UNIVERSITÀ DEGLI STUDI
DI GENOVA

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Università degli Studi di Genova

Scuola di Scienze Mediche e Farmaceutiche

Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili

Master in Riabilitazione dei Disordini Muscoloscheletrici

A.A. 2016/2017

Campus Universitario di Savona

Trattamento conservativo della sindrome del tunnel carpale: revisione della letteratura

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1. Abstract

INTRODUZIONE: la sindrome del tunnel carpale (CTS) è il disturbo a carico della mano a maggiore prevalenza ed ha elevati costi sociali. Caratterizzata da un aumento di pressione all'interno del tunnel carpale con conseguente compressione e ischemia a carico del nervo mediano, recenti RCT hanno evidenziato meccanismi di sensibilizzazione. Numerosi sono i trattamenti conservativi proposti ma solamente l'educazione, farmaci steroidei e 'splinting' sono presenti nelle linee guida. L'**obiettivo** di questa revisione è fare una panoramica dei trattamenti conservativi per la CTS presenti in letteratura e confrontarne l'efficacia, sia tra di loro sia eventualmente con la chirurgia, per evidenziare il miglior approccio terapeutico.

MATERIALI E METODI: ricerca di RCT e revisioni sistematiche degli ultimi 10 anni su MEDLINE, relativi al trattamento conservativo nei soggetti adulti affetti da CTS. Gli articoli inclusi sono stati valutati per il rischio di bias.

RISULTATI/DISCUSSIONE: sono stati inclusi 26 RCT e 8 revisioni sistematiche. Il trattamento conservativo da risultati simili alla chirurgia per riduzione di dolore e incremento funzionalità a breve e lungo termine. Limitate evidenze in favore di terapia manuale, esercizi e tecniche neurodinamiche, laser, elettroterapia e ultrasuoni a breve-medio termine (dolore e funzionalità), ma aggiungono poco alla 'terapia standard' con splint; a causa dell'eterogeneità qualitativa degli studi, i risultati potrebbero essere distorti. A oggi non è possibile stabilire quale sia la migliore scelta terapeutica.

CONCLUSIONI: Sono necessari altri RCT di alta qualità che confrontino l'efficacia di questi trattamenti a lungo termine e, parallelamente, studi che verifichino il meccanismo della sensibilizzazione centrale nella CTS, con l'obiettivo di trovare nuove finestre terapeutiche.

2. Introduzione

La sindrome del tunnel carpale (CTS) è il disordine muscoloscheletrico a carico della mano con maggiore prevalenza; si stima che colpisca lo 0,6% degli uomini e il 5,8% delle donne nella popolazione generale e 1 su 5 tra i soggetti sintomatici(1). La CTS ha un alto impatto sulle attività della vita quotidiana e può essere associata a fattori legati all'attività lavorativa, come l'esposizione prolungata a vibrazioni di alta intensità a braccia e mani, a posizioni di estensione o flessione del polso prolungate nel tempo, ad alte richieste di forza, ripetitività o combinazioni di esse alla mano(1); si stima che i costi relativi ai giorni di lavoro persi a causa di questo disordine si attestino tra $45,000 e $89,000 in 6 anni e che il costo complessivo negli Stati Uniti d'America è di circa $2 miliardi l'anno(2).

Nonostante il meccanismo di insorgenza della CTS sia ancora sconosciuto, la CTS è correlata ad un aumento di pressione all'interno del tunnel carpale con conseguente compressione meccanica e ischemia a carico del nervo mediano(1); oltre al meccanismo puramente meccanico, recenti evidenze suggeriscono che la CTS è una complessa sindrome dolorosa che coinvolge processi di sensibilizzazione, infatti sono stati trovati iperalgesia diffusa (termica e pressoria) in donne con CTS(2).

La CTS è caratterizzata da una varietà di sintomi come numbness/tingling, dolore e perdita di controllo motorio a carico del complesso polso-mano con possibile irradiazione fino al braccio, che portano a diminuzione dello stato funzionale e disabilità(2,3); il Consensus Delphi del 2014, in accordo con le linee guida del 2009 dell' 'American Academy of Orthopaedic Surgeons', approvate dall' 'American Society of Plastic Surgeons', 'American Academy of Physical Medicine and Rehabilitation' e 'American Association of Neuromuscular and Electrodiagnostic Medicine', ha sancito che la diagnosi di CTS è basata principalmente sul quadro clinico e solo in caso di dubbio si può ricorrere ai test elettrodiagnostici(1).

Trattamenti chirurgici e conservativi sono ampiamente utilizzati per la cura della CTS e non sembrano esserci differenze in termini di efficacia tra le 2 opzioni terapeutiche; l'approccio chirurgico continua ad essere il trattamento più

comunemente utilizzato ma c'è molto dibattito attorno alla sua efficacia, dato che il 33% dei pazienti con CTS trattati chirurgicamente non ritornano a lavoro a 2 mesi dall'intervento(2). Nel Consensus Delphi del 2014 si evidenzia come il primo step terapeutico dovrebbe essere il trattamento conservativo e solo in caso di compressioni più gravi si dovrebbe ricorrere alla chirurgia; le modalità di trattamento su cui è stato raggiunto un consenso erano fornire istruzioni al paziente circa la gestione della CTS, lo splinting, le iniezioni di corticosteroidi e in ultima istanza la chirurgia(1); ma, alcuni tra i partecipanti al consensus, avevano menzionato anche altri trattamenti conservativi in aggiunta ai 3 descritti prima, come gli ultrasuoni e l'esercizio terapeutico (compresi esercizi di nerve gliding) e il comitato direttivo aveva proposto di aggiungere una nota alle linee guida: 'a seconda della situazione del paziente e delle sue preferenze, altre modalità terapeutiche possono essere aggiunte' (1). Questa proposta non ha raggiunto il consensus tra gli esperti ma si è cominciato a spostare l'attenzione su altri approcci terapeutici per la gestione del CTS.

L'**obiettivo** di questa revisione è fare una panoramica dei trattamenti conservativi per la CTS presenti in letteratura e confrontarne l'efficacia, sia tra di loro sia eventualmente con la chirurgia, in relazione a tutti gli outcome proposti dagli autori, a breve e lungo termine; particolare attenzione sarà data alle misure di outcome che indagano l'intensità del dolore, la severità dei sintomi, la funzionalità e disabilità. Ci si propone di mettere in luce la migliore scelta terapeutica per i soggetti con CTS.

3. Materiali e Metodi

La ricerca della letteratura è stata condotta sul database scientifico MEDLINE, unico operatore, inserendo la seguente stringa di ricerca:

(((((carpal tunnel syndrome[MeSH Terms]) OR compression neuropathy, carpal tunnel) OR entrapment neuropathy, carpal tunnel) OR medial neuropathy, carpal tunnel)) AND ((((physical therapy modalities[MeSH Terms]) OR physical therapy technique) OR exercise) OR manual therapy)

E' stato deciso di non aggiungere filtri alla ricerca, ma di revisionare manualmente tutti i records trovati per minimizzare il rischio di perdere materiale potenzialmente inerente alla nostra tesi.
Una prima selezione è stata effettuata sulla base del titolo e dell'abstract; degli articoli rimanenti sono stati ricercati i full text e, ove reperibili, questi venivano analizzati; se soddisfacevano i nostri criteri di inclusione e di esclusione ne venivano estrapolati i risultati; inoltre, per ogni studio incluso, è stato valutato il Risk of Bias (Rob) seguendo i criteri del 'The Cochrane Collaboration's tool' (RCT) e AMSTAR (revisione sistematica).

Criteri d'inclusione/esclusione:

- ✓ RCT e Revisioni Sistematiche in lingua inglese pubblicate massimo 10 anni fa.
- ✓ Partecipanti > 18 anni, con diagnosi clinica o clinica ed elettrofisiologica di CTS.
- ✓ Trattamento conservativo della sindrome del tunnel carpale.
- ✓ No pregressa chirurgia per CTS.

Abbiamo deciso di prendere in considerazione tutti i tipi di outcome proposti dagli autori degli studi selezionati, per avere una panoramica più ampia delle misure utilizzate nella valutazione del paziente affetto da CTS e di come i trattamenti proposti riuscivano a modificarli; Comunque gli Outcome di primario interesse sono l'intensità del dolore, la severità dei sintomi, lo stato funzionale e la disabilità.

In sintesi:

Partecipanti: soggetti adulti con diagnosi clinica e/o elettrofisiologica di CTS

Intervento: modalità di trattamento conservativo per la CTS

Confronto: altre modalità di trattamento conservativo e chirurgico per la CTS

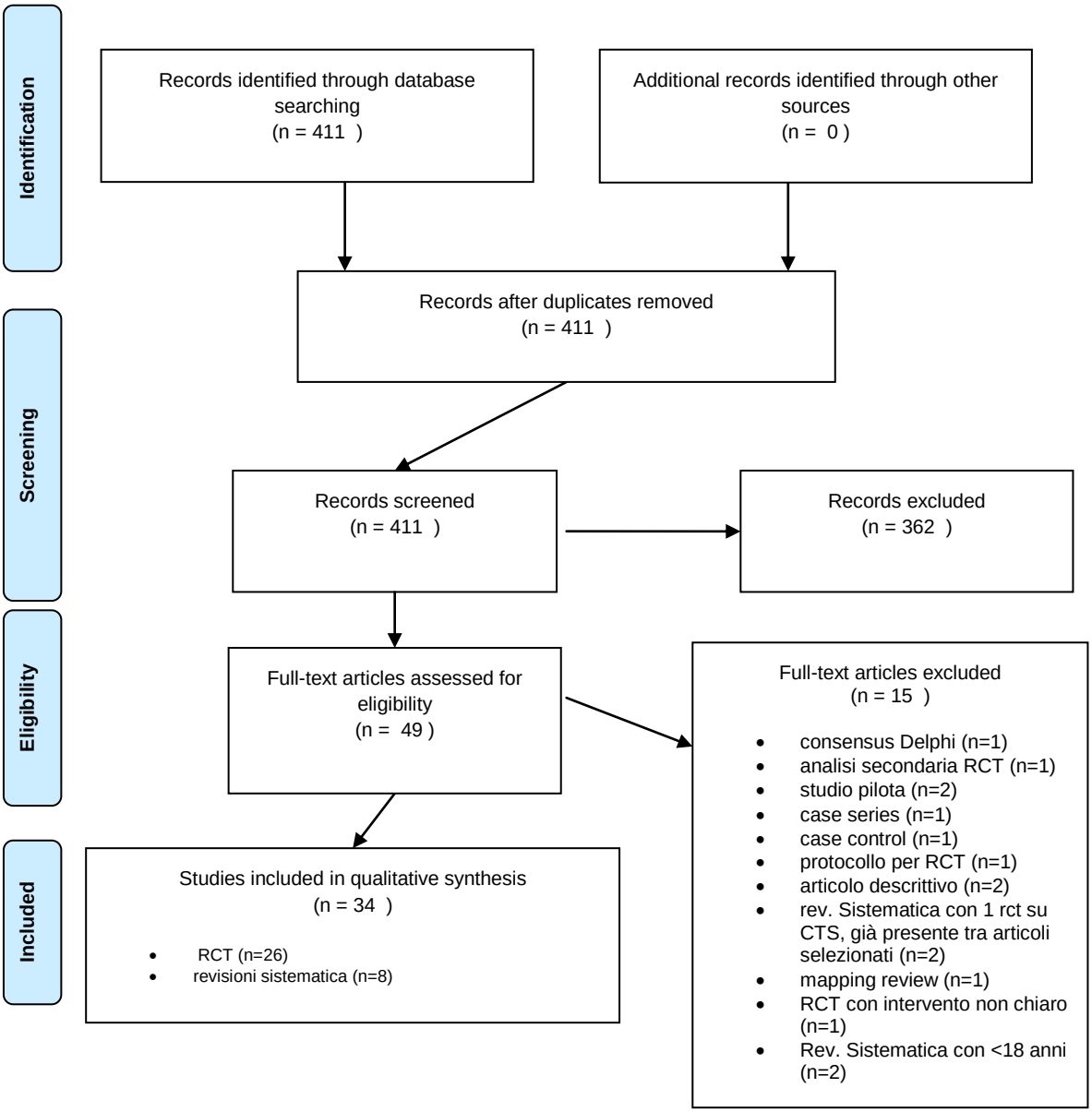
Outcomes primari: intensità del dolore, severità dei sintomi, funzionalità e disabilità.

Outcomes secondari: esame clinico, parametri elettrofisiologici, edema intraneurale, ricorso a chirurgia, eventi avversi

4. Risultati

Un totale di 411 records sono stati trovati inserendo la stringa di ricerca su MEDLINE; 361 sono stati esclusi sulla base del titolo e/o dell'abstract perché non inerenti all'argomento di ricerca o, se inerenti, non soddisfacevano i criteri di inclusione o il full text non era reperibile. 49 full text sono stati valutati e altri 15 articoli sono stati esclusi; le motivazioni per la loro esclusione sono esplicitati nella flow chart (Figura 1). Infine 26 RCT e 8 revisioni sistematiche sono stati inseriti nella nostra revisione.

Figura 1.



Le proposte di intervento e i relativi gruppi di confronto erano molto eterogenei, ma possono essere suddivisi in 6 diverse classi di trattamento.

Splinting

1 RCT(4) comparava l'utilizzo di splint a polso e matacarpo-falangee (MCF) + stretching muscoli lombricali con diverse combinazioni di splint e stretching (splint al polso + stretching lombricali, splint al polso e MCF + stretching generico, splint al polso + stretching generico). In tutti e 4 i gruppi c'era un miglioramento significativo sia nella sintomatologia (CTQ-S) che nella funzionalità (CTQ-F, DASH) a 4, 12 e 24 sett. con una differenza significativa in favore dei gruppi splint al polso + stretching lombricali e splint a polso e MCF + stretching generico nella funzionalità a 12 sett. Lo studio aveva un alto Rob per i dati mancanti relativi agli outcome. Un altro RCT(5) comparava lo splint al poslo con splint al polso e MCF. Il gruppo con splint al polso + MCF mostrava una riduzione del dolore e aumento di forza e funzionalità significativamente superiore all'altro gruppo a 1 mese di follow up; Lo studio aveva un Rob alto per gli items'allocation concealment' e 'blinding of partecipants' e la modalità di randomizzazione non chiara.
1 RCT (6) paragonava l'efficacia dello splint da solo e in associazione con ultrasuoni + esercizi di scivolamento tendineo; in entrambi i gruppi vi erano miglioramenti a 2 mesi per riduzione della severità dei sintomi e aumento funzionalità, senza differenze significative tra i 2 gruppi. I partecipanti e il personale non erano in cieco.

Terapia manuale

9 RCT(2,7–14) e 4 revisioni sistematiche(3,15–17) hanno verificato l'efficacia della terapia manuale nel trattamento della CTS con una vasta gamma di outcome (intensità del dolore, severità dei sintomi, funzionalità, disabilità, aspettativa del paziente, miglioramento percepito, soglia del dolore pressorio e termico, ROM cervicale, forza, qualità della sensibilità tattile, esame fisico,

parametri elettrofisiologici, edema intraneurale, eventi avversi, ricorso alla chirurgia).

Di queste, 6 RCT(2,7,8,12–14) e 4 revisioni sistematiche indagavano l'efficacia di alcune tecniche neuro dinamiche di mobilizzazione del nervo mediano, associate o meno a mobilizzazione dei tessuti molli nei probabili siti di entrapment:

- 2 RCT avevano paragonato tecniche neuro dinamiche (TN) a 'sham' tecniche neurodinamiche, 1 non riscontrava differenze significative tra i 2 gruppi per nessun outcome ad eccezione della riduzione della soglia del dolore termico a 3 sett. in favore del gruppo 'TN'(7), mentre l'altro riportava un miglioramento statisticamente significativo nei parametri elettrofisiologici a 1 mese e nel dolore, nella severità dei sintomi, nella funzionalità e nella qualità della sensibilità tattile a 10 sett., in favore del gruppo 'TN'; entrambi gli studi avevano un basso rischio di Bias per ogni item, ad eccezione dell' 'incomplete outcome data' ad alto rischio per 1 studio(14).
- 2 RCT dello stesso autore paragonavano la 'TN' con l'applicazione di ultrasuoni + laser; miglioramenti statisticamente significativi in entrambi i gruppi per diminuzione dell'intensità del dolore e severità dei sintomi e per miglioramento della funzionalità(13) e qualità della sensibilità tattile(12) a 10 sett., mentre per i parametri elettrofisiologici a 1 mese c'erano miglioramenti significativi solo a favore del gruppo 'TN' (13); entrambi gli studi avevano un basso rischio di Bias per ogni item, ad eccezione dell' 'incomplete outcome data' non chiaro.
- 2 RCT dello stesso autore, paragonavano l'utilizzo di mobilizzazione dei tessuti molli nei siti di entrapment in associazione con 'TN' e tendon-glide rispetto alla chirurgia a 1, 3, 6, 9 e 12 mesi; i risultati dei 2 studi dimostravano un miglioramento significativo nel gruppo di intervento per riduzione del dolore e miglioramento della funzionalità a 1 e 3 mesi(8) e per aumento della soglia del dolore pressorio a livello del tunnel carpale a 3,6 e 9 mesi(2), rispetto al gruppo di controllo; Entrambi gli studi avevano un basso rischio di Bias per ogni outcome, ad eccezione del non chiaro blinding di alcuni outcome, dei partecipanti e personale.

