Sind alle Opioide gleich?

M. Zenz

ehem. Klinik für
Anaesthesiologie,
Intensiv-, Palliativ- und
Schmerzmedizin

Anaesthesist (1983) 32:279–283

Anaesthesist

Die Anwendung von oralem Morphin bei inkurablen Schmerzen

R. Twycross und M. Zenz

Sir Michael Sobell House, The Churchill Hospital (Leiter: R. Twycross), Headington, Oxford, und Zentrum für Anaesthesiologie der Medizinischen Hochschule, Abteilung IV Krankenhaus Oststadt (Leitung: Prof. Dr. Ina Pichlmayr), Hannover

Opioide - Unterschiede

Wirkungsdauer
Verträglichkeit
Applikation (oral – Pflaster)
Nebenwirkungen
Neuropathischer Schmerz

Tramadol - Tumorschmerz

ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2007; 27 (1): 75-83
1173-2563/07/0001-0075/$44.95/0

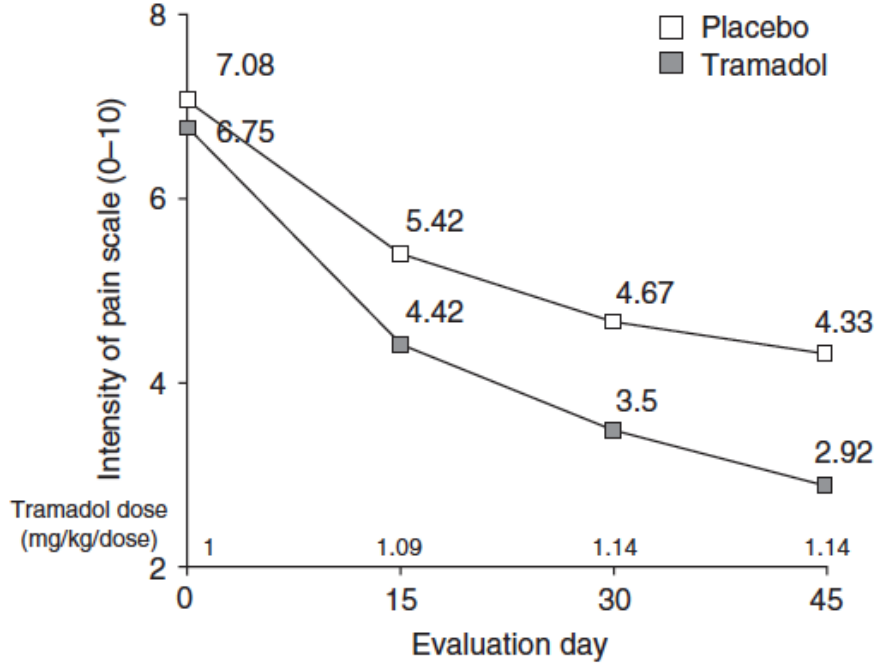
Tramadol in the Treatment of Neuropathic Cancer Pain

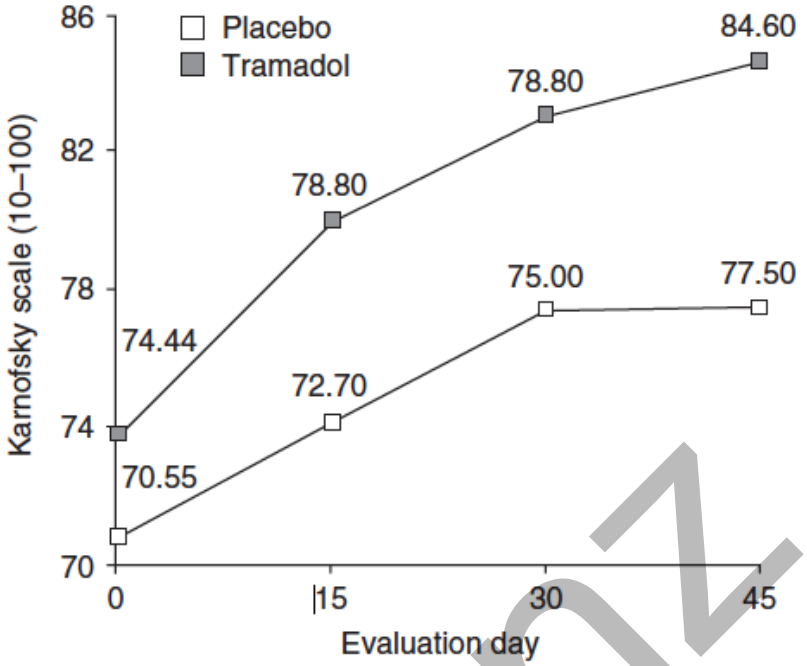
A Double-Blind, Placebo-Controlled Study

Daniel Arbaiza and *Oscar Vidal*

Service of Neuro-Oncology at the National Cancer Institute, Lima, Peru

Tramadol - Tumorschmerz





ORIGINAL RESEARCH ARTICLE
Clin Drug Invest 2007; 27 (1): 75-83
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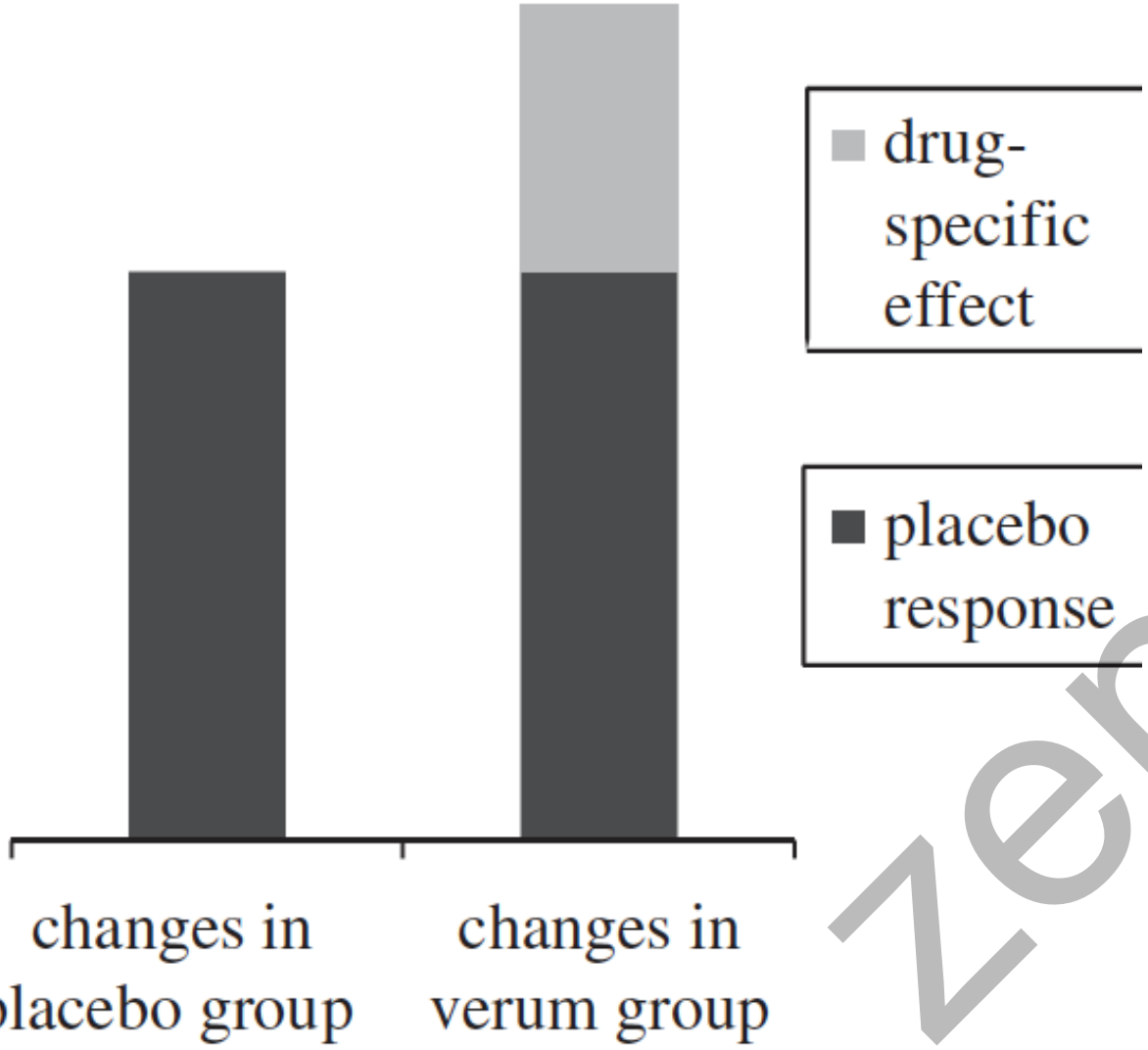
Tramadol in the Treatment of Neuropathic Cancer Pain
A Double-Blind, Placebo-Controlled Study

