Aus der Poliklinik für Zahnärztliche Prothetik
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Die Effektivität von nicht-okklusalen Therapien in Bezug auf die Chronifizierung von Craniomandibulärer Dysfunktionen: eine Systematische Übersichtsarbeit mit Metaanalyse

The effectiveness of non-occlusal therapies in relation to the chronicity of temporomandibular disorders: a systematic review with meta-analysis

Inauguraldissertation
zur Erlangung der Doktorwürde der
Medizinischen Fakultät
der
Julius-Maximilians-Universität Würzburg

vorgelegt von
Helena Held,
aus Kiel
Würzburg, Juni 2023

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Tag der mündlichen Prüfung: 09.01.2024

Die Promovendin ist Zahnärztin

Für meine lieben Eltern Margarete und Tobias

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1 Introduction

1.1 Temporomandibular disorders

1.1.1 Definition

"*Temporomandibular disorders*" (TMDs) is a collective term covering a group of clinical disorders affecting the temporomandibular joint (TMJ) and its surrounding anatomical structures including the masticatory muscles [1]. The term was first described as Costen's syndrome in 1934 [2]. More recently, TMD has been identified as a common pathological disorder and the prevalence of it has increased in the general population [3]. TMD is associated with a number of symptoms such as muscle and/or TMJ pain, TMJ noises, restrictions in the range of motion (ROM) of the mandible and associated headaches [4]. TMDs can often occur in conjunction with other craniofacial/ orofacial pain syndromes. On the other hand, pain or dysfunction not of musculoskeletal origins (e.g., otolaryngologic, neurologic, vascular, neoplastic, or infectious disease in the orofacial region), is not recognised as a primary TMD despite the fact that musculoskeletal pain might also be present [5].

1.1.2 Epidemiology

TMD is considered to be the most common cause of non-dentogenic orofacial pain and is a subset of musculoskeletal disorders [1].

Amongst the various debates surrounding TMD, it has been noted that the approach to the prevalence of TMD in the general population has varied considerably. For example, older studies found a lower percentage of the population with TMD than more recent studies [6]. However, it is significant to note that the prevalence of TMD is rising over the past two decades. This was found in a large epidemiological study in 2012 conducted in Sweden on children and adolescents [7]. A more recent epidemiologic study on a representative sample found that 19.7% of the general Lebanese population had symptoms of TMD [8]. Another study found a 12-month prevalence of 16 % for orofacial pain in a representative adult German population [9]. Conferring to a report by the World Health Organisation (WHO), it is the third stomatological disorder to be considered a common disease after dental caries and periodontal disease [10]. However, studies show that only about 25% of those individuals suffering from TMD pain seek treatment [11]. The outcomes from cross-sectional epidemiological studies show considerable variation between the studies. It could be argued that this is caused by the distinctive terminology used by the researchers, the tools used to identify the disease variations in data collection and diagnostic methods [12]. Nevertheless, it has been shown that individuals suffering from TMD cover a wide age spectrum. The age of subjects and onset of TMD is between 20-40 years of age [9, 13]. TMD is a recurring but

self-limiting condition [14]. It is also known that women predominate in studies of TMD patients. In 2006, Manfredini et al. made similar observations in a study of 433 TMD patients in whom the risk ratio was 2.6:1 (276 females, 73.2%; 101 males, 26.8%) [15]. The sex difference has often been discussed, but it remains largely unexplained. This can partly but not completely explain the overrepresentation of women in clinical materials as women have higher health-seeking behaviours [16] and greater sensitivity to pain than men [17]. Women also tend to suffer more from TMD in the premenopausal years (15-45 years old) [18]. Another contributing factor to this gender difference might be that endogenously or exogenously supplied hormones such as oestrogen and nerve growth factor (NGF) may play also an important role in the development of painful TMD. These new findings, offer a plausible explanation for the long-known observation, supported by epidemiological studies, that women, especially those of childbearing age, are much more frequently affected by pain in the region of the jaw muscles than men [19].

1.1.3 Aetiology

"The cause of the disease is referred to as its aetiology (from the Greek word meaning the study of cause)" [20].

The exact aetiology of TMD is still unknown and the most strategic conventional management of the condition is still a topic of debate [21]. Previously, TMD was considered an occlusal problem. However, currently TMD is understood as a dental/ medical problem, which also influences the diagnostic and management methods for TMD [22]. Several of the ambiguities that cause confusion in the TMD area are due to the multifaceted etiopathogenesis of the disease [23]. From today´s perspective of relevant literature, the influence of occlusion on the emergence and development of TMD signs and symptoms can be considered as rather weak [24, 25]. Several factors are expected to play different roles in the etiopathogenesis of diverse TMD diagnosis [26]. These are categorized into occlusal factors [27], anatomic factors [21, 28], micro- and macro-trauma [29-31], psychosocial factors [32-34], and pathophysiologic factors [35]. Hence the current concept of TMD aetiology is that of a multifactorial aetiology with individually different risk factors playing different roles in initiation, perpetuation, and resolving or chronification of the condition.

1.1.4 Treatment need

The manifestation of signs and symptoms of TMD does not relate to the treatment need. Epidemiology was used to assess the need for treatment for TMD. Variations in the prevalence of TMD, as well as factors involved in decision-making, may influence estimates of the need for treatment due to TMD in the population. A German meta-analysis published in 2008 by Al Jundi et al. [36], stated that the estimated need for treatment for TMD was expected to be 16.2% in adult population in non-patient studies. This demonstrates an

increase in Germany compared to Micheelis' 3 % of individual need for treatment in 1997 [37] based on the results, trends and problem analyses based on population-representative samples.

1.1.5 Cardinal symptoms of TMD

The symptom complex of TMD is composed of three cardinal symptoms: pain from the masticatory muscles and/or the TMJs, TMJ sounds, and restrictions of the lower jaw mobility.

1.1.5.1 Pain from the masticatory muscles and/or the TMJs

Pain occurs predominantly in the masticatory muscles and/ or the TMJs [38].
The literature reports that the most common form of TMD pain in patients is myofascial pain in the masticatory muscles [39]. It is responsible for more than half of the cases treated in specialized clinics worldwide [40]. The management of myofascial pain is challenging for clinicians due to its multifactorial aetiology. The most common therapies for myofascial pain include splint therapies, physical and manual therapies, medication, counselling and behavioural therapies as well as acupuncture [41]. The pain may be imprecisely localised in the muscles, with a dull, pressing or pulling, characteristic, recurrent pain covering the muscles in the jaw, head, and neck [42]. The Diagnostic Criteria for TMD (DC/TMD) muscle pain (myalgia) is based on: pain in the orofacial area in the history within the last 30 days and pain modification by chewing, biting or jaw movements, as well as familiar pain triggered by provocation tests such as palpation of the masticatory muscles or jaw movements during clinical examination [43]. Muscle pain that persists over a long period of time can cause considerable psychosocial stress and reactions. For example, impaired ability to perform everyday activities and contacts, depressive moods and other emotional disorders [44]. The aetiology of muscle pain in TMD is unclear. Common to all hypotheses is that the local release of endogenous substances from participating tissue cells and afferent nerve fibres is at the end of the causal chain (e.g., protons, substance P, glutamate, bradykinin, histamine, prostaglandin E2 (PGE2), serotonin, NGF, adenosine triphosphate). These substances can then stimulate the muscular nociceptors (group III and IV afferences). It is assumed that vasoactive peptides such as substance P and histamine can cause oedema and thus oxygen deficiency (ischemia) in the affected tissues receptors [45, 46]. Of particular importance in this context is that glutamate can cause peripheral sensitization without recognizable signs of inflammation, signs that have often been sought in vain in painful muscles [47, 48]. Despite successful therapy concepts and a large body of literature on the structural changes in the muscles that are clinically referred to as trigger points, there is a generally accepted idea about the cause of such muscular micro lesions. The neurobiologically most plausible hypothesis is the so-called "Cinderella-hypothesis" [49]. It is based on the principle that motor units (MUs) are sequentially stimulated according to their size [50]. As a result, type I fibres,

i.e., small MUs, can be continuously active during long periods of motor activity, even at low force levels. Measurements on the trapezius and the masseter muscle have shown continuous activation of individual MUs (so-called Cinderella MUs) over a period of 30 minutes and longer [51, 52]. It is also known from studies that the long-term active Cinderella's-MUs are particularly frequent in chronic neck pain patients [52, 53]. For therapeutic options, the view that - according to the theory presented - individual MUs can be a source of overload and subsequent painful lesions regardless of the absolute activation level of the original muscle.

Arthralgia, on the other hand, is pain of articular origin modulated by jaw movement, function or parafunction and replicated by provocation testing of the TMJ. According to the DC/TMD it is defined as spontaneously occurring pain in the TMJ in addition to pain on palpation of the lateral pole or posterior attachment of the TMJ on the same side [54]. A dense network of sensory fibres in the synovial membrane of the joint capsule is present, whose receptors react to physical and chemical stimuli, and pain neurons running in the subchondral bone. Accordingly, a possible accompanying synovial inflammation in the context of a degenerative joint remodelling is the most likely cause of pain. When stimulated again, the pain-conducting neurons become increasingly sensitive in the sense of sensitization. Recent studies confirm that peripheral neuroma formation and central nervous sensitization processes are involved in the perception of pain in the context of degenerative and inflammatory joint pain. The subjective experience of pain or impairment is based on peripheral and central neurons. Joint complaints vary greatly over time and pain exacerbations can usually be alleviated by conservative therapy [55].

1.1.5.2 TMJ sounds

TMJ sounds are also common complaints among patients and can be described as clicking, popping, grinding, or crepitating in the joints. In many cases, the joint noises are not accompanied by pain or dysfunction and are merely a nuisance for the patient. Some studies suggest that clicking in the TMJ (without further symptoms) is usually a condition that does not require other treatment except for counselling. Changes in condyle morphology, mechanical disc derangements including disc displacement with reduction may cause TMJ sounds without pain or significant dysfunction. Epidemiological studies have declared an increased prevalence of TMJ sounds among patients in an age range between 15-25 years old [17]. Furthermore, several trials [56, 57] have shown that even in patients with clicks who report other symptoms, severe episodes are not common. The clicking lessens significantly over time and does not lead to a deterioration of the clinical situation. An incidental finding of crepitus or a grinding sound is different as it may indicates a pathological condition, for example osteoarthrosis [58]. Nevertheless, crepitus, which combined with pain and restricts

movement of the lower jaw, should be treated early, and in most cases the disease can be treated with standard methods such as splint therapy, physiotherapy or medication [59].
Disc dysfunction is the second common cause of TMD after myofascial pain [60]. It can be classified according to the DC/TMD into four main types: disc displacement with reduction with or without intermittent locking, disc displacement without reduction with or without limited mouth opening [60, 61]. The most common form of disc dysfunction is displacement with reduction. It occurs in people of all ages, with a higher prevalence in women than in men and in the age range is between 20 to 40 years [62].
The cause of disc displacement is not clear, but possible reasons that could explain changes in TMJ function include anatomical and biomechanical factors [60]. The basis for the models of disc dysfunction pain is also the nociceptor pain. It is hypothesized that this pain is caused by overstrain and by dispositional factors [63]. On the other hand, some authors argue that the cause of intracapsular disorders of the TMJ is most often due to trauma [64]. Trauma can be subtyped in either macro-trauma or microtrauma. In cases of macro-trauma, a single blow to the mandible may result in disruption of the normal biomechanical functions of the TMJ. The traumatic event typically injures the joint structures by stretching the ligaments or damaging the joint surfaces. Once the ligaments have been stretched, their biomechanical function is altered - often leading to instability of the joint [64]. This can eventually lead to disc displacement. On the other hand, in the case of microtrauma, a small amount of repeated loading force over a long period of time can lead to changes in the joint structures. When the teeth are brought into heavy contact and the joint structures are loaded, there is a momentary reduction in blood flow to the small capillaries that supply the joint structures, resulting in hypoxia (a reduced oxygen supply). Under conditions of hypoxia, the metabolism of the local cell populations may change [65, 66]. The subtle changes that may occur could be a decrease in the lubricating quality of the synovial fluid, resulting in more friction during joint movement. It may also affect the articular surfaces of the joint, leading to a softening of tissue called "chondromalacia". The impaired lubrication and softening of the joint surfaces can cause the disc to shift from its normal position between the joint head and socket [67]. Once the disc is displaced, loading of the joint can occur on non-articular surfaces such as the retrodiscal tissue behind the disc. As this tissue is highly vascularised and well innervated, compression often results in pain. With continued loading, this tissue can collapse, allowing the condyle to directly load the glenoid cavity. Continued loading of these structures can lead to loss of the articular surface of the condyle and fossa. The end result of this decline is osteoarthritis or degenerative joint disease [67].

1.1.5.3 Restrictions of the lower jaw mobility

The range of movement of the lower jaw changes in different ways during an individual’s lifetime. It is essentially determined by the rotational and translational freedom of movement

of the condyle, which in turn depends on the structural conditions of the various tissues (fossa, condyle, discus, capsule, ligaments, muscles, etc.) [68].
The term hypomobility indicates a limited mobility of the condyles. It manifests itself in a reduced measured value of the vertical jaw opening. Generally, a passive opening of less than 40 mm is considered an indication of hypomobility, regardless of gender [69]. Regarding nomenclature, the term trismus is recognised as tonic masticatory muscle contractures or a muscular restriction. If mobility is completely restricted, this is then referred to as ankylosis (joint-related restriction) [70]. On the other hand, the term hypermobility stands for an increased mobility of the condyle, whereby no limit between normality and pathology is defined. Their relevance is clinically recognised if the mouth cannot be closed for a short or long time after opening wide (open lock). This problem is due to a shift of the condyle in front of the Eminentia or an obstruction of its return to the fossa. It is partly caused by a reactive contraction of the masticatory muscles. Furthermore, a condyle position in front of the Eminentia alone does not necessarily mean a locked jaw [71]. The diagnosis of a subluxation is given if the affected person can close the mouth again without external help. If this is not possible, the return of the condyle to the fossa requires manipulation by trained personnel (Hippocrate's method) as this is by definition a luxation / dislocation [72]. The clinical problem is clear, and the misalignment of the jaw head can be confirmed by preauricular palpation. In rare unilateral locations the lower jaw deviates to the opposite side. Pain can be intermittent or persistent. The clinical examination of the patient's medical history and the findings are unambiguous, the indication for imaging exists mainly for forensic reasons. For completeness it should be mentioned that a rarely occurring posterior displacement of the disc or a part of it (in case of perforation) can make condyle repositioning difficult and thus also lead to a mouth closure problem [68].

1.1.6 Diagnosis of TMD

1.1.6.1 Helkimo Index

For the diagnosis of TMD one of the first protocols developed was the Helkimo Index in the 1970s [73]. This index distinguished between an anamnestic and a clinical dysfunction sub-index and assigned a disability index score to an individual, based on the findings. The anamnestic evaluation characterizes three criteria I. no anamnestic dysfunction II. mild symptoms III. severe symptoms. Furthermore, a different diagnostic assessment regarding muscle- or joint-related disorders is created by the combination of these findings in a dysfunction index. Also, the lack of calibration and integration of psychosocial aspects points to the shortcomings of this classification system. This index was designed for epidemiological studies. Several amendments have therefore been proposed to the Helkimo Index [74] as the demand for the index is declining.

1.1.6.2 American Academy of Orofacial Pain

The American Academy of Orofacial pain (AAOP) diagnostic criteria for TMD-related masticatory disorders was introduced in 1990. It was based on the International Headache Society's classification of Orofacial Pain. Their focus was on the biomedical factors as opposed to the biopsychosocial factors. For this reason, a separate axis for defining psychosocial factors and diagnosing mental disorders was recommended by the AAOP [75].

1.1.6.3 Research Diagnostic Criteria for TMD

In 1992, many academies, national and international institutes and the expert panel that developed the first version of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) dedicated their study to categorizing the key constellations of signs and symptoms for the diverse TMD subcategories. The RDC/TMD is an endeavour to provide some taxonomic groups to facilitate cross-cultural and multicentre standardization of TMD diagnosis and to provide an assessment of psychosocial factors that weight influence treatment and prognosis [76]. The RDC/TMD integrated the biopsychosocial model of pain by adopting a two-axis model [32]. Axis I consists of a physical examination and axis II includes a psychosocial screening (pain impact, somatization, depression) [13]. Axis I classifies into three different diagnostic categories: muscle disorders, disc displacements or arthrogenous TMD. Axis II estimates the psychosocial dimension of pain and the psychological status of the patient. In contrast to earlier diagnostic systems, where classification was based only on somatic findings, this distinction is intended to facilitate the explanation of pain intensity and severity of limitation [77]. The connection of axis I and axis II is essential and serves a prognostic assessment of the disease [77]. This is because dysfunctional pain can indicate profound psychogenic involvement in the absence of organic causes [78]. Although the RDC/TMD were originally intended for clinical research, they were increasingly being recommended and used in everyday clinical practice for the purpose of diagnosis and classification of TMD [32].

In addition, the diagnosis is also characterized by very different procedures in German-speaking countries. To counteract the wide range of therapy-dependent variations with a scientifically substantiated approach, the interdisciplinary working group Deutsche Schmerzgesellschaft (DGSS) has developed new recommendations in 2000 for standardized diagnostics for patients suffering of TMD. Its concepts are based on the principle of a step-by-step diagnosis: a distinction was made between a minimum, a standard and an extended diagnostic procedure. At each level, both somatic (axis I) and psychosocial aspects (axis II) are diagnosed [79].

In 2014, a detailed evaluation of the RCD/TMD diagnostic criteria demonstrated that despite a high reliability of the axis I diagnosis, the validity was below the proposed target value, while the original RDC/TMD axis II instruments were shown to be both reliable and valid [43]. Based on these findings, a revised version of the DC/TMD was introduced by Schiffman et al. [43].

1.1.6.4 Diagnostic Criteria for TMD (DC/TMD)

Based on these findings and revisions, two international consensus workshops were convened, from which recommendations were obtained for the finalization of new axis I diagnostic algorithms and new axis II instruments [43] for the DC/TMD. The DC/TMD allows refinement of the most common pain related TMD [43]. In addition, the new DC/TMD introduced a more comprehensive classification system that includes both common and less common TMD classifications [43]. The previous diagnoses of osteoarthrosis and osteoarthritis were combined under the term degenerative joint disease and myofascial pain was redefined [43].

Axis I was revised for improved sensitivity and specificity. It consists of diagnostic criteria based on clinical signs and symptoms for the most common pain-related and intra-articular TMD. At the same time, shorter and publicly accessible instruments are available for Axis II, which is why some original RCD/TMD instruments for Axis II can be found with additionally new instruments to asses jaw function, behavioural and additional psychosocial factors [43]. It assesses pain intensity, pain-related disability, psychological factors, limitations in jaw function, parafunctional behaviours and a pain drawing at the pain site [43]**.** Therefore, a detailed assessment will be done with a larger number of instruments. Consequently, clinicians and researchers are currently recommended using DC/TMD when categorizing TMD sub-diagnoses [80]. However, there are some limitations in the new DC/TMD. Therefore, effort is currently underway to create an Axis III to combine genetics, epigenetics and neuroscience and to define standardised diagnostic categories that are pathognomonic for dysfunctional or chronic TMD pain [77].

1.2 Pain

The International Association for the Study of Pain (IASP) Press defined pain as „ an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [81].

1.2.1 Pain characteristics

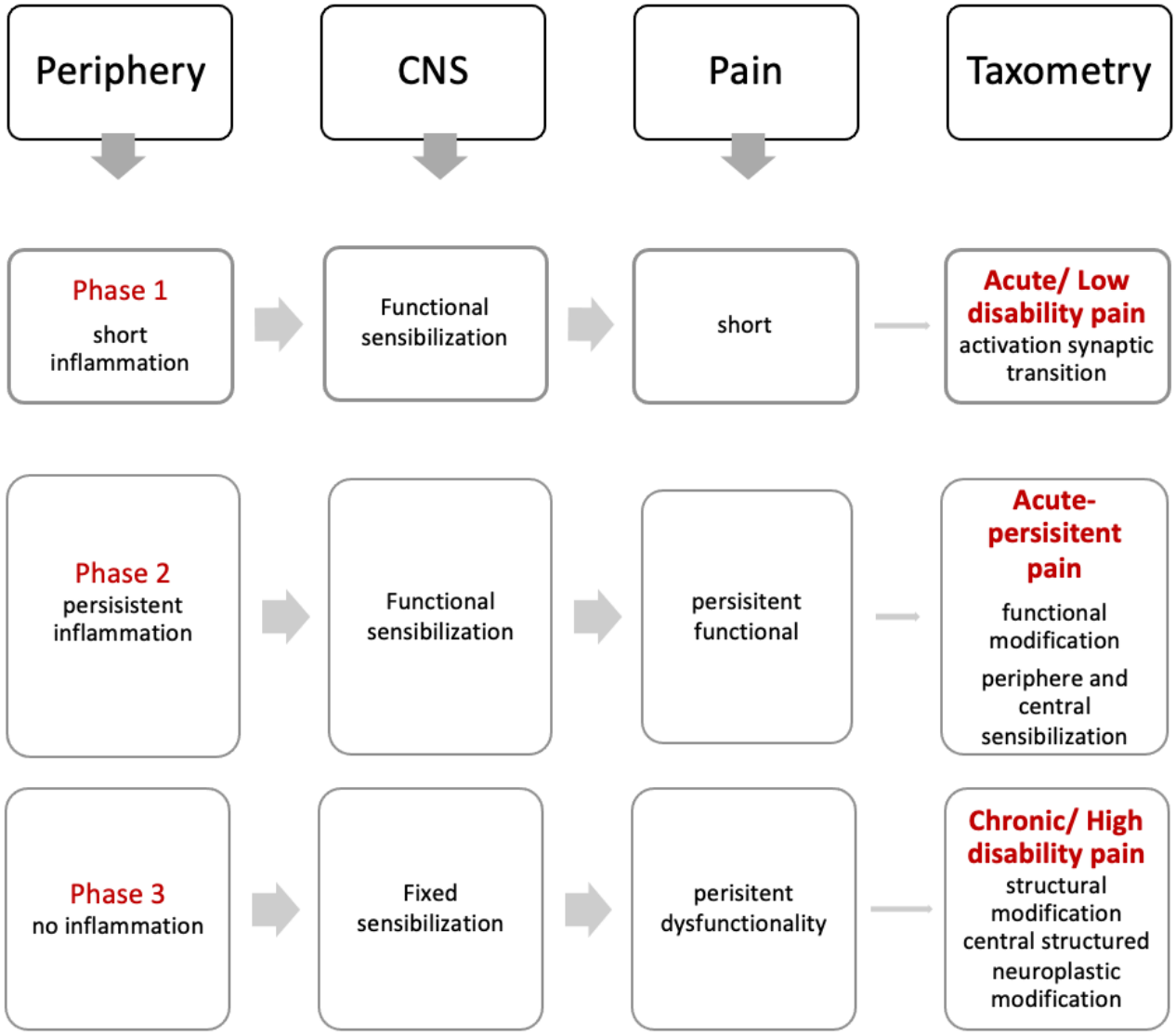


Figure 1: Current taxonomy of pain progression in TMD [82] (modification according to Treede et al. 2011 [83]) (CNS=central nervous system)

To characterize pain into acute/low disability or chronic/high disability pain solely according to the duration of the pain is not clinically purposeful. This is because current literature states that the duration of pain has no uniform significance for the phenomenon of chronification [82]. Other factors such as resistance to previous treatment, widespread pain, psychosocial stress factors (e.g., depression), patients' medication-taking behaviour and demands on the health care system must be considered. The conclusion from these findings is that it seems much more useful to divide pain into the three phases [82]: acute, acute-persistent, and chronic pain [82, 84].

1.2.1.1 Acute pain/ low disability pain

The first phase “acute pain” (low disability pain) is the sensory and emotional experience during the normal healing phase after an injury or endogenous process, such as inflammatory processes. This is a spontaneously occurring pain that is common in everyday life. It is also referred to as transient and protective because of its biological importance in protecting the injured tissue [85]. For this reason, acute pain is usually accompanied by an increase in sympathetic tone [86]. This pain lasts only a short time and diminishes when the stimulus or the healing phase ends [85].
Most often, it is a local pain condition that responds to moderate self-medication. Patients show no family, occupational or psychological impairment and can use coping strategies effectively. As soon as the triggering nociceptive stimulus is eliminated (e.g., with local anaesthetics or anti-inflammatory drugs), the pain is relieved. Pain is particularly triggered by micro or macro trauma and can be eliminated very quickly by removing the triggering factors [82]. In general, the aetiology and pathophysiology of acute pain are easy to understand, diagnosis is not difficult, and therapy is possible. Acute pain has a good prognosis if the cause of the pain is treated or if it heals naturally [86]. It is generally assumed that about 75-95 % of acute TMD patients improve significantly after treatment [87]. An example of this is pain after night-time jaw pressing (sleep bruxism), which disappears after the insertion of a bite splint [82].

1.2.1.2 Acute-persistent pain

The second phase, so called acute-persistent pain can occur with interruptions over weeks, sometimes months or years. It is a continuous pain with little pronounced fluctuations in intensity, which is often widespread and associated with different qualities of pain. Invasive interventions are not uncommon, and the negative influence of the pain on everyday activities is noticeable. However, it is possible to restore a pain-free state as the patients' coping strategies are still intact (pain is in the functional range) [82]. It has been observed in several TMD patients, unlike acute lesions, there is no transient course of pain. Instead, in these cases, the pain becomes acutely persistent (without psychosocial impairment) or chronic / high disabling (with psychosocial impairment). The therapy often has a temporary positive effect. The duration of the pain usually plays a subordinate role [83]. The transition between acute or acute-persistent pain and chronic pain cannot be clearly defined [19]. A typical example of acute persistent pain is active arthrosis of the TMJ, which often lasts for long periods of time (years) and can experience complete remission after arthrocentesis [82].

1.2.1.3 Chronic/ high disability pain

In contrast, the third phase of pain is “chronic pain/ high disability pain”. It is classically defined as pain that persists or recurs beyond the healing phase for more than three months [88, 89]. It should be seen as a health condition and not just a symptom [90]. However, the time factor according to the current understanding of pain processing plays only a subordinate or no role in characterising pain as chronic [91]. It has no warning function of (potential) tissue damage and there is usually no identifiable damaging factor [92]. It is usually a continuous pain without a significant change in intensity, which often spreads to neighbouring regions of the body. Several separate pain locations with comparable pain quality and intensity are usually found. Frequent changes of treating physicians are typical and high medication misuse over years. Treatment resistance to the conservative treatment strategies (which are well suited for acute and acute persistent pain) is frequent and leads to increased frustration and uncertainty among patients and treatment providers. The medical history often includes several pain-related invasive measures [82]. Chronic pain also shows considerable psychosocial impairment in the affected patients [93] and is often overlaid by psychological factors. Social impairments (family, occupation, society) and a lack of adequate coping mechanisms complete the picture [82]. A European population-based surveys have assessed the prevalence of chronic pain in the adult population to be 20-35% [94]. It can be concluded that high disability pain is a greater public health problem than low disability pain and requires special attention and treatment. It is suspected that some patients may also be more prone to pain chronification due to genetic and psychosocial factors.

1.2.2 Pain chronification on neurobiological basis

There are no definitive models to explain the transition from localized to widespread chronic/high disability pain. It is likely that the initial excitation and sensitization of nociceptors due to tissue damage causes sufficient nociceptive input to the central pain systems to cause central sensitization of dorsal horn neurons and/or in higher brain centers. Peripheral and central mechanisms contribute to the chronification of pain, i.e., the transition from acute pain to chronic pain [95, 96]. The mechanisms of central sensitization may involve an imbalance between descending inhibition and facilitation. Reorganization of higher brain centers may also occur in parallel with or after sensitization of second-order neurons [96]. It can be assumed that acute/low disability pain is based on an organic injury on peripheral level, while chronic/ high disability pain is based on a neurological dysfunction on central nervous level.

1.2.2.1 Chronification at the peripheral level (peripheral sensitization)

Sensitization of nociceptors and nociceptive afferent neurons is usually closely related to the presence and concentration of sensitizing substances that, via continuous noxious

stimulation, lead to a lowering of the stimulus threshold and an increase in action potential frequency in the afferents. In addition, the sprouting of new nociceptive terminals contributes to the development of peripheral sensitization (Figure 1). The "neurogenic inflammation" associated with vasodilation and plasma extravasation, which occurs through the mediation of neuropeptides (substance p; calcitonin gene-related peptide; neurokinin A; vasoactive intestinal polypeptide), has a pain-increasing effect [95]. Acute and acute-persistent pain result from peripheral sensitization phenomena and are usually reversible. For instance, a brief pain stimulus activates nociceptive nerve endings. After modulation by descending control systems, the action potentials reach the thalamus and the cerebral cortex. A brief painful sensation occurs [83]. These pain entities are interpreted as low disability pain. Certain local interactions can lead to a chronically increased excitation level of muscle nociceptors. Discrete muscle injuries release serotonin, bradykinin, substance P, PGE2 and histamine that lead to sensitization of nociceptors and the formation of local oedema. The accompanying venous congestion leads to local ischaemia and subsequently causes the further release of analgesic mediators. The consequence of all these mechanisms is an increased sensitivity to pain and classic trigger point [19, 97].

1.2.2.2 Chronification at the central level (central sensitization)

It is assumed that a long-term nociceptive influx of stimuli from the periphery leads to a series of long-term functional changes and sensitization in the CNS (Figure 1), which are accompanied by a permanent increase in the excitability of central nociceptive neurons (CNN). These processes play a crucial role in the development of secondary (central) hyperalgesia (an increased sensation of a painful stimulus) or allodynia (increased sensitivity to pain triggered by minor physiological stimuli), in which persistent pain can be maintained even in the absence of nociceptive information from the periphery [19]. Another mechanism for a persistent increase in excitability of trigeminal neurons can be seen in a dysfunction of descending pain inhibition triggered by the persistent excitatory influx [95]. In high disability chronic pain, additional neurobiological mechanisms are activated. In the case of chronification in the context of somatic lesions or even nerve injuries, there are permanent changes in gene expression in CNN and sensitization of these cells down to the cortical level. The consequence is a long-term altered synaptic connection and/or activation of non-nociceptive afferents that have gained access to CNN in the central nervous system [83]. An example for this would be a light touch stimulus can be felt as pain. Pain is triggered by central neuroplastic changes that have been decoupled from a triggering stimulus signal. Pain dysfunction can have a significant impact on the individual in the form of adaptive behaviours (e.g., to avoid the pain to make a high disability joint work better). While such behaviours may be truly 'adaptive' in the short term, their continued presence leads to further compensatory adaptations that result in expansion of e.g., TMD into the neck region, which

in turn results in pain and limitation in that area, and the continued 'adaptive' behaviours appear to increase the likelihood of high disability pain [83].

1.2.3 Indicators of pain chronification in painful TMD

At present, suggested indicators of pain chronicity have been resistance to previous treatment [79, 98], the concurrent presence of widespread pain in other body areas frequency [99], pain medication overuse [98] and depression [100] as well as the patient's choice of health care [98] but there is no doubt that greater knowledge of the pathophysiology of the different causes for TMD pain is much needed. Once this has been accomplished, the natural course of clinical symptoms can be more fully comprehended. In the following, indicators that could point to pain dysfunction are explained and discussed in more detail. Based on the indicators of pain chronification the authors were able to subtype high disability pain patients from low disability pain patients in this research work.
Von Korff et al. developed an instrument for grading chronic pain “Graded Chronic Pain Scale" (GCPS). The first version of which was integrated into the RDC/TMD and the second version into the DC/TMD classifies pain along two characteristics: pain intensity and impact on psychosocial behaviour [98]. The questionnaire assesses the current and past pain intensity (of the last six months, in the initial version, which changed later to 30 days in the current version of the GCPS) as well as the pain-related impairment of activity in everyday life, social life, and daily work [101]. The diagnostic decision as to whether a musculoskeletal facial pain should be classified as "acute", "acute-persistent" or "chronic-dysfunctional" is made with the help of this simple questionnaire [83]. It distinguishes levels of low disability pain (graded chronic pain, grades I–II) from high disability pain (graded chronic pain, grades III–IV). GCPS has been shown to be associated with psychological impairment, unfavourable appraisal of health status, and more frequent use of pain medications and health care [98]. This addition to the general diagnosis plays an important role in the therapeutic decision making. Currently, it is largely acknowledged in the literature that chronic pain is a multidimensional problem. Pain intensity, pain persistence, pain-related disability and frequency of occurrence can all be striking characteristics of a chronic pain condition [101]. This scale has proven to be a reliable, valid and time-ecological screening instrument for estimating the extent of pain chronification [101]. The instrument consists of seven questions, of which three questions relate to pain intensity and four questions to pain-related restrictions in the performance of normal everyday activities for a past period of 6 months or 30 days [101]. Six items are scored on a 10-point scale and one item is assessed as the number of days of incapacity to work due to facial pain. It is deemed appropriate for self-report use and although the characteristics of the scale may be useful for measuring pain dysfunction as a continuous variable, the authors have provided hierarchical criteria for classifying pain dysfunction into ordinal categories.

The characteristic pain intensity (CPI) score is obtained from the GCPS. It ranges from 0-100 and is calculated from three elements of self-reported TMD pain intensity: (1) pain at the present time, (2) worst pain in the last six months / 30 days, and (3) average pain in the last six months / 30 days. Each item consists of a numerical rating scale (NRS) of 0-10, where 0 means "no pain" and 10 means "worst pain". The three items are divided by three and multiplied by ten to gain the final CPI score [101].

Table 1: The GCPS [102] and [103]

Stage	Definition	Disability Grade
Grade 0	No TMD pain in prior six months	No disability
Grade I	Low impairment and low pain intensity: less than 3 disability points and < 50 Characteristic pain intensity	Low disability pain
Grade II	Low impairment and high pain intensity: less than 3 disability points and > 50 Characteristic pain intensity	
Grade III	Severe impairment and moderate limitation: 3-4 disability points, regardless of characteristic pain intensity	High disability pain
Grade IV	Severe impairment and high degree of restriction: 5-6 disability points regardless of characteristic pain intensity	

1.2.3.1 Resistance to previous treatment

Several authors have discussed a correlation between pain chronification and unsuccessful pre-treatments [98, 104]. Frequent use of medical care has been shown to be more common in patients suffering from severely debilitating pain, especially if they are taking peripherally acting analgesics and change practitioners frequently [98].

Blythe et al. 2004 was able to prove that chronic pain leads to increased use of a range of health services, which is directly related to the degree of pain-related disability and acts independently of other variables [105].

Notwithstanding all the advances in pain management in the 21st century, there are always some pain patients who are resistant to even the best modern therapies [106]. These subjects become highly disabled pain patients, and treatment strategies for such patients are more sophisticated and complex; yet they often do not lead to success. This phenomenon of chronicity and treatment resistance has been described for several regional conditions such as low back pain, headaches, and various types of facial pain, as well as for several pain conditions such as fibromyalgia. Of those patients who initially present with significant symptoms, approximately 75-80% respond positively to conservative treatments. However,

patients with a long history of untreated TMD pain usually prove to be quite difficult to treat [106]. Based on this consideration, frequent use of medical care has been an indication for high disability pain for the authors of this study.

1.2.3.2 Localized or widespread pain

Pain can be classified into local, regional, and widespread pain conditions [107]. Widespread pain is characterised by pain in multiple, distant from each other body regions [108], at seven or more sites in the pain site drawings (widespread pain index) [109]. The multilocularity of the pain, plays a central role in correlation with pain chronification. Studies suggesting associations between pain at sites other than the masticatory system and risk of development of TMD pain as well as lack of response to TMD treatment [110], support the hypothesis that such pain may influence prognosis of TMD pain. In fact, it has been found to correlate with an increased risk of pain disability and thus with a higher GCPS grade [111]. Patients who have myofascial pain and a history of widespread pain suggestive of fibromyalgia appear to have more often persistent and debilitating myofascial pain as compared to patients without a history of widespread pain [110], supporting the hypothesis that widespread pain could cause or increase risk of persistent and disabling TMD pain.

1.2.3.3 Pain medication overuse

Long-term drug abuse is highly correlated with pain chronification [98]. There is clear evidence of dysregulation of our major analgesic and limbic systems in chronic TMD pain [112]. A population-based survey in Europe has estimated that almost half of the subjects suffering of chronic pain were taking 'over the counter' (OTC) analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) (55%), paracetamol (43%), weak opioids (13%) and two-thirds were taking prescription medicines: NSAIDs (44%), weak opioids (23%), paracetamol (18%), cyclooxygenase-2 (COX-2) inhibitors (1-36%), and strong opioids (5%) [94]. Also the graded chronic pain status has been strongly associated with frequent use of pain medication, frequent use of outpatient medical care, unfavourable self-rated health status and psychological impairment [98].

1.2.3.4 Depression

Depression is an affective disorder characterized by a pessimistic sense of inadequacy and a despondent lack of activity. Moderate or severe depression is a very common mental disorder in the general population [100]. Psychological factors such as depression play an

important role in the chronification process of a patient with chronic pain and trigger a specific need for treatment [113], as they increases the pain-perception thresholds [114]. The prevalence of depression in the population of patients with chronic pain has been estimated to be 30–54% [115]. Von Korff et al. found the same strong correlation between limitations in psychological status and a higher degree of chronic pain [98]. Depression is often not recognised and therefore not treated in patients with chronic pain. Even when depression has improved, patients with a history of depression are at higher risk for chronic pain [116]. Chronic pain is considered a possible trigger for psychological changes that can be accompanied by an impairment of life activities [116]. Pain intensity and distribution as well as depressed mood are significant indicator of pain-related impairment [44]. It has also been shown that patients with chronic TMD pain suffer significantly more often from depression compared to the general population, while anxiety seems to be less relevant [100]. It is known that TMD patient populations have a higher prevalence of psychological distress than healthy individuals and chronic TMD pain populations generally produce the highest psychometric scores [106]. This was also shown in the study by Kotiranta et al. in which the patients were divided into the groups no- disability, low disability, and high disability according to the GCPS. In the group no-disability, the patients seemed to function well psychosocially. In contrast, the patients in the high disability group were those who had the highest level of depressive symptoms. The low disability group formed an intermediate group between the patients in the no disability group and the patients in the high disability group in terms of depression [117].

1.2.3.5 Health care setting

According to Schindler et al. there are three levels of care for a TMD patient: primary (e.g. dental practice), secondary (clinic) and tertiary care (mostly university) specialised clinics [79]. The majority of TMD patients are treated in primary care or by general dentists [117]. However, it can be assumed that the proportion of dysfunctional pain patients can be estimated to be much higher in clinics of the third level of care (specialised clinics) than in dental practices. For doctors working in the third level of care, chronic pain patients are not uncommon. They usually exhibit a combination of psychological characteristics. Typically, they seek mechanical explanations for their problem based on the beliefs of previous dentists who emphasised mechanical concepts and did not consider the role of psychological factors. With such patients, it is often difficult to prevent them from being over-treated or from progressing from low disability pain to high disability pain [106]. It is not uncommon for these patients to visit various specialists in order to achieve an improvement in their chronic pain [118]. In the study of Randolph et al. chronic pain patients indicated that they felt that medical care in educational institutions was better than private care. Patients who received dental

care in third level care indicated that they felt the level of care and sharing of information they received in these institutions was superior than in primary care [14]. On the other hand, most studies are conducted within the framework of university hospitals. The high proportion of dysfunctional pain patients is closely associated with university research. This is also supported by the high proportion of the low disability pain TMD population in secondary and tertiary care levels in the study of von Korff et al. [98]. Therefore, in this research, information about the level of care alone could not indicate the presence or absence of pain chronification; it was only considered supportive of the subjects' level of chronification in combination with other indications.

1.3 TMD management

“The estimated need for TMD treatment in the general population is about 16%” [76]. Currently, TMD can be treated by various therapies alone or as a combination of splint therapy, physiotherapy, medication, counselling, laser treatment and surgery, among others [119]. Non-invasive treatments tend to be the first option for approximately 85 to 90% of TMD patients [120]. Despite the existence of clinical studies on the effectiveness of non-occlusal therapies for TMDs, there is yet no data regarding their effectiveness according to the chronification grade of TMD pain. TMD treatment should generally be seen as patient management or symptomatic treatment as signs and symptoms may be the clinical manifestation of a variety of underlying diseases whose aetiology and pathophysiology can rarely be identified. This makes standard treatment challenging in the majority of occasions [76]. Most of the literature on the effectiveness of the treatment of TMD merely distinguish between the duration of pain (three to six month) to the chronicity of TMD and fail to regard the distinction between high disability chronic pain and low disability persistent pain which can be easily assessed by using the GCPS [79]. Regarding the literature that employed the GCPS as an instrument, it was evident that medication combined with physiotherapy and self-therapy following comprehensive consultation seems to be an effective therapeutic tool for non-/low disability facial pain. On the other hand, patients suffering from high-disability pain showed a major decrease in effect from the splint therapy [79]. As we want to find out the effectiveness of non-occlusion therapies on the different pain chronification we have focused on acupuncture, laser, medication, psychosocial interventions, and physiotherapy. The therapies are described in detail in the according section for Acupuncture, Laser, Medication, Psychosocial interventions, and Physiotherapy.

1.4 Systematic reviews and meta-analyses

Systematic reviews of randomized controlled clinical trials are classified as the highest evidence level and provide insights that can contribute to treatment guidelines and improve the quality of clinical research [121, 122]. A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods that are selected in order to minimize bias, thus providing more reliable findings from which conclusions can be drawn and decisions made [123]. It should provide an overview of a well-defined formulated research question from which relevant literature is identified, selected, and evaluated based on explicit criteria. To meet this requirement, the five systematic reviews of this research work were drawn up based on the Cochrane Handbook for Systematic Reviews and the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement. Cochrane is a global network of health and social care professionals, researchers, patient advocates, and others that aims to promote informed decision-making through the production of high-quality, relevant, and accessible systematic reviews and other summarised research. It has played a unique role in adopting the development of methodology for systematic reviews throughout its history. The Cochrane Handbook is an official guide that describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of healthcare interventions [124]. The PRISMA statement consists of a list of 27 items, as well as a flowchart to guide the author to produce a reproducible and high-quality review.

1.5 Research question and aim of this study

It has been shown that protocols for low disability pain therapy often fail in the case of chronic disease (headache or back pain). These include the administration of analgesics or immobilisation of the affected body part up to and including bed rest. Conversely, therapeutic success in high disability pain can be achieved through the concept of a multimodal psychological pain therapy which scarcely plays a role in low disability pain therapy. These clinical experiences led to the suggestion that the treatment of low disability and high disability pain must be based on fundamentally different procedures [92], as the transition from low disability pain to high disability pain is assumed to be an essential clinical feature of the chronification phase i.e. the contribution of peripheral and central mechanisms.
The aim of this research is to gain new understanding into extraoral administered therapies for TMD such as acupuncture, laser, medication, psychosocial interventions, and physiotherapy depending on the degree of chronic pain-related disability. To achieve a differentiated TMD therapy with the aspect of the chronicity of the patient and to evaluate the chronicity of TMD patients and to determine the most beneficial therapy for patients with low and high levels of TMD-pain-related disability.

The aim of this thesis is therefore to examine the differences in the effectiveness of extraoral therapies for the treatment of patients suffering of painful TMD with different pain chronification degrees.

The following hypothesis is put forward:

Hypothesis: Patients with painful TMDs respond differently to extraoral therapeutic methods depending on the degree of chronic pain-related disability. Therefore, the prognosis of therapy is significantly influenced by the degree of chronic pain-related disability of the disease.

2 Material and methods

2.1 Extent of the review and the issues to be addressed

Systematic reviews should address answerable questions and fill important knowledge gaps [125]. To answer the question of whether painful TMDs respond differently to different non-occlusal therapies depending on the degree of pain chronification; the following paper will consist of five systematic reviews and meta-analyses for several non-occlusal therapies of TMDs (acupuncture, laser, medication, psychosocial interventions, and physiotherapy). The methodological steps for the different non-occlusal therapies are discussed together below. This systematic review with meta-analysis is registered in the PROSPERO database under the number CRD420202558.
https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=202558

2.2 Establishing the criteria for the inclusion of studies and their grouping for the synthesis

The PICOS approach, an acronym for Population, Intervention, Comparison(s) and Outcome, is usually used to ask about the effects of an intervention [126].
The **PICOS** scheme was therefore used and defined as follows:

Population: adults diagnosed with painful TMD, no restriction on sex, age (no children) or religion was made. Studies with few adolescents were included if it could be assumed that they were nevertheless predominantly adult subjects.
No specific diagnostic tool was defined, nor the type of TMD. However, as the present study is intended to contribute to the investigation of pain chronification and pain usually conditions the need for treatment of TMD, an important inclusion criterion was that the subjects of the included studies reported pain in the TMJ and/or masticatory muscles. Accordingly, disc displacements with reductions were only included if they were described as painful or occurred simultaneously with pain. Thus, patients with all types of painful TMD were included.

Intervention: five separate systematic reviews with meta-analyses on five different extraoral interventions were conducted. The interventions were acupuncture, laser therapy, drug therapy, psychosocial interventions, and physiotherapy. The authors were interested in all studies that used acupuncture, laser, medication, psychosocial interventions, and physiotherapy. For those five examined non-occlusal interventions, no restriction was imposed on dosage, site of application, frequency, intensity, or duration of treatment. Studies

with combined therapies were also considered relevant if they included any of the five interventions studied.
Acupuncture interventions were considered relevant if the RCT used acupuncture treatment, dry needling, laser acupuncture, electroacupuncture, Traditional Chinese Medicine (TCM) or ear acupuncture. Laser interventions consisted of any type of laser. There was no restriction on medication; all types of medication were accepted for TMD treatment. Psychosocial interventions consisted of self-care, stress management, hypnosis, education, biofeedback, cognitive behavioural therapy, and relaxation. Physiotherapy interventions were accepted if they used manual therapy (MT) by a professional physiotherapist, jaw exercises performed by the patient, physiotherapy equipment (such as Therabite), postural correction or a combination of MT and jaw exercises. Transcutaneous electrical nerve stimulation (TENS) therapy was not studied and studies using solely TENS therapy were excluded.

Comparison: These interventions were compared with either other types of the same intervention, placebo interventions, no therapy or counselling alone, or other therapies. Studies with combined therapies were also considered relevant if they compared one of the investigated interventions (acupuncture, laser, medication, psychosocial interventions, physiotherapy) explored.

Outcomes: Primary outcome: current and unprovoked pain intensity. Short- and long-term changes from baseline to follow-up measurements were considered. Many studies used the visual analogue scale (VAS) for the measurement of pain. Other standardized measuring instruments were also accepted: NRS, 6 point-Likert Scala, GCPS, CPI.
Secondary outcomes: maximum mouth opening (MMO) in millimetres, pain on palpation measured in VAS, clicking (present or absent), depression and somatization.

Study type: According to the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions the author should be using randomized trials as primary literature in a systematic review in order to achieve the highest quality in a systematic review [127]. Therefore, only randomized controlled trials for the systematic review were included. Randomization is the most effective method to avoid systematic differences among the characteristics of the participants in the different intervention groups with regard to known and unknown confounders, so-called biases. [127]. Also, randomization (with blinding of the assignment sequence with respect to the enclosing examiner) avoids systematic bias. Letters to the editor, non-randomized trials, study reports and study protocols were not incorporated in this review.

2.3 Search and selection of the studies

2.3.1 Search strategies

To identify relevant studies, the literature was examined regarding the above criteria. According to the Cochrane Handbook the Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE, together with Embase should be searched for all Cochrane Reviews. The author therefore used MEDLINE via PubMed, EMBASE via Ovid, Cochrane Library: CENTRAL as the main database [128]. It was also recommended to search for relevant trials registers, other bibliographic databases, and ongoing trials. For this reason, LIVIVO, Clinical trials.gov, DKRS.de and Open Grey were also used as further databases. They are an important source for finding further randomized trials [128]. Individual search strategies were created for each of the electronic databases examined and for each of the five interventions separately (acupuncture, laser, medication, psychosocial interventions, and physiotherapy). The search strategy developed for MEDLINE was combined with the Cochrane Highly Sensitive Search Strategy (CHSSS) filter as it is recommended by the Cochrane Handbook [128]. This CHSSS is added to the individual search strategy for identifying randomized trials in MEDLINE. It can be found in the appendix under the search strategy for Pubmed/MEDLINE. The MEDLINE search strategy served as a template for the other databases searched and was revised accordingly for each to consider differences in vocabulary and syntax rules. Thus, specific search strategies were developed for each database. No restriction on language were imposed and no specific time frame was used to have as many eligible studies as possible. Similarly, data provided by the authors of the studies in addition to the respective publications were also used. They included all synonyms for the term TMD in combination with synonyms of the terms of the individual interventions for acupuncture, laser, medication psychosocial interventions and physiotherapy. The literature search for each intervention was performed for the different databases on the 24/01/2019 and on the 31/10/2020 (update). The search strategy for each of the five systematic reviews are presented in the Appendix VII: Search strategy [128].
Furthermore, relevant systematic reviews and meta-analyses were searched to identify further studies that were not found via the search strategies. The manual search (handsearching) was conducted until 31/10/2020.

2.3.2 Selecting studies

The procedure followed for selecting studies for inclusion in this review is as follows:
The first step was to add all search results to the reference management software Endnote X9 [129]. This was done for acupuncture, laser, medication, psychosocial interventions, and physiotherapy separately. Transferral to EndNote X9 also took place on the 24/01/2019 and on the 31/10/2020. The search results from various sources were matched using Endnote

X9, and duplicate entries were removed (e.g., reports with the same journal title, volume, and pages). The articles found were screened in a first screening using the four criteria set at the outset (RCTs, predominantly adult subjects, painful TMD, intervention examined). Two independent reviewers (Helena Held and Dr. Magdalena Dangl) performed the screening for acupuncture, laser, medication, psychosocial interventions, and physiotherapy, as recommended in the Cochrane Handbook, in order to reduce the possibility that relevant reports will be discarded [128]. Titles and abstracts were checked to remove obviously irrelevant reports and retrieved the full text of potentially relevant reports for the second screening. Multiple reports were linked on the same study [127]. Since several studies may have been reported in numerous articles, abstracts or other reports, a comprehensive search of studies for the review may identify many reports from potentially relevant studies [127].
In the second screening phase indetermined studies were re-examined for the four criteria using the full text. Both reviewers read the full text of all the included studies and removed any study which didn't meet the inclusion criteria for the five systematic reviews separately. On some occasions it was necessary to contact the investigators to clarify the eligibility of the studies, we also requested further information at the same time, e.g., missing information on methods or results. If the authors did not respond, a second attempt was made three weeks after the first contact. Failure to respond eventually led to exclusion from the study. To definitively make final decisions on study inclusion and proceed with data collection. In case of any divergence of opinion the estimations were discussed, with the opportunity of requesting a review by a third (Dr. Roldán-Majewski) or fourth review author (PD Dr. Giannakopoulos). If study protocols were available, they were compared with the included RCTs and incorporated or added to the relevant RCT [128].

2.3.3 Excluded studies

According to the Cochrane Handbook, the lists of the excluded studies were included in the Appendix for each intervention examined under "Characteristics of excluded studies". Those lists include all studies that at first glance appeared to meet the eligibility criteria but did not do so on full-text inspection. It also includes studies that do not meet all criteria but are well known and might be considered relevant by some readers [128].
Studies were excluded if:
a) at least one of the four criteria mentioned above was not fulfilled (RCT, painful TMD, investigated intervention, adults)
b) if the full texts were not available nor on request from the authors according to the protocol described above
c) missing or incorrect randomization of the interventions studied
d) majority of underage patients
e) subjects without painful TMD

f) other interventions studied
g) collection of measurement parameters that were not investigated in this study
h) studies with fewer than seven subjects per intervention group
i) a high risk of bias (high RoB) was suspected in the randomization process.
Flow diagrams (Figure 2: Flow Diagram for Acupuncture, Figure 14: Flow Diagram for RCTs on Laser, Figure 27: Flow Diagram for RCT studies on medication) were designed for each review. A summary of the included and excluded studies is shown in APPENDIX VIII: Characteristics of studies.

2.4 Collecting data

All studies meeting the inclusion criteria underwent data extraction. This was completed by two reviewers as recommended by the Cochrane Handbook [127] and was done for acupuncture, laser, medication, psychosocial interventions and physiotherapy separately. Excel was used as software system to obtain all data manually [130].

2.4.1 Which data to collect

Information on the first author and co-authors with contact details, study groups, the control groups, outcomes, indications of the degree of chronification (GCPS score, previous treatment, local or widespread pain, medication misuse, depression, high pain intensity score), country, number of participants, age group, sex, health care, diagnostic instrument used, type of TMD and inclusion/exclusion criteria [130] were extracted.

A draft of the tables and figures that will appear in the review to facilitate the design of the data collection forms were prepared. Forms were created that was easy to use and to collect sufficient and clear data that reflect the source in a structured and organised manner. The data needed for the meta-analyses were also extracted, which needed to be calculated or transformed from data reported in different formats. Data was collected and archived in a form that allows future access and sharing of the data [130].

2.4.2 Correspondence with investigators

At some points, it was not possible to obtain all the desired information about the details of the study design, the full range of outcomes measured and the numerical results from the available reports or desired information about the chronicity of the study population. In such cases, the original investigators were contacted. If the contact details of the study authors were not found in the study reports, recent publications, university or institutional staff directories, professional society membership directories or by a general search on the internet was used to obtain the contact information. If the contact author named in the study report couldn’t be contacted or did not respond, other authors of the studies were contacted [130]. The authors were contacted per email or through http://www.researchgate.com. In the

absence of a response from the authors, a second attempt was made three weeks after the first contact. Failure to respond ultimately led to exclusion of the study if the four essential criteria were not met.

2.4.3 Outcomes

The main outcomes and the most common measuring instruments which were encountered during data extraction are described in more detail below. The parameters examined are shown compactly in Table 2. The primary outcome was pain intensity. The secondary outcomes were MMO, pain upon palpation, TMD sounds, depression and somatization.

Table 2: Measurement parameters investigated (VAS=visual analogue scale; NRS=numeric rating scale; CPI=characteristic pain intensity; mm=millimetres; BDI= Beck Depression Inventory Mean; SCL-90-R= Symptom Checklist-90-R; HADS= Hospital Anxiety and Depression Scale)

Primary outcome	Secondary outcome	Secondary outcome	Secondary outcome	Secondary outcome	Secondary outcome
Pain intensity	**Active MMO**	**TMJ sound**	**Pain on palpation**	**Depression**	**Somatization**
VAS NRS CPI	mm	Present or absent	VAS Number of pressure pain points	BDI SCL-90-R HADS	SCL-90-R

2.4.3.1 Outcomes with corresponding measuring instruments

2.4.3.1.1 Pain intensity at rest

It is measured using different scales (e.g., VAS, NRS or CPI):

VAS

The VAS is an instrument for subjective rating of pain. The VAS is most often used as a unidimensional measure of pain intensity.

The VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient marks on the line the point that they feel represents their perception of their current condition. The VAS score is determined by measuring in millimetres from the left-hand end of the line to the point that the patient marks from “no pain” to the right side for “extreme pain” [131].

NRS

NRS is another quantity estimation for pain. It requires the patient to rate their pain on a defined numerical scale. In contrast to the VAS, the NRS consists of a rating scale in which 11 numbers (0 to 10) are given. Here, the number 0 corresponds to the statement "no pain" and 10 to the statement “worst pain imaginable”. The patient ticks the corresponding number

on the scale. Commonly used NRS are 11 points (0–10), 21 point (0–20) and 101 points (0–100).

CPI

Described in the introduction under the section 1.2.3 “Indicators of pain chronification in painful TMD”.

2.4.3.2 Active maximum mouth opening

MMO is measured in millimetres:

Millimetre (mm)

Measurement of maximum voluntary mouth opening using a ruler in mm: the distance between the mesioincisal angle of the right upper and lower anterior teeth plus the overbite. The overbite refers to the vertical overlap of the anterior teeth and the overbite refers to the horizontal overlap [132].

2.4.3.3 Pain upon palpation

Pain upon palpation was further differentiated into pain intensity of palpation pain and the number of palpation-sensitive muscles or muscle / joint regions. The palpation pain intensity was like the requirements of the main measurement parameter pain intensity with the difference that the pain here was provoked by palpation. The measurement parameter is described in the following as palpation pain and is also differentiated into the number of muscles or muscle or joint surfaces sensitive to palpation and palpation pain intensity.

2.4.3.4 TMJ sound

Presents or absence on TMJ sounds were collected without differentiating between clicking and crepitus.

2.4.3.5 Depression and somatization

The data extraction included the psychosocial parameters on depression and somatization. All valid diagnostic instruments were considered (BDI, SCL-90-R, HADS), for which higher values meant a higher probability of the symptomatology occurring:

2.4.3.5.1 Beck Depression Inventory (BDI)

The BDI is a 21-item, self-rated scale that evaluates key symptoms of depression including mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, body image change, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido.

Each question has a set of four possible choices ranging in intensity.
General guidelines of scores are:
00 – 09 = no or minimal depression
10 – 18 = mild-to-moderate depression
19 – 29 = moderate-to-severe depression
30 – 63 = severe depression

2.4.3.5.2 Symptom Checklist-90-R (SCL-90-R)

The SCL-90-R consists of nine scales (somatization, obsessive-compulsivity, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, psychoticism) and three global parameters (Global Severity (GSI), Positive Symptom Distress Index (PSDI), Positive Symptom Total (PST)) to measure the psychological stress over the previous seven days [133]. In addition to these nine symptomatologic dimensions, the SCL-90-R contains seven additional items relating to appetite and sleep disorder. Currently the SCL-90-R scales are included in the RDC/TMD axis II for psychosocial assessment in both clinical and research settings, which has been extended to include an anxiety scale in the updated version. Two of the subscales (depression and somatization scale) have been added to the psychosocial assessment as part of the research diagnostic criteria for TMD axis III. The SCL-90-R is frequently chosen for self-assessment of psychopathological distress and multiple psychopathological dimensions [76].
Each item is rated on a 5-point scale of distress (0-4) ranging from “Not at All” to “Extremely”. Examinees rate each of 90 items specifying how much each has bothered them during the past seven days [133].

2.4.3.5.3 Hospital Anxiety and Depression Scale (HADS)

HADS is a short self-assessment questionnaire to assess anxiety and depression that has demonstrated good sensitivity and specificity for mental disorders [134]. It is comprised of two subscales: HADS for anxiety scale (HADS-A) and HADS for depression scale (HADS-D). An uncomplicated self-report questionnaire consisting of 14 items comprising seven anxiety items and seven depression items. Separate sub-scales scores can be calculated for anxiety and depression [135]. Each item was answered by the patient on a 4-point (0–3) response category so the possible scores ranged from 0-21 for anxiety and 0-21 for depression, respectively. The test is described as a screening procedure aimed at milder forms of the disorders. The HADS was designed to exclude symptoms of mood disorder which are also likely to be present in patients with physical illnesses such as insomnia and anorexia [136]. The anxiety/depression was defined as HADS-A/HADS-D score ≥8. The anxiety severity was defined as:

00 - 07 = no anxiety
08 - 10 = mild anxiety
11 - 14 = moderate anxiety
15 - 21 = severe anxiety

Similarly, the depression severity was defined as:
00 - 07 = no depression
08 - 10 = mild depression
11 - 14 = moderate depression
15 - 21 = severe depression

2.4.4 Isolating data from figures using a software

Occasionally, the numerical data required for the systematic reviews were only displayed in figures. Data were obtained by contacting the author or alternatively extracted from the figures using a software (WebPlotDigitizer). The WebPlotDigitizer takes an image of a figure and then digitises the data points of the figure using the axes and scales specified by the users. The exported data can be used for systematic overviews [130].

2.5 Degree of chronification

After data extraction from the included RCTs, indications for the degree of chronification was searched separately. The main indicator was the GCPS score. A protocol of indications for high disability pain was designed. The main indications for high disability pain were: (a) GCPS IIb/III/IV; (b) previous therapy, patient still seeking pain relief; (c) widespread pain; (d) medication misuse in ≥ 50% of subjects; (e) depression in ≥ 50% of subjects. The patients' level of care was considered as supportive care, as subjects from specialized clinics are more likely to suffer from high disability pain (actively visited a specialized clinic). Also, high levels of pain intensity were a supportive indication for high disability pain but not sufficient on its own. If the authors did not state the GCPS, the authors with a request for more information about their study population were contracted. Each study was categorised as either “low disability pain”, “high disability pain”, “mixed pain” (low disability and high disability combined) or unclear. Some studies had weak evidence of low disability or high disability pain and were therefore marked as “unclear (low disability)” or “unclear (high disability)”. For the last part, subgroups were formed from “low disability pain”, “high disability pain”, “mixed pain”, and “unclear pain”.

Table 3: Indicators for pain chronification established by the authors study group (GCPS=Graded chronic pain scale)

Low disability TMD pain	High disability TMD pain
1. GCPS Grade I-II 2. No previous TMD therapy 3. Local pain limited to the masticatory muscles or TMJ	1. GCPS: III-IV 2. Previous treatment received before 3. Widespread pain 4. Drug abuse by at least 50% of the subjects 5. Depression present in at least 50% of the subjects
Supportive but not sufficient on its own: - Recruitment of subjects from general practices (primary care level) - Medium pain intensity	Supportive but not sufficient on its own: - Recruitment of subjects from specialized clinics or hospitals (care level II or III) - High pain intensity
If at least 80% of the subjects met a criterion, the study was assigned to the respective category	

2.6 Choosing effect measures and computing estimates of effect

The computer software Review Manager 5.3 (The Cochrane Collaboration, 2014) was used.

2.6.1 Continuous outcome data

The term "continuous" in statistics refers to a variable that can take any value within a certain range. In the context of numerical data, this means that a number can be measured and stated with any number of decimal places [137].

The variable analysed in the meta-analysis phase was pain intensity as well as MMO, depression, and somatization. The measurements taken were the data of baseline and after the treatment of the subject groups and the control groups. As different scales were involved in the measuring instrument for the effect sizes the standardized mean difference (SMD) was chosen [137]. The SMD is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in different ways. We therefore had to standardise our results of the studies to a common scale before we could combine them. The SMD expresses the size of the intervention effect in each study in relation to the variability observed in that study between participants in the outcome measures [137].

$$SMD = \frac{Difference\ in\ mean\ outcome\ between\ groups}{Standard\ deviation\ of\ outcome\ among\ participants}$$

2.6.2 Extracting data for continuous outcomes

The mean of the outcome measures, the standard deviation (SD) of the outcome measurements and the number of participants for whom the outcome was measured was collected for all intervention group. Because of insufficient and varying reporting, it was sometimes challenging to determine these figures from the data summaries provided. Therefore, the author was contacted to obtain the missing data or otherwise different calculations according to the Cochrane Handbook (see below) were used [137].

2.6.3 Obtaining SDs from standard errors and confidence intervals for group means

To estimate the SD of the difference between baseline and postbaseline measurement, the following steps were performed: If the SD was not given, the standard error was used to calculate the SD with the RevMan calculator. If the standard error was not provided, the SD for the baseline and subsequent values was used [137]. This was done according to the Cochrane guidelines, as it can be assumed that the intervention does not increase the variability of the outcome. If the mean values (MV) with SD were not provided, the author of the investigated study was contacted. If there was no response from the author, the missing SD was estimated by calculating the coefficient of variation (CV). This was completed by taking all the given SD and dividing them with the given MV. In the second step the mean value of all the CVs were calculated with the formula:

MWCV= $\sqrt{\frac{CV^2}{n}}$

This MWCV was multiplied by all the MVs with missing SD for each study. This was completed for pain scores, MMO scores, depression scores and somatization scores separately [138] and for each of the five systematic reviews with meta-analysis separately.

2.7 Consideration of bias and conflicts of interest in the included studies

In the five systematic reviews, bias was minimised [139]. Two areas where bias should be considered and distinguished: 1. the results of the individual studies included in the systematic review; 2. the results of the meta-analysis of the results of the included studies. Complications with the design and conduct of individual studies of health care interventions raise questions about the internal validity of their results; empirical evidence supports these concerns [139]. In assessing the internal validity of the included studies, the risk of bias was highlighted in the results, i.e., the risk that an included study over- or underestimates the actual intervention effect (see Assessing risk of bias in a randomized controlled trial) [139].

In addition, the results of the meta-analyses may have been influenced by biases resulting from the absence of results from studies that should have been included in the synthesis. Therefore, consideration of the funding sources and conflicts of interest of the study authors were made, which play a role in examining the immediacy and heterogeneity of study results, assessing the risk of bias within studies, and assessing the risk of bias in syntheses due to missing results [139].

2.8 Assessing risk of bias in a randomized controlled trial

The assessment of the risk of bias for the included studies was carried out independently by the two reviewers (Ms Helena Held, Dr Magdalena Dangl) using the Risk of Bias (RoB) Tool of the Review Manager recommended by the Cochrane Collaboration [140] (RevMan 5.3). The RoB tool was used to rate the included studies according to the quality of their conduct. The RoB tool assesses the risk of bias for each individual study using a fixed set of bias domains that focus on different aspects of study design, conduct and reporting [139].
Within each domain, a series of questions ("signalling questions") aims to obtain information about features of the study that are relevant to the risk of bias.
An algorithm suggests a risk of bias rating for each domain based on the answers to the signalling questions. Responses to the signalling questions and the bias risk assessments should be supported by written rationales. The overall risk of bias for the outcome is the most unfavourable assessment across all areas of bias. Both the proposed domain level judgements and the overall risk of bias judgements can be overridden by the review authors with justification [141].
Relevant studies were rated as “low risk of bias”, “high risk of bias” or “unclear risk of bias” in each of the following five domains, which are described in more detail below:

2.8.1 Random sequence generation

This aspect of possible selection bias describes a predictable allocation to the study groups due to inadequate generation of the randomization list. The qualitative assessment of the generation of the randomization list was conducted according to the rules of the Cochrane Handbook [141].

2.8.2 Allocation concealment

This identified any selection bias caused by predictable allocation to study groups due to inadequate allocation concealment. The quality of the concealed group allocation was also assessed according to the rules of the Cochrane Handbook [141].

2.8.3 Blinding of participants and personnel

The blinding of investigators, subjects and study personnel in the interventions carried out was not considered feasible and thus always assigned a low risk of bias in the evaluation. It

was only considered feasible if it was possible to achieve e.g., medication with placebo medication in the same colour und size. The reason for this was that blinding was impossible to implement in most comparisons. It is not possible to blind the patient and practitioner to different active therapies, for example acupuncture compared to MT. Performance bias could therefore not be prevented in this case in the eyes of the authors of this research [141].

2.8.4 Blinding of outcome assessment

The blinding of the outcome assessment was given more importance. The collection of the measurement parameters separately and independently of the treatment was easy to implement in the included studies. Non-blinded investigators were therefore considered a reason for a high potential for bias [141].

2.8.5 Incomplete outcome data

For the incomplete outcome data publications were screened for information on existing dropouts and intention to treat (ITT). Here we checked the distribution of dropouts among the intervention groups [141]. An ITT analysis could compensate for unbalanced or unexplained dropouts. According to the ITT model, dropouts are also included in the final analysis of the group to which they were originally randomly assigned.

2.8.6 Selective reporting

The assessment of reporting bias examined whether all measurement parameters defined at the beginning of the study were also reported at the end of the publication. Study protocols, hypotheses or the material and methods section of the publication were used for this purpose [141].

2.8.7 Other Risk

All anomalies were noted that were not yet listed in the previous sections and were considered suspicious. If no abnormalities were found in the publication for a further risk of bias, the study was rated with an unclear risk of bias. If there were no other abnormalities, the authors did not admit to any conflicts of interest, and there was no statistically significant difference between the subject characteristics and the baseline of the study, this area was rated with a low risk of other bias. The rating for low risk of bias in this domain was determined by the authors individually for this research and is therefore not subject to the Cochrane Collaboration guidelines.

One study was classified as “high risk of bias” when the randomization was at high risk, or two or more other areas were classified as “high risk of bias”. The same criteria were applied to classify a trial as having “unclear risk of bias”. Otherwise, the study was classified as having a “low risk of bias”.

2.9 Summarizing study characteristics and qualitative synthesis

Synthesising the data from the included studies to draw conclusions about the whole body of the findings was done. This included synthesis of the study characteristics and possibly statistical synthesis of the study results.

Tabulation of study characteristics helped to examine and compare PICOS elements in different studies, facilitated synthesis of these characteristics and grouping of studies for statistical synthesis. This was done using the Excel software and separately for each of the five systematic reviews.

Tabulating the data extracted from the studies allowed it to assess the number of studies that contributed to each meta-analysis (acupuncture, laser, medication, psychosocial interventions or physiotherapy) and helped to decide which other statistical synthesis methods could be used when meta-analysis was not possible [142].

2.10 Analysing data and quantitative synthesis / meta-analysis

Finally, the meta-analyses for the five interventions were conducted. This is a statistical combination of results from two or more separate studies. Most meta-analyses are variations of a weighted average of the effect estimates from the different studies. Accounting for differences between studies (heterogeneity). Random-effects meta-analyses also account for heterogeneity by assuming that the underlying effects follow a normal distribution, but they need to be interpreted carefully. Prediction intervals from random-effects meta-analyses are a useful tool to show the extent of variation between studies [143]. Sensitivity analyses were used to check whether the overall results are robust to potentially influential decisions [143].

2.10.1 Random-effects methods for meta-analysis

The effect sizes were described with a confidence interval of 95%. All the outcome data was processed using RevMan 5.3 (Cochrane Collaboration, London, UK) software. Due to the frequently existing heterogeneity of the results, the random effects model was always applied [137]. A variation of the inverse variance method is to include the assumption that the different studies estimate different but related intervention effects [143].

2.10.2 Heterogeneity

It is inevitable that studies summarised in a systematic review will differ. Any kind of variability between studies in a systematic review can be referred to as heterogeneity. According to the Cochrane Handbook it may be helpful to distinguish between different types of heterogeneity [143].

Interstudy heterogeneity was also assessed, initially by carefully examining the characteristics of the included studies. In addition, in each meta-analysis, the extent and impact of heterogeneity was assessed by calculating Cochran's test I^2 statistics. To quantify

heterogeneity, the I^2 statistic was used, which is standardised to values between 0 and 100 % and follows the recommendations of the Cochrane Collaboration: Values between 0-40 % were classified as low, between 30-60 % as moderate, between 50-90 % as substantial and between 75%-100% as considerable heterogeneity, respectively [143].

2.10.3 Subgroup analysis

Subgroup analyses were conducted for the subjects into “low disability” or “high disability” according to our indications of high disability. By missing interpretation, the study was classified as “unclear disability”. Some studies were marked as “unclear (low disability)” or “unclear (high disability)”. In a sensitivity analysis those studies were allocated to the relevant chronification degree to consider how the studies might interact. In addition, possible factors of heterogeneity of the study results were investigated with the help of subgroup analyses.

2.10.4 Sensitivity analysis

Exclusion criterion for the systematic reviews were a high risk of randomization bias. However, as blinding of the treatment providers and partly also of the patients was assessed as not feasible, this area was always rated as low risk of bias. In addition, possible outlier studies, heterogeneous data collection and the subgroup of subjects with an unclear degree of chronification were subjected to a sensitivity analysis to assess possible effects on the results of the meta-analysis.

2.10.5 Testing publication bias

Publication bias was assessed by creating funnel plots (APPENDIX X: Funnel plots) for each of the interventions in which the natural log was plotted against the standard error. The symmetry of the funnel plots was used to qualitatively determine whether there was publication bias. In a funnel plot, larger studies that provided a more precise estimate of an intervention’s effect from the spout of the funnel, whereas smaller studies with less precision from the cone end of the funnel. Asymmetry in the funnel plot indicates potential publication bias [144].

3 Results

3.1 Acupuncture

3.1.1 Description of the intervention:

A well-known complementary procedure for the primary therapeutic methods mentioned above is acupuncture, a component of TCM. TCM is based on the meridian system. This is an energy structure beyond the physical body, also known as the network of channels, through which the life energy "Qi" flows [145]. With this procedure, the insertion of the needles reorganizes the energy circulation of the entire body. Diseases arise from the disorganization of the low disability energy that controls and dynamizes the organs [146]. In addition to traditional manual acupuncture, other methods of stimulating acupuncture points are also used for therapeutic purposes, such as electro-acupuncture, acupressure, laser acupuncture and moxibustion. Other approaches in TCM include herbal medicine, traditional massage (tut na) and meditation (qi gong). The more frequent use of acupuncture as opposed to other TCM modalities appears to be due to its greater practicability. In TCM diagnosis, the disorders, pain, or dysfunction of an organ system are associated with the meridians. Possible healing responses can then be stimulated using acupuncture points on the meridian pathways associated with the TCM diagnosis [145]. The most recommended acupuncture points for TMD treatment can be divided into local points (ST6, ST7, SI18, GV20, GB20, and BL10) and distant point (LI4) in the face and neck, according to several clinical studies [147]. Controlled clinical trials investigating the effectiveness of acupuncture use different control groups, such as non-penetrating needle or penetrating needle in a non-specific point outside the main meridians [148]. A recent meta-analysis showed that acupuncture was superior to both sham acupuncture (deep or superficial needling of non-acupuncture points) and no acupuncture control for the following chronic pain conditions: non-specific musculoskeletal pain, osteoarthritis, chronic headache, shoulder pain and non-specific lower back pain [149]. According to the World Health Organization (WHO) the use of acupuncture in the treatment of tempomandibular dysfunction has been proposed as an effective pain -relieving treatment with positive results. This has been supported by several studies in systematic reviews. For example, Zhang et. al 2002 and ter Riet et. al 1990 [150, 151] found that acupuncture is an increasingly used treatment modality for the therapeutic management of pain symptoms. Standard acupuncture was found to be more effective than placebo or sham acupuncture. Therefore, it was concluded that acupuncture should be considered a reasonable alternative or addition to current dental practice as an analgesic [152].

Dry needling or intramuscular stimulation is a similar technique to acupuncture. However, it grafts on a different fundament. The needle effect would provide pain relief regardless of the

substance used when a needle is placed directly on the trigger points. Their effectiveness in TMD patients has been established, but there is no evidence of an advantage over other therapeutic procedures [153]. The authors Kao et al. 2006 [154] suggested that some acupuncture points are also myofascial trigger points. Two systematic reviews support the choice of needling (acupuncture and dry needling) as an alternative method for treating TMD [153, 155].

3.1.2 How acupuncture / dry needling might work:

Although the mechanism of action of acupuncture is not fully understood, there are various explanations. Today, it is assumed that acupuncture stimulates small, myelinated nerve fibres in the muscles, which in turn send impulses to the spinal cord and stimulate three centres: the spinal cord, the mesencephalon, and the hypothalamus-hypophysis axis. In addition, several neurotransmitters such as enkephalins, beta-endorphin, dynorphin, serotonin and noradrenaline have been shown to be involved in this process [156].
With dry needling, analgesia can occur through the "needle effect" described by Lewit et al. 1979 [157]. The needle works by mechanically affecting the sensory or motor components of the nerve endings that contribute to atypical function of the contractile parts or trigger point activity. The healing process begins by terminating the trigger point in that region [158]. The stimulation caused by the needle acts through the central nervous system. It has also been suggested that dry needling of myofascial trigger points works by reducing spontaneous electrical activity during local twitches [159]. For high disability pain, a painful stimulus of short duration can provide long-lasting and sometimes permanent relief. It is a cost-effective, harmless, and practical method disabling the myofascial trigger point in myofascial pain syndrome [158].

3.1.3 Study selection

The initial database search yielded 496 entries, of which 166 were retrieved in MEDLINE (via PubMed), 76 in Embase, 205 in Central, 35 in LIVIVO (German and English version), three in Clinicaltrials.gov, eleven in Deutsches Register klinischer Studien (DRKS) and nothing from Open Grey Literature (Table 4). Results of unpublished studies are not included in this review. An additional five articles were identified through cross-reference checking and manual searching summing up to 501 studies. All these studies used acupuncture interventions (Acupuncture, Dry needling, TCM, laser acupuncture, ear acupuncture) for treating TMD. Of these, 411 studies were discarded after review of duplicates, titles and abstracts (because the studies were not using RCTs or included adolescents suffering of TMD). An additional 50 articles were excluded after full-text review and application of the eligibility criteria (reasons for exclusion after full-text analysis are reported in APPENDIX VIII:

Characteristics of studies under Characteristics of excluded studies: Acupuncture). A flowchart that depicts this selection process is displayed in Figure 2.

Database	*Number of studies (n)*
PubMed	166
EMBASE	76
Central	205
LIVIVO (German)	20
LIVIVO (English)	15
Clinicaltrials.gov	3
Deutsches Register klinischer Studien (DRKS)	11
Open Grey Literature	-
Total	496

Table 4: Results of the search strategy for Acupuncture

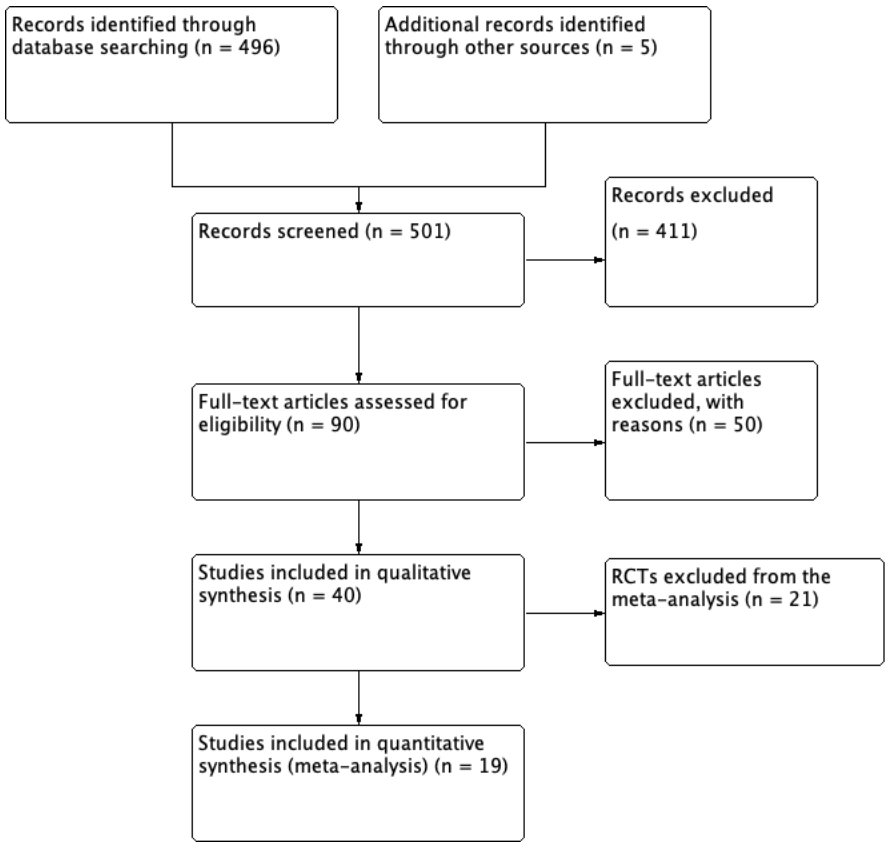


Figure 2: Flow Diagram for Acupuncture

3.1.4 Qualitative synthesis of the included studies

3.1.4.1 Characteristics of the included studies

Finally, 40 studies with 2037 participants, met the inclusion criteria and were included in this systematic review. To check for heterogeneity in advance, characteristics of the population used in the studies, the characteristics of interventions, pain chronification and the excluded studies were strictly reproduced in narrative style. Table 5 represents the general characteristics of the included studies, while APPENDIX VIII: Characteristics of studies, provides detailed information on the participants, the treatment and the comparisons, outcomes, degree of pain and follow up, respectively.

