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REVIEW ARTICLE

# Glyceryl trinitrate patches—An alternative treatment for shoulder impingement syndrome

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**KEYWORDS**
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**Summary** Transdermal glyceryl trinitrate patches have been investigated as an alternative therapeutic intervention for a range of tendinopathies, due to the ease of titration of dosage and the ease of their application. Glyceryl trinitrate has been inferred to reduce pain and inflammation secondary to their nitric oxide-producing action. Shoulder impingement syndrome is a soft tissue condition that manifests as anterior shoulder pain, weakness, and difficulty in daily activities. This review will evaluate the efficacy of glyceryl trinitrate patches in treating a variety of rotator cuff tendinopathies related to shoulder impingement, based on human and animal trials, and suggest its practical application in future trials and management.


## Introduction

Shoulder impingement syndrome (SIS) encompasses a range of pathologies and can simply be defined as a soft tissue condition characterised by entrapment of the rotator cuff soft tissues, including tendons and subacromial bursa, between the coracoacromial arch and the humeral head [1]. It manifests as anterior shoulder pain, weakness, and difficulty in daily activities as a consequence of decreased range of motion (ROM) [2].

This syndrome is managed by either conservative methods (consisting of activity modification and short periods of rest, rotator cuff muscle strengthening, and anti-inflammatory medications) or surgical intervention, both of which are well detailed in the literature [3]. Clinical outcome measures include comparative Visual Analogue Scale (VAS) pain scores, American Shoulder and Elbow Surgery scores, Disability of the Arm Shoulder and Hand scores, ROM, power, and standardised shoulder function tests at different time points, pre- and postintervention.

Glyceryl trinitrate (GTN) patches have been a therapeutic intervention in angina pectoris for over a century.

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Recently, GTN patches have been investigated to treat a range of tendinopathies due to the ease of titration of dosage and the ease of their application [4,5]. These patches have been inferred to reduce pain and inflammation secondary to their nitric oxide (NO)-producing action [6]. This review will evaluate the efficacy of GTN patches in treating a variety of shoulder pathologies, based on human and animal trials, and suggest its practical applications in future trials and management.

NO is an enzymatically produced free radical, which functions as a messenger molecule in small physiological quantities [7]. NO production is dependent on the family of enzymes nitric oxide synthase (NOS), comprising three cofactor-regulated isoforms: eNOS, bNOS, and iNOS, an inducible isoform critical in host defence [7].

Tendon healing relies upon the production of collagen via fibroblasts, and it is thought that NO plays an important role in stimulating collagenous repair [4].

There is limited endogenous generation of NOS in normal tendons; however, it has been demonstrated to be induced in tendon injury [8]. Inhibition of NO has been observed to decrease collagen content and synthesis via fibroblasts, through the systemic inhibition of NOS, resulting in a reduced cross-sectional area of tendon healing histologically [9,10]. In accordance, addition of exogenous NO has been shown to augment tendon healing, improving extracellular collagen matrix organisation [4,11].

NO's involvement in optimising collagen deposition is reinforced through experimentation with human tendon cell cultures, where small doses of exogenous NO and iNOS were shown to enhance collagen and total protein synthesis *in vitro* [12]. The aforementioned mechanisms are demonstrated in greater detail in the NO animal studies discussed later.

## Glyceryl trintrate pharmacokinetics

GTN patches are a potential, easy-to-apply, noninvasive alternative to standard nonoperative treatment options for SISs. GTN is a prodrug; its pharmacological action is attributed to its biotransformation into NO via metabolic enzymes and the consequent localised exogenous NO secretion [5]. The mechanism of NO augmentation in collagen deposition has been discussed previously, and it is postulated that reduction in pain post injury corresponds to enhanced collagen synthesis, an effect potentially extrapolated to GTN patches on impingement syndromes (Fig. 1) [9].

