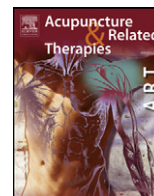




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## Neural therapy—A review of the therapeutic use of local anesthetics

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### ABSTRACT

Neural therapy, or therapeutic local anesthesia (TLA), is the diagnostic and therapeutic use of local anesthetics. This review summarizes the scientific and clinical evidence, indications, methods of application, and possible future research.

In the literature, there is a gap between the multitude of data supporting a number of different molecular effects and the few clinical trials that are available. The available clinical studies and case reports, however, show effectiveness in acute and chronic pain, functional disorders, vegetative diseases such as the complex regional pain syndrome (CRPS), and chronic inflammation.

Five administration methods are described: local, segmental, regional, and systemic application, as well as injections into the so called “stoerfeld” (disturbance field, interference field).

Local anesthetics have been used for therapy for over 120 years, which suggests that this therapy may be an important, effective, and efficient therapy that has few side-effects. Possible clinical studies to reveal the potential effectiveness and benefit-risk ratio of this holistic approach are described.

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### 1. Definition of neural therapy

Neural therapy (neuraltherapy), therapeutic local anesthesia (TLA), or therapeutic neural blockade [1], are common names for the diagnostic and therapeutic use of local anesthetics (LA). In contrast to the well-defined and short-time use for analgesia in surgery, the neural therapy approach aims for long-term relief of pain and functional disorders.

### 2. Neural therapy and acupuncture

There are multiple interrelationships between neural therapy and acupuncture. Both are minimally invasive, both have knowledge of distant phenomena, and both have few side effects. They are both forms of regulatory therapy and aim to influence the whole organism by following a holistic approach. This review summarizes the scientific and clinical evidence, indications, methods of application, and possible future research in this field.

### 3. Scientific evidence

The long-term effects of LA, which are useful in therapy, have been known since the discovery of LA in 1884 by Sigmund Freud and Carl Koller [2]. Freud's goal in investigating cocaine was to find new therapeutic treatments for his patients with chronic pain, particularly a male with severe trigeminal neuralgia. However, Freud's congenial coworker, Koller, immediately recognized cocaine's potential as a perioperative analgesic agent, and 14 days after Koller's historic lecture in Heidelberg in 1884, the whole medical world knew about this fascinating new method for pain-free surgery. Local anesthesia for operations found its way into medical routines worldwide, and its therapeutic use was nearly forgotten. Today, trigeminal neuralgia and similar forms are major indications for the therapeutic application of LA [3], and Freud's idea of therapy with LA is now close to a new renaissance.

Local anesthetics have a multitude of effects on the nervous system. Beside the well-known action on sodium ion channels in excitable cells, they also seem to provide neuroprotection to the CNS [4], protect against sympathetic sprouting in neuropathic pain [5], and reduce intracranial hypertension [6].

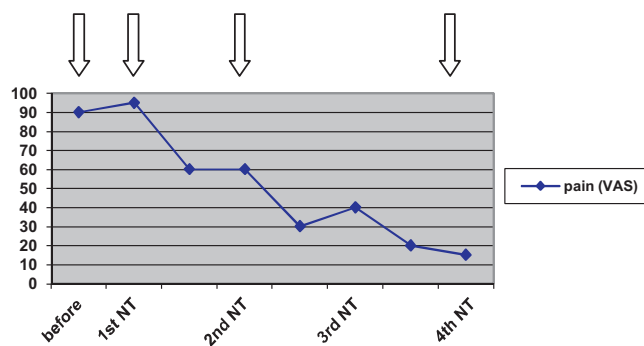
There is some evidence in basic science that pleiotropy (i.e., the “alternative effects”) of LA on non-excitabile cells [7,8] has a longer lasting effect than the pharmacological half-life of the drug in the sodium ion channel.

