Neue Aspekte in der Schmerztherapie

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Conflict of Interest:

Vortragshonorare und Advisory Boards
Wissenschaftsunterstützungen

Grünenthal, Gerot Lannacher, Gebro-Pharma, CSC-Pharma, Böhringer Ingelheim, Sintetico, Reckitt Benkiser, Fresenius,Bionorica,Trigal

1) **Postoperativer Schmerz**
2) Neuropathischer Schmerz
3) Post Covid, Long-Covid
4) Vagusstimulation

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Definition CPSP oder PPP

- **Schmerz,**
- der nach einer Operation neu auftritt,
  - der nach einer Operation >2 Monate persistiert, → **nach 3 Monaten**
  - für den andere Ursachen ausgeschlossen wurden und
- der nicht das Resultat eines kontinuierlichen präexistierenden Problems ist.
- Problem: Zeitliche Definition schwierig!

1,2 Millionen Operationen in Österreich - 10% chronische Schmerzen

**nach:*

***Macrae WA,** Davies HTO. Chronic postsurgical pain. In: Crombie IK, Linton S, Croft P, Von Korff M, LeResche L, editors. Epidemiology of pain. Seattle: IASP Press; 1999; 125–42.)*

***Kehlet H**, Rathmel JP. Persistant postsurgical pain: pathogenic mechanism and preventive strategies. The path forward through better design of clinical studies. Anesthesiology 2010;112.514-15*

***Rappapor**t BA, Cerny I Sanhai WR. **ACTION** on the prevention of chronic pain after surgery: public-private partnerships, the future of analgesic drug development. Anesthesiology2010; 112:509-10*

1. Chronic postsurgical pain is either a continuum of acute postoperative pain or develops after an asymptomatic period;
2. Chronic postsurgical pain shows greater intensity or different pain characteristics than preoperative pain (an important point regarding CPSP after orthopedic procedures, where preoperative pain may affect up to 80% of patients undergoing surgery);
3. **The cutoff for CPSP has now been fixed at 3 months after surgery because healing times differ among different procedures; for major orthopedic surgeries such as hip and knee arthroplasties, pain reaches its lowest level by 3 months after surgery.**

Lavand'homme P, Transition from acute to chronic pain after surgery. PAIN The Journal of the International Association for the Study of Pain. Vol. 158, No.4, April 2017.

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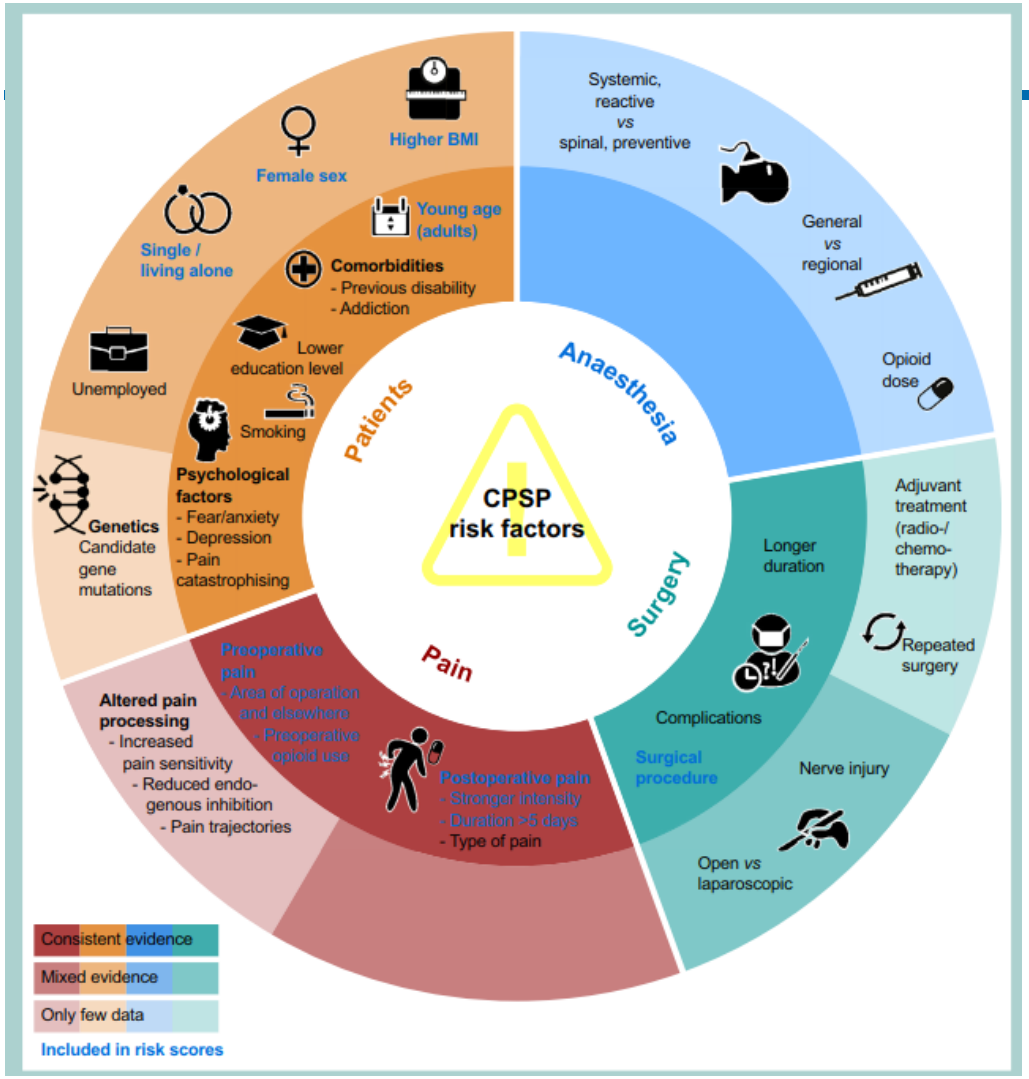
Incidences of CPSP for different types of surgery. Data adapted from several studies. Severe CPSP is defined as painratings of 5 on a scale from 0 (no pain) to 10 (worst possible pain). CPSP, chronic post-surgical pain; NP, neuropathic pain.

Type of surgery	Incidence of all CPSP (%)	Incidence of severe CPSP (>5/10)	Chronic pain up to 12 months	Proportion of NP
Abdominal surgery (bowel and colorectal)	17–21	Not reported	Not reported	Not reported
Amputation	30–85	5–10%	75% (lower limbs)	80%
Caesarean section	6–55	5–10%	Not reported	50%
Cholecystectomy	3–56	Not reported	Not reported	Not reported
Craniotomy	7–65	25%	Not reported	Not reported
Dental surgery	5–13	Not reported	Not reported	Not reported
Hip arthroplasty	7–23	6%	28%	1–2%
Inguinal herniotomy	5–63	2–4%	30%	80%
Knee arthroplasty	13–44	15%	18%	6%
Mastectomy	11–57	5–10%	43–56% (breast cancer surgery)	65%
Sternotomy	7–50	5–10%	27%	13%
Thoracotomy	5–71	10%	41%	45%
Vasectomy	0–37	Not reported	Not reported	Not reported

Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W,Treede R-D. The IASP classification of chronic pain forICD-11: chronic postsurgical or posttraumatic pain. Pain2019; 160: 45e52
Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. Pain Rep 2017; 2: e627
Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet 2019; 393: 1537e46
Richebe P, Capdevila X, Rivat C. Persistent postsurgical pain: pathophysiology and preventative pharmacologic considerations. Anesthesiology 2018; 129: 590e607
Steyaert A, Lavand'homme P. Prevention and treatment of chronic postsurgical pain: a narrative review. Drugs 2018; 78: 339e54
Lavand'homme P. Transition from acute to chronic pain after surgery. Pain 2017; 158: S50e4

Rosenberger D.C., Pogatzki-Zahn E.M.; Chronic post-surgical pain – update on incidence, risk factors and preventive treatment options. BJA Education, 22(5): 190-196 (2022)



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Risk factors for CPSP. Proposed risk factors for development of CPSP and grade of consistency of evidence. Figure adapted from data of Glare and colleagues,
Lavand'homme and Steyaert and Lavand'homme. Dark colours relate to consistent evidence from studies, light colours refer to mixed or low evidence (see colour legend). Text in blue refers to risk factors included in risk scores. CPSP, chronic post-surgical pain.

Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet 2019; 393: 1537e46
Lavand'homme P. Transition from acute to chronic pain after surgery. Pain 2017; 158: S50e4
Steyaert A, Lavand'homme P. Prevention and treatment of chronic postsurgical pain: a narrative review. Drugs 2018; 78: 339e54

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Methods:
PAIN OUT, an international perioperative pain registry, provided standardized methodology for assessing management and multi- dimensional PROs (patient reported outcomes) on the first postoperative day, in patients undergoing orthopaedic, general surgery, obstetric & gynaecology or urological procedures.

Results:
Between 2017 and 2019, data obtained from 10,415 adult patients in 105 wards, qualified for analysis. At the ward level: 50% (median) of patients reported worst pain intensities ≥7/10 NRS, 25% spent ≥50% of the time in severe pain and 20– 34% reported severe ratings for pain- related functional and emotional interference. Demographic variables, country and surgical discipline explained a small proportion of the variation in the PROs, leaving about 88% unexplained. Most treatment processes varied considerably between wards. Ward effects accounted for about 7% and 32% of variation in PROs and treatment processes, respectively.

PAIN OUT Research Group Jena; Chinese PAIN OUT network; Dutch PAIN OUT network; Méxican PAIN OUT network; Serbian PAIN OUT network; Spanish PAIN OUT network; French PAIN OUT network; Italian PAIN OUT network; Swiss PAIN OUT network; Irish PAIN OUT network; Belgian PAIN OUT network; Zaslansky R. Status quo of pain-related patient-reported outcomes and perioperative pain management in 10,415 patients from 10 countries: Analysis of registry data. Eur J Pain. 2022 Nov;26(10):2120-2140. doi: 10.1002/ejp.2024. Epub 2022 Sep 26. PMID: 35996995.

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Conclusions:

This comprehensive evaluation demonstrates that many patients in this international cohort reported poor pain- related PROs on the first postoperative day.

PROs and treatments varied greatly. Most of the variance of the PROs could not be explained.

The findings served as a basis for devising and implementing QI(Quality improvement projects) programmes in participating hospitals

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Non-opioid analgesics and opioids administered on the ward and perioperatively

On the ward, 94.7% (83.5– 98.3) of patients were administered a non- opioid analgesic. Of these, the majority of patients, 57%, received one and 38% received two non- opioids. Paracetamol was the most commonly used non-opioid, administered with a frequency of 65% (6– 95). NSAIDs were the second most commonly administered non- opioid, administered to 57.5% (34.4– 78.8) patients across the wards. The use of metamizole was restricted to five countries in the cohort. In these countries, 12.2% (0.7– 40.2) of patients across wards received this medication.

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A systemic opioid was administered to 48.8% (25– 68.6) of patients across the wards. **The intravenous route was used in 57.9% (n= 2867/4954) and the oral route in 40.7% (n= 2015/4954) of these patients. Median daily doses of the most frequently administered systemic opioids were: 10 mg for oxycodone (10– 20 mg, n= 1892), 100 mg for tramadol (100– 200 mg, n= 1454) and 10 mg for morphine (5– 19 mg, n= 527).**

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The most frequently administered non-opioid analgesics are shown as cumulative doses (intraoperative, PACU, ward) and doses administered on the ward. Median doses, including first (Q1) and third quartile (Q3) and the number of analysed doses are displayed

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	Cumulative			Ward		
Medication	**Median**	**[Q1–Q3]**	***n***	**Median**	**[Q1–Q3]**	***N***
Paracetamol	3000	[2000–4000]	5991	2000	[1200–3000]	5468
Metamizole	3000	[2000–5000]	2231	2500	[2000–4000]	1541
Ketorolac	60	[30–90]	2452	60	[30–90]	1513
Diclofenac	100	[75–150]	1113	100	[75–50]	821
Parecoxib	40	[40–80]	1214	80	[40–80]	741
Flurbiprofen	100	[50–150]	917	147	[100–243]	414
Ketoprofen	160	[100–300]	889	160	[100–200]	487

PAIN OUT Research Group Jena; Chinese PAIN OUT network; Dutch PAIN OUT network; Méxican PAIN OUT network; Serbian PAIN OUT network; Spanish PAIN OUT network; French PAIN OUT network; Italian PAIN OUT network; Swiss PAIN OUT network; Irish PAIN OUT network; Belgian PAIN OUT network; Zaslansky R. Status quo of pain-related patient-reported outcomes and perioperative pain management in 10,415 patients from 10 countries: Analysis of registry data. Eur J Pain. 2022 Nov;26(10):2120-2140. doi: 10.1002/ejp.2024. Epub 2022 Sep 26. PMID: 35996995.

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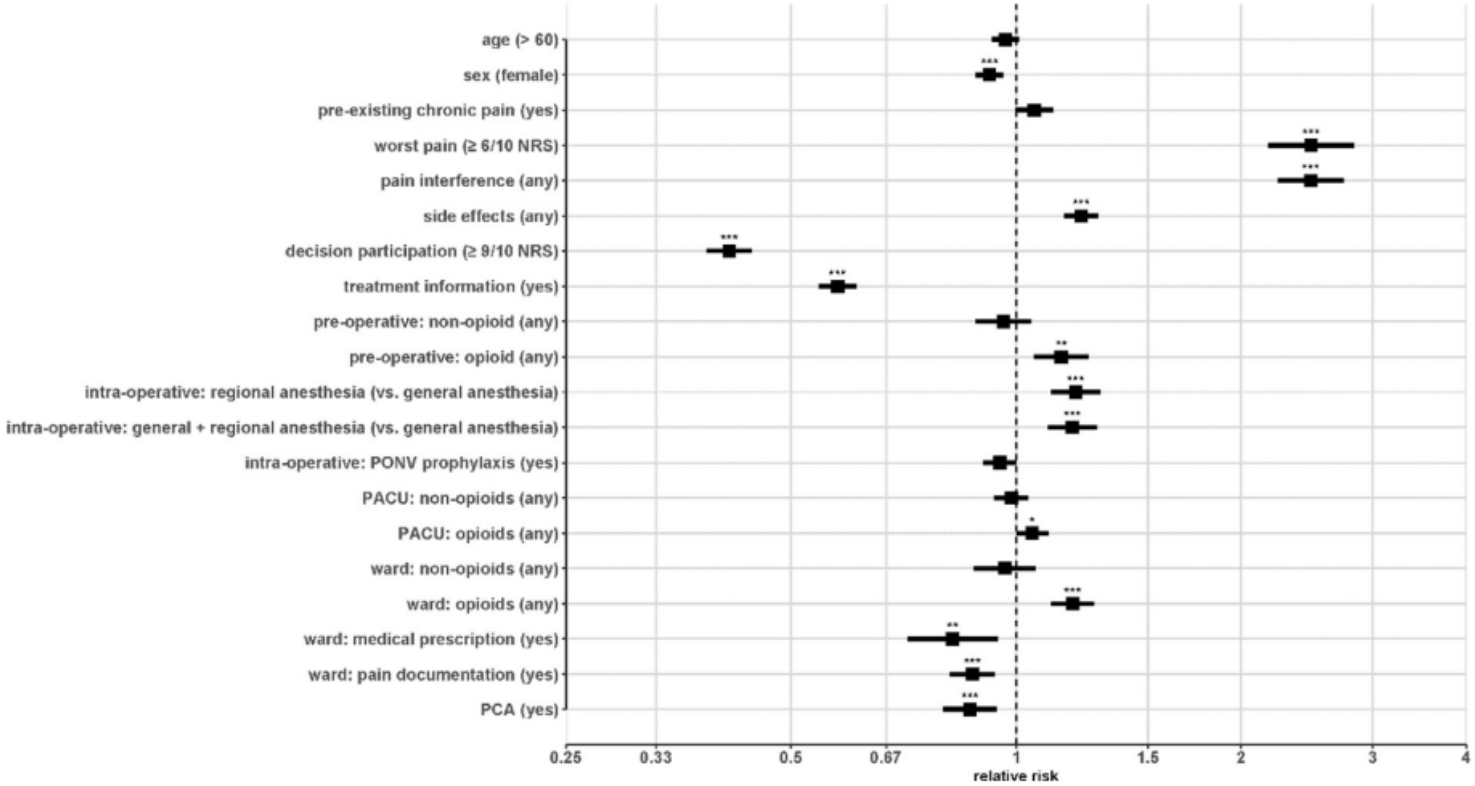
Acute postoperative pain is frequently evaluated by pain intensity scores. However, interpretation of the results is difficult and thresholds requiring treatment are not well defined. Additional **patient reported outcome measures (PROMs)** might be helpful to better understand individual pain experience and quality of pain management after surgery. We used data from the QUIPS pain registry for a cross-sectional study in order to investigate associations between the **desire to receive more pain treatment (D2RMPT)** with pain intensity ratings and other PROMs. Responses from 79,996 patients were analyzed, of whom 10.7% reported D2RMPT. A generalized estimating equation Poisson model showed that women had a lower risk ratio (RR) to answer this question with “yes” (RR: .92, P < .001). Factors that increased the risk most were “maximal pain intensity ≥ 6/10 on a numerical rating scale” (RR: 2.48, P < .001) and “any pain interference” (RR: 2.48, P < .001). **The largest reduction in risk was observed if patients were “allowed to participate in pain treatment decisions” (RR: .41, P < .001) and if they felt that they “received sufficient treatment information” (RR: .58, P < .001). Our results indicate that the (easily assessed) question D2RMPT gives additional information to other PROMs like pain intensity. The small proportion of patients with D2RMPT (even for high pain scores) opens the discussion about clinicians’ understanding of over- und under-treatment and questions the exclusive use of pain intensity as quality indicator. Future studies need to investigate whether asking about D2RMPT in clinical routine can improve postoperative pain outcome**

