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cme: Diagnosis and Treatment of Neuropathic Pain

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SUMMARY

Introduction: Chronic neuropathic pain is common and markedly impairs quality of life. It is important to distinguish it from other chronic pain syndromes. Many chronic pain syndromes are characterized by a mixture of nociceptive and neuropathic components. Methods: Systematic review of articles on neuropathic pain appearing on PubMed, between 1980 and 2006, with a particular focus on metaanalyses, and on a selective literature review. Results: Chronic neuropathic pain arises from damage to sensory neurons in the peripheral or central nervous system. Clinically, these syndromes are characterized by sensory deficits, chronic burning pain, stabbing or shooting pains and allodynia. The diagnosis rests on the neurophysiological demonstration of a neural lesion. Treatment consists varying combinations of four classes of systemic medication, with differing pharmacological modes of action. Effective and timely analgesia at a therapeutic dose is essential. Dtsch Arztebl 2006; 103(41): A 2720–30.

Key words: allodynia, small fibers, nociceptive system, nerve lesion, pharmacotherapy

Chronic neuropathic pain is common in clinical practice. It markedly impairs the patient's quality of life, and carries severe health economic consequences (1). Most recent studies suggest a point prevalence for neuropathic pain syndromes of up to 5% in the general population (2).

The classical peripheral neuropathic pain syndromes – painful diabetic neuropathy and post herpetic neuralgia (*Box 1*) – account for 13% of the case load of pain specialists, and a neuropathic pain component can be demonstrated in up to 35% of all pain syndromes. Central neuropathic pain arises in an estimated 30% of all spinal cord injuries, 20% of patients with multiple sclerosis, and 1.5% of patients suffering from stroke.

To elucidate current evidence based diagnostic and therapeutic recommendations, we carried out a systematic review of the literature from the years 1980 to 2006 (PubMed), with particular attention to available metaanalyses (3-7). Search terms used were: "neuropathic pain, treatment algorithm," "neuropathic pain, treatment recommendations," "or "neuropathic pain, assessment guidelines". The analysis also takes into account the author's clinical experience.

What is neuropathic pain?

A necessary precondition for the development of neuropathic pain is a prior somatosensory nerve injury (8).

This lesion can occur either in the central (brain and spinal cord) or in the peripheral nervous system. A wide range of mechanical, metabolic, toxic or inflammatory agents can cause damage to peripheral nerves. (9) (*Box 1*)

Investigating central neuropathic pain requires a search for a primary pathological process in the CNS. This may arise as a lesion at any point in the neural axis – spinal cord, brain step, thalamus, sub cortical structures, or in the cortex.

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Prevalence

Studies suggest a point prevalence for neuropathic pain syndromes of about 5% in the general population.

BOX 1

Aetiological/anatomically based classification of neuropathic pain*[1]

Peripheral, focal or multifocal painful neuropathies

Post herpetic neuralgia
Post mastectomy pain, post thoracotamy pain, scar pain
Phantom pain, stump pain
Trigeminal neuralgia
Chronic radiculopathies, post discectomy syndrome
Post traumatic neuropathy (territorial neuropathic pain syndrome)
Constriction syndromes
Diabetic mononeuropathy
Morton neuralgia
Ischemic neuropathy
Bannwarth syndrome (Borreliosis/Lyme disease)
Neuralgic shoulder amyotrophy, plexus lesion following irradiation
Tumor related neural plexus damage

Peripheral, generalized painful neuropathies (polyneuropathies)

Metabolic/nutritional
Diabetes mellitus, alcohol, hypothyroidism, vitamin deficiency

Drugs
Chemotherapeutic agents (platins, taxoids, vincristine)
Antiretrovirals
Others (disulfiram, ethambutol, isoniazid, nitrofurantoin, thiouracil, chloramphenicol)

Infectious or post infection, immunological
Chronic inflammatory polyradiculoneuropathy
Bannwarth syndrome (Borreliosis/Lyme disease), HIV neuropathy

Hereditary
Amyloidosis, Fabry's disease, Charcot-Marie-Tooth types 2b and 5
Hereditary sensory-autonomic neuropathies (HSAN) type 1 and 1b

Toxins
Acrylamide, arsenic, clioquinol, dinitrophenol, ethylene oxide, pentachlorophenol, thallium

Malignancy
Paraneoplastic (especially bronchial carcinoma)

CNS based painful neuropathies

Stroke (especially thalamus or brain stem)
Spinal cord injury
Multiple sclerosis
Syringomyelia

„Mixed pain" syndrome

Chronic back pain
Tumor related pain (infiltration)
Complex regional pain syndrome (M. Sudeck, sympathetic reflex dystrophy, causalgia)

*[1] the conditions highlighted in brown are the commonest and together account for more than 80% of cases

Background
Neuropathic pain arises from damage to somatosensory nerves in the peripheral or central nervous system.

History
The diagnosis of neuropathic pain rests on the history of nerve damage, the objective demonstration of a lesion in the nervous system and typical somatosensory symptoms.

