The Efficacy of Cognitive Behavioural Therapy in Reducing Phantom Limb Pain in amputee patients: A Systematic Review

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Abstract

Background: Amputations can result in alterations of both Central Nervous System (CNS) and Peripheral Nervous System (PNS). Frequently it gives rise to Phantom Limb Sensations (PLS) as well. Amputees who experience intense pain over the amputated limb are known as Phantom Limb Pain (PLP). PLP is manifested with sharp stabbing, tingling, cramps, throbbing, and immobile limb sensations. Numerous modal treatment approaches are used, including analgesics, vasodilators, muscle relaxants, sympathetic blocks, surgical revision of the stump, sympathectomies, mirror box therapy, and stimulation-induced analgesia techniques. Predominantly, conservative management is still preferred for treating PLP, and it has exhibited a positive outcome. Cognitive behavioral therapy (CBT) is one of the conventional treatments proved to lessen PLP.

Objective: The study aims to investigate the efficacy of cognitive behavioral therapy in reducing phantom limb pain for amputee patients.

Methods: A systematic review of all randomized controlled trials (RCTs) articles related to cognitive behavioral therapy and amputees with phantom limb pain. The search covered from January 2012 to September 2021 from 7 electronic databases (i.e., PubMed, PubMed Central, Cochrane Library, ClinicalKey, PEDro, SciELO, and Google Scholar). All studies contain information regarding the efficacy of cognitive behavioral therapy in reducing phantom limb pain for amputee patients.

Results: Out of 258 selected articles, 127 articles remained after duplicates removed. A total of 59 studies were excluded due to inability to fulfil the inclusion criteria, and 68 studies remained after studying their titles and abstracts. Subsequently, another 32 studies were excluded after the full-text screening for reasons of no primary outcome, no control, or comparison group. Finally, 39 articles were selected for this study that met the desired inclusion criteria. Further, 7 articles that meet the criteria were included upon further analysis, and 32 articles were then excluded. The eligible studies' analysis revealed that mirror therapy was the most effective intervention in reducing phantom limb pain among various modalities of CBT.

Conclusion: This study concluded that CBT includes mirror therapy (MT), virtual reality (VR) therapy, and other types of intervention such as transcutaneous electrical nerve stimulation (TENS), mental imagery techniques, tactile treatment, and phantom limb exercise can be used in reducing PLP. However, MT was the most effective intervention in comparison with other modalities.

Keywords: Amputation, amputee, cognitive behavioral therapy, mirror therapy, virtual reality, phantom limb pain.

1. Introduction

Phantom limb pain (PLP) is the perception of pain in a limb after limb amputation. Diabetes and peripheral vascular disease are regularly recognized as the leading roots of limb amputation in high-income countries (HICs) (Gupta & Kumar, 2019; Ying et al., 2022). Nonetheless, trauma has been recognized as the chief cause of limb amputation in a few low- and middle-income countries (LMICs). Undeniably, studies display that vascular disease is the reoccurring cause of lower-limb amputations with elevated incident rates among the adult populations aged 65 or older (Chalya et al., 2012). Recent studies have demonstrated that about 60%-80% of amputees will undergo phantom limb sensations (Kaur & Guan, 2018). Amputees that present with PLP outline a range of sensations that include burning, aching, stinging, and piercing pain with alternating cold and warm sensations felt in the amputated region. Initiation of symptoms can be influenced by environmental, physical, and emotional factors. Amputees who experienced PLP attain a lower quality of life (QOL), primarily due to limitations in performing daily activities and an increased level of anxiety, notably among the individuals 18-38 years old, and also depression in the individuals of 60-80 years old (Vaz et al., 2021). The prevalence of lower extremity amputation is high worldwide and remains the leading cause of morbidity and mortality. In 2017, 57.7 million people across the globe had limb amputations due to traumatic reasons (McDonald et al., 2020). The prime traumatic causes of limb amputation were falls (36.2%), road traffic injuries (15.7%), transportation injuries (11.2%), and mechanical injuries (10.4%). South and East Asia had the highest incidence of traumatic cause amputations, accompanied by Western Europe, the Middle East, North Africa, Eastern Europe, and North America (McDonald et al., 2020). There were no definite cases recorded in Malaysia despite the increase in amputation incidence. PLP is more likely to occur to patients who undergo proximal amputations than those with distal amputations. The reason of proximal amputations are more expected to cause PLP than distal amputations remains unclear (Limakatso et al., 2020). Pharmacotherapy, surgical procedure, and adjuvant therapy are frequent treatments used in treating PLP. Additionally, a few medicines may be prescribed to alleviate PLP (e.g., tricyclic antidepressants, NSAIDs, opioids, etc.). Several examples of adjuvant therapy are transcutaneous nerve stimulation (TENS), acupuncture, mirror therapy, electroconvulsive therapy, massage, and biofeedback. Operative management is seldom employed except that all the other approaches have failed to work. Other than operative management, CNS stimulation, including spinal cord stimulation and deep brain stimulation, has been favourable in alleviating PLP to varying extent (Kaur & Guan, 2018). Several studies found patients who experience a history of continuous pre-surgical pain were more likely to obtain PLP than those who did not encounter any constant extremity pain preceding their amputation (Lee et al., 2008; Rathmell et al., 2011). Physiologically, central sensitisation of the nervous system was perceived as mechanism to explain the relation between pre-operative pain and PLP. It was believed that the continuous pre-surgical pain results in the hyper-excitability and functional adaptations within the cortical areas which responsible for pain generation (Lee et al., 2008). The