3 Results

Table 5: Included studies on acupuncture (CPI=characteristic pain intensity; DN=dry needling; LA=local anesthesia; MMO=maximum mouth opening; MPQ= McGill pain questionnaire; NPRS=numeric pain rating scale; NSAID=non-steroidal anti-inflammatory drug; OA=occlusal appliance; PHQ2=patient health questionnaire-2; TCM=traditional chinese medicine; TrPs=trigger points; VAS=visual analogue scale)

Author Year	Patients (n) women %, age (years)	Interventions	Outcomes	Pain chronification	Diagnosis	Application	Follow-up
Aksu et al. 2019 [160]	63 patients 84% women Mean age: 39.4 ±14.9	Group A (n=21): exercise + protection training Group B (n=20): dry needling + exercise + protection training Group C (n=22): trigger point injection + exercise + protection training	Pain (VAS) Changes in the mouth opening level Changes in the low disability limitation level Quality of life and depression scores	Low disability	TMD of muscular origin	Trigger point in the right or left or bilateral masseter and lateral pterygoid muscles	10 days and 1 month
Dalewski et al. 2019 [161]	90 patients 80% women 18-65 years old Mean age: 30.73	Group A (n=30): OA + NSAID Group B (n=30): OA + DN Group C (n=30): OA-control	Pain (VAS)	Low disability	TMD of muscular origin	Myofascial trigger points	After treatment
De Salles-Neto et al. 2020 [162]	40 patients 100% women Mean age: Group A: 37.5 ±13.3 Group B: 41.4 ±12.6	Group A (n=20): acupuncture Group B (n=20): placebo acupuncture (actual insertion did not occur)	Pain (VAS) Pain(SF-MPQ) Mandibular function (MOPDS)	Low disability	TMD of muscular origin	4-Hegu Li4, 34-Yanglingquan, 18-Quanliao 19-Tinggong, 6-Jiache (Ma6), 7-Xiaguam, 20-Fengchi (GB20)	1 month
Dıraçoğlu et al. 2012 [159]	52 patients 87% women Mean age: Group A: 33.00 ±12.70 Group B 35.88 ±9.60	Group A (n=26): DN group Group B (n=26): sham DN	Pain intensity (VAS) Unassisted jaw opening without pain measurement (mm)	Low disability	TMD of muscular origin	Trigger points	1 week
Faria et al. 2014 [163]	30 patients 96.7% women	Group A (n=10): DN therapy Group B (n=10): placebo group (sham DN) Group C (n=10): counselling	Pain intensity (VAS) Unassisted jaw opening without pain	Low disability	TMD of muscular origin	several MTrPs (active and latent)	1 month
Fernández-Carnero et al. 2010 [164]	12 patients 100% women 20-41 years old Mean age: 25 ±6	Group A (n=6): 1. DN, 2. sham acupuncture Group B (n=6): 1. sham acupuncture, 2. DN	Facial pain (NPRS) Pain-free maximal jaw opening (mm)	Low disability	TMD of muscular origin	Active trigger points (TrPs) in the masseter muscle	7 days
Ferreira et al. 2015 [165]	20 patients 100% women 18-60 years old	Group A (n=10): auricular acupuncture associated + occlusal splint Group B (n=10): occlusal splint plate alone	Intensity of pain (VAS)	Low disability	TMD of muscular origin	Shen Kidney E6, ID19, VB20, VB43, IG4, F3, TA3 and Yintang Liver maxillofacial San Jiao	5 weeks
Ferreira et al. 2013 [166]	40 patients 100% women Mean age: 34.17 ±8.83	Group A (n=20): laser acupuncture Group B (n=20): placebo laser associated with occlusal splint therapy	Intensity of pain (VAS)	Low disability	TMD of muscular origin and/or arthrogenic origin	Local, adjacent, and distal acupoints: ST6, SI19, GB20, LI4, LR3, TE3, GB34, and EX-HN3	3 months

Goddard et al. 2002 [167]	18 patients 83% women Mean age: Group A: 35.49 ±10.63 Group B: 34.53 ±6.78	Group A (n=10): acupuncture Group B (n= 8): sham ccupuncture	Changes in masseter muscle pain (VAS) evoked by mechanical stimulation of the masseter muscle	Low disability	TMD of muscular origin	IG4 and E6 (real acupuncture) and points close to IG4 and E6 for placebo Stomach 6 points	No follow-up
Gonzalez-Perez et al. 2015 [168]	48 patients 79.17% women 18-65 years old Mean age: Group A: 34.3 ±13.8 Group B: 35.5 ±11.2	Group A (n=24): deep DN Group B (n=24): drug-treated control group	Pain at rest and upon mastication (VAS) Range of mandibular movements (opening of the mouth, lateral movements, protrusion) (mm) TMJ affectation (100-point scale)	Unclear (low disability)	TMD of muscular origin	Trigger points located in the lateral pterygoid muscle	70 days
Grillo et al. 2015 [169]	40 patients 100% women 18-45 years old Mean age: 30 ±6.59	Group A (n=20): acupuncture Group B (n=20): flat occlusal plane appliance	Pain intensity (VAS) Range of mouth opening (mm)	Low disability	TMD of muscular origin	LI4 (Hegu), LI11 (Quchi), SI19 (Tinggong), LR2 (Xingjian), GB20 (Fengchi), GB21 (Jianjing), GB34 (Yan-glingquan), BL2 (Zanzhu), CV23 (Lianquan), and TE23 (Sizhukong)	4 weeks
Grillo et al. 2018 [170]	40 patients 90% women median age: 38 ±8.7	Group A (n= 20): acupuncture Group B (n= 20): sham acupuncture	Pain (VAS)	Low disability	TMD of muscular origin or mixed origin	ST6 (Jiache), ST7 (Xiagan), SI18 (Quanliao), GV20 (Baihui), GB20 (Fengchi), BL10 (Tiazhu), and LI4 (Hegu)	4 weeks
Han et al. 2015 [171]	120 patients 59% women Mean age: Group A: 40.3 ±12.2 Group B: 35.7 ±10.5	Group A (n=62): acupuncture + medicated cupping Group B (n=58): medicated cupping	Pain (VAS)	Unclear (low disability)	TMD	HegLi (LI 4) Talchong (LR 3)	No follow-up
Hansen et al. 1983 [172]	20 patients 81% women 46-78 years old Mean age: 60.6	Group A (n=10): 1. traditional Chinese acupuncture 2. placebo acupuncture Group B (n=10): 1. placebo acupuncture 2. traditional Chinese acupuncture.	Daily pain	High disability	Facial pain	Yangbai (Gall Blader 14), Taiyand (Extra 2), Waiguan (Sanjiao 5), Sibai (stomach 2), Juliao (stomach 3), Hegu (Large intestine 4), Jiache (Stomach 6), Xiaguan (Stomach 7) and Neiting (Stomach 44)	No follow-up
Itoh et al. 2012 [173]	16 patients 31% women 19-24 years old	Group A (n=7): acupuncture Group B (n=8): sham acupuncture	Pain intensity (VAS) Maximal mouth opening (mm)	High disability	TMD of muscular origin	Ashi points	10 weeks

Iunes et al. 2015 [174]	44 patients 93% women Mean age: Group A: 21.61 ±3.27 Group B: 20.87 ±1.50	Group A (n=31): auriculotherapy Group B (n=13): AA sham	Mobility evaluation of the mouth movements Intensity of pain (VAS)	Low disability	TMD with anxiety	Shen men, rim, sympathetic, brain stem and (TMJ) points	6 weeks
Johansson et al. 1991 [175]	45 patients	Group A (n=15): acupuncture Group B (n=15): splint Group C (n=15): control	Pain (VAS) TMJ sounds	Low disability	TMD of muscular origin	Large intestine 4 (Li4)	3 months
Kang et al. 2012 [176]	42 patients 26% women 18-71 years old Mean age: Group A: 31.43 ±12.48 Group B: 32.14 ±18.96 Group C: 30.14 ±11.41	Group A (n=14): adjacent point acupuncture Group B (n=14): distant point acupuncture Group C (n=14): combination group	Pain intensity (VAS)	Unclear (low disability)	TMD	TE17, GB20, ST7, ST6, SI19, and EX21	4 weeks
Kim et al. 2006 [177]	31 patients 77.42% women	Group A: distance acupuncture Group B: Chuna (Distraction & Translation technique)	Modified Craniomandibular Index (mCMI)	Unclear	TMD	No information	No information
Kütük et al. 2019 [158]	40 patients 72.5 % women 21–54 years old Mean age: 33.8 ±8.1	Group A (n=20): botulinum toxin-A Group B (n=20): dry needling	Pain (VAS) Crepitation (present or absent) Maximum mouth opening (mm)	Low disability	TMD of muscular origin	No information	6 weeks
List et al. 1992 [178]	110 patients 79.% women 19-76 years old	Group A (n=40): acupuncture Group B (n=40): stabilization splint Group C (n=30): waiting list	Pain diary: pain intensity (VAS) TMJ sounds	High disability	TMD of muscular origin	Ex2, St 7, St 6, Gb 20	12 months
Lopez-Martos et al. 2018 [179]	60 patients 87% women 18-62 years old Median age: 39	Group A (n=20): percutaneous needle electrolysis Group B (n=20): deep DN Group C (n=20): sham needling procedure	Pain at rest and pain on mastication (VAS) Maximum interincisal opening (mm)	Low disability	TMD of muscular origin	TPs	28, 42 and 70 days
Ma et al. 2010 [180]	43 patients 51% women Mean age: Group A: 42.3 ±5.1 Group B: 42.2 ±5.3 Group C: 42.6 ±4.9	Group A (n=15, 28 TrPs): miniscapel-needle MSN + self-neck-stretching exercises Group B (n=15, 30 TrPs): acupuncture + self-neck-stretching exercises Group C (n=13, 25 TrPs): self-neck-stretching exercises only	Pain intensity (VAS)	Unclear (high disability)	TMD of muscular origin	Trigger points	2 weeks and 3 months
Madani et al. 2020 [181]	45 patients 71% women 25-71 years old Mean age: 38 ±15.3	Group A (n=15): low-level laser therapy (LLLT) Group B (n=15): laser acupuncture therapy (LAT) Group C (n=15): (placebo) sham laser	Mouth opening and the range of protrusive and lateral excursive movements (mm) Pain intensity (VAS)	Low disability	TMD of muscular origin and/or arthrogenic origin	ST6, ST7, LI4	1 month
McMillan et al. 1997 [182]	30 patients 100% women 23-53 years old	Group A (n=10): Frocaine + simulated dry needling Group B (n=10): dry needling + simulated local anaesthetic Group C (n=10): control (simulated local anaesthetic + simulated dry needling)	Pain intensity (VAS)	Low disability	TMD of muscular origin	n.a.	No follow-up

Özden et al. 2020 [183]	60 patients 52% women	Group A (n=20): needling group Group B (n=20): dryneedling group Group C (n=20): control group (healthy participants)	Pain (VAS) Maximal jaw opening (mm)	Unclear (low disability)	TMD of muscular origin	Trigger points in the masseter	6 weeks
Ritenbaugh et al. 2012 [184]	168 patients 86.1% women Mean age: Group A: 42.9 ±13.0 Group B: 42.3 ±13.5 Group C: 43.7 ±12.4	Group A (n=39): TCM Group B (n=40): self-care Group C (n=88): self-care, not randomized	Facial pain (0–10) Depression (PHQ2)	High disability	TMD	ST7 and/or ST6, GB20 and/or GB21, "yintang", LI4, LV3	18 weeks
Ritenbaugh et al. 2008 [185]	160 patients 100% women 25-55 years old Mean age: Group A: 40.1 ±8.5 Group B: 40.6 ±9.2 Group C: 40.5 ±9.4	Group A (n=50): TCM Group B (n=50): naturopathic medicine Group C (n=60): specialty care	Muscle activity at mouth opening, closing, and clenching	High disability	Concomitant diagnoses of multiple chronic systemic health problems and/or chronic fatigue and fibromyalgia	ST7 and/or ST6, GB20 and/or GB21, yintang, LI4, LV3	3 months
Rodrigues et al. 2019 [186]	89 patients 100% women 18–60 years old Mean age: 31.94 ±9.57	Group A (n=34): active laser (auriculotherapy) Group B (n=33): placebo laser Group C (n=30): control	Pain intensity (VAS)	Low disability	TMD of muscular origin	Shen-men (1-C), TMJ (43-E), heart (60-CL) and the ear of the dominant side of the body	1 month
Schmid-Schwap et al. 2006 [187]	23 patients 100% women Mean age: Group A 35 ±14 (17-59 years old) Group B 40 ±14 (23-68 years old)	Group A (n=11): acupuncture Group B (n=12): sham laser	Subjective pain (VAS) Mouth opening (mm)	Low disability	TMD of muscular origin	Maxilla and mandible retromolar region, mandible, and maxilla vestibular region Extraoral points: IG4, ID2 and ID3	No follow-up
Şen et al. 2020 [188]	49 patients 94% women Mean age: Group A: 41.56 ±17.1 Group B: 39.09 ±16.52	Group A (n=22): acupuncture on specific points Group B (n=27): acupuncture on non-specific points	Pain(CPI) Maximum corrected active mouth-opening without pain Depression	Low disability	TMD of muscular origin and/or arthrogenic	Local: BL2, BL3, SI19, ST7, and TE21 Distal: BL34 and SI3	5 weeks
Shen et al. 2007 [189]	15 patients 93% women Mean age: 43.1 ±13.6	Group A (n=9): acupuncture Group B (n=6): sham acupuncture	General pain (NRS) Pain (VAS)	Unclear (low disability)	TMD of muscular origin	Hegu Large Intestine 4 acupoint	No follow-up
Shen et al. 2009 [190]	28 patients 100% women Mean age: Group A: 36.94 ±13.82 Group B: 44.83 ±11.61	Group A (n=16): acupuncture Group B (n=12): sham acupuncture	Masseter muscle pain (VAS)	High disability	TMD of muscular origin	LI4	No follow-up
Simma et al. 2009 [191]	23 patients 100% women 18-64 years old	Group A (n=11): acupuncture Group B (n=12): sham laser	Pain (VAS)	Low disability	TMD of muscular origin	Ashi points or trigger points	No follow-up

Smith et al. 2007 [192]	27 patients 89% women Mean age: 40.5 ±13.63	Group A (n=15): acupuncture Group B (n=12): sham acupuncture	Pain intensity (VAS) Incisor opening and lateral movement measurement(mm) TMJ sounds (stereo stethoscope)	Unclear (high disability)	TMD of muscular origin	E7	1 month
Speer et al. 2013 [193]	30 patients 67% women 24-60 years old Mean age: Group A: 30.8 Group B: 32.6	Group A (n=15): acupuncture + splint therapy Group B (n=15): splint-therapy	Muscle activity at mouth opening, closing, clenching Pain (VAS)	High disability	TMD of muscular origin	Mg 6-8, Dü 3, Dü 19, Gb 2, SJ 21	No follow-up
Taşkesen et al. 2020 [194]	45 patients 13% women 18–54 years old Mean age: 25.9	Group A (n =15): Masseter Nerve block Group B (n =15): needling therapy Group C (n=15): trigger point injection with LA	Pain on function MMO (mm)	Unclear (low disability)	TMD of muscular origin	No information	12 weeks
Uemoto et al. 2013 [195]	21 patients 100% women 20-52 years old	Group A (n=7): infrared laser Group B (n=7): dry needling Group C (n=7): control	Pain (VAS) MMO (mm)	Low disability	TMD of muscular origin	Trigger points located in the right and left masseter muscles	No follow-up
Vera Zotelli et al. 2017 [196]	40 patients 80% women 20-50 years old Mean age: 36.5 ±8.6	Group A (n=20): acupuncture Group B (n=20): sham treatment	Pain (NVAS) Mouth opening limitation (1) unassisted painless mouth opening (2) unassisted mouth opening (3) assisted mouth opening (mm)	Low disability	TMD of muscular origin or mixed origin	ST6, ST7, SI18, GV20, GB20, BL10, and LI4	4 weeks
Vicente-Barrero et al. 2012 [156]	120 patients 85% women 18-58 years old Mean age 39	Group A (n=10): acupuncture Group B (n=10): decompression splint	Pain (VAS) Measurements of mouth opening and jaw lateral deviation (mm)	Low disability	TMD of muscular origin	Local acupoints: EX-HN5, SJ 21, GB2, SJ17, ST6 Distal acupoints: LI-4, ST-36, SJ5 and GB34	30 days

3.1.4.2 Characteristics of the population used in the studies

3.1.4.2.1 TMD diagnoses of the participants of the included studies

It is evident that a large proportion of the studies (28 studies) falls into the category of TMD with muscular origin [156, 158-165, 167-169, 173, 175, 178-180, 182, 183, 186, 187, 189-195]. Figure 3 categorises the type of TMD of the subjects from the included studies. From the study of Schmid-Schwap et al. 2006, one can deduct from the inclusion criteria and the evaluation of the sample, that the patients had myofascial pain. 18% of the included studies did not give an exact definition of TMD, or did not limit the type of TMD to a specific combination of TMD types at the beginning of the study, so that subjects were allowed to present several types of different painful TMD to be included in the study (seven studies) [171, 172, 174, 176, 177, 184]. Five studies included TMD of muscular origin and/or arthrogenic origin [166, 170, 181, 188, 196].

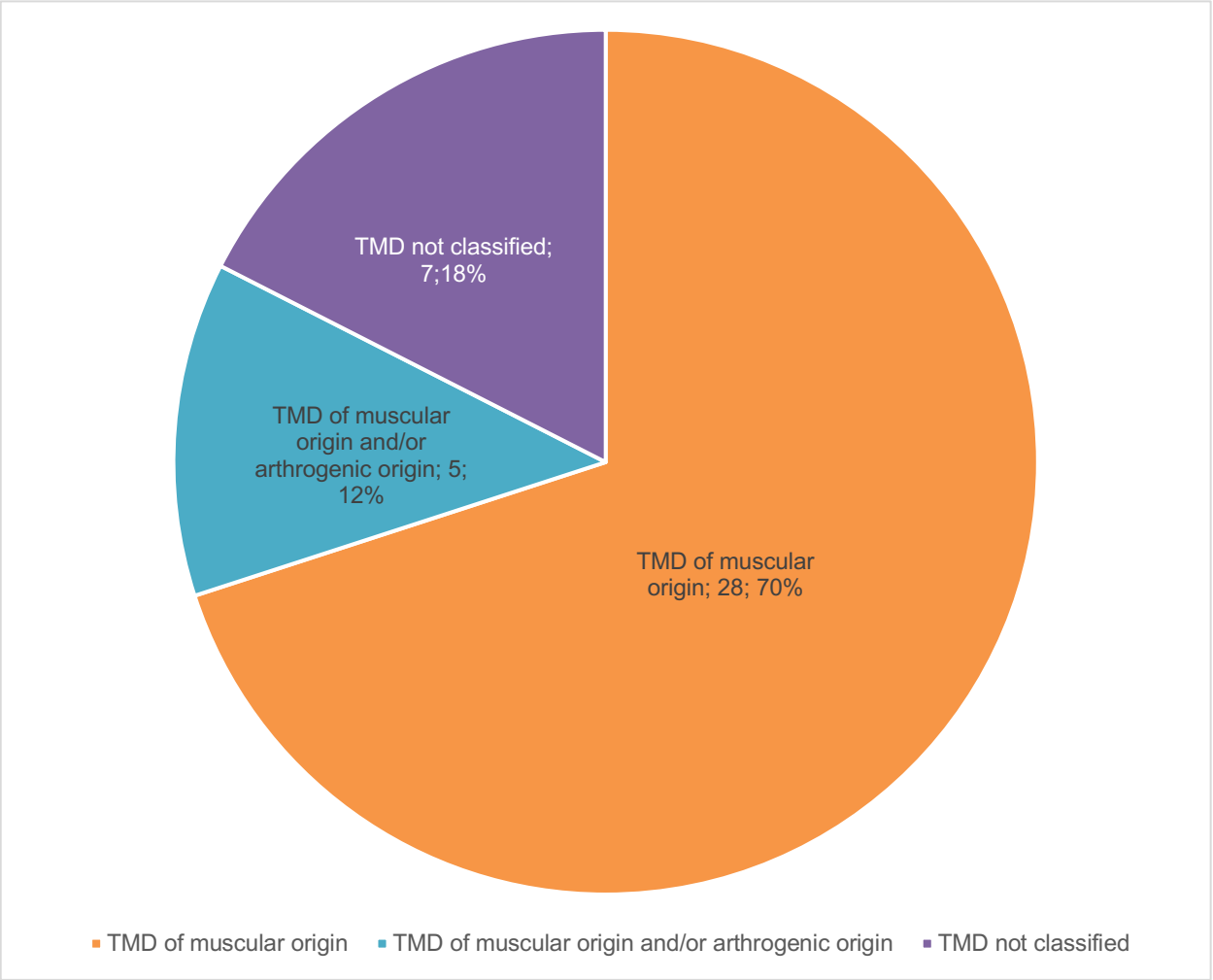


Figure 3: Pie chart presenting the different TMD diagnoses from the included studies on acupuncture therapy (X) with the number of studies included (Y) and the percentage (Z); (X;Y;Z).

3.1.4.2.2 Grade of TMD pain chronification

The degree of TMD pain chronification presented by the patients formed the focus of the present work. The following categories were formed for acupuncture interventions (Figure 4):

- Patients with evidence of a low disability (acute or acute/persistent) pain
- Patients with evidence of high disability pain
- Patients with some evidence of low disability pain (referred to below as: unclear (low disability))
- Patients with some evidence of high disability pain (referred to below as: unclear (high disability))
- Patients with minimum degree of chronicity (referred to below as: unclear)

Most of the publications delivering acupuncture were treating patients with evidence of low disability pain [156, 158-167, 169, 170, 174, 175, 179, 181, 182, 186-188, 191, 195, 196]. Six publications were unclear but with a probability they were diagnosed with low disability pain [168, 171, 176, 183, 189, 194]. Gonzales-Perez et al. 2015 excluded patients suffering from migraine and tension headaches. Han et al. 2015, included patients with short term of pain recorded (34.4 days). Kang et al. 2012 [176] excluded patients if they scored less than four points (or four cm) on the Temporomandibular Function scale and on the VAS. Özden et al. 2020 only included patients with localized pain, Shen et al. 2007 excluded patients with current opioid use; metabolic disease (e.g., diabetes, hyperthyroidism); coagulopathies (e.g., haemophilia, anticoagulants); neurological disorders (e.g., dyskinesia, trigeminal neuralgia) or vascular disease (e.g., migraine, hypertension) and Teskesen et al. 2020 included patients with no history of any invasive procedures in related masseter muscle in the last two years. Seven studies examined patients suffering from high disability pain [173, 178, 184, 185, 190, 193, 197]. On the other hand, two authors included patients with a likelihood of high disability pain [180, 192]. Ma et al. 2010 included patients with extensive pain duration (6 months up to 5 years) and Smith et al. 2007 included patients suffering from headaches in addition to TMD. Out of the 40 studies included, only one publication was unclear about which type of pain the patients were suffering from according to our categories [177].

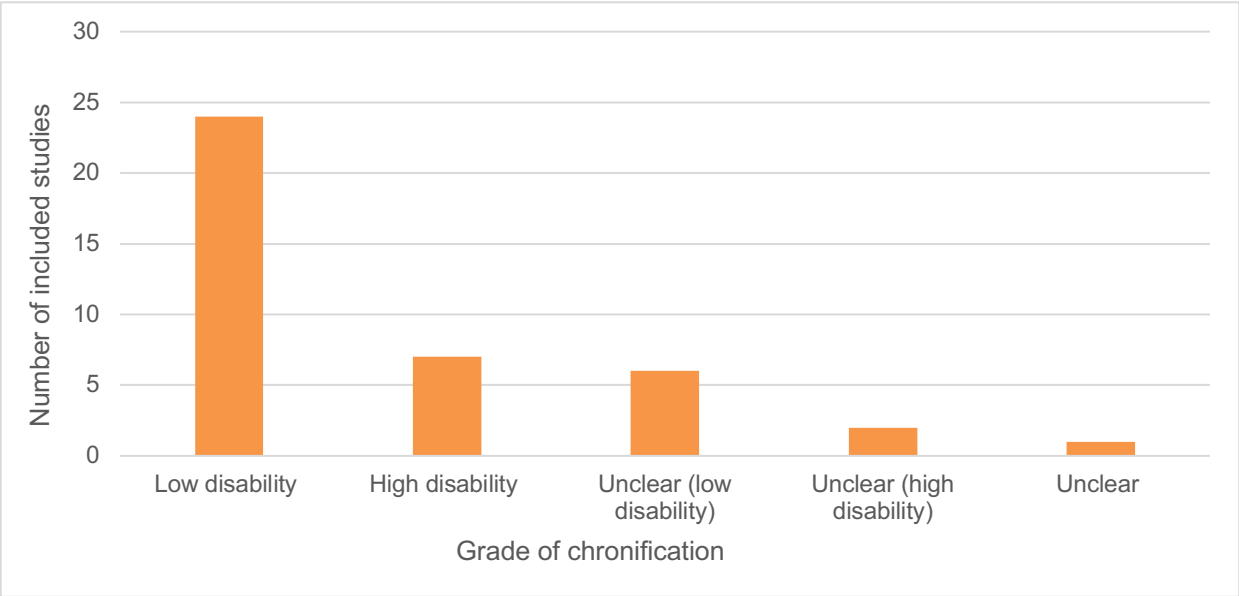


Figure 4: Grade of chronification of the included studies in acupuncture interventions

The participants of the 40 included RCTs were classified according to the indications mentioned above (Figure 5). Several of the studies examined provided multiple clues to the patients' level of chronicity. Consequently, the indications could support or contradict each other. For this reason, the priority list was used for the final basis for classification. In the following table, the priorities of the indications, as well as the studies that was applicable to them, are displayed in Table 6.

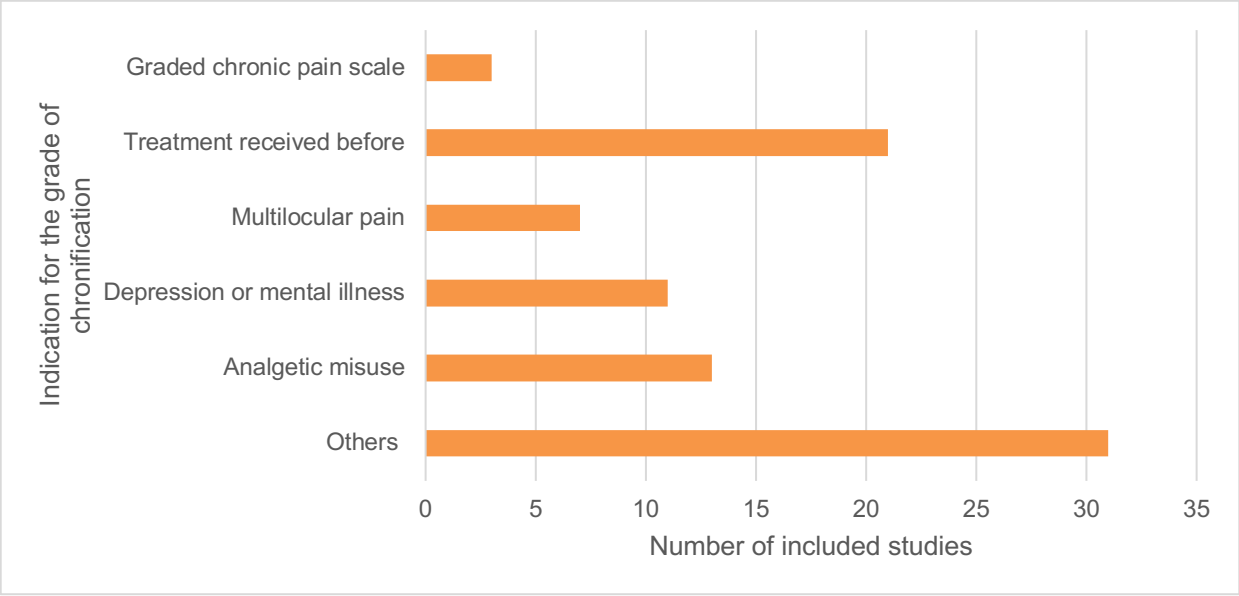


Figure 5: Hints of the degree of chronification, found in the included studies for acupuncture; GCPS= Graded Chronic Pain Scale

Table 6: Indications of the degree of chronification, found in the included studies for acupuncture

Indications	Low disability	High disability	Unclear (low disability)	Unclear (high disability)
Graded chronic pain scale	Grillo 2015 Rodigues 2019 Şen 2020			
Treatment received before	Dalewski 2019 De Salles-Neto 2020 Faria 2014 Fernández-Carnero 2010 Ferreira 2013 Goddard 2002 Grillo 2015 Grillo 2018 Johansson 1991 Kütük 2019 Madani 2020 Rodrigues 2019 Schmid-Schwap 2006 Simma 2009 Uemoto 2013 Vicente-Barrero 2012	Hansen 1983 List 1992 Ritenbaugh 2008 Ritenbaugh 2012 Speer 2013		
Multilocular pain	Faria 2014 Goddard 2002 Simma 2009	List 1992 Ritenbaugh 2008 Ritenbaugh 2012	Özden 2020	
Depression or mental illness	Aksu 2019 Dalewski 2019 Dıraçoğlu 2012 Goddard 2002 Ferreira 2015 Johansson 1991 Lopez-Martos 2018 Madani 2020 Rodrigues 2019 Vicente-Barrero 2012	List 1992 Ritenbaugh 2008 Ritenbaugh 2012		
Analgetic misuse	De Salles-Neto 2020 Faria 2014 Ferreira 2015 Grillo 2018 Iunes 2015 Madani 2020 McMillan 1997 Rodrigues 2019 Uemoto 2013 Vera Zotelli 2017	Itoh 2012 List 1992 Shen 2009		
Others	Aksu 2019 Dalewski 2019 De Salles-Neto 2020 Faria 2014 Fernández-Carnero 2010	Hansen 1983 Itoh 2012 List 1992 Shen 2009 Speer 2013	Gonzalez-Perez 2015 Han 2015 Özden 2020 Shen 2007	Smith 2007 Ma 2010

Indications	Low disability	High disability	Unclear (low disability)	Unclear (high disability)
	Ferreira 2013 Ferreira 2015 Grillo 2015 Johansson 1991 Kütük 2019 Lopez-Martos 2018 Madani 2020 McMillan 1997 Schmid-Schwap 2006 Şen 2020 Simma 2009 Uemoto 2013 Vera Zotelli 2017	Ritenbaugh 2008 Ritenbaugh 2012		

3.1.4.2.3 Recruitment of the subjects

25 of the 40 studies were assigned to tertiary care. This corresponds to a sample of 1087 subjects, but independent of control groups, the diagnostic instrument used, the outcomes measured and the study duration. The subjects were mainly treated in their respective clinic or were referred to this clinic and therefore were included in the respective study. Another 509 subjects from seven studies came from specialized TMD clinics. 172 patients from five studies were recruited from the general population or from dental practices and were thus assigned to primary care. Three trials did not have a description of the care level patients received.

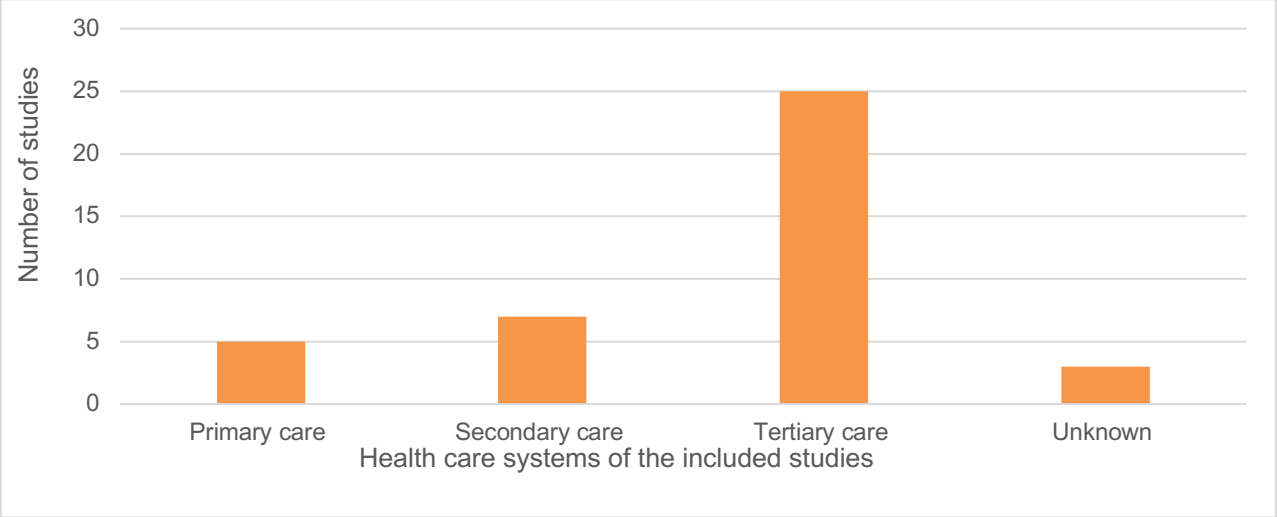


Figure 6: Recruitment of subjects in the included studies of acupuncture

3.1.4.3 Characteristics of interventions

3.1.4.3.1 Outcomes

3.1.4.3.1.1 Primary Outcome – pain at rest

Pain intensity was measured in 33 out of 40 trials using visual analogue scales (VAS). There were several exceptions namely, Şen et al. 2020, who measured pain intensity using the characteristic pain intensity (CPI), Goddard et al. 2002 [167] who measured the change in the masseter muscle pain (VAS), Fernández-Carnero et al. 2010 [164] and Ritenbaugh et al. 2012 who measured facial pain using the NPRS (0-10). Grillo et al. 2008 [170] used the VAS but measured the pain intensity experienced during the needling procedure and could not be added to the meta-analysis as this would interfere with the results. We also had to exclude Hansen et al. 1983 from the meta-analysis because the authors used the period index (PI) (PI=OxA+1xB+2xC+3xD) to measure daily pain. Kim et al. 2006 measured the modified Craniomandibular Index (mCMI).

3.1.4.3.1.2 Secondary outcomes

15 RCTs investigated the MMO measured in millimetres [156, 158, 160, 168, 169, 173, 174, 179, 181, 183, 187, 192-195]. Unassisted jaw opening without pain measurement (mm) was described by five studies [159, 163, 164, 188, 196]. Ten studies investigated pain upon palpation [156, 158, 160, 171, 175, 176, 181, 187, 191, 194]. Three studies examined TMJ sounds [175, 178, 192] and one crepitation (present or absent) [158]. The studies of Ritenbaugh et al. 2012 and Şen et al. 2020 included depression scores. Rithenbaugh et al. 2012 used the Patient Health Questionnaire-2 (PHQ2). No RCT investigated somatization.

3.1.4.3.2 Types of acupuncture interventions

Overall, an initial distribution of the investigated intervention types (Figure 7) was formed into two main blocks, acupuncture, and dry needling. 21 studies examined the effect of acupuncture [156, 162, 167, 169-173, 175-177, 180, 187-193, 196] and 12 used dry-needling as intervention [158-161, 163, 164, 168, 179, 182, 183, 194, 195].

Two studies work with laser acupuncture [166, 181] and three studies analysed ear acupuncture [165, 174, 186]. TCM was investigated by two publications [184, 185].

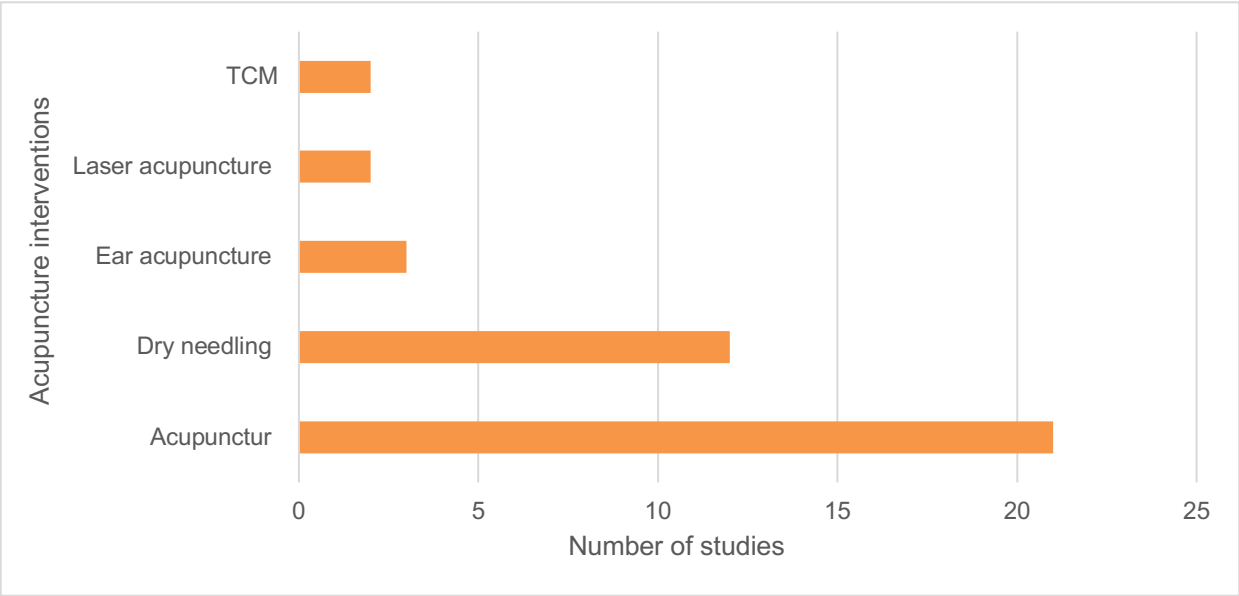


Figure 7: Acupuncture interventions used in the included studies

3.1.4.3.3 Control groups

The interventions in the control groups varied (Figure 8). For example, occlusal splint [156, 161, 165, 169, 178, 186, 193, 198], sham acupuncture [162, 164, 167, 170, 173, 174, 176, 188-190, 192, 196, 197], sham dry needling [159, 163, 179, 194], sham laser treatment [181, 187, 191, 195], medication [158, 161, 168, 182, 194], self-care [184, 185], exercise training [160, 180], no treatment [175, 178, 183], medicated cupping [171] and Chuna therapy [177].

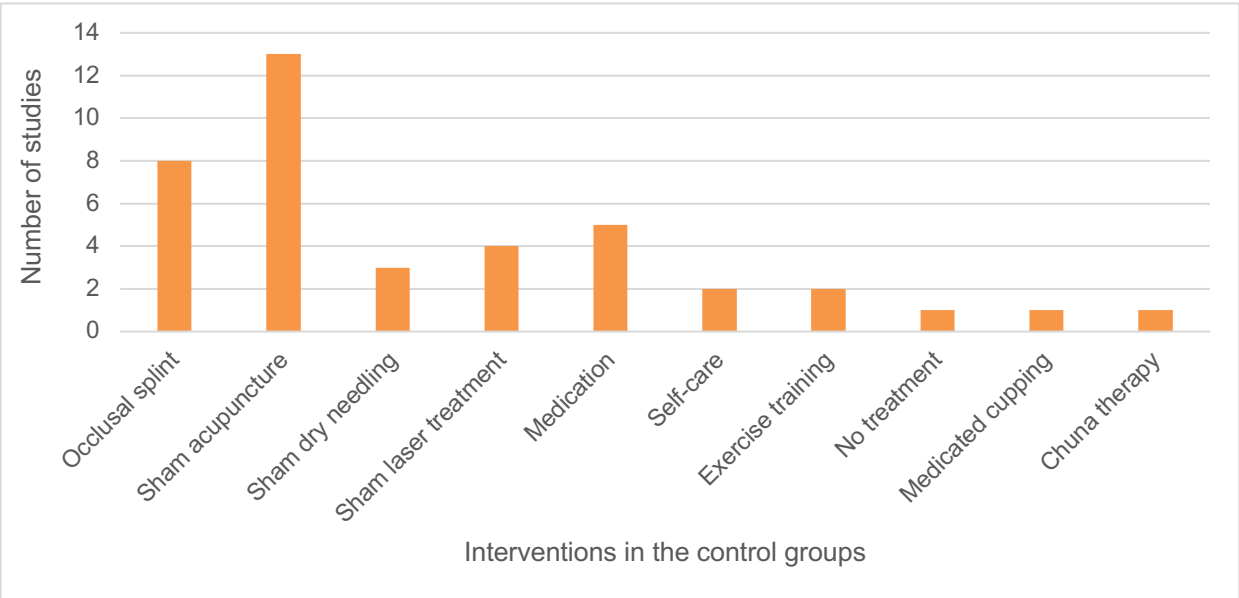


Figure 8: Bar chart of the different interventions serving as controls for acupuncture interventions

3.1.4.3.4 Follow up periods

39 of the studies evaluated the effects of short-term acupuncture treatment. The remaining study [178] evaluated the short and long-term effects, as they re-evaluated the patients at 6

months and 1 year after the study was completed. The study conducted by List et al. was the only study one to show positive long-term effects.

3.1.4.3.5 Treatment sessions

In terms of the technical aspects of the acupuncture treatment used in the RCT, the duration of each session varied between 15 [173, 189, 190, 197], 20 [160-162, 169, 170, 183-185, 187, 192, 196], 30 [156, 167, 175, 178] and 45-50 minutes [166, 188]. 20 minutes being the most common duration for the studies that were reviewed.
15 studies provided no information on the session time [158, 159, 163, 164, 166, 168, 171, 176, 177, 179, 180, 182, 193-195].

3.1.4.3.6 Acupoints

The acupuncture points applied went from proximal points, which are those found in specific anatomic areas of the cranio-cervical-mandibular area ST 6 [156, 166, 167, 170, 176, 178, 181, 184, 185, 196], ST 7 [170, 176, 178, 181, 184, 185, 188, 192, 196], GB 20 [162, 166, 169, 170, 176, 178, 181, 184, 185, 196], EX 2 [176, 178], to distal points, which are mainly found on the upper LI 4 [156, 162, 165-167, 169-171, 175, 176, 178, 181, 184, 185, 187, 189-191, 196, 197], MA 6 [162, 193], SI 2 [187], SI 3 [187, 188] and lower extremities ST 36 [156, 178]. Shen-men piercing was applied in three studies [165, 174, 186].

3.1.4.3.7 Insertion of the needles used

Only 14 of the studies described how deep the needles were inserted [156, 167, 173, 180, 183-185, 188-190, 192, 195, 197]. This insertion depth varied from five to 35mm.

3.1.4.3.8 Adverse effects

Only two trials reported data on adverse effects [188, 199] of acupuncture treatment.

3.1.5 Excluded studies

50 studies were excluded for reasons which are declared in the corresponding table (APPENDIX VIII: Characteristics of studies under Characteristics of excluded studies: Acupuncture)

3.1.6 Assessment of the methodological quality of the included studies

According to this study's two reviewers' analysis, 33 of the study methodologies received no high risk of bias in terms of quality [158-160, 162-167, 169-171, 174, 177, 179-191, 193-198]. Seven trails had one high risk of bias in the assessment of the methodological quality [156, 161, 168, 173, 176, 178, 192]. The evaluation of these trials was rated with a high risk of bias according to the Cochrane Collaboration's risk of bias tool because of the following reasons: There was a baseline imbalance in the study groups in the studies of List et al. 1992 [178] and Smith et al. 2007 [192]. Itoh et al. 2012 [173] considered not adding the drop out data. The outcomes in the trials by Vincente-Barrero et al. 2012 [156], Dalewski et al. 2019 [161], Gonzalez-Perez et al. 2015 [168], were insufficiently reported; Gonzalez-Perez et al. 2015 [168] also had a significant number of withdrawal study subjects (eight patients), with the main reason for dropping out due to personal difficulties associated with patients keeping their scheduled appointments. Kang et al. 2012 [176] described the limitation due to the lack of allocation concealment, possibly leading to bias related to foreknowledge of the treatment assignment. In the case of studies with different therapies as control groups, neither blinding of the examiner nor blinding of the participants and staff was considered relevant, because of technical difficulties. On the other hand, the studies which compared acupuncture with sham acupuncture or placebo the blinding of the participants was expected. The blinding of participants was effectively reported in 16 studies [159, 162, 164, 166, 167, 170, 173, 181, 186-192, 196], Simma, Gleditsch et al. 2009 blinded also the personnel. Six studies failed in achieving the task of blinding [156, 163, 174, 177, 195, 197].

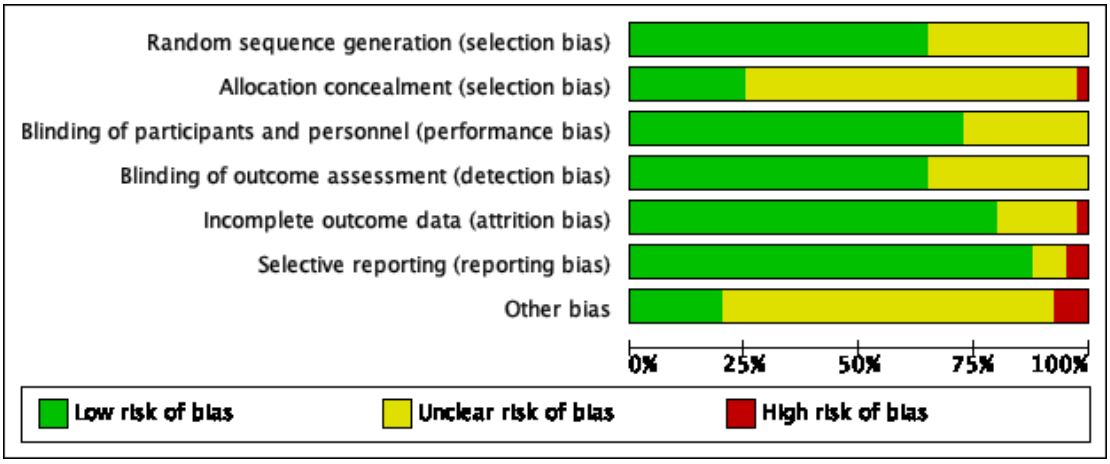


Figure 9: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 10: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

3.1.7 Results of the quantitative synthesis of the included studies (Meta-analysis)

In this section, statistically significant or not statistically significant but relevant results are described. We had to limit ourselves in this area, as the presentation of all results would have been beyond the scope of this work. The remaining forest plots with further results from this study are presented in *APPENDIX IX: Forest plots*. The author decided to only include meta-analysis with a minimum of three studies. For this reason, the author was not able to include eight studies because of the lack of included studies and the heterogeneity of the studies for acupuncture therapy.

For the meta-analysis, 19 RCTs were selected. Of the 40 included studies that were able to pass the full-text screening, a total of 21 studies were excluded for-quantitative comparison. The reasons for exclusion were as follows:

1. Combination of therapies used for the study group [160, 165, 171, 176, 193]
2. Missing data on the outcomes [156, 161, 177, 183]
3. Data collection/presentation was different from the other included studies [165, 166, 171, 174, 184, 185, 192]
4. Study group too small [164] (studies with fewer than seven subjects per intervention group)

A tabular overview of the statistically significant results for the pain group with low disability and with high disability is presented in 3.1.8. for the reduction of pain intensity (Table 7) and MMO (Table 8).

A SMD of zero indicates that the intervention group and the control group have equal effects. For pain reduction, an improvement is associated with lower values in the outcome measure. SMDs less than zero indicate that the intervention group is more effective than the control group. Therefore, a negative direction with lower values corresponds to better performance of the intervention group. Conversely, for MMO improvement, improvement is associated with higher values on outcome measures. A positive direction with higher values corresponding to better performance of the intervention group under study [200].

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guideline states that a 30% pain reduction in chronic pain is necessary to distinguish placebo from verum [201]. This means that the initial pain intensity is considered clinically relevant in clinical studies and the interventions are evaluated as effective in this respect [202]. To

obtain the clinical significance, the author added a small comment on each forest plot obtaining the data from the pain reduction from the baseline compared to the follow up time.

3.1.7.1 Comparison: Effectiveness of acupuncture treatment in comparison with control groups (placebo and other treatment included) on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.1.7.1.1 Primary outcome parameter: pain intensity

3.1.7.1.1.1 Short-term efficacy (treatment duration up to six months)

The effect of acupuncture compared to any control (placebo and other treatment included) in the period up to six months following the start of treatment is demonstrated in Figure 11. Each bar of the forest plot represents the values of the individual studies. Studies with diamonds aligned to the left favour the effect of acupuncture treatment whereas studies with diamonds aligned to the right favour the control intervention. Using the x^2 test, a significant (p=0.02) and moderate heterogeneity of x^2=27.39 (I^2=60%) was calculated. The studies were divided into the following subgroups based on the descriptions of the subjects from the publications or from information acquired directly from the authors: subjects with low disability pain (labelled "low disability" in the Forest Plot), subjects with high disability orofacial pain (labelled "high disability" in the Forest Plot) and subjects with unclear pain chronification level (labelled "unclear" in the Forest Plot).

A total of 12 studies with 385 participants were included in this comparison. Nine trials with a total of 262 participants included patients with low disability orofacial pain. Three trials dealt with high disability pain (n=123 participants), and none were placed in the unclear pain group.

Overall, a statistically significant bigger treatment effect was seen in the acupuncture group for a short period (up to six months) following the start of treatment (SMD=-0.39; 95% CI [-0.73, -0.05]; p=0.02; I^2=60%) regarding pain relief. The low disability pain group (SMD=-0.37; 95% CI [-0.80, 0.06]; p=0.09; I^2=65%) and the high disability pain group (SMD=-0.48; 95% CI [-1.14, 0.18]; p=0.15; I^2=57%) showed no significant difference in the reduction of pain. The overall heterogeneity (I^2=60%) was moderate.

By excluding the one study (Şen et al. 2020) that used a different pain intensity measurement instrument (CPI) than the other included studies that used the VAS and used acupuncture only with non-specific acupuncture points as a control group, the author obtained a lower overall heterogeneity (I^2=57%) and a statistically significant interesting result for the low disability pain group (SMD=-0.47; 95% CI [-0.92, -0.01]; p=0.04; I^2=62; Figure 12).

A clinical significance of 30% pain reduction was observed in the intervention group in the following studies: de Salles-Neto et al. 2020, Goddard et al. 2002, Grillo et al. 2015, Johansson et al. 1991, Schmid-Schwap et al. 2006, Şen et al. 2020, Simma et al. 2009, Vera et al. 2017, Itoh et al. 2012 and List et al. 1992. In the studies of Shen et al. 2007, and 2009 no clinical significance of pain reduction was observed.

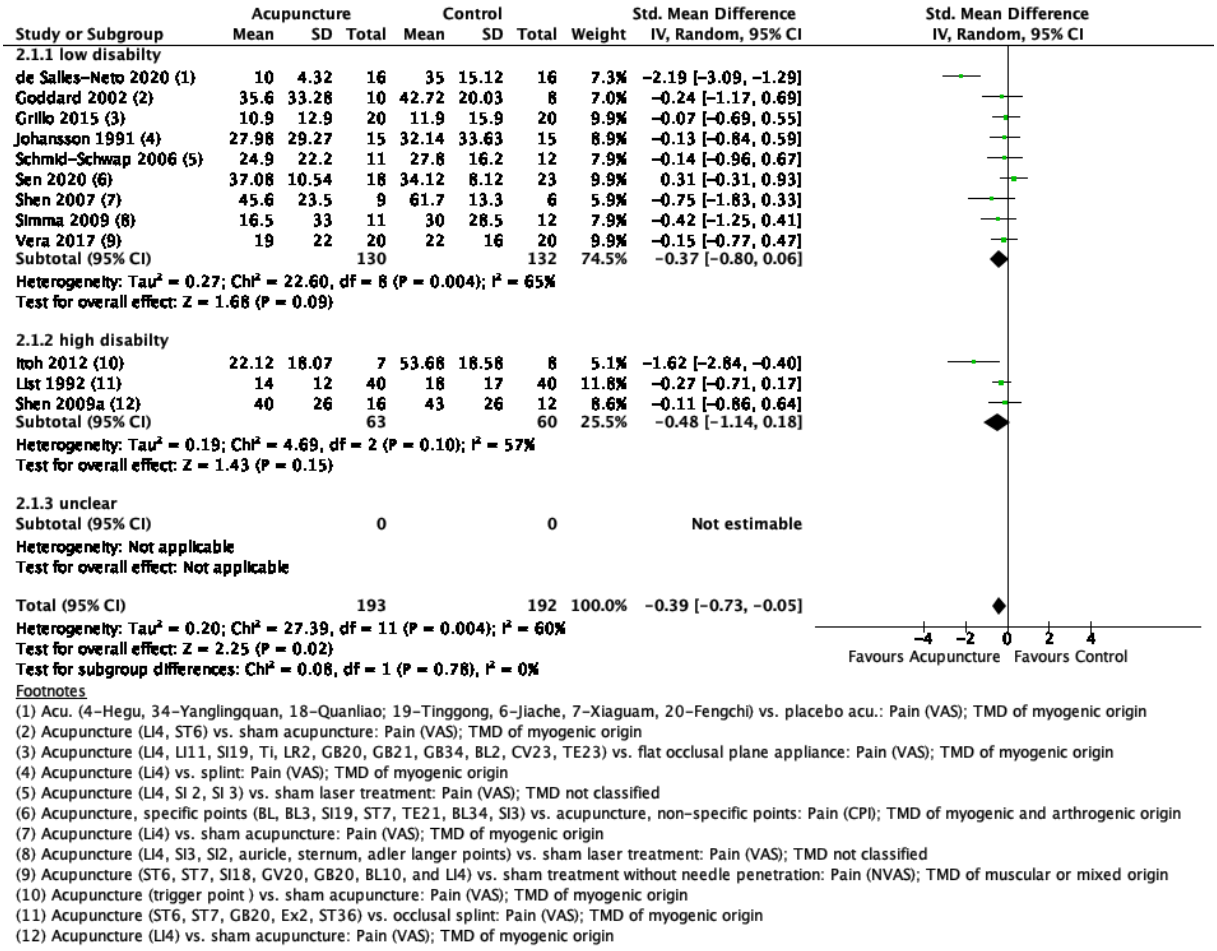


Figure 11: Acupuncture vs. any control (outcome: change in pain intensity; timeframe: less than six months); low disability= acute pain; high disability = chronic pain; unclear = pain not identified

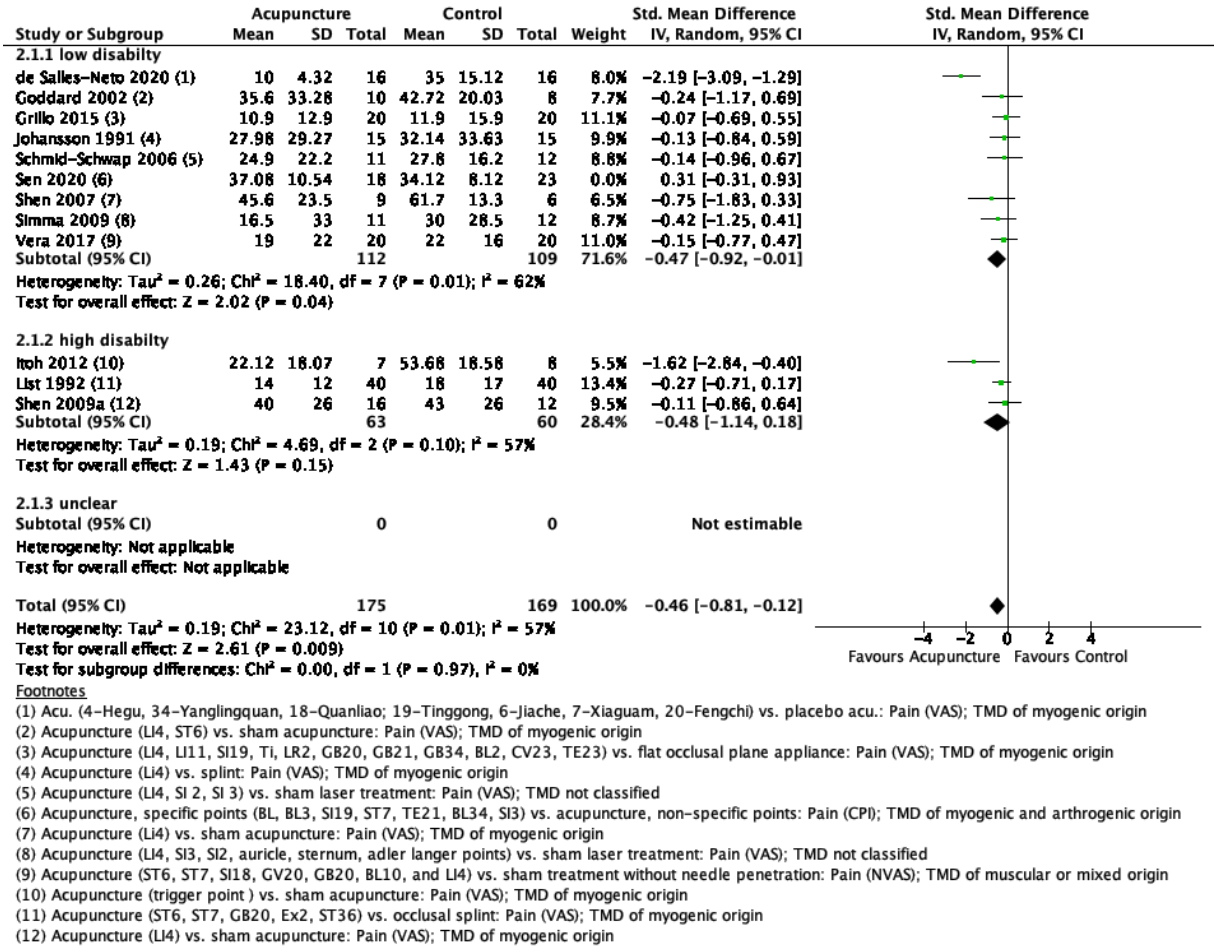


Figure 12: Acupuncture vs. any control (outcome: change in pain intensity; timeframe: less than six months); low disability= acute pain; high disability = chronic pain; unclear = pain not identified; Şen et al. 2020 being removed

3.1.7.1.2 Secondary outcome parameter: MMO

3.1.7.1.2.1 Short-term efficacy (treatment duration up to six months)

The comparison between those groups that received acupuncture treatment versus control groups regarding improvement of MMO in the short term was based on five studies with a total of 159 participants. The results showed no statistically significant difference between acupuncture and the control group (n=5 studies [n=76 for Group A, and n=83 for Group B], SMD=0.30; 95% CI [-0.01, 0.62]; *p*=0.06; I^2=0%). The Figure 71 can be found in the APPENDIX IX: Forest plots. The Group A represents the investigated intervention (acupuncture), while Group B represents the control group (control).

3.1.7.2 Comparison: Effectiveness of acupuncture treatment in comparison to sham acupuncture on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.1.7.2.1 Primary outcome parameter: pain intensity

3.1.7.2.1.1 Short-term efficacy (treatment duration up to six months)

Acupuncture is no more effective than sham acupuncture in reducing pain intensity (n=8 studies [n=107 for Group A, and n=105 for Group B], SMD=-0.54; 95% CI [-1.11, 0.02]; p=0.06, I^2=73%) (Figure 72; APPENDIX IX: Forest plots). Group A represents the investigated intervention (acupuncture treatment), while Group B represents the control group (sham acupuncture). The results for low disability pain (n=6 studies [n=84 for Group A, and n=85 for Group B], SMD=-0.49; 95% CI [-1.17, 0.19]; p=0.16, I^2=77%) and high disability pain (n=2 studies [n=23 for Group A, and n=20 for Group B], SMD=-0.79; 95% CI [-2.25, 0.68]; p=0.29, I^2 =77%) were not significant although both groups showed the same tendency for the reduction of pain using acupuncture intervention.

In the studies by de Salles-Neto et al. 2020, Goddard et al. 2002, Schmid-Schwap et al. 2006, Şen et al. 2020, Vera et al. 2017 and Itoh et al. 2012, a clinical significance of 30% pain reduction was observed in the intervention group. The studies by Shen et al. 2007, and 2009, showed no clinical significance of pain reduction.

3.1.7.2.2 Secondary outcome parameter: Maximum mouth opening (MMO)

3.1.7.2.2.1 Short-term efficacy (treatment duration up to six months)

Acupuncture is not statistically significant more effective than sham acupuncture in increasing MMO (n=4 studies [n=56 for Group A, and n=63 for Group B], SMD=0.34; 95% CI [-0.03, 0.71]; p=0.07, I^2=0% (Figure 73; APPENDIX IX: Forest plots). Low disability pain (n=3 studies [n=49 for Group A, n=55 for Group B], SMD=0.32; 95% CI [-0.12, 0.75]; p=0.15, I^2=16%) may show a non-significant improvement in MMO in the short term (less than six months) using acupuncture interventions. However, here we only included three studies overall.

3.1.7.3 Comparison: Effectiveness of acupuncture treatment in comparison to other treatments on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.1.7.3.1 Primary outcome parameter: pain intensity

3.1.7.3.1.1 Short-term efficacy (treatment duration up to six months)

Acupuncture treatment has no statistically significant effect on reducing pain intensity compared to other treatments (n=4 studies [n=86 for Group A, and n=87 for Group B],

SMD=-0.22; 95% CI [-0.52, 0.08]; p=0.15, I^2=0% (Figure 74; APPENDIX IX: Forest plots). Low disability pain (n=3 studies [n=46 for Group A, and n=47 for Group B], SMD=-0.17; 95% CI [-0.58, 0.23]; p=0.40, I^2=0%).
Observing splint control only, no significant difference was found between the acupuncture and splint therapy regarding the reduction of pain (n=3 studies [n=75 for Group A, and n=75 for Group B], SMD=-0.19; 95% CI [-0.51, 0.13]; p=0.25, I^2=0%; Figure 75; APPENDIX IX: Forest plots).

For all the included the studies for this comparison [169, 175, 178, 191] a clinical significance of 30% pain reduction in the intervention group was observed.

3.1.7.4 Comparison: Effectiveness of dry needling–treatment in comparison with other treatments on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.1.7.4.1 Primary outcome parameter: pain intensity

3.1.7.4.1.1 Short-term efficacy (treatment duration up to six months)

In the meta-analysis of dry needling compared to any other treatment (Figure 13) no significant difference was observed between the interventions aimed at reducing pain intensity in the short term (n=9 studies [n=142 for Group A, and n=138 for Group B], SMD=-0.31; 95% CI [-0.79, 0.18]; p=0.21, I^2=73%). However, dry needling was shown to have a statistically significant bigger effect on reducing pain intensity compared to other treatments in the low disability group (n=7 studies [n=109 for Group A, and n=103 for Group B], SMD=-0.57; 95% CI [-1.03, -0.11]; p=0.02, I^2=60%). High disability pain (n=2 studies [n=33 for Group A, and n=35 for Group B], SMD=0.60; 95% CI [-0.12, 1.32]; p=0.10, I^2=52%) showed a tendency in favour of other treatments in reducing pain intensity in the short term (less than six months). A joint clinical significance of 30% pain reduction was observed in all intervention groups.

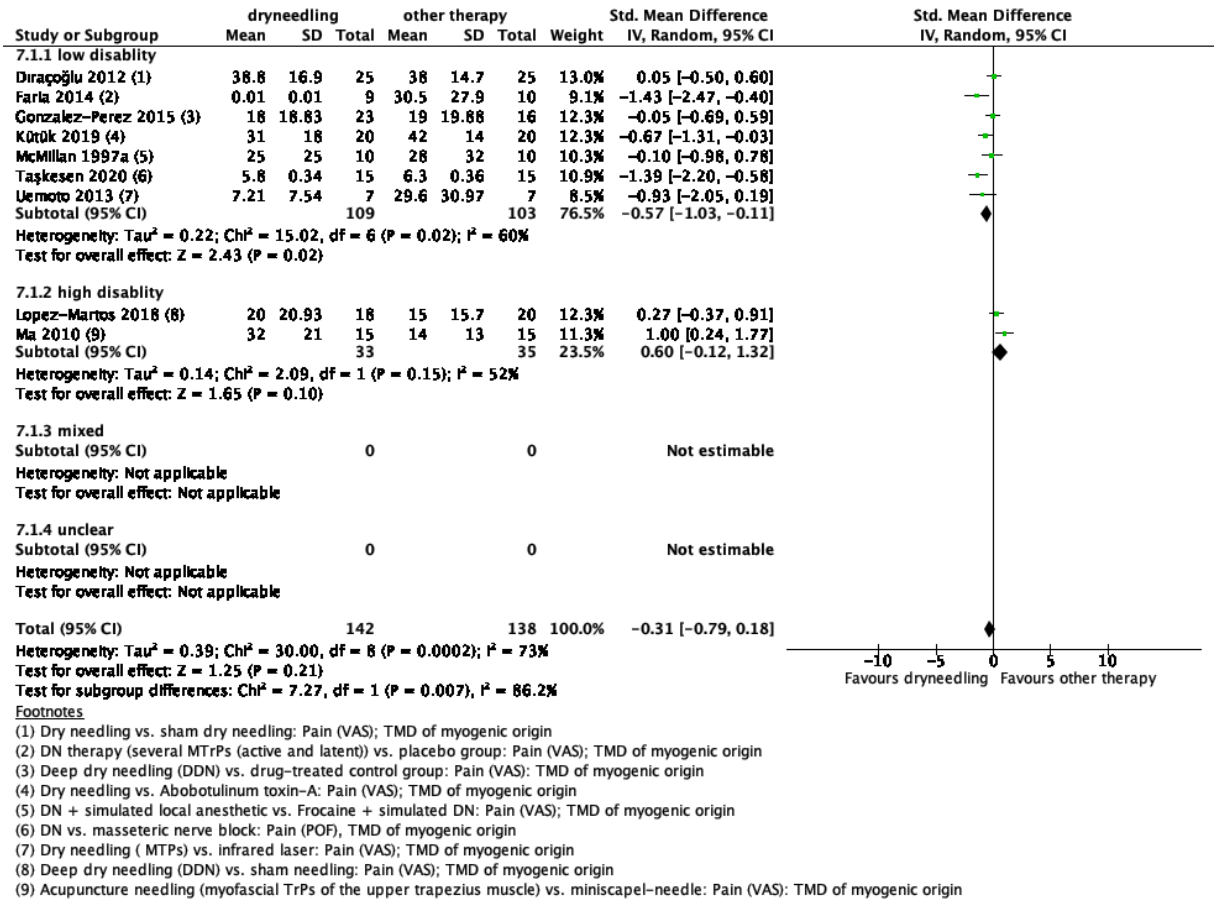


Figure 13: Dry needling vs. other treatment (outcome: change in pain intensity; timeframe: less than six months) low disability= acute pain; high disability = chronic pain; mixed = acute and chronic pain; unclear = pain not identified

3.1.7.4.2 Secondary outcome parameter: Maximum mouth opening (MMO)

3.1.7.4.2.1 Short-term efficacy (treatment duration up to six months)

Dry needling had no statistically significant different effect on the improvement of MMO compared to other treatments (n=6 studies [n=110 for Group A, and n=106 for Group B], SMD=-0.02; 95% CI [-0.29, 0.25]; p=0.89, I^2=0%) shown in Figure 76 in the APPENDIX IX: Forest plots.

3.1.8 Tabular overview of the results of the comparisons for acupuncture

The results of the comparisons performed for acupuncture interventions are listed in Table 7 for pain intensity and Table 8 for MMO.

Table 7: Tabular overview of the results of acupuncture regarding pain intensity categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval; VAS=visual analogue scale

Reduction of pain intensity		
Comparison	**Statistically significant results**	**Data**
Acupuncture vs. (any) control	Short-term: **ss for total pain**, no ss for low disability or high disability pain. ***Sensitivity analysis (Şen et al 2020) removed: ss for low disability pain.***	Short-term: Low disability: (SMD=-0.37; 95% CI [-0.80, 0.06]; *p*=0.09; I^2=65%) **Sensitivity analysis: Low disability: (SMD=-0.47; 95% CI [-0.92, -0.01]; p=0.04; I^2=62%)** High disability: (SMD=-0.35; 95% CI [-0.71, 0.01]; *p*=0.06; I^2=57%) **Total: (SMD=-0.30; 95% CI [-0.51, -0.10]; *p* =0.004; I^2=60%)**
Acupuncture vs. sham acupuncture	Short-term: no ss for low disability, high disability, or total pain.	Short-term: Low disability: (SMD=-0.49; 95% CI [-1.17, 0.19]; *p*=0.16; I^2=77%) High disability: (SMD=-0.79; 95% CI [-2.25, 0.68]; *p*=0.29; I^2=77%) Total: (SMD=-0.54; 95% CI [-1.11, 0.02]; *p*=0.06; I^2=73%)
Acupuncture vs. other treatment	Short-term: no ss for low disability or total pain.	Short-term: Low disability: (SMD=-0.17; 95% CI [-0.58, 0.23]; *p*=0.40; I^2=0%) Total: (SMD=-0.22; 95% CI [-0.52, 0.08]; *p*=0.15; I^2=0%) Sensitivity analysis: (SMD=-0.19; 95% CI [-0.51, 0.13]; *p*=0.25; I^2=0%)
Dry needling vs. other treatment	Short-term: No ss for low disability, high disability, or total pain.	Short-term: Low disability: (SMD=-0.57; 95% CI [-1.03, -0.11]; *p*=0.02; I^2=60% High disability: (SMD=0.60; 95% CI [-0.12, 1.32]; *p*=0.10; I^2=52%) Total: (SMD=-0.31; 95% CI [-0.79, 0.18]; *p* =0.21; I^2=73%)

Table 8: Tabular overview of the results of acupuncture regarding MMO categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval

Improvement of maximum mouth opening		
Comparison	**Statistically significant results**	**Data**
Acupuncture vs. (any) control	Short-term: no ss for low disability or total pain.	Short-term: Low disability: (SMD=0.27; 95% CI [-0.06, 0.60]; *p*=0.11; I^2=0%) Total: (SMD=0.30; 95% CI [-0.01, 0.62]; *p*=0.06; I^2=0%)
Acupuncture vs. sham acupuncture	Short-term: no ss for low disability or total pain.	Short-term: Low disability: (SMD=0.32; 95% CI [-0.12, 0.75]; *p*=0.15; I^2=16%) Total: (SMD=0.34; 95% CI [-0.03, 0.71]; *p*=0.07; I^2=0%)
Dry needling vs. other treatment	Short-term: no ss for low disability or total pain.	Short-term: Low disability: (SMD=0.07; 95% CI [-0.23, 0.36]; *p*=0.66; I^2=0%) Total: (SMD=-0.02; 95% CI [-0.29, 0.25]; *p*=0.18; I^2=0%)

3.2 Laser

3.2.1 Description of the intervention:

Low-level laser therapy (LLLT) has been widely used in the treatment of TMD due to its low energy intensity and wavelengths which enables it to penetrate tissue and exert an effect on the synthesis, release and metabolism of numerous signalling substances involved in analgesia [203]. This is called laser photo biomodulation, which is produced with different laser doses and wavelengths [204]. LLLT may also have anti-inflammatory and stimulant effects [205]. The intensity of the laser does not damage tissue, but can cause biochemical effects on cells, which is why the laser is also called a cold laser or soft laser [206].
It has recently been highlighted in the management of TMD because of its ease of use, short treatment time and limited contraindications [207]. The most commonly used LLLT clinically include the helium-neon laser (632 nm He-Ne) and infrared lasers such as diode gallium arsenide (904 nm Ga-As) or gallium aluminium arsenide (830 nm Ga-Al-As) [208].
A recent network meta-analysis has found that when energy density is not more than 10 J/cm^2, LLLT has statistically significant pain reduction in the initial management of TMD [209]. Looking at previous studies on LLLT and the efficacy on TMD, there have been contradictory results [181]. For example, some results have a positive impact on TMD [210, 211], while other studies show no significant advantage of LLLT over placebo administration in terms of TMD symptoms [212-214].

3.2.2 How laser might work:

The literature search revealed several procedures describing the effects of LLLT, such as an increase in neurotransmitters, an increase in the thermal pain threshold and an increase in local blood flow as well as an increase in the rate of oxidation and reduction of mitochondrial respiratory chain electrons, an increase in the production of adenosine triphosphate at the cell surface and an increase in the production of anti-inflammatory cytokines [215].
The process of pain relief using mid-laser therapy is not clear and several theories have been proposed. One theory from the literature indicates that LLLT can affect the synthesis of prostaglandin, allowing arachidonic acid to enter the endothelial tissue and smooth muscle, causing the vasodilatation and the anti-inflammation [204]. The analgesic effect is due to a decrease in PGE2, one of the major proinflammatory mediators. This theory is based on in vivo and in vitro findings of a reduction of PGE2 both in cultures of ligament cells and in the joint capsule of animals after laser exposure. The PGE2 reduction is likely due to laser-induced inhibition of COX-2, the enzyme involved in the synthesis of PGE2 [208].
Another theory considers the effect of laser therapy on neuronal cells. This involves the possible selective inhibition of nociceptive signals and regulation of microcirculation that could interrupt the onset and development of pain, producing analgesic effects. The

magnitude of the laser effect appears to depend on the wavelength and dose of the laser light. PGE2 reduction has been reported to be observed in a dose range between 0.4-19 J and in a power density range between 5 -21.2 mW/cm2 [208]. In addition to the neuro-pharmacological effects, LLLT leads to C-fibre activity [203].

3.2.3 Study selection

The initial database search yielded 419 entries, of which 105 were retrieved from MEDLINE (via PubMed), 46 from Embase, 214 from Central, 39 from LIVIVO (German and English version), four from Clinicaltrials.gov, eleven from Deutsches Register klinischer Studien (DRKS) and none from Open Grey Literature (Table 9). Results of unpublished studies are not included in this review. An additional seven articles were identified through cross-reference checking and manual searching. All the studies used laser interventions for treating TMD. After exclusion of all duplicates (31 studies), the number of entries was reduced to 395. Of these, 306 studies were discarded after review of the titles and abstracts (no RCTs, no laser interventions, no TMD or children included for most of the participants). An additional 33 articles were excluded after full-text review and application of the eligibility criteria (reasons for exclusion after full-text analysis are reported in Appendix VIII Table 2. A flowchart that depicts this selection process is displayed in Figure 14.

Table 9: Results of the search strategy for Laser

Database	*Number of studies (n)*
PubMed	105
EMBASE	46
Central	214
LIVIVO (German)	36
LIVIVO (English)	3
Clinicaltrials.gov	4
Deutsches Register klinischer Studien (DRKS)	11
Open Grey Literature	-
Total	419

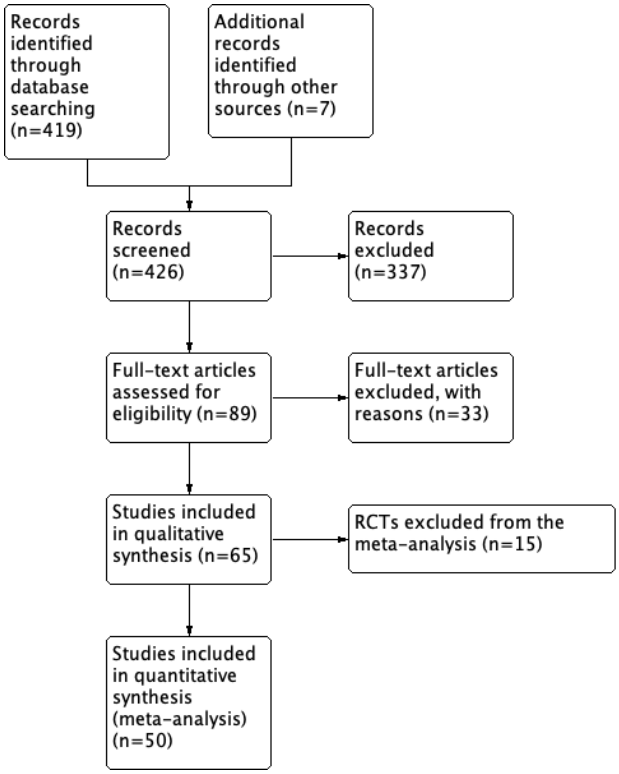


Figure 14: Flow Diagram for RCTs on Laser treatment of patients with painful TMDs

3.2.4 Qualitative synthesis of the included studies

3.2.4.1 Characteristics of the included Studies

65 studies with 3031 participants met the inclusion criteria and were then included in this systematic review. To check for heterogeneity in advance, characteristics of the population used in the studies, the characteristics of interventions and the excluded studies were precisely reproduced in narrative style. Table 10 and Table 11 represent the general characteristics of the included studies. The Appendix VIII, Characteristics of included studies: Laser provides detailed information on the participants, the treatment and the comparisons, outcomes, degree of pain and follow up, respectively.

