

# Clinical effects of spinal manipulation in the management of children and young adults diagnosed with autism spectrum disorder — a systematic review of the literature

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## ABSTRACT

**Background:** Autism spectrum disorders (ASD) are classified as pervasive developmental disorders that permanently affect essential mental functions. Symptoms include quality-related disorders in areas of social interaction, verbal and non-verbal communication, the variability of behaviours and specific learning disabilities. Abnormalities in development are already apparent in early childhood. **Aim:** To identify evidence for the clinical benefits of manual therapy of the musculoskeletal system in children diagnosed with ASD. **Methods:** The following databases and search interfaces were searched from Database start up until October 2015: Bio Med Central, Chiropractic Library Collaboration, Clinical Trials, Cochrane library, Dimdi, EBSCO host, Pubmed, Pubmed central, Medline Plus, Osteopathic research Digital repository, Osteopathic Research Web, and Physiotherapy Evidence Database. Further searches included journals provided by the University of Wales and the University of Duisburg-Essen. Studies were included if participants were children and young adults aged 0-21 years; studies published in English, German, or French; a diagnosis of autism or ASD, and study designs of randomized clinical trial, case-control studies, case series, case reports, and single subject studies (N of 1), which include manual therapeutic interventions of the musculoskeletal system. Two authors independently screened the studies for inclusion criteria, extracted the data and assessed for risk of bias. Methodological quality of randomized clinical trials was assessed by the Downs and Black tool. Quality of reporting for case series and case reports was assessed with the appropriate checklists provided by the QUALity and Transparency Of health Research (EQUATOR) network. **Results:** Included in the review were one randomized clinical trial (uncontrolled), one case series, and 11 case reports. The methodological quality of the included randomised clinical trial was rated as being poor. Quality of reporting for the included case series and case reports was also insufficient. All included studies used spinal manipulation, and indicated an improvement in autistic symptoms after the manual therapeutic intervention. **Conclusion:** The results of this systematic review confirm a general lack of good quality, high level of evidence studies on the topic, as well as no existing experimental studies that have been published in the last 10 years. This review indicates that the literature on the effects of chiropractic interventions to the musculoskeletal system of autistic children and young adults appears to be favourable with respect to the severity of their symptoms. However, the results of this review have to be interpreted with great caution, as the majority of identified studies were case reports. Further feasibility and pilot research is needed to lay the foundation for good quality clinical trials of spinal manipulation in the autistic child population.

## Introduction

Autism spectrum disorders (ASD) are defined as a range of conditions classified as neurodevelopmental disorders, including autistic disorder (autism), Asperger syndrome, and pervasive developmental disorder (PDD).<sup>1</sup> Symptoms are quality-related disorders in the areas of social interaction, verbal and non-verbal communication, and a variety of behaviours and learning disorders.<sup>1</sup> Abnormalities in development are apparent already in early childhood and have a high variability.<sup>1,2</sup> ASD is reported to occur in all racial, ethnic and socioeconomic groups, with about 1 in 68 children

being identified with ASD in 2012 in the US.<sup>3</sup> Boys seem to be 4.5 times more often affected than girls.<sup>3</sup>

With respect to the causation of autism, no universally accepted explanations are currently present. The possibility of a genetic component, environmental triggers and imbalances in the neurophysiological state are all discussed.<sup>4,6</sup> No specific medication is available to address autism. Medication is generally used to treat accompanying symptoms and modify behaviors of the condition.<sup>7</sup> Current clinical guidelines recommend a combination of behavioral, devel-

opmental and educational approaches in order to enhance communication, social and cognitive skills and at the same time minimising autistic symptomology.<sup>8,9</sup> Medication is recommended in case of challenging behaviour and other accompanying symptoms that justify its use.<sup>9</sup>

Use of complementary and alternative treatments is common among children with autism, 50 to 75% of children with autism may be treated with complementary and alternative medicine (CAM). The use of manipulative or body based therapies, such as Craniosacral therapy, osteopathic and chiropractic manipulation were reported by approx 25% of children with ASD.<sup>10,11</sup>

Significant improvements in the symptomology in children with autism are anecdotally reported by chiropractors and other manual therapists, however, the research literature on the effectiveness of manual therapies in ASD is scarce.<sup>12</sup> A previous systematic review on the use of chiropractic care in children with ASD identified five studies (one randomized clinical trial, one case series and three case reports).<sup>13</sup>

All identified studies reported on an improvement in symptoms related to autism after the chiropractic intervention, however, the authors highlighted several limitations of the study designs, particularly of the randomized clinical trial and the case series, and concluded that further research was warranted.<sup>13</sup>

A methodological quality assessment was not formerly conducted in this review, as is recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews.<sup>14</sup> The objective of this present systematic review is to provide an expansion and update of this previous systematic review, aiming to answer whether new research on the topic has emerged, and formerly assess the available evidence for methodological quality and risk of bias, as well as giving detailed recommendations for further research on the topic.