Komann M, Baumbach P, Stamer UM, Weinmann C, Arnold C, Pogatzki-Zahn E, Meißner W. Desire to Receive More Pain Treatment - A Relevant Patient-Reported Outcome Measure to Assess Quality of Post-Operative Pain Management? Results From 79,996 Patients Enrolled in the Pain Registry QUIPS from 2016 to 2019. J Pain. 2021 Jun;22(6):730-738. doi: 10.1016/j.jpain.2021.01.002. Epub 2021 Jan 20. PMID: 33482323.



Results of the multivariable regression model. Relative risks (squares) and corresponding 95% confidence intervals (black lines) are shown for the independent variables (*:P < .05, **: P < .01, ***: P < .001; PACU, postanesthesia care unit; PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting).

Komann M, Baumbach P, Stamer UM, Weinmann C, Arnold C, Pogatzki-Zahn E, Meißner W. Desire to Receive More Pain Treatment - A Relevant Patient-Reported Outcome Measure to Assess Quality of Post-Operative Pain Management? Results From 79,996 Patients Enrolled in the Pain Registry QUIPS from 2016 to 2019. J Pain. 2021 Jun;22(6):730-738. doi: 10.1016/j.jpain.2021.01.002. Epub 2021 Jan 20. PMID: 33482323.

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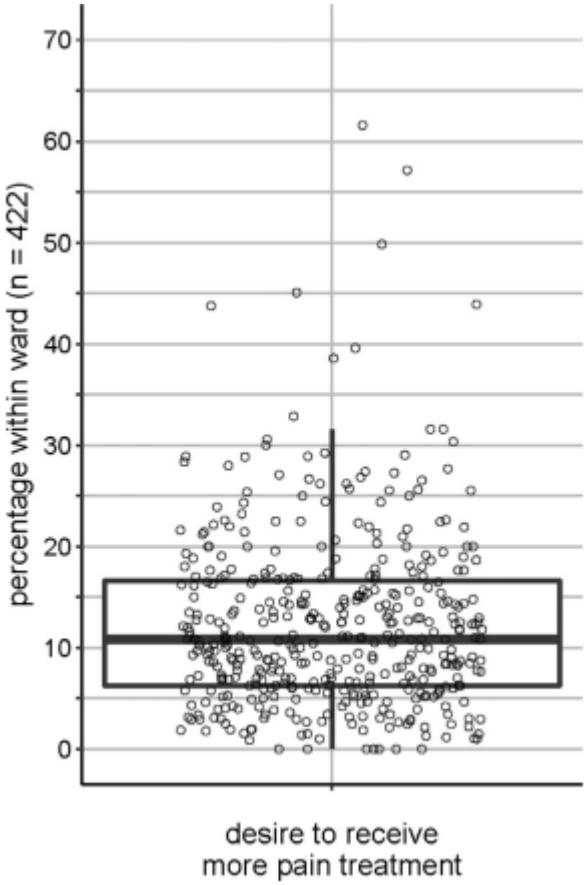
Box-plot of the percentages of desire to receive more pain treatment for each ward (n = 422, open dots). **The median percentage of desire to receive more pain treatment over all wards was 10.8% (thick line in the boxplot).**



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1) Postoperativer Schmerz
2) **Neuropathischer Schmerz**
3) Post Covid, Long-Covid
4) Vagusstimulation

Tabelle 1: Zusammenstellung der Hilfsmittel für Screening, Diagnose und Therapie neuropathischer Schmerzen in der hausärztlichen Praxis. Alle Elemente können unter https://www.cme-point.de/fortbildungen-3/schmerztherapie/neuropathische-schmerzen im PDF-Format abgerufen werden.

DIAGNOSE-/THERAPIEHILFE		WAS?	WER?	WO ZU FINDEN?
DIAGNOSE (KAPITEL 5)				
Schritt 1	GPS – *General Pain Screener* • 5 Basisfragen • Wird vom Patienten im Wartezimmer ausgefüllt	Schmerzscreening • Basisdaten zum Schmerz	Patient und Medizinische Fachkraft	Siehe Abbildung 1
Schritt 2	painDETECT®-Fragebogen • Fragen zu Hinweisen auf neuropathische Schmerzen • Wird vom Patienten im Wartezimmer ausgefüllt	Suchtest für neuropathische Schmerzkomponente	Patient und Medizinische Fachkraft	www.pain-detect.de
Schritt 3	Diagnose-Algorithmus • Diagnose: Neuropathischer Schmerz • Abklärung der Schmerzausbreitung • Wird vom Arzt ausgefüllt	Schmerzursache und -ausbreitung • Peripherer oder zentraler neuropathischer Schmerz? • Schmerz *lokalisiert* oder *diffus*?	Arzt	Siehe Abbildung 2
THERAPIE (KAPITEL 7)				
Schritt 4	Therapie-Algorithmus • Empfehlungen zum therapeutischen Vorgehen • Orientiert sich an Schmerzausbreitung, Komorbiditäten, Komedikation und Kontraindikationen	Einleitung der Behandlung • Bei *lokalisiertem* neuropathischem Schmerz: bevorzugt topische Therapie • Bei *diffusem* neuropathischem Schmerz: bevorzugt systemische Therapie	Arzt	Siehe Abbildung 3

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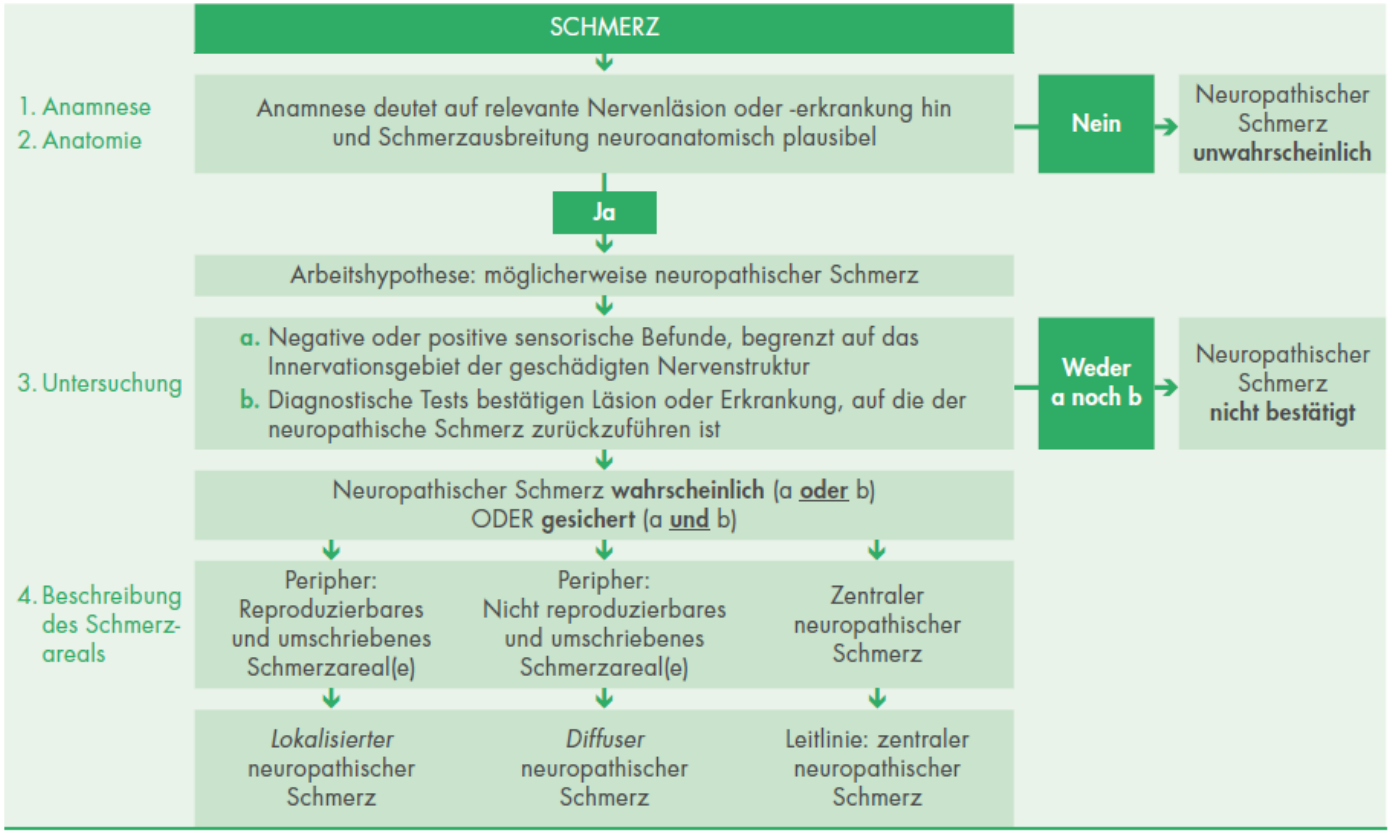

Abbildung 2: Diagnose-Algorithmus für neuropathischen Schmerz. Liegen bei einem Schmerzpatienten anamnestisch Hinweise auf eine relevante Läsion oder eine zugrunde liegende Erkrankung des somatosensorischen Systems vor und zeigt die Schmerzausbreitung eine plausible neuroanatomische Verteilung, ist eine neuropathische Schmerzkomponente möglich (Arbeitshypothese). Findet sich anhand der klinischen Untersuchung zum Nachweis positiver und negativer sensorischer Symptome (*Bedside*-Tests) und/oder spezieller diagnostischer Verfahren ein weiterer Anhaltspunkt für das Vorliegen einer neuropathischen Schmerzkomponente, ist der neuropathische Schmerz wahrscheinlich oder gesichert. In Hinblick auf die Therapieentscheidung erfolgt anhand der Beschreibung des schmerzhaften Areals eine Einordnung in *lokalisierte* oder *diffuse* neuropathische Schmerzen; modifiziert nach [Mick et al. 2012, Treede et al. 2008].

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Tabelle 2: Definition und Untersuchung negativer und positiver sensorischer Symptome bei neuropathischen Schmerzen; modifiziert nach [Baron et al. 2012].

SYMPTOM	DEFINITION/UNTERSUCHUNG (*BEDSIDE*-TESTS)
NEGATIVSYMPTOME	
Hypästhesie	Reduzierte Empfindung nicht schmerzhafter Reize (z. B. Pinsel oder Watteträger)
Hypalgesie	Reduzierte Empfindung schmerzhafter Reize (z. B. *Pinprick*, Zahnstocher)
Pallhypästhesie	Reduzierte Empfindung eines Vibrationsreizes (z. B. Stimmgabel auf Knochen)
Thermhypästhesie	Reduzierte Empfindung eines Wärme- oder Kältereizes (z. B. warmer oder kalter Gegenstand)
POSITIVSYMPTOME (SPONTAN ODER EVOZIERT)	
Parästhesie	Nicht schmerzhafte, unangenehme Missempfindung (z. B. Ameisenlaufen, Stromgefühl)
Dysästhesie	Schmerzhafte Missempfindung
Spontanschmerz	Nicht durch einen Stimulus erzeugt, meist brennend oder elektrisierend
Allodynie	Schmerz auf einen üblicherweise nie schmerzhaften Reiz (z. B. Pinsel oder Watteträger)
Hyperalgesie	Überschießende Reaktion auf leichten Schmerzreiz (z. B. *Pinprick* oder scharfer Zahnstocher, Kälte- oder Wärmereiz)

Pinprick – Nadelstich

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Tabelle 3: Medikamente und Dosierungen bei neuropathischen Schmerzen. Die Tabelle bildet nur eine Auswahl an Substanzen ab. Für eine vollständige Auflistung der Nebenwirkungen und Kontraindikationen, s. [Rote Liste 2018]. Bitte den jeweiligen Zulassungsstatus der Medikamente beachten.