Daniel Arbaiza and *Oscar Vidal*
Service of Neuro-Oncology at the National Cancer Institute, Lima, Peru

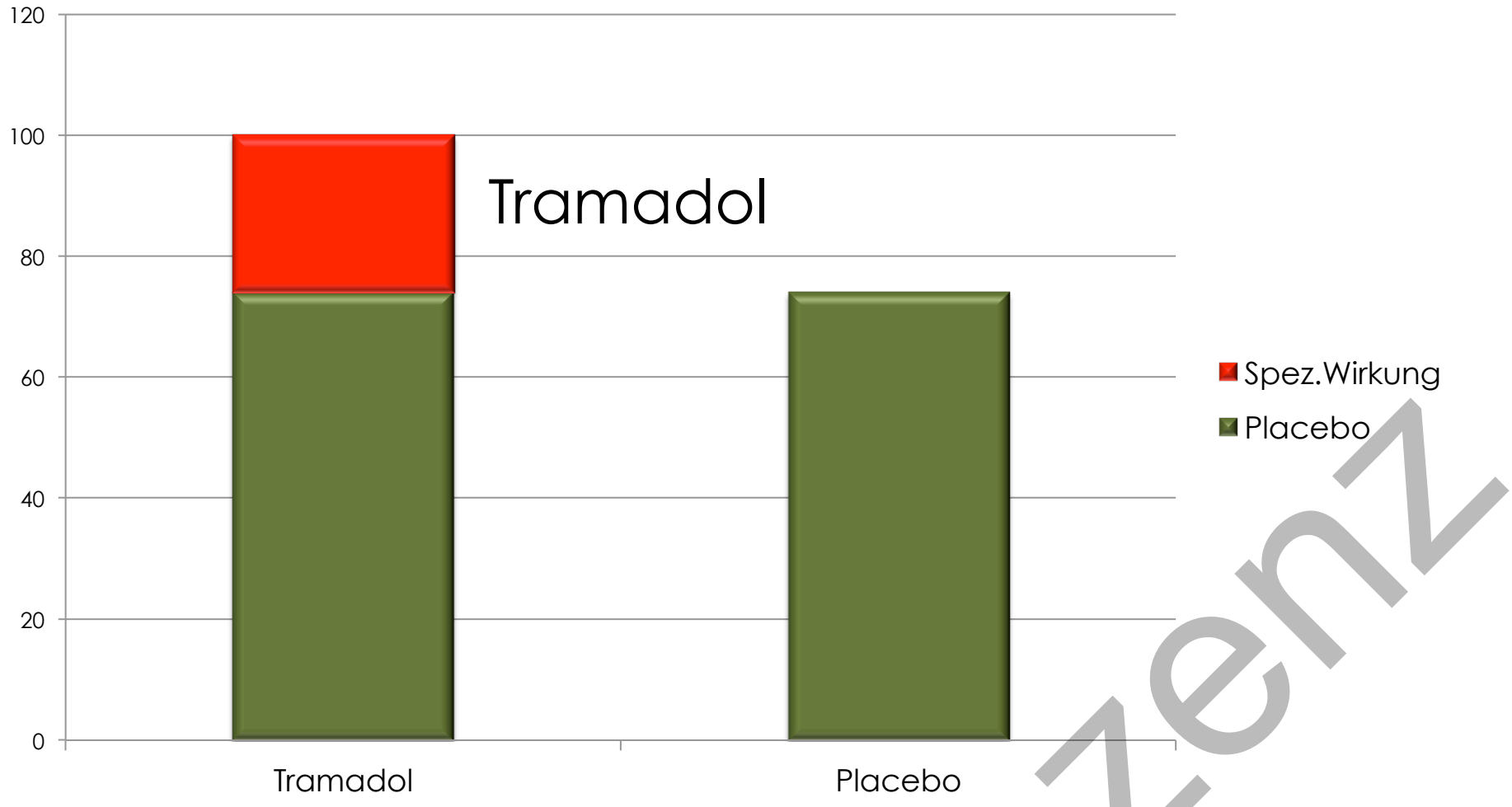
significant difference in favour of tramadol ($p < 0.001$)

