Update aktueller Opiodschmerzmedikation - insbesondere des neuropathischen Schmerzes

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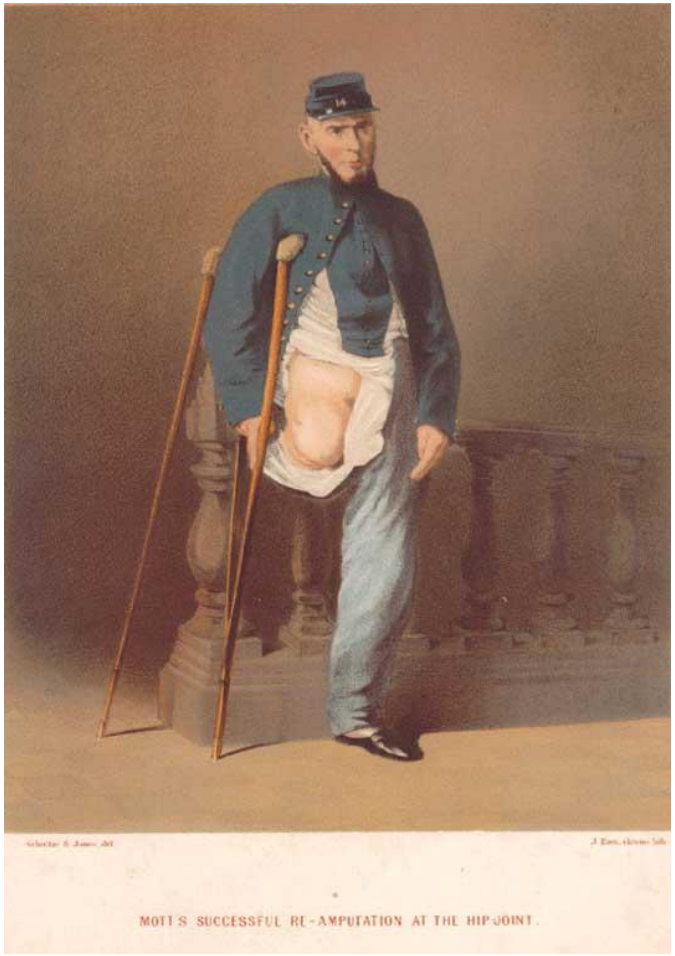
Der nozizeptive Schmerz

- Gewebeschädigung
- Ischämieschmerzen
- Tumorschmerzen
- Kopfschmerzen
- Viszerale Schmerzen
- Arthrose/Arthritis
- Schmerzen in tiefsomatischen Geweben (Band/Bewegungsapparat)

From: René Descartes.
Renatus Des Cartes de homine. Lvgdvni Batavorvm: Petrvm Leffen & Fransciscvm Moyardvm, 1662

Der neuropathische Schmerz

- **Peripher**
  - Engpasssyndrome
  - Postdisketktomiesyndrom
  - CRPS II (Chronic Regional Pain Syndrom …Mb.Sudeck)
  - Posttraumatische Neuropathie
  - Phantomschmerz
  - Postzoster
  - Trigeminusneuralgie
  - Polyneuropathien
- **Zentral**
  - Entzündung z.B. MS
  - Thalamusinfarkt
  - Rückenmarkschädigung



A Civil War Amputee (From: Otis, George A. *A Report on Amputationsof the Hip-Joint, in Military Surgery*. Washington:Govt. Printing Office, 1867)

Prävalenz

- Neuropathischer Schmerz: 7-8% der Bevölkerung (Bouhassira 2008)
- Chronische Schmerzen 20% davon substantieller Anteil neuropathische Schmerzen

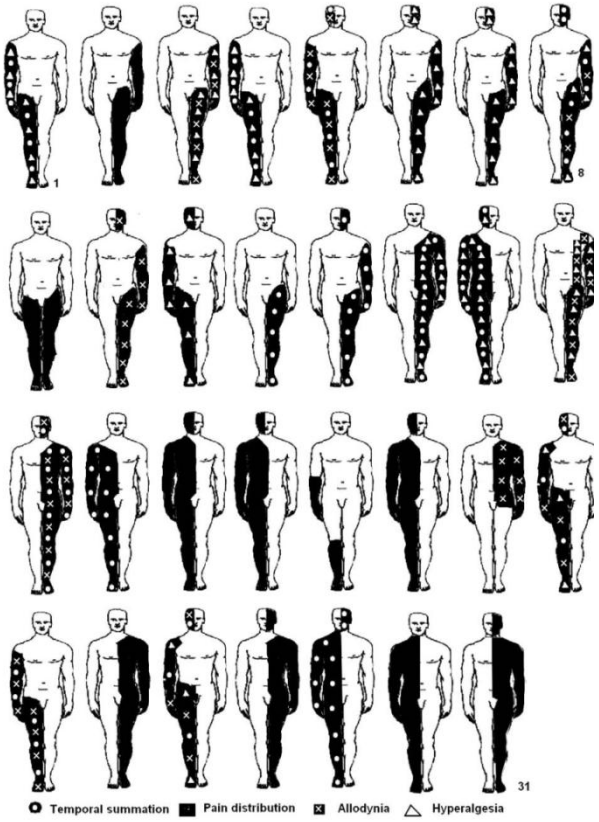
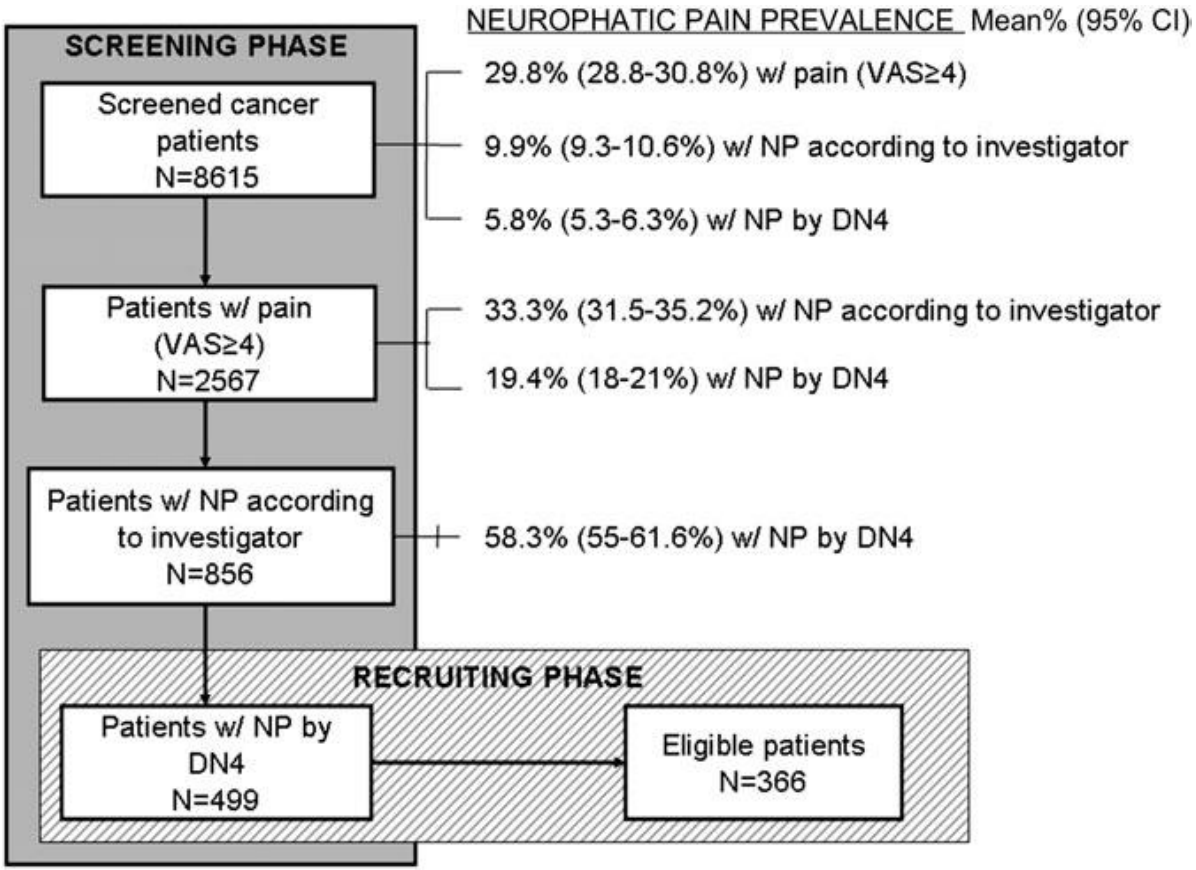