mentioned adaptation might continue to up-regulate the peripheral inputs following limb amputation, hence indirectly developing PLP that mimics the features of pre-operative pain (Rathmell et al., 2011). PLP presents as a distress condition among amputation patients and is frequently neglected by the healthcare team. Among the numerous conservative treatments available, cognitive behavioral therapy (CBT) greatly influences in alleviating PLP. Though, the efficacy of CBT remains unclear. The available literature for CBT treating PLP is insufficient. Hence, it is essential for this systematic review to review the current evidence regarding the efficacy of CBT in alleviating PLP among the affected amputees.

1.1 Rationale

Considering that this topic lacks exploration, we ponder that it is essential to carry out a thorough, systematic review of the accessible article that may clarify the perception of CBT. This study was performed to rule out and determine the effectiveness of CBT in alleviating phantom limb pain for amputee patients. It is also intended to recognize, evaluate and compile the results of all the related individual studies on various CBT (mirror therapy and virtual reality system), thereby creating the available evidence data more reachable to our field of work. Some literature and experimental studies show that mirror therapy is more helpful to diminish phantom limb pain in lower limb amputees when compared with either virtual reality therapy or other conventional treatments. However, there is a study conducted by Ortiz Catalan et al. (2014) lately revealed the occurrence of an individual with chronic upper-limb phantom pain who had failed mirror therapy. They utilized a VR system to produce an appearance of the lost hand on a computer monitor and applied surface EMG data from the remaining limb to let the subject control and implement a series of reaching actions. Employment in this system minimizes the subject's pain. Thus, when deciding about it, we always confuse which interventions should be applied for a better and more effective outcome, which will bring the most benefits to those amputee patients and help reduce the phantom limb pain in a much more effective way?. Within those doubts and queries in all our minds, we finally came out with this systematic review study to act as a guideline for rational decision-making when dealing with the management to reduce phantom limb pain. Much effort is put into it, and this systematic review focuses on determining which types of CBT are most suitable for providing a maximum ideal outcome. Hence this systematic review is to identify relevant randomized controlled trials (RCTs) and determine whether cognitive behavioral therapy (CBT) is an effective intervention in reducing phantom limb pain for amputee

2. Methods

2.1 Search Strategy

Two independent researchers undertook a computerized literature search through 5 electronic databases: PubMed, PubMed Central (PMC), Cochrane Library, PEDro, and ClinicalKey by using different key terms that have been identified using the PICO model as shown below:

Table 1: PICO model

Patient problem (or population)	**P**	Amputee patients

Intervention (or exposure)	**I**	Cognitive behavioral therapy
Comparison (or control)	**C**	Conventional physiotherapy management
Outcome of interest	**O**	Reduce phantom limb pain

The Medical Subject Headings (MeSH) terms such as "cognitive behavioral therapy," "mirror therapy," "virtual reality," and "phantom limb pain" were used. Next, search terms were combined with the Boolean operator "AND" and "OR." To make the search strategy more comprehensive and focused, truncation (*) asterisk and wild cards (#) were utilized for some databases such as PEDro and Pubmed to identify word variants and act as a proxy for a string of characters. Also, phrase searching ("") were used if the specific term has more than one word.

In addition, the restrictions on language were adopted to accept articles in English version only. Furthermore, all searches were conducted separately, using pre-agreed-upon inclusion and exclusion criteria.

2.2 Selection Criteria

Inclusion criteria

(1) Studies include upper or lower limb amputee patients who experienced phantom limb pain.

(2) Any study that evaluates the efficacy of cognitive behavioral therapy.

(3) Studies that are published in English, and evidence within 10 years (2012 - 2021)

(4) Studies are randomized controlled trials (RCT).

(5) Full text available within an electronic database.

(6) Studies with no restriction regarding country, race, gender, etc.

Exclusion Criteria

(1) Studies involving amputees with systemic disease, mental or cognitive impairment, and other neuropathic pain except for PLP, congenital limb absence, and amputation stump anomalies which require surgical reconstructions such as chronic infections, neuroma, or major soft tissue deformities.

(2) Study involving non-human subjects or in vitro studies.

(3) Study with data not reliably extracted, duplicated, or overlapping data.

(4) Abstract-only articles as preceding papers, conference, editorial, and author response theses and books.

(5) Articles that do not have a full text accessible.

(6) Case reports, case series, and systematic review studies.

2.3 Data Extraction

Data were independently extracted from each included study by three investigators. Select the literature or article related and relevant to the research topic, retrieve, synthesize, and appraise it. The details on the title and abstract read, full-text articles rectified, and the excluded and included studies were compared for each author, with any divergent resolution resolved by agreement discussion.

2.4 Data Analysis

Data were analyzed and compared between each experimental study by three investigators. The results and conclusions of the studies were compared and interpreted in table forms. The outcomes of this systematic review have been summarized as the conclusion, and further recommendations have been made during the discussion.

