Alberta Heritage Foundation
for Medical Research

TRIGGER POINT INJECTIONS FOR CHRONIC NON-MALIGNANT MUSCULOSKELETAL PAIN

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January 2005

HTA 35 **Health Technology Assessment**

This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion, and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments related to the report are welcome and should be sent to:

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ISBN 1-894927-06-0 (Print)
ISBN 1-894927-07-9 (On-line)

ISSN 1704-1090 (Print)
ISSN 1704-1104 (On-line)

Alberta's Health Technology Assessment program has been established under the Health Research Collaboration Agreement between the Alberta Heritage Foundation for Medical Research and the Alberta Health Ministry.

CONFLICT OF INTEREST

Conflict of interest is considered to be financial interest, either direct or indirect, that would be affected by the research contained in this report, or creation of a situation where an author's judgement could be unduly influenced by a secondary interest such as personal advancement.

Based on the statement above, no conflict of interest exists with the authors of this report.

The views expressed in the final report are those of the Foundation.

AHFMR is a member of the International Network of Agencies for Health Technology Assessment (INAHTA)

ACKNOWLEDGEMENTS

The Alberta Heritage Foundation for Medical Research is most grateful to the following persons for provision of information and/or comments on the draft report:

Dr. Pamela M. Barton, Clinical Associate Professor, Division of PM&R, The University of Calgary and Consultant, Neuromusculoskeletal Program, Calgary Health Region Chronic Pain Centre, Calgary, Alberta, Canada.

Dr. Gail A. Delaney, Associate Professor, Department of Physical Medicine and Rehabilitation, University of Western Ontario, London, Ontario, Canada.

Dr. Robert D. Gerwin, Department of Neurology, Johns Hopkins University, Baltimore, MD, USA.

Dr. Maria E. Suarez-Almazor, Professor of Medicine, Baylor College of Medicine, Houston, TX, USA.

The Foundation was assisted by an Information Sharing Group on Chronic Pain that provided advice on the scope of the report. Participants in this group were:

Mr. Henry Borowski, Strategy Development, Alberta Health and Wellness, Edmonton, Alberta, Canada.

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Dr. Paul Taenzer, Calgary Health Region Chronic Pain Centre, Calgary, Alberta, Canada.

Information Services Support

Ms. Liza Chan, Research Librarian, Alberta Heritage Foundation for Medical Research, Edmonton, Alberta, Canada.

Ms. Seana Collins, Research Librarian, Alberta Heritage Foundation for Medical Research, Edmonton, Alberta, Canada.

Ms. Leigh-Ann Topfer, Canadian Coordinating Office for Health Technology Assessment, Edmonton, Alberta, Canada.

EXECUTIVE SUMMARY

Background

Chronic pain affects between 10% and 20% of the North American population. Approximately 47% of chronic pain is of musculoskeletal origin. Chronic musculoskeletal pain covers many diagnostic categories including whiplash, fibromyalgia, myofascial pain syndrome, tension headache, and low back pain.

A trigger point is a hyperirritable area of tissue that is tender when compressed and can give rise to referred pain. Trigger points occurring in muscle and fascia are referred to as myofascial trigger points, and they can cause muscle spasm, stiffness, shortening, and fatigue, which hinder muscle lengthening, impair muscle coordination, and reduce range of motion and muscle strength. Trigger points are usually associated with myofascial pain syndrome, but the etiology and pathogenesis of trigger points have yet to be elucidated.

Objective

To assess the efficacy and safety of using trigger point injection (TPI) to treat patients with chronic non-malignant musculoskeletal pain, based on a systematic review of the current published evidence, and to determine the current status of the procedure, the feasibility of delivering it to patients in regional communities, and the clinical accreditation and training required to perform it.

Methodology

Data were collected on patients who underwent TPI and had non-malignant chronic pain of musculoskeletal origin that had persisted for at least three months. All original, published systematic reviews or randomised controlled trials were identified by searching PubMed, EMBASE, CINAHL, The Cochrane Library, Science Citation Index, AMED, BIOSIS, and the web sites of various health technology assessment agencies, research registers, and guidelines sites from root to September 2004. No language restriction was applied.

Results

Ten randomised controlled trials met the inclusion criteria. However, deficiencies in reporting, small sample sizes, and marked inter-study heterogeneity with respect to patient population, treatment regimen, injection site, and experimental protocol precluded a definitive synthesis of the data.

TPI is a safe procedure when used by clinicians with appropriate expertise and training. However, the evidence for its effectiveness when used as the sole treatment for patients with chronic head, neck, and shoulder pain and whiplash syndrome was inconclusive. The combined use of dry needling and trigger point injection with procaine offers no

obvious clinical benefit in the treatment of chronic craniofacial pain, while the effectiveness of trigger point injection for the treatment of cervicogenic headache is unknown. In contrast, trigger point injection with lidocaine may be a useful adjunct to intra-articular injection in the treatment of joint pain caused by osteoarthritis, compared to intra-articular injection alone. There was no proof that trigger point injection is more effective than other less invasive treatments, such as physical therapy and ultrasound, in achieving pain relief, and there is some suggestion that the only advantage of injecting anaesthetic into trigger points is that it reduces the pain of the needling process.

Conclusions and Recommendations

The efficacy of trigger point injection is no more certain than it was a decade ago since, overall, there is no clear evidence of either benefit or ineffectiveness. Trigger point injection was generally analysed as a stand-alone treatment, so it is possible that the effectiveness of trigger point injection was underestimated by analysing it in isolation rather than in the adjunct capacity in which it is routinely used in clinical practice. The advantage of TPI therapy may lie in enabling patients to undergo remedial exercise therapy sooner than other less invasive techniques, such as ultrasound, which may require more treatment sessions to obtain the same result. However, this benefit may be counteracted by the greater skill required to correctly administer TPI, particularly in regional areas where such expertise may be scarce.

The extent of use of trigger point injection in Alberta is unclear, but it is important that physicians understand the importance of not relying on trigger point injection as a sole treatment for chronic non-malignant musculoskeletal pain. Professional bodies, such as The Royal College of Physicians and Surgeons of Canada, should consider providing a training and accreditation program for practitioners wishing to use trigger point injection in Canada. It may also be prudent to tie the successful completion of such training to the ability to apply for reimbursement from the Alberta Health Care Insurance Plan, as this would curb the potential overuse and misuse of trigger point injection therapy.

Since equipoise exists among many of the potential treatments for chronic non-malignant musculoskeletal pain, and the treatments have similar safety profiles, further research should centre on good quality RCTs rather than non-randomised controlled trials. Given the purported popularity of trigger point injection, this research is essential for establishing more realistic expectations of what the treatment can achieve in clinical practice.

CONTENTS

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SCOPE OF THE REPORT

This report is a systematic review and critical appraisal of the literature on the use of trigger point injection, or direct wet needling, for the treatment of chronic non-malignant musculoskeletal pain. Its purpose was to provide information to the Information Sharing Group on Chronic Pain on the available published evidence regarding the short- and long-term efficacy/effectiveness of this treatment for patients with chronic non-malignant musculoskeletal pain, and to determine the feasibility of delivering this procedure to patients in regional communities. The report was intended to provide a distillation of the evidence on the current status of trigger point injection, as well as the clinical accreditation and training required to perform it.

INTRODUCTION

A definitive definition of pain is elusive because the perception of pain is a combination of subjective experience and physical and psychological response [1]. Pain is generally categorised as acute, cancer-related, or chronic. In contrast to acute pain, which is a normal response to tissue damage and resolves as healing progresses, chronic pain persists after the healing process is complete or is associated with progressive non-malignant disease [2]. The most frequently cited definition of chronic pain is "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage*" that has persisted beyond the normal tissue healing time (usually taken to be three months) [3].

Epidemiology of chronic pain

Chronic pain affects between 10% and 20% of the American population [4] and these patients, many of whom have had multiple failed interventions, make 70 million visits to physicians and 425 million visits to alternative healthcare providers each year [5-7]. Similarly, in 1996 the total prevalence of chronic pain in Alberta was approximately 11%. Patients with arthritis, back pain, and migraine headache were the most likely to report moderate to severe levels of pain, and not surprisingly, increasing pain severity was linked with a greater use of health services [8]. It is expected that even if the prevalence rate remains stable, there will be about a 70% increase in the number of individuals suffering from chronic pain in Alberta over the next 25 years [8].

Chronic pain conditions are generally accompanied by coincidental social, behavioural, and psychological problems that either precede or follow the development of the disease. Psychological symptoms encompass frustration, anxiety, depression, mood changes, stress, and anger, while patients may also develop maladaptive behaviours such as pain verbalisation, sleep disturbance, poor dietary habits, avoidance of exercise, poor posture, compulsive teeth grinding, and medication dependency [9, 10]. In addition, the common presence of a financial disincentive to improve, hostile work environment,

and/or dysfunctional family unit [11] can make the treatment of chronic pain complex and often problematic.

Approximately 47% of chronic pain is of musculoskeletal origin [12]. Chronic and recurrent muscle pain is the second most common medical condition behind upper respiratory illness and constitutes the third largest health problem in the United States [1]. Musculoskeletal pain can be generally classified as either articular or non-articular depending on whether it involves inflammation of the joints (rheumatoid arthritis or osteoarthritis) or affects the soft tissues (myofascial pain syndrome) [12]. Chronic musculoskeletal pain covers many diagnostic categories including muscle strain, whiplash, repetitive overuse syndrome, fibromyalgia, myofascial pain syndrome, tension headache, and low back pain [4]. Arthritis and low back syndrome are by far the most common culprits, accounting for 24% and 23% of chronic musculoskeletal pain complaints, respectively [12].

In the United States, 13% of the total workforce experienced a loss in productive time during a two week period due to headache, back pain, arthritis pain, or some other musculoskeletal pain [13]. It has been estimated that approximately 45% of Americans require treatment each year for pain at a cost of US$85 to US$90 billion [14]. This treatment, when combined with the expense of financial compensation and the loss of approximately 700 million work days each year to pain-related disabilities [14], means that the estimated annual cost of chronic pain in the United States alone is over US$100 billion [15].

What is a trigger point?

A trigger point is a hyperirritable area of tissue that is tender when compressed and can give rise to referred pain [16]. Trigger points occurring in muscle and fascia are referred to as myofascial trigger points, but they can also occur in other types of connective tissue, such as ligaments, periosteum, tendons, scars, and skin [17]. A myofascial trigger point is a discrete focal tenderness, 2 to 5 mm in diameter, that is located in distinct tight bands or knots of skeletal muscle or in the muscle's fascia [9, 18-20]. Myofascial trigger points can be felt as hard nodular structures and produce a local twitch response when the muscle knot is palpated or snapped [9, 18, 19, 21]. When palpated, myofascial trigger points can cause pain in distant areas, or referred pain zones, which are specific for each trigger point [18, 21, 22]. This specificity of pain referral is consistent between patients and allows clinicians to find the distantly located trigger points [9, 22]. Sometimes a single myofascial trigger point region may contain several hypersensitive spots [23]. The most sensitive spot in the taut muscle band is called the tender point and differs from a trigger point in that the pain is not referred to a distant area but is experienced in the exact position of the tender point [22].

In humans, myofascial trigger points generally occur in stable anatomic positions, most commonly the head, neck, shoulder girdles, and lower back [18]. Only 20% of trigger

points correspond to the "channel" acupuncture points that are routinely used in acupuncture treatments, whereas all myofascial trigger points correspond to the lesser class of Ah-Shi acupuncture points [24, 25].

A trigger point may be active or latent. Both types are hypersensitive, but the former display continuous pain in the zone of reference with or without palpation, while the latter, which are more common, do not generate spontaneous pain but rather cause restricted movement and muscle weakness [9, 18, 21, 26]. Trigger points are further defined as primary or satellite. Primary trigger points develop independently of other trigger points while satellite trigger points result from the stress and muscle spasm caused by neighbouring trigger points [20].

Patients between the ages of 30 and 49 years have the highest prevalence of trigger points, with women representing a higher proportion of sufferers than men [18]. Trigger points can cause muscle spasm, stiffness, shortening, and fatigue, which hinder muscle lengthening, impair muscle coordination, and reduce range of motion and muscle strength. They can also occasionally lead to motor dysfunction and autonomic phenomena (vasoconstriction, dermal flushing, coldness, lacrimation, abnormal sweating, pilomotor response, ptosis) [10, 27-31]. Other associated neurological symptoms include paresthesias, numbness, blurred vision, twitches, and trembling [10].

Myofascial pain syndrome refers to the cluster of symptoms (pain, autonomic phenomena, and muscle dysfunction) caused by active myofascial trigger points [20]. Primary myofascial pain syndrome usually manifests as overuse syndromes such as tennis elbow, frozen shoulder, and chronic tension type headache, whereas secondary myofascial pain syndrome occurs in the presence of other medical conditions, such as whiplash, temporomandibular joint dysfunction, osteoarthritis, and fibromyalgia [18, 22, 28, 32].

Pathogenesis of myofascial trigger points

The etiology and pathogenesis of trigger points have yet to be satisfactorily explained. It is generally thought that abnormal muscle strain, in combination with emotional stress, in genetically predisposed individuals can cause a latent trigger point to develop in a taut muscle band and subsequent nerve sensitisation [18, 26, 32]. Taut muscle bands commonly occur in pain-free individuals [33, 34]. In addition, latent trigger points may be present in the shoulder girdle and lumbogluteal muscles of up to 45% to 55% of asymptomatic young adults [10].

Several causative factors have been identified in the generation of trigger points including arthritis, strain, trauma, disuse, psychosocial and emotional stressors, fatigue, fever, internal disease, viral infections, inflammatory diseases, scar formation after surgical incision, spinal discogenic diseases, and the cumulative effect of repetitive strain injury [9, 29, 30, 35]. Further aggravating factors can lead to the creation of an active

trigger point, which may recover spontaneously or persist without further development [32].

The presence of perpetuating factors such as psychological problems, chronic infections, or chronic muscle tension due to poor posture may lead to the creation of further trigger points and subsequent chronic myofascial pain syndrome [29]. Several diverse yet complementary models have been proposed to explain the development of trigger points at the cellular level, but it is still not known what the role of each is in the pathogenesis of chronic musculoskeletal pain. Nonetheless, it is clear that the pathogenesis of trigger points is a complex process that involves both the central and peripheral nervous systems.

Trigger point injection

The goal of treatment for chronic musculoskeletal pain is to reduce pain and enable the patient to cope with it, and also to identify the etiological and perpetuating factors that are causing the pain [18, 22]. Non-specific general treatments usually fail to remove the underlying etiological factors causing the pain and associated symptoms [36]. Therefore, a multidisciplinary team approach is often advocated that includes most, if not all, of the following disciplines: physical therapy, clinical psychology, occupational therapy, pharmacy, kinesiology, dietetics, and social work. There are numerous non-invasive methods available to alleviate chronic musculoskeletal pain. These include postural re-training, strengthening and conditioning, stretching, massage, ischemic compression, transcutaneous electrical nerve stimulation, iontophoresis, hydrotherapy, laser therapy, heat, acupressure, ultrasound, magnetic fields, the vapocoolant spray and stretch technique, and pharmacological treatments, such as non-steroidal anti-inflammatory drugs and opioids [9, 10, 18, 27, 30, 37, 38]. This plethora of treatment options is testimony to the fact that no one strategy has proven successful in all patients and that therapy must be tailored to the needs of the individual patient.

The more invasive therapies include acupuncture, electro-acupuncture, and trigger point injection. The latter is the most common interventional technique used in pain medicine [21]. The main objective of trigger point injection is fast pain relief and elimination of muscle spasm in order to break the pain cycle. Elimination of the trigger point and the taut band facilitates physical therapy aimed at regaining muscle length and increasing range of motion [9, 21, 39]. Trigger point injection is generally used as part of a multi-disciplinary approach aimed at treating both the trigger points and all contributing factors. Thus, treatment may also include patient education, psychosocial support, oral medications, and physical therapy to improve the strength and flexibility of the affected musculoskeletal systems [19, 21, 29].

Trigger point injection, or direct wet needling, involves injection of fluid directly into the trigger point located in the taut muscle band. Other needling therapies include indirect wet needling in which fluid is injected into the skin or subcutaneous tissue over

the trigger point; direct dry needling where a hypodermic or solid needle is aimed directly at the trigger point; and indirect dry needling in which a needle is placed superficially or deep into classic acupuncture points but not directly into the trigger point [27]. Injecting a trigger point is painful, but addition of a local anaesthetic to the injected fluid can reduce the pain and tissue irritation caused by the needling [9, 36]. A variety of fluids have been injected into trigger points including water, normal saline, local anaesthetics (procaine, lidocaine, bupivacaine), vitamin B solutions, long-acting corticosteroids, acetylsalicylate, and botulinum toxin, a neurotoxin derived from certain strains of the bacterium, *Clostridium botulinum*, that is responsible for botulism in humans [21, 30, 40].

The effective treatment of pain that originates in musculoskeletal structures requires precise identification of its cause and location [36]. Snapping palpation of a taut muscle band can generate a local twitch response, which is a valuable objective sign that the trigger point has been accurately pinpointed during needle therapy [29]. Currently, opinion on the optimal technique and treatment regimen for trigger point injection varies between practitioners and is largely based on clinical experience. The pain relief conferred by trigger point injection may last for the duration of the anaesthetic to many months, depending on the chronicity and severity of the trigger points and the concomitant treatment of perpetuating factors [9].

Contraindications for trigger point injection include acute cases of muscle trauma, allergies to anaesthetic agents, bleeding disorders, local or systemic infection, and anticoagulant use [18, 29]. Trigger point injections with botulinum toxin are not recommended for patients who are pregnant, lactating, or taking drugs that may interfere with neuromuscular transmission or who have pre-existing disorders of the neuromuscular junction, such as myasthenia gravis, Lambert-Eaton's syndrome, and motor neuron disease [41].

How does trigger point injection work?

The precise mechanism by which trigger point injection inactivates the trigger point is currently unknown. This uncertainty, together with the fact that dry needling is considered by many authors to be as effective as trigger point injection, has led to the suggestion that trigger point injection has little value beyond placebo effect.

Several mechanisms of action have been proposed, each of which may be relevant in different modalities of trigger point injection. These include mechanical disruption of the abnormal muscle fibres and nerve endings; depolarisation of nerve fibres by the intracellular potassium released from disrupted muscle fibres; interruption of the positive feedback mechanism that perpetuates pain; local dilution of nociceptive substances; increased metabolite removal caused by the vasodilatory effect of the local anaesthetic; focal necrosis of the trigger point by the injected substance; and counter-stimulation analogous to the effect of acupuncture [9, 11, 18, 26, 29].

In contrast, more is known about the mechanism of action of botulinum toxin injection, which achieves a reduction in muscle spasm by blocking the release of acetylcholine at the motor end plates [21]. However, the pain relief achieved in patients with cervical dystonia or spasticity seems to be greater than what would be expected from spasm reduction alone, so it is postulated that botulinum toxin may dampen central sensitisation via a direct peripheral antinociceptive effect in these patients [38].

Potential complications

The most common complication of trigger point injection is a vasovagal syncopal episode [21, 42], but this can be avoided if the patient is lying down during the injection procedure. Other complications can include bleeding, transverse cuts or tears in the muscles, injury to nerve fibres, damage to blood vessels (ecchymosis, hematoma), infection, anaphylactic reaction, allergic reactions to the injected fluid [26, 42], and compartment syndrome [42]. In rare instances, injury to internal organs such as the lungs (pneumothorax), intestine, stomach, liver, or kidney can occur [29, 42]. However, the majority of these complications are usually the result of inappropriate technique.

