Peak eVAS (without CS)}]} \times 100\% \quad (1)$$

Temperatures of test and conditioning stimuli of the three treatment groups were compared by one-way analysis of variance. The effect of the conditioning stimulus on peak eVAS was tested by two-tailed *t*-test. To test the effect of treatment on CPM

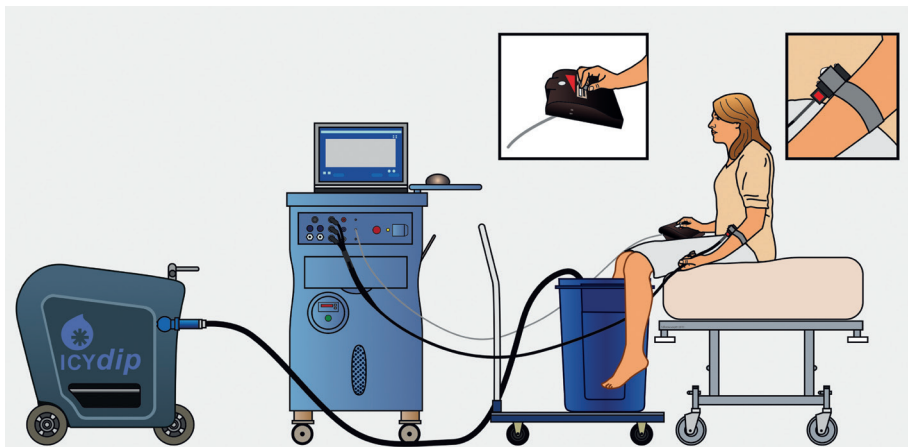


Figure 1 The setup used to induce Conditioned Pain Modulation (CPM). The volunteer sits on the bed while a thermal test stimulus is applied to the arm via a 3x3 cm thermode (insert top right). The leg is placed in a bucket filled with cold water (ie. the conditioning stimulus) and the subject scores the heat pain to the arm using an electronic visual analogue scale (insert top middle). The cold water is applied via the icydip system; the heat pain via Medoc's pathway system.

responses, a mixed effect model was applied to the data (factors: treatment, time and timetreatment) using package “lmerTest” of the R software package (version 2.8, R-project; <http://www.r-project.org>); *post-hoc* a linear mixed model was fit to the data to assess the significance of difference between active treatment and placebo. *p*-values < 0.05 considered significant. Data are presented as mean $\pm$ SEM unless otherwise stated.

RESULTS

Seven men and five women were enrolled from March 2011 to June 2011, aged 26 ± 1 years and with a body mass index of 23 ± 1 kg/m² (mean $\pm$ SD). All twelve volunteers were randomized and dosed and their data were fully analyzed according to protocol (Figure 2). None of the volunteers experienced any side effects following treatment with placebo, morphine and tapentadol, except for one female subject who became nauseous after tapentadol and morphine treatment and vomited after morphine.

The test stimulus temperatures (heat pain) as determined prior to treatment averaged to 47 ± 0.5 °C, 46.6 ± 0.5 °C and 46.9 ± 0.5 °C on placebo, morphine and tapentadol experimental sessions (one-way anova: NS). The target conditioning stimulus temperatures were 7.9 ± 0.5 °C, 8.1 ± 0.6 °C and 8.3 ± 0.6 °C on placebo, morphine and tapentadol experimental sessions (one-way anova: NS).

Effect of the conditioning stimulus of the eVAS of the test stimulus

In Figure 3 the mean eVAS responses to the test stimulus before (blue dots) and after (orange dots) application of the conditioning stimulus are given obtained at 60-90 min after drug intake. At that time period, a significant decrease in peak eVAS for placebo (peak eVAS without CS = 53 ± 4 mm vs. peak eVAS with CS = 43 ± 5 mm, *p* < 0.001) and tapentadol (45 ± 5 mm vs. 36 ± 5 mm with CS, *p* < 0.001) was observed, but not for morphine (48 ± 5 mm vs. 46 ± 6 mm, *p* = 0.48). Similarly, at 120-150 min after drug intake, a significant decrease in peak eVAS for placebo (peak eVAS without CS = 51 ± 5 mm vs. peak eVAS with CS = 40 ± 5 mm, *p* < 0.001) and tapentadol (46 ± 5 mm vs. 33 ± 4 mm with CS, *p* = 0.03) was observed, but not for morphine (51 ± 5 mm vs. 46 ± 6 mm, *p* = 0.12). See also Figure 4A and C.

CPM responses

CPM responses were $22.7 \pm 6.5\%$ (placebo), $4.5 \pm 8.0\%$ (morphine) and $21.2 \pm 8.9\%$ (tapentadol) after 60-90 min and $24.4 \pm 6.0\%$ (placebo), $5.0 \pm 2.8\%$ (morphine) and $23.0 \pm 8.1\%$ (tapentadol) after 120-150 min. A significant treatment effect was observed (*F*_{2,55}

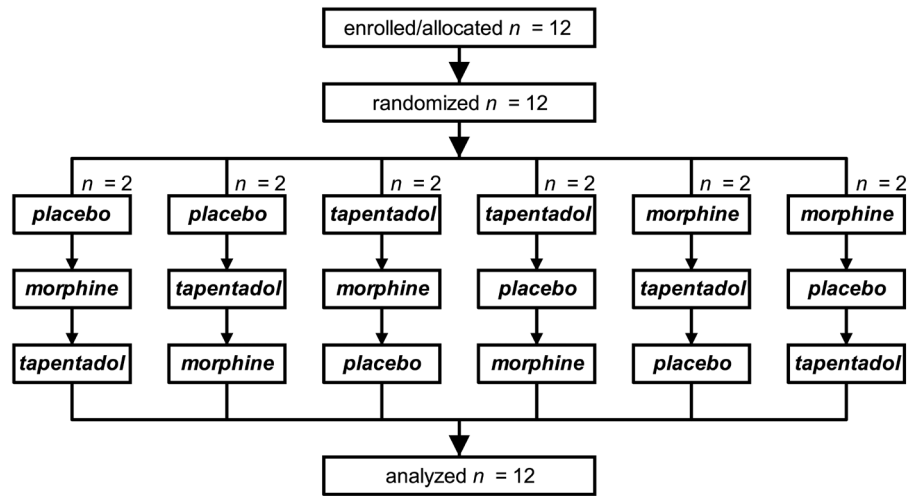


Figure 2 Consort flow diagram.

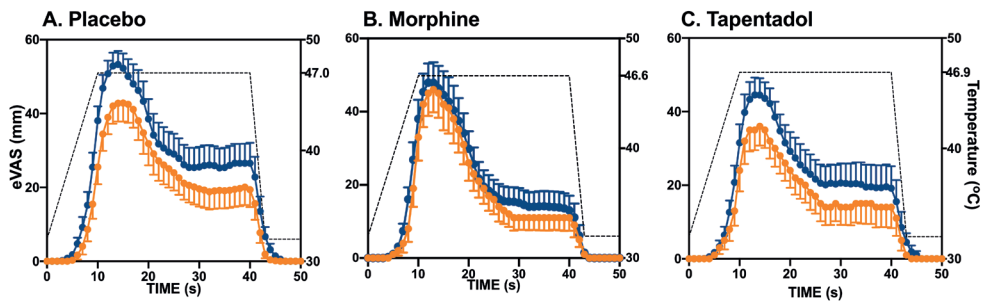


Figure 3 Mean eVAS responses following treatment with placebo (A), oral morphine immediate release 40 mg (B) and oral tapentadol immediate release 100 mg (C) at 60–90 min after drug intake. The blue dots are the responses to the test stimulus without conditioning stimulus, the orange dots the responses to the test stimulus with conditioning stimulus. The broken line is the mean temperature of the test stimulus. Values are $\pm$ SEM.

= 6.2, $p = 0.004$), but there was no time effect ($F_{1,55} = 0.24$, $p = 0.62$) or time $\times$ treatment effect ($F_{2,55} = 0.072$, $p = 0.93$). Treatment effects relative for placebo were -18.8% (95% confidence interval -29.8 to -7.8%, $p = 0.001$) for morphine and -2.9% (95% confidence interval -13.9 to 8.1%, $p = 0.60$) for tapentadol. See Figure 4B and D.

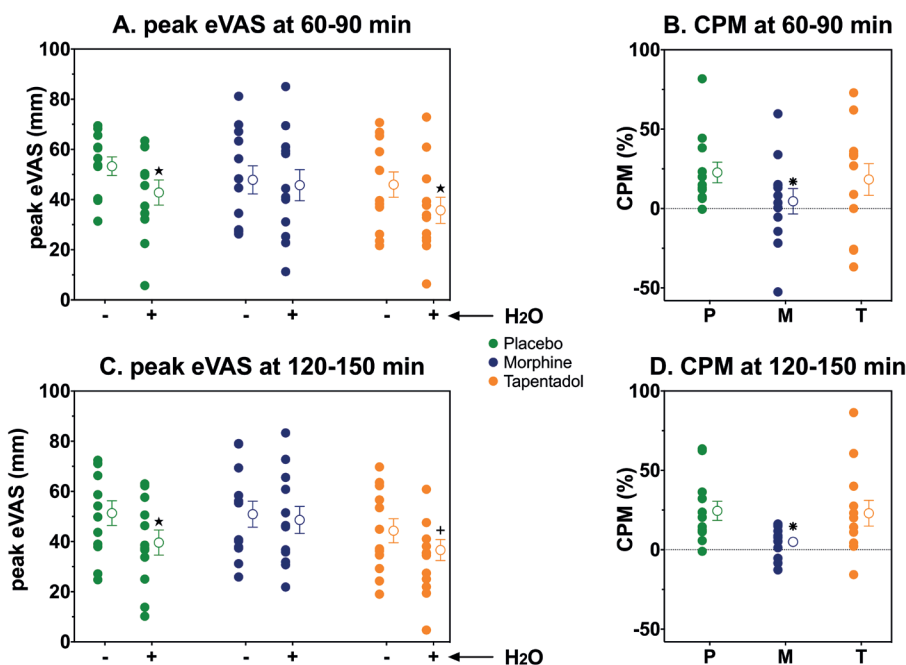


Figure 4 eVAS and CPM responses at 60-90 min (A and B) and 120-150 min (C and D) after drug intake. A and C. Mean peak eVAS responses without (–) and with (+) conditioning stimulus for placebo (green), morphine (blue) and tapentadol (orange). B and D. CPM responses observed following placebo, morphine and tapentadol treatment. Individual data and the mean $\pm$ SEM are presented. □ p < 0.001, * p = 0.001, + p = 0.03.