ARZNEISTOFF	STARTDOSIS	AUFDOSIERUNG ZIELDOSIS (ZD) Maximaldosis pro Tag (d) (Max)	BESONDERHEITEN UND WICHTIGE NEBENWIRKUNGEN	ZULASSUNG FÜR DIE SCHMERZTHERAPIE		
				DE	CH	AT
ANTIKONVULSIVA						
Gabapentin (Kalziumkanal, α2δ)	3 x 100 mg (Beginn mit abendlicher Dosis)	Täglich um 300 mg steigern bis 1.200 mg/d, dann falls erforderlich wöchentlich um 600 mg steigern **ZD:** 1.200–3.600 mg/d, 3–4 Dosen **Max:** 3.600 mg/d	Müdigkeit, Schwindel, Gangunsicherheit, periphere Ödeme, kaum Interaktionen, Dosis an Nierenfunktion anpassen, verzögerter Wirkbeginn	✓[1]	✓[2]	✓[1]
Pregabalin (Kalziumkanal, α2δ)	2 x 50–75 mg (Beginn mit abendlicher Dosis)	Nach 3–7 Tagen Steigerung um 50–75 mg auf 150 mg/d, dann falls erforderlich wöchentlich um 150 mg steigern **ZD:** 150–600 mg/d, 2 Dosen **Max:** 600 mg/d	Müdigkeit, Schwindel, Gangunsicherheit, periphere Ödeme, Gewichtszunahme, wirkt anxiolytisch, kaum Interaktionen, lineare Plasmakonzentration, Dosis an Nierenfunktion anpassen, verzögerter Wirkbeginn	✓[2]	✓[2]	✓[2]
Carbamazepin retard (Natriumkanal)	100–200 mg (abends)	200 mg alle 3–7 Tage **ZD:** 400–800 mg/d, 2 Dosen **Max:** 1.400 mg/d	Goldstandardsubstanz bei Trigeminusneuralgie, kognitive Beeinträchtigung, Blutbildveränderungen, Leberschäden, Hyponatriämie, Hautausschlag, Medikamenteninteraktionen wegen Enzyminduktion, langsame Aufdosierung notwendig	✓[3,4]	✓[3]	✓[3]
Oxcarbazepin	300 mg (abends)	300 mg alle 3–7 Tage **ZD:** 900–1.200 mg/d, 2 Dosen **Max:** 2.400 mg/d	Etwas weniger NW und Interaktionen als Carbamazepin, aber häufiger Hyponatriämien, Dosisäquivalenz Carbamazepin : Oxcarbazepin ~ 1 : 1,5	-	-	-
ANTIDEPRESSIVA						
Amitriptylin (TCA; 5HT, NA)	10–25 mg (abends)	10–25 mg alle 7 Tage **ZD:** 50–75 mg/d als Einmalgabe unretardiert abends, bei begleitender Depression 75–150 mg **Max:** 150 mg/d	Müdigkeit, Schwindel, Sedierung (Sturzgefahr!), Miktions- und Akkommodationsstörungen, Hypotonie, Gewichtszunahme, CYP-Interaktionen, langsame Aufdosierung notwendig, Alter und Gewicht des Patienten müssen bei der Dosierung berücksichtigt werden, kardiale Nebenwirkungen (EKG-Kontrollen!), **Cave:** bekannte Herzrhythmusstörungen, Herzinsuffizienz, Glaukom, Prostatahyperplasie	✓[2]	✓[5]	✓[2]
Clomipramin (TCA; NA)	10–25 mg (morgens)	10–25 mg alle 2–3 Tage **ZD:** 50–75 mg/d als Einmalgabe retardiert morgens **Max:** 250 mg/d	Antriebssteigernd, sonst wie Amitriptylin	✓[3]	✓[5]	-
Duloxetin (sSNRI)	30 mg (morgens)	30 mg alle 4–7 Tage **ZD:** 60 mg/d morgens (evtl. bis 120 mg) **Max:** 120 mg/d	Übelkeit, Erbrechen, Mundtrockenheit, Blutdruckanstieg, CYP-Interaktionen, Dosisanpassung bei Rauchern (Wirkungsverlust), keine Kombination mit Tramadol, Triptanen oder Johanniskrautpräparaten, Einnahme mit dem Essen reduziert Übelkeit	✓[4]	✓[4]	✓[4]
Venlafaxin (sSNRI)	37,5 mg (morgens)	75 mg wöchentlich **ZD:** 150–300 mg/d, 1–2 Dosen **Max:** 300 mg/d	Antriebssteigernd, Übelkeit, Erbrechen, Kopfschmerzen, Nervosität, Mundtrockenheit, vermehrtes Schwitzen, Bluthochdruck, Gewichtsabnahme	-	-	-
Mirtazapin (NaSSA)	7,5 mg (zur Nacht)	7,5 mg alle 4–7 Tage **ZD:** 30–45 mg/d zur Nacht **Max:** 45 mg/d	Schlafanstoßend, Müdigkeit, Schwindel, Kopfschmerzen, Sedierung/Benommenheit, Gewichtszunahme, Alpträume, Harnverhalt, Glaukom, Mundtrockenheit	-	-	-

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OPIOIDE						
Tramadol retard	2(–3) x 50–100 mg	50–100 mg alle 3–4 Tage **ZD:** 100-200 mg/d, 2(–3) Dosen **Max:** 600 mg/d	Übelkeit, Hypotonie, Dosisreduktion bei eingeschränkter Nierenfunktion, **Cave:** keine Kombination mit serotonergen Substanzen oder Duloxetin	✓[6]	✓[6]	✓[6]
Oxycodon retard	2(–3) x 5–10 mg	Individuell	Übliche Opioid-NW, Dosisreduktion bei Leber- oder Niereninsuffizienz	✓[6]	✓[6]	✓[6]
Buprenorphin TTS (Schmerzpflaster)	5–10 µg/Stunde	Individuell	Übliche Opioid-NW, keine Dosisreduktion bei eingeschränkter Nierenfunktion, **Cave:** es gibt Pflaster mit Wirkdauer 3 oder 7 Tage	✓[6]	✓[6]	✓[6]
MOR/NRI						
Tapentadol retard	2(–3) x 50 mg	100 mg alle 3-4 Tage **ZD:** 100–200 mg/d, 2(–3) Dosen **Max:** 500 mg/d	Übliche Opioid-NW bei geringerer Obstipation und Absetzproblematik	✓[5,6]	✓[5,6]	✓[5,6]
TOPISCHE THERAPIEN						
Lidocain-Pflaster (Natriumkanal)	5 % (700 mg); 10 x 14 cm; 1 x täglich, bis zu 12 Stunden Pause	1–3 Pflaster täglich	Erythem und Unverträglichkeitsreaktionen am Applikationsareal, kaum systemische Nebenwirkungen oder Medikamentenwechselwirkungen	✓[7]	✓[7]	✓[7]
Capsaicin-Pflaster (TRPV1-Rezeptor)	8 % (179 mg); 14 x 20 cm; 1 x 30 min bzw. 60 min; mind. 90 Tage Pause	1–4 Pflaster pro Anwendung alle 3 Monate oder später	Erythem, Rötung, Brennschmerz und Unverträglichkeitsreaktionen am Applikationsareal, temporäre Schmerzzunahme ggf. mit Blutdruckanstieg, keine systemischen Nebenwirkungen oder Medikamentenwechselwirkungen	✓[1]	✓[1]	✓[1]

AT = Österreich; CH = Schweiz; CYP = Cytochrom P450; DE = Deutschland; MOR/NRI = µ-Opioid-Rezeptoragonisten/Noradrenalin-Wiederaufnahmehemmer; NA = noradrenerg; NaSSA = noradrenerg und spezifisch serotonerg wirkende Antidepressiva; NW = Nebenwirkungen; sSNRI = selektive Serotonin/-Noradrenalin-Wiederaufnahmehemmer; TCA = trizyklische Antidepressiva; TRPV1 = *Transient Receptor Potential Vanilloid* 1; TTC = transdermales therapeutisches System; 5-HT = serotonerg. [1]periphere neuropathische Schmerzen; [2]neuropathische Schmerzen; [3]Trigeminusneuralgie; [4]diabetische Polyneuropathie; [5]langfristige/chronische Schmerzen; [6]mäßig starke/starke Schmerzen [7]Post-zoster-Neuralgie (PZN).

Gillhausen K. et al.; Diagnose und Therapie neuropathischer Schmerzen: Eine praktische Hilfe für den hausärztlichen Alltag; CME.2019

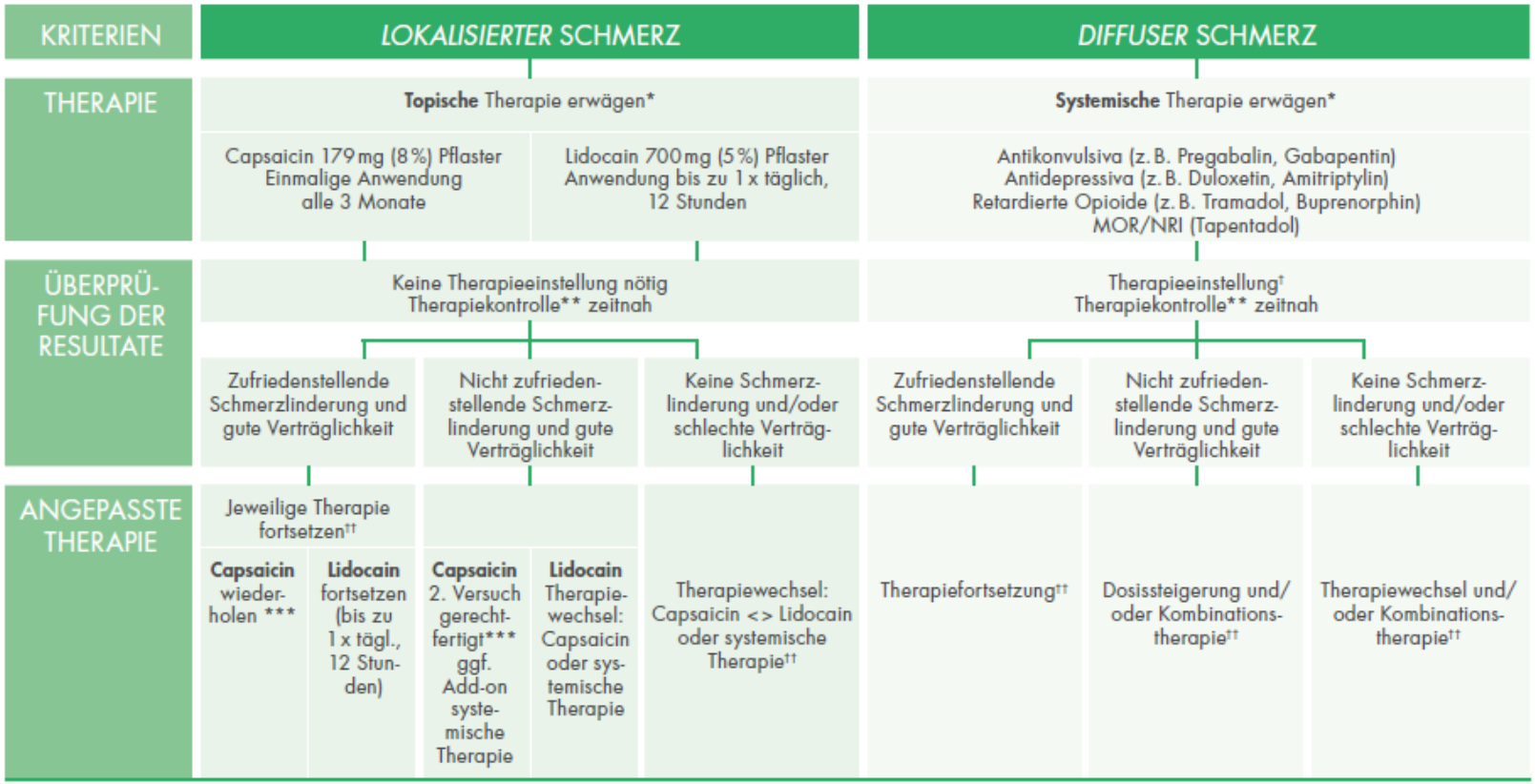
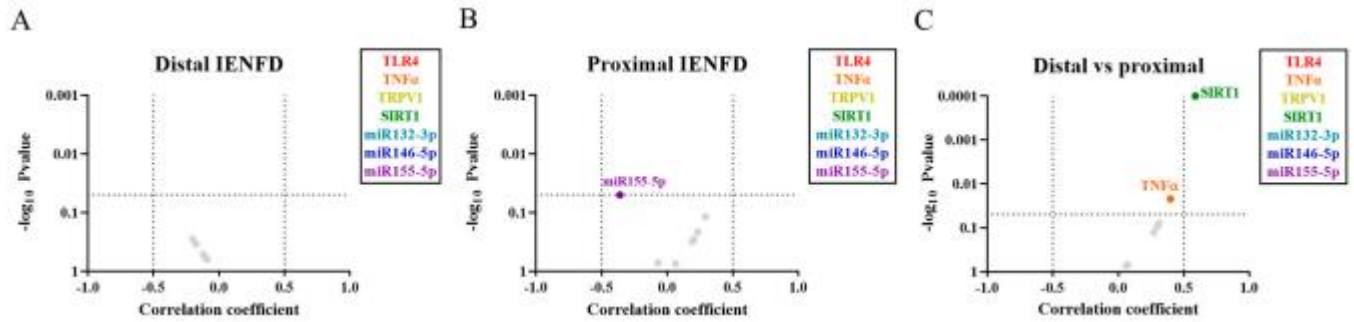


Abbildung 3: Therapie-Algorithmus für neuropathische Schmerzen.*) Aktuelle Zulassungsindikationen sind zu berücksichtigen; **) Schmerzreduktion, Verträglichkeit, Verbesserung von Schlaf, Funktionalität, Lebensqualität und/oder Compliance; ***) Frühestens nach drei Monaten; †) Intensives Therapiemonitoring über die Einstellungsphase von bis zu vier Wochen; ††) Die Therapie sollte in regelmäßigen Abständen bewertet werden. Außerdem bei systemischer Therapie: kritische Reflexion der Therapie nach drei bis sechs Monaten. Die Abbildung bildet nicht exakt die einzelnen Leitlinienstufen ab. Diese sind dem Text zu entnehmen.

Gillhausen K. et al.; Diagnose und Therapie neuropathischer Schmerzen: Eine praktische Hilfe für den hausärztlichen Alltag; CME.2019

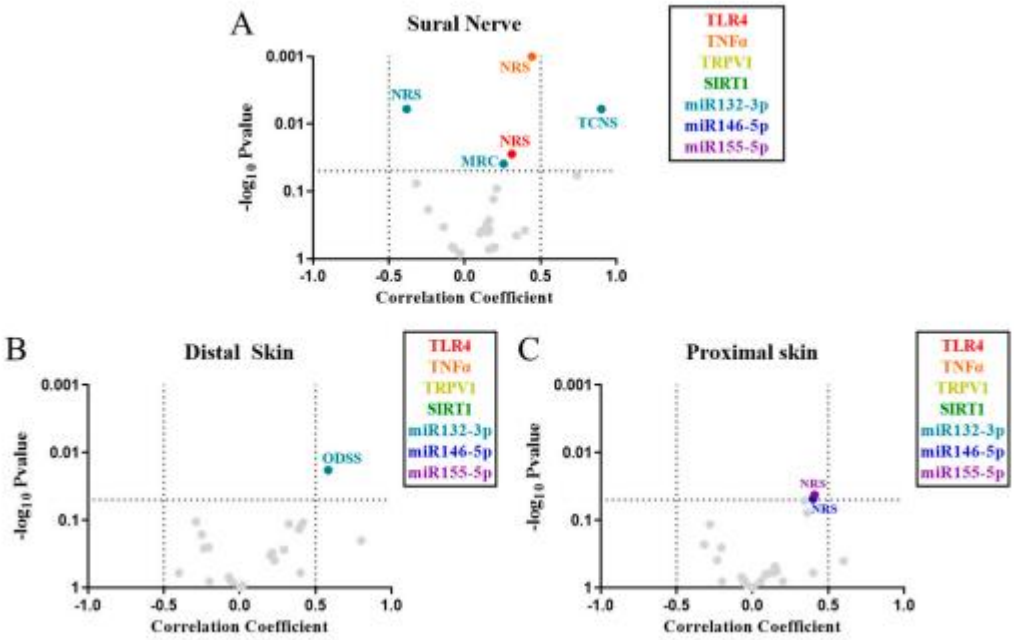
Abstract: Polyneuropathy (PNP) is a term to describe diseases of the peripheral nervous system, 50% of which present with neuropathic pain. In some types of PNP, pain is restricted to the skin distally in the leg, suggesting a local regulatory process leading to pain. In this study, we proposed a pro-inflammatory pathway mediated by NF-κB that might be involved in the development of pain in patients with painful PNP. To test this hypothesis, we have collected nerve and skin samples from patients with different etiologies and levels of pain. We performed RT-qPCR to analyze the gene expression of the proposed inflammatory pathway components in sural nerve and in distal and proximal skin samples. In sural nerve, we showed a correlation of TLR4 and TNFα to neuropathic pain, and an upregulation of TNFα in patients with severe pain. Patients with an inflammatory PNP also presented a lower expression of TRPV1 and SIRT1. In distal skin, we found a reduced expression of TLR4 and miR-146-5p, in comparison to proximal skin. **Our findings thus support our hypothesis of local inflammatory processes involved in pain in PNP, and further show disturbed anti-inflammatory pathways involving TRPV1 and SIRT1 in inflammatory PNP.**

García-Fernández P, Reinhold C, Üçeyler N, Sommer C. Local Inflammatory Mediators Involved in Neuropathic Pain. Int J Mol Sci. 2023 Apr 25;24(9):7814. doi: 10.3390/ijms24097814. PMID: 37175520; PMCID: PMC10178336.