## Methods

A systematic literature search was conducted from Database start up to October 2015, using the following databases and search interfaces: Bio Med Central ([www.biomedcentral.com](http://www.biomedcentral.com)), Chiropractic Library Collaboration (<http://www.chiroindex.org/#results>), Clinical Trials (<http://clinicaltrials.gov>), Cochrane library (<http://www.thecochranelibrary.com/view/0/index.html>), Dimdi (<http://www.dimdi.de/static/de/db/index.htm>), EBSCO host (<http://www.ebscohost.com/>), Pubmed ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)), Pubmed Central (<http://www.ncbi.nlm.nih.gov/pmc/>), Medline Plus (<https://medlineplus.gov/>), Osteopathic Research Digital Repository (<http://ostemed-dr.contentdm.oclc.org/>), Osteopathic Research Web ([www.osteopathic-research.com](http://www.osteopathic-research.com)), Physiotherapy Evidence Database (<http://www.pedro.org.au/>).

Further searches included journals provided by the University of Wales (<http://www.wales.ac.uk/en/OnlineLibrary/OnlineLibrary.aspx>) and the University of Duisburg-Essen ([www.uni-due.de/ub](http://www.uni-due.de/ub)). The investigated journals were: *Advanced Clinical Child Psychiatry*, *Journal of Autism and Developmental Disorders*, *British Journal of Chiropractic*, *Chiropractic and Osteopathy*, *Journal of Clinical Chiropractic Pediatrics*, *Complementary Therapies in Medicine*, *Journal of Complementary and Alternative Medicine*, *The Journal of Manipulative and Physiological Therapeutics*, *The Journal of the American Osteopathic Association*, *Osteopathic Medicine and Primary Care*, *Pediatrics*, *German Journal of Osteopathy*, *International Journal of Osteopathic Medicine*, *Journal Pediatric*, *Maternal & Family Health*, *Journal of Vertebral Subluxation Research*, *the Journal of Upper Cervical Chiropractic Research*.

The search strategy used was: (Chiropractic (MeSH) OR Manual Therapy OR osteopath\* OR OMT OR Physiotherapy OR CAM OR Osteopathic Medicine (MeSH)) AND (Autism OR Autistic disorder (MeSH) OR Autistic spectrum disorder (MeSH)).

Inclusion criteria were children and young adults aged 0-21 years; studies published in peer-review journals in English, German, or French; a diagnosis of autism or ASD, and study designs of randomized clinical trials (either controlled or not), case-control studies, case series, case reports, and single subject studies (N of 1), which include manual therapeutic interventions of the musculoskeletal system. Exclusion criteria were other forms of pervasive developmental disorders, other study designs such as narrative/systematic reviews, and no manual therapeutic interventions of the musculoskeletal system.

### Study selection and data extraction

Two review authors independently screened titles and abstracts of the articles identified through the database search. Full-text articles of potentially eligible studies were obtained and independently evaluated for inclusion. Disagreement between authors was resolved through discussion or by consulting a third review author. Data extraction was performed by two independent reviewers into a data extraction table. Any discrepancies were resolved by discussion.

### Quality assessment of included studies

The methodological quality evaluation of randomized clinical trials was carried out by means of the modified Downs and Black checklist.<sup>15,16</sup> It contains 27 questions that are rated with one point each. The modification relates primarily to the evaluation of the Power Item 14 with 1 point, instead of 0.5 points, as in the original version. This checklist has been evaluated both as a valid and reliable method and

represents a powerful tool for methodological evaluation of clinical studies.<sup>17,18</sup> The quality is evaluated in four domains: reporting, external validity, internal validity/bias and internal validity/confounding. According to the final score of the assessment, the methodological quality of the study is categorised into strong, moderate, limited or poor.<sup>16,19</sup>

For the evaluation of the methodological quality of single subject studies (N of 1), case reports and case series, no checklists are currently available which have been analysed with respect to their validity and reliability. In order to introduce some quality measure, the quality of the reporting of these studies has been assessed in this review instead. The Enhancing the QUALity and Transparency Of health Research (EQUATOR) network states that readers may not be able to make reliable decisions on how relevant this research is with regards to clinical practice, how well the study was conducted and how reliable its findings are without accurate and complete description of methodological aspects of a given study.<sup>14</sup> Accurate reporting may also enhance the usability of research, and if incomplete, would undermine the value and usability of research.<sup>14</sup> For the case series, the reporting quality tool of Carey and colleagues was used.<sup>20</sup> The authors identified characteristics that well-reported case series studies should address: defined study question; well-described study population; well-described intervention; use of validated outcome measures; appropriate statistical analyses; well-described results; discussion/conclusions supported by the data presented; and funding sources acknowledged.<sup>20</sup> For the case reports, the 13-item CAsE REport (CARE) guidelines of the EQUATOR network were utilized.<sup>14</sup> For simplicity reasons, scores of 0-10 out of a total of 30 were rated as poor reporting, scores of 11-20 were rated as moderate, and scores above 20 were considered good reporting.