- 1 revisione sistematica con metanalisi (solo per i self-reported outcome) che comprendeva 12 RCTs inerenti al trattamento conservativo della CTS, confrontava le 'TN' ad altri trattamenti conservativi e le 'TN' non si erano mostrate superiori per gli outcome presenti in metanalisi (VAS, DASH), ma solo nei parametri elettrofisiologici e nella riduzione dell'edema intraneurale(15).
- 2 revisioni sistematiche, che comprendevano 9(16) e 6 (17) RCT, confrontavano le 'TN' con l' uso di splint(16,17), tendon glide + splint(16), splint + ultrasuoni e vero gruppo di controllo(17); tutti e 2 gli studi non rilevavano nessuna differenza significativa tra i gruppi di intervento e gruppi di controllo in termini di dolore, esame clinico, qualità sensibilità tattile, forza e parametri elettrofisiologici, inoltre 1 studio(16) ha evidenziato una migliore performance funzionale nel solo uso di splint e nella combinazione di splint + tendon-glide rispetto al tensionamento distale del nervo mediano + splint.
- 1 Cochrane review , che comprendeva 16 RCT e confrontava esercizi e mobilizzazioni con altri trattamenti conservativi per la CTS, aveva riportato i risultati di 1 RCT di qualità molto bassa (14 pz.) che indagava l' effetto delle 'TN' e mobilizzazione del carpo rispetto al gruppo di controllo; tutti i pazienti del gruppo di intervento avevano riportato un miglioramento generale rispetto alla baseline mentre nessuno nel gruppo di controllo, ma secondo gli autori della revisione la precisione di questo effetto è molto bassa(3).
- 3 RCT verificavano l'effetto di diverse tecniche di terapia manuale senza 'TN': mobilizzazione di tessuti molli nei siti di entrapment, glide laterali e PA cervicali vs chirurgia(9), auto-massaggio 'Madenci' vs splint + esercizi di nerve e tendon glide + paracetamolo(10) e manipolazione fasciale vs laser(11); rispettivamente, il gruppo di intervento del primo studio menzionato, si è mostrato superiore per aumento funzionalità e forza a 1 un mese(9), il secondo per riduzione del dolore e incremento di forza a 6 settimane(10) e il terzo per riduzione del dolore, severità dei sintomi e incremento della funzionalità a 1 e 3 mesi(11). Per il primo studio il Rob era basso per tutti gli item ad esclusione del blinding dei partecipanti che non è chiaro, il terzo studio ha un alto rischio di Rob per l'item 'random

sequence generation', non chiaro per 'allocation concealment' e basso per gli altri item; Il secondo studio invece ha un basso rischio di Rob per l' item 'allocation concealment' e 'incomplete outcome data', non chiaro per 'selective reporting' e alto rischio per gli altri item.

Terapia Strumentale

7 RCT(18–24) e 2 revisioni sistematiche(25,26) avevano come gruppo di intervento diverse tipologie di trattamento mediante terapia strumentale:

- 2 RCT indagavano l'efficacia del Laser a bassa potenza (LLLt); 1 lo confrontava con la magnetoterapia(18) mentre l'altro, in associazione con splint e vitamina B6, lo confrontava con lo 'sham' LLLt + splint e vit. B6 e splint + vit. B6 (19). Nel primo studio sia il gruppo di intervento (L) che il gruppo di controllo (M) hanno avuto riduzione significativa dell'intensità del dolore, solo il gruppo L ha avuto miglioramenti nella positività del Phalen's test e solo nel gruppo M c'era stata una riduzione delle parestesie notturne e diurne a 2, 4, 6 sett. e a 6 mesi di follow up(18); nel secondo studio invece tutti i gruppi sono migliorati significativamente per tutti gli outcome misurati (parametri elettrofisiologici, esame clinico, intensità del dolore, severità dei sintomi e funzionalità) e non sono state trovate differenze significative tra i 3 gruppi a 2 e 8 sett.(19). Il primo studio ha un Rob alto per tutti gli items ad eccezione del 'selective reporting' non chiaro, mentre il secondo ha un rischio non chiaro per 'allocation concealment' e 'incomplete data' e un basso rischio per gli altri items.
- 3 RCT verificavano l'efficacia di diversi tipi di elettroterapia; 1 paragonava le TENS con il placebo(23), 1 le correnti inferenziali (IFC) con le TENS e l'uso di splint(24) e l'ultimo l'elettro-agopuntura in aggiunta allo splint con il solo utilizzo di splint(21). Il primo valutava l'attivazione di specifiche aree cerebrali associate a dolore tramite fRMN e ha riscontrato una riduzione di segnale significativa nel gruppo trattato con TENS dopo 20'(23); il secondo studio riferiva un miglioramento significativamente superiore del gruppo IFC nella intensità del dolore e parametri elettrofisiologici rispetto agli altri 2 gruppi, e nella severità dei sintomi e

funzionalità rispetto al gruppo trattato con TENS a 3 sett.(24). Nel terzo studio il gruppo di intervento si è dimostrato significativamente superiore al gruppo di controllo per riduzione severità dei sintomi a 5 e 17 sett., per riduzione di disabilità,intensità del dolore, destrezza e incremento di forza a 17 sett.(21); Il primo studio ha un alto Rob per i 2 items del 'selection bias', il secondo studio ha alto rischio per la 'random sequence generation' e non chiaro per l' 'Allocation concealment' e 'incompleted outcome data' e l'ultimo ha alto rischio sia per il 'blinding partecipant's' che per il 'blinding of outcome assessment' riferiti ai parametri clinici, e un non chiaro 'incompleted outcome data'.

- 2RCT e 2 revisioni sistematiche hanno riportato evidenze su diversi trattamenti strumentali; 1 RCT, che paragonava splint + ultrasuono, splint + LLLt e solo splint, riferiva che i primi 2 gruppi hanno avuto un miglioramento statisticamente significativo della funzionalità, severità dei sintomi, dolore e parametri elettrofisiologici rispetto al gruppo 'solo splint' a 1 e 3 mesi(27); Il Rob era non chiaro per 'selection bias' ed 'incompleted outcome data' e alto per 'blinding of partecipants' . Nell'altro RCT la diatermia si era rilevata statisticamente superiore al placebo per riduzione del dolore, severità dei sintomi e miglioramento della funzionalità e esame clinico a 3 sett.(22); in questo studio c'era un alto Rob per la voce 'blinding of partecipants' e 'incompleted outcome data'. Le 2 revisioni sistematiche erano dello stesso autore e comprendevano complessivamente 48RCT e 4 revisioni sistematiche sull'efficacia di numerevoli trattamenti conservativi per la CTS; una revisione aveva il 55% di RCT di alta qualità(25) e riportava evidenze moderate sull'efficacia dell'ultrasuono a medio termine, mentre l'altra, che aveva il 77% di articoli di alta qualità(26), rilevava una superiorità significativa dell'ultrasuono vs iniezioni di cortisone + splint nella forza, dell'ipertermia vs placebo nella severità dei sintomi a breve termine e moderate evidenze in favore delle onde d'urto vs splint e placebo (VAS, BCTQ-SSS-FSS) e vs ultrasuoni (BCTQ-SSS) a medio termine; RCT indagava l'effetto a lungo termine.
- 1 RCT aveva come gruppo d' intervento l'utilizzo di onde radio eco-guidate e come gruppo di controllo l'utilizzo di splint. Il dolore diminuiva

significativamente più rapidamente nel gruppo di intervento e a 1-4-8 e 12 sett. l'intensità del dolore e la funzionalità erano migliori(20); la mancanza di 'blinding of partecipants' dava un alto Rob per la scala VAS.

Esercizio

4 RCT(28–31) e 3 revisioni sistematiche(3,32,33) hanno valutato l'efficacia di esercizi neuro dinamici , da soli o in associazione con altri interventi, per il trattamento della CTS:

- 1 RCT e 1 revisione sistematica con 13 RCT, avevano come gruppo d'intervento solo esercizi di neuro-tensione e come gruppo di controllo, rispettivamente, l'utilizzo di splint(31) e altre modalità di trattamento di terapia strumentale e manuale(32). Nell' RCT entrambi i gruppi sono migliorati per riduzione di edema intraneurale e miglioramento dei sintomi e funzione(31), mentre nella revisione veniva riportato un miglioramento per il dolore e soglia del dolore pressorio in seguito ad esercizi neurodinamici ma, se paragonati ad altre terapie, i risultati erano contrastanti: significativamente peggiori in termini di dolore e funzione rispetto a terapia standard e splinting e migliori rispetto ad ultrasuoni e splinting per gli stessi outcome riferiti sopra(32). Nella revisione 6 articoli su 13 avevano punteggi da 5 a 11 al PEDro score, mentre l'RCT aveva un basso Rob, ad eccezione della 'Random sequence generation' non chiara.
- 2 RCT hanno verificato l'efficacia di esercizi neurodinamici in associazione con splint(29) e splint + esercizi di scivolamento tendineo(28) rispetto a il solo esercizio neuro dinamico e splint + iniezioni di cortisone(28) e splint + esercizi di glide tendineo(29), mentre un altro RCT(30) paragonava esercizi neurodinamici + paraffinoterapia + splint con esercizi di scivolamento tendineo + paraffinoterapia + splint e solo paraffino terapia + splint; evidenze in favore della associazione di splint + esercizi neurodinamici e scivolamento tendineo e splint + iniezioni di cortisone, rispetto ai soli esercizi, per riduzione intensità del dolore, positività dell'esame clinico e miglioramento funzionalità ad 8 sett.(28); evidenze in favore di esercizi di glide tendineo + splint nella funzionalità

rispetto a quelli neuro dinamici a 1 e 6 mesi(29); evidenze in favore di esercizi di glide tendineo + paraffino-terapia + splint nella funzionalità rispetto agli esercizi neuro dinamici + paraffino-terapia + splint a 8 sett.(30). Uno studio aveva un alto Rob per 'blinding of partecipants and personnel' e 'selective reporting'(28) e gli altri 2 un alto Rob per 'incomplete outcome data'(29,30).

- 1 Cochrane review, già descritta precedentemente, riporta i risultati di 1RCT (26pz) di qualità molto bassa: nel gruppo in cui i polsi maggiormente affetti da CTS sono stati trattati con esercizi di nerve-glide + splint ed educazione non sono stati trovati parametri elettrofisiologici patologici rispetto al gruppo che aveva ricevuto solo splint + educazione, ma non era stata considerata la correlazione tra i polsi dei pazienti con CTS bilaterale (3); inoltre l'autore della revisione affermava che le evidenze in favore degli esercizi per la CTS sono limitate e di scarsa qualità. Un'altra revisione sistematica di 4 RCT, con Rob da basso a moderato, ha riportato una riduzione della severità dei sintomi e un incremento della funzionalità, nei gruppi trattati con esercizi di nerve e tendon gliding + trattamenti convenzionali, rispetto ai gruppi che avevano ricevuto solo trattamenti convenzionali(33).

Trattamento farmacologico

1RCT(34) e 1 revisione sistematiche(25) (26 RCT e 2 revisioni sistematiche) affrontavano il trattamento farmacologico per la CTS:

- l'RCT paragonava l'efficacia di corticosteroidi (CS) o FANS veicolati tramite fonoforesi e l'utilizzo del solo splint; il gruppo a cui venivano veicolati i CS dimostravano una riduzione significativa dell'edema intraneurale, funzionalità ed esame clinico ma anche un peggioramento di alcuni parametri elettrofisiologici a 3 mesi; mentre entrambi i gruppi hanno riportato una significativa riduzione di dolore e severità dei sintomi a 3 mesi(34). Il Rob, per questo studio, era basso nel blinding of outcome assessment' e 'reporting bias', alto nel 'performance bias' per tutti gli outcome e non chiaro per i rimanenti items.

- Il 55% degli RCT presenti nella revisione sistematica erano di alta qualità e ha riferito evidenze da forti a moderate a breve termine per l'uso di steroidi per via orale (funzionalità) e tramite iniezione (miglioramenti clinici) mentre non avevano alcuna evidenza a lungo termine(25).

Trattamento Multimodale

1RCT verificava l'efficacia di farmaci (FANS e CS) in associazione con splint, esercizi, terapia manuale, ultrasuoni ed educazione sulla CTS, rispetto al trattamento chirurgico(35). Le evidenze a lungo termine erano in favore della chirurgia per riduzione severità dei sintomi e incremento funzionalità a lungo termine, mentre a medio termine non vi erano differenze significative. Lo studio ha un Rob basso per ogni items.

La descrizione dettagliata degli studi inclusi nella revisione è riportata nella tabella riassuntiva (Tab. 1), mentre le tabelle Rob e AMSTAR sono consultabili in Appendice.

Tab.1. Tabella riassuntiva RCT e revisioni sistematiche. Gli studi sono riportati in ordine alfabetico (nome autore), prima RCT e poi Revisioni sistematiche.

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
Baker 2012 'The Comparative Effectiveness of Combined Lumbrical Muscle Splints and Stretches on Symptoms and Function in Carpal Tunnel Syndrome'	RCT	Pz= 124 (d.o. 21), 53.3 ± 11.8 anni, con CTS lieve o moderato, no comorbilità	**LspLst** (n=31, d.o. 5) Splint lombricali notturno + stretching lombricali 6/dia a casa per 4 settimane - **GspLsp** (n=34, d.o. 4) Splint standard notturno + stretching lombricali 6/dia a casa per 4 settimane - **LspGst** (n=31, d.o. 8) Splint lombricali notturno + stretching generico 6/dia a casa per 4 settimane	- **GspGst** (n=28, d.o. 5) Splint standard notturno + stretching generico 6/dia a casa per 4 settimane	-Sintomi e funzione (CTQ-S-F, DASH) -intervento chirurgico a 24 settimane	- 4 sett. - 12 sett. - 24 sett.	Miglioramenti stat. significativi nel tempo per tutti gli outcome a 4,12 e 24 sett. ($p<0.001$) Differenze significative nei gruppi **GspLsp** e **LspGst** rispetto agli altri 2 gruppi nel CTQ-F($p=0.04$) e DASH ($p=0.05$) Sono riportati grafici in cui il gruppo **GspLsp** sembra essere migliore a 24 sett. nel CTQ-F e DASH rispetto alle altre combinazioni, ma non è un dato quantitativo. A 24 sett. il 25% dei pz. è ricorso a chirurgia
Bardak 2009 'Evaluation of the Clinical Efficacy of Conservative Treatment in the Management of	RCT	Pz= 145 (111 mani), 49.14±9.6 età, con diagnosi di CTS moderato, no comorbilità	**-Gruppo 2** (n=35) come gruppo 1 + esercizi di tendon-nerve glide 3/dia per 6 settimane	**Gruppo 1** (n=41) iniezione 3 mg di betamethason e + Splint indossato	- sintomi: punteggio chiamato **STP score** che indaga dolore alla mano,	- 8 sett.	- riduzione positività di tutti i test dell'esame fisico standard in gruppo 1 e 2 (tranne Tinel's test nel 2) ($p<0.05$). - miglioramento STP score e FSS Gruppo 1 e Gruppo 2 comparati con il Gruppo 3 e ($p<0.001$). No differenze statistica mente significative tra Gruppo 1 e gruppo 2.