DISCUSSION

The effect of two opioid analgesics, morphine and tapentadol, on conditioned pain modulation was tested in a single population of healthy young volunteers under identical experimental and placebo-controlled conditions. The main findings of our study are: (1) In agreement with our hypothesis, a single oral dose of morphine reduces CPM responses relative to placebo by 80%; (2) In contrast to our hypothesis, a single dose of tapentadol has no effect on CPM responses compared to placebo treatment.

Tapentadol is a combined μ -opioid receptor (MOR) agonist and inhibitor of the neuronal reuptake of the α_2 -adrenergic receptor agonist NA.²⁶ Noradrenaline, together with other monoamines, plays an important role in mediation of analgesia *via* activation of the α_2 -adrenergic receptor at supraspinal and pre- and postsynaptic spinal sites.^{10,11} Animal data indicate that the combined effect of MOR agonism and NA reuptake inhibition (the so

called MOR-NRI concept) of tapentadol produces synergistic analgesia.²⁷ In contrast to tapentadol, morphine has no effect on NA reuptake. *In vivo* animal data of microdialysis in the ventral hippocampus show that tapentadol but not morphine produces a dose-dependent increase in extracellular levels of NA.²⁶ In mice lacking the MOR, tapentadol's analgesic effect is reduced by about 50% in a model of acute thermal pain and by about 20% in a model of neuropathic pain.³² In contrast, morphine is without any antinociceptive effect in this MOR knockout mouse strain.

In the current study, we tested a single dose of tapentadol (100 mg) and a single dose of morphine (40 mg). The doses chosen were based on equianalgesia data from animal and human studies. For example, in mice the ED₅₀ in the hot plate assay is 11.8 and 4.7 mg/kg for tapentadol and morphine, respectively²⁶ and in the treatment of patients with cancer pain the equianalgesic tapentadol/morphine dose ratio is 2.5.³⁰ Although our data indicate analgesia from morphine and tapentadol (see Figures 3 and 4), our study was not designed to assess (equi)analgesia between treatments and the phasic heat pain may not be the best experimental model to evaluate potency of opioids.³³

The reduction of CPM with morphine is in agreement with an earlier observation of Le Bars et al. from 1992 in healthy volunteers.²⁸ To the best of our knowledge our study is the first to re-assess the effect of morphine on CPM in volunteers. After 0.05 mg/kg morphine, Le Bars et al. observed a complete loss of depression of the spinal nociceptive R_{III}-reflex (elicited by electrical stimulation of the sural nerve) by a contralateral conditioning temperature stimulus. The inhibition returned upon administration of the opioid antagonist naloxone. Animal data, showing similar effects on DNIC, suggest that the effect of morphine on DNIC originates at supraspinal sites.³⁴ The data from Le Bars et al. and ours provide robust proof for an inhibitory effect of morphine on CPM in volunteers without pain.

It is of interest to speculate on the mechanism through which morphine reduces CPM. A specific role from activation of the μ -opioid receptor would be expected in this respect. However, other opioids that have an effect on the μ -opioid receptor (such as oxycodone⁹) do not affect the CPM response as tested within 1-3 hours after the administration of the opioid. Furthermore, three of six human studies on the effect of naloxone or naltrexone on CPM found no effect of opioid receptor blockade on CPM,³⁵⁻³⁷ while three others showed a reduction of CPM.^{31,38,39} This suggests a limited role for the opioid-receptor system in the reduction of CPM. Alternatively, the loss of CPM by morphine may be related to a morphine-specific property such as due to an effect of the pronociceptive metabolite morphine-3-glucuronide. This metabolite appears rapidly in plasma upon the administration of morphine.⁴⁰ Overall, the data on morphine are confusing and presently offer no definite conclusion regarding the involvement of opioid receptors in

the development of descending (inhibitory or facilitatory) controls in humans. We did not observe an increase in CPM by tapentadol. Since monoaminergic receptors play an important role in descending pain inhibition,^{10,11} we expected an increase in CPM. Multiple, nonexclusive mechanisms may have played a role in our finding: (i) In the population of pain-free volunteers, the single administration of tapentadol was insufficient to have a clinical significant effect on neuronal NA reuptake and/or the dose was too low. However, after this single dose we did observe an analgesic effect on peak eVAS (Figures 2 and 3), which we relate to the synergistic effect of MOR activation and NA reuptake inhibition; (ii) Possibly the CPM responses of our healthy volunteers were at their (near) physiological maximum, and a further increase is difficult to attain. In contrast to healthy volunteers, in a recent protocol we observed that in neuropathic pain patients with absent CPM responses, a single treatment with 100 mg immediate release tapentadol treatment did activate CPM to values of similar magnitude as observed in the current study after placebo and tapentadol treatment, while intravenous morphine was without effect in this similar patient population;²² (iii) We cannot exclude that morphine's negative impact on CPM is an opioid receptor-related effect. If so, the apparent absence of effect of tapentadol on CPM may be related to two opposing effects on CPM, one negative (related to an opioidergic effect) and one positive (due to spinal adrenergic stimulation) with a net zero effect. This seems an attractive explanation of our findings and is in agreement with animal data.^{26,27,32,34} Still, further studies are needed to understand the mechanism of tapentadol's absence of effect on CPM in healthy volunteers. For example, specific α_2 -adrenergic and opioid receptor blockers (eg. yohimbine and naloxone) may be used to separate MOR and adrenergic effect on CPM during tapentadol treatment. Just few earlier studies addressed the effect of opioids on CPM responses in human volunteers.^{8,28,41} Comparison with our study is difficult due to differences in dosage, administration route, and dissimilarities in methods to induce CPM. Hence, a significant part of the variability observed in study outcomes may be related to methodological issues. An interesting example is the study by Arendt-Nielsen et al, who studied the effect of fentanyl (25 $\mu\text{g}/\text{h}$) and buprenorphine (20 $\mu\text{g}/\text{h}$), administered by a transdermal patch formulation, on CPM responses after 24, 48 h and 72 h of treatment.⁴¹ They observed an increase in CPM at all time points. Differences with our study include the route of administration (transdermal vs. oral), dose, duration of administration (continuous vs. single delivery), and CPM protocol. Arendt-Nielsen et al. used pressure pain tolerance threshold (test stimulus) applied to the left arm before, during and after immersion of the left hand into a fixed 3 °C water bath (conditioning stimulus). Setting the difference in study CPM protocol aside, these data suggest that sustained but not single deliveries enhance CPM responses in human volunteers. Possibly, the secondary effect of these

opioids on descending control via activation of off-cells in the medulla and release of noradrenaline in the spinal cord takes time to develop,^{10,11,22} and days rather than hours of treatment are required before the CPM increases above baseline levels. Whether this is also true for morphine requires further study. In order to overcome the issue of differences in CPM protocol, which is a general observation that relates to all studies on CPM, adoption of a standardized CPM protocol is required.⁴²

One caveat of our study is that we did not collect plasma levels of morphine and tapentadol. We refrained from blood sampling as this could have affected the study outcome and blood sampling per se is not a good marker of drug effect taken the sometimes relatively long and variable blood-effect-site equilibration half-life (ie. passage of the drug to central sites) of opioids such as morphine and tapentadol.⁴⁰ By performing CPM tests at multiple times in the first three hours following drug intake, we contend that we captured the peak drug effect on CPM for both morphine and tapentadol.

CONCLUSIONS

Our data show that, in agreement with earlier findings, a single oral administration of morphine has a negative impact on the endogenous modulation of nociceptive stimuli in healthy young adult volunteers. In contrast, a single oral administration of tapentadol was without effect on CPM despite the fact that studies were performed under similar controlled conditions in the same study population. These data confirm that tapentadol's main mechanism of action is distinct from that of morphine and likely related to the tapentadol-induced effect of adrenergic stimulation on descending controls.

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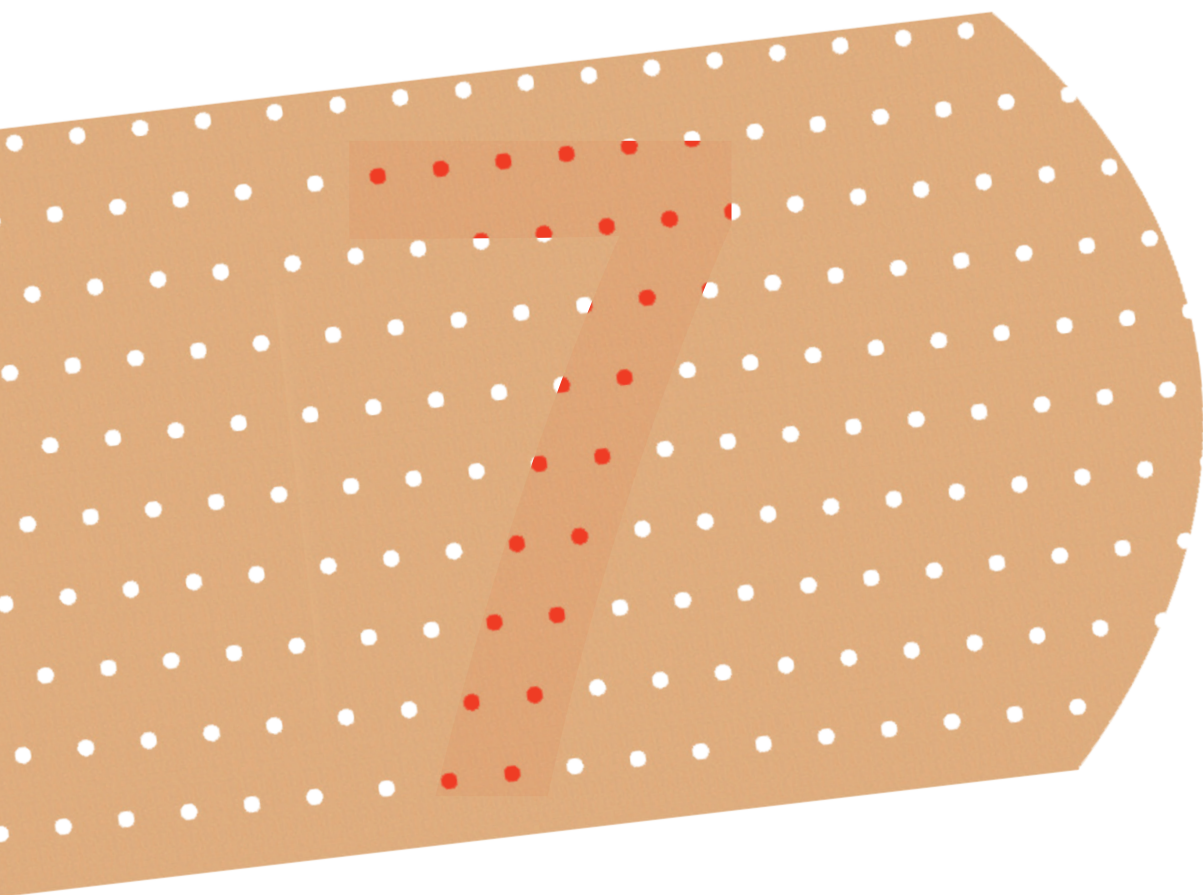
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Chapter
6