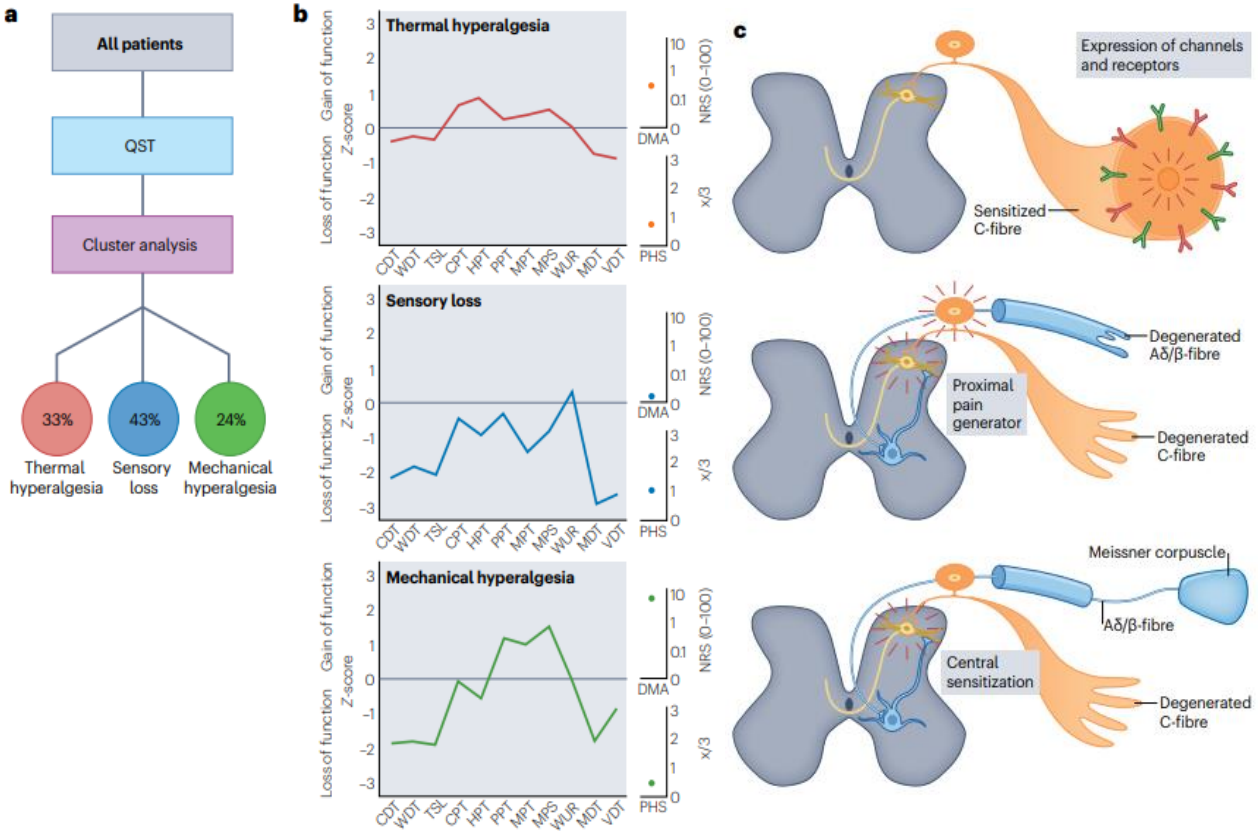
Most inflammatory markers do not correlate to the IENFD in distal and proximal skin regions of PNP patients. Volcano plot of Spearman correlations between IENFD and the gene expression of the inflammatory markers (in legend) in distal (A) and proximal (B) skin from patients with PNP. (C) Volcano plot of Spearman correlations between the gene expression of each inflammatory marker in distal versus proximal skin regions. Correlations with a $p < 0.05$ are colored, while those not significant ($p \geq 0.05$) are marked in grey. **IENFD, intraepidermal nerve fiber density.**

García-Fernández P, Reinhold C, Üçeyler N, Sommer C. Local Inflammatory Mediators Involved in Neuropathic Pain. Int J Mol Sci. 2023 Apr 25;24(9):7814. doi: 10.3390/ijms24097814. PMID: 37175520; PMCID: PMC10178336.



Inflammatory markers correlate with the severity of PNP. Volcano plot of Spearman correlations between the gene expression of the inflammatory markers (in legend) and four neuropathy scores (MRC, NRS, ODSS, and TCNS), in sural nerve (A) and distal (B) and proximal (C) skin. Correlations with a $p<0.05$ are colored, while those not significant ($p\geq0.05$) are marked in grey. MRC, Medical Research Council-sumscore; NRS, numerical rating scale; ODSS, overall disability sum score; TCNS, modified Toronto clinical neuropathy score.

García-Fernández P, Reinhold C, Üçeyler N, Sommer C. Local Inflammatory Mediators Involved in Neuropathic Pain. Int J Mol Sci. 2023 Apr 25;24(9):7814. doi: 10.3390/ijms24097814. PMID: 37175520; PMCID: PMC10178336.



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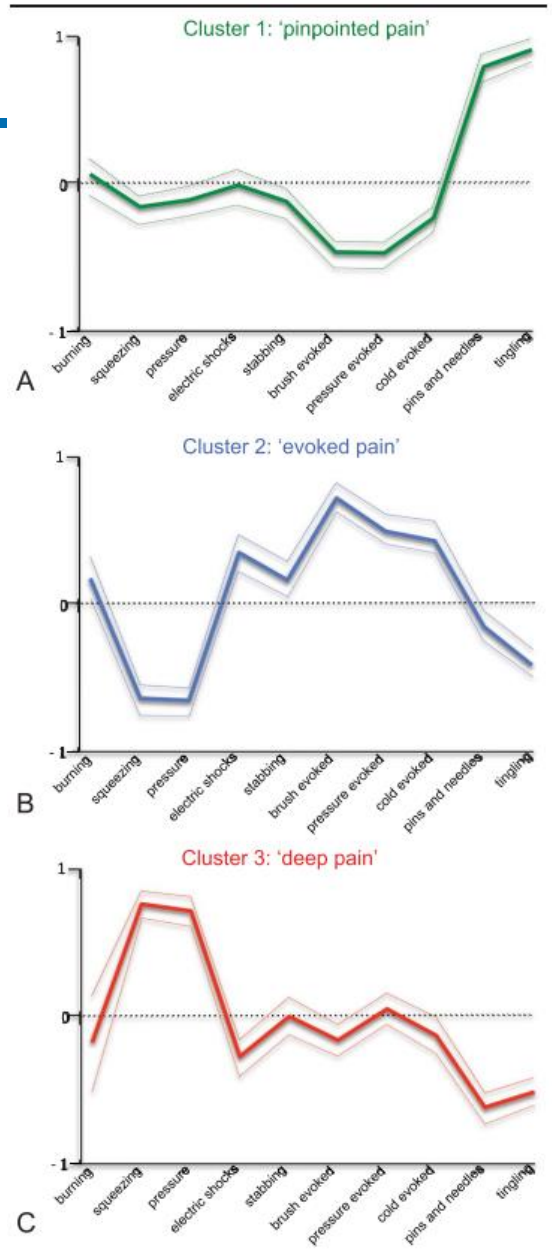
Subgrouping of patients with painful peripheral neuropathy. a, Subgrouping procedure based on quantitative sensory testing (QST) followed by cluster analysis, which was conducted in 902 patients with painful peripheral neuropathy120. b, QST profiles of the three clusters. Sensory profiles are shown as mean Z-scores, which eliminate differences due to test site, sex and age. Positive Z-scores indicate positive sensory signs (hyperalgesia), whereas negative Z-scores indicate negative sensory signs (hypoaesthesia and hypoalgesia). The righthand side of the panel shows ratings for dynamic mechanical allodynia (DMA) on the Numerical Rating Scale (NRS), scored from 0–100 and plotted on a logarithmic scale, and numbers (0–3) of paradoxical heat sensations (PHS) (that is, heat sensations induced by a cold stimulus, as observed during application of alternating warm and cold stimuli). c, Potential underlying pain mechanisms related to the three subgroups. Top: Expression of receptors and channels on primary afferent nociceptors leads to peripheral sensitization and thermal hyperalgesia. Middle: Degeneration of primary afferent small and large fibres leads to sensory loss. Pain generators are located proximally in the spinal ganglion or spinal cord. Bottom: Selective degeneration of small primary afferents is associated with central sensitization, leading to mechanical hyperalgesia via a central switch of Aβ and Aδ primary afferents to central nociceptive projection neurons. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio; ×3, number of paradoxical heat sensations out of three test stimuli.

Baron R, Dickenson AH, Calvo M, Dib-Hajj SD, Bennett DL. Maximizing treatment efficacy through patient stratification in neuropathic pain trials. Nat Rev Neurol. 2023 Jan;19(1):53-64. doi: 10.1038/s41582-022-00741-7. Epub 2022 Nov 18. PMID: 36400867.



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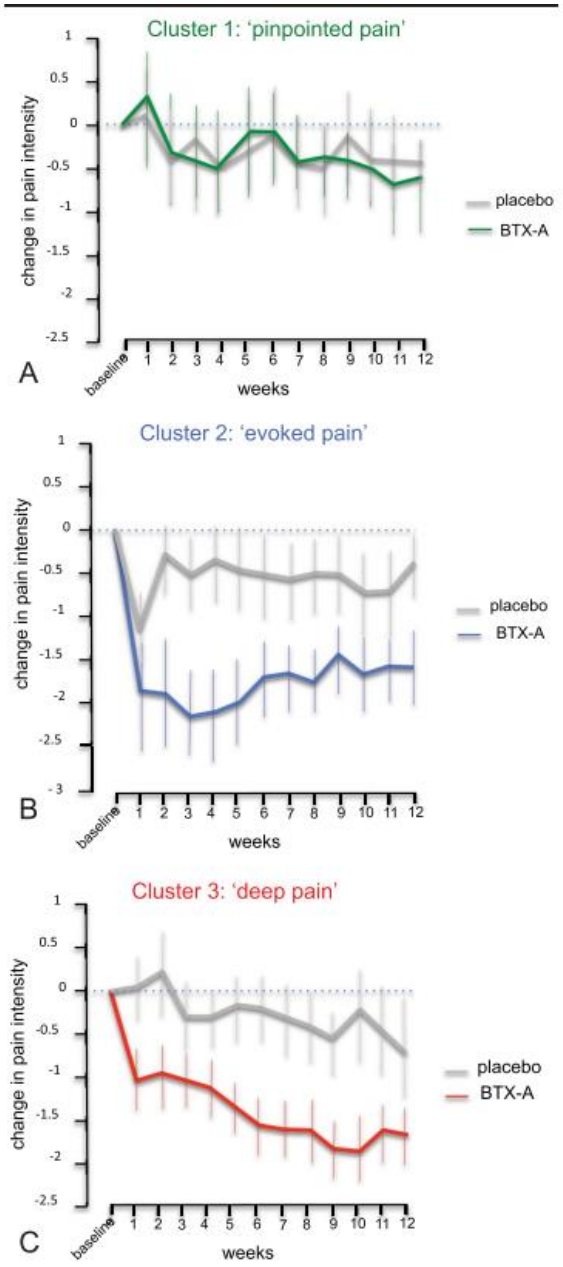
Description of the 3 clusters of patients with distinct sensory profiles (ie, combinations of symptoms assessed with the 10 neuropathic pain descriptors included in the NPSI). Dashed lines represent confidence intervals (95% CI). (A) Cluster 1, "pinpointed pain," was characterized by above average scores for items relating to paresthesia/dysesthesia (ie, tingling and pins and needles) and below average scores for evoked pain (brush allodynia and pressure allodynia). (B) Cluster 2, "evoked pain," was characterized by above average pain provoked by brushing, provoked by cold or pressure and electric shocks and below average deep pain and paresthesia/dysesthesia. (C) Cluster 3, "deep pain," was characterized by above average pressure and squeezing pain and below average paresthesia/dysesthesia. NPSI, Neuropathic Pain Symptom Inventory.

Bouhassira D, Branders S, Attal N, Fernandes AM, Demolle D, Barbour J, Ciampi de Andrade D, Pereira A. Stratification of patients based on the Neuropathic Pain Symptom Inventory: development and validation of a new algorithm. Pain. 2021 Apr 1;162(4):1038-1046. doi: 10.1097/j.pain.0000000000002130. PMID: 33136982.



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Comparisons of the effects, expressed as the mean changes and confidence intervals (95% CI) in pain intensity from baseline, of botulinum toxin A (BTX-A) and placebo injections over 12 weeks after treatment administration in the 3 clusters of patients. The decrease in pain intensity induced by BTX-A was significantly larger than that induced by placebo in cluster 2 (B), "evoked pain" (P 5 0.038 for the treatment effect) and cluster 3 (C) "deep pain" (P 5 0.027 for the treatment effect) but not in cluster 1 (A), "pinpointed pain" (P 5 0.65 for the treatment effect)

Bouhassira D, Branders S, Attal N, Fernandes AM, Demolle D, Barbour J, Ciampi de Andrade D, Pereira A. Stratification of patients based on the Neuropathic Pain Symptom Inventory: development and validation of a new algorithm. Pain. 2021 Apr 1;162(4):1038-1046. doi: 10.1097/j.pain.0000000000002130. PMID: 33136982.

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Validated pain assessment questionnaires for patient stratification

Questionnaire	Description	Ref.
Neuropathic Pain Symptom Inventory (NPSI)	Ten descriptors (each rated 0–10 on the Numerical Rating Scale) Two temporal items (categorical scale) Five dimensions: burning pain, deep pain, paroxysmal pain, evoked pain and paraesthesia	127
Questionnaire for Symptom Assessment in Pain Disorders (Q-SAP) for back pain	12 descriptors for pain in the back, each rated 0–10 for pain intensity, influence on quality of life and influence on activities of daily living	128
painPREDICT	16 descriptors Two items pain intensity One item course of pain One item pain location	129

All three questionnaires are based on patient-reported outcomes.

Baron R, Dickenson AH, Calvo M, Dib-Hajj SD, Bennett DL. Maximizing treatment efficacy through patient stratification in neuropathic pain trials. Nat Rev Neurol. 2023 Jan;19(1):53-64. doi: 10.1038/s41582-022-00741-7. Epub 2022 Nov 18. PMID: 36400867.

