Recommendation of Neurorehabilitation according to the Padovan-Method Neurofunctional Reorganization® for Treating Neurodevelopmental Disorders: A Systematic Review

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Abstract
Objective: The Padovan-Method Neurofunctional Reorganization® is a promising approach in speech therapy treating neurodevelopmental disorders with traumatic or congenital origin. Its use is based on a long-time experience of certified therapists. However, its efficacy and safety has not been assessed in a systematic review. This report aims to gain evidence for the use of the therapy method. The review was registered (PROSPERO: CRD42020156124). Methods and Analysis: Guidelines of PRISMA, the Cochrane Collaboration Handbook, MECIR, and GRADE were followed. General databases (Cochrane Library, PubMed, AWMF, Anthromedics, etc.) and further 38 databases including grey literature were searched. Hand search was done additionally and contact to experts used to retrieve unpublished manuscripts. All trials investigating the effect of the method in comparison to either no intervention, alternative as state of the art, or placebo intervention in English, Portuguese, and German language were included. No restriction regarding study design was applied. Data related to the intervention outcome and the study method was extracted and analyzed independently. Risk of bias was assessed using ROBINS-I for non-RCTs, adherence to CARE-Guidelines was analyzed for case series or reports, and keeping the Declaration of Helsinki was checked for all items. Results are presented both in evidence profiles and summary of findings tables according to GRADE. Results: Amongst 98 records assessed for eligibility, four studies and 14 case reports were identified with a total of n = 196 participants. Duration of reported interventions was between 2 days and 2 years. Microcephalia, down-syndrome, unspecified neurological disorders, and myofunctional disorders were main conditions of the patients with neurodevelopmental disorders. Only indirect overlapping of operationalized criteria was found. Conclusions are therefore limited.

Conclusion: The Padovan-Method® is a holistic therapy approach claiming its feasibility to a large group of disorders making a proof of efficacy difficult. An application of therapy according to the Padovan-Method® by trained therapists might be considered by clinicians (weak recommendation) and a contribution to a relief of symptoms or improvements of condition of named conditions might be gained. Therefore, development and validation of therapy protocols and further investigation are required.

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Neurorehabilitation nach der Padovan-Methode
Neurofunktionelle Reorganisation® zur Behandlung neurologischer Entwicklungsstörungen: Ein systematisches Review

Schlüsselwörter
Neurologische Rehabilitation · Neurologische Entwicklungsstörungen · Rehabilitation von Sprach- und Sprechstörungen · Systematisches Review

Zusammenfassung
Ziel: Neurologische Rehabilitation spielt eine übergeordnete Rolle bei neurologischer Dysfunktion und zentralen Störungen der Sprache und des Sprechens traumatischen oder kongenitalen Ursprungs. Neuroplastizität ist Gegenstand aktueller Forschung und kann durch Training induziert werden. Die auf diesem Prinzip beruhende Padovan-Methode® – Neurofunktionelle Reorganisation ist ein Ansatz in der Logopädie. Sie basiert vornehmlich auf der Expertise und Langzeiterfahrung ausgebildeter TherapeutInnen. Offizielle Reviews oder Behandlungsempfehlungen mit Hinweisen zu Indikation, Durchführung und Wirkungseffizienz liegen aktuell nicht vor. Zielsetzung des vorliegenden Reviews ist die Ermittlung der Evidenz der Methode aus bestehender Forschung. Methoden: Richtlinien von PRISMA, Cochrane Collaboration Handbook, MECIR und GRADE wurden berücksichtigt. Übliche Datenbanken (Cochrane Library, PubMed, AWMF, Anthromedics usw.) und weitere 38 Datenbanken inklusive grauer Literatur wurden durchsucht. Handsuche wurde ebenso durchgeführt sowie ExpertInnen kontaktiert, um unveröffentlichte Arbeiten einschließen zu können. Alle Arbeiten, die die Wirkung der Methode im Vergleich zu entweder keiner Intervention, anderen gängigen Therapien oder Placebo untersuchten, wurden eingeschlossen sofern die Sprache Englisch, Portugiesisch oder Deutsch war. Es gab keine Einschränkung der Eingangsgruppe (alle Altersstufen, Geschlechter und Diagnosen). Insgesamt wurden 196 TeilnehmerInnen in die Analyse eingeschlossen. Die Beobachtungszeitraum lag zwischen zwei Jahren und zwei Jahren. Mikrozephalie, Down-Syndrom, nicht näher bezeichnete neurologische Störungen und myofunktionelle Störungen waren die Haupterkrankungen der Patienten mit neurologischen Entwicklungsstörungen. Es wurden nur indirekte Überschneidungen operationalisierter Kriterien gefunden; daher sind die Schlussfolgerungen begrenzt. Zusammenfassung: Die Padovan-Methode® ist ein ganzheitlicher Therapieansatz mit möglich breitem Indikationsspektrum, was den Wirksamkeitsnachweis erschwert. Eine Anwendung der Therapie nach der Padovan-Methode® durch ausgebildete Therapeuten könnte von BehandlerInnen in Erwägung gezogen werden (schwache Empfehlung) und ein Beitrag zur Linderung von Symptomen oder zur Verbesserung des Zustandes kann erreicht werden. Daher sind die Entwicklung und Validierung von Therapieprotokollen und weitere Untersuchungen erforderlich.

Introduction

Background
Systemic comorbidities and otolaryngologic disorders are frequently detected in children with Down syndrome [1]. Difficulties caused by these comorbidities remain a young field of research [2]. Macroglossia, midface hypoplasia, and narrow nasopharynx are often seen in children with Down syndrome [3]. Quality of life and oral health seem to be related [4]. This was also shown in the context of Down syndrome with significant adverse effects on various effects of quality of life [5, 6]. In a wide analysis of anomalies in Down syndrome the importance of early detection of orofacial dysfunctionality and adequate support were described [7]. Recently an investigation revealed coherences of orofacial myofunctional disorders and childhood apraxia of speech and general sensorimotoric functions [8]. To explore the prevalence of orofacial dysfunctions and temporomandibular disorders, existing literature indicate a range of 2% to 8% for males and 4% to 15% for females [9]. The prevalence of temporomandibular pain ranges from about 2.0% to 4.5% [9].

For treating orofacial dysfunctions regarding closure of mouth, tongue position and speech development in early childhood, the AWMF guideline (s2k) for Down syndrome in childhood and adolescence within the AWMF framework (Association of Scientific Medical Societies)1 [10] names several therapy options. The Padovan-Method Neurofunctional Reorganization® (short: Padovan-Method®) [11] is one of the listed therapy options amongst others like Castillo Morales® Concept [12], NEPA (neurophysiological developmental formation) according to Pörnbacher, 2009 [13], and F.O.T.T.® (Facio-oral-tract-therapy®) [14]. Whilst several studies regarding the Castillo Morales® Concept are presented...
and its application recommended by the guideline for children with abnormal mouth function or tongue protrusion, the Padovan-Method® remains mentioned only with no hint to efficiency [10].

The relevance and usefulness of oral myofunctional therapy in temporomandibular disorders was recently investigated and approved in a systematic review [15] and an early intervention is recommended [10, 16]. The Padovan-Method® is frequently used in children and young patients with myofunctional disorders [17]. This was shown in an inquiry by Ruben and Wittich, 2014 [17], who gained expert evidence for the treatment of myofunctional disorders by reviewing existing therapy concepts (n = 536 experts) [17]. In this report, the Padovan-Method® is the second most used approach after the therapy according to Kittel [17]. Remarkable, Kittel herself recommends applying the Padovan-Method® besides the self-developed approach [18].

Description of the Intervention

The Padovan-Method® was developed as a holistic approach by the speech therapist and Waldorf school teacher Beatriz A.E. Padovan in the 1970s integrating a broad range of neurological functions also described by Abad Bender, 2017 [19]. Some information about the method can be found online [20–22] presumably provided by the umbrella organization of the Padovan-Method® (Brazil)², whereas an imprint and a clear authorship was not provided on the website. Older sources provide some aspects of the therapy [25–27]. The use of the Padovan-Method® can be seen in different countries such as Brazil, Canada, Germany, France, Spain, Greece, and Switzerland amongst others [28]. It is a rehabilitative approach in newborn, children, and adults with neurodevelopmental disorders.

Since no handbook exists covering both the theoretical approach and guidelines to the therapist, describing the model of intervention according the Padovan-Method® remains challenging. The UK society provides a digital brochure [28] and some details are described by Abad Bender, 2019 [29]. The concept is presented as a program which involves the entire body, hands, eyes, and mouth [28, 29]. Physiological movement patterns of ontogenetic development processes would serve as orientation [29]. Adherence to rhythm and a change between tensing and relaxation could be seen as important characteristics [28, 29].