Figure 1. Topography of sensory symptoms in patients with central post-stroke pain.

Misra et al. Journal of Pain 2008

Prävalenz neuropathischer Schmerzen bei Krebspatienten



Garcia de Paredes, Annals of Oncology 2010

Diagnostik – neuropathischer Schmerz

Negativsymptome

- Hypästhesie
- Pallhypästhesie
- Hypalgesie
- Thermhypästhesie

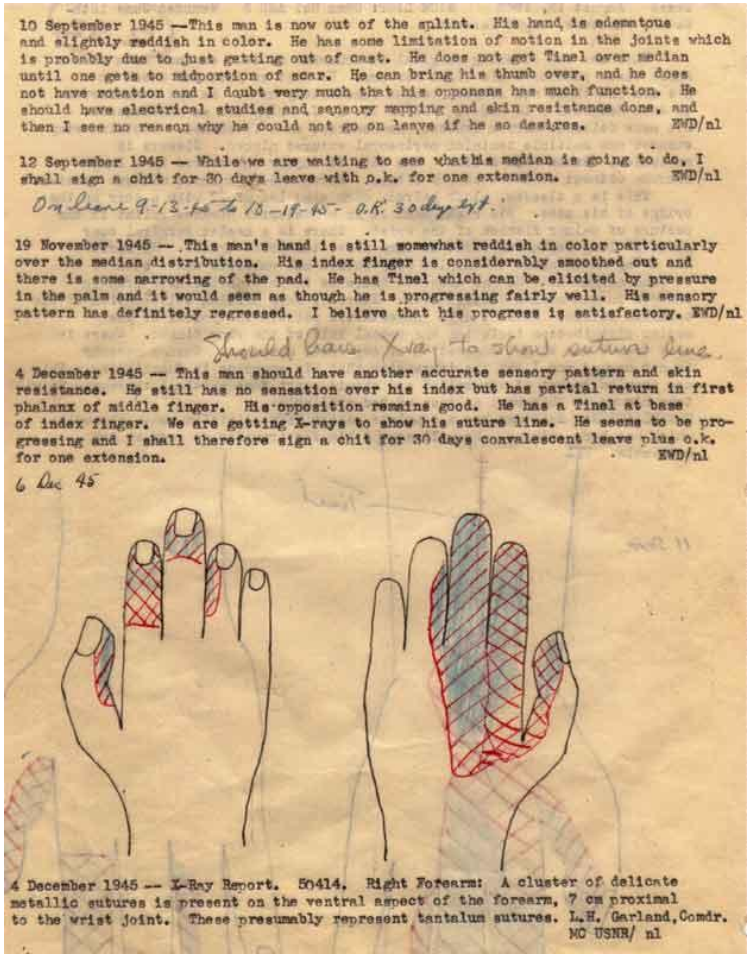
Positivsymptome

Spontan

- Einschiessend
- Parästhesie

Evoziert

- Dynamisch mechanische Allodynie
- Statische mechanische Allodynie
- Mechanische pinprick Hyperalgesie
- Kälte-Allodynie
- Hitze-Hyperalgesie



10 September 1945 —This man is now out of the splint. His hand is edematous and slightly reddish in color. He has some limitation of motion in the joints which is probably due to just getting out of cast. He does not get Tinel over median until one gets to midportion of scar. He can bring his thumb over, and he does not have rotation and I doubt very much that his opponens has much function. He should have electrical studies and sensory mapping and skin resistance done, and then I see no reason why he could not go on leave if he so desires. EWD/nl

12 September 1945 — While we are waiting to see what his median is going to do, I shall sign a chit for 30 days leave with p.k. for one extension. EWD/nl

On leave 9-13-45 to 10-13-45 - O.K. 30 days lvt.

19 November 1945 — This man's hand is still somewhat reddish in color particularly over the median distribution. His index finger is considerably smoothed out and there is some narrowing of the pad. He has Tinel which can be elicited by pressure in the palm and it would seem as though he is progressing fairly well. His sensory pattern has definitely regressed. I believe that his progress is satisfactory. EWD/nl

Should have X-ray to show suture line.