Chapter 7

General Discussion, Summary and Conclusions

The development of new effective and safe analgesics for the treatment of chronic pain is a challenging, time consuming and costly process. Large multicenter trials are needed, as the heterogeneity in pharmacological treatment response is significant, with large within- and between-subject variability in treatment response, which in magnitude may differ among trial centers. This regards not only the effect of the active compound but also the placebo response. Consequently many phase III trials, even the larger ones, of new analgesic medication do fail because of the magnitude of the placebo response. An example is a recent trial that was performed in our institution and one other center (unpublished observation). The effect of a novel compound with analgesic properties was tested in chronic pain patients using a placebo-controlled double-blind randomized design. On average, the novel compound had certainly analgesic effects but the effects were no greater than the placebo-induced analgesic response. Interestingly, the set-up of the trial allows comparison of the effect of the active and placebo treatments between centers. The differences in the outcome between the two recruitment centers were remarkable. One center had low-placebo responses and high-treatment effects (*i.e.* the informative center), while the reverse was true for the other center (*i.e.* the non-informative center). Certainly this relates to differences in experience and training between centers, but one additional observation regarding the patients is of importance as well. The patients recruited in the two centers differed significantly in their body mass index, with severely obese patients almost exclusively recruited in the center with high placebo and low active treatment responses, *i.e.* the non-informative center. The fact that predominantly obese patients were recruited may be mechanistically related to the fact that the outcome of this trial center was negative. The pharmacokinetics of the drug will differ in obese *versus* non-obese patients. And possibly also the pharmacodynamics might differ although this evidently depends on the mechanisms of action of the active treatment (*e.g.* obese patients differ in their metabolic, hormonal and inflammatory status). Furthermore, we have indications that small peripheral nerves in obese patients are less active compared to normal individuals with higher cutaneous stimulus detection and pain thresholds. This will impact trials that rely on intact peripheral nerves when assessing treatment effects through quantitative sensory testing (QST), a test battery consisting of 7 tests measuring 13 variables. Additionally, we recently observed that obese patients have difficulty in rating pain possibly due to a problem with number sensing. Irrespective of the underlying causes for the observed outcome, this trial serves as an example of the difficulties that may arise when performing pain treatment studies, especially when multiple trials centers are involved. We will need to further analyze the data but we are convinced that apart from patient-related factors, the quality of trial centers certainly has an influence on the study outcome. Standardization of patients

(i.e. using patients with predefined weights), application of enrichment trials (in which placebo responders are excluded) or the use of only “informative” or “high quality” trial centers seem possible solutions. If such restrictions are applied in phase III trials, they will certainly influence outcome in a positive fashion. Still, in real life such exclusions do not exist. Physicians and patients outside the trial setting will not benefit from such an approach as it remains unknown which patient will respond to treatment and which will not. Hence it is more important to use these often-large phase III trials to improve our understanding of predictors of effective treatment and/or of the placebo response. This was the goal of the research described in this thesis, in which novel analysis techniques are described to quantify and most importantly **predict** the efficacy of pharmacotherapy for acute and chronic pain. We made use of existing data sets of large multicenter trials (Chapters 3 and 4) or performed experiments in our pain laboratory on healthy volunteers exposed to opioid treatment and experimental nociceptive assays (Chapters 5 and 6). Three important findings of my thesis are that (i) there are multiple responder subgroups to analgesic treatment rather than just “responders” *versus* “non-responders”, (ii) it is important to collect multiple data points over time rather than to collect one end-point at the end of study (e.g. after 12 weeks) and (iii) predictors of analgesic (and placebo) effect differ among response subgroups (and are possibly dependent on the recruitment centers, see above). These findings alone should lead to an “enriched” analysis approach of future phase III trials. And indeed, the approach presented in Chapter 4 has already been proposed by some international regulatory offices.

In this final chapter, I will give a summary of the observations made in the different studies that are presented. Next, I will discuss response (sub)group analyses, the leading theme of this thesis, and the placebo response. Finally, future perspectives and the conclusions of the thesis are presented.

SUMMARY

In **Chapter 2** an overview of the recent literature on pharmacokinetic (PK) and pharmacodynamic (PD) modeling in acute and chronic pain is presented. In this review, novel observations on opioids, NSAIDs, epidural analgesia, ketamine and GABAergic drugs are highlighted. Several mathematical models are discussed that describe and/or predict the time course of analgesic agents and link PK to PD. *Population* PKPD modeling allows, apart from the estimation of fixed effects (the PK and PD model estimates), the quantification of random effects: the within- and between-subject variability. *Effect-*

compartment and *mechanism-based biophase distribution* models incorporate drug association and dissociation kinetics and enable the quantification of the rate-limiting factors in drug effect due to drug distribution versus receptor kinetics. It is a useful technique in understanding the complex behavior of specific compounds, especially with respect to the occurrence and management of side effects. A somewhat different approach in chronic pain studies is the application of *mixture* models. Mixture models allow the identification of specific response subgroups. Combining mixture analysis and (PK)PD modeling or time series analysis leads to the improvement of current therapeutics with respect to dose design, outcome, and understanding the interaction of analgesics within complex chronic pain disease processes and may play an important role in new drug development. For example, the effect of a 100 h intravenous ketamine and placebo infusion on pain in patients with Complex Regional Pain Syndrome type 1 is discussed. Mixture modeling identified 4 treatment-independent response groups, ranging from non- to super-responders. This is an important finding and emphasizes the importance of subgroup analysis and the often large effect of placebo, as is further discussed in Chapters 4 and 5.

In **Chapter 3** a pharmacodynamic model was developed to quantify the magnitude and onset/offset times of a single capsaicin 8% patch in the treatment of painful diabetic peripheral neuropathy in 91 patients. In addition, a mixture model was applied to objectively match patterns in pain-associated behavior. The analysis allowed separation of a heterogeneous neuropathic pain population into homogenous subgroups with distinct behaviors in response to treatment with capsaicin. Four distinct subgroups were identified: (1) 3.3% of patients showed worsening of pain; (2) 31% showed no change in pain; (3) 32% showed a quick reduction in pain that reached a nadir in week-3, followed by a slow return towards baseline ($16 \pm 6\%$ pain reduction in week-12); and finally (4) 34% showed a quick reduction in pain that persisted ($70 \pm 5\%$ reduction in week-12). The response-onset half-life was such that every week the pain score reduced by 50% relative to the score of the previous week ($t_{1/2} \sim 1$ week). In contrast, the response-offset half-life was about 8 weeks (estimated from subjects in groups 2-4). It is argued that this model-based approach may have added value in analyzing longitudinal chronic pain data and allows optimization of treatment algorithms for patients suffering from chronic pain conditions. The small sample size of this study prevented association of specific predictors to the observed distinct responses. The detection of predictors would further enhance treatment selection and optimization.

In **Chapter 4** subgroup analysis (a combination of pharmacodynamic and mixture analyses) was followed by the estimation of significant predictors of response. Longitudinal data from 4 double-blind randomized controlled trials on the efficacy of topical capsaicin 8% (Qutenza, $n = 722$) *versus* an active control (capsaicin 0.04%, $n = 526$) were collected yielding a data set consisting of 1,248 subjects that provided 15,547 numeric pain rating scores (NPRS) over 12 weeks. Five distinct response subgroups were detected with different treatment efficacies: (1) a group with increase in pain response (1.5% Qutenza, 0.8% active control); (2) a group of non-responders (22.7% Qutenza, 39.1% active control); (3) a group showing an initial reduction in pain response with slow return towards baseline (24.7% Qutenza, 17.6% active control); (4) a group showing partial analgesic effect with a reduction in NPRS of 25-30% at week 12 (14.5% Qutenza, 14.3% active control) and finally (5) a group of super-responders showing large analgesic effect with a reduction in NPRS of 67-70% at week 12 (36.6% Qutenza showing 28.2% active control). Active control and Qutenza had similar response profiles but the proportional distribution of patients among the 5 response groups was in favor of Qutenza with 40% less non-responders and 25% more super-responders. For Qutenza important predictors of a super-response were age, duration of disease, concomitant opioid use, pretreatment pain score variability, baseline NPRS, and efficacy of lidocaine pretreatment. These analyses are a major advancement over previous analyses that yield predictors of response *per se* (*versus* non-response) whereas the current analysis allows specification of predictors of distinct response groups. Additionally our results (in terms of treatment effect and predictors) obtained from one treatment (Qutenza) in one disease (post-herpetic neuralgia) with presumably one underlying disease process suggest that pain mechanisms may differ among patients, that possibly require dissimilar treatment approaches. Finally, we observed a large placebo effect, part of which must be also inherent to the active treatment group.