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
Carpal Tunnel Syndrome'			**-Gruppo 3** (n=33) solo esercizi di glide tendineo e nervo mediano 3/dia per 6 settimane	giorno e notte per 3 settimane e solo la notte per altre 3 settimane (tot. 6 sett.)	tingling, numbness, numbness notturno e sonno interrotto - funzione: punteggio chiamato **FSS** che indaga attività come scrivere, abbottonarsi i vestiti, afferrare un telefono, aprire barattoli, fare lavori di casa, portare borse della spesa e fare il bagno - Esame fisco standard (Tinel's test, Phalen's test, reverse Phalen's test, compression test)		
Bialosky 2009 'A Randomized Sham-Controlled Trial of a Neurodynamic	RCT	Pz= 40, donne, 46.90 ±10.25 età, con segni e sintomi di CTS, no comorbilità	- NDT (n=20): tecniche neuro dinamiche (in ULNT1) dirette a stressare significativame	-Sham NDT (n=20): tecniche neurodinamich e con minimo stress su	- aspettativa del paziente (PCOQ) -percezione del dolore	- durante la seduta -3 sett.	-riduzione statistica mente significativa percezione dolorosa durante la seduta di trattamento indipendentemente dal gruppo di assegnazione (p 0.01) -riduzione sommazione temporale statistica mente

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Technique in the Treatment of Carpal Tunnel Syndrome'			nte il nervo mediano + splint al polso per 3 sett.	nervo mediano + splint al polso per 3 sett.	(NRS, MVAS) -soglia dolore alla pressione con presso algometro (MVAS) - soglia dolore termico(MVAS) e sommazione temporale (NRS) -Funzione (DASH) -Stato neurologico (Grip Strength, Semmes-Weinstein monofilament test, NCS)		significativa nella valutazione del dolore termico solo nel gruppo NDT a 3 sett. (P 0.01) - Miglioramento statistica mente significativo nella percezione del dolore (NRS) e nella funzionalità (DASH) in entrambi i gruppi a 3 sett. (p 0.02)
Bulut 2015 'Comparison of static wrist splint with static wrist and metacarpophalangeal splint in carpal tunnel syndrome'	RCT	Pz=33(54 mani), con diagnosi clinica di CTS confermata da esame elettrofisiologico, no comorbilità	-Gruppo 2 pz=17(27 mani), 46.4 ± 7.8 età: splint volare al polso e MCF notturno per 4 sett.	-Gruppo 1 pz=16 (27 mani), 42.4 ± 10.1 età: splint volare al polso notturno per 4 sett.	- dolore (VAS) -forza (grip e pinch strength) -Funzionalità (CTSQ) -test	4-sett.	- differenza statistica mente significativa per la VAS(p 0.029), grip (p 0.001) e pinch strength (p 0.000), CTSQ(0.002) in favore del gruppo 2 rispetto al gruppo 1. Miglioramento statistica mente significativo del test elettrofisiologico in entrambi i gruppi.

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
					elettrofisiologico		
Chen 2015 'Ultrasound-Guided Pulsed Radiofrequency for Carpal Tunnel Syndrome: A Single-Blinded Randomized Controlled Study'	RCT	Pz= 44 (d.o. 8) con diagnosi clinica ed elettromiografica di CTS. No comorbilità	Pz= 22(d.o. 4) 54.8 ± 4.4 età: Splint per 12 sett. da indossare la notte e 8h/dia x 12 sett. + singola esposizione di 120'' a una frequenza (2hz) radio-pulsata (20 ms) eco-guidata del nervo mediano. Il nervo è monitorato anche nei successivi 30' dopo la procedura.	Pz=22(d.o.4) 57.3 ± 5 età: solo splint per 12sett. da indossare la notte e 8h/dia x 12 sett.	Primario -il tempo d'inizio di sollievo dal dolore e severità del dolore (VAS) Secondario -funzionalità e severità dei sintomi (BCTQ) -CSA del nervo mediano (ecografia) -SNVC -Finger pinch (dinamometro)	-1 sett. -4sett. -8 sett. -12 sett.	- il tempo d'inizio di sollievo dal dolore nel gruppo d'intervento era significativamente più breve (2gg vs 14gg, p<0.001), rispetto al gruppo di controllo -Miglioramento significativo nei punteggi VAS e BCTQ (p <0,05) in tutti i follow up, ad eccezione della sottoscala di gravità del BCTQ-SSS alla prima settimana, comparato con il gruppo di controllo.
Chung 2016 'Electroacupuncture and splinting versus splinting alone to treat carpal tunnel syndrome: a randomized controlled trial'	RCT	Pz= 181(d.o.7), con diagnosi clinica di CTS, no comorbilità	Gruppo1 Pz=90 (d.o.5) 51 ±10.2 età: splint prefabbricato con polso in posizione neutra da indossare tutte le sere per 8 ore per 17	Gruppo2 Pz=91 (d.o.2) 51 ± 8.7 età: splint prefabbricato con polso in posizione neutra da indossare tutte le sere per 8 ore per 17	Primario -severità dei sintomi (BCTQ-SSS) Secondari -Funzionalità (BCTQ-FSS) -DASH	-1 sett. -2 sett. -5 sett. -17 sett.	Il gruppo 1 risulta avere un lieve miglioramento stat. significativo rispetto al gruppo 2 nel BCTQ-SSS a 5 e 17 sett. (p=0.04) e BCTQ-FSS (p=0.01), DASH (p<0.01), NRSp (p=0.03), Dellon modified pick-up test (p<0.01), tip pinch strength (p<0.01) alla 17 sett.

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
			sett. + elettro-agopuntura (il protocollo non è disponibile)	sett.	-intensità del dolore (NRSp) -sensibilità (Semmes-Weinstein monofilament test) -destrezza (Dellon-modified pick-up test) -massima tip-pinch strength		
Dakowicz 2011 'Comparison of the long - term effectiveness of physiotherapy programs with low - level laser therapy and pulsed magnetic field in patients with carpal tunnel syndrome'	RCT	Pz= 38 (61 mani), 50.8±10.3 età, con diagnosi clinica confermata da esame elettroneurografico (ENG). No comorbilità	- Gruppo L pz=18 (27 mani): LLLT 904 nm, effettuato per 5 minuti e 33 sec. (non si capisce dove). 2 cicli di 5 sedute a sett. per 2 sett. Tra il Ciclo1 e il Ciclo2 sono trascorse 2 settimane.	-Gruppo M pz=20 (34 mani): magnetoterapia 10-40hz per 15 minuti (non si capisce dove). 2 cicli di 5 sedute a sett. per 2 sett. Tra il Ciclo1 e il Ciclo2 sono trascorse 2 settimane.	- parestesia diurna e notturna -dolore notturno e diurno - Intensità del dolore (VAS) Phalen's, Tinel's e armband tests -ENG	-dopo Ciclo1 -dopo le 2 sett. di stop tra ciclo1 e 2 - dopo Ciclo2 -6 mesi dopo fine Ciclo2	-significativa riduzione di dolore notturno e diurno, della intensità della Vas a tutti i follow up e della positività al Phalen's test al secondo follow up nel gruppo L ($p<0.05$) . L'intensità della Vas era ridotta in modo significativo anche nel gruppo M a tutti i follow up e inoltre risultavano ridotti anche le parestesie notturne e diurne al secondo e quarto follow up ($p<0.05$)
Dincer 2009 'The Effectiveness of Conservative Treatments	RCT	Pz=50 (100 mani), Donne, con diagnosi di CTS lieve e moderato	-Gruppo 2 Pz=15(30 mani), 49.7± 9.5 età: come gruppo 1	-Gruppo 1 Pz= 17(34 mani), 51.8 ± 6.6 età: solo splint	- Sintomi e Funzione (BCTQ-SSS, BCTQ-FSS)	-1 mese -3 mesi	-Il gruppo 2($p=0.04$) e 3($p<0.0001$) hanno dimostrato miglioramenti significativi nel BCTQ-SSS a 1 mese e 3 mesi dal trattamento rispetto al gruppo 1, inoltre risulta significativa anche la differenza tra gruppo 2 e 3 ($p=0.03$).

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
of Carpal Tunnel Syndrome: Splinting, Ultrasound, and Low-Level Laser Therapies'		bilaterale effettuata tramite esame clinico e elettroneuromiografia. No comorbilità	+ 10 applicazioni di US a 3 Hz, 3 minuti nell'area del tunnel carpale, 5 volte a sett. per 2 sett. -Gruppo 3 Pz=18(36 mani), 52.2 ± 9.1 età: come gruppo 2+ applicazioni di LLL therapy 904 nm, in 3 punti (30''per punto) lungo il decorso del nervo mediano, 5 volte a sett. per 2 sett.	notturno e all'aggravarsi dei sintomi anche diurno per 3 mesi.	-Dolore (VAS) -Soddisfazione del paziente -ENMG		-entrambi i gruppi 2-3 hanno dimostrato miglioramenti significativi rispetto al gruppo 1 nel BCTQ-FSS e nella Vas ($p<0.0001$) e all'ENMG ($p=0.006$ gruppo2, $p<0.0001$ gruppo3)
Fernández-de-las-Peñas 2015 'Manual Physical Therapy versus Surgery for Carpal Tunnel Syndrome: a Randomized Parallel-Group Trial'	RCT	Pz=120 (d.o. 9), donne, , con diagnosi clinica ed elettromiografica di CTS, no comorbilità	-Gruppo 1 Pz 60 (d.o. 5), 47 ± 10 età: 3 trattamenti di terapia manuale, incluse manovre di desensibilizzazione del SNC (mobilizzazione tessuti molli nei siti di entrapment, nerve/tendon glide),di 30',1 a sett. per 3 sett. +	-Gruppo 2 Pz 60 (d.o.5), 46 ± 9 età: decompressione e/o release chirurgica del tunnel carpale in endoscopia o a cielo aperto.	Primario: -Dolore a 1 anno (NRSp) Secondario: -severità sintomi e funzione (BCTQ-SSS,BCTQ-FSS) -Miglioramento auto-percepito	-1 mese -3 mesi -6 mesi -12 mesi	-Miglioramento significativo a vantaggio del gruppo 1 rispetto al gruppo 2 sia per il dolore sia per la funzione a 1 e 3 mesi ($p=0.01$) Non ci sono differenze significative tra i due gruppi a 6 e 12 mesi per nessun outcome.

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
			insegnata automobilizzazione a casa.		(GROC)		
Fernández-de-las-Peñas, Mar. 2017 'Effectiveness of manual therapy versus surgery in pain processing due to carpal tunnel syndrome: A randomized clinical trial'	RCT	Pz=100 (d.o.5), donne, con diagnosi clinica ed elettromiografica di CTS, no comorbilità	-Gruppo1 Pz 50 (d.o.3),47 ±10 età: : 3 trattamenti di terapia manuale, incluse manovre di desensibilizzazione del SNC (mobilizzazione tessuti molli nei siti di entrapment, nerve/tendon glide),di 30',1 a sett. per 3 sett. + insegnata automobilizzazione a casa.	-Gruppo2 Pz 50(d.o.2),48 ± 9 età: decompressione e/o release chirurgica del tunnel carpale con metodica a preferenza del chirurgo e del pz. + insegnati gli stessi esercizi da fare a casa del gruppo1	Primario: -PPT a livello del tunnel carpale e nervo mediano (algometro elettronico) Secondario: -HTP (Thermotest System) -intensità del dolore (NRSp)	-1 mese -3 mesi -6 mesi -9 mesi -12 mesi	Il gruppo 1 mostrava un aumento, stat. significativo più alto, di PPT a livello del tunnel carpale (non su nervo mediano) a 3, 6 e 9 mesi (tutti, p <0,01) e maggiore diminuzione della intensità di dolore a 3 mesi (p <0,001) rispetto al gruppo2. Nessuna differenza significativa è stata osservata tra i 2 gruppi per gli outcome rimanenti
Fernández-de-las-Peñas, Aug. 2017 'The Effectiveness of Manual Therapy Versus Surgery on Self-reported Function, Cervical Range of Motion, and Pinch Grip Force in Carpal Tunnel Syndrome: A Randomized Clinical Trial'	RCT	Pz=100 (d.o.6), donne, con diagnosi clinica ed elettromiografica di CTS, no comorbilità	-Gruppo1 Pz 50 (d.o.3), 46 ± 9 età : 3 trattamenti di terapia manuale tra cui manovre mirate al rachide cervicale (glide laterali e pa) e a quelle aree anatomicamente correlate a potenziale	-Gruppo2 Pz 50(d.o.3), 47 ± 8 età: decompressione e/o release chirurgica del tunnel carpale con metodica a preferenza del chirurgo e del pz. + insegnati gli stessi esercizi da fare a casa del gruppo1	Primario: -funzionalità a 12 mesi (BCTQ-FSS) Secondario: -severità dei sintomi(BCTQ-SSS) -ROM cervicale (CROM device)	-1 mese -3 mesi -6 mesi -12 mesi	- Differenza stat. significativa al BCTQ-FSS(*P*<.001) e pinch-tip grip force (P=0.01,P=0.036 a 1 mese in favore del gruppo1. -Non ci sono altri cambiamenti stat. significativi tra i due gruppi per gli altri outcomes nei 4 follow up.

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
			intrappolamento del nervo mediano (cioè spalla, gomito, avambraccio, polso e dita), della durata di 30', una volta a sett. per 3 sett. + insegnato auto mobilizzazione a casa.		-Pinch-tip grip force (dinamometro)		
Heebner 2008 'The Effects of Neural Mobilization in Addition to Standard Care in Persons with Carpal Tunnel Syndrome from a Community Hospital'	RCT	Pz= 60(d.o.31), età compresa 32-75, con diagnosi clinica ed elettromiografica di CTS, no comorbilità	-Gruppo2 Pz= 32 (d.o.18): come Gruppo1+ esercizi neurodinamici per il nervo mediano a casa da effettuare tutti i giorni, 10 rip. da mantenere per 5'' 3-5 volte dia.	-Gruppo1 Pz= 28 (d.o. 13): splint volare con polso in posizione neutra da indossare la notte e nelle ADL pesanti + 8 esercizi di tendon-glide (sviluppati da Totten e Hunter) da effettuare tutti giorni, 10 rip. per 3-5 volte dia.	-Funzionalità (DASH, BCTQ-FSS) -Severità dei sintomi (BCTQ-SSS) - Rom del gomito in ULNT 1	-1 mese -6 mesi	-Gruppo1 ha avuto un miglioramento stat. significativo al BCTSQ-FSS (p=0.016) rispetto al Gruppo2. -Non ci sono differenze per gli altri outcome
Horng 2011 'The Comparative Effectiveness of Tendon and Nerve Gliding	RCT	Pz= 60(d.o.7), con diagnosi clinica ed elettromiografica di CTS, no comorbilità	-Gruppo1 Pz= 20 (d.o.2) 48.9 ± 8.9 età: paraffino-terapia e splint notturno (8	-Gruppo3 Pz= 20 (d.o.4) 52.6 ±9.1 età: paraffino-terapia e splint notturno (8	-Funzionalità (DASH, BCTQ-FSS) -Severità dei sintomi	-8 sett.	-Tutti e 3 i gruppi hanno dimostrato miglioramenti stat. Significativi, rispetto alla baseline, nel BCTQ-SSS,VAS, WHOQOL (dominio ambientale)-BREF-NCS ($p<0.05$), mentre solo il Gruppo1 nel BCTQ-FSS, DASH e WHOQOL (dominio fisico) ($p<0.05$)

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
Exercises in Patients with Carpal Tunnel Syndrome'			sett.) + istruiti su esercizi di tendon-glide da effettuare a casa tutti i giorni, 3 volte dia per 5 volte mantenendo la posizione per 7'' (8 sett.) -Gruppo2 Pz= 20 (d.o.1) 51.9± 9.3 età: paraffino-terapia e splint + istruiti su esercizi di nerve-glide da effettuare a casa tutti i giorni, 3 volte dia per 5 volte mantenendo la posizione per 7'' (8 sett.)	sett.)	(BCTQ-SSS) -Intensità del dolore (VAS) -Stato di salute e qualità della vita (WHOQOL-BREF) - esame fisico: *Phalen's test *Tinel's sign *grip strength (dinamometro) * Semmes-Weinstein monofilament test -NCS		-Il Gruppo1 ha dimostrato differenze stat. Significative rispetto al gruppo2 solo nel BCTQ-FSS.
Incebiyik 2015 'Short-term effectiveness of short-wave diathermy treatment on pain, clinical symptoms, and hand function in patients with mild or moderate idiopathic carpal tunnel	RCT	Pz= 28(52 mani)(d.o.3, 6 mani), donne, con diagnosi clinica ed elettromiografica di lieve o moderato CTS, no comorbilità	-Gruppo1 Pz= 15 (28 mani) 51 ± 10.07 età: 15' d'impacco caldo sul legamento carpale trasverso + 15' di SWD a un intensità variabile (il parametro era la sensazione	-Gruppo2 Pz= 16 (24 mani)(d.o. 3, 6 mani) 44.92±10.84 età: 15' d'impacco caldo sul legamento carpale trasverso + 15' di placebo SWD, con l'apparecchio	-Intensità del dolore (VAS) -Funzionalità (BCTQ-FSS) -Severità dei sintomi (BCTQ-SSS) - esame fisico:	-3 sett.	- Gruppo 1 ha dimostrato una differenza stat. Significativa tra la baseline e la fine del trattamento per tutti gli outcome ($p<0.001$) e rispetto al Gruppo 2 a fine trattamento ($p<0.05$)

