DMCN Developmental Medicine & Child Neurology

Effects, effect duration and adverse effects of extracorporeal shock wave therapy in children with spastic cerebral palsy: A systematic review.

Journal:	*Developmental Medicine & Child Neurology*
Manuscript ID	Draft
Manuscript Type:	Systematic Review
Date Submitted by the Author:	n/a
Complete List of Authors:	Janssen, Thijs; Revalidatiecentrum De Hoogstraat, child & youth Kuijper, Marie-Anne; Rehabilitation center De Hoogstraat, Department of Pediatrics; Revalidatiecentrum De Hoogstraat, Voorman, Jeanine; University Medical Centre Utrecht, and De Hoogstraat Rehabilitation, Centre of Excellence for Rehabilitation Medicine, Brain Centre Rudolf Magnus; University Medical Center Utrecht, Department of Rehabilitation, Physical Therapy Science & Sports, Brain Center Rudolf Magnus Verschuren, Olaf; Rehabilitation Centre DE Hoogstraat, Centre of Excellence;
Keywords:	cerebral palsy, spasticity, extracorporeal shock wave therapy, children, treatment

Effects, effect duration and adverse effects of extracorporeal shock wave therapy in children with spastic cerebral palsy: A systematic review.

Thijs Wim Janssen MSc,[1] Marie-Anne Kuijper MD,[2] Jeanine Voorman MD/PhD[3] & Olaf Verschuren PhD[4]

Corresponding Author:	Thijs Wim Janssen
Mail to:	t.janssen@dehoogstraat.nl
Address:	De Hoogstraat Revalidatie
	Rembrandtkade 10
	3583 TM Utrecht
	The Netherlands

WORD COUNT: 2922 Words

[1] Pediatric Physical Therapist at De Hoogstraat rehabilitation centre
[2] Rehabilitation Docter and Medical Manager at De Hoogstraat rehabilitation centre
[3] Rehabilitation Docter at Wilhelmina Childrens Hospital / Senior Researcher at Centre of Excellence for Rehabilitation Medicine Utrecht
[4] Olaf Verschuren, PhD: Brain Center Rudolf Magnus and Center of Excellence for Rehabilitation Medicine, University Medical Center Utrecht and De Hoogstraat Rehabilitation, Utrecht, The Netherlands

Shortened form of title:

ESWT in children with CP

Abstract

Aim

Spasticity leads to numerous problems in children with cerebral palsy (CP). Therefore, management of spasticity is a major priority. Despite recent publications that examined effects of extracorporeal shockwave therapy (ESWT) in children with spastic CP there is no systematic review about these effects. The aim of this study is to systematically review the literature on effects of ESWT on: 1) Domains of the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY); 2) Effect duration; 3) Adverse effects in children with spastic CP.

Method

Three databases were used (PubMed, Cochrane Library and PEDro library). Search terms were Cerebral Palsy, Muscle Spasticity, Shock Wave Therapy and terms fitting the ICF-CY. Inclusion criteria: 1) Use of ESWT to treat CP related spasticity; 2) Baseline and follow up measurement; 3) At least one outcome on one domain of the ICF-CY.

Results

Seven of initially 33 studies, of overall good and moderate quality, were included.

Interpretation

There is strong evidence that ESWT reduces resistance against passive movement and improves joint mobility and gait cycle. Studies described a sustained significant effect at four, eight and/or twelve weeks on the same outcomes. Only mild tolerable, short lasting adverse effects were mentioned.

What this paper adds

1. This review summarizes the effects of ESWT in children with spastic CP
2. Strong evidence that ESWT reduces resistance against passive movement
3. Strong evidence that ESWT improves joint mobility
4. Strong evidence that ESWT improves walking ability
5. Statements about safety, indications, effect duration and adverse effects of ESWT

Background

Cerebral Palsy (CP) is one of the main causes of posture and movement disorders in pediatric rehabilitation[1] with a pooled overall prevalence of 2.11 cases per 1000 live births.[2] CP describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. Cases are classified by appearance of symptoms in spasticity, dyskinesia and ataxia[3] in which spastic CP is the most common form.[4] Spasticity can lead to problems like pain, insufficient joint range of motion, sleep disturbance and walking disability.[5] Therefore, management of spasticity in children with CP is a major priority in pediatric rehabilitation.

In current medical literature, there is no consensus about the exact definition of spasticity, which leads to multiple definitions of spasticity.[6] Recently the European Support Program for Assembly of database for Spasticity Measurement suggested to define spasticity according to Pandyan[7] as a 'disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermitted or sustained involuntary activation of muscles'. There is a variety of treatment options to reduce spasticity and the symptoms that are related to spasticity. These options include oral medication, botulinum toxin (BTX), orthoses and surgery. The choice of treatment is always complex.[8] A problem with many treatment options is that they can be invasive, painful, expensive, come with unwanted adverse effects and, especially in the case of BTX for children with CP, are performed anesthetized.[9–14]

Recently, it has been shown that Extracorporeal Shock Wave Therapy (ESWT) is also able to reduce spasticity[15–21] and the symptoms related to spasticity in terms of pain,[19] hypertonia,[22] dystonia,[22] but also to improve range of motion,[18–20] motor skills[17,19] and walking ability[18,19] involving patients suffering from spasticity after stroke. Based on these results ESWT seems to be a safe, effective, practical and noninvasive method for reducing symptoms of spasticity. Two recent in vivo studies on Sprague-Dawley rats,[23,24] stated that compound muscle action potential (CMAP) amplitude was, temporarily, significantly smaller (-39%) immediate after treatment without delaying CMAP latency. Morphological changes on the neuromuscular junctions (NMJs) included a temporarily significantly degeneration of acetylcholine receptors (-26%)[23] and a temporarily reduction of the total NMJs in ESWT-exposed muscle by 80% due to destruction of endplates.[24] These results showed that the neurotransmission at affected NMJs was temporarily impaired immediately after one session of ESWT.[23] Until now, there is no systematic review that examined the effects of ESWT in children and youth with spastic CP. Therefore, the purpose of the present paper is to systematically review the literature regarding the use of ESWT in children and youth with spastic CP to address the following questions: 1) what are the effects on body functions and structures, activities and participation; 2); what is the duration of the effect; 3): what are the adverse effects; 4) what is the methodological quality of the studies?

