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Evaluation of Efficacy of Low-Level Laser Therapy

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Abstract

Introduction: Given the inconsistencies in the literature regarding laser performance in non-surgical treatments, this study investigated the available literature to determine the advantages and disadvantages of low-power lasers in treating non-surgical complications and diseases.

Methods: Authentic information from articles was extracted and evaluated to assess low-power laser performance for non-surgical treatments. A systematic search of studies on low-level laser therapy (LLLT) for non-surgical treatments was conducted mainly in PubMed and google scholar articles.

Results: Four categories of diseases, including brain-related diseases, skin-related diseases, cancers, and bone-related disorders, which were treated by LLLT were identified and introduced. The various types of LLLT regarding the studied diseases were discussed.

Conclusion: Positive aspects of LLLT versus a few disadvantages of its application imply more investigation to find better and efficient new methods.

Keywords: Low-level laser therapy; Photobiomodulation; Disorders; Treatment; Side effects.

Introduction

Laser treatment covers various fields in the clinic. Different types of lasers are used in this regard, including cold or low-level laser therapies (LLLT or class III laser) and high-power laser therapy (class IV).[1-4] LLLT is widely used in the clinic and encompasses a range of non-invasive therapeutic aspects. LLLT is commonly used clinically as a red light near-infrared wave with a length of 600 to 1000 nm and 5 to 500 mW.[5] On the contrary, lasers used in surgery have a wavelength of 300 nm.[6] Low-power lasers are capable of penetrating deep into the skin so that the surface of the skin does not burn and damage.[7] Low-power or cold lasers have been enhanced to the point of being able to produce analgesia and healing acceleration for many clinical conditions.[8] A wide range of LLLT and related techniques have been used. Therefore, the results of treatment with low-power lasers may contradict each other.[9] LLLT may be administrated by many dermatologists, physical and occupational therapists, physicians and chiropractic doctors.[10] The biostimulatory healing effect of LLLT may cause the treatment of chronic pain, commonly associated with carpal tunnel syndrome, arthritis, tissue injuries and severe wounds.[11-15] On the other hand skin rejuvenation also may be another administration of lasers.[16] There are many pieces of evidence about LLLT usage for the treatment of wound healing,[17] tuberculosis,[18] pain, tinnitus,[19] epicondylitis,[20] smoking cessation,[21] Achilles tendinitis,[22] back pain,[23] plantar heel pain,[24] Carpal tunnel syndrome,[25] and the primary Raynaud's phenomenon.[26] However, others published documents revealed inadequate efficiency of LLLP for wound healing,[27] arthritis,[28] tinnitus,[29] tuberculosis,[30] epicondylitis,[31] and plantar heeling pain.[32] Therefore, a comprehensive research study on the evaluation of laser function in therapeutic interventions seems necessary.

Methods

Articles that explain the effects of laser therapy on non-surgical disorders and complications in the online journals published from 1990 until 2019 were considered. An online search in google scholar and PubMed using the keywords "Non-surgical", "laser", "side effects" "treatment" "assessment", and "photobiomodulation"

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was performed. The titles and abstracts of 320 collected articles in the English language were studied and 253 appropriate articles were selected to be included in the study. Subsequently, the articles related to the inclusion criteria established previously were chosen. Finally, 164 documents were evaluated and considered as the related article. However, there are many related articles which have overlap with the studied documents.

Results

According to the finding, LLLT is applied to treat at least four categories of diseases including nervous system complications, skin and mucosal disorders, bone and joint disorders, and cancers. These four classes of diseases are tabulated in Table 1. We evaluated and studied the selected articles that have researched these categories of disorders.