Adverse effects from the use of botulinum toxin injection are relatively rare. The most commonly reported side effects are pain at the injection site, a short-lived flu-like syndrome, malaise, local weakness, and dysphagia [21, 43]. However, serious side effects can develop when muscle weakness is greater than intended or occurs in a non-targeted area. For example, it can be potentially dangerous if the toxin spreads into the muscles that control swallowing following an injection into trigger points near the larynx [43].

Current reimbursement arrangement

The Alberta Health Care Insurance Plan for October 1, 2004 lists item numbers for trigger point injections (Table 1).

Table 1: Year 2004 Medical Procedure List for trigger point injection

Category	Item Number
Injection with local anaesthetic of myofascial trigger points (a maximum of three calls applies)	13.59J
Injection with local anaesthetic of myofascial trigger points combined with a spray and stretch technique	95.94A
Intravaginal trigger point injection(s) (benefit includes general gynaecological examination and concurrent specialised physiotherapy)	95.94B

The Centers for Medicare and Medicaid Services in the United States has not issued a national coverage decision regarding trigger point injection. However, in the absence of a formal national reimbursement policy, local Medicare contractors are free to make their own coverage decisions. Consequently, trigger point injection for myofascial pain syndrome is covered by a number of insurance carriers throughout the United States.

Current issues in the use of trigger point injections

The study of treatments for chronic non-malignant musculoskeletal pain has suffered from the diagnostic ambiguity often associated with this malady and a lack of adequate objective measures of severity [11, 18]. It has been suggested that the precise location of the trigger point during injection is more important than the fluid being injected, and that it is essential to elicit a local twitch response during trigger point injection in order to obtain successful pain relief [29]. The results from a number of studies examining the reliability of trigger point examinations clearly show that experienced examiners are more reliable than inexperienced ones and that findings derived from palpation are technique sensitive. Consequently, there is still some controversy surrounding the existence of trigger points because of the lack of reproducibility of diagnosis between different examiners [18, 27].

In addition, it is unclear whether there is any difference in treatment effect between injecting anaesthetic directly into trigger points and merely injecting it in the vicinity of them to numb the whole muscle region. Trigger point injection is a common and deceptively easy treatment to administer, which has led to concern regarding its overuse by under trained practitioners.

Thus, it was the aim of this review to assess the efficacy and safety of using trigger point injection to treat patients with chronic non-malignant musculoskeletal pain, based on a systematic review of the current published evidence, and to determine the current status of the procedure, the feasibility of delivering it to patients in regional communities, and the clinical accreditation and training required to perform it.

RESULTS

The full methodology for this review is detailed in Appendix A. Results were only reported here if they were stated in the text, tables, graphs, or figures of the article, or could be accurately extrapolated from the data presented. Conversely, if a particular complication was not reported, it was assumed to be unreported rather than not having occurred. For example, if the mortality rate was not reported in a study, no value was tabulated. This was done to avoid the bias caused by incorrectly assigning a value of zero to an outcome measurement on the basis of an unverified assumption.

Forty one studies were identified that potentially met the inclusion criteria of the review. On closer examination of the full text article, 31 of these studies were excluded and the reasons documented (Appendix B). A total of ten randomised controlled trials (RCTs) (Table 2) met the inclusion criteria of the review. A meta-analysis was not performed because the studies were very heterogeneous with respect to patient selection, pain etiology, outcome measures, and adjunctive treatments used. When overlapping patient groups were reported in studies, only the paper quoting the most complete data set was used.

Table 2: Summary of included studies

Study	Year	Study Design	Chronic Pain Condition	Intervention	No. of Patients	Length of Follow-up
Byrn et al. [44]	1993	Double-blind RCT	Whiplash syndrome	TPI with sterile water TPI with saline	20 20	8 months
Cheshire et al. [45]	1994	Randomised double-blind crossover trial	Neck and shoulder pain	TPI with botulinum toxin then saline TPI with saline then botulinum toxin	3 3	16 weeks
Esenyel et al. [46]	2000	Non-blinded RCT	Shoulder pain	Neck-stretching exercises US plus neck stretching exercises TPI plus neck stretching exercises	30 36 36	3 months
Ferrante et al. [47]	1998	Randomised double-blind crossover trial	Head, neck, and shoulder pain	SPGB then TPI then SPGB placebo SPGB placebo then TPI then SPGB	13 10	1 week
Freund & Schwartz [48,49]	2000	Double-blind RCT	Chronic headache secondary to whiplash	TPI with saline TPI with botulinum toxin	12 14	4 weeks
McMillan et al. [50]	1997	Double-blind RCT	Craniofacial pain	Simulated dry needling plus simulated TPI Procaine TPI plus simulated dry needling Simulated TPI plus dry needling	10 10 10	24 hours
Schnider et al. [51]	2002	Double-blind RCT	Cervicogenic headache	TPI with saline plus physical therapy TPI with botulinum toxin plus physical therapy	16 17	12 weeks
Wheeler et al. [52]	1998	Double-blind RCT	Neck pain	TPI with saline TPI with 50 U botulinum toxin TPI with 100 U botulinum toxin	11 11 11	4 months
Wheeler et al. [53]	2001	Double-blind RCT	Neck pain	TPI with saline TPI with botulinum toxin	24 21	16 weeks
Yentür et al. [54]	2003	Single-blind RCT	Knee osteoarthritis	Intra-articular injection TPI plus intra-articular injection	16 17	21 days

Abbreviations: RCT – randomised controlled trial; SPGB - sphenopalatine ganglion block; TPI - trigger point injection; US - ultrasound

Methodological quality of included studies

Details of the method used to assess the methodological quality of the included studies and the results are outlined in Appendices A and C, respectively.

Head, neck, and shoulder pain

Two double-blind RCTs [52, 53], one non-blinded RCT [46], and two randomised double-blind crossover trials [45, 47] reported on the use of trigger point injection in patients with head, neck, and shoulder pain. The internal validity of the five trials ranged from poor to moderate. This was largely due to inadequate reporting of aspects of study design, such as the method of randomisation and allocation concealment and how withdrawals and dropouts were handled, together with a lack of detail on whether the outcome assessor was blinded or whether co-interventions were used. Unfortunately, even though the studies may have been conducted appropriately, it is not apparent from the articles, which casts some doubt on the veracity of the data reported. The external validity was good in two studies [52, 53] and poor to moderate in three others [45-47]. The main deficiency in the latter three studies was a failure to report on adverse events or patient baseline parameters. Only two studies [45, 52] did not report point estimates and measures of variability for the primary outcomes.

Whiplash syndrome

The two double-blind RCTs [44, 48, 49] involving patients with whiplash syndrome were of moderate to good quality. Once again, the primary shortcoming was a lack of information on co-interventions and the method of randomisation used. The external validity of the studies was of moderate quality since neither specified any criteria for patient selection. One study [44] did not report baseline parameters for the patient groups, while the other study [48, 49] had a relatively short follow-up period. Only one study [44] failed to report measures of variability for the primary outcomes.

Other chronic musculoskeletal pain conditions

The three RCTs that reported on other types of chronic musculoskeletal pain conditions had only moderate internal validity. Once again, a lack of detail in the study methods made it unclear if randomisation or allocation concealment was adequate, and how withdrawals and dropouts were handled. In two studies [50, 51] the outcome assessors were aware of the treatment allocation, while in the other study [54] the patients knew which intervention they had received. Two studies [51, 54] had good external validity and one study [50] was of moderate quality, largely due to an extremely short follow-up period and deficiencies in the reporting of baseline patient parameters and adverse events. Two studies [50, 51] did not clearly describe the sample size for each treatment group in the results section. In one case [51], where it was revealed in the methods section that a patient was lost to follow-up, the reader was left to guess what the sample sizes were.

Evidence for the safety and efficacy of trigger point injection

A tabulated summary of extracted data from the included studies is provided in Appendix D.

Head, neck, and shoulder pain

Botulinum toxin versus saline trigger point injection

Two RCTs [52, 53] and one randomised crossover trial [45] described the use of trigger point injection with either saline or botulinum toxin type A in the treatment of neck and shoulder pain. The two studies by Wheeler et al. [52, 53] were supported by the Allergan Corporation, which also supplied the botulinum toxin used in the studies. Wheeler et al. [52] tracked outcomes for four months following one trigger point injection of either saline or botulinum toxin (50 or 100 Units) in patients with pain that had persisted for an average of at least three years. It was unclear whether co-interventions were permitted during the study. More of the injuries in the saline treatment group occurred at work than in car accidents, whereas the reverse was true for the patients receiving botulinum toxin. This was most likely related to the higher employment rate noted in the saline group at baseline. However, the mean pain pressure threshold was similar between all treatment groups at the start of the study.

While all treatment groups showed a decline in pain and disability scores and an increase in the pain pressure threshold of the trigger points, there was no appreciable difference between the treatment groups at any time during the four month follow-up period. The neck pain and disability scores were similar for the three groups four months after treatment, as were the number of patients reporting an improvement in their symptoms. A small number of patients in each treatment group requested a further trigger point injection at the end of the study. All of these patients were given 100 Units of botulinum toxin. The sample size was too small to detect any statistically significant difference in treatment effect between the patient groups as a result of the second injection. However, the patients who had previously received a botulinum toxin injection were more likely to report a benefit from the second botulinum toxin treatment than patients who had initially received a saline trigger point injection. The most common adverse events occurring after botulinum toxin injection were mild pain or numbness on the side opposite to the injection site and a shift in the pain site.

In the second study by Wheeler et al. [53], patients with chronic neck pain received injections of either saline or botulinum toxin into multiple trigger points during one treatment session. Physical therapy was not permitted during the study period, and outcomes were reported up to 16 weeks after treatment. The two patient groups had similar pre-treatment parameters at baseline except that the botulinum toxin group had a slightly lower mean SF-36 mental score than the saline group. Both treatment groups showed a significant decline in pain and disability score and an increase in the pain pressure threshold at the trigger points over the follow-up period, but there was no difference in the degree of symptom improvement achieved between the two treatment groups. The patients who received botulinum toxin reported more adverse events than the saline group, which may have accounted for the greater number of patients that were lost to follow-up in the botulinum toxin group. The most commonly reported

complications in the botulinum toxin group were excessive weakness of the injected muscle, pain or soreness at the injection site, and flu-like symptoms.

The crossover trial [45] assessed trigger point injection with either saline or botulinum toxin in selected patients who had chronic neck and shoulder pain for an average of three years. Neither muscle relaxant medication nor physical exercise was prescribed during the study. Unfortunately, it was difficult to discern the raw data values from the graphs presented in the paper because they were displayed in a format that precluded accurate derivation. However, the authors defined a positive response to treatment as reduction in pain of at least 30% from baseline values on at least two occasions. Using this criterion, four of the six patients experienced a reduction in both pain and muscle spasm after botulinum toxin treatment, but not after saline injection. For the other two patients, one reported no change in pain symptoms after either treatment while the other responded favourably to both. Generally, symptom relief occurred within one week after treatment and continued for five to six weeks. In contrast, the beneficial effect in the patient who responded to both treatments lasted for only three to four weeks. While patient outcome was not affected by the order in which the injections were received, a crossover effect was seen in one patient whose pain parameters did not return to pre-treatment values before the second treatment was administered at eight weeks. Therefore, the washout period may have been too short. No side effects occurred after either treatment. The location of the trigger points did not change over the course of the study and they still produced referred pain even after injection with botulinum toxin. This suggests that the treatment merely ameliorated the pain rather than destroying the cause of it. It should be noted that the sample size of this study was very small and the authors stated the results are little more than descriptive [45].

Trigger point injection, ultrasound, and stretching

The study by Esenyel et al. [46] compared a combination of neck stretching and either trigger point injection with lidocaine or ultrasound therapy with neck stretching alone in patients with shoulder pain of at least 6 months' duration. Relatively young patients were selected for this study to ensure that the shoulder pain was not accompanied by degenerative disc or joint disease. The patients who received combined trigger point injection/stretching therapy or ultrasound/stretching therapy had a significant increase in pain threshold and range of motion, as well as a decrease in pain intensity, two weeks and three months after treatment, compared to the stretching only group. These beneficial effects were independent of the severity or duration of the pain present before treatment. There was no significant difference between combined trigger point injection/stretching therapy and ultrasound/stretching therapy with respect to subjective and objective pain measures in patients after three months follow-up, but both treatments were more effective than neck stretching exercises alone. The ultrasound therapy was administered over ten separate treatment sessions, whereas it was not reported how many sessions were required for the trigger point therapy. It was

also unclear if the injected muscles were specifically stretched at the time of injection or on a regular basis afterwards. The study did not report whether any adverse events occurred in the treatment groups.

Levels of depression and anxiety were measured with the Beck Depression Inventory and the Taylor Manifest Anxiety Scale, respectively, but there was no significant correlation between these indices and measures of pain intensity or pain threshold after treatment. However, correlations were significant when compared with pain duration before treatment. The omission of many important details, such as the timing of the treatments and whether the follow-up period was calculated from the initial or final treatment in the protocol, limited the value of the study results. It was also unclear whether the patients were participating in any additional pain management therapy that may have confounded the results.

Sphenopalatine ganglion block and trigger point injection

Ferrante et al. [47] assessed the effectiveness of sphenopalatine ganglion block (SPGB) by comparing it to placebo SPGB and an internal standard, trigger point injection with lidocaine. All patients had chronic musculoskeletal pain of at least six months' duration and had similar characteristics at baseline. There was no difference in analgesic effect between SPGB with 4% lidocaine and placebo SPGB. However, trigger point injection proved to be more effective than either SPGB or placebo SPGB in relieving myofascial pain in the head, neck, and shoulders when outcomes were measured one week after each treatment. A similar number of patients in both treatment groups experienced a placebo response (defined as a simultaneous decrease in pain intensity score and an increase in pain relief score of at least 10 mm after placebo SPGB). The study did not report whether any adverse events occurred in the treatment groups.

Patients were permitted to continue other pre-existing therapies and medication during the course of the trial. Since these co-interventions were not described, the study results must be interpreted cautiously, as the authors themselves acknowledge, given the likelihood of confounding of treatment outcomes by these additional therapies. The authors noted that some patients may have correctly guessed the order of the treatment regimen if they experienced successful local anaesthesia with the active SPGB, particularly those who received this treatment first. In addition, no adjustment for multiple comparisons was made, even though the comparison of SPGB with trigger point injection was a secondary analysis. Since trigger point injection was the internal standard therapy against which active SPGB was compared, it is possible that the benefit of trigger point injection was over estimated by comparing it to an ineffective alternative treatment rather than a true placebo or no treatment control.

Whiplash syndrome

Byrn et al. [44] compared trigger point injection with either sterile water or saline in patients with whiplash syndrome of at least four years' duration that was not associated

with a lesion of the cervical spine. The two patient groups had similar psychological profiles at the start of the study. Other baseline parameters were not compared statistically, but they appeared to be similar between the two groups. The majority of the patients in both treatment groups were already undergoing physiotherapy and/or taking analgesics, benzodiazepines, or antidepressants, although it was unclear if these treatments were continued during the study period. More patients experienced an improvement in symptoms following sterile water injection after three months, compared to saline injection, but there was no difference observed between the groups after eight months. Mean pain intensity scores and mobility were also significantly better following sterile water injection, compared to saline, both immediately after treatment and at the eight month assessment. More patients in the saline group needed the maximum of three treatments and required more injections, compared to the sterile water group. Since up to three treatments were administered within the first two months of the study, according to patient need, the period of time between the last treatment and the follow-up assessment may have varied by up to two months for some patients. In addition, the outcome data were not analysed according to the number of injections a patient received, which made it impossible to assess how many injections were needed to achieve symptom improvement. No side effects occurred in either treatment group.

One RCT, reported in two separate articles [48, 49], compared trigger point injection with either saline or botulinum toxin in the treatment of chronic headache, secondary to cervical whiplash injury, which had persisted for at least six months. Patients in the botulinum toxin treatment group had higher head pain scores prior to treatment than those in the saline group, but there was no difference between the two groups with respect to mean range of motion or total pain score. No other treatments were allowed during the study period. Only patients who received botulinum toxin showed a significant decrease in mean pain intensity and an increase in mean total range of motion four weeks after treatment. However, there was no significant improvement in subjective function in either treatment group after four weeks. The slight improvement in symptoms observed in the saline group over the treatment period was not statistically significant. The fact that the botulinum toxin treatment differed from saline at four weeks but not after two suggests that the maximum muscular relaxation achieved by botulinum toxin may not be reached until at least two weeks after treatment [48]. No side effects or weakness in the injected muscles occurred in either treatment group.

Craniofacial pain

One RCT [50] compared combined procaine trigger point injection and dry needling with combinations of sham trigger point injection and sham dry needling to determine what degree of benefit was conferred by each technique. Only women who had non-malignant craniofacial pain for at least three months were included in the study.

No other medication or treatment was allowed during the study period. There was no difference in treatment effect between trigger point injection, dry needling, and the double sham procedure, even though all of the interventions resulted in lower mean pain intensity and unpleasantness scores and a higher mean pain pressure threshold at the trigger points, relative to baseline values. This suggests that a non-specific placebo-related effect was at work rather than an actual treatment effect. However, the follow-up period for this study was only 24 hours after each treatment over a study period of three weeks. Safety outcomes were not reported. Since the location of the active trigger points changed between treatment sessions, it is likely that the injections were deactivating the trigger points effectively. The patient group in this study was highly selected in that patients with a history of psychiatric illness or drug abuse were excluded. Consequently, the study participants may not be representative of the typical patient presenting with chronic musculoskeletal pain.

Cervicogenic headache

Schnider et al. [51] assessed the efficacy of trigger point injection, with either saline or botulinum toxin, in combination with a standardised physical therapy regimen for treating longstanding (over 6 years on average) cervicogenic headache. Patients were observed for a four week period prior to the start of treatment, and there was no statistically significant difference between the two treatment groups with respect to pain duration, symptoms, or severity, sagittal range of motion, or other potential prognostic factors. The majority of the patients were taking medications, such as antirheumatics and muscle relaxants, at the start of the study and most likely continued taking them throughout the study period.

Sagittal range of motion and biofeedback measurements showed no significant changes over time in either group. Both treatments reduced headache severity, headache free days per month, and headache hours per day; the degree of change was similar in each group. There was also no significant change in analgesic intake per day over time in either group. There was a slight, but statistically non-significant, trend towards improvement in the number of headache free days and headache hours per day in the botulinum toxin group, with a concomitant reduction in analgesic consumption, compared to the saline group. The lack of statistical significance might be explained by the small sample size of the study, the fact that the majority of patients had severe headache, and the effectiveness of physical therapy itself [51]. Unfortunately, without a control arm of physical therapy alone, it is impossible to assess what contribution, if any, trigger point injection made to patient outcomes. The only side effect noted was mild local pain at the injection site in a small number of patients receiving botulinum toxin.

Eighteen patients, nine from each of the two treatment groups, opted for a subsequent trigger point injection with botulinum toxin. Two thirds of these patients reported a beneficial effect that lasted just over three months. Four of the patients who had

initially received a botulinum toxin treatment during the study period did not report an improvement in symptoms until after the second botulinum toxin injection.

Osteoarthritis

Yentür et al. [54] compared a combined treatment regimen of intra-articular injection of sodium hyaluronate and trigger point injection with lidocaine against intra-articular injection alone in a highly selected group of older patients who had suffered with chronic pain for at least a year due to knee osteoarthritis. The two patient groups were similar with respect to potential prognostic indicators at baseline. No other treatments were permitted during the study period. Physical activity assessment results improved significantly for the combined intra-articular injection/trigger point group for all activities, whereas the patients receiving intra-articular injection alone showed a significant improvement in squatting and walking only. Patients in the former group also reported reduced pain, increased range of motion, and an improvement in their ability to undertake daily activities, while the intra-articular injection group had no such improvements. No significant local or systemic side effects were reported in either patient group.