Some studies have revealed additional molecular mechanisms in neural therapy. Local anesthetics induce Gq-protein-complex mediated intracellular anti-inflammatory mechanisms [9],

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**Fig. 1.** The concept of “pain holidays”. Repeated interventions with increasing intervals based on the improvement of patient complaints. Scale: VAS (0–100). Arrows: Treatment session with local anesthetics.

deactivate overactive granulocytes, inhibit the signaling of human NMDA receptors [10], and affect the synthesis and release of inflammatory mediators as eicosanoids, histamine, prostaglandins, and cytokines [11]. LA induce vasodilatation [12], reduce a pathologically increased capillary permeability in a hyperoxic lung injury in rabbits [13], have antimicrobial properties [11], and exhibit a sympatholytic effect [14]. Furthermore, the interesting concept of neurogenic inflammation [15] opens new perspectives into the therapy of chronic sterile inflammation by local anesthetics, thereby reducing the release of pro-inflammatory substances. Although Tracey has already suggested this approach [16], there are no data available proving this idea.

Neural therapy works best if it is repeated several times with increasing intervals as complaints are decreasing. This concept of “*salutogenesis by pain holidays*” (Fig. 1) may reflect the central nervous system action of local anesthetics. Memory effects are important mechanisms in the development of chronic pain disease. A central mechanism of LA action is likely. Procaine, for instance, shows a selective proclivity for activating limbic structures [17] without inducing the adverse effects of cocaine [18].

#### 4. Clinical research

In contrast to this expanded knowledge concerning the underlying mechanisms of neural therapy and its frequent use in Central Europe [19], there is an obvious lack of clinical evidence. A recent systematic review of neural therapy in musculoskeletal diseases [20] could not identify any high-quality studies that proved an effect of neural therapy in this context. The few exceptions to the lack of data are randomized clinical trials (RCTs) on neural therapy in multiple sclerosis [21], on the therapy of distal colitis [22], and on acute pancreatitis [23]. Some reports have also shown high cost effectiveness [24] and a significantly higher treatment and care-related patient satisfaction with primary care for musculoskeletal diseases provided by physicians practicing neural therapy [25]. A HTA report in Switzerland worked-up approximately 3000 case reports from non-peer-reviewed journals (best case analysis) and recommended maintaining this method in the Swiss health system [26]. Since January 2012, Switzerland has reintegrated neural therapy into its basic medical insurance refunding [27].

#### 5. Five groups of indications

Based on clinical experience, at least five indication groups and five administration methods have evolved.

Indications for the therapeutic use of LA can be divided into the following groups:

##### 5.1. Acute pain and chronic pain disorders

**Headache** and migraine can be addressed by injections to the major occipital nerve [3] or by the intranasal or intravenous application of lidocaine [28,29]. Trigeminal neuralgia has been successfully treated with 10% lidocaine injections [30] and with trigger point injections [31].

**Postherpetic neuralgia** (PHN) could be successfully treated with local LA injections. Early reports [32,33] were confirmed by recent studies using neural therapy with procaine in a multifaceted integrated CAM concept [34]. In most recent studies, however, neural therapy was only used in combination with steroids [35,36]; therefore, a clear conclusion on the value of local anesthetics alone cannot be drawn. A promising approach to ophthalmic PHN is the topical use of lidocaine in eye drops [37]. Similarly, the topical use of 5% lidocaine plaster has been established as a first-line option for treating patients with PHN [38].

**Myofascial pain** is characterized by the frequent occurrence of muscular trigger points; in fact, myofascial pain and trigger points are nearly synonymous. One of several publications on successful LA use in this disease was conducted in Taiwan, with cervical facet joint injections for shoulder pain [39].

**Visceral pain.** An important example of abdominal pain conditions is chronic pelvic pain without organic origin. A French group reviewed the literature and found a significant diagnostic effect of autonomic nerve blocks (ganglion impar, hypogastric plexus and L2 lumbar sympathetic blocks) [40]. Further research may reveal a therapeutic effect in repeated interventions.

**Postamputation pain syndrome.** There is some evidence that contra-lateral injections of LA relieve phantom pain in soldiers [41]. Recent observations support the idea of treating postamputation pain with LA [42].

##### 5.2. Functional disorders without organic findings

**Vulvodynia.** Clinical experience in our unit (with 10 patients) yielded the first evidence that LA injections around the pudendal nerve and the hypogastric plexus provided long-term relief of this painful condition [43].