Table 10: Included studies on laser treatment of TMDs; (AlGaAs=aluminium gallium arsenide; GaAlAs=gallium aluminium arsenide; GaAs=gallium arsenide; He-Ne=helium-neon; InGaAlP=indium- gallium-aluminum-phosphide; LLLT= low-level laser therapy; MENS=micro electric neurostimulationMT=manual therapy; Nd:YAG =neodymium-doped yttrium aluminum garnet; PBMT=photo biomodulation therapy)

Author Year	Patients (n) women %, age (years)	Interventions	Outcomes	Pain chronification	Diagnose	Follow-up
Abbasgholizadeh et al. 2020 [216]	45 patients 84% women 18-53 years old Mean age: 29.9 ±9.20	Group A (n=15): splint therapy Group B (n=15): splint therapy with ultrasound-guided arthrocentesis Group C (n=15): splint therapy with LLLT (Nd: YAG)	Pain (VAS) Low disability jaw movements (unassisted mouth opening without pain, maximum unassisted mouth opening, contralateral movements)	Unclear	TMD of muscular and/or arthrogenic origin	6 months
Ahmad et al. 2017 [217]	60 patients 75% women Mean age: Group A: 37.56 ±8.26 Group B: 37.03 ±6.26	Group A (n=30): conventional therapy (active and stretching exercises for mandibular muscles with ultrasound and LLLT application on TMJ area) Group B (n=30): conventional therapy only.	Pain-related limitations in daily functions (LDF-TMDQ)	Low disability	TMD of muscular origin	1 month
Ahrari et al. 2014 [218]	20 patients 100% women Mean age: 35.5	Group A (n=10): laser group Group B (n=10): placebo group	Pain (VAS) Maximum mouth opening (mm)	Low disability	TMD of muscular origin	1 month
Altindiş et al. 2019 [219]	20 patients 100% female 18–45 years old	Group A (n=10): stabilisation splint, Group B (n=10): LLLT	Pain intensity (11-NS)	Low disability	TMD of muscular origin	1 month
Amanat et al. 2013 [220]	60 patients 73% females Mean age: 47.22	Group A (n=30): GaAs laser Group B (n=30): sham laser	Pain (VAS)	High disability	TMD of muscular origin	1 month
Bertolucci et al. 1995 [221]	32 patients n.a. n.a.	Group A (n=16): control (placebo) group Group B (n=16): mid-laser treatment	Mouth opening vertical opening (mm) Pain Index (VAS)	High disability	TMD of arthrogenic origin	No follow-up
Borges et al. 2018 [222]	44 patients 91% women 15-59 years old Mean age: 31.9 ±12.9	Group A (n=11): 8 J/cm2 LLLT (AlGaAs) Group B (n=11): 60 J/cm2 LLLT (AlGaAs) Group C (n=11): 105 J/cm2 LLLT (AlGaAs) Group D (n=11): placebo group	Pain (VAS) TMJ mobility mouth opening (mm)	Low disability	TMD of muscular and/or arthrogenic origin	No follow-up
Brochado et al. 2018 [223]	54 patients 95% women Mean age: 44.5 ±17.1	Group A (n=14): PBM Group B (n=13): MT Group C (n=13): CT	Pain intensity (VAS) Mandibular movements mouth opening Beck anxiety inventory (BAI)	Mixed (separable)	TMD of muscular and/or arthrogenic origin	1 month
Carrasco et al. 2008 [224]	14 patients	Group A (n=7): infrared laser Group B (n=7): placebo treatment	Pain (VAS)	Low disability	TMD of muscular origin	1 month
Carrasco et al. 2009 [225]	60 patients	Group A (n=10): LLLT at 25J/cm2 Group B (n=10): LLLT at 60J/cm2 Group C (n=10): LLLT at 105J/cm2 Group D (n=10): placebo LLLT at 25J/cm2 Group E (n=10): placebo LLLT at 60J/cm2 Group F (n=10): placebo LLLT at 105J/cm2	Pain intensity (VAS)	High disability	TMD of muscular and/or arthrogenic origin	1 month

Cavalcanti et al. 2016 [226]	60 patients 100% women 20–50 years old	Group A (n=20): LLLT Group B (n=20): PDP (hot packs) Group C (n=20): placebo	Presence (P) or Absence (A) of pain (%)	Unclear	TMD of muscular origin	1 month
Chellappa et al. 2020 [227]	60 patients n.a. n.a.	Group A (n=30): LLLT group Group B (n=30): TENS group	Pain (VAS) MMO mouth opening	High disability	TMD of muscular and/or arthrogenic origin	1 month
Costa et al. 2017 [228]	60 patients 90% women 18-76 years old Mean age: 38.8 ±14.2	Group A (n=30): placebo (control) Group B (n=30): PBMT	Mouth opening measurements (mm) Pain (VAS)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Da Cunha et al. 2008 [212]	40 patients 98% Mean age: Group A: 40.15 Group B: 46.6	Group A (n=20): infrared laser Group B (n=20): control group	Pain (VAS)	Low disability	TMD of muscular origin	No follow-up
Da Silva et al. 2012 [229]	45 patients 67% women 25-53 years old Mean age: 39.7	Group A (n=15): laser (52.5 J/cm2) Group B (n=15): laser (105.0 J/cm2) Group C (n=15): placebo (0 J/cm2)	Maximum pain-free mouth opening (mm)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
De Abreu Venancio et al. 2005 [230]	30 patients 83% women Mean age: Group A: 34.9 (15–36 years old) Group B: 37.6 (13–63 years old)	Group A (n=15): infrared laser Group B (n=15): placebo group	Pain (VAS) Range of mandibular movements mouth opening (mm)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
De Carli et al. 2013 [231]	32 patients 91% women 18-58 years old Mean age: 32	Group A (n=11): active laser and placebo piroxicam Group B (n=10): placebo laser and piroxicam Group C (n=11): active laser and piroxicam	Pain (VAS) Maximum mouth opening (mm)	Mixed (separable)	TMD of mixed origin	1 month
De Carli et al. 2016 [232]	15 patients 87% women Mena age: 38	Group A (n=8): LLLT (GaAlAs) Group B (n=7): toxin group (BTX-A)	Pain (VAS) Mouth opening (digital calliper)	Low disability	TMD of muscular origin	1 month
De Moraes Maia et al. 2014 [233]	21 patients 91% women Mean age: 27.76 ±10.44	Group A (n=12): laser (infrared) Group B (n=9): placebo group	Pain intensity (VAS).	Low disability	TMD of muscular and/or arthrogenic origin	1 month
De Oliveira Chami et al. 2020 [234]	20 patients	Group A (n=10): LLLT Group B (n=10): placebo	Pain (spontaneous)	Low disability	TMD of muscular origin	1 month
De Oliveira et al. 2017 [235]	19 patients 79% women 21–55 years old Mean age: 35	Group A (n=15): red laser Group B (n=10): infrared laser	Pain (VAS)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
De Souza et al. 2018 [236]	66 patients 94% women Mean age: 46.14 ± 10.91	Group A (n=33): LLLT (GaAlAs) Group B (n=33): anaesthetic infiltration of lidocaine	Pain (VAS)	Unclear (high disability)	TMD of muscular origin	No follow-up

Del Vecchio et al. 2019 [237]	90 patients 87% women 18-73 years old Mean age: 42.55 ± 14.84	Group A (n=30): LLLT Group B (n=30): sham devices Group C (n=30): conventional drug therapy	Pain (VAS)	Low disability	TMD of muscular and/or arthrogenic origin	No follow-up
Demirkol et al. 2017 [238]	46 patients 50% women 13-65 years old	Group A (n=15): LLLT (Nd: YAG, 1064 nm) Group B (n=16): LLLT (diode laser, 810 nm) Group C (n=16): placebo treatment	Pain (VAS)	Unclear (low disability)	TMD of muscular origin	1 month
Emshoff et al. 2008 [214]	52 patients 81% women 18.58 years old Mean age: 42.9 years	Group A(n=26): active LLLT (He-Ne) Group B(n=26): sham LLLT	Pain (VAS)	High disability	TMD of muscular and/or arthrogenic origin	8 weeks
Fornaini et al. 2015 [239]	24 patients 79% women 17-64 years old	Group A (n=12): LLLT Group B (n=12): inactive laser (placebo group)	Pain (VAS)	Unclear (low disability)	TMD of arthrogenic origin	2 weeks
Frare et al. 2008 [240]	18 patients 100% women Mean age: 27 ±7	Group A (n=10): laser (GaAs) Group B (n=8): manipulated	Pain (VAS)	Unclear (high disability)	TMD of muscular and/or arthrogenic origin	No follow-up
Herpich et al. 2015 [203]	30 patients 100% women 18-40 years old	Group A (n=15): phototherapy (9,96 J/point) Group B (n=15): phototherapy (0 J/point)	Pain (VAS)	Low disability	TMD of muscular origin	48 hours
Herpich et al. 2018 [241]	60 patients 100%women 18-14 years old	Group A (n=15): 2.62 J Group B (n=15): 5.24 J Group C (n=15): 7.86 J Group D (n=15): placebo group	Pain intensity (VAS) Mouth opening (mm)	Low disability	TMD of muscular origin	48 hours
Herpich et al. 2020 [242]	30 patients 50% women Mean age: Group A: 25.44 ±5.76 Group B: 26.55 ±4.6	Group A (n=15): photo biomodulation Group B (n=15): sham photo biomodulation	Mouth opening (mm) Pain intensity (VAS)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Hosgor et al. 2017 [243]	40 patients 90% women 18.59 years old Mean age: 30.35 ±1.97	Group A (n=10): splint therapy Group B (n=10): arthrocentesis therapy Group C (n=10): NSAIDs therapy Group D (n=10): laser therapy (Nd:YAG)	Pain (VAS) Joint noises (clicking, crepitus, or none) Maximum mouth opening (mm)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Juliana Cristina et al. 2008 [244]	20 patients 75% women Mean age: Group A: 28.2 ±7 Group B: 24.01 ±6.04	Group A (n=10): MT Group B (n=10): MT and LLLT (GaAs laser)	Pain intensity (VAS) Mouth opening (mm)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Keskin Tunç et al. 2020 [245]	40 patients 75 % women 18-60 years old Mean age: 22.35	Group A (n=20): NSAID + occlusal splint Group B (n=20): NSAID, occlusal splint + LLLT	Mouth opening (mm) Pain (VAS)	Low disability	TMD of arthrogenic origin (disc displacement with reduction TMJ)	1 month
Khairnar et al. 2019 [246]	42 patients 52 % women 25-45 years old	Group A (n=21): LLLT Group B (n=21): ultrasound therapy	Pain (VAS) Maximum mouth opening (mm)	Unclear (low disability)	TMD of articular origin	post therapy

Khalighi et al. 2016 [247]	40 patients 75% women Mean age: 36 ± 12.34	Group A (n=20): naproxen + placebo laser Group B (n=20): active laser + placebo drug	Pain intensity (VAS) Maximum painless mouth opening (mm)	Low disability	TMD of muscular origin	1 month
Kogawa et al. 2005 [248]	19 patients 100% women Mean age: 26.4	Group A (n=9): LLLT (GaAlAs) Group B (n=10): MENS	Pain (VAS) Active ROM mouth opening (AROM)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Kulekcioglu et al. 2003 [249]	35 patients 80%women 20-59 years old Mean age: 37.0 ±12.3	Group A (n=20): LLLT Group B (n=15): placebo	Pain intensity (VAS) Maximal mouth opening (mm) Joint sounds	Mixed	TMD of muscular and/or arthrogenic origin	1 month
Lassemi et al. 2008 [250]	48 patients 50% women Mean age: Group A: 33 ±9 Group B: 38.6 ±8.37	Group A (n=26): LLLT Group B (n=22): placebo group	Pain (VAS) Clicking (stethoscope)	Unclear (high disability)	TMD of muscular origin	1 month
Machado et al. 2016 [251]	82 patients 93% women	Group A (n=26): LLLT + oral-motor exercises (60J) Group B (n=26): orofacial myofunctional therapy Group C (n=26): placebo + oral-motor exercises Group D(n=26): LLLT (60J) Group E (n=20): healthy control group	TMD severity	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Madani et al. 2014 [213]	20 patients 95% women 35–60 years old	Group A (n=10): LLLT Group B (n=10): placebo	Mouth opening (mm) Pain intensity (VAS) Presence or absence of joint sounds	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Madani et al. 2020 [181]	45 patients	Group A (n=15): LLLT (GaAlAs) Group B (n=15): laser acupuncture therapy (LAT) Group C (n=15): sham laser	Mouth opening (mm) Pain intensity (VAS)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Magri et al. 2017 [252]	91 patients 100% women 18-60 years old Mean age: Group A: 38.45 ±12.56 Group B: 38.87 ±10.88 Group C: 38.67 ±11.18	Group A (n=31): laser Group B (n=30): placebo Group C (n=30): control group (no treatment)	Pain intensity (VAS)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Manfredini et al. 2018 [253]	30 patients 100%women Mean age: 35.3 ± 9.4	Group A (n=10): laser Group B (n=10): oral appliance therapy Group C (n=10): counselling	Pain (VAS) Muscular Index (MI) of the Craniomandibular Index	Low disability	TMD of muscular origin	1 month
Mansourian et al. 2019 [254]	108 patients 81% women 21-60 years old Mean age: 29	Group A (n=36): LLLT (GAAlAr) Group B (n=36): TENS Group C (n=36): control group	Pain intensity (VAS) Maximum mouth opening	Unclear (high disability)	TMD of muscular origin	1 month
Marini et al. 2010 [211]	99 patients 75% women 15-50 years old	Group A (n=30): super pulsed low-level laser (SLLLT) Group B (n=30): ibuprofen Group C (n=30): sham laser	Pain intensity (VAS) Mouth openings (mm)	High disability	TMD of muscular and/or arthrogenic origin	1 month
Mazzetto et al. 2007 [255]	48 patients 88% women 14-50 years old	Group A (n=24): infrared laser Group B (n=24): placebo application (inactive point)	Intensity of pain after palpation (VAS)	Low disability	TMD of muscular and/or arthrogenic origin	1 month

Mazzetto et al. 2010 [210]	40 patients 90% women 14-50 years old	Group A (n=20): effective dose (GaAlAs) Group B (n=20): placebo application (0 J/cm2)	Pain (VAS) Mouth opening (mm)	Low disability	TMD of articular origin	1 month
Molina-Torres et al. 2016 [256]	58 patients 95% women Mean age: Group A: 51.79 ±7.79 Group B: 51.00 ±8.32	Group A (n=29): occlusal splint Group B (n=29): laser	Pain intensity (VAS) Mouth opening (mm) Joint sounds	High disability	TMD of muscular and/or arthrogenic origin	1 month
Nadershah et al. 2020 [257]	202 patients 54% women Mean age: Group A: 34.3 ±10.5 Group B: 33.3 ±10.7	Group A (n=108): LLLT Group B (n=94): sham laser	Pain (VAS)	Low disability	TMD of muscular origin	No follow-up
Öz et al. 2010 [258]	44 patients 85% women 18-60 years old	Group A (n=22): LLLT Group B (n=22): stabilization splint	Pain intensity (VAS) Depression (RDC/TMD) Active and passive mouth opening	Low disability	TMD of muscular origin	3 months
Panhoca et al. 2015 [259]	30 patients 73% women 18-40 years old	Group A (n=10): red LED Group B (n=10): infrared LED Group C (n=10): infrared laser (780 nm)	Mouth opening (maximum oral aperture) Pain (NRS 0-3)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Pereira et al. 2014 [260]	19 patients 80% women Mean age: 35	Group A (n=19 hemiface): red laser therapy Group B (n=19 hemiface): infrared laser therapy	Pain (NRS 0-10)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Pihut et al. 2018 [261]	112 patients 74% women 24-45 years old	Group A (n=56): repositioning splint Group B (n=56): bio stimulation laser	Pain intensity (VNRS)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Rezazadeh et al. 2017 [262]	34 patients 74% women Mean age: Group A: 30.79 Group B: 31.87	Group A (n=19): TENS Group B (n=15): LLLT	Pain intensity (VAS)	High disability	TMD of muscular origin	1 month
Rodrigues et al. 2018 [263]	89 patients 100% women 18–60 years old Mean age: 31.94 ±9.57	Group A (n=34): LLLT Group B (n=33): placebo Group C (n=30): control	Pain intensity (VAS)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Rohlig et al. 2011 [264]	40 patients 60% women Mean age: 43.7 ±1.8	Group A (n=20): LLLT Group B (n=20): placebo group	Mandibular mobility mouth opening (mm) Pain (VAS)	Low disability	TMD of muscular origin	No follow-up
Sancakli et al. 2015 [265]	30 patients 70% women Mean age: 39.2	Group A (n=10): LLLT Group B (n=10) LLLT at pre-established points Group C (n=10): placebo group	Mandibular mobility mouth opening (mm) Pain (VAS)	Low disability	TMD of muscular origin	No follow-up
Sattayut et al. 2012 [266]	30 patients 100% women 20-50 years old Mean age: 35 ±9	Group A (n=10): LLLT (GaAlAs) Group B (n=10): LLLT 820 nm (GaAlAs) Group C (n=10): placebo laser	Unassisted maximum mouth opening without pain (MOSP) Pain rating index (McGill pain questionnaire)	Unclear (low disability)	TMD of muscular and/or arthrogenic origin	3 months

Seifi et al. 2017 [267]	40 patients n.a. 18-50 years old	Group A (n=10): TENS Group B (n=10): LLLT Group C (n=10): sham-TENS Group D (n=10): sham-LLLT	Pain (VAS) Mouth-opening (mm)	High disability	TMD of muscular and/or arthrogenic origin	1 month
Shirani et al. 2009 [268]	16 patients 75% women 16-37 years old Mean age: 23.8	Group A (n=8): laser Group B (n=8): control	Pain (VAS)	Low disability	TMD of muscular origin	1 month
Shobha et al. 2017 [269]	40 patients 78% women 18–40 years old Mean age: Group A: 30.85 ±6.31 Group B: 27.55 ±4.58	Group A (n=20): active LLLT with diode laser Group B (n=20): inactive LLLT	Pain (VAS) Mouth opening (mm) Clicking	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Uemoto et al. 2013 [195]	21 patients 100% women 20-52 years old	Group A (n=7): Infrared laser Group B (n=7): dry needling Group C (n=7): control	Pain (VAS) Mouth-opening (mm)	Low disability	TMD of muscular origin	72 hours
Venezian et al. 2010 [270]	48 patients 90% women Mean age: 41.58	Group A (n=12): 25 J/cm2 LLLT Group B (n=12): 25 J/cm2 LLLT Group C (n=12): 60 J/cm2 LLLT Group D (n=12): 60 J/cm2 Group IV-dose of 60 J/cm2 (60mW for 40 seconds placebo treatment)	Pain to palpation (VAS)	Low disability	TMD of muscular origin	1 month
Wang et al. 2011 [271]	42 patients 76% women Mean Age: Group A: 40.25 ±15.35 Group B: 42.65 ±13.75	Group A (n=21): LLLT Group B (n=21): control group	TMJ pain (VAS) Maximum mouth opening (mm)	Unclear	TMD of muscular and/or arthrogenic origin	3 months
Yamaner et al. 2020 [272]	62 patients 95% women Mean age: 31.51 ±10.32	Group A (n=18): LLLT Group B (n=15): Ozone Group Group C (n=13): Sham Laser Group D (n=16): Sham Ozone	Pain (VAS)	Low disability	TMD of arthrogenic origin (disc displacement with reduction)	3 months

Table 11: Treatment description of included studies on laser treatment of TMD

Author date	Laser type	Treatment time (sec.)	Power (mW)	Dosage (J/cm2)	Frequency and number of sessions
Abbasgholizadeh et al. 2020	Nd: YAG laser 1064 nm	60	500	321	n.a. / 3 sessions per week
Ahmad et al. 2017	diode 905nm	14	550	16	n.a. / n.a.
Ahrari et al. 2014	GaAlAs 810nm	120	50	3.4	12 sessions / three times a week for 4 weeks
Altindiş et al. 2019	970nm diode laser	10	500	5	10 sessions / three times a week for 3 weeks
Amanat et al. 2013	GaAs 980nm	300	1000	12.73	10 sessions / three times a week for 3 weeks
Bertolucci et al. 1995 [221]	COMBY-I infra-red laser 904nm	270	27000	n.a.	n.a. / 3 weeks
Borges et al. 2018 [222]	GaAlAs laser 830 nm	15	30	8 /60 /105	10 sessions / three times a week for 3 weeks
Brochado et al. 2018 [223]	photobiomodulation (PBM) 808 nm	40	100	13.03	12 sessions / 4 weeks
Carrasco et al. 2008 [224]	GaAlAs 780 nm	60	50/60/70	25/ 60/ 105	8 sessions / two times a week for 4 weeks
Carrasco et al. 2009 [225]	GaAlAs 780 nm	60	70	105	8 sessions / two times a week for 4 weeks
Cavalcanti et al. 2016 [226]	GaAlAs 780 nm	20	70	35	12 sessions / four times a week for 3 weeks
Chellappa et al. 2020 [227]	672-nm diode laser	120	50	3	6 sessions / two times a week for 3 weeks
Costa et al. 2017 [228]	photobiomodulation therapy 830nm	28	100	100	1 session
Da Cunha et al. 2008 [212]	GaAlAs 830nm	20	500	4	4 sessions /one a week for 4 weeks
Da Silva et al. 2012 [229]	GaAlAs 780 nm	30 or 60	70	105	10 sessions / five times a week for 2 weeks
De Abreu Venancio et al. 2005 [230]	GaAlAs 780 nm	10	30	6.3	6 sessions / three times a week for 2 weeks
De Carli et al. 2013 [231]	808 nm GaAlAs diode laser (Thera Lase)	28	100	100	twice a week, over a 10-day period
De Carli et al. 2016 [232]	GaAlAs 830nm	28	100	100	4 sessions / 2 weeks
De Moraes Maia et al. 2014 [233]	GaAlAs 808nm	19	100	70	8 sessions / 2 weeks
De Oliveira Chami et al. 2020 [234]	808nm	22	100	80	2 sessions / n.a.
de Oliveira et al. 2017 [235]	red 66nm and infrared 790nm	1.06 and 0.33	120 // 120	8 /4	3 sessions each
De Souza et al. 2018 [236]	GaAlAs 780 nm	40	50	50	12 sessions / 6 weeks
Del Vecchio et al. 2019 [237]	808 nm	n.a.	250	40	12 sessions / 1 week
Demirkol et al. 2017 [238]	Nd: YAG 1064nm	20	250	8	10 sessions / 5 weeks
Emshoff et al. 2008 [214]	HeNe 632,8nm	120	30	1,5	20 sessions: two to three times a week for 8 weeks
Fornaini et al. 2015 [239]	GaAlAs 808nm	900	250	n.a.	14 sessions/ 7 weeks
Frare et al. 2008 [240]	GaAs laser (904 nm)	16	15	6	8 sessions / twice a week, for four consecutive weeks
Herpich et al. 2015 [203]	super-pulsed laser 905 nm, red 640nm, and infrared 875nm	20 Group A, 40 Group B 60 Group C 60 Group D	n.a.	2.62 /5.24 /7.86	n.a.
Herpich et al. 2018 [241]	super-pulsed laser 905 nm, red 640nm, and infrared 875nm	300	n.a.	2.62 / 5.24 /7.86	single session
Herpich et al. 2020 [242]	laser super-pulsed (905 nm)	300	n.a.	35309	1 session/ 1 week
Hosgor et al. 2017 [243]	Nd–YAG laser device 1064 nm	180	500	321	12 sessions / 4 weeks
Juliana Cristina et al. 2008 [244]	GaAs 904 nm	n.a.	n.a.	6	n.a.
Keskin Tunç et al. 2020 [245]	Diode 940 nm	20	300	2.14	8 sessions / two sessions a week for of four weeks

Khairnar et al. 2019 [246]	type Class III B and Class 2M laser machine (Silberbauer) 660-nm laser light	180	60	43863	15 session / n.a.
Khalighi et al. 2016 [247]	GaAlAs 810 nm	60	50000	n.a.	12 sessions / 3 weeks
Kogawa et al. 2005 [248]	GaAlAs 830-904nm	n.a.	100	4	10 sessions/4weeks
Kulekcioglu et al. 2003 [249]	GaAs 904nm	180	17	3	15 sessions / n.a.
Lassemi et al. 2008 [250]	GaAs 980 nm	60	n.a.	n.a.	2 sessions / 2 weeks
Machado et al. 2016 [251]	GaAlAs 780 nm	2700	60	60	12 sessions/ 1 week
Madani et al. 2014 [213]	Laser type NA (Mustang 2000z, Moscow, Russia), 810 nm	120	50	3.4	12 sessions / 3 weeks
Madani et al. 2020 [181]	GaAlAs 810 nm	30	200	21	10 sessions /two times a week for 5 weeks
Magri et al. 2017 [252]	GaAlAs 780 nm	10	TMJ: 20 muscles: 30	5 or 7,5	8 sessions / 2 weeks
Manfredini et al. 2018 [253]	808 and 905 nm	360-600	1100 and 2500	100–200	9 sessions/ 3 weeks
Mansourian et al. 2019 [254]	810 nm wavelength	10	200	2	10 sessions (3 sessions per week
Marini et al. 2010 [211]	GaAlAs 910 nm	20 kHz / 600 18 kHz / 300 16 kHz / 300	45000	n.a.	10 consecutive days (5 days per week
Mazzetto et al. 2007 [255]	GaAlAs 780 nm	10	70	89,7	8 sessions / 2 weeks
Mazzetto et al. 2010 [210]	GaAlAs laser λ 830 nm	10	40	5	twice a week for 4 weeks
Molina-Torres et al. 2016 [256]	n.a.	120	8000	3	1 session / 12 weeks
Nadershah et al. 2020 [257]	940 nm	180	7000	300	every 48 h for 10 days
Öz et al. 2010 [258]	low- intensity semiconductor 820 nm	10	300	3	10 sessions/5weeks
Panhoca et al. 2015 [259]	red LED (630±10 nm) /infrared LED (850±10nm)	60	150 /70	18 /105	8 sessions/4weeks
Pereira et al. 2014 [260]	660 nm (red laser) and 795 nm (infrared laser)		n.a.	4 /8	3 sessions
Pihut et al. 2018 [261]	Biostimulation laser 808 nm	225	n.a.	n.a.	12 sessions/16weeks
Rezazadeh et al. 2017 [262]	GaAlAs 980nm	1200	200	5	8 sessions/2 weeks
Rodrigues et al. 2018 [263]	GaAlAs 780 nm	20 and 50	60	30 /75	8 sessions/4weeks
Rohlig et al. 2011 [264]	GaAs 820 nm	10	300	8	10 sessions/3-4 weeks
Sancakli et al. 2015 [265]	GaAs 820 nm	10	300	3	12 sessions /3 weeks
Sattayut et al. 2012 [266]	GaAlAs 820 nm	n.a.	60	43942	3 sessions each / n.a.
Seifi et al. 2017 [267]	GaAlAs 810 nm	60	500	n.a.	4 sessions/ 4weeks
Shirani et al. 2009 [268]	InGaAlP 660 nm and GaAs 890nm	360 and 600	17.3 and 9.8	6.2 and 1.0	6 sessions: 2x/week for 3 weeks
Shobha et al. 2017 [269]	GaAlAs, 810 nm	60	100	6	8 session/2-3 weeks
Uemoto et al. 2013 [195]	Laser type NA (Infrared laser), 795 nm	n.a.	80	4 or 8	4 sessions/n.a.
Venezian et al. 2010 [270]	GaAlAs 780 nm	20 and 40	50/ 60	25 or 60	8 sessions 2x/week for 4 weeks
Wang et al. 2011 [271]	GaAlAs 650nm/830nm	900	300	n.a.	6 sessions/6weeks
Yamaner et al. 2020 [272]	Infrared radiation 820 nm	10	300	3	three times per week for a total of six sessions

3.2.4.2 Characteristics of the population used in the studies

3.2.4.2.1 TMD diagnoses of the participants in the included studies

The types of TMD of the subjects from the included studies of laser therapy were divided into the three main diagnosis of TMD (Figure 15). The largest proportion of the studies were of mixed TMD of muscular and/or articular origin (34 studies) [181, 211, 213, 214, 216, 222, 223, 225, 227-231, 233, 235, 237, 240, 242-244, 248, 249, 251, 252, 255, 256, 259-261, 263, 266, 267, 269, 271, 273]. Kulekcioglu et al. 2003 [249] distinguished in the sample 50% of myogenous TMD and was therefore added to the mixed TMD group.
25 studies included TMD of muscular origin according to the RDC/TMD [195, 203, 212, 217-220, 224, 226, 232, 234, 236, 238, 241, 247, 250, 253, 254, 257, 258, 262, 264, 265, 268, 270]. Patients suffering from TMD of articular origin were treated in six studies [210, 221, 239, 245, 246, 272]. The trials of Keskin et al. 2020 [245] and Yamaner et al. 2020 [272] included patients with disc displacement with reduction according to DC/TMD.

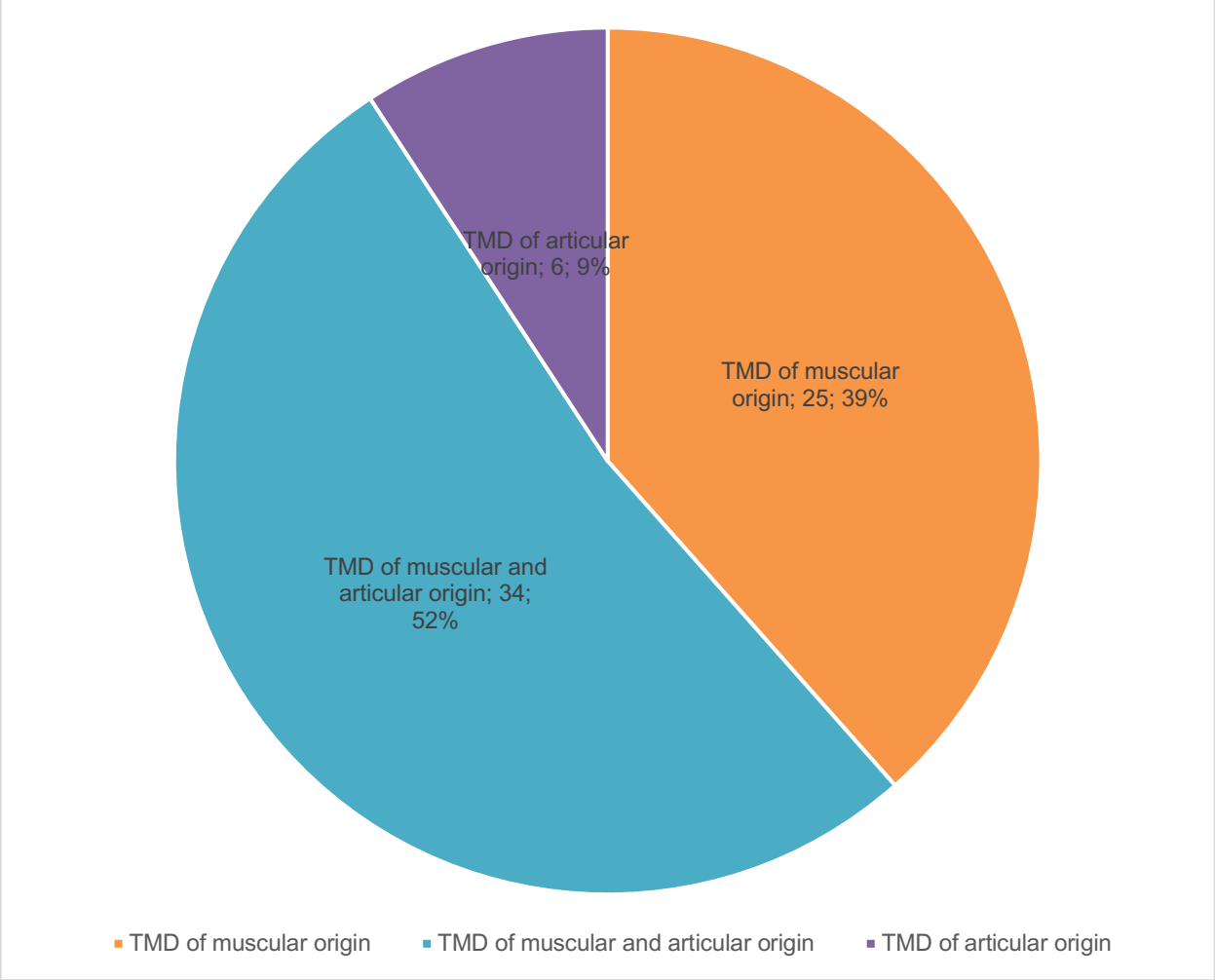


Figure 15: Pie chart presenting the different TMD diagnoses from the included studies on laser therapy (X) with the number of studies included (Y) and the percentage (Z); (X;Y;Z).

3.2.4.2.2 Grade of pain chronification

The degree of TMD pain chronification of the subjects formed the focus of the present work. The following categories were formed for laser therapy treatment (Figure 16):

- Patients with evidence of a low disability (acute or acute/persistent) pain
- Patients with evidence of high disability pain
- Patients with different degrees of chronicity, where results were presented separately by the authors (referred to below as: mixed)
- Patients with slight evidence of low disability pain (referred to below as: unclear (low disability))
- Patients with slight evidence of high disability pain (referred to below as: unclear (high disability))
- Patients with limited degree of chronicity (referred to below as: unclear)

The majority of the studies were treating low disability pain in the LLLT studies [181, 195, 203, 210, 212, 213, 217-219, 222, 228-230, 232-235, 237, 241-245, 247, 248, 251-253, 255, 257-261, 263-265, 268-270, 272], and four studies were likely to have included patients with low disability pain [238, 239, 246, 266] as Fornaini et al. 2015 [239] described the patients in the study with “acute pain” and suffering from localised pain as did Sattayut et al. 2012 [266]. Demirkol et al. 2017 [238] excluded participants suffering from orofacial pain for more than six months and Khairnar et al. [246] included participants not taking any antidepressant medications patients but using other forms of medication. Interestingly, only a small number of studies included patients suffering from high disability pain [211, 214, 220, 227, 256, 262, 267, 274]. A probability of high disability pain [224, 236, 240, 250, 254] was identified by de Souza et al. 2018 [236] as the patients were treated through secondary care and were excluded if they altered their systemic medications 3 months before beginning the treatment and by Lassemi et al. 2008 [250] as the patients included in the trial were experiencing high pain level (8.9 +/-.5). Carrasco et al. 2008 [224], Frare et al. 2008 [240] and Mansourian et al. 2019 [254] involved participants that were recruited from tertiary care. A diversity of pain types were observed in three studies [223, 231, 249]. Consequently, it was unclear from three of the studies what type of pain the patients were suffering from and we had no indications [216, 226, 271].

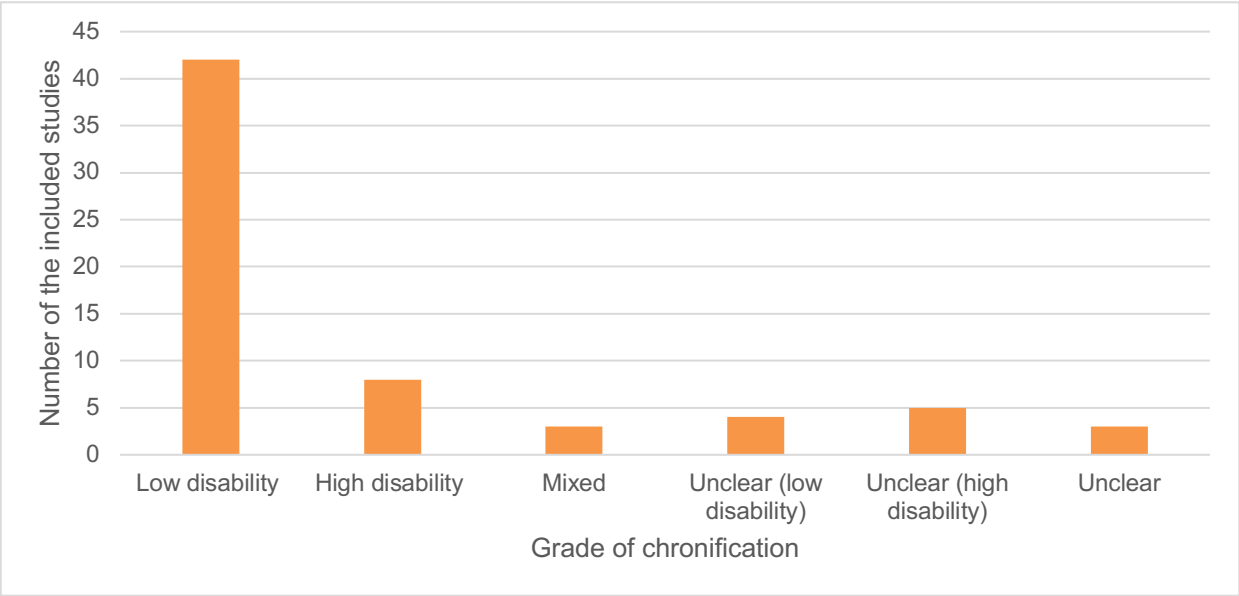


Figure 16: Grade of chronification of the included studies for laser therapy

The participants in the 65 included RCTs were classified according to the indications mentioned above. Several of the studies examined, provided multiple indications of the subjects' level of chronicity. Consequently, the indications could support or contradict each other. For this reason, priority list was employed for the final decision on classification. In the following tables and charts, the priorities of the indications, as well as the studies that applied them, are listed below:

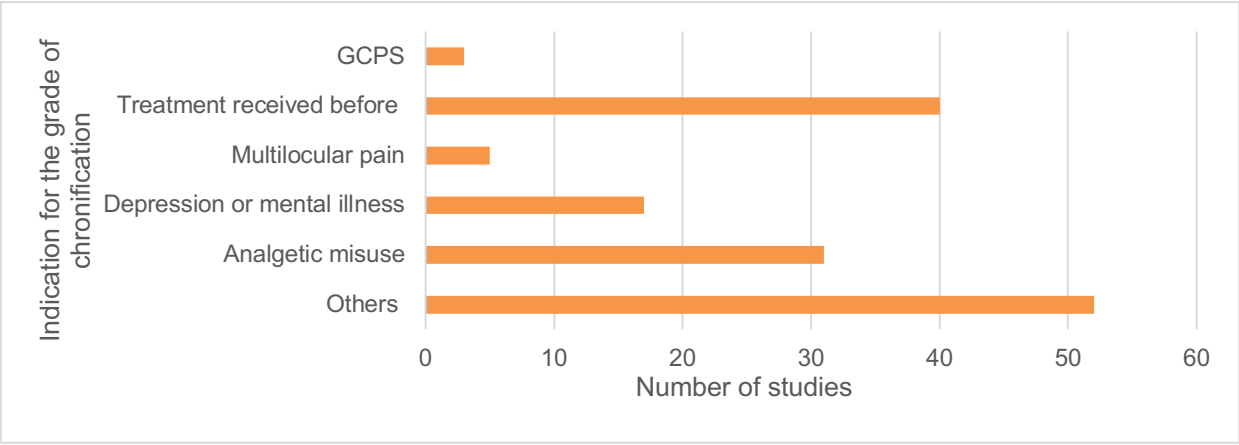


Figure 17: Hints of the degree of chronification, found in the included studies for laser; GCPS= Graded Chronic Pain Scale

Table 12: Hints of the degree of chronification, found in the included studies for laser

Hints	Low disability	High disability	Mixed	Unclear (low disability)	Unclear (high disability)
Graded chronic pain scale	Manfredini, 2018 Öz, 2010		Brochado 2018		
Previous treatment	Ahmad 2017 Ahrari 2014	Amanat 2013 Bertolucci 1995	Kulekcioglu 2003	-	-

Hints	Low disability	High disability	Mixed	Unclear (low disability)	Unclear (high disability)
	Borges 2018 Costa 2017 De Cunha 2008 De Abreu Venancio 2005 De Carli 2016 De Moraes Maia 2014 De Oliveira 2017 De Oliveira 2020 Del Vecchio 2019 Herpich 2015 Herpich 2018 Juliana Cristina 2008 Khalighi 2016 Kogawa 2005 Machado 2016 Madani 2014 Madani 2020 Magri 2017 Mazzetto 2007 Mazzetto 2010 Öz 2010 Panhoca 2015 Pihut, 2018 Rohling 2011 Shirani 2009 Shobha 2017 Uemoto 2013 Venezian 2010 Yamaner 2020	Chellappa 2020 Emshoff 2007 Marini 2010 Molina-Torres 2016 Seifi 2017			
Multilocular pain	Hosgor 2017 Shobha 2017		Kulekcioglu 2003	Fornaini 2015 Sattayut 2012	
Depression or mental illness	Altindis 2019 Da Silva 2012 De Abreu Venancio De Carli 2016 Del Vecchio 2019 Kogawa 2005 Madani 2014 Madani 2020 Nadershah 2020 Öz, 2010 Panhoca 2015 Rohling 2011 Sancakli 2015 Shobha 2017 Yamaner 2020	Amanat 2013 Rezazadeh 2017	-	-	-
Analgetic misuse	Ahrari 2014 Borges 2018 Carrasco 2008 Costa 2017 Da Silva 2012 de Oliveira 2017 Del Vecchio 2019 Herpich 2018 Herpich 2020 Hosgor 2017 Juliana Cristina 2008 Keskin 2020 Khalighi 2016 Madani 2014 Madani 2020 Magri 2017 Mazzetto 2007	Marini 2010 Rezazadeh 2017	de Carli 2013	Khairmar 2019	De Souza 2018

Hints	Low disability	High disability	Mixed	Unclear (low disability)	Unclear (high disability)
	Mazzetto 2010 Panhoca 2015 Pereira 2014 Rodrigues 2018 Rohling 2011 Shirani 2009 Shobha 2017 Uemoto 2013 Venezian 2010				
Others	Ahmad 2017 Ahrari 2014 Altinis 2019 Carrasco 2008 De Cunha 2008 Da Silva 2012 De Abreu Venancio 2005 De Carli 2016 De Moraes Maia 2014 De Oliveira 2017 De Oliveira 2020 Del Vecchio 2019 Herpich 2015 Herpich 2018 Herpich 2020 Juliana Cristina 2008 Khalighi 2016 Kogawa 2005 Machado 2016 Madani 2014 Madani 2020 Magri 2017 Mazzetto 2007 Mazzetto 2010 Nadershah 2020 Pereira 2014 Pihut, 2018 Rohling 2011 Sancakli 2015 Shirani 2009 Shobha 2017 Uemoto 2013 Venezian 2010 Yamaner 2020	Amanat 2013 Bertolucci 1995 Chellappa 2020 Emshoff 2008 Marini 2010 Molina-Torres 2016 Rezazadeh 2017 Seifi 2017	De Carl 2013 Kulekcioglu 2003	Demirkol 2017 Sattayut 2012	Carrasco 2009 De Souza 2018 Frare 2008 Lassemi 2008 Mansourian 2019

3.2.4.2.3 Recruitment of the subjects

51 of the 65 studies could be assigned to tertiary care (Figure 18). This corresponds to a sample of 2380 subjects, but independent of control groups, the diagnostic instrument used, the outcomes measured and the study duration. The subjects were mainly treated in a specialized clinic or were referred to this clinic and thus were able to participate in the respective study. In some cases, it was stated by the author that the study had taken place in the clinic. 186 subjects from five studies came from specialized TMD clinics. Another 74 patients from two studies were recruited from the general population or from dental practices and were thus assigned to primary care. Eight trials did not have a description of the care level from which the subjects originated.

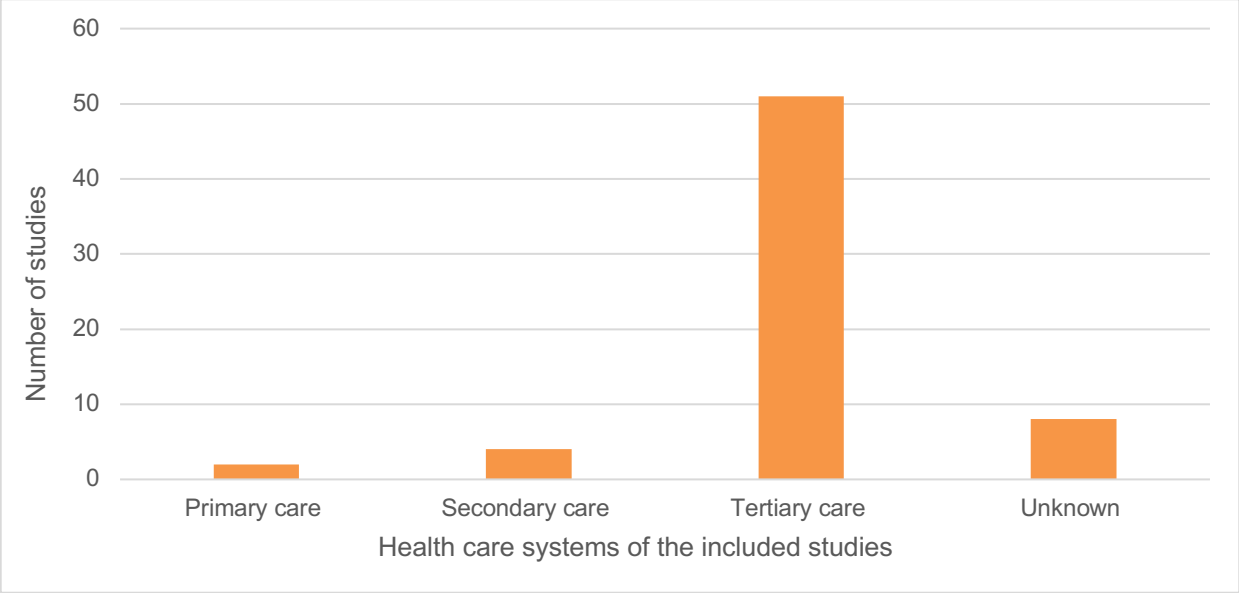


Figure 18: Recruitment of subjects in the included studies of laser therapy

3.2.4.3 Characteristics of the interventions

3.2.4.3.1 Outcomes

3.2.4.3.1.1 Primary outcome – pain at rest

Pain was assessed using the VAS [181, 195, 203, 210-214, 216, 218, 220-225, 227-233, 236-250, 252-258, 262-265, 267-272], the number of trigger points [213, 249, 260], pain related limitations in daily function (LDF-TMDQ), numerical scale (NS) [219, 235, 259, 261], presence or absence of pain (%), pain rating index (McGill pain questionnaire) [266] or the craniomandibular index [212, 253].

3.2.4.3.1.2 Secondary outcomes

30 RCTs investigated mouth opening (MO) [181, 210, 211, 213, 216, 218, 221, 222, 227-232, 242-247, 249, 254, 256, 258, 259, 264-266, 269, 271]. 16 studies investigated pain upon palpation using the VAS score [181, 212, 219, 228, 229, 231, 234, 236, 247, 248, 251, 255, 258, 260, 264, 270]. Six studies focused on joint noises either present or absent [213, 243, 249, 250, 264, 269]. Öz et al. 2010 [258] was the single study which investigated depression using the RCD/TMD for the laser studies. No study to date investigated somatization.

3.2.4.3.2 Laser interventions

There were ten different types of laser treatment among the 65 included studies. GaAlA laser was applied in 29 studies [181, 210-212, 218, 222, 224-226, 229-233, 236, 239, 247, 248, 251, 252, 254, 255, 262, 263, 266, 267, 269-271], GaAs laser in eight studies [220, 240, 244, 249, 250, 264, 265, 268], and Nd:YAG laser in three studies [216, 238, 243]. He-NE laser [214], InGaAlP laser [268], and diode laser [217, 219, 227, 245, 257, 258] were applied in three studies. Bio -stimulation laser was used in three studies [223, 228, 261] and infrared

laser in six studies [195, 221, 235, 259, 260, 272]. Herpich et al. used super-pulsed laser [203, 241, 242]. The type of laser used was not stated in six studies [213, 217, 234, 237, 246, 253, 256-258].

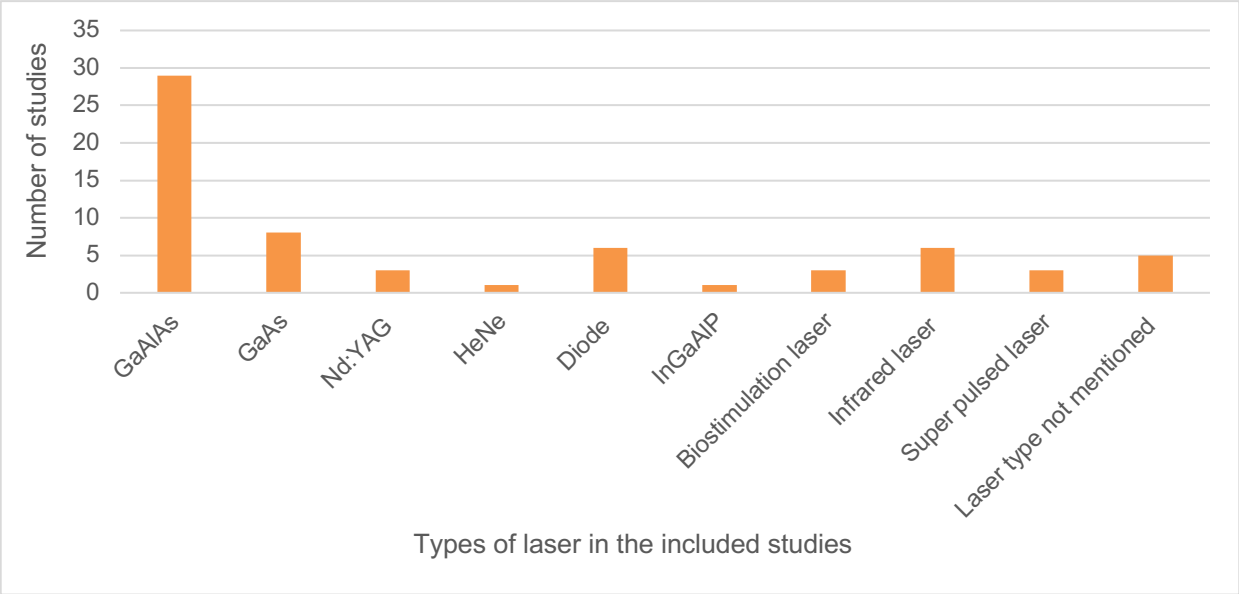


Figure 19: Types of laser therapy used in the included studies

3.2.4.3.3 Control groups

The majority of the included studies compared LLLT and placebo groups [181, 195, 210-213, 218, 220-222, 224-226, 228-230, 252, 255, 257, 259, 263-266, 268-271]. Two of these studies included combined interventions applied equally to both LLLT and placebo groups. In one study, LLLT was combined with piroxicam [231] and in the other, it was combined with oral motor (OM) exercises [251]. Three studies compared red laser versus infrared laser [235, 259, 260]. Two studies using a placebo group investigated the combination of two types of laser: one study applied indium-gallium-aluminium-phosphide laser (InGaAlP) (660 nm) and GaAs laser (890 nm) [268], while the other applied neodymium-doped yttrium aluminium garnet (Nd:YAG) laser (1064nm) and diode laser (810nm) [238]. One combined Ga-Al-A laser at two wavelengths (650 nm/830 nm) [271]. Six studies used only one laser type, but with two or three laser dosages [203, 222, 229, 241, 266, 270]. There was one study that applied one type of laser, but at two application sites [265]. Seven studies included other interventions to the placebo group, namely, drugs [211, 237], acupuncture or needling [181, 195], controls (no treatment or healthy) [252, 263] and physiotherapeutic and drug protocol (PDP) [226]. The remainder of the included studies used different combined interventions: splint therapy [216, 219, 243, 245, 253, 256, 258, 261], TENS [227, 254, 262, 267], MT [217, 223, 244], drugs [232, 236, 247], ultrasound [246], Microcurrent Nerve Stimulation (MENS) [248], Ozon therapy [272].

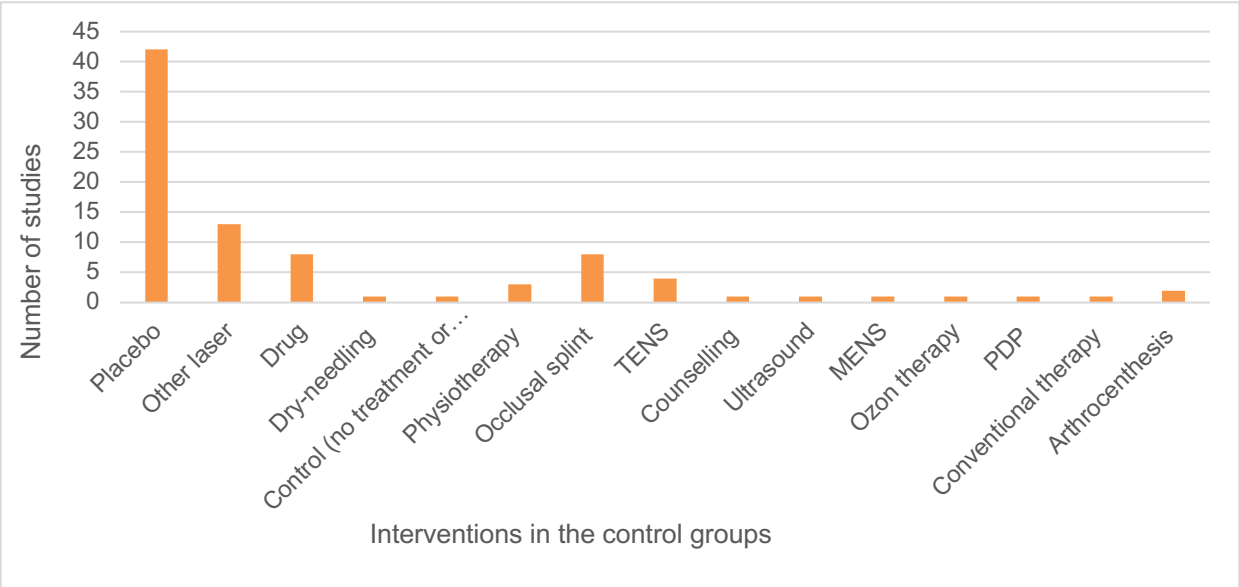


Figure 20: Bar chart of the different interventions in the control groups of laser interventions; TENS= Transcutaneous electrical nerve stimulation; MENS= Microcurrent Electrical Nerve Stimulation; PDP=Physiotherapeutic and Drug Protocol

3.2.4.3.4 Follow up periods

The final follow-up time point varied from immediately following the intervention [212, 221, 222, 236, 237, 240, 246, 257, 264, 265], up to 1 month [181, 195, 203, 210, 211, 213, 217-220, 223-235, 238, 239, 241-245, 247-254, 256, 259-263, 267-270], up to 3 months [214, 258, 266, 271, 272] or up to 6 months [216] after completing the treatment.

3.2.4.3.5 Application site

The LLLT application site was the treatment condition that diverged most among the studies. LLLT was applied to the TMJ in eleven studies [210, 211, 214, 217, 221, 225, 230, 239, 245, 246, 269, 271, 272], to the masticatory muscles in 17 studies [195, 203, 218, 224, 228, 231, 233, 234, 236, 238, 247, 253, 261, 264, 265, 268, 270], to a combination of TMJ and masticatory muscles [181, 212, 213, 216, 219, 223, 226, 227, 229, 232, 234, 241, 243, 248-252, 257, 259, 260, 262, 263, 266], to the tender points or trigger points [237, 256, 258, 267] or to the pre auricular points [222, 240, 244, 255]. Three studies did not state the application site [220, 242, 254].

3.2.4.3.6 Wavelengths

The wavelength of the laser treatment was placed into four categories 660-779nm [227, 246], 780-799nm [195, 214, 224-226, 229, 230, 234, 236, 251, 252, 255, 259, 263, 268, 270], 800-830nm [181, 210, 212, 218, 222, 223, 228, 231-234, 237, 239, 247, 253, 254, 258, 260, 261, 264-267, 269, 271, 272], >831nm [203, 211, 216, 217, 219-221, 238, 240-245, 248-250, 257, 262, 268] and one RCT didn't report the wavelength [256].

3.2.4.3.7 Laser dosage

Laser dosage varied from 1.5 J/cm2 to 300 J/cm2. Eight studies did not report the dosage [211, 221, 239, 247, 250, 261, 267, 271].

3.2.4.3.8 Treatment sessions

Participants received a total of between 1 to 20 treatment sessions. The number of applications and the treatment time differed considerably among the studies, ranging from a single application of 20 seconds, and 20 seconds to 1200 seconds.

3.2.5 Excluded studies

33 studies were excluded for reasons declared in the corresponding table in Appendix VIII (Characteristics of excluded studies: Laser).

3.2.6 Assessment of the methodological quality of the included studies

High heterogeneity was observed between studies of the laser therapy application. Most of these trials inadequately described the demographics of the participants and the randomization methods. The included RCTs were mainly at risk of unclear bias. (See Figure 21, Figure 22). Because of the relatively simple design of the studies, blinding was not reported in all trials comparing LLLT with sham LLLT (not active laser) [195, 210, 212, 217, 222, 226-228, 233, 236, 238, 245, 246, 248-250, 254, 259, 262, 267, 269, 271]. An exception was Marini et al. [211] who described intention-to-treat (ITT) analysis. Moreover, nine studies were deemed at high risk according to the risk of bias tool [211, 220, 223, 243, 251, 259, 261, 262, 266]. Five RCTs [211, 220, 243, 259, 266] did not fulfil all the outcomes from the study protocol. Two trials [223, 261] informed the patients or the examiner about the treatment they were receiving or providing. At baseline, in the RCT of Machado et al. [251], an intergroup comparison indicated a significant difference between the treatment group and the control group and the study by Rezazadeh et al. [262] only partly described the drop out numbers participating in the study. Pihut et al. [261] was the one trial that received two high risk evidence of bias (allocation concealment and blinding of outcome assessment), and needed to be appraised carefully in the meta-analysis.

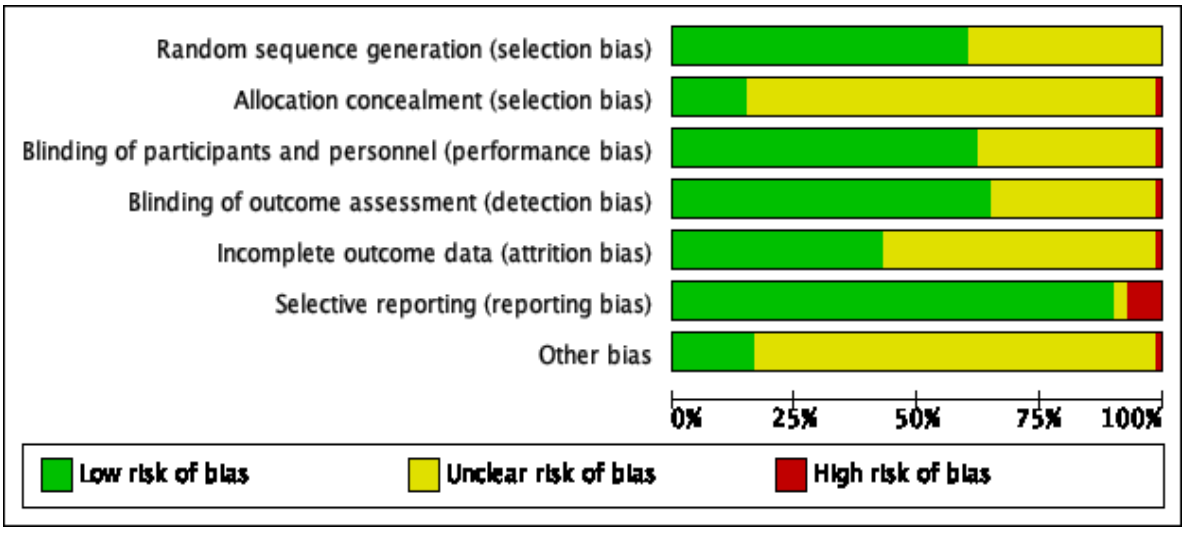


Figure 21: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

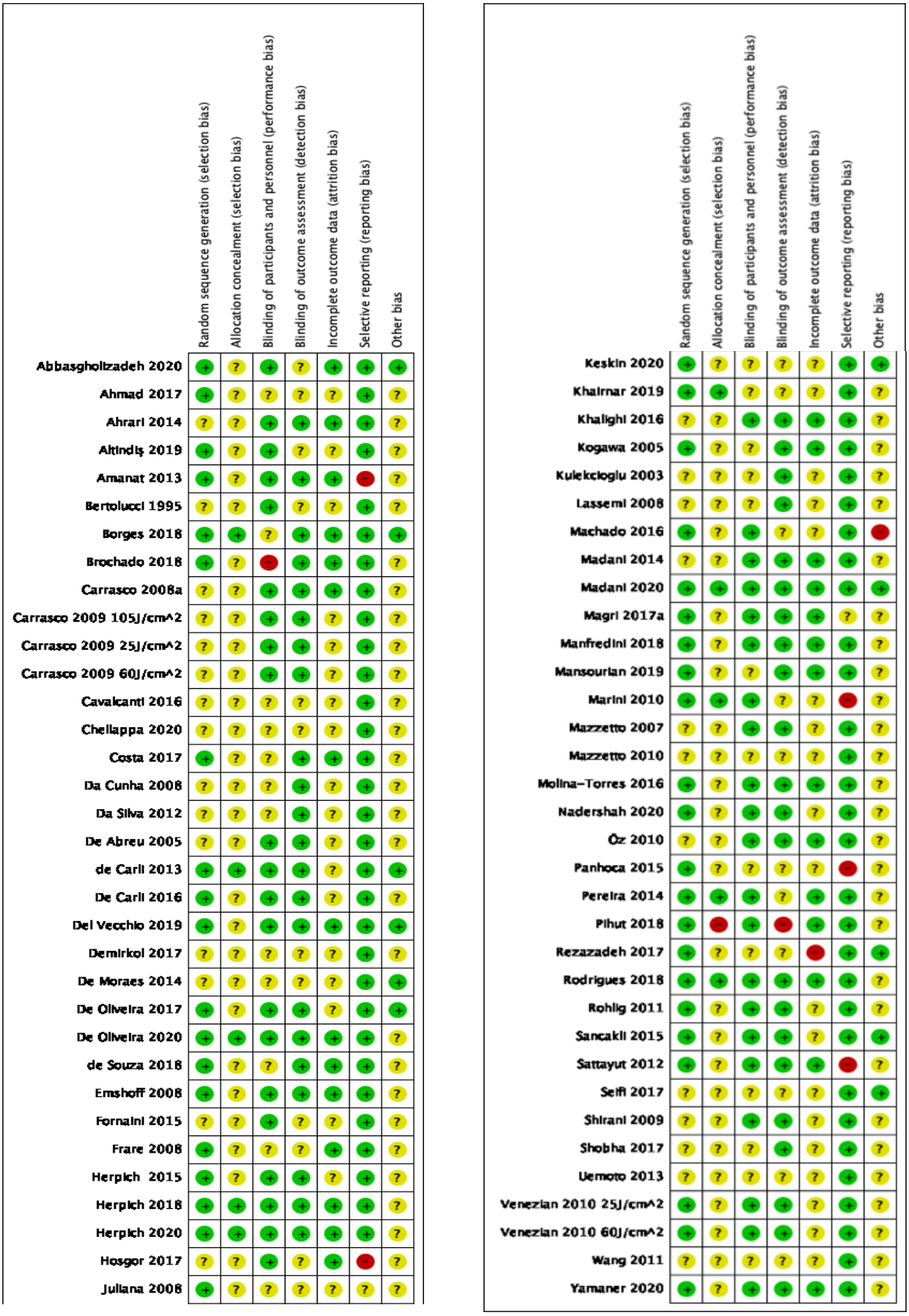


Figure 22: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

3.2.7 Results of the quantitative synthesis of the included studies (Meta-analysis)

In this section of the paper, statistically significant or not statistically significant with relevant results are described below. We had to restrict ourselves to only include the major meta-analysis. The presentation of all results would have gone beyond the scope of this paper. For the sake of comprehensiveness, the remaining forest plots with further results from this study are presented in *APPENDIX X: Funnel plots*.

We decided to only include meta-analysis with a minimum of three studies.

For the meta-analysis, 50 RCTs were selected. Out of the 65 included studies that were able to pass the full-text screening, a total of 15 studies were excluded for the quantitative comparison. The reasons for exclusion were as follows:

1. Combination of therapies used for the study group (five studies) [216, 217, 244, 245, 251]
2. Missing data on the outcomes (two studies) [211, 257]
3. Data collection/presentation was different from the other included studies (six studies) [226, 229, 235, 255, 259, 260, 263]
4. Study group too small (one study) [224] (studies with fewer than seven subjects per intervention group)

A tabular overview of the statistically significant results for the pain group with low disability and with high disability is presented in 3.2.8 for the reduction of pain intensity (Table 13) and MMO (Table 14).

A SMD of zero indicates that the intervention group and the control group have equal effects. For pain reduction, an improvement is associated with lower values in the outcome measure. SMDs less than zero indicate that the intervention group is more effective than the control group. Therefore, a negative direction with lower values corresponds to better performance of the intervention group. Conversely, for MMO improvement, improvement is associated with higher values on outcome measures. A positive direction with higher values corresponding to better performance of the intervention group under study [200].

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guideline states that a 30% pain reduction in chronic pain is necessary to distinguish placebo from verum [201]. This means that the initial pain intensity is considered clinically relevant in clinical studies and the interventions are evaluated as effective in this respect [202]. To

obtain the clinical significance, the author added a small comment on each forest plot obtaining the data from the pain reduction from the baseline compared to the follow up time.

3.2.7.1 Comparison: Effectiveness of laser treatment in comparison to other treatments per type of chronicity (low disability, high disability, mixed or unclear pain)

3.2.7.1.1 Primary outcome parameter: pain intensity

3.2.7.1.1.1 Short-term efficacy (treatment duration up to six months)

Meta-analysis of data from 852 participants across 22 studies indicated no statistically significant different reduction in total pain scores with LLLT versus other treatment, as seen in Figure 23. The overall effect for pain favoured LLLT (n=22 studies [n=427 for Group A, and n=425 for Group B], SMD=-0.30; 95% CI [-0.66, 0.07]; p=0.11), yet with substantial heterogeneity Ch^2=0.55 (I^2=84%). Subgroup analysis showed no significant differences between LLLT and other treatment groups of patients suffering from low disability pain (n=14 studies [n=252 for Group A , and n=249 for Group B], SMD=-0.42; 95% CI [-0.99, 0.15]; p=0.15, I^2=88%), high disability pain (n=6 studies [n=150 for Group A, and n=153 for Group B], SMD=-0.20; 95% CI [-0.65, 0.26]; p=0.40, I^2=73%) or mixed pain group (n=2 studies [n=25 for Group A, n=23 for Group B], SMD=0.09; 95% CI [-0.48, 0.66]; p=0.76, I^2=0%). The low disability pain subgroup and the high disability pain subgroup showed the same predisposition to favour laser in reducing pain in the short term (less than six months).

By undertaking sensitivity analysis and excluding the outlier Khalighli et al. 2016 (Figure 77, APPENDIX IX: Forest plots), no change was observed in the low disability pain group. However, the total pain group, showed no significant result following the exclusion. We found no explanation for the outlier as the study was not at high risk of bias. The study used a GaAIA laser for the experiment group and naproxen as the control group.

All included studies on low disability pain and mixed pain showed a clinical significance of 30% pain reduction in the intervention group. On the other hand, half of the included studies on high disability pain [256, 262, 267] did not show clinical significance of 30% pain reduction.

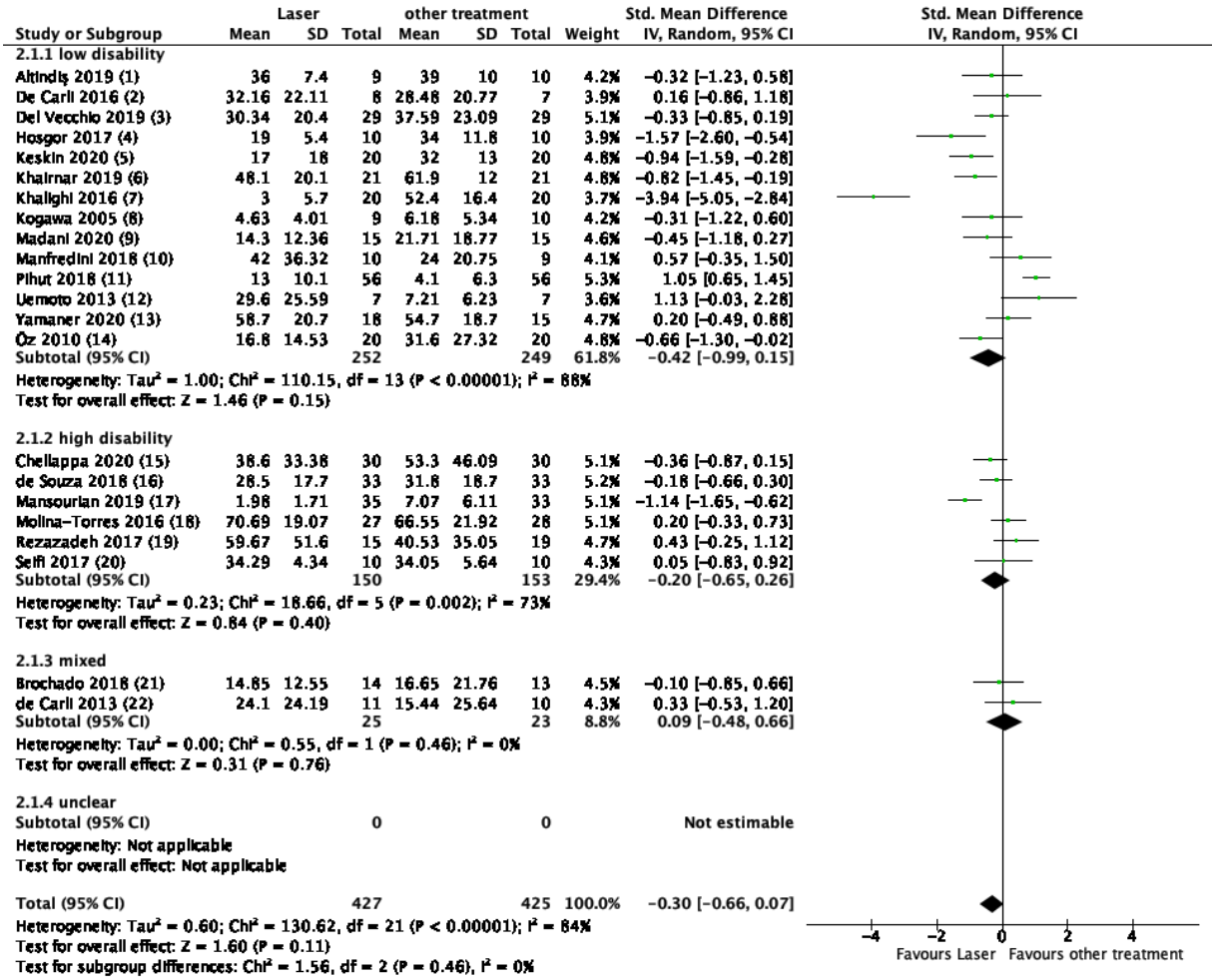


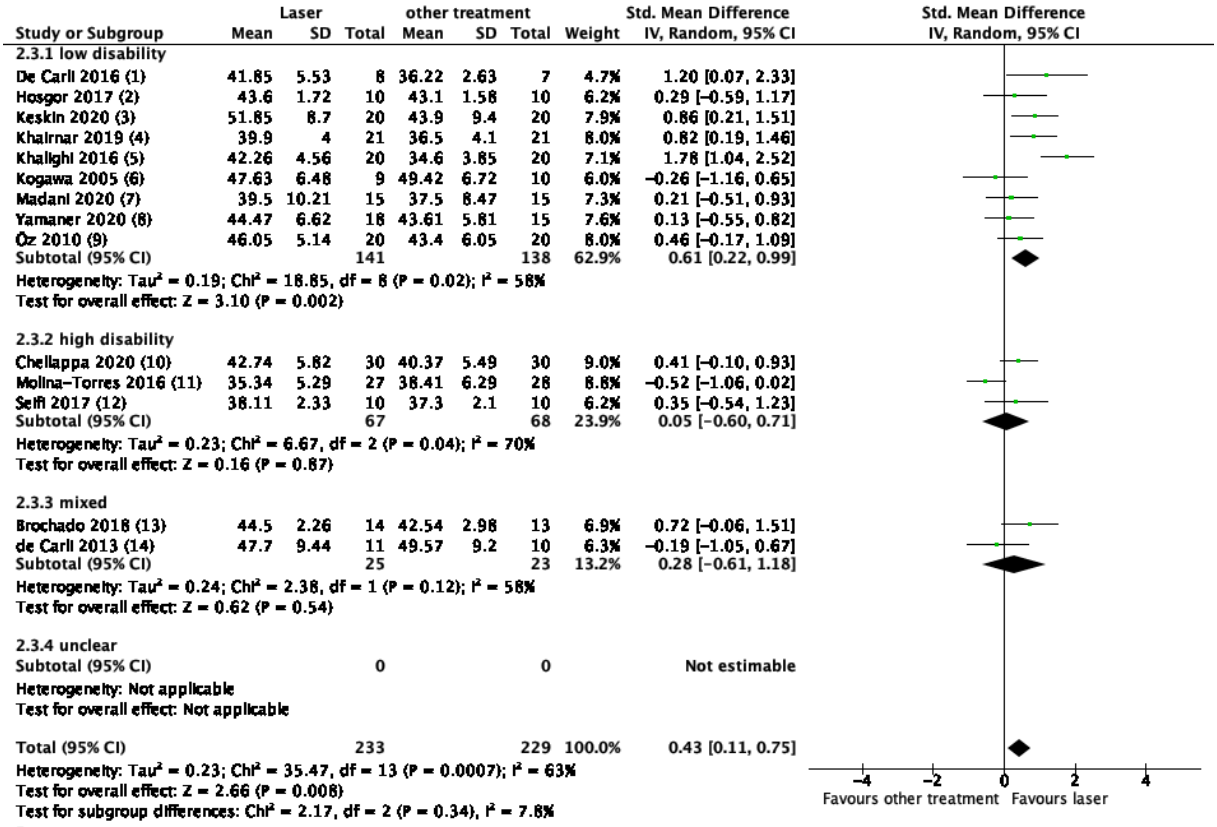
Figure 23: Laser vs. other treatment (outcome: change in pain intensity, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.2.7.1.2 Secondary outcome parameter: MMO

3.2.7.1.2.1 Short-term efficacy (treatment duration up to six months)

Laser is statistically significant more effective than other treatment in increasing MMO in a timeframe of less than six months (n=14 studies [n=233 for Group A, n=229 for Group B], SMD=0.43; 95% CI [0.11, 0.75]; p=0.008, I^2=63%), seen in Figure 24. The subgroup analysis

for low disability pain also showed a significant bigger difference favouring the laser treatment (n=9 studies [n=141 for Group A, n=138 for Group B], SMD=0.61; 95% CI [0.22, 0.99]; p=0.002, I^2=58%), whereas the subgroup of high disability pain (n=3 studies [n=67 for Group A, n=68 for Group B], SMD=0.05; 95% CI [-0.60, 0.71]; p=0.87, I^2=70%) showed no significant difference. The population with mixed pain demonstrated the same tendency as the low disability subgroup (n=2 studies [n=25 for Group A, n=23 for Group B], SMD=0.28; 95% CI [-0.61, 1.18]; p=0.54, I^2=58%). By examining the application of laser to the low disability group, we detected a pattern as all nine studies used the painful region or trigger points as the application site; none used acupuncture points.



Footnotes
(1) GaAlAs laser vs botulinum toxin: Mouth opening (mm); TMD of muscular origin
(2) Nd:YAG laser vs splint: Maximum mouth opening (mm); TMD of muscular and articular origin
(3) NSAID and occlusal splint vs NSAID, occlusal splint and laser: MMO (mm); disc displacement with reduction
(4) Type Class III B and Class 2M laser machine LLLT vs ultrasound therapy: Maximum mouth opening (mm); TMD of articular origin
(5) GaAlAs laser vs Naproxen : Maximum painless mouth opening (mm); TMD of muscular origin
(6) GaAlAs laser vs MENS: Active range of motion mouth opening (AROM); TMD of muscular and articular origin
(7) GaAlAs LLLT vs laser acupuncture therapy: Mouth opening (mm); TMD of muscular and articular origin
(8) Infra red laser LLLT vs Ozone Group: Maximum mouth opening (mm); disc displacement with reduction
(9) Diode laser vs OA: active and passive mouth opening (mm); TMD of muscular origin
(10) Diode LLLT vs TENS: MMO (mm); TMD of muscular and articular origin
(11) Laser vs OA: Active and passive mouth opening (mm); TMD of muscular and articular origin
(12) GaAlAs laser vs TENS : Mouth-opening (mm); TMD of muscular and articular origin
(13) Biostimulation laser vs manual therapy: Maximum mouth opening (mm); TMD of muscular and articular origin
(14) GaAlAsLaser + piroxicam vs laser + placebo piroxicam vs placebo laser + piroxicam: Maximum mouth opening (mm); TMD of mixed origin

Figure 24: Laser vs. other treatment (outcome: change in MMO, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.2.7.2 Comparison: Effectiveness of laser treatment in comparison to placebo per type of chronicity (low disability, high disability, mixed or unclear pain)

3.2.7.2.1 Primary outcome parameter: pain intensity

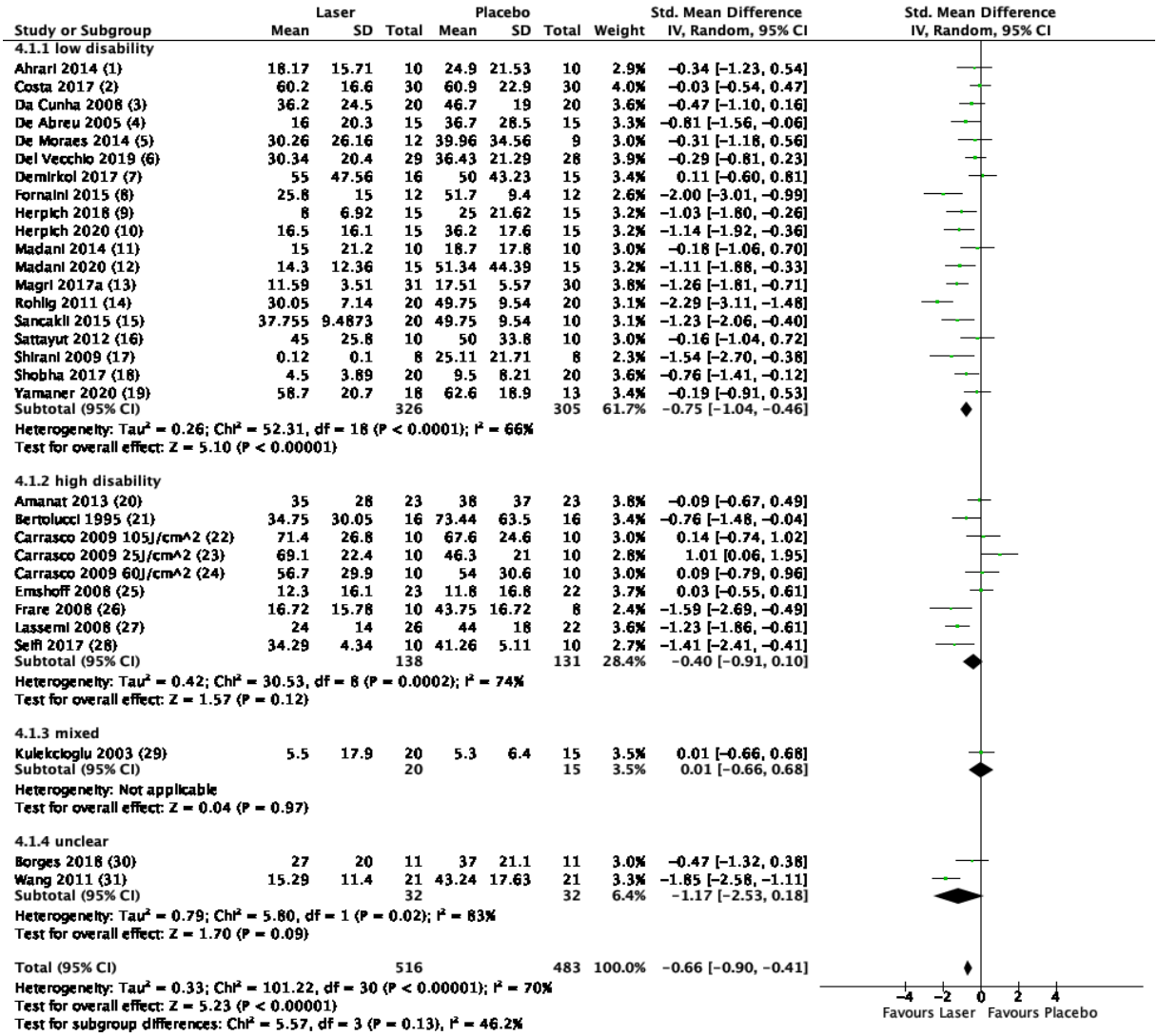
3.2.7.2.1.1 Short-term efficacy (treatment duration up to six months)

Laser is statistically significant more effective than placebo in reducing pain intensity in a timeframe of less than six months (n=31 studies [n=516 for Group A, and n=483 for Group B], SMD=-0.66; 95% CI [-0.90, -0.41]; p<0.00001, I^2=70%) (Figure 25).
The subgroup of low disability pain (n=19 studies [n=326 for Group A, and n=305 for Group B], SMD=-0.75; 95% CI [-1.04, -0.46]; p <0.0001, I^2 =66%) showed a statistical significance superiority in reducing pain intensity using the laser treatment. The subgroup with high disability pain (n=9 studies [n=138 for Group A, and n=131 for Group B], SMD=-0.40; 95% CI [-0.91, 0.10]; p=0.12, I^2=74%) favoured laser treatment but without bigger statistical significance. The unclear pain subgroup (n=2 studies [n=32 for Group A, and n=32 for Group B], SMD=-1.17; 95% CI [-2.53, 0.18]; p=0.09, I^2=83%) showed no statistical significance in the laser group. The mixed pain group was not further investigated due to the lack of studies in this pain group (n=1).

We decided to create another sub-group analysis and focus on the different wavelengths of the included studies to ascertain if there was a difference upon chronification. We therefore classified the wavelengths into 780-799 nm, 800-830 nm and over 831 nm.
The subgroup of lasers with 780-799 nm (Figure 78, APPENDIX IX: Forest plots) showed the same tendency as laser treatment compared to placebo above, without significance in reducing pain intensity for total pain (n=6 studies [n=99 for Group A, and n=97 for Group B], SMD=-0.18; 95% CI [-0.84, 0.47]; p=0.59, I^2=79%). The number of studies with this subgroup was limited. Low disability pain (n=2 studies [n=46 for Group A, and n=45 for Group B], SMD=-1.10; 95% CI [-1.55, -0.66]; p<0.00001, I^2=0%) and the high disability pain group (n=4 studies [n=53 for Group A, and n=52 for Group B], SMD=0.23; 95% CI [-0.17, 0.64]; p=0.26, I^2=6%) showed the opposite tendency in favour of placebo treatment. The mixed group and the unclear group were not assessed because no suitable studies with a wavelength of 780-799 nm were available.
Lasers with the wavelengths of 800 to 830 nm (Figure 79, APPENDIX IX: Forest plots) are statistically significant more effective compared to placebo in reducing pain intensity (n=17 studies [n=293 for Group A, and n=269 for Group B], SMD=-0.78; 95% CI [-1.12, -0.45]; p<0.00001, I^2=71%). It also showed a statistically significant superiority for the low disability pain group (n=11 studies [n=231 for Group A, and n=212 for Group B], SMD=-0.75; 95% CI [-1.11, -0.38]; p<0.0001, I^2=69%), for the unclear pain group (n=2 studies [n=32 for Group A, and n=32 for Group B], SMD=-1.17; 95% CI [-2.53, 0.18]; p=0.09, I^2=83%) in reducing pain

intensity compared to placebo. The population with high disability pain (n=1) and mixed pain was not assessed because no suitable studies with the wavelengths of 800nm to 830nm were available for the subgroup.
The number of studies for the last subgroup was also limited. We found the same effect as with 800-830nm. Lasers with the wavelengths > 831 nm were statistically more significant and found to be more effective than placebo in pain relief in immediate to six months change~~s~~ in clinical outcomes (n=8 studies [n=151 for Group A, and n=139 for Group B], SMD=-0.77; 95% CI [-1.26, -0.28]; p=0.002, I^2=74%, Figure 80, APPENDIX IX: Forest plots). This was also shown for the high disability pain (n=4 studies [n=75 for Group A, and n=69 for Group B], SMD=-0.85; 95% CI [-1.49, -0.20]; p=0.01, I^2=69%). In the low disability pain group (n=2 studies [n=24 for Group A, and n=23 for Group B], SMD=-0.65; 95% CI [-2.26, 0.96]; p=0.43, I^2=82%), and the subgroups of mixed (n=1) unclear pain (n=2) a positive tendency was seen in favour of laser therapy with a wavelength more than 831nm compared to placebo therapy.

Apart from Costa et al. 2017 and Sattayut et al. 2012, a clinical significance (30% pain reduction) was observed in all included studies on low disability pain. In the high disability pain group, the studies of Carrasco et al. 2009 and Seifi et al. 2017 showed no clinical significance.