3.0 Results

3.1 Study Selection

A total of 258 papers are screened from the following database: PubMed, Cochrane Library, and PEDro. There are 127 articles remaining after duplicates were removed. A total of 59 studies were excluded, and 68 studies remain after studying their titles and abstracts. The search identified a total of 68 articles for potential inclusion, the other 59 studies do not meet the inclusion criteria. Then, 32 studies were excluded after the full-text screening for reasons: no primary outcome, no control, or comparison group. Finally, 39 articles were selected for this study that met the desired inclusion criteria. 7 articles were included upon further analysis, and 32 articles were excluded. 7 articles met the criteria in the final selection for further analysis.

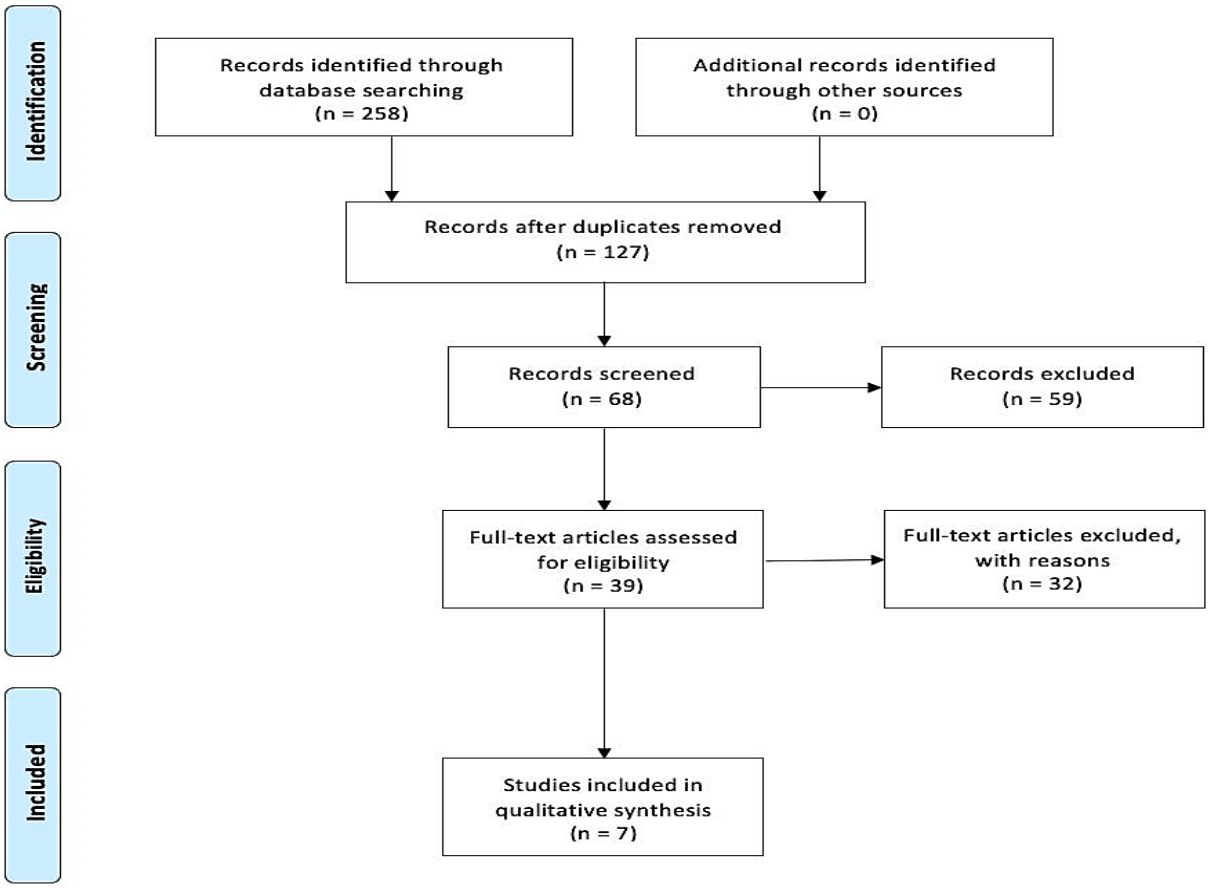

Figure 1: Prisma Flow Diagram

3.2 Qualitative Evaluation of Clinical Trials

The quality assessment of the 7 trials used in this study is shown in the table below. The magnitude of this scale was between 6 and 9, with an average score of 7.14/11. In 7 articles, the criterion is provided, and there is a list of criteria used to determine the participants in the study. In 5 articles, the allocation of the participants was concealed. In 7 articles, the reports explain at least one outcome measurement at baseline and at least one measure of the severity of the condition being treated. In 1 article, the

subject was blinded, there are no articles that the therapist was blinded, and in 3 articles, the examiner was blinded. In 7 articles, at least one outcome measurement was obtained from more than 85% of the initially allocated participants into groups.

Table 2 below shows the Cognitive Behavioral Therapy (CBT) Assessment of Quality of Studies by PEDro Scale.