The training program consists of different sections addressing the extremities, coordination of hand and eye, and functionality of the oral system. The first units are leg movements in supine position and arm tasks in prone position. Thereby joints and muscle chains from the feet up to the rotation of the head are being activated. To maintain rhythm and coordination this is accompanied by poems spoken by the therapist. The further steps involve homolateral and crossed coordination tasks which put the process of straightening up from crawling to standing and walking in the picture. The following tasks address gripping motor skills, hand eye coordination, and mouth functions such as chewing, sucking, and swallowing [19, 21, 22, 30].

The concept is based on (i) interdependencies of anthropological development phases and a rule-like running through development stages [19, 21, 22, 30] and (ii) neuroplasticity, its trainability, and the idea to initiate, regulate, and strengthen elementary functions and motions using movement exercises in a multidisciplinary setting in order to facilitate the progress of speech development as well as sensorimotor and higher cognitive functions [21, 29, 31].

Even if the assumption of functional and structural neuroplasticity is not new as a basic idea, the number of publications has risen considerably in recent years³ and can be considered a fact more than a theory [32]. Mechanisms of neuroplasticity [33, 34] and its intervention-dependent trainability highlighted in the context of early brain lesions as well as rehabilitation after brain damage [35–38] are under examination. In poststroke patients neuroplasticity was shown [39] and a systematic review indicates the presence of neuroplasticity following intervention in children with congenital hemiplegia [40].

Assuming neuroplasticity as a reasonable assumption [29, 31, 37, 41–43], the method can be seen as a combination of whole-body physio- and logopedic speech therapy [19, 44] following a hierarchic set of units addressing the entire body (motoric functions of hands, arms and legs, coordination, arbitrary and automatic movements, reflex system) as well as mouth functions (breathing, suction, chewing, swelling) [18, 45, 46] taking also sensory body function as well as cognitive functions into account. Part of the concept is based on myofascial chains and their interconnection between different parts of the body [19, 47, 48]. Some of the units regarding the mouth function units can be found published by the founder [27]. One of the core aspects of the method is to accomplish the development to the upright by repeating the physiological development stages, i.e., roll, crawl, pull up, walk, etc. [19, 25, 30, 49–52].

This construct leads to an multi-indication suitability where study approaches regarding breathing and sleep apnea [53, 54], sucking and feeding condition in preterm new-born babies [31, 55–57], myofunctional disorders [58], and also congenital syndromes [53, 56, 59–64] could be found. A contextualization to other therapy approaches is given by Jasmin et al., 2012, Finkbeiner, 2008, and

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² This is also supported by the fact, that the previous domain http://site.prosinapse.com.br [23] used to declare its ownership and is now forwarded to [24].
³ PubMed with search term [neuroplasticity].
Bergt et al., 2017 [48, 65, 66]. The target group of the Padovan-Method® includes patients of all ages following curative, supportive, or preventive aims [29, 31, 48, 56, 57, 67].

Due to a missing guideline of the therapy, no clear information about the principal intervention design was available. Existing literature indicates a protocol with therapy sessions of 45–60 min each ranging from 2 to 7 times a week for a period of several weeks up to several months [19, 44, 68] or even longer up to 3 years [69]. A certain set of equipment is required for the intervention and described by Abad Bender, 2017 [19]. The Padovan-Method® can be applied by people with healthcare degree [28], mainly logopedists, physiotherapists, ergotherapists, and osteopaths who run through a multi-step qualification program [28, 70–72].

State of the Art and Description of the Condition
The Padovan-Method® has only been published incompletely [27] and no comprehensive therapy guide is available. Nevertheless the concept was recently described exemplarily by Abad Bender, 2017 and 2019 [19, 29], Pereira, 2015 [31], and von Treuenfels, 2003 [30].

Target group of the therapy are patients with neurodevelopmental disorders such as motoric impairment, language, learning and behavioral alterations, orofacial disorders leading to dysphagia, and additionally other complications caused by brain damage, syndromes, or other congenital reasons [21, 29–31, 44, 73, 74]. For a definition of the concept of neurodevelopmental disorders see Cioni et al., 2016 [75]. The method appears in a few scientific publications in patients with orofacial or myofunctional disorders (dysphagia, closure of mouth, tongue position, and speech development in early childhood [30, 76–79]; also related to Down syndrome [10]; lack of coordination of sucking, breathing, and swallowing [31, 57]), and neurological dysfunctions or development disorders with different origin (autism [52, 80]; cerebral palsy [57]; microcephalia [60–62, 81]; stroke [82]; fatigue as well as mental and physical disability [29, 48, 83, 84]; habits [85]). The Padovan-Method® is also used in stationary settings for inpatients [31, 57]. A small increase of scientific publications including information on its effectiveness can be noticed in the last decade [57, 58, 64, 86–90].

Why It Is Important to Do This Review
The Padovan-Method® remains a relatively unknown therapy approach. Data about the Padovan-Method® and its evidence is thin or not scientifically substantiated [19, 91–93]. The background of the therapists (logopedists, physiotherapists, ergotherapists) [19], which is frequently non-academic per se, might be considered as one of the reasons of the lack of available trials. Whereas Starrost and Schilling, 2013 [79] list the approach in an overview article of therapy approaches in dysphagia [79], no publication concerning the Padovan-Method® met the inclusion criteria for a systematic review focusing interventions for oropharyngeal dysphagia by Morgan et al., 2012 [94].

In view of the burden of the targeted groups of patients, more evidence regarding the potentially appropriate therapy methods is highly desired. An abstract announcing a literature review about the Padovan-Method® and its evidence was found [95] and continuing or updating existing reviews is recommended [96]. No results were available or published. Hence we decided to set up a new systematic review regarding the effectiveness of the Padovan-Method®, which is to our knowledge the first of its kind on this topic. Adherence to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [97], The Cochrane Collaboration Handbook [98], the guidelines of the Grading and Recommendations Assessment, Development and Evaluation working group (GRADE) [99] and in parts to Methodological Expectations of Cochrane Intervention Review (MECIR) [100] was considered in the design.

Objective
This systematic review aims to access available scientifically published studies or case reports dealing with the explicit application of a therapy according to the Padovan-Method® to newborn, children, and adults. Due to the explorative character of this project, design restrictions regarding the included studies were dispensed. Both experimental studies as well as observational design were of interest. Studies with either no intervention, alternative intervention as state of the art, or placebo intervention were included. It is sought to clarify the application spectrum and effectiveness of the Padovan-Method® to gain evidence of usability. Trials with comparison were of interest as well as single case reports.

Methods

Until now, no guidelines for creating systematic reviews in the field of rehabilitative medicine exist. Challenges as well as opportunities are seen and a guideline is being worked out by the Cochrane Rehabilitation Group and creation of recommendations is ongoing [101]. Upcoming updates of this review will be able to take not yet available guidelines into account [101]. For now, available concepts were obeyed [102] to ensure methodologic quality [103]. We therefore follow the available guidelines of PRISMA [97], The Cochrane Collaboration Handbook [98], MECIR in parts [100], and GRADE [99] (see online supplement E for the PRISMA-P Checklist [104]). The review has been registered at PROSPERO database (registration number: CRD42020156124). A protocol following PRISMA-Protocols (PRISMA-P) [105] was set up [106] and can be requested from the authors at any time. A preprint but not a published version of this article is available at Research Square [107].
Eligibility Criteria
As the context of the Padovan-Method® refers to rehabilitative medicine, difficulties were present [108] in setting up a PICOT search strategy (short for Patient Problem, Intervention, Comparison, Outcome and Time) [102] as needed for a systematic review [109]. Scientific reports on efficacy of the Padovan-Method® meeting the PICOT question hereinafter defined were included.

Participants
To define the target group (P, patient) a set of relevant diagnoses for the Padovan-Method® would be needed but is not clearly provided by existing literature. Consequently, P was set broadly as follows. All studies examining newborn, children, and adults regardless of sex and age (i) in a neuro-rehabilitative setting due to neuropsychomotoric dysfunctions or development disorders OR (ii) with orofacial or myofunctional disorders OR (iii) with any other not yet listed diagnosis will be included.

Intervention
All setups using the Padovan-Method® were of interest. If other treatment was applied in conjunction, the reports were included too. The interventions had to be applied by trained therapists [72]. No further limitations were set for duration of each therapy session, frequency, and overall duration of the intervention.