Footnotes

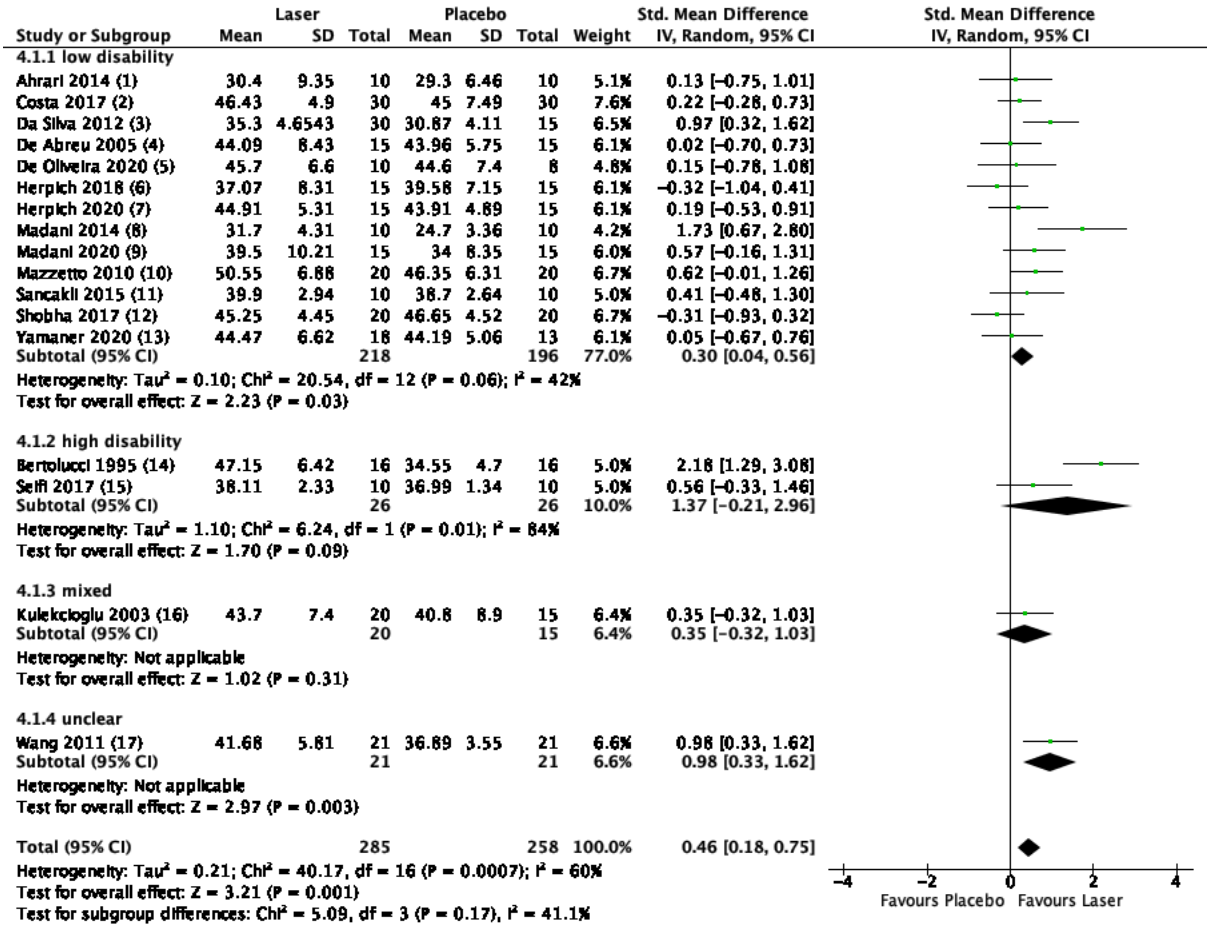
(1) GaAlAs laser vs placebo: Pain (VAS); TMD of muscular origin
(2) Biostimulation laser vs placebo: Pain (VAS); TMD of muscular and articular origin
(3) GaAlAs laser vs placebo: Pain (VAS); TMD of muscular origin
(4) GaAlAs laser vs placebo; Pain (VAS); TMD of muscular and articular origin
(5) GaAlAs laser vs placebo: Pain (VAS); TMD of muscular and articular origin
(6) Laser vs placebo: Pain (VAS); TMD of muscular and articular origin
(7) Nd:YAG laser vs placebo: Pain (VAS); TMD of muscular origin
(8) GaAlAs laser vs placebo: Pain (VAS); TMD of articular origin
(9) Laser superpulsed vs placebo: Pain (VAS); TMD of muscular origin
(10) Laser superpulsed vs placebo: Pain (VAS); TMD of muscular and articular origin
(11) Mustang 2000z, Moscow, Russia Laser vs placebo: Pain (VAS); TMD of muscular and articular origin
(12) GaAlAs LLLT vs placebo: Pain (VAS); TMD of muscular and articular origin
(13) GaAlAs laser vs placebo: Pain (VAS); TMD of muscular and articular origin
(14) GaAs laser vs placebo: Pain (VAS); TMD of muscular origin
(15) GaAs laser vs placebo: Pain (VAS); TMD of muscular origin
(16) GaAlAs laser vs placebo: Symptom severity index (SSI); TMD of muscular and articular origin
(17) GaAs laser vs placebo: Pain (VAS); TMD of muscular origin
(18) GaAlAs laser vs placebo: Pain (VAS) pain; TMD of muscular and articular origin
(19) Infra red laser LLLT vs Sham Laser: Pain (VAS); diagnosed with disc displacement with reduction
(20) GaAs laser vs placebo: Pain (VAS); TMD of muscular origin
(21) Infra red laser vs placebo: Pain Index (VAS); TMD of articular origin
(22) GaAlAs laser vs placebo: Pain (VAS); TMD of muscular and articular origin
(23) GaAlAs laser vs placebo: Pain (VAS); TMD of muscular and articular origin
(24) GaAlAs laser vs placebo: Pain (VAS); TMD of muscular and articular origin
(25) HeNe laser versus placebo: Pain (VAS); TMD of muscular and articular origin
(26) GaAs laser vs placebo: Pain (VAS); TMD of muscular and articular origin
(27) GaAs laser vs placebo: Pain (VAS); TMD of muscular origin
(28) GaAlAs laser vs sham laser: Pain (VAS); TMD of muscular and articular origin
(29) GaAs laser vs placebo: Pain (VAS), TMD of muscular and articular origin
(30) GaAlAs laser vs placebo: Pain (VAS); TMD of muscular and articular origin
(31) GaAlAs laser vs placebo: Pain (VAS); TMD of muscular and articular origin

Figure 25: Laser vs. placebo (Outcome: change in pain intensity, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.2.7.2.2 Secondary outcome parameter: MMO

3.2.7.2.2.1 Short-term efficacy (treatment duration up to six months)

Laser is statistically significant more effective than a placebo in increasing MMO within a timeframe of less than six months (n=17 studies [n=285 for Group A, and n=258 for Group B], SMD=0.46; 95% CI [0.18, 0.75]; p=0.001, I^2=60%), as seen in Figure 26. The subgroup of low disability pain (n=13 studies [n=218 for Group A, and n=196 for Group B], SMD=0.30; 95% CI [0.04, 0.56]; p=0.03, I^2=42%) showed a significant difference favouring laser treatment. The subgroup with high disability pain (n=2 study [n=26 for Group A, and n=26 for Group B], SMD=1.37; 95% CI [-0.21, 2.96]; p=0.09, I^2=84) favoured laser without statistical significance difference. The population with mixed pain and unclear pain were represented by only one study each and therefore not examined any further. All four subgroups had the same tendency toward favouring the laser group within a timeframe of less than six months compared to the placebo group.



Footnotes

(1) GaAlAs laser vs placebo: Maximum mouth opening (mm); TMD of muscular origin
(2) Biostimulation laser vs placebo: Mouth opening measurements (mm); TMD of muscular and articular origin
(3) Low energy laser vs high energy laser vs placebo: Maximum pain-free mouth opening (mm); TMD of muscular and articular origin
(4) GaAlAs laser vs placebo; Maximum mouth opening (mm); TMD of muscular and articular origin
(5) LLLT vs placebo: Maximum mouth opening; TMD of muscular origin
(6) Laser superpulsed vs placebo: Vertical mouth opening mandibular movement (mm); TMD of muscular origin
(7) Laser superpulsed vs placebo: Maximum mouth opening (mm); TMD of muscular and articular origin
(8) Mustang 2000z, Moscow, Russia Laser vs placebo: Maximum mouth opening (mm); TMD of muscular and articular origin
(9) GaAlAs LLLT vs placebo: Maximum mouth opening (mm); TMD of muscular and articular origin
(10) GaAlAs laser vs placebo: Maximum mouth opening (mm); TMD of articular origin
(11) GaAs laser vs placebo: Maximum mouth opening (mm); TMD of muscular origin
(12) GaAlAs laser vs placebo: Maximum mouth opening (mm); TMD of muscular and articular origin
(13) Infra red laser LLLT vs Sham Laser: Maximum mouth opening (mm); diagnosed with disc displacement with reduction
(14) Infra red laser vs placebo: Maximum mouth opening (mm); TMD of articular origin
(15) GaAlAs laser vs sham laser: Maximum mouth opening (mm); TMD of muscular and articular origin
(16) GaAs laser vs placebo: Maximum mouth opening (mm), TMD of muscular and articular origin
(17) GaAlAs laser vs placebo: Maximum mouth opening (mm); TMD of muscular and articular origin

Figure 26: Laser vs. placebo (outcome: maximum mouth opening, timeframe: less than six months); low disability= acute pain; high disability = chronic pain; mixed = acute and chronic pain; unclear = pain not identified

3.2.8 Tabular overview of the results of the comparisons for laser

The results of the comparisons performed for laser interventions are listed below in Table 13 for pain intensity and in Table 14 for MMO:

Table 13: Tabular overview of the results of laser regarding pain intensity categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval

Reduction of pain intensity		
Comparison	**Statistically significant results**	**Data**
Laser vs. (any) other treatment	Short-term: no ss less pain for low disability, high disability, or total pain by using laser therapy compared to any other treatment.	Short-term: Low disability: (SMD=-0.42; 95% CI [-0.99, 0.15]; *p*=0.15; I^2=88%) High disability: (SMD=-0.20; 95% CI [-0.65, 0.26]; *p*=0.40; I^2=73%) Total: (SMD=-0.30; 95% CI [-0.66, 0.07]; *p*=0.11; I^2=84%)
Laser vs. placebo	Short-term: **significant less pain after laser treatment than after placebo treatment for low disability and total pain.** No ss less pain in the high disability pain group and unclear pain group using laser treatment. *Subgroup analysis: no ss less pain using laser (wavelengths of 780-799 nm) treatment than using placebo treatment.* *Subgroup analysis:* ***significant less pain after laser treatment (800-830 nm) than after placebo treatment for low disability and total pain.*** *Subgroup analysis:* ***significant less pain after laser treatment (>831 nm) than after placebo treatment for high disability and total pain.***	Short-term: **Low disability: (SMD=-0.75; 95% CI [-1.04, -0.46]; *p*<0.0001; I^2=66%)** High disability: (SMD=-0.40; 95% CI [-0.91, 0.10]; *p*=0.12; I^2=74%) **Total: (SMD=-0.66; 95% CI [-0.90, -0.41]; *p*<0.0001; I^2=70%)**

Table 14: Tabular overview of the results of laser regarding MMO categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval

Improvement of maximum mouth opening		
Comparison	**Statistically significant results**	**Data**
Laser vs. other treatment	Short-term: **Significant less pain after laser treatment than after placebo treatment for low disability and total pain.** No ss less pain in the subgroups of high disability using laser therapy compared to other treatment.	Short-term: **Low disability: (SMD=0.61; 95% CI [0.22, 0.99]; *p*=0.002; I^2=58%)** High disability: (SMD=0.05; 95% CI [-0.60, 0.71]; *p*=0.87; I^2=70%) **Total: (SMD=0.43; 95% CI [0.11, 0.75]; *p*=0.008; I^2=63%)**
Laser vs. placebo	Short-term: **Significant improvement in MMO after laser treatment than after placebo for low disability and total pain.** No ss improvement for the subgroups of high disability pain using laser treatment compared to placebo treatment.	Short-term: **Low disability: (SMD=0.30; 95% CI [0.04, 0.56]; *p*=0.03; I^2=42%)** High disability: (SMD=1.37; 95% CI [-0.21, 2.96]; *p*=0.09; I^2=84%) **Total: (SMD=0.46; 95% CI [0.18, 0.75]; *p*=0.001; I^2=60%)**

3.3 Medication

3.3.1 Description of the intervention:

Pharmacological management of TMD has been widely adopted with approximately every second patient reporting usage [275]. Generally, however, the evidence on efficacy of pharmacological treatment in patients with TMD pain is weak and diverging results have been reported [276]. Diverse medications have been investigated for the treatment of TMD e.g., paracetamol and NSAIDs, benzodiazepines and opioids, anti-depressants, muscle relaxants and capsaicin. The route of administration also varies according to the main effect expected of the drug. According to the routes of administration, the author has divided pharmacotherapy into three groups: oral administration, topical administration, and intramuscular injections. The most prescribed medications are those administered orally, including analgesics (NSAIDs and COX-2 inhibitors), anticonvulsants (benzodiazepines and antiepileptics), muscle relaxants or other drugs such as antidepressants (tricyclic antidepressants). Topical medications such as NSAIDs and capsaicin are also typically used to treat TMD, while intramuscular injection of Botulinum toxin (BTX) or local anaesthesia have also been shown to be effective. Hormone treatment has recently received attention in the treatment of TMD. The author will mention the most common ones in detail below with an explanation how the medication might work:

3.3.2 How the medication might work:

Paracetamol and NSAIDs

Analgesic substances such as paracetamol (acetaminophen) and NSAIDs are widely used for acute pain and are considered the first approach for chronic pain. NSAIDs inhibit cyclooxygenase (COX) 1 and 2 and are divided into selective COX-2 inhibitors and non-selective COX-1/2 inhibitors. Since prostaglandins are important inflammatory mediators and nociceptors have prostaglandin receptors, COX-inhibitors reduce both the inflammatory process and nociceptor sensitization. As COXs also occur in the spinal cord, the prostaglandins formed there contribute to central sensitization [277]. The best-known COX-1/2 inhibitors include, for example Acetylsalicylic acid, ibuprofen, naproxen, diclofenac, indomethacin, mefenamic acid and piroxicam. Selective COX-2 inhibitors include celecoxib, parecoxib and etoricoxib. Paracetamol is better tolerated than NSAIDs (e.g., hardly any gastrointestinal adverse effects), but has a weaker analgesic effect compared to COX inhibitors. Recent in-vitro studies have shown that paracetamol has also selective COX-2 inhibitory properties, although its anti-inflammatory effect is weak compared to NSAIDs. Paracetamol can also be dose-adapted in children and adolescents and used during pregnancy.

Oral administration

Study data are available for the use of the NSAID piroxicam, which has a favourable adverse effect spectrum and is used successfully for TMD. This has been shown in a randomized trial by Carli et al. 2013, in which piroxicam was compared with laser therapy [231].

Another study investigating the effectiveness of NSAIDs in TMD treatment, here diclofenac (3x50mg daily) was compared to splint therapy over 3 months. After one week, there was a significant reduction in pain in the group treated with diclofenac. However, after one month, this effect was also achieved with the splint therapy [278]. Furthermore, in Ta el al. 2014, celecoxib (2x100 mg daily) was compared with naproxen (2x500 mg daily) and placebo in a double-blind, placebo-controlled, randomized trial over 6 weeks. Naproxen showed a significant analgesic effect that lasted throughout the treatment period. Celecoxib was only slightly more effective than placebo. The side effects of naproxen and celecoxib did not differ [279]. The effect of analgesics on TMD patients is poorly studied. In the short term, the oral use of NSAIDs is justified in case of acute pain. NSAIDs are not suitable for long-term treatment, as long-term gastrointestinal side effects and the increase in cardiovascular morbidity and mortality must be considered.

Topical administration

Topical applications of NSAIDs in the form of plasters, creams, ointments, and gels are increasingly the drug of choice for the treatment of painful TMD. It has been proven that there is no difference in the efficacy of diclofenac, ibuprofen, ketoprofen and piroxicam [280]. Systemic adverse effects and local skin reactions are generally mild. For the treatment of TMD, di Rienzo et al. 2004, compared the effect of topical (solution 4xdaily) and oral (2x50 mg daily for 14 days) diclofenac in 2 groups of 18 patients each. The treatment outcomes of the two groups did not differ significantly, but gastrointestinal adverse effects occurred in 16 of 18 patients in the oral treatment group [281].

Benzodiazepines and opioids

Oral administration

Furthermore, the use of benzodiazepines is attracting more attention. Anxiety and stress have been found to be important risk factors in TMDs [275]. It has been suggested that myofascial pain is associated with sleep disturbances [282] and the frequency of everyday use of sleeping aids in TMD has been reported [283]. Benzodiazepines bind receptors in the CNS and proliferate the effectiveness of the inhibitory neurotransmitter g-aminobutyric acid (GABA) for its receptor, thus causing an inward drive of negatively charged chloride ions across nerve cell membranes. The resulting hyperpolarization and neuronal inhibition are thought to contribute to the anxiolytic, sedative and hypnotic properties of these drugs [284].

While NSAIDs are classified as weak analgesics, opioids have a stronger analgesic effect. Therapeutic opioids such as morphine act on μ -opioid receptors, which are found in many parts of the nociceptive system. It has been suggested that a peripheral subtype of the μ-opioid receptor exists in TMJ tissue, explaining the potential benefits of this treatment method [285]. In a randomized double-blind trial, intra-articular morphine significantly increased the pain threshold in the diseased joint [286]. However, the effectiveness of opioids on pain reduction could not be concluded by some other studies [287, 288].

Tricyclics and other antidepressants

Oral administration

Tricyclic antidepressants (e.g., amitriptyline, nortriptyline) have been used in pain therapy for decades. The opinion that depression is overrepresented in TMD patients has been psychometrically verified in numerous studies over the years and confirmed in more recent clinical investigations [289]. Most data are available on the use of amitriptyline for musculoskeletal and neuropathic pain as well as headache. Tricyclics are thought to have good antidepressant effects in higher doses. In the mostly low doses in which they are predominantly used in pain therapy, they initially have a sleep-inducing effect and have hardly any antidepressant effects. Central aspects of pain processing could explain why Tricyclic antidepressants also show good efficacy in TMJ disorders. They enhance endogenous pain inhibition by modulation of sodium channels, postsynaptic NMDA receptors and intracellular signalling cascades inhibiting the reuptake of the neurotransmitter's noradrenalin and serotonin [55]. The latter and other psychotropic drugs not only influence the nociceptive system, but also contribute to pain relief by combating depression and tension [290]. Treatment with 10 mg amitriptyline in the evening, which can be increased to 25 mg if needed, is well tolerated by most patients. The efficacy and side-effect profile of tricyclics strongly depend on the genotype of the p-450 enzyme that metabolise this group of drugs [55]. However, there is limited evidence for the effectiveness of antidepressants pain management of TMD [291].

Muscle relaxants

Oral administration

The effect of muscle relaxants is not yet fully understood. Muscle relaxants exert a calming effect on muscle spasms and also have a sedative effect that plays an important role in the treatment of TMD patients [292]. Methocarbamol is a centrally acting muscle relaxant. It inhibits reflex relaxation in the spinal cord and in certain brain centres, which leads to a slackening of tense muscles. It is assumed that there is a general weakening of the CNS,

which leads to an inhibition of reflex relaxation at the level of the spinal column by inhibition of the internal neurons. No study results are yet available on its use for jaw muscle pain [79].

Botulinum Toxin Injections and Local Anaesthetic

Injected administration

BTX is a neurotoxin made by the anaerobic bacterium *Clostridium botulinum* [293].
BTX is an established therapy for cervical dystonia and is also an option for several other muscle-related disorders, including blepharospasm and hemifacial spasm [294]. It is injected intramuscularly and acts on presynaptic cholinergic nerve terminals by blocking the release of acetylcholine until new synaptic connections are formed, resulting in a temporary (3-4 months) blockage of motor fibres and weakening of muscle contractions. [295]. Moreover, BTX has been shown to block the release of inflammatory mediators such as substance P and glutamate, resulting in an antinociceptive effect and treatment of chronic migraine with BTX is also well documented, with suspected antinociceptive mechanisms of action beyond inhibition of neuromuscular transmission. These muscle-relaxing and pain-relieving properties, as well as the reduction in compliance-related problems, have led to an increasing number of clinicians using BTX as a treatment for myogenous TMD [296].
The mechanisms by which the use of botulinum toxin achieves pain relief are the subject of current research. BTX showed a positive effect after three months of observation in two studies [297, 298] and was not superior to the placebo in the study of Ernberg et al. 2011 [299]. In another study on the treatment of TMD, a direct comparison between BTX and fascia manipulation therapy showed comparable significant results in pain relief [40].
Trigger point infiltrations are performed as part of neural therapy treatments with local anaesthetics. The specific action of anaesthetics is to reversibly block the nerve impulses, eliminating local sensitivity and in some cases the motor response. On mucous membranes, a local anaesthetic can be used for surface sedation. However, the blocking of the transmission of action potentials cannot be applied permanently, since not only nociceptors, but also other sensory, motor, and efferent nerve fibres are affected by the transmission [300]. Local anaesthetics are classified by their local ester or amide linkage. Among anaesthetics with ester or amide linkages, only benzocaine is used as a local ester anaesthetic in dentistry. Anaesthetics with amide linkages include lidocaine, mepivacaine, prilocaine, articaine, and bupivacaine [301]. Injections of 1mL of lidocaine 2% without vasoconstrictor into the TMJ or into the muscle´s trigger points have been used to treat localized and acute TMD pain.
Kang's study, lidocaine demonstrated no significant difference in the pain levels between intramuscular morphine or lidocaine on TMD patients with myofascial pain [302]. Also, intramuscular morphine elevated mechanical pain threshold and tolerance in the masseter

only in male patients, suggesting sex differences in local morphine effects [302]. Another study compared trigger point infiltration with lidocaine to splint therapy in the treatment of myofascial pain and showed additive effects [303].

Capsaicin

Topical administration

An important molecule for the absorption of heat stimuli is the vanilloid receptor (VR1). It is activated by the substance capsaicin, which is component of Chili peppers and causes the typical burning pain when consuming this spice. When capsaicin binds to the receptor, a cation channel is opened through which an inward current with depolarizing effect flows. This ion channel is also opened by heat stimulation and is therefore considered one of the heat transfer molecules. How the thermal stimulus opens the channel is still unknown [304]. Winocur's study showed a comparative effectiveness of capsaicin cream in the management for chronic musculoskeletal diseases however compared to NSAIDs there was no significant difference [305].

Corticosteroids

Injected administration

Corticosteroids are phospholipase A2-inhibiting drugs that reduce plasma extravasation, while regulating hyperalgesia when-compared to the effect of steroidal hormones. Corticosteroids reduce the accessibility of arachidonic acid in the cells of enflamed tissue and diminish the synthesis of their metabolites through COX-2. Corticosteroids are primarily proposed in the treatment of TMD where there is inflammatory conditions and produce a side effect of immunosuppressive effects [306].

Palmitoylethanolamid and Hormones

Oral administration

Palmitoylethanolamid (Peapure, PEA) is a substance produced naturally in the body and was first used around 20 years ago as a remedy for neuropathic and chronic pain. There are numerous scientific study results on PEA, including TMD [307]. PEA acts as an endogenous agent with an autacoid local inflammatory antagonism and modulates the behaviour of mast cells by controlling both acute and chronic inflammation [307].

The role of female reproductive hormones in TMD has attracted much attention [308]. Hormonal differences, including exogenous hormones, have been proposed as a potential risk factor. It is thought that hormones could modulate the risk of TMD through several possible peripheral joint- or central pain-related mechanisms [275]. In addition, the effect of melatonin on reducing pain in TMD was demonstrated in a randomized double-blind study

with 32 women over four weeks. Melatonin was shown to have a pain-relieving effect that went beyond simply improvement of sleep [309].

3.3.3 Study selection

The initial database search yielded 1743 entries, of which 768 were retrieved from MEDLINE (via PubMed), 249 from Embase, 656 from Central, 49 from LIVIVO (German and English version), ten from Clinicaltrials.gov, eleven from Deutsches Register klinischer Studien (DRKS) and none from Open Grey Literature (Table 15). Results from four unpublished studies found through the database search were not included in this review. An additional 34 articles were identified through cross-reference checking and manual searching. All the studies used medication interventions for treating TMD. After exclusion of all duplicates (28 studies), the number of entries was 1749. Of these, 1580 studies were discarded after a review of the titles and abstracts. An additional 79 articles were excluded after full-text review and application of the eligibility criteria (reasons for exclusion after full-text analysis are reported in Appendix VIII Table 3. A flowchart that depicts this selection process is displayed in Figure 27. The systematic literature search realised the results shown in Table 15.

Table 15: Results of the search strategy for Medication

Database	*Number of studies (n)*
PubMed	768
EMBASE	249
Central	656
LIVIVO (German)	29
LIVIVO (English)	20
Clinicaltrials.gov	10
Deutsches Register klinischer Studien (DRKS)	11
Open Grey Literature	-
Total	1743

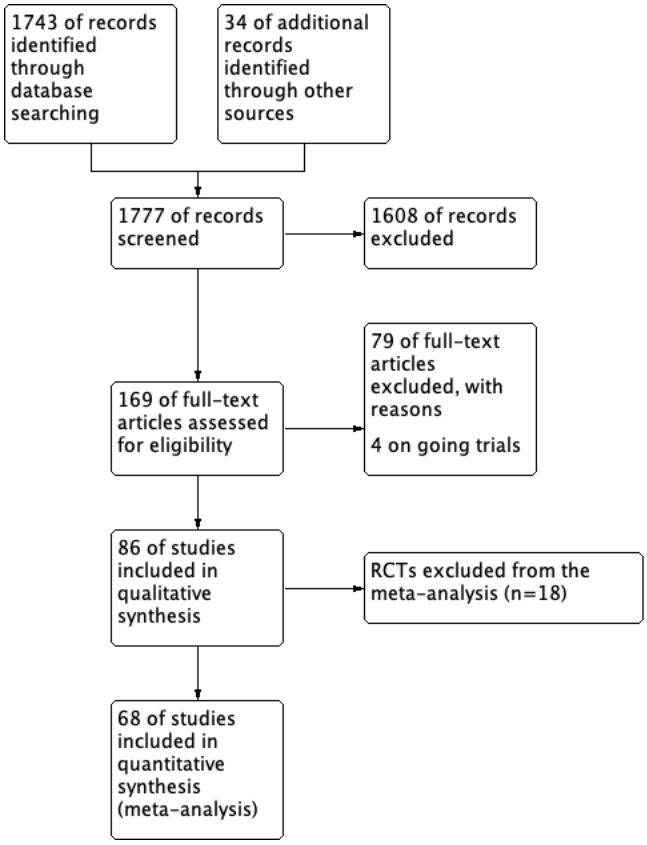


Figure 27: Flow Diagram for RCT studies on medication treatment of patients with painful TMDs

3.3.4 Qualitative synthesis of the included studies

3.3.4.1 Characteristics of the included studies

Ultimately, 86 RCTs with 4895 participants met the inclusion criteria and were then included in this systematic review. To check for heterogeneity in advance, the characteristics of the population used in the studies, the characteristics of the interventions, the characteristics of interventions, and the excluded studies were precisely reported in narrative style. Table 14 demonstrates the general characteristics of the included studies, Characteristics of Included Studies I, provides detailed information on participants, treatment and comparisons, outcomes, pain severity, and follow-up.

In the appendix APPENDIX VII-X one can find the detailed search strategy, characteristics of the included and excluded studies, further forest plots and funnel plots.

Table 16: Included studies on medication treatment for TMD; (BTX-A=botulinum toxin A; CBT=cognitive behavioural therapy; CS=corticosteroid injections; DDR=reducing displaced disc; DDwoR=disk displacement without reduction; DDwR=disk displacement with reduction; DJD=degenerative joint disease; DON=nonreducing displaced disc; GH=glucosamine hydrochloride; GS=glucosamine; HA=hyaluronic acid; JME=jaw movement exercise; LLLT=low-level laser therapy; LPM= lateral pterygoid muscle; NOS=non-occlusal splint; NSAID=non-steroidal anti-inflammatory drug; OA= occlusal appliance; PEA=palmitoylethanolamid; PI=psychological intervention; SH=sodium hyaluronate; SPGB=sphenopalatine ganglion block; SS=stabilization splint; TCM= traditional chinese medicine; TENS=transcutaneous electrical nerve stimulation; TMD=temporomandibular disorder)

Author Year	Patients (n), %women, age: mean±SD (years)	Interventions	Outcomes	Pain chronification	Diagnosis	Follow-up
Ahmed et al. 2016 [310]	26 patients 35% women Mean age: Group A: 32.92 ±10.9 Group B: 36.00 ±14.21	Group A (n=13): occlusal splint Group B (n=13): medications (analgesia and muscle relaxants) + supportive care	Palpatory tenderness at rest and during various jaw movements (VAS) Maximum comfortable mouth opening (mm) Clicking sound	Unclear	TMD of arthrogenic origin (internal derangement of TMJ)	4 months
Alajbeg et al. 2018 [311]	21 patients n.a. Mean age: Group A: 57.25 ±8.13 Group B: 46.5 ±18.15 Group C:42.8 ±12.45	Group A (n=7): amitriptyline Group B (n=7): placebo pill Group C (n=7): stabilization splint	Pain (VAS) Maximal comfortable mouth opening (mm)	Low disability	TMD of mixed origin	3 months
Alencar Jr et al. 2014 [312]	45 patients 91.33% women Mean age: Group A: 37.1 Group B: 36.5 Group C: 36.9	Group A (n=15): placebo group Group B (n=15): tizanidine 4 mg Group C (n=15): cyclobenzaprine	Pain intensity (VAS) Frequency and duration (Severity Symptoms Index)	Low disability	TMD of muscular origin	3 weeks
Alpaslan et al. 2012 [313]	79 patients 84% women 17–52 years old Mean age: 32	Group A (n=15): chlorzoxazone Group B (n=15): phenprobamate Group C (n=15): mephenoxalone Group D (n=15): baclofen Group E (n=19): no medication	Severity of pain (VAS)	Low disability	TMD of muscular origin	1 month
Altaweel et al. 2019 [314]	14 patients 71% women Mean age: 23.13	Group A (n=7): LPM extra orally Group B (n=7): LPM intraorally	Maximum active mouth opening (mm) TMJ clicking Pain (VAS)	Unclear (low disability)	TMD of arthrogenic origin (TMJ disc displacement)	6 months
Ayesh et al. 2008 [315]	18 patients 83% women 20–39 years old Mean age: 26.5 ±1.4	Group A (n=9): intra-articular injection of ketamine (crossover study) Group B (n=9): normal saline (crossover study)	Spontaneous pain (VAS) (24h) Pain on jaw function (VAS) (24h) Jaw opening (mm)	Unclear (high disability)	TMD of arthrogenic origin (arthralgia)	24 hours
Basterzi et al. 2009 [316]	33 patients 88% women Mean age; Group A: 28.3 ± 9.3 (16 - 52 years old) Group B: 34.83 ± 14 (16 - 55 years old)	Group A (n=20): intraarticular SH Group B (n=20): intraarticular SH	Pain intensity (VAS) Joint sounds Maximal mouth opening	High disability	TMD of arthrogenic origin (Disc displacement)	12 months

Bertolami et al. 1993 [317]	121 patients 94% women Mean age: Group A: 36.0 Group B: 40.7	Group A (n=80): sodium hyaluronate Group B (n=41): USP physiologic saline, (placebo group)	Level of pain (VAS) Joint noises	High disability	TMD of arthrogenic origin (DJD, DDR, or DON)	6 months
Bjornland et al. 2007 [318]	40 patients 85% women Mean age: Group A 53.4 ±12.9 Group B 50.0 ±13.3	Group A (n=20): Synvisc Group B (n=20): Celestone Chronodose	Pain intensity (VAS) Joint sounds Mandibular function and complications (mm)	High disability	TMD of mixed origin (Osteoarthritis of the TMJ, TMD of muscular origin)	6 months
Bouloux et al. 2017 [319]	102 patients 87% women Mean age: Group A: 39.6 Group B: 44.3 Group C: 51.8	Group A (n=36): hyaluronic acid Group B (n=35): corticosteroid Group C (n=31): lactated ringer solution	Pain (VAS) Maximum incisal opening (MIO)	Low disability	TMD of arthrogenic origin (Arthralgia, internal derangement, or degenerative joint disease)	3 months
Cahlin et al. 2011 [320]	95 patients 86% women women Mean age: 60 ±13 men Mean age: 57±11	Group A (n=30): oral glucosamine sulphate Group B (n=29): placebo	Pain (VAS) Opening capacity (mm)	Unclear (high disability)	TMD of arthrogenic origin (Osteoarthritis)	6 weeks
Calderon et al. 2011 [321]	47 patients 17-52 years old Mean age: 35.6	Group A (n=11): amitriptyline Group B (n=12): amitriptyline + CBT Group C (n=11): placebo + CBT Group D (n=13): placebo only (control)	Pain intensity (VAS) Depression (BDI)	Low disability	TMD of muscle origin and/or arthrogenic origin	1 months
Campbell et al. 2017 [322]	70 patients 100% women 18-65 years old	Group A (n=8): capsaicin TMD Group B (n=21): capsaicin (healthy) co Group C (n=8): vehicle TCM Group D (n=23): vehicle (healthy)	Pain intensity (VAS)	Unclear (low disability)	Group IIIa, arthralgia of the TMJ criteria	1 week
Celakil et al. 2017 [323]	40 patients 100% women Mean age: 31.7	Group A (n=20): ozone therapy Group B (n=20): sham ozone therapy	Mandibular movements (mm) Pain levels (VAS)	Low disability	TMD of muscular origin	3 months
Cen et al. 2018 [324]	144 patients 87% women Mean age: Group A: 40.1 ±15.8 Group B: 36.2 ±15.8	Group A (n=72): oral GS (Glucosamine) + HA injection (intra-articular injection of 1.0 ml sodium HA) Group B (n=72): oral placebo + HA injection	Maximum interincisal mouth opening (MMO) (mm) TMJ pain (VAS)	Low disability	Osteoarthritis	1 year
Cigerim et al. 2020 [325]	169 patients 78% women 18–69 years old Mean age: 27.04 ±10.56	Group A (n=42): naproxen Group B (n=40): naproxen sodium + codeine phosphate Group C (n=40): naproxen + single-dose dexamethasone + Kordexa Group D (n=47): paracetamol	Pain (VAS)	Low disability	TMD of muscular origin	1 month
Daif et al. 2012 [326]	60 patients 81% women 22-46 years old Mean age: 32	Group A (n=30): injection of ozone gas Group B (n=30): nonsteroidal anti-inflammatory drugs and muscles relaxants	Helkimo's clinical dysfunction index: Joint noises and pain Masticatory muscle tenderness Range of mandibular motion Pain during mandibular movements	Unclear (high disability)	TMD of arthrogenic origin (Internal derangement of the TMJ)	2 weeks

Dalewski et al. 2019 [161]	90 patients 80% women 18-65 years old Mean age: 30.73	Group A (n=30): occlusal appliance (OA) + NSAID Group B (n=30): occlusal appliance + dry needling (DN) Group C (n=30): occlusal appliance therapy (OA-control group)	Pain (VAS)	Low disability	TMD of arthrogenic origin	3 weeks
Damlar et al. 2015 [327]	34 patients 100% women 18-40 years old Mean age: 28.6 ±6.89	Group A (n=16): glucosamine + chondroitin sulphate Group B (n=15): tramadol HCl	Levels of pain (NRS) Maximum mouth opening (mm)	Low disability	TMD of arthrogenic origin (Internal derangement of TMJ)	2 months
De Carli et al. 2013 [231]	32 patients 90,63 % women 18-58 years old Mean age: 32.4	Group A (n=11): active laser + placebo piroxicam Group B (n=10): placebo laser + piroxicam Group C (n=11): active laser + piroxicam	Pain (VAS) Maximum mouth opening (mm)	Mixed	TMD of mixed origin	1 month
De Carli et al. 2016 [232]	15 patients 87% women Mean age: 38	Group A (n=8): LLLT (830 nm) Group B (n=7): botulinum toxin	Pain (VAS) Mouth opening (digital calliper)	Low disability	TMD of muscular origin	15 days
De la Torre Canales et al. 2020 [328]	100 patients 100% women Mean age: 36.8 ± 5.6	Group A (n=20): OA Group B (n=20): saline solution Group C (n=20): BTX-A -Low Group D (n=20): BTX-A -Medium Group E (n=20): BTX-A -High	Pain intensity (VAS) Masticatory Performance (MP)	High disability	TMD of muscular origin or mixed origin	6 months
De Souza et al. 2018 [236]	66 patients 94% women Mean age: 46.14 ±10.91	Group A (n=33): LLLT (780nm) Group B (n=33): aesthetic infiltration of lidocaine 2%	Pain (VAS)	High disability	TMD of muscular origin	4-6 weeks
DeNucci et al. 1998 [329]	20 patients 90% women 20-55 years old Mean age 39.2 ± 9.7	Group A (n=10): triazolam Group B (n=10): placebo (matching placebo tablets)	Pain Intensity (VAS) Mandibular ROM (mm)	Low disability	TMD of muscular origin and/or arthrogenic origin	2 weeks
Di Rienzo Businco et al. 2004 [281]	36 patients 53% women 34-61 years old Median age: 43	Group A (n=18): oral diclofenac sodium Group B (n=18): topical diclofenac	Pain (VAS) Low disability limitation of mouth opening (VAS)	High disability	TMD of arthrogenic origin	n.a.
Dogan et al. 2014 [330]	63 patients 86%women Mean age: Group A: 32.7 ±9.2 Group B: 34.7 ±10.0	Group A (n=33): ozone therapy Group B (n=30): ketoprofen + thiocolchicoside	Pain (VAS) Interincisal mouth opening (MMO) (mm) Clicking sounds	Unclear (high disability)	TMD of arthrogenic origin	1 week
Ekberg et al. 1996 [331]	32 patients 84% women 27-82 years old Mean age: 47	Group A (n=16): diclofenac sodium (Voltaren) Group B (n=16): placebo	Pain (VAS) TMJ sounds (clicking and crepitation) Maximum opening capacity<40mm	Low disability	TMD of arthrogenic origin	2 weeks
Ernberg et al. 2011 [332]	21 patients 90.5% women Mean age; 38 ±12	Group A (n=12): BTX-A then saline (control) Group B (n=9): isotonic saline (control)	Pain intensity at rest (VAS) Global improvement Depression (SCL-90R) Somatization (SCL-90R)	Low disability	TMD of muscular origin	3 months

Ferrante et al. 1998 [333]	23 patients 73.9% women Mean age: Group A: 42.2 ±3.1 Group B: 37.8 ±2.9	Group A (n=13): SPGB (lidocaine) Group B (n=10): SPGB (saline placebo)	Intensity of pain (VAS)	High disability	TMD of muscular origin	1 month
Gencer et al. 2014 [334]	100 patients 55% women 20-65 years old Mean age: 42.5 ±10.2	Group A (n=25): hyaluronic acid Group B (n=25): betamethasone Group C (n=25): tenoxicam Group D (n=25): control group	Pain (VAS)	High disability	TMD of arthrogenic origin	1st and 6th week
Gerschman et al. 1984 [335]	32 patients 73% women Mean age: Group A: 34.6 ±11.2 Group B: 29.7 ±9.4	Group A (n=14): mersyndol + diazepam Group B (n=16): placebo + diazepam	Pain (VAS)	Unclear (high disability)	TMD of arthrogenic origin	1 week
Gokçe Kutuk et al. 2019 [336]	31 patients 68% women Mean age: Group A: 36.4 ±8.2 Group B: 37.4 ±9.9 Group C: 34.5 ±9.3	Group A (n=13): platelet-tich plasma Group B (n=12): HA Group C (n=6): CS	Pain (5- point pain scale) Presence of crepitation	Unclear (high disability)	TMD of arthrogenic origin (Osteoarthritis)	3 months
Gokçe Kutuk et al. 2019 [336]	43 patients 54% women Mean age: Group A: 33.7 ±10.4 Group B: 34.7 ±10.1 Group C: 34.6 ±10.0	Group A (n=13): platelet-rich plasma Group B (n=12): HA Group C (n=6): CS	Pain (5- point pain scale) Presence of crepitation	Unclear (high disability)	TMD of arthrogenic origin	3 months
Goncalves et al. 2013 [337]	111 patients 100% women Mean age: 34.3 ±8.8	Group A (n=22): propranolol + SS Group B (n=23): propranolol placebo and SS Group C (n=23): propranolol + NOS Group D (n=21): propranolol placebo + NOS	Mean intensity of facial pain VAS) Mandibular vertical ROM (mm) (unassisted)	Mixed	Migraine and TMD	6 months
Gonzalez-Perez et al. 2015 [168]	48 patients 79% women 18 - 65 years old Mean age: Group A 34.3 ±13.8 Group B 35.5 ±11.2	Group A (n=24): deep dry needling Group B (n=24): methocarbamol + paracetamol	Pain at rest and upon mastication (VAS) Range of mandibular movements (opening of the mouth, lateral movements, protrusion) (mm)	Low disability	TMD of muscular origin	70 days
Guarda-Nardini et al. 2004 [338]	27 patients 74% women Mean age: 53.9 ±11.8	Group A (n=19): sodium hyaluronate Group B (n=8): Ringer's lactate solution	Intensity of pain (VAS) Maximal mouth opening and lateral jaw movements	Unclear	TMD of arthrogenic origin (Osteoarthritis)	6 months
Guarda-Nardini et al. 2005 [339]	60 patients 92% women Mean age: Group A: 49.8 Group B: 51.4 Group C: 46.4	Group A (n=20): injections of 1 mL SH Group B (n=20): bite-plane treatment Group C (n=20): no treatments	Maximum mouth opening (mm) Pain at rest and mastication (VAS)	Low disability	TMD of arthrogenic origin (Osteoarthrosis)	6 months

Guarda-Nardini et al. 2008 [297]	20 patients 50% women 25-45 years old	Group A (n=10): botulinum toxin Group B (n=10): saline placebo	Pain at rest and at chewing (VAS) Maximum non-assisted and assisted mouth opening, protrusive and laterotrusive movements (mm)	Low disability	TMD of muscular origin	6 months
Guarda-Nardini et al. 2012 [40]	30 patients 73%women 23-69 years old Mean age: 45.45	Group A (n=15): botulinum toxin Group B (n=15): fascial manipulation	Maximum pain level (VAS) Maximum mouth opening, protrusion, right and left laterotrusion (mm)	Unclear (high disability)	TMD of muscular origin	3 months
Gupta et al. 2016 [340]	74 patients 70.27% women Mean age: 44.54 ±15.98	Group A (n=37): local anaesthetic Group B (n=36): combined trigger point injection therapy + 50 mg of tablet Levosulpiride	Pain (VAS) Depression (Beck's depression inventory (BDI))	High disability	TMD of muscular origin	3 months
Harkins et al. 1991 [341]	20 patients 80% women Mean age: 31	Group A (n=10): clonazepam orally Group B (n=10): placebo	Pain (VAS) Vertical mandibular ROM (maximum passive interincisal opening, mm)	Low disability	TMD of muscular origin	1 month
Hepguler et al. 2002 [342]	38 patients 68% women Mean age: Group A: 31.94 ±12.67 Group B: 31.94 ±12.67	Group A (n =19): intra-articular injections of HA Group B (n =19): intra-articular injections of placebo	Pain and sound intensity of the joint (VAS)	High disability	TMD of arthrogenic origin (displaced disc of the TMJ)	6 months
Herman et al. 2002 [343]	41 patients 80% women 21-79 years old	Group A (n=13): self-care program + medication Group B (n=15): self-care program + placebo Group C (n=13): self-care program + medication	Pain (Symptom Severity Index (SSI))	Low disability	TMD of muscular origin	3 weeks
Hosgor et al. 2017 [243]	40 patients 90% women 18-59 years old Mean age: 30.35 ±1.97	Group A (n=10): splint therapy Group B (n=10): arthrocentesis therapy Group C (n=10): tenoxicam NSAID Group D (n=10): LLLT	Pain (VAS) Joint noises (clicking, crepitus, or none) Maximum mouth opening (MMO, mm)	Low disability	TMD of arthrogenic origin (anterior disc displacement of the TMJ)	6 months
Jayachandran et al. 2017 [344]	30 patients 57% women 40-60 years old Mean age: 49	Group A (n=10): diclofenac sodium Group B (n=10): oral enzymes (bromelain, trypsin, rutoside trihydrate) + diclofenac sodium combination Group C (n=10): oral enzymes (bromelain 90 mg, rutoside trihydrate)	Pain (Numeric Rating Scale)	Unclear	TMD of arthrogenic origin (OA)	10 days
Kang et al. 2018 [302]	51 patients 47% women Mean age: Men: 29 ±6.3 Women: 28 ±8.5	Group A (n=11): saline masseter Group B (n=13): morphine Group C (n=11): morphine 5 mg Group D (n=11): lidocaine masseter Group E (n =5): morphine 5 mg trapezius	Pain intensity (VAS)	Low disability	TMD of muscular origin	48 hours
Khalighi et al. 2016 [247]	40 patients	Group A (n=20): naproxen Group B (n=20): active laser (810 nm)	Pain intensity (VAS) Maximum painless mouth opening (mm)	Low disability	TMD of muscular origin	2 months
Kimos et al. 2007 [345]	50 patients 100% women. Mean age: 33.58	Group A (n=25): gabapentin Group B (n=25): placebo	Pain intensity (VAS)	High disability	TMD of muscular origin	3 months
Kopp et al. 1985 [346]	33 patients 88% women Mean age: 46 years	Group A (n=18): hyaluronate Group B (n=15): corticosteroid	Effect on subjective symptoms (VAS)	High disability	TMD of arthrogenic origin	4 weeks 1st and 2nd year

Kopp et al. 1991 [347]	33 patients 88% women Mean age: 46	Group A (n=18): intra-articular injections of sodium hyaluronate Group B (n=15): intra-articular injections of corticosteroid (betamethasone)	Effect on subjective symptoms (VAS)	High disability	TMD of arthrogenic origin (rheumatoid arthritis of the TMJ)	1 month
Korkmaz et al. 2016 [348]	51 patients 69% women 18- 48 years old, Mean age: Group A: 32.38 ±8.7 Group B: 32 ±9.73 Group C: 32.08 ±9.79 Group D: 28.67 ±10.21	Group A: self-designated control group (not randomized) Group B: single HA injection Group C: double HA injection Group D: stabilization splint	Pain at rest and during mastication (VAS) TMJ noise Level of jaw movements ROM: max. mouth opening, protrusion, excursion movements	Low disability	TMD of arthrogenic origin (painful disc displacement with reduction)	6 months
Kurtoglu et al. 2008 [298]	24 patients 83.3%women 16-53 years old Mean age: 26.5	Group A (n=12): BTX (bilateral injections) Group B (n=12): placebo	RDC/TMD axis II	High disability	TMD of muscular origin	1 month
Kütük et al. 2019 [158]	40 patients	Group A (n=20): BTX-A Group B (n=20): dry needling	Pain (VAS) Crepitation (present or absent) Maximum mouth opening (mm)	Low disability	TMD of muscular origin	6 weeks
Li et al. 2009 [349]	45 patients 71% women Mean age: Group A: 43.96 ±13.13 Group B: 47.14 ±9.30	Group A (n=23): Ping On ointment Group B (n=22): placebo cream	Pain diary (VAS) Mandibular function, vertical mouth opening without pain	Low disability	TMD of muscular origin and/or arthrogenic origin	1 month
List et al. 2001 [286]	53 patients 83% women Mean age: Group A: 49.5 Group B: 40 Group C: 49.5	Group A (n=18): 1.0 mg morphine–HCl Group B (n=17): 0.1 mg morphine–HCl Group C (n=18): saline (placebo)	Pain at maximum mouth opening and pain at jaw rest (VAS diary) Vertical opening of the mouth (mm)	High disability	TMD of arthrogenic origin (arthralgia/osteoarthritis)	1 week
Lobo Lobo et al. 2004 [350]	52 patients 90% women n.a.	Group A (n=26): Theraflex cream Group B (n=26): placebo cream	Maximum mouth opening (mm)	Low disability	TMD of muscular origin and/or arthrogenic origin	20 days
Makino et al. 2014 [351]	39 patients 69% women Mean age: Group A: 40 Group B: 42 Group C: 53	Group A (n=13): control group Group B (n=13): exercise therapy (JME) at home Group C (n=13): ET-PI group (continue JME at home + PI)	Pain intensity (NRS) Jaw movement	High disability	TMD of arthrogenic origin	98 days
Marini et al. 2010 [211]	99 patients 75% women 15–50 years old	Group A (n=30): LLLT Group B (n=30): ibuprofen Group C (n=30): sham laser	Pain intensity (VAS) Active and passive mouth openings right and left lateral motions	Low disability	TMD of arthrogenic origin (disc displacement without reduction or osteoarthritis)	15 days 1 month
Marini et al. 2012 [307]	24 patients 67% women 24-54 years old	Group A (n=12): PEA Group B (n=12): Ibuprofen	Intensity of spontaneous pain (VAS) Maximum mouth opening (mm)	Low disability	TMD of arthrogenic origin (arthralgia or Osteoarthritis)	14 days

Marzook et al. 2020 [352]	60 patients	Group A (n=8): arthrocentesis technique Group B (n=8): hyaluronic acid and corticosteroid	Pain (VAS) Maximum interincisal opening (MIO) Range of lateral mandibular excursions Clicking was recorded as present or absent	Low disability	TMD of arthrogenic origin (TMJ internal derangement with reduction)	3 months
Mejersjö et al. 2008 [278]	29 patients 93% women 36–76 years old	Group A (n=15): splint Group B (n = 14): diclofenac (Voltaren)	Maximum opening (mm) Pain intensity (VAS, NRS 0-5)	Low disability	TMD of arthrogenic origin (Osteoarthritis of the TMJ)	1 year
Minakuchi et al. 2001 [353]	69 patients 91% women Mean age: 34.0 +15.4	Group A (n=23): self-care/NSAIDs Group B (n=25): occlusal appliance/jaw mobilization + self-care/NSAID Group C (n=21): control group	Pain Levels at rest / during mastication (VAS) Maximum comfortable / active / passive mandibular opening	Low disability	TMD of arthrogenic origin (Painful anterior dislocation of the disc without reduction)	2 months
Nguyen et al. 2001 [354]	45 patients 88% women Mean age: Group A: 43 ±14 Group B: 46 ±15	Group A (n=23): GH + chondroitin sulphate Group B (n=22): placebo	Pain (McGill Pain Questionnaire, VAS) ROM (mm) TMJ sounds	Low disability	TMD of arthrogenic origin	3 months
Nitecka-Buchta et al. 2014 [355]	79 patients 73% women 22–34 years old Mean age: 23	Group A (n=37): bee venom Group B (n=42): placebo (Vaseline)	Pain intensity (VAS)	Unclear	TMD of muscular origin	14 days
Oliveras-Moreno et al. 2008 [356]	41 patients 78% women 20-65 years old Mean age: Group A: 25 ±11 Group B: 33 ±14	Group A (n=20): SH Group B (n=21): control group	Pain at rest, on jaw opening, and on mastication (VAS)	Low disability	TMD of arthrogenic origin (internal derangement)	14, 28, 56, and 84 days
Ozkan et al. 2011 [303]	50 patients 88% women Group A: 30.36 ±8.94 Group B: 30.4 ±9.22	Group A (n=25): ss Group B (n=25): ss + lidocaine + saline	Pain intensity (VAS) Maximal incisal opening (MIO)	Low disability	TMD of muscular origin	3 months
Patel et al. 2017 [357]	19 patients n.a. n.a.	Group A (n=10): BTX-A Group B (n=9): placebo	Pain (VAS) Muscle tenderness scores	High disability	TMD of muscular origin and/or arthrogenic origin	4 months
Pramod et al. 2011 [358]	35 patients 60% women up to 50 years old	Group A (n=10): placebo Group B (n=25): diazepam	Pain intensity (VAS) Maximum Mouth opening (mm)	High disability	TMD of muscular origin	5 weeks
Ramakrishnan et al. 2019 [359]	50 patients n.a. n.a.	Group A (n=25): plain ultrasound acoustic gel Group B (n=25): phonophoresis (with aceclofenac gel)	Pain (VAS)	High disability	TMD of arthrogenic origin	2 weeks

Schiffman et al. 2007 [360]	106 patients women: Group A: 90% Group B: 100% Group C: 85% Group D: 96% Mean age: Group A: 33.7 ±1.8 Group B: 30.0 ±1.7 Group C: 31.8 ±1.7 Group D: 31.4 ±1.9	Group A (n=29): medical management Group B (n=25): nonsurgical rehabilitation Group C (n=26): arthroscopic surgery Group D (n=26): arthroplasty	Pain (Symptom Severity Index (SSI)) Depression (only at Baseline SCL-90-R) Somatization (only at Baseline SCL-90-R) Mandibular ROM (mm) TMJ sounds (clicking, crepitus)	Low disability	TMD of muscular origin and/or arthrogenic origin	3, 6, 12, 18, 24, and 60 months
Shanavas et al. 2014 [361]	40 patients 60% women 20-55 years old	Group A (n=20): analgesics + muscle relaxants (ultrazox tablet-chlorzoxazone 250 mg, diclofenac potassium 50 mg, paracetamol 325 mg 3xdaily, for five days) Group B (n=20): TENS therapy + drugs	Intensity of pain (VAS)	Unclear (high disability)	TMD of mixed origin	5 days
Sharav et al. 1987 [362]	28 patients 79% women Mean age: 41.5	Group A (n=8): low dose amitriptyline versus placebo Group B (n=11): high dose amitriptyline versus Group C (n=9): high dose versus low dose	Pain (VAS, McGill Pain Questionnaire (MPQ)) Depression (Hamilton Depression Inventory)	High disability	TMD of muscular origin	2 months
Shin et al. 1997 [363]	20 patients 75% women Mean age: Group A: 18.70 ±4.64 Group B: 26.20 ±13.48	Group A (n=10): ultrasound massage Group B (n=10): ultrasound massage (+ 1% indomethacin cream)	Pain (VAS)	Unclear (high disability)	TMD of arthrogenic origin	2 days
Singer et al. 1997 [364]	39 patients 90% women Mean age: 36.1	Group A: placebo Ibuprofen Group B: Diazepam Group C: Ibuprofen Group D: Diazepam Ibuprofen	Pain intensity (VAS) Maximal interincisal opening Mood Changes (Zung Depression Scale, Depression)	High disability	TMD of muscular origin	1 month
Sousa et al. 2020 [365]	80 patients 80% women Mean age: 43.1 ±17.7	Group A (n=20): splint Group B (n=20): betamethasone +splint Group C (n=20): sodium hyaluronate + splint Group D (n=20): platelet-rich plasma + splint	Pain intensity (VAS) Maximum pain-free mouth opening (mm)	Low disability	TMD of arthrogenic origin	6 months
Ta et al. 2004 [279]	68 patients 68% women 18–65 years old	Group A (n=24): celecoxib 100 mg twice a day Group B (n=22): naproxen, 500 mg twice a day Group C (n=22): placebo for 6 weeks	Pain intensity (VAS) Maximal comfortable mandibular opening Quality of life (SF-36)	Low disability	TMD of arthrogenic origin	6 weeks
Tchivileva et al. 2020 [366]	199 patients 78% women Mean age: Group A: 33.9 ±12.19 Group B: 34.2 ±13.29	Group A (n=100): propranolol hydrochloride Group B (n=100): placebo	Pain (facial pain index (FPI)) Emotional functioning (HADS) Somatization (SCL-90R)	Mixed	TMD of muscular origin and/or arthrogenic origin	1 week
Thie et al. 2001 [367]	45 patients 89% women Mean age: 37.5	Group A (n=21): Glucosamine Sulphate (500 mg) Group B (n=18): Ibuprofen (400 mg)	TMJ pain with function (CAS) Pain-free (CAS) Voluntary maximum mouth opening (mm)	Low disability	TMD of arthrogenic origin (Osteoarthritis)	3 months

Turner et al. 2011 [368]	191 patients 100% women Mean age: Group A: 29.1 ±7.4 Group B: 25.4 ±5.7 Group C: 28.6 ±6.9	Group A (n=60): self-management Group B (n=57): targeted self-management training Group C (n=74): continuous oral contraceptive therapy	Pain intensity (CPI) Depression (BDI)	Low disability	TMD of mixed origin	1 year
Vidor et al. 2013 [309]	32 patients 100% women 20-40 years old Mean age: Group A: 29.47 ±5.01 Group B: 32.27 ±4.65	Group A (n=16): placebo Group B (n=16): melatonin (5 mg)	Pain intensity (VAS) Depression (Beck Depression Inventory)	Low disability	TMD of muscular origin	1 month
von Lindern et al. 2003 [369]	90 patients n.a. n.a.	Group A (n=60): botulinum toxin Group B (n=30): placebo	Subjective pain (VAS)	High disability	TMD of muscular origin	1-3 months
Winocur et al. 2000 [305]	30 patients 80% women Mean age: Group A: 35.6 ±14.2 Group B: 37.5 ±16,7	Group A (n=17): capsaicin cream Group B (n=13): placebo	Pain (present pain, most severe pain, effect of pain on daily activities, and pain relief) (VAS) Maximal mouth opening (assisted/passive and non-assisted/active)	Low disability	TMD of arthrogenic origin	1 month
Yang et al. 2018 [370]	144 patients 83% women 16-70 years old	Group A (n=72): hyaluronate sodium injections + oral glucosamine hydrochloride Group B (n=72): hyaluronate sodium injections + oral placebo	Pain during TMJ movement (VAS) Maximum interincisal mouth opening (MMO)	Unclear	TMD of arthrogenic origin (Osteoarthritis)	1 year
Yilmaz et al. 2019 [371]	45 patients 78% women 15-82 years old Mean age: 33.9	Group A (n=18): arthrocentesis + HA Group B (n=18): single HA Group C (n=9): control	Maximum non-assisted and assisted mouth opening (mm) TMJ sounds	Low disability	TMD of arthrogenic origin (DDwR or DDwoR)	6 months
Yilmaz et al. 2019 [371]	45 patients 78% women 15-82 years old Mean age: 33.9	Group A (n=19): arthrocentesis + HA Group B (n=18): single HA Group C (n=8): control	Maximum non-assisted and assisted mouth opening (mm) TMJ sounds	Low disability	TMD of arthrogenic origin (DDwR or DDwoR)	6 months
Yuasa et al. 2001 [372]	60 patients 80% women 16-69 years old, Median age: 28	Group A (n=30): NSAID + physical therapy Group B (n=30): no treatment	Pain (VAS) Maximum mouth opening (mm)	Low disability	TMD of arthrogenic origin (DDwoR)	1 month
Yurttutan et al. 2019 [373]	73 patients 45% women Mean age: Group A: 31,0 ±7.33 Group B: 30.5 ±9.95 Group C: 30.2 ±8.63	Group A (n=32): occlusal splint Group B (n=31): BTX Group C (n=31): occlusal splint + BTX injections	Pain (VAS) Graded Chronic Pain Scale (GCPS) Jaw Function	Mixed	TMD of muscular origin (myofascial pain due to bruxism)	6 months
Ziegler et al. 2010 [374]	48 patients n.a. 21-79 years old	Group A (n=12): morphine (5 mg) Group B (n=12): morphine sulphate (10 mg) Group C (n=12): bupivacaine 0.5% Group D (n=12): isotonic saline solution as a placebo	Pain (VAS) Interincisal distance under active mouth opening and registration of the laterotrusion and protrusion	Low disability	TMD of arthrogenic origin (single-side articular complaints in the region of the TMJ)	1 week

3.3.4.2 Characteristics of the included studies' population

3.3.4.2.1 TMD diagnoses of the participants in the included studies

Among the included studies, there was considerable diversity in the clinical performances and analyses of the participants suffering from TMD. The Figure 28 below demonstrate the distribution of TMD diagnoses between the subjects from the included studies using medication. 26 of the studies assessed the effectiveness of medication for myofascial pain [40, 158, 168, 236, 247, 297, 298, 302, 303, 309, 312, 313, 323, 325, 332, 333, 340, 341, 343, 345, 355, 358, 362, 364, 369, 373], 20 studies assessed effectiveness in patients with disc displacements [243, 279, 310, 314, 316, 317, 326, 327, 330, 342, 348, 352-354, 356, 360, 371, 372, 374], and 18 studies assessed effectiveness in patients with arthralgia or arthritis [278, 286, 307, 315, 318, 320, 322, 324, 336, 338, 339, 344, 347, 365, 367, 370, 375]. Nine studies [231, 311, 321, 328, 329, 349, 350, 357, 366] investigated both myogenic and arthogenic TMD and 13 studies did not classify TMD [161, 281, 305, 331, 334, 335, 337, 346, 351, 359, 361, 363, 368].

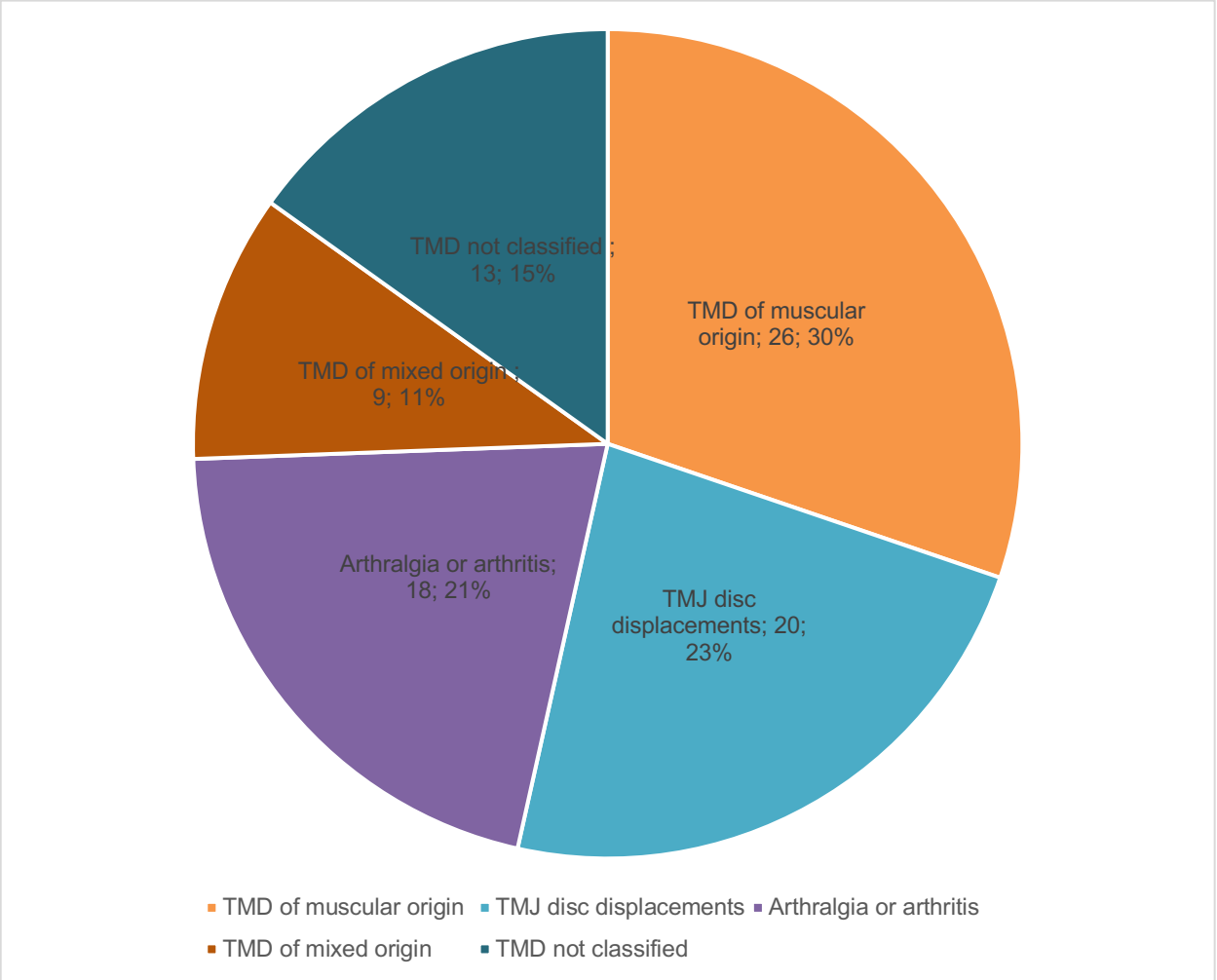


Figure 28: Pie chart presenting the different TMD diagnoses from the included studies on medication therapy (X) with the number of studies included (Y) and the percentage (Z); (X;Y;Z).

3.3.4.2.2 Grade of pain chronification

The degree of TMD pain chronification of the subjects formed the focus of the current work. The following categories were formed for medication therapy (Figure 29):

- Patients with evidence of low disability (acute or acute/persistent) pain
- Patients with evidence of high disability pain
- Patients with different degrees of chronicity, where the results were presented separately by the authors (referred to below as: mixed)
- Patients with slight evidence of low disability pain (referred to below as: unclear (low disability))
- Patients with slight evidence of high disability pain (referred to below as: unclear (high disability))
- Patients with minimum or no degree of chronicity (referred to below as: unclear)

Many studies included RCTs using drug intervention were studies with participants suffering from acute pain. Therefore, 45 studies were flagged as "low disability pain" [158, 161, 168, 243, 247, 278, 279, 297, 302, 303, 305, 309, 311-313, 319, 321, 323-325, 327, 329, 331, 332, 339, 341, 343, 348-350, 352-354, 356, 360, 365, 367, 368, 371, 372, 374]. In 23 studies [247, 278, 297, 302, 303, 305, 311, 313, 323, 327, 331, 332, 341, 348, 350, 352-354, 360, 365, 367, 372, 375], it was unobjectionable that patients suffered from "high disability pain." Information was obtained from the RCTs or by contacting the authors of the studies. Similarly, we found four studies that treated patients with a mixed population of patients suffering from high disability and low disability pain [231, 337, 366, 373]. It should be noted that eight studies did not directly report the characteristics of the pain, but provided some evidence of high disability pain [315, 320, 326, 335, 336, 361, 363, 376]. They were therefore marked as "unclear (high disability)." The participants from the eight studies were all recruited from tertiary care (university hospitals) to seek help. Two RCTs were unclear but with suggestions of low disability pain. The authors excluded patients with either regular drug use such as (opioid, muscle relaxants, calcium channel blockers, immunosuppressive drugs or aminoglycoside antibiotics or hypersensitivity to any botulinum toxin preparation, human albumin or sodium chloride) [314] or any subjects who had taken any pain medications (e.g., ibuprofen, acetaminophen, opioids) within 48 hours prior to participating in the trial [322]. Five trials reported no information relating to the chronicity of pain [310, 338, 344, 355, 370].

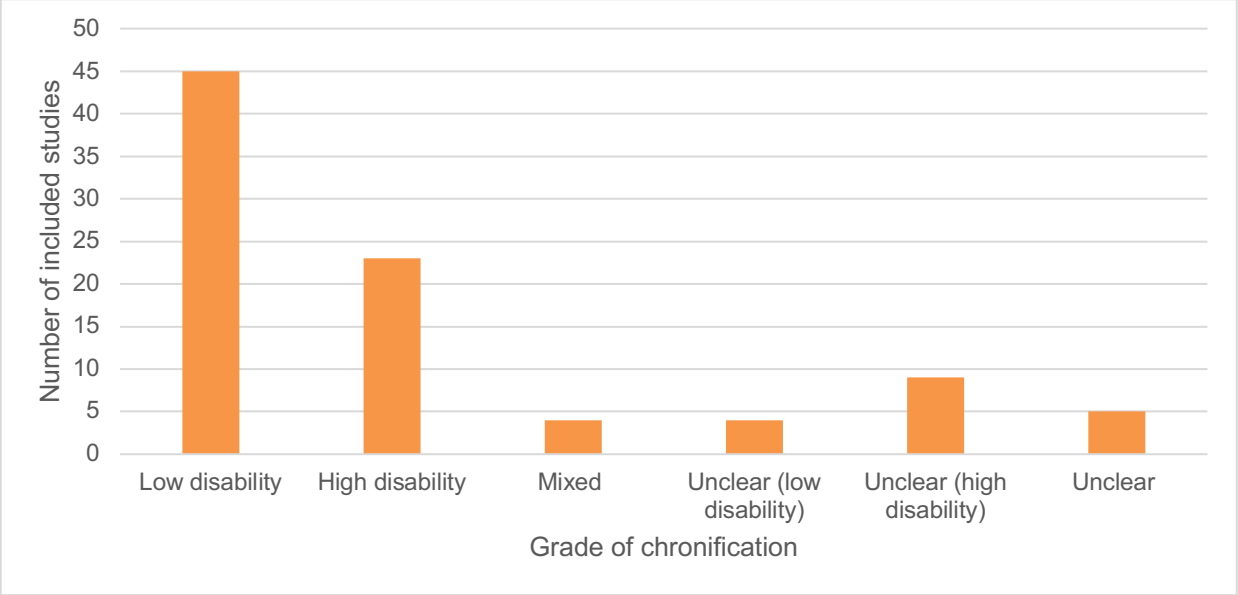


Figure 29: Grade of chronification of the included studies in medication.

The included RCTs were classified according to the indications mentioned above illustrated in Figure 30. Several of the studies examined provided multiple evidence of the subjects' level of chronicity. Consequently, the indications could support or contradict each other. For this reason, the priority list was used for the final inclusion in the classification. In the following Table 17, the priorities of the indications and the studies related to them are displayed.

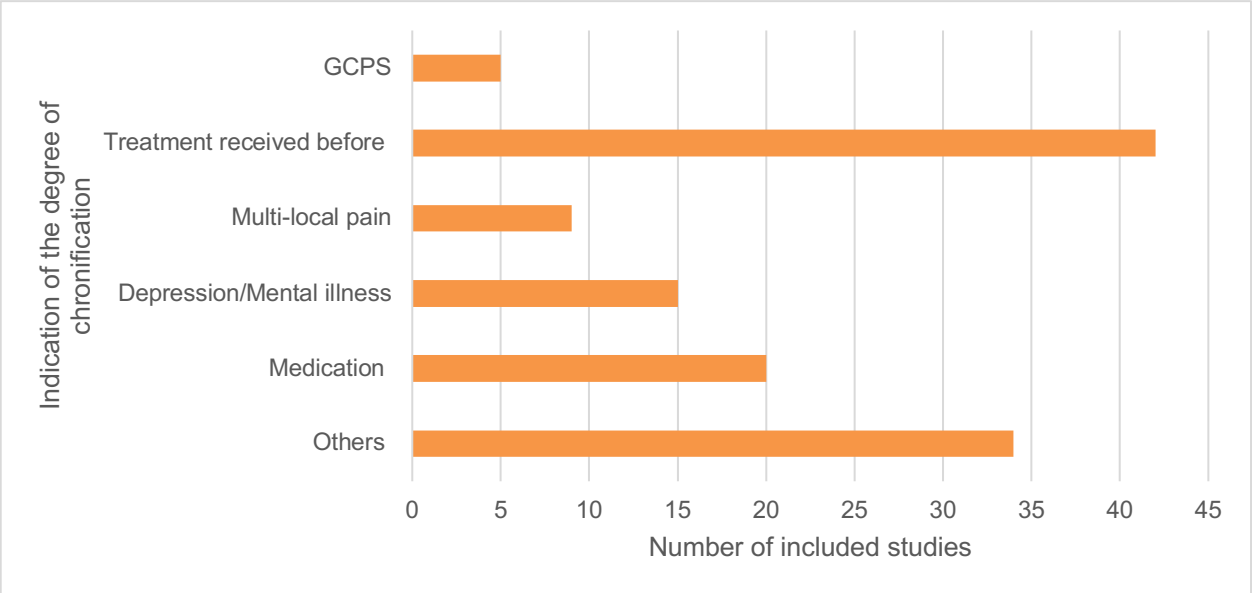


Figure 30: Hints of the degree of chronification, found in the included studies for medication; GCPS= Graded Chronic Pain Scale

Table 17: Indications of the degree of chronification, found in the included studies for medication

Indications	Low disability	High disability	Mixed	Unclear (low disability)	Unclear (high disability)
Graded chronic pain scale	Ernberg 2011		Goncalves 2013 De Carli 2013 Tchivileva 2020 Yurttutan 2019		
Treatment received before	Alajbeg 2018 Alpaslan 2012 Bouloux 2017 Celakil, 2017 Can 2018 Cigerim 2020 Dalewski 2019 Damlar 2015 De Carli 2016 Ekberg 1996 Guarda-Nardini 2008 Harkins 1991 Khalighi 2016 Korkmaz 2016 Marzook 2020 Mejersjö 2008 Minakuchi 2001 Nguyen 2001 Oliveras-Moreno 2008 Ozkan 2011 Sousa 2020 Winocur 2000 Yilmaz 2019 Yuasa 2001	Basterzi 2009 Bjornland 2007 De la Torre Canales 2020 Dogan 2014 Ferrante 1998 Gencer 2014 Hepguler 2002 Kopp 1985 Kopp 1991 Kurtoglu 2008 List 2001 Patel 2017 Ramakrishnan 2019 Sharav 1987 Singer 1997 Von Lindern 2003			Cahlin 2011
Multilocular pain	Dalewski 2019 Ekberg 1996 Gonzalez-Perez 2015 Guarda-Nardini 2005 Herman 2002 Nguyen 2001 Winocur 2000	List 2001 Makino 2014			
Depression or mental illness	Alajbeg, 2018 Alencar 2014 Bouloux 2017 Calderon 2011 DeNucci 1998 Herman 2002 Li 2009 Lobo Lobo 2004 Marini 2010 Marini 2012 Marzook 2020 Schiffman 2007 Ta 2004 Thie 2001	Gupta 2016			

Indications	Low disability	High disability	Mixed	Unclear (low disability)	Unclear (high disability)
Analgetic misuse	Cigerim 2020 Dalewski 2019 De Carli 2016 Hosgor 2017 Kang 2018 Khalighi 2016 Lobo Lobo 2004 Nguyen 2001 Schiffman 2007 Thie 2001 Turner 2011 Ziegler 2010	De Souza 2018 Di Rienzo Businco 2004 Ferrante 1998 Kimos 2007 Pramod 2011 Singer 1997		Altaweel 2019 Campbell 2017	
Others	Calderon 2011 Cen 2018 DeNucci 1998 Guarda-Nardini 2008 Herman 2002 Marini 2010 Marinin 2012 Minakuchi 2001 Oliveras-Moreno 2008 Ozkan 2011 Ta 2004 Yuasa 2011 Ziegler	Basterzi 2009 Bjornland 2007 Dogan 2014 Gencer 2014 Gupta 2016 Hepguler 2002 Kimos 2007 Kopp 1985 Koppp 1991 Kurtoglu 2008 List 2001 Makino 2014			Ayesh 2008 Cahlin 2011 Daif 2012 Gerschman 1984 Kütük 2019 Guarda-Nardini 2012 Shanavas 2014 Shin 1997

3.3.4.2.3 Study setting

75 of the 86 studies took place in tertiary care setting. This corresponds to a sample of 3340 subjects, but independent of control groups, the diagnostic instrument used, the outcomes measured and the study duration. The subjects were mostly treated in a specialized clinic or were referred to this clinic and thus found their place of participation in the respective study. In some cases, it was stated that the study had taken place in the clinic. Another 208 subjects from four studies came from specialized TMD clinics. Another 273 patients from six studies were recruited from the general population or from dental practices and were thus assigned to primary care. 16 trials did not have a description of the care level from which the subjects originated. Two studies recruited patients from primary and secondary care, one study included participants from primary and tertiary care, and one study used all three (primary, secondary, and tertiary care).

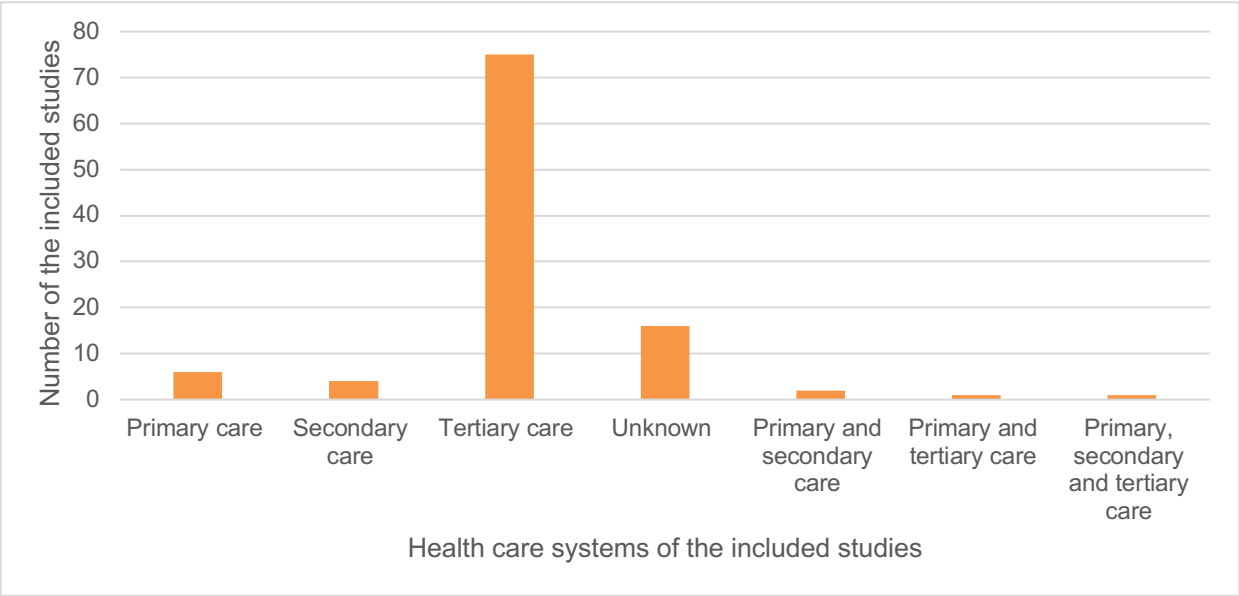


Figure 31: Recruitment of subjects in the included studies of medication

3.3.4.3 Characteristics of Interventions

3.3.4.3.1 Diagnostic instruments

It is noteworthy that 44 studies used the RCD/TMD according to Dworkin and LeResche criteria to categories patients at risk of developing TMD [40, 158, 168, 231, 236, 243, 247, 278, 279, 286, 298, 302, 303, 309, 311, 313, 315, 318, 320-325, 328, 329, 332, 336, 337, 340, 343, 345, 349, 355, 365, 366, 368, 370, 373, 375]. Seven used the magnetic resonance imaging (MRI) as diagnostic criteria [314, 316, 326, 327, 338, 352, 353, 360, 371], while others used the American Academy of Orofacial Pain [312, 367, 372], the Helkimo Index [317], or the Wilkes category [334, 356]. Ferrante et al. [333] used the diagnostic protocol after Simons, Jayachandran et al. 2017 [344] after Okeson and Pramod et al. 2011 [358] used Truelove's standard criteria. 16 used their own (based on participants signs and symptoms) [281, 297, 305, 310, 317, 330, 339, 341, 342, 346-348, 354, 359, 361, 363, 374] and nine studies did not specify the diagnostic protocol used [161, 331, 335, 350, 351, 357, 362, 364, 369].

3.3.4.3.2 Outcomes

3.3.4.3.2.1 Primary outcome – pain at rest

When considering the outcomes examined by the included studies it was observed that quite a few differences occurred. The primary outcome of pain intensity was frequently measured with the VAS instrument. 75 studies used the VAS [40, 158, 161, 168, 211, 231, 232, 236, 243, 247, 278, 279, 281, 286, 297, 302, 303, 305, 307, 309-318, 320-325, 328-335, 337-343, 345-349, 352-359, 361-365, 367, 369, 370, 372-375], while five studies used the NRS [158, 327, 344, 350, 351]. Other measuring instruments for pain intensity were the Helkimo's

clinical dysfunction index [326], the SSI [360], the CPI [368] or the Facial pain index (FPI) [366]. Two studies did not measure pain intensity [298, 371].

3.3.4.3.2.2 Secondary outcomes

MMO (mm) was measured by 50 RCTs [158, 243, 247, 278, 279, 286, 303, 305, 307, 310, 311, 314-316, 320, 323, 329, 348-354, 356, 358, 364, 365, 367, 370-372, 374, 375]. Ten studies investigated pain or tenderness upon palpation [231, 236, 247, 278, 303, 305, 310, 314, 331, 345]. 13 studies examined the improvement of TMJ sounds [243, 310, 314, 316-318, 328, 330, 331, 342, 352, 354, 360, 371]. Depression was measured in nine studies using the BDI [309, 321, 340, 368], SCL-90-R [332, 360], Hamilton Depression Inventory [362], Zung Depression Scale [364] or the HADS [366]. Somatization was investigated by three studies using the SCL-90-R [332, 360, 366].

3.3.4.3.3 Medication interventions

The variety of the medication employed was extensive. We divided the different medications into 13 subgroups Figure 32: Eleven trials investigated the effect of botulinum toxin [40, 158, 297, 298, 314, 328, 332, 357, 369, 373], 24 studies worked with NSAIDs [161, 168, 211, 231, 243, 247, 278, 279, 281, 310, 317, 325, 326, 330, 331, 334, 344, 353, 359-361, 363, 364, 367, 372], five studies dealt with opioids [286, 302, 325, 327, 374], anaesthetic agents were used by six trials [236, 303, 315, 333, 374, 377], different kind of Benzodiazepines were investigated in ten studies [311, 312, 321, 329, 335, 341, 343, 345, 358, 364], while 16 studies worked with natural drugs [307, 309, 320, 323, 324, 334, 336, 347, 349, 350, 354, 355, 365, 366, 370, 375]. Alpaslan et al. [313] compared different muscle relaxants. Ten studies worked with hyaluronic acid [158, 316, 324, 334, 348, 352, 371, 375]. Nine studies looked at sodium hyaluronate [317, 318, 338, 339, 342, 346, 347, 356, 370]. Goncalves et al. 2013 investigated propranolol [337]. Two studies used capsaicin [305, 322]. Turner et al. 2011 [368] focused on hormonal therapy and investigated the effect of contraceptive pills on TMD. Sharav et al. 1987 [362] used anti-depressives (amitriptyline). Finally, Makino et al. 2014 [351] described the study group with conventional medication but without further information.