**Chronic colitis.** In a review with description of their own experience, a Swedish group [22] described the results of a treatment of colorectal mucosa with a topical application of 2% lidocaine gel. The clinical results were promising and no side effects were observed.

Reportedly, **tinnitus** may respond well to the application of local anesthetics. The first known publication reported on successful nasal application of procaine (Barany, 1935). In a recent report, a Japanese group performed intravenous lidocaine injections with good success [44].

##### 5.3. Vegetative (systemic) disorders

“Sympathetic pain” describes sympathetically induced vasoconstriction, ischemia, tissue damage, and chronic pain in the respective area. Well-known examples are reflex or vasospastic disorders, such as Raynaud’s phenomenon and thromboangiitis obliterans (Buerger’s disease). Early sympatholysis with LA injections or infusions to the respective ganglion or artery is an auspicious method of relieving these conditions [45,46]. Also causalgia and reflex dystrophy (Sudeck’s disease, CRPS) are vegetative disorders. Therapy with LA injections to sympathetic ganglia is a promising approach for relieving these severe conditions [45,47–49].

Probably, based on clinical experience, also non-specific vegetative disorders, such as menopausal flushes, can be addressed with LA injections to the sympathetic ganglia. Case reports are available, but there is no available RCT data.

#### 5.4. Chronic inflammation

Following the encouraging results on the anti-inflammatory effects of LA in basic research, a Swedish group has collected 227 publications on the physiological and clinical effects of LA in inflammation [11]. They report on its strong effects, e.g., in treating interstitial cystitis [50], major burn injuries [51], and in recurrent HSV-1 and HSV-2 infection [52].

#### 5.5. Miscellaneous indications

**Oncology.** Some clinical units in Central Europe use the systemic application of procaine infusions for secondary prevention. They report on good results and refer to *in vitro* findings that support an anti-tumor effect of this substance in different tumor cell lines [53,54] and in mesenchymal stem cells [55]. Obviously, the amid-linked LA lidocaine has DNA-demethylating properties [56], too.

**Alzheimer's disease** may also be a promising indication for neural therapy. Lecanu et al. in Washington, DC, demonstrated *in vitro* that procaine protects rat cells against beta-amyloid-induced neurotoxicity [57], which suggested a potential preventive application of procaine in early Alzheimer's disease. However, no clinical trials have been published yet.

**Hypercortisolemia and stress therapy.** An increase of ACTH-cortisol and prolactin by procaine was suspected by an NIH group in the 1980s [17]. In contrast, the Lecanu group showed the inhibition of adrenal cortical steroid formation by procaine [74]. Further studies are necessary to explain this discrepancy.

**Wound healing** can be improved by local anesthetics *in vitro* [55]. In our university hospital, the systemic application of local anesthetics was shown to reduce the length of postoperative hospital stays after colorectal surgery [58].

The majority of these data can only provide first hints to possible clinical effectiveness. Clinical trials in many subspecialties will be necessary to outline the indications and non-indications of the therapy with local anesthetics. Perhaps the wide spectrum of indications is connected with the possibility that local anesthetics can be administered in several different manners.

### 6. Five administration methods of LA for therapeutic means

For didactic reasons, the application of LA can be divided into five different administration methods. Similar to acupuncture, in daily use, these methods are not purely applied; instead, most physicians combine two or more methods in their therapeutic regimen.

#### 6.1. Local and trigger point infiltration

Injections into trigger points and tender areas (ligaments, fascia) were first described by the authors of *The Trigger Point Manual* [59] and are frequently used in pain therapy, e.g., in chronic pelvic pain [60]. This approach is similar to the acupuncture of ASHI-points.

#### 6.2. Segmental therapy

This form of neural therapy aims to exploit segmental reflexes and referred pain mechanisms. It resembles needling of the bladder meridian in acupuncture. Administering wheels ("quaddles") into the HEAD zones and infiltrations into intervertebral (facet) joints [39] are the main techniques in this context.