Table 2: Results of assessment on quality of studies

Author	Cri 1	Cri 2	Cri 3	Cri 4	Cri 5	Cri 6	Cri 7	Cri 8	Cri 9	Cri 10	Cri 11	Total
Anaforoğlu Külünkoğlu, B. (2019)	1	1	1	1	0	0	0	1	0	1	1	7
Mallik, A.K. (2020)	1	1	0	1	0	0	0	1	0	1	1	6
Ramadugu, S. (2017)	1	1	0	1	0	0	1	1	0	1	1	7
Tilak, M. (2016)	1	1	1	1	0	0	1	1	0	1	1	8
Rothgangel, A. (2018)	1	1	1	1	0	0	1	1	1	1	1	9
Finn S.B. (2017)	1	1	1	0	1	0	0	1	0	1	1	7
Ol, H.S. (2018)	1	1	1	0	0	0	0	1	0	1	1	6

Note: Cri: Criteria

At first, 40 post-traumatic unilateral transtibial amputation patients aged 18-45 years old were studied in a randomized controlled trial by Anaforoğlu Külünkoğlu et al. (2019). By using the closed envelop randomization technique, the amputees were assigned into 2 groups: mirror therapy (MT) and phantom exercises (PE) with each group consisted of 20 subjects. This article was rated 7 out of 10 on the Pedro scale. Thus, it is considered a good article. Randomization, concealed allocation, baseline comparability, adequate follow-up, between-group statistical comparisons, reporting of point estimates, and variability are all included. Next, 92 amputees aged between 12-75 years old were studied in a prospective randomized controlled trial by Mallik et al. (2020). The amputees were randomly assigned into 2 groups with non-blinded: mirror therapy and mental imagery, with each group consisting of 46 subjects. This article was rated 6 out of 10 on the Pedro scale. Thus, it is considered a good article. Randomization, baseline comparability, adequate follow-up, between-group statistical comparisons, reporting of point estimates, and variability are all included. 64 amputees with PLP, aged between 15-75 years old, were studied in a randomized controlled trial by Ramadugu et al. (2017). Participants were randomly assigned into two groups, either the mirror therapy or control groups, with each group consisting of 32 subjects. This article was rated 7 out of 10 on the Pedro scale. Thus, it is considered a good article. Randomization, baseline comparability, blind assessors, adequate follow-up, between-group statistical comparisons, reporting of point estimates, and variability are all included. Furthermore, 26 subjects presented with PLP of any duration with unilateral upper limb or lower limb amputation aged 18-60 years old were studied in a single-blinded randomized control trial by Tilak et al. (2016). Using a computer-generated simple randomization sequence. Participants were randomly allocated into 2 groups: mirror therapy and

TENS, with each group consisting of 13 subjects. This article was rated 8 out of 10 on the Pedro scale. Thus, it is considered a good article. Randomization, concealed allocation, baseline comparability, blind assessors, adequate follow-up, between-group statistical comparisons, reporting of point estimates, and variability are all included. 75 subjects who had a unilateral lower-limb amputation were studied in a three-arm multicenter randomized controlled trial by Rothgangel, et al. (2018). Using a blocked random number sequence, participants were randomly allocated into 3 groups: Group A (Four weeks of traditional MT followed by six weeks of teletreatment utilising augmented reality MT), Group B (Four weeks of traditional MT followed by six weeks of self-delivered MT) and Group C (Four weeks of sensorimotor exercises to the intact limb followed by six weeks of self-delivered exercises). This article was rated 9 out of 10 on the Pedro scale. Thus it is considered an excellent article. All included are randomization, concealed allocation, baseline comparability, blind assessors, adequate follow-up, intention-to-treat analysis, between-group statistical comparisons, point estimates, and variability reporting. 15 subjects with unilateral upper extremity amputees were studied in a randomized controlled trial by Finn et al. (2017). Using a computer-generated number, participants were randomly assigned into 3 groups: either the mirror therapy or control groups that included covered mirror or covered mirror or mental visualization therapy. This article was rated 7 out of 10 on the Pedro scale. Thus it is considered a good article. Randomization, concealed allocation, blind participants, adequate follow-up, between-group statistical comparisons, reporting of point estimates, and variability are all included. Last but not least, 45 patients aged more than 16 years old who presented with unilateral transtibial amputation were studied in a randomized controlled trial by Ol et al. (2018). By using the computer-generated random numbers, the subjects were randomly assigned into 3 groups: mirror therapy, tactile treatment, combined mirror therapy and tactile treatment with each group consisted of 15 subjects. This article was rated 6 out of 10 on the Pedro scale. Thus, it is considered a good article. Randomization, concealed allocation, adequate follow-up, between-group statistical comparisons, reporting of point estimates, and variability are all included.

3.3 Data Presentation

Summary of data analyses are presented as in Table 3 below.