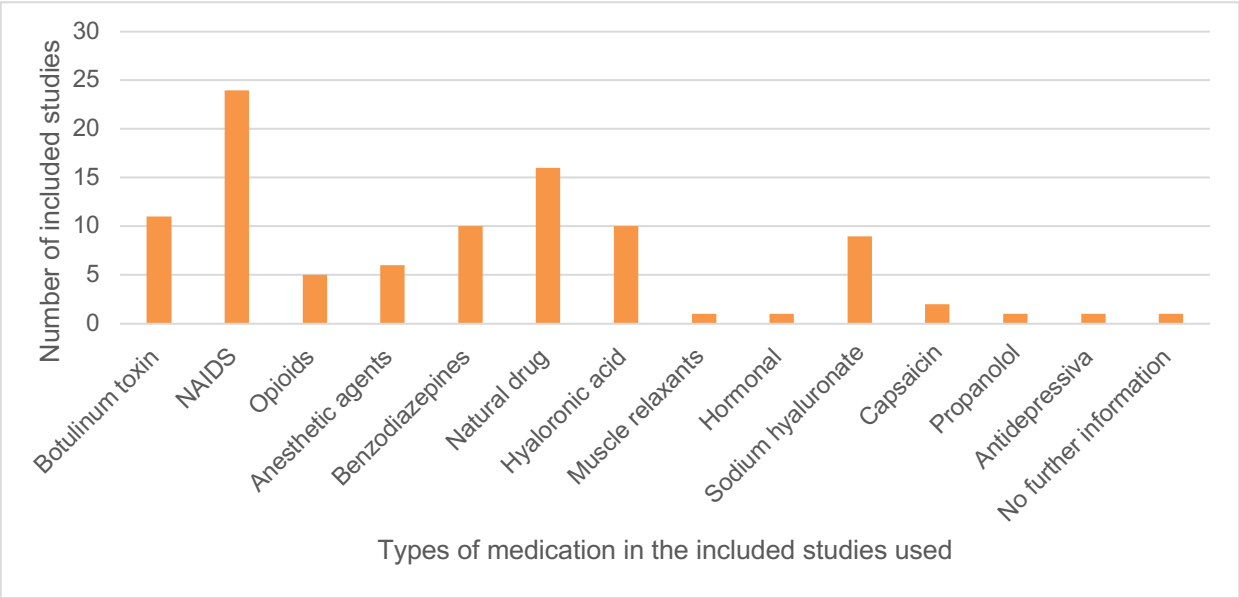


Figure 32: Types of medications used in the included studies in medication therapy

3.3.4.3.4 Way of medication administration

The included RCTs investigating medication treatment for TMD were very heterogeneous, regarding not only the medication investigated, but also the administration routes and follow-up periods. Medication with topical applications were investigated by seven studies [305, 322, 349, 350, 355, 359, 363]; oral administration and injectable medication were investigated by 40 studies and 38 studies each [161, 232, 243, 247, 278, 279, 281, 307, 309-313, 317, 320, 321, 324, 325, 327, 329-331, 337, 341, 343-345, 351, 353, 354, 358, 360-362, 364, 366-368, 372] [40, 158, 236, 286, 297, 298, 302, 303, 314-318, 326, 328, 332-336, 338-340, 342, 346-348, 352, 356, 357, 365, 369-371, 373-375]. One study focused on ozone therapy [323].

3.3.4.3.5 Control groups

Predominantly, the authors compared medication treatment with placebo therapy [231, 279, 286, 297, 298, 302, 305, 309, 311, 312, 315, 317-322, 324, 329, 331-335, 337, 338, 341-343, 345, 349, 350, 354, 355, 357-359, 363, 366, 369-371, 374]. The second biggest control groups used different medication other than the drug investigated in 27 studies [279, 281, 286, 302, 307, 312-314, 316, 325, 327, 328, 334, 336, 340, 344, 346-348, 356, 362, 364, 365, 367, 374, 378]. Splint was used in 12 studies as controls [243, 278, 303, 310, 311, 328, 337, 339, 348, 353, 365, 373] and laser therapy in six trials [231, 236, 243, 247]. The other controls used no treatment [313, 339, 372], TENS [361], CBT/self-management [321, 368], arthrocentesis [243, 352, 360], DN [158, 168], facial manipulation [40], exercise [351] and ozone therapy [317, 326, 330]. The bar chart (Figure 33) below displays the therapies that were compared with medications treatment.

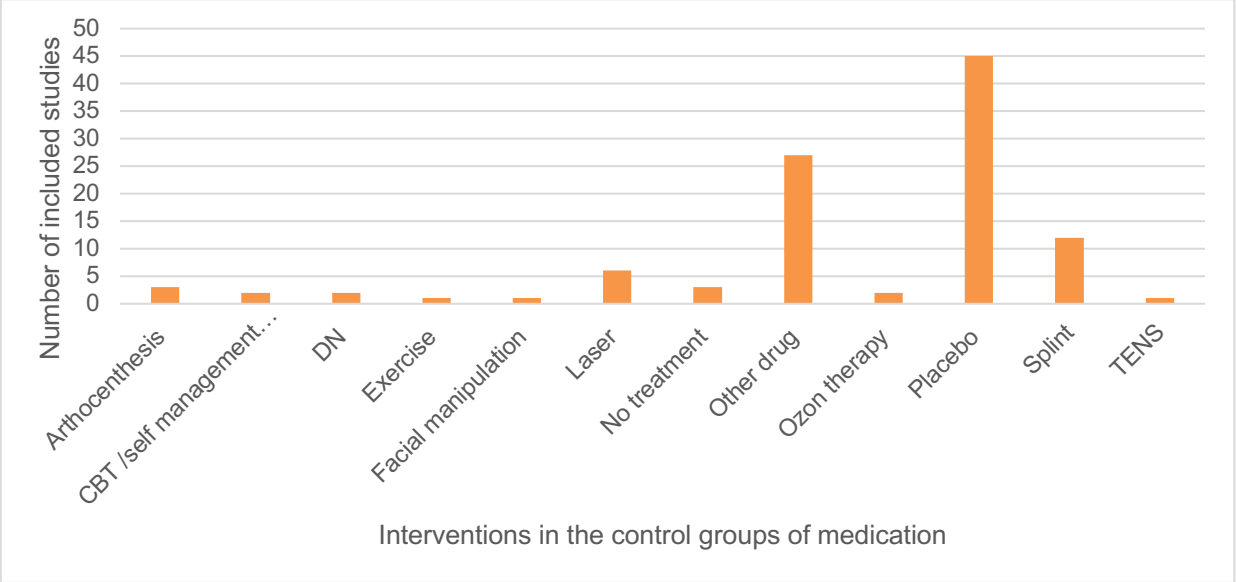


Figure 33: Controls used in the included studies for medication therapy

3.3.4.3.6 Follow up periods

Follow-up intervals differed from 24 hours up to five years. The majority of the included studies were short term investigations (less than six months), while six studies had a follow-up period for more than one year [278, 316, 324, 360, 368, 370]

3.3.5 Excluded studies

79 studies were excluded for which reasons are declared in the corresponding table (Appendix VIII, section Characteristics of excluded studies).

3.3.6 Assessment of the methodological quality of the included studies

The assessment of risk of bias in the studies was conducted by two independent reviewers (Ms. Held and Dr. Dangl) as previously described. Figure 34 and Figure 35 summarise the risk of bias of the evidence according to the guidelines established by the Cochrane Collaboration for the RCTs using medications in the treatment of TMD. Most studies did not meet the criteria of important methodological indicators of risk of bias, such as randomization, allocation concealment, blinding, and ITT. Randomization generation was rated as low risk of bias by 62.8% of the included studies. One study [316] was classified as high risk for randomization because the author declared that it was a randomized trial, but the groups were divided according to their symptoms. The category of allocation concealment was inadequately described, although we contacted each author for further details. Only 19.8% of the included studies provided information on the allocation concealment procedure. More than half of the included studies (55.8%) blinded participants

and staff or outcome assessment (52.2%), while four trials [281, 317, 330, 344, 356] were rated with a high risk of bias for blinding of participants. For instance: Dogan et al. 2014 [330] did not blind the patients, Di Rienzo Businco et al. 2004 [281] and Jayachandran et al. 2017 [344] stated by email that neither the patients nor the investigator in the studies were blinded. In addition, Oliveras-Monera et al. 2008 [356] conducted an open trial study and was therefore also classified as high-risk for both blinding categories. The included studies reported quite well regarding the incomplete outcome data. Eight studies [309, 320, 337, 345, 353, 366, 368, 370] used ITT and 67.4% were classified as low risk in the incomplete outcome data category. Three studies did not report sufficient information. For example, in the study by Nguyen et al. 2001 [354] there were many dropouts and unequal distribution between groups. This was also observed in the trials of Gonzales-Perez et al. 2015 [168] and Harkins et al. 1991 [341], with the majority of the dropouts arising from the control group. Out of the 86 included studies, 87% were rated as low risk of bias, while four studies did not report all stated outcomes. Bertolami et al. 1993 [317] was classified as high risk for incomplete outcome as the author did not report actual linear values of mandibular displacement (arthrophonometry) in the results. Dogan et al. 2014 [330] and Hosgor et al. 2017 [243] reported no results to the joint sounds, and Gonzales-Perez et al. [168] only reported on pain and MMO. A low risk of bias for other bias was achieved by 15% of the studies. Three studies met all criteria of low-risk bias using the Cochrane Collaboration's tool [161, 325, 366].

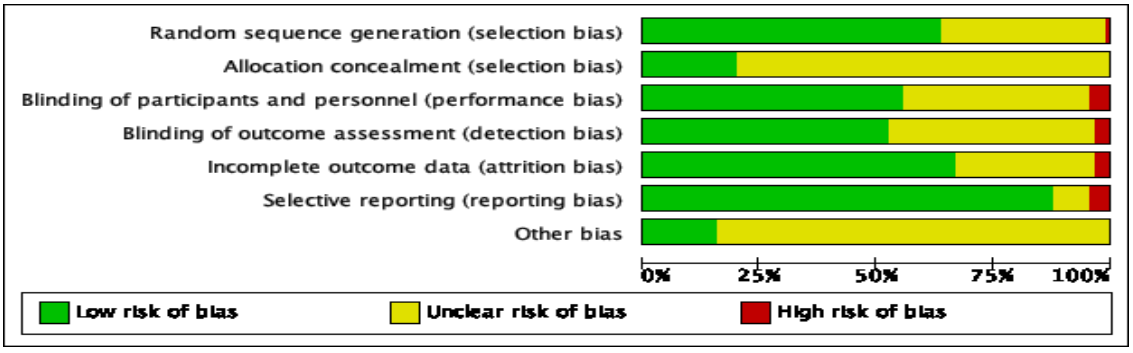


Figure 34: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

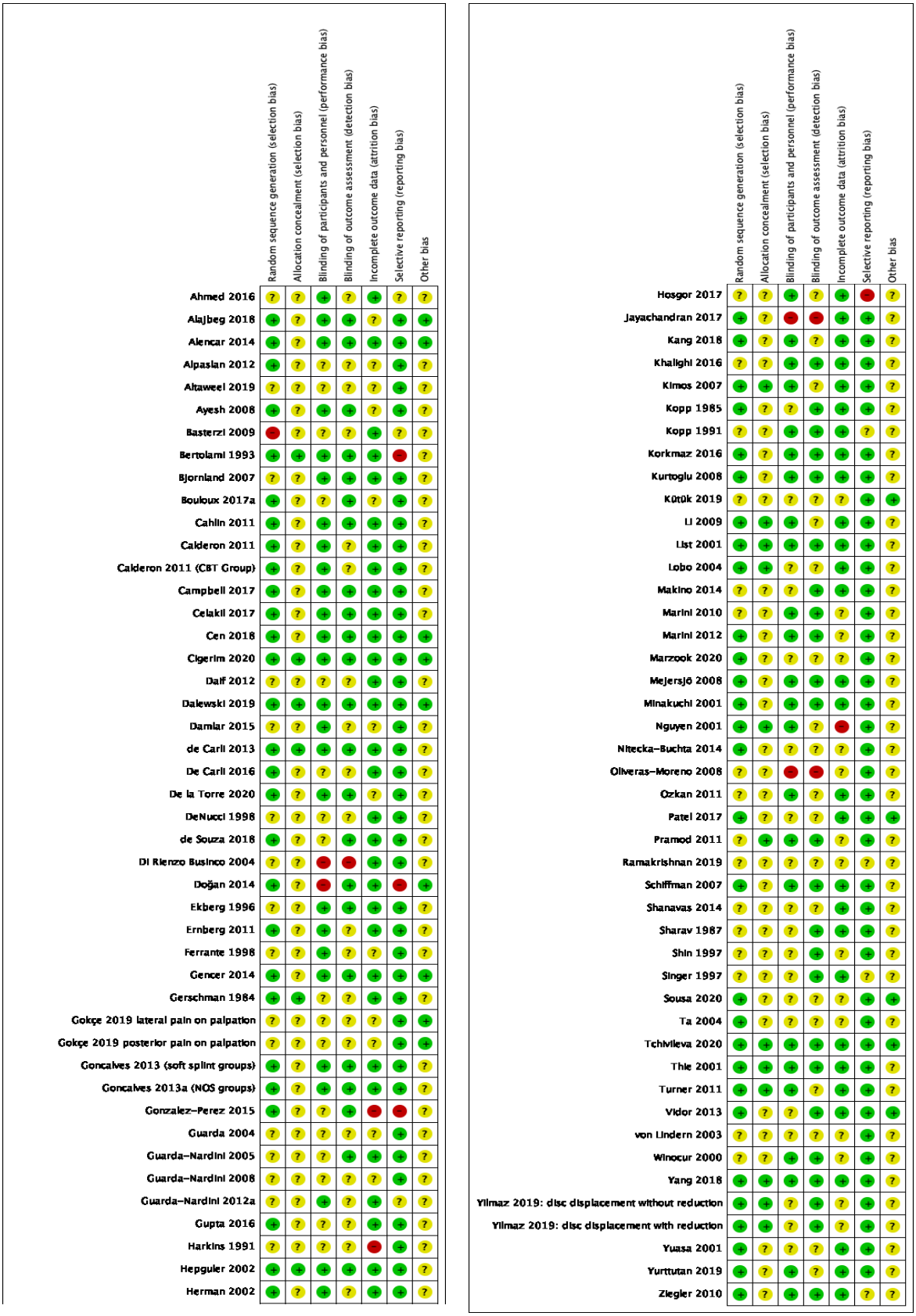


Figure 35: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

3.3.7 Results of the quantitative synthesis of the included studies (Meta-analysis)

In general, the meta-analysis for medications was very difficult to compile because the included studies used different medication, different dosages, and different control groups. This led to very heterogeneous results and a low number of trials for single comparisons. For this reason, in this part of the paper we included the two main comparisons (1. Medication vs. other treatment and 2. Medication vs. placebo) with sensitivity analysis, despite the heterogeneity being extensive. Statistically significant or not statistically significant but relevant results are described below in detail. For comprehensiveness, the remaining forest plots for the smaller analysis (minimum three studies for each subgroup) with further results from this study are presented in Appendix (IX).

For the meta-analysis, 68 RCTs were selected. The study of Calderon et al. 2011 [321] and Goncalves et al. 2013 [337] were added twice as both studies had four groups (two interventions and two controls). Of the 86 included studies that could pass the full-text screening, a total of 18 studies were excluded from the quantitative comparison. The reasons for exclusion were as follows:

1. Combination of therapies used for the study group [303, 353, 360, 365, 372]
2. Missing data on the outcomes [161, 338, 373]
3. Data collection/presentation differed from the other included studies [298, 317, 326, 333, 346, 379]
4. Compared different symptoms in the trial [316, 371]
5. Used the same medication with different dosage or application site in the included study [314, 362]

A tabular overview of the statistically significant results for the pain group with low disability and with high disability is presented in 3.3.8 for the reduction of pain intensity (Table 18) and for MMO (Table 19).

A SMD of zero indicates that the intervention group and the control group have equal effects. For pain reduction, an improvement is associated with lower values in the outcome measure. SMDs less than zero indicate that the intervention group is more effective than the control group. Therefore, a negative direction with lower values corresponds to better performance of the intervention group. Conversely, for MMO improvement, improvement is associated with higher values on outcome measures. A positive direction with higher values corresponding to better performance of the intervention group under study [200].

The IMMPACT guideline states that a 30% pain reduction in chronic pain is necessary to distinguish placebo from verum [201]. This means that the initial pain intensity is considered clinically relevant in clinical studies and the interventions are evaluated as effective in this respect [202]. To obtain the clinical significance, the author added a small comment on each forest plot obtaining the data from the pain reduction from the baseline compared to the follow up time.

3.3.7.1 Comparison: Effectiveness of medication treatment (orally administered) in comparison to other treatment on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.3.7.1.1 Primary outcome parameter: pain intensity

3.3.7.1.1.1 Short-term efficacy (treatment duration up to six months)

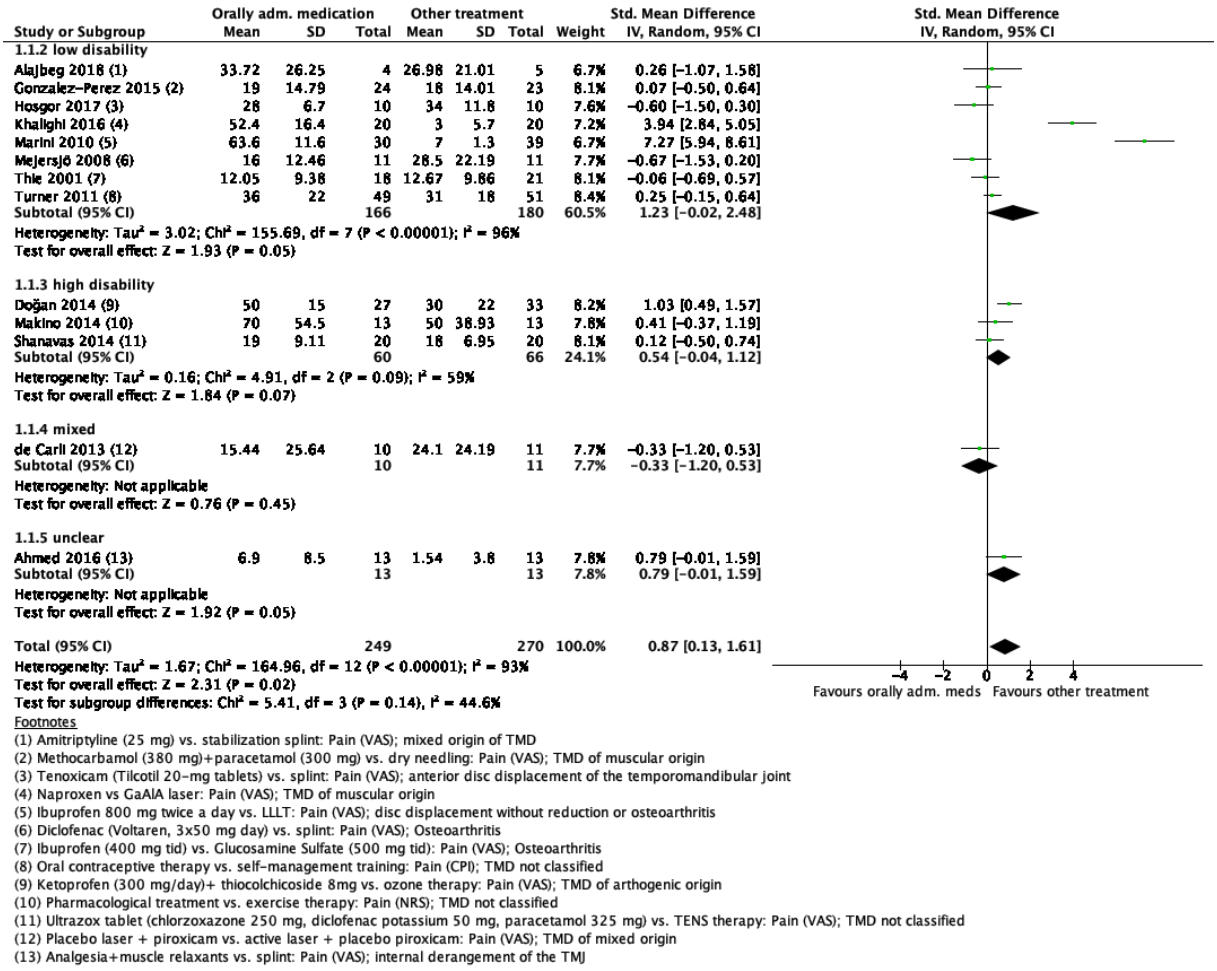
The effect of medication orally administered compared with other treatments in the period from 0 to 6 months following the start of treatment is demonstrated in Figure 36. Surprisingly, the meta-analysis of data from 519 participants across 13 trials showed a statistically significant bigger reduction in total pain scores using other treatments compared to medication treatment (n=13 studies [n=249 for Group A, and n=270 for Group B], SMD=0.87; 95% CI [0.13, 1.61]; p=0.02), yet with a substantial heterogeneity x^2=164.96 (I^2=93%).
A subgroup analysis showed no significant bigger pain reduction between orally administered medications and other treatment for patients with low disability pain (n=8 studies [n=166 for Group A, and n=180 for Group B], SMD=1.23; 95% CI [-0.02, 2.48]; p=0.05, I^2=96%), or high disability pain (n=3 studies [n=60 for Group A, and n=66 for Group B], SMD=0.54; 95% CI [-0.04, 1.12]; p=0.07, I^2=59%).

It is important to note that it appears that the low disability pain group had two outliers Khalighli et al. 2016 and Marini et al. 2010 [211]. By removing these two studies no change in the low disability pain group was found. The overall total pain result, shifting more to the left side to the orally administered medication resulted in no significance difference Figure 81, APPENDIX IX: Forest plots.

Due to the high heterogeneity of the results, we made further investigations:
Consequently, only studies that included analgetic medication were included in the analysis. These were the eight studies [243, 247, 278, 307, 310, 317, 330, 361, 367]. The result was statistically significantly bigger for other treatment in the pain relief (SMD=1.40; 95% CI [0.12, 2.69]; p=0.03; Figure 82, APPENDIX IX: Forest plots) yet with a high heterogeneity Chi^2=154.07 (I^2=95%). However, in the low disability pain group (n=5 studies [n=89 for Group

A, and n=101 for Group B], SMD=1.93; 95% CI [-0.56, 4.42]; *p*=0.13, I^2=97%) and in the high disability pain group (n=2 studies [n=47 for Group A, and n=53 for Group B], SMD=0.59; 95% CI [-0.30, 1.48]; *p*=0.20, I^2=79%) no significant difference was found between analgetic orally administered medication and other treatment, however.

A clinical significance of 30% pain reduction was observed in all the studies except for the studies of Khalighi et al. 2016, Dogan et al. 2014 and Makino et al. 2014.



Footnotes
(1) Amitriptyline (25 mg) vs. stabilization splint: Pain (VAS); mixed origin of TMD
(2) Methocarbamol (380 mg)+paracetamol (300 mg) vs. dry needling: Pain (VAS); TMD of muscular origin
(3) Tenoxicam (Tilcotil 20-mg tablets) vs. splint: Pain (VAS); anterior disc displacement of the temporomandibular joint
(4) Naproxen vs GaAlA laser: Pain (VAS); TMD of muscular origin
(5) Ibuprofen 800 mg twice a day vs. LLLT: Pain (VAS); disc displacement without reduction or osteoarthritis
(6) Diclofenac (Voltaren, 3x50 mg day) vs. splint: Pain (VAS); Osteoarthritis
(7) Ibuprofen (400 mg tid) vs. Glucosamine Sulfate (500 mg tid): Pain (VAS); Osteoarthritis
(8) Oral contraceptive therapy vs. self-management training: Pain (CPI); TMD not classified
(9) Ketoprofen (300 mg/day)+ thiocolchicoside 8mg vs. ozone therapy: Pain (VAS); TMD of arthogenic origin
(10) Pharmacological treatment vs. exercise therapy: Pain (NRS); TMD not classified
(11) Ultrazox tablet (chlorzoxazone 250 mg, diclofenac potassium 50 mg, paracetamol 325 mg) vs. TENS therapy: Pain (VAS); TMD not classified
(12) Placebo laser + piroxicam vs. active laser + placebo piroxicam: Pain (VAS); TMD of mixed origin
(13) Analgesia+muscle relaxants vs. splint: Pain (VAS); internal derangement of the TMJ

Figure 36: Medication (orally administered) versus (any) other treatment (outcome: change in pain intensity, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

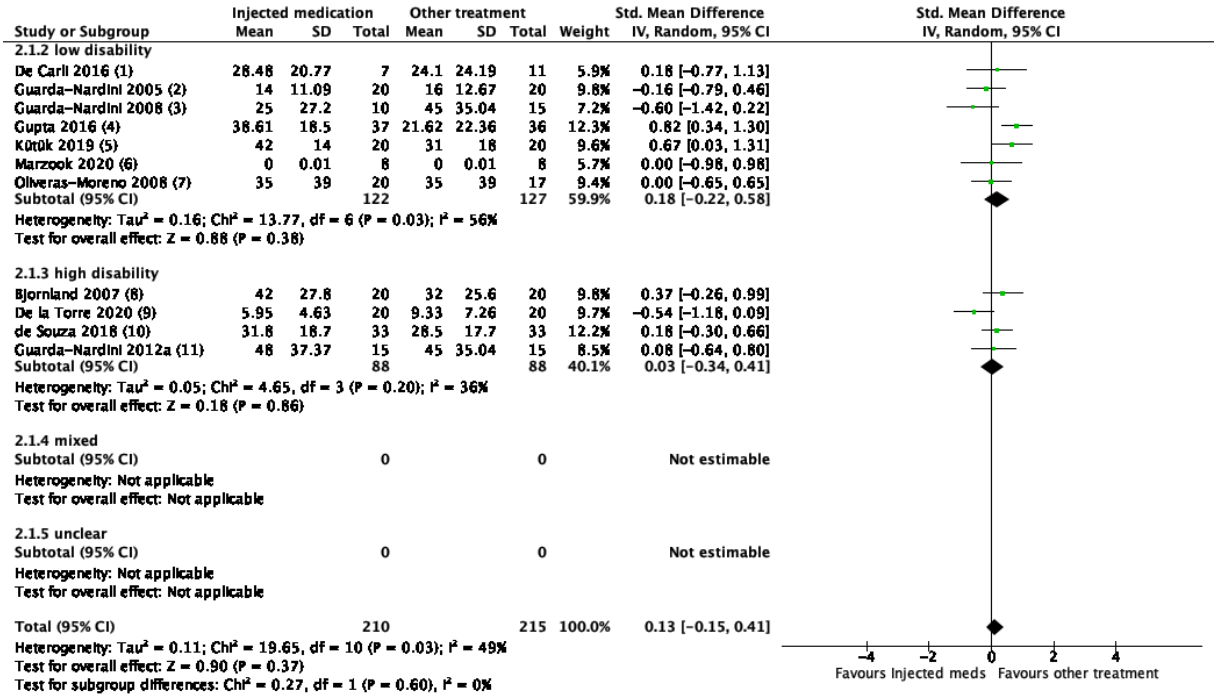
3.3.7.2 Comparison: Effectiveness of the medication treatment (injection only) in comparison to other treatment on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.3.7.2.1 Primary outcome parameter: pain intensity

3.3.7.2.1.1 Short-term efficacy (treatment duration up to six months)

In this comparison we concentrated on the injected medication. Figure 37 demonstrates the effect of injected medication compared to other treatment n in the period from 0 to 6 months following the start of treatment. The meta-analysis of data from 425 participants across 11 trials showed no statistically significant bigger reduction in total pain scores using injected medication versus other treatment. Unexpectedly, the overall effect for pain favoured other treatment (n=11 studies [n=210 for Group A, and n=215 for Group B], SMD=0.13; 95% CI [-0.15, 0.41]; p=0.37), with moderate heterogeneity Chi^2=19.65 (I^2=49%).
A subgroup analysis showed no significant difference between injected medications and other treatment groups for patients with low disability pain (n=7 studies [n=122 for Group A, and n=127 for Group B], SMD=0.18; 95% CI [-0.22, 0.58]; p=0.38, I^2=56%) or high disability pain (n=4 studies [n=88 for Group A, and n=88 for Group B], SMD=0.03; 95% CI [-0.34, 0.41]; p=0.86, I^2=36%). The mixed pain and unclear pain had limited studies in this category.

For the studies of De Carli et al. 2016, Guarda-Nardini et al. 2005, Guarda-Nardini et al. 2008, Gupta et al. 2016, Marzook et al. 2020, Oliveras-Moreno et al. 2008, Björnland et al. 2007, De la Torres et al. 2020, De Souza et al. 2018 and Guarda-Nardini et al. 2012 a clinical significance of 30% pain reduction in the intervention group was observed. The study of Kütük et al. 2019, did not have a clinical significance in pain reduction.



Footnotes

(1) Botulinum toxin (30 U after 15 days 15 U) vs. GaAlAs laser: Pain (VAS); TMD of muscular origin
(2) Injections of 5x1 mL SH vs. splint: Pain (VAS); osteoarthrosis
(3) Botulinum toxin (total 100 U) vs. saline placebo injections: Pain (VAS); TMD of muscular origin
(4) Anesthetic (0.5% bupivacaine) vs. trigger point injection+50 mg Levosulpiride orally: Pain (VAS); TMD of muscular origin
(5) Abobotulinum toxin−A (total 150 U) vs. dry needling: Pain (VAS); TMD of muscular origin
(6) Intra−articular injection (HA + corticosteroid) vs. arthrocentesis: Pain (VAS); TMJ internal derangement with reduction
(7) 1l A infiltration of Sodium Hyaluronate (SH) vs. control (combination of methocarbamol 380 mg and paracetamol 300 mg): Pain (VAS); internal derangement
(8) Celestone Chronodose vs. Synvisc: Pain (VAS); osteoarthritis of the TMJ and myofascial pain
(9) BoNT−A−Median (temporal:20 U;masseter:50 U) vs. oral appliance (OA): Pain (VAS); TMD of mixed origin
(10) Anaesthetic infiltration vs. GaAlAs laser: Pain (VAS); TMD of muscular origin
(11) Botulinum toxin injections (total 150 U) vs. Fascial manipulation: Pain (VAS); TMD of muscular origin

Figure 37: Medication (injection only) vs. other treatment (outcome: change in pain intensity, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.3.7.3 Comparison: Effectiveness of medication treatment (injection excluded) in comparison to placebo treatment on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.3.7.3.1 Primary outcome parameter: pain intensity

3.3.7.3.1.1 Short-term efficacy (treatment duration up to six months)

The meta-analysis of data from 1277 participants across 26 trials showed a statistically significant bigger reduction in total pain scores in medication (excluding injectable medication) versus placebo. Figure 38 demonstrates the effect of medication (injections excluded) compared with placebo medication in the period from 0 to 6 months following the start of treatment. The overall effect for pain favoured the treatment of medication with a statistically significant bigger result (n=26 studies [n=648 for Group A, and 629 for Group B], SMD=-0.38; 95% CI [-0.60, -0.15]; p=0.001), yet with a high heterogeneity (I^2=71%).
A subgroup analysis showed significant differences between drugs and placebo groups for patients with low disability pain (n=12 studies [n=185 for Group A, and n=180 for Group B], SMD=-0.47; 95% CI [-0.80, -0.14]; p=0.005, I^2=56%) and high disability pain (n=9 studies [n=230 for Group A, and n=215 for Group B], SMD=-0.49; 95% CI [-0.92, -0.07]; p=0.02, I^2=73). Surprisingly, there was no significant difference between drugs (injectable excluded) and placebo in pain relief for the mixed disability pain subgroup (n=3 studies [n=127 for Group A, and n=128 for Group B], SMD=0.14; 95% CI [-0.11, 0.39]; p=0.26, I^2=0) and the unclear pain subgroup (n=2 studies [n=106 for Group A, and n=106 for Group B], SMD=-0.26; 95% CI [-0.70, 0.18]; p=0.25, I^2=57%). The mixed pain population showed the opposite trend to the other subgroups.

Due to the high heterogeneity evident in the results, sensitivity analysis was performed on the following:
First, studies that used cremes as a medication form were excluded from the analysis (Figure 83, APPENDIX IX: Forest plots). Six studies were excluded [305, 349, 350, 355, 359, 363]. The result for orally administered medication showed statistically significantly bigger result in favour of medication for high disability pain (SMD=-0.39; 95% CI [-0.78, -0.00]; p=0.05; I^2=49) and total pain (SMD=-0.24; 95% CI [-0.43, -0.04]; p=0.02; I^2=42%) but not in the low disability pain group (SMD=-0.25; 95% CI [-0.54, 0.03]; p=0.08; I^2=15%) for reducing pain intensity. The mixed pain and unclear pain group showed no change between the medication group and placebo.

Secondly, to reduce the heterogeneity we excluded all studies [321, 335, 337, 343, 363, 366] in which the patients received medication in combination with another treatment or medication. Consequently, we had 26 studies for sensitivity analysis (SMD=-0.48; 95% CI [-

0.75, -0.22]; *p*=0.0003; I^2=70%, Figure 84). The result was statistically significant bigger in favour of the medication therapy for pain relief compared to placebo.

A clinical significance of 30% pain reduction in the intervention group was observed in all the included studies except for DeNucci et al. 1998 and Cahlin et al. 2011.

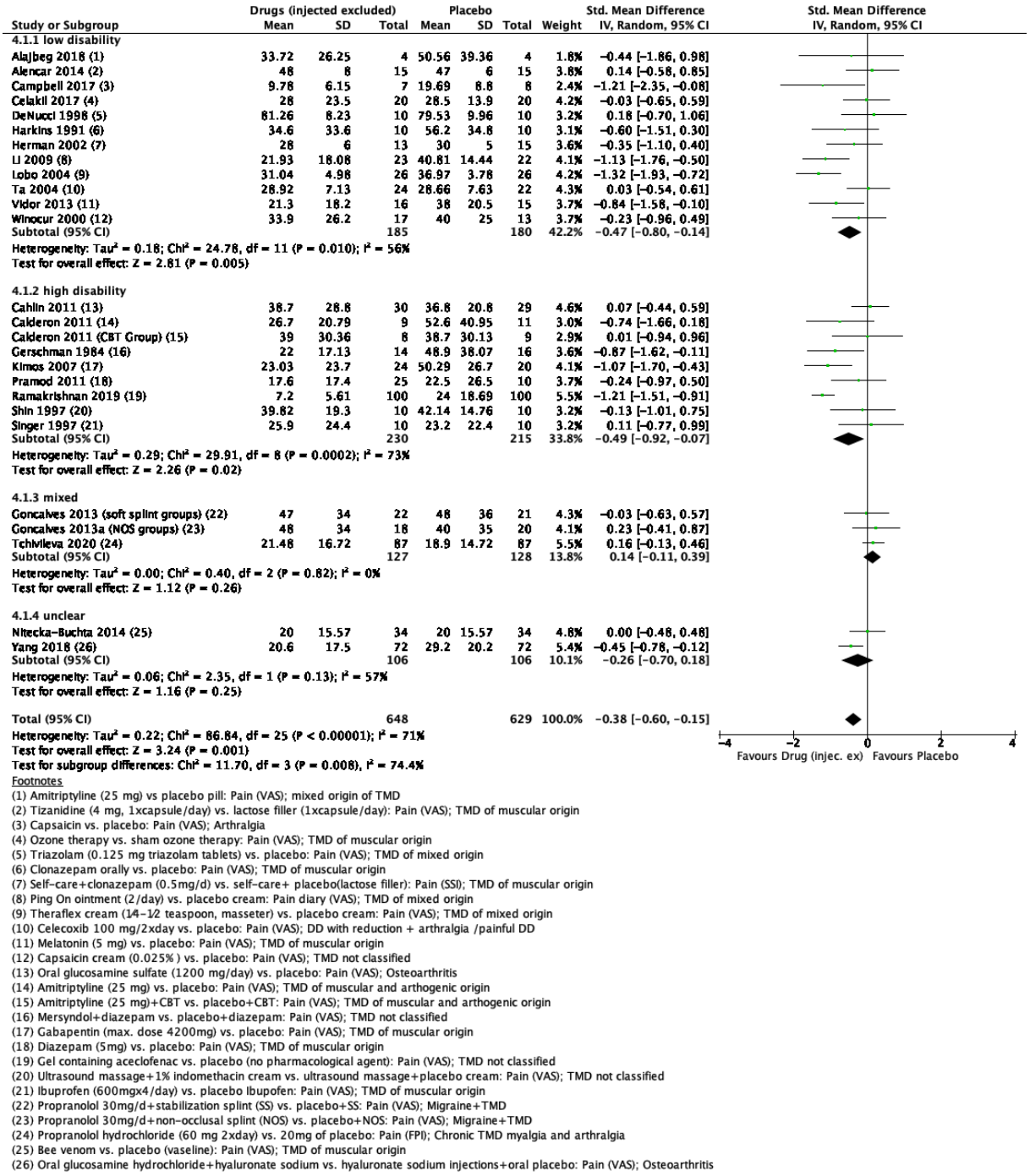


Figure 38: Medication (injectables excluded) versus placebo (outcome: change in pain intensity, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain-related disability not identified

3.3.7.3.2 Secondary outcome parameters: Maximum mouth opening

3.3.7.3.2.1 Short-term efficacy (treatment duration up to six months)

Surprisingly, there was no effect in the meta-analysis (Figure 85) for improving MMO using medication (injections excluded) compared to placebo within the timeframe of less than six months (n=11 studies [n=252 for Group A, and n=234 for Group B], SMD=0.01; 95% CI [-0.17, 0.19]; p=0.93, I^2=0%). This was observed in all three subgroups in low disability pain (n=6 studies [n=147 for Group A, and n=144 for Group B], SMD=0.01; 95% CI [-0.27, 0.28]; p=0.97, I^2=19%), high disability pain (n=3 studies [n=65 for Group A, and n=49 for Group B], SMD=-0.00; 95% CI [-0.38, 0.38]; p =0.99, I^2=0%), mixed pain population (n=2 studies [n=40 for Group A, n=41 for Group B], SMD=0.06; 95% CI [-0.38, 0.50]; p=0.78, I^2=0%).

3.3.7.4 Comparison: Effectiveness of medication treatment (injection only) in comparison to placebo on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.3.7.4.1 Primary outcome parameter: pain intensity

3.3.7.4.1.1 Short-term efficacy (treatment duration up to six months)

A significant bigger pain relief was found in the comparison of injectable medications versus placebo (Figure 39) in the short-term period (less than six months) in favour of medication (n=14 studies [n=300 for Group A, and n=274 for Group B], SMD=-0.39; 95% CI [-0.76, -0.03]; p=0.04, I^2=76%). No significant results were seen for low disability (n=6 studies [n=125 for Group A, and n=131 for Group B], SMD=-0.18; 95% CI, [-0.43, 0.07]; p=0.15, I^2 =0%) or for high disability pain (n=8 studies [n=175 for Group A, and n=143 for Group B], SMD=-0.49; 95% CI [-1.09, 0.17]; p=0.15, I^2=85%). The tendency for both pain groups were in favour of injectable medication.

In terms of clinical significance, a worrying five out of 14 studies failed to reach the 30% mark. In the studies of Cen et al. 2018, Gurada-Nardini et al. 2008, Kang et al. 2018, Ziegler et al. 2010, de la Torre et al. 2020, Gencer et al. 2014, Hepguler et al. 2002, Patel et al. 2017 and von Lindern et al. 2003, clinically significant pain reduction of 30% was observed in the intervention group. The studies by Ernberg et al. 2011, Nguyen et al. 2001, Ayesh et al. 2008, Kopp et al. 1991, List et al. 2001 had no clinical relevance for pain relief.

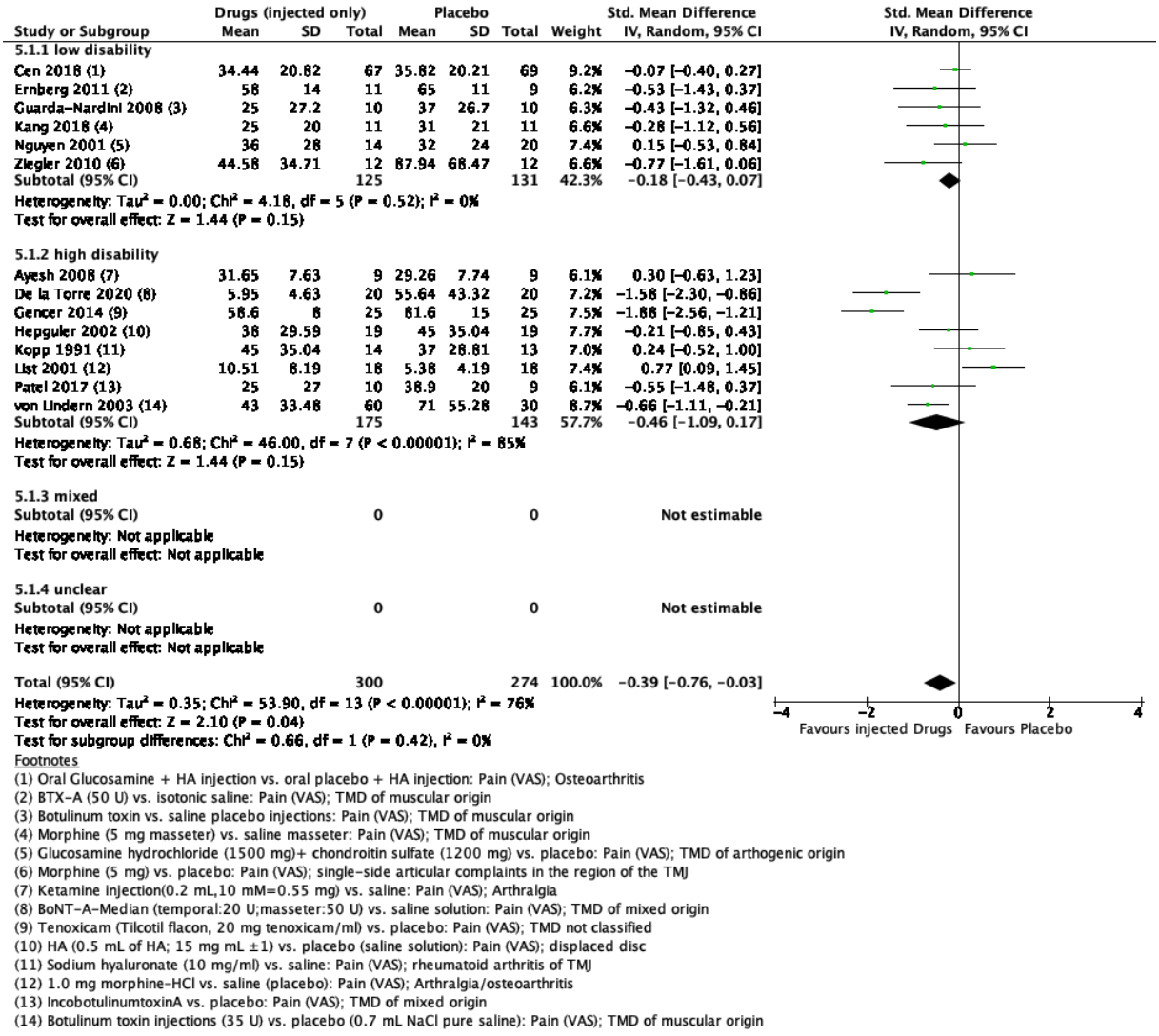


Figure 39: Medication (injected only) versus placebo (outcome: change in pain intensity, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.3.7.4.2 Secondary outcome parameters: Maximum mouth opening

3.3.7.4.2.1 Short-term efficacy (treatment duration up to six months)

There was no bigger effect seen in the meta-analysis (Figure 86, APPENDIX IX: Forest plots) for improving MMO using medication (injections only) compared to placebo in the timeframe of less than six months (n=6 studies [n=147 for Group A, and n=141 for Group B], SMD=-0.03; 95% CI [-0.26, 0.21]; *p*=0.82, I^2 =0%). This was also seen for low disability pain (n=4 studies [n=124 for Group A, n=119 for Group B], SMD=-0.03; 95% CI [-0.28, 0.22]; *p*=0.81, I^2=0%) and for high disability pain (n=2 studies [n=23 for Group A, and n=22 for Group B], SMD=-0.00; 95% CI [-0.59, 0.59]; *p*=1.00, I^2=0).

Comparison: Effectiveness of Botulinum toxin treatment in comparison to other treatments on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.3.7.4.3 Primary outcome parameter: pain intensity

3.3.7.4.3.1 Short-term efficacy (treatment duration up to six months)

The comparison of botulinum toxin injections versus other treatments showed no statistical significance bigger difference in reducing pain intensity within a timeframe of less than six months follow up (n=5 studies [n=72 for Group A, and n=81 for Group B], SMD=-0.04; 95% CI [-0.54, 0.47]; *p*=0.88), seen in Figure 87, APPENDIX IX: Forest plots. The heterogeneity was moderate Chi^2=9.27 (I^2=57%) but neither for low disability pain (n=3 studies [n=37 for Group A, and n=46 for Group B], SMD=0.11; 95% CI [-0.67, 0.89]; *p*=0.78, I^2=65%) nor for high disability pain (n=2 studies [n=35 for Group A, and n=35 for Group B], SMD=-0.26; 95% CI [-0.87, 0.36]; *p*=0.41, I^2=39%) a significant larger improvement in pain intensity using botulinum toxin was found.

All the included studies ha a clinically significant pain reduction on the intervention group except for the study of Kütük et al. 2019.

3.3.7.5 Comparison: Effectiveness of Botulinum toxin treatment in comparison to placebo on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.3.7.5.1 Primary outcome parameter: pain intensity

3.3.7.5.1.1 Short-term efficacy (treatment duration up to six months)

Five studies [297, 328, 332, 357, 369] were included for the meta-analysis of botulinum toxin versus placebo in the short-term reducing pain intensity shown in Figure 88, APPENDIX IX: Forest plots. A statistically significant bigger result in favour of botulinum toxin was found for pain relief compared to placebo (n=5 studies [n=111 for Group A, and n=78 for Group B], SMD=-0.78; 95% CI [-1.19, -0.37]; *p*=0.0002, I^2=35%). There was also a significant bigger difference for the high disability pain group (n=3 studies [n=90 for Group A, and n=59 for Group B], SMD=-0.93; 95% CI [-1.55, -0.31]; *p*=0.003, I^2=60%). The low disability pain group (n=2 studies [n=21 for Group A, and n=19 for Group B], SMD=-0.48; 95% CI [-1.11, 0.16]; *p*=0.14, I^2=0%) also showed a positive favour of botulinum toxin, but without statistical significance. The subgroup of mixed pain was not evaluated due to the lack of studies in this area. For all included the studies was of a clinical significance of 30% pain reduction in the intervention group observed.

3.3.7.6 Comparison: Effectiveness of NSAIDs treatment in comparison to placebo on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.3.7.6.1 Primary outcome parameter: pain intensity

3.3.7.6.1.1 Short-term efficacy (treatment duration up to six months)

A positive tendency towards NSAIDs was seen in the meta-analysis of NSAIDs versus placebo in the short-term (less than six months) in reducing pain intensity in Figure 89 (APPENDIX IX: Forest plots) (n=5 studies [n=169 for Group A, and n=167 for Group B], SMD=-0.65; 95% CI [-1.40, 0.09]; *p*=0.09). There was considerable heterogeneity with I^2=87%. However, looking at the subgroups, a statistically significant superiority of NSAIDs was found for the high disability pain group in reducing pain intensity (n=4 studies [n=145 for Group A, and n=145 for Group B], SMD=-0.84; 95% CI [-1.62, -0.07]; *p*=0.03, I^2=83%). Low disability pain was represented in one trial only. For all included the studies was of a clinical significance of 30% pain reduction in the intervention group observed.

3.3.7.7 Comparison: Effectiveness of NSAIDs treatment in comparison to other treatment on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.3.7.7.1 Primary outcome parameter: pain intensity

3.3.7.7.1.1 Short-term efficacy (treatment duration up to six months)

A significant difference was seen in favour of other treatments in reducing pain intensity in the analysis of NSAIDs versus other treatment in the follow up period of less than six months (n=9 studies [n=159 for Group A, and n=178 for Group B], SMD=1.20; 95% CI [0.04, 2.37]; P=0.04, I^2=95%; Figure 90, APPENDIX IX: Forest plots). Surprisingly, the low disability pain group (n=5 studies [n=89 for Group A, and n=101 for Group B], SMD=1.93; 95% CI [-0.56, 4.42]; *p*=0.13, I^2=97%) and the high disability pain group (n=2 study [n=47 for Group A, and n=53 for Group B], SMD=0.59; 95% CI [-0.30, 1.48]; *p*=0.20, I^2=79%) reacted both positive in favour of other treatment without significance. The mixed pain group and the unclear pain group were only represented by one study each.

By removing the studies that received another drug in addition to the NSAIDs [310, 330, 361], a statistically significant bigger result in favour of other treatments (n=6 studies [n=99 for Group A, and n=112 for Group B], SMD=1.54; 95% CI [-0.50, 3.59]; *p*=0.09, I^2=97%) was no longer obtained. For the studies of Hosgor et al. 2017, Mejersjö et al. 2008, Thie et al. 2001, Shanavas et al. 2014, de Carli et al. 2013 and Ahmed et al. 2016 a clinical significance of 30% pain reduction in the intervention group was observed. The studies of Khalighli et al. 2016, Marini et al. 2010, and Dogan et al. 2014 did not have a clinical significance in pain reduction.

3.3.7.7.2 Secondary outcome parameter: MMO

3.3.7.7.2.1 Short-term efficacy (treatment duration up to six months)

Surprisingly, a clear statistically bigger significant result was seen in the meta-analysis of NSAIDs versus other treatment in improving MMO in favour of other treatments in the follow up time of less than six months demonstrated in Figure 91, APPENDIX IX: Forest plots (n=8 studies [n=139 for Group A, n=158 for Group B], SMD=-0.86; 95% CI [-1.52, -0.19]; p=0.01, I^2=85%). Other treatments also showed a statistically significant superiority compared to NSAIDs in the low disability pain group (n=5 studies [n=89 for Group A, and n=101 for Group B], SMD=-1.07; 95% CI [-2.02, -0.13]; p=0.03, I^2=88%). The high disability pain group, the mixed pain group and the unclear pain group were represented by only one study each.

3.3.7.8 Comparison: Effectiveness of benzodiazepines treatment in comparison to placebo on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.3.7.8.1 Primary outcome parameter: pain intensity

3.3.7.8.1.1 Short-term efficacy (treatment duration up to six months)

A positive trend for the treatment of benzodiazepines was observed in the meta-analysis of benzodiazepines versus placebo in the short-term in reducing pain intensity (n=6 studies [n=87 for Group A, and n=76 for Group B], SMD=-0.45; 95% CI [-1.36, 0.46)]; p=0.33, I^2=86%). Low disability pain (n=4 studies [n=48 for Group A, and n=50 for Group B], SMD=-0.41; 95% CI [-1.90, 1.07]; p=0.58, I^2=91%) and high disability pain (n=2 studies [n=39 for Group A, and n=26 for Group B], SMD=-0.55; 95% CI [-1.16, 0.07)]; p=0.08, I^2=27%) also showed a bigger result in favour of benzodiazepines use compared to placebo therapy, however without statistical significance (Figure 92, APPENDIX IX: Forest plots). All the included studies except for DeNucci et al. 1998 had a clinical significance of 30% pain reduction in the intervention group.

3.3.8 Tabular overview of the results of the comparisons for medication

The results of the comparisons performed for medication interventions are listed below for pain intensity (Table 18) and for MMO (Table 19):

Table 18: Tabular overview of the results of medication regarding pain intensity categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval

Reduction of pain intensity with medication treatment for TMD		
Comparison	**Statistically significant results**	**Data**
Medication (orally administered) vs. (any) other treatment	Short-term: **Significant less pain after the treatment of other treatment than after orally administered medication treatment for total pain.** No ss result found for low disability or high disability pain.	Short-term: Low disability: (SMD=1.23; 95% CI [-0.02, 2.48]; *p*=0.05; I^2=96%) High disability: (SMD=0.54; 95% CI [-0.04, 1.12]; *p*=0.07; I^2=59% **Total: (SMD=0.87; 95% CI [0.13, 1.61]; *p*=0.02; I^2=93%)**
Medication (injected only) vs. other treatment	Short-term: No ss superiority in the comparison for low disability pain, high disability pain or total pain.	Short-term: Low disability: (SMD=0.18; 95% CI [-0.22, 0.58]; *p*=0.38; I^2=56%) High disability: (SMD=0.03; 95% CI [-0.34, 0.41]; *p*=0.86; I^2=36%) Total: (SMD=0.13; 95% CI [-0.15, 0.41]; *p*=0.37; I^2=49%)
Medication (injected excluded) vs. placebo	Short-term: **Significant less pain after medication treatment than after placebo treatment for the low disability, the high disability, and the total pain groups.** No ss for mixed and unclear pain. *Subgroup analysis:* ***significant less pain in medication with only orally administered medication treatment than after placebo treatment in the high disability pain group and for total pain.*** *Subgroup analysis:* ***significant less pain after medication treatment as a single intervention than after placebo treatment in the low disability pain, high disability pain, and total pain groups.***	Short-term: **Low disability: (SMD=-0.47; 95% CI [-0.80, -0.14]; *p*=0.005; I^2=56%)** **High disability: (SMD=-0.49; 95% CI [-0.92, -0.07]; *p*=0.02; I^2=73%)** **Total: (SMD=-0.38; 95% CI [-0.60, -0.15]; *p*=0.001; I^2=71%)**
Medication (only injectable) vs. placebo	Short-term: **Significant less pain after injected medication treatment than after placebo treatment for total pain.** No ss superiority for medication treatment in low disability pain or high disability pain.	Short-term: Low disability: (SMD=-0.18; 95% CI [-0.43, 0.07]; *p*=0.15; I^2=0%) High disability: (SMD=-0.46; 95% CI [-1.09, 0.17]; *p*=0.15; I^2=85%) **Total: (SMD=-0.39; 95% CI [-0.76, -0.03]; *p*=0.04; I^2=76%)**
Botulinum toxin vs. other treatment	Short-term: No ss superiority for botulinum toxin in the treatment for low disability, high disability, or total pain.	Short-term: Low disability: (SMD=0.11; 95% CI [-0.67, 0.89]; *p*=0.78; I^2=65%) High disability: (SMD=-0.26; 95% CI [-0.87, 0.36]; *p*=0.41; I^2=39%) Total: (SMD=-0.04; 95% CI [-0.54, 0.47]; *p*=0.88; I^2=57%)
Botulinum toxin vs. placebo	Short-term: **Significant less pain after botulinum toxin treatment than after placebo treatment for high disability pain and total pain.** No ss superiority for botulinum toxin treatment for low disability pain.	Short-term: Low disability: (SMD=-0.48; 95% CI [-1.11, 0.16]; *p*=0.14; I^2=0%) **High disability: (SMD=-0.93; 95% CI [-1.55, -0.31]; *p*=0.003; I^2=60%)** **Total: (SMD=-0.78; 95% CI [-1.19, -0.37]; *p*=0.0002; I^2=35%)**

NSAIDs vs. placebo	Short-term: **Significant less pain after NSAIDs treatment than after placebo treatment for high disability pain.** No ss superiority for NSAIDs in the treatment of total pain.	Short-term: **High disability: (SMD=-0.84; 95% CI [-1.62, -0.07]; *p*=0.03; I^2=83%)** Total: (SMD=-0.65; 95% CI [-1.40, 0.09]; *p*=0.09; I^2=87%)
NSAIDs vs. other treatment	Short-term: **Significant less pain after other treatment than after NSAIDs treatment for total pain.** No ss superiority for NSAIDs in the treatment of low disability pain or high disability pain.	Short-term: Low disability: (SMD=1.93; 95% CI [-0.56, 4.42]; *p*=0.13; I^2=97%) High disability: (SMD=0.59; 95% CI [-0.30, 1.48]; *p*=0.20; I^2=79%) **Total: (SMD=1.20; 95% CI [0.04, 2.37]; *p*=0.04; I^2=95% for other treatment)**
Benzodiazepines vs. Placebo	Short-term: No ss superiority for benzodiazepines in the treatment of for low disability pain, high disability pain, or total pain.	Short-term: Low disability: (SMD=-0.41; 95% CI [-1.90, 1.07]; *p*=0.58; I^2=91%) High disability: (SMD=-0.55; 95% CI [-1.16, 0.07]; *p*=0.08; I^2=27%) Total: (SMD=-0.45; 95% CI [-1.36, 0.46]; *p*=0.33; I^2=86%)

Table 19: Tabular overview of the results of medication regarding MMO categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval

Improvement of maximum mouth opening after medication treatment of TMD		
Comparison	**Statistically significant results**	**Data**
Medication (injected excluded) vs. placebo	Short-term: No ss superiority for medication in the treatment for low disability pain, high disability pain, mixed or total pain.	Short-term: Low disability: (SMD=0.01, 95% CI [-0.27, 0.28]; *p*=0.97, I^2=19%) High disability: (SMD=-0.00; 95% CI [-0.38, 0.38]; *p*=0.99, I^2=0% Mixed: (SMD=0.06; 95% CI [-0.38, 0.50]; *p*=0.78, I^2=0%) Total: (SMD=0.01; 95% CI [-0.17, 0.19]; *p*=0.93; I^2=0%)
Medication (injections only) vs. placebo	Short-term: No ss superiority for medication in the treatment for low disability, high disability, mixed or total pain.	Short-term: Low disability: (SMD=-0.03, 95% CI [-0.28, 0.22]; *p*=0.81, I^2=0%) High disability: (SMD=-0.00; 95% CI [-0.59, 0.59]; *p*=1.00, I^2 =0%) Total: (SMD=-0.03; 95% CI -0.03 [-0.26, 0.21]; *p* =0.94; I^2=0%)
NSAIDs vs. other treatment	Short-term: **Significant improvement in MMO after other treatment than after NSAIDs treatment for low disability pain and total pain.**	Short-term: **Low disability: (SMD=-1.07; 95% CI [-2.02, -0.13]; *p*=0.03; I^2 =88%)** **Total: (SMD=-0.86; 95% CI [-1.52, -0.19]; *p*=0.01; I^2=85%)**

3.4 Psychosocial interventions

3.4.1 Description of the intervention:

A psychological element is a common feature of painful TMDs, and is the reason why the DC/TMD includes psychometric assessments [32]. Recognizing that psychosocial and physical factors have an impact on the aetiology and preservation of TMD has led to a range of biopsychosocial treatment modalities [380]. Truelove et al. 2006 showed that conservative therapy which consisted of jaw relaxation, suggestions about stress reduction, and self-care strategies were just as efficient as splint therapy in the reduction of pain in treating TMD, thus prompting the question of whether expensive splint therapy is necessary and the actual influence of the conservative approach with self-treatment strategies and counselling [381]. Recent studies have reported the importance of assessments of psychological disorders and psychosocial dysfunction, which are particularly associated with chronic pain [382]. Psychosocial interventions consist of cognitive behavioural therapy (CBT), self-care, education, and counselling, electromyographic biofeedback and hypnoses to mention the most important ones. These treatments are often given in combination, which makes it difficult to establish which was most effective in reducing pain in individual cases [382].

Cognitive behavioural therapy (CBT)

CBT essentially aims to improve the patient's coping skills by changing the patient's perception of themselves and their relationship to the symptoms of TMD. In general, some of the basic components of CBT are educating the patient about pain and their specific syndrome, providing a perspective of self-management and coping skills in relation to pain, teaching relaxation and stress management techniques, emphasising the identification and elimination of maladaptive thoughts, guiding the patient to improve activities of daily living with appropriate goal setting, teaching relapse prevention strategies to manage possible future relapses, and teaching relaxation and stress management techniques [76].

CBT was found to produce significantly better changes in self-reported pain and cognitive coping among the available biological-behavioural treatments. In addition, there was a reduction in behavioural expressions of pain among patients on the waiting list and in the alternative treatment control conditions [383]. A recent study showed significant results in the short and long-term using a combination of CBT and Biofeedback as a comprehensive pain-management technique [384]. An overall increase in the importance and interest in the studies of CBT and TMD has been seen in the last decade. Systematic reviews of CBT have revealed an expansion in the number of meta-analyses from ten in the early 2000s to on average 40–50 within the last 10 years [385].

Counselling, self-care, and education

Counselling is primarily a means of providing basic information to the patient about the possible aetiology and pathogenesis of TMD and of teaching avoidance behaviours that may risk exacerbating the associated symptomatology. Counselling is usually used as a secondary intervention to the main effect of other therapies. Counselling with guidance on self-care is superior to training alone and may even outperform splint therapy alone [386, 387]. Some of the self-care and educational strategies are closely related to counselling, such as guidance to reduce parafunctional jaw activities. It is difficult to separate the definition of self-care, education, and counselling in the treatment of TMD as the terms are not well defined and get mixed up in the TMD treatment. However, the results show the effectiveness of these simple interventions. They also confirm the importance of education about an adequate, i.e., tooth-contact-free mandibular resting position, about malpositions involved in the development of pain and stereotypical oral (also occlusal) habits and their active avoidance as dispensable therapy components [388].

Biofeedback and hypnosis

Biofeedback, autogenic training, and progressive muscle relaxation according to Jacobson are often used successfully in other body parts. Biofeedback is the most used and studied relaxation technique [388]. It brings unconscious body functions into consciousness through measurements of pulse, skin conductance and muscle tone and coupled feedback in the form of visual or acoustic signals and has been proven to be effective for myogenic facial pain compared to placebo [389, 390]. However, the mechanism of action is non-specific, as the effect occurs independently of tonus reduction and is probably cognitive in nature. Biofeedback can also help those patients learn correct mandibular posture who have difficulty relaxing the elevators through self-observation alone [388].

Medical hypnosis is an ego-strengthening treatment method for TMD. It is an old psychosomatic therapy method. Today it is increasingly scientifically proven and enjoys a high level of acceptance among TMD patients [391, 392]. Communication is used on a verbal and non-verbal level to put the patient into a trance state. Trance states are deeper natural states of consciousness that differ from everyday thinking. The patient's attention is focused with the support of the therapist. It therefore leads to a high level of mindfulness, which is used in hypnosis to increase or decrease feelings or change perceptions such as pain. Creativity for problem solving can be increased in the trance state [391, 393]. In this sense, medical hypnosis is suitable for cognitive pain management and for changing behavioural patterns in TMD. The study by Abrahamsen et al. 2009 was able to show that hypnosis

achieves a significant and clinically relevant reduction in pain compared to relaxation alone [394].

3.4.2 How psychosocial interventions might work:

Psychosocial interventions for chronic orofacial pain can be based on two possible suspect models of pain development: a) Inactivity (avoidance behaviour) and b) overactivity (emotional distress) [395].

Inactivity model: demonstrates the avoidance of physical activity in response to persistent and prolonged pain and fear of worsening symptoms in the affected region. The negative cognitive and behavioural responses in turn prolong and worsen the symptoms. CBT, Counselling, self-care, or education would target this fear-avoidance behaviour to alleviate symptoms through a return to normal functioning. This mechanism considers the main mechanisms of pain processing [395]. CBT works on two levels: it helps the patient to change their response to situations that trigger or exacerbate pain by learning new coping strategies, and to build a positive, manageable attitude towards pain. Feelings of helplessness and uncontrollability are reduced, and the patient can better control the pain. The patient needs to understand that the affective, emotional, cognitive, and behavioural components of pain are as important as the somatic components. The primary goal of therapy is therefore not to reduce pain but to improve pain management, and therefore to improve quality of life despite pain [388]. Counselling, self-care, and education are the use by patients of a range of strategies that enable them to live well with pain, minimising pain as much as possible while reducing its impact on their lives.

Overactivity model: demonstrates the emotional stress (anxiety, depression, anger) due psychological factors that trigger oral habits leading to muscle hyperactivity and facial pain. Interventions such as biofeedback, relaxation training or hypnosis can target these emotional stress levels [395]. The effectiveness of biofeedback is explained by several factors: specific improvement of physiological self-control, non-specific relaxation induction, change of important expectations and attitudes, increase of self-efficacy. The procedure can be useful to train unconscious behavioural patterns that maintain the discomfort [390]. Hypnosis is better related to the emotional stress model and primarily targets parafunctional habits in TMD treatment. In this way, the patient can be dissociated from the pain in trance. This offers the patient the opportunity to analyse the pain from a new position under the guidance of a trained hypnotherapist and to find creative cognitive solutions to change the quality, quantity, and frequency of the pain. The guidance to self-hypnosis can achieve significant relief and better management of the discomfort, and on the other hand, it can promote the patient's self-competence by regaining a certain degree of control over the pain process [391].

3.4.3 Study Selection

The initial database search yielded 681 entries, 206 of which were retrieved from MEDLINE (via PubMed), 63 from Embase, 334 from Central, 63 from LIVIVO (German and English version), four from Clinicaltrials.gov, eleven from Deutsches Register klinischer Studien (DRKS) and none from the Open Grey Literature (Table 20). Results of unpublished studies are not included in this review. An additional three articles were identified through cross-reference checking and manual searching. All studies used psychosocial interventions (counselling, stress management, education, hypnosis, relaxation, and biofeedback) for treating TMD. After exclusion of all duplicates (17 studies), the number of entries was 667. Of these, 548 studies were discarded after a review of the titles and abstracts. An additional 77 articles were excluded after a full-text review and application of the eligibility criteria (reasons for exclusion following a full-text analysis are reported in Appendix VIII. A flowchart that depicts this selection process is displayed in Figure 40.

The systematic literature search achieved the results shown Table 20.

Table 20: Results of the search strategy for Psychosocial interventions for TMD

Database	*Number of studies (n)*
PubMed	206
EMBASE	63
Central	334
LIVIVO (German)	26
LIVIVO (English)	37
Clinicaltrials.gov	4
Deutsches Register klinischer Studien (DRKS)	11
Open Grey Literature	-
Total	681

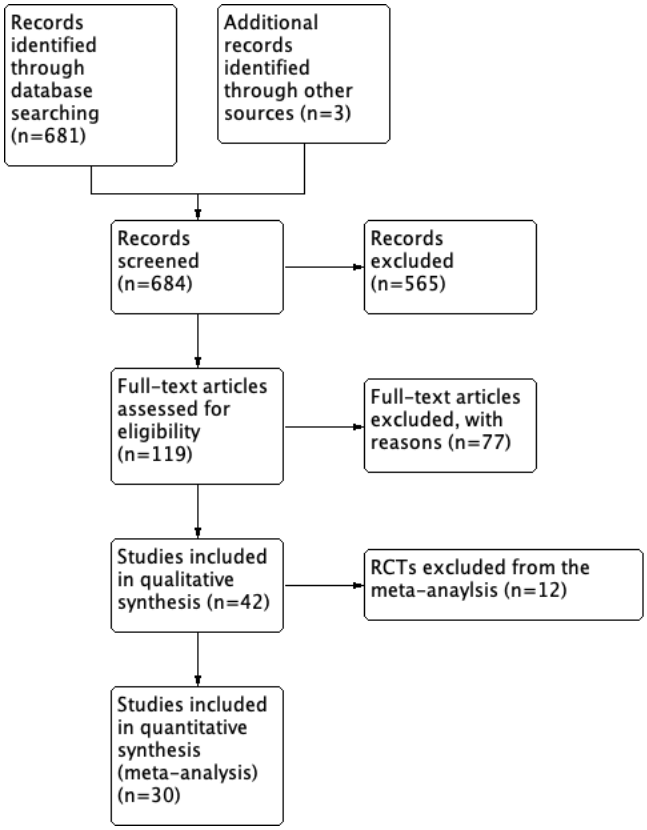


Figure 40: Flow Diagram for Psychosocial interventions for TMD patients

3.4.4 Qualitative synthesis of the included studies

3.4.4.1 Characteristics of the included Studies

Ultimately 42 studies with 3004 participants met the inclusion criteria and were consequently included in this systematic review. To check for heterogeneity in advance, the characteristics of the population used in the studies, the characteristics of the interventions, the pain chronification, and the excluded studies were accurately reported in narrative style. **Table 21** presents the general characteristics of the included studies. Appendix VIII, Characteristics of Included Studies I, provides detailed information on participants, treatment and comparisons, outcomes, pain severity, and follow-up.

Table 21: Included studies on psychosocial interventions for TMD treatment (BDI=back depression inventory; BFB=biofeedback; BI=brief information; CBST=cognitive-behavioral skills training; CBT=cognitive-behavioral therapy; CPI=characteristic pain intensity; CS=counselling; EMG=electromyography; GCPS=graded chronic pain scale; HADS=hospital anxiety and depression scale; IMT=intra-oral myofascial therapy; JME=jaw movement exercise; MPI=multidimensional pain inventory; MT=manual therapy; NRS=numerical pain rating scale; NTI-TSS=trigeminal inhibition-tension suppression system; OS=occlusal splint; PSS=pain severity scale; RDC=research diagnostic criteria; RIST=reversible interocclusal splint therapy; SCL-90-R=symptom checklist-90-R; STD=standard treatment; TENS=transcutaneous electrical nerve stimulation; TMD=temporomandibular disorders; VAS=visual analogue scale)

Author Year	Patients (n), %women, age mean±SD (years)	Interventions	Outcomes	Pain chronification	Diagnoses	Follow-up
Abrahamsen et al. 2009 [394]	43 patients 100% women Mean age: 38 ±10.8	Group A (n=20): hypnosis Group B (n=20): relaxation	Pain diary (NRS) Maximum unassisted jaw opening, Maximum assisted jaw opening (mm) Somatization (SCL-90-R) Depression (SCL-90-R)	Unclear (high disability)	TMD of muscular origin	Data before and after treatment
Bartleya et al. 2019 [396]	33 patients 41% women Mean age Group A: 38.1 ±14.3 Group B: 39.7 ±14.0	Group A (n=15): hope 3-session intervention Group B (n=14): education about pain and stress	Pain/disability (GCPS) Pain (NRS) Centre for Epidemiological Studies–Depression Scale	Mixed	TMD (not identified)	3 weeks
Brandão et al. 2020 [397]	23 patients 100 % women Mean age: Group A: 38.1 ±14.3 Group B: 39.7 ±14.0	Group A (n=12): Isotonic exercises and relaxing techniques Group B (n=11): self-care	Pain intensity and depression (GCPS, RDC)	Mixed	TMD of muscular and/or arthrogenic origin	1 month
Calderon et al. 2011 [321]	47 patients gender not given 17-52 years old Mean age: 35.6	Group A (n=11): amitriptyline Group B (n=12): amitriptyline + CBT Group C (n=11): placebo and CBT Group D (n=13): placebo only (control)	Pain intensity (VAS) Depression (BDI)	Low disability	Orofacial pain	1 month
Conti et al. 2014 [398]	15 patients 80 % women Mean age: Group A: 37.3 ±8.9 Group B: 31.9 ±12.3	Group A (n=7): biofeedback treatment using a CES paradigm (active group) Group B (n=8): inactive device (control group)	Pain intensity (VAS)	Low disability	TMD of muscular origin	1 month
Crockett et al. 1986 [399]	21 patients 100% women older than 19 years	Group A (n=7): splint + physiotherapy Group B (n=7): relaxation program utilizing progressive muscle relaxation, biofeedback, stress management technique Group C (n=7): TENS	Interincisal opening (mm) Pain intensity (VAS)	Mixed	TMD of muscular origin	immediately

Dalen et al. 1986 [400]	19 patients 95% women Mean age: Group A: 29.6 ±12.8 Group B: 25.9 ±8.14	Group A (n=10): biofeedback training sessions Group B (n=9): received no feedback	Pain intensity (10-point scale)	Low disability	TMD of muscular origin	6 months
DeVocht et al. 2013 [401]	80 patients 80% women 21 and older	Group A (n=20): "self-care" and "RIST" Group B (n=20): "self-care" and "Chiropractic AMCT" (Activator Method Chiropractic Technique) Group C (n=20): "self-care" and sham AMCT Group D (n=20): "self-care" only	TMD-related pain (NRS)	Mixed	TMD of muscular origin	6 months
Dohrmann et al. 1978 [402]	24 patients 84% women 20-71 years old Mean age: Group A: 38 Group B: 36 Group C: 32	Group A (n=16): fully familiarized with the theory of EMG feedback Group B (n=8): not informed about EMG biofeedback Group C (n=7): mean masseter EMG levels of a group of normal subjects also was determined	Pain value Maximum opening Presence of joint sounds on opening or closing	Unclear (high disability)	TMD of muscular origin	12 months
Dworkin et al. 2002 [403]	124 patients 85% women Mean age: Group A: 37.4 ±4.2 Group B: 38.0 ±3.6	Group A (n=61): self-care intervention Group B(n=63): usual treatment	Pain intensity (CPI) GCPS Somatization (SCL-90-R) Depression (SCL-90-R) Unassisted jaw opening without pain (mm)	Low disability	TMD of muscular origin	12 months
Dworkin et al. 2002 [404]	117 patients 81% women 18-70 years old Mean age: 38.8 ±10	Group A (n=59): comprehensive care Group B (n=58): usual treatment	Pain intensity (CPI) GCPS Somatization (SCL-90-R) Depression (SCL-90-R) Unassisted jaw opening without pain (mm)	High disability	TMD of muscular origin	12 months
Dworkin et al. 1994 [405]	185 patients 85% women Mean age: 37 ±10.3	Group A (n=66): 2 sessions Group B (n=73): usual treatment	Pain intensity (CPI) GCPS Somatization (SCL-90-R) Depression (SCL-90-R) Unassisted jaw opening without pain (mm)	Mixed and separatable	TMD of muscular origin	12 months
Ferrando et al. 2012 [406]	72 patients 90% women Mean age: 39	Group A (n=41): 6-session CBT program Group B (n =31): conservative standard treatment for TMD	Pain intensity (von Korff, 1979) Subjective pain index (MPQ) Pain severity (Multidimensional Pain Inventory, 1985) Emotional distress (including subdimensions anxiety, somatization, and depression)	Low disability	TMD of muscular origin	9 months
Funch et al. 1984 [407]	57 patients 90% women Mean age: Group A: 35.6 ±12.7 Group B: 43.0 ±15.0	Group A (n=30): biofeedback therapy Group B (n=27): relaxation	Pain (6- point scale)	High disability	TMD (not identified)	2 years

Gardea et al. 2001 [408]	108 patients 83% women Mean age Group A: 35.1 ±9.49 Group B: 37.4 ±10.8 Group C: 35.1 ±8.56 Group D: 36.5 ±11.4	Group A (n=24): CBST Group B (n=27): Biofeedback Group C (n=29): combined treatment (CBST + Biofeedback) Group D (n=28): no treatment	Pain (CPI) GCPS	Low disability	TMD (not identified)	12 months
Gatchel et al. 2006 [409]	101 patients 80% women Mean age: Group A: 36.7 ±11.47 Group B: 39.1 ±11.17	Group A (n=56): CBT and biofeedback Group B (n=45): no treatment	Pain (CPI) Depression (BDI)	Low disability	TMD of muscular origin	12 months
Giro et al. 2016 [410]	52 patients 100% women Mean age: 36.4 ±8.8	Group A (n=16): 1.no treatment, 2. Education and self-care instructions 3. education and self-care instructions Group B (n=18): 1. education instructions 2. Education and self-care instructions 3. education and self-care instructions Group C (n=18): 1. Education and self-care instructions 2. education and self-care instructions 3. Review of education and self-care instructions	Mandibular movements during MMO and mastication	Mixed	TMD of muscular and/or arthrogenic origin	2 months
Goldthorpe et al. 2017 [411]	37 patients 86% women Mean age Group A: 52 (22-73 years old) Group B: 47 (21-66 years old)	Group A (n=19): self-help manual “Managing Chronic Orofacial Pain” supported and guided by a facilitator Group B (n=18): treatment as usual	Anxiety and depression (HADS) Pain intensity (Brief Pain Inventory)	Unclear (high disability)	TMD of muscular origin	3 months
Göller et al. 2017 [412]	44 patients 78% women 20-60 years old Mean age: Group A: 26.21 ±6.87 Group B: 28.33 ±11.2	Group A (n=22): biofeedback-therapy Group B (n=22): splint + physiotherapy	GCPS	High disability	TMD of muscular origin	12 months
Harrison et al. 1997 [413]	178 patients 84% women Mean age: 38.8 ±12.2	Group A (n=45): placebo alone Group B (n=44): fluoxetine Group C (n=46): cognitive-behavioural therapy plus placebo Group D (n=43): cognitive behavioural therapy plus fluoxetine	Pain (MPQ) Depression (BDI)	Low disability	Chronic idiopathic facial pain	3 months
Hasanoglu et al. 2017 [414]	40 patients 83% women Mean age: Group A: 24.6 ± 9.2 Group B: 32.25 ±11.9	Group A (n=20): guidance only, assurance, counselling, and behavioural changes Group B (n=20): guidance, assurance, counselling, and behavioural changes + NTI-TSS device	Pain intensity (VAS)	Low disability	TMD of muscular origin	immediately

Herman et al. 2002 [343]	41 patients 80% women Mean age: Group A: 26.9 ±10.1 Group B: 24.0 ±4.8 Group C: 30.3 ±8.6	Group A (n=13): self-care program + Clonazepam 0.5mg daily Group B (n=15): self-care program + placebo (lactose filler) Group C (n=13): self-care program + Cyclobenzaprine 10mg daily	Pain (SSI)	Low disability	TMD of muscular origin	3 weeks
Kalamir et al. 2012 [415]	93 patients 54% women Mean age: Group A: 35 ±6.7 Group B: 34 ±6.1 Group C: 35 ±5	Group A (n=31): IMT Group B (n=31): IMT plus education + "self-care" exercises Group C (n=31): wait-list control	Pain (11-point GPCS) Incisal opening range (mm)	Low disability	TMD of muscular origin	6 months
Komiyama et al. 1999 [416]	60 patients 82% women Mean age: 25.68	Group A (n=20): control group Group B (n=20): cognitive behavioural treatment Group C (n=20): cognitive behavioural treatment with posture correction group	Pain-free unassisted mouth opening (mm) Pain intensity (VAS)	Low disability	TMD of muscular origin	12 months
Lam et al. 2020 [417]	43 patients 79% women Median age: 27 IQR: 23-37 years	Group A (n=20): cognitive behaviour therapy + self-management principles Group B (n=23): occlusal splint therapy	Pain intensity (CPI) Jaw low disability limitation Depression	Mixed	TMD of muscular and/ arthrogenic origin	3 and 6 months
Litt et al. 2010 [418]	101 patients 84% women 18-65 years old, Mean age: 39.4 ±12.1	Group A (n=49): STD Group B (n=52): STD+ cognitive-behavioural	Pain (MPI, CPI) Depression (CES-D) Somatization (SCL-90-R)	Mixed	TMD of muscular and/or arthrogenic origin	12 months
Makino et al. 2014 [351]	39 patients 69% women Mean age: Group A: 40 Group B: 42 Group C: 53	Group A (n=13): control group (pharmacological treatment) Group B (n=13): JME at home Group C (n=13): ET-PI group (continue JME at home + psychological intervention)	Pain intensity (NRS) Jaw movement	High disability	Craniocervical chronic pain	3 months
Manfredini et al. 2018 [253]	30 patients 100% women Mean age: 35.3 ±9.4	Group A (n=10): laser therapy Group B (n=10): oral appliance (OA) Group C (n=10): counselling	Pain intensity (VAS)	Low disability	TMD of muscular origin	3 weeks 3 months 6 months
Melo et al. 2020 [419]	89 patients	Group A (n=25): OSCS Group B (n=24): OS Group C (n=21): MT Group D (n=19): CS	Pain (VAS) Depression (HADS)	Low disability	TMD of muscular and/or arthrogenic origin	1 month
Michelotti et al. 2012 [386]	44 patients 89% women Mean age: 31.2 ±11.8	Group A (n=10): habit reversal treatment (home-based minimal therapist contact) Group B (n=18): stabilization splint	Pain intensity (VAS) Unassisted jaw opening without pain (mm) Pain during chewing (VAS)	Low disability	TMD of muscular origin	3 months

Michelotti et al. 2004 [387]	70 patients 89% women Mean age: Group A: 31.8 ±13.0 Group B: 28.2 ±8.8	Group A (n=34): education only Group B (n=36): education + self-supportive exercise program	Pain intensity (VAS) Pain-free maximal jaw opening (mm)	Low disability	TMD of muscular origin	3 months
Roknic et al. 2010 [420]	36 patients 75% women 14-79 years old	Group A (n=12): splint treatment Group B (n=12): splint + neurofeedback Group C (n=12): splint + BFB	Mouth opening, low disability range (mm) Muscle pain (maximum opening, active and passive in each case) Joint noises (opening, closing, moving)	High disability	TMD of muscular origin	6 weeks
Shedden et al. 2013 [421]	58 patients Group A: 86.2% women Group B 70.4% women 18-70 years old	Group A (n=29): BFB-CBT Group B (n=29): splint	Pain and Disability (CPI)	Mixed	TMD (not identified)	6 months
Stam et al. 1984 [422]	61 patients 84% women 15-41 years old Mean age: 25.7 ±7	Group A (n=12): hypnosis + cognitive coping skills Group B (n=15): relaxation + cognitive coping skills Group C (n=14): no-treatment	Intensity of pain (VAS) Frequency of sounds Extent of limitations (if any) in opening their mouths on three 140-mm visual analogue scales (mm)	Unclear (high disability)	TMD (not identified)	4 weeks
Townsen et al. 2001 [423]	20 patients 100% women Mean age: Group A: 35.4 ±9.5 Group B: 38.9 ±8.2	Group A (n=10): habit reversal treatment Group B (n=10): wait-list control	Pain (6-point Likert-type scale)	High disability	TMD (not identified)	8–24 months
Turk et al. 1993 [424]	80 patients 82% women 18 – 55 years old Mean age: 34.1 ±8.4	Group A (n=30): intraoral appliance Group B (n=30): biofeedback and stress management Group C (n=20): wait list control	Pain (PSS) Depression (depression scale from the Profile of Mood state)	Low disability	TMD of muscular origin	6 months
Turner et al. 2011 [368]	191 patients 100% women Mean age: Group A: 29.1 ±7.4 Group B: 25.4 ±5.7 Group C: 28.6 ±6.9	Group A (n=60): self-management training Group B (n=57): targeted self-management training Group C (n=74): continuous oral contraceptive therapy	Pain intensity (CPI) Depression (BDI)	High disability	TMD of muscular origin	12 months
Turner et al. 2005 [425]	158 patients 88.1% women Mean age: Group A: 39.3 ±11.1 Group B: 35.4 ±10.5	Group A (n=61): CB pain management training Group B (n=65): education/attention self-care management	Pain intensity (VAS) Jaw use limitations	High disability	TMD of muscular and/or arthrogenic origin	4 weeks
Vallon et al. 1991 [426]	50 patients 88% women 15-55 years old Mean age: 28.5	Group A (n=25): occlusal adjustment Group B (n=25): comforted ("reassurance of occlusion")	Pain (Likert-Skala 0-5) Range of mandibular mobility Joint sounds	Unclear	TMD and a history of headache	3 and 6 months
Wahlund et al. 2003 [427]	122 patients 76% women Mean age: 15.3	Group A (n=41): BI + OA Group B (n=42): BI + relaxation therapy Group C (n=39): BI	Pain intensity (VAS)	Unclear (high disability)	TMD of muscular and/or arthrogenic origin	6 months

Wright et al. 1995 [428]	30 patients 19-51 years old Mean age: Group A: 34 Group B: 36 Group C: 31	Gruppe A (n=10): soft splint Gruppe B (n=10): palliative treatment Gruppe C (n=10): no treatment	Pain (Modified Symptom Severity Index) Maximum pain-free opening (mm)	Unclear	TMD of muscular origin	6 weeks
Yu et al. 2016 [429]	168 patients 89% women Mean age: 32.5 ±9.8	Group A (n=42): Michigan Splint Group B (n=42): combination of manipulative and physical therapies group Group C (n=42): stabilization splint combination of manipulative + physical therapies group Group D (n=42): control group (consulting only)	Spontaneous masticatory muscle pain (VAS) Pain-free maximum active mouth opening (mm)	Low disability	TMD of arthrogenic origin (disc displacement without reduction)	3 months

3.4.4.2 Characteristics of the population recruited in the studies

3.4.4.2.1 TMD diagnoses of the participants from the included studies

In the RCTs of psychosocial interventions more than half of the authors (24 studies) concentrated on myofascial pain according to the RCD/TMD [253, 343, 368, 386, 387, 394, 398-406, 409, 411, 412, 414-416, 420, 424, 428], one study included TMJ disc displacement without reduction [429], seven studies were of myogenous and arthrogenous origin [397, 410, 417-419, 425, 427] while seven RCTs simply described the condition as TMD without any further explanation [396, 407, 408, 421-423, 426]. Three studies described different types of pain and were therefore also added to the group of unclassified TMD. Calderon et al. [321] described it as orofacial pain, while other authors focused on chronic idiopathic facial pain [413] or craniocervical chronic pain [351]. Figure 41 below categorises the type of TMD of the subjects from the included studies of psychosocial interventions.

