

Prospective Evaluation

A Novel Mini-invasive Approach to the Treatment of Neuropathic Pain: The PENS Study

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Background: Peripheral neuromodulation is often used as chronic neuropathic pain treatment. Percutaneous electrical nerve stimulation (PENS) is generally utilized with several probes at the same time and repeated treatments.

Objectives: Evaluate the short- and long-term efficacy of a single probe and single shot PENS approach.

Study Design: Multicenter, prospective, observational study.

Setting: Four Italian pain therapy centers.

Methods: Inclusion criteria were age ≥ 18 and ≤ 80 years, presence of severe peripheral neuropathic pain lasting more than 3 months, localized and refractory to pharmacological therapies. Patients with infection, coagulopathies, psychiatric disorders, pacemakers, or implantable cardiac defibrillators were excluded.

Patients: Seventy-six patients (47 women, 29 men), mean age 62 ± 14 years, affected by neuralgia (21 herpes zoster infection, 31 causalgia, 24 postoperative pain) were enrolled in the study.

Intervention: After localization of trigger point and/or allodynic/hyperalgesic area, PENS therapy was achieved with a single 21 gauge conductive probe tunneled percutaneously and a neurostimulator device.

Measurement: Numerical Rating Scale (NRS) and Neuropathic Pain Scale (NPS) were assessed at baseline, 60 minutes after PENS, at one week, after one, 3, and 6 months; perceived health outcome was measured with Euroqol-5 dimension (EQ-5D) questionnaire at baseline and at 6 months. Adverse events and patient satisfaction were reported.

Results: NRS and NPS decreased significantly after 60 minutes and the reduction remained constant over time at follow-up. EQ-5D increased significantly with respect to the baseline. Two nonclinically significant adverse events (one contralateral dysesthesia and one self-resolving hematoma) were observed.

Limitations: Small sample size and non-randomized observational study; high prevalence of post-herpetic and occipital neuralgias.

Conclusion: PENS therapy produced significant and long-lasting pain relief in chronic peripheral neuropathic pains of different etiology. The present study confirms the feasibility, safety, and repeatability of this minimally invasive technique.

Key words: Neuropathic pain, neuromodulator, peripheral nerve, percutaneous stimulation

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Chronic neuropathic pain, isolated or in association with a somatic nociceptive component, looks like a difficult pain that chronically afflicts thousands of patients with different pathologies. Very often pharmacological therapies are insufficient to treat it, and more invasive options have to be considered, up to spinal cord stimulation (1-3). In fact, neuromodulation has become an effective option when chronic neuropathic disorders are refractory to traditional treatments and the phenomena of central sensitization and hyperexcitability become established in a definitive form (4).

The action of electricity for relieving pain is based on mechanisms of inhibition of painful signals in the dorsal horn of the spinal cord, and activation of the descending inhibitory pathways, even if they are still not well explained (5-7). However central neuromodulation is invasive, requires particular skills, and has high costs. Peripheral neuromodulation represents an increasingly common approach, and 3 methods are available in clinical practice: implanted peripheral nerve stimulation, peripheral nerve field stimulation, and percutaneous electrical nerve stimulation (PENS) (8-12). PENS uses fine gauge needles inserted through the skin of the painful area providing an alternate electrical stimulation for a prefixed period of time (13). There are randomized controlled trials and case series available on PubMed about PENS for headache disorders, peripheral neuropathic pain (sciatica, diabetic, surface hyperalgesia), and other chronic pain (neck, low back, pelvic, osteoarthritis of the hip), but almost all of them utilized several probes at the same time, and programs of stimulation lasting for several weeks (14-20).

The aim of this observational multicenter study was to evaluate the efficacy in the short, medium, and long term of a recently introduced device for PENS using a single probe for a single shot treatment, in patients suffering from chronic neuropathic pain with circumscribed allodynic/hyperalgesic areas, refractory to conventional drug therapies.

METHODS

The study was performed in 4 Italian pain therapy centers, each one charged with recruiting at least 15 patients, and obtaining previous local Ethics Committee approval and patient informed consent.