The reporting of this present systematic review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>14</sup>

## Results

Database searches revealed a total of 2,232 citations, and 1,569 records were screened after duplicate removal, with 1,528 articles excluded (Figure 1, Table 1). Out of 41 articles which were evaluated by full-text assessment, 13 articles were selected for this review, including one randomized clinical trial, one case series, and 11 case reports, involving a total of 52 study participants/subjects (Table 2). Compared with the systematic review by Alcantara and colleagues,<sup>13</sup> no new experimental studies have been published to date, although a series of new case reports are now available in the literature which have been published in the last five years.

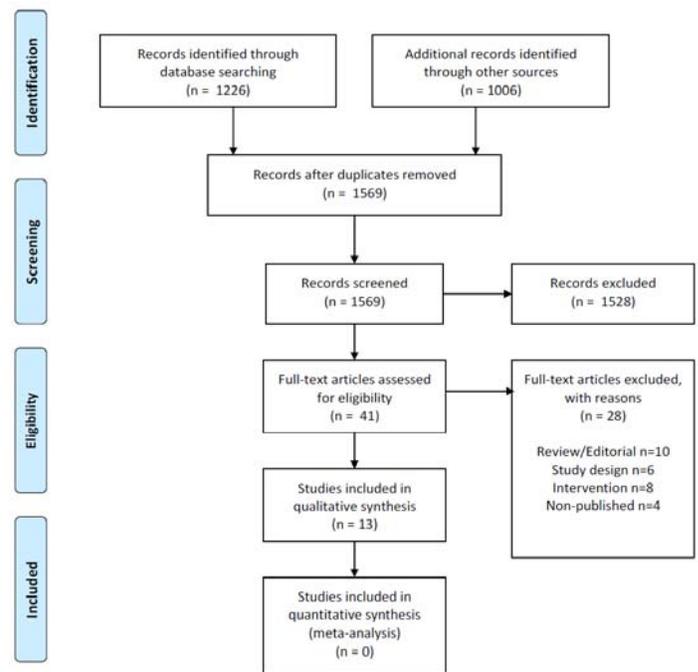


Figure 1: PRISMA Flow diagram of study selection.

Table 1. Database search results

Source	Number of studies retrieved
Clinical trials	3
Pubmed	154
Dimdi	569
Cochrane library	1
Pubmed Central	250
Medline Plus	28
EBSCO Host	79
Chiropractic Library Collaboration	33
Osteopathic research web	2
OstMed DR	3
BioMed Central	103
PEDro	1
Journals	1,006
<b>Total</b>	<b>2,232</b>

In all identified articles of this current review, chiropractic treatment was performed, with all of the studies describing manipulative techniques to the spine, either to the cervical or entire spine. Common to all studies is that positive effects, such as improvement in autistic symptoms, were observed in patients with ASD after treatment.

In all 11 case reports, chiropractic manipulation was performed one to three times per week, for up to 8 months (Ta-

**Table 2. Overview of included articles**

Study design	Number	Study
Randomised Comparison Trial	1	Khorshid (2006) <sup>21</sup>
Case series	1	Aguilar (2000) <sup>22</sup>
Case report	11	Amalu (1998) <sup>23</sup> Warner (1999) <sup>24</sup> Neally (2003) <sup>25</sup> Mc Cormick (2008) <sup>26</sup> Hoffman (2008) <sup>27</sup> Marini (2010) <sup>28</sup> Cohn (2011) <sup>29</sup> Cleave (2011) <sup>30</sup> Scelfo (2011) <sup>31</sup> Noriega (2012) <sup>32</sup> Zielinski (2013) <sup>33</sup>
<b>Total</b>	<b>13</b>	

ble 3, next page). Age of patients ranged from 3-20 years. In two case reports, the cervical spine was treated and in the remaining nine other case reports, treatment of the entire spine was carried out. Thrust techniques were used in all studies (Table 3).

Likewise, the age range in the case series of 26 patients, conducted by Aguilar et al., ranged from 3 to 13 years, with similar frequency and duration of the treatment period (Table 3). Patients in this case series were treated by upper cervical spine chiropractic manipulation.

Participants in the randomized clinical trial, performed by Khorschid et al, were 4-16 years old, and treated in two groups twice each week for 3 months (Table 3). One group received upper cervical spine adjustment and the other group received spinal manipulation of the whole spine. The techniques commonly used in all studies were high velocity, low amplitude (HVLA) thrusts to correct segmental dysfunction; Thompson drop-assisted technique using a segmental 'drop table' for thrust enhancement; Activator method using an instrument to deliver a specific low force thrust; Atlas orthogonal adjustment using an instrument that transmits a mechanical impulse to the patient's atlas; and Torque release technique using a hand-held device for a torque and recoil-based adjustment. In the included studies, different assessment and outcome measures were used for the evaluation of data, both objective and subjective (Table 3).

In all studies, palpation was used to investigate the mobility of the spine, generally revealing improved flexibility of the spine by the end of the study (Table 3).