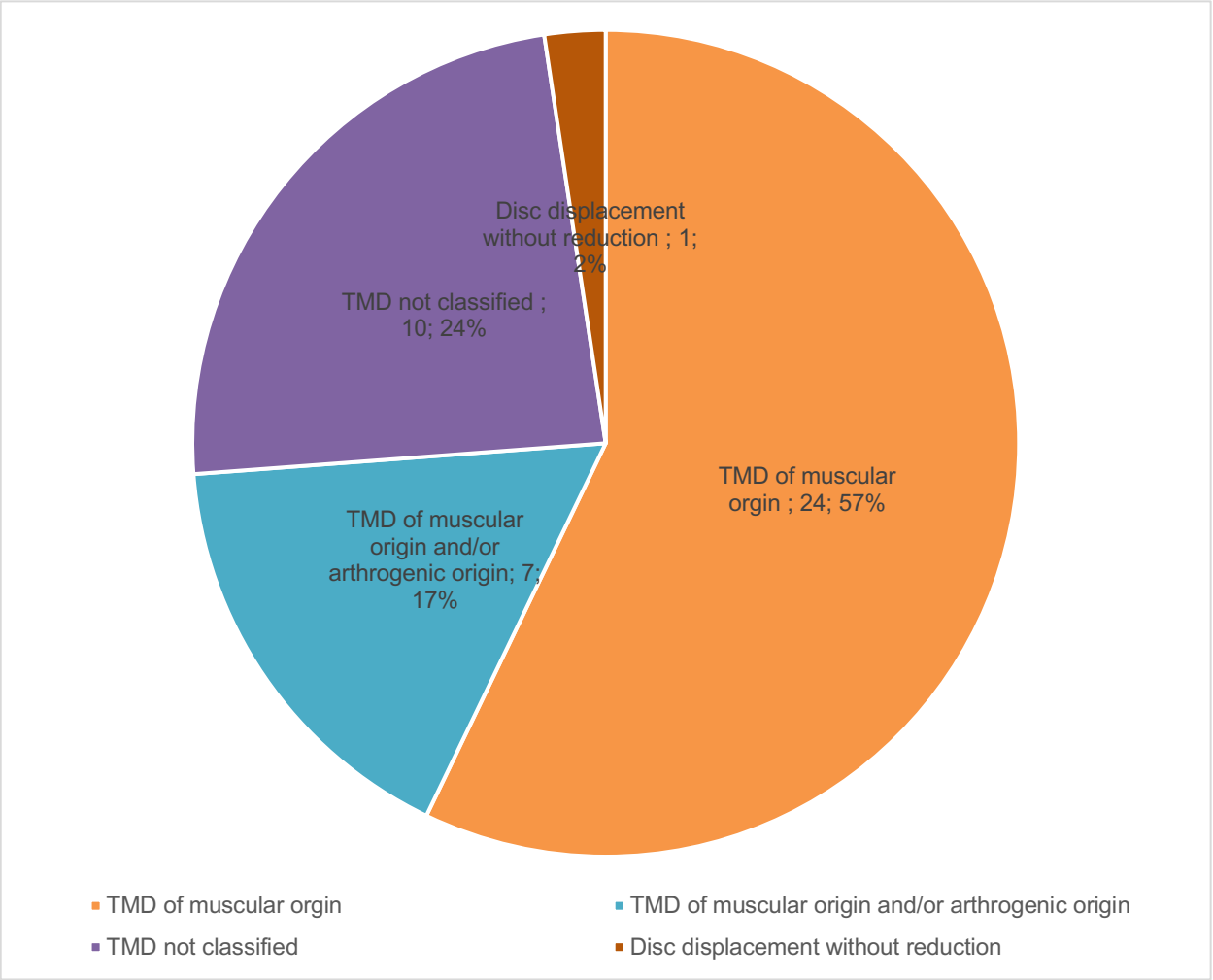


Figure 41: Pie chart presenting the different TMD diagnoses from the included studies on psychosocial intervention therapy (X) with the number of studies included (Y) and the percentage (Z); (X;Y;Z).

3.4.4.2.2 Grade of chronification

The degree of TMD pain chronification of the subjects formed the focus of the present work. The following categories were formed from those that used psychosocial interventions (Figure 42):

- Patients with evidence of a low disability (acute or acute/persistent) pain
- Patients with evidence of high disability pain
- Patients with different degrees of chronicity, whose results were presented separately by the authors (referred to below as: mixed)
- Patients with slight evidence of high disability pain (referred to below as: unclear (high disability))
- Patients with minimum or no degree of chronicity (referred to below as: unclear)

The population from the included RCTs showed a consistent distribution of the different types of degrees of pain. 18 studies [253, 321, 343, 386, 387, 398, 400, 403, 406, 408, 409, 413-416, 419, 424, 429] focused on acute pain/ low disability pain. High disability pain was evident in eight trials [351, 368, 404, 407, 412, 420, 423, 425]. A probability of high disability pain was also observed in five studies [394, 402, 411, 422, 427]: participants in Abrahamsen et al. 2009's [394] study had a mean duration of pain of more than 11.9 years (SD 9.9). On the other hand, the other four studies included patients who sought help through secondary care or tertiary care for professional treatment. A mixed distribution of low disability and high disability pain was observed in nine RCTs [396, 397, 399, 401, 405, 410, 417, 418, 421, 423]. For the reminding two trials the pain degree was unspecified [426, 428].

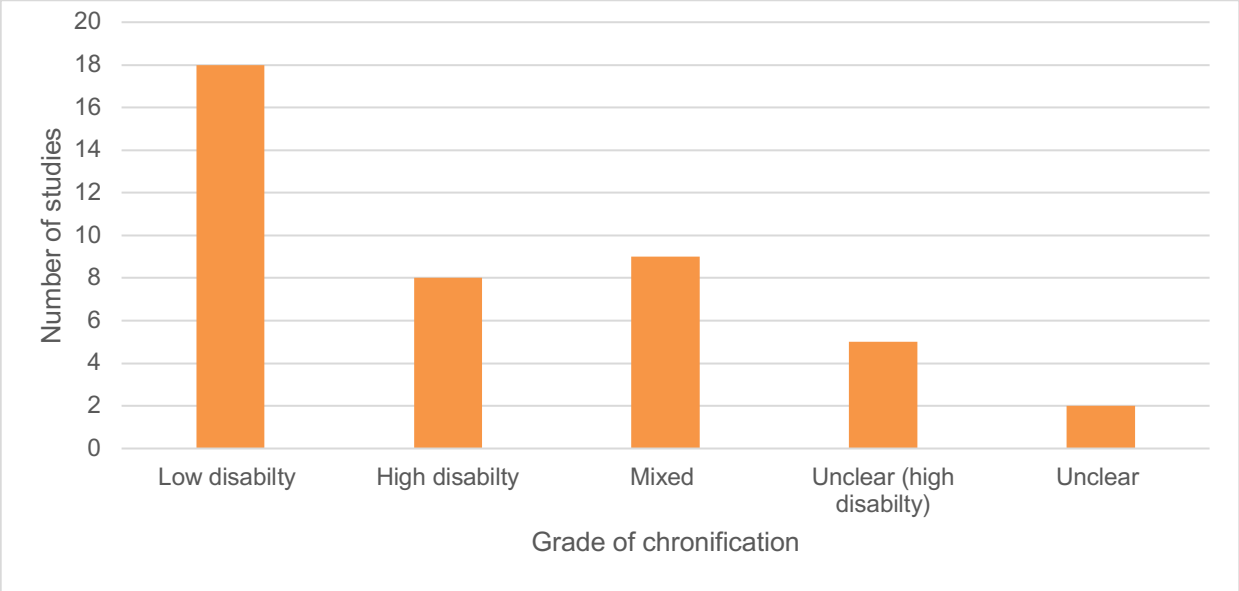


Figure 42: Grade of chronification of the included studies in psychosocial interventions

The participants from the 42 included RCTs were classified according to the indications mentioned above illustrated in Figure 43. Several of the studies examined provided multiple indications of the subjects' level of chronicity. Consequently, the indications could support or

contradict each other. For this reason, the priority list was used for the final decision on classification. In the following Table 22, the priorities of the indications, as well as the studies that investigated them, are displayed below:

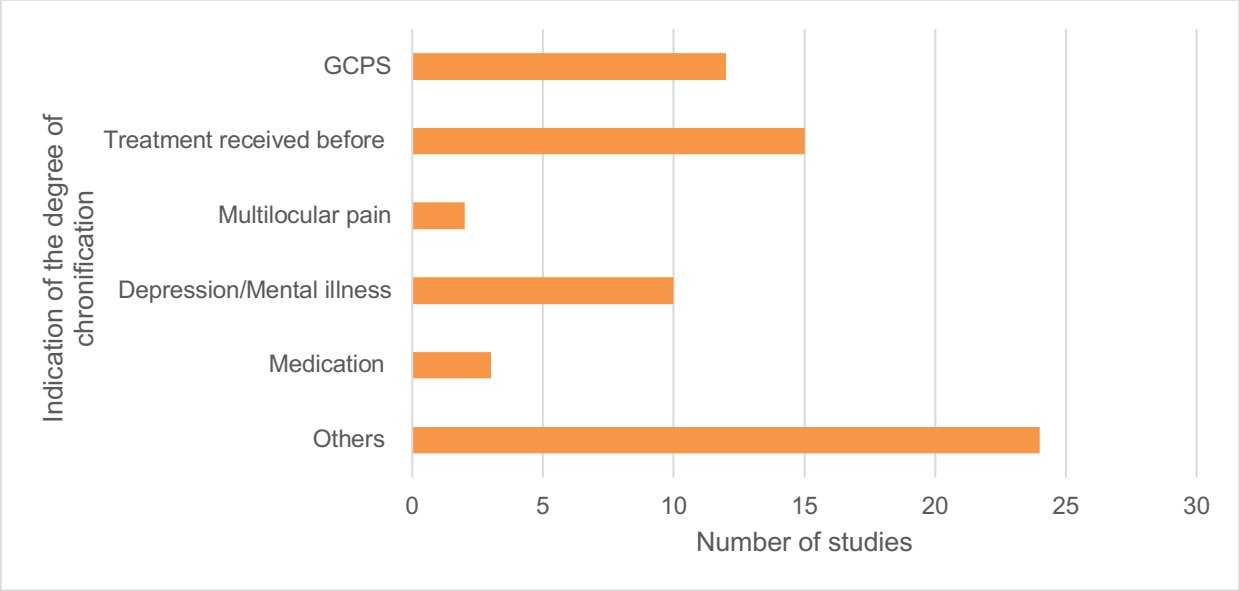


Figure 43: Indications of the degree of chronification, found in the included studies for psychosocial interventions; GCPS= Graded Chronic Pain Scale

Table 22: Indications of the degree of chronification, found in the included studies for psychosocial interventions

Indications	Low disability	High disability	Mixed	Unclear (high disability)
Graded chronic pain scale	Dworkin, 2002 Gardea 2001 Kalamir 2012 Manfredini 2018	Dworkin 2002a Turner 2005	Bartleya 2019 Brandão 2020 Dworkin 1994 Giro 2016 Lam 2020 Litt 2010	
Treatment received before	Conti 2014 Hasanoglu 2017 Komiyama 1999 Melo 2020 Michelotti 2012 Michelotti 2004 Yu 2016	Funch 1984 Göller 2017 Roknic 2010 Townsen 2001	Crocket 1986 DeVocht 2013 Shedden, 2013	Goldthrope 2017
Multilocular pain	Gatchel 2006	Makino 2014		
Depression or mental illness	Calderon 2011 Conti 2014 Dalen 1986 Ferrando 2012 Harrison 1997 Herman 2002 Kalamir 2012 Michelotti 2004 Turk 1993 Yu 2016			
Analgetic misuse	Conti 2014 Hasanoglu 2017 Michelotti 2004			

Indications	Low disability	High disability	Mixed	Unclear (high disability)
Others	Calderon 2011 Conti 2014 Dworking 2002 Ferrando 2012 Harrison 1997 Hasanoglu 2017 Melo 2020 Michelotti 2012 Michelotti 2004 Turk 1993	Dworking 2002 Funch 1984 Göller 2017 Makino 2014 Roknic 2010 Turner 2011	DeVocht 2013 Dworking 1994 Giro 2016	Abrahamsen 2009 Dohrmann 1978 Goldthrope 2017 Stam 1984 Wahlund 2003

3.4.4.2.3 Recruitment of the subjects / study settings

23 of the 42 studies could be assigned to tertiary care. This corresponds to a sample of 1780 subjects, but independent of control groups, the diagnostic instrument used, the outcomes measured and the study duration. The subjects were mainly treated in a clinic or were referred to this clinic and thus were included in the study. In some cases, it was stated that the study had taken place in the clinic. Another 356 subjects from seven studies came from specialized TMD clinics. 391 patients from seven studies were recruited from the general population or from dental practices and were thus assigned to primary care. Two trials did not have a description of the care level from which the subjects originated. Three studies recruited patients from a primary and tertiary care. Figure 44 displace the number of studies according to the different health care systems seeked by the participants.

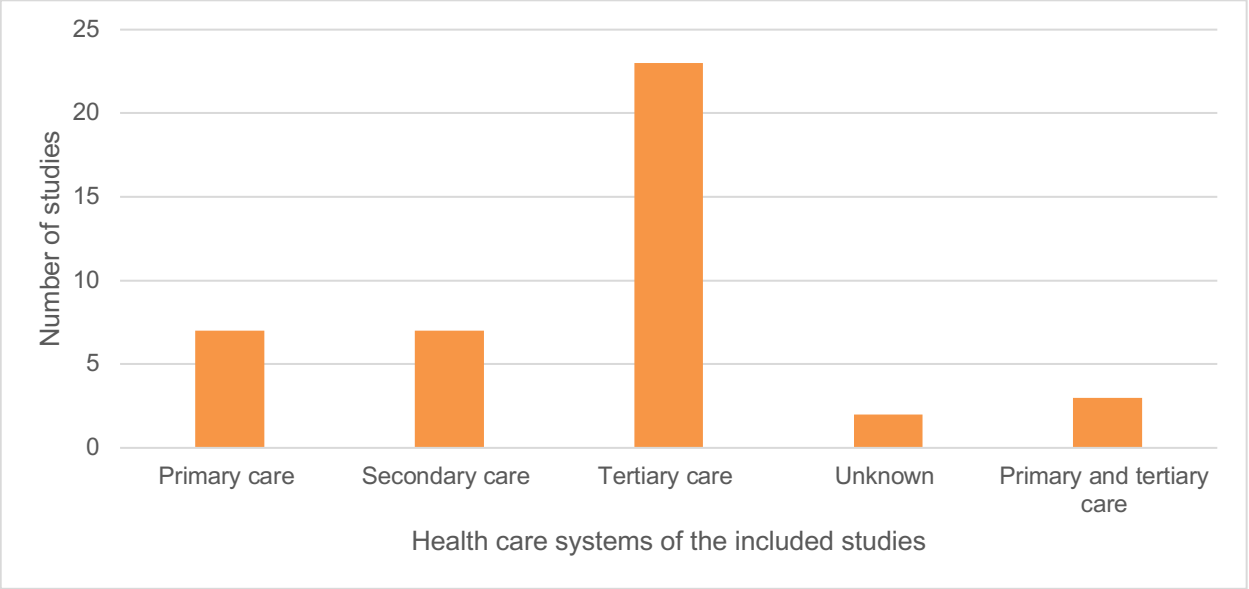


Figure 44: Recruitment of subjects in the included studies of psychosocial interventions

3.4.4.3 Characteristics of the interventions

3.4.4.3.1 Outcomes

3.4.4.3.1.1 Primary outcome -pain at rest

To measure pain intensity a variety of measuring scales were used in the included trials. 15 RCT's treated pain intensity with VAS [253, 321, 387, 398, 399, 402, 414, 416, 419, 422, 427, 429, 430], nine trials were working with CPI to evaluate pain intensity [368, 403-405, 408, 409, 417, 418, 421], five [397, 403, 405, 408, 412] authors included the GCPS and four practiced with NRS [351, 394, 396, 401]. Townsen et al. 2001 [423] and Funch et al. 1984 [407] preferred the 6-point Likert-type scale. The Symptom Severity Index (SSI) in four trails [343, 406, 424, 428], 10-point scale was engaged by Dalen et al. 1986 [400], while Goldthrope et al. 2017 [411] measured pain intensity and interference with life using the Brief Pain Inventory.

3.4.4.3.1.2 Secondary outcomes

Mouth opening was evaluated in 17 studies [351, 386, 387, 394, 399, 402-405, 410, 415, 416, 420, 422, 428-430]. Seven studies investigated pain upon palpation. Crocket et al. 1986 used the Likert-Skala 0-4, Dworkin et al. 2002a und 2002b counted the number of muscle sites tender upon palpation, Turk et al. 1993 [424] used the muscle palpation pain index (PPD), Yu et al. 2016 [429] used the VAS score for pain upon palpation. The final two studies Roknic et al. 2010 [420] and Vallon et al. 1991 [426] did not state the instrument used for measuring pain upon palpation. Clicking was measured in three trials [402, 422, 430]. The authors did not report how the TMD sound was measured. 16 RCTs [321, 368, 394, 397, 403-406, 409, 411, 413, 417, 418, 421, 424] measured depression with different scales: SCL-90-R [394, 403-405], RCD/TMD Axis II [396, 397], Back depression inventory (BDI) [321, 368, 409, 413], HADS [411], CES-D [418, 421] and depression scale from the Profile of Mood state [424]. Somatization was evaluated in six RCTs using the SCL-90-R [394, 403-406, 418].

3.4.4.3.2 Psychosocial interventions

In the included RCTs, different preferences for psychosocial interventions were described. The interventions can be divided into seven different categories. The first category included psychotherapies aimed at improving coping skills and behavioural management, namely CBT [321, 403-406, 408, 409, 411, 413, 416, 418, 421, 425], isolated or combined with other treatments. Gardea et al. 2001 used CBT [408], Calderon et al. 2011 [321] and Harrison et al. 1997 [413] focused on CBT compared with pharmaceutical placebo, three trials worked with CBT and EMG-biofeedback [408, 409, 421], one RCT investigated CBT with self-care strategies [403], Komiyama et al. 1999 [416] compared CBT with posture correction and four trials compared CBT with „usual treatment" or standard treatment [368, 404, 406, 418]. Stam

et al. 1984 [422] investigated CBT with hypnosis versus a relaxation program. The next three categories are relatively simple interventions aimed at improving patient self-control, i.e. counselling [253, 396, 414, 419, 429], self-care [343, 351, 368, 386, 397, 401, 403, 410, 415, 417, 423, 425, 426, 428] and education [387, 396, 410]. In addition to their mutual reinforcement, and their association with other therapeutics. These interventions can be carried out by qualified professionals other than psychologists. We found four studies on counselling: three compared occlusal splint and counselling alone [253, 419, 429] and one trial compared education treatments [396] and 14 studies focused on self-care strategies with or without additional treatments or placebos. The final categories was a set of procedures closer to physiotherapeutic interventions that target harmful behaviours and increase awareness of muscular activity, e.g. stress management [394, 399, 424, 425, 430], biofeedback [398, 400, 402, 407-409, 412, 420, 424] and hypnosis [394, 422].

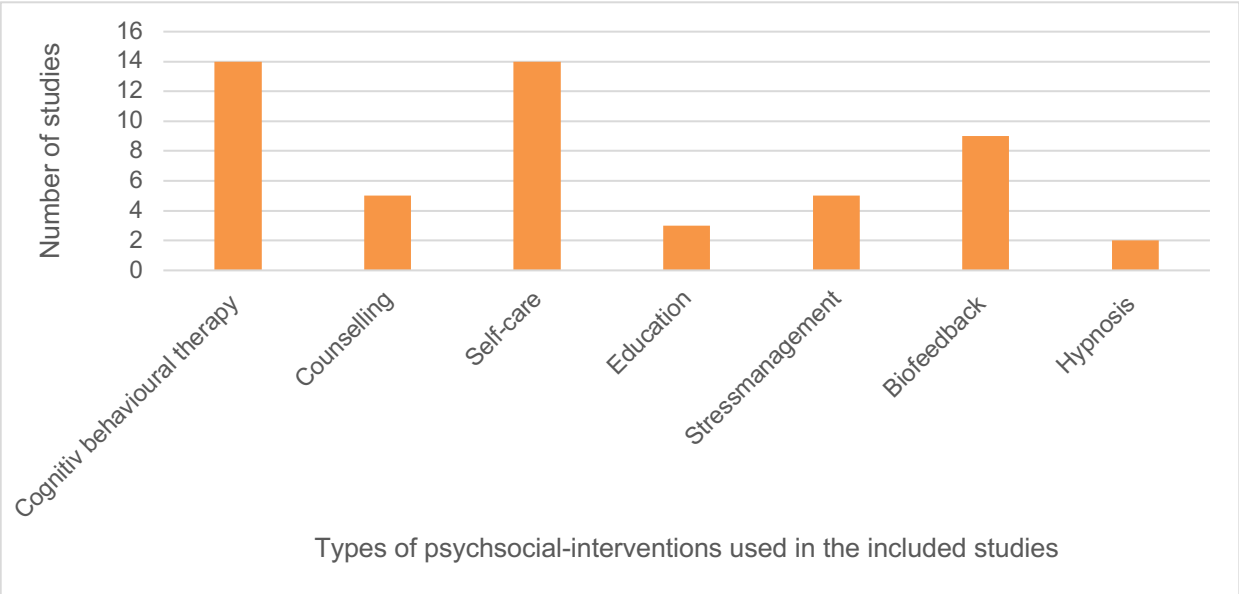


Figure 45: Types of psychosocial interventions used in the included studies

3.4.4.3.3 Controls for psychosocial interventions

The bar chart (Figure 46) below displays the comparative therapies that were compared with the psychosocial interventions. Predominantly, the authors compared psychosocial interventions treatments with splint treatment [253, 386, 399, 412, 414, 417, 419-421, 424, 426-429] and other psychosocial interventions (Biofeedback, self-care, relaxation or education) [387, 394, 396, 397, 407-410, 422, 425, 427] as controls. Other controls were physiotherapy [401, 415, 416], drugs [321, 343, 351, 368, 413], laser [253], standard [406, 418] and usual therapy [403-405, 411]. Placebo [321, 343, 398, 400, 402, 413], waiting list [415, 423, 424] and no treatment [410, 428] were also observed in several studies.

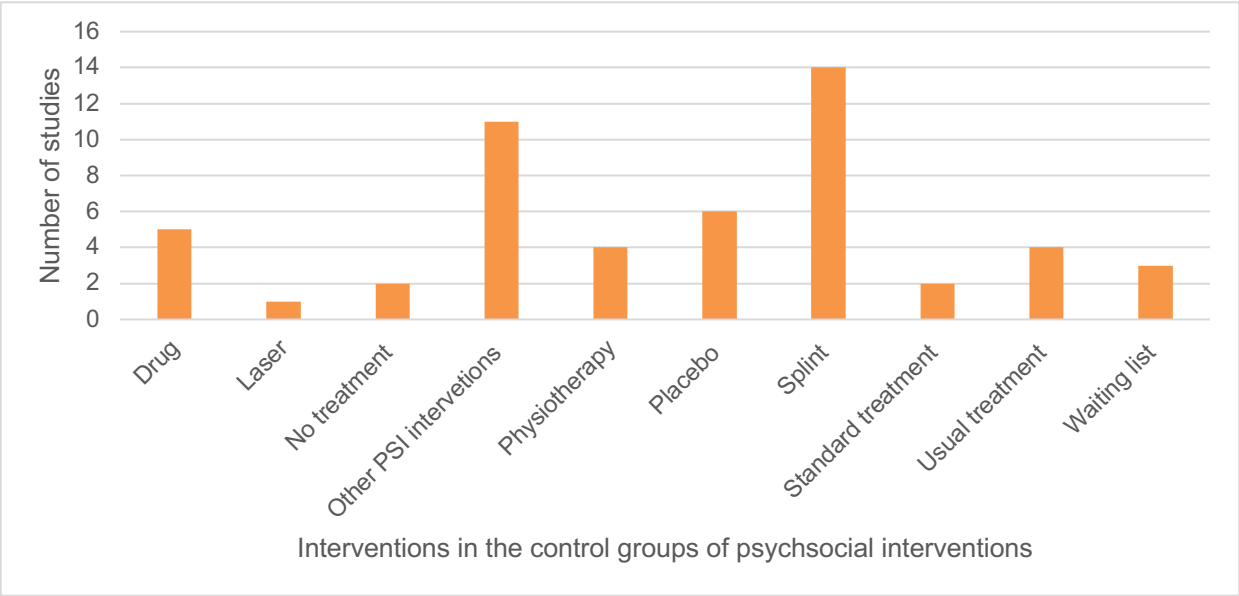


Figure 46: Control groups used in the included studies for psychosocial interventions

3.4.4.3.4 Follow up periods

Follow up times varied from immediately after treatment [394, 396, 399, 414, 422, 425, 428], to three weeks [253, 343], one month [321, 397, 398, 419], two months [410, 420], three months [253, 351, 386, 387, 411, 413, 417, 429, 430], six months [253, 400, 401, 415, 417, 421, 424, 427, 430], nine months [406], twelve months [368, 402-405, 408, 409, 412, 416, 418] up to two years [407] after treatment. Turk et al. 1993 [424] had a follow up period from eight to 24 months.

3.4.5 Excluded studies

77 studies were excluded the reasons for which are declared in the corresponding table (Appendix II, section Characteristics of excluded studies).

3.4.6 Assessment of the methodological quality of the included studies

The risk of bias according to the Cochrane Collaboration of the included studies is presented in figures 47 and 48. An overall result of 54.71% for low risk of bias was observed among the included studies. Eight [368, 403, 404, 408, 409, 415, 418, 421] out of the 43 included RCTs conducted ITT analysis. However, despite the additional information from many authors, 35.7% of the included studies presented an unclear risk of bias adopting the criteria for “Random sequence generation”, 81% for “Allocation concealment”, 33.3% for “Blinding of participants and personnel”, 35.7% for “Blinding of outcome assessment” and “Incomplete outcome data”. Three trials [408, 422, 430] reported omitted outcome results and were therefore judged as high risk in the “Selective reporting category”. One study applied a weighting of the results according to the compliance of the treatment rather than using ITT

analysis and “Other bias” was inadequately reported with only 4.76% being judged as low risk of bias.

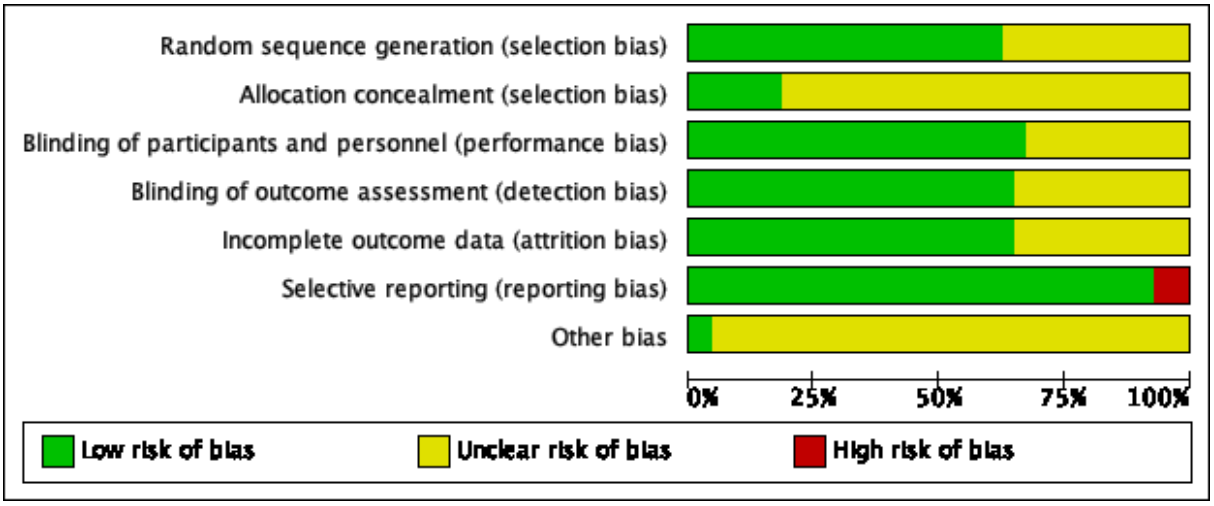


Figure 47: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

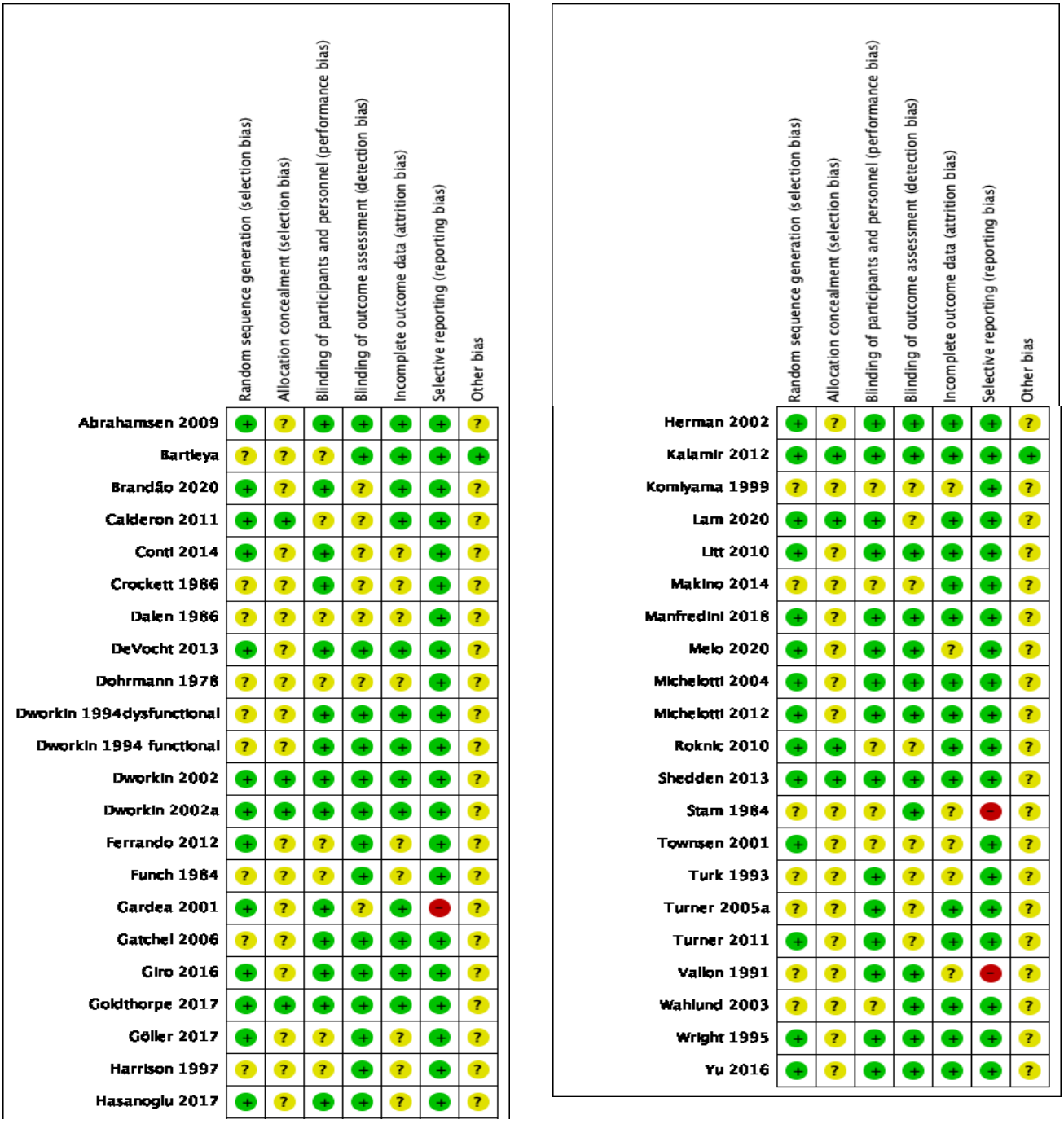


Figure 48: Risk of bias summary: review of authors' judgements about each risk of bias items for each included study

3.4.7 Results of the quantitative synthesis of the included studies (Meta-analysis)

In this section of the paper, statistically significant or not statistically significant but clinically relevant results are described. There were some limitations, as the presentation of all results would have been beyond the scope of this paper. For the sake of completeness, the remaining forest plots (minimum of three studies included) with further results from this study are presented in *APPENDIX IX: Forest plots*.

For the meta-analysis, 30 RCTs were selected. Out of the 42 included studies that passed the full-text screening, a total of eleven studies were excluded for quantitative comparison. The reasons for exclusion were as follows:

1. Combination of therapies used for the study group [343, 401, 413, 414, 418, 420, 422]
2. Missing data on the outcomes [397, 400, 402, 407, 412]

The study of Dworkin et al. 1994 was added twice as the population was capable of being divided into low disability and high disability groups.

A tabular overview of the statistically significant results for the pain group with low disability and with high disability is presented in 3.4.8 for the reduction of pain intensity in Table 23, in Table 24 for MMO and in Table 25 for depression.

A SMD of zero indicates that the intervention group and the control group have equal effects. For pain reduction and depression, an improvement is associated with lower values in the outcome measure. SMDs less than zero indicate that the intervention group is more effective than the control group. Therefore, a negative direction with lower values corresponds to better performance of the intervention group. Conversely, for MMO improvement, improvement is associated with higher values on outcome measures. A positive direction with higher values corresponding to better performance of the intervention group under study [200].

The IMMPACT guideline states that a 30% pain reduction in chronic pain is necessary to distinguish placebo from verum [201]. To obtain the clinical significance, the author added a small comment on each forest plot obtaining the data from the pain reduction from the baseline compared to the follow up time.

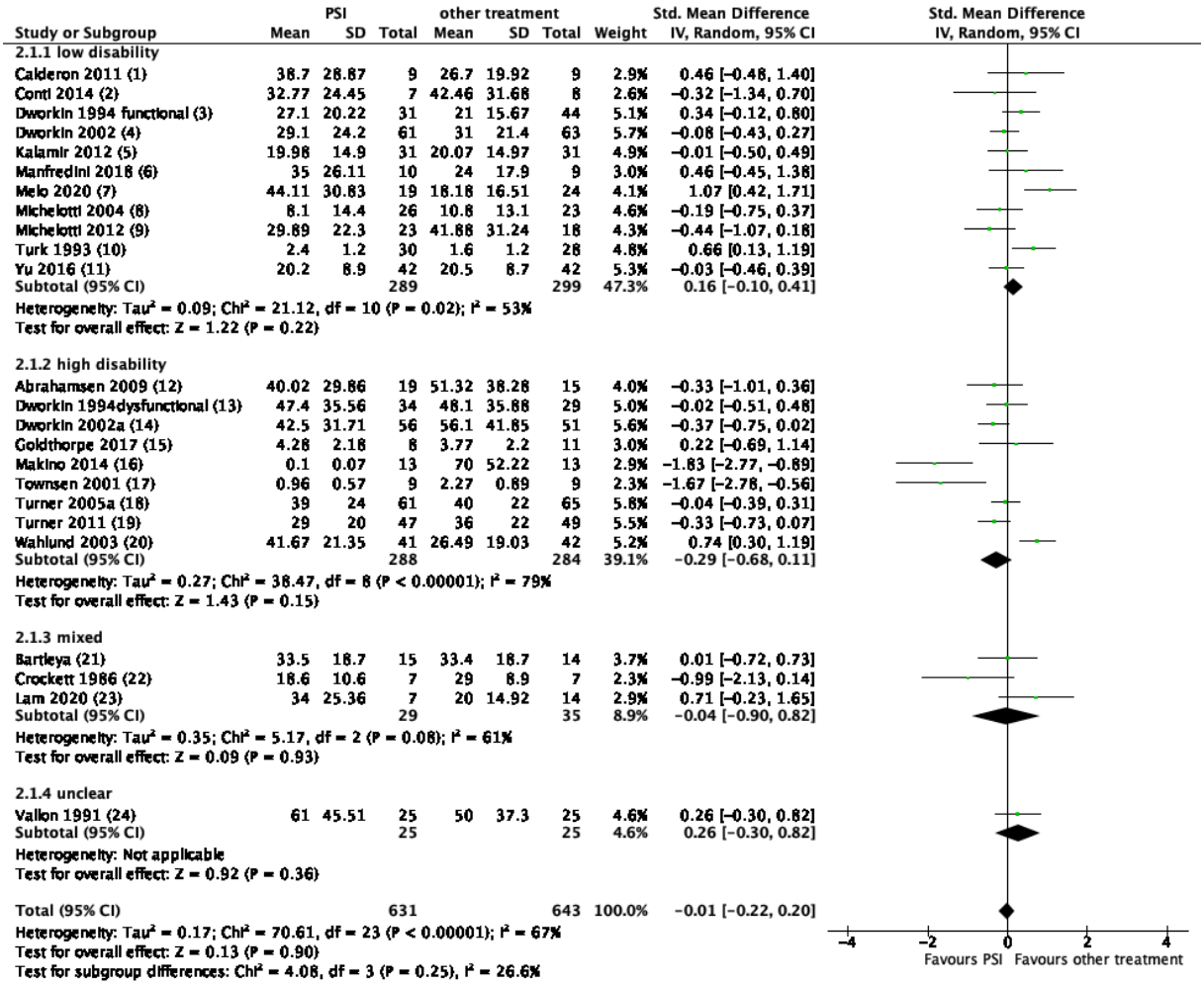
3.4.7.1 Comparison: Effectiveness of psychosocial treatment (of any kind) in comparison to other treatments on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.4.7.1.1 Primary outcome parameter: pain intensity

3.4.7.1.1.1 Short-term efficacy (treatment duration up to six months

Meta-analysis of data from 1274 participants across 24 studies indicated no statistically significant bigger reduction in total pain scores in psychosocial interventions versus other treatment as seen in Figure 49. The overall effect for pain showed no significant difference between psychosocial interventions and other treatment (n=24 studies [n=631 for Group A, and n=643 for Group B], SMD=-0.01; 95% CI [-0.22, 0.20]; *p*=0.90), yet with moderate heterogeneity Ch^2=70.61 (I^2=67%). Subgroup analysis showed no statistically significant differences between psychosocial interventions and other treatment of patients suffering from low disability pain (n=11 studies [n=289 for Group A, and n=299 for Group B], SMD=0.16; 95% CI [-0.10, 0.41]; *p*=0.22, I^2=53%), high disability pain (n=9 studies [n=288 for Group A, and n=284 for Group B], SMD=-0.29; 95% CI [-0.68, 0.11]; *p*=0.15, I^2=79%, mixed pain subgroup (n=3 studies [n=29 for Group A, and n=35 for Group B], SMD=-0.04; 95% CI [-0.90, 0.82]; *p*=0.93, I^2=61%). The unclear pain group was represented by one study, and therefore there was no need to describe it any further.

Nearly half of the included studies showed no clinical significance in pain reduction (30%) in the intervention group. The studies of Dworkin et al. 1994 functional, Melo et al. 2020, Michelotti et al. 2012, Turk et al. 1993, Dworkin et al. 1994 dysfunctional, Goldthrope et al. 2017, Turner et al. 2005a, Wahlund et al. 2003, Lam et al. 2020 and Vallon et al. 1991 did not have a clinical significance in pain reduction.



Footnotes

(1) CBT and Placebo vs. amitriptyline: Pain (VAS); Orofacial pain
(2) Biofeedback vs. placebo: Pain (VAS); TMD of muscular origin
(3) CBT vs. usual treatment: Pain (CPI); TMD of muscular origin
(4) Self-care intervention vs. usual treatment :Pain (CPI): TMD of muscular origin
(5) IMT + education and "self- care" exercises (IMTESC) vs. : Pain (11-point GPCS); TMD of muscular origin
(6) Councelling vs. laser therapy vs. OA: Pain (VAS); TMD of muscular origin
(7) Counselling (CS) vs. splint: Pain (VAS); TMD of muscular and articular origin
(8) Education only vs. education + self-supportive exercise: Pain (VAS): TMD of muscular origin
(9) Habit reversal treatment vs. Splint: Pain (VAS): TMD of muscular origin
(10) Combination of biofeedback+stress management vs.OA: Pain (PSS); Muscle TMD of muscular origin
(11) Councelling vs. slint: Pain (VAS); disc displacement without reduction
(12) Hypnosis vs. relaxation only: Pain (NRS); TMD of muscular origin
(13) CBT vs. usual treatment: Pain (CPI); TMD of muscular origin
(14) Comprehensive care vs. usual treatment: Pain (CPI); TMD of muscular origin
(15) CBT vs. usual treatment: Pain (Brief Pain Inventory); TMD of muscular origin
(16) Home+psychological intervention vs. pharmacological: Pain (NRS); craniocervical chronic pain
(17) Habit reversal treatment vs. wait-list control: Pain (6-point Likert-type scale); TMD (not identified)
(18) CB pain management training vs. self-care management: Pain (VAS); TMD of muscular and articular origin
(19) Self-management training vs. oral contraceptive therapy: Pain (CPI); TMD of muscular origin
(20) Relaxation therapy vs. occlusal appliance: Pain (VAS); TMD of muscular and articular origin
(21) Hope session vs. EDC involving education about pain and stress: Pain (NRS); TMD (not identified)
(22) Relaxation vs. splint and physiotherapy: Pain (VAS); TMD of muscular origin
(23) CBT and self-management principles vs. OA: Pain (CPI); TMD of muscular and articular origin
(24) Comforted ("reassurence of occlusion") vs. occlusal adjustment: Pain (VAS); craniomandibular disorders and a history of headache

Figure 49: Psychosocial interventions versus other treatment (outcome: change in pain intensity, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.4.7.1.1.2 Medium-term efficacy (treatment duration six till 12 months)

A high degree of heterogeneity (I^2=78%, p<0.00001) was seen in Figure 93, APPENDIX IX: Forest plots. Eight studies [253, 368, 403, 404, 415, 417, 421, 424] reporting pain intensity exhibited no significant bigger differences in the overall effect of the interventions (p=0.92). All three subgroups with low disability, high disability and mixed pain group also showed no statistically significant difference between psychosocial interventions treatment compared to other treatment for the reduction of pain intensity.
In all the included studies except for Manfredini et al. 2018 a clinical significance of 30% pain reduction in the intervention group was observed.

3.4.7.1.1.3 Long-term efficacy (treatment duration over 12 months)

Psychosocial interventions is statistically significant more effective than other treatment in reducing pain intensity within a timeframe more than 12 months (n=7 studies [n=292 for Group A, and n=286 for Group B], SMD=-0.31; 95% CI [-0.58, -0.05]; p=0.02, I^2=59%, Figure 50). The subgroup with low disability pain (n=5 studies [n=202 for Group A, and n=206 for Group B], SMD=-0.41; 95% CI [-0.75, -0.07]; p=0.02, I^2 =64%) showed a statistically significant bigger effect in reducing pain intensity in the intervention group. The subgroup with high disability pain (n=2 studies [n=90 for Group A, and n=80 for Group B], SMD=-0.08; 95% CI [-0.38, 0.23]; p=0.62, I^2=0%) also favoured psychosocial interventions treatment without a statistical significance result. The subgroups showed the same tendency in favour of psychosocial interventions for reducing pain intensity within a time frame of over 12 months. In all the included studies was a clinical significance of 30% pain reduction in the intervention group observed.

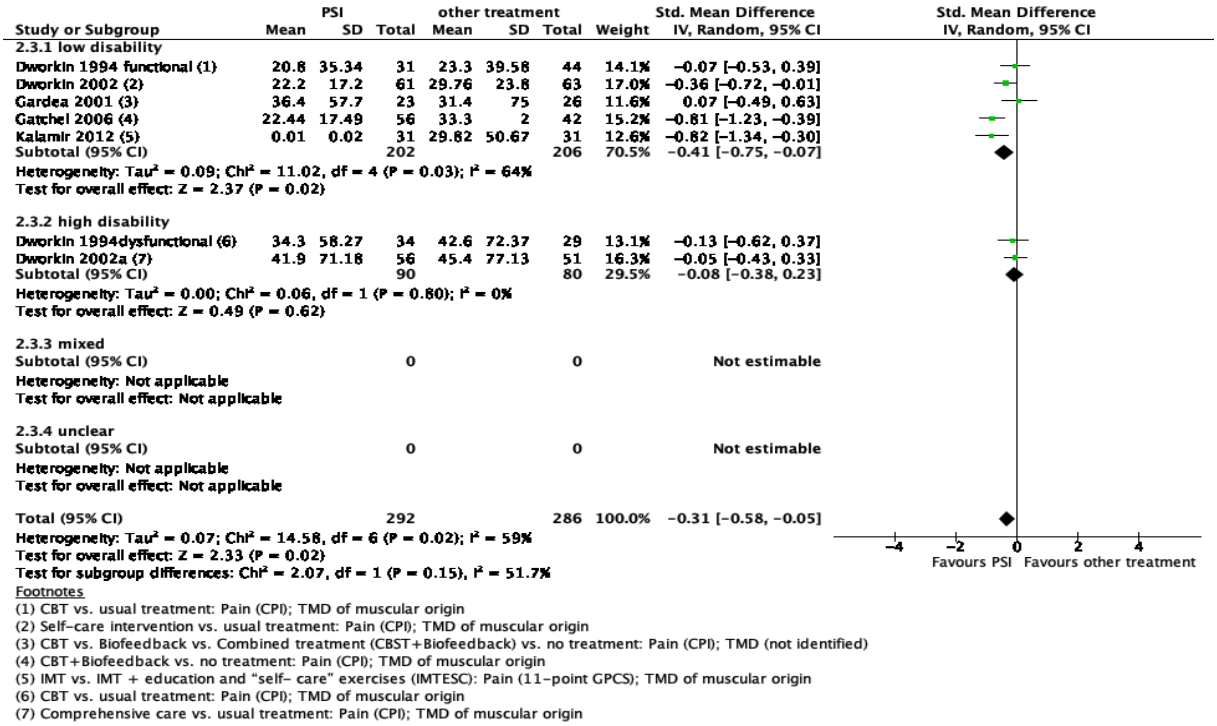


Figure 50: Psychosocial interventions versus other treatment (outcome: change in pain intensity, timeframe: over twelve months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.4.7.1.2 Secondary outcome parameter: MMO

3.4.7.1.2.1 Short-term efficacy (treatment duration up to six months)

Psychosocial interventions was not statistically significant more effective than other treatments in increasing MMO within a timeframe of less than six months (n=11 studies [n=289 for Group A, and n=274 for Group B], SMD=0.03; 95% CI [-0.20, 0.26]; *p*=0.79, I^2=42%) as this can be seen in Figure 94, APPENDIX IX: Forest plots. The subgroup analysis with low disability pain (n=5 studies [n=171 for Group A, and n=164 for Group B], SMD=0.08; 95% CI [-0.27, 0.43]; *p*=0.66, I^2=58%), high disability pain (n=2 studies, *p*=0.47) and mixed pain group (n=3 studies [n=48 for Group A, and n=43 for Group B], SMD=0.24; 95% CI [-0.18, 0.65]; *p*=0.27, I^2 =0%) showed no significance difference. The unclear pain subgroup was represented by one study and therefore not described any further.

3.4.7.1.3 Secondary outcome parameter: Depression

3.4.7.1.3.1 Short-term efficacy (treatment duration up to six months)

Depression in the short term (less than six months) showed no significance difference between psychosocial interventions and other treatments (n=7 studies [n=205 for Group A, and n=197 for Group B], SMD=-0.28; 95% CI [-0.57, 0.02], Figure 51), without statistical significance (*p*=0.07). Heterogeneity was moderate with *p*=0.06 (I^2=51%) for this analysis. By looking at the subgroup with high disability pain a significant difference was observed in

favour of psychosocial interventions for the improvement of depression (n=4 studies [n=130 for Group A, and n=126 for Group B], SMD=-0.49; 95% CI [-0.85, -0.13]; *p*=0.008, I^2=43%).

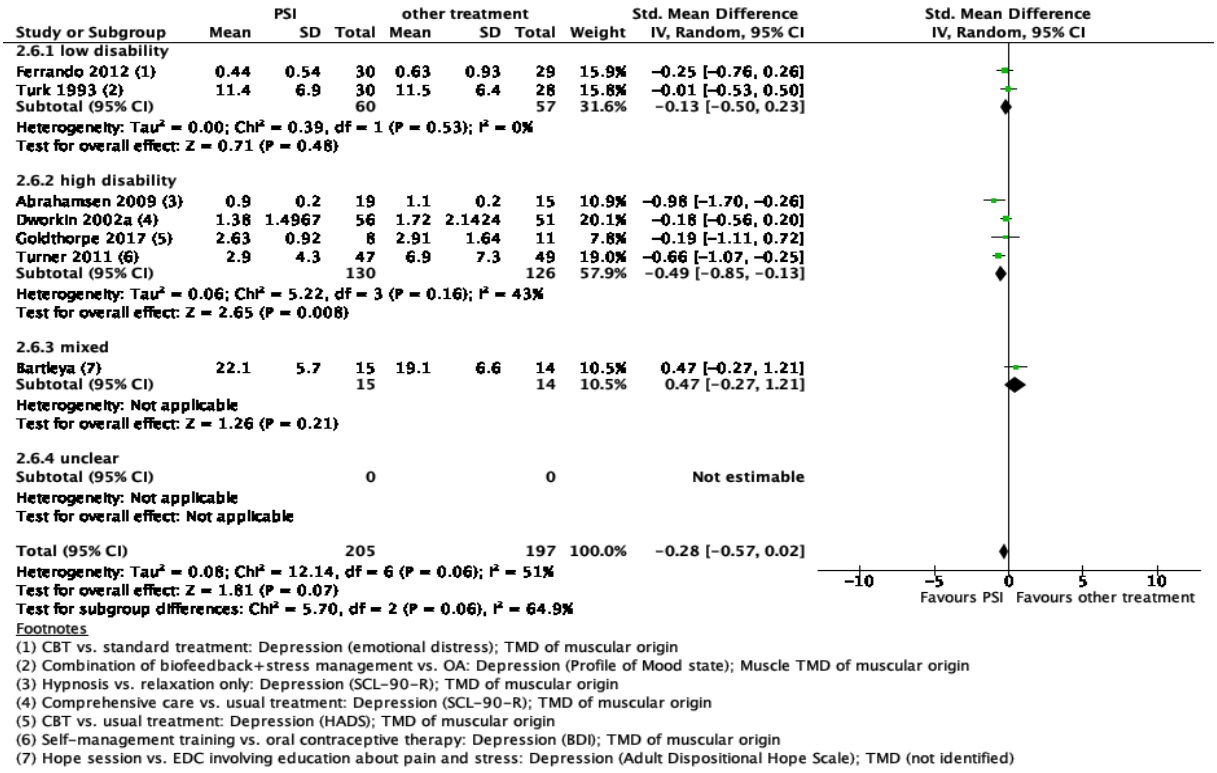


Figure 51: Psychosocial interventions versus other treatment (outcome: change in depression, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.4.7.2 Comparison: Effectiveness of self-care treatment, counselling, and education in comparison to other treatments on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.4.7.2.1 Primary outcome parameter: pain intensity

3.4.7.2.1.1 Short-term efficacy (treatment duration up to six months

For the analysis of self-care, counselling and education compared to other treatment (Figure 95, APPENDIX IX: Forest plots) a positive tendency can be seen favouring self-care, counselling, and education in reducing pain intensity in the short term (n=11 studies [n=311 for Group A, and n=312 for Group B], SMD=-0.07; 95% CI [-0.37, 0.22]; *p*=0.63, I^2=68%). The subgroup with low disability pain indicates a definite predisposition in support of self-care with a low heterogeneity of I^2=57% (n=7 studies [n=212 for Group A, and n=210 for Group B], SMD=0.06; 95% CI [-0.25, 0.37]; *p*=0.70), whereas the high disability pain category suggests substantial heterogeneity of I^2=88% (n=2 studies [n=60 for Group A, and n=62 for Group B], SMD=-1.02; 95% CI [-2.49, 0.45]; *p*=0.17, I^2=88%). The mixed and unclear group were represented by one study each. All the included studies had a clinical significance pain

reduction (30%) except for the studies of Melo et al. 2020, Michelotti et al. 2012 and Vallon et al. 1991.

3.4.8 Tabular overview of the results of the comparisons for psychosocial interventions

The results of the comparisons performed for psychosocial interventions are listed below in Table 23 for pain intensity, in Table 24 for MMO and in Table 25 for depression:

Table 23: Tabular overview of the results of psychosocial interventions regarding pain intensity categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval; VAS=visual analogue scale

Reduction of pain intensity		
Comparison	**Statistically significant results**	**Data**
Psychosocial interventions (of any kind) vs. (any) other treatment	Short-term: No ss bigger effectiveness for the treatment of psychosocial interventions for low disability, high disability, mixed or total pain compared to other treatment. Medium-term: No ss bigger effectiveness for the treatment of psychosocial interventions for low disability, high disability, mixed or total pain compared to other treatment. Long-term: **Significant less pain after psychosocial interventions than after other treatment for low disability pain and total pain.** No ss bigger effectiveness for the treatment of psychosocial interventions for high disability pain compared to other treatment.	Short-term: Low disability: (SMD=0.16; 95% CI [-0.10, 0.41]; *p*=0.02; I^2=53%) High disability: (SMD=-0.29; 95% CI [-0.68, 0.11]; *p=0.15*; I^2=79%) Mixed: (SMD=-0.04; 95% CI [-0.90, 0.82]; *p*=0.93; I^2=61%) Total: (SMD=-0.01; 95% CI [-0.22, 0.20]; *p*=0.90; I^2=67%) Medium-term: Low disability: (SMD=0.18; 95% CI [-0.49, 0.86]; *p*=0.59; I^2=84%) High disability: (SMD=-0.35; 95% CI [-0.75, 0.05]; *p*=0.09; I^2=52%) Mixed: (SMD=0.29; 95% CI [-1.26, 1.83]; *p*=0.71; I^2=87%) Total: (SMD=0.02; 95% CI [-0.37, 0.41; *p*=0.92; I^2=78%) Long-term: **Low disability: (SMD=-0.41; 95% CI [-0.75, -0.07]; *p*=0.02; I^2=64%)** High disability: (SMD=-0.08; 95% CI [-0.38, 0.23]; *p* =0.62; I^2=0%) **Total: (SMD=-0.31; 95% CI [-0.58, -0.05; p=0.02; I^2=59%)**
Self-care, counselling, and education vs. other treatment	Short-term: No ss bigger effectiveness for the treatment of self-care, counselling or education for low disability, high disability, or total pain compared to other treatment.	Short-term: Low disability: (SMD=0.06; 95% CI [-0.25, 0.37]; *p*=0.70; I^2=57%) High disability: (SMD=-1.02; 95% CI [-2.49, 0.45]; *p*=0.17; I^2=88%) Total: (SMD=-0.07; 95% CI [-0.37, 0.22]; *p*=0.63; I^2=68%)

Table 24: Tabular overview of the results of psychosocial interventions regarding MMO categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval

Improvement of maximum mouth opening		
Comparison	**Statistically significant results**	**Data**
Psychosocial interventions vs. other therapy	Short-term: no ss bigger effectiveness for the treatment of psychosocial interventions for low disability, high disability, mixed or total pain compared to other treatment.	Short-term: Low disability: (SMD=0.08; 95% CI [-0.27, 0.43]; *p*=0.66; I^2=58%) High disability: (SMD=-0.30; 95% CI [-1.14, 0.53]; *p* =0.47; I^2=76%) Mixed: (SMD=0.24; 95% CI [-0.18, 0.65]; *p* =0.27; I^2=0% Total: (SMD=0.03; 95% CI [-0.20, 0.26]; *p* =0.79; I^2=42%)

Table 25: Tabular overview of the results of psychosocial interventions regarding depression score categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval

Reduction of depression scores		
Comparison	**Statistically significant results**	**Data**
Psychosocial interventions vs. other therapy	Short-term: **significant less depression after psychosocial interventions than after other treatment for high disability pain.** No ss bigger effectiveness of psychosocial interventions treatment for low disability or total pain for the reduction of depression compared to other treatment.	Short-term: Low disability: (SMD=-0.13; 95% CI [-0.50, 0.23]; *p*=0.48; I^2=0%) **High disability: (SMD=-0.49; 95% CI [-0.85, -0.13]; *p*=0.008; I^2=43%)** Total: (SMD=-0.28; 95% CI [-0.57, 0.02]; *p*=0.07; I^2=51%)

3.5 Physiotherapy

3.5.1 Description of the intervention:

A national survey in 2013 demonstrated that despite limited evidence, 72% of respondents considered physical therapy to be an effective treatment option for TMD, with orthodontics (79%), ultrasound (52%), MT (48%), acupuncture (41%) and laser therapy (15%) considered the most effective modalities for treating TMD in the UK [351]. Physical therapy is among the ten most commonly used treatment modalities for TMD, focusing on reducing neck and jaw pain, improving ROM, and promoting movement to maintain healthy function [431]. Due to the harmful effects of NSAIDs, interest in physical therapy has increased considerably today that the AAOP has recommended physical therapy as the main treatment modality for TMD management [181, 432]. It is reversible and non-invasive, providing self-care management in a manner that encourages patient accountability for their own health. Physical therapy modalities include exercise therapy programs, electrophysical modalities (ultrasound, microwaves), electro analgesic modalities (TENS, biofeedback) and physical devices [433]. The exercise programme for TMD can be divided into three parts: (a) manual techniques for the TMJ and masseter muscles (performed by a trained physiotherapist), (b) home exercise programme for the above areas (performed by a trained physiotherapist), (c) home exercise programme for correction of body parts (requires careful instruction and repetitive control of the techniques so that they can be performed correctly by the patient). MT may consist of traction for the TMJ, a return technique for the intervertebral disc and trigger point therapy for the masseter muscles [434]. It has been the subject of many studies in the literature [431]. The home exercise programme for the TMJ and masseter muscles consists of self-massage of the masseter, temporalis, and digastricus muscles, stretching exercises for the jaw muscles and coordination exercises for the jaw joints. The home exercise programme to correct posture can consist of mobilisation of the cervical spine, strengthening exercises for the neck muscles and stretching exercises for the sternocleidomastoid muscle [435]. The treatment may include and focus on poor posture, cervical spasm or pain, and treatment of orofacial pain of cervical origin (pain originating from the upper levels of the cervical spine) [436]. The effectiveness of electrophysical modalities has been questioned by some scholars [437] (as the results showed that electrophysical modalities seemed not to be significantly better in reducing pain when compared other therapies). However, the theory that all forms of therapy are similar in their effect is supported by a German study [438]. This study investigated the effectiveness of MT and compared it to a more complex multimodal physiotherapy program on patients. Both types of therapy led to a significant reduction in pressure and pain. For an improvement in symptoms, 15-20 min of physiotherapeutic

treatment techniques at regular intervals are sufficient to bring about a significant reduction in pain [439].

3.5.2 How physiotherapy might work:

"The aim of physiotherapy treatment in the management of TMD is to relief persistent pain, enable muscle relaxation, reduce muscular hyperactivity, and restore muscle function and joint mobility" [248]. The intention is to reduce inflammation and thus improve the pain and function of the TMJ and the masticatory muscles. In addition, physiotherapy focuses on coordination exercises of the TMJ, stretching of the masticatory muscles and correction of posture, as the cervical spine and the craniomandibular complex are closely connected [435].

3.5.3 Study Selection

The initial database search yielded 911 entries, of which 228 were retrieved from MEDLINE (via PubMed), 115 from Embase, 412 from Central, 129 from LIVIVO (German and English version), 16 from Clinicaltrials.gov, eleven from Deutsches Register klinischer Studien (DRKS) and none from the Open Grey Literature (Table 26). Results of unpublished studies are not included in this review. An additional 27 articles were identified through cross-reference checking and manual searching. All the studies used physiotherapy interventions (posture corrections, MT, jaw exercise, physiotherapy devices) for treating TMD. After exclusion of all duplicates (169 studies), the number of entries was 769. Of these, 642 studies were discarded after a review of the titles and abstracts. An additional 68 articles were excluded following full-text review and application of the eligibility criteria (reasons for exclusion after full-text analysis are reported in Appendix VIII). A flowchart depicting the selection process is displayed in Figure 52. The systematic literature search achieved the results shown in Table 26.

Table 26: Results for the search strategy for Physiotherapy

Database	*Number of studies (n)*
PubMed	228
EMBASE	115
Central	412
LIVIVO (German)	50
LIVIVO (English)	79
Clinicaltrials.gov	16

Deutsches Register klinischer Studien (DRKS)	11
Open Grey Literature	-
Total	911

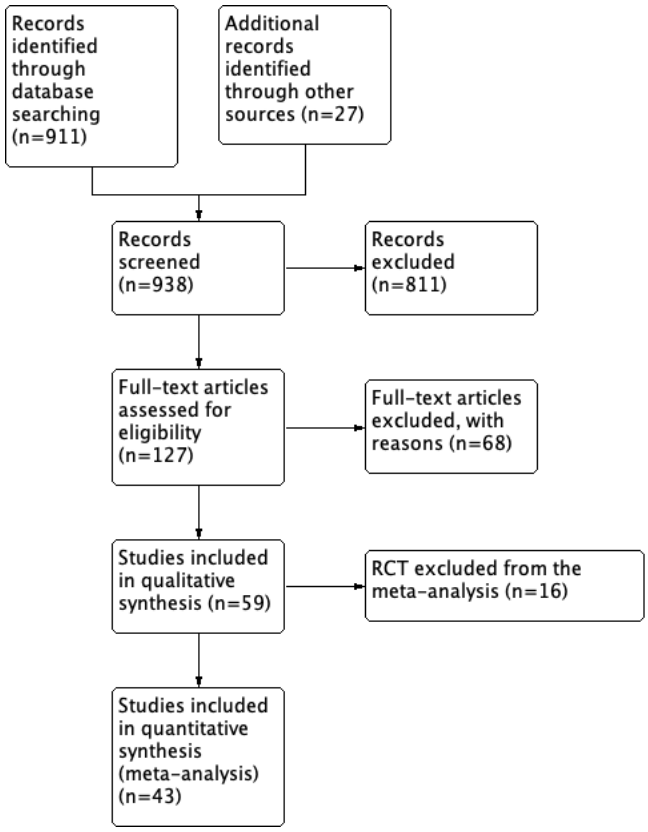


Figure 52: Flow Diagram for RCTs with Physiotherapy treatment for patients with painful TMDs

3.5.4 Qualitative synthesis of the included studies

3.5.4.1 Characteristics of the included studies

59 studies with 3217 participants were included for this review from the search of databases. 27 studies were obtained through a manual search. Details of included studies are provided in Appendix VIII and **Table 27** depicts the general characteristics of the included studies. Characteristics of the Population Used in the Studies, the characteristics of interventions, the pain chronification and the excluded studies were accurately reproduced in narrative style.

Table 27: Included studies physiotherapy treatment for TMD (AMCT=activator method chiropractic technique; CS=counselling; HE=home exercise; LLLT= low-level laser therapy; MMO=maximal mouth opening; MPQ=McGill pain questionnaire; MT=manual therapy; NPRS= numeric pain rating scale; OMT=oral myofunctional therapy; OMT=orofacial myo-low disability therapy; OS=occlusal splints; RIST=reversible interocclusal splint therapy; ST=splint therapy; TB=thera bite; TENS=transcutaneous electrical nerve stimulation; TMD= temporomandibular disorder;VAS= visual analogue scale; WTD =wooden tongue depressors therapy)

Author Year	Patients (n) women %, age (years)	Interventions	Outcomes	Pain chronification	Diagnose	General group therapy	Follow-up
Barbosa et al. 2019 [440]	46 patients 100% women	Group A (n=23): biting endurance exercises Group B (n=23): placebo	Pain (VAS)	Low disability	TMD of muscular origin	General jaw exercise alone or combined with other exercise program	8 weeks
Benli et al. 2020 [441]	91 patients 82% women Mean age: Group A: 39.1 ±3.4 Group B: 39.2 ±3.3 Group C: 39.1 ±4	Group A (n=30): aromatherapy massage therapy with lavender oil Group B (n=30): massage therapy with sweet almond oil Group C (n=31): without massage therapy	Pain (VAS) Maximal mouth opening (MMO)	Low disability	TMD of muscular origin	manual therapy targeted to the orofacial region	2-month
Berguer et al. 2008 [442]	56 patients 94% women 18-45 years old	Group A (n=27): Neuro-reflexotherapy Group B (n=24): Sham interventions	Level of pain (VAS)	High disability	TMD of muscular origin	manual therapy targeted to the orofacial region	n.a.
Brandão et al. 2020 [397]	23 patients 100% women Mean age: Group A: 36.7 ±11.2 Group B: 35.4 ±10.4	Group A (n=12): Isotonic exercises and relaxing techniques Group B (n=11): self-care	Pain severity Pain intensity and depression (GCPS, RDC)	Mixed	TMD of muscular origin	General jaw exercise alone or combined with other exercise program	30 days
Brochado et al. 2018 [223]	51 patients 95% women Mean age: 44.5 ± 17.1	Group A (n=18): photo biomodulation Group B (n=16): manual therapy group Group C (n=17): combined therapy	Pain intensity (VAS) Mandibular movements (mm)	Mixed	TMD of muscular and/or arthrogenic origin	Manual therapy	8 weeks
Burgess et al. 1988 [443]	29 patients 74% women Mean age: 34	Group A (n=10): masticatory and neck muscle chilling with ethyl chloride followed by stretch Group B (n=11): reflexive inhibition Group C (n=8): non-intervention control	Subjective pain (MPQ) non-painful mandibular opening (mm)	High disability	TMD of muscular origin	General jaw exercise alone or in combined with neck exercise program	3 weeks
Calixtre et al. 2019 [444]	61 patients 100% women Mean age: Group A: 26.3 ±4.6 Group B: 26.1 ±5.7	Group A (n=30): mobilisations and neck motor control and stabilisation exercises Group B (n=31): no treatment	Pain intensity (VAS) Mandibular function impairment questionnaire (MFIQ)	Low disability	TMD of mixed origin	Manual therapy + exercise	5 weeks
Capan et al. 2017 [445]	31 patients 97% women Mean age: Group A: 31.0 ±5.9 Group B: 32.2 ±6.0	Group A (n=20): supervised exercise Group B (n=20): home-based exercise	Maximum mouth opening (MMO) Pain (VAS)	High disability	TMD of arthrogenic origin (disc displacement without reduction)	Jaw + neck exercise alone/part of a conservative regime. Home-based exercise	No follow-up

Carlson et al. 2001 [446]	44 patients 77% women Mean age: 34.6	Group A (n=23): Physical self-regulation training Group B (n=21): splint and self- care instructions	Pain intensity (Pain diary 3x/d VAS) Maximum interincisal opening with/without pain (mm) Depression scale (SCL-90-R) Somatization scale (SCL-90-R)	High disability	TMD of muscular origin	general jaw exercise alone or combined with neck exercise Home-based exercise	5 months
Carmeli et al. 2001 [447]	36 patients 72% women 19-43 years old Mean age: 30.3 ±5.5	Group A (n=18): soft flat plane occlusal repositioning splint Group B (n=18): manual mobilisation and active exercises	Active ROM for maximum mouth opening (mm) Pain levels (PPI)	Unclear	TMD of arthrogenic origin anterior (displaced temporomandibular discs)	Manual therapy plus jaw exercise	No follow-up
Coskun et al. 2016 [448]	33 patients 83% women Mean age: Group A: 31.6 ±11.5 Group B: 31.1 ±10.1	Group A (n=17): Kinesio taping + counselling and jaw exercise Group B (n=16): regimen of counselling and exercise alone	Active mouth opening (mm) TMJ pain at rest (VAS) Biobehavioural Questionnaire (Pain-related disability, pain intensity, depression level)	Low disability	TMD of mixed origin	Manual therapy + exercise	6 months
Craane et al. 2012 [449]	53 patients 74 % women Mean age: Group A: 36.6 ±15.5 Group B: 42.9 ±15.1	Group A (n=26): physical therapy Group B (n=27): education on the evaluation days only	Pain (VAS) Active and passive maximal mouth opening	Low disability	TMD of muscular origin	General Jaw exercise alone or in combined with neck exercise program	
Cuccia et al. 2010 [450]	50 patients 56% women Mean age: Group A: 40.6 ±11.03 Group B: 38.4 ±15.33	Group A (n=25): osteopathic manual therapy Group B (n=25): conventional conservative therapy	Pain intensity (VAS) Range of maximal mouth opening (mm)	Low disability	TMD of mixed origin	Manual therapy	2 months
Cunali et al. 2011 [451]	32 patients 56% women Mean age: Group A: 53 ±9 Group B: 44 ±12	Group A (n=16): mandibular exercises with mandibular advancement device therapy Group B (n=16): placebo therapy	Intensity of pain (NRS)	High disability	TMD not classified	Physiotherapy device	120 days
Dalen et al. 1986 [400]	19 patients 95% women Mean age: Group A: 29.6 ±12.82 Group B: 25.9 ±8.14	Group A (n=10): 8x biofeedback training Group B (n=9): received no feedback	Pain intensity (10-point scale)	Low disability	TMD of muscular origin	Physiotherapy device	6 months
De Felicio et al. 2008 [452]	28 patients 100% women Mean age: 31.46	Group A (n=10): OMT Group B (n=10): waiting list Group C (n=8): asymptomatic subjects	Joint noises Self-assessment of TMD severity signs and symptoms	Unclear	TMD of arthrogenic origin	jaw and neck exercise alone/ part of a conservative regime	135 days
De Felicio et al. 2010 [453]	40 patients 100% women 13-68 years old Mean age: Group A: 31 Group B: 29 Group C: 34 Group D: 27	Group A (n=10): OMT Group B (n=10): occlusal splint Group C (n=10): symptomatic control (no treatment) Group D (n=14): asymptomatic control (not randomised)	Mandibular range Muscular pain, TMJ pain TMJ noise	Low disability	TMD of mixed origin	General jaw exercise	120 days

De Paula Gomes et al. 2014 [454]	42 patients 71% women 18-40 years old Mean age: Group A: 30.10 ±5.80 Group B: 29.70 ±3.10 Group C: 30.87 ±6.20	Group A (n=14): massage group Group B (n=14): occlusal splint Group C (n=14): asymptomatic comparison group (not randomized)	Maximum active mouth opening	Low disability	TMD of mixed origin	Manual therapy	No follow-up
de Resende et al. 2019 [455]	89 patients 81% women Mean age: 28 ±9.34	Group A (n=24): OS Group B (n=21): manual therapy Group C (n=19): counselling therapy Group D (n=25): OS associated with C	Pain (VAS)	Low disability	TMD of mixed origin	Manual therapy + exercise	1 month
Delgado de la Serna et al. 2020 [456]	61 patients 59% women Mean age: Group A: 44.0 ±10.5 Group B: 42.5 ±12.0	Group A (n=31): physiotherapy and manual therapy group Group B (n=30): physiotherapy	Pain intensity NPRS Depressive symptoms (BDI-II) Mandibular ROM	Low disability	TMD of mixed origin with tinnitus concomitant	Manual therapy + exercise	6 months
DeVocht et al. 2013 [401]	80 patients 80% women >21 years old Mean age: Group A: 36.9 ±13.5 Group B: 38.0 ±12.7 Group C: 31.7 ±7.9 Group D: 33.1 ±11.4	Group A (n=20): "self-care" and "RIST" Group B (n=20): "self-care" and "Chiropractic AMCT" Group C (n=20): "self-care" and sham AMCT Group D (n=20): "self-care" only	TMD-related pain (NRS)	Mixed	TMD of muscular origin	Manual therapy targeted to the orofacial region. Home based exercise	n.a.
Espejo-Antúnez et al. 2016 [457]	42 patients 67 % women Mean age: 21.2 ±1.6	Group A (n=21): stretching technique Group B (n=21): stretching plus the ischemic compression	Active mouth opening (mm) Pain intensity (VAS)	Low disability	TMD of muscular origin	manual therapy targeted to the orofacial region. Home based exercise	No follow-up
Espí-López et al. 2020 [458]	16 patients 81% women Mean age: 29.9 ±12.4	Group A (n=8): MT plus ST-Experimental Group B (n=8): ST alone - Control	Pain perception (VAS)	Low disability	TMD of muscular origin	Manual therapy targeted to the orofacial region	135 days
Garrigos-Pedron et al. 2018 [459]	52 patients 83% women Mean age: Group A: 48.2 ±11.3 Group B: 46.0 ±9.1	Group A (n=26): Control group Group B (n=26): COG	Pain intensity (VAS) Maximal mouth opening (MMO)	Low disability	TMD of muscular origin	Manual therapy targeted to the orofacial region	12 weeks
Gavish et al. 2006 [460]	20 patients 100% women Mean age: Group A: 27.1 ±10.1 Group B: 27.3 ±5.9	Group A (n=10): exercise chewing group Group B (n=10): control (only support and encouragement)	Pain intensity (CPI)	Low disability	TMD of muscular origin	General Jaw exercise alone or in combined with neck exercise program	8 weeks
Giannakopoulos et al. 2018 [433]	45 patients 100% women 18-45 years old Mean age: Group A: 28.2 ±6.4 Group B: 24.7 ±3.4	Group A (n=23): sensorimotor training: RehaBite Group B (n=22): splint	Pain (CPI via GCPS)	Low disability	TMD of muscular origin	Physiotherapy device	No follow-up

Guarda-Nardini et al. 2012 [40]	30 patients 73%women 23-69 years old Mean age: 45.5	Group A (n=15): Botulinum toxin Group B (n=15): Fascial manipulation	Maximum pain level (VAS) Maximum mouth opening	Unclear (high disability)	TMD of muscular origin	Manual therapy targeted to the orofacial region	3 months
Haketa et al. 2010 [461]	52 patients 89% women 18 years and older Mean age: 37.6 ±14.9	Group A (n=28): Stabilization Splint Group B (n=24): Mobilization training for the jaw joint	Mouth opening with / without pain Maximum daily pain intensity (VAS)	Unclear (low disability)	TMD of arthrogenic origin anterior disc displacement without reduction	Manual therapy plus jaw exercise	8 weeks
Ibanez Garcia et al. 2008 [462]	57 patients 30% women 18-50 years old Mean age: 30.14 ±10.08	Group A (n=19): control group, placebo technique Group B (n=17): neuromuscular technique Group C (n=21): jones group strain / counterstain technique	Pain (VAS) Active mouth opening	Low disability	TMD of muscular origin	Manual therapy targeted to the orofacial region	3 weeks
Ismail et al. 2007 [463]	26 patients 88% women Mean age: Group A: 44.5 ±14.1 Group B: 41.7 ±16.5	Group A (n=13): Michigan splint Group B (n=13): physical	Maximum jaw opening (mm) Total pain intensity (VAS)	Low disability	TMD of arthrogenic origin	Manual therapy plus jaw exercise	1, 4, 8 and 12 weeks
Kalamir et al. 2013 [464]	46 patients 63% women 18-50 years old	Group A (n=23): intra-oral myofascial therapy education Group B (n=23): self-care and exercise	Pain at rest, upon opening and clenching (11-point scale) Maximum voluntary opening range (mm)	Low disability	TMD of muscular origin	Manual therapy targeted to the orofacial region	No follow-up
Kalamir et al. 2012 [415]	93 patients 56% women 18-50 years old Mean age: Group A: 35 ±6.7 Group B: 34 ±6.1 Group C: 35 ±5	Group A (n=31): waiting-list control Group B (n=31): intra-oral myofascial therapies Group C (n=31): Intra-oral myofascial therapy (IMT) + self-care	Resting pain (11-point GCPS) Interincisal opening range (mm)	Low disability	TMD of muscular origin	Manual therapy targeted to the orofacial region	6 months
Klobas et al. 2006 [465]	94 patients 71% women Mean age: Group A: 38.5 Group B: 36.2	Group A (n=25): jaw exercise group Group B (n=30): control group	Maximum active mouth-opening capacity, mean value (mm) Pain on mandibular movement (%) Clicking (%)	Unclear	TMD of mixed origin and chronic whiplash-associated disorders	General jaw exercise	6 months
Komiyama et al. 1999 [416]	60 patients	Group A (n=20): Control group Group B (n=20): cognitive behavioural treatment intervention group Group C (n=20): cognitive behavioural treatment intervention with posture correction group	Pain-free unassisted mouth opening (mm) Pain intensity (VAS)	Low disability	TMD of muscular origin	Posture Correction	12 months
Kraaijenga et al. 2014 [466]	96 patients 86% women 17–73 years old Mean age: 38	Group A (n=46): TB device Group B (n=50): standard physical therapy	Pain (VAS) Maximum interincisal (mouth) opening (MIO)	Unclear	TMD of muscular origin	Physiotherapy device	6 weeks

La Touche et al. 2013 [467]	32 patients 66% women Mean age: Group A: 33.19 ±9.49 Group B: 34.56 ±7.84	Group A (n=16): mobilization of the upper cervical Group B (n=16): sham therapy	Depression (BDI) Pain intensity (VAS)	Unclear (high disability)	TMD of muscular origin	Manual therapy mobilization of cervical spine	8 months
Machado et al. 2016 [251]	102 patients	Group A (n=20): healthy control group Group B (n=21): laser + oral-motor exercises Group C (n=22): OMT and OM-exercises Group D (n=21): LLLT placebo + OM-exercises Group E (n=18): LLLT	TMD severity Orofacial myo-low disability status	Low disability	TMD of mixed origin	General jaw exercise alone or combined with other exercise program	3 months
Magnusson et al. 1999 [468]	26 patients gender not stated Mean age: Group A: 37 Group B: 32	Group A (n=14): Michigan splint Group B (n=12): therapeutic jaw exercises	Maximal jaw opening capacity Pain on movement of the jaw Joint sounds	Low disability (+5 subjects with probably high disability pain in combined treatment group)	TMD of muscular origin	General Jaw exercise alone or in combined with neck exercise program	6 months
Maloney et al. 2002 [469]	35 patients 96% women Mean age: 44.5 ±17.1	Group A (n=10): Thera bite Group B (n=7): WTD Group C (n=7): control group	Mandibular ROM Pain level (NRS)	High disability	TMD of muscular and/or arthrogenic origin	Physiotherapy device	4 weeks
Maluf et al. 2010 [470]	28 patients 100% women Mean age: Group A: 30.0 ±4.3 Group B: 30.08 ±7.07	Group A (n=14): global posture Group B (n=14): static stretching	Severity symptoms for TMJ pain (VAS)	Low disability	TMD of muscular origin	Posture Correction	8 weeks
Melo et al. 2020 [419]	89 patients 82% women Mean age: 28 ±9.34	Group A (n=25): OSCS Group B (n=24): OS Group C (n=21): MT Group D (n=19): CS	Pain (VAS) HADS, BAI and State-Trait Anxiety Inventory (STAI)	Low disability	TMD of mixed origin	Manual therapy	1 month
Michelotti et al. 2004 [387]	70 patients 89% women Mean age: Group A: 31.8 ±13.0 Group B: 28.2 ±8.8	Group A (n=34): education only Group B (n=36): education + self-supportive exercise program	Pain intensity (VAS) Pain on chewing (VAS Pain-free maximal jaw opening (mm)	Low disability	TMD of muscular origin	General Jaw exercise alone or in combined with neck exercise program	3 months
Mulet et al. 2007 [471]	45 patients 95% women Mean age: Group A: 23.4 ±2.1 Group B: 25.1 ±2.3	Group A (n=20): self-care Group B (n=22): self-care + 6x6 exercises	Self-report pain intensity in masticatory muscles (NGRS)	Low disability	TMD of muscular origin	General Jaw exercise alone or in combined with neck exercise program	1 month
Nagata et al. 2018 [472]	61 patients 82% women Mean age: 49.6 ±25	Group A (n=30): conventional treatment (cognitive behavioural therapy for bruxism + education) Group B (n=31): conventional treatment + manipulation	Mouth-opening limitation (mm) Orofacial pain (NRS) TMJ sounds	Low disability	TMD of muscular and/or arthrogenic origin	Manual therapy targeted to the orofacial region	10 weeks

Nambi et al. 2020 [473]	30 patients 18-40 years old	Group A (n=15): Maitland joint mobilization Group B (n=15): home based training	Pain (NPRS) Maximal mouth opening (MMO)	Unclear	TMD of mixed origin following cervicofacial burn	Manual therapy	3 months
Nascimento et al. 2013 [474]	20 patients 100% women 25-56 years old Mean age: 41.5 ±10.1	Group A (n=10): 8xcycle of anaesthetic blockages of auriculotemporal Group B (n=10): anaesthetic blockage + physical therapy (massage + muscular stretching exercises)	Maximal mouth opening and jaw protrusion (mm) Pain (VAS)	Low disability	TMD of arthrogenic origin	Manual therapy plus jaw exercise	2 months
Packer et al. 2014 [475]	32 patients 100% women Mean age: Group A: 23.5 (21.3-25.6 years old Group B: 26.0 (22.6-29.4 years old)	Group A (n=16): upper thoracic manipulation Group B (n=16): thoracic region with no therapeutic effect	Vertical mouth opening (mm) Pain (VAS, Algometer)	Low disability	TMD of mixed origin	Manual therapy	48-72 hours
Patil et al. 2017 [476]	36 patients 64% women Mean age: Group A: 32.9 ±12.57 Group B: 34 ±7.4	Group A (n=18): TENS therapy Group B (n=18): HE therapies	Muscle pain (VAS) Maximum mouth opening (mm)	Unclear	TMD (not classified, osteoarthritis excluded)	general jaw exercise home-based exercise	4 weeks
Reynolds et al. 2019 [477]	50 patients 86% women Mean age: Group A: 32.2 ±11.3 Group B: 38.8 ±14.8	Group A (n=25): Cervical Thrust Joint Manipulation plus education + exercise Group B (n=25): Sham Manipulation plus education + exercise	Jaw range of motion (ROM) Pain (NPRS)	Low disability	TMD of mixed origin	Manual therapy + exercise	n.a.
Rodriguez-Blanco et al. 2015 [478]	60 patients 68% women Mean age: 35 ±11.22	Group A (n=30): suboccipital muscle inhibition technique Group B (n=30): neuromuscular technique over the masseter muscles and passive hamstring muscle stretching	Vertical mouth opening	Low disability	TMD of mixed origin	Manual therapy	n.a.
Sherman et al. 1997 [479]	21 patients 86% women	Group A (n=10): relaxation training Group B (n=10): rested for an equivalent time	Pain (MPQ-SF)	Unclear (low disability)	TMD of mixed origin	General jaw exercise	No follow-up
Tavera et al. 2012 [480]	175 patients 80% women Mean age: Group A: 37.3 ±10 Group B: 38.0. ±11.0 Group C: 36.3 ±13.0	Group A (n=67): TMDes (ear system) device Group B (n=71): stabilization splint Group C (n=37): jaw exercise + heat application for 10 min	Pain (VAS)	Low disability	TMD of mixed origin	General jaw exercise	3 months
Taylor et al. 1994 [481]	15 patients 93% women No information given	Group A (n=8): sham treatment Group B (n=7): mobilisation	Changes in mandibular movement capacity	Low disability	TMD of muscular and/or articular origin	Manual therapy targeted to the orofacial region	No follow-up
Tegelberg et al. 1988 [482]	60 patients 85% women Mean age: Group E: 48 Group C: 49	Group E (n=28): physical training Group C (n=32): comparison	Mean maximum voluntary mouth opening (mm)	Unclear	TMD of mixed origin and rheumatism	General jaw exercise	3 years

Tuncer et al. 2013	40 patients 78% women 18-72 years old Mean age: Group A: 34.8 ±12.4 Group B: 37.0 ±14.6	Group A (n=20): home physical therapy Group B (n=20): MT	Pain intensity at rest, at stress (VAS) Pain-free maximum mouth opening (mm)	Low disability	TMD of mixed origin	Manual therapy + exercise	No follow-up
Wänman et al. 2020 [483]	90 patients 70% women Mean age: 39.2 ±15.2	Group A (n=30): bite splint Group B (n=30): HE Group C (n=30): supervised exercise program	TMJ clicking sounds % Pain in jaw Severity of jaw pain (0-50) Depression sum mean Somatisation sum mean Jaw opening (mm)	Low disability	TMD of arthrogenic origin (disc displacement with reduction)	Jaw + neck exercises alone/part of a conservative regime. Home-based exercise	3 months
Wright et al. 2000 [484]	60 patients 85% women 18-56 years old Mean age: Group A: 32.7 Group B: 30.8	Group A (n=30): posture training and TMD self-management instructions Group B (n=30): TMD self-management instructions only	Pain (modified SSI) Maximum pain-free opening	Low disability	TMD of muscular origin	Posture Correction	4 weeks
Yoshida et al. 2011 [485]	148 patients 100% women 19-75 years old Mean age: Group A: 41 Group B: 39	Group A (n=74): exercises of the mandibular condyle Group B (n=74): control group	MMO (mm)	Low disability	TMD of arthrogenic origin (internal derangement of the TMJ)	jaw and neck exercises alone/ part of a conservative regime	No follow-up
Yu et al. 2016 [429]	168 patients 89% women Mean age: 32.5 ±9.8	Group A (n=42): Michigan Splint Group B (n=42): manipulative and physical therapies Group C (n=42): splint +manipulative and physical therapies Group D (n=42): control (consulting only)	Spontaneous masticatory muscle pain (VAS) Pain-free maximum active mouth opening (mm)	Low disability	TMD of arthrogenic origin (Disc displacement without reduction)	Manual therapy plus jaw exercise	3 months

3.5.4.2 Characteristics of the studies' population

3.5.4.2.1 TMD diagnoses of the participants in the included studies

There was a substantial variety in the clinical performances and analyses of participants with TMD among the included studies. 27 [40, 387, 397, 401, 433, 440-443, 446, 449, 457-460, 462, 464, 466-468, 470, 471, 484, 486, 487] of the studies graded the effectiveness of the physiotherapy interventions in myogenous TMD. Nine studies examined the effectiveness in patients with TMD of arthrogenic origin [429, 445, 447, 452, 461, 463, 474, 483, 485], and 22 studies assessed the effectiveness in patients with mixed diagnoses of TMD (including both myogenous and arthrogenous TMD) [251, 419, 444, 448, 450, 451, 454-456, 465, 473, 475, 476, 479, 480, 482, 488, 489]. Included in the mixed TMD group, one trial investigated TMD with tinnitus concomitant [456] while other trails included mixed TMD and chronic whiplash-associated disorder [465], mixed TMD following cervicofacial burn [473] and mixed TMD together with rheumatic [482]. Two studies did not classify the type of TMD. The Figure 53 shows the type of TMD of the subjects from the included studies of physiotherapy.