Comparators
With regard to the wide area of the intended review, several comparators were set to be relevant. Thereby comparison with either no intervention, alternative intervention as state of the art, or placebo was analyzed.

Outcome
Consequently, the outcome (O, outcome) is widespread and was likewise wide set, considering this review aims to investigate expectable results presented in existing studies. Improvement of condition or alleviation of symptoms were of interest. Response to treatment regarding motoric functions, psychomotor development, speaking, swallowing, and eating as well as suction were defined as primary outcomes. Definitions of outcomes were extracted as reported in the included studies. A list of rating instruments used was set up and comes along with this paper.

Timing
Items were included regardless of the length of intervention or follow-up. This was decided again due to expected little available data.

Summarizing, the following PICOT question was formulated: “In newborn, children, and adults regardless of sex and age, patients (i) in a neuro-rehabilitative setting due to neuropsychomotoric dysfunctions or development disorders OR (ii) with orofacial or myofunctional disorders OR (iii) with any other not yet listed diagnosis (P), how does an application of the Padovan-Method® or myofunctional disorders OR (iii) with any other not yet listed diagnosis will be included.

A recommendation for an updated PICOT question with special regards to P and O was set up.

Study Design
As a piloting of the search revealed, little data was available and no randomized controlled trials (RCT) were to be expected [110]. This is not a rare situation in rehabilitation research [101, 108] and eligibility therefore was set to include all types of intervention reports. Both qualitative and quantitative studies were sought. Included items were RCTs, controlled (non-randomized) clinical trials (CCTs), cluster trials, controlled before-after (CBA) studies, prospective and retrospective comparative cohort studies, and case-control, nested case-control studies (CCS) as well as case series (CS) and case reports (CR).

Language
We conducted the search in English and included all results in English. Additionally results in Portuguese and German were taken in. Titles in other languages were identified and listed for further consideration.

Publication Status
Scientific documents regardless of their publication status (published, in preparation, or unpublished manuscripts) were included.

Information Sources
Search was carried out within general databases (MEDLINE via PubMed, Cochrane Library, AWMF, Embase, Epistemonikos, UpToDate, BIREME, SciiLEO, DARE, SAGE, Scopus, SpeechBite, EBSCO/Ovid [CINAHL, Psynex, TOC Premier, E-Journal Database, PsycInfo, PsyArticles, PsyBooks]). Complementary and alternative medicine (CAM) based databases [111] were included (Cambase, Oseeker, PEDro, Antromedics). Additionally, clinical trial registers (CTR) were scanned (Cochrane Central Register of Controlled Trials CENTRAL, ISRCTN registry, WHO CTR, ANZCTR, Brazilian CTR, ChiCTR, ClinicalTrials.gov, India CTR, EU CTR, FACTR) as well as PROSPERO to find ongoing or recently completed trials/reviews. According to the protocol of this review [106] a hand search as well as grey literature was conducted to retrieve more relevant data [112–114]. Therefore relevant databases were used (Google Scholar, GoogleBooks, Open Grey, NTIS, AHRQ, Grey Source Index, OpenDOAR). We inspected the references of all identified studies for more results. We contacted the Society of the Padovan-Method® Brazil [23, 24] and Germany [71] to ask for further studies or missing information.

Search Strategy
Regarding the thin data the search term was set up in a general manner: “padovan” in title or abstract. It was adapted, where necessary, for each database. Exemplary the term used in Cochrane Library was padovan[title] OR padovan[abstract]. The search was conducted from June 2019 until end of November 2019. Some delay occurred during the project due to covid.

A re-run of the search prior to the final analysis (MEDLINE, Embase via Cochrane Library and PsycINFO) was carried out in August 2020.

Study Records
Data Management
Results from different sources were collected in Excel first. In this step duplicates were removed by finding identical titles. Excel was also used for the further review process. Citavi (version 6, Swiss Academic Software GmbH) was used as a reference manager.

Selection Process
Titles were screened for duplicates (D.V.). Titles and abstracts of the remaining results were screened independently for further duplicates and eligibility check (D.V., H.V.). In the case of disagreement, a third member of the team was consulted (T.O.). On-going, all selected items were retrieved (D.V.) if possible as full text to be fully analyzed (D.V., K.L.) to identify the hits to be included in the systematic review.
Data Collection Process
Data was extracted basing on principles of PRISMA [97]. Further data extraction for study quality and ethical evaluation was based on ROBINS-I (a tool for assessing risk of bias in non-randomized studies of interventions) [115, 116], the CARE-Guidelines [117], and the items proposed by Weingarten et al., 2004 [118]. For further description of ROBINS-I and CARE see section Study Quality and Risk of Bias.

A standardized form and a detailed instruction manual was developed and piloted (D.V.) and then introduced and explained to the second reviewer (K.L.). Both reviewers understand English, German, and Portuguese. Authors of articles for which no full text was available or any other important data was missing were contacted electronically if contact details were identifiable. In case of disagreement, a third member of the team was consulted (K.F.).

Data Items
Data was extracted with respect to reference, status of publication, country (where the treatment was carried out), sample (number of participants), dropout, groups, blinding (if any), age of participants, diagnosis/indication (characteristics of the participants), diagnostic instruments, research design of the treatment study, duration per session (D), frequency, duration of overall intervention period (D), therapist (qualification) and main outcome, specification of the numerical result being assessed, length of follow-up, confounding domain(s), measured treatment outcome variable(s), co-intervention(s). Consensus was sought in case of disagreements and if necessary a third reviewer was consulted (H.V.). Relevant information for assessing ethical considerations, the study quality, and risk of bias was extracted in the same workflow (see section Study Quality and Risk of Bias and Ethical Considerations). Qualitative data was recorded and dichotomously analyzed.

Outcomes
Outcomes in the setting of rehabilitative medicine evidence are difficult to define [108]. Therefore little restriction regarding sought outcomes was done. All outcomes were collected as reported. All quantitative data were extracted as reported (e.g., dichotomous, continuous). Qualitative data were screened for additional information and interpreted dichotomously.

Primary Outcomes
Due to the explorative character of the current review, a list of outcomes could not be given in advance. Improvements of motoric functions, psychomotor development, speaking, swallowing, and eating as well as suction were relevant. Expectable results by the Padovan-Method® are defined and are presented in the results section. Qualitative data was interpreted dichotomous and was analyzed to list potential outcomes. This can be used for further updates of the review. In terms of clarification of the potential outcomes, which might report various time points of the trial, we have decided to subdivide treatment indices as follows:

Secondary Outcomes
Secondary outcomes were set according to GRADE [99]: death due to intervention side effects, quality of life, acceptability of treatment (dropout to any reason), and overall tolerability.

Study Quality and Risk of Bias
To assess the quality and risk of bias, we followed the recommendations of the Cochrane Collaboration [98] and used ROBINS-I [115, 116] by two reviewers (D.V., K.L.). ROBINS-I [115] uses different domains to assess the risk of bias: (1) bias due to confounding, (2) bias in selection of participants, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, (7) bias in selection of the reported result, and (8) overall bias. The assessment was documented in a table and explanations given in the case of serial or critical risk of bias. Bias was assessed per study rather than per outcome [119]. To make these judgements, we used the criteria listed in ROBINS-I [115] for judging low risk of bias, moderate risk of bias, serious risk of bias, and critical risk of bias. See Table B1 (online supplement B) for the definition of each domain and for a description of the overall bias judgment both described by Sterne et al., 2016 [115]. The Newcastle-Ottawa Scale (NOS) [120] is criticized for its validity to measure the quality of case reports and observational studies [121] and was therefore not assessed. For further quality assessment the adherence of case reports to the CARE guidelines [117] was judged instead. The CARE guidelines outline advice concerning the following domains: keywords, abstract, introduction, patient information, clinical findings, timeline, diagnostic assessment, therapeutic interventions, follow-up and outcomes, discussions, patient perspective [117]. According to Sanderson et al., 2007 [122] no scoring but only descriptive report on adherence to CARE was done [122]. Retraction statements and errata were checked if available for further information of limitation or potential exclusion [100]. As no RCTs were available, RoB 2 (Cochrane Collaboration tool for assessing the risk of bias) [123] was not applied.

Data Synthesis
Due to the explorative character of this systematic review and the heterogeneity of the data, a meta-analysis was not performed and is not planned. A model of how the intervention works was set up in the first step according to the findings.

Studies are described textually following the guidelines on the conduct of narrative synthesis in systematic reviews [124] and details of all included items are presented tabulated to develop a preliminary synthesis of the results.