4 December 1945 — This man should have another accurate sensory pattern and skin resistance. He still has no sensation over his index but has partial return in first phalanx of middle finger. His opposition remains good. He has a Tinel at base of index finger. We are getting X-rays to show his suture line. He seems to be progressing and I shall therefore sign a chit for 30 days convalescent leave plus o.k. for one extension. EWD/nl

6 Dec 45

4 December 1945 — X-Ray Report. 50414. Right Forearm: A cluster of delicate metallic sutures is present on the ventral aspect of the forearm, 7 cm proximal to the wrist joint. These presumably represent tantalum sutures. L.H. Garland, Comdr. MC USNR/ nl

William K. Livingston's Case Notes from

a WWII Peripheral Nerve Injury Patient, 1945

Diagnose
Fragebögen

Comparison of items within five neuropathic pain screening tools (*shaded boxes highlight features shared by two or more tools*)

	LANSS[a]	DN4[a]	NPQ	pain*DETECT*	ID Pain
Symptoms					
Pricking, tingling, pins and needles	•	•	•	•	•
Electric shocks or shooting	•	•	•	•	•
Hot or burning	•	•	•	•	•
Numbness		•	•	•	•
Pain evoked by light touching	•		•	•	•
Painful cold or freezing pain		•	•		
Pain evoked by mild pressure				•	
Pain evoked by heat or cold				•	
Pain evoked by changes in weather			•		
Pain limited to joints[b]					○
Itching		•			
Temporal patterns				•	
Radiation of pain				•	
Autonomic changes	•				
Clinical examination					
Brush allodynia	•	•			
Raised soft touch threshold		•			
Raised pin prick threshold	•	•			

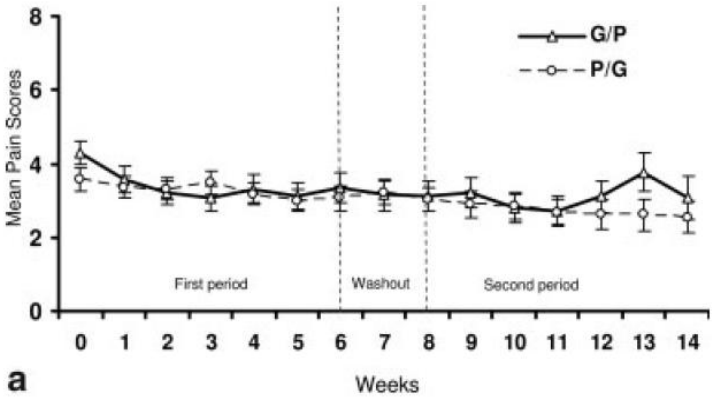
Sens -	82-91%	83%	66%	85%
Spez -	80-94%	74%	74%	80%

Bennett, Pain (2007)

Therapie neuropathischer Schmerzen

- **Nur 40-60% der Patienten erzielen eine teilweise Besserung ihrer neuropathischen Schmerzen**
- **Die meisten Studien sind für diabetische Polyneuropathie oder für die postherpetische Neuralgie → Uebertragung auf andere schmerzhafte Zustände nicht selbstverständlich**
- **Studien wurden meistens für mittel bis sehr starke Schmerzen durchgeführt**
- **Meistens nur für 3 Monate**
- **Wenig Studien für Kombinationstherapien**

Gabapentin nicht effektiv für Chemotherapie induzierte PNP

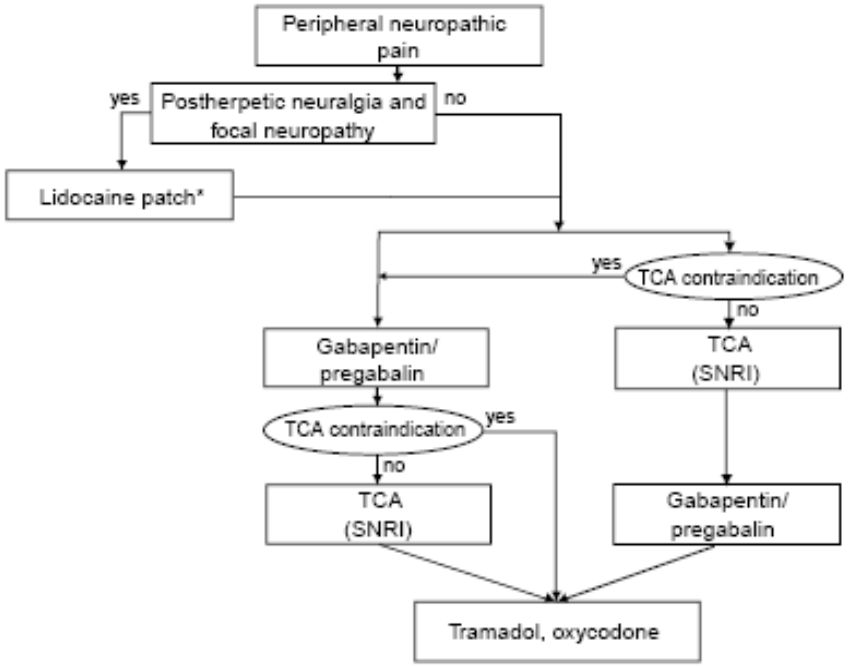


Rao, Cancer 2007

Therapie neuropathischer Schmerzen

Ca-Kanal (α2-δ) modulierende Antikonvulsiva	Pregabalin, Gabapentin
Na-Kanal-Blocker an primär afferenten und zentralen Neuronen	Carbamazepin, Lamotrigin, Lidocain
Trizyklische Antidepressiva → fördern Funktion der deszendierenden inhibierenden Bahnen	z.B. Nortryptilin, Imipramin, Amitryptilin
SSNRI (Serotonin-Noradrenalin Wiederaufnahmehemmer)→fördern Funktion der deszendierenden inhibierenden Bahnen	Duloxetin, Venlafaxin
Opiate → aktivieren die μ Rezeptoren im Rückenmark und Gehirn (inhibiert Neurotransmitterfreisetzung von Glutamat und Substanz P	Codein, Morphine, Tramadol

Behandlungsalgorithmus



Finnerup NJ et al. Pain (2005)