#### 6.3. Regional therapy

Regional therapy comprises all injections in or around nerves and ganglia. Many complex pain syndromes are induced or maintained by sympathetic overweight. Injecting local anesthetics into

the respective ganglia can reduce an increased sympathetic tone and re-establish the autonomic balance. In a doctoral thesis, our group demonstrated this effect through the enhancement of heart rate variability (HRV) shortly after neural therapy compared to a waiting group [61]. A well-known example for the clinical application of regional therapy is the successful treatment of CRPS and chronic pelvic pain (see above publications). Another example for regional therapy is performing paraurethral injections in motor or sensory urgency in female patients [62].

#### 6.4. Systemic infusion therapy

The main indications of LA infusions are chronic pain disease, tinnitus, the prevention of post-surgery ileus [63] for lidocaine, and acute pancreatitis [23] for procaine. LA infusions also seem to increase the general pain threshold, which is usable in otherwise intractable chronic pain [64].

#### 6.5. Stoerfeld therapy

The most sophisticated but otherwise irritating concept is stoerfeld injection therapy. A stoerfeld (German: "Störfeld", English also "interference field", "disturbance field") is defined as "any disturbed structure of the body being asymptomatic but inducing or maintaining another disorder by remote effects" [65]. Important examples for stoerfelds are scars, as well as organs with chronic inflammation, particularly the teeth, sinuses, and pharynx. The autonomous nervous system (ANS) seems to play an important role in the information transfer from the disturbed area to the target region of complaints. Case reports suggest that stoerfelds and their remote adverse effects can be temporarily or permanently eliminated by injections of LA [66]. These authors used LA injections into the area of the wisdom teeth for diagnostic methods to prove or exclude remote effects. In cases of repeated positive responses to this "stoerfeld test", the wisdom teeth were removed, with remarkable improvement of clinical complaints in these patients. In another approach, our group showed that LA injections to the sinuses and the oropharyngeal region significantly reduced the tenderness in the cervical spine. We called this special type of tender points of the cervical region *neck reflex points* (NRP). These results will be published in a doctoral thesis [67]. There is some evidence that oropharyngeal disturbances may be a preferred site of developing stoerfelds and may become a major remote cause of chronic diseases [68], perhaps based on the intensive interrelation between the dental region and the ANS [69]. *Neuralgia inducing cavitation osteonecrosis* (NICO) is a term coined by Bouquot from Houston, TX, for a dental focal disease that induces remote adverse effects, thus precisely meeting the definition of a stoerfeld [70,71].

### 7. Need for clinical studies

The continuous usage of LA for therapy worldwide for over 120 years suggests that neural therapy may be an important, effective, and efficient therapy with little side-effects. Clinical education for safe and secure application will be necessary. At the moment, an up-to-date and scientific-based textbook of neural therapy is only available in German [72]. Clinical studies are highly recommended to reveal the potential effectiveness and benefit-risk-ratio of this systemic approach [73].

A number of questions evolve from this puzzling gap between the abundance of basic research results and the obvious lack of clinical data. For instance, clinical trials are necessary in the following areas:

- **Methodology:** Are RCTs adequate for investigating this type of complex intervention?
- **Method safety:** What is the rate of adverse effects? To what extent are they influenced by various factors, such as the LA used, the experience of therapists, and the administration method?
- **What is the effectiveness of neural therapy in different indications?**
- **Cost effectiveness:** Can neural therapy help reduce the cost of basic medical supplies in emerging countries?

In basic research, there are also interesting questions to answer:

- **Neurobiology:** Is there a difference between the mechanism of action of local anesthetics in the autonomous nervous system and in the peripheral sensory neurons?
- **Neurogenic inflammation:** Do local anesthetics interrupt the liberation of pro-inflammatory substances at the terminal plate?
- **Neuroanatomy:** What underlying neuronal connection between the trigeminal nerve and the cervical region explains the effects of neural therapy on the neck reflex points?
- **Molecular biology:** Is the DNA-demethylating effect of procaine and lidocaine reproducible in other cell lines? Are there similar *in vivo* effects?
- **Pathophysiology:** The stoerfeld phenomenon – myth or clinical entity?

It is no exaggeration to predict that young and open-minded researchers will further explore this promising field of complex interventions in future medicine.

#### Conflict of interest

None.

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