Spez. Wirkung = Wirkung - Placebo



Rief 2011

Tramadol = Wirkung - Placebo



Nach Rief 2011

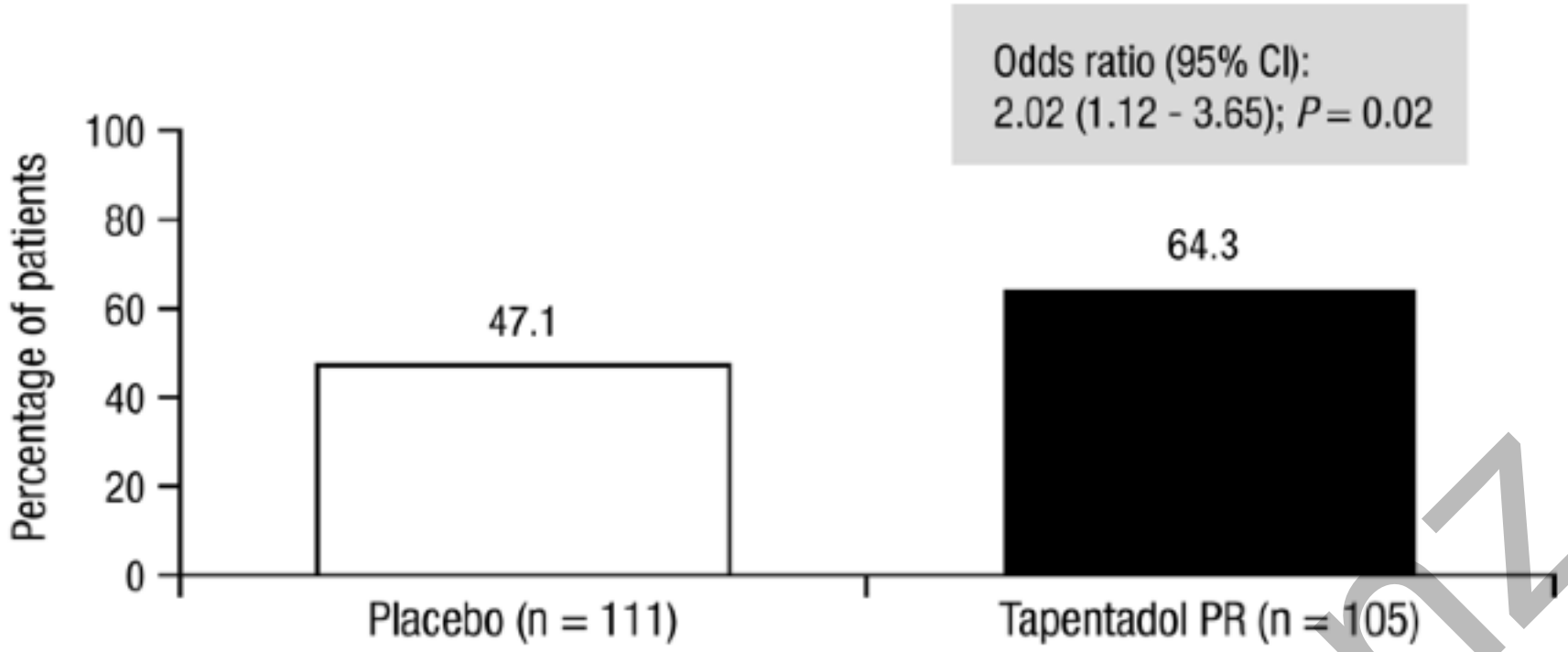
Tramadol

- Duale Wirkung: Opioid + Serotonin-Freisetzung
- Neuropathischer Schmerz durch mehrere Studien belegt
- Eine Studie bei Tumorschmerz
  - NNT 4.6 (3.6-6.4) 50% Schmerzreduktion

Tilidin-Naloxon

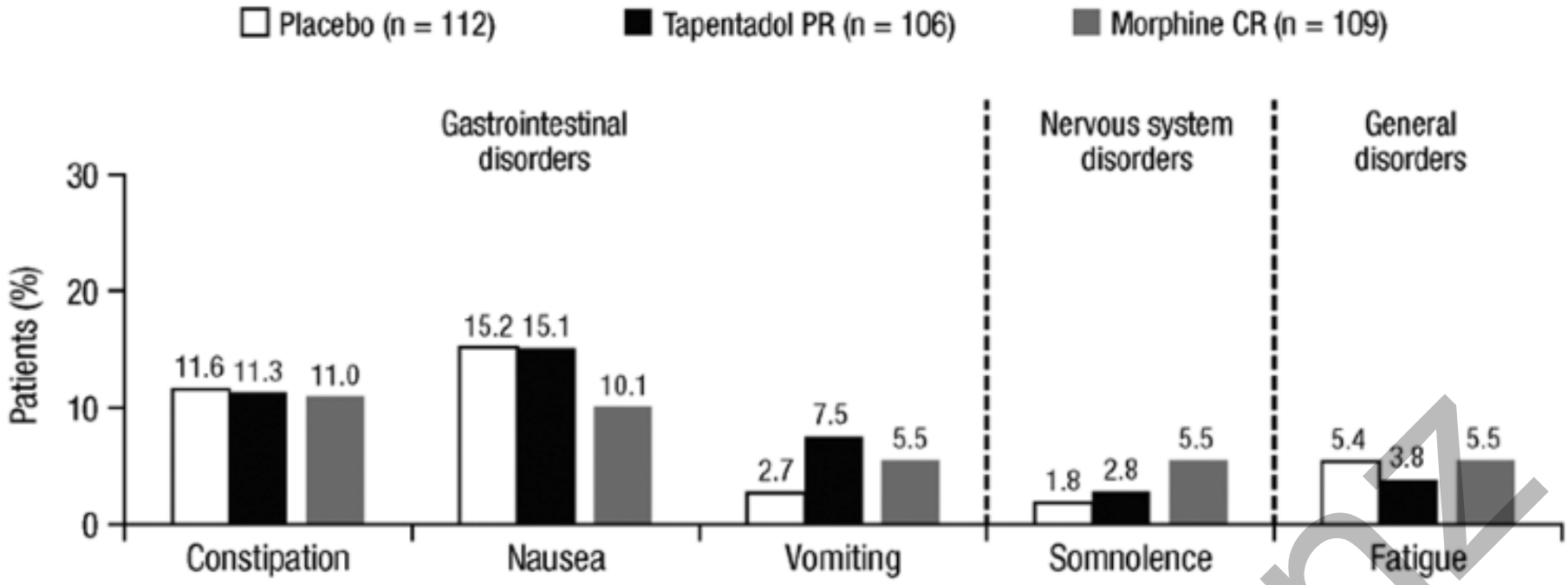
- Stark lipophil - Cave: Nicht-retardiert
- Kaum/keine Obstipation
- Keine Studien