Positive und negative Studien

	Painful poly-neuropathy	Postherpetic neuralgia	Peripheral nerve injury[a]	HIV neuropathy	Central pain	Mixed neuropathic pain	Combined NNH
Antidepressants							
TCAs	**11+** 2.1 (1.9-2.6)	**4+** 2.8 (2.2-3.8)	**1+/1–**	**2–**	**2+** 2.7 (1.7-6.1)	**2+** NA	15.9 (11-26)
SNRIs	**5+** 5.0 (3.9-6.8)		**1–**			**1–**	13.1 (9.6-21)
SSRIs	**3+/1–** 6.8 (3.9-27)						ns
Anticonvulsants							
Gabapentin	**3+/1–** 6.4 (4.3-12)	**2+** 4.3 (3.3-6.1)	**1+/2–**	**1–**	**1+/1–**	**1+/1–**	32.5 (18-222)
Pregabalin	**5+** 4.5 (3.6-5.9)	**4+** 4.2 (3.4-5.4)	**1+** ns	**1–**	**2+** 5.6 (3.5-14)	**1+** 3.8 (2.6-7.3)	10.6 (8.7-14)
Lacosamide	**1+/3–**						7.8 (5.9-12)
Valproate	**2+/2–**	**1+** 2.1 (1.4-4.2)			**1–**		ns
Lamotrigine	**1+/3–**			**1+/1–**	**1+/2–**	**2-**	11.7 (8.5-19)
Topiramate	**1+/3–**						6.3 (5.1-8.1)
Levetiracetam			**1–**		**1–**		ns
Carbamazepine/ Oxcarbazepine	**3+/2–** 3.7 (2.6-6.4)				**1–**	**1+** NA	6.6 (4.9-10)
Opioids							
Opioids	**2+** 2.6 (1.7-6.0)	**2+** 2.6 (2.0-3.8)	**2+** 5.1 (2.7-36)			**2+/1–** 2.1 (1.5-3.3)	17.1 (9.9-66)
Tramadol	**3+** 4.9 (3.5-8.0)	**1+** 4.8 (2.6-27)	**1+** NA		**1+** ns		13.3 (8.8-27)
Various							
Cannabinoids	**1–**		**1+** ns		**2+** 3.4 (1.8-23)	**2+** 8.3 (4.5-45)	ns
Topical lidocaine		**2+** NA	**1+/1–**	**1–**		**1+/1–**	ns
NMDA antagonists	**2+/1–** 3.4 (2.1-9.0)	**4–**	**2–**	**1–**		**3–**	12.5 (7.5-36)
Mexiletine	**1+/3–**		**1+/1–**	**2–**	**1–**	**1–**	ns
Topical capsaicin	**3+/2–** 11 (5.5-316)	**2+** 3.2 (2.2-5.9)	**1+/1–**	**1–**		**1+** NA	11.5 (8-20)
NGX capsaicin		**2+** ns		**1+** 6.5 (3.9-20)			ns
BTX-A	**1+** 2.3 (1.5-4.7)					**1+** 3.0 (1.6-22)	ns
Nitrate spray	**3+** NA						ns

TCAs: tricyclic antidepressants; SNRIs: serotonin noradrenaline reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; BTX-A: Botulinum Toxin Type A; NA: dichotomized data are not available; ns: absolute risk difference not significant.

[a] Includes postamputation pain and brachial plexus avulsion.

Negative Studien

- VIH
  - A randomized trial of **amitriptyline** and **mexiletine** for painful neuropathy in HIV infection. Neurology 1998; 51(6): 1682-1688
  - Acupuncture and **amitriptyline** for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. JAMA 1998; 280 (18): 1590-1595.
  - A randomized controlled tiral of **5% lidocaine gel** for HIV-associated distal symmetric polyneuropathy. J Acquir Immune Defic Syndr 2004; 37 (5): 1584-1586
  - **Pregabalin** for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology 2010; 74: 413-420.
- **Polyneuropathie durch Chemotherapie induziert**
  - Phase III evaluation of **nortriptylin** for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. Pain 2002; 98 (1-2): 195-203
  - **Amitriptyline** in the treatment of chemotherapy induced neuropathic symptoms. J Pain Symptom Mange. 2008; 35 (1): 31-39
  - Efficacy of **gabapentin** in the management of chemotherapy- induced peripheral neuropathy: a phase 3 randomized, double blind, placebo-controlled, crossover trial. Cancer 2007; 110: 2110-2118.

Negative Studien

- Radikulopathien
  - **Morphine, nortriptyline** and their combination vs. Placebo in patients with chronic lumbar root pain. Pain 2007; 130: 66-75.
  - **Topiramate** in chronic lumbar radicular pain. J Pain 2005; 6: 829-836
  - A randomized placebo-controlled trial of the efficady and safety of **pregabalin** in the treatment of subjects with neuropathic pain asociated with lumbo-sacral radiculopathy.Pain 2010; 150: 420-7.

Opiate

- Mehrzahl der Opiatverschreibungen bei nicht-tumorbedingten Schmerzen
- Tägliche Dosis nicht über 200mg Morphin-Aequivalent
- Schmerzreduktion bei nozizeptiven und neuropathischen Schmerzen mindestens 30%
- 80% klagen ueber Nebenwirkungen: Obstipation (81%), Uebelkeit (32%), Somnolenz (29%)

Opiate und Mortalität

Tägliche Opiatdosis	OR Mortalität
50-100mg	1.92
100-200mg	2.04
>200mg	2.88

Gesteigerte Vefügbarkeit von Opiaten
akzidentellen Ueberdosierung
häufigster Unfalltod von jungen Menschen
In den USA (Gomes 2011)

Opiate Cochrane I

Study or subgroup	Opioid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gilron 2005	44	37 (22.6)	43	44.9 (22.3)		14.9 %	-7.90 [-17.33, 1.53]
Gimbel 2003	82	41 (27)	77	53 (26)		19.5 %	-12.00 [-20.24, -3.76]
Huse 2001	12	33 (16)	12	40 (12)		10.3 %	-7.00 [-18.32, 4.32]
Morley 2003	19	60 (20)	19	64 (19)		8.6 %	-4.00 [-16.40, 8.40]
Raja 2002	76	44 (24)	76	60 (20)		26.9 %	-16.00 [-23.02, -8.98]
Watson 1998	38	35 (25)	38	54 (25)		10.5 %	-19.00 [-30.24, -7.76]
Watson 2003	36	26.3 (24.7)	36	46.7 (26.9)		9.3 %	-20.40 [-32.33, -8.47]
Total (95% CI)	**307**		**301**			**100.0 %**	**-12.77 [-16.41, -9.13]**

