



## Effectiveness of High Intensity Laser Therapy in managing Neck related painful conditions: A Scoping Review

1. Diggaj Shrestha<sup>1</sup>, 2. Hem Jiwani<sup>2</sup>, 3. Upneet Kaur<sup>1</sup>, 4. Parul Dalal<sup>1</sup>, 5. Rahul Kumar<sup>1</sup>, 6. Kunal Setia<sup>1</sup>, 7. Pardeep<sup>1</sup>, 8. Manalisa Kalita<sup>1</sup>, 9. Ankita Sharma<sup>1</sup>, 10. Sunita Sharma<sup>3\*</sup>

### Authors:

1. Diggaj Shrestha BPT, MPT (Musculoskeletal physiotherapy)
2. Hem Jiwani, Resident, General Medicine
3. Upneet Kaur BPT, MPT (Musculoskeletal physiotherapy)
4. Parul Dalal BPT, MPT (Musculoskeletal physiotherapy)
5. Rahul Kumar BPT, MPT (Musculoskeletal physiotherapy)
6. Kunal Setia BPT, MPT (Musculoskeletal physiotherapy)
7. Pardeep BPT, MPT (Musculoskeletal physiotherapy)
8. Manalisa Kalita BPT, MPT (Musculoskeletal physiotherapy)
9. Ankita Sharma BPT, MPT (Musculoskeletal physiotherapy)
10. Sunita Sharma\* BPT, MPT (Orthopaedic Physiotherapy), (Ph.D Scholar)

### Author(s) affiliation:

1. MPT student, Department of Musculoskeletal Physiotherapy, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana-133207. Haryana, India.
2. PG Resident, Department of General Medicine, MMIMSR, Maharishi Markandeshwar (Deemed to be University), Mullana-133207. Haryana, India.
3. Associate Professor, Department of Musculoskeletal Physiotherapy, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana-133207. Haryana, India. (<https://orcid.org/0000-0002-1761-6691>)

**Address Correspondence to:** 3. Sunita Sharma, Associate Professor, Department of Musculoskeletal Physiotherapy, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana-133207. Haryana, India.

**[drsunita.sharma@mmumullana.org](mailto:drsunita.sharma@mmumullana.org)**

**Co-corresponding author:** Diggaj Shrestha, MPT student, Department of Musculoskeletal Physiotherapy, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation. Maharishi Markandeshwar (Deemed to be University), Mullana-133207. Haryana, India.

**[physiodiggaj@gmail.com](mailto:physiodiggaj@gmail.com)**

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### Abstract

**Background:** Neck pain is the most prevalent musculoskeletal condition, affecting individuals of all ages and etiologies. Numerous studies have been conducted on High Intensity Laser Therapy (HILT) and neck pain, but no synthesis has been published as of yet. This study aims to evaluate the efficacy of HILT for the treatment of neck pain caused by a wide range of conditions.

**Methods:** PubMed, Scopus, and PEDro (Physiotherapy Evidence Database) databases were searched using an array of keywords and medical subject headings to identify relevant articles. The included articles discussed HILT and neck-related conditions. Two evaluators extracted data and assessed the eligibility of studies. The PEDro scale was used to evaluate the risk of bias, and Sackett's levels of evidence were used to evaluate the evidence regarding neck-related disorders.

Among the articles examined, seven met all eligibility requirements and were included in the final qualitative synthesis. These articles included a total of 602 patients treated with HILT for neck pain.

**Conclusion:** HILT in conjunction with a comprehensive and individualized exercise program is undeniably beneficial for addressing functional deficits. HILT is a feasible, safe intervention for enhancing function in patients with neck pain caused by a variety of conditions.

**Keywords:** Laser, Pain Management, Exercise Therapy, Neck Pain, HILT.

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## **Introduction**

Neck pain is one of the most prevalent pain related to musculoskeletal conditions, with only one-third of individuals experiencing complete symptom alleviation [1, 2]. Several modifiable and non-modifiable risk factors for neck pain include age, gender, lack of social support, inactivity, a history of neck or back pain, duration of daily computer usage, and perceived stress. Identifying risk factors is essential for the early identification and avoidance of neck pain, which has a tendency to become chronic [3].