The five studies that used X-ray analysis show varying re-

sults.<sup>21,22,23,31,32</sup> In the case report by Amalu, the subluxations of the spine were corrected after chiropractic intervention. Likewise, in the case report by Noriega, a decrease in subluxation of the atlas complex could be shown. Scelfo (2011), however, performed x-ray analysis only at the beginning of the treatment series and did not repeat it at the end, so no assessment of a change after spinal manipulation could be made (Table 3). In the study by Khorschid and colleagues, X-ray analysis was performed before and after the first cervical adjustment. Aguilar and colleagues performed X-ray analysis before the first treatment and prior to the fifth visit, when no subluxation was detected anymore, as assessed by leg length difference.

The leg length measurement in the prone position was applied in three of the studies assessed in this current review,<sup>21,22,32</sup> resulting in the existing difference of leg lengths being corrected by the manipulative intervention.

The objective examination of patients with paraspinal thermography (thermal scan) was used in seven studies (Table 3). This diagnostic method is used to measure changes in temperature along the spine that may occur due to subluxations of spinal vertebrae. In the seven studies that applied the thermal scan, at the end of the investigation the spinal temperature was normalised and the vertebral subluxations were reduced or adjusted.<sup>23,24,26,27,29,32,33</sup>

Surface electromyography (SEMG) was used in four studies as an evaluation tool for paraspinal muscle tension in vertebral subluxations; chiropractic treatments led to normalized values and thus to compensation of asymmetries (Table 3).<sup>24,26,27,29</sup>

In four studies, the Autism Treatment Evaluation Checklist (ATEC) was used to assess the severity of autistic symptoms (Table 3).<sup>21,26,28,31</sup> This checklist has been designed to monitor children with autism over time in order to evaluate potential effects of a given therapy.<sup>34</sup> This simple scoring scale with 77 items is filled in by parents or carers. It consists of four subdomains: speech/language, sociability, sensory and cognitive awareness, and health/physical/behaviour, providing a possible total score range of 0-180, with a higher score generally indicating a greater degree of impairment in symptoms. Total scores of less than 30 indicate that the child may lead a normal and independent life, scores of less than 50 indicate that the child may lead a semi-independent life, scores between 50 and 104 hint to moderate autistic symptoms, and with scores above 104 the child would be considered severely autistic.<sup>34</sup>

Within the scope of this review, the clinical changes after chiropractic treatment were demonstrated by a decrease in the ATEC scores, with a reduction of the total scores from

**Table 3. Overview of included studies**

Study	N	Male: female	Study design	Age	Treatment approach	Techniques used	Outcome measures/diagnostic test applied	Results
Khorshid (2006)	14	13 : 1	Randomized clinical trial	4-16 yrs	Chiropractic treatment: Group 1: upper cervical spine; Group 2: entire spine, twice each week for 3 months	Instrument-assisted atlas orthogonal adjustment of cervical spine, no other techniques/ approaches described	ATEC; X-rays; spinal palpation; leg length difference; palpation in motion	Manipulation of the upper cervical spine led to reduction of ATEC scores by 32% in group 1 compared to 19% in group 2; in both groups, X-rays were normal, free movement of spine, leg length difference was resolved
Aguilar (2000)	26	21:5	Case series	3-13 yrs	Chiropractic treatment of upper cervical spine for 9 months 3 times per week	Orthospinology specific upper cervical technique	X-rays, leg length difference, CARS, modified autism rating scale	Statistically significant reduction of CARS scores after 9 months by 10%; statistically significant reduction of modified autism rating scores after 9 months by 22%; leg length difference resolved
Amalu (1998)	1	0:1	CR	5 yrs	Chiropractic treatment of upper cervical spine for 12 weeks	Thrust techniques for correction of Occipito-atlanto region	Thermalscan upper cervical spine; X-rays upper cervical spine; palpation in motion	Neurophysiological symptoms and temperature of the spine normalized, subluxations of spine resolved, follow-up after 8 and 11 weeks confirmed results; Diagnosis of autism reversed
Warner (1999)	1	0:1	CR	5 yrs	Chiropractic treatment of the spine for 3x per week, after 2 years 1x per week	Thrust techniques	SEMG; thermal scan; Palpation of spine in motion	Autistic symptoms positively influenced; reduction of vertebral subluxation; normalised thermal scan and SEMG
Neally (2003)	1	0:1	CR	19 rs	Six chiropractic treatments of the spine	Occiput: Drop-headpiece; thrust techniques to spine	Palpation of spine in motion	Reduction of autistic behavioural symptoms, improved spinal movement, patient started to speak
McCormick (2008)	1	1:0	CR	4 yrs	Chiropractic treatment of spine for 6 months	Thompson-Drop-Assisted Technique for S2; Thrust C1; Activator for Thoracic spine	ATEC; thermal scan; SEMG; palpation in motion	Reduction of autistic behavioural symptoms; social behaviour, language and understanding of environment improved; ATEC reduced from 97 to 90; normalised movement, temperature and EMG of spine
Hoffman (2008)	1	0:1	CR	3.5 yrs	Chiropractic treatment of the spine for 10 weeks	Torque Release Technique	SEMG; thermal scan; palpation in motion	Improved symmetry and balance of the nervous system after treatment series and follow-up after 2 months; normalised EMG and thermal scan; subluxations of spine resolved; subjective and objective change in behaviour, as reported by parents
Marini (2010)	1	1:0	CR	6 yrs	Chiropractic treatment of spine and pelvis for 16 weeks	Thompson-Drop-Assisted Technique for SIJ; thrust techniques for thoracic and lumbar spine	ATEC; palpation in motion	Reduction of ATEC scores in: language from 16 out of 28 to 9 out of 28; social behaviour from 16 out of 40 to 7 out of 40; perception from 15 out of 36 to 6 out of 36; health from 23 out of 75 to 10/ out of 75; total from 70 out of 180 to 32 out of 180 (improvement of 54,3%); improvement of symmetries of spine and pelvis
Cohn (2011)	1	1:0	CR	3 yrs	Chiropractic treatment once per week for 10 weeks	Correction of spine, not described in detail	SEMG; thermal scan; palpation in motion	Muscle tonus and posture, reading, stereotypes and social behaviour positively influenced; language development positively influenced; SEMG and thermal scan normalized reconstitution of spinal symmetry
Cleave	2	1:1	mCR	17 yrs (female) and 20 yrs (male)	20 chiropractic treatments of spine and pelvis for 5 months	Patient 1 (male): Activator method chiropractic technique Patient 2 (female): Thompson-Drop-Assisted Technique, AMCT	Palpation in motion	Improvement of social behaviour; ability to concentrate; reduction of aggressive behaviour; increase of tolerance to frustration and perception, reported by caregivers improvement of symmetry of spine and pelvis