Inclusion criteria were:

- age ≥ 18 or ≤ 80 years
- peripheral neuropathic pain as defined according to the 2008 IASP Pain Terminology (21)

- pain lasting more than 3 months
- pain severe in grade (NRS ≥ 7)
- pain localized, feasible to be treated with a single needle
- pain refractory to pharmacological therapies
- possibility of a follow-up of 24 weeks.

Exclusion criteria were:

- infections
- coagulopathies or therapies with oral anticoagulants (INR > 2)
- psychiatric disorders or treatment with drugs that would act on the central nervous system
- patients with pace-maker or implantable cardiac defibrillator

All the procedures were performed on patients admitted to a surgical day hospital before their ambulatory evaluation. Pulse oximetry, noninvasive blood pressure, and EKG were monitored. The first step was to find the peripheral area of neuropathic pain and localize a trigger point and/or an allodynic/hyperalgesic area. Then a 21 gauge neurostimulator PENS therapy conductive probe was introduced and tunneled percutaneously along the peripheral nerve pathway or the major axis of the painful area, within the subcutaneous tissue at a depth between 0.5 and 3 cm. The probe was connected to the neurostimulator device (Neuro-Stimulator PENS therapy®, Algotec Research and Development Limited, Crawley West Sussex, UK), and the program A of sensitive stimulation at 100 Hz, intensity 0.2 V, was started. Immediately after obtaining the paresthesia along the nerve pathway, the program C of the neurostimulator was applied as the main treatment, with the following parameters: pulse frequency 2 Hz – 100 Hz automatically changed every 3 seconds; intensity 0.5 V; duration of stimulation 25 minutes for all the patients enrolled in the study. The intensity of stimulation could be changed according to the patient perception. At the end of the electrical stimulation the probe was removed and the patients were kept under observation for 2 hours, and then discharged home.

Adverse events related to PENS procedure were reported. At the times T0 (baseline), T1 (60 minutes after PENS), T2 (one week after PENS), T3-T4-T5 (respectively one, 3, and 6 months after PENS), the pain intensity was assessed with the Numerical Rating Scale (NRS, 0 – 10). At the times T0-T2-T3-T4-T5 the neuropathic pain intensity was assessed with the Neuropathic Pain Scale (NPS) (22). At baseline and T5 the perceived health outcome

of the patients was measured with Euroqol-5 dimension (EQ-5D) questionnaire, which includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (23).

The patient satisfaction level with the PENS treatment was defined as negative, sufficient, good, or excellent, and was detected at T2-T3-T4-T5. At the end of the follow-up (T5) any variation in drug therapies were reported according the definitions unchanged, reduced, discontinued. The following outcomes were outlined:

- full success, NRS pain reduction $\geq 50\%$ at 6 months
- partial success, NRS pain reduction $< 50\%$ at 6 months
- failure, severe pain $<$ one month after treatment
- need of a second PENS treatment
- need of other types of treatment
- need of increase of the pharmacological support.

Data were expressed as median and interquartile ranges for ordinal categorical values. Non parametric tests (Chi-square test, Mann-Whitney U-test and Friedman test) were used as appropriate, a $P < 0.05$ was defined as significant.

RESULTS

Eighty-two patients were enrolled in the study, and 76 (47 women, 29 men), mean age 62 ± 14 years, completed the follow-up at 6 months. The causes of neuralgia were 21 patients with herpes zoster infection; 31 patients with causalgia, 5 of them diabetic; 24 patients with post-operative pain (7 after inguinal herniorrhaphy, 4 after lumbar surgery, 4 after mastectomy, 3 after upper limb surgery, 2 after hip surgery, 2 after safenectomy, one after thoracotomy, one after dorsal discectomy).

Sixty-eight patients (89%) showed a trigger point and a well-defined nerve pathway. In the remaining 8 patients a specific trigger point was not found, but an allodynic/hyperalgesic area was well defined and circumscribable. Thirty-two patients (42%) complained of episodes of breakthrough pain (BTP).

The specific nerve pathways responsible for neuralgias are reported in Table 1.

The mean duration of the neuropathic pain referred by the patients was 39.7 ± 17.6 months. All the patients enrolled in the study had been previously subjected to therapies with opioids, antiepileptics and adjuvants in different combinations and compositions. Eight patients took tapentadol without benefits. Fourteen patients had stopped all therapies at enrollment.