Table 3: Data analysis and presentation

Summary of data analysis		
Study Type	**Title + Author + Year**	**Results**
Randomized Controlled Trial	1. A Comparison of the Effects of Mirror Therapy and Phantom Exercises on Phantom Limb Pain. *Anaforoğlu Külünkoğlu et al. (2019)*	**Results:** - The analysis of all variables improved remarkably in both groups ($P < 0.05$). - The comparison of both groups disclosed significant changes for all

		measures of VAS and BDI, and conjointly in the results before and after treatment for all SF-36 criteria in favor of the MT group. **Conclusion**: - The overall treatment in this study reduced PLP, improved QoL and psychological status within a short period. However, upon comparing, better results were shown in the MT group than in the PE group.
	2. Comparison of Relative Benefits of Mirror Therapy and Mental Imagery in Phantom Limb Pain in Amputee Patients at a Tertiary Care Centre. *Mallik, A. K. e. al. (2020)*	**Results:** - There was no significant difference in VAS score between both groups at baseline, but the researcher found a significant reduction of pain in each group at follow-up. - However, upon comparing the improvement in both groups, there was a better improvement revealed in the MT group compared with the other group. **Conclusion:** - Both mirror and mental imagery therapy are beneficial and low-cost rehabilitation tools for the amputee to lessen PLP. - However, mirror therapy emerged to be more effective than mental imagery in this study.
	3. Intervention for phantom limb pain: A randomized single crossover study of mirror therapy. *Ramadugu, S et al. (2017)*	**Results:** - A significant reduction in PLP was observed in the test group compared to the control group after 4 weeks. - A significant reduction was observed in the control group after the switchover and lasted for 12 weeks in both. No harm was reported. **Conclusion:** - Mirror therapy has been reported to reduce the intensity, duration, frequency, and overall PLP. The improvement persists up to 12 weeks after treatment.

	4. Mirror Therapy and Transcutaneous Electrical Nerve Stimulation for Management of Phantom Limb Pain in Amputees — A Single Blinded Randomized Controlled Trial. *Tilak, M. et al. (2016)*	**Results:** - Both participants in Group I and Group II also showed a significant reduction in pain for the measures in VAS and UPS. - However, no difference was observed between the two groups. **Conclusion:** - It reported that both mirror therapy and TENS were found to be effective in pain reduction on a short-term basis. - However, the article has no evidence to prove which intervention is superior to the others.
	5. Traditional and augmented reality mirror therapy for patients with chronic phantom limb pain (PACT study): results of a three-group, multicentre, single-blind randomized controlled trial. *Rothgangel, A. et al. (2018)*	**Results:** - Based on primary and secondary outcomes, there were no significant treatment effects in favor of either group on the mean PLP intensity in the first four weeks. The mean PLP intensity reduction will only show at 10 weeks and 6 months. - Upon comparing, MT had shown considerably reduced duration of PLP at six months compared to the teletreatment and control group. **Conclusion:** - The clinical foundation for MT that was employed in this study for both traditional MT and the teletreatment using augmented reality MT appears to be feasible and showed some results at 4 weeks and 6 months.
	6. A Randomized Controlled Trial of Mirror Therapy for Upper Extremity Phantom Limb Pain in Male Amputees. *Finn SB et al. (2017)*	**Results:** - Subjects in the MT group had a significant reduction in pain scores and total daily time spent experiencing PLP. - The control group experienced no significant change in pain over the course of treatment, with only two subjects showing improvement. - A pain decrement response could be observed by the 10th treatment session, predicted ultimate efficacy.

		Conclusion: - The existing results endorse the hypothesis that mirror therapy may reduce PLP in upper limb amputees. In contrast, the use of covered mirrors and mental imagery techniques do not significantly reduce PLP and, in some cases, may worsen the pain. - The article concluded that mirror therapy is considered an effective intervention to reduce the severity of PLP and the duration of daily episodes.
	7. Mirror Therapy for Phantom Limb and Stump Pain: A Randomized Controlled Clinical Trial in Landmine Amputees in Cambodia. *Ol, H. S. et al. (2018)*	**Results:** - During the first 4 weeks of treatment, PLP and residual limb pain were reduced in all three treatment arms. All three interventions were associated with a VAS reduction greater than 50%. **Conclusion:** - Combined mirror-tactile had shown a significantly better effect on PLP than either mirror or tactile therapy alone.

3.4 Risk of Bias in Included Studies

A total of 7 articles have been included in this systematic review. Only the study by Mallik et al. (2020), which randomization process was not clearly stated. Only 1 study by Finn et al. (2017) reported blinding participants. The other 6 articles did not blind the participants, which may affect the results of the studies as a placebo effect may occur among participants. Apart from that, there were no studies reported blinding therapists. Last but not least, only 3 articles (Ramadugu et al., 2017; Tilak et al., 2016; Rothgangel et al., 2018) had blinded the assessors.

4. Discussions

The eligible studies showed that mirror therapy was the most effective intervention in reducing phantom limb pain with CBT. However, the outcome measures for all 7 studies included were different, hence, the data analysis couldn't be carried out successfully. As the data collection tools were inconsistent, the data was not able to interpret together. The outcome measure used for the study of Anaforoğlu Külünkoğlu et al. (2019) was the Visual Analog Scale (VAS), Short-Form 36 (SF-36) questionnaire, and also Beck Depression Inventory (BDI). The VAS was the most common tool used in clinical rehabilitation settings to identify pain intensity. It consists of a 100-mm line, with two endpoints representing “no pain at all” to “the most severe pain. As a result, a higher score may indicate a greater pain intensity. Next for Short-Form 36 (SF-36) questionnaire is mainly used to evaluate patients’ quality of life. The questionnaires will consist of physical functioning (PF),