Chapters 5 and 6 present data obtained from our laboratory on the effect of opioids on experimental pain models applied to healthy volunteers. **Chapter 5** deals with the antinociceptive profile of an orodispersible oxycodone tablet (OOT) compared to an active comparator (paracetamol orodispersible tablet, POT). The OOT is marketed for acute breakthrough pain when a rapid onset of analgesia is important. In a randomized, double blind, crossover study, twelve healthy volunteers received 20 mg OOT and 500 mg POT sublingually on two separate occasions. Three pain parameters were obtained at regular intervals for 5 hours: Electrical pain threshold (EPTh), electrical pain tolerance (EPTol) and pressure pain threshold (PPT). Time-response data were analyzed with a novel mathematical (pharmacodynamic) model of analgesia evolution that bears some

similarities with the models described in Chapters 2 to 4; no pharmacokinetic data were obtained in this study. Important observations were that paracetamol displayed 14% of the analgesic efficacy of oxycodone. For the OOT the population analysis revealed a 30% increase from baseline response at $t = 15$ min and $t = 41$ min (after drug intake) for EPTol and EPTh, respectively. For pressure pain a 30% increase from baseline was found at $t = 18$ min. We argue that the 30% increase in pain parameter values (onset of action) bears clinical significance albeit further studies are needed to validate this statement. The observed onset times ranging from 15 to 41 min do suggest a rather similar antinociceptive profile of OOT compared to conventional oral oxycodone. How OOT compares to other rapidly acting opioids such as intranasal fentanyl requires further study.

Another relatively new approach is the application of dynamic psychophysical tests as predictor of drug efficacy and to better understand the analgesic mechanism. One such test is Conditioned Pain Modulation (CPM), a biomarker of descending inhibition. CPM reduces the perception of pain from a primary test stimulus during application of a secondary stimulus, *ie.* the conditioning stimulus, according to the concept “pain inhibits pain”. Previous studies showed that chronic pain patients who are unable to activate CPM benefit most from medication that interacts with the endogenous pain modulatory system such as duloxetine and *vice versa* patients that have an active CPM have little analgesic benefit from these drugs. In **Chapter 6** the effects of the analgesics tapentadol (100 mg immediate release tablet), a combined μ -opioid receptor agonist and noradrenaline reuptake inhibitor, and morphine (40 mg immediate release tablet), a strong μ -opioid receptor agonist, were tested on CPM in a randomized, double-blind, placebo-controlled crossover trial in 12 healthy pain-free volunteers, to understand possible differences in mechanism of action between these opioids. CPM was detectable after treatment with placebo and tapentadol (peak pain ratings reduced by 20-30% after application of the conditioning stimulus) but not after morphine. Compared to placebo morphine displayed significantly less CPM. This indicates that in volunteers morphine negatively affects CPM, while tapentadol was without effect despite identical experimental conditions. These data confirm that tapentadol’s main mechanism of action is distinct from that of morphine and likely relates to the effect of adrenergic stimulation on descending control.

RESPONSE GROUPS

In chapter 3 we proposed the use of PD mixture models to identify response groups and separate the heterogeneous neuropathic pain population into responders and non-responders. Four distinct response groups were found for the DPN population (chapter 3), whereas five response groups were recognized in PHN patients (chapter 4). Subgroup 4 (a group of PHN patients showing partial analgesic effect with a reduction in NPRS of 25-30% at week 12) was lacking in DPN patients. In fact, the response to capsaicin treatment as observed at the end the trial in patients with DPN was dichotomous, with patients showing either no effect of treatment (subgroup 2 and 3) or a full analgesic effect (subgroup 4). These differences may relate to differences in the underlying disease process. DPN is regarded as a classical denervation neuropathy (long-term dying back of nerve fibers) whereas PHN is considered an inflammatory mediated 'dynamic' denervation neuropathy (consisting of partial nerve injury, post-nerve repair, denervation and nerve sprouting).¹ Since our findings (and those of others) suggest that, in contrast to patients with fully damaged peripheral nerves, patients with diseased but (partly) intact nerve fibers are likely responders to active treatment, questionnaires and quantitative sensory testing may hold predictive power as they are able to detect specific symptoms (such as the occurrence of allodynia or burning pain) related to the state of nerve damage.² Future studies should address this issue, focusing on the integrity of sensory nerve endings by means of immuno-histochemical analyses.^{3,4}

Published subgroup analyses have been restricted so far to DPN, PHN (treated with capsaicin, Chapters 3 and 4) and complex regional pain syndrome type 1 (CRPS 1, treated with ketamine, Chapter 2). In terms of the numbers the response groups in CRPS 1 patients were similar to those observed in DPN patients. In contrast to the comparison of DPN *versus* PHN, both treated with capsaicin (see above), comparison of DPN treated with capsaicin *versus* CRPS 1 treated with ketamine is difficult due to the use of two very distinct drugs (capsaicin acting at TRPV1 receptors *versus* ketamine acting at NMDA receptors) in two distinct chronic illnesses. Hence predictors of effect will differ between treatment of DPN with capsaicin and treatment of CRPS 1 with ketamine. I have to conclude that the use of treatment predictors in clinical practice is still rather premature. Treatment of one pain syndrome (*e.g.* DPN) with drugs with distinct mechanisms of action (*e.g.* opioids *versus* capsaicin *versus* ketamine *versus* GABAergic medication *versus* SSRI's *versus*) in large randomized trials will allow detection of predictors of a specific drug-related treatment response (*e.g.* super-response). For example, it might well be that such an analysis would find that the presence of burning pain predicts a high probability of falling into a super-responder group when being treated with capsaicin but not with

opioids. Alternatively, it might be that the presence of wind-up in the QST will result in a good response to ketamine. Evidently, further research on this topic is required. Possibly, data mining strategies in data sets from existing (published and non-published) clinical trials will allow such comparisons.

We defined the response groups by the course of the onset and offset of the pharmacodynamic response and observed presence of 4 to 5 subgroups in our analyses. However, the number of true response groups may be much larger and may not have been captured by our analysis in relatively small populations. Additionally, pain in chronic pain patients is not constant and this variability was not included in our analysis. Also the quality of the pain sensation and perception might differ over time with variations in symptomatology. Examples are patients that present with nightly allodynia and daytime burning pain (or the reverse) *versus* patients that have a constant tingling or electrical pain sensation. This is not readily caught in numerical ratings but may be addressed in questionnaires. The above suggests that variability in the pain response as pharmacodynamic end-point may yet be another item that deserves further study and that possibly will further improve the prediction of treatment effect.

Finally, it is important to realize that the response group analysis as performed in Chapters 3 and 4 is only possible when data points are collected over time (such as at 1 week intervals). Using just the end-of-study data point (one measurement at week 12) does not allow the pharmacodynamic or time-series analyses that were performed in chapters 2, 3 and 4. Consequently, when using just end-of-study data, only responders and non-responders are detected. This indicates that a proper study design with multiple measurement points during and following treatment is essential for the full understanding of the effect of a drug treatment in the study population; this regards detection of subgroups and predictors.

THE PLACEBO RESPONSE

As indicated above, the relative large confounding placebo response in randomized controlled trials is responsible for the lack of success of many studies in observing an effect of active treatment greater than placebo. Many studies have focused on understanding the large placebo response. Predictors include long treatment duration,⁵ type of neuropathic pain condition (DPN trials consistently show a higher placebo response compared to PHN trials),⁶ high variability in baseline pain scores,⁷ trials involving opioids as active treatment, a high number of face-to face visits and randomization ratio.⁸ Some

of these factors clearly enhance patients expectation (*e.g.* treatment duration, face-to-face visits). These findings relate to the example I gave earlier in this chapter. It is possible that any of these factors may have caused a large placebo response in this one “non-informative” center mentioned above. It is our understanding that increasing experience in performing pain trials and training of personnel will be highly effective in reducing the placebo response.

Clearly, the general term “placebo response” should be separated into a more genuine psychosocial and physiological “placebo effect” and “placebo *related* behaviors” such as spontaneous remission of disease, regression to the mean and natural waxing and waning of an illness.⁹⁻¹¹ A means to do so is to introduce a no-treatment control (NTC) arm in RCT design.¹² An NTC arm (also referred to as the “waiting list”) is defined as an arm of a RCT in which randomly allocated subjects receive no treatment or intervention and in which subjects are only observed during the time of the trial. By doing so, predictive factors for the true placebo effect and mechanistic pathways that mediate the placebo (or nocebo, an occurrence that is opposite to placebo) effect may be identified. Current known pathways of placebo effect in chronic pain conditions include endogenous analgesic mechanisms with endogenous opioid and dopaminergic involvement.¹²⁻¹⁵ Mechanisms for the nocebo effect include activation of cholecystokinin and deactivation of dopamine pathways.¹⁶⁻¹⁸

It is important to realize that the data presented in Chapter 4 were obtained from more than 160 recruitment centers. Some of these centers may be more informative than others, *i.e.* some centers effectively separate placebo response from active treatment response, while other find large placebo effects often not very different from the response to active treatment. Merlo-Pich et al.^{19,20} reviewed data from multicenter trials on the efficacy of antidepressants in patients with major depressive disorder. They applied a *post-hoc* enrichment filter that reduced between-center heterogeneity by excluding those centers that have a placebo response that equals or exceeds the response to active treatment. Such a filter could easily be applied to the current data set, not to inflate the response to active treatment but rather to assess which predictors are specific to placebo or to active treatment response efficacy. I speculate that baseline pain variability is a predictor of a large placebo response but not of a large response to active treatment.

FUTURE PERSPECTIVES: WHAT TO MEASURE, HOW TO MEASURE

The pharmacological effect of analgesics is dependent on various complex and interacting factors. These factors can be subdivided into substance, subject and disease related. Examples of substance related factors include pharmacokinetic-associated variables such as equilibrium delay between plasma and biophase concentrations, receptor association/dissociation kinetics and delay between receptor occupancy and onset of subsequent analgesic effect. Subject related factors may consist of age, sex, weight, duration of disease, severity of pain symptoms and comorbidity. We already know from clinical practice that some individuals do not respond to opioid treatment. We confirmed this in Chapter 5 showing that 20% of subjects did not respond to oxycodone in several nociceptive models. We relate the later to pharmacogenetic factors, probably due to reduced activity of the CYP2D6 enzyme, which causes less production of oxycodone's active metabolite oxymorphone. Indeed inter-individual variability in pharmacokinetics is a well-known phenomenon.^{21,22} However, also variability in pharmacodynamics should be considered.²³⁻²⁵ Population-based PK-PD models in conjunction with pharmacogenetics (PG) are important tools to describe and predict the analgesic effect and the interaction of specific pharmacological agents within the often complex disease states. Future developments may make the use PK-PD-PG analyses easier to apply in pain trials and possibly even in clinical pain patients.