Method

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[25] In this systematic review, evidence will be gathered and results will be categorized according International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) domains body functions and structures, activities and participation.[26] The data related to adverse effects and effect duration will also be collected.

Data sources and searches

Using a PICO search string, the authors searched PubMed, Cochrane Library and PEDro library. These databases were searched from their respective inceptions until August 2018. Search terms, or used synonyms derived from these terms, that were used were Cerebral Palsy, Muscle Spasticity, Shock Wave Therapy, Abnormal Reflex, Muscle hypertonia, Spasm, Articular Range Of Motion, Dystonia, Pain, Myalgia, Muscle Weakness, Muscle Strength, Contracture, Fatigue, Gait, Gait Disorders Neurologic, Motor Skills, Child Developmental Disorders, Sleep, Quality of Life, Social Problems, Social Participation, International Classification of Fuctioning, Disability and Health for Children and Youth, Refusal To Participate, Clonus, Withdrawel Response, Possitive Support Reaction, Associated Reaction, Co-Contractions, Ataxia, Diskinetic, Discomfort and Muscle Stiffness. The full searchstring can be send upon request by the first author.

Study selection

In the search string, articles were unlimited regarding study design and publication date. Titles and abstracts were assessed by the first author. The study selection was independently performed by two authors (TJ & OV). Conflicting opinions were

resolved through discussion until consensus was reached. Included studies were read in full text by two authors (TJ & OV) who are both experienced with CP rehabilitation. In addition, reference lists were checked by the first author to identify potential relevant publications. Studies were included if they met the following criteria: (1) The study used ESWT to treat (symptoms of) CP related spasticity; (2) Studies performed baseline and follow up measurements; (3) At least one study outcome according to the ICF-CY domains body functions and structures, activities & participation, personal factors and/or environmental factors must be presented; (4) Patients must be under eighteen years of age; (5) The language of the publication was English. Studies were excluded if they met the following criteria: (1) Studies using ESWT combined with invasive treatment such as BTX injection, phenol treatment, baclofen treatment or other chemical nerve blocks; (2) Studies exclusively treating adults; (3) Studies about the use of ESWT on spasticity caused by other pathology than CP such as stroke and multiple sclerosis; (4) Studies without a control group.

Data extraction

Data extraction was done by the first author and later checked by the fourth author. Statements conducted in the included studies regarding outcomes were not altered except the statement that spasticity was reduced by ESWT according to the Modified Ashworth Scale (MAS). Although the MAS is internationally the most commonly used clinical measure of spasticity, this ordinal scale is limited by poor inter-rater reliability. Furthermore, it does not measure spasticity according to Pandyans definition.[27–30] Therefore, the authors of this review decided to change the outcome of the MAS as an assessment for spasticity to an assessment for resistance against passive movement. This will be reflected as such in the results of this article. Both authors

recorded details of the number-, age-, sex-, pathology- and Gross Motor Function Classification System (GMFCS) of participants. Also, data about therapy parameters, treated muscles, placebo treatment and other therapy were extracted. Outcome measures, significant outcome of treatment, effect duration and adverse effects were recorded. Outcomes were categorized in the ICF-CY domains by the first author.

Quality assessment

In this systematic review, obtained reports were assessed by the same two authors that performed the data extraction. To assess the quality of included studies, the authors used the Physiotherapy Evidence Database (PEDro) score and categorized the studies according to the levels of evidence as stated by the American Association of Cerebral Palsy and Developmental Medicine (AACPDM).[31] PEDro is recommended for inclusion in health care practice and for library resource pages at institutions with professional preparation programs for rehabilitation professions[32] and is regarded as a valid measure of the methodological quality of clinical trials.[33] To make a statement the authors used the best evidence synthesis according to van Peppen et al. 2004[34] (Table 1). Obtained articles were independently reviewed in full texts by the same two reviewers that performed the data extraction for each specific paper. After this the PEDro scores and classification of the level of evidence for each single study was calculated separately. To improve the reliability of both scales, any disagreement between the reviewers was resolved by discussion until consensus was reached.

Here Table 1

Results

The initial search of the electronic databases and the manual search of reference lists identified 33 citations. After removing 11 duplicates, title and abstract of the remaining 22 studies were screened. Based on title and abstract 14 studies were excluded for not meeting the inclusion criteria in terms of language, pathologies, patient type or ESWT combined with invasive treatment. The remaining eight studies were read full text after which one study was excluded for not meeting the inclusion criteria because of the study design, which was a non-comparative study without control group.[35] The seven studies that remained contained a total of 190 participants. Figure 1 shows the flow chart which represents the search work.

Here figure 1.

The methodological quality was assessed with the PEDro scale and classified in levels of evidence according to the AACPDM (Table 2). The median score was six out of ten, and no study scored more than six points, indicating moderate to good quality. Four out of seven included studies were randomized controlled trials.[36–39]

Here Table 2.

Details of the number-, age-, sex-, pathology and GMFCS of participants are shown in Table 3. Also, data about therapy parameters, treated muscles, placebo and other therapy is shown in Table 4. Outcome measures, significant outcome of treatment, effect duration and adverse effects are placed in Table 5.

Here Table 3

Here Table 4

Here Table 5

Body functions and structures

Resistance against passive movement

All but one of the included studies used the MAS to evaluate the effect of ESWT on the resistance against passive movement. Two RCTs of good quality,[37,38] one RCT of moderate quality,[39] two clinical controlled trials (CCT) of good quality[40,41] and one CCT of poor quality[42] concluded that there was a significant decrease in the resistance against passive movement measured with the MAS.