Tapentadol – Responder Tumorschmerz



Kress et al 2014

Tapentadol

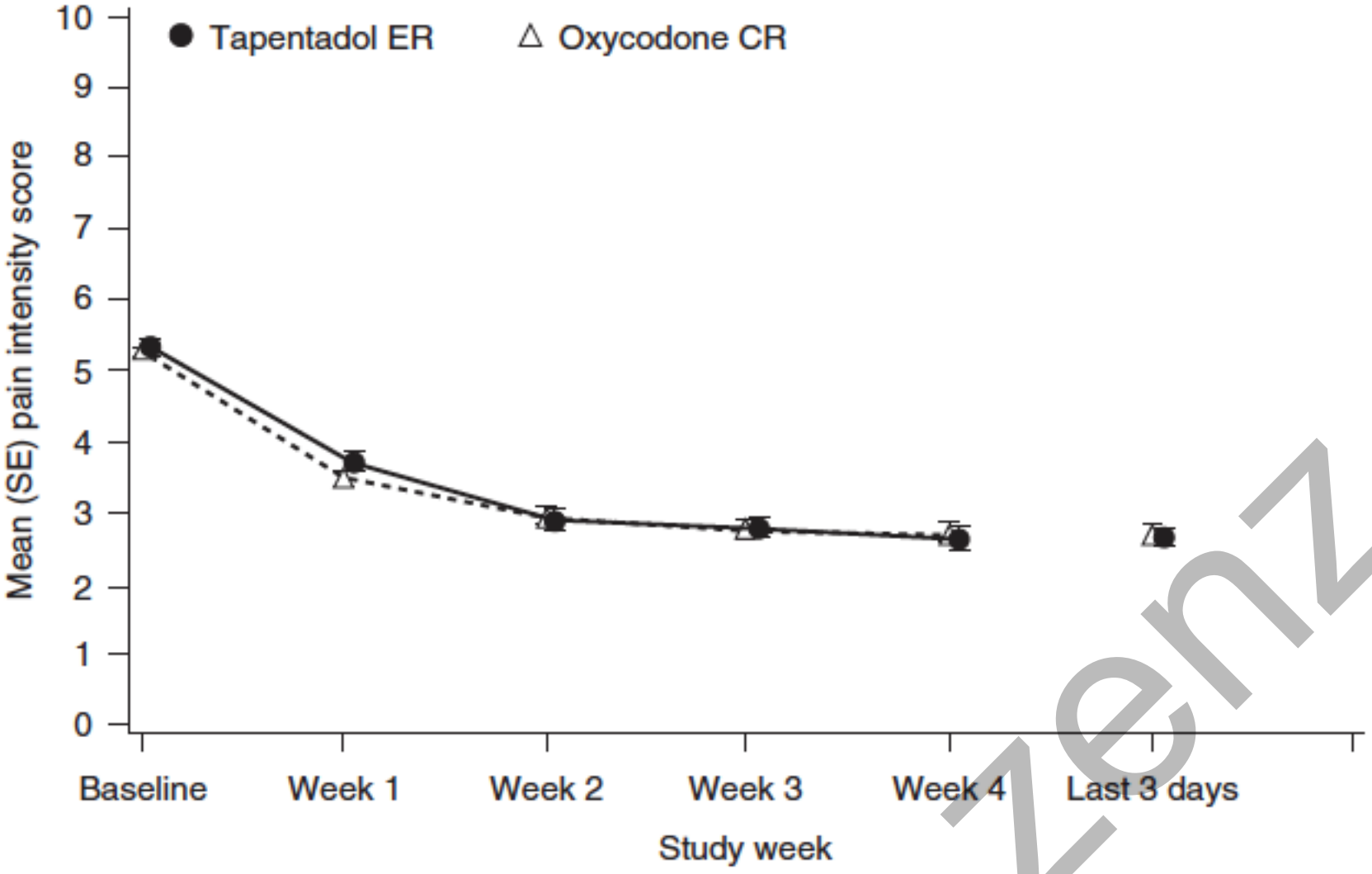


B. Maintenance period

„improved gastrointestinal tolerability“ ???

Kress et al 2014

Tapentadol - Tumorschmerz



Imanaka et al Current Medical Research & Opinion Vol. 29, No. 10, 2013, 1399–140

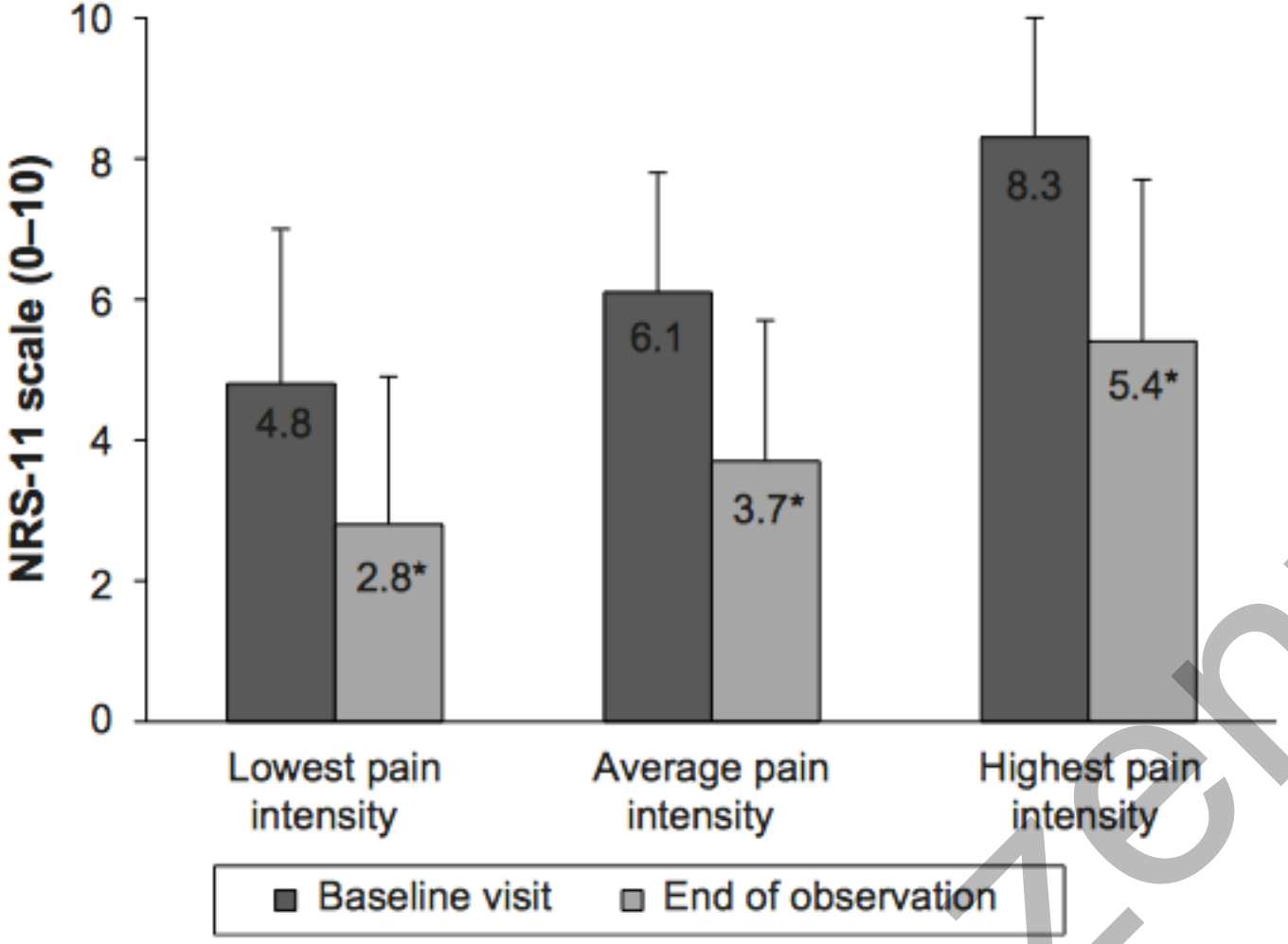
Tapentado - Tumorschmerz

...better gastrointestinal tolerability profile than oxycodone CR..

The incidences of some gastrointestinal TEAEs were numerically lower in the tapentadol ER group than in the oxycodone CR group...

Imanaka et al Current Medical Research & Opinion Vol. 29, No. 10, 2013, 1399–140

Tapentadol - Tumorschmerz



Schikowski et al 2014 Cancer pain

Tapentadol

- Duale Wirkung: Opioid
  +Noradrenalin reuptake-Hemmer
- Neuropathischer Schmerz
  wenig belegt
- 3 Studien bei Tumorschmerz
- NNT ~ 2 – 3

Morphin

Review

PALLIATIVE MEDICINE

Palliative Medicine
25(5) 402–409

DOI: 10.1177/0269216310392102
pmj.sagepub.com
SAGE

Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project

Augusto Caraceni *Palliative Care, Pain Therapy and Rehabilitation Unit, Fondazione IRCCS Istituto Nazionale Tumori, Italy*
Alessandra Pigni *Palliative Care, Pain Therapy and Rehabilitation Unit, Fondazione IRCCS Istituto Nazionale Tumori, Italy*
Cinzia Brunelli *Palliative Care, Pain Therapy and Rehabilitation Unit, Fondazione IRCCS Istituto Nazionale Tumori, Italy*

„....oral morphine, oxycodone and hydromorphone have similar efficacy and toxicity in this patient population.“

Cochrane Database Syst Rev. 2013 Jul 22;7:CD003868. doi: 10.1002/14651858.CD003868.pub3.

Oral morphine for cancer pain.

Wiffen PJ, Wee B, Moore RA.