In the near future various advances in pain measurement and evaluation of therapy are foreseen. The use of questionnaires, such as the 'Patient Reported Outcomes' (PRO) or painDETECT questionnaires,²⁶ allows detection and quantification of sensory neuropathic symptoms. The association between pain symptoms and treatment response may be used to further elucidate pathophysiological mechanisms of disease and identify novel drug targets. Moreover, QST enables the mapping of different sensory patterns in neuropathic pain syndromes. Analysis of these profiles may allow a distinction between responders and non-responders to specific treatments. Additionally, the application of dynamic psychophysical tests, such as Conditioned Pain Modulation (CPM) or Offset Analgesia (OA), may predict which patients benefit most from medication that interacts with the endogenous pain modulatory system (chapter 6). Until recently, large and complex experimental devices were needed to test CPM and OA. Recently, new devices were introduced on the market that allow rapid and reliable assessment of CPM and OA

in the clinical setting. One example is Medoc's Qsense CPM device, a mobile system built to test CPM and additionally allows assessment of a large part of the QST battery. The use of such systems by pain clinicians in the ambulatory setting will allow a choice of medication based on the presence or absence of CPM. For example in chapter 1 I showed that DPN patients with inactive CPM benefit from tapentadol (a combined opioid and noradrenaline reuptake inhibitor, see chapter 6) while patients with active CPM do not. Finally, novel techniques such as cornea confocal microscopy,^{27,28} identifying small fiber disease in the cornea and point-of-care sural nerve conduction test,²⁹ identifying large nerve disease, hold promises for the detection of painful neuropathic disease and its resolve during treatment.

CONCLUSIONS

From the data presented in this thesis several conclusions can be formulated:

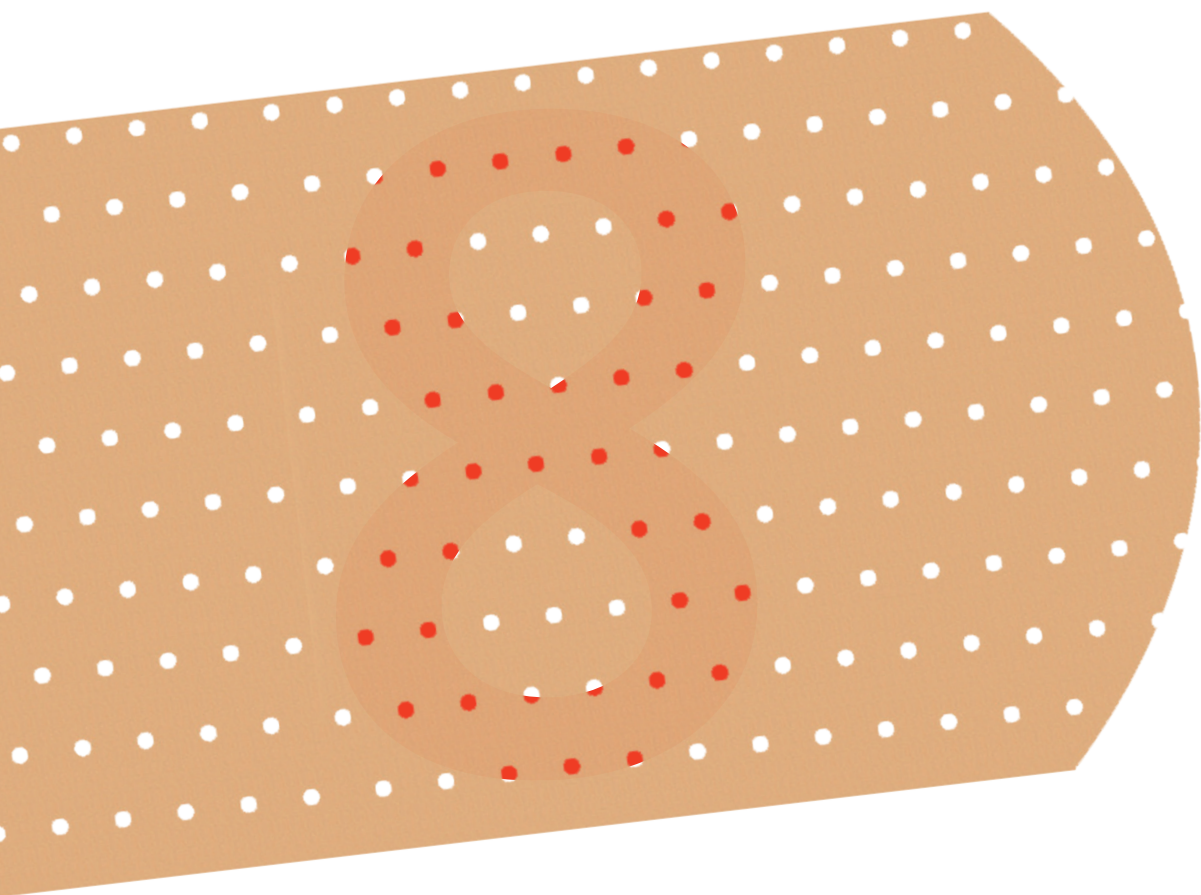
1. Longitudinal pharmacodynamic modeling can be used to describe the antinociceptive/analgesic time course of analgesic medication. This approach yields more information than traditional assessment of treatment effect at specific endpoints at preset times.
2. Mixture modeling analysis allows separation of a heterogeneous pain population into homogenous subgroups with distinct behaviors in response to analgesic treatment.
3. Covariate analysis within different distinct response subgroups may identify important predictors of treatment effect. This will eventually allow optimization of individual pain therapy with specific predictors linked to specific pharmacotherapies.
4. The onset of action of an analgesic compound may be quantified by a longitudinal pharmacodynamic model from sparse data sets without the need of PK sampling.
5. In future, the application of dynamic psychophysical tests, such as Conditioned Pain Modulation – a marker of descending pain inhibition – may be used as a predictor of drug efficacy.

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Chapter 8

**Algemene discussie, samenvatting
en conclusies**

Het ontwikkelen van nieuwe, effectieve en veilige pijnstillers voor de behandeling van chronische pijn is een uitdagend, tijdrovend en kostbaar proces. Onderzoekers zijn aangewezen op grote multicenter studies, aangezien er een grote variatie bestaat in farmacologische respons op behandeling. Zowel de intra- als inter-subject variabiliteit is groot, waarbij deze kan verschillen tussen de behandelcentra. Deze variatie is niet alleen van toepassing op het effect van het nieuw te ontwikkelen actieve middel, maar ook op de placebo behandeling. Veel fase III studies, zelfs de grotere, slagen er niet in een voordeel van nieuwe pijnstillers aan te tonen door de grootte van dit placebo effect. Een voorbeeld hiervan betreft een recente studie die zowel in onze instelling als in een ander centrum is uitgevoerd (ongepubliceerde data). Het pijnstillend vermogen van een nieuw medicijn werd getest in chronische pijnpatiënten door gebruik te maken van een placebo gecontroleerd, dubbelblind, gerandomiseerd design. Gemiddeld genomen had het nieuwe middel een pijnstillend effect, maar niet meer dan in de placebo groep. Er was echter een opvallend verschil in behandel-effect van het actieve middel en de placebo pijnstiller *tussen* de beide centra. Het ene centrum had een laag placebo effect en groot actief behandel-effect (dit centrum werd geclassificeerd als informatief centrum), terwijl het omgekeerde het geval was voor het andere centrum (een non-informatief centrum). Een verklaring voor dit verschil kan liggen in de ervaring met het doen van pijnonderzoek en de training van de medewerkers, maar er was nog een belangrijke bevinding. De patiënten in het non-informatieve centrum hadden allen een verhoogde body mass index (BMI), wat zowel de farmacokinetiek als de farmacodynamiek kan hebben beïnvloed. Daarnaast is aangetoond dat kleine perifere zenuwen in obese patiënten minder actief zijn dan in de normale populatie met een hogere prikkel detectiegraad en hogere pijndrempel. Dit kan van belang zijn voor studies die de functie van intacte zenuwen bestuderen door gebruik te maken van quantitative sensory testing (QST), een testbatterij van 7 testen met 13 variabelen. Afgezien van de onderliggende oorzaak voor het verschil in behandeluitkomst, illustreert dit voorbeeld goed hoe lastig pijnonderzoek in het algemeen - en multicenter pijnonderzoek in het bijzonder - kan zijn. Hoewel de nadere grondoorzaken nog onderzocht moeten worden, zal behalve patiënt gerelateerde factoren ook zeker de onderzoekskwaliteit van de instelling een mogelijke rol hebben gespeeld. Toekomstige oplossingen liggen in het standaardiseren van patiënten (bv. alleen patiënten met een normaal tot licht verhoogd BMI includeren), het toepassen van verrijkingstechnieken (waarbij placebo responders worden geëxcludeerd) en gebruik maken van informatieve of 'high quality' centra. Dit zal zeker het behandel-effect van het actieve middel in fase III studies ten goede komen. Echter, in het werkelijke leven zijn deze exclusies niet toegestaan. Patiënten en artsen in de behandelkamer profiteren niet van deze aanpak, aangezien van tevoren niet voorspeld kan worden wie wel en wie niet op

de voorgestelde behandeling gunstig zal reageren. Daarom is het van belang deze fase III studies te gebruiken om voorspellende factoren te destilleren voor behandeluitkomst van zowel het actieve als het placebo middel. Dit was ook het doel van het onderzoek zoals beschreven in dit proefschrift waarbij nieuwe analyse technieken zijn toegepast om niet alleen de grootte van het behandel-effect te beschrijven maar ook te *voorspellen*. Er is zowel gebruik gemaakt van bestaande datasets (hoofdstuk 3 en 4) als van nieuwe data verkregen uit studies in ons eigen pijnlaboratorium naar opiaten en experimentele pijntesten in gezonde vrijwilligers (hoofdstuk 5 en 6). De drie belangrijkste bevindingen van mijn proefschrift zijn dat: i) er meerdere responder subgroepen bestaan in pijnstillend effect in plaats van alleen responders en non-responders, ii) het belangrijk is om meerdere data punten van pijnstilling in de tijd te verzamelen in plaats van alleen na een vooraf gedefinieerde einddatum (bv. na 12 weken) en iii) voorspellers van pijnstilling (en placebo) verschillen in de responsgroepen en studiecentra. De bevindingen zouden moeten leiden tot een verrijkingstechniek voor toekomstige fase III studies. Momenteel wordt deze techniek zoals voorgesteld in hoofdstuk 4 al door diverse internationale regulerende instanties toegepast.