Heterogeneity: $Chi^2 = 7.54$, df = 6 (P = 0.27); I^2 =20%

Test for overall effect: Z = 6.88 (P < 0.00001)

CochraneReview 2006

- Signifikant wirksam auch auf mechanische Allodynie
- NW 11-33%
- Keine Information zu Gewöhnung und Abhängigkeit → insbesondere Langzeit!
- Effekt auf Lebensqualität nicht belegt

Cochrane II (McNicol 2013)

Analysis 2.1. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 1 Number of participants with at least 33% pain relief.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome: 1 Number of participants with at least 33% pain relief

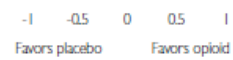
Study or subgroup	Opioid n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Gilron 2005	35/44	13/42		16.3 %	0.49 [0.30, 0.67]
Gimbel 2003	37/82	20/77		19.1 %	0.19 [0.05, 0.34]
Hanna 2008	68/121	52/127		20.9 %	0.15 [0.03, 0.28]
Khoromi 2007	13/32	11/33		13.1 %	0.07 [-0.16, 0.31]
Watson 1998	22/38	7/38		15.2 %	0.39 [0.20, 0.59]
Wu 2008	33/50	19/43		15.3 %	0.22 [0.02, 0.42]
Total (95% CI)	**367**	**360**		**100.0 %**	**0.25 [0.13, 0.37]**

Total events: 208 (Opioid), 122 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.65$, df = 5 (P = 0.02); $I^2 = 63\%$

Test for overall effect: Z = 4.18 (P = 0.000030)

Test for subgroup differences: Not applicable



Opiate und Cochrane II

- Opiate wirksam in Schmerzreduktion von mindestens 33% und 50%
- Viele Lebensqualitätkriterien nicht erfüllt
- Verglichen mit aktivem Plazebo (z.B. Amitryptiline) nicht unbedingt besser
- Allerdings wahrscheinlich mit geringeren Dosen (Wu 2008)

Kein Einfluss auf Depression

Analysis 2.7. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 7 Beck Depression Inventory.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

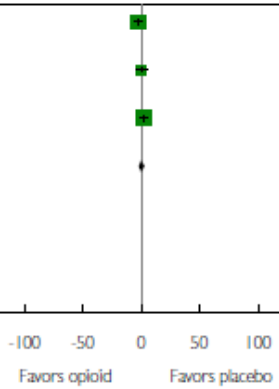
Outcome: 7 Beck Depression Inventory

Study or subgroup	Opioid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Gilron 2005	44	6.7 (6.6)	42	8.5 (6.5)		39.0 %	-1.80 [-4.57, 0.97]
Khoromi 2007	32	9.6 (8.5)	33	9 (8.5)		24.6 %	0.60 [-3.53, 4.73]
Raja 2002	66	12.1 (8.9)	56	10 (7.8)		36.4 %	2.10 [-0.86, 5.06]
Total (95% CI)	**142**		**131**			**100.0 %**	**0.21 [-2.29, 2.71]**

Heterogeneity: $Tau^2 = 2.18$; $Chi^2 = 3.61$, df = 2 (P = 0.16); $I^2 = 45\%$

Test for overall effect: Z = 0.17 (P = 0.87)

Test for subgroup differences: Not applicable



Opiate Sicherheit Cochrane 2013

- Mortalität nicht unterschiedlich (wahrscheinlich zu geringe Dosen und insgesamt zu geringe Fallzahlen)
- Abhängigkeit kein Unterschied (wahrscheinlich vorsorglicher Ausschluss in den Studien und geringe Häufigkeit

Opiate Cochrane 2013

- Kurzzeitapplikation inkonklusive Resultate → kein guter Prädiktor
- NNTB 4.0-5.9 (umstrittener outcome s.u.)
- Eindimensionaler outcome (Lebensqualität kein Unterschied, evozierter Schmerz nicht besser)
- Kein Unterschied zwischen zentral und peripher neuropathischen Schmerz
- Studien in niedrigen bis mittleren Opiatbereich

Kombinationsstudien mit Opiaten Cochrane (Chaparro 2012)

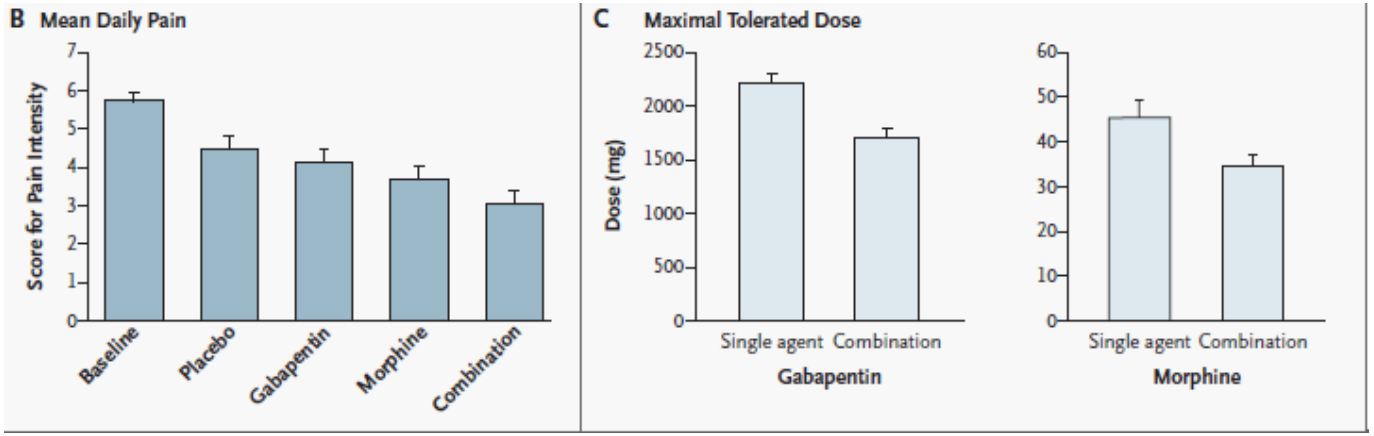
- Nur 21 randomisierte kontrollierte Studien (nur 4 mit Opiaten)
- Oft besser als Monotherapie
- Allerdings einige methodologische Probleme (nur die Hälfte verglich mit jeder Monotherapie)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Morphine, Gabapentin, or Their Combination for Neuropathic Pain

Ian Gilron, M.D., Joan M. Bailey, R.N., M.Ed., Dongsheng Tu, Ph.D., Ronald R. Holden, Ph.D., Donald F. Weaver, M.D., Ph.D., and Robyn L. Houlden, M.D.