DISCUSSION

Good studies are defined by rigid inclusion criteria, extensive evaluation, highly standardised treatment, validated and clinically relevant outcomes, an adequate follow-up period, and impartial investigators [55, 56]. All of the studies available for review failed in at least one of these requirements. The primary deficiency of the included studies was inadequate reporting, which made it impossible to tell if the study was actually deficient in design and execution or if it was conducted appropriately but just not reported as such. The result was a dearth of information regarding the randomisation method used, the co-interventions permitted during the study period, and the independence, or lack thereof, of the outcome assessor(s). Most of the studies provided scant information on baseline patient parameters, which made inter-study comparisons problematic and cast doubt on whether the randomisation process had resulted in evenly matched treatment groups. However, the majority of the studies did conduct a statistical comparison, albeit sometimes limited, of preoperative patient characteristics for each of the study groups prior to treatment.

The evidence base was also limited by the fact that seven out of the ten studies had very small sample sizes, with less than 20 patients in each study arm. In addition, most of the studies used an 'active' treatment for the control rather than a physiologically inert placebo, which made it impossible to quantify the substantial placebo effect that is purportedly associated with trigger point injection. Thus, the heterogeneous nature of the pain etiologies assessed, together with the small sample size and limited reporting in the majority of the included studies, meant that only very general conclusions could be drawn from the data. In addition, the very different, and sometimes inadequately

reported, treatment regimens used in the studies precluded the formulation of any specific determinations on the dose or intensity of trigger point injection therapy required to obtain optimal benefit.

Efficacy/effectiveness of trigger point injection

A summary of the RCT results is presented in Table 3.

Head, neck, and shoulder pain

Limited evidence from two moderate to good quality RCTs [52, 53] showed that botulinum toxin type A, administered in concentrations ranging from 50 U to over 200 U during one treatment session, was as effective as saline trigger point injection in reducing the pain and disability associated with chronic neck and shoulder pain at up to four months after treatment. Another moderate quality randomised crossover trial [45] that compared botulinum toxin and saline trigger point injection in only six patients with chronic neck and shoulder pain reported equivocal results. Given that the only adverse events reported occurred after botulinum toxin injection, it is likely that saline injection would be the more attractive treatment option since it is cheaper and has no apparent side effects. The results suggested that trigger point injection with botulinum toxin did not destroy the trigger points and that a sequential botulinum toxin injection regimen may be more effective than a single injection treatment, but this needs further investigation.

Very limited evidence from a moderate quality RCT [46] suggested that combined trigger point injection with lidocaine and neck stretching therapy achieved the same improvement in pain symptoms as combined ultrasound/neck stretching therapy, compared to neck stretching alone, after three months. However, poor reporting meant that it was impossible to judge whether trigger point injection required more treatment sessions than ultrasound to achieve this result. It was also unclear if the results were confounded by the use of co-interventions, and whether the stretching therapy was generalised or directed specifically at the injected muscles, which would have influenced the effectiveness of the trigger point injections.

A poor to moderate quality randomised crossover trial [47] found that trigger point injection with lidocaine was more effective than either SPGB or placebo SPGB in relieving myofascial pain in the head, neck, and shoulders up to one week after treatment. However, it is likely that other medications and therapies used by the patients during the study confounded this treatment effect.

Table 3: Summary of the RCT results

Treatment	Condition	Comparator	Evidence	Efficacy/Safety Results
TPI (lidocaine) plus intra-articular injection	Osteoarthritis pain (knee)	Intra-articular injection	One moderate to good quality RCT Follow-up = 21 days	TPI plus intra-articular injection is more effective than intra-articular injection alone. There was no difference in safety between the two treatments.
TPI (botulinum toxin)	Head, neck, and shoulder pain	TPI (saline) TPI (different botulinum toxin concentrations)	Three moderate to good quality RCTs Follow-up = 4 months	No difference in effectiveness between botulinum toxin TPI and saline TPI, regardless of botulinum toxin concentration (50 U to over 200 U). No difference in effectiveness between 50 U and 100 U of botulinum toxin. Saline TPI produced fewer adverse effects than botulinum toxin TPI.
	Whiplash syndrome	TPI (saline)	One moderate quality RCT Follow-up = 4 weeks	No difference in safety or effectiveness (subjective function) between the two treatments.
TPI (botulinum toxin) plus physical therapy	Cervicogenic headache	TPI (saline) plus physical therapy	One moderate to good quality RCT Follow-up = 12 weeks	No difference in safety or effectiveness between the two treatments.
TPI (water)	Whiplash syndrome	TPI (saline)	One moderate to good quality RCT Follow-up = 3 months	Water TPI is more effective than saline TPI. There was no difference in safety between the two treatments.
TPI (lidocaine)	Head, neck, and shoulder pain	Sphenopalatine ganglion block	One poor to moderate quality RCT Follow-up = 1 week	Lidocaine TPI is more effective than sphenopalatine ganglion block. Safety outcomes were not reported.
TPI (lidocaine) plus neck stretching	Head, neck, and shoulder pain	Ultrasound plus neck stretching	One moderate quality RCT Follow-up = 3 months	No difference in effectiveness between the treatments, but combined TPI/neck stretching and ultrasound/neck stretching was more effective than neck stretching alone. Safety outcomes were not reported.
TPI (procaine) plus dry needling	Craniofacial pain	Sham treatment	One moderate quality RCT Follow-up = 24 hours	No difference in effectiveness between the treatments. Safety outcomes were not reported.

RCT – randomised controlled trial; TPI – trigger point injection

Whiplash syndrome

One moderate to good quality RCT [44] showed that the symptoms of whiplash syndrome were significantly improved after trigger point injection with sterile water, compared to saline, three months after treatment. However, the effect was not durable at eight months follow-up. This is to be expected if trigger point injection was the sole treatment, but it is unclear if co-interventions were used.

A moderate quality RCT [48, 49] suggested that trigger point injection with botulinum toxin was more effective at reducing pain and increasing range of motion than saline trigger point injection in patients with chronic headache secondary to whiplash. However, the clinical significance of this is unclear since neither treatment resulted in an improvement of subjective function.

Craniofacial pain

The results of one moderate quality RCT [50] with a 24 hour follow-up period suggested that the combined use of dry needling and trigger point injection with procaine offers little beyond a placebo effect in the treatment of craniofacial pain.

Cervicogenic headache

One moderate to good quality RCT [51] found no difference in treatment benefit between botulinum toxin trigger point injection performed in conjunction with physical therapy and combined saline trigger point injection/physical therapy in patients with cervicogenic headache. However, in the absence of a control group that received only physical therapy, it is impossible to tell to what degree, if any, the trigger point injection component contributed to the overall treatment effect. In addition, co-interventions may have confounded the results.

Osteoarthritis

One moderate to good quality RCT [54] showed that intra-articular injection combined with lidocaine trigger point injection was more effective than intra-articular injection alone in relieving pain and improving knee function. This suggests that trigger points may be a substantial contributor to the pain experienced by patients suffering osteoarthritis and may be the primary cause of pain in other joint diseases. However, the authors were careful to point out that trigger point therapy in isolation is not likely to be a sufficient treatment for osteoarthritis pain, since it does not resolve any of the underlying perpetuating factors [54].

The Bottom-line: Very limited evidence suggested that the combined use of dry needling and trigger point injection with procaine offers no obvious clinical benefit in the treatment of chronic craniofacial pain. The effectiveness of trigger point injection for the treatment of cervicogenic headache is unknown. In contrast, trigger point injection with lidocaine may be a useful adjunct to intra-articular injection in the

treatment of joint pain caused by osteoarthritis, compared to intra-articular injection alone.

The evidence for the effectiveness of trigger point injection when used as the sole treatment for patients with chronic head, neck, and shoulder pain and whiplash syndrome was inconclusive. This was true regardless of whether sterile water, saline, or botulinum toxin was injected. There is also some suggestion that trigger point injection is no more effective than other less invasive treatments such as physical therapy and ultrasound.

Safety of trigger point injection

Trigger point injection appears to be a relatively safe procedure since very few adverse events were reported in the included RCTs (Table 3). However, the small sample size, focussed objective, highly selected patient group, and specialised clinical setting of most RCTs makes them ill equipped to detect unusual outcomes in procedures with a high safety profile. Therefore, it is not surprising that very few complications were reported in the small number of RCTs included in this review. However, it should be noted that some unusual, and potentially dangerous, complications that have occurred following trigger point injection have been published in case reports. These include: cervical epidural abscess that required urgent cervical laminectomy [57]; accidental intrathecal injection resulting in pneumocephalus [58]; muscle atrophy at the injection site [59]; pneumothorax that necessitated needle aspiration and chest tube drainage [60]; and development of asystole in a patient with a history of panic attacks [61]. This emphasises the fact that inappropriate technique and limited expertise can render an apparently harmless procedure potentially debilitating, if not lethal.

The Bottom-line: Trigger point injection is a safe procedure when used by clinicians with appropriate expertise and training.

Clinical practice guidelines

A number of position statements and practice guidelines for the treatment of non-malignant chronic pain have been published since 1995, the majority of which recommend an inter-disciplinary team approach to treatment that includes physicians, psychologists, and physical/occupational therapists [62]. Trigger point injections are generally considered to be an adjunctive rather than a primary form of treatment for chronic musculoskeletal pain [63, 64].

In 1999, an evidence-based revision of practice guidelines specifically designed for chronic non-malignant pain syndrome patients was published [62]. The original guidelines, published in 1995, were adopted by the American Academy of Physical Medicine and Rehabilitation in 1996. However, these were based primarily on common practice and consensus among the original authors. The updated evidence-based guidelines found no evidence to support the routine application of trigger point

injection for the treatment of patients suffering from chronic pain syndrome. While the guidelines acknowledged that trigger point injection may be widely used in practice, its routine use in chronic pain syndrome patients was not recommended until further evidence demonstrated its efficacy. The routine use of botulinum toxin injections was also not recommended for these patients because of a similar dearth of evidence [62].

The College of Physicians and Surgeons of Ontario published guidelines for the medical management of chronic non-malignant pain in November 2000 [65]. Since the evidence for the use of trigger point injection in the management of chronic neck, back, and myofascial pain is contradictory and based on poor quality studies, The College suggests that trigger point injection should only be pursued if the patient shows improvement after a short trial. However, trigger point injection is not recommended as a first line treatment for chronic musculoskeletal pain. Guidelines for the management of chronic non-malignant pain have also been published by the College of Physicians and Surgeons of Alberta [66], but these provide guidance on the overall management strategy for patients with chronic pain and do not provide any specific recommendations on the use of trigger point injection.

Issues surrounding trial design

A prospective blinded RCT is considered the most scientifically rigorous method of evaluating a new therapy [67]. However, this trial design is often not applicable or feasible to undertake in studies of treatments for chronic musculoskeletal pain. In the case of trigger point injection, it is sometimes difficult to blind patients to the therapy that they received and impossible to conceal this from the clinicians administering it, unless different injectant solutions are being compared. Even when the patients are unaware of the treatment that they are receiving, there is always the possibility that the behaviour of an informed provider could inadvertently unmask the treatment allocation [68].

Even with a multicentre randomised study design, there are aspects of trigger point injection therapy that can still introduce bias. These include variations in the degree of interaction and rapport that each clinician achieves with the patient during the treatment sessions, and the different treatment and patient management regimens that may exist between centres. This variability can be minimised somewhat by conducting the trial with one clinician at a single site, but in the case of chronic musculoskeletal pain, it is often difficult to get a critical mass of homogeneous patients in one practice site. The scientific rigour of a study can also be improved by using strict eligibility criteria for patient selection; employing a standard treatment duration for all study groups; and having patient outcomes assessed by independent analysts who are blinded to treatment allocation [17, 69]. It may also be necessary to stratify patients according to whether or not they have previously undergone trigger point injection [70]. It is possible that patients who are naïve to trigger point injection therapy will have different expectations and responses to treatment, compared to more experienced

patients, and they are also less likely to correctly guess their treatment allocation in a blinded RCT.

Strict eligibility criteria for patient selection, particularly with respect to the definition of chronic pain, are essential. A number of RCTs on trigger point injection therapy were excluded from this review either because they did not clearly define chronic pain or because results for patients with chronic pain were pooled with those of patients with acute or sub-acute pain. While it can be argued that the boundaries between acute, sub-acute, and chronic pain are somewhat arbitrary, it has been shown that, in the case of low back pain, there is an 80% to 90% probability that patients will recover spontaneously within three months [71]. This can significantly confound RCT results when the active treatment is compared to a placebo group that has an inherently high recovery rate [72]. Since this is likely to be the case for patients with other types of chronic musculoskeletal pain as well, defining chronic pain as being of at least three months' duration will reduce the 'noise' in comparisons between active therapy and placebo or sham treatments.

It is often difficult to devise an adequate placebo for physical forms of treatment, and there has been continued debate over what is the most appropriate inert control or placebo treatment for studies assessing trigger point injection. Ideally, a placebo should equalise the non-specific effects of the treatment, such as physical contact, and maintain the illusion that the patient is receiving the active treatment in order to minimise the effect of patient expectation on outcomes, while exerting little or no specific treatment effect itself [69, 70]. However, there is currently no placebo or sham treatment available for trigger point injection that fulfils all of these criteria, since it is often difficult to ensure that the placebo is not actually an active treatment itself [69]. Obvious choices for a sham treatment (such as non-specific dry or wet needling) or a physiologically inert control (trigger point injection with saline or water) are considered by many to be active therapies that are somewhat effective in their own right. For example, sham acupuncture, which involves inserting needles into the skin away from true acupuncture points and is similar to sham dry needling, has been shown to produce analgesic effects in up to 50% of patients, compared with 60% to 75% for real acupuncture [73].

Since there is a significant non-specific placebo effect associated with subcutaneous needle insertion and injection, a control group is essential in studies on trigger point injection therapy [17, 50]. Studies that use inappropriate placebos or sham treatments really only provide information about the most effective needling site rather than the specific effect of trigger point injection itself [74]. Only one of the included studies used a control treatment that was truly inert [47]. Consequently, the strength of the placebo effect of trigger point therapy as an isolated treatment is still unknown, which makes it difficult to know if the injection therapy itself is effective or not. The absence of a comparison with dry needling alone in the included studies also prevented an

assessment of whether the injection of liquid or the tissue irritation caused by the needling, or both, results in the treatment effect observed during trigger point injection, and whether the main contribution of the injected fluid is merely to reduce the pain of needle insertion.

Another complicating factor is that some solutions cause more pain upon injection than others. For example, saline by itself is more painful than saline with lidocaine or procaine, and sterile water is more painful than saline [44, 75]. This has implications both for maintaining ignorance of treatment allocation and for selecting a physiologically inert control solution, since a painful injection is likely to cause a greater placebo response than a benign one [44].

If an acceptable placebo treatment cannot be found, the alternative is to minimise the placebo effect by designing studies with adequate sample sizes that will take into account the high proportion of patients likely to improve in the placebo group [50, 76]. Unfortunately, it is not ethical to include a 'no treatment' control group for patients suffering from chronic musculoskeletal pain, so it is impossible to determine how much of the observed treatment effect is contributed by the spontaneous improvement in symptoms often associated with the cyclical fluctuations that occur as part of the natural progression of myofascial pain [50].

Further considerations

Technical issues

Reliable identification of trigger points

The results of a survey of American Pain Society members [77] showed that over 88% of respondents thought that myofascial pain syndrome was a legitimate diagnosis, and over 90% regarded the presence of regional pain, taut muscle bands, and trigger points as being essential for its identification. Despite this emboldening clinical consensus, the diagnosis of myofascial pain continues to be undermined by the absence of a standardised examination technique for identifying trigger points [17, 78]. There is currently no satisfactory objective biochemical, electromyographic, or diagnostic imaging test available for diagnosing trigger points, although the use of ultrasonography, electromyography, thermography, and muscle biopsy has been explored [79-82]. The identification of trigger points still largely relies upon the knowledge and palpatory skill of the examiner, particularly since trigger points can be missed if palpation is too gentle [80, 82]. In studies that do not clearly report the method used to identify trigger points, it is difficult ascertain whether the trigger points were correctly located and injected.

The diagnostic criteria for identifying myofascial trigger points are now considered to be: spot tenderness, reproduction or aggravation of the pain usually experienced by the patient, and location of a taut muscle band. Eliciting referred pain and a local twitch response at the trigger point confirms the diagnosis [25]. However, identification of a

palpable taut band and referred pain are highly sensitive to the extent of examiner training, and eliciting the twitch response is the most demanding of all [32]. Acquiring these skills requires training and repetition, as well as a knowledge of referred pain patterns [80, 82, 83]. While the validity and reliability of using palpation as a means of identifying trigger points is still questioned, studies have shown that extensive clinical experience, together with a short period of specific training in trigger point identification to establish uniform examination techniques, can improve the reliability of trigger point identification between examiners [80, 82, 84].

Training is clearly important since even expert examiners differ in their interpretation of physical findings, examination technique, and the definition of the criteria used to identify a trigger point. The pressure applied to muscle sites during an examination differs between examiners, as does the technique used to elicit a local twitch response, and the former is particularly difficult to standardise [80]. Manual pressure algometry has been suggested as a way to objectively quantify the tenderness of a trigger point and overcome the imprecision of manual palpation, but this technique is still fraught with inter-examiner variation [81, 85].

Dosage/intensity of treatment

The published literature is rife with recommendations from various authors on the number of injections that should be administered per treatment session; the maximum volume of fluid that should be injected per session and per trigger point; how frequently the patient should be treated and for how long; and the best method for needling the trigger point itself. However, these recommendations, while replete with experience, are not reflected in the RCT evidence. Unfortunately, few of the included RCTs provided enough detail about the trigger point injection regimen and technique to assess what is optimal.

In addition, most of the included studies attempted to quantify the effects of trigger point injection as an isolated therapy. Since myofascial pain syndromes are often multifactorial and usually involve groups of muscles, trigger point injection is not generally recommended as the sole primary treatment for chronic musculoskeletal pain, but rather as a short-term adjunctive treatment that facilitates the use of exercise and other therapy [63, 64]. Therefore, the RCTs offered little in terms of understanding the efficacy of trigger point injection as part of the multi-disciplinary approach to chronic pain management that currently seems most promising [86]. It has also been suggested that when trigger point therapy is used as the primary therapy, patients are at risk of becoming dependent on it for pain relief [10], which may divert them from tackling the underlying factors that are causing and perpetuating their pain. This may be particularly likely if the newly acquired increase in range of motion provided by the trigger point injection therapy is not maintained by remedial stretching or exercise therapy. The current evidence base does not identify what, if any, treatment(s) would be augmented by the adjunctive use of trigger point injection, and it is possible that the

effectiveness of trigger point injection was underestimated by analysing it in isolation rather than in the adjunct capacity in which it is routinely used in clinical practice. Thus, there seems to be a significant disconnect between how trigger point injection is examined in the research literature and its advocated use in clinical practice.