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
syndrome'			confortevole di calore del pz.) + 10 rip. di nerve/tendon glide per 3 sett.	spento + 10 rip. di nerve/tendon glide per 3 sett.	*Phalen's test *reverse Phalen's test *carpal compression *Tinel sign		
Jarvik 2009 'Surgery versus non-surgical therapy for carpal tunnel syndrome: a randomised parallel-group trial'	RCT	Pz =116(d.o.13) 50,7 età media, con diagnosi clinica ed elettromiografica di CTS, no comorbilità	Pz. 57 (d.o. 8) 51,2 età media: terapia multimodale medica e fisioterapica. therapist: ibuprofene 200 mg/3x /dia), oppioidi e corticosteroidi + brochure con indicazioni su gestione del CTS, esercizi, stretching, tendon gliding, splint al polso e modifica delle attività lavorative(6 visite/6 sett.) + ultrasuono (pulsato, 1Mhz) se non si riscontrano miglioramenti dopo 6 sett. di trattamento (max. 12-15 min a sessione; 2–4 applicazioni a sett./6 sett.)	Pz 57 (d.o.5) 50,2 età media: Chirurgia aperta o in endoscopia a discrezione del chirurgo + esercizi di tendon/nerve gliding	Primario: -Funzione (BCTQ-FSS) Secondario: -Severità dei sintomi (BCTQ-SS S) -intensità dolore (NRS); -interferenza del dolore nel lavoro o lavori di casa(NRS) - assenteismo da lavoro (0–28) - limitazione ADL e qualità di vita generale (SF-36).	-6 mesi -12 mesi	- A 12 mesi il gruppo chirurgico ha dimostrato una migliore funzionalità (BCTQ- fss, p=0.0081) e una riduzione della severità dei sintomi (BCTQ-SS S, p=0.0357) stat.significativa rispetto al gruppo di terapia multimodale. Non ci sono differenze stat. Significative per gli altri outcome a nessun follow up.
Kara 2010	RCT	Pz = 20 (d.o. 2),	Gruppo TENS	Gruppo 'sham'	differenza di	-20 minuti	Riduzione del segnale di attivazione aree corticali

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'Quantification of the Effects of Transcutaneous Electrical Nerve Stimulation With Functional Magnetic Resonance Imaging: A Double-Blind Randomized Placebo-Controlled Study'		donne, con diagnosi clinica ed elettromiografica di CTS, no comorbilità	Pz = 10 (d.o. 1) 49 ± 16.7 età: valutazione attivazione aree corticali del dolore con fMRI e successivo trattamento di 30' TENS a livello del nervo mediano (100 hz). 20' dopo il trattamento viene rivalutata l'attivazione corticale con fMRI	TENS Pz = 10 (d.o. 1), 51.8 ± 3.2 età: valutazione attivazione aree corticali del dolore con fMRI e successivo trattamento di 30' di 'Sham 'TENS (senza passaggio di corrente) a livello del nervo mediano (100 hz). 20' dopo il trattamento viene rivalutata l'attivazione corticale con fMRI	attivazione aree corticali del dolore (fMRI)		associate al dolore solo nel gruppo TENS ($p<0.001$)
Koca 2014 'Assessment of the effectiveness of interferential current therapy and TENS in the management of carpal tunnel syndrome: a randomized controlled study'	RCT	Pz= 75 (d.o. 12) con diagnosi clinica ed elettromiografica di CTS, no comorbilità	Gruppo2: Pz= 25 (d.o. 5) 34.2±5.2 età: 20' di TENS (100HZ) con elettrodo - su legamento carpale e quello + sulla faccia palmare della mano, 5 volte /sett. per 3 sett. Paracetamolo al bisogno	Gruppo 1: Pz= 25 (d.o. 3) 35.4±4.2 età: splint notturno per 3 sett. Paracetamolo al bisogno (1g/dia)	-Esame elettroneurofisiologico (mMDL e mSNCV) -livello medio di dolore a mano e dita (VAS) -Severità dei sintomi (BCTQ-SSS)	3 sett.	-tutti e 3 i gruppi hanno avuto miglioramenti stat. Significativi nella VAS, BCTQ e mSNCV ($p<0.05$) - il gruppo 3 si è dimostrato significativamente superiore al gruppo1 nella VAS (P=0.001), mMDL(P=0.001) e mSNCV (p=0.01) e al gruppo 2 nella VAS ($p = 0.001$), BCTQ-SSS ($p = 0.015$), BCTQ-FSS($p = 0.039$), mMDL($p = 0.003$) e mSNCV ($p = 0.021$). -No differenze tra gruppo 2 e gruppo 1

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
			(1g/dia) Gruppo 3 Pz= 25 (d.o. 4) 34.9± 4.8 età: 20' di IFC (4000hz con range di modulazione di 20 hz), 2 elettrodi posizionati sul 1/3 medio faccia volare avambraccio + 1 su faccia palmare della mano e 1 su eminenza tenar. 5 volte /sett. per 3 sett. Paracetamolo (1g/dia) al bisogno		-Funzionalità (BCTQ-FSS)		
Madenci 2012 'Reliability and efficacy of the new massage technique on the treatment in the patients with carpal tunnel syndrome'	RCT	Pz= 84 (151 mani) (d.o. 4) con diagnosi clinica ed elettromiografica di CTS. No comorbilità	Gruppo 1 Pz=42 (d.o. 2)43.4 ± 7.6 età : Splint (come gruppo 2) + auto-massaggio chiamato 'Madenci' (30'' effleurage + 30'' frizioni + 30'' petrissage + 30'' scuotimento +	Gruppo 2 Pz= 42 (d.o. 2) 44.2 ± 7.8 età: spint notturno polso-mano per 6 mesi, esercizi di tendon/nerve gliding giornalieri; paracetamolo, (1g/dia) al bisogno.	-funzionalità e severità dei sintomi (BCTQ-FSS e SSS); -Intensità del dolore (PGA 0-10mm, MDPGA 0-10mm) - grip strength della mano (dinamometr	- 6 sett	-L'intensità del dolore (PGA, MDPGA) e la grip strength sono significativamente migliorati in entrambi i gruppi (p=0.001) rispetto alla baseline, ma confrontando i 2 gruppi, il gruppo 1 risulta avere un miglioramento significativamente superiore per questi 2 outcome (p<0.05) -No differenze stat. significative per gli altri outcome

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
			30'' effleurage) insegnato da un fisioterapista o da un fisiatra, per 6 sett.; esercizi di tendon/nerve gliding; paracetamolo, (1g/dia) al bisogno.		o) - Esame elettroneurofisiologico (mMDL e mSNCV)		
Pratelli 2015 'Conservative treatment of carpal tunnel syndrome: Comparison between laser therapy and fascial manipulation'	RCT	Pz= 42 (70 mani), età media 54.2 (38-74anni), con diagnosi clinica ed elettromiografica di CTS. No comorbilità	Gruppo A 35 mani : tre sessioni di manipolazione fasciale per 45', 1/sett. per 3 sett. La tecnica consiste in frizioni profonde su punti specifici (da 4 a 8) della superficie massima di 2 cm. I punti vengono selezionati in base alla palpazione del terapista. Ai pazienti è permesso assumere i loro abituali farmaci.	Gruppo B 35 mani: 5 sedute giornaliere di LLLT (780-830 nm) della durata di 10' ciascuna. Ai pazienti è permesso assumere i loro abituali farmaci.	- intensità del dolore (VAS) -funzionalità e severità dei sintomi (BCTQ)	-10gg dopo ultimo trattamento -3 mesi	Il Gruppo A, rispetto al GruppoB, ha dimostrato risultati stat. Significativi in termini di riduzione di dolore (VAS), severità dei sintomi e incremento della funzionalità (BCTQ) a 10 gg e 3 mesi di follow up ($p<0.0001$)
Rayegani SM 2013 'The Effects of	RCT	Pz= 50 , con diagnosi clinica ed elettromiografica	Laser Pz=18, 52±12 età:	Sham laser Pz= 15, 49±11 età:	- parametri elettrofisiologici (mMDL,mM	-2 sett. -8 sett.	-Tutti e 3 i gruppi hanno dimostrato miglioramento stat. Significativo in tutti gli outcome a entrambi i follow up ($p<0.05$)

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
Low Intensity Laser on Clinical and Electrophysiological Parameters of Carpal Tunnel Syndrome'		di CTS lieve e moderato. No comorbilità	10 sessioni di Laser(880 nm) della durata di 10' ciascuna, su 5 punti (120'' a punto) lungo il decorso del nervo mediano, per 2 sett. + splint con polso in posizione neutra, da indossare giornalmente per 4 sett.+ vitamina b6 giornalmente	10 sessioni di Sham-laser con l'apparecchio spento + splint con polso in posizione neutra, da indossare giornalmente per 4 sett .+ vitamina b6 giornalmente Splint Pz= 17, 47.±7 età: splint con polso in posizione neutra, da indossare giornalmente per 4 sett. .+ vitamina b6 giornalmente	CV, SNAP) - Phalen's and Tinel's tests - intensità del dolore (VAS) -Severità dei sintomi e funzione (BCTQ-SSS-FSS)		Non ci sono differenze significative fra i tre gruppi.
Schmid 2012 'Effect of Splinting and Exercise on Intraneural Edema of the Median Nerve in Carpal Tunnel Syndrome-An MRI Study to Reveal Therapeutic Mechanisms'	RCT	Pz= 21 (d.o.1) con diagnosi clinica ed elettromiografica di CTS lieve e moderato. No comorbilità	ESERCIZI Pz=11(d.o.1) 49.9±12.5 età: esercizi domiciliari di nerve gliding (descritti da Totten e Hunter) e tendon gliding (descritti da Wehbe). 10 sessioni/dia per 1 sett.	SPLINT Pz=10, 57.9± 16.3 età: splint prefabbricato notturno per 1 sett. STORIA NATURALE CTS (esperimento parallelo allo studio):	Primario -Edema intraneurale(intensità di segnale nervo mediano alla RMN) -misurazione legamento arcuato (RMN)	-10' dopo esercizi o splint -1 sett.	- stat. Significativo: Riduzione di edema intraneurale e (p= 0.03), miglioramento nei sintomi e funzione (p<0.004) in entrambi i gruppi

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
			Ogni sessione era composta da 10 rip. per ogni esercizio della durata di 2'.	Pz=5, 53.4±9.7 età: nessun intervento, solo indicazioni a rimanere attivi per 1 sett. Gli outcome alla RMN non hanno subito variazioni stat. Significative (p > 0.27, p= 0.81). Viene usato come confronto ma non ha fatto parte di questo studio per ragioni etiche.	Secondario: -severità dei sintomi e funzione (BCTQ-SSS,FSS) -intensità dolore e numbness (VAS)		
Sim S.E. 2018 'Short-term clinical outcome of orthosis alone vs combination of orthosis, nerve, and tendon gliding exercises and ultrasound therapy for treatment of carpal tunnel syndrome'	RCT	Pz=51(66 mani)(d.o.10, 10 mani), con diagnosi clinica ed elettromiografica di CTS lieve e moderato. No comorbilità	SPLINT+TERAPIA MULTIMODALE: Pz= 26 (34 mani)(d.o.5, 5 mani) 50.41±9.92 età: Splint (come altro gruppo)+ esercizi di tendon glide (descritti da Wehbe) e nerve glide (basati su studi biomeccanici	SOLO SPLINT: Pz=25(32 mani)(d.o.5, 5 mani) 56.6±13.9 età: Splint palmare da indossare tutto il giorno per 2 mesi. Lo splint può essere tolto per 1 ora al giorno	-severità dei sintomi e funzionalità (BCTQ-SSS-FSS)	-2 mesi	La severità dei sintomi e la funzionalità risultano significativamente migliorate in entrambi i gruppi: solo splint (BCTQ-SSS p=0,001,BCTQ-FSS p=0.001) splint + terapia multimodale (BCTQ-SSS p<0.001, BCTQ-FSS p<0.001) No differenze significative tra i 2 gruppi

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
			di Coppieters), 10 ripetizione per esercizio 10 volte/dia + 5' di ultrasuoni pulsati (1Mhz) nell'area carpale 1 volta/sett. per 8 sett.				
Soyupek 2011 'Determining the effectiveness of various treatment modalities in carpal tunnel syndrome by ultrasonography and comparing ultrasonographic findings with other outcomes'	RCT	Pz=47(74 mani)(d.o.4pz), con diagnosi clinica ed elettromiografica di CTS lieve e moderato. No comorbilità	FONOFORESI con CORTISONE (PCS) Pz=? (28 mani)(d.o.1 pz) 50.50 ± 8.71 età: betamethasone valerate % 0.1 in crema viene veicolato tramite fonoforesi. 10' 5 volte/sett. per 3 sett. Non sono ammessi altri trattamenti. FONOFORESI CON FANS (PNSAI) Pz=? (23 mani)(d.o. 1 pz) 53.79 ± 10.40 età: diclofenac diethylammonium in gel	SPLINT Pz=? (23 mani)(d.o.3pz) 47.95 ± 6.93 età: splint volare rigido con polso in posizione neutra da indossare giorno e notte per 2 sett. e poi solo quando il dolore è presente.	Primario -CSA, diametro trasverso e antero-posteriore del nervo mediano (ecografia) Secondari - Esame elettrofisiologico (mSDL, mMDL, mSNCV, mMNCV ,SNAP) - Phalen's e Tinel's Signs - intensità del dolore(VAS) - severità dei sintomi e funzionalità(BCTQ-SSS-	3 mesi	Le riduzioni della CSA, del diametro trasverso e AP del nervo mediano sono stati significativi solo nel gruppo PCS(p= 0.004) e sono correlati negativamente ad alcuni parametri elettrofisiologici (mMNCV e mSNCV p<0.05). Non ci sono altre correlazioni tra l'outcome primario e i secondari. -Il gruppo PCS e PNSAI hanno mostrato un miglioramento significativo nella intensità del dolore (P = 0,001) e al BCTQ-SSS (p=0.000), mentre solo il gruppo PCS anche al BCTQ-FSS (p=0.000) e presenza Phalen's(p=0.003) e Tinel's (p=0.001) Signs. -Il gruppo Splint ha avuto miglioramenti stat. significativi solo al BCTQ-SSS (p<0.017)

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
			viene veicolato tramite fonoforesi. 10' 5 volte/sett. per 3 sett. Non sono ammessi altri trattamenti.		FSS) Correlazione tra outcome primario e secondari		
Wolny 2016 'Effect of manual therapy and neurodynamic techniques vs ultrasound and laser on 2PD in patients with CTS: A randomized controlled trial'	RCT	Pz=160 (d.o.20), con diagnosi clinica ed elettromiografica di CTS lieve e moderato. No comorbilità	Gruppo1 Pz=80(d.o.10) TERAPIA MANUALE 53.1± 8.7 età: terapia manuale (massaggio funzionale del trapezio inferiore 30', tecniche di apertura e chiusura del polso 15' come descritto da Shacklock) e tecniche neurodinamiche (slider e tensioner nervo mediano in ULNT1 12') 2 volte a sett. per 10 sett.	Gruppo2 Pz=80(d.o.10) LASER 51.5±10.3 età: Red Laser 658 nm su 3 punti nell'area del legamento carpale trasverso per 120''+ laser infrarosso 808 nm per 60''(l'intera procedura ha durata di 8') + 15' di ultrasuono 1Mhz in modalità pulsata sulla superficie del legamento carpale trasverso. 2 volte a sett. per 10 sett.	-qualità della sensibilità tattile(2PD)	10 sett.	Entrambi i gruppi hanno dimostrato un miglioramento stat. significativo al 2PD ($p<0.001$) Nessuna differenza tra i due gruppi
Wolny 2017 'Efficacy of Manual Therapy Including Neurodynamic	RCT	Pz=160 (d.o. 20), con diagnosi clinica ed elettromiografica	Gruppo1 Pz=80 (d.o.10) 53.1± 8.7 età: terapia	Gruppo2 Pz=80 (d.o.10) 51.5 ±10.3 età: Red Laser	-NCS -intensità del dolore (NRSp)	1 mese (NCS) -10 sett. (NRSp,	Il guppo1 ha dimostrato miglioramenti significativi al NCS ($p<0.01$), mentre non ci sono state differenze significative nel gruppo2. Entrambi i gruppi hanno dimostrato miglioramenti

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
Techniques for the Treatment of Carpal Tunnel Syndrome: A Randomized Controlled Trial'		di CTS lieve e moderato. No comorbilità	manuale (massaggio funzionale del trapezio inferiore 30', tecniche di apertura e chiusura del polso come descritto da Shacklock) e tecniche neurodinamiche (slider e tensioner nervo mediano in ULNT1 3 serie per 60 rip.) 2 volte a sett. per 10 sett.	658 nm su 3 punti nell'area del legamento carpale trasverso per 120''+ laser infrarosso 808 nm per 60''(l'intera procedura ha durata di 8') + 15' di ultrasuono 1Mhz in modalità pulsata sulla superficie del legamento carpale trasverso. 2 volte a sett. per 10 sett.	- severità dei sintomi e funzionalità (BCTQ-SSS-FSS)	BCTQ-SSS-FSS)	significativi in tutti gli altri outcome a 10 sett. ($p<0.01$)
Wolny 2018 'Neurodynamic Techniques Versus "Sham" Therapy in the Treatment of Carpal Tunnel Syndrome: A Randomized Placebo-Controlled Trial'	RCT	Pz=180 (d.o. 30), con diagnosi clinica ed elettromiografica di CTS lieve e moderato. No comorbilità	TECHNICHE NEURODINAMICHE(TN) Pz=90 (d.o. 12), 54.2±9.48 età: gliding e tensioner mirati al nervo mediano con il braccio in posizione ULNT1; 3 serie di 60 rip. intervallate da 15'' di riposo, 2 volte a sett. per 10 sett.	TERAPIA-''SHAM''(TS) Pz=90 (d.o. 18), 52.2±10.4 età: tecniche neurodinamiche in posizione intermedia per ogni articolazione rispetto all'ULNT1 e senza una sequenza corretta. 3 serie di 60 rip. intervallate	-NCS -intensità del dolore (NRSp) - qualità sensibilità tattile (2PD) - Grip and pinch strength (dinamometro) -severità dei sintomi e funzionalità(	-1 mese(NCS) -10 sett. (NRSp,2PD,Grip and pinch strength, BCTQ-SSS-FSS)	Miglioramento stat. significativo nella NCS a 1 mese, NRSp, 2PD, BCTQ-SSS-FSS, a fine trattamento solo per il gruppo TN ($p<0.01$). No differenze significative tra i due gruppi per pinch e grip strength.