Nervous System Complications

Brain Photobiomodulation

Researches in intracranial photobiomodulation have shown that the use of infrared or near-infrared light can promote cell repair.[33] Near-infrared waves are capable of passing through the human skull and the cerebral cortex which could receive a small amount of energy.[34] The abundant mitochondria present in neurons are the primary receptors for near-infrared and infrared wave energy. Subsequently, mechanisms such as increased ATP production, CMP activity and increased oxidative activation work together to prevent cell death during ischemic failure, brain injury, and neurodegeneration.[35,36] This process can be mediated by increased expression of genes involved in the cell survival process, such as the production of antioxidant enzymes, heat shock proteins, and cell death-preventing proteins.[37] Transcranial light therapy has been developed to increase neuron proliferation in the hippocampus following a stroke or ischemia.[38]

Trigeminal Nerve Neuralgia

Trigeminal nerve neuralgia (TN) is the major cause of face and mouth pains.[39] The pathogenesis of TN neuralgia is not well understood and high vascular pressure causes demyelination of nerves following pons entrance.[40] LLLT could decrease acute neuralgia via mechanisms such as decreasing histamine, serotonin, and bradykinin and increasing acetylcholinesterase, aerobic metabolism, ATP, encephalin, and endorphins production.[41,42] Lasers could significantly increase the pain threshold and stimulate the synthesis of endorphins.[43] Limited studies have been designed to assess the effects of LLLT on TN analgesia treatment with controversial results.

Traumatic Brain Injury

Traumatic brain injury (TBI) — the other subject that is treated via LLLT — is one of the main causes of morbidity and mortality in young military staff or athletes along with accidents.[44] Several cell and tissue interactions lead to inflammation and brain edema and cerebral perfusion. The combination of defects results in brain ischemia and diminishing oxygen and glucose transportation to the neurons. Membrane channel transportation changes together with voltage postsynaptic enhancement.[45] Calcium rises inside the neurons with mitochondrial malfunction and apoptosis happens simultaneously in TBI.[46]

Neuropathic Pain

Primary lesions and dysfunctions of the nervous system may cause neuropathic pain. It seems that LLLT may cause the treatment of this kind of pain; however, there are controversies between different applications. LLLT is a suitable method for neuropathic pain treatment; different wavelengths of lasers which are reported in several studies revealed increased analgesia significantly.[47-50] The importance of LLLT in the treatment of diabetic neuropathy was investigated due to the antioxidant and biomodulation effects of lasers as a non-pharmacological treatment.[51, 52] Another study carried out different mechanisms of LLLT in pain relief as inflammatory process modulation, excitation alteration, and endorphins secretion.[53] Bradykinin reduction with the modulation of the inflammatory process according to the LLLT pain relief mechanism is reported through researches.[54,55] The β-endorphin expression seems to be a secondary action of LLLT in analgesia.[56] Red and infra-red laser effects on analgesia amplification have been reported with a controversy between two lasers.[57,58] The density of LLLT energy seems to be an effective value in pain relief. However, there are some discrepancies between the results of the assessments.[48, 59]

Table 1. Summary of Different Complications Treated by LLLT

Nervous System Complications	Skin and Mucosal Disorders	Cancers	Bone and Joint Disorders
Brain photobiomodulation	Skin burn	Breast cancer lymphoma	Bone disorders
Trigeminal nerve neuralgia	Hair loss	Head & neck cancer	Tendon repair
Traumatic Brain Injury	Pemphigus vulgaris		Carpal tunnel syndrome
Neuropathic pain	Diabetic foot ulcers		
	Herpes labialis		

Skin And Mucosal Disorders

Skin Burns

Burn with the thermal origin which is a traumatic injury could affect human organs.[60] LLLT is a useful method for treating burning injuries, especially skin burns; however, there are some controversies between application parameters of LLLT in the treatment of skin burns. There are many factors causing skin burns, such as chemical, physical and biological factors, which lead to pain, infection, and even death.[61] The mechanism of wound healing in cutaneous burns is the interaction between the cascade release of cytokines and the extracellular matrix and involves these steps: spontaneous and interdependent inflammation, proliferation, and remodeling.[62] Early stages of repair are proliferation and edema and may modulate complications such as the reduction of leukocytes and macrophages, fibroblasts, and angiogenesis simultaneously.[63] Those complications may lead to scar and tissue adhesions.[64] Recent studies have shown that LLLT can be effective in the treatment of skin burns as a low-price and non-invasive treatment.[65] The mechanism of laser action on biological tissues is mainly related to stimulating cytochrome oxidase releasing, and it activates intracellular cascade reactions and increases the intracellular and molecular synthesis and subsequently increases the synthesis of RNA and DNA which, in turn, increases cell proliferation and migration in the injured tissue restoration.[66-68] Lab experimental researches revealed that LLLT increases fibroblasts proliferation and collagen synthesis along with tissue granulation. These cellular events resulted in the acceleration of wound contraction and re-epithelization.[69-71] The study on laser therapy for wound healing has been the subject of researches since its inception and its first report was published in 1971.[66] In the following years, many studies were performed in this area and the upward trend of laser burn and wound healing methods was studied too; however, differences in the methods, including the wavelength and energy used and the power of radiation and duration of treatment in different studies, were significant.[72,73] The 600-700 nm wavelengths have less penetrating power than the 700-1000 nm wavelengths within the tissue.[68] Researchers have used different wavelengths for LLLT.[74, 75] Some researchers have considered the 660 nm wavelength for the initial stages of skin wound healing and the 780 nm wavelength effective for the formation of tissue granulation.[76]