The morphological distortion in the peripheral and central nervous system caused by the lesion can become fixed and irreversible over time (10-12) (*see additional material at the end of this article for a diagram illustrating this phenomenon*). It is essential to distinguish neuropathic pain from chronic pain of other aetiologies – so called "nociceptive" pain – such as visceral or joint pain arising from inflammatory processes, because neuropathic pain requires specific treatment.

TABLE 1

Definition and examintation of negative and positive sensory symptoms in neuropathic pain

		Symptom	Definition	Bed side test	Expected answer
Negative symptoms		Hypoesthesia	Reduced sensation of non painful stimuli	Stroke skin with brush or cotton wool	Reduced sensation, numbness
		Pallhypoesthesia	Reduced sensation of vibration	Apply tuning fork over joint or bone	Reduced sensation
		Hypoalgesia	Reduced sensation of painful stimuli	Touch skin with pin	Reduced sensation, numbness
		Thermhypoesthesia	Reduced sensation of heat or cold	Touch skin with cold object (metal object, tiptherm, water glass, acetone spray at 10°C, metal object, tiptherm or water glass at 45°C)	Reduced sensation (higher temperature thresholds), with damage to cold fibers also paradoxical sensation of heat
Positive symptoms	**Spontaneous sensation or pain**	Paresthesia	Non painful chronic "crawling" sensation	Ask about intensity on scale*1 of 0-10 and area in cm^2	–
		Stabbing pain	Electric shock-like sensations lasting seconds	Ask about frequency and intensity (0-10)	–
		Superficial pain	Chronic painful sensation, often burning	Ask about intensity on scale of 0-10 and area in cm^2	–
	Evoked pain	Mechanically dynamic allodynia	Normally non painful stimulus causes pain	Stroke skin with brush or cotton wool	Burning, stabbing pain in the primary area and surrounding area (secondary zone)
		Mechanically static allodynia	Normally non painful static pressure stimulus causes pain	Light touch of finger on skin	Dull pain in the primary area
		Mechanical pinprick allodynia (hyperalgesia)	Normally non painful or minimally painful, light, pricking stimulus causes marked pain	Touch skin with pin prick or sharp toothpick	Stabbing pain in the primary area and surrounding area (secondary zone)
		Cold allodynia (hyperalgesia)	Normally non painful or minimally painful cold stimulus causes marked pain	Touch skin with cold object (metal object, tiptherm, water glass, acetone spray at 10°C)	Painful burning misperception of temperature in the primary zone, paradoxical heat sensation
		Heat allodynia (hyperalgesia)	Normally non painful or minimally painful heat stimulus causes marked pain	Touch skin with warm object (metal object, tiptherm or water glass at 45°C)	Painful burning misperception of temperature in the primary zone

*1 VAS: Visual analog scale for the assessment of pain intensity. 0= no pain, 10=strongest pain imaginable

Diagnosis

Neuropathic pain is characterized by a combination of negative and positive symptoms and signs which can be demonstrated using simple bedside tests.

Symptoms

Patients frequently complain of mechanical hypersensitivity – so called allodynia.

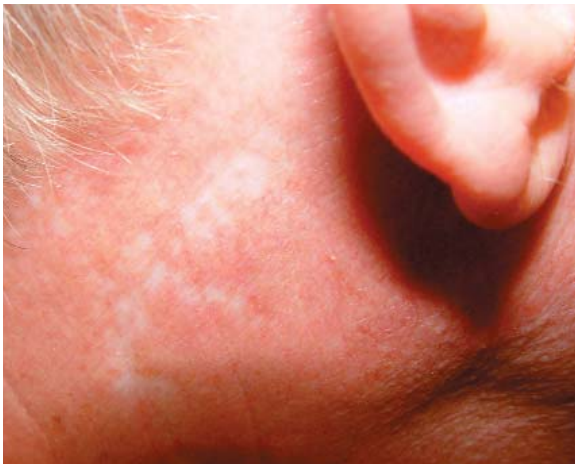

Figure:
post herpetic neuralgia following acute infection with herpes zoster (shingles) in C3 dermatome on the right, with scar formation. In theory shingles can occur in any dermatome, but is commonest in the thoracic and trigeminal dermatomes.

However, many chronic pain symptoms show both nociceptive and neuropathic pain components, and clear categorization is not always possible (13). A classic example would be back pain syndromes, where chronic irritation of afferent nerves in joints, ligaments and muscles (nociceptive components) are combined with compression and damage to nerve roots via hyperostosis, fibrotic tissue, or intervertebral disc tissue (neuropathic component) (14).

A further example of mixed neuropathic and nociceptive pain is tumor pain, where, on the one hand, intact nociceptor fibers are stimulated by neuroactive substances released by the tumor, and on the other hand, the tumor can damage neural tissue via direct infiltration. In these mixed conditions it is important to estimate the degree of neuropathic component.

History and diagnosis

The cornerstone of diagnosis in neuropathic pain is the elucidation of the underlying cause and the characterization of the pain syndrome itself, in particular, the degree of neuropathic pain, as opposed to nociceptive pain, in which neural structures are intact. It rests primarily on the history, particularly, any history of trauma involving nerve damage, and wherever possible on the objective demonstration of a lesion in the nervous system, in combination with the type of somatosensory symptoms typical in neuropathic pain (5,6). A full neurological examination to establish any neurological deficits (motor, sensory or autonomic) is essential. The sensory examination is particularly important, both to identify sensory deficits, and to reveal any positive signs of sensory irritation. (15).