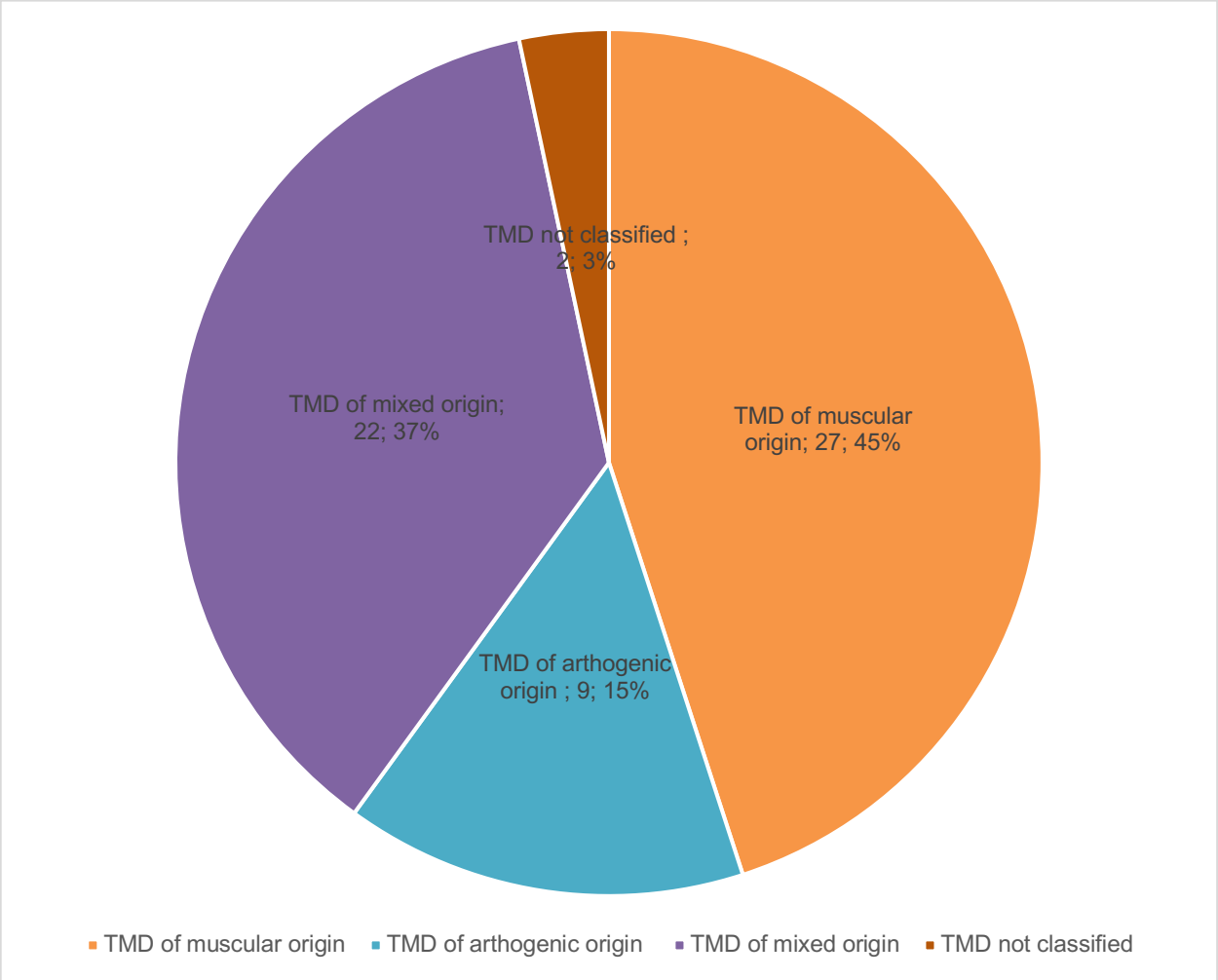


Figure 53: Pie chart presenting the different TMD diagnoses from the included studies on physiotherapy therapy (X) with the number of studies included (Y) and the percentage (Z); (X;Y;Z).

3.5.4.2.2 Grade of chronification

The degree of TMD pain chronification of the subjects formed the focus of the present work. The following categories were formed for physiotherapy interventions (Figure 54):

- Patients with evidence of a low disability (acute or acute/persistent) pain.
- Patients with evidence of high disability pain
- Patients with different degrees of chronicity, where results were presented separately by the authors (referred to below as: mixed)
- Patients with slight evidence of low disability pain (referred to below as: unclear (low disability))
- Patients with slight evidence of high disability pain (referred to below as: unclear (high disability))
- Patients with limited or no degree of chronicity (referred to below as: unclear)

Overall, the majority of participants for physiotherapy treatment were suffering from low disability pain according to the pain indications [251, 387, 416, 419, 429, 433, 440, 441, 444, 448-450, 453-460, 462-464, 468, 470-472, 474, 475, 477, 478, 480, 481, 483-486, 489]. The second largest group of participants of the included RCTs were of high disability pain [442, 443, 445, 446, 451, 467, 469]. The study of Guarda-Nardini et al. 2012 [40] was rated as unclear (high disability) as the study recruited their-participants from tertiary care. It was unclear which pain characteristics the included patients had in the five studies despite contact being made with each of the authors. Finally, three RCTs included a mixed population with low disability and high disability pain [223, 397, 401]. The studies of Haketa et al. 2010 [461] and Sherman et al. 1997 [479] were rated as unclear (low disability) as both studies excluded participants who took medication on a regular basis.

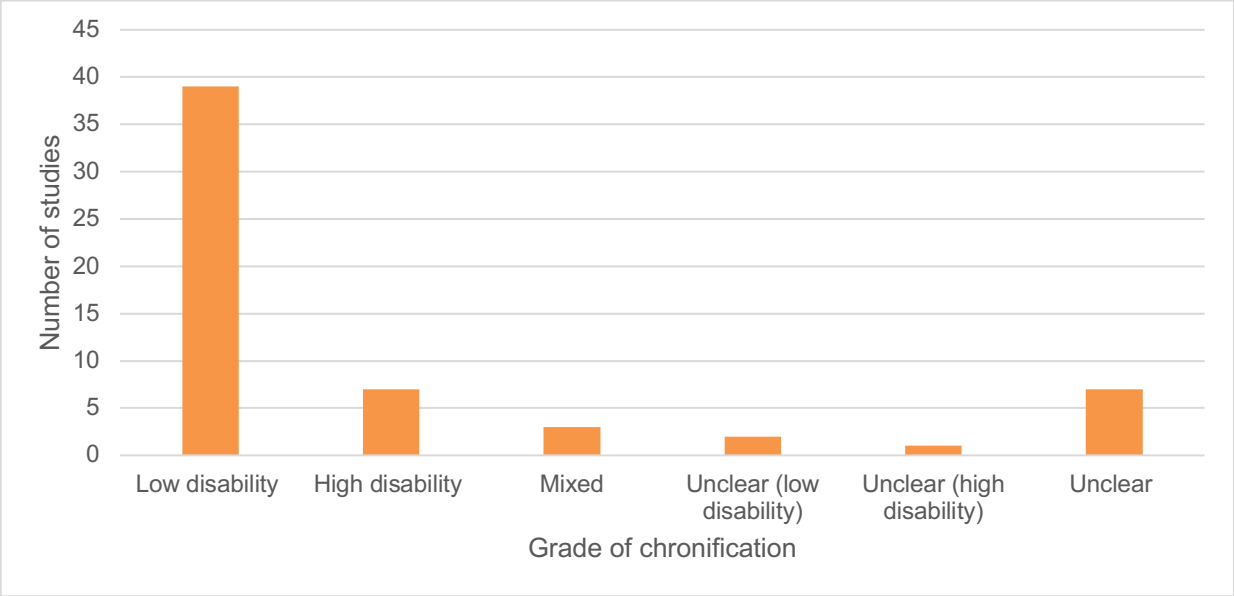


Figure 54: Grade of chronification of the included studies for physiotherapy

The participants of the 59 included RCTs were classified according to the indications mentioned above (Figure 55). Several of the studies examined provided multiple indications of the subjects' level of chronicity. Consequently, the indications could support or contradict each other. For this reason, a priority list was used for the final decision on classification. In the following table the priorities of the indications, together with the studies that investigated them, are displayed below:

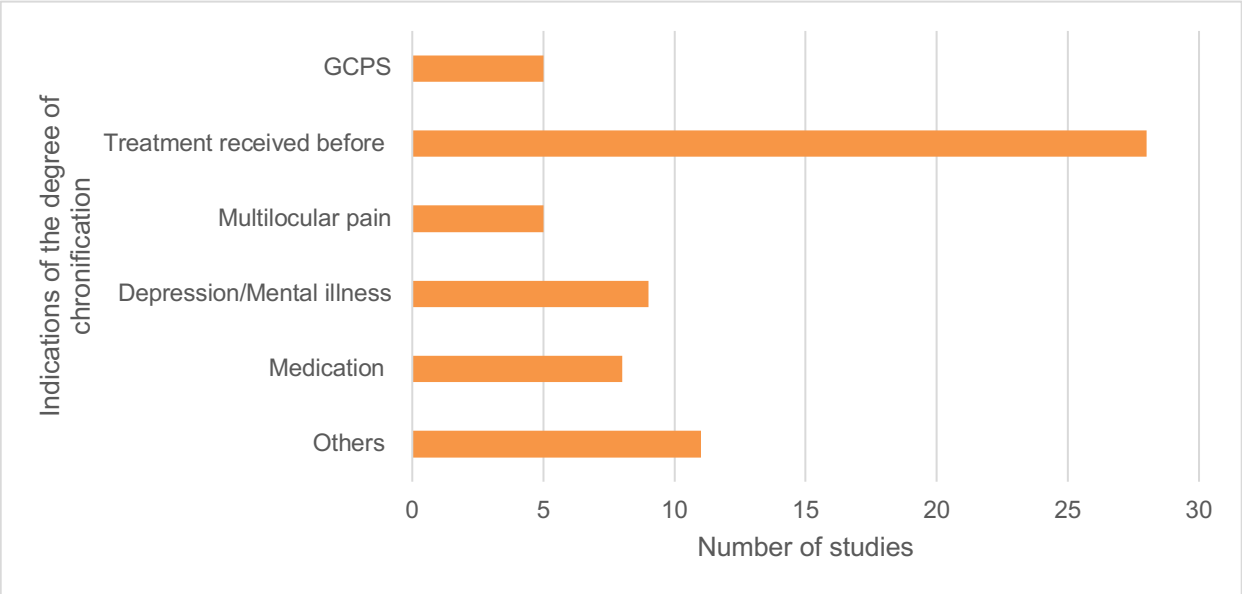


Figure 55: Indications of the degree of chronification, found in the included studies for Physiotherapy; GCPS= Graded Chronic Pain Scale

Table 28: Indications of the degree of chronification, found in the included studies for physiotherapy

Indications	Low disability	High disability	Mixed	Unclear (low disability)	Unclear (high disability)
Graded chronic pain scale	Giannakopoulos 2018 Kalamir 2012 Wänman 2020		Brandao 2020 Brachado 2018		
Treatment received before	Calixtre 2019 Craane 2012 Cuccia 2010 De Felicio 2010 Dalgado 2020 Gomes 2014 Espejo-Antúnez 2016 Garrigos-Pedron 2018 Gavish 2006 Ibanez Garcia 2008 Ismail 2007 Komiyama 1999 Machado 2016 Magnusson 1999 Maluf 2010 Michelotti, 2004 Nascimento 2013 Packer 2014 Rodriguez-Blanco 2015 Tavera 2012	Capan 2017 Maloney 2002	DeVocht, 2013 Brachado 2018		

Indications	Low disability	High disability	Mixed	Unclear (low disability)	Unclear (high disability)
	Tuncer 2013 Wright 2000 Yu 2016				
Multilocular pain	Craane 2012 Espejo-Antúnez 2016 Packer 2014 Rodriguez-Blanco 2015				Carlson 2001
Depression or mental illness	Cuccia 2010 Garrigos-Pedron 2018 Ibanez Garcia 2008 Kalamir 2012 Michelotti, 2004 Nagata 2018 Rodriguez-Blanco 2015 Tuncer 2013 Yu 2016	Berguer 2008 Capan 2017	Brachado 2018		
Analgetic misuse	Craane 2012 Espejo-Antúnez 2016 Gavish 2006 Mulet 2007 Reynolds 2019 Rodriguez-Blanco 2015	List 1992	Brachado 2018	Haketa 2010 Melo 2020	
Others	Coskun 2016 Gomes 2014 Mulet 2007 Nagata 2018 Reynolds 2019				Benli 2020 Burgess 1988 Dalen 1986 La Touche 2013

3.5.4.2.3 Health care / study setting

23 of the 42 studies could be assigned to tertiary care. This corresponds to a sample of 1780 subjects, but independent of control groups, the diagnostic instrument used, the outcomes measured and the study duration. The subjects were mainly treated in university clinics. Another 356 subjects from seven studies came from specialized TMD clinics. Another 391 patients from seven studies were recruited from the general population or from dental practices and were thus assigned to primary care. Two trials did not have a description of the care level from which the subjects originated. Three studies recruited patients from primary and tertiary care.

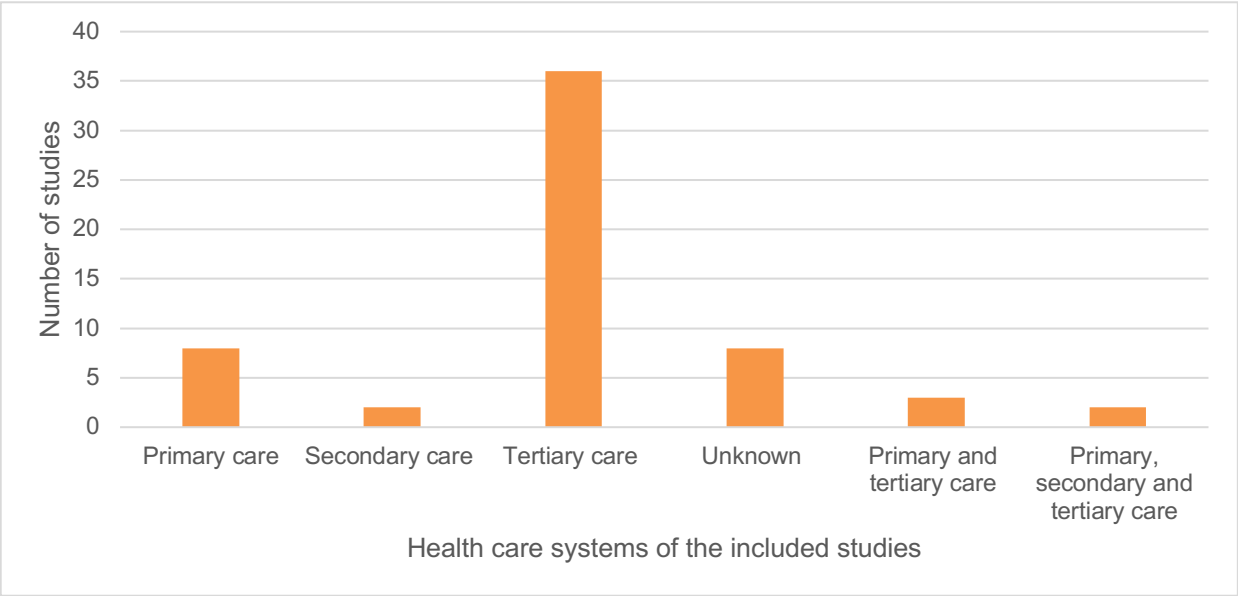


Figure 56: Recruitment of subjects in the included studies of physiotherapy

3.5.4.3 Characteristics of the interventions

3.5.4.3.1 Outcomes

3.5.4.3.1.1 Primary outcome -pain at rest

With regard to measuring pain intensity, the majority used the VAS [223, 387, 415, 416, 419, 429, 440-442, 444-446, 448, 455, 457-459, 461-463, 466, 467, 470, 474-476, 480, 490]. Other measuring tools for pain intensity were: the GCPS [397, 415, 433], the MPQ [443, 479], the pain-physiopathology instrument (PPI) [447], the 10-point scale , the 11-point scale [464], the NRS [401, 451, 456, 469, 471-473, 477, 483], Pain on mandibular movement (%) [465], the modified SSI [484] and the severity signs and symptoms of pain [452, 453]. Furthermore, seven RCTs did not report pain intensity [251, 454, 468, 478, 481, 482, 485].

3.5.4.3.1.2 Secondary outcomes

MMO was measured by 36 studies [223, 387, 429, 441, 445-450, 454, 457, 459, 461-466, 468, 469, 472-478, 482-487, 489]. Ten studies used different instruments to measure pain upon palpation [251, 429, 443, 446, 448, 452, 453, 460, 465, 468]. Joint noise was measured by four RCTs [452, 453, 465, 483]. Depression was measured using the RCD [397, 448], SCL-90-R [446] and BDI [456, 467] by five trials. Somatization was measured with the SCL-90-R by one trial only [446].

3.5.4.3.2 Diagnostic instruments

41 studies used the RDC/TMD established by Dworkin and LeResche to categorize patients at risk of developing TMD [40, 223, 251, 387, 397, 401, 415, 416, 419, 429, 433, 440, 441, 444, 446, 448, 449, 451-453, 455-460, 463, 464, 467, 469, 471, 472, 474-478, 480, 483, 484, 490], three studies used the Helkimo index [465, 470, 491], one RCT used the

diagnostic based on the criteria of Laskin [443], two studies were using the MRI [445, 461] as diagnostic criteria, while others were using the Fonseca Patient History Index [492] or the Temporomandibular index [450]. The last ten studies used either their individual diagnostic criteria [442, 447, 462, 481, 482, 485] (based on signs and symptoms of the participants) or gave no information relating to the diagnostic method [466, 468, 473, 479].

3.5.4.3.3 Physiotherapy interventions

The included 59 RCTs can be divided into five different categories according to the intervention type employed: jaw exercise by itself or combined with neck exercise program, MT (directed to orofacial region or cervical spine), MT and jaw exercise, physiotherapy device for TMD and posture corrections (Figure 57):

We took a closer look at the diagnosis of TMD (myogenic, arthrogenic or mixed TMD) and the targeted treatment for each category. Eleven RCTs [251, 387, 397, 440, 443, 446, 449, 460, 468, 471] looked at the effect of general jaw exercises alone or combined with other therapies for myogenous TMD. For example, Barbosa et al. 2019 [440] and Machado et al. 2016 compared exercise therapy to stimulated laser or in the case of Machado et al. 2016 to active laser [251]. Cunali et al. 2011 [451] used jaw exercise training to improve the advancement device against placebo. Furthermore, five other [387, 397, 449, 460, 471] RCTs used self-care or education as a control intervention, while Magnusson et al. 1999 [468] and Carlson et al. 2001 [446] measured exercise therapy against splint therapy and Burgess et al. 1988 [443] compared general exercise to reflexive inhibition. Four trails [445, 452, 483, 485] that assessed participants suffering from TMD of arthrogenic origin focused on jaw and neck exercises solitary or combined with other treatments. Yoshida et al. 2011 [485] focused on exercise therapy alone, Felicio et al. 2010 looked at the effectiveness of orofacial myofunctional therapy compared to a waiting list and the studies of Capan et al. 2017 [445] and Wänman et al. 2020 [483] compared exercise to home-based exercise alone. Six studies [453, 465, 476, 479, 480, 482] looked at exercise alone or as part of a general therapeutic regimen to treat patients with mixed TMD. The treatment was compared to splint therapy [453], rehabilitation program [465], TENS therapy [476], resting therapy [479], stabilization splint and TMDes (ear system device) [480] or sham therapy [482].

Furthermore, five trials [429, 447, 461, 463, 474] looked at the combined effect of MT plus exercise for patients suffering from arthrogenous pain. Four authors investigated MT and exercises combined with splint therapy [429, 447, 461, 463] while Nascimento et la. 2013 [474] compared MT combined with exercise with anaesthetic blockage of the auriculotemporal nerve with bupivacaine. Six RCTs investigated the effect of MT in combination with exercises in patients suffering of mixed TMD. Calixtre et al. 2019 [444], Tuncer et al. 2013, Delgado de la Serna et al. 2020 [456] and Reynold et al. 2019 researched the specific effect of orofacial and cervical MT combined with stretching

techniques for the masticatory and neck muscles compared with home physical therapy [456, 489], sham manipulation [477] or no therapy [444]. Two studies compared MT in combination with exercise to either splint therapy [455] or counselling [448].

Twelve RCTs [401, 441, 442, 457-459, 462, 464, 472, 481, 486, 493] observed MT procedures, like facial manipulation versus botulinum toxin [40], stretching versus stretching plus the ischemic compression [457], MT versus splint therapy [401, 458], aromatherapy versus massage with sweet almond oil or no treatment [441], MT versus sham interventions [442, 462, 481], MT in the orofacial and cervical region versus treatment only in the cervical region [459] or intraoral myofascial therapy versus waiting list [415], and self-care education and exercises [464, 472] for people with myogenous TMD. La Touche et al. 2013 [467] performed a more precise methodology directed to the cervical spine to treat patients with cervico-craniofacial pain compared to sham treatment. Seven studies [223, 419, 450, 454, 473, 475, 478] investigated MT alone compared to laser [223], conventional conservative therapy [450], splint [419, 454], home based training [473], suboccipital muscle inhibition technique [478] or sham technique [475] for treating patients with mixed TMD.

Four studies [433, 466, 469, 491] used a physiotherapy device to treat TMD of mostly muscular origin. The devices and the control group differed for each study. Two trials made use of Therabite device versus regular physiotherapy [466] or wooden tongue depressors therapy [469]. One author compared RehaBite device versus splint therapy [433].

Furthermore, one RCT [400] made use of biofeedback versus no treatment and finally, three RCTs [416, 470, 484] evaluated the effectiveness of posture correction exercises for patients with low disability pain of myogenic origin. All three studies showed positive results for postural exercises for improving the symptoms of muscular TMD.

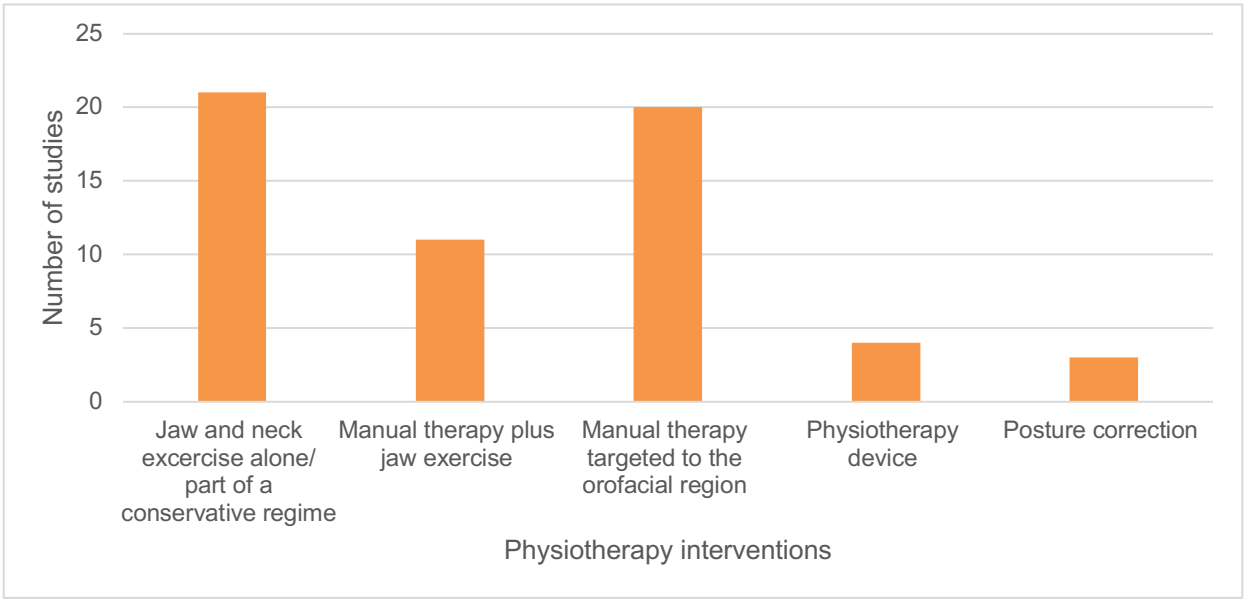


Figure 57: Types of physiotherapy in the included studies of physiotherapy

3.5.4.3.4 Controls

As briefly described above, the controls of the included studies on physiotherapy interventions were very different. Splint therapy and placebo therapy were the main controls. psychosocial interventions (CBT, counselling, education, and self-care) were also a popular intervention, while drug treatment and laser therapy were rarely used compared to physiotherapy. Other physiotherapies included TENS therapy, rehabilitation programme, standard physiotherapy, wooden tongue depressor therapy, neuromuscular technique, stretching or rest technique. Five RCTs did not use any treatment, while conventional therapy and waiting list were used in only two studies. Figure 58 demonstrates the number of studies and the according control groups used.

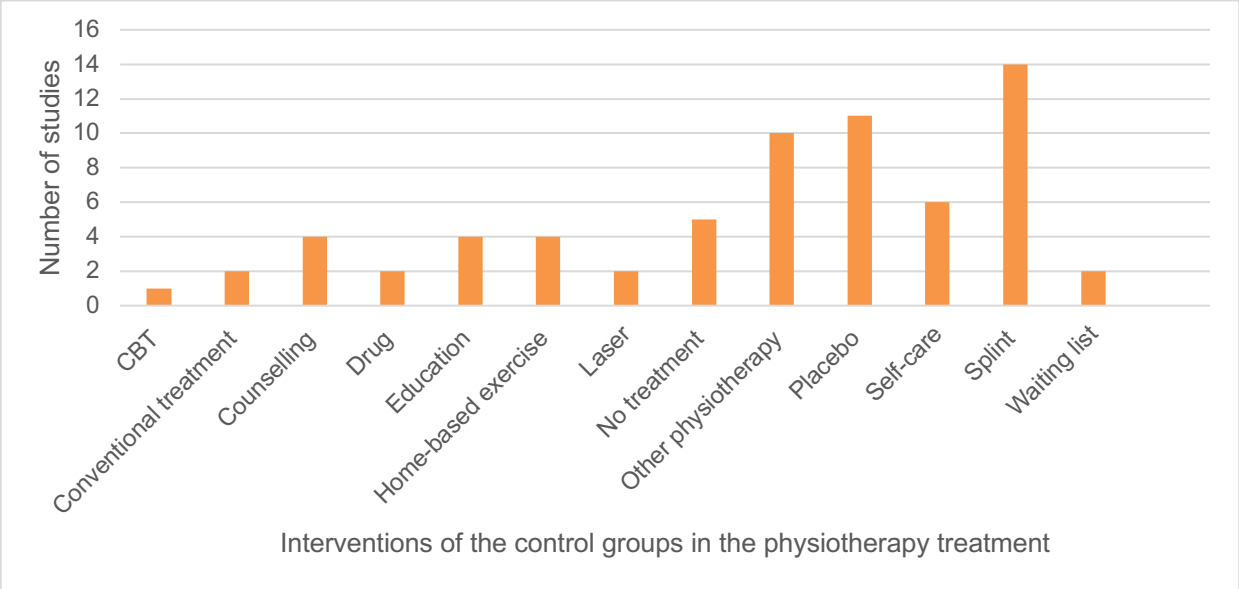


Figure 58: Control groups used in the included studies for Physiotherapy interventions

3.5.5 Excluded studies

67 studies were excluded for which reasons are declared in the corresponding table (Appendix II, section Characteristics of excluded studies).

3.5.6 Assessment of the methodological quality of the included studies

The risk of bias according to the Cochrane Collaboration of the included studies is presented in figures 59 and 60. Assessments of (risk of bias) were fulfilled by two independent reviewers. We followed the guidelines established by the Cochrane Collaboration to perform assessments of risk of bias. Most of the studies did not include items with important methodological indicators of risk of bias, such as randomization, allocation concealment, blinding, and ITT. For instance, study flaws regarding patient selection were mainly related to description and appropriateness of the randomization procedure and concealment of

allocation, with only 67.8% and 15.3% of these studies meeting these criteria. For blinding of participants, a score of 67.8% in low risk of bias was observed. We considered this category as not relevant in the cases of different therapies administered. Three studies failed the criteria of risk of bias blinding of outcome assessment [453, 480, 493], as the examiners were not blinded, while 66.1% scored low risk of bias for this category. Despite the fact that the adequate handling of dropouts is considered an important method used to prevent bias in data analysis, four RCTs reported incomplete outcome data [433, 469, 480, 494], 72.9% was rated as at low risk of bias and five studies used ITT analysis [415, 456, 461, 472, 483]. In the trial of Giannakopoulos et al. 2018 [433] the withdrawals were not equally balanced and the causes of drop out were directly related to the treatment [433]. Maloney et al. 2002 [469], Tavera et al. 2012 [480] and Wright et al. 2000 [484] poorly described about the dropouts. Furthermore, Maloney et al. 2002 [469] reported insufficient information for the selective reporting category and was supported by the “Therabite Corporation”, which could lead to a risk of bias. For this reason, we marked the study with unclear risk of bias for selective reporting and high risk for other bias. 98.3% of the included studies reported low risk of bias for selective reporting and 15.3% of the included RCTs for other bias.

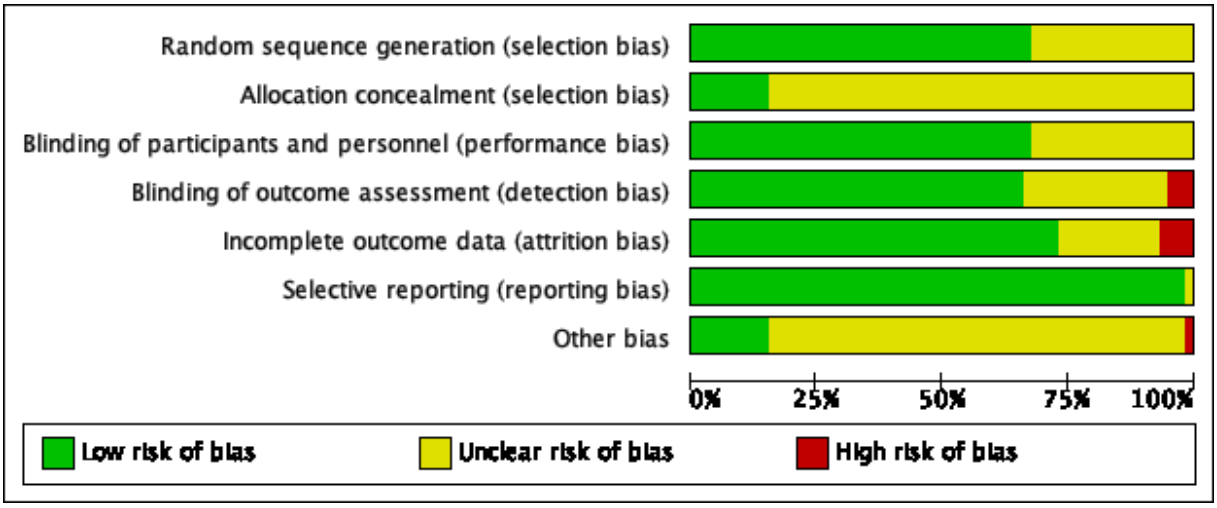


Figure 59: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

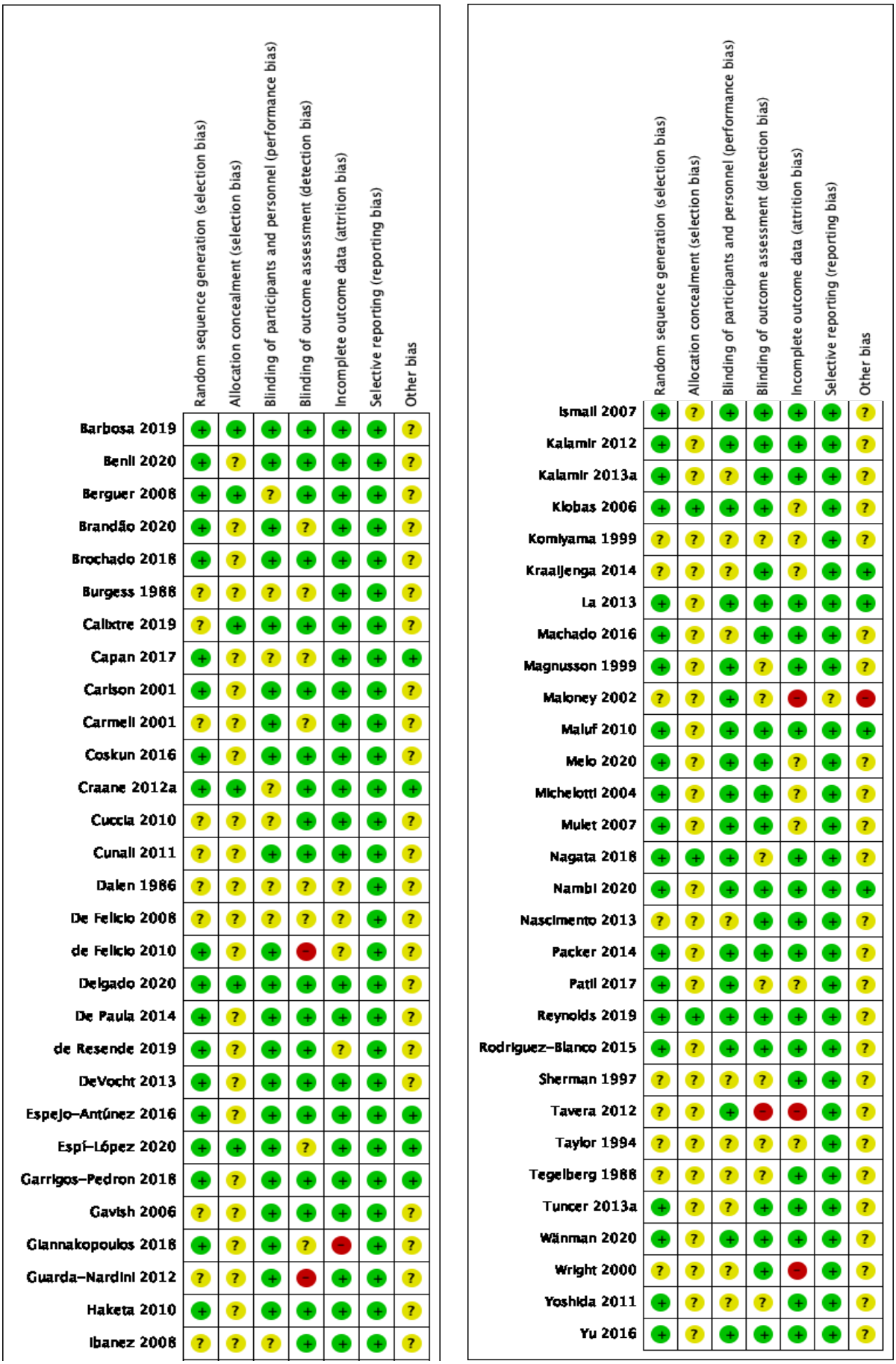


Figure 60: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

3.5.7 Results of the quantitative synthesis of the included studies (Meta-analysis)

The meta-analysis for physiotherapy treatment was very difficult to compile because the included studies used different physiotherapy interventions and diverse control groups. This led to very heterogeneous results and a low number of trials using single comparisons. For this reason, in this part of the paper we included the main comparative measures 1. Physiotherapy vs. any other therapy, 2. Physiotherapy + tx (other treatment) vs. other treatment, 3. Physiotherapy vs. placebo 4. Jaw exercise vs. other treatment 5. MT + exercise vs. control, 6. MT vs. control 7. Physiotherapy vs. splint therapy 8. Physiotherapy vs. psychosocial interventions with sensitivity analysis, although the heterogeneity was extensive. We were unable to compile an analysis for posture corrections and physiotherapy device as the studies were too heterogenic to conduct a meta-analysis. Statistically significant or not statistically significant but clinically relevant results are described below in detail. For the sake of comprehensiveness, the remaining forest plots with reduced analysis (minimum three studies) with further results this study are presented in Appendix (IX, Physiotherapy).

For the meta-analysis, 43 RCTs were selected. Out of the 59 included studies that passed full-text screening, a total of 16 studies were excluded for the quantitative comparison. The reasons for exclusion were as follows:

1. Missing data on the outcomes [251, 397, 452, 479-481, 485, 491]
2. Data collection/ presentation was different from the other included studies [469]
3. RCTs compared physiotherapy versus another physiotherapy intervention [445, 459, 466, 470, 473, 478, 489].

A tabular overview of the statistically significant results for the pain group with low disability and with high disability is presented in 3.5.8 for the reduction of pain intensity displayed in Table 29 and in Table 30 for MMO.

A SMD of zero indicates that the intervention group and the control group have equal effects. For pain reduction, an improvement is associated with lower values in the outcome measure. SMDs less than zero indicate that the intervention group is more effective than the control group. Therefore, a negative direction with lower values corresponds to better performance of the intervention group. Conversely, for MMO improvement, improvement is associated with higher values on outcome measures. A positive direction with higher values corresponding to better performance of the intervention group under study [200].

The IMMPACT guideline states that a 30% pain reduction in chronic pain is necessary to distinguish placebo from verum [201]. To obtain the clinical significance, the author added a small comment on each forest plot obtaining the data from the pain reduction from the baseline compared to the follow up time.

3.5.7.1 Comparison: Effectiveness of physiotherapy treatment in comparison to other treatments on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.5.7.1.1 Primary outcome parameter: pain intensity

3.5.7.1.1.1 Short-term efficacy (treatment duration up to six months)

The results of the meta-analysis of the data from 634 participants across 16 studies is presented in Figure 61: no statistically significant bigger reduction in total pain scores using physiotherapy versus other treatments could be observed. The overall effect for pain significantly favoured physiotherapy (n=16 studies [n=308 for Group A, and n=328 for Group B], SMD=-0.02; 95% CI [-0.25, 0.21]; p=0.85), with moderate heterogeneity (I^2=52%). Subgroup analysis showed no statistically significant bigger differences between physiotherapy and other treatment of patients suffering from low disability pain (n=9 studies [n=209 for Group A, and n=221 for Group B], SMD=-0.10; 95% CI [-0.29, 0.09]; p=0.32, I^2=0%), high disability pain (n=2 studies [n=28 for Group A, n=34 for Group B], SMD=0.01; 95% CI [-0.49, 0.51]), mixed pain (n=3 studies [n=35 for Group A, n=37 for Group B], SMD=0.14; 95% CI [-0.32, 0.60]; p=0.55) or unclear pain (n=2 studies [n=36 for Group A, n=36 for Group B], SMD=0.28; 95% CI [-2.07, 2.63]; p=0.81, I^2=95%).

For the studies of Craane et al. 2012a, Cuccia et al. 2010, de Resende et al. 2019, Haketa et al. 2010, Kalamir et al. 2013a, Melo et al. 2020, Yu et al. 2016, Brochado et al. 2018, DeVocht et al. 2013, Magnusson et al. 1999, and Carmeli et al. 2001 a clinical significance of 30% pain reduction in the intervention group was observed. The other part of the studies of Gavish et al. 2006, Wänman et al. 2020, Carlson et al. 2001, Guarda-Nardini et al. 2012 and Patil et al. 2017 did not have a clinical significance in pain reduction.

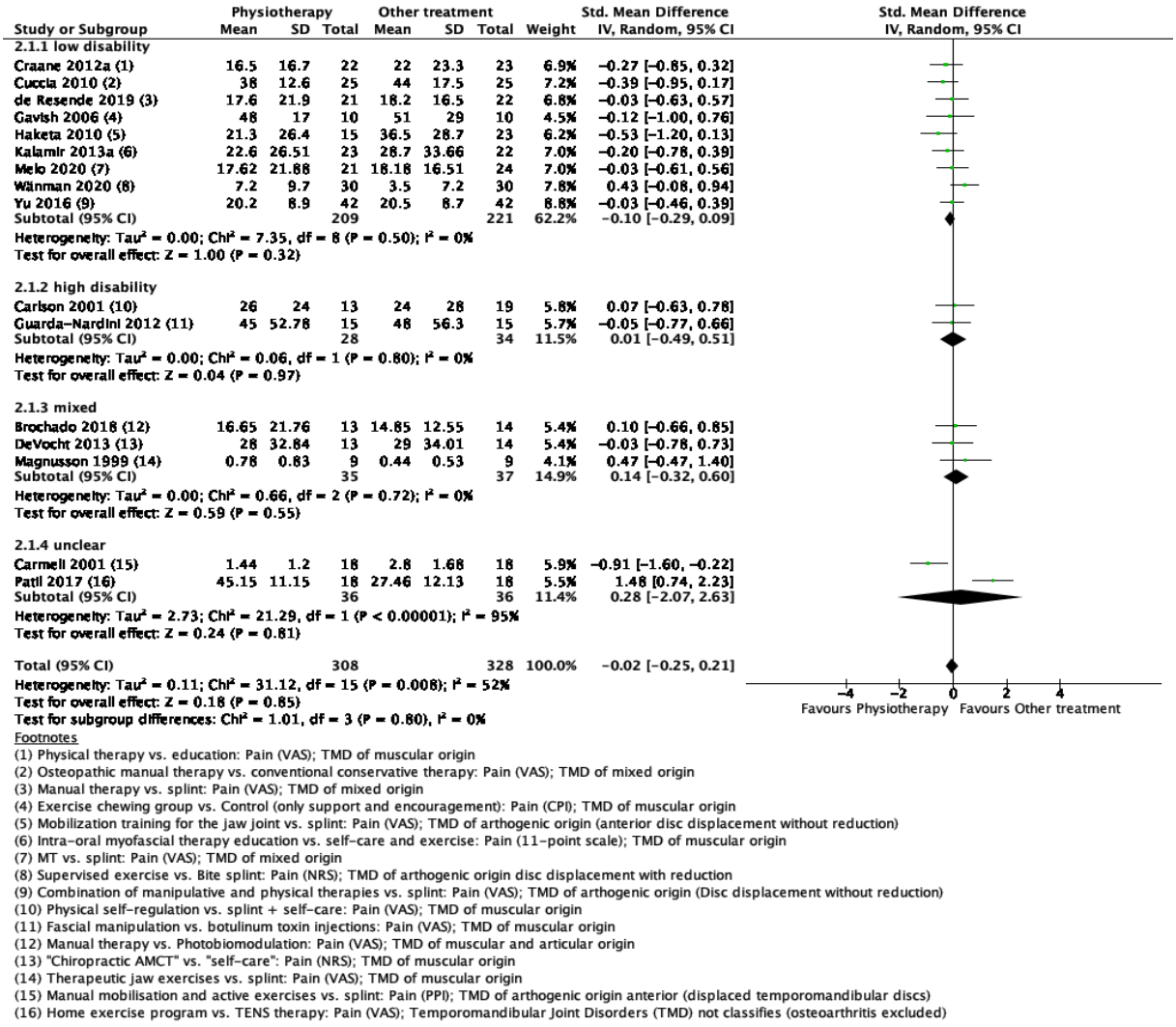


Figure 61: Physiotherapy versus other treatment (Outcome: change in pain intensity, Timeframe: less than six months); low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.5.7.1.2 Secondary outcome parameter: maximum mouth opening

3.5.7.1.2.1 Short-term efficacy (treatment duration up to six months)

Meta-analysis of data from 633 participants across 14 studies indicated a non-statistically significant larger improvement in MMO when physiotherapy was compared to other treatment (n=14 studies [n=303 for Group A, and n=330 for Group B], SMD=0.19; 95% CI [-0.05, 0.42]; *p*=0.12, Figure 62), yet with moderate heterogeneity (I^2=53%). In this analysis, low disability pain patients had a significantly bigger improvement being treated with physiotherapy compared to other treatments in the short-term efficacy (n=7 studies [n=178 for Group A, and n=187 for Group B], SMD=0.42; 95% CI [0.11, 0.74]; *p*=0.008, I^2= 53%).

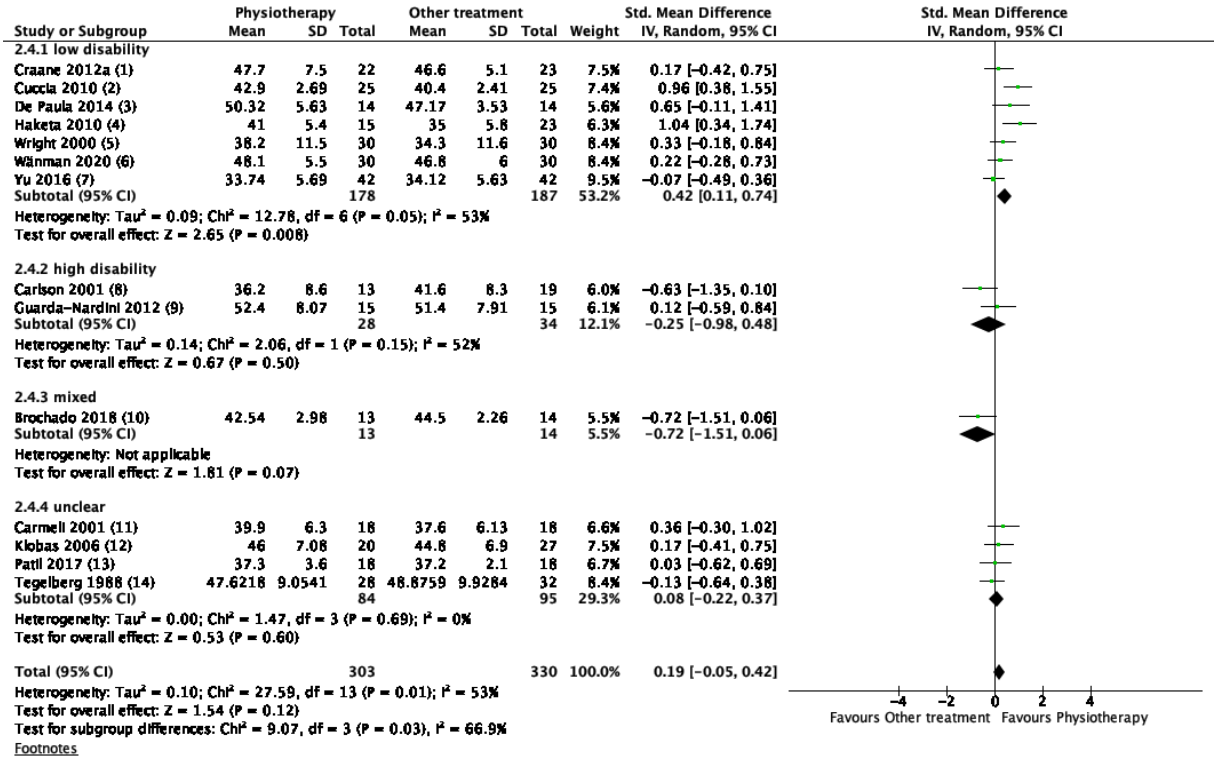


Figure 62: Physiotherapy vs. other treatment (outcome: change in MMO, timeframe: less than six months); low disability= acute pain; high disability = chronic pain; mixed = acute and chronic pain; unclear = pain not identified

3.5.7.2 Comparison: Effectiveness of physiotherapy treatment combined with another treatment in comparison to another treatment alone on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.5.7.2.1 Primary outcome parameter: pain intensity

3.5.7.2.1.1 Short-term efficacy (treatment duration up to six months)

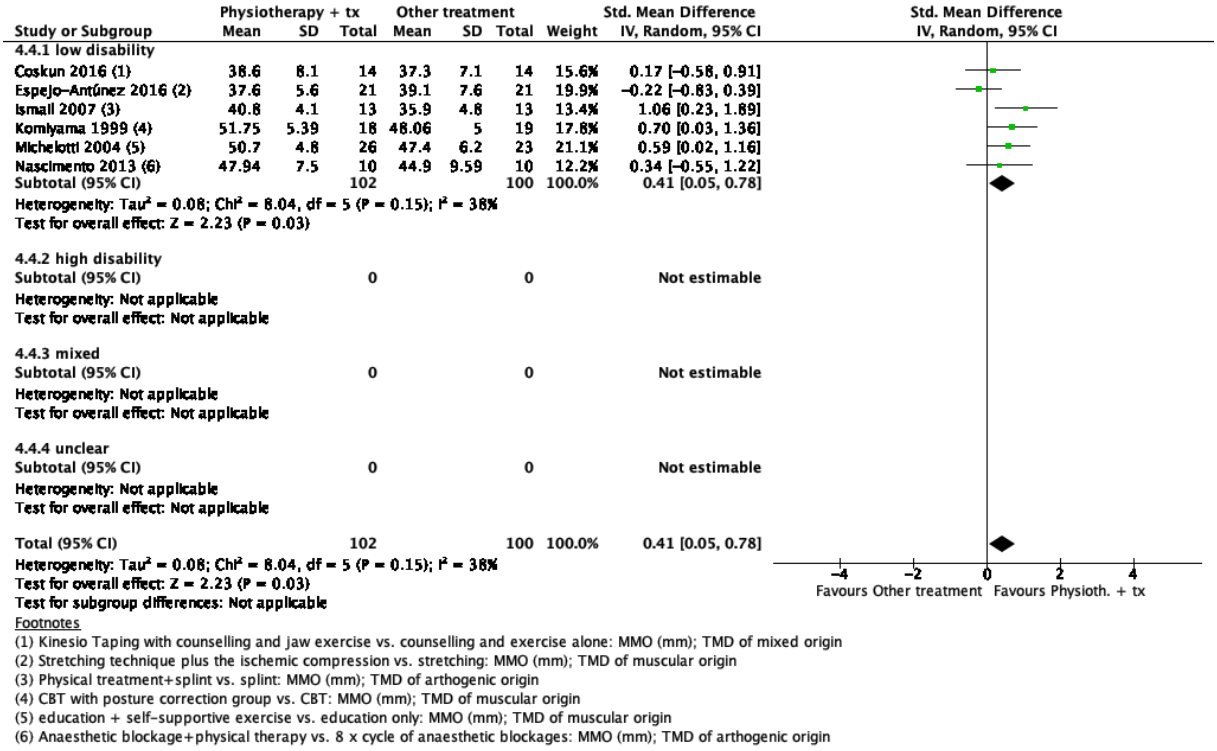
No statistically significant difference was found by comparing physiotherapy combined with an extra treatment versus other treatments (Figure 96, APPENDIX IX: Forest plots) in the reduction of pain intensity (n=6 studies [n=96 for Group A, n=97 for Group B], SMD=-0.24; 95% CI [-0.96, 0.48]; p=0.51, I^2=82%). In this analysis we only had low disability pain patients.

For all the studies of Coskun et al. 2016, Espi-Lopez et al. 2020, Ismail et al. 2007, Mulet et al. 2007, Nagata et al. 2018 and Nascimento et al. 2013 a clinical significance of 30% pain reduction in the intervention group was observed.

3.5.7.2.2 Secondary outcome parameter: maximum mouth opening

3.5.7.2.2.1 Short-term efficacy (treatment duration up to six months)

Meta-analysis of data from 202 participants across six studies indicated a statistically significant bigger improvement in MMO when physiotherapy was combined with another treatment versus a single other treatment. The overall effect for MMO favoured physiotherapy (n=6 studies [n=102 for Group A, and n=100 for Group B], SMD=0.41; 95% CI [0.05, 0.78]; *p*=0.03, I^2=38%, Figure 63), yet with moderate heterogeneity. Similarly, only patients with low disability pain were included in this analysis.



Footnotes
(1) Kinesio Taping with counselling and jaw exercise vs. counselling and exercise alone: MMO (mm); TMD of mixed origin
(2) Stretching technique plus the ischemic compression vs. stretching: MMO (mm); TMD of muscular origin
(3) Physical treatment+splint vs. splint: MMO (mm); TMD of arthogenic origin
(4) CBT with posture correction group vs. CBT: MMO (mm); TMD of muscular origin
(5) education + self-supportive exercise vs. education only: MMO (mm); TMD of muscular origin
(6) Anaesthetic blockage+physical therapy vs. 8 x cycle of anaesthetic blockages: MMO (mm); TMD of arthogenic origin

Figure 63: Physiotherapy + tx vs. other treatment (outcome: MMO, timeframe: less than six months); low disability= acute pain; high disability = chronic pain; mixed = acute and chronic pain; unclear = pain not identified

3.5.7.3 Comparison: Effectiveness of physiotherapy treatment in comparison to placebo on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.5.7.3.1 Primary outcome parameter: pain intensity

3.5.7.3.1.1 Short-term efficacy (treatment duration up to six months)

A clear superiority in the treatment of physiotherapy was seen in Figure 97, APPENDIX IX: Forest plots comparing physiotherapy to placebo in the change of pain intensity in the short term (n=5 studies [n=100 for Group A, and n=97 for Group B], SMD=-0.88; 95% CI [-1.58, -0.18]; *p*=0.01, I^2=81%). The low disability pain subgroup (n=3 studies [n=58 for Group A, and n=58 for Group B], SMD=-0.43; 95% CI [-1.02, 0.16]; *p*=0.15, I^2=59%) and the high disability subgroup (n=2 study [n=42 for Group A, and n=39 for Group B], SMD=-1.66; 95% CI [-3.26, -

0.06]; p=0.04, I^2=88%) showed the same tendency of benefiting more with the treatment of physiotherapy compared to placebo, but only in high disability pain a significance difference was found. It should also be noted that high disability pain was represented by only two studies.

For all the studies of Barbosa et al. 2019, Packer et al. 2014, Reynolds et al. 2019, Berguer et al. 2008, and La Touche et al. 2013 a clinical significance of 30% pain reduction in the intervention group was observed.

3.5.7.4 Comparison: Effectiveness of the treatment of jaw exercise in comparison to other treatment on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.5.7.4.1 Primary outcome parameter: pain intensity

3.5.7.4.1.1 Short-term efficacy (treatment duration up to six months)

Surprisingly, no significant difference of jaw exercise to other treatments was observed in the meta-analysis of jaw exercises compared to other treatment in the reduction of pain intensity (n=7 studies [n=110 for Group A, n=117 for Group B], SMD=0.08; 95% CI [-0.42, 0.57]; p=0.76, I^2=69%). No significant difference was seen in the low disability pain group for the effectiveness of jaw exercise compared to other treatment for the reduction of pain (n=4 studies [n=78 for Group A, and n=78 for Group B], SMD=0.18; 95% CI [-0.56, 0.91]; p=0.64, I^2=80%).

In Figure 64, one can see a difference between low disability pain and high disability pain (n=2 studies [n=42 for Group A, and n=39 for Group B], SMD=-0.31; 95% CI [-1.15, 0.53]; p=0.47, I^2=54%). As all the included studies except for Gavish et al. (2006) and Carlson et al. (2001) had a clinical significance of pain reduction one can say that other treatments have a bigger effectiveness in reducing pain of low disability patients, while jaw exercise have a bigger effectiveness in high disability pain patients in the reduction of pain intensity. Both results were without statistical significance.

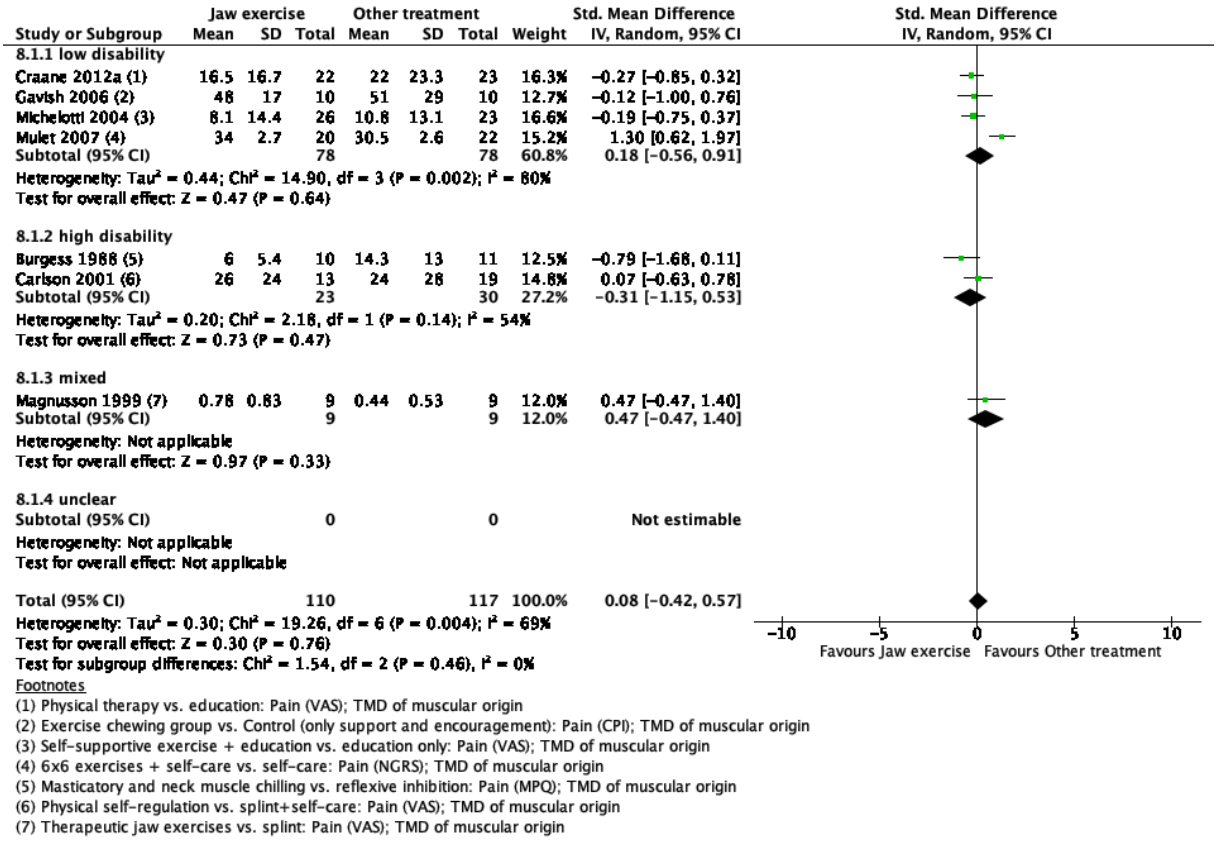


Figure 64: Jaw exercise versus other treatment (outcome: change in pain intensity, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.5.7.4.2 Secondary outcome parameter: MMO

3.5.7.4.2.1 Short-term efficacy (treatment duration up to six months)

No statistical difference was seen in the analysis in the Figure 98, APPENDIX IX: Forest plots (n=6 studies [n=119 for Group A, n=135 for Group B], SMD=0.04; 95% CI [-0.27, 0.36]; *p*=0.79, I^2=35%). No statistical difference was seen in the low disability pain group in the short-term improving MMO (n=2 studies [n=48 for Group A, and n=46 for participants], SMD=0.38; 95% CI [-0.03, 0.80]; *p*=0.07, I^2 =1%), nor in the high disability pain group (n=2 studies [n=23 for Group A, and n=30 for Group B], SMD=-0.42; 95% CI [-0.98, 0.13]; *p*=0.13, I^2=0%).

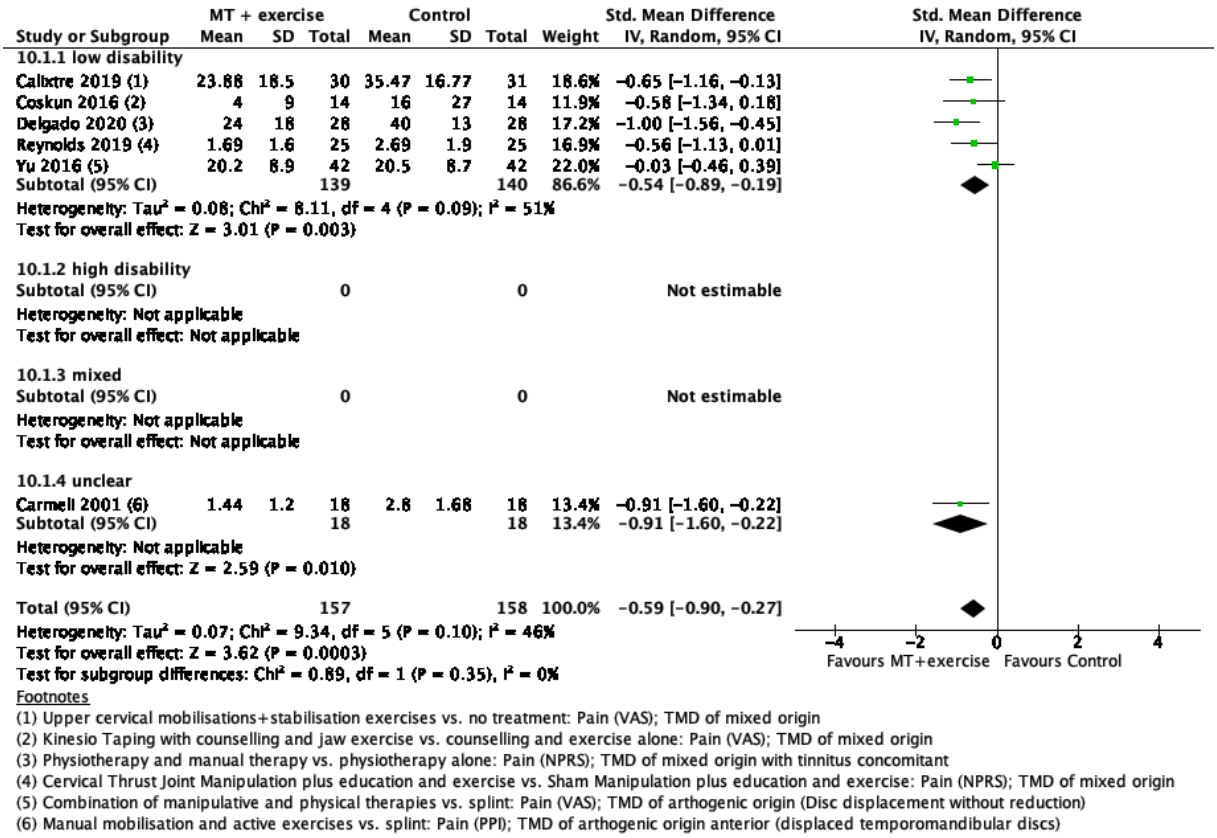
3.5.7.5 Comparison: Effectiveness of manual therapy treatment combined with exercise in comparison to control on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.5.7.5.1 Primary outcome parameter: pain intensity

3.5.7.5.1.1 Short-term efficacy (treatment duration up to six months)

A statistically significant bigger difference was seen in the analysis of MT combined with exercise compared to control, for the outcomes of changes in pain intensity in a follow up

period of less than six months (n=6 studies [n=157 for Group A, and n=158 for Group B], SMD=-0.59; 95% CI [-0.90, -0.27]; *p*=0.0003, I^2=46%, Figure 65). The low disability subgroup (n=5 studies [n=157 for Group A, n=158 for Group B], SMD=-0.54; 95% CI [-0.89, -0.19]; *p*=0.003, I^2=51%) significantly favoured a combination of MT and exercise for the relief of pain intensity. For all the studies of Calixtre et al. 2019, Coskun et al. 2016, Delgado et al. 2020, Reynolds et al. 2019, Yu et al. 2016 and Carmeli et al. 2001 a clinical significance of 30% pain reduction in the intervention group was observed.



Footnotes
(1) Upper cervical mobilisations+stabilisation exercises vs. no treatment: Pain (VAS); TMD of mixed origin
(2) Kinesio Taping with counselling and jaw exercise vs. counselling and exercise alone: Pain (VAS); TMD of mixed origin
(3) Physiotherapy and manual therapy vs. physiotherapy alone: Pain (NPRS); TMD of mixed origin with tinnitus concomitant
(4) Cervical Thrust Joint Manipulation plus education and exercise vs. Sham Manipulation plus education and exercise: Pain (NPRS); TMD of mixed origin
(5) Combination of manipulative and physical therapies vs. splint: Pain (VAS); TMD of arthogenic origin (Disc displacement without reduction)
(6) Manual mobilisation and active exercises vs. splint: Pain (PPI); TMD of arthogenic origin anterior (displaced temporomandibular discs)

Figure 65: Manual therapy combined with exercise versus control (outcome: change in pain intensity, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.5.7.5.2 Secondary outcome parameter: MMO

3.5.7.5.2.1 Short-term efficacy (treatment duration up to six months)

There was no statistically significant bigger result in the Figure 66, for MT combined with exercise in improving mouth opening in the short term. The intervention was compared to controls and included 204 patients and four studies (n=4 studies [n=102 for Group A, and n=102 for Group B], SMD=0.40; 95% CI [-0.17, 0.97]; *p*=0.17, I^2=74%). MT plus exercise had no statistically significant bigger result in the low disability pain group but still showed a positive tendency in the effectiveness of pain relief (n=3 studies [n=84 for Group A, and n=84

for Group B], SMD=0.41; 95% CI [-0.37, 1.19]; *p*=0.30), but with a high heterogeneity (I^2=82%).

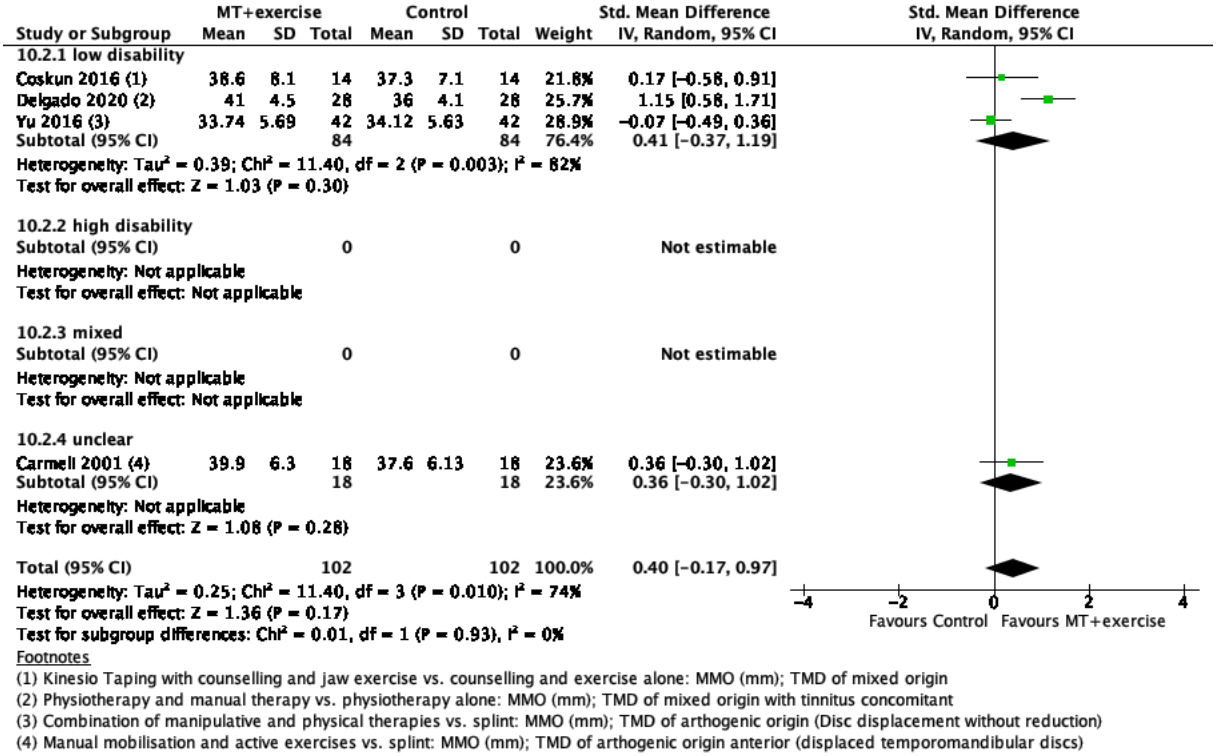


Figure 66: Manual therapy combined with exercise versus control (outcome: change in MMO, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.5.7.6 Comparison: Effectiveness of manual therapy treatment in comparison to controls on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.5.7.6.1 Primary outcome parameter: pain intensity

3.5.7.6.1.1 Short-term efficacy (treatment duration up to six months)

Overall a superiority was also observed in the analysis comparing MT alone against the controls in reducing pain intensity within a time frame of less than six months (n=16 studies [n=342 for Group A, n=355 for Group B], SMD=-0.33; 95% CI [-0.58, -0.07]; *p*=0.01, I^2=64%), seen in Figure 67. Looking at the subgroups separately, the low disability pain subgroup (n=10 studies [n=229 for Group A, n=243 for Group B], SMD=-0.12; 95% CI [-0.31, 0.06]; *p*=0.18, I^2=0%) shows a slight improvement using the MT intervention compared to other treatments. One can clearly see a striking statistically significant result in the high disability subgroup (n=4 studies [n=87 for Group A, and n=84 for Group B], SMD=-1.03; 95% CI [-1.81, -0.24]; *p*=0.01, I^2=82%). The mixed subgroup showed no difference (n=2 studies [n=26 for Group A, n=28 for Group B], SMD=0.04; 95% CI [-0.50, 0.57]; *p*=0.90, I^2=0%). All the

included studies showed a clinical significance of 30% pain reduction in the intervention group except for the study of Guarda-Nardini et al. 2012.

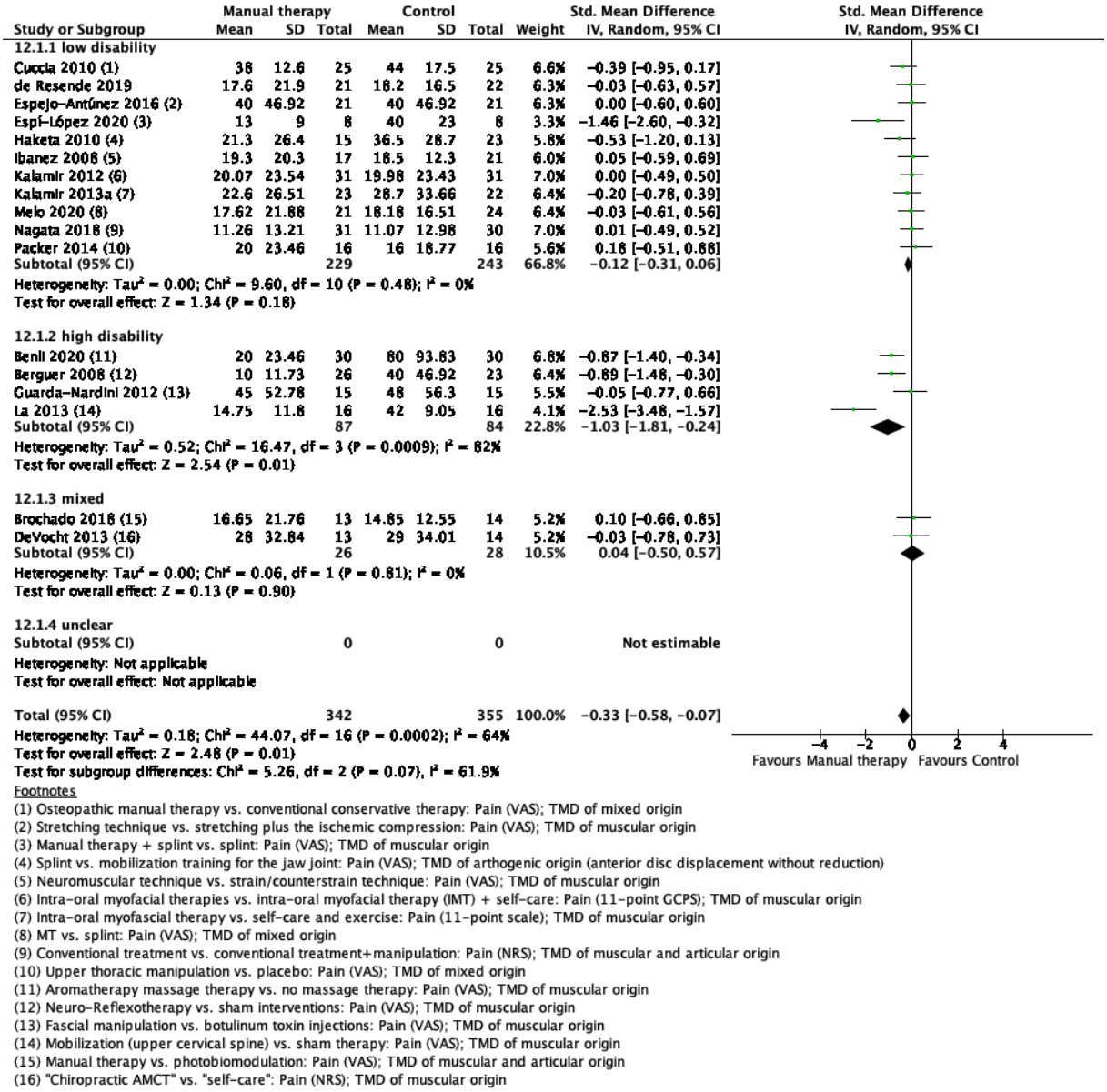


Figure 67: Manual therapy versus controls (outcome: change in pain intensity, timeframe: less than six months months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.5.7.6.2 Secondary outcome parameter: MMO

3.5.7.6.2.1 Short-term efficacy (treatment duration up to six months)

With a substantial heterogeneity (I^2=95%, p<0.00001), six studies reporting improvement of MMO exhibited no statistically significant bigger differences in the overall effect from the interventions (p=0.06). A statistically significant result was observed in the subgroup with low disability pain (n=4 studies [n=92 for Group A, and n=91 for Group B], SMD=2.14; 95% CI [0.23, 4.04]; p=0.03; I^2=96%, Figure 68) for MT for improving MMO.