Hair Loss

Recent investigations have revealed that LLLT could evaluate hair growth stimulation. Studies on hair loss of male and female cases, chemotherapy-induced alopecia and alopecia aerate have demonstrated the effectiveness of LLLT in hair re-growth. The first study about hair growth was published by Ferrando et al in 2002.[77] They used IPL photomodulation to remove unwanted hair but the results were paradoxically positive for hair growth. However, studies on the LLLT treatment of alopecia are limited in numbers of documents and the wavelengths from 600 to 1000 nm were in preference. Leavitt et al assessed the effects of a laser with the wavelengths of 635 and 660 nm and a combination of both on the hair growth of the forearm. The results revealed the positive effects of LLLT on hair follicle growth compared to the control group.[78] In another study, it was revealed that evaluated laser devices could increase hair growth elongation on day 3 of treatment compared to the control group.[79] The very low incidence of LLLT side effects made it safe to use for hair growth.[80] In animal experiments, results revealed the positive effects of LLLT on hair growth for alopecia aerate AA),[81] and chemotherapy-induced alopecia.[82] On the other hand, King et al did not have positive results for AA treatment by LLLT in mice, as opposed to the results of a study by Wikramanayake et al.[83] Clinical trials revealed the positive effects of LLLT on hair re-growth.[84-90]

Pemphigus Vulgaris

Pemphigus vulgaris (PV) is a chronic blistering disease with antibodies directed against keratinocytes.[91] Management of PV is difficult. Steroid therapy is still the basic treatment of disease with some adverse effects.[92] Various laser devices have been used to treat PV. There are some reports about wounds that are related to PV.[93] Based on previous investigations the mouth is affected by PV. Lesions of gingiva and mucosa of mouth and the other parts of body are reported in the PV patients.[94,95] The assessment of LED laser therapy of PV with a 660 nm wavelength in a continuous wave and 30 mW energy in 10 patients revealed the efficiency of LLLT in the treatment of PV ulcers.[96]

Diabetic Foot Ulcers

One of the complications in diabetes mellitus is long-lasting or non-healing skin ulcers of the foot and the results of treatments are not satisfactory for patients.[97] LLLT as an effective and noninvasive tool could be seemingly manageable for a diabetic foot ulcer.[98] Multifactorial occurrences such as peripheral neuropathy and arterial occlusive disorders may cause foot diabetic syndrome.[99] As it is shown in Table 2, diabetic ulcers (DUs) could be classified according to Wagner and Armstrong ulcer classifications.[100]

Conventional treatments as wound cleaning, skin grafting, vasodilators, and antibiotics could be still unsatisfactory.[101] LLLT has been introduced as a painless and noninvasive treatment without major side effects for DU treatment. Low-power lasers with low-energy radiation stimulate cell activity, but high-power lasers have adverse effects on cell activity, and in non-healing DUs, the application of lasers to stimulate wound healing has been recommended.[102] The laser needle is a new method of laser acupuncture which its therapeutic effects are similar to manual needle acupuncture.[103] A unique