The transdermal patch is applied on the skin proximal to the site of pain or tenderness, delivering GTN at a constant rate [7]. The GTN plasma concentration is maintained over a period of 24 hours, via continuous absorption into vasculature, albeit interindividual variation exists [5]. It is considered a "safe" treatment, due to the absence of

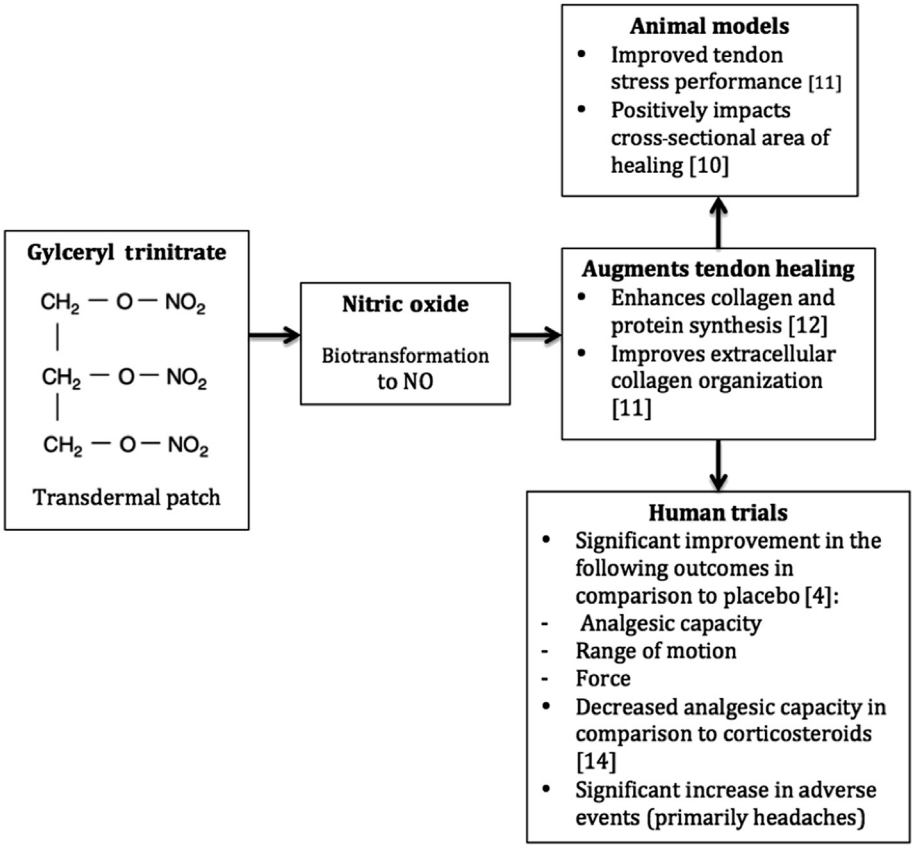


**Figure 1** Flow chart demonstrating the mechanism of action of GTN patches in tendon healing explored throughout this review. CRAAP = currency, relevance, authority, accuracy, and purpose; PICO = population, intervention, control, and outcome.

severe or chronic adverse events, with symptoms primarily constituting of headaches and mild rash, characterised by their "reversal upon cessation" nature [9]. The administrating dosage can be titrated simply to facilitate the treatment intention, in the context of the clinical trials below a 5 mg/24-hour patch is subdivided into equal quarterly 1.25 mg/24-hour patches, replaced daily [14].

## Treatment rationale

The presentation of shoulder impingement is often concurrent to rotator cuff tendinitis, and may progress to chronic inflammation or tendinopathy if it remains untreated [17]. Thus, a mainstay of treatment involves restoring rotator cuff function [18]. A systematic approach to rehabilitation of SIS is divisible into three chronological stages: the initial reduction of pain and inflammation, followed by the maintenance of the "normal" ROM, and finally strengthening of the involved and supporting rotator cuff muscles [17].

Thus, the therapeutic effect of transdermal GTN on shoulder impingement may be attributed to the role it plays in augmenting tendon remodelling and healing, which will cause a natural decline in inflammation of the affected rotator cuff tendon, reducing the symptoms associated with impingement and discontinuing the cycle of chronic injury progression into tendinopathy. The therapeutic outcome is potentially augmented by the analgesic effect, which may accelerate mobilisation, promoting the maintenance of ROM and muscle strength.

## Inclusion criteria

Human studies included were randomised control trials (RCTs) comparing efficacy of GTN patches with either placebo or a currently recognised treatment control. No restriction on dosage, time frame, or concurrent treatments was made. RCTs addressing shoulder pathology related to SIS, verified via clinical examination or imaging, were included in this review. Animal studies demonstrating the involvement of NO in any form of tendon healing were also included.