In the year 2017, there were 122.7 million male and 166.0 million female cases of neck pain. Furthermore, more women (16.4 million) than men (12.2 million) lived with neck pain-related disabilities. Globally, the prevalence of problems with the neck increased until 70–74 years of age, after which it declined [4]. The conservative treatment for neck pain includes NSAIDs, cervical and scapular stretching and strengthening exercises, spinal manipulations, acupuncture, traction, yoga, massage therapy, and electrotherapy like TENS, ultrasound, laser, etc [5].

Modern physical therapy employs Laser photobiomodulation (PBM) therapy, a non-invasive, simple form of therapy that may have localized and systemic effects on patients [6]. Low-power lasers (class III; b, or low intensity laser therapy [LILT]) and high-power lasers (or high intensity laser therapy [HILT]) are distinguished by the laser's emission power, less than or greater than 500 milliwatts (0.5 watts) [7]. The ability of laser therapy to decrease inflammation, promote microcirculation, activate immunological functions and nerve regeneration, as well as increase endorphin secretion, is believed to be the reason for the pain management experienced after

treatment [1]. HILT devices are differentiated by strong photothermic and photochemical reactions, resulting in a less concentrated and more diffusely focused energy emission with the slowest chromophores' absorption and average depths of 10–12 cm [8,9].

HILT has wavelengths greater than 1000 nm and high power; this is an advantage over LLLT and allows it to penetrate deeper into joints and muscles to improve outcomes. The higher the power, the higher the effectiveness of pulsed analgesic therapy is observed in acute conditions, as well as the higher the delivery of intense thermic therapies for chronic conditions [10]. Additionally, in a short time, it allows higher delivery of energy in the patient's body, resulting in more practical benefits [11]. Although the efficacy of HILT in the management of various neck pain conditions has been documented, not much data has been published on the topic to date. No review has been published to date evaluating the efficacy of HILT for neck pain. Consequently, the purpose of this scoping review was to assess the efficacy of HILT in the treatment of neck pain.

## **Materials and Methods**

### **Inclusion Criteria**

To qualify, the article had to discuss high-intensity laser therapy for cervical conditions and be published in English. Randomized controlled trials were employed to gather information about the treatment of neck pain. Traumatic neck pain conditions are excluded from this study. Using the databases listed in the "Information Sources and Search Strategy" section, we concluded our search in March 2023. Two researchers independently extracted data from the included studies. To clarify any concerns or misunderstandings, we discussed the extracted categories on an ongoing basis.

### **Literature Search Technique**

The articles were searched from 2014 to 2022 for articles related to HILT interventions. High-intensity laser therapy, myofascial neck pain, chronic neck pain, mechanical neck pain, cervical spondylosis, and cervical pain are among the search strategies. To reduce the number of irrelevant articles regarding neck pain and high-intensity laser therapy, filtering techniques were used to eliminate those containing the term "low-intensity laser therapy." Only full-text articles written in English were included in the scoping review. In addition to searching relevant databases, we manually searched each included article for other articles. In addition, a textual search was conducted in a university library. Finally, to ensure full inclusion, physical therapy clinicians were consulted.

## Information sources and search techniques

We began our search for articles on neck pain and high-intensity laser therapy in September 2022 and finalized it in March 2023. We extracted and summarized data using the "descriptive-analytic" methodology of Arksey and O'Malley [12]. The databases PubMed, SCOPUS, and PEDro were utilized for searching for articles. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [13] were adhered to throughout the research and reporting process. High intensity laser therapy, neck pain, cervical radiculopathy, chronic neck pain, cervical spondylosis, non-specific neck pain, and myofascial pain were used as MeSH search terms. Boolean terms "AND", "OR," and "NOT" were used to link the keywords. We searched across the bibliographies of the articles and review papers we discovered to determine whether we overlooked any sources. In addition, we consulted with experts in the discipline to determine whether there was additional relevant research.