Recommendations
We devised a strong recommendation for DN4, I-DN4, and LANSS, and a weak recommendation for S-LANSS and PainDETECT.

Recommendations
We devised a weak recommendation for using QST to diagnose neuropathic pain.

Recommendations
We devised a weak recommendation for using nociceptive evoked potentials (laser- and contact heat-evoked potentials) to diagnose neuropathic pain in patients with chronic pain.Trigeminal reflex testing received a strong recommendation in diagnosing secondary trigeminal neuralgia.

Recommendation
The use of skin biopsy is strongly recommended in the diagnosis of neuropathic pain, particularly in patients with suspected small-fibre neuropathy.

Truini A, Aleksovska K, Anderson CC, Attal N, Baron R, Bennett DL, Bouhassira D, Cruccu G, Eisenberg E, Enax-Krumova E, Davis KD, Di Stefano G, Finnerup NB, Garcia-Larrea L, Hanafi I, Haroutounian S, Karlsson P, Rakusa M, Rice ASC, Sachau J, Smith BH, Sommer C, Tölle T, Valls-Solé J, Veluchamy A. Joint European Academy of Neurology-European Pain Federation-Neuropathic Pain Special Interest Group of the International Association for the Study of Pain guidelines on neuropathic pain assessment. Eur J Neurol. 2023 Aug;30(8):2177-2196. doi: 10.1111/ene.15831. Epub 2023 May 30. PMID: 37253688.

Summary of recommendations.

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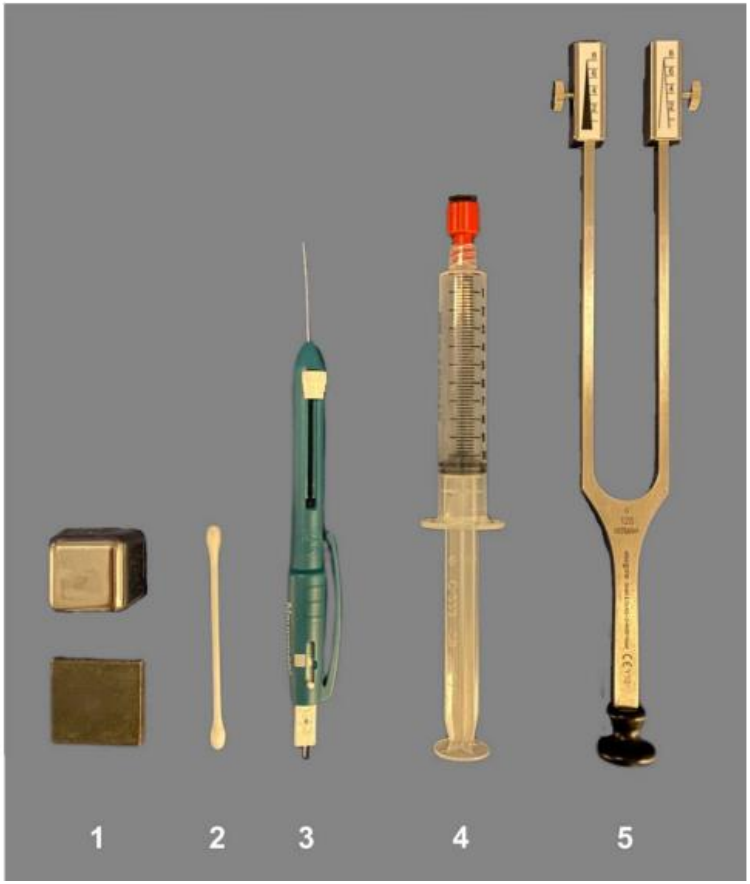
	Conditions	Studies included, *n*	Diagnostic accuracy		Strength of recommendation for use
			Sensitivity	Specificity	
Screening questionnaires					
DN4	All neuropathic pain conditions	27	0.89 (0.68–0.92)	0.88 (0.83–0.92)	Strong
I-DN4	All neuropathic pain conditions	9	0.83 (0.75–0.88)	0.81 (0.76–0.84)	Strong
LANSS	All neuropathic pain conditions	16	0.70 (0.70–0.70)	0.93 (0.93–0.93)	Strong
S-LANSS	All neuropathic pain conditions	7	0.72 (0.42–0.90)	0.92 (0.81–0.97)	Weak
PainDETECT	All neuropathic pain conditions	13	0.73 (0.56–0.84)	0.81 (0.66–0.91)	Weak
Quantitative sensory testing[a]	All neuropathic pain conditions	14	NA	NA	Weak
Nociceptive evoked potentials[b]	All neuropathic pain conditions	3	0.66–0.79	0.82–0.90	Weak
Trigeminal reflex testing	Trigeminal neuralgia	4	0.95 (0.58–1.00)	0.94 (0.90–0.97)	Strong
Skin biopsy	Neuropathic pain associated with small-fibre neuropathy	6	0.84 (0.75–0.90)	0.86 (0.70–0.94)	Strong
Corneal confocal microscopy	Neuropathic pain associated with small-fibre neuropathy	Insufficient and inconclusive evidence; further studies needed			
Functional neuroimaging	All neuropathic pain conditions	Not currently a diagnostic tool but could provide insight in pathophysiology; further studies needed			
Peripheral nerve blocks	Neuropathic pain associated with peripheral nervous system diseases	Intraforaminal nerve root blocks for cervical radiculopathy and genitofemoral blocks for genitofemoral neuralgia may have a prognostic value for surgical success; further studies needed			
Genetic testing	Neuropathic pain associated with peripheral nervous system diseases	Established role in monogenic disorders (e.g., erythromelalgia); it might be also considered in selected cases (e.g., "idiopathic" small-fibre neuropathy), but not for the routine assessment of neuropathic pain			

Note: Corneal confocal microscopy, functional neuroimaging, peripheral nerve blocks, and genetic testing did not undergo GRADE assessment to derive a strength of recommendation. Abbreviations: DN4, Douleur Neuropathique en 4 Questions; I-DN4, self-administered version of DN4; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; NA, not applicable; S-LANSS, self-administered version of LANSS.

[a]Pooled analysis of sensitivity and specificity not provided due to the characteristics of the studies selected for the analysis.

[b]Pooled analysis of sensitivity and specificity not provided due to the small sample of subjects included in the three studies selected.

Truini A, Aleksovska K, Anderson CC, Attal N, Baron R, Bennett DL, Bouhassira D, Cruccu G, Eisenberg E, Enax-Krumova E, Davis KD, Di Stefano G, Finnerup NB, Garcia-Larrea L, Hanafi I, Haroutounian S, Karlsson P, Rakusa M, Rice ASC, Sachau J, Smith BH, Sommer C, Tölle T, Valls-Solé J, Veluchamy A. Joint European Academy of Neurology-European Pain Federation-Neuropathic Pain Special Interest Group of the International Association for the Study of Pain guidelines on neuropathic pain assessment. Eur J Neurol. 2023 Aug;30(8):2177-2196. doi: 10.1111/ene.15831. Epub 2023 May 30. PMID: 37253688.



Bedside-QST devices.

Displayed are the devices used for the final bedside-QST protocol.
(1): 3 3 3-cm metal piece or 2.7 3 2.7 3 2.7-cm metal cube for thermal perception/pain,
(2): Q-tip for touch sensation and dynamic mechanical allodynia,
(3): Neuropen with a Neurotip for touch sensation and pinprick pain sensitivity,
(4): 10-mL syringe for pressure pain sensitivity,
(5): tuning fork c 128/C 64 Hz for vibration detection. QST, quantitative sensory testing

Sachau J, Appel C, Reimer M, Sendel M, Vollert J, Hüllemann P, Baron R. Test-retest reliability of a simple bedside-quantitative sensory testing battery for chronic neuropathic pain. Pain Rep. 2023 Jan 13;8(1):e1049. doi: 10.1097/PR9.0000000000001049. PMID: 36660554; PMCID: PMC9842225.

1) Postoperativer Schmerz
2) Neuropathischer Schmerz
3) **Post Covid, Long-Covid**
4) Vagusstimulation

Überblick über COVID-19 Nomenklatur (in Anlehnung an NICE 2020

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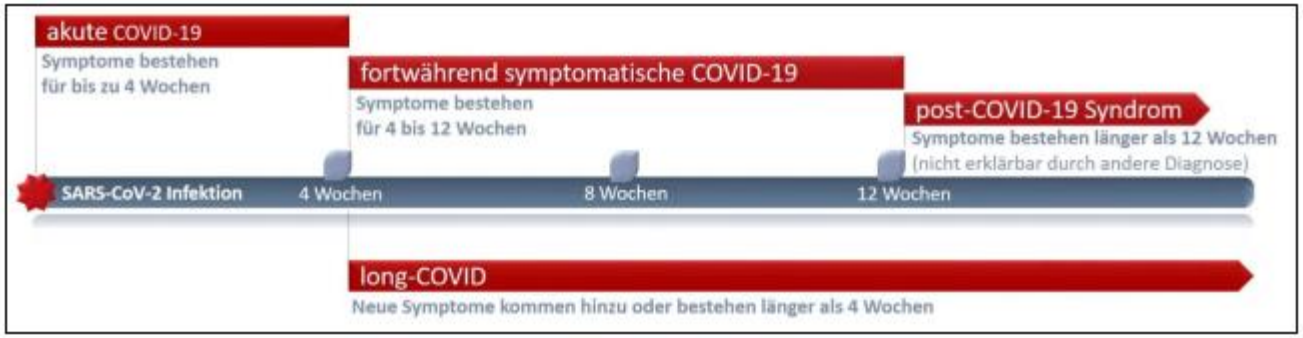

Sivan M, Taylor S. NICE guideline on long covid. BMJ 2020; 371: m4938. DOI:10.1136/bmj.m4938

Was ist „Long Covid“?

Eine verlässliche Definition fehlt nach wie vor

Die WHO[1] schlägt folgende 3 Hauptsymptome vor

- **Fatigue**
- **Kurzatmigkeit**
- **Kognitive Dysfunktion**

[1] *https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1*

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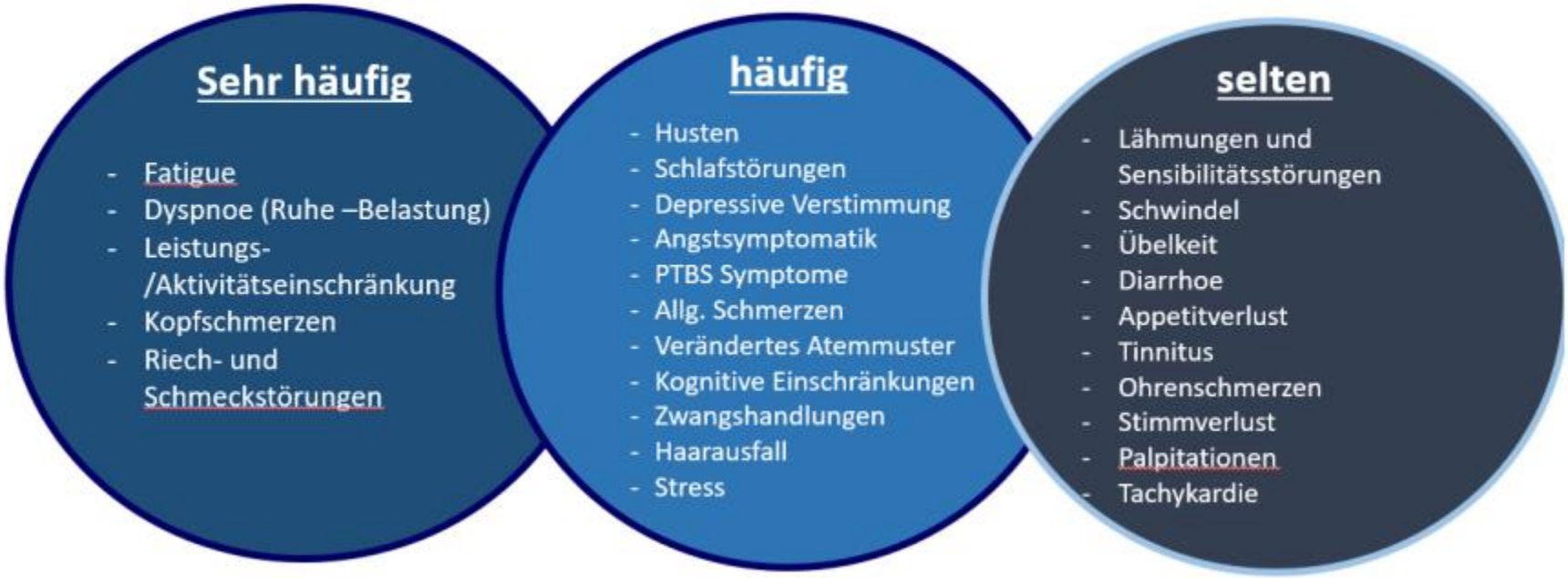
Häufigkeit von long-COVID Symptomen



Pragmatische Einteilung der Symptomhäufigkeit nach aktueller Literatur ohne Anspruch auf Vollständigkeit nach

Wong AW, Shah AS, Johnston JC et al. Patient-reported outcome measures after COVID-19: a prospective cohort study. European Respiratory Journal 2020; 56.
Huang C, Huang L, Wang Y et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021; 397: 220-232. DOI: 10.1016/S0140-6736(20)32656-8
Carfi A, Bernabei R, Landi F et al. Persistent Symptoms in Patients After Acute COVID-19. JAMA 2020; 324: 603-605. DOI: 10.1001/jama.2020.12603
Goërtz YM, Van Herck M, Delbressine JM et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ open research 2020; 6.
Halpin S, O'Connor R, Sivan M. Long COVID and chronic COVID syndromes. J Med Virol 2021; 93: 1242-1243. DOI: 10.1002/jmv.26587
Cares-Marambio K, Montenegro-Jimenez Y, Torres-Castro R et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Chron Respir Dis 2021; 18: 14799731211002240. DOI: 10.1177/14799731211002240

S1-Leitlinie Post-COVID/Long-COVID AWMF online 020/027. Stand 12.07.2021

Abstract

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A total of 40 articles (11,196 patients) were included in the meta-analysis. Fatigue/ muscle weakness, dyspnea, pain and discomfort, anxiety/depression and impaired concentration were presented in more than 20% of patients reported. In conclusion, PCS is mainly characterized by musculoskeletal, pulmonary, digestive and neurological involvement including depression. PCS is independent of severity of acute illness and humoral response. Long-term antibody responses to SARS-CoV-2 infection and a high inter-individual variability were confirmed. Future studies should evaluate the mechanisms by which SARS-CoV-2 may cause PCS and the best therapeutic options

Anaya J.M, Rojas M., Salinas M.L. et al. Post-COVID syndrome. A case series and comprehensive review. Autoimmunity Reviews 20 (2021).