Bedside tests of sensory function

By establishing the classic somatosensory pattern it is possible to distinguish neuropathic from nociceptive pain (*Table 1*). Since nerve injury is a prerequisite for neuropathic pain, most patients describe negative sensory symptoms, i.e. a reduction of touch, pain or temperature or proprioceptive sensation, or complete anaesthesia. These negative sensory symptoms are usually experienced as unpleasant, but are not painful per se.

The characteristic symptoms requiring specific treatment are known as positive sensory symptoms. These include parasthesiae such as "crawling skin" (a sense of ants running over the skin), dysaesthesiae (painful paraesthesiae) and evoked pain. Many patients with chronic neuropathic pain suffer from spontaneous pain unprovoked by any external stimulus,

Somatosensory symptoms are:
Sensory deficits, negative symptoms such as reduced sensitivity to touch and pain, and positive symptoms such as chronic burning pain, attacks of stabbing pain, and evoked pain.

Characteristic complaints:
"Crawling" skin, dysesthesias, and both spontaneous and evoked pain.

characteristically burning in nature, which may be constant (spontaneous chronic pain). Stabbing pains can also occur suddenly and spontaneously. This pattern is characteristic in trigeminal neuralgia, but is also found in acute and chronic herpetic neuralgia, in stump and phantom limb pain, and following mechanical nerve lesions (*figure*). In the case of polyneuropathies, the pain may be experienced simply as a feeling of pressure or constriction in the extremity itself. Crawling sensations and other dysaesthesiae are among the classic symptoms of polyneuropathy. Some patients describe distressing itching, muscle cramps, or restless leg syndrome.

Alongside spontaneous pain, patients often complain of evoked pain, which can be extremely unpleasant. In contrast with spontaneous pain this is triggered by an external stimulus. In the case of allodynia, this can take the form of pain evoked by the application to an unaffected part of the body of a non-painful stimulus such as touch, warmth or cold. Mechanical allodynia is typical of post herpetic neuralgia and rapidly developing polyneuropathies; cold allodynia is common in posttraumatic nerve lesions, some polyneuropathies, in the acute phase of oxaliplatin treatment, and in central pain syndromes following stroke. Hyperalgesia is the term used for an intense pain arising in response to a stimulus inadequate to produce severe pain. Simple clinical tests can distinguish between different types of evoked pain (*table 1*).

Questionnaire to estimate the neuropathic component

A number of questionnaires have been developed to define the symptoms of neuropathic pain qualitatively and quantitatively. Using these can help estimate the component of a chronic pain syndrome which is attributable to neuropathic pain, in order to inform treatment. In general it is advisable to use those measures which summarize symptoms characteristic for neuropathic pain (positive and negative symptoms), which measure pain intensity, and which use a whole body diagram to describe the localization and radiation of symptoms. A screening questionnaire in German has recently been developed for self-administration by patients, without the need for medical tests (PainDetect) (16).

Investigations

Where a neuropathic pain syndrome is suspected, attempts should be made to document the lesion with neurophysiologic or imaging technologies.

The nociceptive pain fibers implicated in neuropathic pain syndromes belong to the category of fine, unmyelinated or partially myelinated fibers. Conventional neuro imaging is for technical reasons only able to demonstrate thick, rapidly conducting fibers, which means that fine fibers escape routine diagnosis. For this reason a specialized form of small fiber polyneuropathy which account for around 10% of diabetic polyneuropathy, especially in its early stages, is invisible to neuroimaging techniques. It is therefore important, even where the results of neuro imaging are unremarkable, to conduct bedside tests in all patients with symptoms suggestive of polyneuropathy, to gain what information is available about small fiber function (such as via pinprick testing, or testing temperature sensation (*table 1*). Confirmation and quantitative analysis of the fine pain pathways can be achieved via special neurophysiologic investigations such as the quantitative thermo test (QST) (17) or the analysis of laser-pain evoked potentials (LEP).

Where a CNS based pain syndrome is suspected the lesion must be sought using definitive imaging in the form of MRI, evaluation of the cerebrospinal fluid, especially in the case of multiple sclerosis, and/or neurophysiologic methods such as sensory evoked potentials, QST and LEP.

Diagnostic tools

Where symptoms suggest polyneuropathy bedside testing should be carried out even where neuroimaging is unremarkable.

General principles of treatment

Patience is needed in establishing effective treatment at an effective dose. Long term monitoring is needed to detect side effects and tolerance.

Pharmacological treatments for neuropathic pain

General principles (18,19)

Patience in doctor and patient: With many chronic pain conditions, the right agent or combination of agents must be sought on an individual, case-by-case basis via trial and error. (individual titration against effect and side effects). With neuropathic pain in particular, there are cases where antidepressants are ineffective, but anticonvulsants or a combination of the two offer satisfactory pain relief. It must be emphasized that a medication should not be dismissed as ineffective before giving it a fair trial of two to four weeks, as chronic morphological distortions in the nervous system are not susceptible to rapid correction. These problems are best discussed with the patient in advance, in the interest of establishing a long term therapeutic partnership. Too rapid a cessation of treatment can risk losing a treatment option which could have proven helpful.