Joint range of motion

One RCT of good quality,[38] two RCTs of moderate quality,[36,39] two CCTs of good quality[40,41] and one CCT of poor quality[42] concluded that there was a significant increase in joint range of motion regarding dorsal flexion of the ankle[36,38–42] and regarding elbow extension, wrist extension, hip abduction and knee extension.[39] Measurements were taken using a goniometer[38–42] or using 3D gait analysis to examine ankle dorsal flexion in gait cycle.[36]

Activities & participation

Walking ability measured by a 3D gait analysis system

One RCT of good quality[37] and one RCT of moderate quality[36] concluded that the walking ability significantly improved after a combined therapy of ESWT and physical

therapy compared to a control group that received only physical therapy. Measurements were conducted using a 3D gait analysis system. Significant improvements were found in terms of speed,[36,37] cadence,[36,37] stride length,[36,37] single limb support,[36] double limb support,[36] gait cycle time,[37] stance phase percentage[37] and swing phase percentage.[37]

Gross motor function

Only one CCT of good quality[40] examined the effect of ESWT on gross motor skills by using the Gross Motor Function Measure (GMFM). The study compared an intervention group that received combined ESWT and traditional conservative therapy with a control group that received stand-alone traditional conservative therapy. Measurements were done at baseline and after twelve weeks. Although GMFM improved, it showed no statistically significant difference between the groups.

Personal factors & environmental factors

None of the included studies made any comments about personal factors, environmental factors, quality of life and/or participation.

Effect Duration

Depending on the moment of follow-up measurements, studies described a sustained significant positive effect at four weeks on resistance against passive movement,[38,41] joint range of motion[36,38,41] and gait cycle[36] and at eight weeks on resistance against passive movement and joint range of motion[39] and at twelve weeks on resistance against passive movement,[37,40] joint range of motion[40] and gait cycle.[37] One study described significant positive effects on resistance against passive

movement and joint range of motion measured at four weeks that were lost at twelve weeks.[42]

Adverse effects

Five out of seven included studies indicated that ESWT is painless and does not require any kind of anesthesia or the use of analgesic drugs.[37,38,40–42] One study did not report any comments about adverse effects[36] and one study described adverse effects in order of small superficial hematomas, petechial and light pain during the therapy which was expressed by three out of fifteen patients. These side effects were tolerated by all the patients and disappeared after one to seven days.[39]

Evidence statement

According to the best evidence synthesis according to van Peppen et al. 2004[34] it can be concluded that there is strong evidence that ESWT reduces resistance against passive movement measured by the MAS[37–39] and improves joint mobility regarding ankle dorsal flexion measured by goniometry in children with CP.[36,38,39] Furthermore, we can conclude that there is strong evidence that walking ability, measured by a 3D gait analysis system, significantly improves in terms of speed, cadence and stride length, in a combined ESWT and physical therapy program when compared to physical therapy as a stand-alone treatment in children with CP.[36,37]

There is limited evidence that walking ability, measured by a 3D gait analysis system, significantly improves in terms of single limb support, double limb support,[36] gait cycle time, stance phase percentage and swing phase percentage,[37] in a combined ESWT and physical therapy program when compared to physical therapy as a stand-

alone treatment in children with CP.[36,37] No significant evidence has been found that ESWT combined with traditional therapy improves gross motor function compared to traditional therapy as stand-alone treatment.[40]

Discussion

Although the evidence base is weak due to small sample sizes of the included studies, the results of the present systematic review support the use of ESWT as being beneficial for reducing spasticity related symptoms in children with CP. All but one[39] of the included studies focused on children under the age of 12 which makes it difficult to predict treatment outcome on adolescents. There is strong evidence for reduction of resistance against passive movement and improvement in joint range of motion and walking ability. This review shows similar results when compared with studies that examine the effects from ESWT on resistance against passive movement,[15–21] joint range of motion[18–20] and walking ability[18,19] on adult patients that suffer from spasticity after stroke. Therefore, ESWT presents itself as a suitable treatment option with the advantage that it is a cheap, non-invasive, pain free treatment. Although ultrasound guided BTX injections might be a more precise treatment, especially with transcutaneous electric nerve stimulation, there are some benefits in favor of ESWT when compared to BTX. Known adverse effects involving BTX are such as generalized weakness, non-specific pain, dysphagia and aspiration pneumonia.[11–14,43–45] These adverse effects have a reported incidence of at least 3% of the injected episodes.[11,45,46] Also, a recent study shows a reduction of muscle volume after the first BTX treatment in all participants.[47] This review supports the statement made by Guo[15] and Mori[22] that ESWT is considered a safe, effective, practical and noninvasive treatment to reduce spasticity related symptoms.

There are, however, some limitations regarding the included studies. All included studies were monocentral studies with modest studies groups varying from 12 to 66 participants. Therefore, none of the studies are qualified as levels of evidence I according to the AACPDM. There is a wide or unknown spread of GMFCS levels of the participants in the included studies. This makes it difficult to specify treatment indications related to GMFCS level. Future studies should ideally be multicenter studies with large subject groups (>100) that make strong statements about GMFCS classification regarding study participants to further specify treatment indications. One included study of moderate quality had a range regarding age from 10 to 46 years with a mean age of 31 years.[39] Because this study included children it was included in this systematic review. However, one should be careful to draw conclusions based on this study about the effects of ESWT on symptoms of spasticity regarding children with spastic CP. Most goals set in rehabilitation are related to the ICF-CY domains activity and daily life participation. Most of the included studies however, focused on the ICF-CY domain body functions and structures in terms of resistance against passive movement and joint range of motion.[38,39,41,42] Only three included studies measured the ICF domain activities in terms of walking[36,37] and gross motor skills.[40] There is no consensus among the included studies regarding stimulus parameters in terms of Bar (0.6 – 2.0), Herz (4 – 8), total impulses given (700 – 2000) and kinetic energy (0.03 mm/mj^2 – 0.32 mm/mj^2). The results seem unaffected by this wide spread of stimulus parameters. One study included in this review uses a placebo treatment in the control group using 100 shots with the lowest stimulus parameters possible and using two cushions between the body part and the ESWT device.[41] Although unlikely, effects on the muscle tissue in the control group receiving this placebo treatment cannot be