Author information

Pain Research and Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK. phil.wiffen@ndcn.ox.ac.uk.

AUTHORS' CONCLUSIONS:The effectiveness of oral morphine has stood the test of time, but the randomised trial literature for morphine is small given the importance of this medicine.

.....New studies added to the review reinforce the view that it is possible to use modified release morphine to titrate to analgesic effect. There is qualitative evidence that oral morphine has much the same efficacy as other available opioids.

Morphin

Original Article

American Journal of Hospice
& Palliative Medicine®
30(7) 712-716

DOI: 10.1177/1049909112469823
ajhpm.sagepub.com
SAGE

Correlation Between the Administration of Morphine or Oxycodone and the Development of Infections in Patients With Cancer Pain

Miharu Suzuki[1], Tomoya Sakurada, PhD[1], Kazumi Gotoh[2], Satoshi Watanabe, MD[3], and Nobunori Satoh, PhD[1]

.....morphine's immunosuppressive effect may contribute to the development of infections in patients with cancer pain.

Oxycodon

Review

PALLIATIVE MEDICINE

Palliative Medicine
25(5) 454–470

DOI: 10.1177/0269216311401948
pmj.sagepub.com
SAGE

A systematic review of oxycodone in the management of cancer pain

Samuel James King *Department of Palliative Medicine, University of Bristol, UK*
Colette Reid *Department of Palliative Medicine, University Hospitals Bristol NHS Foundation Trust, UK*
Karen Forbes *Department of Palliative Medicine, University of Bristol, UK, Department of Palliative Medicine, University Hospitals Bristol NHS Foundation Trust, UK*
Geoffrey Hanks *Department of Palliative Medicine, University of Bristol, UK*

Conclusions: There is no evidence from the included trials of a significant difference in analgesia or adverse effects between oxycodone and morphine or hydromorphone.

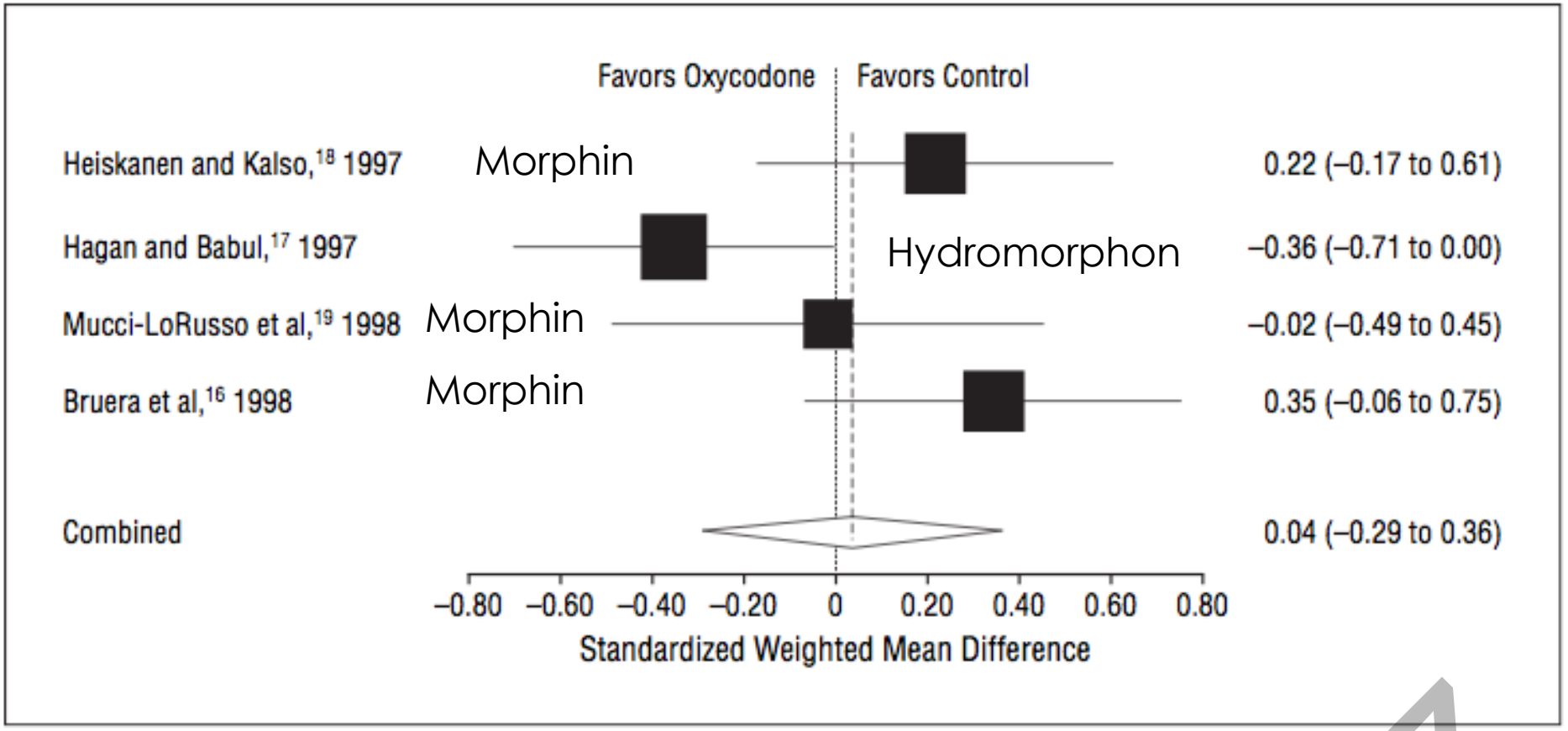


Figure 4. Standardized weighted mean differences (95% confidence intervals) in pain intensity scores in patients with cancer, comparing oxycodone minus control in all 4 trials with analyzable data.

REVIEW ARTICLE

Oxycodone for Cancer-Related Pain

Meta-analysis of Randomized Controlled Trials

Colette M. Reid, MB; Richard M. Martin, BM, PhD; Jonathan A. C. Sterne, PhD; Andrew N. Davies, MD; Geoffrey W. Hanks, DSc

Oxycodon

...oxycodone offers similar levels of pain relief and adverse events to other strong opioids including morphine, which is commonly considered the gold standard strong opioid....

Oxycodone for cancer-related pain (Review)

Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS

Oxycodon

The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy

Art Van Zee, MD

Review

PALLIATIVE MEDICINE

Palliative Medicine
25(5) 488–493

DOI: 10.1177/0269216310397687
pmj.sagepub.com
SAGE

Is oral methadone better than placebo or other oral/transdermal opioids in the management of pain?

Nathan Cherny *Department of Medical Oncology, Shaare Zedek Medical Center, Jerusalem, Israel*

(1) Kein Unterschied zu anderen Opioiden
(2) Preiswerter
(3) Sedierung und Kumulation
(4) Morphin:Methadon 4:1.

Methadon - Kumulation

HWZ bis zu 100 Std.

Methadon - Herz

2013 Dec **Prolonged QT interval by methadone: relevance for daily practice? A prospective study in patients with cancer and noncancer pain.**

J Opioid Manag
J Opioid Manag 2013 Jul-Aug;9(4):263-7
Marieke H J van den Beuken-van Everdingen, José W Geurts, Jacob Patijn

The study found that in our patients with pain, with relatively low doses of methadone, 5 percent had QTc times ≥500 ms and were thus at serious at risk for TdP.