Patient selection

The variability in the inclusion criteria used by the included studies precluded the derivation of any definitive conclusions regarding the possible contraindications for trigger point injection. It is also not clear what the effects of patient age, which can influence outcomes such as range of motion, or pain etiology and location have on the efficacy of trigger point injection therapy. In addition, some of the studies excluded patients with psychological problems, which made the results less generalisable to the 'typical' chronic pain sufferer. The literature suggests that patients who are unemployed because of their pain, have a longer duration of pain, and have pain that is constant rather than intermittent are less likely to respond to treatment [87]. Thus, it is obvious that the control of perpetuating and contributing factors is important in the treatment of chronic non-malignant musculoskeletal pain [88]. Patients are more likely to have a successful treatment outcome if they are motivated; do not have a psychosocial disorder; and have musculoskeletal pain of less than one year duration that is located in a specific area, is associated with few trigger points, and has caused a significant reduction in mobility [44].

Trigger point injection in Alberta

Expert Opinion

There was no information in the literature on the current use of trigger point injection therapy among practitioners in Alberta, so we obtained expert opinion from a physician practising in Alberta who specialises in physical medicine and musculoskeletal rehabilitation. In his opinion, trigger point injection is not commonly performed in Alberta and is not generally considered to be a mainstream treatment for patients suffering chronic non-malignant musculoskeletal pain. However, the technique is routinely used by certain specialised clinician groups such as interventional anaesthetists and physical medicine and rehabilitation specialists practicing pain management.

From the clinical perspective, trigger point injection is considered to be an adjunct treatment for chronic soft tissue pain disorders. Trigger point injection acts to dampen the pain enough to allow patients to be more effective in their exercise program and, as such, trigger point injection is a short-term treatment option that compliments rehabilitation or self-applied physical treatments. Even though the art of injecting trigger points is not commonly taught in medical school, expert opinion suggests that it is not difficult to learn and is within the skill set of most general practitioners. In the physician's opinion, the diagnosis of myofascial pain (in particular, the correct

identification of underlying primary sources of pain that are contributing to the secondary myofascial pain), the palpatory examination required to identify the trigger point(s), and the implementation of appropriate rehabilitation modalities are the most demanding aspects of trigger point injection in terms of the skill and expertise of the practitioner.

Expert opinion was also obtained from an anaesthetist practising in Alberta who specialises in pain medicine. His views on trigger point injection contrast slightly with those of the other expert in that he believes that this technique is used widely within Alberta by a variety of medical practitioners, most commonly as an isolated treatment rather than as part of a multi-disciplinary pain program. In the anaesthetist's opinion, trigger point injection is safe, easy to learn, requires minimal equipment, and offers enough pain relief to allow patients to participate in guided exercise therapy. Therefore, it is a good partial solution to pain management for patients in regional areas who may not have access to a multi-disciplinary pain management program, provided that there is a general practitioner available who can offer guidance in remedial exercise therapy.

Training, accreditation, and reimbursement

Currently, no medical specialty formally trains students in the diagnosis and treatment of myofascial trigger points, and no standards for training and practice have been established [20]. Given the importance of training for the reliable identification and diagnosis of myofascial trigger points, there is a clear need for further research into developing a validated, standardised teaching method that is effective in training physicians, both expert and non-expert, in the skills required to reliably identify trigger points and perform trigger point injection [84, 89]. Thorough training in the relevant anatomy, particularly in areas such as the thorax and cervical spine, should also be incorporated to ensure that potentially dangerous complications, such as pneumothorax, are avoided [42]. The needling technique used may also be important, and it has been suggested that clinicians should hone their skills by injecting cadavers with a coloured dye in order to learn correct needle placement [90]. The advent of such a training program would also require the development of methods to evaluate competency in the various skills at the end of the training period.

There is some concern that the inappropriate use of trigger point injection may inadvertently encourage patients to keep returning for a never ending program of trigger point injections to relieve their pain, rather than using the injections to augment a structured program of treatment that addresses the underlying etiological and perpetuating factors as well. It is important that physicians are aware of the importance of not relying on trigger point injection as a sole treatment for chronic non-malignant musculoskeletal pain. Therefore, professional bodies, such as The Royal College of Physicians and Surgeons of Canada, should consider providing a training and accreditation program for practitioners wishing to use trigger point injection in Canada.

It may also be prudent to tie the successful completion of such training to the ability to apply for reimbursement from the Alberta Health Care Insurance Plan, since this would curb the potential overuse and misuse of trigger point injection therapy.

Use of trigger point injection in regional communities

It is clear that any benefit of trigger point injection is inextricably linked to the training and expertise of the provider. The current literature was unclear as to what type of provider achieves the best results. Since there is disagreement between the published literature and expert opinion as to the degree of skill and provider experience required to achieve good results with trigger point injection, it remains unclear whether this will be an important aspect of trigger point injection in regional areas where specific clinical expertise may not be available.

The goal of treatment for chronic non-malignant musculoskeletal pain is not only to reduce pain but also to enable the patient to cope with it [18]. Non-specific general treatment procedures usually fail to remove the etiological factors causing the pain and associated symptoms [36]. Trigger point injection is only one of a number of therapies available to alleviate chronic musculoskeletal pain. This plethora of treatment options is testimony to the fact that no one strategy has proven successful in all patients and that therapy must be tailored to the needs of the individual patient.

It has become increasingly accepted that chronic musculoskeletal pain is most successfully managed with a multi-disciplinary approach that requires expertise from a number of medical and non-medical specialties, with trigger point injection comprising only one small facet of such a management program. However, trigger point injection may be used widely in regional areas in Alberta because it is perceived as a simple and safe way of providing patients with enough pain relief to enable them to participate in exercise therapy. Therefore, it is not known whether a lack of availability of multi-disciplinary pain management programs in regional areas currently limits the use of trigger point injection or encourages it. Physicians in regional areas could potentially offer effective trigger point injection therapy provided that they had adequate knowledge, training, and skill as well as access to an appropriately trained physical therapist that could provide suitable post-injection follow up to gain maximum benefit from the treatment.

Considerations for further research

To date, the safety and efficacy data most commonly quoted for the use of trigger point injection therapy for chronic non-malignant musculoskeletal pain are usually derived from studies that do not define what they mean by the term "chronic pain" [91, 92], only recorded outcomes for acute pain [71], or pooled patient outcomes for acute and chronic pain [93]. When the most commonly used definition of chronic pain [3] is applied to the published RCTs on trigger point injection, the dearth of evidence on its efficacy becomes apparent. Consequently, many questions regarding the use of trigger point

injection therapy for patients with chronic non-malignant musculoskeletal pain have yet to be addressed satisfactorily. These include:

1) Is there a cumulative dose response to trigger point injection, and if so, what is the minimum dose/intensity required to achieve a clinically significant treatment effect?
2) Is there a difference in treatment effect between specific wet needling of the trigger point and non-specific injection of fluid into the region surrounding the trigger point?
3) How strong is the placebo effect in trigger point injection therapy?
4) What does needling of the trigger point itself, in comparison to injecting fluid into the trigger point, contribute to the treatment effect?
5) Does the type, concentration, or volume of fluid injected affect treatment outcomes?
6) Does the needling technique used affect treatment outcomes?
7) What is the optimum treatment regimen with respect to frequency, treatment duration, number of injections per session, and needle size?
8) Which patient subgroups would receive the most benefit from trigger point injection?

The study of treatments for chronic non-malignant musculoskeletal pain has suffered from the diagnostic ambiguity often associated with this malady and a lack of adequate objective measures of severity [11, 18]. A comprehensive clinical description of patients entering trials using a universally accepted grading scale would enable comparisons between the pre- and post-treatment status of patients both within and between studies. Without this, any observed changes in patient status are virtually meaningless. In addition, even though there is evidence that educational and employment status, pain duration, somatisation, and depression are all potential prognostic factors in chronic pain outcomes, many studies fail to stratify or control these factors in their study design [11]. More detail is also needed on the treatment regimens used, the activity level of the patients while undergoing treatment, the co-interventions used by the patients during the study, and the method used to identify the trigger points [80, 94]. In addition, it has been suggested that the credibility of the technique used to identify the trigger points can be enhanced by using two examiners, who are blinded to treatment allocation, and reporting the inter-examiner reliability [78].

Pain relief is not necessarily associated with positive changes in daily functioning, work status, or use of health care, so studies should include these outcomes in addition to pain relief and physiological measures [11]. The comparability of examination results after trigger point injection is often compromised by the different inclusion criteria and examination methods, as well as the lack of standardised well-defined outcomes. However, it was notable that the majority of the RCTs included in this assessment used

a visual analog scale to quantify subjective pain and/or used objective measures to assess changes in pain threshold and range of motion. Given the difficulty of measuring something as subjective as an individual patient's perception of pain and improvement in function, it is commendable that researchers are using standardised and reproducible measures to report study outcomes.

Many of the problems evident in the evidence base for trigger point injection can be remedied if researchers follow the Consolidated Standards for Reporting Trials (CONSORT) recommendations [95] in tandem with the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) [96] when designing and reporting studies. The STRICTA guidelines are particularly applicable to trials of trigger point injection because they cover specific aspects of reporting that are peculiar to needling therapies.

CONCLUSIONS

Diagnosing and effectively treating trigger points in the absence of a clear understanding of their etiology and pathogenesis is a challenge. Thus, despite having been around for decades, trigger point injection is still an evolving therapy, and debate continues over various aspects of its use. Obtaining unalloyed data on the treatment of chronic musculoskeletal pain with trigger point injection was hampered by poor reporting and the inappropriate pooling of outcomes from both chronic and acute pain patients. In addition, small sample sizes and marked inter-study heterogeneity with respect to patient population, treatment regimen, injection site, and experimental protocol precluded a definitive synthesis of the data.

Trigger point injection is a relatively safe procedure when used by clinicians with appropriate expertise and training. However, the evidence for its effectiveness when used as the sole treatment for patients with chronic head, neck, and shoulder pain and whiplash syndrome was inconclusive, regardless of whether sterile water, saline, or botulinum toxin is injected. It is clear that more work is needed to quantify dose response for active injectants like botulinum toxin and anaesthetic. The combined use of dry needling and trigger point injection with procaine offers no obvious clinical benefit in the treatment of chronic craniofacial pain, while the effectiveness of trigger point injection for the treatment of cervicogenic headache is unknown. In contrast, trigger point injection with lidocaine may be a useful adjunct to intra-articular injection in the treatment of joint pain caused by osteoarthritis, compared to intra-articular injection alone. There was no proof that trigger point injection is more effective than other less invasive treatments, such as physical therapy and ultrasound, in achieving pain relief, and there is some suggestion that the only advantage of injecting anaesthetic into trigger points is that it reduces the pain of the needling process.

Even though trigger point injection is not a new technique, the rigour and validity of its evidence base is still relatively immature. Trigger point injection was generally analysed as a stand-alone treatment, so it is possible that the effectiveness of trigger point injection was underestimated by analysing it in isolation rather than in the adjunct capacity in which it is routinely used in clinical practice. The value of trigger point injection within the kind of multi-disciplinary approach to chronic pain management that is currently advocated in clinical practice is unknown.

The true value of trigger point injection therapy may lie in enabling patients to undergo remedial exercise therapy sooner than other less invasive techniques, such as ultrasound, which may require more treatment sessions to obtain the same result. However, this advantage may be counteracted by the greater skill required to correctly administer trigger point injections, particularly in regional areas where such expertise may be scarce. Formal guidance, training, and accreditation in the identification of trigger points and the use of injection therapy is necessary to ensure that misuse and overuse of trigger point injection therapy is not perpetuated.

The efficacy of trigger point injection is no more certain than it was a decade ago since, overall, there is no clear evidence of either benefit or ineffectiveness. Since equipoise exists among many of the potential treatments for chronic non-malignant musculoskeletal pain, and the treatments have similar safety profiles, further research should centre on good quality RCTs rather than non-randomised studies. Given the purported popularity of trigger point injection, this research is essential. A greater understanding of trigger point injection may help define better patient outcomes and establish more realistic expectations of what the treatment can achieve in clinical practice.

APPENDICES

APPENDIX A: METHODOLOGY

Inclusion criteria

Types of studies

Systematic reviews or RCTs were included for analysis. Non-randomised comparative studies, case series studies, and case reports detailing trigger point injection were excluded from review because of the limited data they could offer in comparison to the number of higher quality RCTs available.

An article was deemed to be a systematic review if it met all of the following criteria as defined by Cook et al. [97]:

1) focused clinical question;
2) explicit search strategy;
3) use of explicit, reproducible and uniformly applied criteria for article selection;
4) critical appraisal of the included studies;
5) qualitative or quantitative data synthesis.

Only full peer-reviewed articles were included because abstracts do not provide adequate detail on patient selection, treatment allocation, outcome and measurement methods, and study design to allow an accurate, unbiased assessment and comparison of the study results.

Background information

Where appropriate, additional relevant published material in the form of letters, conference material, commentary, editorials and abstracts were included as background information.

Participants

Data were collected on patients with chronic non-malignant pain of musculoskeletal origin that had persisted for at least three months. Patients with acute pain or pain secondary to a defined systemic disease, such as cancer, AIDS, diabetes, or sickle cell anemia were excluded unless the data subset for the patients with chronic musculoskeletal pain could be separated from the aggregate data. However, patients with non-malignant disorders of the skeletal system, such as osteoarthritis, were included. Animal studies were not included.

Index Intervention

Trigger point injection, or direct wet needling, involving the injection of fluid directly into a trigger point(s) located within a taut muscle band.

Comparative intervention

Any medical, mechanical, or surgical intervention designed to treat patients with chronic musculoskeletal pain. Placebo and no treatment comparisons were also included, as were studies comparing different treatment regimens within the therapeutic modality of trigger point injection.

Outcomes

The papers included must contain information on at least one of the following outcomes of the new or comparative intervention. In addition, at least one of these outcomes must be reported for both the index and the comparative intervention to allow for comparison between the treatment groups. These outcomes may include but not be limited to:

- Post-treatment morbidity of patients;
  - bleeding
  - nerve injury
  - infection
  - vasovagal syncope
  - allergic reaction
- Post-treatment efficacy measures;
  - pain pressure threshold
  - range of motion
  - subjective pain

Literature search strategy

The medical literature was searched to identify relevant studies and reviews. Searches were conducted without language or date restriction (Table A.1). Additional searches were also run in September 2004 on HealthSTAR, SUMSearch, Google.com, Copernic.com, and AlltheWeb.com to locate grey literature using the key terms trigger point, trigger point injection, and needling.

The bibliographies of all articles retrieved in full hard copy form were manually searched for relevant references that may have been missed in the database searches.

Literature database

Study selection was conducted by one reviewer (AS). Articles were excluded that, on the basis of their abstract, clearly did not meet the inclusion criteria. Copies of the full text of potentially eligible studies were retrieved. In some cases, when the full text of the article was retrieved, closer examination revealed that it did not meet the inclusion criteria specified by the review protocol. Consequently these papers were not used to

formulate the evidence base for the systematic review (Appendix B). However, relevant information contained in these excluded papers was used to inform and expand the review discussion. For RCTs in which the definition of chronic pain was unclear, we contacted the authors to verify whether any of the study participants had chronic pain of less than three months' duration when treatment began.

Assessment methods

Study methodology appraisal

The included trials were assessed with respect to various methodological aspects using the criteria list recommended in the method guidelines of the Cochrane Back Review Group for systematic reviews [98]. This list has been used in a number of systematic reviews [99-101] in the field of chronic pain and includes all the criteria from the lists generated by Jadad et al. [102] and Verhagen et al. [103]. It consists of internal and external validity criteria, as well as statistical criteria. The list was modified by removing items E (Was the care provider blinded?) and G (Was compliance acceptable?), since blinding of the care provider is often not possible in trigger point injection and compliance is not a relevant issue when trigger point injection is the sole treatment. In addition, some instructions were reworded or supplemented with more detailed criteria descriptions from Downs and Black [104]. Given the potential dangers of using numerical scores to evaluate the quality of trials [105, 106], a simple nominal rating scale was used such that the studies were scored as positive (yes), negative (no), or unclear (don't know) for each quality criterion. Aspects of the scientific quality of systematic reviews and meta-analyses were similarly assessed using a validated checklist developed by Oxman and Guyatt [107].

The study quality assessments were undertaken by two independent reviewers (AS and BG). Any disagreements that could not be resolved by discussion were referred to a third reviewer for mediation until consensus was reached. The two reviewers discussed the checklists with respect to the interpretation of the questions prior to assessing the studies. Critical appraisal results for all included studies are tabulated in Appendix C. For descriptive purposes, the included RCTs were referred to as being good, moderate, or poor quality with respect to internal and external validity according to the total number of criteria met as follows (see also Appendix C, Table C.1):

- Internal validity (total number of criteria = 9) – good (at least 7 criteria met), moderate (between 4 and 6 criteria met), poor (less than 4 criteria met);
- External validity (total number of criteria = 6) – good (at least 5 criteria met), moderate (3 or 4 criteria met), poor (less than 3 criteria met).

Outcome measures and data extraction

Study profile information as well as safety and efficacy data were extracted by one reviewer (AS) using standardised data extraction forms developed *a priori*.

In terms of efficacy, the question was whether the index intervention produced equivalent clinical outcomes, in comparison to the comparator procedure. Post-treatment efficacy outcomes included changes in range of motion, pain pressure threshold at the trigger points, and pain and subjective function scores. If any other efficacy outcome was reported in the study it was also tabulated.

The question of safety was addressed in terms of whether the index intervention was more or less likely to cause injury or harm to the patient, in comparison to the comparator procedure. This aspect was considered a subsidiary aim of the review. However, since trigger point injection is invasive, it can, in rare instances, be potentially dangerous. Therefore, it was considered pertinent to tabulate any outcome related to patient safety.

Data analysis

The analyses for binary and continuous outcomes included all patients with available data, using the last reported observed response. Thus, the data analysis was by treatment rather than intention-to-treat. The denominator used to calculate proportions was the number of patients remaining in the study at each follow-up period, and did not include dropouts or withdrawals.

A meta-analysis was planned if the RCTs had comparable outcomes, inclusion criteria, treatment regimen, and follow-up period. However, the small number of studies and variety of treatment regimens precluded this.

Expert review

External reviewers with clinical expertise in trigger point injection therapy and health technology assessment methodology evaluated the draft review and provided feedback. In selecting reviewers, the practice of the AHFMR is to choose experts who are well recognised and published in the peer-reviewed literature, and who can offer a provincial and/or national perspective with respect to the use of trigger point injection in patients with chronic non-malignant musculoskeletal pain.