## Study Selection

DS and SS independently screened and reviewed the retrieved articles. Articles were selected if they addressed any causes of neck pain, including myofascial pain, radicular pain, and spondylosis that was treated directly with high-intensity laser therapy. Articles that did not discuss the topic and HILT treatment for traumatic neck conditions were eliminated. Pre-defined inclusion and exclusion criteria were defined before the beginning of the search process (Table 1). Two researchers independently assessed the suitability of studies based on the list of criteria. The study investigators dealt with the criteria for inclusion and exclusion to better understand any questions or discrepancies that showed up. The full articles of all summaries that met the first criteria were evaluated. Articles that fulfilled the standards for inclusion were taken into account in the final data analysis based on full-text evaluation by both extractors.

**Table No 1:** Inclusion and exclusion criteria of this study

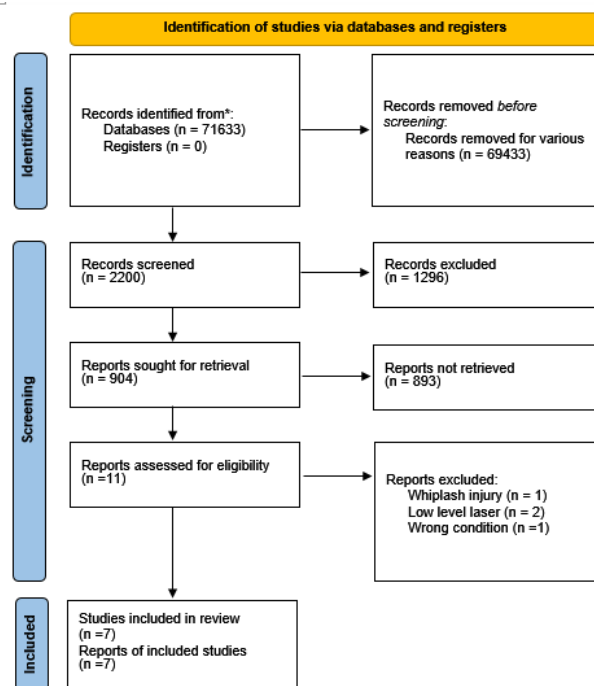
Criteria	Inclusion criteria	Exclusion criteria
Types of study	Only randomized clinical and randomized controlled trial are involved	Clinical commentary, Editorials, Letters to editor, narrative review ,grey literature
Intervention	High intensity Laser Therapy	Medical or pharmacological management, interventions including alternative medicine
Language	English	Other language literature
Participants	Both gender with age above 18 years old of age	Age less than 18 years old
Articles	Only full text article included	abstract
Outcome measures	VAS, NDI, cervical ROM	Other outcomes

\*VAS- Visual analogue scale; NDI- Neck disability index; ROM- Range of motion

## Results

### Charting the data

The results of our preliminary search approach were 71,633 articles. Following the elimination of duplicates and completion of all available RCTs, 2,200 articles were left. Following the application of filters, there are a total of 904 items that have been preserved. After thoroughly examining the articles, only 11 articles remained as most of them were excluded due to methodology and non-neck-related conditions. 11 articles are analyzed properly, and among them, 7 articles are taken for this scoping review as they deal directly with HILT on the treatment of neck-related pain conditions, and these articles match the inclusion criteria of our study. The review team submitted the data into the Microsoft® Excel program and analyzed it under the following headings: author(s), year of publication, investigation site, treatment type, and a comparison (if any); period of the intervention; participants; study goals; methodology; outcome measures; and significant findings. The flowchart of article selection is shown in **Figure 1**. **Table 2** displays an overview of the identified studies for the study.



**Figure 1** PRISMA 2020 flow diagram of the study.

### Methodological Quality Assessment

The PEDro scale was applied to do a qualitative analysis of the study that was listed [14]. The internal validity of the papers that were found was assessed using the PEDro scale (Table 3). Studies that investigate the efficacy of physical therapy treatments are compiled in a database

known as PEDro. For the purpose of assessing the dependability and outstanding methodological quality of randomized clinical trials, an 11-item scale was developed. If an item has not been taken into consideration, it should receive a rating of "0," whereas if it has, it should receive a rating of "1" for a positive response. The ultimate rating is arrived at by totaling up all of the points received. Every correct response is worth one point, with the exception of the very first question, which is different from the others because it has to do with the internal and external validity of the study.