Hydromorphon

- niedrige Plasmaeiweißbindung
- weniger Interaktionen
- weniger Metaboliten
- bei polymorbiden / alten Patienten
- bei Niereninsuffizienz

Hydromorphon

Review

PALLIATIVE MEDICINE

Palliative Medicine
25(5) 471–477

DOI: 10.1177/0269216310387962
pmj.sagepub.com
SAGE

The role of hydromorphone in cancer pain treatment: a systematic review

Alessandra Pigni *Fondazione IRCCS Istituto Nazionale Tumori-Milano, Italy*
Cinzia Brunelli *Fondazione IRCCS Istituto Nazionale Tumori-Milano, Italy*
Augusto Caraceni *Fondazione IRCCS Istituto Nazionale Tumori-Milano, Italy*

....there is no evidence to demonstrate its superiority or inferiority in comparison with morphine as the first choice opioid for the same indication.

Hydromorphon - Osteoarthitis

Table 3. Change from baseline for pain intensity and WOMAC measures at maintenance week 12 for OROS hydromorphone ER (16 mg) and placebo (LOCF imputation)

	Change from baseline, LS mean (SEM)				
Measure	Placebo (n = 331)	OROS hydromorphone ER 8 mg (n = 319)	OROS hydromorphone ER 16 mg (n = 330)	P value (8 mg vs. placebo)	P value (16 mg vs. placebo)
Pain intensity	−1.9 (0.16)	−2.0 (0.16)	−2.5 (0.16)	0.774	0.007
WOMAC overall score	−1.3 (0.11)	−1.6 (0.11)	−1.7 (0.11)	0.0633	0.003
Pain	−1.3 (0.12)	−1.6 (0.12)	−1.8 (0.12)	0.143	0.005
Stiffness	−1.4 (0.13)	−1.7 (0.13)	−1.9 (0.13)	0.0753	0.004
Physical function	−1.3 (0.11)	−1.6 (0.11)	−1.7 (0.11)	0.0587	0.006

~ Morphin 60 mg 120 mg

OROS hydromorphone ER failed to achieve statistical significance for the primary endpoint using the prespecified imputation method ...When data were analyzed according to an alternate method of imputation (LOCF), OROS hydromorphone ER demonstrated statistically significant improvements in pain, stiffness, and physical function.

Rauck et al Pain Practice 2012

Hydromorphon

- Hydromorphone neuroexcitation.

Thwaites D, McCann S, Broderick P. J Palliat Med. 2004 Aug;7(4):545-50.

Hydromorphon

•A possible mechanism for these findings is hydromorphone-3-glucoronide, a metabolic product of hydromorphone, which has been implicated in neuroexcitatory symptoms in laboratory investigations.

Thwaites D, McCann S, Broderick P. J Palliat Med. 2004 Aug;7(4):545-50.

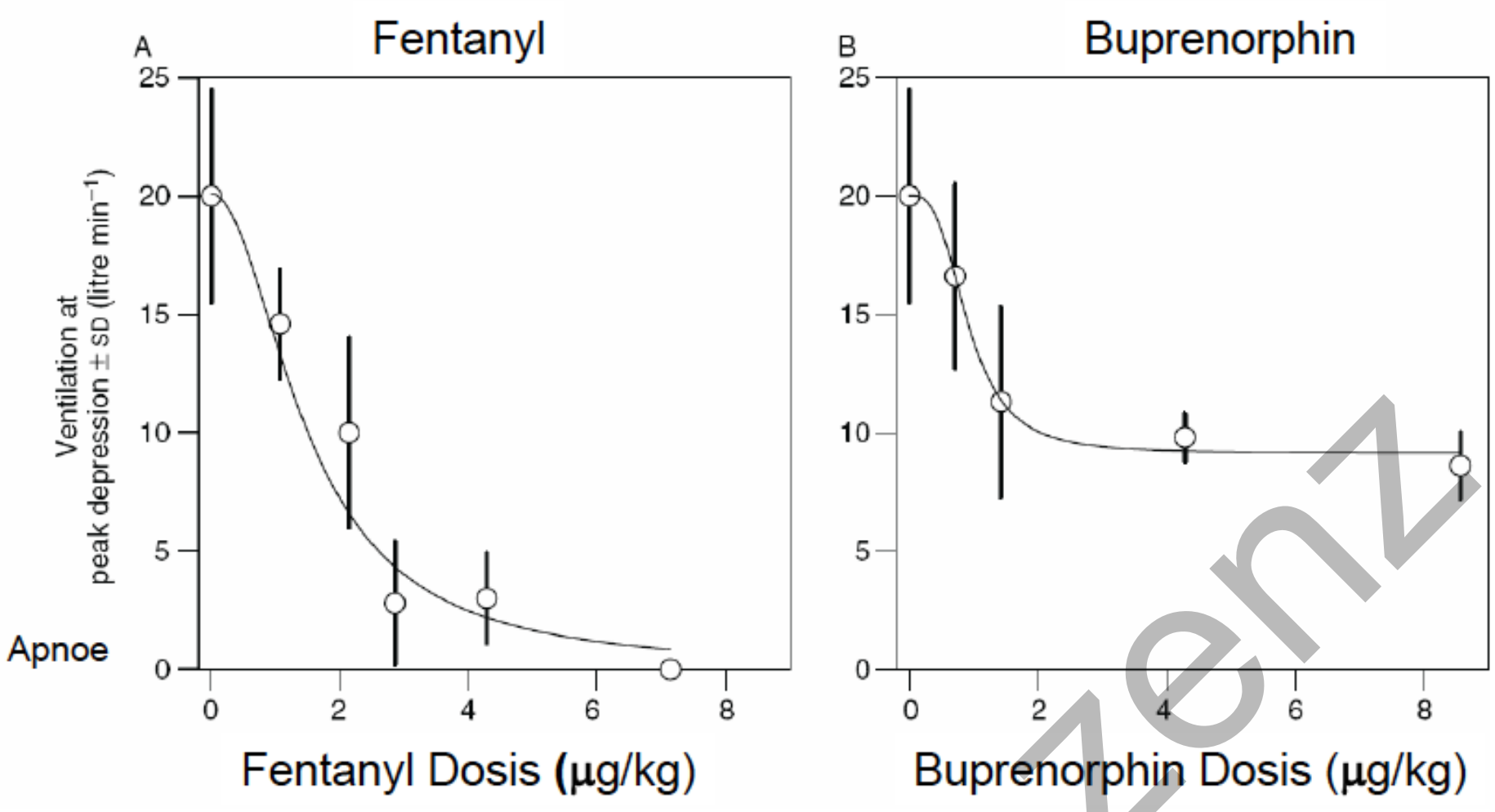
Buprenorphin sublingual

Erstes langwirkendes Opioid in Deutschland (1980)

Buprenorphin

- Partieller Agonist
- Stufe 2 – 3
- Schwer antagonisierbar
- Weniger Atemdepression