## Search strategy

Medline and Embase (via Ovid Platform), and the Cochrane library were searched using key search terms to identify relevant trials. Relevant articles' references and citations were also searched (Fig. 2). The combination of search terms utilised was "Glyceryl Trinitrate" AND "Rotator Cuff" OR "Shoulder Impingement", which presented the results discussed in the following section.

The 68 database results and 83 references or citations were scanned manually for titles relating to "GTN in tendon healing", and the abstracts of those articles were screened utilising the currency, relevance, authority, accuracy, and purpose (CRAAP) assessment tool to determine if they met the inclusion criteria. Studies not detailing pathology, treatment routine, or outcomes were ineligible and excluded. Four RCTs extracted from the databases and references met the inclusion and eligibility criteria, and were included in this review.

## Animal studies

The effects of NO and NOS on tendon healing have been investigated in animal studies, principally via rat Achilles tendon injury rather than shoulder pathologies, the mechanisms of which may be extrapolated to the rotator cuff tendons.

The bulk of experiments performed can be categorised as those demonstrating the correlation between injury and the influx of NO or NOS, and monitoring the effect of NOS inhibition or exogenous administration on tendon healing. This has been followed by a spurt in clinical trials. In the following subsections, we explore the animal data first.

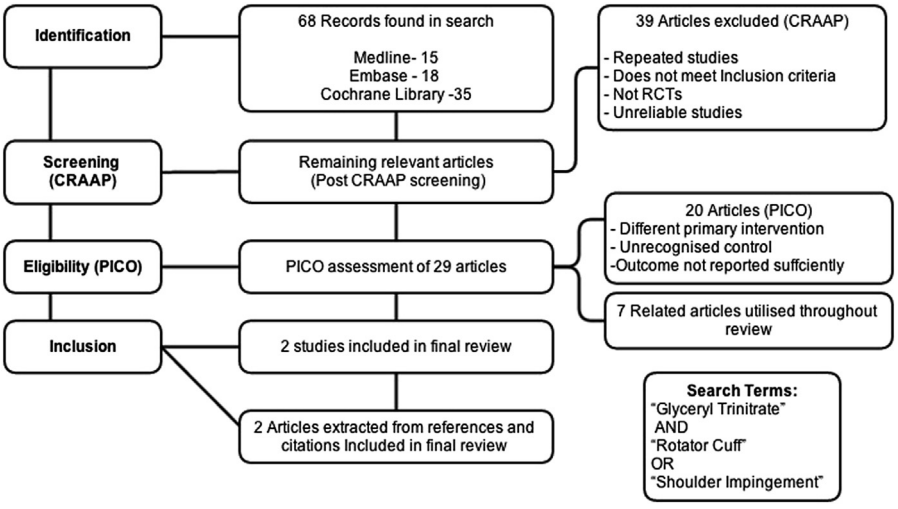


**Figure 2** Search strategy flow chart illustrating sequence of events, database results, and exclusion process; utilising CRAAP and PICO evaluating tools. CRAAP = currency, relevance, authority, accuracy, and purpose; PICO = population, intervention, control, and outcome.

## Injury-induced NOS

Murrell et al [8] conducted a foundational investigation in rats' Achilles tendons, demonstrating the absence of NOS activity in uninjured tendons, and a five-fold increase in NOS activity after surgical division within the healing tendon. Subsequent inhibition of NOS decreased failure loads and cross-sectional area of the healing tendon ($p < 0.01$ on Day 7). The proposition of NOS expression in tendon injury or tendinopathy was supported by the conclusions made using the "overuse" model—when rats stimulated to run 1 hour/day on a treadmill were compared with controls, an overexpression of NO precursors was observed in the supraspinatus tendon post 14 days in the experimental group [6].