In dit laatste hoofdstuk wordt een samenvatting gegeven van de observaties uit de eerder gepresenteerde studies. Daarna volgt een discussie over de belangrijkste thema's van dit proefschrift: responsgroep analyse en placeborespons. Tot slot worden mogelijke toekomstperspectieven geschetst en conclusies geformuleerd.

SAMENVATTING

In **hoofdstuk 2** wordt een overzicht gegeven van de recente literatuur over farmacokinetisch (FK) en farmacodynamisch (FD) onderzoek in acute en chronische pijn. In deze review worden nieuwe bevindingen over opiaten, NSAIDs, epiduraal analgesie, ketamine en medicijnen aangrijpend op de GABA receptor toegelicht. Verschillende wiskundige modellen worden behandeld die het dynamische tijdsverloop van een pijnstillert kunnen beschrijven en/of voorspellen en een brug slaan tussen FK en FD. *Populatie* FK-FD modellen maken het mogelijk om – naast het kwantificeren van de zogeheten fixed effects (de vaste FK-FD model parameter waarden) ook een inschatting te geven van de zogeheten random effects: de intra- en interindividuele variabiliteit. *Effect compartiment en mechanistische biophase distributie* modellen passen medicamenteuze associatie en dissociatie kinetiek toe en geven hiermee inzicht in de snelheid beperkende factoren in medicatie effect, zoals verdelingssnelheid en receptor kinetiek. Het is een gebruikelijke

techniek om de complexe eigenschappen van sommige middelen te doorgronden, met name het optreden en behandelen van bijwerkingen. Een andere toepassing in chronische pijn studies is het gebruik van *mixture* modellen. Mixture modellen maken het mogelijk om specifieke subgroepen te identificeren. Wanneer mixture en FK-FD modellen worden gecombineerd, kan dit een sterke verbetering geven van het huidige therapeutische arsenaal op het gebied van doseringsschema, effectiviteit, het mechanisme achter het effect van pijnstillers binnen bekende complexe chronische pijnsyndromen en kan dit nieuw pijnonderzoek stimuleren. Een voorbeeld hiervan is het effect van een 100-uur durende infusie van ketamine voor patiënten met het Complex Regionaal Pijn Syndroom type 1 (CRPS type 1). Met behulp van mixture modellering werden 4 onafhankelijke responsgroepen geïdentificeerd, variërend van non-responders tot super-responders. Dit is een belangrijke bevinding en onderstreept het belang van subgroep analyse en het dikwijls relatief grote placebo effect, zoals verder wordt behandeld in hoofdstuk 4 en 5.

In **hoofdstuk 3** werd een farmacodynamisch model opgesteld om de mate van pijnstilling en snelheid van in- en uitwerken te bepalen van een capsacine 8% pleister voor de behandeling van diabetische perifere neuropathie (DPN) in 91 patiënten. Daarnaast werd een mixture model toegepast om subgroepen te onderscheiden. Vier specifieke subgroepen werden onderscheiden: (1) 3,3% van de patiënten vertoonde verergering van pijnklachten; (2) 31% had geen verandering van pijnklachten; (3) 32% toonde een snelle afname van pijnklachten met een maximale afname na drie weken waarna de pijn terugkeerde naar uitgangsniveau ($16 \pm 6\%$ pijnafname in week 12); (4) 34% had een snelle afname van pijnklachten die aanhield ($70 \pm 5\%$ afname in week 12). De inwerk halfwaardetijd was zodanig dat iedere week de pijnscores afnamen met 50% ten opzichte van de week ervoor ($t_{1/2} \approx 1$ week). De uitwerk halfwaardetijd was ongeveer 8 weken (op basis van respons profielen van patiënten in groepen 2-4). Deze modelmatige aanpak biedt extra voordelen ten opzichte van de reguliere analyses (zoals bv. afname van 30% of 50% van de pijnklachten ten opzichte van uitgangsniveau) en kan de behandelduur en interval tussen behandelingen optimaliseren voor de verschillende subgroepen. Door de relatief kleine onderzoekspopulatie was het niet mogelijk voorspellende covariaten te onderscheiden. Deze covariaten analyse wordt verder uitgediept in hoofdstuk 4.

In **hoofdstuk 4** wordt dieper ingegaan op subgroep analyse (door gebruik te maken van farmacodynamische en mixture modellen) en voorspellende factoren voor behandel-effect. Longitudinale pijndata van vier dubbelblinde, gerandomiseerde, placebo gecontroleerde studies naar het effect van capsacine 8% (Qutenza, $n = 722$) en actief placebo (capsacine 0.04%), $n = 526$) werden samengevoegd. In totaal werden 1248

patiënten geïncludeerd die 15.547 pijnscores gedurende 12 weken aanleverden. Vijf verschillende respons subgroepen werden onderscheiden: 1) een groep met pijntoename (1,5% Qutenza, 0,8% actief placebo); 2) een groep van non-responders (22,7% Qutenza, 39,1% actief placebo); 3) een groep met initieel een pijnafname met geleidelijk terugkeer naar uitgangsniveau (24,7% Qutenza, 17,6% actief placebo); 4) een groep met gedeeltelijke pijnafname tot 25-30% in week 12 (14,5% Qutenza, 14,3% actief placebo) en 5) super-responders met een groot pijnstillend effect van 67-70% in week 12 (36,6% Qutenza, 28,2% actief placebo). Actief placebo en Qutenza toonden vergelijkbare respons profielen maar de verdeling over deze profielen was in het voordeel van Qutenza met 40% minder non-responders en 25% meer super-responders. In de Qutenza super-responder groep waren belangrijke voorspellers van behandeling: leeftijd, ziekteduur, gelijktijdig gebruik van opiaten, uitgangsvariabiliteit in pijnscores, uitgangspijnscore en effectiviteit van voorbehandeling met lidocaïne. Deze studieopzet maakt het mogelijk voorspellende factoren per subgroep te identificeren in plaats van alleen in responders in de *totale* studiepopulatie. Daarnaast laten de resultaten van één behandeling (Qutenza), in één aandoening (post-herpetische neuralgie) met waarschijnlijk één onderliggend ziekteproces zien dat pijnmechanismes kunnen verschillen tussen patiënten en dat mogelijk verschillende behandelstrategieën noodzakelijk zijn. Tot slot was er sprake van een groot placebo effect wat ook zichtbaar was in de actieve behandeling groep.

Hoofdstuk 5 en 6 tonen data uit ons eigen pijnlaboratorium naar het effect van opiaten op experimentele pijnmodellen in gezonde vrijwilligers. **Hoofdstuk 5** beschrijft het anti-nociceptieve profiel van oxycodon zuigtablet (OZT) in vergelijking met een actief placebo (paracetamol zuigtablet, PZT). OZT is geregistreerd voor de behandeling van acute doorbraakpijn wanneer een snelle intrede van pijnstilling noodzakelijk is. In een gerandomiseerde, dubbelblinde, cross-over studie kregen 12 gezonde vrijwilligers 20 mg OZT en 500 mg PZT toegediend. Drie verschillende pijntesten werden gedurende 5 uur op vaste tijden verricht: elektrische pijndrempel (EPD), elektrische pijntolerantie (EPT) en drukpijndrempel (DPD). Beloop van pijnstilling in de tijd werd geanalyseerd met een nieuw wiskundig (farmacodynamisch) model wat enige gelijkenis vertoont met de modellen zoals gebruikt in hoofdstuk 2 t/m 4. Er werden geen farmacokinetische data gebruikt. Belangrijke uitkomsten waren dat paracetamol 14% van het analgetisch effect van oxycodon bezit. OZT liet een 30% toename in EPD en EPT zien op respectievelijk $t = 15$ min en $t = 41$ min na inname. Voor DPD werd 18 min na inname een 30% toename gevonden. Een 30% toename wordt als mogelijk klinisch significant beschouwd, hoewel toekomstige studies dit verder moeten valideren. Met een inwerktijd van 15 tot 41 min lijkt OZT een vergelijkbaar analgetisch profiel te vertonen als conventionele orale oxycodon.

Hoe OZT zich verhoudt tot andere snelwerkende opiaten zoals intranasale toediening van fentanyl dient toekomstig onderzoek uit te wijzen.

Relatief nieuw in de pijngeneeskunde is het toepassen van experimentele pijntesten als voorspeller van pijnstillend effect en om het onderliggend analgetisch mechanisme beter te doorgronden. Een voorbeeld van een dergelijke test is Conditioned Pain Modulation (CPM), een maat voor endogene inhibitie van afferente input. CPM vermindert de pijnvaring van een primaire test stimulus gedurende de toepassing van een secundaire stimulus, de zogeheten conditionele stimulus, volgens het concept 'pijn vermindert pijn'. Eerdere studies toonden aan dat chronische pijnpatiënten met een inactieve CPM het meest profiteren van medicatie die het endogene modulatoire pijnsysteem activeert zoals duloxetine. Het omgekeerde is waar voor patiënten die reeds een actieve CPM hebben. In **hoofdstuk 6** worden het effect van tapentadol (100 mg immediate release tablet, een gecombineerde mu-opiaat receptor agonist en noradrenaline reuptake inhibitor) en morfine (40 mg immediate release tablet) op CPM onderzocht in een gerandomiseerde, dubbelblinde, placebo gecontroleerde studie in 12 gezonde proefpersonen om een verschil in werkingsmechanisme tussen beide opiaten vast te stellen. CPM kon worden vastgesteld na behandeling met placebo en tapentadol (piek pijnscores waren 20-30% lager na toediening van de conditionele stimulus), maar niet na behandeling met morfine. Vergeleken met placebo gaf morfine significant minder CPM. Dit toont aan dat in vrijwilligers morfine CPM vermindert, terwijl tapentadol onder gelijke condities dit effect niet laat zien. Deze data bevestigt dat het belangrijkste werkingsmechanisme van tapentadol verschilt van morfine en zeer waarschijnlijk gerelateerd is aan het noradrenerge effect op endogene inhibitie van pijnstimuli.