Gilron I NEJM 2005

Morphine, Nortriptyline and their Combination vs. Placebo in Patients with Chronic Lumbar Root Pain

Suzan Khoromi, MD, MHS1, **Lihong Cui, MS**2, **Lisa Nackers, BS**3, and **Mitchell B. Max, MD**4

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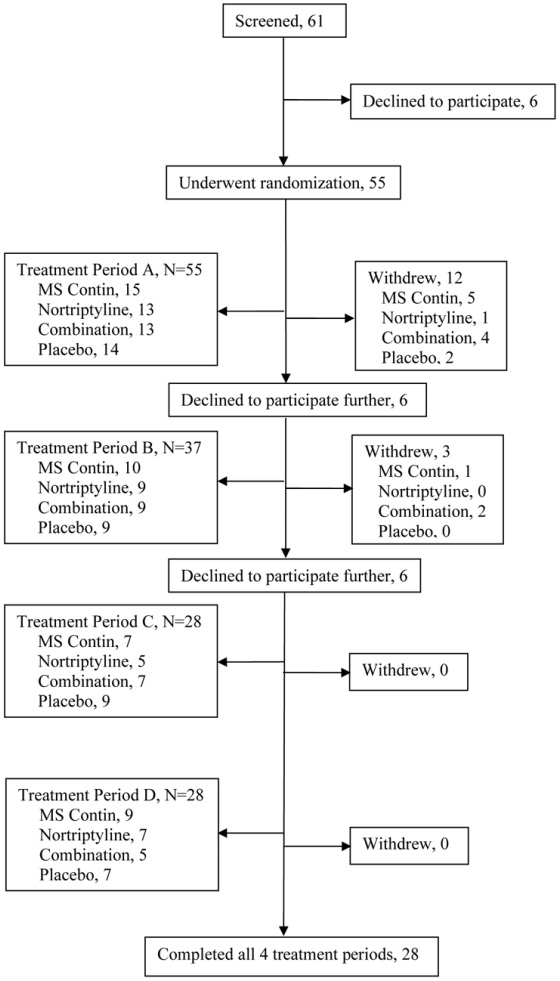
2 *Biostatistics, National Institute of Mental Health, Bethesda, MD 20892*

3 *Laboratory of Clinical Investigation, Division of Intramural Research, National Center for Complementary and Alternative Medicine, Bethesda, MD 20892*

4 *Clinical Pain Research Section, National Institute of Dental and Craniofacial Research, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892*

Pain. 2007 July ; 130(1-2): 66–75



Mean doses were: nortriptyline alone, 84 +/− 24.44 (SD)mg/day; morphine alone, 62 +/−29mg/

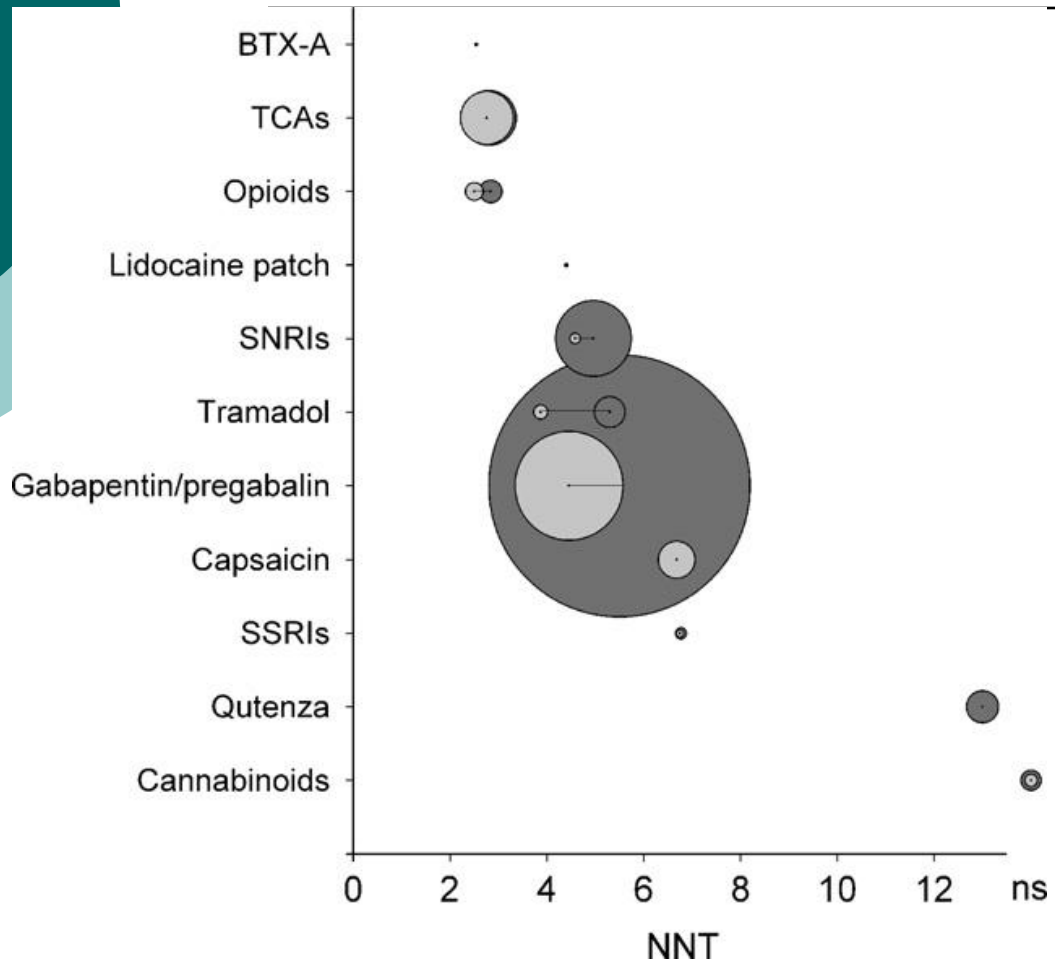
day; and combination, morphine, 49 +/−27 mg/day plus nortriptyline, 55 mg+/− 33.18 mg/day.