## Inhibition of NOS

Xia et al [10] performed a follow-up study on 29 mice, evaluating the effect of deleting the *NOS* gene on Achilles tendon healing. Twenty-one *NOS* gene-deficient mice were divided into two groups, the first of which was treated with an NOS inhibitor (intraperitoneal) and the second remained without treatment. The remaining eight "wild" mice with intact *NOS* gene constituted the third control group. Transection of the right Achilles tendon was performed in all mice, and the tendons were subsequently harvested 7 days postsurgery. Outcome measures were the cross-sectional area, biomechanical force, and displacement of the tendon. The *NOS* gene-deficient mice that were further treated with an NOS inhibitor (Group 1) showed a significant reduction in the cross-sectional area of healing, whereas no significant difference was observed between the other two groups ($p < 0.01$). No difference in failure or stress load was elicited between the three groups. Thus, the study concluded that the *NOS* gene deletion alone did not play a significant role in healing; however, systemic NOS inhibition reduced healing, inferring the importance of local NOS in tendon healing and the presence of alternate pathways for its production [10].

## Administration of NO

Yuan et al [11] histologically assessed the effect of exogenous NO administration via the vehicle compound flurbiprofen (NO-flurbiprofen), in comparison to flurbiprofen alone, on healing of surgically divided rat Achilles tendons. They found improved extracellular collagen matrix organisation postsurgery in the NO-flurbiprofen and flurbiprofen groups and improved tendon stress performance only in the NO-flurbiprofen group, but no statistically significant change in collagen mass in any of the experimental groups.

The aforementioned findings were supported by a trial comparing subcutaneous injection of NO-paracetamol, paracetamol, and the vehicle compound, reporting that injection of paracetamol and the vehicle alone had a similar effect, and no significant change in failure load was elicited by any of the experimental groups. The NO-paracetamol subcutaneous injection was shown to improve tendon properties, including collagen organisation and content, in comparison to the other test groups, reportedly consistent with the findings of human trials in which NO improved tendinopathy-related signs and symptoms [13].

Thus, oral vehicle transmission of NO may not provide the ideal platform for drug delivery. Transdermal patches may offer an easy-to-use and proven alternative.

## GTN human trials

There has been a paucity of clinical data on GTN patches in tendon healing. However, this field has been exploded over the last decade, with many institutions currently conducting research on the same, including our own. There is an absence of published RCTs in the literature exploring the effect of GTN on SIS explicitly; thus, this review will evaluate the available RCTs that measure the efficacy of transdermal GTN in a range of rotator cuff tendinopathies involved in shoulder impingement (Table 1).

## Shoulder tendinopathy

Giner-Pascual et al [14] conducted a double-blinded clinical trial evaluating the efficacy of transdermal GTN patches in treating shoulder pain and functionality, in 45 wheel-chair-bound spinal cord injury patients presenting with concurrent shoulder tendinopathy. Diagnosis of rotator cuff tendinitis or partial tears was made based on magnetic resonance imaging findings (or ultrasonography when magnetic resonance imaging was contraindicated), in concordance with the complaint of chronic shoulder pain ($> 3$ months) prior to inclusion in the study.

The participants were randomly assigned to an experimental group ($n = 33$) and a placebo group ($n = 12$), each respectively administered a quarter (1.25 mg) GTN patch or placebo patch daily, on the lateral aspect of the shoulder. This treatment pattern was maintained for over 6 months in absence of additional pharmacotherapy or physical therapy [14].

Outcome measures included awareness of pain (assessed via a 0—10 VAS), functional movement [assessed via Spinal Cord Injury Measurement (SCIM)], functional movement-induced pain [assessed via Wheelchair Users Shoulder Pain Index (WUSPI)], and manual assessment of ROM via goniometry. Assessment of outcomes was performed before and after treatment [14].

Comparison of the mean outcome scores revealed significant improvement in the GTN experimental cohorts' ROM (abduction, antepulsion, retropulsion, and internal and external rotation) post-treatment ($p < 0.005$), whereas a reduction in ROM was elicited in the placebo cohort ($p < 0.005$). The mean pain scores (VAS and WUSPI) were improved in the experimental group ($p < 0.001$) throughout treatment; however, the placebo cohort demonstrated no significant change in VAS scores and an increase in WUSPI (increased pain induced by functional movement). There was no significant difference in functional movement via SCIM post-treatment in either group [14].