excluded because the ESWT did produce some kinetic energy. Studies measuring joint range of motion of the ankle measured with a stretched knee[36,38,40] or don't describe body positioning during this measurement[39,41,42]. Measurement with a stretched knee only gives information about change in the m. gastrocnemius and not the m. soleus due to its bi-articular anatomy. This point is highly relevant because no comment can be made about effects on the m. soleus. There are studies published that study the effect of BTX on deep tissue musculature[48,49]. The included studies used in this systematic review however, all treated superficial muscles. The effects from ESWT on deep tissue musculature are unknown and need further investigation.

In conclusion, ESWT seems to be a promising treatment to reduce symptoms of spasticity with strong evidence for improving walking ability when combined with physical therapy and joint range of motion as standalone treatment. There is also strong evidence that ESWT reduces resistance against passive movement as standalone treatment.

Authors disclosure

The authors thank Avans plus, de Hoogstraat rehabilitation centre, Centre of Excellence for Rehabilitation Medice Utrecht and the Wilhelmina Childrens hospital. The authors have stated that they had no interests which might be perceived as posing a conflict or bias. No funding was provided to perform this systematic review.

References

1. Koman LA, Smith BP, Shilt JS. Cerebral palsy. *Lancet*. 2004;363(9421):1619–1631. doi:10.1016/S0140-6736(04)16207-7.
2. Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: A systematic review and meta-analysis. *Dev Med Child Neurol*. 2013;55(6):509–519. doi:10.1111/dmcn.12080.
3. Cans C. Fourth World Fisheries Congress • Vancouver , Canada • 2004 Development of a Bottom-set Gillnet to Catch Dusky Flathead (Platycephalus fuscus) Whilst Minimizing Bycatch. *Fish*. 2004:2004–2004. doi:10.1111/j.1469-8749.2000.tb00695.x.
4. Hagberg B, Hagberg G, Olow I. the Changing Panorama of Cerebral-Palsy in Sweden .4. Epidemiological Trends 1959-78. *Acta Paediatr Scand*. 1984;73(4):1–2. doi:10.1111/j.1651-2227.1984.tb09951.x.
5. Shamsoddini A, Amirsalari S, Hollisaz MT, Rahimniya A, Khatibi-Aghda A. Management of spasticity in children with cerebral palsy. *Iran J Pediatr*. 2014;24(4):345–351. doi:10.3944/AOTT.2009.081.
6. Malhotra S, Pandyan AD, Day CR, Jones PW, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. *Clin Rehabil*. 2009;23(7):651–658. doi:10.1177/0269215508101747.
7. Pandyan AD, Gregoric M, Barnes MP, e.a. Spasticity: Clinical perceptions, neurological realities and meaningful measurement. *Disabil Rehabil*. 2005;27(1–2):2–6. doi:10.1080/09638280400014576.
8. Matthews DJ, Birol B. Management of spasticity in children with cerebral palsy Beyin felçli çocuklarda spastisitenin tedavisi. *Acta Orthop Traumatol Turc*. 2009;43(2):81–86. doi:10.3944/AOTT.2009.81.
9. Brin MF, Mallett M JJ. *Scientific and Therapeutic Aspects of Botulinum Toxin*.; 2002.
10. Karp BI, Cole R a, Cohen LG, Grill S, Lou JS, Hallett M. Long-term botulinum toxin treatment of focal hand dystonia. *Neurology*. 1994;44(1):70–76. doi:10.1212/WNL.44.1.70.
11. O'flaherty SJ, Janakan V, Morrow AM, Scheinberg AM, Waugh MCA. Adverse events and health status following botulinum toxin type A injections in children with cerebral palsy. *Dev Med Child Neurol*. 2011;53(2):125–130. doi:10.1111/j.1469-8749.2010.03814.x.
12. Albavera-Hernández C, JM R, AJ I. Safety of botulinum toxin type A among children with spasticity secondary to cerebral palsy: a systematic review of randomized clinical trials. *Clin Rehabil*. 2009;23(5):394–407. doi:10.1177/0269215508099860.
13. Love SC, Novak I, Kentish M, e.a. Botulinum toxin assessment, intervention and after-

care for lower limb spasticity in children with cerebral palsy: International consensus statement. *Eur J Neurol*. 2010;17(SUPPL. 2):9–37. doi:10.1111/j.1468-1331.2010.03126.x.