To evaluate relationships in the data, grouping of studies according to similar characteristics was done and described afterwards.

Meta-Bias
In order to evaluate if reporting or publication bias is present [97, 125], we determined, whether protocols of studies are available and published before the start of the study. In case of included abstracts reporting about intended studies, we documented if the results are published to evaluate whether the results were reported as planned.

Confidence in Cumulative Estimate
To judge the quality of the evidence for all important outcomes GRADE methodology [99] was used. GRADE recommends to evaluate the quality of evidence of the outcomes by assessing the domains of risk of bias, consistency, directness, precision, and publication bias before summarizing the overall response to treatment, acceptability of treatment (dropout due to any reason), quality of life, death, overall tolerability [99]. To define the overall quality of evidence and assigning grades we used the definitions according to GRADE [126] (also see Tables B2 and B3, online supplement C). GRADE evidence profiles (EP) [99] were set up to provide information on outcomes of each subgroup. The main findings were presented as “summary of findings” tables in a transparent and simple format providing relevant information regarding the quality of evidence, the effect of the interventions, and the sum of available and included data on the main outcomes [99, 119, 126–128].
**Ethical Considerations**

No approval of an ethical committee for a systematic review was required as no patient data is processed. Included trials were checked if they were approved by an ethic committee and informed consent was given. The ethical standard of all items and adherence to the Declaration of Helsinki [129] was outlined. See Table B4 (online supplement B) for the hereby used checklist for ethical assessment of trials in systematic reviews as proposed by Weingarten et al., 2004 [118]. Studies were included even though adherence to ethical standards were poor or simply not reported. This was done to reveal some possible risk of bias due to unpublished trials [130] and in order to bring light in the little noticed field of research regarding the Padovan-Method®.

**Results**

A total number of \( n = 533 \) items were found using scientific databases (\( n = 229 \)), grey literature databases (\( n = 233 \)), trial registries (\( n = 2 \)), and other sources (\( n = 69 \)). See Table C1 (online supplement C) for a list of the databases used and the number of results. After removal of duplicates (\( n = 114 \)) a total number of \( n = 419 \) items was screened for title and abstract and exclusion was made where necessary (\( n = 321 \)). 98 titles were analyzed for eligibility and exclusion (\( n = 80 \)) was made according to the protocol [106] in case of missing full text (\( n = 4 \)) [87, 88, 90, 95], whereas three of them were abstracts of relevant trials [87, 88, 90], and one of them was an announced review concerning the Padovan-Method® [95]. The authors were contacted but no further full text was available. Further items did not meet inclusion criteria but contained information about basic principles of the Padovan-Method® (\( n = 22 \)) as primary literature (\( n = 8 \)) [25, 49–51, 131–134] or secondary literature (\( n = 14 \)) [19, 44, 48, 68, 69, 74, 135–142], recommended the Padovan-Method® context dependent (\( n = 29 \)) [10, 27, 29, 52, 65, 76, 78, 80, 82–85, 89, 93, 143–157], mentioned the therapy as a possible option for certain indications without any proof of evidence (\( n = 10 \)) [16, 79, 92, 158–164], or simply contained some unspecified information about the method (\( n = 7 \)) [91, 165–170]. Due to manuscript language, eight potentially relevant items had to be excluded [46, 86, 171–176]. See Table C2 (online supplement C) for a reference list of excluded items. Finally four studies (no RCT, one pseudo-RCT [58], one non-RCT/CCT [64], one CBA [53], and one retrospective self-compared cohort study [57]) and \( n = 14 \) case documentations (10 CR [55, 56, 59–62, 81, 177–179] and 4 CS [31, 45, 63, 180]) remained for inclusion. Divergent from the protocol no further exclusion was made in the case of CS or CR with unclear documentation of the therapists’ qualification (therapy under supervision [61, 62, 81] or NI [59, 60, 63, 177–180]).
Table 1. Characteristics of the sample

| Author/year | Status | Country/language | Sample, n | Dropout | Groups | Blinding | Age | Diagnosis/indication | Diagnostic instruments | Design | Duration D1 in minutes | Frequency | Duration D2 | therapist/setting | Length of follow-up | Confounding domain(s) |
|-------------|--------|------------------|-----------|---------|--------|---------|-----|-----------------------|-----------------------|--------|----------------------|-----------|-------------|---------------------|---------------------|---------------------|
| Barbosa 2019 [59] publ | BRA/pt | 1 | NR | NR | NR | 2 y | microcephalia | MRI, EEG, audiometry | CR | NI | 2 m, 7 sessions | NI/NI | NI | Padovan-Method® | other not specified; 2nd to 7th session with Padovan-Method® |
| Braga 2019 [60] publ | BRA/pt | 1 | NR | NR | NR | 2,2 y | microcephalia | ultrasonography during pregnancy (31 weeks), CT scan with 5 days of life | CR | 60 | NI | 3 m, 7 sessions | NI/univ | NI | Padovan-Method® starting in session 4 | kinesiotaping |
| Buson 2019 [61] publ | BRA/pt | 1 | NR | NR | NR | NI | microcephalia | collection of liquor and CT scan within first 3 days of life | CR | 60 | NI | 3 m, 9 sessions | supervised/univ | NI | kinesiotherapy; sessions 2–9 with Padovan-Method® |
| Carmo 2019 [62] publ | BRA/pt | 1 | NR | NR | NR | 2,5 y | microcephalia | ultrasonography during pregnancy, physical examination with inspection, palpation, respiratory examination, test of reflex actions and global movements | CR | NI | NI | 3 m, 6 sessions | supervised/univ | NI |
| Delmondes 2018 [56] publ | BRA/en | 1 | NR | NR | NR | 6 d | Treacher Collins syndrome | NI | CR | NI | 1/d | 5 d | q/ip | 3 y |
| Freisthaller 2010 unp | NLide | 1 | NR | NR | NR | 2,4 y | teratogenesis, open bite | NI | CR | NI | NI | 1,2 y | NI |
| Groißwieschede 2000 [178] unp | GER/de | 1 | NR | NR | NR | 8,9 y | audiogenic dyslalia | patients’ records | CR | NI | 1/w | 2 y | student/amb |
| Kunert 2003 [179] unp | GER/de | 1 | NR | NR | NR | 6 y | speech development disorder | NI | CR | NI | NI | NI | speech therapist/amb |
| Menezes 2019 publ | BRA/pt | 9 | NI | NR | NR | M = 10 m; SD = 5,4 m; Min = 0,3 y; Max = 1,7 y | microcephalia | AIMS [182] | CS | NI | 2/w | 1 y; Min = 28; Max = 64 sessions | NI/ip | NI |
| Oertel 2015 [45] unp | GER/de | 8 | S | NR | none | M = 8,3; SD = 8,3; Min = 4,9; Max = 29 y | myofunctional disorder | logopedic assessment tool (Kölner Diagnostik Bogen) [142, 183], sheet for therapeutic objective clarification [184], results and progress log (IPVP) [142, 183] | CS | 45–60 | 1–2/w | 1 y | q/amb | NR | variation in frequency of therapy; ci: osteopathy, physiotherapy, LWZ tool [185] |
| Oliveira 2019 [81] publ | BRA/pt | 1 | NR | NR | NR | 2,4 y | microcephalia | ultrasonography during pregnancy, physical examination, behavior, respiratory examination, test of reflex actions and global movements | CR | 60 | 1/w | 4 m, 9 sessions | supervised/univ | NI |
| Pereira 2015 [31] publ | BRA/en | 11 | NI | NR | NR | Min = 5 d; Max = 5,12 | neonatal hypoxic-ischemic encephalopathy (10), neurological alteration by kernicterus (1) | CS | NI | NI | 8 d–1 m (5 m) | q/ip | NI |
| Pereira 2018 [180] publ | BRA/pt | 2 | NI | NR | NR | 3,5 m, 24 d | fetal alcohol syndrome | physical examination | CS | NI | NI | 1 m, 28 d | q/ip | NI |
| Author/ year | Status | Country/ language | Sample, n | Dropout Groups | Blinding Age | Diagnosis/ indication | Diagnostic instrumentsa | Design | Duration D1 in minutes | Frequency | Duration D2 | Therapist/ setting | Length of follow-up | Confounding domain(s) |
|-------------|--------|------------------|-----------|----------------|--------------|----------------------|----------------------------|--------|-----------------------|------------|---------------|---------------------|---------------------|---------------------|
| Wilson 2016 [55] | publ  | GBR/en | 1 | NR | NR | 28 y | brain injury | CT scan | CR | 45–60 | 2/w | NI | q/ip | NI | multi-modal therapy setting |
| Bellingen 2017 [56] | publ | GER/de | 12 | 1 | 8 ig/4 cg | none | M1 = 11.1 y; SD1 = 2.6 y; M2 = 8.8 y; SD2 = 1.4 y | myofunctional disorders | IOPR [186], BOT-2 [187], LPB [188], mouth strengthening tool (MFT: Lippenwaage) [189], therapists observation parental questionnaire [58] | pseudo-RCT | 45 | 2/w | 11 w | q/amb | NI |
| Lukowicz 2019 [53] | publ | GER/en | 42 | 24 | NR | M = 6.3 y; SD = 2.5 y | Down syndrome with obstructive sleep apnea | MO-4H [190], D1/BW [53] | CBA | 45 | 2/d | 1 w | q/ip | NI | noticeably short intervention |
| Pereira et al. 2015 publ [57] | BRA/en | 92 | 10 | NR | Min = 2 d; Max = 102 d | newborns with symptoms summarized as alterations in neurological examination or presenting difficulties in sucking | neurological examinations | retrospective self-controlled cohort study | 5/w | 2 d–5 m | q/ip | NI |
| Rodenacker 2007 unp [64] | GER/en | 10 | 0 | 5 ig/5 cg | none | M = 5.2 y; SD = 1.1 y; Min = 3.11 y; Max = 6.7 y | Down syndrome | MOT-4-6 [191], SETK-3-5 [192] | non-RCT/ CCT | 1–2/w | 10 w | q/amb | NI | short setup; data collection limited due to bilingualism of participants; impairments due to infections; ci: speech therapy, kindergarten, dancing, gymnastics, recreational activities |