Nine of the initial 33 patients in the experimental group did not complete the 6-month treatment routine, five due to improvement of symptoms and four due to inability to

**Table 1** Summary of the controlled trials conducted with GTN patches and a control—a comparison of the efficacy of the EG (in all cases GTN patch cohort) and the CG (other treatment).

| Trial | Shoulder tendinopathy [14] | | Supraspinatus tendinopathy [4] | | Rotator cuff tendinitis [15] | | Supraspinatus tendinitis [16] | |
|---|---|---|---|---|---|---|---|---|
| Patient no. | 45 | | 53 | | 48 | | 20 | |
| Control | Placebo | | Rehabilitation exercise | | Corticosteroid injection | | Placebo | |
| Dosage | 1.25 mg/24 h | | 1.25 mg/24 h | | 5 mg/24 h (3d) | | 5 mg/24 h | |
| Time | 6 mo | | 6 mo | | 3-, 15-d intervals | | 3 d | |
| Pain score (VAS)[a] EG | 5.42[b] | 2.25 | 5[b] | 1.75 | 21% 5 + point reduction | | 7.05[b] | 2 |
| Pain score (VAS)[a] CG | 5.33[b] | 4.6 | 5.5[b] | 4.25 | 79% 5 + point reduction | | 6[b] | 5.9 |
| *p* | <0.001 | | <0.05 | | <0.05 | | <0.0001 | |
| ROM (EG) | Improved in every direction ($p < 0.05$) | | Increased in abduction and internal rotation ($p = 0.02, 0.04$) | | Not reported | | Significant improvement in joint mobility ($p < 0.0001$) | |
| Special test (EG) | SCIM ($p > 0.05$) | | Increase in supraspinatus force ($p = 0.05$) | | Not reported | | Pain duration decreased ($p < 0.0001$) | |
| % Adverse effects (EG/CG) | 33% (7H + 2 other) | 16.6% (2H) | 65% (15H + 3 R) | 33% (9H + 1 R) | 62% (15H) | 16% (4 mild pain) | 20% (2H) | Nil reported |
| Authors' conclusion regarding GTN patches | Safe alternative for controlling pain in shoulder pathology | | Significantly improves pain symptoms, ROM, and force, in comparison to tendon rehabilitation | | Analgesic efficacy is less than corticosteroid injection, with increased adverse events | | Analgesic action in musculoskeletal disorders, albeit it induces adverse effects such as headaches | |

CG = control group; EG = experimental group; GTN = glyceryl trinitrate; H = headache; R = rash; ROM = range of motion; SCIM = Spinal Cord Injury Measurement; VAS = visual analogue scale.

[a] Adjusted among all studies (0—10).

[b] Baseline recording of score (pretreatment).

tolerate the treatment. Ten patients (33%) in this group reported adverse events, seven of whom experienced headaches and the other three reported single cases of facial reddening, dizziness, and tachycardia. Six of the initial 12 patients in the placebo group discontinued treatment, five due to no improvement in symptoms and one due to an inability to tolerate the treatment. Two patients (16.6%) in this group experienced headaches, which was the only adverse event reported [14].

## Supraspinatus tendinopathy

Paoloni et al [4] conducted a double-blind controlled trial in 53 patients (57 shoulders) with chronic supraspinatus tendinopathy, over a period of 6 months, assessing the efficacy of sustained GTN (1.25 mg/24 hours) application in comparison to rehabilitation exercise. The outcome parameters, including severity of shoulder pain (0—4), power, ROM, strength and ADL-related symptoms, concurrent monitoring of compliance, and headaches, were assessed based on daily diary entries.

The intention-to-treat cohort in comparison to the rehabilitation-only cohort reported an overall reduction in pain ($p < 0.05$); at 12 weeks, there was a decrease in shoulder pain at night and at rest (0.03 and 0.04, respectively) and further reduction in both cases by 24 weeks ($p = 0.01$ and $p = 0.03$, respectively). The GTN group also demonstrated increases in supraspinatus and external rotation force ($p < 0.01$ and $p < 0.05$, respectively). No significant differences were noted in subacromial tenderness ($p = 0.53$), external rotation impingement ($p = 0.24$), and flexion ROM ($p = 0.36$) in either cohort. Patients in the treatment cohort experienced a significant increase in headache-affected days ($p = 0.001$) and consequently in the amount of paracetamol used ($p = 0.001$) throughout the course of treatment, with 8% of patients (2/26) in the GTN cohort ceasing treatment due to severe headaches. Effect size was reported to be 0.26 for all outcomes [4].