social functioning (SF), role limitation due to physical problems (RP), role limitation due to emotional problems (RE), mental health (MH), vitality (V), pain (P), and general health perception (GH) domains. The scores are range between 0-100, and a higher score denotes better health related to the patient's QoL. At the same time, Beck Depression Inventory (BDI) was used to assess the patient's psychological status. This contains 21 items. Each scored between 0 and 3. The total possible score will in between 0 and 63, with higher scores indicating higher levels of depression. According to a result from the study of Anaforoğlu Külünkoğlu et al. (2019), there was a remarkable reduction in both VAS and BDI scores. A substantial improvement in SF-36 PF, SF, MH, and V subscale scores was shown on the side of the MT group during an assessment at the end of treatment, 3 months, and 6 months after treatment ($P < 0.05$). Besides that, there was also manifested a variation between both groups, which was observed for the SF-36 RE subscale score after 3 months and 6 months of treatment ($P = 0.035$) and the SF-36 P and GH subscale score throughout assessment at the end of treatment ($P = 0.001$ and $P = 0.020$, respectively). Next, there was no dissimilarity between both groups regarding the baseline pain intensity, which VAS measured over 28 days of the period ($P = 0.804$). Even though the pain intensity is reduced in both groups across the 28 days, the extent of the decline was 0.501 (SE: 0.175) units more in the MT group for each measuring point when compared to the PE group ($P = 0.004$). Thus, the results were proved that the MT group was had better outcomes than the PE group. There are two studies in the literature using PE (phantom exercise). First, in the Ulger O et al. study, 20 subjects were randomly distributed into two groups. As a result, PLP was significantly reduced in the PE group after 4 weeks. Next, Brunelli et al. practice modified PE incorporated with progressive muscle relaxation and mental imagery exercises twice weekly for 4 weeks constant. A significant reduce in the intensity of PLP was noticed in the treatment group compared with the control group. However, in the study of Anaforoğlu Külünkoğlu et al., pain intensity was decreased in both groups, but the decrease level was higher in the MT group. Meanwhile, the only outcome measure used for the study of Mallik et al. was the Visual Analog Scale (VAS). According to the study, each subject's phantom pain intensity will be assessed using the VAS on a scale of 0 to 10 points in both the groups at baseline, then at the 4th, 8th, and 12th of the months. As a result, there was no significant variation in VAS score between both groups at the baseline. However, a significant decrease in pain was then observed in both groups during the follow-up session. Upon comparing the improvement in both MT and mental imagery groups, we realized that the MT group was implied a more significant improvement (from 7.07 +/- 1.74 to 2.74 +/- 0.77). Thus we conclude that MT was appeared to be more effective than mental imagery in this study. Afterward, in the study of Ramadugu et al., the VAS and Short-form version of the McGill Pain Questionnaire (SF-MPQ) was being utilized as the outcome measures for this study. SF-MPQ was demonstrated to be a highly reliable measure of pain containing 15 descriptors (4 affective and 11 sensories), which are graded on a scale from 0 = none; 1 = mild; 2 = moderate, and 3 = severe. Regarding the evaluation of pain by SF-MPQ, the score was reduced gradually from the mean baseline score (3.65) to the lowest level (0.15) at the end of the 16th week in the test group. Whereas the

initial mean pain score in the control group was 2.37, and at the end of the 16th week after treatment, it has reduced to 0.33. This result showed a significant decrease in average pain scores in the test group. However, during the initial 4 weeks of covered mirror therapy in the control group, no significant change was noted in the average pain score. There was only shown a significant reduction in the average pain score at 8 weeks when the control group swapped to uncovered mirror therapy after 4 weeks. Therefore, this declares that mirror therapy does help in reducing PLP.The outcome measures used in the upcoming study of Tilak et. al. were the Visual Analog Scale (VAS) and Universal Pain Score (UPS). The UPS combines six hand-drawn faces from the Wong-Baker Pain assessment tool with activity tolerance. Activity tolerance statements will be provided in various languages, and the six faces scores will range on a scale of 1–10, with an explanation for each face. There was a comparison between initial and final pain intensity using these scales for both groups for this study. Based on the collected outcomes, there was a significant reduction in PLP in the MT group. The VAS value has went down from 5.46 to 2.08 (p-value = 0.003) and a reduction of UPS from 5.50 to 1.83 (p-value = 0.003) was observed. While on the contrary, participants allocated to the TENS group also had a significant reduction in PLP. The VAS value reduced from 5.00 initially to 2.46 finally (p-value = 0.001) and UPS reduced from 5.69 to 2.08 (p-value = 0.002). Again, the researcher was carried on with both groups' pre and post-treatment pain scores. The mean difference between VAS and UPS was not found to have a significant difference (VAS, p-value = 0.223 and UPS, p-value = 0.956). Moreover, we had observed a significant reduction in PLP in both groups after 4 days of treatment. In the MT group, there was a significant reduction in PLP, which is consistent with the findings of Chan et al. (2007) in which, PLP decreased significantly in eight out of nine patients (89%) who received mirror therapy. Furthermore, a case study carried out by MacLachlan et al. (2004), in which the PLP reduced from 6 out of 10 on the VAS to 0 after mirror therapy, also supports these findings. Conversely, the TENS group also manifested a significant reduction in PLP, which is consistent with the results of previous studies (Giuffrida et al., 2010). However, no between groups statistically significant differences were detected in pain intensity using either outcome. In an adjacent study by Rothgangel et al., 7 outcome measures were used in this study. First and foremost is the Numeric Rating Scale (NRS), which ranges from 0-10, 0 indicating no pain, and 10 indicating worst pain. Both duration and frequency of PLP are measured with a 6 point scale. 0 indicates none, and 5 indicates constantly. Next is the Neuropathic Pain Symptom Inventory (NPSI), comprised of five subscales, each representing different aspects of neuropathic pain such as burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain, and paraesthesia or dysesthesia. Each item was scored on an 11-point NRS. 0 indicates no symptom, and 10 indicates worst symptom. Higher scores may indicate more severe neuropathic pain symptoms. Thirdly is the Patient-Specific Functional Scale (PSFS), which measures the patient's function with different levels of independence. Patients were asked to rate the present level of difficulty corresponding with each activity on the scale. Continued proceed to the following outcome measure in the study of Rothgangel et al. were the Pain Disability Index (PDI). Patients were asked