RESPONGROEPEN

In hoofdstuk 3 toonden wij aan dat met behulp van FD mixture modellen het mogelijk is responsgroepen te identificeren in een heterogene neuropathische pijnpopulatie en zo responders van non-responders te scheiden. Vier verschillende responsgroepen werden gevonden voor de DPN populatie (hoofdstuk 3) en vijf groepen voor PHN patiënten (hoofdstuk 4). Subgroep 4 (een groep van PHN patiënten met een partieel pijnstillend effect van 25-30% afname ten opzichte van de uitgangssituatie) ontbrak in de DPN populatie. De respons op capsäicine behandeling in DPN patiënten was min of meer dichotoom, met ofwel geen effect van behandeling (subgroep 2 en 3), danwel een groot pijnstillend effect (subgroep 4). Dit verschil kan verklaard worden door het onderliggende

ziekteproces. DPN wordt beschouwd als een klassieke denervatie neuropathie (waarbij zenuwen gedurende een lange periode langzaam afsterven), terwijl PHN valt onder inflammatie gemedieerde 'dynamische' denervatie neuropathieën (met gedeeltelijke schade en partieel herstel van zenuwen, terugtrekken van oude en aangroei van nieuwe zenuwvezels).¹ Aangezien onze bevindingen (en die van anderen) suggereren dat patiënten met gedeeltelijke zenuwschade in tegenstelling tot patiënten met volledig aangedane zenuwen het meest profiteren van behandeling met capsaïcine, kunnen vragenlijsten en QST een voorspellend vermogen voor behandelings-effect bezitten, aangezien hiermee specifieke symptomen voor zenuwschade kunnen worden aangetoond (zoals allodynie en brandende pijn).² Toekomstige studies moeten dit verder onderzoeken, waarbij met name aandacht besteed dient te worden aan de integriteit van de zenuwuiteinden door middel van immunohistochemische analyses.^{3,4}

Reeds gepubliceerde subgroep analyses zijn tot op heden verricht in DPN, PHN (behandeld met capsaïcine, hoofdstuk 3 en 4) en CRPS type 1 (behandeld met ketamine, hoofdstuk 2). Voor wat betreft de aantallen lijken de responsgroepen in CRPS type 1 sterk op die in DPN. In tegenstelling tot de vergelijking tussen DPN en PHN, die beide behandeld zijn met capsaïcine, is het vergelijken van DPN (behandeld met capsaïcine werkend op de TRPV1 receptor) met CRPS 1 (behandeld met ketamine aangrijpend op de NMDA receptor) lastig aangezien het om twee verschillende middelen in twee verschillende aandoeningen gaat. Daardoor zullen voorspellers van effect verschillen tussen beide behandelingen. Tot slot moet worden opgemerkt dat het gebruik van voorspellers van effect nog erg ongebruikelijk is in de klinische praktijk. Grote gerandomiseerde studies zullen moeten aantonen of de behandeling van een pijnsyndroom (bv. DPN) met verschillende werkzame medicijnen (zoals opiaten, capsaïcine, ketamine, GABA-agonisten, SSRI's, etc.) een middel-afhankelijke voorspeller van effect (bv. met relatief veel super-responders) kan opleveren. Het kan bijvoorbeeld zijn dat de aanwezigheid van brandende pijn een voorspeller is van een succesvolle respons op behandeling met capsaïcine maar niet met opiaten. Of dat de aanwezigheid van het wind-up fenomeen in de QST een goede respons op ketamine voorspelt. Meer onderzoek hiernaar is noodzakelijk, bijvoorbeeld door gebruik te maken van patroonanalyse in datasets van bestaande (gepubliceerde en niet-gepubliceerde), grote klinische studies.

Responsgroepen werden door ons gedefinieerd op basis van het inwerk- en uitwerkpatroon van de farmacodynamische respons. Hiermee werden 4 tot 5 subgroepen aangetoond. Het kan echter zijn dat de werkelijke hoeveelheid subgroepen veel groter is en nog onontdekt is in onze relatief kleine onderzoekspopulatie. Daarnaast is de mate

van pijn in chronische pijnpatiënten niet constant in de tijd en deze natuurlijke variatie is niet meegenomen in onze analyses. Voorbeelden hiervan zijn patiënten die nachtelijke allodynie vertonen en overdag brandende pijn (of andersom) of patiënten die continu wisselend een tintelend of elektrisch prikkelend gevoel ervaren. Deze variabiliteit en kwalitatieve beschrijving van pijn komt niet goed tot uitdrukking in numerieke waarden maar kan beter door middel van vragenlijsten worden gescoord. De mate van variabiliteit kan een mogelijke voorspeller van behandel-effect zijn en verdient verdere aandacht in toekomstige farmacodynamische studies.

Tot slot moet worden opgemerkt dat responsgroep analyse (zoals beschreven in hoofdstuk 3 en 4) alleen mogelijk is wanneer meerdere datapunten in de tijd verzameld worden (zoals pijnscores met wekelijkse intervallen). Wanneer alleen de scores aan het eind van de behandeling worden meegenomen (1 meting aan het eind van de 12 weken behandelperiode), is farmacodynamische analyse zoals beschreven in hoofdstuk 2, 3 en 4 niet mogelijk. Met een dergelijke studieopzet is het alleen mogelijk om te spreken over algemene responders en non-responders. Een studieopzet daarentegen met longitudinale data is essentieel om het werkelijke behandel-effect in de gehele populatie te doorgronden, inclusief subgroepen en voorspellers van effect.

DE PLACEBO RESPONS

Zoals eerder beschreven is de relatief grote bijdrage van het placebo effect in veel gerandomiseerde studies verantwoordelijk voor het niet kunnen aantonen van een voordeel van actieve behandeling boven placebo. Veel studies probeerden een verklaring te geven voor deze grote placebo respons. Voorspellers zijn onder andere lange behandeluur,⁵ type neuropathische pijn-aandoening (DPN studies laten aanzienlijk vaker een grote placebo respons zien dan PHN studies),⁶ hoge variabiliteit in uitgangspijnscore,⁷ studies naar opiaten,⁸ veel contactmomenten en randomisatie verhouding (hoe meer patiënten in de actieve behandelgroep ten opzichte van placebo, hoe kleiner de placebo respons).⁸ Sommige van deze factoren beïnvloeden het verwachtingspatroon (zoals behandeluur en contactmomenten). Mogelijk hebben een of meerdere van deze factoren een rol gespeeld bij het eerder genoemde onderzoek met informatieve en non-informatieve centra. Wij zijn van mening dat een grondige training van medewerkers en ruime ervaring in het doen van pijnonderzoek hoogst effectief zijn in het verminderen van het placebo effect.

De algemene term ‘placebo respons’ zou gescheiden moeten worden in een psychosociaal en fysiologisch ‘placebo effect’ en ‘placebo *gerelateerd* gedrag’ zoals regressie naar het gemiddelde en het natuurlijk fluctuerend beloop en spontaan herstel van ziekte.⁹⁻¹¹ Een methode om dit bereiken is het introduceren van een no-treatment controle (NTC) groep in gerandomiseerde placebo gecontroleerde studies. Een NTC groep (ook wel de ‘wachtgroep’ genoemd) is gedefinieerd als een groep waarin willekeurig toegewezen proefpersonen geen behandeling of interventie krijgen en waarin personen alleen worden geobserveerd in de tijd. Hierdoor kunnen voorspellende factoren voor het werkelijke placebo effect en mechanismen achter het placebo (of nocebo, het tegenovergestelde van placebo) effect worden vastgesteld. Huidige bekende mechanismen van het placebo effect in chronische pijnandoeningen zijn endogene pijnstillers met opioïde en dopaminerge betrokkenheid.¹²⁻¹⁵ Mechanismen achter het nocebo effect zijn activatie van cholecystokinines en deactivatie van dopaminerge aangrijpingspunten.¹⁶⁻¹⁸

Het is belangrijk om te beseffen dat de data uit hoofdstuk 4 is verkregen uit meer dan 160 onderzoekscentra. Sommige van deze centra zijn informatiever dan andere. Sommige centra zijn in staat de placebo respons te scheiden van actieve behandeling, terwijl andere een relatief grote bijdrage van de placebo behandeling vinden welke niet significant verschilt van actieve behandeling. Merlo-Pich et al. hebben data geanalyseerd van multicenter studies over de effectiviteit van antidepressiva bij mensen met ernstige depressies.^{19,20} Zij hebben *post-hoc* een verrijkingsfilter toegepast waarbij centra werden geëxcludeerd met een placebo effect dat groter of gelijk aan behandelings-effect was. Een dergelijk filter zou gemakkelijk kunnen worden toegepast op de huidige dataset, niet om het behandelings-effect te vergroten maar om voorspellers van effect van placebo en van actieve behandeling aan te wijzen. Het zou goed kunnen zijn dat sommige van de eerder gevonden variabelen, zoals uitgangsvariabiliteit in pijnscore, meer een voorspeller is van placebo dan van actieve behandeling.

TOEKOMSTPERSPECTIEVEN: WAT TE METEN, HOE TE METEN?

Het farmacologische effect van pijnstillers is afhankelijk van verschillende complexe en samenhangende factoren. Deze factoren kunnen worden onderverdeeld in middel, patiënt en ziekte gerelateerd. Voorbeelden van middel gerelateerde factoren zijn farmacokinetische variabelen, zoals de tijd om een evenwicht in te stellen tussen plasma en plaats het middel werkzaam is, receptor kinetiek en tijd na receptorbinding tot daadwerkelijk pijnstillend effect. Patiëntgebonden factoren zijn bijvoorbeeld leeftijd,

geslacht, gewicht, ziekte duur, ernst van de pijnklachten en comorbiditeit. Vanuit de kliniek is bekend dat sommige personen niet op behandeling met opiaten reageren. Dit werd herbevestigd in hoofdstuk 6 waarbij 20% van de proefpersonen geen reactie op oxycodon liet zien in verschillende pijnmodellen. Wij denken dat dit veroorzaakt wordt door farmacogenetische (FG) eigenschappen, zoals verminderde activiteit van het CYP2D6 enzym wat minder productie geeft van oxycodon's actieve metaboliet oxymorfon. Grote inter-individuele variabiliteit in farmacokinetiek is een bekend fenomeen.^{21,22} Echter, ook de variabiliteit in farmacodynamiek moet in ogenschouw worden genomen.²³⁻²⁵ Populatie FK-FD modellen in combinatie met farmacogenetica zijn belangrijke middelen om het effect en de interactie van medicijnen binnen complexe ziektebeelden te beschrijven en te voorspellen. Toekomstige ontwikkelingen maken wellicht het gebruik van FK-FD-FG analyses gemakkelijker toe te passen in pijnstudies en misschien zelfs in klinische pijnpatiënten.