## Rotator cuff tendinitis

Pons et al [15] performed a randomised controlled trial in 48 patients comparing the efficacy of transdermal GTN (5 mg patch) and corticosteroid infiltration (1 mL triamcinolone acetonide with a local anaesthetic) in rotator cuff tendinitis. The diagnostic inclusion criteria consisted of pain, positive impingement sign, and a positive rotator cuff tendon minor test; patients were also not responsive to oral non-steroidal anti-inflammatory drugs (NSAIDs). Patients were randomly distributed into two groups of 24: "Group A" patients received a posterior-approach corticosteroid injection and "Group B" patients were administered GTN patches over the shoulder region with the most severe pain for 3 days. Complete improvement corresponded with cessation of treatment; otherwise, procedures were repeated up to three times at 15-day intervals [15].

The primary outcome measured pain (via a VAS, 0—10), treatment failure (defined as a reduction in pain score by $< 3$ points), partial improvement (a reduction by 3—5 points), and complete improvement (>5-point reduction). An outcome assessment was performed at baseline and 7 days post each treatment routine to measure the adverse effects as a secondary outcome [15].

In Group A, consisting of intention-to-treat patients receiving corticosteroids, 19 patients (79%) demonstrated complete improvement, three patients (12.5%) demonstrated partial improvement, and two patients (8.3%) demonstrated treatment failure. The adverse event elicited was pain (mild) at the site of injection in four patients (16.6%). In the GTN patch cohort, Group B, five patients (20.8%) demonstrated complete improvement, five patients (20.8%) showed partial improvement, and 14 patients (58.3%) had failure of treatment. Fifteen patients (62.5%) in the GTN cohort experienced headaches, causing eight patients (33.3%) to abandon treatment. The difference between Groups A and B was reported to be statistically significant. Pons et al [15] concluded that GTN patches were not as efficacious as corticosteroid infiltration and led to a significant increase in adverse events, resulting in abandonment of treatment; thus, treatment failure were not a suitable alternative.

## Supraspinatus tendinitis

Berrazueta et al's [16] double-blinded placebo-controlled trial assessed GTN's analgesic capacity, in supraspinatus tendinitis-induced "shoulder pain syndrome". Twenty patients (10 M/10 F) were randomised, and equal numbers of patients received either a 5 mg GTN patch or a placebo equivalent, applied proximal to the region with the most severe pain, over 3 consecutive days. Pain evaluation was carried out before treatment and 24—48 hours subsequently via an analogue scale (0—10). Patients were also monitored for duration of the pain (hours) and joint motion restriction (% restriction) [16].

Post-treatment follow-up demonstrated a significant reduction in pain intensity in the GTN cohort at the 24-hour mark (from 7 to 4.5; $p < 0.001$), with further reduction at 48 hours (to 2; $p < 0.0001$); however, no change in pain was elicited in the placebo group. The mean duration of pain also reduced with GTN (from 1.7 to 0.1; $p < 0.0001$), with no significant variation in the placebo group. Joint mobility improved significantly with GTN (from 2.0 to 0.1; $p < 0.0001$), but did not change in the placebo group. Adverse effects were limited to two patients experiencing headaches with GTN administration. Further assessment after 15 days demonstrated the entire GTN cohort and five placebo patients (on analgesic medication) to be symptom free, while the remaining placebo patients remained with a slight pain (intensity 3.6) [16].

## Discussion

This review has explored the evidence surrounding NO's effect on tendon healing, its application in a variety of animal studies, and the efficacy of its administration via GTN patches in clinical trials. The literature suggests that NO is an important biochemical factor in collagen deposition and organisation. Animal studies demonstrate that its inhibition impedes healing and addition augments it. This has sparked a variety of clinical trials, which have reported significant pain reduction with GTN.

A common primary outcome of the four trials related to SIS pathology explored in this review was the analgesic capacity of the treatment, measured from the differences in VAS pain scores before and after intervention. The results have been converted to the mean pain reduction from baseline, as demonstrated by graph of Fig. 3. Three of the four trials show a significant ($p < 0.05$) reduction in the mean pain in the GTN cohort in comparison to the placebo cohort, while the trial conducted by Pons et al [15] showed a significant reduction in pain for the control cohort (corticosteroid injection) in comparison to the GTN cohort.