Monitoring treatment effect: Long term monitoring is essential both to document treatment efficacy and to detect early any development of tolerance. This should not only include documentation of analgesic efficacy using instruments such as pain diaries, but possible effects of treatment on other areas of daily living such as sleep and mood. It is realistic to aim for a pain reduction of 30 to 50%, an improvement in sleep quality, the preservation of social activity and the capacity to maintain relationships, and to work. Complete freedom from pain is seldom achievable. All pharmacological treatments will be ineffective in between 20 to 40% of patients (so called non-responders), or produce unacceptable side effects. The therapeutic goals must be discussed openly with patients, to forestall unrealistic expectations and disappointment. Exclusion tests for each medication are usually recommended after a year.

Even where neuropathic pain is chronic, the first priority is to look for a treatment based on the underlying cause, such as optimizing diabetic control or decompression surgery in the case of carpal tunnel syndrome. Symptomatic, pharmacological treatment is broadly similar between chronic pain syndromes of varying etiologies (5, 20, 21). The one notable exception is trigeminal neuralgia, which is not discussed in detail here. At the present time four systemic therapies with differing modes of action are used, delivered either orally or transdermally. These form the mainstay of treatment, with topically prescribed treatments as an adjunct where appropriate (8, 22) (*table 2*). Not all of these substances are licensed for pain of neuropathic pain in Germany.

A blueprint for a gradual process of diagnosis and treatment is set out in *box 2*. The choice of agents and combinations must take account of co morbidity and other medications.

Basic pharmacological treatment

- Calcium channel modifying anticonvulsants work mainly presynaptically on CNS calcium channels. Examples: pregabalin, gabapentin.
- Sodium channel blockers act on sodium channels in primary afferent and CNS neurones. Examples: carbamazepine, lamotrigine.
- Tricyclic antidepressants such as amitryptilline and selective serotonin and noradrenalin reuptake inhibitors (SSNRIs), such as duloxetine and venlafaxine, block the reuptake of these neurotransmitters in desensitizing inhibitory pathways.
- Opiates activate μ receptors in the brain and spinal cord.

Clinical experience suggests that these agents can often usefully be combined, albeit with care in relation to mutual potentiation of side effects such as tiredness or dizziness.

Topical treatments

- The effect of systemic agents can be augmented via the use of topical agents such as lidocaine or capsaicin which act locally on pain fibers in the affected area of skin, without causing systemic side effects.

Drug treatments

Four systemically active classes of drug are helpful in managing neuropathic pain, given orally or transdermally.

Medications

Basic treatment (antidepressants, anticonvulsants, opioids) can be augmented with topical agents. Non opioid analgesics are of little benefit.

TABLE 2

Evidence based drug treatment in neuropathic pain, dose recommendations in adults

Medication	Evidence	Initiatl dose (mg)	Effective Dose (maximum dose) (mg/d)	Comments
Antidepressants				
TCA (5-HT, NA) Amitryptylline, nortryptilline TCA (NA) Desipramine	PHN ⇑⇑ PNP ⇑⇑ PTN ⇑ STR ⇑	10–25 0–0–1	50–75 (150)	SEs: micturition disturbances, hypotension Weight ↑, Caution: AV block, glaucoma Amitryptilline: sedating Nortryptilline: slightly stimulating Desipramine: markedly stimulating
SSNRI Duloxetine Venlafaxine	PNP ⇑⇑	 (30)–60 1–0–0 37.5 1–0–0	 60 75–225 retard (375)	SEs Nausea, dry mouth SEs Nausea, vomiting, Weight ↓ Restlessness
Antiepileptics (calcium channel)				
Gabapentin	PHN ⇑⇑ PNP ⇑⇑ HIV ⇑ CRPS ⇑ PHAN ⇑ SC ⇑ MIX ⇑ CANC ⇑	300 0–0–1 up to 1–1–1	1 200–2 400 (3 600)	SEs: sedation, dizziness, edema Minimal interactions
Pregabalin	PHN ⇑⇑ PNP ⇑⇑ SC ⇑	75 1–0–1	150 (600)	SEs: sedation, dizziness, edema Minimal interactions, linear plasma Concentration, rapid onset of action Effect on sleep and anxiety
Antiepileptics (sodium channel)				
Carbamazepine	PNP ⇑ TGN ⇑⇑	100–200 0–0–1	600–1 200 retard (1 400)	SEs: Hematological derangement Liver damage, hyponatremia, Drug interactions due to enzyme Induction
Lamotrigine	HIV ⇑ PNP ⇑ STR ⇑	25 0–0–1	100–200 (400)	SEs: rash, Extremely slow dose increase
Opiates				
Tramadol retard	PHN ⇑ PNP ⇑⇑	100–200 1–0–1	Titration (400)	SEs: Nausea, hypotension
Morphine retard	PHN ⇑ PHAN ⇑	10–30 1–0–1	Titration (none)	Accumulation in renal disease and Old age
Oxycodon	PHN ⇑ PNP ⇑⇑	5–20 1–0–0	Titration (none)	Dual mode of action, well tolerated
Cannabinoids				
Tetrahydrocannabinol	PA ⇔ MS ⇑⇑ MIX ⇑	2.5 1–0–0	Titration (40)	SEs: tachycardia, hypotension, sedation
Topical treatment				
Lidocaine plaster	PHN ⇑⇑ MIX ⇑	5 % 1 × daily minimum of 12 hours' gap	Up to 3 plasters daily	Effective in allodynia, No systemic effects, No interactions
Capsaicin cream/ointment	PHN ⇑ PNP ⇑ PTN ⇑	0.025–0.01 % 3–4 × daily	3–4 × daily	Initial burning sensation