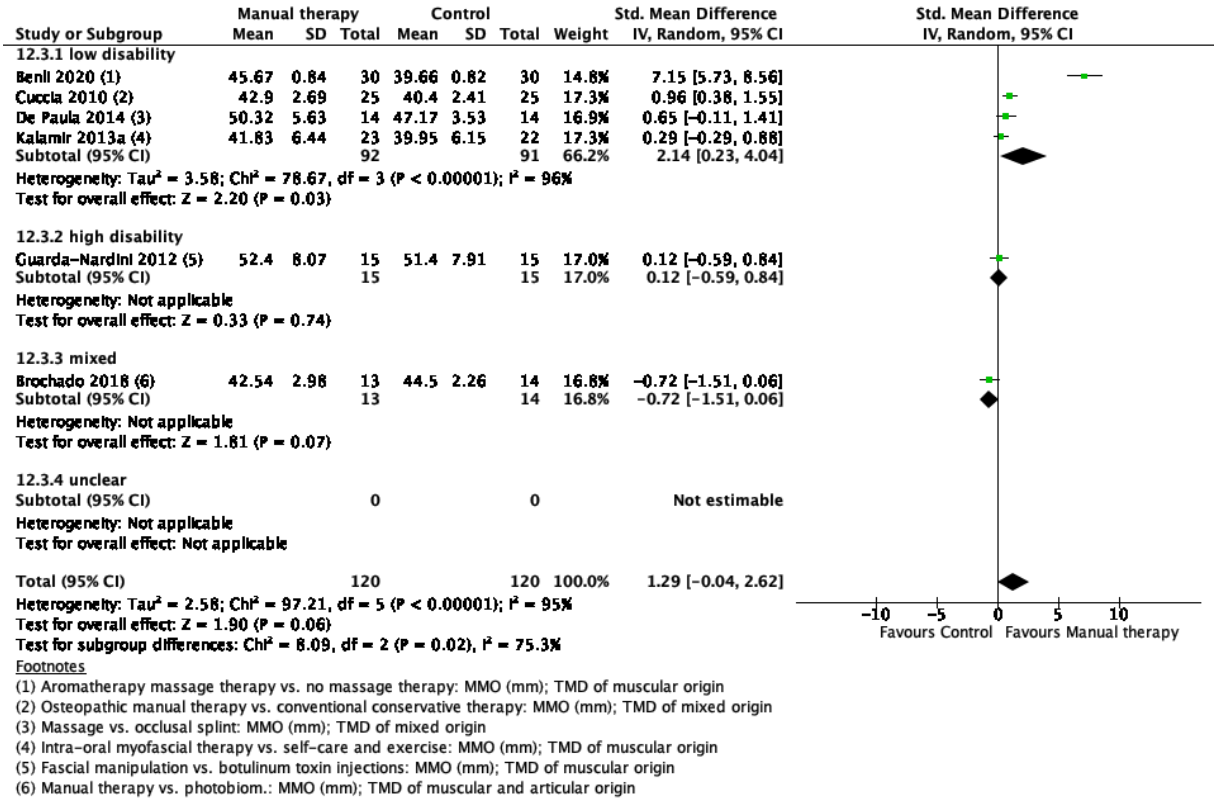


Figure 68: Manual therapy versus control (outcome: change MMO, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.5.7.7 Comparison: Effectiveness of physiotherapy treatment in comparison with splint therapy per type of chronicity (low disability, high disability, mixed or unclear pain)

3.5.7.7.1 Primary outcome parameter: pain intensity

3.5.7.7.1.1 Short-term efficacy (treatment duration up to six months)

Meta-analysis of data from 337 participants across 9 studies indicated no statistically significant bigger reduction in total pain scores using physiotherapy treatment compared to splint therapy (Figure 69). The overall effect for pain reduction was bigger for physiotherapy (n=9 studies [n=159 for Group A, and n=178 for Group B], SMD=-0.25; 95% CI [-0.55, 0.04]; *p*=0.09) with a low heterogeneity (I^2=39%). Subgroup analysis also showed no statistically significant differences between physiotherapy treatment and other splint therapy with patients suffering from low disability pain (n=6 studies [n=119 for Group A, n=132 for Group B], SMD=-0.25; 95% CI [-0.55, 0.05]; *p*=0.10, I^2=24%). The other subgroups were represented by one study each and therefore not explained any further. A clinical significance of 30% pain reduction in the intervention group was observed in all studies except for the study of Carlson et al. 2001.

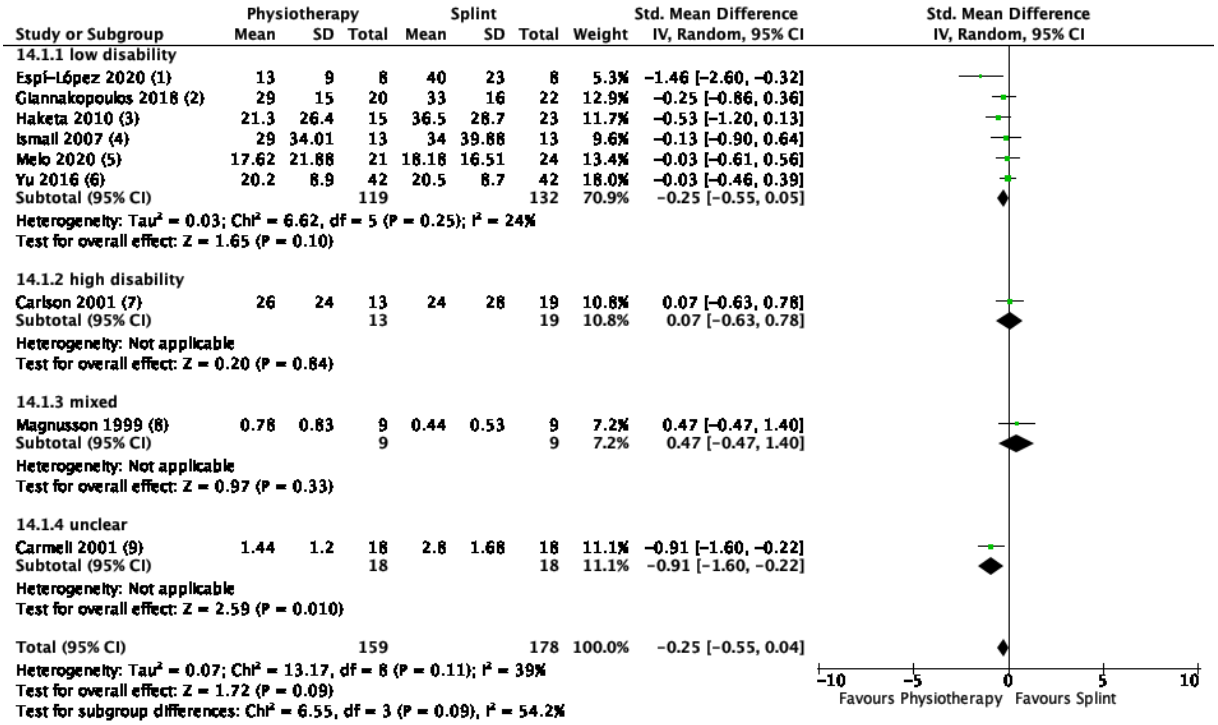


Figure 69: Physiotherapy versus splint (outcome: change pain intensity, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.5.7.7.2 Secondary outcome parameter: MMO

3.5.7.7.2.1 Short-term efficacy (treatment duration up to six months)

No statistical difference was observed in the analysis (n=7 studies [n=145 for Group A, and n=159 for Group B], SMD=0.34; 95% CI [-0.07, 0.75]; p=0.10, I^2=66%), seen in Figure 70. A statistically significant bigger result was observed in the low disability pain group in favour of physiotherapy in the short-term improving MMO (n=5 studies [n=114 for Group A, and n=122 for Group B], SMD=0.51; 95% CI [0.05, 0.97]; p=0.03, I^2=64%).

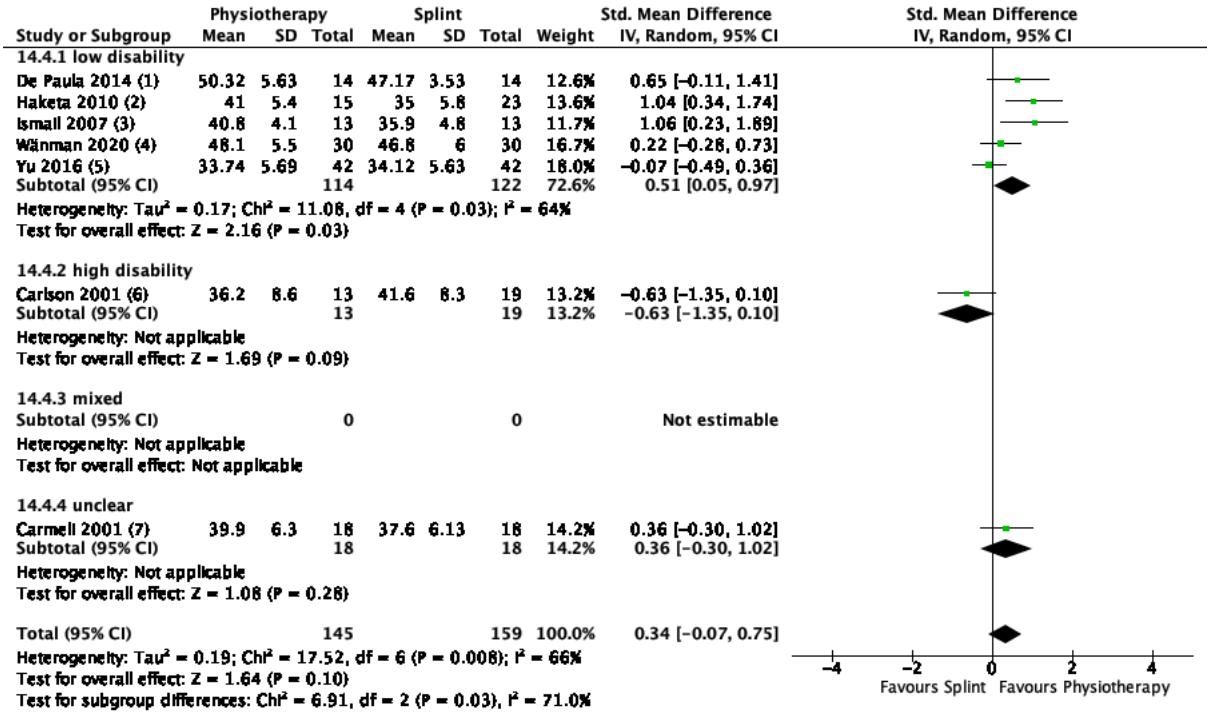


Figure 70: Physiotherapy versus splint (outcome: change MMO, timeframe: less than six months) low disability= acute pain; high disability = chronic pain; unclear = pain not identified

3.5.7.8 Comparison: Effectiveness of physiotherapy treatment in comparison to psychosocial interventions therapy on the type of chronicity (low disability, high disability, mixed or unclear pain)

3.5.7.8.1 Primary outcome parameter: pain intensity

3.5.7.8.1.1 Short-term efficacy (treatment duration up to six months)

No statistically significant difference (Figure 99, APPENDIX IX: Forest plots) was found in the comparison of physiotherapy treatment versus psychosocial interventions in the reduction of pain intensity for low disability pain n=7 studies [n=143 for Group A, n=142 for Group B], SMD=-0.15; 95% CI [-0.61, 0.32]; *p*=0.54, I^2=75%) or high disability pain (n=0). A clinical significance of 30% pain reduction in the intervention group was observed in all studies except for the study of Gavish et al. 2006.

3.5.8 Tabular overview of the results of the comparisons for physiotherapy

The results of the comparisons made for physiotherapy interventions are listed below in Table 29 for pain intensity and in for MMO:

Table 29: Tabular overview of the results of physiotherapy regarding pain intensity categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval

Reduction of pain intensity		
Comparison	**Statistically significant results**	**Data**
Physiotherapy vs. other therapy	Short-term: No ss effectiveness for physiotherapy for the treatment for low disability, high disability, or total pain compared to other therapy.	Short-term: Low disability: (SMD=-0.10; 95% CI [-0.29, 0.09]; *p*=0.32; I^2=0%) High disability: (SMD=0.01; 95% CI [-0.49, 0.51]; *p*=0.97; I^2=0%) Total pain: SMD=-0.02; 95% CI [-0.25, 0.21]; *p* =0.85; I^2=52%)
Physiotherapy + tx vs. other treatment	Short-term: No ss effectiveness for physiotherapy combined with another treatment for the treatment for low disability or total pain compared to other treatment. High disability was not evaluated.	Short-term: Low disability: (SMD=-0.24; 95% CI [-0.96, 0.48]; *p*=0.51; I^2=82%) Total pain: (SMD=-0.24; 95% CI [-0.96, 0.48]; *p*=0.51; I^2=82%)
Physiotherapy vs. placebo	Short-term: **Significant less pain after physiotherapy treatment than after placebo for high disability and total pain.** No ss effectiveness for physiotherapy for the treatment of low disability pain compared to placebo.	Short-term: Low disability: (SMD=-0.43; 95% CI [-1.02, 0.16]; *p*=0.15; I^2=59%) **High disability: (SMD=-1.66; 95% CI [-3.26, -0.06]; *p*=0.04; I^2=88%)** **Total pain: (SMD=-0.88; 95% CI [-1.58, -0.18]; *p*=0.01; I^2=81%)**
Jaw exercise vs. other treatment	Short-term: No ss effectiveness for jaw exercise for the treatment of low disability pain, high disability pain, or total pain compared to other treatment.	Short-term: Low disability: (SMD=0.18; 95% CI [-0.56, 0.91]; *p*=0.64; I^2=80%) High disability: (SMD=-0.31; 95% CI [-1.15, 0.53]; *p*=0.47; I^2=54%) Total pain: (SMD=0.08; 95% CI [-0.42, 0.57]; *p* =0.76; I^2=69%)
Manual therapy + exercise vs. control	Short-term: **Significant less pain after manual therapy combined with exercise than after control treatment for low disability and total pain.**	Short-term: **Low disability: (SMD=-0.54; 95% CI [-0.89, -0.19]; *p*=0.003; I^2=51%)** **Total pain: (SMD=-0.59; 95% CI [-0.90, -0.27]; *p*=0.0003; I^2=46%)**
Manual therapy vs. control	Short-term: **Significant less pain after manual therapy than after control treatment for high disability pain and total pain.** No ss effectiveness for manual therapy for the treatment of low disability pain compared to controls.	Short-term: Low disability: (SMD=-0.12; 95% CI [-0.31, 0.06]; *p*=0.18; I^2=0%) **High disability: (SMD=-1.03; 95% CI [-1.81, -0.24]; *p*=0.01; I^2=82%)** **Total pain: (SMD=-0.33; 95% CI [-0.63, -0.05]; *p*=0.01; I^2=64%)**
Physiotherapy vs. splint	Short-term: No ss effectiveness for physiotherapy for the treatment of low disability pain, or total pain compared to splint therapy.	Short-term: Low disability: (SMD=-0.25; 95% CI [-0.55, 0.05]; *p*=0.10; I^2=24%) Total pain: (SMD=-0.25; 95% CI [-0.55, 0.04]; *p*=0.09; I^2=39%)
Physiotherapy vs. psychosocial interventions	Short-term: No ss effectiveness for physiotherapy for the treatment of low disability pain, or total pain compared to psychosocial interventions therapy.	Short-term: Low disability: (SMD=-0.16; 95% CI [-0.69, 0.37]; *p*=0.55; I^2=79%) Total pain: (SMD=-0.15; 95% CI [-0.61, 0.32]; *p*=0.54; I^2=75%)

Table 30: Tabular overview of the results of physiotherapy regarding MMO categorised according to the comparisons made; ss=statistical significance; SMD=standard mean difference; CI=confidence interval

Improvement of maximum mouth opening		
Comparison	**Statistically significant results**	**Data**
Physiotherapy vs. other therapy	Short-term: **Significant improvement of MMO after physiotherapy treatment than after other treatment for low disability.**	Short-term: **Low disability: (SMD=0.42; 95% CI [0.11, 0.74]; *p*=0.008; I^2=53%)** High disability: (SMD=-0.25; 95% CI [-0.98, 0.48]; *p*=0.50; I^2=52%) Total pain: (SMD=0.19; 95% CI [-0.05, 0.42]; *p*=0.12; I^2=53%)
Physiotherapy + tx vs. other treatment	Short-term: **Significant improvement of MMO after physiotherapy treatment + tx than after other treatment for low disability and total pain.** High disability pain was not evaluated.	Short-term: **Low disability: (SMD=0.41; 95% CI [0.05, 0.78]; *p*=0.03; I^2=38%)** **Total pain: (SMD=0.41; 95% CI [0.05, 0.78]; *p*=0.03; I^2=38%**
Jaw exercise vs. other treatment	Short-term: No ss effectiveness for jaw exercise for the treatment of low disability pain, high disability pain, or total pain compared to other treatment in the improvement of MMO.	Short-term: Low disability: (SMD=0.38; 95% CI [-0.03, 0.80]; *p*=0.07; I^2=1%) High disability: (SMD=-0.42; 95% CI [-0.98, 0.13]; *p*=0.13; I^2=0%) Total pain: (SMD=0.04; 95% CI [-0.27, 0.36]; *p*= 0.79; I^2=35%)
Manual therapy + exercise vs. control	Short-term: No ss effectiveness for MT+ exercise for the treatment of low disability pain and total pain. High disability was not evaluated.	Short-term: Low disability: (SMD=0.41; 95% CI [-0.37, 1.19]; *p*=0.30; I^2=82%) Total pain: (SMD=0.40; 95% CI [-0.17, 0.97]; *p*=0.17; I^2=74%)
Manual therapy vs. control	Short-term: **Significant improvement of MMO after manual therapy than after control treatment for low disability pain.** No ss effectiveness for MT+ exercise for the treatment of total pain.	Short-term: **Low disability: (SMD=2.14; 95% CI [0.23, 4.04]; *p*=0.03; I^2=96%)** Total pain: (SMD=1.29; 95% CI [-0.04, 2.62]; *p*=0.06; I^2=95%)
Physiotherapy vs. splint	Short-term: **Significant improvement of MMO after physiotherapy compared to splint therapy for low disability pain.** No ss effectiveness for physiotherapy for the treatment of total pain compared to splint therapy.	Short-term: **Low disability: (SMD=0.51; 95% CI [0.05, 0.97]; *p*=0.03; I^2=64%)** Total pain: (SMD=0.34; 95% CI [-0.07, 0.75]; *p*=0.10; I^2=66%)

4 Discussion

4.1 Summary of the findings

Within this review, the research question was structured using the PICOS format and specific eligibility criteria were set in advance. A widespread and detailed literature search was conducted to identify potentially appropriate trials from several electronic databases for each of the five interventions (acupuncture, laser, medication, psychosocial interventions, and physiotherapy). The author also conducted five meta-analyses to determine the overall effect sizes of the treatments for TMD according to the pain chronification status. This ensured that this review could serve as a useful summary of the currently available evidence.

In each intervention group, individual forms of therapy showed positive effects in reducing pain intensity, MMO and depression, depending on the degree of chronicity.

However, in each intervention group, some forms showed no effects or different effects. Therefore, the author cannot derive an overall result for the interventions studied (acupuncture intervention, laser, medication, psychosocial interventions, physiotherapy).

Table 31: Summary of the results of the five interventions investigated on the degree of chronification for pain intensity in the short time. (yes=statistically significant results; X=no statistically significant result; PSI= psychosocial interventions)

Improvement in pain intensity for the short time (up to six months)			
	Low Disability	**High Disability**	**Total**
Acupuncture interventions			
Acupuncture > control	X	X	yes
Acupuncture > control	yes	X	yes
Acupuncture > sham acupuncture	X	X	X
Acupuncture > other treatment	X	X	X
Dry needling > other treatment	yes	X	X
Laser			
Laser > other treatment	X	X	X
Laser > placebo	yes	X	yes
Laser treatment (800-830 nm) > placebo	yes	X	yes
Laser treatment (>831 nm) > placebo	X	yes	yes
Medication			
Medication (orally administered) < other treatment	X	X	yes
Medication (injected only) < other treatment	X	X	X
Medication (injected excluded) > placebo	yes	yes	yes
Medication with only orally administered	X	yes	yes
Medication treatment as a single intervention	yes	yes	yes
Medication (injected only) > placebo	X	X	yes
Botulinum toxin > other treatment	X	X	X
Botulinum toxin > placebo	X	yes	yes
NSAIDs > placebo	X	yes	X
NSAIDs < other treatment	X	X	X
Benzodiazepines > placebo	X	X	X
Psychosocial Interventions			
PSI (of any kind) vs. other treatment			
PSI (of any kind) > other treatment *(short time)*	X	X	X
PSI (of any kind) < other treatment *(medium time)*	X	X	X
PSI (of any kind) > other treatment *(long time)*	yes	X	yes
Self-care, counselling, and education > other treatment	X	X	X
Physiotherapy			
Physiotherapy > other therapy	X	X	X
Physiotherapy + tx > other treatment	X	X	X
Physiotherapy > placebo	X	yes	yes
Jaw exercise < other treatment	X	X	X
Manual therapy + exercise > control	yes	X	yes
Manual therapy > control	X	yes	yes
Physiotherapy > splint	X	X	X
Physiotherapy > PSI	X	X	X

Table 32: Summary of the results of the five interventions investigated on the degree of chronification for maximum mouth opening in the short time. (yes=statistically significant results; X=no statistically significant result; PSI= psychosocial interventions)

Improvement in maximum mouth opening for short term period (zero till six months)			
	Low Disability	**High Disability**	**Total**
Acupuncture interventions			
Acupuncture > control	X	X	X
Acupuncture > sham acupuncture	X	X	X
Dry needling < other treatment	X	X	X
Laser			
Laser > other treatment	yes	X	yes
Laser > placebo	yes	X	yes
Medication			
Medication (injected excluded) > placebo	X	X	X
Medication (injections only) < placebo	X	X	X
NSAIDs < other treatment	yes	X	yes
Psychosocial Interventions			
Psychosocial interventions > other therapy	X	X	X
Physiotherapy			
Physiotherapy > other therapy	yes	X	X
Physiotherapy + tx > other treatment	yes	X	yes
Jaw exercise > other treatment	X	X	X
Manual therapy > exercise vs. control	X	X	X
Manual therapy > control	yes	X	X
Physiotherapy > splint	yes	X	X

Table 33: Summary of the results of psychosocial interventions on the degree of chronification for depression in the short time. (yes=statistically significant results; X=no statistically significant result; PSI= psychosocial interventions)

Improvement in depression (zero till six months)			
	Low Disability	**High Disability**	**Total**
Psychosocial Interventions			
PSI > other therapy	X	yes	X

4.2 Acupuncture

4.2.1 Discussion of the systematic review / descriptive findings

Most of the included studies (70%) on acupuncture treatment were TMD of muscular causes. The fact that 18% of the included studies could not define the type of TMD of the subjects more precisely led to an often-inaccurate analysis of the effectiveness of acupuncture therapy. The diagnostic tools used in many studies were RDC/TMD, followed by clinical examinations. The type of diagnostic tool used is not expected to influence the results in any way. Pain in the lower jaw muscle or TMJ was an important inclusion criterion, which was met in all included studies. A major lack of current data, however, is the small number of studies in which patients with high disability pain were treated (22.5% of the included studies had a potential high disability pain). Although the TMD of patients was mostly diagnosed by RDC/TMD, details of GCPS could not be seen which is cause of concern (7.5% of included studies reported the GCPS). Most authors replied that they did not have any data. As a result, the sample size of patients with high disability pain was very small and subgroup comparisons between patients with low disability pain and those with high disability pain were hardly possible. Our indications of possible pain chronification were based on logical considerations and observations from previous data. To date, TMD patients have not been diagnosed with high disability pain at the neurobiological level. Therefore, it was assumed that patients with the indications defined by the author show pain chronification and thus may respond less well to acupuncture therapy. In most cases, the criterion for diagnosing high disability pain was the mention of previous treatments (52.5% of the included studies). Whether the treatments already performed were unsuccessful has generally not been described. Nevertheless, these subjects evidently thought it useful to seek further therapies or to participate in the studies investigated here, which is why it is assumed that the previous treatments were at least insufficiently successful. Unfortunately, there are no systematic reviews in the current literature, whose results would be comparable to ours. The present paper is therefore intended to encourage future study authors to examine and publish the evidence for pain chronification investigated here. 62.5% of the included studies recruited participants from tertiary institutions, which corresponds to the assumption that most RCTs are conducted at universities. Another aspect which should not be overlooked in the critical analysis of the methodology is the non-exclusive and well-defined application of the measures examined. All acupuncture therapies with sometimes very heterogeneous combinations and control groups were investigated and the data obtained were compared. The author included all kinds of acupuncture interventions. Classical acupuncture was studied by only 52.5% of the included studies. In the quantitative analysis of the studies, the author has always opted for the random effect model. The reason for this was the great

methodological and numerical heterogeneity of the included studies. Over-interpretation of some studies should be avoided by applying the random effects method.
Most studies compared the effectiveness of acupuncture interventions with that of sham acupuncture or various other therapies. This explains the great heterogeneity of the studies, which made it difficult for the author to investigate a larger patient pool. For ethical reasons, real control groups are rarely analyzed or only in short observation periods (e.g., control group=patients with waiting lists). Many of the included studies had a very short follow-up time. 97.5% of the included studies followed patients for less than six months. Therefore, the long-term efficacy of acupuncture could not be investigated.

4.2.2 Quality of the studies

The findings of this review and meta-analysis should be treated with caution. The quality of the included studies of acupuncture is acceptable and can be compared with the quality of other studies of different extraoral interventions (laser, medication, psychosocial interventions, physiotherapy). The quality of the studies was significantly increased by the additional material we received from the research team for each study. We were able to reduce the risk of bias assessment because we methodically contacted every author of the included studies and the studies awaiting classification. It showed that 65% of the included trials had a low risk of bias for randomization. Allocation concealment, on the other hand, was poorly reported which is a common deficiency in existing RCTs for the treatment of TMD. For acupuncture, 25% showed a low risk of bias. The area of blinding of participants and staff, which is due to the nature of the therapies proposed difficult to proceed was under-reported. Therefore, for all studies where blinding of patients and staff was not appropriate due to differences in therapies, we assessed a low risk of bias. Thus, the quality of evidence in the meta-analysis was equal to those in older reviews, which can be explained by the blinding of participants and staff and the additional information collected from the individual authors [495]. However, 72.5% of the included studies had a low risk of bias for participants and personnel, while 65% of the investigators were blinded. The report on dropouts (80% of low risk of bias) was more advanced than in other extraoral interventions cited below. The positive result can be explained by the fact that the follow-up period was short and there were no dropouts in many studies. Furthermore, only one trial used intention-to-treat analysis. Selective reporting of acupuncture treatment was comparable to the other interventions with a high value 87.5% of low risk of bias. In addition, less than 25% of the studies presented a low risk of bias that could affect the quality of the results, as most RCTs did not report the non-significance statistical difference in intervention groups at baseline or did not report a conflict of interest.

4.2.3 Discussion of the meta-analysis

Despite widespread use in clinical practice, acupuncture remains a controversial treatment option for chronic pain. Acupuncture is frequently used as an integrative or complementary pain therapy. It is well accepted and conducts little risk of serious adverse effects. It has been demonstrated that traditional acupuncture and non-traditional techniques, such as electroacupuncture and dry needling, often improve pain. Several factors may contribute to the inconsistency of the therapeutic effect of acupuncture, including the needling technique, the number of needles used, the dwell time of the needles, the specificity of the acupuncture points, the number of sessions, and psychological factors. Many controlled studies have been published on pain syndromes, e.g., acupuncture for acute and chronic low back pain, knee osteoarthritis, headaches, myofascial pain, neck pain or fibromyalgia [496]. Our objective was to provide an update on individual patient data meta-analysis to determine the effect size of acupuncture for TMD disability pain conditions. Our meta-analysis estimated 19 clinical trials for acupuncture treatment that included TMD patients. To reduce bias on the efficiency of acupuncture interventions and to discover whether the cumulative effects of other techniques impacted on the results, we excluded RCTs that included combined treatments. This reduced the outcomes but permitted an improved support from the results of acupuncture treatment separately and the impact of acupuncture interventions in TMD treatment [119].

In this review, a statistically significant advantage of acupuncture therapy over control therapy (placebo and other treatment combined) was found, as measured by the VAS in the short-term. The specific subgroup results helped to refine the findings and reveal factors that may be beneficial in the clinical practice of acupuncture for the management of pain in patients suffering from low disability. A subgroup analysis, according to the classification of chronicity of pain, showed that patients with low disability pain being measured with the VAS had a statistically significant advantage being treated with acupuncture, while high disability pain had the same tendencies towards acupuncture treatment and was more likely to benefit from acupuncture treatment compared to the control group at reducing pain intensity in the short term. A clinical significance was observed by all the included studies except for two included studies [189, 190].

Interestingly, also no significant advantage was observed in the comparison of acupuncture to sham acupuncture or other treatment in terms of pain reduction and improving MMO in the short-term. Sham acupuncture has a known analgetic effect, therefore, it is not surprising that the sham therapy had an effectiveness on the management of pain. Opposite results have been found in older reviews [146, 497] and meta-analyses [148, 498], suggesting that acupuncture is an effective tool for managing pain in patients with TMD compared to controls or other treatments. In the review of La Touche et al. [499] in 2010, in which four studies

were included, a statistically significant difference was also found between acupuncture to sham therapy in short-term pain reduction for myofascial TMD, which is contrary to the results of this meta-analysis. This can be explained by the different number of studies, as in this meta-analysis the author performed the comparison with twice the number of included studies (n=8). Furthermore, all types of TMD were included.

On the other hand, dry needling was shown to have greater benefit in comparison to other treatments in the short-term for the subgroup with low disability pain. The results suggest that dry needling may provide a similar benefit, at least in the short term, in patients with acute pain, potentially resulting in a faster recovery. However, further studies with longer follow-up periods are required for more conclusive results. The high disability pain group benefited more from other treatments (without significance). All the studies for this comparison had a clinical significance in pain reduction in the intervention groups.

Similar results were found in previous studies on acute neck pain [500] and came to the same conclusion that dry needling is an effective treatment for low disability pain, having an hypoalgesia effect in the short term.

The hypothesis can be confirmed that painful TMDs respond differently to acupuncture therapy depending on the degree of chronic pain-related disability, as well as for dry-needling therapy. Therefore, the prognosis of therapy of acupuncture and dry-needling is significantly influenced by the degree of chronic pain-related disability of the disease.

4.3 Laser

4.3.1 Discussion of the systematic review / descriptive findings

Most of the included laser therapy studies (65%) involved TMD of muscle and joint pain. Only 39% were of muscular origin, which is very interesting as myofascial pain is the most common diagnosis of TMD. The diagnostic tool used in many studies was the RDC/TMD. Painful TMD was an important inclusion criterion that was met in all included studies. However, a major lack of up-to-date data on laser therapy is the small number of studies in which patients with high disability pain have been treated. Although patients' TMD was primarily diagnosed by RDC/TMD, details of GCPS were hardly presented (4.6% of included studies reported GCPS). Most authors replied that they had no data. As a result, the sample size of patients with high disability pain during laser therapy was very small (20% including studies with potentially high disability pain) and subgroup comparisons between patients with low disability and those with high disability pain were hardly possible during this intervention. The highest criterion in laser therapy for the diagnosis of high disability pain was also the mention of previous treatments (61.5% of the included studies). Whether the treatments already performed were unsuccessful has generally not been described. Nevertheless, these subjects apparently thought it useful to search for further therapies or to participate in the studies investigated here, which is why it is assumed that the previous therapies were at least insufficiently successful. 78% of the included laser therapy studies recruited participants from tertiary institutions, which corresponds to the assumption that most RCTs, as mentioned above, are conducted at universities. Another aspect which should not be overlooked in the critical analysis of the methodology is the non-exclusive and well-defined application of the measures examined. All types of laser therapies with sometimes very heterogeneous combinations, applications sites, frequencies, wavelengths, and control groups were investigated and the data obtained were compared. The author included all kinds of laser interventions. The GaAlA laser (44.6%) was the most common laser type in the included studies. In the quantitative analysis of the studies, the author has always opted for the random effect model. The reason for this was the great methodological and numerical heterogeneity of the included studies. Over-interpretation of some studies should be avoided by applying the random effects method. Most studies compared the effectiveness of laser therapy with placebo or other types of lasers. This explains the great heterogeneity of the studies, which made it difficult for the author to investigate a larger patient pool. Many of the included studies had a very short follow-up period. No long-term follow-up study has been studied. In the included studies, patients were followed for less than six months. Therefore, the long-term efficacy of lasers could not be investigated.

4.3.2 Quality of the studies

The risk of bias of the articles was significantly improved by the supplementary material we received from the research team of the respective studies. We were able to make the changes in the risk of bias assessment because we methodically contacted all authors of the included studies and the studies not yet classified. However, not all authors responded, leading to many uncertainties in the Cochrane Library's assessment of risk of bias and to most of the included studies having unclear risk. However, the overall result of low risk of bias was adequate and in line compared to other interventions investigated. For example, random sequence generation was rated at 60.3% and allocation concealment at 14.7%. Blinding of participants and staff was also underreported (61.2%-64.7%), as it is technically difficult to achieve in this type of comparison. For all studies where blinding of patients and staff was problematic due to the diversity of therapies, we assessed the risk of bias as low. Thus, the quality of evidence in the meta-analysis improved significantly compared to older reviews, which can be explained by blinding of participants and staff as well as additional information obtained by the individual authors. Incomplete outcome data were rated as 42.6% at low risk of bias, while selective outcomes had a high percentage (89.7%) of low risk of bias. Other biases were also poorly reported (16.2%) in the laser studies and is in line with the other four interventions investigated.

4.3.3 Discussion of the meta-analysis

This systematic review and meta-analysis showed that laser therapy is not significantly better than other treatments in reducing pain intensity. On the other hand, LLLT was superior to placebo therapy for pain relief in the short term. The subgroup analysis showed a significant effect on low disability pain. The high disability pain subgroup showed no effect with the treatment. Having to say that double the number of included studies in the high disability pain group showed no clinical significance to only two studies in the low disability pain group. LLLT is thought to reduce pain by decreasing biochemical markers and oxidative stress. Numerous studies have demonstrated analgesic and anti-inflammatory effects of photobiomodulation in acute pain, both in experimental and clinical trials [501, 502]. The analgesic effect of LLLT in the treatment of TMD pain depends mainly on the wavelength of the laser and the radiation dose. Lasers with an infrared wavelength are the most suitable due to their greater penetration for TMD. Red light (below 700 nm) is more easily absorbed by the superficial skin, while the infrared LLLT (> 700 nm) can penetrate deeper into the tissue with a longer wavelength and are suitable for deeper injuries [503]. The most commonly used are in the electromagnetic spectrum of 780 nm to 904 nm [230]. This is consistent with the results of this meta-analysis. LLLT with wavelengths of 800-830nm and >831nm showed an overall statistical significance superiority in favour of laser compared to placebo therapy in reducing short term pain intensity. The wavelengths of 800-830nm

showed a significant bigger pain reduction in the subgroup analyses with low disability pain. Interestingly, it was found an advantage in the subgroup with high disability pain for the wavelengths of > 831nm compared to placebo. One study [504] examined the penetration depth and attenuation of different wavelengths in different animal tissues and concluded that the attenuation of light was greater at about 600nm, while the wavelength of about 900nm penetrated more strongly. A recent meta-analysis even recommended the use of a higher wavelength between 910nm and 1100nm to achieve better results in the short term [503]. Further studies with longer follow-up periods are recommended for these results. In terms of MMO improvement, a statistical significance was observed comparing laser either to other treatment or placebo. LLLT also produced a statistically significant bigger difference in MMO in the short-term in comparison to placebo use as well as to other treatments for the low disability pain group. This is likely due to the anti-inflammatory modifications and the change in pain muscle inhibition, in addition to the alteration in inflammation of the hyperactive sensory receptors of the joint capsule [221]. In general, the result of the superiority of LLLT to placebo therapy for pain relief in the short term is consistent with the results of the work by Herpich et al. 2015 [203] and Xu et al. 2018 [207]. Conversely, the results of this systematic review partly contradict the results of a different systematic review by Petrucci et al. 2011 [208], who reported that there is no evidence to recommend the treatment of TMD with LLLT compared to placebo. However, the authors urge for caution as the latter review included a small number of papers, the lack of definition of the used dose, the power density in several studies and a high degree of heterogeneity. In addition, the meta-analysis by Chang et al. 2014 [204] demonstrated that the wavelengths of 830 nm and 780 nm are moderate or superior in reducing pain intensity of TMD, which is consistent with the results of this meta-analysis. This review also found a relationship between low disability pain and laser effectiveness for pain relief and function. This finding is credible as the laser application sites were based on the trigger points of pain. It showed to have the same effect as dry needling. Low disability pain is more likely to resolve spontaneously than high disability pain and, once central sensitization occurs, a condition may become unresponsive to LLLT. Other publications found the same effect for acute back pain and similarly reported a decline in functional disability and pain after three weeks of LLLT, which confirms the results of the current study [215, 505]. However, this needs to be explored further in future research.

The hypothesis can be confirmed that painful TMDs respond differently to laser therapy and the usage of different wavelength depending on the degree of chronic pain-related disability. Therefore, the prognosis of therapy is significantly influenced by the degree of chronic pain-related disability of the disease.

4.4 Medication

4.4.1 Discussion of the systematic review / descriptive findings

Most of the included medication treatment studies (30%) involved TMD of muscular origin and followed by TMJ disc displacement (20%). Over half of the studies (51%) used the RDC/TMD as diagnostic tools. Painful TMD was an important inclusion criterion that was met in all included studies. However, a major lack of up-to-date data on medication treatment is also the small number of studies in which patients with high disability pain have been treated. Although patients' TMD was primarily diagnosed by RDC/TMD, details of GCPS were hardly present (5.8% of included studies reported GCPS). Most authors replied that they had no data. As a result, the sample size of patients with high disability pain in the drug therapy was also very small (26.7% of the included studies with potentially high disability pain) and subgroup comparisons between patients with low disability pain and those with high disability pain were hardly possible in this intervention. The highest criterion for the medication treatment diagnosis of high disability pain was also the mention of previous treatments (48.8% of the included studies) as the author has seen it in acupuncture und laser treatment. Whether the treatments already performed were unsuccessful has generally not been described. Nevertheless, these subjects apparently thought it useful to look for further therapies or to participate in the studies investigated here, which is why it is assumed that the previous treatments were at least insufficiently successful. 87.2% of the included medication treatment studies recruited participants from tertiary institutions, which corresponds to the assumption that most RCTs, as mentioned above, are conducted at universities. Another aspect which should not be overlooked in the critical analysis of the methodology is the non-exclusive and well-defined application of the measures examined. All medication studies with sometimes very heterogeneous combinations, administration (oral, injected, creams), dosages and control groups were examined, and the data obtained were compared. The author included all sorts of medical interventions. NSAIDs (27.9%) were the most common medication in the included studies. In the quantitative analysis of the studies, the author has always chosen the random effect model. The reason for this was the great methodological and numerical heterogeneity of the included studies. Over-interpretation of some studies should be avoided by applying the random effects method.

Most studies compared the effectiveness of treatment with placebo (52.3% of the included studies) or another medicine (31.4%).

This explains the great heterogeneity of the studies, which made it difficult for the author to investigate a larger patient pool. Many of the included studies had a very short follow-up time. Only 7% of the included drug trials were investigated in long-term follow-ups.

4.4.2 Quality of the studies

Considering the Cochrane risk of bias tool, it was found that 54 studies had a low risk of bias for randomization. It is even more worrying that when the allocation concealment was evaluated, only 17 RCTs showed low risk of bias. Selection bias or allocation bias occurs when there are systematic differences between comparison groups in terms of prognosis or response to treatment. Allocation bias prevents investigators from predicting which intervention will be allocated next and using this information to select which participant receives which treatment. Errors in randomization and the allocation concealment can lead to serious biases and affect the quality of the evidence generated, potentially translating into selection biases [506]. In terms of blinding of participants and personnel, 48 studies marked a low risk of bias and 45 trails used blinding of the investigator. Nevertheless, in 15 studies, blinding of the participants was not possible due to the various treatments and nature of the endorsed therapies [40, 161, 243, 297, 303, 310, 311, 323, 337, 348, 353, 360, 365, 368, 373]. Regarding incomplete outcome data, 59 studies satisfactory stated dropouts, while only 11% of the included studies used ITT. This is an additional potential bias that could hypothetically hinder the perceived outcomes, as the effect sizes from studies that used ITT analysis are more highly valued compared to trails without ITT analysis [507]. The included trials adequately reported selective reporting with 75 studies showing low risk. In addition, less than 25% of the studies had scored a low risk of bias for other bias that could affect the quality of the results, as most studies did not report the non-significance statistical difference in intervention groups at baseline. When comparing the included studies of medication to the other extraoral interventions for TMD (acupuncture, laser, psychosocial interventions), the author found out that the studies focusing on medication reported less on blinding of participants and blinding of the investigator than the other interventions mentioned above. They scored above 60% for both categories. This is striking as medication is easily blinded compared to placebo. In view of this, the interpretation of the included studies must be made with caution, as the general risk of bias was present.

4.4.3 Discussion of the meta-analysis

The aim of this review and meta-analysis was to provide validated scientific evidence on the effectiveness of extraoral therapies on different degrees of pain chronification in TMD patients. Nevertheless, taking a closer look at medication, the results were limited due to the lack of primary studies of acceptable scientific quality and the heterogeneity of the available material. 86 studies were included in the systematic review and 68 studies were included in the meta-analysis for medication.

The meta-analysis showed some interesting results: In the broad meta-analysis of orally administered medication compared to other treatments, a significant bigger difference in

favour of other treatments in pain relief in the short term (less than six months) was found. Both subgroups with low disability pain and high disability pain showed no statistically significant result for orally administrated medication. A clinically significant pain reduction was found in almost all low disability pain groups but not in the high disability pain group. Comparing injected medication only to other treatment no statistically significant result was being observed for total pain, low disability pain nor for high disability pain. An overall clinical pain reduction was observed in the included studies for the comparison. When medication treatment (injected medication excluded) was compared to placebo in relieving pain, an advantage with significance in favour of medication was found. Both subgroups with low and high disability pain showed a statistically significant difference in favour of medication. An overall clinical pain reduction was observed in the included studies. A sensitivity analysis was undertaken for this comparison (seen in Figure 84) and closer look was taken at excluding the cream medication and a significance difference was found for the oral medication compared to placebo. High disability pain also showed a benefit from medication (injectable excluded + creams excluded) compared to placebo. On the other hand, low disability groups showed no significant difference. Some trials used a combination of medication cocktails. Consequently, another subgroup analysis (Figure 85) was used showing the superiority of medication as a single intervention compared to placebo. Both low and high disability groups showed bigger significant results. For an improvement in MMO no significant difference was seen between medication (injections excluded) and placebo. The injected medication compared to placebo showed a statistically significant difference in the overall comparison for pain relief. However, neither low nor high disability subgroups demonstrated significant results. From the results of the study, injections are not superior to placebo for the improvement of MMO.

Subgroup analyses were done by subdividing the medications into subgroups of BTX, NSAIDs, and benzodiazepines. When botulinum toxin treatment alone was compared to other treatments, no advantage in terms of pain relief was found. However, it was interesting to note that there was a statistically significant difference when compared to placebo. Botulinum toxin was found to be superior in the high disabled subgroup. A clinical significance was observed entirely in the included studies using BTX. For the treatment of BTX, it has been demonstrated by Sahoo et al. 2021, that botulinum toxin also showed a significant improvement in all scores that continued for up to six months post-injection ($P<0.001$) [508]. The effect of BTX can last up to six months, so future studies should focus on longer follow-up periods to get the greatest results. Previous reviews on the efficacy of botulinum toxin in the treatment of TMD have shown comparable results for BTX [296, 509]. The results for NSAIDs were also interesting as they showed a weak to no efficacy in treating painful TMD, except for groups with high disability pain. NSAIDs was compared with other

treatments and found a significant difference in favour of other treatments in pain relief and improvement in function. NSAIDs were found to be superior to placebo in the high disability subgroup, which is very interesting and needs further investigation. A clinical significance pain reduction was observed in all the included studies in this comparison.
Looking at previous reviews and meta-analysis, Kulkarni et al. 2020 reached similar conclusions regarding the effectiveness of NSAIDs and suggested heterogeneity of results for the lack of significant findings [510]. A meta-analysis by Enthoven et al. 2017 also supports the findings of this meta-analysis. It found that NSAIDs were associated with greater improvement in pain intensity and disability compared to placebo in patients with chronic low back pain [511]. Benzodiazepines showed no significant result in terms of pain reduction for low disability pain nor high disability pain in the short term compared to placebo. However, it is important to point out that the benefits of benzodiazepines are limited by the loss of efficacy that can occur with continued use and by adverse effects, including physiological dependence, which develops in 20-100% of those who take these agents for longer than one month [512].

The hypothesis can be confirmed that painful TMDs respond differently to orally administered medication, BTX therapy and NSAIDs therapy depending on the degree of chronic pain-related disability. Therefore, the prognosis of therapy is significantly influenced by the degree of chronic pain-related disability of the disease.

4.5 Psychosocial interventions

4.5.1 Discussion of the systematic review / descriptive findings

Most of the included studies on psychosocial intervention treatment (57%) concerned TMD of muscular origin. Most studies used the RDC/TMD as diagnostic tools. Painful TMD was an important inclusion criterion that was met in all included studies. However, a major lack of current data on treatment with psychosocial interventions is also the small number of studies that treated patients with high disability pain. However, details on GCPS (28.6% of included studies reported GCPS) were best described in this intervention category compared to the other interventions studied in this work (acupuncture, laser, medication, physiotherapy). The sample size of patients with high disability pain in psychosocial intervention therapy was still very small (19% of included studies with potentially high disability pain), and subgroup comparisons between patients with low disability pain and those with high disability pain were also hardly possible for this intervention. The highest criterion for a diagnosis of high disability pain was also the mention of previous treatments (35.7% of included studies), as seen by the author in acupuncture, laser, and drug intervention studies. Whether the previously performed treatments were unsuccessful was generally not described. 54.8% of the included studies on psychosocial intervention treatment recruited participants from tertiary institutions, which is in line with the studies to acupuncture, laser and medication treatment and the assumption that most RCTs are conducted at universities. Another aspect that should not be ignored in the critical analysis of the methodology is the non-exclusive and well-defined application of the interventions studied. All psychosocial intervention studies with sometimes very heterogeneous combinations and control groups were examined and the data obtained compared. The author included all types of psychosocial interventions. CBT (33%) and self-care (33%) were the most common psychosocial interventions in the included studies. In the quantitative analysis of the studies, the author always chose the random effects model. The reason for this was the great methodological and numerical heterogeneity of the included studies. Overinterpretation of some studies was to be avoided by using the random effects method.

Most studies compared the efficacy of psychosocial interventions to splint therapy (33% of included studies) or to another psychosocial intervention (26%).

This explains the large heterogeneity of the studies, which made it difficult for the author to examine a larger patient pool. Many of the included studies had a very short follow-up period. However, the studies on psychosocial interventions (28.6 %) had the highest proportion of long-term follow-up (12 months or more) studies compared to the other extraoral interventions investigated (acupuncture, laser, medication, and physiotherapy).

4.5.2 Quality of the studies

The risk of bias from the articles was significantly enriched by the supplementary material received from the research team of the respective studies. The author was able to apply the modifications to the risk-of-bias assessment because the author methodically contacted each author of the included trials and studies awaiting classification. However, not all authors responded, leaving many uncertainties in the Cochrane Library's Risk of Bias, and resulting in most of the included studies to be at unclear risk. The author also under-reported the blinding of participants and staff, as it is technically difficult to do in this type of comparison. For all studies where the different therapies made blinding of patients and staff difficult, the author assessed a low risk of bias. The quality of evidence in the meta-analysis was therefore significantly improved over older reviews, due to the blinding of participants and staff and the further information gathered from the individual authors.

4.5.3 Discussion of the meta-analysis

The results showed no superiority in the short term or medium-term pain reduction when comparing psychosocial interventions with other treatments in the low disability pain or high disability pain group. In the long term, the author found an overall clinically and statistically significant result in favour of psychosocial interventions compared to other treatments in reducing pain intensity. A statistically significant result was also found in the low disability pain group but not in the high disability pain. The results showed no differences in MMO improvement when comparing psychosocial interventions with other treatments. Further studies may be needed to determine whether the lack of statistical significance within the analysis is due to low statistical power or chance. On the other hand, looking at the improvement in depression scales in the short term: a superiority to the psychosocial interventions group was seen in the high disability pain group compared to other treatments, while no effect was seen in the other subgroups with low disability pain. These results must be considered with caution due to the high heterogeneity of the studies and the limited number of studies.

Psychosocial interventions are an umbrella term for all interventions that highlight psychological or social factors [513]. Looking at the effectiveness of self-care, counselling, and education alone, the author was unable to clarify the efficacy of those therapies in this meta-analysis. In the results the author conducted a meta-analysis in the short term against other treatments and no difference was observed between the two therapies in the follow-up periods. In the subgroup analysis no statistically, significant difference was observed in the low disability or high disability pain group.

For the treatment of patients with a painful anterior disc displacement without reduction as well as for patients with TMD pain without major mental disorders, the null hypothesis of Türp at al. 2007 can be accepted, stating that a simple therapy is equally efficient as the

multimodal approach in resolving the disorder of patients with disc displacement without reduction, which appears to be a predominantly mechanical problem. However, it must be rejected for patients with TMD pain and major mental disorders. According to Türp et al. 2007, patients without major mental problems do not need more than a simple therapy. In contrast, patients with major mental disorders need to be identified, as the best outcome is achieved with a multimodal, interdisciplinary therapy strategy [514]. As psychosocial interventions mainly use more than one therapy the findings of this meta-analysis are in some part according to the findings of Türp et al. [514]. Another author hypothesised that patients reporting emotional and physical difficulties (e.g., depression) would benefit more from treatment with psychosocial interventions than from similar comparative treatment without psychosocial interventions, which is in line with our findings regarding the depression scale. Turk et al. 1996 also concluded that psychosocial interventions was effective for highly distressed TMD patients [515].

The overall statistically significant result in favour of psychosocial interventions compared to other treatments in reducing pain intensity, does not undermine the hypotheses that patients suffering from high disability pain respond better to psychological interventions in terms of pain relief than patients suffering from acute/low disability short-term pain [515]. However, it can be explained through one that the fact that the control groups were very heterogeneous and difficult to compare. Additionally, the impact of CBT was investigated by Turner et al. 2007 on possible predictors for outcomes by patients' baseline characteristics. Several patients with more somatization, depressive symptoms and a greater number of pain sites were more impaired in their activities after one year. Previous studies in different populations also found that these factors were associated with greater concurrent and future disability and poorer treatment outcomes [516]. Patients with severely debilitating pain may require more intensive psychosocial interventions, and treatment for depression may be advisable before or in conjunction with CBT for pain [516].

The hypothesis can be confirmed that patients with painful TMDs respond differently in the long-term pain reduction and short-term improvement of depression through psychosocial interventions therapy depending on the degree of chronic pain-related disability. Therefore, the prognosis of therapy is significantly influenced by the degree of chronic pain-related disability of the disease.

4.6 Physiotherapy

4.6.1 Discussion of the systematic review / descriptive findings

Most of the included studies on physiotherapy treatment concerned TMD of muscular origin (45% of the included studies). 69% of the included studies used the RDC/TMD as diagnostic tools. Painful TMD was an important inclusion criterion that was met in all included studies. However, a major lack of current data on treatment with physiotherapy is also the small number of studies that treated patients with high disability pain. Details on GCPS was only reported by 8.5%. The sample size of patients with high disability pain in physiotherapy treatment was very small (12% of included studies with potentially high disability pain), and subgroup comparisons between patients with low disability pain and those with high disability pain were also hardly possible for this intervention. The highest criterion for a diagnosis of high disability pain was also the mention of previous treatments (47.5% of included studies), as seen by the author in acupuncture, laser, drug intervention and psychosocial intervention studies. Whether the previously performed treatments were unsuccessful was generally not described. 61% of the included studies on physiotherapy treatment recruited participants from tertiary institutions, which is in line with the studies to acupuncture, laser, medication and psychosocial intervention treatment and the assumption that most RCTs are conducted at universities. Another aspect that should not be ignored in the critical analysis of the methodology is the non-exclusive and well-defined application of the interventions studied. All physiotherapy studies with sometimes very heterogeneous combinations and control groups were examined and the data obtained compared. The author included all types of physiotherapy: jaw and neck exercise alone/ part of a conservative regime (36%) and manual therapy targeted to the orofacial region (34%) were the most common physiotherapy in the included studies. In the quantitative analysis of the studies, the author always chose the random effects model. The reason for this was the great methodological and numerical heterogeneity of the included studies. Overinterpretation of some studies was to be avoided by using the random effects method. Most studies compared the efficacy of physiotherapy treatment to splint therapy (24% of included studies) or to placebo (19%).
This explains the large heterogeneity of the studies, which made it difficult for the author to examine a larger patient pool. Many of the included studies had a follow up period of six months and less. Therefore, the meta-analysis for physiotherapy were only on short follow up periods (less than six months).

4.6.2 Quality of the studies

In general, the included studies on physiotherapy are similar in methodological quality compared to the other interventions in the review (acupuncture, laser, medication, and psychosocial interventions). As mentioned above, the author contacted each author for

further information and adjusted the risk-of-bias tool accordingly to improve the quality of the overall risk-of-bias tool. Nevertheless, the methodological biases common to the contained trials could have an influence on the outcomes. Selection bias may have occurred as only 40 studies recorded adequate randomization and just nine studies described concealed allocation. In addition, insufficient information about blinding, especially blinding of patients and investigators, could also be considered critical bias. Therefore, it is possible that the absence of blinding influenced the outcomes of the included trials. However, the author labelled the studies as low risk of bias when blinding was not possible due to the different therapies as mentioned before in the other interventions (acupuncture, laser, medication, or psychosocial interventions). A previous meta-epidemiological study found that clinical and policy decisions should be more circumspect when based on studies in which blinding was not reported and outcome measures were assessed subjectively. It states that studies lacking adequate randomization, allocation concealment and double blinding were more likely to issue an inaccurate treatment effect compared to RCTs that met these categories [317, 517]. Therefore, the results should also be considered cautiously as not all studies reported everything accurately.

A substantial number of 43 studies reported appropriate handling of withdrawals and drop out. This was higher in comparison to other interventions assessed in this review such as laser and medication. However, there was another potential bias that could affect the observed results, as only five trials reported on ITT. It has been shown that effect sizes from studies that used intention-to-treat analysis are more valuable compared to studies that did not use ITT analysis [507]. On the other hand, all included trials except for one reported fully about the outcomes compared to the other interventions in this review. Finally, nine studies reported no conflict of interest and stated that there was no statistically significant difference of the included groups at baseline. This was similar when compared to the other interventions.

4.6.3 Discussion of the meta-analysis

The aim of this systematic review and meta-analysis was to analyse the effectiveness of physiotherapy interventions in patients with different degrees of pain. To our knowledge, the meta-analysis procedure applied in this study is the first to identify the effectiveness of physiotherapy according to different degrees of pain chronification. A total of 43 RCTs were included in this meta-analysis. The outcomes obtained in the present review and meta-analysis show however, a considerable heterogeneity between the included trials. Therefore, the results need to be evaluated with caution because of the large clinical differences between the interventions performed and the measurement instruments used for comparisons. The analysis was difficult to conduct because there is no standardisation for the individual treatments in physiotherapy. In addition, many RCTs only present short-term

results. The experimental group (physiotherapy) was also subdivided into MT combined with exercise, MT alone and jaw exercise alone, while the control group (other treatment) was also categorized into other treatment, placebo group, splint therapy and psychosocial interventions therapy. To focus without bias on the efficiency of physiotherapy interventions and to determine the cumulative effects from other techniques, the author used the same procedure as a previous review and excluded RCTs that included combined therapies except for studies using MT combined with exercise training and physiotherapy combined with another treatment. This reduced the outcomes but permitted an improved support for the results of physiotherapy separately and the impact of physiotherapy interventions in TMD treatment [119].

In the meta-analysis the author found out that there was no significance difference comparing physiotherapy to other therapy in pain relief, but a statistically significant difference was found in the improvement of MMO compared to other therapy in the short term (less than six months) in patients suffering from TMD. The results from the specific subgroups helped to refine the findings and highlight factors that may be beneficial in the clinical practice of physiotherapy for the treatment of pain in patients with low or high disability pain. A subgroup analysis according to the classification of chronicity of pain showed to be significantly superior in the improvement of MMO in the low disability pain group. This is in line with the short treatment effects of physiotherapy. These results are not in accordance with the findings of Paco et al. 2016 who stated that in the case of MMO they found no statistically significant result in favour of physiotherapy in improving MMO only in the short term [119].

By comparing physiotherapy combined with another treatment with any control treatment, the combination treatment had a statistically significant effect on the improvement of MMO but similarly, not on pain intensity. All of the included studies in this comparison showed a clinical significant pain reduction. Observing physiotherapy treatment combined with another treatment the author only had studies with low disability pain. No significant difference was found in short-term pain relief compared with another single treatment, whereas a significant result was found in MMO improvement and low disability pain.

Another salient point was that physiotherapy rarely uses placebo control groups compared to the other extraoral interventions. When the author compared physiotherapy with placebo, an advantage for physiotherapy treatment was found in pain relief. The subgroup showed a statistically significant result for the high disability pain group, but controversially not in the low disability pain group. MMO was not evaluated due to the lack of studies for that comparison.

Jaw exercises showed no advantage compared to other treatment in pain relief or function. Nevertheless, looking at MT combined with exercise and MT alone compared to other

treatment the author found a significance difference in pain relief in the short term (less than six months) in favour of MT as well as MT combined with exercise. However, the subgroup analysis showed that MT therapy alone had a significant result in pain reduction in the high disability group. For MMO improvement, MT alone proved to be superior in the low disability group. MT in combination with pain exercises proved to be significantly more effective in the low disability group in pain management and showed no significant difference for MMO compared to the control group. Finally, when the author compared physiotherapy against the two main controls (splint and psychosocial interventions), the author wanted to see whether there was evidence in favour of physiotherapy as splint and psychosocial interventions were the main treatments. Physiotherapy works differently than the other two controls as physiotherapy focuses on the muscles and the position of the condyle. The author perceived a significant difference in the improvement of MMO in favour of physiotherapy treatment compared to splint therapy. This was also found in the low disability subgroup. However, no significant results were found when the author compared physiotherapy with psychosocial interventions.

Comparable effects have been determined in previous reviews regarding the effectiveness of treatments based on MT [431, 518]. A direct difference between the low disability and high disability pain group was also found for MT. The reduction in pain could be explained by peripheral and central pathways according to Bialosky et al. 2009. In response to impairment, peripheral nociceptors and inflammatory mediators might interact and MT may directly influence this mechanism [519]. In addition, MT has been shown to induce mechanical hypoalgesia (changes associated with sympathetic nervous system activation) and a reduction in temporal summation (suggesting mechanisms involving the periaqueductal grey and spinal dorsal horn). Compelling evidence was found to support the involvement of the central nervous system in mediating the response to MT [519, 520]. Nevertheless, further investigation needs to be conducted on MT and TMD combined.

The hypothesis can be confirmed that painful TMDs respond differently to physiotherapy depending on the degree of chronic pain-related disability. Therefore, the prognosis of therapy is significantly influenced by the degree of chronic pain-related disability of the disease.

4.7 Degree of chronification depending on the different therapies investigated

The aim of this meta-analysis was to find out whether patients with low or high pain disability in painful TMD show different healing response to extraoral therapies. Knowledge of the patient characteristics of pain chronification that predict or attenuate improvement with extraoral therapies could help direct limited resources to those most likely to benefit, match patients to the most appropriate treatments, and tailor interventions to patient characteristics. Clinical concepts such as the division into different phases of pain clarify the process of chronification. Furthermore, consideration of psychosocial components through dual-axis diagnostic schemes (Axis I: somatic findings, Axis II: psychosocial parameters) in the classification of pain patients allows for a better assessment of the severity of the pain condition, independent of the time factor [19]. Remarkable results were found, and it was concluded that there is some evidence that low disability pain and high disability pain have different responses to extraoral therapies for TMD (Table 31, Table 32, Table 33).

For example, acupuncture therapy showed a significant difference in pain reduction in the low disability pain group compared to the control group, while dry needling showed a significant difference in pain reduction in the low disability pain group compared to other treatment. In contrast, acupuncture and dry needling showed no significant effect in the high pain disability group. In addition, no significance difference was seen for the improvement of mouth opening in the low disability pain group nor in the high disability pain group using acupuncture or dry needling. These results demonstrate that acupuncture and dry needling have a positive short-term effect on pain relief in low disability pain groups.

LLLT had the same effect as acupuncture and dry needling in the low disability group, as the author found significant advantage for LLLT in the low disability pain group over placebo in pain reduction. Dry needling and LLLT both use the trigger points as application site.

Laser therapy also showed a significant difference in the improvement of mouth opening in the low disability pain group in the short term. For high disability pain, there was no effect for either outcome. When considering the different wavelengths, the author discovered another difference between the two pain groups. The low disability pain group showed a statistically significant result at a wavelength of 800-830 nm in terms of short-term pain relief compared to placebo, while the high disability group showed a significant result at a wavelength of >831 nm. While acupuncture, dry needling and LLLT appear to have greater effects on low disability pain, medication and psychosocial interventions had a better healing effect on the high disability group in several meta-analyses. For example, medication orally administered showed a significant difference from placebo in the high disability group, while there was no significant result in low disability pain. Botulinum toxin and NSAIDs also showed a significant effect on pain relief in high disability pain, while there was no significant difference from placebo in low disability pain. In addition, psychosocial interventions had a statistically

significant better effect on pain reduction in the long time in the high disability pain group than in the low disability group. Depression score improved significantly in the short term in the high disability pain group with psychosocial interventions compared to other treatments. Physiotherapy also showed some interesting results in the different healing processes in the low and high disability pain group. Overall, the low disability pain group showed significant advantages in improving MMO using physiotherapy interventions such as physiotherapy alone or in combination with another treatment and using manual therapy. In contrast, high disability pain did not show any advantage towards physiotherapy in improving function.
In terms of reducing pain relief, physiotherapy compared to placebo and MT achieved significant results in the high disability pain group. Controversial MT combined with exercise had a significant result in the low disability pain group.
Considering these results, the need to treat patients with low disability pain and those with high disability pain in a different way is evident. Too many differences were found between the pain characteristics. It must be said that further studies need to focus on the diversity of pain characteristics and that the results should be considered with caution due to the heterogeneity of the studies and outcomes.

4.8 Limitations

The results of the current literature on extraoral therapies for the treatment of TMD have some limitations that should be noted. In general, several shortcomings were found in the five interventions reviewed. A primary limitation of the work was the large heterogeneity between the pooled studies that was evident in the observed results. Despite the considerable heterogeneity in some cases, the observations were not excluded from the discussion. In addition, controls varied widely. Most studies used sham or placebo controls, but some used splints, lasers or even medication. This makes comparison difficult, as some clinical trials lacked data on baseline characteristics, potentially falsely increasing heterogeneity. Although the author estimated the missing SD from other SDs for each intervention, this could lead to errors. Another limitation was the partially different measurement parameters of the included studies. Data from the CPI or NRS were compared with simple surveys of current pain intensity using the VAS. However, the sensitivity analysis did not reveal any suspicion of bias in the results. Standardisation of measurement tools would allow researchers to pool data from multiple studies and thereby draw consistent conclusions about the effectiveness of treatment for TMD. Many studies have used the VAS as a pain measurement tool, which has been shown to be an effective measurement tool for low disability pain. However, it has also been criticised for being used as a unidimensional measure of pain intensity and not capturing the complex experience of high disability pain. This is because high disability pain in adults has been poorly measured with the VAS [521]. Considering that pain is the most common reason for consultation, further studies should

revise the current knowledge to account for the multidimensionality of pain. In this regard, the psychological profile of the patient may be crucial to determine the most effective therapy for a personalised TMD diagnosis. The lack of use of the GCPS in the included studies underscores this notion and was a limiting factor in categorising patients into their individual levels of chronification, leaving many studies in the "unclear pain" category. The categorisation of the degree of chronification itself could lead to some errors, as the information only comes from the authors' publications and statements, not from the study authors themselves. In addition, the treatment effects could be overestimated due to the small sample size. To avoid this phenomenon, several studies with fewer than 15 candidates needed to be excluded. In addition, studies with predominantly unclear or partially high risk of bias were not excluded from the quantitative analysis unless they suggested questionable randomization.

In summary, several limitations were identified in the included studies of extraoral therapies in the treatment of TMD, leading to several potential errors in the resulting outcomes. For this reason, the results must be interpreted with caution. However, the author attempted to limit the errors by contacting each study group and systematically grouping the included studies into categories to limit heterogeneity. Despite these limitations, the results of this study are not expected to be biased.

Further researchers should focus on the major complications of TMD, recognise the multidimensionality of pain and focus more on patient severity and chronicity.

4.9 Conclusion

The present study makes an important contribution to the differentiated consideration of subjects with low-disability and high-disability TMD pain. A general conclusion on the general forms of intervention in extraoral therapy (acupuncture, laser, medication, psychosocial interventions, and physiotherapy) cannot be made. This review strived for a clearer view at the level of individual interventions. Some interventions showed no difference between low disability pain and high disability pain, with no significant outcome. However, individual interventions demonstrated a significant difference in the effectiveness for low disability pain or high disability pain. Thus, individual interventions of the five interventions studied confirm the hypothesis that painful TMDs respond differently to established therapies depending on the degree of chronic pain-related disability and that the prognosis of therapy is significantly influenced by the degree of chronic pain-related disability of the condition, according to the GCPS.

4.10 Outlook

The overall results of this meta-analysis show differences between the subgroups of low disability pain and high disability pain. For this reason, the next studies should focus on better diagnostics of painful TMD. Many studies used the DC/TMD, but only a handful of

authors described the GCPS, leaving the multifactorial nature of TMD pain unclear. It is recommended that future studies on TMD and related secondary diagnoses should use the recommended diagnostic material to apply the most appropriate treatment for the specific pain stage the patient is suffering from.

From the results, it is also suggested that upcoming research needs to clarify the ambiguous issues of extraoral therapy and work against the absence of a specific protocol for acupuncture, laser, medication, psychosocial interventions, and physiotherapy in the management of painful TMD.

Also, further studies should focus on correct satisfactory randomization methods, allocation concealment, blinding of participants and investigators, ITT and long term follow up periods. In addition, future RCTs should report key outcomes to allow comparisons. This meta-analysis proposes an approach to compare the effectiveness of extraoral therapies for the different types of chronicity of TMD, for pain (pain intensity), physical outcomes (MMO) and psychological outcomes (depression).

5 Abstract

Background: That a differentiated treatment of subjects with low and high levels of disabling pain might be necessarily has only been suspected but not sufficiently confirmed so far. Furthermore, the effectiveness of extraoral therapy methods for TMD is still controversial in the literature. The present work could make an important contribution to this.

Objectives: Five systematic reviews with meta-analysis were conducted to investigate the efficacy of extraoral therapies (acupuncture, laser, medication, psychosocial interventions, and physiotherapy) in the treatment of TMD in relation to the degree of chronicity of pain.

Literature sources: With this objective, the databases Pubmed/MEDLINE, EMBASE, Cochrane Library, Livivo, OpenGrey, drks.de, Clinicaltrials.gov. were searched.

Criteria for the selection of suitable studies: Adults suffering from painful TMD and treated with either acupuncture, laser, medication, psychosocial interventions, or physiotherapy. The studies were then examined for evidence in the subjects' characteristics suggesting that they were suffering from chronic TMD in terms of pain dysfunction. These included a high score on the GCPS, resistance to undergone treatments, multilocular pain, depression, and regular use of pain medication. The effectiveness of the five interventions was then differentiated according to the suspected degree of chronicity. Effectiveness was assessed by the following outcomes: patient-related current pain intensity, MMO, pain on palpation, temporomandibular joint sounds, depression, and somatization.

Study evaluation: After the assessment of the studies, the quality assessment (Risk of Bias Tool of the Cochrane Institute) and the extraction of the data were conducted. After that five meta-analyses were carried out for each of the five interventions using the Review Manager of the Cochrane Institute (RevMan 5.3)

Results: Acupuncture and dry needling were statistically significantly more effective in providing short-term pain relief compared to the control group in patients with low disability pain ($p=0.04$) and ($p=0.02$), respectively. Acupuncture or dry needling did not show a significant result in the improvement of MMO in the short-term period. Laser therapy is more effective in relieving pain ($p<0.0001$) and functional outcomes ($p=0.03$) in the short term compared to placebo for low disability pain. Botulinum toxin ($p=0.003$) and NSAIDs ($p=0.03$) showed significantly better short-term improvement in pain intensity for high disability pain. Low disability pain is significantly better treated by psychosocial interventions than by other treatments in terms of long-term pain relief (more than 12 months) ($p=0.02$). Patients with high disability pain had significantly lower depression scores after psychosocial interventions than after other treatments ($p=0.008$). Physiotherapy showed a statistically significant short-term analgesic effect in patients with high disability pain compared to placebo ($p=0.04$). Manual Therapy (MT) showed a statistically significant short-term analgesic effect in high disability pain compared to the control group ($p=0.01$). Patients with low disability pain showed a statistically significant short-term pain-relieving effect with the single intervention of MT in combination with exercise compared to the control groups ($p=0.003$). A statistically significant result in the improvement of MMO was found in the short-term period in low disability pain for the single interventions of physiotherapy ($p=0.008$) and physiotherapy in combination with another treatment compared to other treatments ($p=0.03$), MT compared to the control group ($p=0.03$) and physiotherapy compared to splint therapy ($p=0.03$). **Clinical conclusion:** Individual interventions of the five extraoral therapies confirm the hypothesis that painful TMDs respond differently to established therapies depending on the degree of chronic pain-related disability and that the prognosis of therapy is significantly influenced by the degree of chronic pain-related disability of the condition, according to the GCPS.

Registration number of the review at PROSPERO: CRD42020202558

Keywords: meta-analysis, systematic review, temporomandibular disorders, extra oral therapy, acupuncture, laser, medication, psychosocial interventions, physiotherapy, low disability, high disability, pain, chronification

Zusammenfassung

Hintergrund: Das eine differenzierte Behandlung von Probanden mit funktionalem (fS) und dysfunktionalem Schmerz (dS) notwendig sein könnte, wurde bisher nur vermutet, aber nicht ausreichend bestätigt. Darüber hinaus ist die Wirksamkeit extraoraler Therapiemethoden bei CMD in der Literatur noch umstritten. Die vorliegende Arbeit könnte hierzu einen wichtigen Beitrag leisten. **Ziele:** Fünf systematische Übersichten mit Metaanalyse wurden durchgeführt, um die Wirksamkeit extraoraler Therapien (Akupunktur, Laser, Medikamente, psychosoziale Interventionen und Physiotherapie) bei der Behandlung von einer schmerzhaften CMD in Abhängigkeit von dem Chronifizierungsgrad zu untersuchen. **Literaturquellen:** Die Datenbanken Pubmed/MEDLINE, EMBASE, Cochrane Library, Livivo, OpenGrey, drks.de und Clinicaltrials.gov wurden durchsucht. **Auswahlkriterien:** Erwachsene PatientInnen, die an schmerzhaften CMD leiden und entweder mit Akupunktur, Laser, Medikamenten, psychosoziale Interventionen oder Physiotherapie behandelt wurden. Die Studien wurden dann auf Hinweise in den Probandenmerkmalen untersucht, die darauf schließen lassen, dass die ProbandInnen unter chronischer CMD im Sinne einer Schmerzdysfunktion leiden. Dazu gehörten ein hoher Wert im GCPS, Behandlungen, die die Probanden bereits erfolglos durchgeführt hatten, multilokuläre Schmerzen, Depressionen und regelmäßige Einnahme von Schmerzmitteln. Anschließend wurde die Wirksamkeit der fünf Interventionen nach dem vermuteten Grad der Chronifizierung differenziert. Die Wirksamkeit wurde anhand der folgenden Ergebnisse untersucht: patientenbezogene aktuelle Schmerzintensität, MMO, Schmerz bei Palpation, Kiefergelenkgeräusche, Depression und Somatisierung. **Studienbewertung**: Nach der Bewertung der Studien, der Qualitätsbeurteilung (Risk of Bias Tool des Cochrane-Instituts) und der Extraktion der Daten wurden für jede der fünf Interventionen fünf Meta-Analysen mit dem Review Manager des Cochrane-Instituts (RevMan 5.3) durchgeführt **Ergebnisse:** Akupunktur und Dry Needling waren statistisch signifikant wirksamer bei der kurzfristigen Schmerzlinderung im Vergleich zur Kontrollgruppe bei Patienten mit geringem Grad an beeinträchtigendem Schmerz (p=0,04) bzw. (p=0,02). Akupunktur oder Dry-Needling zeigten im kurzfristigen Zeitraum kein statistisch signifikantes Ergebnis in der Verbesserung der Kieferöffnung. Die Lasertherapie ist im Vergleich zu Placebo bei funktionalem Schmerz kurzfristig wirksamer bei der Reduktion der Schmerzintensität (p<0,0001) und funktionellen Ergebnissen (p=0,03). Botulinumtoxin (p=0,003) und NSARs (p=0,03) zeigten eine signifikant bessere kurzfristige Verbesserung der Schmerzintensität bei dS. FS werden durch die psychosozialen Interventionen signifikant besser behandelt als durch andere Behandlungen, was die langfristige Schmerzlinderung (mehr als 12 Monate) betrifft (p=0,02). PatientInnen mit dS wiesen nach psychosozialen Interventionen signifikant niedrigere Depressionswerte auf als nach anderen Behandlungen (p=0.008). Physiotherapie zeigte eine statistisch signifikante kurzfristige schmerzlindernde Wirkung bei PatientInnen mit dS im Vergleich zu Placebo (p=0,04). Manuelle Therapie (MT) zeigte eine statistisch signifikante kurzfristige schmerzlindernde Wirkung bei dS im Vergleich zur Kontrollgruppe (p=0,01). Bei PatientInnen mit fS zeigte sich im Vergleich zu den Kontrollgruppen eine statistisch signifikante kurzfristige schmerzlindernde Wirkung bei der Einzelintervention von MT in Kombination mit Bewegung (p=0,003). Ein statistisch signifikantes Ergebnis bei der Verbesserung der MMO wurde im Kurzzeitzeitraum bei fS für die Einzelinterventionen der Physiotherapie (p=0,008) und der Physiotherapie in Kombination mit einer anderen Behandlung im Vergleich zu anderen Behandlungen (p=0,03), der MT im Vergleich zur Kontrollgruppe (p=0,03) und der Physiotherapie im Vergleich zur Schienentherapie festgestellt (p=0,03). **Schlussfolgerung:** Einzelne Interventionen der fünf extraoralen Therapien bestätigen die Hypothese, dass schmerzhafte CMD je nach Grad der Schmerz Chronifizierung unterschiedlich auf etablierte Therapien ansprechen und dass die Prognose der Therapie signifikant durch den Grad der Chronifizierung der Erkrankung beeinflusst wird. **Registrierungsnummer der Review bei PROSPERO**: CRD42020202558.

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APPENDIX I: Abbreviations

AAOP ..... ***American Academy of Orofacial pain***
ATP ..... ***Adenosine triphosphate***
BDI ..... ***Beck Depression inventory mean***
BTX ..... ***Botulinum toxin***
CBT ..... ***Cognitive behavioural therapy***
CENTRAL ..... ***Cochrane Central Register of Controlled Trials***
CHSSS ..... ***Cochrane Highly Sensitive Search Strategy***
CNN ..... ***Central nociceptive neurons***
COX ..... ***cyclooxygenase***
COX-2 ..... ***Cyclooxygenase-2***
CPI ..... ***Characteristic pain intensity***
CV ..... ***Coefficient of variation***
DC/TMD ..... ***Diagnostic Criteria for TMD***
DGSS ..... ***Deutsche Schmerzgesellschaft***
FPI ..... ***Facial pain index***
Ga-Al-As ..... ***Gallium aluminium arsenide***
Ga-As ..... ***Gallium arsenide***
GABA ..... ***G-aminobutyric acid***
GCPS ..... ***Graded Chronic Pain Scale***
GSI ..... ***Global Severity Index***
HADS ..... ***Hospital Anxiety and Depression Scale***
He-Ne ..... ***Helium-neon***
IASP ..... ***International Association for the Study of Pain***
InGaAlP ..... ***Indium- gallium-aluminium-phosphide***
ITT ..... ***Intention-to-treat***
LDF-TMDQ ..... ***Limitations in daily function***
LLLT ..... ***Low-level laser therapy***
MENS ..... ***Microcurrent Nerve Stimulation***
mm ..... ***Millimetre***
MMO ..... ***Maximum mouth opening***
MO ..... ***Mouth opening***
MRI ..... ***Magnetic resonance imaging***
MT ..... ***Manual therapy***
MUs ..... ***Motor units***
MV ..... ***Mean value***
Nd:YAG ..... ***Neodymium-doped yttrium aluminium garnet***

APPENDIX I: Abbreviations

NGF ..... ***Nerve growth factor***
NRS ..... ***Numerical rating scale***
NS ..... ***Numerical scale***
NSAIDs ..... ***Non-steroidal anti-inflammatory drugs***
OM ..... ***Oral motor***
PDP ..... ***Physiotherapeutic and drug protocol***
PGE2 ..... ***Prostaglandin E2***
PHQ2 ..... ***Patient Health Questionnaire-2***
PICO ..... ***Population, Intervention, Comparison(s) and Outcome***
PPI ..... ***Pain-physiopathology instrument***
PRISMA ..... ***Preferred Reporting Items for Systematic reviews and Meta-analysis***
PSDI ..... ***Positive Symptom Distress Index***
PST ..... ***Positive Symptom Total***
RCD/TMD ..... **Research Diagnostic Criteria for Temporomandibular Disorders**
RCT ..... ***Randomized controlled trials***
ROM ..... ***Range of motion***
SCL-90-R ..... **Revised Symptom Checklist-90**
SD ..... ***Standard deviation***
SMD ..... ***Standardized mean difference***
TCM ..... ***Traditional Chinese medicine***
TENS ..... ***Transcutaneous electrical nerve stimulation***
TMDs ..... ***Temporomandibular disorders***
TMJ ..... **temporomandibular joint**
VAS ..... ***visual analogue scale***
WHO ..... ***World Health Organisation***
WSP ..... ***widespread pain***

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APPENDIX IV: Acknowledgements

I would like to express my sincere thanks to Dr. Giannakopoulos for providing me with the topic and for his always friendly and helpful support in carrying out my work.

I would like to thank Dr. Roldán-Majewski. Her constructive criticism and suggestions were instrumental in the success and completion of the thesis.

I would like to thank Prof. Dr. Schmitter for making it possible for me to carry out this thesis in the Department of Prosthodontics.

I would like to thank all the staff at the Würzburg Dental Clinic and especially the Department of Prosthodontics who supported me in various ways in carrying out this work. In this regard, I would also like to thank Mrs Eichhorn, who assisted me many times with the full text search with full dedication and reliability.

Dr. Dangl I would like to thank for her help and cooperation in removing the duplicates.

I would like to thank Dr. Marion McGinn for her initial review and correction of the grammar of the manuscript.

Finally, I would like to thank my family and my partner Jan for their great support during my thesis, which is only a small part of the support I have received in my personal career so far.

APPENDIX VI: Publications

Title:

"Do occlusal splints statistically significantly improve jaw opening in CMD patients? Partial results of a systematic review with meta-analysis".

Authors:

Magdalena Stimmer, Nikolaos Nikitas Giannakopoulos, **Helena Held**, Hans Jürgen Schindler, Carolina Roldán-Majewski.

Journal:

Journal of Craniomandibular Function (CMF)

Published:

12.11.2021