Additional outcomes, including ROM, functionality, and force, were not standardised across the trials; however, the three placebo control trials demonstrated a significant improvement in these functions in the GTN cohort. Overall, a significant increase in GTN-related side effects, namely, headaches, was observed, impeding treatment in a number of patients in each trial.

## Heterogeneity of trial design

There is heterogeneity in the available clinical trials, in terms of GTN administration, dosage and time, diagnostic criteria for inclusion, comparative controls, and final outcome measures. This confounds attempts to formulate *a priori* conclusions of efficacy from the results.

## Administration

The application of a 5 mg GTN patch over 3 consecutive days in earlier studies deviates from the daily application of a 1.25 mg patch utilized in recent studies. This creates variability in the pharmacokinetics, whereby the absorption in the vasculature is changed. The consequent inconsistency in plasma concentration, compounded by the pre-existing interindividual variation, leads to an unpredictable treatment effect.

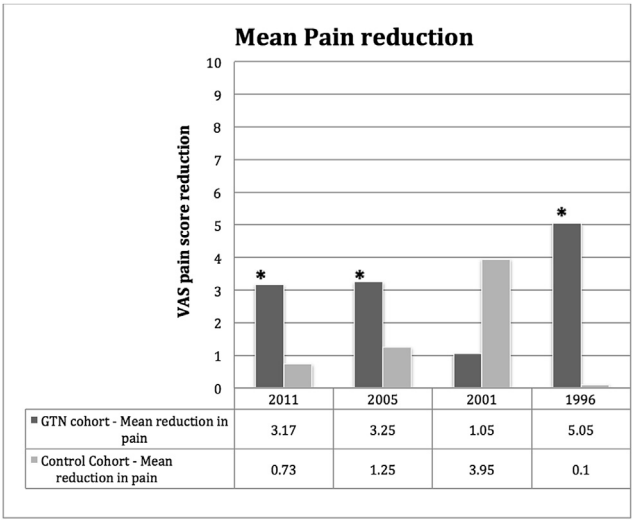


**Figure 3** Graphs comparing the mean pain reduction between the GTN patch experimental cohort and the control cohort, categorised by trial dates. Pain reduction was calculated from VAS end outcomes. * Statistically significant ($p < 0.05$) pain reduction in GTN cohort. GTN = glyceryl trinitrate; VAS = visual analogue scale.

## Outcome time points

The diversity of the outcome assessment time points potentially confounds the reported results. The 6-month postintervention assessment in Giner-Pascual et al [14] and Paoloni et al [4] demonstrate a positive effect in the GTN cohort's pain scores and ROM. Berrazueta et al [16] assessed the pain and restriction of joint motion 3 days postintervention, perceivably a measure of acute analgesic capacity rather than an adequate quantification of GTN's healing aptitude.

Pons et al [15] assessed outcomes at 7-day intervals post 3-day GTN application or corticosteroid injections. Discontinuity of GTN application in between follow-ups and short-term assessment do not effectively gauge the healing potential of GTN, in comparison to the control in which this is sufficient time to alleviate symptoms. Therefore, the healing capacity of GTN may have been underestimated in the two initial studies [15,16].

## Control

The use of a consistent control in studies allows the validation of results that can be replicated. The available studies that we have reviewed lack consistency, comparing GTN to placebo, rehabilitation, or corticosteroid controls, making it difficult to evaluate the validity of each individualised study, as the results are not standardised.

## Randomisation

Giner-Pascual et al [14] and Paoloni et al [4] utilised patient arrival time points and coding randomisation, respectively, to eliminate bias. Pons et al [15] significantly reduced the risk of randomisation bias by assigning patients through a random number table. There was no description of randomisation in the study of Berrazueta et al [16]; thus, there remains an unpredictable risk of randomisation bias.

## Blinding

Trials of Giner-Pascual et al [14], Paoloni et al [4], and Berrazueta et al [16] had adequate double blinding of patients and clinical examiners, utilising identical placebo patches in the control group. Pons et al's [15] paper did not describe any blinding of either patients or examiners, the variable invasiveness of the intervention rendering the process difficult, albeit a replica patch or injection may have sufficed.