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
				da 15'' di riposo, 2 volte a sett. per 10 sett.	BCTQ- SSS-FSS)		
Ballestero-Pérez 2016 'Effectiveness of Nerve Gliding Exercises on Carpal Tunnel Syndrome: A Systematic Review'	Revisione sist.	Periodo di ricerca: fino maggio 2014 Motori di ricerca: PubMed, PEDro, Web of Knowledge, Cochrane Plus, and CINAHL. Parole chiave : nerve tissue, gliding, exercises, carpal tunnel syndrome, neural mobilization, and neurodynamic mobilization. Criteri inclusione: >18 anni, gestiti con esercizi neuro dinamici, diagnosi clinica o elettrofisiologica di CTS Criteri esclusione: chirurgia,	mobilizzazione nervo mediano con incremento pressione neurale (1 art.) -nerve gliding (12 art.)	- mobilizzazione del nervo con diminuzione pressione neurale (1 art.) -splint volare al polso + medicamenti (8 art.) - mobilizzazione polso o tendini (2 art.) -ultrasuono (1 art.) -nessuna comparazione (3 art.)	-Intensità del dolore : NRSp (2art.),VAS(4 art.),pain relief scale (1 art.) -Funzione: DASH(3 art.),BCTQ-FSS(6 art.), functional status box(1 art.), 4 art. considerano pinch e grip strength come parametri funzionali - Dolore e funzione insieme: BCTQ-SSS (5 art.), 24-hour symptom diary (1art.),Carpal Tunnel Specific Questionnaire(3 art.), Symptom Total Point	Non riportato	PEDro score: 6 su 13 articoli hanno punteggio da 5 a 11. La maggior parte degli studi riportava miglioramenti nel dolore, nella soglia del dolore alla pressione e nella funzione dopo nerve gliding , combinato o meno con altre terapie nerve gliding vs altre terapie: -peggiori risultati in termini di dolore e funzione rispetto a terapia standard(2art.) e splinting(1 art.)., - migliori risultati in termini di dolore e funzione rispetto a Ultrasuoni e splinting (3 art.)

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		comorbilità, gravidanza. Studi inclusi: 13 RCT Valutati con PEDro scale			Score(2 art.) - % di pz. Che ricorreranno a chirurgia (2art.)		
Basson 2017 'The effectiveness of neural mobilisation for neuro-musculoskeletal conditions: A systematic review and meta-analysis'	Revisione sist. con metanalisi	Periodo di ricerca: gennaio 1980- aprile 2016 Motori di ricerca: PubMed, PEDro, Cochrane Controlled Trial Registered, CINAHL plus, ProQuest Central (Family Health, Health and Medical Complete), Nursing and Allied Health Source, EBSCO MasterFile Premier, Science Direct Parole chiave : neural, nerve, mobilization, manipulation, physical therapy, physiotherapy, manual therapy, exercises, treatment,	-tecniche neurodinamiche secondo Totten e Hunter (7 art.) -diverse tipologie di tecniche per gli altri studi	-solo splint (4 art.) -splint e ultrasuoni (1 art.) -splint e iniezioni di cortisone (1 art.) -splint e ''sham''Tecniche neuro dinamiche (1 art.) -splint, raccomandazioni ed esercizi di tendon glide (1 art.) -splint e paraffino terapia (1 art.) -splint, ultrasuoni e TENS (1 art.) L'autore ha	Primario: - dolore(VAS), presente in metanalisi - disabilità(DASH), presente in metanalisi -funzione (?) Secondario: - edema intraneurale (CSA) - Parametri elettrofisiologici		Low Rob 5 studi Unclear Rob 4 studi High Rob 3 studi Le tecniche neuro dinamiche non si sono mostrate superiori per gli outcome primari (VAS p=0.40,DASH p=0.63) ma mostra miglioramenti nella CSA e parametri elettrofisiologici.

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
		intervention, management, modality, stretching, tension, neurodynamics Criteri inclusione: RCT in lingua inglese , >18 anni, con affezioni neuro-muscolo scheletriche indicative di disfunzione del tessuto neurale Criteri esclusione: Case report, studi di coorte, case-control, disordini del sistema nervoso centrale, polineuropatie e malattie sistemiche. Studi inclusi: 40 RCT, 12 per CTS Metanalisi: 19 RCT (10 per CTS) Valutato Rob		riportato solo articoli presenti in metanalisi.			
Huisstede 2010	Revisi	Periodo di	Splint:	Splint:	-intensità	-breve	55% degli studi sono di alta qualità

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'Carpal Tunnel Syndrome. Part I: Effectiveness of Nonsurgical Treatments-A Systematic Review'	one sist.	ricerca: Motori di ricerca: Cochrane Library, PubMed, EMBASE, CINAHL, PEDro Parole chiave: "carpal tunnel syndrome," "median nerve entrapment," "interventions" Criteri inclusione: revisioni sit. e RCT, pz con diagnosi di CTS, il trattamento sia stato valutato, dolore-funzione e recupero riportato, Criteri esclusione: traumi, comorbilità, studi su efficacia sul dolore di analgesici pre-intra e post operatori. Studi inclusi: 26 RCT, 2 revisioni sist.	- in posizione neutra polso - notturno -solo polso, - + LLLT, - + tendon/nerve glide Ultrasuono Farmaci e vitamine Mobilizzazione e terapia manuale Trattamenti chiropratici tastiera ergonomica Magneto-terapia Agopuntura Massaggio Impacchi caldi Cupping therapy	- in estensione polso -no trattamento,giornaliero - polso-mano cortisone per via orale Yoga frequenze ultrasuono LLLT Infiltrazioni di cortisone FANS Fonoforesi steroidi	dolore (VAS) -miglioramenti clinici (non specificati) -Severità dei sintomi e Funzione (BCTQ-FSS-SSS, Globl sympton score, Levine Questionnaire) -Disabilità (DASH) -Funzionalità della mano -Hand - grip strength Le scale di valutazione non sempre sono riportate	termine -medio termine -lungo termine	Evidenze da forti a moderate sono state trovate per l'efficacia di steroidi per via orale (BCTQ-FSS), iniezioni di steroidi (miglioramenti clinici), ultrasuoni vs laser (vas, grip strenght), magneto-terapia, splint notturno (sintomi e funzione) e l'uso di tastiere ergonomiche (dolore e funzionalità mano) rispetto a una tastiera standard e coppettazione tradizionale vs termo-coppettazione (dolore, Levine Questionnaire) a breve termine. Evidenze moderate su efficacia di ultrasuoni (sintomi) a medio termine. L'outcome a lungo termine è stato studiato solo per il cortisone, e steroidi, sia orale sia per iniezione, ma non hanno riportato evidenze.

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		Valutato Rob (Cochrane Reviewers Handbook)	Insulina Iontoforesi Infiltrazioni cortisone				
Huisstede 2017 'Carpal Tunnel Syndrome: Effectiveness of Physical Therapy and Electrophysical Modalities. An Updated Systematic Review of Randomized Controlled Trials'	Revisione sit.	Periodo di ricerca: Motori di ricerca: Cochrane Library, PubMed, EMBASE, CINAHL, PEDro Parole chiave: 'carpal tunnel syndrome', 'median nerve entrapment', and 'interventions Criteri inclusione: revisioni sit. e RCT, pz con diagnosi di CTS, fisioterapia e terapia strumentale, dolore-funzione e recupero riportati con scale validate. Criteri	Fisioterapia: -Tendon and Nerve Gliding Exercises -Tendon Gliding Exercises versus -mobilizzazione e terapia manuale -massaggio -splint Terapia strumentale: -Ultrasuono -LLLT -onde d'urto -magneto-terapia -ipertermia	-placebo -intensità e diverse frequenze ultrasuono -Nerve Gliding Exercises -iniezione corticosteroidi -crio-ultrasuoni -onde d'urto -preparati erboristici -fonoforesi -TENS -splint	Primari -intensità dolore (VAS) -Severità dei sintomi e Funzione (BCTQ-FSS-SSS) -Disabilità (DASH) Secondari -grip e pinch strenght	-breve termine (<3mesi) -medio termine (4-6 mesi) -lungo termine (>6 mesi)	77% degli studi sono di alta qualità, 23% di bassa qualità Evidenze a breve termine (in favore): massaggio vs LLLT (VAS, BCTQ-FSS-SSS) ultrasuoni vs iniezioni di cortisone + splint (grip strenght), ipertermia vs placebo (BCTQ-SSS), ionoforesi vs fonoforesi (VAS,grip e pinch strenght, BCTQ-SSS), radiofrequenza pulsata + splint(VAS,BCTQ-SSS-FSS) diatermia vs placebo (BCTQ-SSS) e corrente interferenziale vs TENS(VAS, BCTQ-SSS-FSS) vs splint (VAS) notturno (Evidenze a medio termine (in favore): moderate in onde d'urto + splint vs placebo (VAS,BCTQ-SSS-FSS), onde d'urto vs ultrasuoni e crio-ultrasuoni (BCTQ-SSS) e ultrasuoni vs placebo (sintomi) Lungo termine: nessun RCT indagava l'effetto a lungo termine

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
		esclusione: . traumi, comorbilità Studi inclusi: 22 RCT, 2 revisioni Valutati per Rob (Criteri di Furlan, Cochrane Reviewers Handbook)	-ionoforesi fonoforesi -luce polarizzata -radio frequenza pulsata -diatermia -correnti inferenziali				
Kim 2015 'Efficacy of tendon and nerve gliding exercises for carpal tunnel syndrome: a systematic review of randomized controlled trials'	Revisione sist.	Periodo di ricerca: 1963 – gennaio 2015 Motori di ricerca: Cochrane Library, PubMed, EMBASE, CINAHL Parole chiave: carpal tunnel syndrome AND tendon and nerve gliding exercises OR tendon gliding exercises OR nerve gliding exercises Criteri inclusione:	Esercizi di tendon e nerve gliding : - paraffina + splint + esercizi di tendon glide -paraffina + splint + esercizi di nerve glide -SCT + esercizi di tendon e nerve gliding - esercizi di tendon e nerve gliding --splint polso e metacarpofalangee +	Altre modalità di trattamento: -paraffina + splint -trattamento conservativo standard (SCT) -splint polso e metacarpofalangee -splint cock-up - splint con polso in posizione neutra	-Severità dei sintomi (BCTQ-SSS) -Stato funzionale (BCTQ-FSS)	Da 4 sett. a 11 mesi	Rob da basso a moderato La severità dei sintomi e lo stato funzionale sono migliorati nei gruppi che hanno ricevuto esercizi di tendon e nerve gliding + trattamenti convenzionali rispetto a quei gruppi che hanno ricevuto solo trattamenti convenzionali.

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
		diagnosi di CTS, RCT che avevano come gruppo d'intervento 'esercizi di tendon e nerve gliding' e come gruppo di controllo 'nessun esercizio di tendon e nerve gliding, severità dei sintomi e stato funzionale come outcome. Criteri esclusione: non specificati . Studi inclusi: 4 RCT Valutati con 'Cochrane Collaboration's risk of bias tool'	esercizi di tendon e nerve gliding -splint con polso in posizione neutra + esercizi di tendon gliding				
Lim 2017 'Median nerve mobilization techniques in the treatment of carpal tunnel syndrome: A systematic review'	Revisione sist.	Periodo di ricerca: 2000 - aprile 2015 Motori di ricerca: CINAHL, Scopus, MEDLINE	Mobilizzazione nervo mediano: - tensionamento distale del nervo + splint - tensione	Altri trattamenti: -splint - tendon gliding + splint	-test elettrodiagnostico (NCS, intensità di segnale) - performance funzionale (BCTQ-		Qualità studi: 3 strong, 2 good, 4 adequate Performance funzionale migliore nel gruppo di controllo (splint) rispetto al gruppo tensionamento distale del nero ($p<0.001$). Performance funzionale migliore nel gruppo di controllo (splint+tendon glide) rispetto al gruppo

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
		(Ovid), EMBASE, and Cochrane Library electronic databases Parole chiave: (Mesh) "carpal tunnel syndrome" and "nerve mobilization" Criteri inclusione: Confronto tra mobilizzazione del nervo mediano con gruppo di controllo o altri trattamenti per CTS, individui con diagnosi clinica ed elettrofisiologica di CTS Criteri esclusione: non-RCT, (2) CTS trattato chirurgicamente, revisioni sistematiche, report di conferenze, abstract, tesi, o relazioni	prossimale del nervo + splint -nerve sliding		SSS-FSS, Brigham and Woman's Hospital Carpal Tunnel Syndrome Questionnaire, DASH, symptom total point, and Functional Box Scale) -intensità del dolore (VAS, pain relief scale, irritabilità nervo mediano) -esame fisico (Tinel's test, Phalen's test, reverse Phalen's test, compression test, upper limb tension test 2a, ROM) -sensibilità (VAS, 2PD, Semmes-Weinstein Monofilament test)		tensionamento distale del nervo + splint Non ci sono altre evidenze

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
		tecniche. Studi inclusi: 9 RCT Valutati con : 'Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields'			-forza (vigori metro, dinamometr o, test manuale)		
McKeon 2008 'Neural Gliding Techniques for the Treatment of Carpal Tunnel Syndrome: A Systematic Review'	Revisi one sist.	Periodo di ricerca: 1964 – April 2008 Motori di ricerca: CINAHL, MEDLINE (Ovid), EMBASE, Cochrane Central Register of Controlled Trials, SPORTDiscus Parole chiave: "nerve glides," "nerve gliding exercises," "nerve mobilization exercises," "upper limb neuropathy," "therapy,"	Gliding neurale (6 art.)	- vero gruppo di controllo (1 art.) -splint+ ultrasuono (1 art.) - splint (4 art.)	-Dolore (VAS) -severità dei sintomi (BCTQ-SSS) -stato funzionale (BCTQ-FSS) - Esame clinico (Tinel's test, Phalen's test) -2PD - grip e pinch strenght		PEDro score più alto era 5/10 con una media tra gli studi di 4,6/10. Per tutte le variabili, nessuna evidenza consistente in favore del gliding neurale rispetto ai trattamenti alternativi

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
		"entrapment neuropathy," "nerve gliding exercises" and "carpal tunnel decompression exercises." Criteri inclusione: studi in lingua inglese che confrontano la mobilizzazione del nervo mediano con gruppo di controllo o altri trattamenti per CTS e utilizzato almeno una delle otto misure di outcome selezionate. Criteri esclusione: non specificati . Studi inclusi: 6 RCT metanalisi Valutati con PEDro scale					
Page MJ 2012 'Exercise and mobilisation interventions for	Cochrane review	Periodo di ricerca: 1937-gennaio 2012	Esercizi e mobilizzazione: -	Placebo o altri trattamenti conservativi: -Placebo	Primario: - miglioramento generale a	-breve termine (<3mesi) -lungo	Gli studi erano eterogenei in termini di Rob (da alto a basso: solo 3 studi riportavano esplicitamente il blinding dell'allocazione e 4 quello dei partecipanti) e in termini d'intervento, outcome misurati (solo 4 riportavano l'outcome primario

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
carpal tunnel syndrome (Review)'		Motori di ricerca: Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL, MEDLINE, EMBASE, CINAHL Plus, AMED, reference list RCT trovati. Parole chiave: physical therapy modalities, exercise movement techniques, musculoskeletal manipulations, mobilisation, osteopathic Massage, Carpal Tunnel Syndrome, nerve entrapment, nerve compression, entrapment neuropath Criteri inclusione: RCT e quasi-RCT, diagnosi di CTS Criteri esclusione:	mobilizzazione nervo mediano - mobilizzazione del carpo - tecniche neurodinamiche -esercizi di nerve gliding -esercizi di tendon gliding - mobilizzazione tessuti molli mirata ai siti di entrapment - mobilizzazione tessuti molli assistita da strumenti -trattamenti chiropratici -Yoga	-massaggio generale - mobilizzazione standard tessuti molli -splint -splint + iniezioni di farmaci steroidei -ultrasuoni - paraffinoterapia -educazione - ibuprofene	breve termine;tutte le misure in cui il pz. indica l'intensità della sua soddisfazione rispetto alla baseline (ad es. la global rating scale)breve termine Secondari: -eventi aversi. - miglioramento nei sintomi (Es. dolore, parestesie, parestesie notturne)breve e lungo termine - miglioramenti dello stato funzionale o nella qualità della vita;breve e lungo termine -. Parametri neurofisiolog	termine (>3 mesi)	della revisione) e follow-up; gli autori non sono riusciti a raggruppare i risultati. Outcome primario: -1 RCT di qualità molto bassa (14 pz.): tutti i pz trattati con mobilizzazione neurodinamica o del carpo hanno riportato un miglioramento generale rispetto alla baseline e nessuno nel gruppo di controllo (RR 15.00, 95% CI 1.02 to 220.92); la precisione di questo effetto stimato è molto bassa. - 1 RCT di bassa qualità (22pz): la possibilità di essere molto soddisfatti o soddisfatti del trattamento era del 24% più alta nei pz. Trattati con mobilizzazione dei tessuti molli ,assistita da strumenti', rispetto a una mobilizzazione dei tessuti molli 'standard' (RR 1.24, 95% CI 0.89 to 1.75); non era però presente il blinding dei partecipanti e la sequenza di allocazione non era chiara. - 1 RCT di qualità molto bassa (26pz):nel gruppo in cui i polsi più affetti da CTS sono stati trattati con esercizi di nerve glide+ splint e educazione non sono stati trovati valori patologici nella mSDL a fine trattamento rispetto al gruppo che ha ricevuto splint + educazione (RR 1.26, 95% CI 0.69 to 2.30); non è stata considerata la correlazione tra i polsi dei pz. con CTS bilaterale. - solo 2 RCT avevano come outcome la misurazione di eventi avversi. Outcome Secondari: in generale, i risultati tra i gruppi di confronto avevano un 95% IC a vantaggio di entrambi i gruppi. Le evidenze a favore di mobilizzazioni ed esercizi per i pz. affetti da CTS sono di scarsa qualità e

Autore anno 'Titolo'	Tipo	Partecipanti	Intervento	Controllo	Outcome	Follow-up	Risultati
		chirurgia Studi inclusi: 16 RCT Valutati con 'The Cochrane Collaboration's'			ici; breve termine - necessità di ricorrere a chirurgia.		limitate.