pub, published; unp, unpublished; M, mean; SD, standard deviation; y, years; m, months; w, weeks; d, days; BRA, Brazil; GBR, United Kingdom of Great Britain and Northern Ireland; GER, Germany; en, English; pt, Portuguese; de, German; NI, no information given; NR, not relevant; ig, intervention group; cg, control group; MRI, magnetic resonance imaging; CT, computed tomography; EEG, electromyolograms; CR, case report; CS, case series; RCT, randomized controlled trial; CCT, controlled clinical trial; q, qualified; univ, university; ip, inpatient; amb, ambulatory; ci, co-interventions; LWZ, lip-cheek-tongue trainer (Lippen Wangen Zungen Träner) [183]. For main outcomes and numerical results please see Table 2. a See Table D1 (online supplement D). b As stated in original document.
179]). A flowchart following the PRISMA guidelines [181] was created to illustrate the process and is shown in Fig. 1. The characteristics of the sample are shown in Table 1 and an overview of the quantitatively evaluated primary outcomes is given in Table 2.

**Study Quality and Risk of Bias**

The risk of bias using ROBINS-I [115, 127] is presented in Table 3. See Tables D2–D5 (online supplement D) for details and authors’ judgement. Although Bellingen [58] described the design as pseudo-randomized controlled trial, it was not clear, to what extend it could be interpreted as randomized or non-randomized. Therefore we decided to classify and rate it as non-RCT. None of the included studies had a low risk of bias. One item each was at moderate [53] and serious [58] risk of bias. Two items had a critical risk of bias [57, 64]. Bias due to confounding was present due to too short study design [53], multi-therapy setting [57, 64]. Selection bias occurred due to retrospective design and selection into the study in relation to intervention [57]. Bias in classification of interventions was overall at low risk. Deviations from intended interventions caused moderate risk of bias due to non-balanced co-interventions [57, 64] and critical risk of bias due to potential effect of non-controlled co-interventions [57]. Missing data for any participant led to a critical risk of bias [57]. Unclear conditions in measurements of outcomes were rated with moderate risk of bias due to observers’ knowledge of the intervention [57, 58] and serious risk of bias due to language barriers and limited condition of patients at certain measurements [64] and no available outcome data [57]. Bias in selection of reported results was detected moderate due to no available study protocol [57, 58, 64], serious due to deviations between methods and results section [58], and critical due to rare outcome data in the results section [57]. Limita-

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**Table 2.** Table of primary outcomes quantitatively evaluated

| Early response, between 1 and 4 weeks | Acute phase treatment response, between 6 and 12 weeks | Long-term and follow-up response, between 4 and 6 months (or more) |
|--------------------------------------|-------------------------------------------------------|---------------------------------------------------|
| Decrease of D100 [53] | Changes of tongue and lip coordination exercises [58] | Improvement condition of lips [45] |
| | Swallowing examination [58] | Reduced habit of |
| | Position of tongue tip whilst swallowing [58] | – licking lips [45] |
| | Position of tongue edge whilst swallowing [58] | – biting objects [45] |
| | Articulation (s-sound formation [188]) [58] | Improved |
| | Time to get up in the morning [193] | – sitting posture [45] |
| | | – swallowing patterns [45] |
| | | Improved axis symmetry of |
| | | – eyes [45] |
| | | – zygomatic bone [45] |
| | | – shoulders [45] |
| | | Gained as ability |
| | | – pull the lips wide [45] |
| | | – move the tongue to the right or in a circle [45] |
| | | Reduced lateral posture [45] |
| | | No preferred side of chewing [45] |
| | | Rise of the AIMS score [63, 182] |

Details of measurements and outcomes are described in the text.

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**Table 3.** Risk of bias ROBINS-I of the included studies

| Author/year | Bias due to confounding | Bias in selection of participants into the study | Bias in classification of interventions | Bias due to deviations from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall bias |
|-------------|-------------------------|-----------------------------------------------|----------------------------------------|-----------------------------------------------|-------------------------|---------------------------------|--------------------------------------|------------|
| Bellingen 2017 [58] | + | + | + | + | + | ? | × | × |
| Lukowicz 2019 [53] | ? | + | + | + | + | + | ? | ? |
| Pereira et al. 2015 [57] | ! | × | + | ! | ! | × | ! | ! |
| Rodenacker 2007 [64] | ! | + | + | ? | + | × | ? | ! |

Assessment according to the ROBINS-I tool [115]. +, low risk of bias; ?, moderate risk of bias; ×, serious risk of bias; !, critical risk of bias.
tions were set according to the overall risk of bias, if no further limitations existed. Imprecision was judged according to GRADE [126] (see Table 4).

The results of the CARE [117] evaluation of the CS and CR were evaluated as shown in Table 5. No retraction statements were found. One CS was found including an erratum as appendix with some corrections of the manuscript (master thesis), taken into consideration by this work [45]. None of the included CS and CR fulfilled the CARE [117] recommendations completely. Critical limitations were present in all items regarding at least one of the following domains: diagnostic assessment [31, 56, 59–62, 177], follow-up and outcomes (all items) [31, 45, 55, 56, 59–63, 81, 177–180], and discussion [56, 59–62, 81, 177, 179]. Limitations of CS and CR where therefore considered to be moderate [45, 55, 63, 81, 178–180] or high [31, 56, 59–62, 177]. For an overview see also Table 4.

### Ethics Assessment

The results of the ethics screening are presented in Table 6. Approval by an ethics committee was reported only in two papers [63, 194]. No information about agreement was found in all other items [31, 45, 55–62, 64, 81, 177–180]. Patient informed consent given prior to the intervention was documented in four of the results [45, 55, 63, 178]. Lukowicz et al., 2019 [53] reported no patient informed consent had been required. Documentation was unclear in one case [179] and no information was found in all others [31, 55, 56, 58–62, 64, 81, 177, 180].

### Funding

Only one item reported on sources of funding and stated to not have received any funding [53].

### Declaration of Interest

Only one item reported on the declaration of interest declaring none [53].

### Textual Descriptions of Included Items and Reported Outcomes

The included studies and case reports are described textually in this section giving general information about the setting, participants, indicating diagnoses, intervention, comparisons, variables, and outcomes. If applicable further information is presented in Table 1.