14. Naidu K, Smith K, Sheedy M, Adair B, Yu X, Graham HK. Systemic adverse events following botulinum toxin A therapy in children with cerebral palsy. *Dev Med Child Neurol*. 2010;52(2):139–144. doi:10.1111/j.1469-8749.2009.03583.x.
15. Guo P, Gao F, Zhao T, Sun W, Wang B, Li Z. Positive Effects of Extracorporeal Shock Wave Therapy on Spasticity in Poststroke Patients: A Meta-Analysis. *J Stroke Cerebrovasc Dis*. 2017;26(11):2470–2476. doi:10.1016/j.jstrokecerebrovasdis.2017.08.019.
16. Lee J-Y, Kim S-N, Lee I-S, Jung H, Lee K-S, Koh S-E. Effects of Extracorporeal Shock Wave Therapy on Spasticity in Patients after Brain Injury: A Meta-analysis. *J Phys Ther Sci*. 2014;26(10):1641–1647. doi:10.1589/jpts.26.1641.
17. Li T-Y, Chang C-Y, Chou Y-C, e.a. Effect of Radial Shock Wave Therapy on Spasticity of the Upper Limb in Patients With Chronic Stroke. *Medicine (Baltimore)*. 2016;95(18):e3544. doi:10.1097/MD.0000000000003544.
18. Sawan S, Abd-Allah F, Hegazy MM, Farrag MA, El-Den NHS. Effect of shock wave therapy on ankle plantar flexors spasticity in stroke patients. *NeuroRehabilitation*. 2017;40(1):115–118. doi:10.3233/NRE-161396.
19. Taheri P, Vahdatpour B, Mellat M, Ashtari F, Akbari M. Effect of Extracorporeal Shock Wave Therapy on Lower Limb Spasticity in Stroke Patients. 2017;20(6):338–343.
20. Wu Y-T, Chang C-N, Chen Y-M, Hu G-C. Comparison of the effect of focused and radial extracorporeal shock waves on spastic equinus in patients with stroke: a randomized controlled trial. *Eur J Phys Rehabil Med*. 2017:1–27. doi:10.23736/S1973-9087.17.04801-8.
21. Yoon SH, Shin MK, Choi EJ, Kang HJ. Effective site for the application of extracorporeal shock-wave therapy on spasticity in chronic stroke: Muscle belly or myotendinous junction. *Ann Rehabil Med*. 2017;41(4):547–555. doi:10.5535/arm.2017.41.4.547.
22. Mori L, Marinelli L, Pelosin E, e.a. Shock Waves in the Treatment of Muscle Hypertonia and Dystonia. *Biomed Res Int*. 2014;2014:1–9. doi:10.1155/2014/637450.
23. Kenmoku T, Ochiai N, Ohtori S, e.a. Degeneration and recovery of the neuromuscular junction after application of extracorporeal shock wave therapy. *J Orthop Res*. 2012;30(10):1660–1665. doi:10.1002/jor.22111.
24. Kenmoku T, Nemoto N, Iwakura N, e.a. Extracorporeal shock wave treatment can selectively destroy end plates in neuromuscular junctions. *Muscle and Nerve*. 2018;57(3):466–472. doi:10.1002/mus.25754.

25. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Bmj-British Med J*. 2009;339(2):1–13. doi:Artn B2535\rDoi 10.1136/Bmj.B2535.
26. Schiariti V, Selb M, Cieza A, O'Donnell M. International Classification of Functioning, Disability and Health Core Sets for children and youth with cerebral palsy: A consensus meeting. *Dev Med Child Neurol*. 2015;57(2):149–158. doi:10.1111/dmcn.12551.
27. Alibiglou L, Rymer WZ, Harvey RL, Mirbagheri MM. The relation between Ashworth scores and neuromechanical measurements of spasticity following stroke. *J Neuroeng Rehabil*. 2008;5:1–14. doi:10.1186/1743-0003-5-18.
28. Blackburn M, van Vliet P, Mockett S. People With Stroke Modified Ashworth Scale in the Lower Extremities of Reliability of Measurements Obtained With the. *Phys Ther*. 2002;82(1):25–34.
29. Pandyan AD, Johnson GR, Price CIM, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil*. 1999;13(5):373–383. doi:10.1191/026921599677595404.
30. Fleuren JFM, Voerman GE, Erren-Wolters C V., e.a. Stop using the Ashworth Scale for the assessment of spasticity. *J Neurol Neurosurg Psychiatry*. 2010;81(1):46–52. doi:10.1136/jnnp.2009.177071.
31. Butler C, Darrah J. Format : Abstract Effects of neurodevelopmental treatment (NDT) for cerebral palsy : an AACPDM evidence report . 2002;10(11):778–790.
32. Blobaum P, Librarian HP. Physiotherapy Evidence Database (PEDro) ADVANTAGES / DISADVANTAGES. 2005;10(8):8–10.
33. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother*. 2009;55(2):129–133. doi:10.1016/S0004-9514(09)70043-1.
34. Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? *Clin Rehabil*. 2004;18(8):833–862. doi:10.1191/0269215504cr843oa.
35. Mirea A, Onose G, Padure L, Rosulescu E. Extracorporeal shockwave therapy (ESWT) benefits in spastic children with cerebral palsy (CP). *J Med Life*. 2014;7(3):127–132. doi:10.1016/j.rehab.2014.03.1262.
36. Abdel Gawad HA, Abdel Karim AE, Mohammed AH. Shock wave therapy for spastic plantar flexor muscles in hemiplegic cerebral palsy children. *Egypt J Med Hum Genet*. 2015;16(3):269–275. doi:10.1016/j.ejmhg.2014.12.007.
37. El-Shamy SM, Eid MA, El-Banna MF. Effect of Extracorporeal Shock Wave Therapy

on Gait Pattern in Hemiplegic Cerebral Palsy. *Am J Phys Med Rehabil*. 2014;93(12):1065–1072. doi:10.1097/PHM.0000000000000133.