Table 2. Wagner & Armstrong Ulcer Classification in Summary

Wagner Grade	Lesion	Armstrong Ulcer Grades
0	No open wounds	A: Without infection or ischemia
1	Superficial wounds	B: With infection
2	Ulcer extension	C: With Ischemia
3	Deep ulcer	D: With infection and ischemia
4	Localized Gangrene	
5	Extensive Gangrene	

laser therapy mode determination to treat diabetic foot ulcers is not explained yet. Kajagar et al compared pulsed LLLT on 85 diabetic wound healing patients on the basis of wound size, duration of exposure and used energy in the surface of the wound (2-4 J/cm^2 at 60 mW for 15 days). There was a significant ulcer reduction in LLLT compared with traditional treatment methods.[98] Another review of wound treatments focusing on venous leg ulcers and decubitus ulcers claimed LLLT could not improve wound healing and suggested that researches should focus on molecular and cellular mechanisms of wound healing with more investigation in humans to find precise laser parameters and treatment protocols.[104]

Herpes Labialis

This is a viral disease, which could not be treated completely and anti-viral drugs acyclovir, valacyclovir, and famciclovir could not eliminate the virus.[105] Different kinds of laser therapy and several protocols have been proposed for the treatment of herpes labialis (HL) based on successful clinical trials recently. Different studies reported the wavelengths between 630 and 980 nm and power of 20 to 300 mW with radiation duration between 10 seconds and 15 minutes respectively for HL treatment.[106] All the researchers reported that LLLT is an effective tool in the management of HL prevention without any side effects.

Cancers

Breast Cancer Lymphedema

Early diagnosis and treatment of breast cancer result in the survival of more than 82% patients in developed countries.[107] However, more survived patients suffer from secondary lymphedema due to the following cancer therapies.[108] Despite efforts to reduce breast cancer lymphedema (BCL) by treatments such as surgery or radiotherapy, BCL remained relevant.[109] During the past few years, LLLT has been introduced as suitable noninvasive phototherapy for the treatment of BCL, with the wavelength between 650 and 1000 nm to be delivered into the target tissue to reduce inflammation and promote lymphatic vessel regeneration and lymphatic mortality reduction.[110-112] LLLT was more effective than compression bandage for pain relief in BCL post-treatment [113]. Based on previous studies infrared radiation (808 to 905 nm) is applied to LLLT of BCL post treatment (Table 3). The range of energy usage was 1.5 J/ cm^2 to 2.4 J/cm^2.[114].

Head and Neck Cancer

Several types of related complications of head and neck cancer (HNC), which are treated via LLLT, are tabulated in Table 3.

1. Oral Mucositis

Most of the patients with HNC treated by radiotherapy (RT) or chemotherapy (CT) suffered from orofacial and oropharyngeal complications.[115] Most patients confront multiple complications, leading to a negative impact on their lifestyle.[116] Supportive care for these complications should be considered in different stages of the disease. Photobiostimulation with various kinds of light energy as LLLT and LED and visible light has shown a promising efficiency for the treatment of HNC complications.[117] Oral mucositis almost appears in all of the HNC patients treated by CT.[118] Some investigations have claimed that photobiomodulation is efficient for oral mucositis, a complication that appears after HNC routine treatments.[119,120] There are several complications resulted from HNC such as "Oral mucositis,[121] dermatitis,[122] dysphagia,[123] hyposalivation and xerostornia,[124] taste alterations,[125] osteoradionecrosis,[126] trismus,[127] soft tissue necrosis,[128] head and neck lymphedema,[129] and voice alterations."[130] All of those complications could be treated by photomodulation (see Table 3). Oral mucositis affects patients with HNC, treated by oral CT from mild to severe conditions.[131] ROS production starting cascade reactions leads to microvascular injuries and ECM alterations in mucositis.[132] Different meta-analysis assessments revealed

Table 3. Different Complications Resulted From Head and Neck Cancer Treated by Photobiomodulation

Head & Neck Cancer Complications	Photobiomodulation Therapy	Wavelengths	Power Supply	Efficiency
Oral mucositis	IR & NIR & LLLT	630-830 nm	10-150 mW	Positive
Dermatitis	IR LED	630-680 nm	20-150 mW	Positive
	Red & IR LED	630-680 nm	20-80 mW	Positive
Dysphagia	IR-NIR	980nm	-	Positive
Osteoradio necrosis	Red & IR	660-800 nm	100 mW	Positive
Trismus	Diode Laser	980 nm	30 mW	Positive
	Ga-Al-As	830 nm	30 mW	Negative
Head & neck lymphedema	LLLT	650-1000 nm	20-80 mW	Positive
	LLLT	808-905 nm	20-80 mW	Positive

the efficiency of photobiomodulation in mucositis reduction and pain-relieving with different doses of light energy consumption.[133] IR (630-680 nm) and NIR (780-830 nm) lights had the same efficiency for the treatment of mucositis.[134]