Using the Sackett levels of evidence scale, which can be found in Table 4, we analyzed the amount of evidence provided by the articles [15]. This program offers a numerical rating for every article based on the type of study that was conducted, with lower numbers suggesting a decreased risk of bias [16]. The papers were examined for information regarding their populations, formats, and data evaluation methods so that it could be determined which level of evidence was used in each study. This was done so that it could be determined which degree of evidence was applied to every study.

**Table 2** Characteristics of studies included in the review

Author s	Objectives	Parti cipants	Study design	Interventions	Outco me measur es	Conclusion
<b>Dunde r U. et al. (2014) [17]</b>	To investigate the efficacy of HILT in chronic Myofascial pain syndrome of the trapezius muscle.	76 female	Rando mized control led, double -blind study	Total energy delivered = 1,060 J/session in three phases. 1st phase = (100 cm <sup>2</sup> per 30 s) fast manual scanning of the trapezius muscles with total energy dose of 500 J. 2nd phase = 10 J with time of 6 s at each trigger point on trapezius, for a total of 60 J. 3rd phase involved (100 cm <sup>2</sup> per 60 s) slow manual scanning of the trapezius muscles for a total energy of 500 J. Total time: 15 min/ session. HILT was applied once a day for 15 days during a period of 3 weeks	VAS, NDI, SF-36	Patients who suffer from chronic Myofascial pain syndrome of the trapezius muscle can be effectively treated with HILT.
<b>Alayat MSM et al. (2016) [1]</b>	To evaluate the effectiveness of HILT in reducing symptoms of chronic neck pain (CNP).	60 male	Rando mized double -blinde d, control led study	Total energy delivered in one session= 2250 J in three phases. 1st phase was total of 1025 J performed with fast manual scanning. 2nd phase, HILT (25 J) was applied to eight trigger points (four points on each side) with a fluency of 510 mJ/cm <sup>2</sup> each; a total of 200 J for 14 s administered. 3 <sup>rd</sup> phase is same as the 1 <sup>st</sup> phase with slow manual scanning. Total time: approximately 15 min. HILT was applied 12 sessions twice a week for 6 weeks.	Cervica l ROM, VAS, NDI	HILT and EX is effective method in the reducing symptoms of patients with chronic neck pain.
<b>Halada j R. et al. (2017) [18]</b>	To assess the analgesic effectiveness and improvement of active mobility of the cervical	174 (114 women and 60 men)	Rando mized Contro lled Trial	Ten times in one series, analgesic and biostimulation treatments were used (1 per day, 5 times a week for 2 weeks) Total energy for analgesia = 195 J with pulse mode at 25 Hz, wavelength at 980 nm, and radiation power density at 600 mW in 3.5 minutes and 5 J/cm <sup>2</sup> is the energy density. For Biostimulation application,	VAS and the Polish Version NDI	In patients with cervical spondylosis, both interventions were effective and analgesic in the short and medium term,

	spine following traction therapy using the Saunders device and HILT in patients with cervical spondylosis.			Continuous hand piece motion parallel to muscle fibres in the continuous wave mode, with power density $P=300$ mW, from C4 to Th4. At a wavelength of 980 nm, 6.5 minutes of operation time, and 1250 J of supplied energy, the average Ed was 50 J/cm <sup>2</sup> .		but HILT was superior to the Saunders approach in the long-term follow-up.
<b>Venosa M. et al. (2019) [19]</b>	To evaluate how patients with cervical spondylosis respond to HILT and a combination of US and TENS in terms of pain, range of motion, and functional activity.	84 (52 women and 32 men)	Randomized Controlled Trial	Total energy administered = 2050 J for approximately 30 minutes in three phases for 12 sessions. Powerful laser with peaks of 3 kW, pulsed emission at 1064 nm, frequency of 10–40 Hz, short pulse duration (120–150 s), and high levels of fluency (510–1780 mJ/cm energy density) with a 5-mm luminous spot diameter.. In first phase, fast manual scanning was done with a total of 1000 J/cm <sup>2</sup> . A total of 200 J were provided in the second phase, which involved applying HILT in four stages to each of the eight trigger points until a pain reduction of 70–80% was achieved. The final phase involved slow manual scanning similar to first phase.	Cervical ROM, VAS, and NDI	HILT with exercise is more effective than US combined with TENS plus exercise.
<b>Yilmaz M. et al. (2020) [20]</b>	To evaluate and compare the efficacy of TENS and US combined with HILT for treating cervical pain caused on by	40 (22 women, 18 men)	Randomized single-blind controlled clinical trial	Total energy delivered during one session = 1850 joules For each 25 cm <sup>2</sup> of painful area, 1.02 min of treatment, with an energy of 8.0 W, frequency of 25 Hz, a dose of 5 J / cm <sup>2</sup> and a total energy of 125 joules. Total time: 15 min per session. HILT was applied 20 therapeutic sessions 5 days in a week, for 4 week.	VAS, and cervical ROM	The HILT plus exercise programme and the TENS/US plus exercise programme are both effective in reducing