Legenda

2PD: two point discrimination sensation; **BCTQ-FSS**: Boston Carpal Syndrome Questionnaire Functional status scale; **BCTQ-SSS**: Boston Questionnaire Carpal sympton severity scale; **NCS**:nerve conduction study; **CSA**: cross sectional area; **CTQ:** carpal tunnel syndrome questionnaire -**S:** syntom, **-F** function ; **d.o**.: drop out; ; **ENMG**: esame neuro miografico; **fMRI**: risonanza magnetica funzionale**; HPT**: thermal pain thresholds; **IFC**: Corrente interferenziale; **MDPGA**: physician global evaluation; **mMDL**:median motor distal latency; **PPT**: pressure pain thresholds;; **SWD**: short-wave diathermy; **PGA**: Patient global evaluation; **mMNCV**: median nerve motor conduction velocity; **mSDL**: median sensory distal latency; **mSNCV**: median sensory nerve conduction velocity; **Rob**: risk of bias; **SNAP**: sensory nerve action potential peak latency; **SNVC**: sensory nerve conduction.

5. Discussione

Gli studi analizzati in questa revisione hanno proposto una grande varietà di trattamenti conservativi per la gestione della CTS e molteplici sono gli outcome con cui ne misurano l'efficacia.

L'utilizzo del tutore al polso, associato o meno ad altre terapie, è presente nel 61% degli RCT revisionati (16/26) e 15 lo includevano nel gruppo di controllo; infatti lo 'splinting', insieme all'educazione del paziente, è l'unica terapia conservativa non farmacologica presente nelle linee guida per il trattamento della CTS stilate dal Consensus Delphi del 2014 (Huisstede 2014):

- 2 RCT confrontavano l'utilizzo di splint notturno al polso con splint notturno a polso e MCF: nel primo non vi erano differenze tra i 2 gruppi per funzionalità e severità dei sintomi a 4 e 12 sett.(4) mentre nel secondo lo splint a MCF si era dimostrato superiore per incremento funzionalità a 4 sett.(5). Risulta comunque difficile comparare i 2 risultati perché vi erano grandi differenze nel numero di partecipanti (124 vs 54) e nel primo studio lo splint era associato a stretching dei muscoli lombricali; inoltre nello studio in cui sono emerse evidenze in favore dello splint MCF, la randomizzazione non era stata decritta e l'allocazione e i partecipanti non erano in cieco.
- 4 RCT invece verificavano l'efficacia di esercizi neurodinamici rispetto allo splint associato o meno ad altri trattamenti: uno (Schmidt) non ha trovato differenze significative tra i 2 gruppi(31), due hanno trovato un incremento di funzionalità in favore dei gruppi che indossavano lo splint in associazione con iniezione di CS o esercizi(28,30) e anche l'ultimo ha trovato un incremento della funzionalità nel gruppo che effettuava esercizi di scivolamento tendineo rispetto a quelli neurodinamici (29); i risultati dei 4 studi sono piuttosto concordanti e lo studio che non ha trovato differenze tra i 2 gruppi è quello con meno partecipanti (21 vs 111 vs 60) ma con minor rischio di Bias. Un altro RCT con 40 partecipanti e basso rischio di Bias (Bialosky 2009) ha verificato che tecniche neurodinamiche, questa volta somministrate dal terapista, non hanno portato alcun giovamento rispetto al solo splinting + placebo in termini di riduzione del dolore e disabilità, ma solo nella riduzione del dolore

termico a breve termine(7). Un altro RCT con 51 partecipanti (66 mani) ha provato ad associare l'esercizio di scivolamento tendineo a sedute di ultrasuonoterapia e splint, ma ha osservato gli stessi effetti in quei pazienti che ricevevano il solo splint (miglioramento al BCTQ a 2 mesi)(6); i partecipanti e il personale non erano pero in cieco.

- 1 RCT con un elevato numero di partecipanti (151 mani) ha confrontato l'efficacia di un massaggio auto-somministrato in aggiunta a splint ed esercizi di glide tendineo e neurale; entrambi i gruppi miglioravano significativamente ma con il massaggio il miglioramento era maggiore per riduzione del dolore ed incremento della forza a breve termine(10). I limiti di questo studio sono l'assoluta mancanza di cieco e il possibile conflitto d'interessi dell'autore, dato che il massaggio porta il suo nome.
- 1 RCT ha trovato evidenze in favore della leserterapia e ultrasuonoterapia, in aggiunta allo splinting, rispetto al solo splinting per la riduzione della severità dei sintomi e miglioramento della funzionalità e parametri elettrofisiologici a breve termine(27). In contrasto con lo studio precedente un altro RCT (Rayegani) non ha rilevato differenze statisticamente significative tra l'utilizzo di laser,placebo e splint, i 3 gruppi hanno avuto miglioramenti significativi negli stessi outcome dello studio precedente a breve termine(19). Il numero dei pazienti era uguale (50) per entrambi gli studi, ma il primo studio aveva trattato 100 mani senza aver riportato alcuna informazione sulla bilateralità del CTS dei partecipanti e la sua gestione. Nel primo studio i partecipanti non erano in cieco e la randomizzazione e allocazione non sono chiare mentre il secondo studio non ha riportato informazioni sul cieco di chi valuta gli outcomes.
- 2 RCT hanno verificato l' apporto di Tens, correnti inferenziali(24) ed elettro-agopuntura(21) rispetto allo splinting: le Tens sembrano aggiungere niente, in termini di riduzione del dolore e sintomi ed incremento funzionalità e parametri elettrofisiologici, mentre le IFC sembrano migliori rispetto al solo splint per gli outcome citati a breve termine(24) (Koca); lo studio ha un alto numero di partecipanti (75) ma le modalità con cui sono stati randomizzati ha un alto rischio di Bias. Anche l'elettro-agopuntura sembra migliorare la sintomatologia dolorosa e la

severità dei sintomi oltre alla disabilità, forza e destrezza rispetto al solo splint a breve e medio termine(21); lo studio aveva un grande numero di partecipanti (181) ma non era in cieco.

- 1 RCT con 22 partecipanti ha trovato evidenze in favore ad una singola esposizione di radiofrequenza pulsata a livello del nervo mediano rispetto al solo splint, con sollievo dal dolore dopo 2 gg dal trattamento e riduzione VAS e severità dei sintomi e incremento funzionalità a breve e medio termine(20); Il Rob per questo studio è basso ma il numero dei partecipanti è esiguo e il trattamento invasivo, anche se non sono stati riportati eventi avversi.
- In fine un altro studio, che non ha una chiara descrizione metodologica della randomizzazione dei partecipanti e aveva solo il cieco di chi valutava gli Outcome, ha trovato evidenze in favore della veicolazione tran-dermica di CS e FANS rispetto allo splinting, per riduzione di dolore a 3 mesi(34); la fonoforesi con CS era migliore anche per incremento della funzionalità e forza ma mostrava un peggioramento dei parametri elettrofisiologici mentre nel gruppo 'splint' diminuiva solo la severità dei sintomi(34). Il gruppo splint indossava il tutore giorno e notte per 2 settimane e questo è in contrasto con le linee guida del Consensus Delphi del 2014, che suggeriscono l'utilizzo di splint per almeno 4 settimane e preferibilmente solo la notte(1).

Tra gli 11 RCT che non avevano lo splint come gruppo di controllo, 7 (11–14,18,22,23) comparavano tra di loro diverse metodologie di trattamento:

- 3 recenti RCT dello stesso autore verificavano l'efficacia della terapia manuale (TM), comprendenti anche tecniche neurodinamiche, rispetto al Laser (12,13) e di tecniche neurodinamiche rispetto al placebo(14); non ci sono differenze tra la 'TM' e il Laser al 2DP, NRSp e BCTQ a 10 settimane ed entrambi i gruppi mostravano miglioramenti significativi per questi outcomes; l'unica differenza significativa tra i 2 gruppi era il miglioramento della conduzione nervosa a 1 mese e quindi, questo risultato, non sembra essere correlato al miglioramento dei nostri outcomes di primario interesse(12,13). Il terzo studio dimostrava come l'applicazione di tecniche neurodinamiche porti ad un miglioramento di

tutti gli outcomes indagati negli studi precedenti rispetto al placebo(14). Il miglioramento dei parametri elettrofisiologici a vantaggio delle sole tecniche neurodinamiche rispetto al laser, ma il concomitante miglioramento nel dolore e funzionalità in entrambe le modalità di trattamento, conferma quanto descritto da Fernandez de-las-Peñas in uno studio del 2017, circa eventuali meccanismi di sensibilizzazione centrale, dato che anche il gruppo che non aveva miglioramenti negli outcome strumentali ha avuto gli stessi benefici in termini di dolore e funzionalità. L'elevato numero di partecipanti (180-180-160), la buona descrizione sia del gruppo d'intervento che di controllo e il basso rischio di Bias dei tre studi fanno si che i risultati siano attendibili.

- 1 RCT con randomizzazione dei partecipanti ad alto rischio di Bias condotto su 42 pz (70 mani) ha trovato una superiorità statisticamente significativa del trattamento con manipolazione fasciale rispetto al LLLt (VAS, BCTQ)(11). In un altro studio il laser (LLLt) è stato confrontato con la magnetoterapia e si è dimostrato superiore nella VAS a breve, medio e lungo termine(18) ma aveva un rischio di Bias molto alto. Anche l'effetto a breve termine della diatermia è stato indagato e sembra essere significativamente positivo nei risultati di VAS, BTCQ e esame clinico rispetto al placebo e l'inizio del trattamento(22), ma c'e' il rischio che il cieco dei partecipanti possa essere stato infranto.
- Un' ultimo RTC (20 pz), con randomizzazione ad alto rischio di bias, aveva come outcome la variazione di attivazione di alcune aree cerebrali legate al dolore valutata con risonanza magnetica funzionale, dopo una seduta di TENS o 'sham' TENS sul nervo mediano; solo in chi aveva effettuato le TENS si riscontravano differenze significative(23). L'autore dunque suggerisce che questa terapia è utile nell'inibire alcune aree cerebrali associate al dolore nei pazienti affetti da CTS

I rimanenti 4 RCT(2,8,9,35) confrontavano diverse tipologie di trattamento conservativo con la chirurgia:

- 3 recenti RCT dello stesso autore, con elevato numero di partecipanti (120-100-100) e basso rischio di Bias, hanno evidenziato una lieve superiorità della terapia manuale (con tecniche di desensibilizzazione

centrale) a breve termine, per riduzione dell'intensità di dolore e miglioramento funzionalità(2,8,9). L'autore conclude che gli effetti della terapia manuale e della chirurgia sono simili, soprattutto nel lungo periodo.

- 1 altro RCT con 116 partecipanti e basso rischio di bias ha trovato moderate evidenze in favore della chirurgia rispetto ad un trattamento multimodale medico e fisioterapico a lungo termine (BCTQ-FSS-SSS); nella intensità ed interferenza del dolore nel lavoro, assenteismo dal lavoro ed SF-36 non vi erano differenze(35).

Delle 8 revisioni sistematiche incluse nella revisione, tra cui una Cochrane review del 2012(3), 6(3,15,17,32,33) hanno cercato prove di efficacia per mobilizzazioni ed esercizi neurodinamici nel trattamento della CTS. Le revisioni sono uscite tra il 2008 e il 2017 e tutte sono concordi nel ritenere molto limitate le evidenze in favore di questi approcci terapeutici, anche perché la qualità degli RCT da loro revisionati è piuttosto bassa. Le rimanenti 2 revisioni sono dello stesso autore e trovano evidenze moderate per diversi tipologie di trattamenti strumentali (ultrasuoni, onde d'urto, laser) nella riduzione del dolore ed incremento funzionalità, ma solo a breve e medio termine(25,26); l'autore suggerisce come studi futuri debbano concentrarsi su follow up a lungo termine.
In generale, tutti gli autori mettono alla luce la necessità di futuri trial clinici di alta qualità e, per quanto riguarda il trattamento di tipo neurodinamico, di individuare sotto-gruppi nella popolazione che potrebbero rispondere meglio a questa tipologia di trattamento(17,32).
Gli autori della Cochrane review sottolineano come la scelta terapeutica debba essere guidata dall'esperienza del clinico e dalle preferenze del paziente(3).
Gli studi sono molto eterogenei tra di loro, sia per tipologia d'interventi e confronti proposti, sia per qualità metodologica.
Dei 26 RCT proposti, solo 9 hanno un rischio di Bias molto basso(2,7–9,12–14,31,35) e tra questi nessuno aveva come gruppo d'intervento la terapia strumentale, mentre delle 8 revisioni sistematiche solo 3 (3,25,26) avevano una alta qualità metodologica; per questi motivi i risultati potrebbero essere distorti.

6. Conclusioni

Da questa revisione della letteratura degli ultimi 10 anni si evince che il trattamento conservativo è una valida alternativa alla chirurgia nel trattamento della sindrome del tunnel carpale e non ci sono chiare prove di superiorità tra i due approcci terapeutici per riduzione del dolore e incremento funzionalità a breve e lungo termine.

Se confrontiamo le diverse modalità non chirurgiche, la terapia standard con tutore sembra essere ancora oggi una valida scelta terapeutica e l'addizione di alcune terapie, come tecniche ed esercizi neuro dinamici, laser, elettroterapia, ultrasuoni e laser, apportino un minimo contributo a breve termine in relazione ai nostri outcome primari.

Inoltre è emerso che il miglioramento dei parametri elettrofisiologici non sono sempre correlati ad un miglioramento della funzionalità e riduzione del dolore(2,13) e questo potrebbe essere spiegato con il meccanismo della sensibilizzazione centrale (2).

La letteratura revisionata non aiuta ad individuare la migliore scelta terapeutica per i pazienti affetti da CTS ma ad oggi, come già emerso nella Cochrane review del 2012 e proposto da alcuni esperti nel Consensus del 2014, l'aggiunta di altre terapie a quella standard dovrebbe essere guidata dalla esperienza del clinico e dalle preferenze del paziente(1,3).

Sono necessari altri trial randomizzati di alta qualità che confrontino l'efficacia dei trattamenti conservativi già utilizzati a lungo termine e, parallelamente, studi che indaghino il meccanismo della sensibilizzazione centrale nella CTS e verificare la presenza di fattori psicologici e sociali nei soggetti che ne sono affetti, con l'obiettivo di trovare nuove finestre terapeutiche.