TCA, tri or tetracyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SSNRI, selective serotonin and noradrenalin reuptake inhibitor; PHN, post herpetic neuralgia; PNO, polyneuropathy; PTN, posttraumatic neuralgia; CRPS, complex regional pain syndrome; SC, spinal cord lesion; STR, stroke; HIV, HIV neuropathy; PHAN, phantom pain; MIX, mixed group; PA, plexus damage; MS, multiple sclerosis; CANC, neuropathic cancer pain; TGN, trigeminal neuralgia; SE, side effects.

Classification of levels of evidence and strength of recommendation

⇑⇑ Recommendations based on several valid clinical studies (such as randomized controlled trials) or on one or more metaanalyses or systematic reviews – recommendations well founded

⇑ Recommendations based on at least one adequate clinical study (e.g. RCT) – recommendation based on some evidence

⇔ No reliable data exist to suggest a positive or negative effect. This may be due to lack of evidence, or to conflicting evidence.

Caution:
Not all of the named preparations are licensed in Germany for the treatment of neuropathic pain. This table summarizes the results of 110 scientific studies. The key meta-analyses are Dworkin et al. (5) and Finnerup et al. (20). German language publications in Baron R, et al. (22).

● The above treatments are supported by non-pharmacological measures such as transcutaneous electrical nerve stimulation (TENS), other interventional measures, physiotherapy, ergotherapy and psychotherapy.

Analgesics

Non opioid analgesics (NSAIDS, paracetamol and metamizole) are of little efficacy in neuropathic pain. These substances are not contained in treatment algorithms for neuropathic pain due to lack of evidence and possible serious side effects in long term use, such as gastrointestinal ulceration or nephrotoxicity. However, in contrast to widespread opinion, neuropathic pain has been shown to be opioid sensitive. Tramadol has been shownto be effective in painful diabetic polyneuropathy. Oxycodon for example demonstrated a positive treatment effect in patients suffering from post herpetic neuralgia and diabetic polyneuropathy. Strong opiates should be reserved for severe or refractory pain. Chosen using these criteria, and with careful supervision, patients with chronic, non-malignant pain can be treated safely and effectively over long periods with strong opiates, without developing tolerance or tachyphyllaxis.

Antidepressants

Tricyclic antidepressants have been shown to be effective both in painful polyneuropathy and in post herpetic neuralgia and CNS based pain syndromes. The moderate dose required for analgesia is lower than that required to achieve an antidepressant effect. The analgesic effect cannot therefore be attributed to antidepressant activity. In addition, the analgesic

BOX 2

Algorithm for the diagnosis and treatment of neuropathic pain

Diagnosis

Screening for neuropathic pain and diagnostic distinction from nociceptive pain (possible referral to pain specialist or neurologist)
Diagnosis of relevant co morbidity (cardiac, renal, depression)

Treatment

If possible treatment of the underlying cause (e.g. optimization of diabetic control)
Symptomatic treatment according to age, co morbidity and co medication with one or more medications from the four systemic groups (a-d):
a) Ca channel modulating anticonvulsants (pregabalin, gabapentin)
b) Na channel blockers (carbamazepine, lamotrigine)
c) Tricyclic antidepressants (amitryptilline) or SSNRIs (duloxetine, venlafaxine)
d) weak opioids (e.g. tramadol, tilidin) in combination with 1 or more medication from groups a–d.

Treatment failure

Persistent pain and/or intolerable side effects ⇨ other combinations of the four major groups (a–d).
Persistent pain and/or intolerable side effects ⇨ strong opiates (e.g. morphine, oxycodon, fentanyl) in combination with 1 or more medication from groups a–c.

Antidepressants
The moderate dose required to deliver analgesia is lower than that required for antidepressant activity.

Anticonvulsants
Anticonvulsants have differing modes of action and can be combined.

effect is in evidence from between a few days and two weeks, whereas the antidepressant effect takes several weeks at a higher dose to become apparent. Benefit has also been shown in diabetic polyneuropathy with duloxetine and venlafaxine, which have fewer side effects than the tricyclics. In contrast, no definite effect was able to be demonstrated for SSRIs (fluoxetine, citalopram and paroxetine) in painful polyneuropathy.

Anti convulsants with membrane stabilizing activity (sodium channel blockers)

The efficacy of carbamazepine in trigeminal neuralgia has long been familiar. A handful of studies suggest positive results for carbamazepine in painful diabetic neuropathy, whereas for oxcarbazepine no effect could be demonstrated.

Lamotrigine is effective in post ischaemic CNS pain syndromes as well as in spinal lesions and painful diabetic neuropathy.