	cervical disc herniation (CDH).					cervical pain caused on by a herniated cervical disc in terms of range of motion and quality of life.
<b>Kenareh R. et al. (2021) [21]</b>	To evaluate the effectiveness of a HILT and ultrasound physiotherapy in office workers diagnosed with chronic non-specific neck pain.	60(43 females, 17 males)	Single-blind randomized control trial	Two phases. 1 <sup>st</sup> phase was performed at 10 W, 25 Hz and 15 J/cm <sup>2</sup> respectively for 3 minutes and 2 <sup>nd</sup> phase continued for 6 minutes with 7 W power and 100 J/cm <sup>2</sup> dosage. Total time: 9 min per session. HILT was applied 10 sessions over a two week period.	VAS, NDI	HILT is effective method in treating office workers with chronic non-specific neck pain.
<b>Ahi ED. et al. (2022) [22]</b>	To compare the effectiveness of HILT and dry needling options in patients with myofascial pain syndrome on neck.	108 (76 male and 32 female)	Randomized Controlled Trial	In each of the 15 sessions, the HILT group received HILT at high peak power (3 kW) with wavelength of 1064 nm to the cervical region for 15 min (1.02 min for each 25 cm <sup>2</sup> pain area, analgesic portion, at 8.0 W, a dose of 5 J/cm <sup>2</sup> , a frequency of 25 Hz, with altogether 125 J.	VAS, NDI and Cervical ROM	HILT is just as effective as dry needling in the treating of MPS when used in conjunction with exercise to decrease pain and minimize disability.

\*HILT- High intensity laser therapy; VAS- Visual analogue scale; NDI- Neck disability index; ROM- Range of motion, kw- Kilowatt; J- Joules; MPS- Myofascial pain syndrome; nm- nanometer

**Table 3** Assessment of quality of the methodology by PEDro.

<b>TRIAL</b>	<b>SELECTION CRITERIA SPECIFIED</b>	<b>RANDOM ALLOCATION</b>	<b>CONCEALED ALL OCATION</b>	<b>GROUPS SIMILAR AT BASELINE</b>	<b>PARTICIPANT BLINDING</b>	<b>THERAPEUTIC BLINDING</b>	<b>ASSESSOR BLINDING</b>	<b>&lt;15% DROP OUT</b>	<b>INTENTION TO TREAT ANALYSIS</b>	<b>BETWEEN GROUP DIFFERENCE REPORTED</b>	<b>POINT ESTIMATE AND VARIABILITY</b>	<b>TOTAL (0-10)</b>
<b>DUNDER U. ET AL. (2014) [17]</b>	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	8
<b>ALAYAT MSM ET AL. (2016) [1]</b>	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
<b>HALADAJR. ET AL. (2017) [18]</b>	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5
<b>VENOSAM. ET AL. (2019) [19]</b>	No	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
<b>YILMAZ M. ET AL. (2020) [20]</b>	No	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5

<b>KENAREH R. ET AL. (2021) [21]</b>	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	5
<b>AHI ED. ET AL. (2022) [22]</b>	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6

\*Total PEDro scores of 0-3 are considered ‘poor’, 4-5 ‘fair’, 6-8 ‘good’, and 9-10 ‘excellent’