to rate on an 11-point scale with 0 indicating no limitation and 10 indicating complete limitation on how much pain had interfered in 7 areas of life activity, including family or home, recreation, social, occupation, sexual, and self-care life-support, and average. The fifth outcome measure was the Pain Self-Efficacy Questionnaire (PSEQ) which enquires into the level of self-efficacy regarding a range of functions, including household chores, socializing, work, and coping with pain without medication. Total scoring for PSEQ ranged from 0-60, where high scores stipulate greater confidence levels when dealing with pain. Next, the overall treatment effect will be measured using the Global Perceived Effect scale (–5 = vastly worse; 0 = unchanged; 5 = completely recovered). Lastly, 5 - Dimensional EuroQol Questionnaire (EQ-5D-5L) is used to evaluate the patient's quality of life. It mainly comprises five dimensions, including mobility, self-care, regular activities, pain/discomfort, and anxiety/depression with each dimension consists of 5 levels which are categorized into no problems, slight problems, moderate problems, severe problems, and extreme problems. As the consequences based on the above study of Rothgangel et al., the intention-to-treat analysis showed no significant treatment outcome of MT over the control group regarding the mean intensity of PLP in the previous four weeks (treatment effect: – 1.2; 95% confidence interval (CI): – 2.4 to 0.0; P = 0.054) after rectification for baseline differences based on the primary outcomes. In addition, at 10 weeks and 6 months, all groups did show a decline in the mean intensity of PLP. No statistically significant differences between both groups were noticed in the mean intensity of PLP according to the intention-to-treat and per-protocol analyses. Subsequently, at 6 months, eight patients in the teletreatment group, fourteen patients in the MT group, and finally five patients in the control group showed a decrease in the duration of PLP episodes. Regarding the period of PLP at 6 months, the generalized estimating equation analysis had discovered a significant treatment impact on MT over both control (P = 0.019) and teletreatment groups (P = 0.050). On top of that, the secondary outcomes showed no significant effects in favor of any group in the first four weeks. In opposition, the majority of secondary outcomes also showed no significantly different among the groups during 6 months. For reference, patients in the teletreatment group showed significant and clinically worthy advantages over the control group concerning their general health status at six months measured with the VAS of the EuroQol form, and both experimental groups showed significant and clinically worthwhile effects on the control group regarding the intrusion of PLP in existence at all follow-up measures. To conclude, the impact of MT at four weeks on PLP was not significant. MT significantly lessens the duration of PLP at six months compared to the teletreatment (P=0.050) and control group (P=0.019). Simultaneously, the outcome measure that had been used in the study of Finn SB et al. was the VAS. In the MT group, eight subjects experienced a decrease in pain, while one subject experienced increased in pain. The group pain score decreased from an average of 41.4 (SD = 17.6) to 27.5 (SD = 17.2) mm on a 100-mm VAS (p = 0.001). The control group did not encounter a significant reduction in pain all-round way of treatment [mean 35.2 (SD = 25.5) to 48.5 (SD = 29.0) mm; p = 0.601], with only two subjects showing improvement. In calculating the estimated effect size regarding the initial and final VAS scores for