Anticonvulsants with calcium channel activity

Benefit has been shown for gabapentin in painful diabetic neuropathy and post herpetic neuralgia. Further randomized controlled trials have shown benefit in patients with spinal cord injury, painful Guillain-Barré syndrome, phantom limb pain and other pain.

Pregabalin is a potent ligand of the $\alpha 2$-δ subgroup in the potential difference-dependent calcium channels in nociceptive neurons, and so reduces the release of mediators from the synapse. Pregabalin has been shown to be an effective analgesic in post herpetic neuralgia, diabetic neuropathy and in patients with CNS pain due to spinal cord injury. In addition, a clear improvement in sleep and anxiety was reported. This allows common accompanying symptoms to be co treated.

Topical treatments

Topical application of lidocaine, for example in the form of a lidocaine plaster, is useful as adjuvant therapy, especially where pain is well localised with allodynia. Because it acts only locally and is only minimally systemically absorbed, it is a particularly useful adjuvant treatment option in elderly patients. In certain focal neuropathies mono therapy with local anaesthetic may be appropriate, such as in post herpetic neuralgia, or pain following mastectomy.

Capsaicin is a vanilloid receptor agonist occurring naturally in chilli pepper, which after long term application leads to a reversible desensitization of nociceptive afferent fibers. It generally causes a strong burning sensation on the skin, and is therefore not usually considered a treatment of first choice.

Cannabinoids

Controlled trials on cannabis extracts such as tetrahydrocannabinol showed a significant reduction in pain in patients with CNS pain in multiple sclerosis and in a mixed group of patients with chronic neuropathic pain. Further studies in individual patient groups are needed to elucidate the mode of action of these agents.

Combination studies

Since the different classes of drug have different mechanisms of action, it makes theoretical sense to combine several agents. In reality this option is often restricted to no more than two drugs at a time, by the mutual potentiation of side effects across classes. A recent study investigated the combination of gabapentin and morphine in a mixed group of patients with painful diabetic polyneuropathy and post herpetic neuralgia. In support of the study hypothesis, the data showed an additive effect on pain reduction when compared with

Prevention

Effective analgesia must be initiated as early and as effectively as possible to prevent pain becoming chronic.

Conclusion

Many patients benefit from a combination of medications from different classes.

monotherapy, at a low dose of the individual agents. No other combination studies have been completed to date.

Prevention

The modern understanding of chronification of pain is based on the understanding that every nociceptive stimulus which acts on the central nervous system is capable of reinforcing pain in the long term (23). Hence the important principle of all chronic pain management: effective analgesia must be commenced as early and as effectively as possible. This is particularly important in conditions which can be treated early and prophylactically in the acute phase, such as herpetic neuralgia and phantom limb pain. This strategy has revolutionized our thinking about pain management. Blandishments offered to patients about "grinning and bearing it" are inappropriate, unhelpful to patients and promote the development of acute into chronic pain. Only if this is consistently applied will prevention of chronic pain be effective.

A recent contribution has suggested a new strategy for the prevention of post herpetic pain (24). Based on the assumption that acute zoster infection arises from an age related immune susceptibility to varicella zoster virus, the hypothesis was tested that an immunological boost using zoster vaccination in the over 60s might reduce the incidence of shingles and therefore of post herpetic neuralgia. A double blind study was conducted in almost 40 000 elderly people over 5 years, showing a reduction in the cumulative incidence of zoster of 50% and of post herpetic neuralgia of 70%.

Conclusions

The aim in neuropathic pain should always be to identify a causal neurological lesion, establish an aetiological explanation, and instigate a treatment based on the underlying cause. In addition, symptomatic analgesia should be initiated with a view to preventing chronification of pain and improving quality of life.

At present four classes of systemic agent (antidepressants, anticonvulsants with calcium channel activity, anticonvulsants with sodium channel activity, and opioids) and two of topical agent with different modes of action, are in use.

Combination therapy with drugs of different classes is advisable where pain is severe or refractory.

Conflict of Interest Statement
The author has received research funding and honoraria from the following firms: Allergan, Genzyme, Grünenthal, Novartis, Pfizer, Sanofi, Pasteur, Schering AG und Lilly.

Manuscript received on 8 June 2006, final version accepted on 18 July 2006.

Translated from the original German by Dr. Sandra Goldbeck-Wood.

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FURTHER INFORMATION

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education.

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www.leitlinien.net
Guidelines of the German Neurological Society

www.neuropathischer-schmerz.de
German Neuropathic Pain Research Group

www.dgss.org
The German Society for the Study of Pain

www.deutsche-schmerzgesellschaft.org
German Pain Society

www.gesundheitsforschung-bmbf.de/de/139.php
Information about chronic pain courtesy of the Federal Ministery of Education and Research

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Which of the following statements is true for neuropathic pain:

a) The point prevalence is 20% in the general population.
b) Neuropathic pain accounts of 5% of all chronic pain.
c) Chronic pain often involves a mixture of nociceptive and neuropathic pain components.
d) "Restless legs syndrome" is a common complication of central nervous system pain following stroke.
e) 10% of patients with hemiplegia suffer from CNS derived neuropathic pain.