Study	N	Male: female	Study design	Age	Treatment approach	Techniques used	Outcome measures/diagnostic test applied	Results
Scelfo (2011)	1	1:0	CR	9 yrs	16 Chiropractic treatments 2x per week	Thrust and later toggle-recoil for Atlas; Thrust SIJ	ATEC; palpation in motion; x-rays	Improved ATEC scores in: language from 16/28 to 14/28; behaviour from 20/40 to 15/40; perception from 18/36 to 15/36; health from 42/70 to 22/70 and total from 96/180 to 66/180; reconstitution of spinal symmetry; reduction of medication use, no X-ray assessment at end of study
Noriega (2012)	1	1:0	CR	6 yrs	Chiropractic treatment of upper cervical spine 2x per week for 12 weeks, additional 3 weeks 1x per week	Thrust (triceps pull)	Static Palpation; palpation in motion; postural pelvis-evaluation; weight distribution; leg length difference; thermal scan; X-rays	No neurological and musculoskeletal findings reported; leg length difference restored; symmetric thermal scan, reduction of subluxation of atlas complex; resolution of nocturnal enuresis; improvement of ASD by 70% particularly in areas of school performance and social behaviour
Zielinski (2013)	1	0:1	CR	3 yrs	Chiropractic treatment of cervical and thoracic spine 1x per week for 8 months	Treatment 1-11: Activator-method; from 12th treatment: manual thrust techniques	Palpation in motion; postural evaluation; thermal scan	Subluxations decreased; thermal scan more balanced; vegetative imbalance reduced; ASD-symptoms improved in area of behaviour; child started to speak; eye contact has been established; total resolution of bilateral headache, reflux, nausea and insomnia; no epileptic fits; use of medication terminated

Abbrev.: ASD — Autism Spectrum Disorders; AMCT - Activator Method Chiropractic Technique; ATEC - Autism Treatment Evaluation Checklist; CARS — Childhood Autism Rating Scale, CR — Case Report; mCR — multiple case report; RCT — Randomised Comparison Trial; SEMG — Surface Electromyography; SIJ — Sacro-iliac joint

97 to 90 out of 180,<sup>26</sup> from 70 to 32 out of 180 (corresponding to a reduction by 54.3%),<sup>28</sup> and from 96 to 66 out of 180.<sup>31</sup> In the study by Khorschid et al., mean ATEC values in the full spine adjustment Group changed from 68 to 46 out of 180 (calculated by the authors of this current review, as only individual values of participants were given in the original publication), and the mean values of the cervical spine adjustment Group changed from 41 to 30 out of 180.<sup>21</sup> In regard to the safety of the spinal manipulative treatment approach, no adverse events were reported in the studies. The assessment of the methodological quality of the ran-

domized clinical trial revealed 6 out of 27 points, corresponding to an overall poor methodological quality. In all domains (reporting, internal and external validity), serious shortcomings were detected, including selective recruitment of the study population and an absence of a sample size calculation, lack of blinding, no statistical analysis of data rather than individual patient data being presented in tables. Neither probability values (p-values) nor confidence intervals were calculated or reported (Table 4).

