Multimodal stepped care approach with acupuncture and PPAR-α agonist palmitoylethanolamide in the treatment of a patient with multiple sclerosis and central neuropathic pain

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ABSTRACT
Central neuropathic pain is a common debilitating symptom in patients with multiple sclerosis. Side effects of analgesics often limit reaching therapeutic dosages. In this case report, a 61-year-old woman with chronic central neuropathic pain due to multiple sclerosis is described. Acupuncture could only partly and temporarily reduce the pain. However, after adding the natural compound palmitoylethanolamide, a glial modulator and peroxisome proliferator-activated receptor-α agonist, pain reduction was more pronounced and the interval between acupuncture sessions could be increased. A multimodal stepped care approach is demonstrated, with acupuncture and palmitoylethanolamide both influencing non-neuronal cells, such as activated glial cells, which are key factors in the development and maintenance of neuropathic pain.

INTRODUCTION
We report on a patient with multiple sclerosis (MS) whose neuropathic pain responded only for short periods to acupuncture treatments. However, when palmitoylethanolamide (PEA) was first marketed in the Netherlands and was used in combination with acupuncture, she gained sustained pain relief.

CASE REPORT
A 61-year-old woman experienced in July 2003 sudden sight disturbances on the right side, weakening of the right leg and pain in the upper legs and thumbs. In March 2004, after lumbar puncture and MRI scan she was diagnosed with MS. The complaints resolved gradually, except for the pain, which increased progressively. At the end of 2005 her pain had become severe: 8 on the 11-point numerical rating scale (NRS). The prescribed analgesic acetaminophen did not relieve her pain.

In October 2006 the patient came for the first time to our Institute for Neuropathic Pain to be treated with acupuncture. At physical examination the pain in the upper legs appeared to be musculoskeletal, characterised as sore, dull and deep, aggravated by pressure on tender points. For the pain in her thumbs, she scored 4 on the Douleur Neuropathique 4 questionnaire (DN4: total score 10), which indicates that the pain was of neuropathic origin. The characteristics of the pain were tingling, pins and needles, numbness, and aggravation when rubbing or grabbing an object. At that time she did not have any other complaints related to MS. Her only medication was subcutaneous glatiramer acetate (Copaxone) once daily. In 2009 the fine motor skills of her fingers diminished gradually.

The patient did not experience any clinical pain relief after several types of acupuncture, including traditional Chinese acupuncture and microsystem acupuncture. Pain reduction in the upper legs was only experienced after puncturing local tender points (ah shi point acupuncture). Acupuncture needles (25 mm×0.22 mm) were not stimulated and left in place for 30 min. The neuropathic pain in the thumbs was only reduced after placing two long wrist needles subcutaneously, according to the Chinese Wrist and Ankle acupuncture. In total, four long acupuncture needles (40 mm×0.25 mm) were placed, at position 3 and 4 on the medial and lateral borders of the radius near to the wrist for 30 min. The needles were inserted subcutaneously and completely (up to the handle), parallel with the radius towards the thumb so that the tip of the needle was 1 cun from the wrist. During the insertion no sensations were provoked, such as pain, soreness or tingling. Pain in both the upper legs and the wrists diminished in the following days, from 9 to 3 and 7 to 2, respectively (NRS). However, these effects weakened after time and 3–4 weeks after acupuncture the pain gradually increased again. After 5 weeks she had to return to our clinic for new acupuncture treatments, because the pain was again severe.

In January 2011 PEA (brand name Normast) was introduced into the Dutch market, and in September 2011 into the German market. It has been available as food for medical purposes in Italy and Spain for some years now. To date, nearly 40 clinical trials have been reported, mostly in Italian medical journals. PEA is an endogenous molecule, with anti-inflammatory and analgesic properties and is widely present in humans and other mammals.

Because no sustained pain reduction was seen in this patient with acupuncture alone, we decided to add PEA 600 mg twice daily in March 2011. For personal reasons she was unable to visit our clinic after the scheduled 5 weeks, though returned after 9 weeks. The patient reported she was feeling well. Since starting PEA her pain scores remained low and were reduced even further. In the last week before visiting our clinic the average score on the NRS for the upper legs was 1 and for the thumbs 0. The tender points on the upper leg were only moderately painful when pressed. We advised her to reduce PEA to 300 mg twice daily, which resulted in aggravation of the pain again.

Sustained alleviation of her pain was accomplished with PEA 600 mg in the morning and PEA 300 mg in the evening. We decided to extend
the treatment interval to 10 weeks. In September 2011 she started to cough and stopped PEA to evaluate whether PEA was the cause of the coughing. After 3 weeks she started PEA again because the coughing did not diminish, though the pain was aggravated. In the last visit, 23 November 2011, the patient reported that 5 weeks after the last acupuncture session and taking PEA 900 mg daily, her pain score fluctuated on the NRS from only 2 to 4 and her pain did not increase to the previous severe pain levels. Our advice was to increase PEA again to 1200 mg daily. In case this profound pain reduction persists, appointments for acupuncture will be only on demand.

DISCUSSION

Pain in MS is common and occurs in 40–65% of all patients. Several types of pain can be present in MS with specific treatments required for each. Neuropathic pain can be treated with neuroleptics, antidepressants and opioids, whereas musculoskeletal pain can be treated with acetaminophen and non-steroidal anti-inflammatory drugs. Chronic use of analgesics is often limited by side effects, toxicity and reduced patient compliance and is a problem, particularly in older patients.