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8.Appendice

Tabelle Risk of bias (Rob) RCT

Baker 2012

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a priori– blocked randomization schedule was developed by a researcher not involved in subject consent or assessment.
Allocation concealment (selection bias)	Low risk	The randomization sequence was concealed in sequentially numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias)	Low risk: CTQ-F-S, intervento chirurgico a 24 sett.	No blinding of participants and personnel but the lack of blinding can not influenced the outcome
Blinding of outcome assessment (detection bias) (patient-reported outcomes	Low Risk	No blinding of outcome assessment but the outcomes (CTQ, DASH) measurement is not likely to be influenced by lack of blinding;
Incomplete outcome data	High risk	21 drop outs
Selective reporting (reporting bias	Low risk	The study protocol is available and the outcome that is of interest (BCTQ) is reported
Other bias	Low risk	We not found other bias

Bardak 2009

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"For randomization of the patients into treatment groups, a biostatistician created a computer-generated randomization list."
Allocation concealment (selection bias)	Unclear	''According to this list, numbered, sealed envelopes containing one of the treatment groups were prepared. When patients entered the study, the corresponding envelope was opened and the enclosed card determined the treatment group" It is not clear whether the sealed, numbered envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants and personnel and the lack of blindig can influenced the outcomes
Blinding of outcome assessment (detection bias) (patient-reported outcomes All outcomes	Low Risk	"Two investigators were assigned to this study. One of the investigators was blind to the therapy given to the patient and only evaluated the subjective symptoms, clinical examinations, and the functional status of the patient. These evaluations

		were carried out pretreatment and 8 weeks posttreatment. The second investigatorswas blind to the functional status and symptoms of the patients and only applied the treatment"
Incomplete outcome data	Low risk	No drop-outs or losses to follow-up were reported in the trial publication, and the tables of outcome data clearly indicate that data reported are based on a complete sample of participants who were randomised
Selective reporting (reporting bias	low risk	the outcome VAS pain score was not reported in the results.
Other bias	Low risk	We not found other bias

Bialosky2009

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was computer generated
Allocation concealment (selection bias)	Low risk	The randomization sequence was concealed in sequentially numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias)	a)NRS, DASH, PCOQ :Low risk b) **Grip Strength,** Semmes-Weinstein monofilament Testing: Low risk c)NCS:Unclear	a)Blinding of partecipants. It is impossibile to have a personnel's blind, but the outcome measurement is not likely to be influenced by lack of blinding b) Assessment at the 3-week follow-up session was performed by an examiner blinded to group assignment c) NCS was performed by a medical doctor (K.R.V.) experienced in this assessment, the blind of medical doctor is not reported
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)NRS:low risk b)DASH:low risk **c)Grip Strength,** Semmes-Weinstein monofilament Testing: low risk	a) Blinding of partecipants b)self-administered c) Assessment at the 3-week follow-up session was performed by an examiner blinded to group assignment
Incomplete outcome data	Low Risk	Only one partecipant did not keep followup appointments
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Bulut 2015

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	After satisfying inclusion criteria, patients were admitted to the study and assigned a number. The generetion of number is not described.
Allocation concealment (selection bias)	High Risk	Odd numbers used to indicate allocation to Group 1 and even numbers to indicate allocation to Group 2.
Blinding of participants and personnel (performance bias)	High Risk per (CTSQ), (VASp)	No blinding of partecipants and personnel.
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)Electrophysiological ev.: Low risk b) (CTSQ), (VASp): Low risk c) grip strength, pinch strength: high risk	a) evalueted by the physician who was not aware of the splint allocated to the patient b) self-administered c) evalueted by same physician pre and post intervention
Incomplete outcome data	Unclear	Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk'
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
Other bias	Low risk	We not found other bias

Chen 2015

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Referring to a random-number table
Allocation concealment (selection bias)	Low risk	allocation using a fixed block size of 4 to divide into 11 blocks from 44 participants, one block could determine two intervention groups and two control groups) by a research assistant who drew numbers from a sealed envelope
Blinding of participants and personnel (performance bias)	a)VAS-BCTQ: high risk b)CSA,SNCV, Finger pinch strength: low risk	No Blinding of partecipants and personnel a)the lack of partecipants blinding can be influenced the outcomes b) the lack of blinding can not influenced the outcomes: All the measurements were performed by the same physician (Dr. Sun), who was blinded to the randomization and treatment procedure
Blinding of outcome assessment (detection bias) (patient-reported outcomes	Low risk	All the measurements were performed by the same physician (Dr. Sun), who was blinded to the randomization and treatment procedure
Incomplete outcome data	Low risk	Missing outcome data balanced in numbers across intervention groups,

		with similar reasons for missing data across groups
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Chung 2016

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	''We used the Random Allocation Software random block sizes option and did not prespecify the block size range''
Allocation concealment (selection bias)	Low risk	''We used a sequentially numbered procedure with opaque sealed envelopes to conceal the random sequence.32 The sequence was generated and concealed by a trained research assistant, independent of the study, who was supervised by one of the authors (S.L.).''
Blinding of participants and personnel (performance bias)	BCTQ-sss(primario), Functional Status Scale, DASH, NPRS, Semmes– Weinstein monofilament test, Dellon-modified pick-up test, maximal tip pinch strength (secondari): High risk	No blinding of partecipants and personnel. In both groups, all participants had the expectation of receiving electroacupuncture, because the study procedures were explained to all potential participants before enrolment.
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)BCTQ(primario), Functional Status Scale, DASH: low risk b)NPRS, Semmes– Weinstein monofilament test, Dellon-modified pick-up test, maximal tip pinch strength (secondari): High risk	The blinding of outcome assessment is not reported. a)self-administered
Incomplete outcome data	Unclear	All patients were included in the intention-to-treat analysis. We defined a patient as having dropped out of the trial if they did not complete assessment at week 17. Five patients dropped out of the treatment group. Two patients dropped out of the control group
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Dakowicz A 2011

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	High risk	'' All patients were randomly assigned to 2 groups''. Not reported the random sequence generation.
Allocation concealment (selection bias)	High risk	Not reported

Blinding of participants and personnel (performance bias)	High risk	Not reported
Blinding of outcome assessment (detection bias) (patient-reported outcomes	Day and night parestesia-Day and night pain-Pain intensity based on the VAS-Phalen's, Tinel's and armband tests- ENG examination: High risk	Not reported
Incomplete outcome data	High risk	Not reported
Selective reporting (reporting bias	Unclear	The study did not address this outcome
Other bias	Low risk	We not found other bias

Dincer 2009

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Randomization was performed by the use of numbered envelopes. Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk
Allocation concealment (selection bias)	Unclear	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk
Blinding of participants and personnel (performance bias)	a)BCTQ,patient satisfation inquiry: High Risk b)ENM:Low risk c)VAS:high risk	No blind o f partecipants
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)BCTQ,patient satisfation inquiry:Low Risk b)ENM:Low risk c)VAS:Low risk	a) self-administered b) Electrodiagnostic evaluations were performed by another physiatrist c) At the beginning, all of the patients were assessed by the same physiatrist and at the first and third month the assessments were performed by another physiatrist who was blinded to treatment modality (M.Z.K.).
Incomplete outcome data	Unclear	Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk'
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
Other bias	Low risk	We not found other bias

Fernández-de-las-Peñas 2015

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was conducted using a computer-generated randomized table of numbers created by a statistician who was not otherwise involved in the trial and did not participate in analysis or interpretation of the results
Allocation concealment (selection bias)	Low risk	Individual and sequentially numbered index cards with the random

		assignment were prepared. The index cards were folded and placed in sealed opaque envelopes. Another researcher opened the envelope and proceeded with allocation
Blinding of participants and personnel (performance bias)	Unclear	''We blinded assessed clinicians who obtained follow-up information to allocation''. The blind procedure is not reported.
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a) Nprs (primario): Unclear b) (BCTQ, GROC): Low risk	a) ''Outcomes were blinded assessed at baseline, and 1, 3, 6, and 12 months after the end of therapy''. The blind procedure is not reported b) self-administered
Incomplete outcome data	Low risk	plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
Other bias	Low risk	We not found other bias

Fernández-de-las-Peñas 2017, Mar.

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was conducted using a computer-generated randomized table of numbers created prior to the start of the data collection by a researcher not involved in subject recruitment
Allocation concealment (selection bias)	Low risk	Individual and sequentially numbered index cards with the random assignment were prepared, folded, and placed in sealed opaque envelopes.
Blinding of participants and personnel (performance bias)	Unclear	''We blinded clinicians who obtained follow-up information to group allocation'' The blind procedure is not reported
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)the functional status subscale of BCTQ (primario), BCTQ symptom severity subscale: Low risk b)cervical Arom, pinch-tip grip force: Unclear	a) self-administered b)Insufficient information to permit judgement of 'Low risk' or 'High risk'
Incomplete outcome data	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
Other bias	Low risk	We not found other bias

Fernández-de-las-Peñas 2017, Aug.

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was conducted using a computer-generated randomized table of numbers created prior to the start of the data collection by a researcher not involved in subject recruitment
Allocation concealment (selection bias)	Low risk	Individual and sequentially numbered index cards with the random assignment were prepared, folded, and placed in sealed opaque envelopes.
Blinding of participants and personnel (performance bias)	Unclear	''We blinded clinicians who obtained follow-up information to group allocation'' The blind procedure is not reported
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a) PPTs(primario):Unclear b) NPRS: Unclear c) TPT :Thermotest System: Unclear	a)b)c) Insufficient information to permit judgement of 'Low risk' or 'High risk'
Incomplete outcome data	Low risk	plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Heebner 2008

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants were randomly assigned to one of two groups by means of a coin toss
Allocation concealment (selection bias)	Unclear	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias)	Unclear	The study did not address this outcome
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a) DASH, CTSQ:Low risk b) Elbow extention in Ulnt1:Unclear	a) self-administered b) The study did not address this outcome.
Incomplete outcome data	High risk	The attrition rate in this study neared 50%, much higher than the anticipated 25% used to calculate the required sample size. Therefore, it is possible that there was inadequate power to find a difference between groups if one was present
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have

		been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Horng 2011

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All consecutive patients were invited, and the participants were assigned to three groups in the order of group 1, 2, and 3 by a nurse who was not involved in the study design and blind to the preassigned treatment
Allocation concealment (selection bias)	Low risk	The allocations were concealed with the use of packages of prescription orders, which were given by the nurse to the physical therapists, who did not know the sequences of randomization
Blinding of participants and personnel (performance bias)	Low risk	.No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)BTCQ-DASH-WHOQOL-BREF:Low risck b)NCS-PE	a) self-administered b)The outcomes of the physical examinations and NCS were evaluated by physiatrists who were not aware of the group assignments.
Incomplete outcome data	High Risk	In group 1 and group 2 only one subject lost followup for similar reason, but in group 3, three subject lost followup
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Incebiyik 2015

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	The random generetion is not described
Allocation concealment (selection bias)	Low risk	Patients were allocated randomly to two groups using the closed envelope method
Blinding of participants and personnel (performance bias)	A)BCTQ: High risk B)Clinical ev., static2PD test: Low risk C)VAS:High risk	Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. '' The dosage was adjusted to the level at which the patient felt a comfortable heat.With the device

		switched off, 15-min placebo SWD treatment was applied to the placebo group patients in the same position'' by the same Therapist
Blinding of outcome assessment (detection bias) (patient-reported outcomes	A)BCTQ: low risk B)Clinical ev., static2PD test: Low risk C)VAS:low risk	A) self-administered B)The clinical evaluation and static2PD test were performed, prior to treatment and immediately following the end of the 3-week treatment, by the same physician who was blinded to the type of treatment. C) Unclear who administer VAS
Incomplete outcome data	High risk	The SWD group consisted of 15 patients (28 wrists, 13 bilateral) while the control group consisted of 16 patients (30 wrists, 14 bilateral). Three patients (6 wrists) withdrew from the study in the control group
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Jarvik 2009

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	''A systems analysis with no contact with patients generated the computerised random allocation with block sizes varying between 4 and 12 (concealed from research personnel involved with recruitment), stratifi ed by site''.
Allocation concealment (selection bias)	Low risk	''We placed assignments in opaque sealed envelopes opened by research assistants after patients' baseline questionnaire assessment. We masked staff who obtained follow-up information to patient allocation. At the beginning of each interview, the interviewer reminded the patient not to reveal his or her treatment group.''
Blinding of participants and personnel (performance bias)	Low risk	No blinding of partecipants but the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) (patient-reported outcomes	functional status scale of BCTQ(primary), symptom severity scale of BCTQ, hand/wrist pain intensity (NRS 0–10); hand/ wrist pain interference (NRS 0–10); work days lost (0–28) SF-36(secondary), : low risk	interview in person or telephone by a blinded person
Incomplete outcome data	Low risk	intention-to-treat analysis for patients in the group to which they were allocated,

		regardless of compliance with the intended intervention
Selective reporting (reporting bias	LOW risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Kara 2010

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The random sequence generation is not reported
Allocation concealment (selection bias)	High risk	The al location concelment is not reported
Blinding of participants and personnel (performance bias)	Low risk	Blinding of partecipants, no blinding of personnel but not influenced the outcome
Blinding of outcome assessment (detection bias) (patient-reported outcomes	FMRI:low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Incomplete outcome data	Low risk	Missing outcome data balanced in numbers across intervention groups(1-1) for similar reason (artefact and undetected cortical activity)
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified outcome that is of interest in the review have been reported in the pre-specified way;
Other bias	Low risk	We not found other bias

Koca 2014

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	High risk	randomization was performed by a second investigator using a simple randomization method based on the sequential admission of patients
Allocation concealment (selection bias)	Unclear	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk
Blinding of participants and personnel (performance bias)	Low risk	Blinding of the partecipans, no blinding of the personnel and the outcomes could not influenced,
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a) BCTQ:low risk b) VAS:low risk c) mMDl, mSncV:unclear	a) self-administered b) the partecipants where blind to the treatment c) Insufficient information to permit judgement of 'Low

		risk' or 'High risk
Incomplete outcome data	Unclear	Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Madenci 2012

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Simple randomization according to the hospital admission order of the patients
Allocation concealment (selection bias)	Low risk	The allocotion concealment was performed by a different physician
Blinding of participants and personnel (performance bias)	a)Electroneurophysiological examinations: low risk b)PGA and MDPGA: high risk c)Evaluation of strength; Hand grip strength: low risk d)Boston symptom severity scale and the functional capacity scale: High risk	No blinding of partecipants and personnel: a)c) no blinding could not have influenced the outcome b,d) No blinding of partecipants could have influenced the outcome
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)Electroneurophysiological examinations: High risk b)PGA and MDPGA: high risk c)Evaluation of strength; Hand grip strength: high risk d)Boston symptom severity scale and the functional capacity scale: low risk	No blinding of outcome assessors could have influenced the outcomes a)b)c), not d)because was self-administered
Incomplete outcome data	Low risk	''Among the patients, two patients from group I and two patients from the group II were excluded from the study because of poor compliance with the therapy and follow-up visits''
Selective reporting (reporting bias	Unclear	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Other bias	High risk	The massage used in the study called ''Madenci'' was problably conceived By the author of the study.