### Studies

The included studies [53, 57, 58, 64] covering the period from 2007 to 2019 were found as published [53, 57, 58] or grey literature [64]. For two of the published studies [53, 58] detailed underlying thesis manuscripts were available as grey literature [54, 193]. The manuscripts were used to gain further information about the studies. Three of the studies were carried out in Germany [53, 64] and one in Brazil [57]. The setting was clinical (inpatients) [53, 57] and ambulatory [58, 64]. The number of participants reached from \( n = 10 \) [64] to \( n = 92 \) [57] and was \( n = 156 \) in total. Amongst the prospective trials [53, 58, 64] a controlled setup was found in two cases [58, 64]. One trial was set up retrospectively self-controlled and descriptively [57]. The age of the participants reached from 2 days [57] to 15 years [58]. Indicating diagnoses

### Table 4. Quality of evidence regarding risk of bias, limitations, and imprecision

| Author/year         | Risk of bias | Limitations | Imprecision |
|---------------------|--------------|-------------|-------------|
| Bellingen 2017 [58] | serious risk | moderate    | low         |
| Lukowicz 2019 [53] | moderate risk| low         | very low    |
| Pereira et al. 2015 [57] | critical risk | high      | high        |
| Rodenacker 2007 [64] | critical risk | high      | moderate    |
| Barbosa 2019 [59]  | –            | high        | high        |
| Braga 2019 [60]    | –            | high        | high        |
| Buson 2019 [61]    | –            | high        | high        |
| Carro 2019 [62]    | –            | high        | high        |
| Delmontes 2018 [56] | –            | high        | high        |
| Froitzheim 2010 [177] | –            | high        | high        |
| Großweischede 2000 [178] | –            | moderate    | high        |
| Kunert 2003 [179]  | –            | moderate    | high        |
| Menezes 2019 [63]  | –            | moderate    | moderate    |
| Oertel 2015 [45]   | –            | moderate    | moderate    |
| Oliveira 2019 [81] | –            | moderate    | high        |
| Pereira 2015 [31]  | –            | high        | high        |
| Pereira 2018 [180] | –            | moderate    | high        |
| Wilson 2016 [55]   | –            | moderate    | high        |

*According to ROBINS-I [115]. *b According to GRADE [126].
Table 5. Adherence of the included CR and CS to the CARE guidelines

| Author/year | Key-words available? | Abstract | Introduction/Patient information | Clinical findings | Timeline | Diagnostic assessment | Therapeutic interventions | Follow-up and outcomes | Discussion | Patient perspective |
|-------------|----------------------|----------|-----------------------------------|------------------|---------|-----------------------|-------------------------|------------------------|-----------|---------------------|
|             |                      |          |                                    |                  |         |                       |                         |                        |           |                     |
|             |                      |          | Core presentation (symptoms, findings, diagnoses, etc.) |                  |         |                       |                         |                        |           |                     |
|             |                      |          | Conclusion: what were the main takeaway lessons? |                  |         |                       |                         |                        |           |                     |
| Barros 2019 [95] | N                  | N        | N                                  | Y                | Y      | Y                    | Y                       | Y                      | Y         | Y       |
| Braga 2019 [96]    | Y                  | N        | N                                  | Y                | Y      | Y                    | Y                       | Y                      | Y         | N       |
| Busson 2019 [97]   | Y                  | N        | N                                  | Y                | Y      | Y                    | Y                       | Y                      | Y         | Y       |
| Camara 2019 [98]   | N                  | N        | N                                  | Y                | Y      | Y                    | Y                       | Y                      | Y         | Y       |
| Delmendo 2018 [34] | Y                  | Y        | Y                                  | PY               | PY     | PY                   | Y                       | Y                      | Y         | Y       |
| El-Fatihah 2010 [177] | N          | N        | N                                  | N                | N      | N                    | N                       | N                      | N         | Y       |
| Großreihen 2006 [178] | Y           | N        | N                                  | Y                | Y      | Y                    | Y                       | Y                      | Y         | N       |
| Kurken 2015 [99] | N                  | N        | N                                  | N                | N      | N                    | N                       | N                      | N         | N       |
| Meneses 2015 [100] | Y               | N        | N                                  | N                | N      | N                    | N                       | N                      | N         | N       |
| Oertel 2015 [101] | N                  | N        | N                                  | Y                | Y      | Y                    | Y                       | Y                      | Y         | Y       |
| Oboziera 2015 [102] | Y               | N        | N                                  | Y                | Y      | Y                    | Y                       | Y                      | Y         | Y       |
| Pavone 2013 [103] | Y                  | N        | N                                  | Y                | Y      | Y                    | Y                       | Y                      | Y         | Y       |
| Pavone 2018 [104] | Y                  | N        | N                                  | Y                | Y      | Y                    | Y                       | Y                      | Y         | Y       |
| Wilson 2016 [105] | N                  | N        | N                                  | Y                | Y      | Y                    | Y                       | Y                      | Y         | Y       |

Table according to the CARE guidelines [117]. Y, yes; PY, partly yes; PN, partly no; N, no; NI, no information provided.
## Table 6. Assessment of ethics in included items

| Author/year          | Goal-related considerations | Duty-related considerations | Rights-related considerations | Global considerations |
|----------------------|------------------------------|------------------------------|--------------------------------|------------------------|
|                      | Is there a clear declaration on financial support in all trials? | Is there a statement that relates to potential conflicts of interest in all trials? | Was there a clear declaration on potential conflicts of interest in all trials? |                      |
|                      | Is there a statement that relates to potential conflicts of interest in all trials? | Was the size of the study sufficient to achieve adequate statistical power? | Were the comparators appropriate? |                      |
|                      | Were any of the trials superfluous? | Could the results have been obtained by laboratory or animal experiments? | If a placebo was used, was it justified? |                      |
|                      | Publication bias               | Justification                | Safety                          |                      |
|                      | Is the trial published?        | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Is the trial published? | Did participants have reduced competence, were appropriate measures taken to protect their best interests? |                      |
|                      | Was informed consent obtained? | Was the trial published? | Was the trial published? |                      |
|                      | Could the results have been obtained by laboratory or animal experiments? | Was the trial published? | Were the comparators appropriate? |                      |
|                      | Were any of the trials superfluous? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Publication bias               | Could the results have been obtained by laboratory or animal experiments? | Was the trial published? |                      |
|                      | Is the trial published?        | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Could the results have been obtained by laboratory or animal experiments? | Was the risk for participants appropriate to the importance of the research? |                      |
|                      | Was the risk for participants appropriate to the importance of the research? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Could the results have been obtained by laboratory or animal experiments? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
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|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
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|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |
|                      | Was the size of the study sufficient to achieve adequate statistical power? | Was the risk for participants appropriate to the importance of the research? | Was informed consent obtained? |                      |

Table according to Weingarten et al. [118]. Y, yes; PY, partly yes; PN, partly no; N, no; NI, no information provided; NR, not relevant. 1Not superfluous, but reporting has methodological flaws. 2More declared. 3The intervention protocol was set up too short and known in advance as described by the authors. 4No control group. 5Study period too short and too intensive leading to inappropriate burden for the patients. 6Stated by the author as not necessary. 7Status of patient was coma when treatment was applied.
were Down syndrome [64], Down syndrome with obstructive sleep apnea [53], myofunctional disorders [58], and newborns with symptoms which are summarized as alterations in neurological examination or presenting difficulties in sucking [57]. Nevertheless myofunctional disorders were also present in the three other studies at the level of condition of included patients [53, 57, 64]. Dropouts \((n = 35)\) were reported because of upper respiratory infections or recording of less than 3 h of sleep \((n = 24)\) [53], death due to sepsis in the context of newborn \((n = 7)\) [57], transfer \((n = 2)\) [57], surgery \((n = 1)\) [57], or too large intervals between therapy sessions \((n = 1)\) [58]. All therapists were documented to be qualified for the Padovan-Method® [72]. The measured items were totally heterogeneous without any conformity. The rating instruments used in the included papers are listed in Table D1 (online supplement D). Rodenacker et al., 2007 [64] used the motoric test (MOT 4-6) [191], speech development test (Sprachentwicklungstest, SETK 3-5) [192], and a parental questionnaire regarding the development of the participants and their influence on the family, self-developed by Rodenacker et al., 2007 [64]. Pereira et al., 2015 [57] documented and evaluated neurological examinations [57]. Bellingen, 2017 [58] used the Iowa Oral Performance Instrument (IOPI) [186], assessment of mouth closure by the therapists using a three-point scale, lip strength using the MFT-Lippenwaage (tool to strengthen and measure the muscles for closure of lip and mouth) [189], measurement of suction power and speed using the suction trainer developed by Beatriz A.E. Padovan and described at Abad Bender, 2017 [19], coordination of tongue and lips using certain tasks from a toolkit developed by and described at Kittel and Förster, 2010 [195], swallowing examination using an own system with different types of fluid and color [193], observation of teeth and jaw position by therapists [193], Bruinincks-Oseretsky Test of motoric proficiency (BOT-2) [187], articulation (Lautprüfbogen, LPB) [188], therapists observation and parents questionnaire developed by the author described at Bellingen, 2017 [58] with the following items: time needed for homework, concentration during homework, difficulties with orthography, difficulties with building sentences, difficulties with finding the right words, building unstructured sentences, time to get up in the morning, awakening during night, needed time to fall asleep, preference of certain food consistency, chewing [58]. Von Lukowicz et al., 2019 [53] used the mixed-obstructive-apnea/hypopnea index (MOAHI [53, 54], defined as the sum of obstructive and mixed apnea and hypopnea per hour of corrected estimated sleep time\(^4\) (CEST) [53, 54]), DI\(_90\) (desaturation index <90%, events per hour of corrected estimated sleep time) [53, 54], DI\(_3\) (desaturation index ≥3%, events per hour of corrected estimated sleep time) [53, 54], DI\(_90\) (desaturation index ≥90%, events per hour of corrected estimated sleep time) [53, 54], arterial oxygen saturation (SpO\(_2\)) [53].