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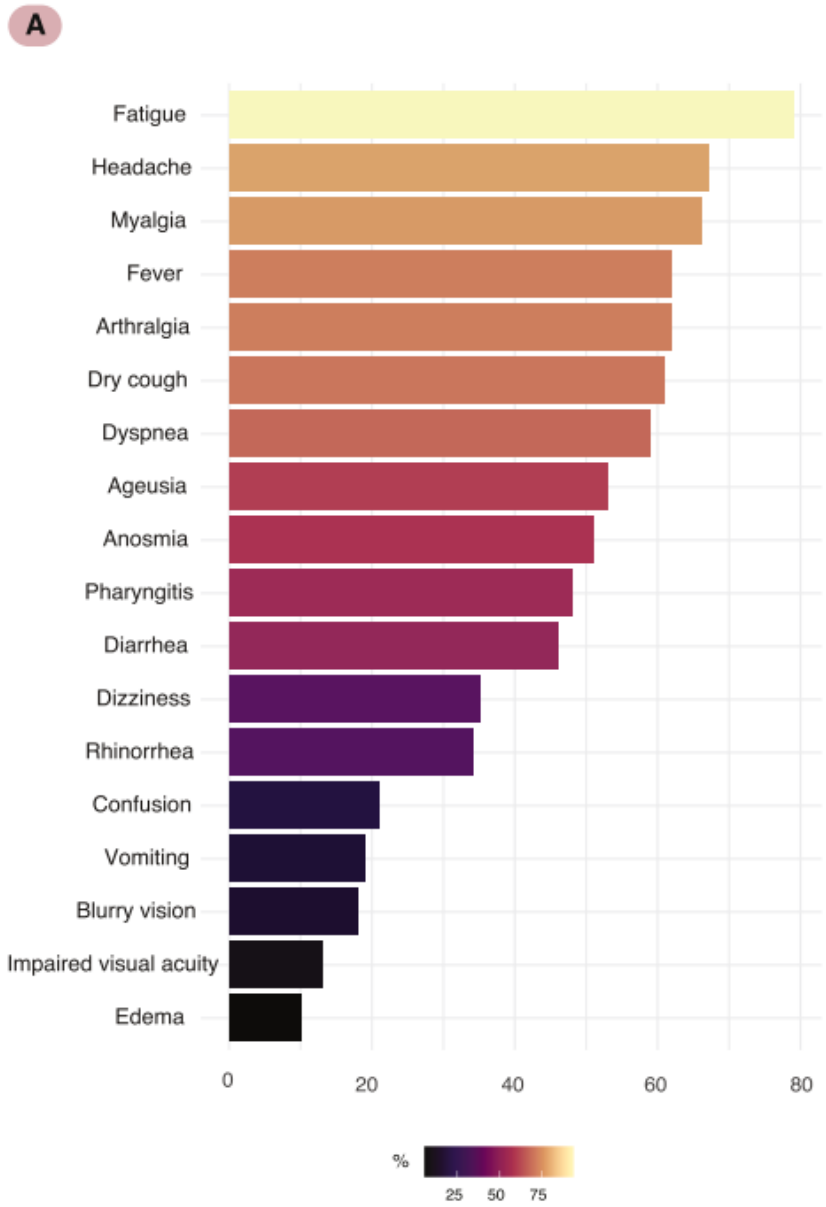

Acute and post-COVID symptoms.
A. Frequency bar plot for clinical manifestations on acute COVID-19.

Anaya J.M, Rojas M., Salinas M.L. et al. Post-COVID syndrome. A case series and comprehensive review. Autoimmunity Reviews 20 (2021).

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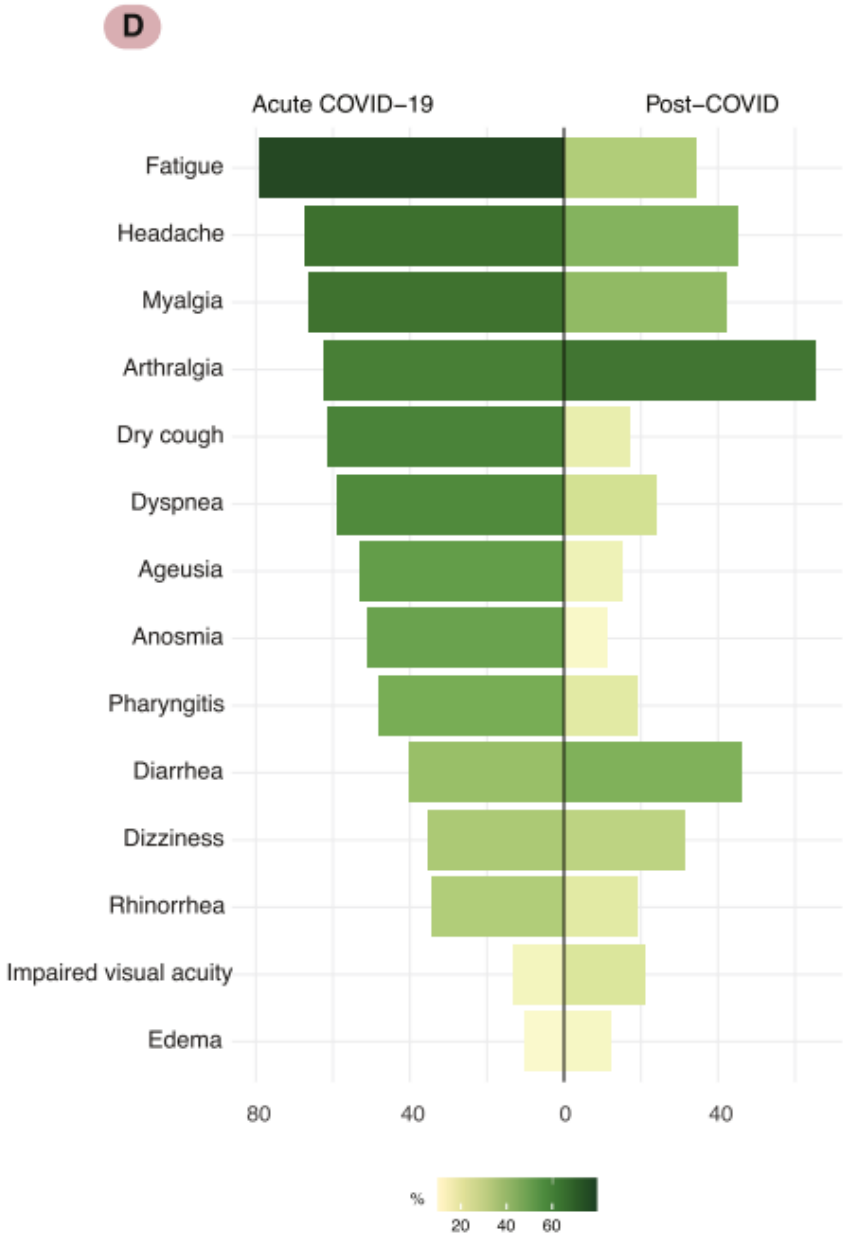

D. Mirrored bar plot for symptoms on acute COVID-19 and post COVID syndrome

Anaya J.M, Rojas M., Salinas M.L. et al. Post-COVID syndrome. A case series and comprehensive review. Autoimmunity Reviews 20 (2021).

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Background: **The COVID-19 pandemic has forced sweeping social and behavioral changes that have adversely affected the general population. Many changes, such as business closures, working from home, increased psychological distress, and delayed access to health care, could have unique adverse effects on patients diagnosed with chronic pain (CP). The present study sought to examine perceived changes in the CP experience brought about by the COVID-19 pandemic.**

Design: Participants included 487 self-reported patients with musculoskeletal, neuropathic, or postsurgical pain recruited using CloudResearch. A 53-item survey was created to assess changes in perceived pain, mood, control over pain, physical activity, employment, and medical access since the onset of the pandemic.

Chatkoff D. K., Leonhard M. T., Najdi R. R. et al. A Brief Survey of the COVID-19 Pandemic's Impact on the Chronic Pain Experience. Pain Management Nursing. 2021.

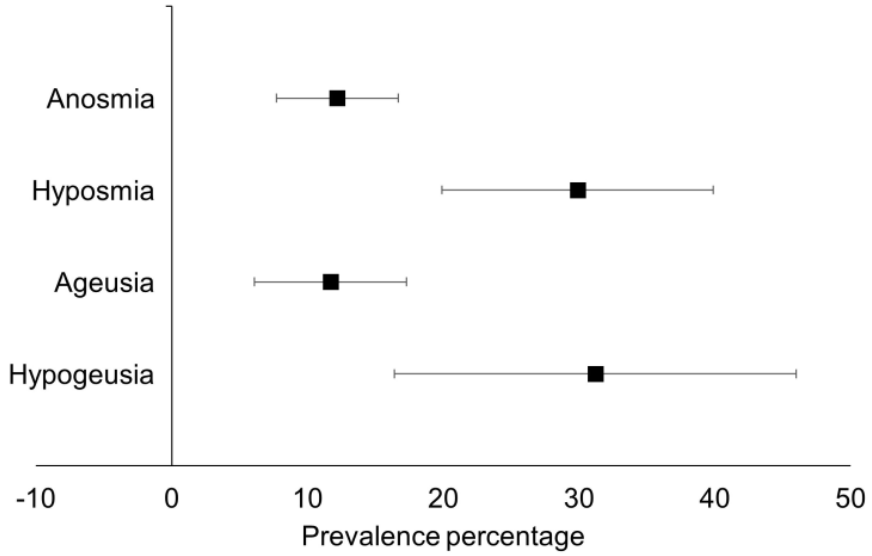

FIGURE 2
Meta-analytic prevalence of smell and taste related sensory loss in post-COVID syndrome.

Trott M, Driscoll R, Pardhan S. The prevalence of sensory changes in post-COVID syndrome: A systematic review and meta-analysis. Front Med (Lausanne). 2022 Aug 25;9:980253. doi: 10.3389/fmed.2022.980253. PMID: 36091707; PMCID: PMC9452774.

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Conclusion

While anosmia and ageusia appear to be present in around 12% of people 12 weeks post COVID-19, the prevalence of hyposmia and hypogeusia appears to be much higher, with prevalence rates being 30% and 31% respectively.
Considering that changes in taste, smell, vision, and hearing are associated with decreases in quality of life and also reduced overall well-being, future research is required to ascertain the mechanisms behind this phenomenon and the creation of therapeutic interventions.

Trott M, Driscoll R, Pardhan S. The prevalence of sensory changes in post-COVID syndrome: A systematic review and meta-analysis. Front Med (Lausanne). 2022 Aug 25;9:980253. doi: 10.3389/fmed.2022.980253. PMID: 36091707; PMCID: PMC9452774.

Die Ergebnisse von 4 000 COVID-19-Patienten zeigen, dass die meisten von ihnen einen Verlust ihrer Riech- und Schmeckfähigkeit während der Erkrankung erlebten, viele auch den der Chemethesis.. Die Probanden beschrieben dabei einen massiven Rückgang der Empfindlichkeit ihres Geruchs- oder Geschmackssinns – von einer Skala von 0 bis 100 zum Teil um 90 Punkte, erklärt Ohla. Parosmien – wenn etwas als schlecht riechend empfunden wird, was vorher gut roch, oder umgekehrt – und Phantosmien – Geruchswahrnehmungen ohne Geruchsreiz – traten in der Umfrage bisher sehr selten auf, so Ohla. **Noch sei es zu früh, Aussagen darüber zu machen, ob die Sinnesstörungen so rasch und plötzlich auftreten wie in den bisherigen Berichten. Dies sei erkennbar anders als der postgrippale Geruchsverlust, der meist schleichend auftrete und wieder verschwinde. Inzwischen wurde Anosmie (auch ohne Rhinitis) als gelegentliches Symptom in die Hinweise vom Robert Koch-Institut aufgenommen.**

Forschungszentrum Jülich: Geschmacks und Geruchsstörungen bei COVID-19. Pressemitteilung vom 9. April 2020. https://www.fz-juelich.de/SharedDocs/Pres semitteilungen/UK/DE/ 2020/2020–04–09-onlineumfrage-covid19.html (last accessed on 30 April 2020). Link zur Umfrage: https://gcchemosensr. org/surveys/
Robert Koch-Institut: Hinweise zu Erkennung, Diagnostik und Therapie von Patienen mit COVID-19. Stand: 17. April 2020. https://www.rki.de/DE/Content/Kommissionen/Stakob/Stellungnahmen/Stellungnahme-Covid-19_Therapie_Diagnose.html (last accessed on 30 April 2020)

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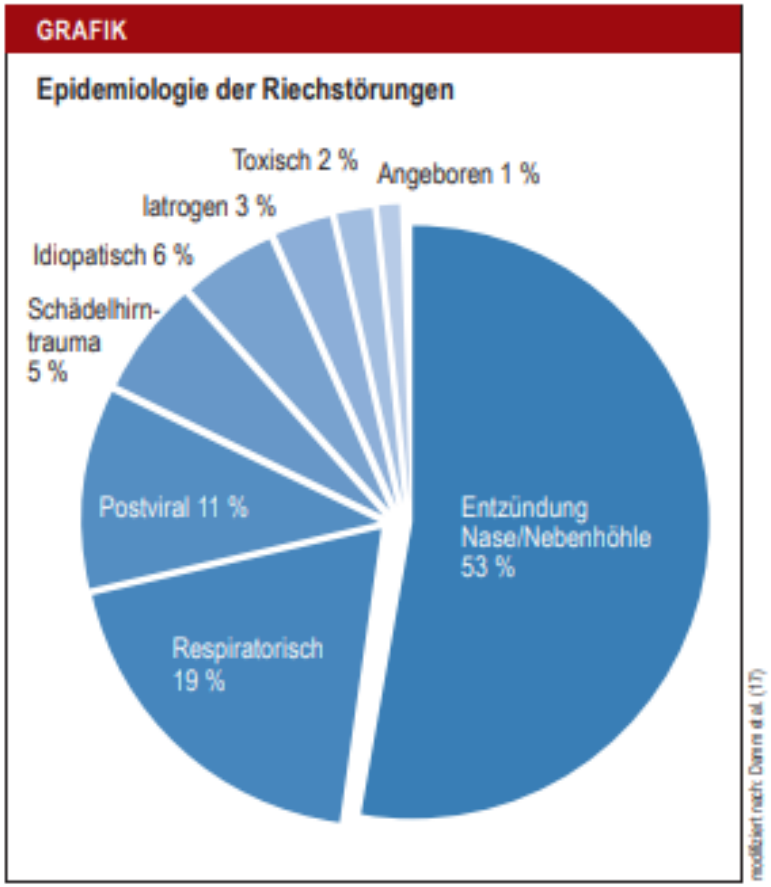
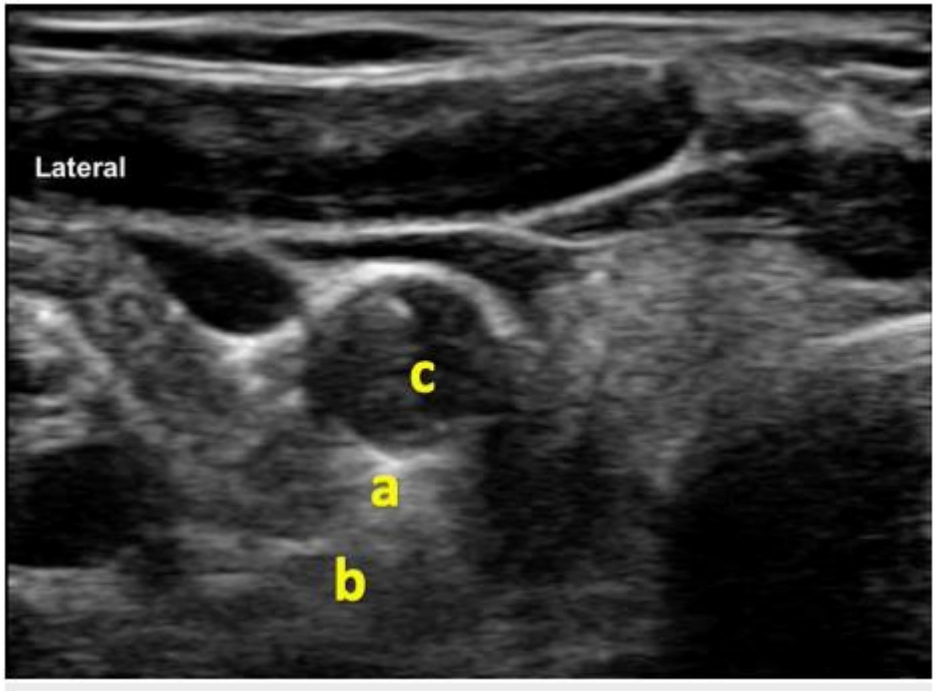


Wie COVID-19 die Nerven tangiert. Deutsches Ärzteblatt, Jg. 117, Heft 19, 8. Mai 2020



Ultrasonographic image of the right side of the neck depicting stellate ganglion
a: stellate ganglion above the longus colli muscle. Site for deposition of local anesthetic solution.
b: longus colli muscle.
c: right carotid artery

Chauhan G, Upadhyay A, Khanduja S, Emerick T. Stellate Ganglion Block for Anosmia and Dysgeusia Due to Long COVID. Cureus. 2022 Aug 8;14(8):e27779. doi: 10.7759/cureus.27779. PMID: 36106285; PMCID: PMC9450932.