The reporting quality of the included case series achieved

<b>Reporting</b>									
1	2	3	4	5	6	7	8	9	10
N/U	Y	N/U	Y	N/U	Y	N/U	N/U	N/U	N/U
<b>External Validity</b>									
11	12	13	14						
N/U	N/U	Y	N/U						
<b>Internal Validity/Bias</b>									
15	16	17	18	19	20	21			
N/U	N/U	N/U	N/U	N/U	N/U	Y			
<b>Internal Validity/Confounding</b>									
22	23	24	25	26	27				
Y	N/U	N/U	N/U	N/U	N/U				
<b>Total Score = 6/27</b>									
<b>Methodological Quality: Poor</b>									
*Modified Downs and Black checklist <sup>15,16</sup> ; Abbrev.: Y — Yes, N/U — No/Unclear									

a poor three points out of a possible eight points, with a clearly defined study question, study population and intervention as well as appropriate statistics missing (Table 5).

Reporting of all 11 case reports was assessed using the 13-item (including several subitems) CARE checklist. Out

of a total possible 30 points, one study achieved under 10 points, corresponding to overall poor reporting (Table 6). Seven case reports achieved scores between 10 and 20, corresponding to overall moderate reporting. Three case reports achieved scores of 20 and higher, corresponding to good reporting.

**Discussion**

This systematic review update included in total one randomized clinical trial, one case series, and 11 case reports. Since the publication of the randomized clinical trial by Khorschid and colleagues in 2006, no new experimental evidence has been generated/published in the last 10 years.

Reasons for this can only be speculated on, which may form part of resource implications of chiropractic research, i.e. a lack of highly qualified and experienced research staff and research funding, a lack of public interest on the topic, or a

**Table 5: Reporting quality of case series by Aguilar et al (2000)**

Study characteristic	Presence
Study Question	No
Study population	No
Well-described Intervention	No
Valid outcome measure	Yes
Appropriate statistical analysis	No
Well-described results	Yes
Discussion/Conclusion supported by data	No
Funding source acknowledged	Yes

SOURCE: (Carey 2003) 20

**Table 6: Reporting quality of case reports**

	Amalu 1998	Warner 1999	Neally 2003	McCormick 2008	Hoffman 2008	Marini 2010	Cohn 2011	Scelfo 2011	Cleave 2011	Noriega 2012	Zielinski 2013
1	N	Y	N	N	N	N	N	N	N	N	N
2	N	N	N	Y	N	Y	Y	Y	Y	Y	Y
3a	N	N	N	N	N	N	N	N	N	N	Y
3b	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
3c	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
3d	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5c	Y	N	N	Y	Y	Y	N	Y	N	Y	Y
5d	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8a	Y	Y	N	N	Y	Y	N	N	N	Y	Y
8b	N	N	N	N	N	N	N	N	N	N	N
8c	N	N	N	N	N	N	N	N	N	N	Y
8d	N	N	N	N	N	N	N	N	N	N	N
9a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9b	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
9c	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y
10a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10b	N	N	N	N	N	Y	N	N	N	Y	Y
10c	N	N	N	N	N	N	N	N	N	N	N
10d	N	N	N	N	N	N	N	N	N	N	N
11a	N	N	N	N	N	Y	N	N	N	N	Y
11b	Y	N	N	Y	Y	Y	N	Y	Y	Y	Y
11c	N	N	N	N	Y	Y	N	N	Y	Y	Y
11d	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
12	N	N	N	N	N	N	N	N	N	N	N
13	N	N	N	N	N	N	N	N	N	N	N
<b>Total 13</b>	<b>15</b>	<b>7</b>	<b>16</b>	<b>17</b>	<b>21</b>	<b>15</b>	<b>17</b>	<b>16</b>	<b>16</b>	<b>20</b>	<b>23</b>

SOURCE: (Gagnier 2013) 14,54, Abbrev.: Y – Yes, N – No

misinterpretation of the available evidence in itself.

### ***Effects of chiropractic treatment on symptoms***

Common to all studies/reports within the scope of this review is that positive effects such as improvements of autistic symptoms have been observed in patients with ASD after treatment. However, due to a lack of statistical data and poor study design of the included randomized clinical trial, no comments on the effectiveness/efficacy of the chiropractic intervention can be made.

In four studies of this review, the ATEC was used to assess the severity of autistic symptoms. According to the Autism Research Institute, ATEC is a validated and reliable instrument, available free of charge for research purposes.<sup>34</sup> This questionnaire is particularly suitable for the detection of improvement or decline of autistic symptoms, provided the same person fills out the questionnaire.<sup>34</sup> The advantage of the ATEC is the extent to which a treatment leads to changes in the expression of autism in the assessment. Other checklists, such as the Childhood Autism Rating Scale (CARS), the Gilliam Autism Rating Scale (GARS) or the Autism Behaviour Checklist (ABC) can be used to establish the diagnosis of autism, but do not judge the benefits of having a therapy for an autistic child.<sup>35</sup> ATEC is an ideal measuring tool for the collection of reliable data in the context of interventional studies.<sup>34,35</sup>