Question 2

Which of the following can be described as a positive sensory symptom:

a) Reduced touch sensation
b) Reduced temperature sensation
c) Reduced vibration sensation
d) Disordered proprioception
e) Paresthesia

Question 3

Which of the following statements is correct:

a) Neuropathic pain is defined as a pain syndrome arising from a lesion in the central or peripheral nervous system
b) Neuroimaging allows a functional assessment of all peripheral nerve fiber groups
c) The investigation of choice for a CNS lesion is computerized tomography
d) Most pain fibers are myelinated
e) The eliciting of sensory evoked potentials investigates conductivity in the central pain pathways

Question 4

Which of the following is true of the symptomatology of neuropathic pain syndromes?

a) Paresthesia is classed as a negative symptom
b) Neuropathic pain often involves a mixture of positive and negative symptoms
c) Spontaneous burning pain is rare in neuropathic pain
d) The presence of evoked pain (elicited by an external stimulus) makes neuropathic pain unlikely
e) Mechanical allodynia is a negative symptom

Question 5:

Neuropathic pain syndromes are accompanied by typical patterns of pain and sensation. Which of the following definitions is correct?

a) Dynamic mechanical allodynia – a usually painful pressure stimulus on the skin causes greater pain than in a healthy individual
b) Cold allodynia – a normally painless cold stimulus elicits a sensation of heat in the skin
c) Heat hyperalgia – a normally mildly painful heat stimulus is experienced as more painful than in a healthy individual
d) Pallhypoesthesia (reduced sensitivity to vibration) – describes the condition where vibration is experienced as painful
e) Thermhypoesthesia describes an increased sensitivity to heat and cold.

Question 6:

Which of the following counts as a neuropathic syndrome?

a) Osteoarthritis
b) Inflammatory arthritis
c) Visceral pain
d) Painful diabetic polyneuropathy
e) Angina pectoris

Question 7:

The evidence of efficacy in the treatment of neuropathic pain is weakest in which of the following?

a) Opiates
b) Gabapentin
c) Amitryptilline
d) Carbamazepine
e) Diclofenac

Question 8:

General therapeutic guidelines for the treatment of neuropathic pain include:

a) The daily dose of anticonvulsants should be titrated strictly against the serum levels.
b) A non response rate of 80% is to be expected.
c) Combining agents from different groups should be avoided because if increased risk of side effects.
d) Before evaluating the efficacy of any one agent, a treatment duration of at least 12 weeks is needed.
e) A combination of oral and topical preparations (such as lidocaine) can be useful

Question 9:

Anatomical components of the nociceptive system include:

a) The dorsal columns
b) The corticospinal tract
c) Fast conducting, large diameter A-fibers
d) Small diameter, unmyelinated C-fibers
e) The superior and inferior colliculi

Question 10:

Which of the following are possible causes for neuropathic pain?

a) Diabetes mellitus
b) Vincristine treatment
c) Fabry's disease
d) Plexus lesion following radiotherapy
e) All of the above

Important Information

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The correct answers to this CME questionnaire will be published in Issue 49/2006 under this heading.

The planned CME topic in Issue 45/2006 is "Diagnosis of headache"

ADDITIONAL MATERIAL

Case report:

Diagnosis and treatment of neuropathic pain

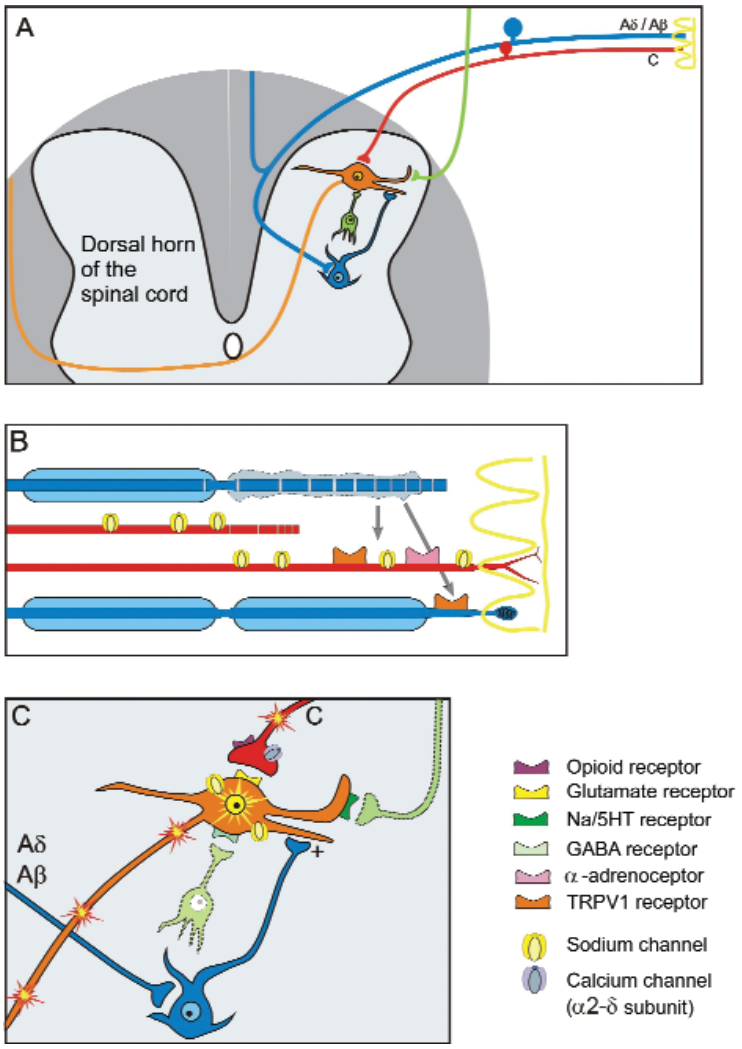
A 65 year old woman complained of feeling generally unwell. She felt exhausted and described an increasing generalized physical malaise. Over the next few days she developed a left sided paravertebral pain at the level of T 5/6/7, radiating anteriorly to behind the sternum. The pain was described as burning, sharp, and stabbing. The skin in the affected area was extremely sensitive: gentle touch elicited a burning pain.