Conclusions

The mechanistic factors related to the dramatic improvement of anosmia due to SGB are still debatable; however, SGB may be an effective treatment option for patients with olfactory and taste issues associated with post acute sequelae of SARS-CoV-2 infection(PASC). **At this point, the evidence for using SGB to alleviate anosmia and dysgeusia associated with Long COVID is anecdotal and limited to a few case reports. Collaborative multi-institutional research might be required to gather more evidence to support using SGB as a treatment modality for anosmia and dysgeusia due to Long COVID.**

Chauhan G, Upadhyay A, Khanduja S, Emerick T. Stellate Ganglion Block for Anosmia and Dysgeusia Due to Long COVID. Cureus. 2022 Aug 8;14(8):e27779. doi: 10.7759/cureus.27779. PMID: 36106285; PMCID: PMC9450932.

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Small Fiber Neuropathie

- Neuropathie der Aδ-Fasern und unmyelinisierten C-Fasern
- Betrifft sensorische und/oder autonome Fasern
- Bei Long Covid beschrieben[1,2]
- Diagnostik z.B. per Hautbiopsie in Kombination mit Klinik
- Kann prinzipiell Dysautonomie und häufige neuropathische Schmerzen[3] erklären

[1] *Novak P et al. Multisystem Involvement in Post-acute Sequelae of COVID-19 (PASC). Ann Neurol 2021; doi.org/10.1002/ana.26286*

[2] *Oaklander AL et al. Peripheral Neuropathy Evaluations of Patients With Prolonged Long COVID. Neurol Neuroimmunol Neuroinflamm 2022; 9:e1146*

[3] *Odozor C et al. Post-acute sensory neurological sequelae in patients with severe acute respiratory syndrome coronavirus 2 infection: the COVID-PN observational cohort study. Pain 2022; doi: 10.1097/j.pain.0000000000002639*

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Therapie bei Neuroinflammation

Low Dose Naltrexon (off-label)[1]

- Moduliert Mikroglia[2]
- Hat oft positiven Effekt bei ME/CFS[3]
- Dosierung:
  - Beginn mit 0,5mg abends
  - Steigerung um 0,5mg alle 7-14 Tage
  - Merkbarer Effekt meist bei 1,5-2,5mg
  - Max. 5mg/d
- Nebenwirkungen hauptsächlich schlechterer Schlaf, gastrointestinal

[1] *Toljan K, Vrooman B. Low-Dose Naltrexone (LDN)—Review of Therapeutic Utilization. Med Sci 2018; 6:82*
[2] *Younger J et al. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol 2014; 33:451*
[3] *Bolton MJ et al. Low-dose naltrexone as a treatment for chronic fatigue syndrome. BMJ Case Rep 2020; 13: e232502*

Conclusions for clinical practice

- The consequences of COVID-19 can be diverse and prolonged. Our results suggest that most patients will experience a self-limited acute infection with full recovery, but every third patient develops symptoms that persist for at least 1 year. For some COVID-19 survivors, persisting symptoms are sufficiently severe to preclude return to employment.

- **New-onset headache and pain in muscles and joints are frequently associated with each other and with physical fatigue and cognitive disturbances.**

- **The severity of acute COVID-19 might increase the risk of post-COVID-19 conditions.**

- Some post-COVID-19 symptoms such as shortness of breath can be explained by persistent structural changes of the pulmonary systems.

- The most frequently reported PCS, namely fatigue and cognitive disturbances, are common symptoms in the general population and should not be solely attributed to infection by SARS-CoV-2 virus.

- Acute COVID-19 can worsen pre-existing diseases, e.g., chronic obstructive pulmonary disease (COPD), dementia or FMS.

- **Pain medicine physicians should be involved in the management of chronic pain (headache, musculoskeletal system) and mental health care specialist in the management of fatigue and cognitive problems after COVID-19.**

Zuschlag D., Grandt D., Custodis F., et al.; Spontaneously reported persistent symptoms related to coronavirus disease 2019 one year after hospital discharge – A retrospective cohort single-center study. Schmerz 2022.

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Abstract

This survey investigated the prevalence of de novo widespread musculoskeletal post-COVID pain and risk factors for its development in non-hospitalized COVID-19 survivors. A nationwide exploratory cross-sectional study was conducted including a cohort of 593,741 Danish residents that had suffered from a SARS-CoV-2 infection from March 2020 to December 2021. A questionnaire was distributed to the Danish population via digital mail system (e-Boks). Self-reported demographic data, previous medical comorbidities (diagnosed), socioeconomic data, time of infection, prior chronic pain conditions (diagnosed), development of de novo widespread pain after infection, pain medication, and pain intensity information were collected. Responders consisted of 130,443 non-hospitalized participants (58.2% women; mean age: 50.2 years). **At a mean of 14.4 (SD 6.0) months after infection, 6,875 (5.3%) patients reported the presence of de novo widespread musculoskeletal post-COVID pain. Almost 75% of the patients reported a moderate to severe intensity of the pain. In conclusion, de novo widespread post-COVID pain was present in 5.3% of non-hospitalized COVID-19 survivors one year after infection (14.4±6.0 months). Older age, female sex, higher body mass index, and history of migraine, whiplash, stress, type-2 diabetes, neurological disorders, and lower socioeconomic status, were risk factors associated with the development of de novo widespread post-COVID pain in non-hospitalized patients. As de novo widespread pain is considered a sign of sensitization, this group will require specialized pain management attention.**

Ebbesen BD, Giordano R, Valera-Calero JA, Hedegaard JN, Fernández-de-Las-Peñas C, Arendt-Nielsen L. Prevalence and Risk Factors of de Novo Widespread Post-COVID Pain in Non-Hospitalized COVID-19 Survivors: A Nation-Wide Exploratory Population-Based Survey. J Pain. 2023 Aug 24:S1526-5900(23)00512-6. doi: 10.1016/j.jpain.2023.08.011. Epub ahead of print. PMID: 37633573.

Our meta- analysis shows that the frequency of neuropathic pain associated with COVID- 19 in the acute/sub-acute phase ranges between 0.4 and 25%, with a pooled estimated frequency of 10%. This finding should be con-sidered with caution due to the high heterogeneity across studies and the poor description of neuropathic pain di-agnostic criteria applied. Nevertheless, indirect evidence and multiple clinical observations suggest that COVID- 19 has the potential to trigger neuropathic pain. Ongoing studies with good quality protocols (Odozor et al., 2021) and further longitudinal studies enrolling consecutive patients with COVID- 19 and detailing neuropathic pain diagnostic criteria might eventually clarify the burden of neuropathic pain in patients with COVID-19.Our systematic review also indicates that recovered COVID- 19 patients might develop long COVID syndrome manifesting with small fibre neuropathy and pain. Further large case–control studies including consecutively recov-ered COVID- 19 patients are therefore needed to clarify how small fibre neuropathy affects recovered COVID- 19 patients.

Di Stefano G, Falco P, Galosi E, Di Pietro G, Leone C, Truini A. A systematic review and meta-analysis of neuropathic pain associated with coronavirus disease 2019. Eur J Pain. 2023 Jan;27(1):44-53. doi: 10.1002/ejp.2055. Epub 2022 Nov 23. PMID: 36367322; PMCID: PMC9877974.

Forest plot showing overall pooled frequency estimates of neuropathic pain associated with COVID- 19.

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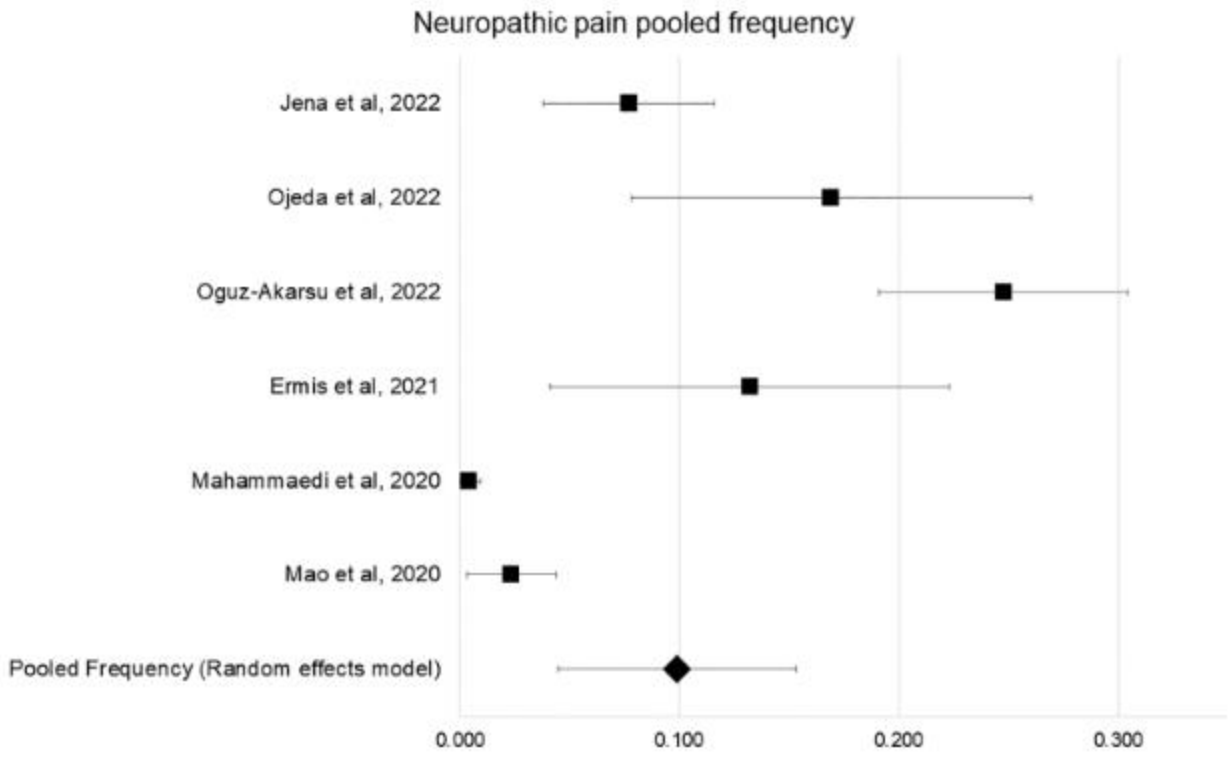

Di Stefano G, Falco P, Galosi E, Di Pietro G, Leone C, Truini A. A systematic review and meta-analysis of neuropathic pain associated with coronavirus disease 2019. Eur J Pain. 2023 Jan;27(1):44-53. doi: 10.1002/ejp.2055. Epub 2022 Nov 23. PMID: 36367322; PMCID: PMC9877974.

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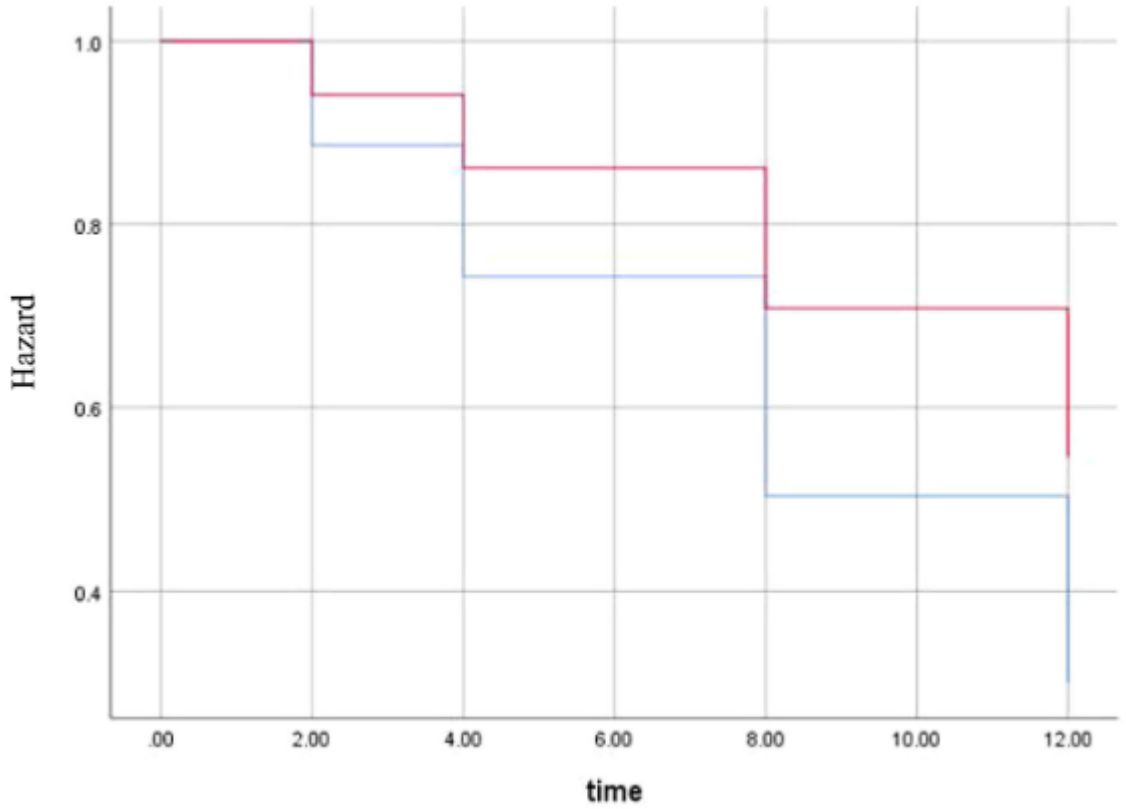
Results:
Of 270 enrolled patients, 52% developed long-COVID and 32% post-COVID-syndrome.When only considering the presence of moderate or (very) severe symptoms at weeks 8 and 12,these percentages were 28% and 18%, respectively. Fatigue was the most often reported symp-tom during follow-up. The impact of lingering symptoms was most evident in sports and house-hold activities. About half (53%) had at least one general practice contact during follow-up. Obese patients took twice as long to return to usual health (HR: 0.5, 95%CI: 0.3–0.8); no otherrisk profile could predict lingering symptoms.

Conclusion:
Long-COVID and post-COVID are also common in outpatients. In 32%, it takesmore than 12 weeks to return to usual health.