Table A.1: Databases and search terms used in the search strategy

Database	Platform	Edition	Search Terms
Core Databases			
The Cochrane Library	Issue 3, 2004	September 18, 2004	trigger* AND pain AND (inject* OR trigger point*)
CRD (UK)	http://nhscrd.york.ac.uk/ welcome.htm	September 18, 2004	(trigger OR trigger point OR trigger-point) AND (pain OR chronic pain OR myofascial pain syndromes OR fibromyalgia) AND (inject OR needling)
PubMed	http://www.pubmed.gov	September 18, 2004	((pain/[MeSH] NOT malignant) OR ("chronic pain" NOT malignant) OR myofascial pain syndromes[MeSH] OR fibromyalgia[MeSH]) AND ((injection/[MeSH] OR inject* OR needling) AND (trigger* OR "trigger point* OR "trigger point inject*"))
ECRI	www.ecri.org	September 18, 2004	(trigger* AND (inject* OR needling)) OR (trigger point* AND pain)
EMBASE	OVID	Week 38, 2004	((inject* OR needling OR exp INJECTION/) AND (trigger* OR trigger point* OR trigger-point*) AND (exp CHRONIC PAIN/ OR exp PAIN/) NOT malignant.mp)
Science and Social Sciences Citation Index	Web of Science	September 18, 2004	TS=(trigger* AND point* OR trigger-point*) AND (inject* OR needling) AND (pain OR chronic pain) NOT (TS=malignant)
Library Catalogues			
NEOS (Central Alberta Library Consortium Catalogue)	http://www.neoslibraries.ca/	September 18, 2004	"trigger point inject*" AND (pain OR myofascial pain syndrome*)
AMICUS (National Library of Canada Public Catalogue)	http://www.nlc-bnc.ca/amicus	September 19, 2004	"trigger point inject*" AND (pain OR myofascial pain syndrome*)
NLM LocatorPlus	http://locatorplus.gov/	September 18, 2004	((Trigger* OR trigger point*) AND inject* AND (pain OR chronic pain OR myofascial pain syndrome*)) NOT malignant
Canadian Resources			
Canadian Theses Portal, National Library of Canada	http://www.nlc-bnc.ca/thesescanada	September 18, 2004	trigger point injection
AETMIS	http://www.aetmis.gouv.qc.ca	September 18, 2004	trigger point injection OR (trigger* AND injection*)
CCOHTA	http://www.ccohta.ca	September 18, 2004	trigger point injection OR (trigger* AND injection*) OR ((pain OR chronic pain) AND injection*))

Database	Platform	Edition	Search Terms
Canadian Resources (cont'd)			
Health Quality Council of Saskatchewan	http://www.hqc.sk.ca/	September 18, 2004	"trigger point injection" OR (pain AND inject*)
ICES	http://www.ices.on.ca/	September 18, 2004	trigger point injection OR (trigger* AND inject*)
Evidence-based Resources			
ACP Journal Club	OVID	March/April 2004	(trigger point injection* OR ((trigger* OR trigger point*) AND inject*))
ATTRACT (UK)	http://www.attract.wales.nhs.uk	September 21, 2004	trigger point injection* OR ((trigger* OR (trigger point)) AND inject*)
Bandolier	http://www.jr2.ox.ac.uk/bandolier/	September 20, 2004	trigger point injection* OR ((trigger* OR (trigger point)) AND inject*)
Clinical Evidence	http://www.clinicalevidence.com	September 22, 2004	trigger point injection* OR ((trigger* OR trigger point) AND inject*)
TRIP Database	http://www.tripdatabase.com	September 18, 2004	trigger point injection* OR ((trigger* OR trigger point) AND inject*)
Clinical Practice Guidelines			
AMA Guidelines (Alberta Medical Assoc.)	http://albertadoctors.org	September 18, 2004	trigger point injection* OR ((trigger* OR trigger point) AND inject*) OR ((pain OR chronic pain) AND inject*)
CMA Clinical Practice Guidelines Database	http://mdm.ca/cpgsnew/cpgs/index.asp	September 18, 2004	trigger point injection* OR ((trigger OR trigger point) AND inject*) OR ((pain OR chronic pain) AND inject*)
National Guideline Clearinghouse	http://www.ngc.gov	September 18, 2004	trigger point injection* OR ((trigger* OR trigger point) AND inject*) OR ((pain OR chronic pain) AND inject*)
Clinical Trials			
ClinicalTrials.gov (US)	http://clinicaltrials.gov	September 18, 2004	trigger point injection* OR ((trigger* OR trigger point) AND inject*) OR ((pain OR chronic pain) AND inject*)
CenterWatch Clinical Trials Service (US)	http://www.centerwatch.com/	September 18, 2004	trigger point injection* OR ((trigger* OR trigger point) AND inject*) OR ((pain OR chronic pain) AND inject*)
National Research Register (UK)	http://www.updatesoftware.com/national	September 18, 2004	trigger point injection* OR ((trigger* OR trigger point) AND inject*) OR ((pain OR chronic pain) AND inject*)

Database	Platform	Edition	Search Terms
Other Subject Databases			
CINAHL	OVID	September Week 3, 2004	trigger* AND pain AND (inject* OR needling) AND (exp "PAIN (NANDA)"/ or exp CHRONIC PAIN/ or exp "CHRONIC PAIN (SABA HHCC)"/ or exp "CHRONIC PAIN (NANDA)"/ or exp PAIN/) AND exp Injections/ AND (trigger OR trigger point* OR trigger-point*)
Dissertations Abstracts UMI (US)	http://www.lib.umi.com/dissertations	September 22, 2004	trigger point injection OR (myofascial pain AND treatment)
AMED	OVID	September 23, 2004	trigger point injection* OR (trigger* point AND inject*) OR ((pain OR chronic pain) AND inject*))
BIOSIS	http://www.biosis.org/	1999-2003	(trigger point injection* AND pain)
NLM Gateway	http://gateway.nlm.nih.gov/gw/Cmd	September 22, 2004	(trigger point injection* OR ((trigger* OR trigger point*) AND inject*)) OR ((pain OR chronic pain) AND inject*)
Regulatory Agencies/Licensing Agencies/Coverage Agencies			
Alberta Health and Wellness	http://www.health.gov.ab.ca	September 20, 2004	(trigger point injection* OR ((trigger* OR trigger point*) AND inject*)) OR ((pain OR chronic pain) AND inject*)
Health Canada Medical Devices Active Licence Listing	http://www.mdall.ca/	September 20, 2004	(trigger point injection* OR ((trigger* OR trigger point*) AND inject*)) OR ((pain OR chronic pain) AND inject*)
NICE (UK)	http://www.nice.org.uk/	September 20, 2004	(trigger point injection* OR ((trigger* OR trigger point*) AND inject*)) OR ((pain OR chronic pain) AND inject*)
US Food and Drug Administration	http://www.fda.gov	September 20, 2004	(trigger point injection* OR ((trigger* OR trigger point*) AND inject*)) OR ((pain OR chronic pain) AND inject*)
Medicare/Medicaid Coverage Database (US)	http://www.cms.hhs.gov/mcd/search.asp?	September 20, 2004	(trigger point injection* OR ((trigger* OR trigger point*) AND inject*)) OR ((pain OR chronic pain) AND inject*)

Note: * is a truncation character that retrieves all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc. In databases accessed via the Ovid platform the truncation character is $.

APPENDIX B: EXCLUDED STUDIES

Table B.1: Summary of excluded studies

Study	Study Type	Reason for Exclusion
Alo et al. (1997) [108]	Non-randomised comparative study	Study participants not randomised to the intervention groups.
Bourne (1984) [91]	Double blind RCT	Definition of "chronic" not stated so unable to determine whether the pain symptoms had been present for a minimum of three months. Publication date precluded contacting the authors for further information.
Cummings & White (2001) [27]	Systematic review	The review pooled results from studies of patients with chronic and acute (<3 months' duration) pain. It was impossible to separate the results for the chronic pain patients from those with acute pain.
Ezzo et al. (2000) [76]	Systematic review	None of the included studies used TPI as an intervention.
Fine et al. (1988) [109]	Double blind crossover RCT	The study population comprised patients with acute (<3 months' duration) and chronic pain. The results for the patients with chronic pain could not be separated from the aggregate data.
Freund and Schwartz (1998) [110]	Randomised comparative study	Definition of "chronic" not stated so unable to determine whether the pain symptoms had been present for a minimum of three months. Unable to find current contact details for the study authors.
Frost et al. (1980) [111]	Double blind RCT	Patients had acute (<3 months' duration) not chronic pain.
Frost et al. (1980) [112]	Double blind RCT	Duplication of data presented in Frost et al. [111].
Frost (1986) [113]	Single blind RCT	The study population comprised patients with acute (29%) (<3 months' duration) and chronic pain. The results for the patients with chronic pain could not be separated from the aggregate data.
Garvey et al. (1989) [71]	Double blind RCT	Patients did not have chronic pain (symptom duration of four weeks prior to study enrolment).
Hameroff et al. (1981) [92]	Randomised double blind crossover trial	Definition of "chronic" not stated so unable to determine whether the pain symptoms had been present for a minimum of three months. Publication date precluded contacting the authors for further information.
Hawk and Long (2000) [70]	Single blind RCT	Trigger point therapy involved manual ischemic compression rather than TPI.
Hollingworth et al. (1983) [114]	Double blind crossover RCT	The study population comprised patients with acute (<3 months' duration) and chronic pain. The results for the patients with chronic pain could not be separated from the aggregate data.

Table B.1: Summary of excluded studies (cont'd)

Study	Study Type	Reason for Exclusion
Hong (1994) [93]	Double blind RCT	The study population comprised patients with acute (<3 months' duration) and chronic pain. The results for the patients with chronic pain could not be separated from the aggregate data.
Hong & Hsueh (1996) [115]	Non-randomised comparative study	Study participants not randomised to the intervention groups. A few patients with myofascial pain syndrome had pain duration of less than three months (Pers. Comm.. C.Z. Hong).
Hubbard (1996) [4]	Non-randomised comparative study	Study participants not randomised to the intervention groups.
Imamura et al. (1998) [81]	Non-randomised comparative study	Study participants not randomised to the intervention groups.
Iwama & Akama (2000) [116]	Double blind RCT	The pain duration of the study participants was unknown (Pers. Comm. H. Iwama) so it was impossible to determine whether the pain symptoms had been present for a minimum of three months.
Iwama et al. (2001) [117]	Double blind RCT	Patients had acute (<3 months' duration) not chronic pain (Pers. Comm. H. Iwama).
Lang (2003) [118]	Non-randomised comparative study	Study participants not randomised to the intervention groups.
Mariot et al. (1985) [119]	Case series study	Not an RCT.
Nelemans et al. (1999) [72]	Systematic review	The review inclusion criteria comprised patients with acute (<3 months' duration) and chronic low back pain. The results for the patients with chronic pain could not be separated from the aggregate data.
O'Reilly and Pollard (1996) [120]	RCT	Trigger point therapy involved manual ischemic compression rather than TPI.
Porta (2000) [121]	Double blind RCT	Local muscle injection rather than TPI.
Prateepavanich et al. (1999) [122]	RCT	Patients did not have chronic pain.
Ready et al. (1983) [123]	Single blind crossover RCT	Definition of "chronic" not stated so unable to determine whether the pain symptoms had been present for a minimum of three months. Publication date precluded contacting the authors for further information.
Tschopp & Gysin (1996) [124]	Double blind RCT	The study population comprised patients with acute (<3 months' duration) and chronic pain. The results for the patients with chronic pain could not be separated from the aggregate data.
Vad et al. (2002) [125]	Non-randomised comparative study	Study participants not randomised to the intervention groups. The study population comprised patients with acute (< 3 months' duration) and chronic pain. The results for the patients with chronic pain could not be separated from the aggregate data.

Table B.1: Summary of excluded studies (cont'd)

Study	Study Type	Reason for Exclusion
van Tulder et al. (1997) [126]	Systematic review	None of the included studies used TPI as an intervention.
van Tulder et al. (1999) [127]	Systematic review	Only included one RCT involving TPI (Garvey et al. [71]), which was excluded from the current review.
van Tulder et al. (1999) [128]	Systematic review	Duplication of data presented in van Tulder et al. [127].

APPENDIX C: METHODOLOGICAL ASSESSMENT RESULTS

Study Quality Assessment Checklist

(Adapted from the list recommended in the method guidelines of the Cochrane Back Review Group for systematic reviews [98], with additional guidance derived from Downs and Black [104])

Patient Selection

A. *Were the eligibility criteria specified?*

Inclusion and/or exclusion criteria should be given.

B. *Treatment allocation*

1) Was a method of randomisation performed?

Studies stating that patients were randomised should be answered 'yes' except where the method of randomisation would not ensure random allocation. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation are not regarded as appropriate.

2) Was the treatment allocation concealed?

Assignment generated by an independent person not responsible for determining the eligibility of the patients.

C. *Were the groups similar at baseline regarding the most important prognostic indicators?*

To receive a 'yes', groups must be similar at baseline regarding age, gender, duration of pain, and at least one of the following: patient comorbidities, pain pressure threshold, mobility, or pain intensity.

Interventions

D. *Were the index and control interventions explicitly described?*

The description should include (when applicable) type, modality, application technique, intensity, and duration as well as the number and frequency of sessions so that others can replicate the treatment. If any of the treatments are described by name only, with no further detail given, the question should be answered 'no'.

E. *Were co-interventions avoided or comparable?*

Co-interventions should either be avoided in the trial design or comparable between the index and control groups.

F. *Was the patient blinded to the intervention?*

For studies where the patients would have no way of knowing which intervention they received, this should be answered 'yes'. For studies that do not state whether blinding was attempted, the answer should be 'unclear'.

Outcome measurement

G. *Was the outcome assessor blinded to the intervention?*

For studies where the outcome assessor would have no way of knowing which intervention the patients received, this should be answered 'yes'. For studies that do not state whether blinding was attempted, the answer should be scored as 'unclear'.

H. *Were the outcome measures relevant?*

Outcome measures should be clearly described. Relevant measures for non-malignant chronic pain include changes in pain, mobility, and pain pressure threshold; generic functional status; global measure of improvement; and return to work.

I. *Were adverse effects described?*

Each event should be described and correctly attributed to the allocated treatment. If it was explicitly reported that no adverse events occurred then a 'yes' should be scored. When adverse events are described but not clearly attributed to a particular treatment, the answer should be scored as 'unclear'.

J. *Was the withdrawal/dropout rate described and acceptable?*

Patients included in the study but who did not complete the observation period or were not included in the analysis must be described. If the numbers of patients lost to follow-up were not reported, the question should be answered as 'unclear'. If the proportion lost to follow-up was too small (≤10% in each treatment group for short-term follow-up and ≤20% for long-term follow-up) to affect the main findings, the question should be answered 'yes'. (**Note:** These percentages are arbitrary and are not supported by literature).

K. *Timing of follow-up measurements*

1) Was a short-term follow-up measurement performed?

Outcome assessment at the end of the intervention period.

2) Was a long-term follow-up measurement performed?

Outcome assessment >3 months after randomisation.

L. *Was the timing of the outcome assessment comparable in both groups?*

The timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments. Where follow-up was the same for all study patients, the answer should be 'yes'. If the results were adjusted to account for different lengths of follow-up (for example by survival analysis), the answer should be 'yes'. Studies where differences in follow-up were ignored should be answered 'no'.

Statistics

M. *Was the sample size for each group described?*

Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.

N. *Did the analysis include an intention-to-treat analysis?*

All randomised patients are reported/analysed for the most important effect measurements (minus missing values) irrespective of non-compliance and co-interventions.

O. *Were point estimates and measures of variability presented for the primary outcome measures?*

Both point estimates and measures of variability should be presented separately for each important outcome. In non-normally distributed data the median and inter-quartile range should be reported. In normally distributed data the mean plus standard error, standard deviation, or confidence interval should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes'.

Table C.1: Study quality assessment results

Study Characteristic		Byrn et al. [44]	Cheshire et al. [45]	Esenyel et al. [46]	Ferrante et al. [47]	Freund & Schwartz [48,49]
Patient Selection	A. Were the eligibility criteria specified?	-	+	+	+	?
	B1. Was randomisation performed adequately?	?	?	?	?	?
	B2. Was treatment allocation concealed?	+	?	?	?	+
	C. Were the groups similar at baseline?	?	?	?	?	-
Interventions	D. Were the index and control interventions explicitly described?	+	+	+	+	+
	E. Were co-interventions avoided or comparable?	?	+	+	?	+
	F. Was the patient blinded to the intervention?	+	+	?	+	+
Outcome measurement	G. Was the outcome assessor blinded to the intervention?	+	?	?	?	+
	H. Were the outcome measures relevant?	+	+	+	+	+
	I. Were adverse events described?	+	+	-	-	+
	J. Was the withdrawal/dropout rate described and acceptable?	+	+	+	?	-
	K1. Was a short-term follow-up measurement performed?	+	+	+	+	+
	K2. Was a long-term follow-up measurement performed?	+	-	+	-	-
	L. Was the timing of the outcome assessment comparable in both groups?	+	+	+	+	+
Statistics	M. Was the sample size for each group described?	+	+	+	+	+
	N. Did the analysis include an intention-to-treat analysis?	+	+	+	?	-
	O. Were point estimates and measures of variability presented for the primary outcome measures?	-	-	+	+	+

Key: Yes = +; No = -; Unclear = ?; Not applicable or not possible because of the nature of the intervention = NA

Internal validity criteria: b, e, f, g, h, j, l, n; External validity criteria: a, c, d, i, k; Statistical criteria: m, o

Table C.1: Study quality assessment results (cont'd)

Study Characteristic		McMillan et al. [50]	Schnider et al. [51]	Wheeler et al. [52]	Wheeler et al. [53]	Yentür et al. [54]
Patient Selection	A. Were the eligibility criteria specified?	+	+	+	+	+
	B1. Was randomisation performed adequately?	?	?	?	?	?
	B2. Was treatment allocation concealed?	?	?	+	?	?
	C. Were the groups similar at baseline?	?	+	?	+	+
Interventions	D. Were the index and control interventions explicitly described?	+	+	+	+	+
	E. Were co-interventions avoided or comparable?	+	+	?	?	+
	F. Was the patient blinded to the intervention?	+	?	?	+	?
Outcome measurement	G. Was the outcome assessor blinded to the intervention?	?	?	+	?	+
	H. Were the outcome measures relevant?	+	+	+	+	+
	I. Were adverse events described?	-	+	+	+	+
	J. Was the withdrawal/dropout rate described and acceptable?	?	+	+	+	+
	K1. Was a short-term follow-up measurement performed?	+	+	+	+	+
	K2. Was a long-term follow-up measurement performed?	-	+	+	+	?
	L. Was the timing of the outcome assessment comparable in both groups?	+	+	+	+	+
Statistics	M. Was the sample size for each group described?	-	-	+	+	+
	N. Did the analysis include an intention-to-treat analysis?	?	-	+	-	?
	O. Were point estimates and measures of variability presented for the primary outcome measures?	+	+	-	+	+

Key: Yes = +; No = -; Unclear = ?; Not applicable or not possible because of the nature of the intervention = NA

Internal validity criteria: b, e, f, g, h, j, l, n; External validity criteria: a, c, d, i, k; Statistical criteria: m, o

APPENDIX D: DATA EXTRACTION TABLES

Glossary for Appendix D

Measurement Abbreviations

SD – standard deviation

SE - standard error of the mean

General Abbreviations

FU – follow-up

IA – intra-articular

ROM – range of motion

TENS - transcutaneous electrical nerve stimulation

TPI - trigger point injection

US - ultrasound

VAS - visual analog scale

Table D.1: Intervention study profile

Authors/Location	Intervention	Study Design	Study Population
Byrn et al. (1993) [44] Department of Anaesthesia and Department of Psychiatry, Sahlgrenska Hospital, University of Gothenburg, Gothenburg, Sweden Traffic Injury Register, Department of Orthopaedics, East Hospital, University of Gothenburg, Sweden Back Health, Gothenburg, Sweden Department of Neurology, Lundby Hospital, Gothenburg, Sweden **Financial support** Not stated	**1) TPI with sterile water** Technique: Trigger and tender points were located by palpation and marked with a ballpoint pen. Subcutaneous injections (2 to 3 mm below the skin) of 0.3 to 0.5 mL of sterile water were made at every tender and trigger point. Three to five subcutaneous injections (2 to 3 mm below the skin) of 0.3 to 0.5 mL of sterile water were given in rapid succession, emptying the syringe. After this there was a pause of one or two minutes to allow any stinging sensation to pass. Then the injections were continued until all tender and trigger points were treated. If the patient still indicated pain in a particular area during a certain movement a second palpation and at least one more injection at other trigger and tender points was given during the same session. All treatments and assessments took place between 9:00 AM and midday to minimise activity related discomfort. Treatment Regimen: Treatments given within first two months of study according to patient indicated need: one treatment - 15%; two treatments - 55%; three treatments - 30%. Mean Number of Tender/Trigger Points Treated: First treatment - 29 (range 5 to 80); Second treatment - 13 (range 2 to 47); Third treatment - 5 (range 3 to 38)	Prospective randomised double-blind concurrently controlled trial Intention-to-Treat Analysis: Not stated but intention-to-treat analysis conducted by default since there were no losses to follow-up. Method of Randomisation: Not stated Time of Randomisation: Not stated Method of Allocation Concealment: Not stated Details of Blinding: The injections solutions were supplied by the hospital pharmacy in coded ampoules but the patient's pain reaction on being injected with sterile water made it inevitable that the treating physician would know the content of the ampoule since saline does not hurt. No further details of blinding were given. Participation Rate: Not stated Eligibility Rate for Study: Not stated Follow-up: 1, 3 and 8 months after first treatment Lost to Follow-up: 0% Study Period: Not stated Provider: All injections were given by one anaesthetist.	Sample Size: **1)** n = 20; **2)** n = 20 There was no statistically significant difference between groups 1 and 2 with respect to depression, anxiety and personality trait scores (which were in the normal range) (p not stated). Statistical comparison of other pre-treatment parameters for the patient groups was not reported. Patient Diagnosis: Typical whiplash syndrome with pain and impaired mobility in the neck and shoulders. Diagnostic Definitions: Not stated Pre-treatment Mean Pain Pressure Threshold: Not measured Pre-treatment Mean VAS Rating for Pain Intensity (scale 0 to 10): **1)** 4.0 (range 0 to 9); **2)** 3.6 (range 0 to 9) Pre-treatment Mean Total Cervical Mobility: **1)** 288° (range 120 to 390) **2)** 291° (range 140 to 440) Mean Age: **1)** 45.5 yrs (range 25 to 73) **2)** 46.3 yrs (range 24 to 72)