Recently, multimodal pharmacotherapy in pain management has become regarded as the most optimal therapeutic option. In this approach drugs from different analgesic classes are prescribed, targeting a wider range of receptors, aiming at higher efficacy and fewer side effects owing to the use of reduced dosages of each treatment modality. However, even if we follow this modern paradigm, many patients still have intractable pain, and thus the search for innovative, safe and well-tolerated treatments as well as for synergistic combinations has to continue.

Because acupuncture is safe and effective in several chronic pain states, it can be added to other treatments. Some studies show the synergistic effect of acupuncture and analgesics such as non-steroidal anti-inflammatory drugs and opioids.

The second described treatment is PEA, the body’s own lipid and a natural modulator of chronic pain and inflammation states. PEA has high affinity to the nuclear peroxisome proliferator-activated receptor-α (PPAR-α), and PEA has induced analgesic and anti-inflammatory effects in a great variety of animal paradigms and clinical pilot trials. Biosynthesis of PEA in various tissues, such as neurons and glial cells, occurs on demand in inflammatory and chronic pain states. PEA acts as a negative feedback molecule preventing escalation of pain and/or inflammation via activation of PPAR-α. When PEA docks on PPAR-α, genes which activate inflammatory cascades leading to the production of tumour necrosis factor α and interleukins are switched off. When given orally, PEA has almost no clinically relevant side effects, though it has clear pain-reducing properties in several pain states.

In a multimodal stepped care approach every treatment step is evaluated for its additional analgesic effect. When a newly added intervention has reliable and profound effects, tapering of previously prescribed analgesics with less tolerability might become feasible.

Our case report illustrates how treatments with minimal side effects, such as acupuncture and PEA, can be used in a multimodal stepped care approach. These two modalities might have a synergistic effect, though this can only be demonstrated in a randomised clinical trial and not with a single case. To our knowledge this is the first description of the above-mentioned therapeutic combination.

Acupuncture treatments temporarily reduced the pain. PEA, in addition to acupuncture, reduced the pain further, and with 900 mg daily (one 600 mg tablet and one 300 mg tablet) the pain intensity no longer rose above a score of 4 on the NRS in the 5-week period after an acupuncture session. PEA 1200 mg daily might be the optimal dosage for this patient since on this dosage her pain scores remained very low. Following the multimodal stepped care approach, for this patient acupuncture sessions will be only on demand, in case the pain aggravates again.

It seems that PEA reduces pain via the natural modulation pathways and acupuncture sessions can enhance the analgesic effects, when the analgesic response wavers.

Besides modulation of the central nervous system through the release of mainly endorphines, serotonin, norepinephrine and dopamine, pain-reducing effects of acupuncture can also be explained by suppression of activated glial cells. Interestingly, in rat models inhibitory effects of acupuncture on glial cell activation were significantly enhanced after adding glial cell inhibitors propentofylline and fluoroacetate. Thus, acupuncture and PEA may have a synergistic effect in modulating glial cells, mast cells and neurons.

Recently, the importance of non-neuronal cells such as the glial cells in pain processing has become quite clear, especially in neuropathic pain. Released chemokines and cytokines, from the damaged nerves after a nerve injury, activate glial cells in the spinal cord. In response, the activated glial cells also release pro-inflammatory cytokines, including interleukin 1β, tumour necrosis factor α and interleukin 6 and other neuromodulatory signals, such as substance P, excitatory amino acids, nitric oxide and adenosine triphosphate. This neuroinflammation causes sensitisation and leads to neuropathic pain.

In our clinic, we often observe pain reduction when we add PEA to our treatments. PEA also enhances the analgesic effects of compounds such as pregabalin and amitriptyline. Based on a dose-finding study and our experience the optimal dose seems to be between 600 mg and 1200 mg daily. Dose reduction of PEA from 1200 mg to 600 mg PEA daily in this patient, however, resulted in aggravation of the pain again. The dosage of 900 mg daily was partially effective. Therefore, in our clinic we now routinely combine acupuncture with PEA. We start treating patients with sublingual granules of PEA 600 mg twice daily for the first 10 days. Patients should not swallow so that
PEA can quickly dissolve in the saliva and can enter the bloodstream without the first-pass effect. After 10 days patients can be treated with 600 mg PEA tablets twice daily. So far, after treating several hundreds of patients, we have not seen any troublesome side effects, or any clinically relevant drug interactions.

Acupuncturists use the innate analgesic system of our body, via various endogenous analgesic pathways. PEA also follows such an innate analgesic system. Therefore we could even claim that both acupuncture and PEA are natural remedies.

In 1986 the famous neuroscientist professor Erminio Costa delivered a keynote lecture in Washington, bearing the title ‘To follow where nature leads’. In this lecture Costa talked with great vision about how nature itself can become our tutor in developing new drugs. PEA is one of these molecules entering the clinic and developed according to Costa’s vision. That is why PEA seems such a good compound to combine with other treatment modalities, such as acupuncture. PEA is available without a prescription, but one should always inform the treating physician about its use.

CONCLUSION
This multimodal stepped care approach influencing neuropathic pain through a new target, the modulation of non-neuronal cells, such as glial and mast cells, is a promising strategy. Both acupuncture and PEA are safe and tolerated treatments for the reduction of neuropathic pain and can easily be combined as well as added to classical analgesic medication, without fear of negative interactions.

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Contributors DJK treated the patient and wrote the manuscript. JMKH advised in the treatment plan and also wrote the manuscript.

Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement All the relevant data concerning the treatment of the patient is included in the case report.

Accepted 12 January 2012
Published Online First 1 February 2012


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Acupunct Med 2012 30: 53-55 originally published online February 1, 2012
doi: 10.1136/acupmed-2011-010119

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