It was noted, that in the randomized clinical trial by Khorschid and colleagues, children with different severities of autism were participating, based on ATEC scale assessments. Due to the very small sample size of 14 patients in this trial, random group allocation of these patients was not uniform, resulting in 2 and 1 severely impaired patients (scores >104), 2 and 0 moderately affected patients (scores >50), 1 and 2 patients with scores >30 and 1 and 4 patients with very mild symptoms (scores <30) in the groups of full spine adjustment vs cervical spine adjustment, respectively. These imbalances in symptom severity are to be avoided in future clinical trials in order to avoid skew of data. This can be achieved by strictly defining the inclusion and exclusion criteria, taking into account the practicalities of patient recruitment for clinical studies in real-world settings. Severely autistic children may not be easily accessible, and ethical considerations in the future study design must be taken into account, such as supply of standard care for all patients in the study, regardless of group allocation. Since no other randomized clinical trial exist other than the study by Khorschid et al, it is difficult to predict which patient group with a given symptom severity may benefit most from chiropractic treatment, if there is an effect after all.

Analysis of a considerable number of single case studies on autistic children may be the way forward in establishing

which patient group may be most suitable for engagement in future clinical trials, which techniques to use and which areas of the spine to treat. Single subject studies (N of 1) are ideal for exploring treatment conditions for individual patients, and where heterogeneity of the patients may limit generalisability from trial data.<sup>36,37</sup>

On practical grounds, for example a group of chiropractors who regularly treat children with autism could be engaged by performing simple single subject studies (N of 1), whereby each parent of a presenting autistic child is asked to fill in the ATEC online before each treatment, so that a potential change in symptom severity can be closely monitored. Additionally, participating chiropractors should report on techniques used and body areas treated.

The case series by Aguilar and colleagues report on the changes of each individual child after chiropractic intervention, and in several cases parents reported a decrease of medication use and improvement on chronic infections.<sup>22</sup> Since these aspects are not monitored within the ATEC questionnaire, they could be assessed and reported as part of the case note taking prior to treatment, and reassessed before each subsequent follow-up treatment, with these data also feeding into future study results.

The randomized clinical trial in this current review did not incorporate a follow-up assessment after the end of the treatment period, hence the duration of treatment effects, if any, are not clear. Future studies could address this question, again by initially performing single subject studies (N of 1) in order to explore the number of treatments needed and time for potential treatment effects to last. Additionally, potential confounders and the feasibility of study procedures, such as number and time required and adherence to fill out questionnaires, as well as attendance at study appointments can be explored. Since outcome measures with respect to autism symptoms will mainly be based on questionnaires and medication use, the acquisition of robust baseline data during 3-5 weeks before the first chiropractic intervention (run-in phase) may be indicated, in order to assess the variance in change of these data during day-to-day life of the participants.

### ***Influence of confounders***

One common problem in clinical studies is the reporting of confounding factors which have the potential to influence study results. According to Skelly, confounders commonly may indicate an association between a treatment modality and an outcome, when in fact, there is no real association.<sup>38</sup> Confounding variables such as age, sex, diet, exercise, natural course of disease, lifestyle changes, emotional events, comorbidities etc should be considered in the design and reporting of clinical studies. Skelly recommends adequate

reporting of patient characteristics/demographics as well as definition of inclusion criteria by specific confounding variables.<sup>38</sup> However, it is noted that there always will be residual confounding, no matter how many variables one accounts and adjusts for, most likely due to unknown factors.<sup>38</sup>

In the included studies in this current review, no attention to confounding factors was paid. In order to address and explore this issue for future clinical trials, parents and carers may be most suitable to answer questions with respect to effects of diet changes, emotional events, lifestyle changes such as holidays etc on the symptoms of their autistic child. They also may be able to report on patterns of symptom changes which may be related to season of the year or specific weather conditions, or change of symptoms over the last few years. These questions can be best explored as part of a qualitative interview study where parents/carers have the opportunity to express their feelings/attitudes/beliefs about the subject of discussion, but findings of these qualitative studies should be verified by larger scale surveys of parents with autistic children, in order to get a more realistic picture of the population to be studied.

#### ***The ethics of effective treatment supply***

In the randomized clinical trial of Khorshid and colleagues, two different treatment approaches were compared. It is not clear, whether the participating children received other forms of treatment, such as usual care. Since chiropractic care in autism cannot be considered effective to date due to lack of evidence, other existing effective treatments, if applicable, should be provided for future study participants. In order to meet the rigorous ethical requirements for the conduct of clinical trials involving children, the current clinical guidelines on the treatment of children and young adults with autism should be taken into account in any future study design, in that all study participants should receive the recommended therapies, and additionally the chiropractic manipulation as the specific intervention to be explored. Importantly, this would avoid the deprivation of effective care of all study participants, independent of group allocation, but also would likely encourage interdisciplinary communication and increase acceptance for such studies within the medical profession.