**Table 4** Evaluation of the methodological quality of studies using the Sackett level of evidence

Level of Evidence	Dunder U. et al	Alayat MSM et al.	Kenareh R. et al.	Yilmaz et al.	M. Haladaj R. et al.	Venosa M. et al.	Ahi ED. et al.
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<b>1a (Strong)</b>							
<b>1b (Moderate)</b>	✓						✓
<b>2a (Limited)</b>		✓	✓	✓	✓	✓	
<b>2b (Limited)</b>							
<b>3 (Consensus)</b>							
<b>4 (Conflicting)</b>							
<b>5 (No Evidence)</b>							

\*Criteria: 1a (strong)—well designed meta-analysis, high-quality RCT; 1b (moderate)—one RCT of “high” quality; 2a (limited)—at least one “fair” quality RCT (PEDro scale score=4–5); 2b (limited)—at least one well-designed non-experimental study: non-randomized controlled trial; quasi-experimental studies; cohort studies with multiple baselines; single subject series with multiple baselines; 3 (consensus)—agreement by an expert panel; 4 (conflicting)—conflicting evidence of two or more equally designed studies; 5 (no evidence)—no well-designed studies

### Discussion

This scoping review aimed to examine the scientific evidence regarding the efficacy of HILT as a therapeutic treatment for patients with neck pain caused by a variety of conditions.

It's been proven that a number of diseases and conditions cause neck pain. People with conditions such as cervical spondylosis, fibromyalgia, cervical radiculopathy, and whiplash-related issues frequently and distinctly complain of neck pain [4]. Numerous additional comorbidities, including migraines, vertigo, anxiety, and depression, have been associated with neck pain [23]. It has been reported that kids and teens with non-specific neck pain demonstrate strong neck flexion during activities such as sitting, studying, viewing television, and playing with cellphones (or other portable devices) [24]. Additionally, research across different backgrounds and socioeconomic levels indicates people with CNP are additionally prone to experience psychiatric illnesses (such as anxiety, depression, and alcohol disorders) in comparison to those without such conditions [25].

In patients with CNP, the combination of exercise and HILT reduces pain, decreases neck disability, and improves cervical range of motion. HILT dosage includes a total of 1025 J per session, divided into three phases: the first phase of fast manual scanning, the second phase of direct over trigger points for 14 seconds, and the third phase of slow manual scanning twice a week for 6 weeks for a total of 12 sessions with stretching and strengthening exercises [1].

Dunder et al. found HILT to be effective in the treatment of trapezius myofascial pain syndrome; there was a significant decrease in the visual analogue scale (VAS) from  $6.1 \pm 1.6$  to  $3.1 \pm 1.1$  and the neck disability index (NDI) from  $32.6 \pm 6.6$  to  $21.1 \pm 6.3$  over a 4-week period, as well as an increase in cervical ROM and quality of life. The HILT treatment regimen includes a total of 1060 J in 3 phases of treatment per session, one time a day for 15 days over three weeks, along with active cervical range-of-motion (ROM) exercise, cervical isometric strengthening exercise, and stretching exercises [17].

In a 2013 study by Haadaj et al., it was determined that HILT is effective in the short, medium, and long term for reducing disability and pain index in patients with cervical spondylosis. The dosage consisted of an average energy density of 5 j/cm<sup>2</sup> and 50 J/cm<sup>2</sup> at a wavelength of 980 nm for analgesic and biostimulation procedures, respectively, with a total treatment time of 10 minutes and a total energy of 1445 J for a total of 10 sessions administered five times per week for two weeks [18].

30-minute specific exercise sessions of active ROM, stretching, and strengthening exercises of the cervical region combined with HILT dosage of total 2050 J divided into three phases of treatment for approximately 30 minutes for 12 total sessions significantly reduced the VAS score from  $7.96 \pm 0.68$  to  $1.56 \pm 0.71$  and decreased the neck disability from  $46.84 \pm 3.18$  to  $6.68 \pm 2.12$  in a 4-week time period in patients with cervical spondylosis [19].