Table 1. *Specific nerve pathways of neuralgias.*

Gender n. (%)	Male	29 (38)
	Female	47 (62)
Age year (SD)		62 (14)
Nerve pathways of neuralgias n. (%)		
	Occipital nerve neuralgia	25 (33)
	Greater occipital nerve	22
	Lesser occipital nerve	3
	Trigeminal herpes zoster	12 (16)
	Maxillary branch	4
	Mandibular branch	1
	Lower limb	15 (20)
	Ilioinguinal nerve	7
	Peroneal nerve	3
	Saphenous nerve	2
	Lateral femoral cutaneous nerve	2
	Posterior tibial nerve	1
	Intercostal nerve	7 (9)
	Upper limb	5 (6,5)
	Musculocutaneous nerve	3
	Median nerve	1
	Axillary nerve	1
	Thoracic nerve	4 (5)
	Not assessed	8 (10,5)

All the patients underwent first the trial with program A of the neuromodulator, and subsequently the program C for 25 minutes. The range of stimulation was comprised within 1 – 1.3 V. A 100 mm conductive probe was used in 41 patients, 50 mm in 32 patients, 20 mm in 3 patients.

Adverse events related to PENS were contralateral dysesthesia in one patient treated for intercostal pain, resolved in 24 hours; hematoma on the point of needle insertion without further spillage in another patient treated for occipital neuralgia.

A second PENS treatment was needed in 7 patients: 6 after 2 months (4 occipital, one infrapatellar, one lumbar); one after one month (lumbar).

NRS, NPS, and Euroqol behaviors are reported in Table 2. Pain intensity measured with NRS, showed a significant reduction at T1 (3 [IQ 7 – 10] vs 8 [IQ 7 – 10] at T0, $P < 0.001$), which remained constant over time (3 [IQ 0 – 6] at T5), without significant differences from T1 to T5 (Fig. 1). Fourteen patients (18.4%) referred NRS 0 – 1 at T1: 6 great occipital nerve, 5 trigeminal her-

Table 2. Main results of the study.

	Baseline (T0)	After 60 minutes (T1)	At 1 week (T2)	At 1 month (T3)	At 3 months (T4)	At 6 months (T5)
Numerical Rating Scale (median, interquartiles range)	8 (7-10)	3* (0-5)	4* (2-6)	3* (2-6)	3* (1-6)	3* (0-6)
Neuropathic Pain Scale (median, interquartiles range)	6.4 (4.7-8.2)		2.9* (1.5-4.1)	2.10* (1.1-3.5)	2.0* (1.0-4.2)	2.1* (0.8-4.1)
Euroqol-5 dimension (median, interquartiles range)	0.30 (0.02-0.62)					0.76* (0.55-1.00)

* T1,T2,T3,T4,T5 vs T0 : P < 0.0001

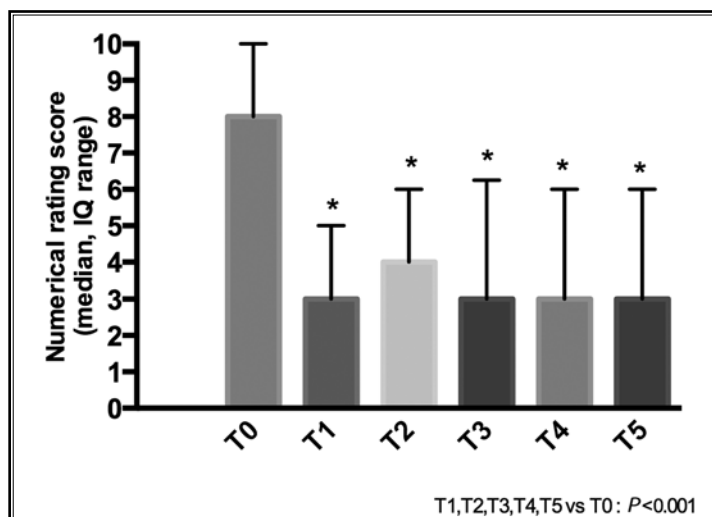


Fig. 1. Numerical rating score at times of the study.