#### ***Safety aspects***

Assessment of adverse events as part of the chiropractic treatment was not mentioned in the identified studies. This could be interpreted as no adverse events were taking place, or that adverse events occurred but have not been reported. Incidences of serious neurological and/or vertebrobasilar complications in all patient groups were estimated as one in 250 million chiropractic visits<sup>39</sup> which was challenged by other authors, stating that they feel it was inaccurate and

likely to be underestimating risk.<sup>40</sup> Survey data from chiropractic practices indicate that one child per 100-200 attending may have a mild adverse event not lasting longer than 24 hours, with no serious adverse events reported.<sup>41-43</sup> Since the literature on the safety of spinal manipulation as part of experimental studies in children is scarce and controversial, it is vital that, regardless of study design, adverse events are assessed and reported on; even if no adverse events occurred, this should be equally stated.

#### ***Methodological quality and reporting***

The assessment of the methodological quality of the randomized clinical trial in this review was performed by means of the Downs and Black assessment tool which is valid and reliable and can serve as a strong methodological instrument for the evaluation of methodological quality.<sup>15-18</sup> The weakness of this instrument, however, is the reliability in the field of external validity, which is rated as low.<sup>15</sup> The advantage of this checklist is that it can be used for the evaluation of randomized and non-randomized trials in health research<sup>15</sup> and currently is in this respect one of the best assessment tools for studies involving public health interventions.<sup>18</sup>

Although the RCT by Khorshid and colleagues is rated by design on top of the hierarchy of evidence,<sup>44</sup> the methodological quality evaluation resulted in only 6 out of 27 points, achieving a poor quality rating. Furthermore, it only achieved a low scoring in the categories of internal and external validity. No statistical methods were applied so that the effects of chiropractic treatments of the upper cervical spine compared with those of the whole spine in autistic children are unclear. Since this trial compared two different treatments with each other, blinding of subjects with respect to a 'real' intervention and a sham procedure was perhaps not anticipated by the the study authors. Nevertheless, future clinical trials should make an attempt to control for non-specific effects, by taking an appropriate sham control as well as a 'no intervention' control into account, all in addition to usual care, as only then one can conclude on the effectiveness of the chiropractic intervention and a potential placebo effect of non-specific elements of such a treatment session, such as patient expectations, practitioner-patient relationships, practice environment, and the manual touch itself.<sup>45</sup> Appropriate sham controls in clinical trials of spinal manipulation have been described in previous studies.<sup>46-53</sup>

Future studies with randomized clinical trial design should adhere to the CONSORT reporting guideline as specified by the EQUATOR network.<sup>14</sup> Likewise, in order to improve the quality of reporting for future single subject studies (N of 1) and case reports, the appropriate guidelines should also be considered and adhered to.<sup>14</sup> In the current review, the reporting of the case reports in general lacked information

on diagnostic challenges and reasoning, prognostic features of the condition and a shared patient perspective as well as informed consent. Arguably, these aspects may not be seen as being relevant in the day-to-day practice encounter of autistic children and young adults or are performed as part of the routine assessment and treatment anyway, however, they should be reported on in order to meet the rigorous standards of reporting to guide clinical practice.<sup>54</sup>

### Future directions

This review highlights a scarcity and poor methodology of clinical trial data. In order to move forward and establish a solid base for future research, single steps in the form of initial pilot work need to be taken. Several authors have emphasized a focus on treatment outcomes research being best conducted in phases.<sup>55-57</sup> Phase 1 would be the exploration of a new treatment with a small number of individual patients to test the therapeutic effect. As previously mentioned, this could be achieved by performing single subject studies (N of 1). After optimization through further studies and determining the optimal treatment candidates, the potential efficacy of the treatment should further be explored in small pilot studies (Phase 2). The third phase would then be well-controlled trials that test the efficacy under ideal conditions, and if efficacy has been shown in this phase, the treatment then should be tested within the real-world setting and a cost-effectiveness analysis would be added (Phase 4 and 5).<sup>55-57</sup>

### Review limitations

This present systematic review has the following limitations which may have influenced the results presented: Only English, German and French language articles were included, which may have led to the exclusion of relevant articles in other languages. Authors of original publications were not contacted for additional information on data, and database searches were restricted to peer-reviewed literature only. Additionally, inclusion of so-called 'grey literature' may reduce potential publication bias in future systematic reviews on the topic.

### Conclusion

The results of this systematic review update confirm a previously reported general lack of good quality, high level of evidence studies on the topic, as well as no existing experimental studies that have been published in the last 10 years. The authors' interpretation of the results of this review indicate that chiropractic intervention to the musculoskeletal system of autistic children and young adults may have the potential to create a positive effect on the severity of their symptoms. However, the majority of study designs identified were case reports/series with only individual patients studied and reported on, hence generalisation of results to the autistic child/youth population are not indicated.

Therefore, the results of this study have to be interpreted with caution, despite positive results being presented with regards to autistic symptoms. Further feasibility and pilot research is needed in order to formulate a robust study hypothesis and design a high quality randomized controlled trial to explore the effectiveness and efficacy of spinal manipulation in the autistic child and young adult population.

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