In all studies the core intervention were therapy sessions according to the Padovan-Method®. The duration of the sessions was 45 min [53, 58] (NI: [57, 64]), with an application frequency varying in all studies between three times a day [53], five times per week [57], two times per week [58], and in one case accelerating from one to two times per week [64]. The intervention periods were heterogeneous with 1 week [53], 10 weeks [64], 11 weeks [58], and due the retrospective setup 2 days to 5 months [57].

The trials came up with different and heterogeneous outcomes. Statistically significant changes of tongue and lip coordination exercises (tongue exercise 2 [195] likelihood-ratio test \([LR]\) \(\chi^2\) [2, \(n = 12\)], \(p = 0.001\) [58]; lip exercise 1 [195] \(LR\) \(\chi^2\) \([n = 12]\), \(p = 0.005\) [58], swallowing examination (swallowing fluids [193] test for independent samples: \(t(10) = -5.331, p < 0.000\) [58], position of tongue tip whilst swallowing [193] test for independent samples: \(t(10) = -3.429, p = 0.006\) [58], position of tongue edge whilst swallowing [193] test for independent samples: \(t(10) = -9.163, p < 0.001\) [58]), articulation (sound formation [188]) test for independent samples: \(t(10) = -2.525, p = 0.010\) [58] and time to get up in the morning (parental questionnaire, Chi-square test \(\chi^2\) [3, \(n = 12\), \(p = 0.023\) [193], decrease of DI\(_90\) (2.7 [SD 4.5] to 2.1 [SD 3.7], \(p < 0.05\) [53]. Not statistically significant but described as noticeable was a rising of lip strength (MFT-Lippenwaage [189] T1 = initial examination: 500–1,017 g; T2 = examination after intervention: 850–1,367 g) [58] and a subjective boost of development described by some of the parents [64]. No data provided and thereby only descriptively reported were the following: a shortening of hospital stay, an avoidance of gastrostomy, and palliative procedure of feeding for discharge of the treated newborns [57]. Furthermore no statistically significant effect of Padovan-Method® on obstructive sleep apnea in Down syndrome patients was shown [53] and no difference between therapy according to Padovan-Method® and Psychomotor Performance Therapy was revealed [64]. Moreover a change of the tongue pressure, lip strength, suction power and speed, quality of mouth closure, physiologically swallowing of food, fine and gross motor skills was not shown or not evaluable due to small sampling size [58]. None of the studies came up with a follow-up testing or documentation.

Case Reports
The included case reports [31, 45, 55, 56, 59–63, 81, 177–180] covering the period from 2000 to 2019 were found as published [31, 55, 56, 59–63, 81, 179, 180] or grey literature [45, 177, 178], one of which [45] was later

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\(^4\) For more information regarding MOAHI see Arthasana, 2019 [190].
published as abstract only [196]. Nine of the cases were collected in Brazil [31, 56, 59–63, 81, 180], three in Germany [45, 178, 179], one in Great Britain [55], and one did not provide any information about the country [177]. The context of the cases were university [60–62, 81], in-patients [31, 55, 56, 63], and ambulatory setting [45, 178, 179] (no information provided [59, 177, 180]). The number of participants reached from \( n = 1 \) to \( n = 11 \) [31] and was \( n = 40 \) in total. The items contained four case series [31, 45, 63, 180] and ten single case reports [55, 56, 59–62, 81, 177–179]. The age of the participants reached from 5 days [31] to 28 years [55]. Indicating diagnosis were microcephalia (with total \( n = 14 \) in six case reports [59–63, 81]), neonatal hypoxic-ischemic encephalopathy (\( n = 10 \) [31]), myo-functional disorder (\( n = 8 \) [45]), fetal alcohol syndrome (\( n = 2 \) [180]), neurological alteration by kernicterus (\( n = 1 \) [31]), speech development disorder (\( n = 1 \) [179]), audiogenic dyslalia (\( n = 1 \) [178]), Treacher Collins syndrome (\( n = 1 \) [56]), tetraparesis and open bite (\( n = 1 \) [177]), and brain injury (\( n = 1 \) [55]). Dropouts (\( n = 5 \)) were reported in one case series due to lack of time to adhere to the therapy protocol [45]. The therapists were either certified for the Padovan-Method® [31, 45, 55, 56, 180], under supervision [61, 62, 81], or no information given [59, 60, 63, 177–179].

The measured items were totally heterogeneous without any conformity. See Table D1 (online supplement D) for the rating instruments utilized. Menezes et al., 2019 [63] used the Alberta Infant Motor Scale (AIMS) [182] and dichotomous assessment of physical assessment (grab objects, reflux, don’t follow objects, lack of cervical control, convulsion/spasm, lack of thoracical control) [63] analyzed descriptively. Oertel, 2015 [45] used a logopedic assessment tool developed for quality assessment in logopedic therapies (Kölner Diagnostikbogen described at [184]), the report sheet from the results and progress log for neurofunctional reorganization (Befund- und Verlaufsprotokoll zur Neurofunktionalen Reorganisation, IPVP [142, 183]), and a clarification of therapeutic objectives sheet (Therapeutische Auftragsklärung following [184]). The case report of Wilson et al., 2016 [55] is mainly descriptive, but used tools were the Wessex Head Injury Matrix (WHIM) [197] and the JFK Coma Recovery Scale-Revised (CRS-R) [198] and throughout the hospital stay replaced by the Putney Auditory Comprehension Screening Test (PACST) [199], the Functional Assessment Measure (FAM) [200], and the Functional Independence Measure (FIM) [201]. No information about measured variables were given in all other items (11) [31, 56, 59–62, 81, 177–180].

Within all reports the patients received therapy sessions according to the Padovan-Method®. The duration of each session was 45–60 min [45, 55, 60, 61, 81, 179] or not specified [31, 56, 59, 62, 63, 177, 178, 180], with divergent application frequencies of 1 or 2 times per week (1–2/w) [45, 55, 63, 81, 178], 5–6/w, [56, 62], and 7/w [59–61] (NI: [31, 177, 180]). The intervention periods were heterogeneous between 5 days [56] and 2 years [178] (NI: [55]). In some case reports other therapies were applied too and are to be accounted as confounding domains (ki-nesiology [60, 61], osteopathy or physiotherapy [45], multi-disciplinary setting [55], use of a lip-cheek-tongue trainer (Lippen-Wangen-Zungen [LWZ]-Trainer [185]) [45], manual therapy not further specified [59]).

The reports presented different outcomes, again very heterogeneous. Statistically significant changes were presented in two case reports [45, 63] though with moderate imprecise documentation according to GRADE Rating [202]. Fisher’s exact test [194] and Wilcoxon Test [203] was used to measure statistical significance between first and third (last) examination [45] and revealed the following results: no preferred side of chewing (\( p = 0.025 \)), condition of lips (\( p = 0.024 \)), pull the lips wide gained as ability (\( p = 0.046 \)), move the tongue to the right or in a circle gained as ability (each \( p = 0.046 \)), reduced habit of licking lips (\( p = 0.034 \)), habit of biting objects reduced (\( p = 0.038 \)), improved sitting posture (\( p = 0.046 \)), reduced lateral posture (\( p = 0.020 \)), improved swallowing patterns (\( p = 0.026 \)), improved axis symmetry of eyes (\( p = 0.038 \)), zygomatric bone (\( p = 0.025 \)), and shoulders (\( p = 0.026 \)). A rise of the AIMS Score [182] between the first and third testing was described and postulated as statistically significant without giving a definition of the confidence interval (\( t \text{ test}(8) = 2.927, p = 0.19\ CI:NI [63] \) [63]).