Hedin K, van der Velden AW, Hansen MP, Moberg AB, Balan A, Bruno P, Coenen S, Johansen E, Kowalczyk A, Kurotschka PK, van der Linde SR, Malania L, Rohde J, Verbakel J, Vornhagen H, Vellinga A. Initial symptoms and three months follow-up after acute COVID-19 in outpatients: An international prospective cohort study. Eur J Gen Pract. 2023 Dec;29(2):2154074. doi: 10.1080/13814788.2022.2154074. Epub 2023 Jan 19. PMID: 36655704; PMCID: PMC10249456.



Cox regression for time to return to usual health for obese patients compared to non-obese. Graph shows the hazardfor obese patients (red) and non-obese patients (blue). Outcomes were adjusted for age, sex, sore throat and gastrointestinal man-ifestations (variables included in the final model,p-value¼0.007).Y-axis starts at 0.3 to better visualise the difference betweenlines. TheX-axis shows number of weeks

Hedin K, van der Velden AW, Hansen MP, Moberg AB, Balan A, Bruno P, Coenen S, Johansen E, Kowalczyk A, Kurotschka PK, van der Linde SR, Malania L, Rohde J, Verbakel J, Vornhagen H, Vellinga A. Initial symptoms and three months follow-up after acute COVID-19 in outpatients: An international prospective cohort study. Eur J Gen Pract. 2023 Dec;29(2):2154074. doi: 10.1080/13814788.2022.2154074. Epub 2023 Jan 19. PMID: 36655704; PMCID: PMC10249456.

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Fazit für die Praxis

- COVID-19 erhöht das Risiko, anhaltende Kopf- und muskuloskeletale Schmerzen zu entwickeln.
- Long/Post-COVID-19-Schmerzen sind häufig mit Fatigue und kognitiven Störungen assoziiert.
- Long/Post-COVID-19-Schmerzen können durch eine Interaktion von biologischen, psychischen und sozialen Faktoren in Prädisposition, Auslösung und Chronifizierung erklärt werden.
- Die Diagnostik von Long/Post-COVID-19- Schmerzen sollte gemäß schmerzmedizinischen Standards durchgeführt werden.
- Bei Long/Post-COVID-19-Schmerzen sollte zwischen nozizeptiven, neuropathischen, noziplastischen Schmerzmechanismen und Mischformen dieser Mechanismen unterschieden werden.
- Long/Post-COVID-19-Schmerzen sollen entsprechend den Leitlinien der AWMF behandelt werden

Lemhöfer C, Koczulla AR, Meissner W, Häuser W. Aktualisierte S1-Leitlinie Long/Post-COVID: Relevante Aspekte für die Schmerzmedizin [Updated S1 guideline on long/post-COVID: relevant aspects for pain medicine]. Schmerz. 2023 Mar 16:1–8. German. doi: 10.1007/s00482-023-00704-x. Epub ahead of print. PMID: 36929455; PMCID: PMC10019417.

1) Postoperativer Schmerz
2) Neuropathischer Schmerz
3) Post Covid, Long-Covid
4) **Vagusstimulation**

Die AuriMod Studie

personalisierter pVNS bei Patient*innen mit **chronischem Kreuzschmerz** in einer multizentrischen, prospektiven, offenen, randomisierten, kontrollierten **Pilotstudie**.

Studienzentren: Klinikum Klagenfurt am Wörthersee (Univ.-Prof. Dr. Likar) | La Tour Hopital Genf (PD Dr. Perruchoud)

Studienaufbau:

Screening Phase: Evaluierung der Schmerzqualität, Anpassung der Schmerzmedikation, Beurteilung der Compliance im Therapiemanagementsystem (TMS)

8 Wochen Behandlung mit pVNS in 3 Gruppen (untersch. Grad der Personalisierung)

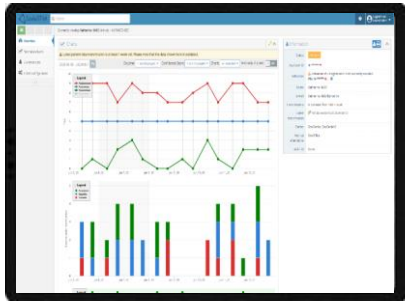
12 Wochen Follow-Up

Visit / Assessment	Screening	Baseline	Treatment							EoT/ ET[i]	FU		
Visit	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Time Window (W=week, D=day)	-1W ±2D	0	1W ±2D	2W ±2D	3W ±2D	4W ±2D	5W ±2D	6W ±2D	7W ±2D	8W ± 2D	EOT+4W ±7D	EOT+8W ±7D	EOT+12W ±7D

Studiengruppen:

Gruppe A	Gruppe B	Gruppe C
Personalisierung (Dosis)	Personalisierung (Stärke)	Aktive Kontrolle
Amplitude & Behandlungszyklus	Amplitude	einmalige Einstellung der Amplitude zu V1

AuriMod CT01 (AURIMOD GmbH)



Patient*innen dokumentieren

- VAS
- Notfallmedikation
- Wohlbefinden
- Blutdruck
- **Herzrate**, **HRV**, **Schritte**, **Schlafdauer** (vom Gerät)

Primärer Endpunkt: Veränderung der **mittleren VAS** von Baseline zu **EoT**

Sekundäre Endpunkte: Follow-Up| **Notfallmedikation** | **painDETECT** | **EQ-5D-5L** | **HADS** | **Schlafqualität** | Veränderung Herzrate, Herzratenvariabilität, Motilität | unerwünschte Ereignisse

Einschlusskriterien: m/w | 18-65 Jahre | **chronischer Kreuzschmerz für min. 3 Monate** | konstante Schmerztherapie in Screening Woche | mittlere **VAS ≥ 4** in Screening Woche

Ausschlusskriterien: Indikation zur Operation | hochgradige Spinalstenose | autonome Dysfunktion | Diabetes | Beta-Blocker | vorherige VNS | Arrhythmien

Notfallmedikation: Ibuprofen (400-800 mg) | Naproxen (500 mg) | Tramadol (50 mg / 15% der tägl. Dosis)

Details siehe Poster

Demographie:

	Statistic	Not Randomized Subjects (N=10)	Group A (N=13)	Group B (N=10)	Group C (N=10)	Randomized Subjects (N=33)	All Subjects in Database (N=43)
Screened	n (%)	10 (100)	13 (100)	10 (100)	10 (100)	33 (100)	43 (100)
Randomized	**n (%)**	**0 (0.0)**	**13 (100)**	**10 (100)**	**10 (100)**	**33 (100)**	**33 (76.7)**
Full Analysis Population	**n (%)**	**0 (0.0)**	**13 (100)**	**10 (100)**	**10 (100)**	**33 (100)**	**33 (76.7)**
Performance Population	**n (%)**	**0 (0.0)**	**11 (84.6)**	**9 (90.0)**	**8 (80.0)**	**28 (84.8)**	**28 (65.1)**
Per Protocol Population	**n (%)**	**0 (0.0)**	**7 (53.8)**	**7 (70.0)**	**7 (70.0)**	**21 (63.6)**	**21 (48.8)**
Study site							
Hopital de la tour	n (%)	1 (10.0)	5 (38.5)	3 (30.0)	3 (30.0)	11 (33.3)	12 (27.9)
KABEG-Klinikum Klagenfurt am WS	n (%)	9 (90.0)	8 (61.5)	7 (70.0)	7 (70.0)	22 (66.7)	31 (72.1)

bis EoT (n=25)

inkl. Follow-Up

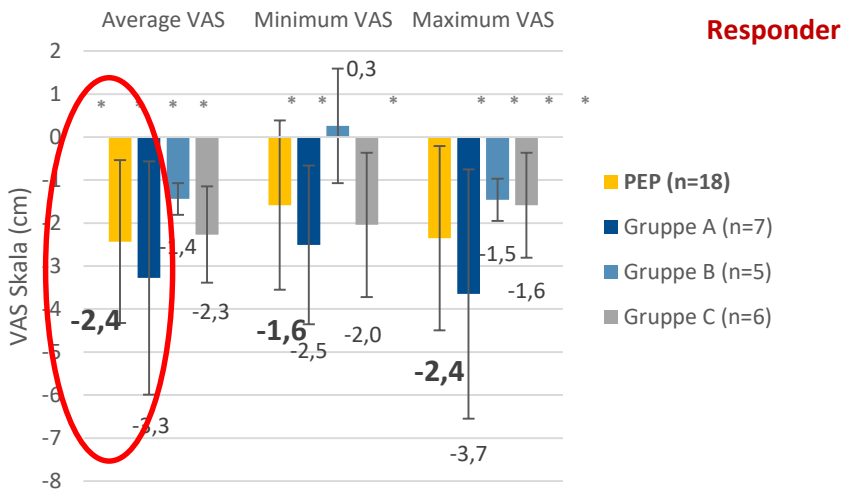
Performance Population: n = 28, **22 Frauen** | 46.9 (±10.75) Jahre | BMI = 28.5 (±5.41)

signifikante Unterschiede bei BMI in den Gruppen (p = 0.0154)

Gruppe A übergewichtig | Gruppe B normalgewichtig | Gruppe C stark übergewichtig

Primärer Endpunkt – VAS EoT:

- **Signifikante Reduktion mittlere VAS** Werte EoT vs. Baseline **Performance Population** sowie **Gruppe A und C**
  - **Stärkste Reduktion in Gruppe A,** jedoch keine signifikanten Unterschiede zwischen den Gruppen
- **72%** der Patient*innen zeigen eine Reduktion der VAS (**Responder**) | **28% Non-Responder**
- Subanalyse Responder (n=18) | Veränderung mittlere **VAS -2.4 Punkte** | mittlere Schmerzreduktion um 36%



Sekundärer Endpunkt – Notfallmedikation:

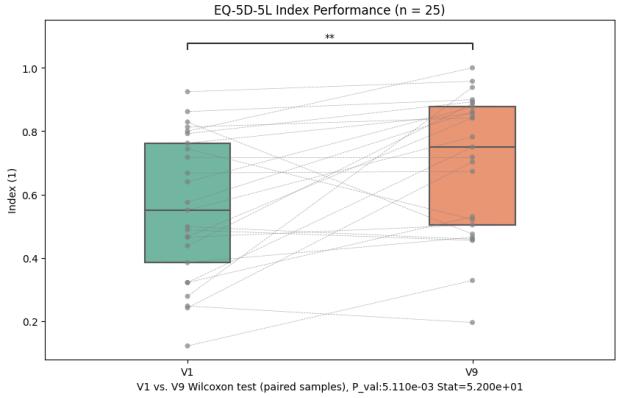
- 11 von 25 Patient*innen haben **Notfallmedikation** genommen (**44%**)
- 3 von 25 Patient*innen haben während der Therapie **Tramadol** genommen (**12%**)
- Patient*innen konnten **Notfallmedikation mit Ibuprofen** in allen Gruppen von Screening vs. EoT **reduzieren**
- In der **Respondergruppe bleibt dieser Trend** in Gruppe A und C **auch im Follow-Up erhalten**

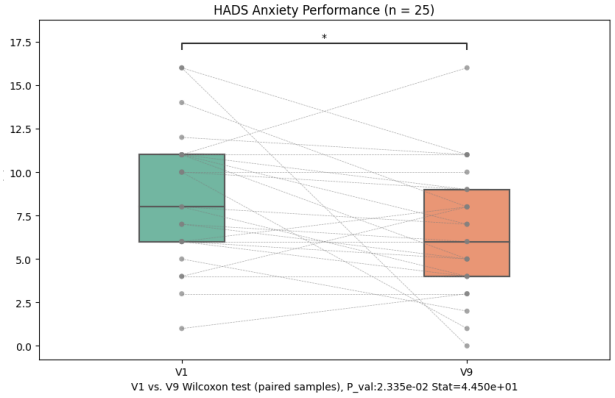
Ibuprofen	**n**	**Screening** Mean/Tag (SD)	**EoT** Mean/Tag (SD)	**Relative Änderung**
Gruppe A	4	375 mg (±249)	301 mg (±193)	**-20% (±40)**
Gruppe B	3	375 mg (±288)	262 mg (±346)	**-30% (±41)**
Gruppe C	1	113 mg	24 mg	**-79%**

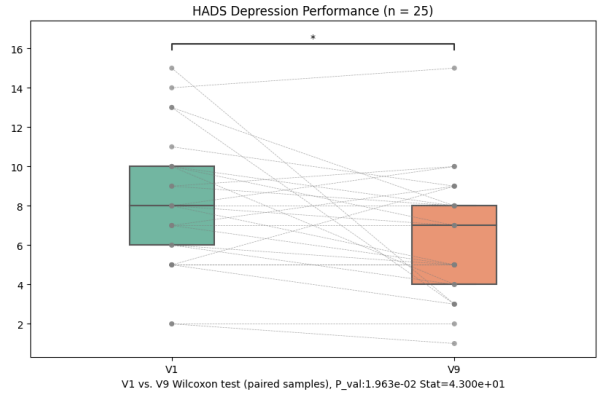
Tramadol	**n**	**Screening** Mean/Tag (SD)	**EoT** Mean/Tag (SD)
Gruppe A	1	0	4,46 mg
Gruppe B	2	0	4,04 mg (±4,57)
Gruppe C	0	0	0

Sekundärer Endpunkt – Fragebögen:

- **EQ-5D-5L** & **HADS**: **signifikante Verbesserung** bei EoT, Trend hält an über Follow-Up
- **Schlafqualität** verbessert sich in Gruppe A und C bei EoT
- **painDETECT**: neuropathische Schmerzkomponenten weniger frequent bei EoT







Sicherheit und Verträglichkeit:

- 60 NW: davon **23 NW in Verbindung mit der Behandlung** (mild/moderat)

23 Behandlungsrelevante NW	n
Lokal (Stimulationsort)	11
Kopfschmerz	3
Schwindel	1
Tinnitus	2
Übelkeit	1
Infektion am Stimulationsort	1
Hypertonie	1
Prozeduraler Kopfschmerz	2

- Die **Anwendbarkeit** wurde von Proband*innen als **sehr gut** bewertet (84,1 ± 15,6 von 100)
- Die **Verträglichkeit** wurde als **gut** bewertet (31,9 ± 4,6 von 40 Punkten).

- **Bestätigt bisherige Wirksamkeit** pVNS bei **chronischem Kreuzschmerz**
  - **Signifikante Verbesserung** VAS | EQ-5D-5L | HADS | Schlafqualität
- pVNS ist **sicher und gut verträglich** – Einsatz digitales Tagebuch wurde als sehr gut bewertet
- Patient*innen mit **höherem Baseline VAS** (6-8) und **neuropathischem Schmerz** scheinen **besser anzusprechen**

- *Detailanalyse* noch ausstehend inkl. Follow-Up
- Die *geringe Fallzahl* und *heterogene Patientengruppe* erlaubt nicht genug statistische Trennschärfe um Unterschiede zwischen den Behandlungsgruppen zu detektieren

  -> Ergebnisse werden nun für das **Design weiterer Studien** herangezogen

  -> weitere **Erforschung optimaler Patientenauswahl** und **objektiver Biomarker**

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Dr. Rudolf Likar
Dr. Herbert Janig Dr. Georg Pinter
Michael Schmieder, MAE Dr. Reinhard Sittl
Dr. Slaven Stekovic

VORSORGEN statt behandeln

Gesund bleiben ohne Verzicht

ueberreuter

Danke für Ihre Aufmerksamkeit