38. Park DS, Kwon DR, Park GY, Lee MY. Therapeutic effect of extracorporeal shock wave therapy according to treatment session on gastrocnemius muscle spasticity in children with spastic cerebral palsy: A pilot study. *Ann Rehabil Med*. 2015;39(6):914–921. doi:10.5535/arm.2015.39.6.914.
39. Vidal X, Morral A, Costa L, Tur M. Radial extracorporeal shock wave therapy (rESWT) in the treatment of spasticity in cerebral palsy: A randomized, placebo-controlled clinical trial. *NeuroRehabilitation*. 2011;29(4):413–419. doi:10.3233/NRE-2011-0720.
40. Wang T, Du L, Shan L, e.a. A Prospective Case-Control Study of Radial Extracorporeal Shock Wave Therapy for Spastic Plantar Flexor Muscles in Very Young Children With Cerebral Palsy. *Medicine (Baltimore)*. 2016;95(19):1–13. doi:10.1097/MD.0000000000003649.
41. Gonkova MI, Ilieva EM, Ferriero G, Chavdarov I. Effect of radial shock wave therapy on muscle spasticity in children with cerebral palsy. *Int J Rehabil Res*. 2013;36:284–290. doi:10.1097/MRR.0b013e328360e51d.
42. Amelio E, Manganotti P. Effect of shock wave stimulation on hypertonic plantar flexor muscles in patients with cerebral palsy: A placebo-controlled study. *J Rehabil Med*. 2010;42(4):339–343. doi:10.2340/16501977-0522.
43. Kolaski K. Botulinum toxin: Did the black box warning change how we treat children with cerebral palsy? *Dev Med Child Neurol*. 2018;60:440–441. doi:10.1111/dmcn.13719.
44. Apkon SD, Cassidy D. Safety Considerations in the Use of Botulinum Toxins in Children With Cerebral Palsy. *PM R*. 2010;2(4):282–284. doi:10.1016/j.pmrj.2010.02.006.
45. Paget SP, Swinney CM, Burton KLO, Bau K, O'Flaherty SJ. Systemic adverse events after botulinum neurotoxin A injections in children with cerebral palsy. *Dev Med Child Neurol*. 2018:1–6. doi:10.1111/dmcn.13995.
46. Papavasiliou AS, Nikaina I, Foska K, Bouros P, Mitsou G, Filiopoulos C. Safety of botulinum toxin a in children and adolescents with cerebral palsy in a pragmatic setting. *Toxins (Basel)*. 2013;5(3):524–536. doi:10.3390/toxins5030524.
47. Alexander C, Elliott C, Valentine J, e.a. Muscle volume alterations after first botulinum neurotoxin A treatment in children with cerebral palsy: a 6-month prospective cohort study. *Dev Med Child Neurol*. 2018;i(11). doi:10.1111/dmcn.13988.
48. Choi JY, Jung S, Rha DW, Park ES. Botulinum toxin type a injection for spastic equinovarus foot in children with spastic cerebral palsy: Effects on gait and foot pressure distribution. *Yonsei Med J*. 2016;57(2):496–504.

doi:10.3349/ymj.2016.57.2.496.

49. Bollens B, Gustin T, Stoquart G, Detrembleur C, Lejeune T, Deltombe T. A randomized controlled trial of selective neurotomy versus botulinum toxin for spastic equinovarus foot after stroke. *Neurorehabil Neural Repair*. 2013;27(8):695–703. doi:10.1177/1545968313491002.

Tables

Table 1. Beste evidence synthesis according to van Peppen et al. 2004

Strong evidence	Provided by statistically significant findings in outcome measures in - At least two high quality RCTs, with PEDro scores of at least 4 points
Moderate evidence	Provided by statistically significant findings in outcome measures in - At least one high-quality RCT and - At least one low quality (3 points on REDro or less) RCT or one high quality CCT
Limited evidence	Provided by statistically significant findings in outcome measures in - At least one high-quality RCT or - At least two high quality CCTs (in the absence of high quality RCTs)
Indicative findings	Provided by statistically significant findings in outcome measures in at least - One high-quality CCT of low-quality RCTs (in the absence of high-quality RCT), or - Two studies of a non-experimental nature with sufficient quality (in absence of RCTs and CCTs)
No or insufficient evidence	- In the case that results of eligible studies do not meet the criteria for one of the above stated levels of evidence, or - In the case of conflictiing (statistically significant positive and statistically significant negative) results among RCTs and CCTs, or - In the case of no eligible studies

- If the number of studies that show evidence <50% of the total number of studies found within the same category of methodologigal quality and study design (RCT, CCT or non-experimental studies), no evidence will be classified.
- CCT: Clinical controlled trial; RCT: Randomized controlled trial

Table 2. Levels of evidence according to the AACPDM

Reference	Published in	Design	Pedro score	Classification	Levels of evidence
Park et al.	2015	RCT	6/10	Good	Level II
El-Shamy et al.	2014	RCT	6/10	Good	Level II
Gawad et al.	2015	RCT	4/10	Moderate	Level II
Vidal et al.	2011	RCT	4/10	Moderate	Level II
Wang et al.	2016	CCT	6/10	Good	Level III
Gonkova et al.	2013	CCT	6/10	Good	Level IV
Amelio & Manganotti	2010	CCT	3/10	Poor	Level IV

Table 3 Subject parameters

Study	Participants				
Reference	***N***	***Age, range, mean±SD***	***M/F***	***Participants***	***GMFCS level participants***
Abdel Gawad et al. 2015	30	Range 5 - 7 years old Mean±SD Control 5.83±0.34 Study 5.75±0.51	Control 6/9 Study 6/9	Spastic CP (hemiplegic)	Unknown (all patients were able to stand with support)
Amelio & Manganotti 2010	12	Range 6 - 11 years old Mean±SD 8±2.31	6/6	Spastic CP (unilateral spastic equinus foot)	Unknown (all patients were able to ambulate, assisted or unassistent)
El-Shamy et al. 2014	30	Range 6 - 8 years old Mean±SD Control 6.8±0.7 Study 6.93±0.8	Control 9/6 Study 9/6	CP (hemiplegic)	Unknown (all patients were able to walk without walking device)
Gonkova et al. 2013	25	Range unknown Mean±SD 4.84±3.11	16/9	Spastic CP (hemiplegic)	Unknown
Park et al. 2015	12	Range unknown Mean±SD Control 7.0±3.1 Study 6.8±2.3	Control 4/2 Study 3/3	Spastic CP (diplegia & hemiplegia)	Control Level II/2 Level III/4 Study Level II/2 Level III/4
Vidal et al. 2011	15	Range 10 - 46 years old Mean±SD 31 ±unknown	12/3	Spastic CP	Unkown
Wang et al. 2016	66	Range Control 1.1 - 5 years old Study 1 - 4.79 years old Mean±SD Control 2.25±1.18 Study 2.24±1.09	Control 21/11 Study 23/11	Spastic CP	Unknown

- CP: Cerebral palsy; GMFCS: Gross Motor Function Classification System; M/F: Male / Female; N: Norm; SD: Standard Deviation