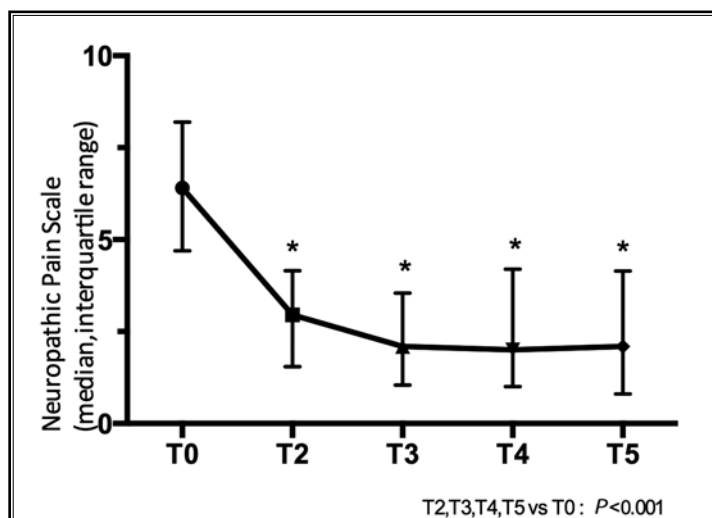


Fig. 2. Neuropathic Pain Scale at times of the study.

pes zoster, 2 ilioinguinal nerve, one thoracic nerve.

The NPS data behaved in the same way, decreasing significantly at T2 in comparison with the basal value (2.9 [IQ 1.5 – 4.1] vs 6.4 [IQ 4.7 – 8.2] at T0, $P < 0.001$) and maintaining this reduction over time (2.1 [IQ 0.8 – 4.1] at T5) (Fig. 2).

EQ-5D increased significantly at T5 compared to the baseline (0.76 [IQ 0.55 – 1.00] vs 0.30 [IQ 0.02 – 0.62] at T0, $P < 0.001$), specifically for the dimensions pain/discomfort, anxiety/depression, and mobility (Fig. 3). No differences in pain relief were detected between the trigger point subgroup and allodynic area subgroup.

Pharmacological therapies were discontinued in 11 patients and reduced in 19. Nine patients out of 14 not on therapy at T0, started again with drug treatment after PENS application. All the 8 patients without a localizable trigger point were comprised among the 32 patients who did not show any reduction in drug requirements, of which 58% of cases had episodes of BTP, 60% reported a predominant allodynia.

Fifty-seven patients (75% of cases) reported a good (35 patients) or excellent (the remaining 22) satisfaction with PENS treatment, while the level of satisfaction was considered sufficient in 9 patients and negative in 10 patients (13.1% of cases). Among the patients who reported a good or excellent level of satisfaction after the treatment with PENS, 74% of cases had an history of BTP and 64% showed a prevalent allodynia. The 7 patients who needed a second PENS treatment reported

a negative level of satisfaction at the end of the follow-up of 6 months, NRS and NPS values at T5 showed a reduction of less than 50% in comparison with the T0 value (6 ± 2 vs 8 ± 1 , and 4.8 ± 2.0 vs 6.6 ± 1.2 , respectively, NS).

Discussion

The control of chronic pain in patients with circumscribed allodynic or hyperalgesic areas can be difficult to achieve. The use of more potent analgesics, such as opiates, may in turn lead to problems, such as immediate adverse effects or prolonged exposure, in the absence of a proven effectiveness. Actually failure of the pharmacological approach varies depending on the disease occurrence, however it oscillates between 13 and 49% in post-herpetic neuralgia and some diabetic neuropathies (24).

Local therapies such as topical applications of anesthetic or anti-inflammatory agents, or infiltrations, generally lead to a benefit of short duration and require a subsequent repetition of the treatment with consequent discomfort for the patient. Procedures such as electrical stimulation of the nerve through leads connected to a pulse generator provide a surgical approach of different complexity, and the risk of displacement of the lead. These procedures also have high costs, and the indications for their use are not yet well defined. On the contrary PENS does not require an implantable device and does not need a surgical preparation. This is the main difference from PNS and PNFS. PENS is not the same as TENS where electrical stimulation is delivered through the skin. PENS utilizes bipolar needle-like electrodes inserted into the tissues and removed at the end of treatment session. It does not require a particular technical ability or long training.