## Methodology

Heterogeneity of end outcomes makes it difficult to validate individualised results and compare the overall efficacy of the treatment cohorts. Pons et al [15] assessed only the VAS pain score and the adverse event rate; we do not believe that subjective pain assessment alone is sufficient to

indicate the efficacy of GTN, particularly when significant symptoms of shoulder impingement have been ignored, compared to the other studies all of which measured pain, adverse events, and ROM. The subjectivity in outcome selection potentiates reporting bias, whereby significant outcomes may be selectively expressed in the method.

Supplementary measures included shoulder functional movements (via SCIM) and muscle force [14]. Pain scale intertrial variation also exists, albeit it is the only outcome comparable across all trials.

The absence of the aforementioned clinically significant secondary outcomes will negatively impact the clinician's decision-making process in trialling this treatment.

Standardised long-term follow-up assessment is absent in all four studies; this would be a valuable addition to the literature, permitting a paralleled comparison with current interventions. It would also reduce the risk of reporting bias, where positive effects may have been temporary. Long-term assessment would also facilitate the application of GTN as a definitive intervention and not just an adjuvant.

### Outcome reporting

The outcomes reported by Giner-Pascual et al [14] and Paoloni et al [4] parallel those detailed in methodology; though there is a selective reporting of numerical *p* values at time points of significance, the reader may assume that non-numerical outcomes are insignificant. Pons et al [15] deviates from the methodological plan utilizing a defined categorical scale, consisting of the three-components; complete improvement, partial improvement and treatment failure. This is ineffective in comparison to the initial baseline to post-treatment continuous scoring system.

### Statistical analysis

Giner-Pascual et al's [14] trial was the only trial to detail the multivariate analysis of variance of the "intention-to-treat" group in their methodology, adequately evaluating the association between the independent variable (i.e., GTN) and the dependent variables [VAS pain, ROM, and function (SCIM)]. Paoloni et al [4] and Berrazueta et al [16] utilised the Mann—Whitney *U* test, a nonparametric test showing greater efficiency than a simple *t* test in the non-normal distributions. The non-normal distribution is predictable in the context of pre-existing interindividual variation of NO plasma concentration and responses to treatment. Pons et al's [15] trial did not provide sufficient information regarding their statistical analysis, a prospect for analytical bias.

## Future implications in clinical practice and research

The results explored throughout this review are promising; there is evidence that GTN shows analgesic effects in SIS, as well as increasing ROM and function, facilitating a platform for further research to validate findings and increase their statistical power for application in the clinical setting.

Based on a systematic review of the available treatment modalities, we concluded that the first-line therapy should consist of NSAIDs, which provide temporary short-term relief and physical therapy (stretching and strengthening exercises), whereas therapeutic adjuvants such as phonopheresis, ionophoresis, and ultrasound lack appropriate evidence [19]. A meta-analysis by Arroll [20] revealed subacromial corticosteroid injections to be more effective than NSAIDs. Corticosteroids were found to provide short-term relief; however, there was not sufficient evidence to demonstrate longer-term benefits. Andres and Murrell [19] suggested transdermal GTN as a viable alternative if other treatments failed and surgical debridement as a final option subsequent to exhausting all other interventions, as it is associated with significant morbidity and cost, with only "modest" success.

In future research, high-quality trials should maintain a consistent GTN dosage regimen and interventional time span. Comprehensive secondary outcome measures and long-term follow-up are highly recommended, enabling valuable comparison with currently recognised interventions. Nonbiased randomisation and double blinding are essential, the physical appearance of the placebo replicating that of the treatment. GTN is a simple-to-apply, noninvasive, low-morbidity intervention, with great potential to become a mainstay treatment, if larger, multicentre trials with greater strength reproduce the aforementioned results.

## Conclusion

The clinical effect of GTN patches in SIS needs to be substantiated through supplementary high-quality trials, with larger cohorts and consistent pathology. The primary contingency is counteracting the common adverse consequence of headaches. Little evidence exists for its equitable therapeutic capacity to current treatment, such as corticosteroid use or muscle strengthening; thus, future comparative trials will reveal the overall efficacy of this treatment.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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