After about a week she developed small itchy red blisters covering the left side of her chest, in the midclavicular line. These developed into fluid filled blisters covering around a hand's area, which had the classic appearance of herpes zoster. The patient was by now markedly unwell, febrile with a temperature of 37.9°C and suffering from pain related sleep disturbance and low mood. After three weeks the rash disappeared leaving an area of increased sensitivity to touch. The affected segments showed marked mechanical allodynia (Visual analog score 8 on a scale of 0-10). In addition, the patient complained of sharp, stabbing pains radiating to the sternum, as well as a dull, burning pain which was continuous.

Six month follow up revealed scars from the rash which were lighter in colour at the center than at the periphery. Both the scars and the surrounding area were sensitive to light touch (cotton wool) or pain stimuli (pinprick) (signs of dynamic mechanical allodynia and pinprick hyperalgesia). This pain scored 7 on the visual analog scale. The stabbing pains were no longer a primary concern, but the burning constant pain was given a score of 6. The patient moved extremely circumspectly, in an effort to avoid pain. Wearing clothes caused her significant difficulty and distress. The remainder of the physical examination was normal for the patient's age.

A diagnosis of postherpetic neuralgia was made.

Treatment with a combination of amitryptilline 50mg nocte and pregabalin 2x 75mg increasing to 2x 150 mg, was able to achieve a reduction of about 50% in her spontaneous pain and allodynia, and an improvement in her sleep. The combination of both medications was needed. The treatment was continued for 6 months to good effect, and discontinued at a year. The patient now reported only mild hypersensitivity and occasional itch in the affected area.



Pathophysiological mechanisms of chronification of pain in neuropathy, and therapeutic target receptor sites (Diagram).

A) Neuronal connections in the dorsal horn of the spinal cord. C fibers transmit pain and temperature stimuli, and end in the upper laminae of the spinal cord (orange neuron). A fibers from the periphery transmit non pain stimuli (pressure, touch) and end in the laminae of the spinal cord. The spinothalamic projection neuron is of the WDR (wide dynamic range) type because it receives direct synaptic input from nociceptive fibers and multisynaptic input from A fibers (blue neuron system). GABAergic interneurons (green neuron) inhibit WDR neurons. Descending modulating neurons (green descending ending) also modulate (often inhibit) the WDR neuron.

B) Peripheral mechanisms of sensitization following partial nerve injury. Damaged afferent nociceptive C fibers (red) express sodium channels (leading to ectopic excitation). The release of neural growth factor from degenerating nerve sheaths leads to the expression of receptors and channels in intact adjacent C and A fibers.

C) Central sensitization of WDR neurons. Pathological rest activity in afferent C nociceptors leads to central sensitization of the secondary afferent dorsal horn neurones (star in the orange neuron) and thereby to a transformation of the functionally effective synaptic structures in the dorsal horn. Impulses from low threshold afferent Aß and A touch fibers (blue system) can now activate central nociceptive neurons.

Exhaustion of descending and intraspinal control mechanisms. The nociceptive system in the spinal cord is physiologically under constant inhibitory control, to prevent nociceptive over

activity. Descending pathways from the brain stem (for example arising in the peri aqueductal grey matter) inhibit activity in nociceptive dorsal horn neurones via noradrenalin and serotonin. GABAergic interneurones have an inhibitory role in the dorsal horn. Chronic nociceptive activity can lead to a loss of function and even to degeneration of this inhibitory system, which leads to unmoderated transmission of nociceptive impulses, and to pain chronification. Pharmacologic treatment options: calcium channel blockers (e.g. carbamazepine, lidocaine, lamotrigine) act on newly expressed sodium channels on primary afferent and central neurones. Capsaicin on vanilloid receptors (TRPV1) in primary afferent neurones. Pregabalin and gabapentin modulate central calcium channels both pre and postsynaptically. Opiates activate receptors occurring primarily presynaptically, but to a lesser extent postsynaptically, in the spinal cord. Antidepressants block the reuptake of noradrenalin and serotonin in the descending inhibitory pathways.

Modified from: Baron, R: Disease mechanisms in neuropathic pain: a clinical perspective. Nature Clinical Practice Neurology 2006; 2:95-106.

This text is a translation from the original German which should be used for referencing. The German version is authoritative.