2. Dermatitis

HNC patients treated by RT mostly have dermatitis. Radiotherapy leads to the release of inflammatory cytokines as interleukin I & VI and this process causes the development of edema, erythema and possibly ulceration.[135] Radiation of the skin could damage basal epithelial cells and connective tissue vascular components. Photobiomodulation may reduce the severity of radiation dermatitis.[68] Damage to the skin developed by radiation may be ameliorated by multi-wavelength photobiomodulation.[136] In a review by Bensadon et al, the effects of the red laser diode cluster and the IR LED cluster on radiation dermatitis were evaluated positively due to reduction of pain and inflammation and also promotion of tissue repair after LLLT administration. However, more investigations were suggested to reduce the side effects of LLLT and the photobiomodulation treatment of dermatitis.[137]

3. Dysphagia

Dysphagia is an impairment of swallowing and could be seen in patients with head and neck malignancy as a side effect of cancer therapy.[138] Dysphagia is associated with inflammation, edema, and fibrosis.[139] Photobiomodulation is a promising technique for dysphagia treatment.[140] Dysphagia has different stages from 0 to V. According to references, treatment could be intraoral and extraoral photobiomodulation.[141] Using an IR laser with a wavelength of 980 nm (Table 3), Mobadder et al reported the effectiveness of LLLT in cancer resulted from a dysphagia case in pre- and post-operative stages.[141]

4. Osteoradionecrosis

Oral cancers may need different treatments such as surgery, radiotherapy, chemotherapy or a combination of these techniques. Chronic side effects of an oral cavity may cause bone repair capacity to diminish.[142, 143] Osteoradionecrosis (ORN) means a condition that the irradiated bone be exposed into the oral cavity more than 12 weeks and this process occurs in the suppression of tumor recurrence or tumor necrosis in RT.[144] There is no cure for ORN and only clinical control treatments as surgical debris removing, antibiotic therapy, and ultrasound could be performed.[144-146] LLLT with increasing metabolism capacity, cell proliferation, angiogenesis and wound healing is a suitable method for assisting ORN treatment.[147] LLLT also has analgesic effects and improves lymphatic flow.[148] Riberio et al in a study analyzed ORN treatment by LLLT. The objective of the study was the stimulation of the affected area to homeostasis, leading to oral mucosa healing. Red light and IR lasers (see Table 3) were used for bone exposure and the affected jaw subsequently. LLLT improved the healing process of bone and accelerated the covering of bone with oral mucosa in most cases.[149] Positive results of LLLT as an adjuvant therapy suggested for ORN treatment.

5. Trismus

Lockjaw or trismus is a limited jaw range of motion. It may be caused by HNC. LLLT is an efficient tool to reduce pain, edema and inflammation without adverse effects to promote damaged tissue repairing.[150] Petrini et al revealed the effect of LLLT treatment with the aid of an 890 nm (Table 3) diode laser on pain and edema reduction.[151]

Bone and Joint Disorders

Bone Disorders

Bone regeneration is accelerated by laser treatment in Wistar rats relative to the controls.[152] Improvement of closed bone fracture healing in human wrist and hand via LLLT is reported by Chang et al.[153]

Tendon Repair

As it is reported, a low-level laser in combination with adipose-derived mesenchymal stem cells improves the initial phase of tendon repair.[154] Based on the investigation by Badawy et al, laser therapy can be used to recover hand flexor tendon repair.[155]

Carpal Tunnel Syndrome

Tezcan et al investigated the effect of LLLT on 34 patients with carpal tunnel syndrome. On the basis of this report, the LLLT strain ratio and the cross-sectional area of the median nerve in patients decreased after LLLT. They concluded that nerve regeneration and development of the vascular supply effects of laser therapy led to the improvement of patients' condition.[156]