In a 2020 study by Yilmaz et al., the combination of HILT and exercise was found to alleviate cervical symptoms associated with cervical radiculopathy. The laser dosage was 8.0 watts with a total of 1850 joules per session for approximately 15 minutes for 20 sessions, along with 30

minutes of cervical stretching of the suboccipital, trapezius, pectoral, and rhomboid muscles and isometric strengthening exercises of the cervical muscles. Significant reductions in pain, disability, and cervical ROM were observed [20].

Photobiomodulation has demonstrated efficacy in the management of chronic, nonspecific neck pain when coupled with postural correction and exercise training. The HILT settings of power, frequency, and dosage were 10 W, 25 Hz, and 15 J/cm<sup>2</sup> for three minutes each, followed by six minutes of seven W power and 100 J/cm<sup>2</sup> dosage, which significantly decreased the VAS score and neck disability score, as well as the Neck Pain and Disability Scale (NPDS) and Bournemouth Questionnaire (BQN) scores, which measured the various aspects of chronic neck pain [21].

A recent study compared the HILT to dry needling among individuals with neck and upper back myofascial pain syndrome. Both the intervention groups received exercise with dry needling or Laser and the control group received exercise only. The HILT group received a powerful peak power HILT (3 kW) with a wavelength of 1064 nm to the cervical region for 15 minutes (1.02 minutes for each 25 cm<sup>2</sup> pain area, analgesic portion, at 8.0 W, a dose of 5 J/cm<sup>2</sup>, with a rate of 25 Hz, and 125 J in total). In the HILT and dry needling groups, there was a significant reduction in pain and disability, as well as an increase in cervical range of motion, compared to the exercise-only control group [22].

HILT is a relatively novel technology that has only recently been utilized in physical therapy. HILT stands out for having a wavelength of 1064 nm, a maximum output of 3 kW, and a mean power of 10.5 W. Moreover, it is a non-painful, non-invasive therapeutic technology that can deliver a therapeutic dose to deep joints and large areas [1]. Stimulation by HILT causes the chromophores in the tissue to absorb laser light delicately. This event stimulates the synthesis of ATP, RNA, or DNA and initiates the oxidative processes within mitochondria. HILT regulates the discharge of bradykinin, histamine, and substance P from damaged tissues and peripheral nociceptors, respectively, resulting in an increased pain threshold and delayed pain conduction [21].

As mentioned above, it has been used and found effective for various neck-related conditions. Therapists who manage individuals with HILT may find, depending on more advanced evidence linked with equivalent feedback, improved results. There are insufficient studies regarding HILT and neck-related conditions. In general, our evaluation revealed that the little research supporting the use of high-intensity laser therapy to treat painful neck conditions is of poor quality. Due to the poor quality of the RCTs, firm conclusions about HILT cannot be drawn at this time. On the basis of a systematic review and meta-analysis, additional research can be conducted to determine the true magnitude of the effect of HILT on neck pain.

## **Limitations**

The limitations of this scoping review may have added a few possible biases. The lack of certainty in the proof is due to the poor methodological quality of a few of the cited articles. Participant numbers were modest for a number of results across time periods. Another cause for concern is that review contributors have inconsistently evaluated the methodology quality of multiple papers. In addition, there's a paucity of proof concerning neck-related conditions and HILT.

### **Clinical Implication**

Neck pain is one of the most common reasons for patients and their parents to consult a physical therapist for general medical care. The treatment of conditions affecting the neck must be precise, prompt, and efficient. This scoping review revealed that the combination of HILT and exercise reduces pain and improves patients' functional status. In any of the comparisons, HILT did not have any side effects that were more significant than the stated minimally significant difference for pain and function.

### **Conclusion**

Implementing a structured and customized program of physical therapy with HILT improves functional disability. An overview of the development and impacts noted in the study's conclusions demonstrates that HILT-based physical therapy reduces pain and improves functionality. The final outcomes, which are underscored by the gathered data, demonstrate the value of HILT for individuals with painful neck conditions.

**Data Availability:** Not applicable.

**Code Availability:** Not applicable.

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#### ***Declarations***

**Ethics Approval:** Not applicable.

**Conflict of Interest:** The authors declare no competing interests.

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