In our observational study the common presentation in all the patients enrolled was a peripheral neuropathic pain with a well-defined allodynic/hyperalgesic area. In fact this represented the main inclusion criteria for the use of PENS, because the technique acts specifically at a peripheral level. PENS treatment, to the best of our knowledge, has proven to be an effective procedure, easy to perform,

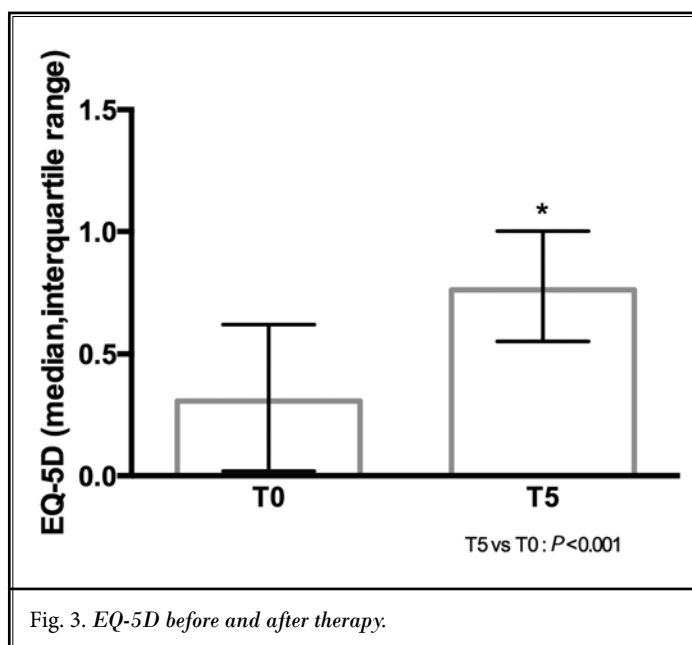


Fig. 3. EQ-5D before and after therapy.

repeatable, and safe. This is demonstrated by the positive response at the end of treatment in terms of reduction in pain intensity (NRS) and in its neuropathic characteristics. NPS analyzes several aspects of pain, such as sharpness, heat/cold, dullness, intensity, overall unpleasantness, and surface vs deep pain. All of them depict the complexity and difficulty of treatment of neuropathic pain. Reduction in NRS and NPS was confirmed at the end of follow-up, testifying to the full success of PENS treatment. Six months is a reasonable period to ensure the stabilization of a pain framework notoriously unstable and capricious. The figure is even more significant when considering the period of chronic pain endured by the patients (39.7 months).

PENS is a form of peripheral nerve stimulation and is a relatively noninvasive neuromodulation approach. The mechanism of action of PENS as well as that of the spinal cord stimulation, or the PNS, is not fully understood. It is hypothesized that electrical impulses modulate peripherally the activity of the nerve, disrupting the arrival of the pain signal to the brain. This would be a mechanism resembling to the gate control theory (25). Another option should be the stimulation of the release of endogenous opioids induced by the electrical current. The neurostimulator device can apply 2 different pulse rates of electrical stimulation. The stimulation at low pulse rate (2 Hz) should induce release of enkephalins but not of dynorphins, while the stimulation at high pulse rate (100 Hz) should induce the release of dynorphins but not of enkephalins. Thus the analgesic effects at 2 Hz should be induced through the action on mu and delta receptors, while the high pulse rate current (100 Hz) should act on kappa receptors (26). For this reason the alternation between 2 and 100

Hz is considered more effective than a constant current at low or high frequency. These mechanisms are based mainly on laboratory findings, but some clinical experience in humans is available (27). On the contrary there is no current evidence of different effectiveness based on duration or intensity of stimulation.

The pain relief obtained immediately after PENS application probably relies on the ability to find a trigger point and a well-defined peripheral nerve pathway in almost all the patients enrolled in the study (89%). This allowed the proper introduction and positioning of the needle, and increased the possibility of applying the current directly on the peripheral nerve or the most peripheral branches of the peripheral nerve. All patients were subjected to the test phase (optional) via program A of the neuromodulator device at continuous 100 Hz. We think this pretreatment is advisable because it allows confirmation of correct placement of the needle, obtaining paresthesia along the nerve pathway and bordering properly on the painful area.

According to this pathophysiologic point of view, the action on the peripheral sensitization of nociceptors may therefore be assumed as a primary element of the beneficial effects of PENS on peripheral neuropathic pain (28).