Table 4 Intervention parameters

Study	**Intervention program**					
Reference	***Number of sessions***	***Frequency***	***Treatment***	***Treateed muscles***	***Placebo***	***Other treatment***
Abdel Gawad et al. 2015	3 sessions	1 session a week	700 shots / session 0.32 mJ/mm2	Gastrocnemius muscles and soleus muscles mainly in the middle of the belly		The designed therapeutic exercises program used for the control and study groups included changing position exercises, balance training, manual standing on the mat, grasping the child around his knees, manual standing on the mat with step forward and step backward grasping the child around both knees, standing on the mat by slightly pushing the child forward, backward and laterally to increase standing balance. Also the use of balance board and medical ball is useful to improve equilibrium, protective and righting reactions, strengthening exercises of the weak muscles like dorsiflexors using manual resistive exercises, stoop and recovery exercises from standing position, quatting to standing exercise and gait training exercise.
Amelio & Manganotti 2010	1 session	-	1500 shots 0.03 mJ/mm2	Gastrocnemius muscles and soleus muscles mainly in the middle of the belly using an ultrasound pointerguide	One placebo treatment session in which no shock waves were applied	-
El-Shamy et al. 2014	12 sessions	1 session a week	1500 shots / muscle 5 Herz 0.03 mJ/mm2	Gastrocnemius muscles and soleus muscles mainly in the middle of the belly using an ultrasound pointer-guide	-	Both treatment groups received conventional physical therapy program, which included neurodevelopmental techniques,muscle stretching, strengthening exercises, pro-prioceptive training, and balance and gait training, for three months (1 hour/day, 3 days/week).
Gonkova et al. 2013	1 session	-	1500 shots 5 Herz 1.5 Bars	gastrocnemius and soleus muscle of the lower limb, mostly in the middle of the muscle belly. (not treated seperatly)	Before the active stimulation 4 weeks later, a placebo session was applied. For this treatment, two cushions were inserted between the large head of the applicator and the muscles and 100 shots were applied with the lowest intensity.	-
Park et al. 2015	Control One true session in week 1 and 2 sham sessions in	1 session a week	1500 shots / session 4 Herz 0.03	gastrocnemius muscle mainly in the middle of the muscle belly	One true session in week 1 and 2 sham sessions in week 2 & 3	In addition, patients received outpatient rehabilitation treatment during the treatment and after ESWT treatment, including twice weekly sessions of stretching exercises, strengthening

	week 2 & 3 Study 3 sessions		mJ/ mm2			exercises, functional electrical stimulation, and progressive gait training.
Vidal et al. 2011	3 sessions	1 session a week	2000 shots in each spastic muscle in group I 4000 shots in group II (2000 in spastic muscle and 2000 in antagonist muscle). 8 Herz 0.1 mJ/mm2. 2 Bar.	6 biceps brachii, 6 wrist flexors, 5 hip adductors, 10 gastrocnemius, 10 soleus and 3 hamstrings	Group I (14 muscles): received rESWT in spastic muscle. Group II (13 muscles): received rESWT in spastic muscle + rESWT in antagonist muscle. Group III (13 muscles): received placebo via application of a sham rESWT with sound in spastic muscle	-
Wang et al. 2016	12 sessions	1 session a week	1500 shots per session and leg 8 Herz 0.030 mJ / mm2 0.6 Bar	Gastrocnemius and soleus muscle (evenly distributed)	-	Patients in both groups received traditional conservative therapy consisting of physical therapy, Chinese massage, meridian mediation, and muscle stimulation for 3 months (6 days per week, 30 minutes per type of therapy).

- mJ/mm2: Millijoule per square millimeter; rESWT: radial Extracorporeal Shock Wave Therapy

Table 5 Outcome measures, significant outcome of treatment, effect duration and adverse effects

Study	**Results**			
Reference	***Outcome measures***	***Significant outcome after treatment***	***Effect duration***	***Side effects***
Abdel Gawad et al. 2015	H/M ratio measurement 3D gait analysis	**H/M ratio** MD 1.80 **Gait measurements** speed MD 0.23, cadence MD -1.20, stride length MD 0.25, single limb support MD 0.03, double limb support MD -0.049 **Maximum ankle dorsiflexion** Intitial contact MD 11.07 midstance 7.00 stance phase 6.67 mid swing 10.93	Results were measured at the 4th week after shock wave treatment	Unknown
Amelio & Manganotti 2010	PROM of the ankle by an electric goniometer MAS of the plantar foot flexors Pedobarometric measures	**PROM** increased from 20° to 50° **MAS** outcome went from 3.3 (SD 0.49) to 1.8 (SD 0.38) **Pedobarometric evaluation** plantar surface area (cm2) increased from 40.3 to 80.2 kPa on the hindfoot increased from 20.6 to 99.6	Effects persisted between baseline and after 4 weeks. There were no stastically significant group differences after 12 weeks	The therapy is painless and does not require any kind of anaesthesia or the use of analgesic drugs
El-Shamy et al. 2014	MAS Gait parameters	**MAS** 1.86 (0.22) control- vs. 1.63 (0.23) studygroup **The gait parameters** stride length 0.5 m. control- vs. 0.74 m. studygroup cadence 125 steps/min control- vs. 119 steps/min studygroup speed 0.6 m/sec control- vs. 0.75 m/sec studygroup cycle time 0.48 sec control- vs. 0.65 sec studygroup stance phase percentage 50.4% control- vs. 55.9% studygroup were 0.5 m, 125 steps/min, 0.6 m/sec, 0.48 sec, and 50.4% and 0.74 m, 119 steps/min, 0.75 m/sec, 0.65 sec, and 55.9% for the control group and the study group	Evaluation was done at the end of 3 months of treatment	The therapy is painless and does not require any kind of anesthesia or the use of analgesic drugs.
Gonkova et al. 2013	PROM MAS	**PROM** increased after ESWT (47.00±2.298 versus 33.25±2.208) **MAS score** decreased from 2.77	Assessment was done before, after, and 2 and 4 weeks. Results persisted at 4 weeks.	The treatment was not painful and no anesthesia was needed.