Discussion

As noted in the introduction, the types of complications which can be treated with low-power lasers include disorders of the nervous system, skin and mucous membranes of the body, bones and joints, and finally cancers. It should be noted that according to the reviewed articles, one of the common treatments for the above complications by low-power laser is pain relief. Given the variety of sources studied, the conclusion that the wavelengths and energy used in different low-power lasers for the treatment of these diseases are different is a point that needs to be considered because there are no specific protocols to treat each of the above-introduced side effects by low-laser and much research is still needed in this regard. As it is presented in Table 1, four types of nervous system complications

including Brain photobiomodulation, trigeminal nerve neuralgia, traumatic brain injury, and neuropathic pain are treated via LLLT. According to the studied sources, photobiomodulation modulates nerve cells, but in relation to trigeminal neuralgia, some articles reported positive effects of LLLT on TN treatment and others didn't have any significant difference between tested groups. The wavelength of light and the size of samples are the factors that need more investigations.[39] TBI treated by LLLT leads to increasing the brain neurotrophic factor and synaptogenesis.[157] LLLT may cause neuropathic pain treatment but there are some controversies. However, there is a lack of detail on laser and energy density parameters in the reviewed articles to assess the LLLT effect on analgesia. According to Arnold Shultz law, the biological responses in tissues could change (stimulate or inhibit) according to the dose of energy absorption[158] and more investigation is necessary to define the protocols for optimizing LLLT in neuropathic pain relief as different doses of energy are provided by different instruments. In the field of skin and mucosal disorders, skin burns revealed that the size of the wound and classification of the lesion may explain total energy discrepancy in different studies; however, it could be concluded that LLLT could promote the wound healing process, but the gap in the current literature may cause the limitation of opening a window to suggest a suitable and precise method for the specifications of skin burn healing by LLLT. Hair loss treatment with LLLT also reminds us that the phenomenon named "paradoxical hypertrichosis" was the result of low influences of different types of lasers, being enough for hair growth but not enough to induce thermolysis with the range of 0.6% to 10 %.[159] Suitable randomized controlled trials in a clinic are required to assess the efficiency of LLLT for hair growth.[160] However, more studies are required to create optimal protocols for such parameters as wavelengths, flounce, pulse type, time and power density of LLLT evaluation for hair re-growth.[80] Combined treatment of drugs and LLLT needs more clinical trials suggested by researchers.[80] Diabetic foot ulcer treatment with LLLT is a subject of controversy. Unique laser therapy mode determination to treat diabetic foot ulcers is not explained yet. It could be generally concluded that the laser effects are generally different in certain ulcers,[161] and animal studies revealed the promotion of wound healing by laser irradiation due to different factors such as cellular, morphological and collagen synthesis improvement.[162, 163] However, further investigations and clinical trials are required to understand efficacy of LLLT on diabetic wound healing according to the available positive results of studies. HL has different treatments and dissimilar protocols which implies more precise clinical trials with standard laser parameters be considered. As mentioned in Table 3 for breast cancer, different wavelengths and power supplies to use in LLLT treatments should be considered. A need to identify the optimal parameters of photobiomodulation for oral mucositis and dermatitis treatment is still required because of the controversies in different laser parameters that have been used by researchers (see Table 3) and the reduction of treatment side effects is still a problem. ORN treatment by LLLT is suggested by clinicians because of the proliferation and angiogenesis characters of laser therapy in this regard. Trismus treatment by LLLT was suggested, but some studies have not confirmed the effect of low-power lasers on muscle spasm reduction, which may be due to differences in sample type and other standards such as radiation intensity and the dose and depth of penetration.[164] Further research is required to introduce standard LLLT therapy for trismus treatment. It can be concluded that LLLT is in the initial step to be applied in a clinic in spite of the considerable development of related methods and theories.

Conclusion

Based on the studies of the low-power laser in the treatment of non-surgical diseases, it can be concluded that most studies have shown its positive effects on the treatment of such diseases, but lack of consistency in the choice of laser standards such as the wavelength, the amount of energy consumed, the surface of laser contact, and the duration of treatment is seen. Most researchers believe that in relation to each of the diseases, the efficiency of the low-power laser is positive. Standard research with qualitative and quantitative assumptions in the clinical setting should be undertaken to achieve original protocols to treat non-surgical diseases with LLLT and photobiomodulation. It seems that LLLT is a useful therapeutic method with a high degree of capacity for progression in future.

Ethical Considerations

Not applicable.

Conflict of Interests

The authors declare no conflict of interest.

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