The improved performance of the patients treated with PENS should not be a surprise, as shown by the Euroquol score at 6 months. The pain relief obtained was associated with lower levels of anxiety and depression, and the resumption of adequate physical activity. The overall high level of satisfaction further confirms the effectiveness of PENS and the achievement of a better psycho-physical status. It is reasonable to think that in patients with chronic pain the minimal impact of the technique gave an important contribution to the level of satisfaction.

The safety of the method is worthy of reporting because there were only 2 complications among the 76 cases, which were not clinically significant. A second treatment was required only in 7 patients (below 10% of the total). The data should not be surprising because the complexity of the nervous lesion includes the possibility of reentry circuits, which can reactivate after an initial apparent control. The patients who needed a second treatment reported a negative level of satisfaction at the end of the follow-up of 6 months, and showed NRS values at T5 reduced by less than 50% in comparison with the T0 value. This suggested the importance of a subjective involvement and the confidence about treatment. There are no data in the literature about re-

peated schemes of treatment with the modified PENS, since most of the papers protocols included percutaneous electrical stimulation cycles lasting several weeks (16-18). The new device, combined with the best quality of the probe needles, has certainly contributed to the success of the treatment based on a single application. Again it must be stressed the importance of researching carefully the trigger point and/or the precise boundaries of the allodynic/hyperalgesic area.

A not insignificant percentage of patients reduced or discontinued drug therapies at the end of the period of follow-up (39%). Neuropathic pain syndromes are often undertreated, and appropriate therapies are difficult to achieve (29). Being chronic therapies, their discontinuation or reduction can be related to a better quality of life and the high level of satisfaction reported at the end of the study. In the group of patients who did not change their therapies, 60% had marked allodynia and 58% reported episodes of BTP. So, it is possible that drug therapies were not changed more for a prudential behavior than for a true need of the patient.

As previously said, in some cases (14 patients, suffering for occipital and trigeminal neuralgias) the complete disappearance of pain immediately after the procedure has been observed, and it is legitimate to ask what prognostic meaning to give this clinical finding (30). Another important question is whether there are clinical conditions that can predict the prolonged pain relief which has been observed in most patients. A fundamental aspect is the tight selection of the patients. In fact PENS is viable only in the presence of a peripheral neuropathy. Future studies should test the mode of insertion of the probes and their subcutaneous positioning, since an advantage of PENS is the reduction of skin resistance. Also the choice of the length of the probe could correlate to a positive outcome, in fact the longer the probe the greater is the area of stimulation. An echo-guided approach may be hypothesized even if it could complicate the easy access of the technique (31).

The present study has several limitations, the first one being an observational study and the relatively small sample size, even if other experiences reported in literature were smaller. A possible placebo effect cannot be excluded. Actually data from the literature show PENS vs sham PENS had better performances in terms of pain relief, level of activity, and quality of sleep (15-16,18).

More than half of the patients enrolled in the study suffered from post-herpetic or occipital neuralgias, the efficacy of PENS in other types of neuropathic pain has

to be proven, for example in post-radiotherapy or chemotherapy localized nerve injury. Moreover cost-effectiveness of the technique has to be confirmed.

The present study showed the feasibility of this minimally invasive technique, its safety and repeatability, for the treatment of chronic peripheral neuropathic pains. PENS adds another weapon at the disposal of the pain therapist, before resorting to harmful and/or more invasive techniques. Our data confirm the statements of the National Institute for Clinical Excellence on March 27, 2013: "... Current evidence on the safety of percutaneous electrical nerve stimulation (PENS) for refractory neuropathic pain raises no major safety concerns and there is evidence of efficacy in the short-term. Therefore this procedure may be used with normal arrangements for clinical governance, consent and

audit ..." (32). It is hoped that in future other experiences with PENS treatment for neuropathic pain could be planned, selecting homogeneous groups of patients, performing prospective sham controlled studies and randomized comparisons with non-invasive options such as medicated patches or with other minimally invasive approaches.

CONCLUSION

In conclusion, PENS therapy for chronic peripheral neuropathic pain was associated with a significant pain relief immediately after the treatment and lasting for several months. This result improved the perceived quality of life of the patients and allowed a decrease in drug therapies in the majority of cases.

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