	Baropodometria	to 2.00 points **Baropodometria** Increase in plantar surface contact area (81.32±6.14 to 101.58±5.41 cm2) and heel pressure (50.47±6.61 to 75.17±3.42 N/cm2)		
Park et al. 2015	MAS PROM median gastrocmenius RPI	**MAS** score decreased in both groups after the first session. lower immediately and at 4 weeks after the third session (1.0±0.4 vs. 2.0±0.7, 1.1±0.5 vs. 2.3±0.8) **PROM** score increased in both groups after the first session. (13.3° ±3.7° vs. 13.6°±3.8°) mean PROM of ankle dorsiflexion in studygroup was higher immediately and at 4 weeks after the third ESWT (22.5°±2.7° vs. 7.9°±1.3°, 19.1°±3.7°vs. 7.3°±1.8°) mean **RPI** of the medial GCM was decreased signif- icantly immediately after the first ESWT in both groups. (130.7±6.1 vs. 134.8±8.5) However, the mean RPI of the medial GCM in group 2 was significantly lower than that in group 1 im- mediately and at 4 weeks after the third ESWT (127.6±9.8 vs. 146.6±7.4, p≤0.001; 136.6±7.6 vs. 147.9±5.0)	Effect of ESWT on spastic medial gastrocnemius in children with spastic CP is dependent on the number of ESWT sessions.	ESWT is not painful. It does not require anesthesia or analgesic drugs. Adverse events were monitored throughout the treatment and after treatment. No side effect was observed until 4 weeks after the third ESWT.
Vidal et al. 2011	PROM Ashworth Scale	A decrease in the Ashworth Scale and in- crease in the PROM were observed in all patients treated with rESWT.	Positive results were maintained for at least 2 months after treatment and at three months the results were the same as those obtained just before treatment.	Observed side effects were 3 small superficial hematomas, petechial, and light pain during the therapy expressed by 3 patients. All side effects were tolerated by all the patients and disappeared after 1–7 days
Wang et al. 2016	MAS PROM GMFM-88	**MAS** scores decreased with -42% (2.6±1.0 to 1.5±1.0) on the left side and -37% 1.9±0.6 to 1.2±0.7) on the right side **PROM** increased with +87% (18.0±11.6 degrees at to 33.6±11.1) on the left side and +57% (21.9±12.6 to 34.4±10.0) on the right side	Evaluation was done after 12 weeks of treatment	Local or general anesthesia was not applied

- CM2: Square Sentimeter; CP: Cerebral Palsy; ESWT: Extracorporeal Shock Wave Therapy; GCM: Gastrocnemius muscle; GMFM: Gross Motor Function Measure; H/M: Hoffman reflex/Motor response; kPA: Peak pressure volume; m: Meter; MAS: Modified Ashworth Scale; MD: Mean Mifference; mJ/mm2: Millijoule per square millimeter; m/sec: Meters per second; N/cm2: Newton per square centimeter; PROM: Passive Range Of Motion; rESWT: radial Extracorporeal Shock Wave Therapy; RPI: red pixel intensity; SD: Standard Deviation; steps/min: Steps per minute; vs: Versus

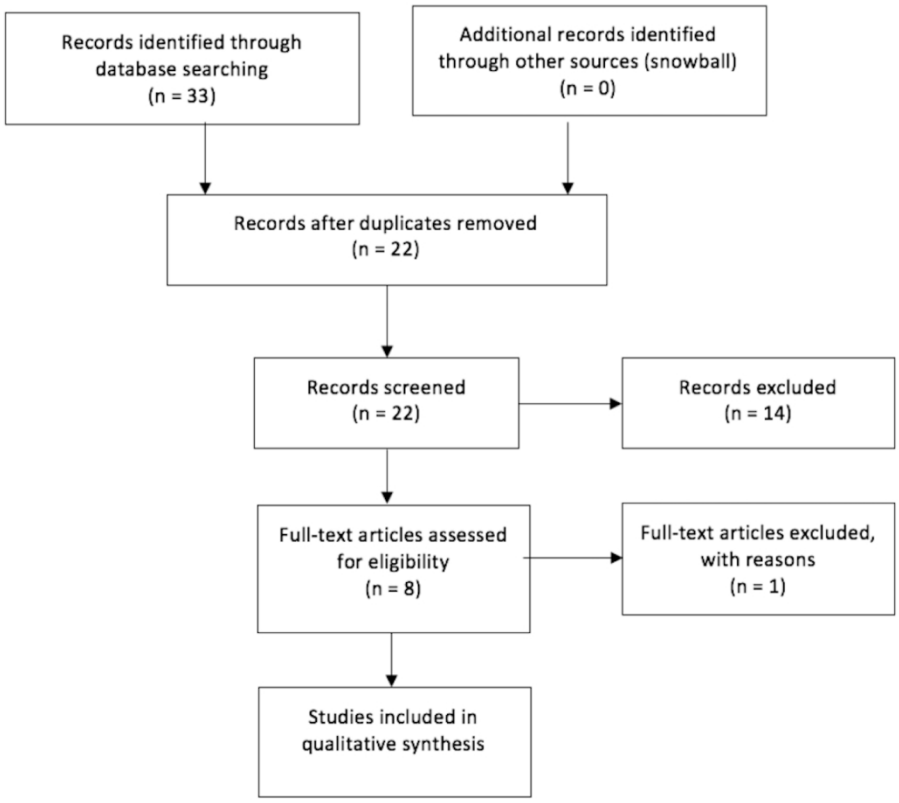

Figure 1. Flow chart study selection

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2 / 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4 / 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 / 7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7, 8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 10, 11, 12, 13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 13, 14, 15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 14 & 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.