Continued next page

Authors/Location	Intervention	Study Design	Study Population
Byrn et al. (1993) [44] (cont'd)	**2) TPI with saline** Technique: As for group 1 above but with saline. Treatment Regimen: Treatments given within first two months of study according to patient indicated need: one treatment - 10%; two treatments - 25%; three treatments - 65%. Mean Number of Tender/Trigger Points Treated: First treatment - 36 (range 10 to 110); Second treatment - 31 (range 6 to 116); Third treatment - 20 (range 20 to 98) **1) & 2)** Equipment: 2 mL syringe and a 27 gauge cannula Sites Treated: Not specifically stated but trigger and tender points were usually located over the lateral cervical muscles, the superior margin of the trapezius, and on the anterior rotator cuff. Several patients also had tender and trigger points along the medial rim of the scapulae and the anterior and posterior aspect of the upper arm. Co-interventions: Not stated Pre-treatment Evaluation: Pain intensity using a VAS; mobility measured with a Myrin goniometer; psychological examination with the NEO personality inventory (Swedish version), Beck depression inventory, Spielberger anxiety test, and the mode adjective checklist. Post-treatment Evaluation: Same as for pre-treatment evaluation.	Assessor Details: Mobility and pain were evaluated by one physiotherapist; the psychological analysis was conducted by one clinician (specialty not stated); and data were analysed by another physician who had not seen the patients. Setting: Not stated Inclusion/Exclusion Criteria: Not stated	Gender Mix: **1)** M/F = 10 (50%)/10 (50%) **2)** M/F = 9 (45%)/11 (55%) Duration of Pain: Not specifically stated but all patients were involved in car accidents 4 to 6 years earlier. Since whiplash syndrome is characterised by cervical spine injury resulting from a traffic accident, it was assumed that the duration of pain for this patient group was equivalent to 4 to 6 years, i.e. as beginning from the time of their car accidents. Patient Co-morbidities: **1) & 2)** Traumatic lesion of the cervical spine - 0% Patient Details: **1)** Sleep disturbances - 70%; Headache - 65%; Vertigo - 35%; Fatigue - 45%; Tinnitus - 5%; Full sick leave - 15%; Half sick leave - 15%; Retired - 10% **2)** Sleep disturbances - 80%; Headache - 70%; Vertigo - 35%; Fatigue - 50%; Tinnitus - 30%; Full sick leave - 30%; Half sick leave - 5%; Retired - 5%; Previous Treatment: **1)** Acupuncture - 40%; TENS - 35%; US - 30%; Laser - 15%; Chiropraxis - 30%;Physiotherapy - 100% **2)** Acupuncture - 25%; TENS - 45%; US - 30%; Laser - 25%; Chiropraxis - 15%;Physiotherapy - 100% Treatments at the Start of the Study: **1)** Analgesics - 95%; Benzodiazepines - 55%; Antidepressants - 55%; Physiotherapy - 75% **2)** Analgesics - 90%; Benzodiazepines - 80%; Antidepressants - 35%; Physiotherapy - 80%

Table D.1: Intervention study profile (cont'd)

Authors/Location	Intervention	Study Design	Study Population
Cheshire et al. (1994) [45] Department of Neurology, University of North Carolina, Chapel Hill, North Carolina, USA **Financial support** Not stated	**1)** **a) TPI with botulinum toxin** **b) TPI with saline** Technique: Trigger points were injected with a total dose of 50 mouse units of botulinum toxin type A in 4 mL of normal saline divided equally among 2 or 3 sites. Eight weeks later the same sites were injected with normal saline only. **2)** **a) TPI with saline** **b) TPI with botulinum toxin** Technique: As for group 1 but in reverse order **1) & 2)** Equipment: Not stated Treatment Regimen: Injections on two occasions, 8 weeks apart, one of botulinum toxin and the other of normal saline, in random order. Number of Trigger Points Treated: 2 or 3 Sites Treated: The same sites were injected each time as located by carefully drawn anatomic charts for each patient. Co-interventions: Oral muscle relaxant medication and vigorous standardised physical exercise were not prescribed during the study. Pre-treatment Evaluation: Pain intensity using a VAS, pain intensity and unpleasantness measured with verbal pain descriptors, palpable muscle spasm grading, pressure pain threshold with a pressure algometer Post-treatment Evaluation: Same as for pre-treatment evaluation.	Prospective randomised double-blind controlled crossover trial Intention-to-Treat Analysis: Not stated but intention-to-treat analysis conducted by default since there were no losses to follow-up. Method of Randomisation: Not stated Time of Randomisation: Not stated Method of Allocation Concealment: Not stated Details of Blinding: Patients and investigators were blinded but no details given. Since botulinum toxin produces no immediate side effects or sensations different from placebo, it was considered unlikely that patients or investigators could distinguish between the two injections. Participation Rate: Not stated Eligibility Rate for Study: Not stated Follow-up: Weekly intervals for four weeks after each injection and 8 weeks after the final injection. Lost to Follow-up: 0% Study Period: Not stated Provider: Not stated Assessor Details: Not stated Setting: Patients were recruited from a Pain Clinic	Sample Size: **1)** n = 3; **2)** n = 3 Statistical comparison of pre-treatment parameters for groups 1 and 2 was not reported. Patient Diagnosis: Focal pain involving the cervical paraspinal or shoulder girdle muscles with discrete trigger points. Diagnostic Definitions: Based on the Travell and Simons criteria [16]. Pre-treatment Mean Pain Pressure Threshold: Unable to derive raw data from graphical presentation Pre-treatment Mean VAS Rating for Pain Intensity (scale 0 to 100): Unable to derive raw data from graphical presentation Pre-treatment Mobility: Not stated Mean Age: **1)** 43.0 yrs (SD ± 8.5); **2)** 44.7 yrs (SD ± 9.6) Gender Mix: **1)** M/F = 0%/100% **2)** M/F = 2 (66.7%)/1 (33.3%) Mean Duration of Pain: **1)** 3.0 yrs (SD ± 1.0); **2)** 3.5 yrs (SD ± 0.9) Patient Co-morbidities: Not stated Patient Details: Not stated Previous Treatment: **1)** Cervical discectomy – 33.3% **1) & 2)** Non-steroidal anti-inflammatory drugs and muscle relaxant medication. Treatments at the Start of the Study: Not stated

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Authors/Location	Intervention	Study Design	Study Population
Cheshire et al. (1994) [45] (cont'd)		Inclusion/Exclusion Criteria: *Inclusion Criteria:* Focal pain involving the cervical paraspinal or shoulder girdle muscles with discrete trigger points, the palpation of which reproduced a typical pattern of radiating pain. *Exclusion Criteria:* Diffuse pain or neurological deficits	

Table D.1: Intervention study profile (cont'd)

Authors/Location	Intervention	Study Design	Study Population
Esenyel et al. (2000) [46] Department of Physical Medicine and Rehabilitation and the Anesthesiology and Pain Clinic, Vakif Gureba Teaching Hospital, Istanbul, Turkey **Financial support** Not stated	**1) Neck-stretching exercises (control)** No further details were stated. **2) Ultrasound therapy plus neck stretching exercises** Technique: Ultrasound therapy (1.5 W/cm^2) directed to the trigger point and to the pain referral zone. Neck stretching exercises were also assigned to these patients but no details were given. Equipment: Not stated Number of Trigger Points Treated: Not stated Treatment Regimen: Six minutes' duration for 10 sessions **3) TPI plus neck stretching exercises** Technique: 1% lidocaine TPI. Neck stretching exercises were also assigned to these patients but no details were given. Equipment: Not stated Number of Trigger Points Treated: Not stated Treatment Regimen: Not stated **1), 2) & 3)** Sites Treated: One side of the upper trapezius muscle Co-interventions: Not stated Pre-treatment Evaluation: Clinical examination; pain intensity using a VAS; pressure pain threshold with a pressure algometer using the technique recommended by Fischer; ROM of the cervical spine using a large scale goniometer; Beck Depression Inventory and Taylor Manifest Anxiety Scale Post-treatment Evaluation: Clinical examination; pain intensity using a VAS; pressure pain threshold with a pressure algometer using the technique recommended by Fischer; ROM of the cervical spine using a large scale goniometer	Prospective randomised non-blinded concurrently controlled trial Intention-to-Treat Analysis: Not stated but intention-to-treat analysis conducted by default since there were no losses to follow-up. Method of Randomisation: Not stated Time of Randomisation: Not stated Method of Allocation Concealment: Not applicable Details of Blinding: Not applicable Participation Rate: Not stated Eligibility Rate for Study: Not stated Follow-up: 2 weeks and 3 months after treatment (it was unclear whether the follow-up time started from the initial or final treatment) Lost to Follow-up: 0% Study Period: Not stated but patients recruited over a 2.3 year period. Provider: Not stated Assessor Details: Not stated Setting: Patients recruited from the outpatient clinic of the Physical Medicine and Rehabilitation Department and the Pain Clinic of a hospital.	Sample Size: **1)** n = 30; **2)** n = 36; **3)** n = 36 There was no statistically significant difference between groups 1, 2, and 3 in duration of pain (p not stated). Statistical comparison of other pre-treatment parameters for the patient groups was not reported. Patient Diagnosis: Myofascial trigger points in one side of the upper trapezius muscle. Diagnostic Definitions: Diagnosis of an active myofascial trigger point was based on the Travell and Simons criteria [16] as follows: tender spots in one or more palpable taut bands; a typical pattern of referred pain in the ipsilateral posterolateral cervical spine, mastoid, or temporal areas; palpable or local twitch responses on snapping palpation at the most sensitive spot in the taut band; restricted ROM in lateral bending of the cervical spine to the opposite side. Pre-treatment Mean Pain Pressure Threshold (units not stated): **1)** 3.3 kg/cm^2 (SD ± 0.33); **2)** 3.1 kg/cm^2 (SD ± 0.52); **3)** 3.1 kg/cm^2 (SD ± 0.48) Pre-treatment Mean VAS Rating for Pain Intensity (scale 0 to 10): **1)** 6.5 (SD ± 0.93); **2)** 7.2 (SD ± 1.62); **3)** 7.2 (SD ± 1.66) Pre-treatment Mobility: Not stated

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Authors/Location	Intervention	Study Design	Study Population
Esenyel et al. (2000) [46] (cont'd)		Inclusion/Exclusion Criteria: *Inclusion Criteria*: Myofascial trigger points in one side of the upper trapezius muscle. *Exclusion Criteria:* Symptoms and signs meeting the 1990 American College of Rheumatology criteria for fibromyalgia; received myofascial TPIs or physical medicine in the year preceding the study; history of acute trauma, inflammatory joint or muscle disease, infection, or malignancy; evidence of neurologic deficit; exhibited inadequate co-operation.	Mean Age: **1)** Not stated; **2)** 32 yrs (SD ± 5.5); **3)** 30 yrs (SD ± 7.7) Gender Mix: **1)** M/F = 8 (26.7%)/22 (73.3%) **2)** M/F = 16 (44.4%)/20 (55.6%) **3)** M/F = 14 (38.9%)/22 (61.1%) Duration of Pain: **1), 2) & 3)** Range 6 months to 7 years Patient Co-morbidities: Not stated Patient Details**: 1), 2) & 3)** Forward head tilt - 89.2%; Shoulder protraction – 80.4%; Increased lordosis - 37.3%; Scoliosis – 7.8%; No structural abnormality – 6.9%; Depression - 22.6%; Severe depression - 4.9%; High anxiety scores - 88.2% Previous Treatment: Not stated Treatments at the Start of the Study: Not stated

Table D.1: Intervention study profile (cont'd)

Authors/Location	Intervention	Study Design	Study Population
Ferrante et al. (1998) [47] Pain Medicine Center, Hospital of the University of Pennsylvania, The University of Pennsylvania, Philadelphia, Pennsylvania, USA **Financial support** Not stated	**1)** **a) Sphenopalatine ganglion block (SPGB) with 4% lidocaine** **b) TPI with 1% lidocaine** **c) SPGB with normal saline (placebo)** Sites Treated: Trapezius – 100%; Levator scapulae – 38.5%; Deltoid – 30.8%; Masseter – 0%; Sternocleidomastoid – 0%; Occipitofrontalis – 0% **2)** **a) SPGB with normal saline (placebo)** **b) TPI with 1% lidocaine** **c) SPGB with 4% lidocaine** Sites Treated: Trapezius – 100%; Levator scapulae – 60%; Deltoid – 20%; Masseter – 10%; Sternocleidomastoid – 10%; Occipitofrontalis – 10% **1) & 2)** Technique: *SPGB:* Four cotton tip applicators were saturated with either normal saline or 4% lidocaine. Two applicators were placed in each nare. The first was passed in the horizontal plane until contact was made with the nasopharyngeal mucosa behind the inferior turbinate. The second applicator was passed through the nare at an angle to make contact behind the middle turbinate. Applicators were left in place for 20 minutes. *TPI:* 3 mL of 1% lidocaine was injected in each head, neck, and shoulder trigger point that met the criteria of Simons [129] and could be elicited by palpation. Equipment: Not stated Treatment Regimen: Each respective treatment within each protocol was given sequentially at one week intervals.	Prospective double-blind placebo-controlled randomised crossover study Intention-to-Treat Analysis: Not stated but intention-to-treat analysis conducted by default since there were no losses to follow-up. Method of Randomisation: Not stated Time of Randomisation: After trigger points were localised to specific muscles. Method of Allocation Concealment: Not stated Details of Blinding: Both patient and provider were blinded to the SPGB blocks but not TPI. Participation Rate: Not stated Eligibility Rate for Study: Not stated Follow-up: 30 minutes, 6 hours, 24 hours, and one week after each treatment Lost to Follow-up: 0% Study Period: Not stated Provider: Not stated Assessor Details: Not stated Setting: Pain Medicine Centre Inclusion/Exclusion Criteria: *Inclusion Criteria:* Myofascial pain in the head, neck, and shoulders for ≥ 6 months *Exclusion Criteria:* Patients with fibromyalgia as defined by the American College of Rheumatology criteria.	Sample Size: **1)** n = 13; **2)** n = 10 There was no statistically significant difference between groups 1 and 2 in demographic data, muscle involvement, or pain intensity ($p \geq 0.05$). Patient Diagnosis: Myofascial pain in the area of the head, neck, and shoulders Diagnostic Definitions: Diagnostic criteria for myofascial pain syndrome based on Simons [129]. Pre-treatment Mean Pain Pressure Threshold: Not stated Pre-treatment Mean VAS Rating for Pain Intensity (scale 0 to 100): **1)** 62.7 (SD ± 22.7) **2)** 47.4 (SD ± 26.6) Pre-treatment Mobility: Not stated Mean Age: **1)** 42.2 yrs (SE ± 3.1); **2)** 37.8 yrs (SE ± 2.9) Gender Mix: **1)** M/F = 3 (23.1%)/10 (76.9%) **2)** M/F = 3 (30%)/7 (70%) Duration of Pain: **1) & 2)** ≥ 6 months Patient Co-morbidities: Not stated Patient Details: **1)** Employed - 38.5%; **2)** Employed - 50% Previous Treatment: Not stated

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Authors/Location	Intervention	Study Design	Study Population
Ferrante et al. (1998) [47] (cont'd)	Number of Trigger Points Treated: Not stated Co-interventions: Patients were permitted to continue stretch and spray exercises and to engage in prescribed physiotherapy during the study period but no further details of these adjunctive therapies were given. Pre-treatment Evaluation: Subjective pain intensity measured on a VAS Post-treatment Evaluation: Same as for pre-treatment evaluation		Treatments at the Start of the Study: Pre-existing medications, such as antidepressants and non-steroidal anti-inflammatory drugs, were not stopped prior to enrolment.