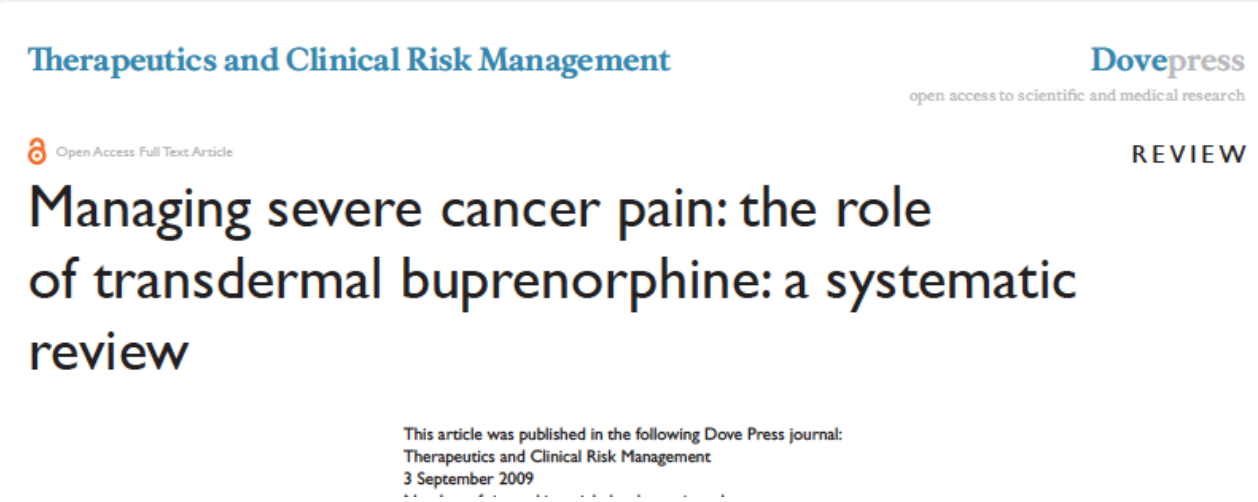
Buprenorphin – Atemdepression „Ceiling-effect“



Dahan et al 2005

Transdermale Opioide

Buprenorphin transdermal



Therapeutics and Clinical Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

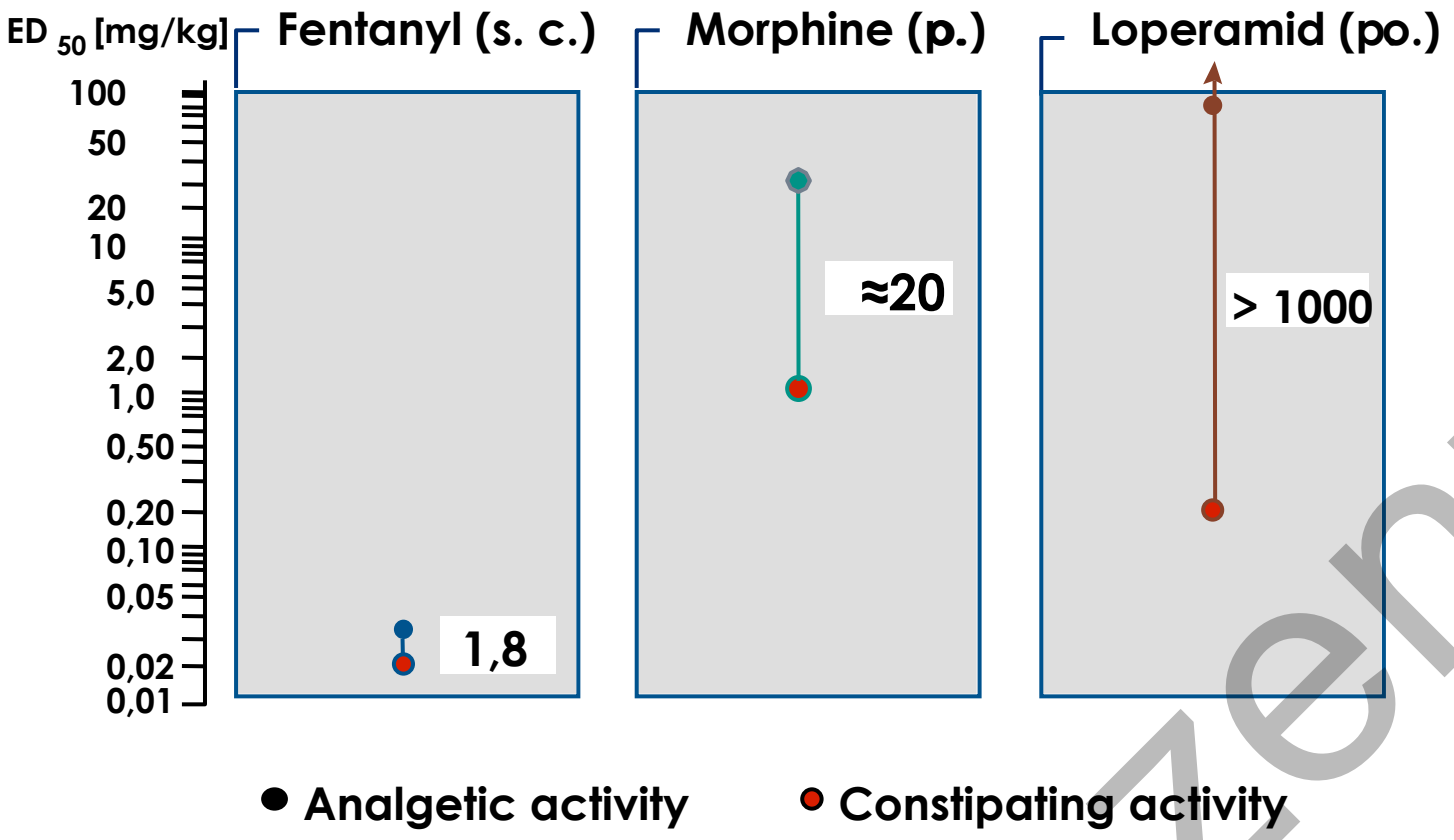
REVIEW

Managing severe cancer pain: the role of transdermal buprenorphine: a systematic review

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
3 September 2009

In conclusion, although the narrative appraisal of each study suggests a positive risk benefit profile, well designed and statistically powered controlled clinical trials are needed to confirm this preliminary evidence.

Analgetische – Obstipierende Aktivität



Megens A et al.: J Pain Symptom Manage 1998; 15: 253-258.

Buprenorphin/Fentanyl TTS

Although no difference in the overall adverse effect profile exists between transdermal opiates and slow release oral morphine, the difference in some adverse effects (mainly constipation) seems to favor transdermal opiates in the preference of patients with moderate-severe cancer pain.

Tassinari et al

Adverse Effects of Transdermal Opiates Treating Moderate-Severe Cancer Pain in Comparison to Long-Acting Morphine: A Meta-Analysis and Systematic Review of the Literature

Journal of Palliative Medicine. April 2008, 11(3): 492-501

Buprenorphin/Fentanyl TTS

Transdermal opioids showed no benefit over oral controlled-release hydromorphone with regard to gastrointestinal symptoms.

Gastrointestinal symptoms under opioid therapy: A prospective comparison of oral sustained-release hydromorphone, transdermal fentanyl, and transdermal buprenorphine

Stefan Wirz [a,b,*], Maria Wittmann [a], Michael Schenk [c], Andreas Schroeck [d], Nico Schaefer [e], Marcus Mueller [e], Jens Standop [e], Norbert Kloecker [f], Joachim Nadstawek [a]

European Journal of Pain 13 (2009) 737–743

Buprenorphin/Fentanyl TTS

Conclusions: .....the use of transdermal opioids to be reserved for selected patients.