The number of patients reporting moderate pain relief or better on the Global Pain Relief questionnaires for, morphine, nortriptyline, the combination treatment and placebo were 13 (42%), 12 (40%), 18 (67%), and 11 (37%) respectively.

→ Problem: oft kombinierter Schmerz neuropathisch/Plazebo

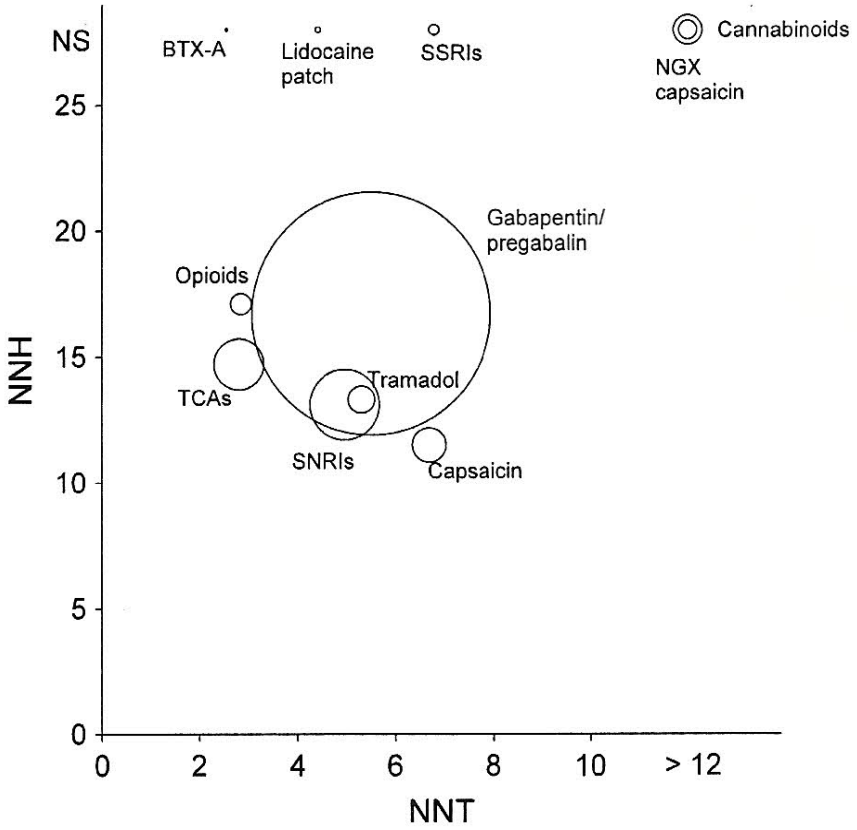
.

Number needed to treat (NTT) in peripheral neuropathic pain



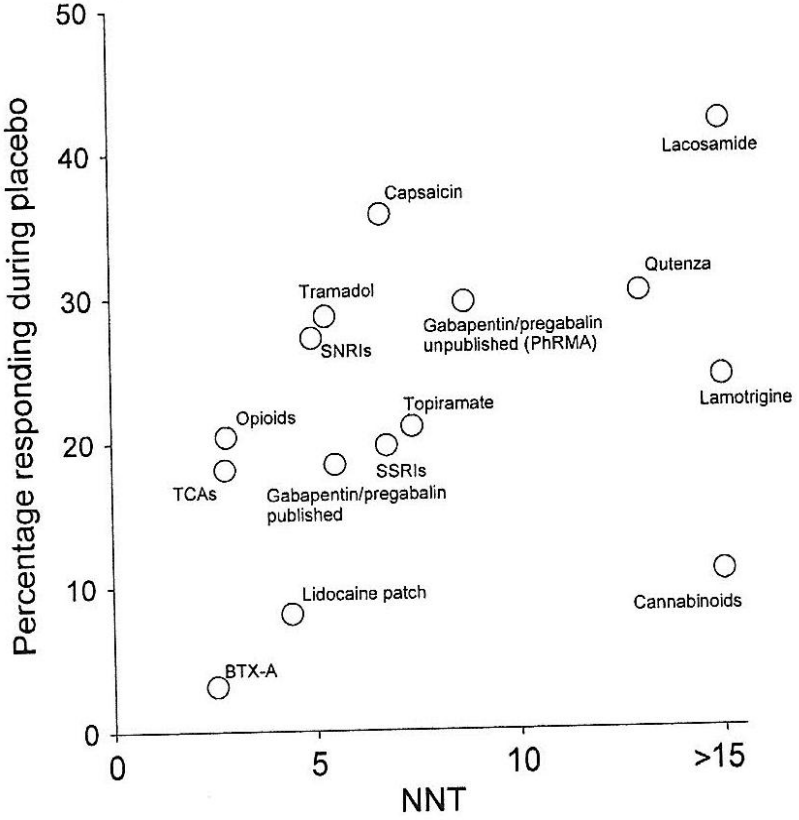
Finnerup NJ et al. Pain (2005) et (2010)

Number needed to harm (NNH) vs Number needed to treat (NNT)