Table D.1: Intervention study profile (cont'd)

Authors/Location	Intervention	Study Design	Study Population
Freund and Schwartz (2000) [48,49] Crown Institute and University of Toronto, Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada **Financial support** Not stated	**1) TPI with saline** Technique: 1 mL of saline with each trigger point receiving 0.2 mL. **2) TPI with botulinum toxin** Technique: 100 U (40 ng) of botulinum toxin A reconstituted and diluted in 1 mL of saline; each trigger point received 0.2 mL **1) & 2)** Equipment: Tuberculin syringe with 30 gauge needle. Treatment Regimen: Not stated but appeared to be a single treatment session. Number of Trigger Points Treated: Five injection sites were chosen by palpation which corresponded to the five most tender cervical muscular trigger points. Sites Treated: One or more of the following (bilaterally): splenius capitis, rectus capitis, semispinalis capitis, and trapezius Co-interventions: Patients were asked to refrain from any form of co-intervention during the trial period. Pre-treatment Evaluation: Pain measured on a VAS for neck pain, headache and shoulder pain (total scores from the 3 VAS were pooled for a total pain score); objective mean ROM of the neck based on measurements of rotation, flexion, extension, and lateral bending measured with an in-house technique that has not been validated; subjective function measured with the Vernon-Mior function index. Post-treatment Evaluation: Same as for pre-treatment evaluation	Prospective randomised double-blind concurrently controlled trial Intention-to-Treat Analysis: No - results for 4 patients were lost to follow-up (reasons were given) and their data were not included in the final analysis. Method of Randomisation: Identical syringes were prepared and labelled in code by a nurse not associated with the study and then placed in a cup. Each patient selected the syringe to be used. Time of Randomisation: Immediately prior to treatment. Method of Allocation Concealment: As per randomisation method above. The botulinum toxin solution was indistinguishable from the saline to both the patient and provider. Details of Blinding: As per randomisation method above. Botulinum toxin solution is visually indistinguishable from saline and elicits no subjective or objective tissue reaction on injection. Participation Rate: Not stated Eligibility Rate for Study: Not stated Follow-up: 2 and 4 weeks post-treatment Lost to Follow-up: **1)** 20%; **2)** 6.7% Two patients were disqualified because they sustained injury in motor vehicle accidents during the follow-up period and 2 did not return for follow-up due to personal reasons. Study Period: Not stated Provider: Not stated	Sample Size: **1)** n = 12; **2)** n = 14 Group 2 had significantly higher pre-treatment head pain scores than group 1 (p not stated). There was no statistically significant difference between the two groups with respect to mean ROM and mean subjective total pain score ($p < 0.01$). Statistical comparison of other pre-treatment parameters for the patient groups was not reported. Patient Diagnosis: Chronic headache secondary to a cervical whiplash injury (Quebec Classification of Whiplash Associated Disorders (WAD) grading II) Diagnostic Definitions: Headaches met all the characteristic diagnostic criteria of cervicogenic headache [130] (except for confirmation by anesthetic block) as follows: precipitation of head pain with external pressure over the cervical or occipital region of the affected side, restricted ROM of the neck (subjective and objective), and ipsilateral neck pain. Since not all criteria were met, chronic headache could not be differentiated from tension headache so the headaches were referred to as cervical associated headaches. Pre-treatment Mean Pain Pressure Threshold: Not measured

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Authors/Location	Intervention	Study Design	Study Population
Freund and Schwartz (2000) [48] (cont'd)		Assessor Details: Not stated Setting: Not stated. Patients recruited from the general population and private practice. Inclusion/Exclusion Criteria: *Inclusion Criteria:* Chronic headache secondary to a cervical whiplash injury *Exclusion Criteria:* Not stated	Pre-treatment VAS Rating for Pain Intensity (scale 0 to 10): *Headache:* **1)** Median 3 (range 0 to 8); **2)** Median 6.5 (range 2 to 9) *Total Pain (headache, neck and shoulder):* **1)** Mean 13.3 (SE ± 20.0); **2)** Mean 16.2 (SE ± 1.7) Pre-treatment Total ROM: **1)** Median 337˚ (range 225 to 380); Mean 316˚ (SE ± 15.8) **2)** Median 312˚ (80 to 400); Mean 310˚ (SE ± 21.7) Pre-treatment Mean Subjective Function: **1)** 13.7 (SE ± 1.9); **2)** 18.1 (SE ± 25.0) Mean Age: **1) & 2)** 46 yrs (range 29 to 75) Gender Mix: **1) & 2)** M/F = 11 (42.3%)/15 (57.7%) Mean Duration of Pain: **1) & 2)** > 6 months; injury occurred at least 2 years prior to enrolment (mean 3.1 yrs). Patient Co-morbidities: Not stated Patient Details: **1) & 2)** Unilateral head pain without side shift – 80%; Bilateral pain that behaved as independent unilateral cervicogenic headache – 20% Previous Treatment: **1) & 2)** Extensive conservative therapy (including massage, physiotherapy, and chiropractic adjustment) – 100% Treatments at the Start of the Study: Not stated

Table D.1: Intervention study profile (cont'd)

Authors/Location	Intervention	Study Design	Study Population
McMillan et al. (1997) [50] The Department of Restorative Dentistry and the Department of Oral Medicine, University of Newcastle, Newcastle upon Tyne, United Kingdom Centre for Health and Medical Research, University of Teesside, Middlesborough, Teesside, United Kingdom **Financial support** Not stated	**1) Simulated dry needling plus simulated TPI (control)** Technique: Insertion of an acupuncture needle just into the skin over a non-tender part of the muscle and then removed immediately. A drop of isotonic saline was also injected in the same area. **2) Procaine TPI plus simulated dry needling** Technique: Injection of 0.5 mL of 1% Procaine into the active trigger point. An acupuncture needle was also placed just into the skin over a non-tender part of the muscle and then removed immediately. **3) Simulated TPI and dry needling** Technique: Insertion of an acupuncture needle into an active trigger point which was then left in situ for 1 to 2 minutes. A drop of isotonic saline was also injected just below the skin over a non-tender part of the muscle. **1), 2) & 3)** Equipment: Syringe and a 27 gauge needle; an acupuncture needle Treatment Regimen: Treatment administered in three sessions one week apart. Number of Trigger Points Treated: Not stated Sites Treated: Right or left masseter Co-interventions: No other medication or treatment was permitted during the study period. Pre-treatment Evaluation: Pain intensity and unpleasantness using a VAS; pressure pain threshold measured five minutes after treatment with a pressure algometer Post-treatment Evaluation: Same as for pre-treatment evaluation	Prospective randomised double-blind concurrently controlled trial Intention-to-Treat Analysis: Not stated but intention-to-treat analysis conducted by default since there were no losses to follow-up. Method of Randomisation: Not stated Time of Randomisation: Not stated Method of Allocation Concealment: Not stated Details of Blinding: Not stated Participation Rate: Not stated Eligibility Rate for Study: Not stated Follow-up: 5 minutes, 1 hour, and 24 hours after each treatment over the three week treatment period Lost to Follow-up: 0% Study Period: Not stated Provider: One doctor administered all treatments. Assessor Details: A clinician blinded to trigger point location, patient symptoms and treatment conducted all pain measurements. Setting: Patients recruited from those attending a dental hospital admissions department and Temporomandibular Joint Clinic	Sample Size: **1)** n = 10; **2)** n = 10; **3)** n = 10 Statistical comparison of pre-treatment parameters for groups 1, 2, and 3 was not reported. However, patients were stratified by age (<35 yrs or >35 yrs) prior to randomisation. Patient Diagnosis: Craniofacial pain of myogenous origin defined on the basis of the International Headache Society's classification of myofascial pain. Diagnostic Definitions: The pain pressure threshold was defined as the point when the pressure stimulus applied to the skin first changed from a pressure sensation to a pain sensation. Pre-treatment Mean Pain Pressure Threshold (units not stated): *Masseter muscle:* **1)** 0.8 (SD ± 0.3); **2)** 0.8 (SD ± 0.3); **3)** 0.8 (SD ± 0.4) *Temporalis muscle:* **1)** 1.2 (SD ± 0.6); **2)** 1.2 (SD ± 0.3); **3)** 1.3 (SD ± 0.7) Pre-treatment Mean VAS Rating for Pain Intensity (scale 0 to 100): **1)** 34 (SD ± 25); **2)** 39 (SD ± 24); **3)** 37 (SD ± 18) Pre-treatment Mobility: Not measured Age Range: **1), 2) & 3)** 23 to 53 yrs

Continued next page

Authors/Location	Intervention	Study Design	Study Population
McMillan et al. (1997) [50] (cont'd)		Inclusion/Exclusion Criteria: *Inclusion Criteria:* Women of 20 to 50 years of age with a primary complaint of frequent pain (at least four times per week) in the jaw muscles of at least 12 weeks' duration; tenderness to palpation at a minimum of three sites in the jaw muscles, including at least one in the masseter; palpation of a tender area in the masseter which led to changes in the pattern of referred pain. *Exclusion Criteria:* Clinical and/or radiographic signs of pathology in the temporomandibular joint; metabolic disease; neurologic disorders; vascular disorders such as migraine; bleeding diastheses; neoplasia; a history of psychiatric illness or drug abuse; recent facial or neck trauma; medication or adjunctive treatment that could not be stopped during the study; allergy to local anesthetic solutions.	Gender Mix: **1), 2) & 3)** M/F = 0%/100% Duration of Pain: **1), 2) & 3)** At least three months Patient Co-morbidities: **1), 2) & 3)** Not stated Patient Details: Not stated Previous Treatment: Not stated Treatments at the Start of the Study: Not stated

Table D.1: Intervention study profile (cont'd)

Authors/Location	Intervention	Study Design	Study Population
Schnider et al. (2002) [51] Department of Neurology, Faculty of Medicine, University of Vienna, Vienna, Austria Department of Physical Medicine and Rehabilitation, Faculty of Medicine, University of Vienna, Vienna, Austria **Financial support** Not stated	**1) TPI with saline plus physical therapy** Technique: 0.9 mL of saline; each trigger point received 0.15 mL. Standardised physical therapy (massage and hot packs) for nine sessions over three weeks in the 2 to 4 week period after treatment. **2) TPI with botulinum toxin plus physical therapy** Technique: 90 mouse units of botulinum toxin A reconstituted and 0.9 mL of saline; each trigger point received 0.15 mL. Physical therapy regimen as for group 1. **1) & 2)** Equipment: Not stated Treatment Regimen: One injection treatment only Number of Trigger Points Treated: Six Sites Treated: The most painful tender or trigger points in the cervical muscles. Co-interventions: Not stated Pre-treatment Evaluation: Patients were examined four weeks prior to treatment: patients kept a headache diary recording presence of headache (hours per day), number of headache free days per four week period, number of analgesics per day, and the daily pain intensity using a VAS score; sagittal ROM; pain pressure threshold measured by scoring the six most painful tender or trigger points of the neck and shoulder muscles on a four point scale; biofeedback measurements. Post-treatment Evaluation: Same as for pre-treatment evaluation	Prospective double-blind randomised concurrently controlled trial Intention-to-Treat Analysis: No - one patient in group 1 was lost to follow-up and was excluded from analysis. Method of Randomisation: Not stated Time of Randomisation: Not stated Method of Allocation Concealment: Not stated Details of Blinding: Not stated Participation Rate: Not stated Eligibility Rate for Study: Not stated Follow-up: 4, 8, and 12 weeks after injection Lost to Follow-up: **1)** 5.9%; **2)** 0% One patient in group 1 refused to come for further control visits and was excluded from analysis. Study Period: Not stated Provider: Not stated Assessor Details: Not stated Setting: Not stated	Sample Size: **1)** n = 16; **2)** n = 17 There was no statistically significant difference between the two groups with respect to age, gender, duration of headache, headache pain severity, headache free days, headache hours per day, or daily analgesic intake (p not stated). Patient Diagnosis: Cervicogenic headache diagnosed according to the International Headache Society classification Diagnostic Definitions: Not stated Pre-treatment Mean Pain Pressure Threshold*: **1)** 3.3 (SE ± 0.06); **2)** 3.5 (SE ± 0.06) Pre-treatment Mean VAS Rating for Pain Intensity (scale 0 to 100): **1)** 50.7 (SE ± 3.8); **2)** 53.0 (SE ± 3.7) Pre-treatment Sagittal Mobility: Data not reported Mean Age: **1)** 50.0 yrs (SD ± 8.8); **2)** 51.4 yrs (SD ± 12.2) Gender Mix: **1)** M/F = 6 (37.5%)/ 10 (62.5%) **2)** M/F = 7 (41.2%)/ 10 (58.8%)

*Scored on a four point scale as follows: 1 = no local tenderness to pressure; 2 = moderate local tenderness to pressure; 3 = pronounced local tenderness to pressure; 4 = pronounced local tenderness to pressure with pain radiation

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Authors/Location	Intervention	Study Design	Study Population
Schnider et al. (2002) [51] (cont'd)		Inclusion/Exclusion Criteria: *Inclusion Criteria:* Cervicogenic headache for at least 6 months diagnosed according to the International Headache Society classification; headaches present for > 15 days per month; age > 19 years; inadequate or no response to previous treatment; and the presence of painful trigger or tender points. *Exclusion Criteria:* Other symptomatic headache forms; excessive consumption of analgesics as defined by the International Headache Society; and pregnancy.	Mean Duration of Pain: **1)** 6.1 yrs (SD ± 7.2); **2)** 6.1 yrs (SD ± 7.2) Patient Co-morbidities: **1) & 2)** Migraine - 12.1% (patients were able to distinguish between the two headache types) Patient Details: **1) & 2)** Unilateral headache without side shift – 48.5%; Bilateral headache with marked unilateral dominance - 27.3%; Bilateral headache – 24.2%; History of excessive analgesic intake - 9.1% Previous Treatment: Not stated Treatments at the Start of the Study: **1) & 2)** Salicylates, para-aminophenol derivatives, antirheumatics, and muscle relaxants were taken by the majority of patients. No further details were given.

Table D.1: Intervention study profile (cont'd)

Authors/Location	Intervention	Study Design	Study Population
Wheeler et al. (1998) [52] Charlotte Spine Center and the Department of Psychology, University of North Carolina, Charlotte, North Carolina, USA **Financial support** Supported in part by an educational grant from the Allergan Corporation, which also supplied botulinum toxin type A and financial support for two statisticians.	**1) TPI with normal saline** Technique: Target trigger points were identified, mapped, and then injected with 2 mL of normal saline. **2) TPI with 50 Units botulinum toxin A** Technique: Target trigger points were identified, mapped, and then injected with 50 U of Botulinum toxin A in 2 mL of normal saline without preservative. **3) TPI with 100 Units botulinum toxin A** Technique: Target trigger points were identified, mapped, and then injected with 100 U of Botulinum toxin A in 2 mL of normal saline without preservative. **1), 2) & 3)** Equipment: Not stated Treatment Regimen: One injection treatment only Number of Trigger Points Treated: Not stated, but appears to be only one. Sites Treated: Not stated Co-interventions: Not stated Pre-treatment Evaluation: Subjective pain measured on a VAS (Neck Pain and Disability Scale); pain pressure threshold measured using an algometer Post-treatment Evaluation: Subjective pain measured on a VAS (Neck Pain and Disability Scale); pain pressure threshold measured using an algometer; subjective assessment of improvement.	Prospective randomised double-blind concurrently controlled trial Intention-to-Treat Analysis: Not stated but intention-to-treat analysis conducted by default since there were no losses to follow-up. Method of Randomisation: Not stated Time of Randomisation: Not stated Method of Allocation Concealment: Not stated Details of Blinding: Patient and provider blinded to substance injected. Participation Rate: Not stated Eligibility Rate for Study: Not stated Follow-up: 1, 3, 6, and 9 weeks; 3 and 4 months Lost to Follow-up: 0% Study Period: Not stated Provider: One physician performed all injections and was blinded to the identity of the injected substance. Assessor Details: Not stated Setting: Spine Centre	Sample Size: **1)** n = 11; **2)** n = 11; **3)** n = 11 Work-related injuries were more prevalent in group 1, which also had a higher employment rate, while the percentage of automobile accidents was lower, in comparison to groups 2 and 3 (p not stated). There was no difference between the three groups with respect to mean pain pressure threshold (p = 0.10). Statistical comparison of other pre-treatment parameters for the patient groups was not reported. Patient Diagnosis: Chronic unilateral neck pain predominantly localised to a unilateral primary trigger point in cervicothoracic paravertebral musculature. Diagnostic Definitions: Trigger points were identified by palpation of a tender taut band, which reproduced the patient's pain locally and by regional referral, and the presence of a "jump sign". Pre-treatment Mean Pain Pressure Threshold (units not stated): **1)** 3.5; **2)** 4.0; **3)** 4.4 Pre-treatment Mean VAS Rating for Pain Intensity (scale 0 to 100): Unable to derive raw data from graphical presentation

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Authors/Location	Intervention	Study Design	Study Population
Wheeler et al. (1998) [52] (cont'd)		Inclusion/Exclusion Criteria: *Inclusion Criteria:* Non-operative condition and trigger points of > 3 months' duration; no benefit from previous treatments. *Exclusion Criteria:* Age < 21 years; presence of a systemic inflammatory disorder; impending surgical pathology; a known allergy or sensitivity to Botulinum toxin A; pregnancy or planning a pregnancy; diagnosed with any significant disease that might interfere with neuromuscular transmission; received anaesthetic or corticosteroid injections to the target trigger point within four weeks of study enrolment; presence of diffuse tender and trigger points; diagnosed with fibromyalgia.	Pre-treatment Mobility: Not measured Mean Age: **1)** 38 yrs (SD ± 9.0); **2)** 41 yrs (SD ± 11.1) **3)** 43 yrs (SD ± 8.0) Gender Mix: Not stated Mean Duration of Pain: **1)** 1067.5 days; **2)** 930.2 days; **3)** 1038.3 days Patient Co-morbidities: Not stated Patient Details: **1)** Employed - 90%; Work injury - 50%; Automobile accident - 10%; **2)** Employed - 64%; Work injury - 18%; Automobile accident - 46%; **3)** Employed - 60%; Work injury - 0%; Automobile accident - 70% Previous Treatment: Not stated Treatments at the Start of the Study: Not stated

Table D.1: Intervention study profile (cont'd)

Authors/Location	Intervention	Study Design	Study Population
Wheeler et al. (2001) [53] Charlotte Spine Center and the Department of Psychology, University of North Carolina, Charlotte , North Carolina, USA Georgia School of Professional Psychology, Atlanta, Georgia, USA **Financial support** Study supported by a grant from Allergan Pharmaceutical Corporation	**1) TPI with saline** Technique: Mean dosage = 206.8 U (SD ± 39.1) Sites Treated: Injections were placed in multiple sites in symptomatic muscles at the discretion of the physician as follows: Mid-upper cervical - 0%; Mid-lower cervical - 28%; Trapezius - 72%; Thoracic - 0% **2) TPI with botulinum toxin A** Technique: Mean dosage = 231.2 U (SD ± 50.1) Sites Treated: Injections were placed in multiple sites in symptomatic muscles at the discretion of the physician as follows: Mid-upper cervical - 4%; Mid-lower cervical - 24%; Trapezius - 68%; Thoracic - 4% **1) & 2)** Equipment: Not stated Treatment Regimen: One injection treatment only Number of Trigger Points Treated: Not sated Co-interventions: Physical therapy was not administered during the treatment period. No further details given. Pre-treatment Evaluation: SF-36 health survey; Beck depression inventory; subjective pain measured on a VAS (Neck Pain and Disability Scale); pain pressure threshold measured with spring loaded pressure algometer Post-treatment Evaluation: SF-36 health survey; Beck depression inventory; subjective pain measured on a VAS (Neck Pain and Disability Scale); pain pressure threshold measured with spring loaded pressure algometer; patient's and physician's subjective global assessment of improvement; diary record of the frequency and intensity of adverse events	Prospective randomised double-blind concurrently controlled trial Intention-to-Treat Analysis: No - one patient in group 1 and four patients in group 2 were lost to follow-up and were excluded from analysis (reasons not given). Method of Randomisation: Based on a coded number that was assigned to the patient. Time of Randomisation: When they arrived at the clinic for their injection. Method of Allocation Concealment: Not stated Details of Blinding: Neither the patient, physician or clinical assistant were aware of the nature of the injections. No further details given. Participation Rate: 76% of the people who responded to the recruitment drive were willing to participate in the study. Eligibility Rate for Study: 19.9% of the 251 people who responded to a newspaper advertisement. Follow-up: 4, 8, 12 and 16 weeks Lost to Follow-up: **1)** 4%; **2)** 16% Study Period: Not stated Provider: Physician Assessor Details: Not stated	Sample Size: **1)** n = 24; **2)** n = 21 There was no significant difference between the two groups with respect to pre-treatment parameters except for the SF-36 mental score, in which group 2 scored slightly below group 1 ($p<0.05$). Patient Diagnosis: Chronic neck pain Diagnostic Definitions: Target trigger points were identified by palpation of a tender taut band which reproduced the patient's pain locally and by regional referral. Pre-treatment Mean Pain Pressure Threshold (algometer score*): **1)** 1.62 (SD ± 1.04); **2)** 1.60 (SD ± 0.60) Pre-treatment Mean VAS Rating for Pain Intensity (scale 0 to 100): **1)** 49.0 (SD ± 12.7); **2)** 54.0 (SD ± 13.8) Pre-treatment Mobility: Not measured Mean Age: **1)** 45 yrs (SD ± 10.2); **2)** 43 yrs (SD ± 11.4) Gender Mix: **1)** M/F = 7 (28%)/18 (72%) **2)** M/F = 5 (20%)/20 (80%) Mean Duration of Pain: **1)** 96.8 months (SD ± 113.1) **2)** 111.0 months (SD ± 121.0) Patient Co-morbidities: Not stated

*Calculated by taking the difference between the pressure threshold measurement obtained form a non-tender control muscle and the tenderest trigger point.