those receiving mirror therapy, Cohen's *d* is 0.971, indicating that MT had a greater impact on pain reduction. Next, a study participant's response to MT approximately after five sessions was widely predictive of the response at 4 weeks. Six participants reported a directional change in their pain scores on the day 5 evaluation that was in step with their directional change after 4 weeks. Of the three remaining subjects, all reported a directional change at the day 10 evaluation that admit with that of their day 20 evaluation. Moreover, there was also a significant alteration in total daily time spent experiencing PLP by the MT group, declining from a mean of 1,022 (SD = 673) to 448 (SD = 565) minutes (p = 0.003). Subsequently, no significant change in daily time experiencing pain could also be noted in the control group, from a mean of 743 (SD = 806) to 726 (SD = 825) minutes (p = 0.49). In reference to the seven MT subjects who initially reported constant pain, five of them have no longer reported this during the end of treatment. In calculating the estimated effect size of the initial and final time experiencing pain per day for the therapy group, Cohen's d is 0.924, signifying that MT had a more significant effect in reducing the time experiencing pain. Lastly, in the study of Ol et al. (2018), VAS was being utilized as the outcome measure to determine the pain intensity. Based on the results, the compliance rates during the first-round treatment were high, with a mean of 89.9% (SD 16.6). During the initial 4 weeks of the treatment period, reduced PLP and stump pain were observed in all three treatment arms, except for one patient in the MT group and one in the Tactile Treatment group. The mean reduction in VAS ratings for phantom and limb pain in all three treatment arms was >50%. No significant differences were observed between the three subsamples. In a nutshell, the mean delay between the conclusion of round one and the start of round two was 33 days. The compliance rate during the round two treatment was 100%. All initial non-responders reacted to the second-round treatment with a reduction in VAS rating of >90% for phantom and stump pain. A table in the study also demonstrates a tendency toward a better effect of combined mirror-tactile treatment compared to the monotherapies as estimated by the percentage reduction in VAS scores. Consequently, the 95% CI for the difference in percentage PLP reduction between T and M + T was 2.8 – 20.3; between M and M + T 10.0 – 8.6; and between M and T −11.5 – 31.0. Also, regarding stump pain, the combined treatment had a slightly better effect than the monotherapies as estimated by percentage VAS reduction, the 95% CI for the difference between T and M + T being 5.0 – 15.7; between M and M + T 4.9 – 22.8. No significant change was spotted between the monotherapies, the 95% CI for the difference between the M and T subsample regarding percentage VAS reduction being −10.0 – 17.0. To wind up, four weeks of practice of MT and tactile treatment causes a sustained reduction of PLP and stump pain in the majority of transtibial amputees. The most efficient method seems to be simultaneous mirror therapy and tactile treatment, or the two interventions serially.

4.1. Strengths

This study is a systematic review of randomised controlled trials (RCT), ranked at the highest level in the hierarchy of evidence. It provides a comprehensive and unbiased pooling of the information from similar research articles to answer a particular research question. This systematic review involves transparency throughout the

conduction of each phase so that readers can have a clear-cut understanding or better practical decision-making based on the evidence. Furthermore, discussions were being conducted by three researchers (two students and a supervisor) throughout the process until it reached a consensus. Besides, it has undergone peer- or professionals review along with the approval of the proposal to validate the idea. This systematic review has evaluated all the relevant articles in the available electronic databases, yielding a more reliable result than a single study. It is considered one of the substantial designs to evaluate the affecting relations. This systematic review was conducted efficiently by investigating the efficacy of different CBT in reducing phantom limb pain among amputees. No similar review or research was discovered in the published or registered articles.

4.2. Limitations

The main challenge in conducting this systematic review is the lack of standardization between the included studies. There are varieties of intervention classifications for CBT and are broadly used for different conditions or disorders (either in neuromuscular or neurological related conditions; or psychological conditions). Despite the significant findings, different characteristics vary among the studies that cannot be directly compared, thus causing difficulty in retrieving the results. All analyzed studies, for example, used various assessment tools for the evaluation of pain. This review does present some limitations. There is a lack of detailed investigation into the long-term effects of reducing phantom limb pain after applying conventional, and different CBT approaches. Besides that, systematic bias may arise in our study because there was one article in which the randomization process was not clearly stated. Other than that, 6 articles did not blind the participants, and 4 articles did not blind the outcome assessors. This may affect the result of the studies as a placebo effect may occur among participants and cause publication bias to emerge. Lastly, our initial intention was to investigate the relationship between all CBT, which includes mirror therapy (MT), and virtual reality (VR) systems in reducing phantom limb pain; however, our search strategy was not fruitful since there were no suitable relevant articles regarding virtual reality (VR) system in the past 10 years and we failed to search for randomized controlled trials as we only included RCTs in our study.

4.3. Recommendations

Based on the apparent increasing use of CBT in various fields or areas, better guidelines with evidence-based should be figured out. Hence, there is an urgent need for high-quality, well-reported research. Thus, we ponder that it is essential to carry out a thorough, systematic review concerning CBT will certainly benefit all therapists by producing the best desirable clinical result for the patient with reliable evidence. Further research with larger sample sizes and a longer follow-up period is needed. The patient's psychological problems should be included as an outcome measure to the result of the intervention as emotional stress may trigger phantom limb pain. It is also essential to incorporate health-related quality of life measures to detect improvements in participants' activity limitations in the community setting. These measures can also provide meaningful results to the participants and may aid in engaging participants to continue the long-term exercise program after the intervention.

5. Conclusion

The outcomes of the study are expected to

benefit practitioners. This study concluded that CBT, such as mirror therapy (MT), and other types of intervention such as transcutaneous electrical nerve stimulation (TENS), mental imagery techniques, tactile treatment, and phantom limb exercise, can reduce phantom limb pain. However, most studies had proven that MT was the most effective intervention when dealing with PLP. Hence, mirror therapy can be the first choice of treatment to relieve phantom limb pain among amputees other than conventional therapy.

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