Pratelli 2015

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Each patient was given a consecutive number

Allocation concealment (selection bias)	Unclear	Insufficient information to permit judgement of 'Low risk' or 'High risk
Blinding of participants and personnel (performance bias)	Low risk	No blinding of partecipants and personnel who performed the treatment but not influenced the outcomes
Blinding of outcome assessment (detection bias) (patient-reported outcomes	Low risk	All patients were evaluated by physician P.C. who was blinded from the original patient group
Incomplete outcome data	Low risk	None of the patients dropped out of the study and no collateral effects were observed in patients after the application of FM and LLLT
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Rayegani 2013

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Referring to a random number table
Allocation concealment (selection bias)	Unclear	the method of concealment is not described
Blinding of participants and personnel (performance bias)	a) Electrophysiological parameters:Unclear b) Phalen's and Tinel's tests:Unclear c)VAS, Symptoms Severity Score, Functional Status Scale:low risk	Patients were blinded to the treatment used in Laser and Sham Laser group. The blinding of personnel was impossibile.
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)Electrophysiological parameters:Un clear b)Phalen's and Tinel's tests:Unclear c)VAS, Symptoms Severity Score, Functional Status Scale:low risk	a)b)The blinding of outcome assessment is not reported c)self-administred
Incomplete outcome data	UNclear	Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk'
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Schmid 2012

Entry	Judgement	Support for judgement
Random sequence generation	Unclear	''Patients who met clinical20 and

(selection bias)		electrodiagnostic21,22 criteria for mild or moderate CTS were randomly allocated to receive either night splinting or nerve and tendon gliding exercises . Allocation was stratified for CTS severity based on electrodiagnostic test results.''
Allocation concealment (selection bias)	Low risk	Concealed random allocation was performed by an independent investigator using sealed envelopes
Blinding of participants and personnel (performance bias)	Low risk	No blinding of partecipants and personnel who performed the treatment but not influenced the outcomes
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)MRI:low risk b)VAS,BCTQ:low risk	a)''All MRI scans were coded and an investigator blinded to the group allocation took all measurements (AS). To verify the inter-tester reliability of the measures, a second investigator blinded to group allocation independently evaluated all MRI scans (JE)'' c) Self-administred
Incomplete outcome data	Low risk	Only one partecipant of ''exercises group'' leave the study for time constraints and in this way the numbers of partecipants were 10 for each Group.
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Sim 2018

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization sequence was created by Microsoft excel
Allocation concealment (selection bias)	Low risk	1:1 allocation using random block size of 4. In cases of bilateral CTS, the patients were allocated to the next block of 4, and both wrists involved received the same treatment.
Blinding of participants and personnel (performance bias)	High risk	Both patients and investigator were aware of the treatment group chosen
Blinding of outcome assessment (detection bias) (patient-reported outcomes	Low Risk	No blinding of outcome assessment but the outcome (BCTQ) measurement is not likely to be influenced by lack of blinding;
Incomplete outcome data	Low Risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias	Low risk	The study protocol is available and the outcome that is of interest (BCTQ) is reported

Other bias	Low risk	We not found other bias

Soyupek 2011

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear	the method of concealment is not described
Blinding of participants and personnel (performance bias)	Ultrasonographic evaluation:High risk Electrophysiological studies:High risk Phalen's and Tinel's Signs: high risk VAS: high risk BCTQ:high risk	No blinding of personnel and partecipants
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)Ultrasonographic evaluation, Electrophysiological studies, Phalen's and Tinel's Signs: Low risk b) VAS, BCTQ: Low risk	a)The investigators who evaluated ultrasonographic, electrodiagnostic and clinical measurements were blinded to allocated treatments and blinded to each other. b) Self-administred
Incomplete outcome data	Unclear	'' Three patients in the splinting group, one patient in PCS group and one patient in PNSAI did not attend the follow-up protocol'' no reasons for missing data provided
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Wolny 2016

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Subjects were randomly assigned to either the NM group or the EPM group by drawing lots using the group numbers
Allocation concealment (selection bias)	Low risk	Individuals who drew the number 1 were assigned to the NM group and those who drew number 2 were assigned to the EPM Group. The procedure in which the patient drew his or her group number was supervised by a secretary who was not otherwise involved in the study
Blinding of participants and personnel (performance bias)	2PD: Low risk	No blinding of partecipants . A physical therapist was informed by the secretary of the treatment to be performed and completed the regimes without knowledge of the assessment results.

Blinding of outcome assessment (detection bias) (patient-reported outcomes	2PD: Low risk	The same physical therapist performed preand post-treatment assessments of 2PD but was blinded as to treatment allocation.
Incomplete outcome data	Uncler	This out come was not sufficient described
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Wolny 2017

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned by drawing lots with the group number
Allocation concealment (selection bias)	Low risk	Individuals who drewthe number 1 were assigned to the MT group, and those who drew number 2 were assigned to the EM group. The procedure in which the patient drew his or her group number was supervised by a secretary who was not otherwise involved in the study
Blinding of participants and personnel (performance bias)	Low risk	No blinding of partecipants and personnel but The therapists conducting the initial physical examination and delivering the therapy were not members of the research team and knew nothing about the experiment. Not influenced the outcomes.
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a) NCS:low risk b) NPRS: low risk c) BCTS:low risk	a)The NCS was performed by specialists in an independent, off-site electromyography laboratori. The specialists who performed the NCS were not aware of the nature of the therapy administered to participants. b) the patient was directed to a physical therapist who performed a physical examination, and the patient and therapist completed the relevant questionnaires and documentation. The physical therapy procedures were performed by other physical therapists. d) Self-administered
Incomplete outcome data	Unclear	Both groups had 70 Hans to analysed but the missing data was not sufficiently described
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes

		that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

Wolny 2018

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	random number generator
Allocation concealment (selection bias)	Low risk	who were randomly assigned 1 were allocated to the neurodynamic techniques group, and those who were randomly assigned 2 were allocated to the sham therapy group. Randomization and allocation were performed by persons who were not otherwise involved in the trial
Blinding of participants and personnel (performance bias)	a)NCS b)NPRS c) 2PD, Grip and pinch strength d)BCTQ Low risk	Blinding of partecipants, not of personnel but the lack of blinding not influenced the outcomes
Blinding of outcome assessment (detection bias) (patient-reported outcomes	a)NCS b)NPRS c) 2PD, Grip and pinch strength d)BCTQ Low risk	NCS was performed in an independent laboratory, and the staff did not know anything about the experiment. The diagnosis was made by a physician before being allocated to the appropriate research group. The rest of the parts of the examination were conducted by several physiotherapists who did not know anything about patient allocation. Eight other physiotherapists performed the physiotherapy procedures
Incomplete outcome data	High risk	imbalance in numbers for missing data across intervention groups
Selective reporting (reporting bias	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	We not found other bias

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Ballestero-Pérez 2016

1-Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☑Population ☑Intervention ☑ Comparator Group ☑ Outcome	Optional (Recommended) ☐ Timeframe for follow-up	☑ Yes ☐ No
2-Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☑ review question(s) ☑ a search strategy ☑inclusion/exclusion criteria ☑ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☑ Partial Yes ☐No
3-Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☐ Yes ☑No	
4-Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): ☑ searched at least 2 databases (relevant to research question) ☑ provided key word and/or search strategy ☑ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☑ searched the reference list / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☑ Partial Yes ☐ No
5-Did the review authors perform study selection in duplicate?		

For Yes, either ONE of thefollowing: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.		☐ Yes ☑ No
6-Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.		☐ Yes ☑No
7-Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full - text form but excluded from the review	For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☑ No
8-Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☑ described populations ☑ described interventions ☑described comparators ☑ described outcomes ☑ described research designs	For Yes, should also have ALL the following: ☑ described population in detail ☑ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting timeframe for follow-up	☐ Yes ☑ Partial Yes ☐ No
9-Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs For Partial Yes, must have assessed RoB from: ☑ unconcealed allocation, and ☑ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: ☐allocation sequence that was not truly random, and ☐selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☑ Partial Yes ☐ No Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☑ from confounding, and ☑ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☑ Partial Yes ☐ No Includes only RCTs

10-Did the review authors report on the sources of funding for the studies included in the review?		
For Yes: ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☑ No	
11-If meta-analysis was justified did the review authors use appropriate methods for statistical combination of results?		
RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☑ No meta-analysis conducted	
NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☑ No meta-analysis conducted	
12-If meta-analysis was performed did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?		
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☑ No meta-analysis conducted	
13-Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?		
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐ Yes ☑ No	
14-Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?		

For Yes: ☑There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☑Yes ☐ No
15-If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☑No meta- analysis conducted
16-Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☑The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☑Yes ☐ No

Basson 2017

1-Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☑Population ☑Intervention ☑ Comparator Group ☑ Outcome	Optional (Recommended) ☐ Timeframe for follow-up	☑ Yes ☐ No
2-Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☑ review question(s) ☑ a search strategy ☑inclusion/exclusion criteria ☑ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☑ a meta-analysis/synthesis plan, if appropriate, *and* ☑ a plan for investigating causes of heterogeneity ☑ justification for any deviations from the protocol	☑ Yes ☐ Partial Yes ☐No
3-Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☑ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☑ Yes ☐No	
4-Did the review authors use a comprehensive literature search strategy?		

For Partial Yes (all the following): ☑ searched at least 2 databases (relevant to research question) ☑ provided key word and/or search strategy ☑ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☑ searched the reference list / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☑ Partial Yes ☐ No
5-Did the review authors perform study selection in duplicate?		
For Yes, either ONE of thefollowing: ☑ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☑ Yes ☐ No	
6-Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☑ Yes ☐No	
7-Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes: ☑ provided a list of all potentially relevant studies that were read in full - text form but excluded from the review	For Yes, must also have: ☑ Justified the exclusion from the review of each potentially relevant study	☑ Yes ☐ Partial Yes ☐ No
8-Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☑ described populations ☑ described interventions ☑described comparators ☑ described outcomes ☑ described research designs	For Yes, should also have ALL the following: ☑ described population in detail ☑ described intervention in detail (including doses where relevant) ☑ described comparator in detail (including doses where relevant) ☑ described study's setting timeframe for follow-up	☑ Yes ☐ Partial Yes ☐ No
9-Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		

RCTs For Partial Yes, must have assessed RoB from: ☑ unconcealed allocation, and ☑ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: ☑allocation sequence that was not truly random, and ☑selection of the reported result from among multiple measurements or analyses of a specified outcome	☑ Yes ☐ Partial Yes ☐ No Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, and ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☑ No Includes only RCTs
10-Did the review authors report on the sources of funding for the studies included in the review?		
For Yes: ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☑ No	
11-If meta-analysis was justified did the review authors use appropriate methods for statistical combination of results?		
RCTs For Yes: ☑ The authors justified combining the data in a meta-analysis ☑AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☑ AND investigated the causes of any heterogeneity	☑ Yes ☐ No ☐ No meta-analysis conducted	
NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☐ No meta-analysis conducted	
12-If meta-analysis was performed did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?		

For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☑ No ☐ No meta-analysis conducted
13-Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☑ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☑ Yes ☐ No
14-Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐There was no significant heterogeneity in the results ☑ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☑Yes ☐ No
15-If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☑ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☑ Yes ☐ No ☐No meta- analysis conducted
16-Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☑The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☑Yes ☐ No

Huisstede 2010

1-Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☑Population ☑Intervention ☑ Comparator Group ☑ Outcome	Optional (Recommended) ☑ Timeframe for follow-up	☑ Yes ☐ No
2-Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		

For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☑ review question(s) ☑ a search strategy ☑ inclusion/exclusion criteria ☑ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☑ Partial Yes ☐ No
3-Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☑ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☑ Yes ☐ No	
4-Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): ☑ searched at least 2 databases (relevant to research question) ☑ provided key word and/or search strategy ☑ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☑ searched the reference list / bibliographies of included studies ☑ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☑ Partial Yes ☐ No
5-Did the review authors perform study selection in duplicate?		
For Yes, either ONE of thefollowing: ☑ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☑ Yes ☐ No	
6-Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: ☑ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☑ Yes extract from included studies ☐ No	
7-Did the review authors provide a list of excluded studies and justify the exclusions?		

For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full - text form but excluded from the review	For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☑ No
8-Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☑ described populations ☑ described interventions ☑described comparators ☑ described outcomes ☑ described research designs	For Yes, should also have ALL the following: ☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☑ described study's setting timeframe for follow-up	☐ Yes ☑ Partial Yes ☐ No
9-Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs For Partial Yes, must have assessed RoB from: ☑ unconcealed allocation, and ☑ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: ☐allocation sequence that was not truly random, and ☐selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☑ Partial Yes ☐ No Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☑ from confounding, and ☑ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☑ No Includes only RCTs
10-Did the review authors report on the sources of funding for the studies included in the review?		
For Yes: ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☑ No	
11-If meta-analysis was justified did the review authors use appropriate methods for statistical combination of results?		

RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☑ No meta-analysis conducted
NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☑ No meta-analysis conducted
12-If meta-analysis was performed did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☑ No meta-analysis conducted
13-Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☑ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☑ Yes ☐ No
14-Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐There was no significant heterogeneity in the results ☑ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☑Yes ☐ No
15-If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	

For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☑No meta- analysis conducted
16-Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☑The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☑Yes ☐ No

Huisstede 2017

1-Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☑Population ☑Intervention ☑ Comparator Group ☑ Outcome	Optional (Recommended) ☑ Timeframe for follow-up	☑ Yes ☐ No
2-Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☑ review question(s) ☑ a search strategy ☑inclusion/exclusion criteria ☑ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☑ Partial Yes ☐No
3-Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☑ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☑ Yes ☐No	
4-Did the review authors use a comprehensive literature search strategy?		

For Partial Yes (all the following): ☑ searched at least 2 databases (relevant to research question) ☑ provided key word and/or search strategy ☑ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☑ searched the reference list / bibliographies of included studies ☑ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☑ Partial Yes ☐ No
5-Did the review authors perform study selection in duplicate?		
For Yes, either ONE of thefollowing: ☑ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☑ Yes ☐ No	
6-Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: ☑ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☑ Yes extract from included studies ☐ No	
7-Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full - text form but excluded from the review	For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☑ No
8-Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☑ described populations ☑ described interventions ☑described comparators ☑ described outcomes ☑ described research designs	For Yes, should also have ALL the following: ☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☑ described study's setting timeframe for follow-up	☐ Yes ☑ Partial Yes ☐ No
9-Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		

RCTs For Partial Yes, must have assessed RoB from: ☑ unconcealed allocation, and ☑ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☑ Partial Yes ☐ No Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☑ from confounding, and ☑ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☑ No Includes only RCTs
10-Did the review authors report on the sources of funding for the studies included in the review?		
For Yes: ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☑ No	
11-If meta-analysis was justified did the review authors use appropriate methods for statistical combination of results?		
RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☑ No meta-analysis conducted	
NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☑ No meta-analysis conducted	
12-If meta-analysis was performed did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?		

For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☑ No meta-analysis conducted
13-Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: ☐ included only low risk of bias RCTs ☑ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☑ Yes ☐ No
14-Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: ☐There was no significant heterogeneity in the results ☑ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☑Yes ☐ No
15-If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☑No meta- analysis conducted
16-Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☑The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☑Yes ☐ No

Kim 2015

1-Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☑Population ☑Intervention ☑ Comparator Group ☑ Outcome	Optional (Recommended) ☐ Timeframe for follow-up	☑ Yes ☐ No
2-Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		

For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☑ review question(s) ☑ a search strategy ☑ inclusion/exclusion criteria ☑ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☑ Partial Yes ☐ No
3-Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☑ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☑ Yes ☐ No	
4-Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): ☑ searched at least 2 databases (relevant to research question) ☑ provided key word and/or search strategy ☑ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☐ searched the reference list / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☑ Partial Yes ☐ No
5-Did the review authors perform study selection in duplicate?		
For Yes, either ONE of thefollowing: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☐ Yes ☑ No	
6-Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☐ Yes extract from included studies ☑ No	
7-Did the review authors provide a list of excluded studies and justify the exclusions?		

For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full - text form but excluded from the review	For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☑ No
8-Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☑ described populations ☑ described interventions ☑described comparators ☑ described outcomes ☑ described research designs	For Yes, should also have ALL the following: ☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting timeframe for follow-up	☐ Yes ☑ Partial Yes ☐ No
9-Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs For Partial Yes, must have assessed RoB from: ☑ unconcealed allocation, and ☑ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: ☐allocation sequence that was not truly random, and ☐selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☑ Partial Yes ☐ No Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, and ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☑ No Includes only RCTs
10-Did the review authors report on the sources of funding for the studies included in the review?		
For Yes: ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☑ No	
11-If meta-analysis was justified did the review authors use appropriate methods for statistical combination of results?		

RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☑ No meta-analysis conducted
NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☑ No meta-analysis conducted
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For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☑No meta- analysis conducted
16-Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☑The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☑Yes ☐ No

Lim 2017

1-Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☑Population ☑Intervention ☑ Comparator Group ☑ Outcome	Optional (Recommended) ☐ Timeframe for follow-up	☑ Yes ☐ No
2-Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
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3-Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☑ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☑ Yes ☐No	
4-Did the review authors use a comprehensive literature search strategy?		

For Partial Yes (all the following): ☑ searched at least 2 databases (relevant to research question) ☑ provided key word and/or search strategy ☑ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☐ searched the reference list / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☑ Partial Yes ☐ No
5-Did the review authors perform study selection in duplicate?		
For Yes, either ONE of thefollowing: ☑ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☑ Yes ☐ No	
6-Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: ☑ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☑ Yes extract from included studies ☐ ☑ No	
7-Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full - text form but excluded from the review	For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☑ No
8-Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☑ described populations ☑ described interventions ☑described comparators ☑ described outcomes ☑ described research designs	For Yes, should also have ALL the following: ☑ described population in detail ☑ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting timeframe for follow-up	☐ Yes ☑ Partial Yes ☐ No
9-Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		

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NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, and ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☑ No Includes only RCTs
10-Did the review authors report on the sources of funding for the studies included in the review?		
For Yes: ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☑ No	
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Mckeon 2008

1-Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☑Population ☑Intervention ☑ Comparator Group ☑ Outcome	Optional (Recommended) ☐ Timeframe for follow-up	☑ Yes ☐ No
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7-Did the review authors provide a list of excluded studies and justify the exclusions?		

For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full - text form but excluded from the review	For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☑ No
8-Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☑ described populations ☑ described interventions ☑described comparators ☑ described outcomes ☑ described research designs	For Yes, should also have ALL the following: ☐ described population in detail ☑ described intervention in detail (including doses where relevant) ☑ described comparator in detail (including doses where relevant) ☐ described study's setting timeframe for follow-up	☐ Yes ☑ Partial Yes ☐ No
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NRSI For Partial Yes, must have assessed RoB: ☑ from confounding, and ☑ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☑ Partial Yes ☐ No Includes only RCTs
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Page 2012

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4-Did the review authors use a comprehensive literature search strategy?		

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16-Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: ☑The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☑Yes ☐ No