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Authors/Location	Intervention	Study Design	Study Population
Wheeler et al. (2001) [53] (cont'd)		Setting: Not applicable. Patients were recruited from the general population via a newspaper advertisement. Inclusion/Exclusion Criteria: *Inclusion Criteria:* Significant neck pain, defined as a Neck Pain and Disability score ≥ 23, for at least three months; no other serious medical or psychological conditions *Exclusion Criteria:* age <21 years or >70 years; previous neck surgery.	Patient Details: **1) & 2)** No injury - 36%; Work-related injury - 4%; Automobile related injury - 40%; Personal injury - 14%; Other type of injury - 6% **1)** Education - 15.0 yrs (SD ± 2.2); Employed - 76% **2)** Education - 14.0 yrs (SD ± 2.7); Employed - 92% Previous Treatment: Not stated Treatments at the Start of the Study: Not stated

Table D.1: Intervention study profile (cont'd)

Authors/Location	Intervention	Study Design	Study Population
Yentür et al. (2003) [54] Anaesthesiology and Intensive Care Department and the Orthopaedics and Traumatology Department, School of Medicine, Celal Bayar University, Manisa, Turkey Anaesthesiology and Intensive Care Department, Pain Clinic, School of Medicine, Ege University, Izmir, Turkey **Financial support** Not stated	**1) Intra-articular injection** Technique: 2 mL of high molecular weight sodium hyaluronate was injected into the affected knee joints. Sites Treated: Not stated **2) TPI plus intra-articular injection** Technique: 2 mL of high molecular weight sodium hyaluronate was injected into the affected knee joints. Trigger points were then injected with 0.5% lidocaine. A local twitch response was induced when introducing the needle into the muscle. Number of Trigger Points Treated: Not stated Sites Treated: The rectus femoris, vastus medialis, vastus lateralis, sartorius, adductor longus, tensor fasciae latal, gracilis, pectineus, iliopsoas, biceps femoris, semitendinosus, semimembranosus, adductor magnus, gastrocnemius, and soleus. **1) & 2)** Equipment: Not stated Treatment Regimen: Injections on three separate occasions at weekly intervals. Patients were told to rest for two days after each injection treatment to avoid taxing the injected joint. Co-interventions: No other treatments allowed during study period. Pre-treatment Evaluation: Joint ROM measured by goniometry; pain intensity and activity restrictions evaluated with a five point scale. Post-treatment Evaluation: Same as for pre-treatment evaluation	Prospective randomised single-blind concurrently controlled trial Intention-to-Treat Analysis: No – one patient in group 1 did not complete the treatment cycle (reason not given). Method of Randomisation: Not stated Time of Randomisation: Not stated Method of Allocation Concealment: Not stated Details of Blinding: Not stated Participation Rate: Not stated Eligibility Rate for Study: Not stated Follow-up: 7 days after the third injection (21 days) Lost to Follow-up: **1)** 5.9%; **2)** 0% Study Period: Not stated Provider: Not stated Assessor Details: Physician blinded to treatment allocation. Setting: Not stated Inclusion/Exclusion Criteria: *Inclusion Criteria:* Primary knee osteoarthritis diagnosed according to the American College of Rheumatology criteria. *Exclusion Criteria:* Knee joint disease other than osteoarthritis, severe concomitant diseases, diseases that interfere with the evaluation of knee joint function, skin infections, joint instability, hemorrhagic diathesis, or major neuroses.	Sample Size: **1)** n = 16; **2)** n = 17 There was no significant difference between the two groups with respect to age, weight, height, joint ROM, or physical activity assessment results (p not stated). Patient Diagnosis: Primary knee osteoarthritis diagnosed according to the American College of Rheumatology criteria. Diagnostic Definitions: Trigger points were identified according to the Travell and Simons criteria [16]. Pre-treatment Mean Pain Pressure Threshold: Not measured Pre-treatment Mean Rating for Pain Intensity (scale 0 to 4):**1)** 2.56; **2)** 2.9 Pre-treatment Mean Knee Mobility: **1)** 116.2°; **2)** 103.8° Mean Age: **1)** 59.8 yrs; **2)** 62.1 yrs Gender Mix: **1) & 2)** M/F = 0%/100% Mean Duration of Pain: **1) & 2)** At least one year prior to the study (Pers. Comm. EA Yentür) Patient Co-morbidities: Not stated Patient Details: Not stated Previous Treatment: **1) & 2)** Used non-steroidal anti-inflammatory drugs for more than one year without any beneficial effect. No patient had received physical therapy or intra-articular injections within six months of the study. Treatments at the Start of the Study: Non-steroidal anti-inflammatory drugs; no further details given.

Table D.2: Post-treatment pain and mobility measures

	Byrn et al. (1993) [44]		Esenyel et al. (2003) [46]		
Post-treatment Outcome Measures	**Sterile Water n = 20**	**Saline n = 20**	**Stretching n = 30**	**US plus stretching n = 36**	**TPI plus stretching n = 36**
End Of Study Outcome Relative To Baseline					
Change in mean pain pressure threshold (masseter muscle)					
Change in mean pain pressure threshold (temporalis muscle)					
Change in mean pain pressure threshold			↑0.6% (2 wks)** ↑18.4% (3 mths)**	↑35.9% (2 wks) §# ↑34.3% (3 mths) §#	↑39.9% (2 wks)§#†† ↑35.6% (3 mths)§#††
Change in mean algometer score					
Change in mean pain intensity (VAS)	↓80.0% (Immediate) ↓47.5% (1 mth) ↓42.5% (3 mths) ↓40.0% (8 mths)	↓44.4% (Immediate)† ↓5.6% (1 mth) ↑11.1% (3 mths)‡ ↑30.6% (8 mths)§	↓0.6% (2 wks)** ↓11.1% (3 mths) **	↓58.0% (2 wks)§# ↓57.5% (3 mths)§#	↓57.4% (2 wks)§#†† ↓55.5% (3 mths)§#††
Change in mean pain intensity					
Change in mean pain intensity for headache (VAS)					
Change in mean pain intensity for neck and shoulder pain, and headache (VAS)					
Change in mean pain unpleasantness (VAS)					
Change in mean mobility	+54 (Immediate) +36 (1 mth) +39 (3 mths) +20 (8 mths)	+23 (Immediate)‡ +5 (1 mth) +6 (3 mths)† -11 (8 mths)†			
Change in mean total ROM					
Change in mean subjective function					

	Byrn et al. (1993) [44]		Esenyel et al. (2003) [46]		
Post-treatment Outcome Measures	**Sterile Water n = 20**	**Saline n = 20**	**Stretching n = 30**	**US plus stretching n = 36**	**TPI plus stretching n = 36**
Change in mean global assessment rating					
Change in mean headache free days/four week period					
Change in mean headache hours per day					
Change in mean daily analgesic intake					
Change in mean Beck depression inventory					
Change in mean SF-36 (mental) score					
Change in mean SF-36 (physical) score					
Clinical improvement					
Physician's subjective assessment					
Patient's subjective assessment					
No change	5% (3 mths) 45% (8 mths)	70%[§] (3 mths) 60%* (8 mths)			
Improved	45% (3 mths) 25% (8 mths)	15%[§] (3 mths) 25%* (8 mths)			
Much improved	50% (3 mths) 30% (8 mths)	15%[§] (3 mths) 15%* (8 mths)			
Desire for re-treatment with active intervention					

*No statistically significant difference between the interventions at $p \geq 0.05$; [†]Statistically significant difference between the interventions at $p < 0.05$; [‡] $p < 0.01$; [§]$p < 0.001$

**No statistically significant difference compared to baseline $p \geq 0.05$; [#]Statistically significant difference compared to baseline at $p < 0.001$

[††]No statistically significant difference between the US plus stretching and TPI plus stretching treatments at $p \geq 0.05$

Table D.2: Post-treatment pain and mobility measures (cont'd)

	Freund and Schwartz (2000) [48,49]		McMillan et al. (1997) [50]		
Post-treatment Outcome Measures	**Saline n = 12**	**Botulinum toxin n = 14**	**Double placebo n = 10**	**TPI plus simulated dry needling n = 10**	**Simulated TPI plus dry needling n = 10**
End Of Study Outcome Relative To Baseline					
Change in mean pain pressure threshold (masseter muscle)			0% (wk 1)* ** ↑25% (wk 2)* ** ↓12.5% (wk 3)* **	↑12.5% (wk 1)* ** ↑25.0% (wk 2)* ** ↑25.0% (wk 3)* **	0% (wk 1)* ** ↑12.5% (wk 2)* ** ↑25.0% (wk 3)* **
Change in mean pain pressure threshold (temporalis muscle)			0% (wk 1)* ** ↑16.7% (wk 2)* ** ↑8.3% (wk 3)* **	0% (wk 1)* ** ↑16.7% (wk 2)* ** ↑8.3% (wk 3)* **	0% (wk 1)* ** 0% (wk 2)* ** ↑7.7% (wk 3)* ** ††
Change in mean pain pressure threshold					
Change in mean algometer score					
Change in mean pain intensity (VAS)			↓11.8% (wk 1) ↓29.4% (wk 2) ↓44.1% (wk 3)*‖	↓10.3% (wk 1) ↓28.2% (wk 2) ↓28.2% (wk 3)*‖	↓23.3% (wk 1) ↓5.4% (wk 2) ↓32.4% (wk 3)*‖
Change in mean pain intensity					
Change in mean pain intensity for headache (VAS)					
Change in mean pain intensity for neck and shoulder pain, and headache (VAS)	↓25.6% (2 wks)** ↑6.0% (4 wks)**	↓25.3% (2 wks) ** ↓38.3% (4 wks)¶			
Change in mean pain unpleasantness (VAS)			↓20.5% (wk 1) ↓25.6% (wk 2) ↓46.2% (wk 3)*‖	↓20.4% (wk 1) ↓42.9% (wk 2) ↓46.9% (wk 3)*‖	↓30.8% (wk 1) ↓19.2% (wk 2) ↓46.2% (wk 3)*‖
Change in mean mobility					
Change in mean total ROM	↑6.6% (2 wks)** ↓2.5% (4 wks)**	↑4.8% (2 wks)** ↑10.7% (4 wks)¶			
Change in mean subjective function	↓12.4% (4 wks)**	↓16.0% (4 wks)**			
Change in mean global assessment rating					

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	Freund and Schwartz (2000) [48,49]		McMillan et al. (1997) [50]		
Post-treatment Outcome Measures	**Saline n = 12**	**Botulinum toxin n = 14**	**Simulated TPI plus simulated dry needling n = 10**	**TPI plus simulated dry needling n = 10**	**Simulated TPI plus dry needling n = 10**
Change in mean headache free days/four week period					
Change in mean headache hours per day					
Change in mean daily analgesic intake					
Change in mean Beck depression inventory					
Change in mean SF-36 (mental) score					
Change in mean SF-36 (physical) score					
Clinical improvement					
Physician's subjective assessment					
Patient's subjective assessment					
Desire for re-treatment with active intervention					

*No statistically significant difference between the interventions at $p \geq 0.05$

**No statistically significant difference compared to baseline $p \geq 0.05$; ‖Statistically significant difference compared to baseline at $p < 0.05$; ¶$p < 0.01$

††Thresholds in the anterior temporal region were consistently higher than in the masseter before and after treatment

Table D.2: Post-treatment pain and mobility measures (cont'd)

	Schnider et al. (2002) [51]		Wheeler et al. (1998) [52]		
Post-treatment Outcome Measures	**Saline plus physical therapy n = 16**	**Botulinum toxin plus physical therapy n = 17**	**Saline n = 11**	**Botulinum toxin 50 U n = 11**	**Botulinum toxin 100 U n = 11**
End Of Study Outcome Relative To Baseline	**FU = 9 to 12 weeks**				
Change in mean pain pressure threshold (masseter muscle)					
Change in mean pain pressure threshold (temporalis muscle)					
Change in mean pain pressure threshold	↓22.7%**	↓25.7%** *	↑3.5% (wk 1) ↓3.7% (wk 3) ↑10.1% (wk 9) ↑0.3% (4 mths)	↑15.0% (wk 1) ↑1.3% (wk 3) ↑16.8% (wk 9) ↑28.0% (4 mths)	↓5.5% (wk 1)* ↑1.1% (wk 3)* ↑2.3% (wk 9)* ↑2.7% (4 mths)*
Change in mean algometer score					
Change in mean pain intensity (VAS)					
Change in mean pain intensity	↓18.2%‖	↓21.8%‖*			
Change in mean pain intensity for headache (VAS)					
Change in mean pain intensity for neck and shoulder pain, and headache (VAS)					
Change in mean pain unpleasantness (VAS)					
Change in mean mobility					
Change in mean total ROM					
Change in mean subjective function					
Change in mean global assessment rating (baseline value = one week after treatment)			↓3.5% (wk 3) ↓3.9% (wk 9) 0% (4 mths)	↓14.5% (wk 3) ↓11.0% (wk 9) ↓3.5% (4 mths)	↓3.8% (wk 3)* ↓3.8% (wk 9)* ↓7.6% (4 mths)*
Change in mean headache free days/four week period	↑50.0%¶	↑185.7%¶*			
Change in mean headache hours per day	↓16.2%‖	↓31.3%‖*			

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	Schnider et al. (2002) [51]		Wheeler et al. (1998) [52]		
Post-treatment Outcome Measures	**Saline plus physical therapy n = 16**	**Botulinum toxin plus physical therapy n = 17**	**Saline n = 11**	**Botulinum toxin 50 U n = 11**	**Botulinum toxin 100 U n = 11**
Change in mean daily analgesic intake	↑8.6%**	↓14.3%** *			
Change in mean Beck depression inventory					
Change in mean SF-36 (mental) score					
Change in mean SF-36 (physical) score					
Clinical improvement			36.4%	36.4%	54.6%
Physician's subjective assessment					
Patient's subjective assessment					
Desire for re-treatment with active intervention	n = 9	n = 9	n = 4	n = 5	n = 4
Clinical improvement	Combined groups = 66.7%		25%	80%	75%

*No statistically significant difference between the interventions at $p \geq 0.05$

**No statistically significant difference compared to baseline $p \geq 0.05$; ‖Statistically significant difference compared to baseline at $p < 0.05$; ¶$p < 0.01$

Table D.2: Post-treatment pain and mobility measures (cont'd)

	Wheeler et al. (2001) [53]		Yentür et al. (2003) [54]	
Post-treatment Outcome Measures	**Saline n = 24**	**Botulinum toxin n = 21**	**IA Injection n = 16**	**IA Injection plus TPI n = 17**
End Of Study Outcome Relative To Baseline			**FU = 21 days**	
Change in mean pain pressure threshold (masseter muscle)				
Change in mean pain pressure threshold (temporalis muscle)				
Change in mean pain pressure threshold				
Change in mean algometer score[††]	↓60.0% (wk 4) ↓42.5% (wk 8) ↓52.5% (wk 12) ↓52.5% (wk 16)[¶]	↓47.1% (wk 4) ↓44.1% (wk 8) ↓50.0% (wk 12) ↓44.1% (wk 16)[¶*]		
Change in mean pain intensity (VAS)	↓19.1% (wk 4) ↓24.1% (wk 8) ↓28.2% (wk 12) ↓31.7% (wk 16)[¶]	↓3.7% (wk 4) ↓15.9% (wk 8) ↓29.9% (wk 12) ↓26.0% (wk 16)[¶*]		
Change in mean pain intensity			↓12.1%**	↓82.1%[#§]
Change in mean pain intensity for headache (VAS)				
Change in mean pain intensity for neck and shoulder pain, and headache (VAS)				
Change in mean pain unpleasantness (VAS)				
Change in mean mobility				
Change in mean total ROM			↑0.34%**	↑19.9%[#§]
Change in mean subjective function				
Change in mean global assessment rating				
Change in mean headache free days/four week period				
Change in mean headache hours per day				

Continued next page

	Wheeler et al. (2001) [53]		Yentür et al. (2003) [54]	
Post-treatment Outcome Measures	**Saline n = 24**	**Botulinum toxin n = 21**	**IA Injection n = 16**	**IA Injection plus TPI n = 17**
Change in mean daily analgesic intake				
Change in mean Beck depression inventory	↓3.8% (wk 8) ↓15.0% (wk 16)**	↓26.1% (wk 8) ↓21.7% (wk 16)**		
Change in mean SF-36 (mental) score	↑2.6% (wk 16)**	↑3.8% (wk 16)** ‡		
Change in mean SF-36 (physical) score	↑1.0% (wk 16)**	↑8.7% (wk 16)**		
Clinical improvement				
Physician's subjective assessment (mean)	1.1 [1.1] (wk 4) 1.2 [1.4] (wk 8) 1.3 [1.4] (wk 12) 1.2 [1.5] (wk 16)	0.2 [1.6] (wk 4) 0.9 [1.4] (wk 8) 1.4 [1.2] (wk 12) 1.0 [1.4] (wk 16)¶		
Patient's subjective assessment (mean)	1.2 [1.5] (wk 4) 1.3 [1.6] (wk 8) 1.5 [1.8] (wk 12) 1.3 [1.9] (wk 16)	0.2 [1.6] (wk 4) 0.8 [1.9] (wk 8) 1.4 [1.6] (wk 12) 1.0 [1.7] (wk 16)‖		
Desire for re-treatment with active intervention				

[] = Standard deviation

*No statistically significant difference between the interventions at $p \geq 0.05$; ‡Statistically significant difference between the interventions at $p < 0.01$; §$p < 0.001$

**No statistically significant difference compared to baseline $p \geq 0.05$; ‖Statistically significant difference compared to baseline at $p < 0.05$; ¶$p < 0.01$; #$p < 0.001$

††Calculated by taking the difference between the pressure threshold measurement obtained form a non-tender control muscle and the tenderest trigger point.

Table D.3: Safety outcomes

	Byrn et al. (1993) [44]		Cheshire et al. (1994) [45]		Freund & Schwartz (2000) [48,49]		Schnider et al. (2002) [51]	
Post-treatment Outcomes	**Sterile Water n = 20**	**Saline n = 20**	**Botulinum toxin/ Saline n = 3**	**Saline/ Botulinum toxin n = 3**	**Saline n = 12**	**Botulinum toxin n = 14**	**Saline plus physical therapy n = 16**	**Botulinum toxin plus physical therapy n = 17**
	FU = 8 months		**FU = 16 weeks**		**FU = 4 weeks**		**FU = 9 to 12 weeks**	
Side effects	0%	0%	0%	0%	0%	0%		
Symptomatic weakness in injected muscles			0%	0%	0%	0%	0%	0%
Symptomatic weakness in non-injected muscles			0%	0%				
Dysphagia							0%	0%
Mild local pain at the injection site								5.9%
Mild local pain opposite the injection site								
Pain shift								

Table D.3: Safety outcomes (cont'd)

	Wheeler et al. (1998) [52]			Yentür et al. (2003) [54]	
Post-treatment Outcomes	**Saline n = 11**	**Botulinum toxin 50 U n = 11**	**Botulinum toxin 100 U n = 11**	**IA Injection n = 16**	**IA Injection plus TPI n = 17**
	FU = 4 months			**FU = 21 days**	
Side effects				0%	0%
Symptomatic weakness in injected muscles					
Symptomatic weakness in non-injected muscles		Combined groups = 9.1%			
Dysphagia					
Mild local pain at the injection site					
Mild local pain opposite the injection site		Combined groups = 9.1%			
Pain shift		Combined groups = 9.1%			

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