Review

PALLIATIVE MEDICINE

Palliative Medicine
25(5) 478–487

DOI: 10.1177/0269216311404274
pmj.sagepub.com
SAGE

Transdermal opioids as front line treatment of moderate to severe cancer pain: a systemic review

Davide Tassinari *Supportive and Palliative Care Unit, Department of Oncology, City Hospital, Rimini, Italy*
Fabrizio Drudi *Department of Oncology, City Hospital, Rimini, Italy*
Marta Rosati *Palliative Care Unit, Valerio Grassi Hospice, Forlimpopoli, Italy*
Marco Maltoni *Palliative Care Unit, Valerio Grassi Hospice, Forlimpopoli, Italy*

2011

Buprenorphin/Fentanyl TTS

- Lange Wirkungsdauer
- Compliance
- Weniger Obstipation
- Problem Schmerzspitzen

Kurz wirksames Fentanyl

- Kurze Wirkungsdauer
- Durchbruchschmerzen

Fentanyl Buccaltabletten

Pain Medicine

Section Editor: **Spencer S. Liu**

The Efficacy and Safety of Fentanyl Buccal Tablet Compared with Immediate-Release Oxycodone for the Management of Breakthrough Pain in Opioid-Tolerant Patients with Chronic Pain

Michael A. Ashburn, MD, MPH,* Kieran A. Slevin, MD,* John Messina, PharmD,† and Fang Xie, PhD†

(Anesth Analg 2011;112:693–702)

Fentanyl Buccaltabletten

CONCLUSION: FBT resulted in more rapid onset of analgesia and was generally well tolerated in comparison with oxycodone for the treatment of BTP in opioid-tolerant patients.
(Anesth Analg 2011;112:693–702)

Fentanyl-Buccaltabletten hatten schnelleren Beginn der Analgesie und wurden „grundsätzlich“ gut vertragen.

Ashburn et al 2011

FDA - Indikation

for the treatment of breakthrough pain in cancer patients

Fentanyl Buccaltabletten

Primary diagnosis of chronic pain, *n* (%)		
Back pain	187 (58)	105 (57)
Osteoarthritis	33 (10)	20 (11)
Neck pain	26 (8)	14 (8)
Fibromyalgia	22 (7)	16 (9)
Traumatic injury	20 (6)	8 (4)
Complex regional pain syndrome	9 (3)	7 (4)
Diabetic peripheral neuropathy	6 (2)	1 (<1)
Chronic pancreatitis	2 (<1)	1 (<1)
Postherpetic neuralgia	1 (<1)	1 (<1)
Cancer	1 (<1)	0
Other[a]	16 (5)	10 (5)

1 Tumorpatient – Rest Nicht-Tumorschmerz

Ashburn et al 2011

Kurz wirksames Fentanyl

Preis/Einzeldosis
€ 6.63 – €11.22

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

Augusto Caraceni, Geoffrey Hanks*, Stein Kaasa*, Michael I Bennett, Cinzia Brunelli, Nathan Cherny, Ola Dale, Franco De Conno, Marie Fallon, Magdi Hanna, Dagny Faksvåg Haugen, Gitte Juhl, Samuel King, Pål Klepstad, Eivor A Laugsand, Marco Maltoni, Sebastiano Mercadante, Maria Nabal, Alessandra Pigni, Lukas Radbruch, Colette Reid, Per Sjogren, Patrick C Stone, Davide Tassinari, Giovambattista Zeppetella, for the European Palliative Care Research Collaborative (EPCRC), on behalf of the European Association for Palliative Care (EAPC)*

Lancet Oncol 2012; 13: e58–68

Here we provide the updated version of the guidelines of the European Association for Palliative Care (EAPC) on the

Recommendation for WHO step II opioids

For patients with mild to moderate pain or whose pain is not adequately controlled by paracetamol or a non-steroidal anti-inflammatory drug (NSAID) given regularly by mouth, the addition of a step II opioid (eg, codeine or tramadol; table 1) given orally might achieve good pain relief without troublesome adverse effects. Alternatively, low doses of a step III opioid (eg, morphine or oxycodone; table 1) may be used instead of codeine or tramadol. The data permit a weak recommendation to start a step II opioid in these circumstances.

Empfehlung bei unzureichender Wirkung von Paracetamol oder NSAIDs

Caraceni et al 2012

Recommendation for WHO step III opioid of first choice

The data show no important differences between morphine, oxycodone, and hydromorphone given by the oral route and permit a weak recommendation that any one of these three drugs can be used as the first choice step III opioid for moderate to severe cancer pain.

Keine Unterschiede zwischen Oxycodon, Morphin, Hydromorphon

Caraceni et al 2012

Recommendation for opioid titration

The data permit a weak recommendation that immediate release and slow-release oral formulations of morphine, oxycodone, and hydromorphone can be used for dose titration. The titration schedules for both types of formulation should be supplemented with oral immediate release opioids given as needed.

Auch mit retardierten Opioiden kann titriert werden

Caraceni et al 2012

Recommendation for the use of transdermal opioids

Transdermal fentanyl and buprenorphine are alternatives to oral opioids. The data permit a weak recommendation that either drug may be the preferred step III opioid for some patients. For patients unable to swallow they are an effective, non-invasive means of opioid delivery.

Buprenorphin und Fentanyl TTS
Alternativen
Patienten mit Schluckstörungen

Caraceni et al 2012

Recommendation for use of methadone

Methadone has a complex pharmacokinetic profile with an unpredictably long half-life. The data permit a weak recommendation that it can be used as a step III opioid of first or later choice for moderate to severe cancer pain.It should be used only by experienced professionals.

Unvorhersehbare Halbwertszeit
Nur von erfahrenen Ärzten

Caraceni et al 2012

Recommendation for opioid switching

The data permit a weak recommendation that patients receiving step III opioids who do not achieve adequate analgesia and have side-effects that are severe, unmanageable, or both, might benefit from switching to an alternative opioid.

Schwache Empfehlung zum Wechsel bei unzureichender Analgesie oder Nebenwirkungen

Caraceni et al 2012

Recommendation for opioids for breakthrough pain

Starke Empfehlung für schnell freisetzendes Opioid oder buccales/nasales Fentanyl

Vor Therapie von Durchbruchschmerzen immer erst Versuch, die retardierten Opioide anzupassen

Caraceni et al 2012

Opioide

- Die sichersten Medikamente der WHO Essential Drug List

Opioide

- Kein Todesfall bei richtiger Applikation

J. Med. Toxicol. (2012) 8:417–423
DOI 10.1007/s13181-012-0257-8

REVIEW ARTICLE

"Safe and Effective When Used As Directed": The Case of Chronic Use of Opioid Analgesics

Jane C. Ballantyne

Opioidanalgetika
Differenzierte Indikation

- Preiswert = Morphin ret.

Opioidanalgetika
Differenzierte Indikation

- Orale Aufnahme = Oxycodon

Opioidanalgetika
Differenzierte Indikation

- Stoffwechsel = Hydromorphon

Opioidanalgetika
Differenzierte Indikation

- Obstipation = TTS
- Obstipation = Opioid+Naloxon
  Tapentadol

Opioidanalgetika
Differenzierte Indikation

- Bekanntes Opioid nehmen
- Wechseln nur nach Notwendigkeit
- Ausreichende Einstellung mit ret.Opioid

Opioide

Alle Opioide nach Wirkung titrieren

Sind alle Opioide gleich?

Die gepoolten Direktvergleiche von Opioiden des Sponsors einer Studie vs. Standardopioide liefern keine Begründung für die Bevorzugung eines Opioids und/oder Applikationswegs in der Behandlung von Patienten mit CNTS.

Lauche et al 2015