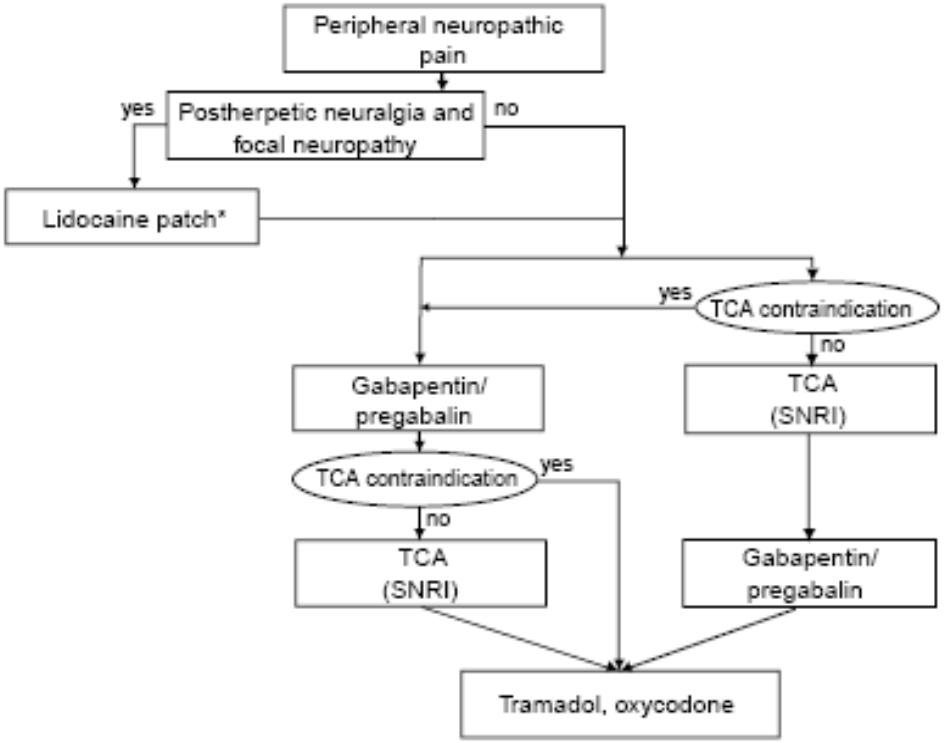
Finnerup NJ et al. Pain (2005
et (2010)

NNT für das Plazebo



Finnerup NJ et al. Pain (2005) et (2010)

Der Behandlungsalgorithmus hat seit 2005 nicht geändert



Finnerup NJ et al. Pain (2005) et Pain (2010)

Nicht publizierte Studien

- www.clinicalstudyresults.org
- Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database
- Important pour des études non publiées

Probleme der Guidelines

- Sehr wenig Vergleichsstudien zwischen den einzelnen Substanzen
- NNT/NNH haben ihre Probleme
  - Ausschluss der Studien ohne Plazebo
  - Verschiedene Schwellen zur Messung der Schmerzreduktion
  - Schmerzreduktion eindimensional
  - Unterschiedliches Studiendesign

Finnerup 2005 et 2010, Dworkin 2010

Warum haben sich die Guidelines nicht geändert

- Wenig Studien mit den neuen Medikamenten und mit rareren Erkrankungen
- Klassifikation nach Krankheiten und nicht nach Mechanismen
- Schmerzintensität als alleinige „outcome measure“
- Unbekannte Mechanismen der Chronifizierung
- Wenig Kombinationsstudien

Moleküle in der Pipeline

Drug	Company	Mechanism	Phase	Indications
Prialt (ziconotide)	Elan/Eisai	N-type Ca-channel blocker, intrathecal	Launched	Severe chronic pain
Lacosamide (Vimpat, Harkoseride)	Schwarz Pharma	Nav block	Ph3	Positive in PDN. Evaluation in fibromyalgia and OA ongoing
Ralfinamide Alipamide NW1029	Newron	Nav blocker MAO-inhibitor	Ph2	Evaluation in several NP conditions
Topamax topiramate	J&J	Glut antag/GABA agonist/Na blocker	Ph3 (PDN)	Launch for epilepsy and migraine. Effective in PDN
ADX10059, ADX48621	Addex	mGluR5 inhibitor	Ph2	Efficacy in acute migraine. Ph2 planned for NP
AZD 2066	AstraZeneca	mGluR5 inhibitor	Ph1	Ongoing
XP13512	GSK/Xenoport	Pro-gabapentin	Ph 2	Recruiting Ph2
Tezampanel NGX426	TorreyPines	AMPA/kinate antagonist	Ph2	Ongoing
TC6499	GSK/ Targacept	Neuronal nicotinic receptor agonist	Ph1	Recruiting Ph1
Retigabine	Valeant	Potassium channel KCNQ2/3 opener	Ph3	Efficacy in epilepsy, PHN
NGD8243 (MRK2295)	Merck/ Neurogen	TRPV1 antag	Ph2	Postop dental pain
GRC-6211	Lilly/ Glenmark	TRPV1 antag	Ph2	Ongoing for NP and OA
AMG 986	Amgen	TRPV1 antag	Ph1	In progress
AZD1386	AstraZeneca	TRPV1 antag	Ph1	In progress
Transacin (Transdolor, NGX-4010) (topical)	NeurogesX	TRPV1 agonist (capsaicin)	Ph3 (PHN, HIV) and Ph2 (PDN)	Pain reduction in HIV and PHN
Sativex, GW-1000, Buccal spray	GW Pharma	Cannabinoid-receptor agonist	Ph3, Ph2 in PDN	Approved for cancer and MS pain. Effective in NP with allodynia
IP 751, CT-3, ajulemic acid	Indevus	CB1 receptor-agonist/CoX-2/IL-1 block	Ph2	Reduces spinal and nerve injury pain
KDS2000 (topical)	Kadmus Pharma	Cannabinoid	Ph 2	Progress in PHN and PDN
AZD 1940	AstraZeneca	Cannabinoid-receptor agonist	Ph1	Progress
TRO-19622 (oral)	Trophos	Unknown	Ph2a	Recruiting PDN patients
RN624 PF-4383119	Pfizer/Rinat	Anti-NGF mAb	Ph2 (OA)	Recruiting for PHN, LBP, bone pain, cystitis
AMG403	Amgen	Anti-NGF mAb	Ph2 starting	
SB-509	Sangamo	Plasmid DNA to up-regulate VEG-F	Ph2 (PDN)	Disease modifying for diabetes

Dray A, British Journal of Anaesthesia 101 (1): 48-58 (2008)

Zusammenfassung

- Dem Patienten die Krankheit erklären (auch wenn wir sie nicht ursächlich behandeln können)
- Seine Ressourcen und Prioritäten verstehen
- Realistische Ziele
- Frühzeitige multidisziplinäre Arbeit
- www.pain.ch
- **Schweizerische Gesellschaf zum Studiem des Schmerzes (SSGS)**
  - Nationale Sektion der l'IASP (International Association for the Study of Pain)
  - lEFIC (European Federation of IASP Chapters).

Sir Charles Bell.
The Anatomy and Philosophy ofExpression: as Connected with the Fine Arts. 5th ed.

London : Henry G. Bohn, 1865