In de nabije toekomst is vooruitgang te verwachten op het gebied van pijnmetingen en beoordelen van pijntherapie. Het gebruik van vragenlijsten zoals de 'Patient Reported Outcomes' (PRO) of de painDETECT maken het mogelijk op grote schaal neuropathische pijnsymptomen te identificeren en kwalitatief te beschrijven.²⁶ De relatie tussen pijnsymptomen en behandelrespons kan gebruikt worden om pathofysiologische mechanismen bloot te leggen en aangrijpingspunten voor nieuwe medicijnen te introduceren. Daarnaast zal het gebruik van QST het mogelijk maken patronen in pijnsymptomen in diverse chronische pijnandoeningen te herkennen. Met behulp van deze patronen kan een eerste aanzet gegeven worden responders van non-responders te voorspellen. Daarnaast kan het toepassen van psychofysische testen zoals CPM en offset analgesia (OA) mogelijk voorspellen welke patiënten het meest profiteren van medicatie die aangrijpt op het endogene modulatorische pijnsysteem (hoofdstuk 6). Tot vrij recent waren grote en logge apparaten nodig om CPM en OA te testen. Tegenwoordig zijn kleinere apparaten op de markt verschenen die snel en betrouwbaar in de klinische setting CPM en OA kunnen beoordelen. Een voorbeeld hiervan is Medoc's Qsense CPM, een mobiel systeem wat naast CPM ook een groot deel van de QST batterij kan testen. Het gebruik van een dergelijk apparaat op de pijnpoli maakt een keuze mogelijk tussen verschillende medicatie afhankelijk van de aan- of afwezigheid van CPM. Bijvoorbeeld, in hoofdstuk 1 werd aangetoond dat DPN patiënten met een inactieve CPM baat hebben van tapentadol (een gecombineerde opiaat en noradrenaline reuptake inhibitor, zie hoofdstuk 6), terwijl dit niet het geval is bij een actieve CPM. Tot slot zijn nieuwe diagnostische technieken, zoals cornea confocal microscopy,^{27,28} die kleine zenuwvezel aandoeningen aantoon, en de point-of-care suralis zenuw geleidingstest,²⁹ die grote zenuwvezel

aandoeningen aantoont, veelbelovend voor het aantonen van zenuwaandoeningen en voor het vervolgen gedurende behandeling.

CONCLUSIES

Uit de data gepresenteerd in dit proefschrift kunnen de volgende conclusies worden getrokken:

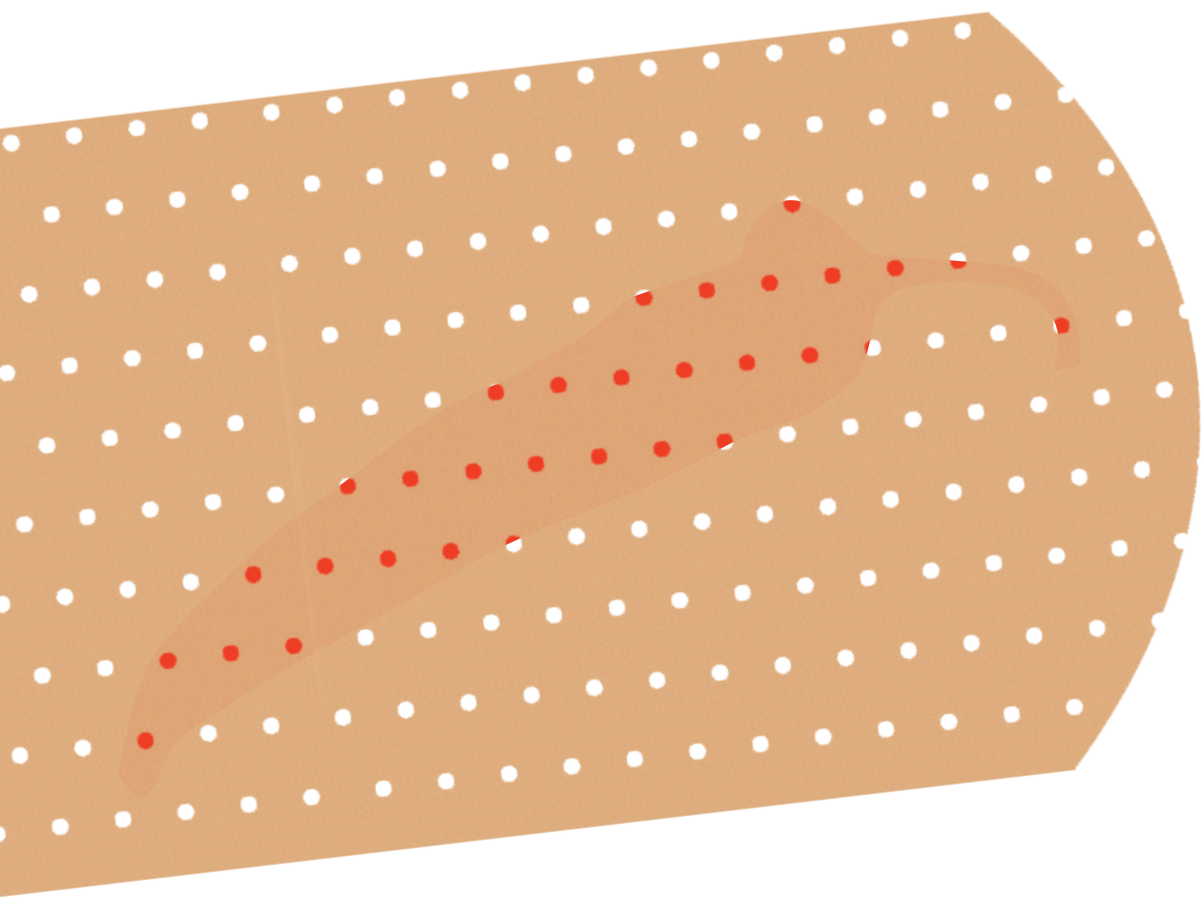
1. Longitudinale farmacodynamische modellen kunnen worden gebruikt om het anti-nociceptieve/analgetisch tijdbeloop van pijnstillers te beschrijven. Deze aanpak geeft meer informatie dan de tot nu toe gebruikelijke beoordeling van behandel-effect op een tevoren vastgesteld moment in de tijd.
2. Mixture modellen maken het mogelijk een heterogene pijnpopulatie te scheiden in homogene subgroepen met elk een eigen respons op pijnbehandeling.
3. Covariaten analyse binnen de verschillende subgroepen maakt het mogelijk voorspellers van behandeling te identificeren. Dit kan uiteindelijk een geoptimaliseerd individueel behandelprofiel opleveren met voorspellers voor iedere medicamenteuze therapie.
4. De snelheid van inwerken van een pijnstiller kan worden beschreven middels een longitudinaal farmacodynamisch model met beperkte datapunten zonder de noodzaak van FK samplen.
5. In de toekomst kan het toepassen van experimentele pijntesten, zoals CPM, als maat voor endogene inhibitie van afferente input, gebruikt worden om medicatie effect te voorspellen.

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Addenda

Curriculum Vitae

List of publications

CURRICULUM VITAE

Christian Martini was born on the 13th of January 1980 in Rotterdam, the Netherlands. He attended the Stedelijk Gymnasium Leiden and obtained his VWO degree in June 1998 (cum laude). He was immediately admitted to University College Utrecht (international Honours College of Utrecht University) for one year following a pre-medical major program. One year later he started his medical studies at the Leiden University Medical Center (LUMC), during which he deployed several extra-curricular activities.

In 2000 he participated in the setup of an exchange program for undergraduate students with the Karolinska Institutet, Stockholm, Sweden. One year later he became member of the board of the medical students association (M.F.L.S.), where he was involved in finance and sponsor acquisition. He led a curriculum exploration at Harvard Medical School, Boston, USA (2002) and in the same year he attended the Honours Class programme of the LUMC “Marktwerking en gezondheidszorg”. In 2003 he was elected for a position in the students council and worked as assistant co-ordinator at the International Office for undergraduate students.

During his studies he performed a research project at the department of Clinical Epidemiology, LUMC, (Prof. dr. F.R. Rosendaal) on the role of genetic variants in the TAFI gene on the development of venous thrombosis. As a result he was accepted as a research fellow at the Hemophilia and Thrombosis Center Angelo Bianchi Bonomi, University of Milan, Italy, (Prof. dr. P.M. Mannucci) to perform a subanalysis of prothrombotic genes on myocardial infarction in young adults without cardiovascular risk factors. Moreover, he studied the effects of factor VII gene polymorphisms on the risk of myocardial infarction in young women.

After his return from Italy he graduated from Medical School in August 2006. In October 2006 he was appointed at the department of Anesthesiology, LUMC, combining both residency (Prof. dr. L.P.H.J. Aarts) and research (Prof. dr. A. Dahan) for which he received a grant from the Netherlands Organisation for Health Research and Development (Agikobeurs ZonMw, 2007). Since October 2013 he is a staff member of the department of Anesthesiology, LUMC. He is currently involved in many ongoing research projects, in Crew Resource Management training and a member of the National Organ Transplantation team (ZUT).

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1. **Martini CH**, Doggen CJ, Cavallini C, Rosendaal FR, Mannucci PM. No effect of polymorphisms in prothrombotic genes on the risk of myocardial infarction in young adults without cardiovascular risk factors. *J Thromb Haemost* 2005; 3: 177-9.
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