Not statistically significant but noticeable effects such as reducing dysphagia and bronchial aspirations, spasms, improvement of the abilities to roll, crawl, and sit were reported [63] nonetheless imprecisely [202]. An improvement of the body condition (tone, posture, axial symmetry, occurrence of tension and pain) was qualitatively described as observed changes between initial and final testing [45]. A rise of the CRS-R [197] from three (T1: 4 months post injury, equal to vegetative state [198]) to eight (T2: 14 months post injury) was documented [55]. Throughout the hospital stay of the reported case, CRS-R [198] and WHIM [197] were discontinued because of ceiling both tests [55] followed by measuring PACST [199], FAM [200], and FIM [55, 201] with no further information regarding development of number. A high bias of missing data (according to GRADE [204]) exists as only results of the CRS-R [198] are reported [55]. A progress in verbal expression and improvement in cognition and speech within a multimodal therapy setting was reported qualitatively [55].

All other reports did not provide any measurements but reported improvements in the fields of psycho- and motoric development, speech, and vegetative functions. Details are listed in Tables D20 and D21 (online supple-
therapy in the meantime as no Padovan-Therapy® due to confounding domains: physiotherapy and speech good motorial and speech development (high risk of bias low-up after 3 years without detailed testing showing explicit results [179]. One of the reports mentioned a fol-
ment D). One report described a case but did not contain explicit results [179]. One of the reports mentioned a fol-
low-up after 3 years without detailed testing showing good motorial and speech development (high risk of bias due to confounding domains: physiotherapy and speech therapy in the meantime as no Padovan-Therapy® had been available) [56].

To define the primary and secondary outcomes (see Table 2 and online supplement D, Tables D20–21), the results of the studies and case reports were used. Outcomes documented to be statistically significant are listed separately (see Table 2). To extract the early response from acute phase treatment, response at the length of in-
tervention was used (cutoff duration of treatment process ≤1 month [31, 56, 57, 64, 180] and ≤3 months for acute phase treatment [31, 58–62, 180], >3 months for long-
term response [45, 55, 56, 63, 81, 177, 178]). As some of the included trials or reports extended over a long period, by derogation from the protocol [106] the section “fol-
low-up response between 4 and 6 months” was extended to “long-term and follow-up response between 4 and 6 months and more.” Secondary outcomes in the case of dropouts were listed in Table D21 (online supplement D). The reported death in seven cases [57] was caused by sep-
sis in the context of preterm babies. No adverse side ef-
effects or contraindications were found in any of the in-
cluded trials or reports.

Evaluation of Relationships and Subgroup Analysis

Even if there were methodological weaknesses in the included items, relationships and subgroup analysis was evaluated regarding diagnosis, outcomes, comparison, and duration of the intervention.

There was some accumulation of leading diagnoses in of the studies. (I) Microcephalia [59–63, 81], (II) Down syndrome [53, 64], (III) neurological disorders (high het-
erogeneity) [31, 53, 55–57, 59–64, 81, 177–180], and (IV) myofunctional disorders [45, 53, 57, 58, 64] appeared to be research focus. Due to very heterogenic setting and in-
cclusion criteria (addressing inconsistency [205]) and dif-
fferences in study population, intervention protocol, mea-
ured outcomes (addressing indirectness [206]) a com-
parison or subgroup analysis for indication diagnoses cannot expect a high or moderate ranking according to GRADE guidelines [99]. Nevertheless a GRADE evidence profile (EP) [99] was set up for I–IV regarding the out-
come “condition improvement or alleviation of symp-
toms.”

In a similar way, a further analysis of the potential out-
comes of the studied therapy approach was to be carried out with appropriate caution given the limitations, risk of bias, and methodological weaknesses of the included items. Nevertheless it was not left out in order to shed more light on the ongoing research and study approach-
es. Therefore the three domains of outcomes formulated in the initial PICOT question [106] (see the introduction section) were taken and addressed: (A) motoric dysfunc-
tion, (B) neuropsychomotoric development disorder, (C) orofacial or myofunctional disorder, and (D) any other not yet listed diagnoses. By analyzing the outcomes (see Tables 2 and D21 of online supplement D), speech or articulation difficulties are addressed several times. It was set as separate type of outcome (D). For each of the out-
come domains (A–D) several primary outcomes (see Ta-
ble D21 of online supplement D) can be assigned, where-
as each primary outcome can be assigned to one or more outcome domains. Mapping all primary outcomes led to a subdivision of A into A.i, motoric development and co-
ordination and A.ii, posture and axial symmetry impair-
ment. C contains IV as per inclusion criteria and was des-
tination of all outcomes in the context of swallowing or eating excluding speech or articulation, as this was do-
main D. Table D22 (online supplement D) shows the as-
ignment of the primary outcomes and the relevant pa-
pers. The GRADE evidence profiles (EP) [99] for each subgroup are listed in Tables 7 (I–IV) and 8 (A–D).

Regarding the comparison of intervention little data is available as most of the included papers do not provide a control group or placebo, though, considering a hands-
on physical therapy approach, placebo would be difficult to realize. Only two of the included studies had a control group [58, 64]. All other items have to be considered as observational studies in terms of GRADE evidence rating [99].

The outcome of the PICOT question “modify the ex-
sisting symptoms and quality of life within what time” contains the treatment duration as further variable. With-
in the included studies, the duration of the applied ther-
apy was very heterogenic and reached from few days to multiple years. Outcomes were qualitatively described as partly emerging already after a few therapy sessions with further results visible after at least a few months (see Ta-
bles 2 and D20 of online supplement D). Building sub-
groups for further analysis was not considered due to het-
erogeneity, very serious indirectness [206], and inconsis-
tency [205].

Confidence in Cumulative Estimate

According to the EP of I, I), III, and A–D summaries of findings according to GRADE [99] are shown in Tables 9 (I), 10 (II), 11 (III), and 12–15 (A–D). IV is not present-
ed separately as included in C (Table 14). A downrating was inevitable in all items due to inconsistency, indirect-
ness, imprecision, and risk of bias regarding an evaluation of evidence and in most of the cases due to study design, small sample sizes, heterogeneity, methodological weak-
nesses. The absence of large magnitude effect, dose re-
sponse in more than one item, or confounders likely to
minimize the effect in more than one item an uprating was not to be considered. Consequently the GRADE quality rating [126] was very low for every defined item (very uncertain about the estimate of effect). This might confuse involved therapists and trainers but should be seen in the scientific context and high standard of evaluation this review is based on. No discouragement but rather occasion and impulse for further research and study design with high quality standards shall be derived.

Table 16 contains the derived PICOT recommendations for clinicians.

Meta-Bias
Publication bias is present and possibly serious. During the research process announcements for trials [90], trial reports [87, 88], and a systematic review [95] were found as conference poster or abstracts without any hint for full-text publication. Requests for more information provided no further data. Even though 14 of the included items were published, only three of the included items were found through database research (MEDLINE via PubMed [53], Embase [179], EBSCO/Ovid TOC Premier [58]) whereas all others were found searching grey literature, cross-reference, or offline research throughout the network of therapists. The language used by the authors was English only in six cases [31, 53, 55–57, 64]. The accessibility of many items was restricted as beside the included items composed in Portuguese [59–63, 81, 180] or German [46, 86, 171–175] only, French [46, 86, 171–175] or Spanish [176] only, [38] whereas all others were found searching grey literature.

Outcome reporting bias is present but difficult to estimate. No study protocol or trial register was found. In two cases of published articles [53, 58] a prior thesis manuscript was available [54, 193] providing more information on outcome as in the final article. Deficits in presentation of results were present in a large number of included items (see Tables 3–5).

PICOT Recommendation
Regarding the included studies and case reports and analysis of the data considering the EP and SoF of each outcome (see Tables 8–15) the PICOT question was used to build recommendations (see Table 16, online supplement Large Tables).

Updated PICOT Question
Derived by the results of the review and the information of the umbrella organization of the Padovan-Metho® (Brazil) [21] an overview of the target group (P) can be set as stated in Table D23 (online supplement D) adding also information from articles identified through research process but not included into the analysis due to research character [19, 30].

Table 7. GRADE evidence profile for conditions I–IV: condition improvement or alleviation of symptoms

| Quality assessment | Number of studies (design) | Limitationsa | Inconsistencyb | Indirectnessc | Imprecisiond | Publication biasd | Large magnitude effect/ dose response/confounders likely to minimize the effect | Number of patients (after dropout) | Outcome measurement | Outcome quality |
|--------------------|-----------------------------|--------------|----------------|--------------|--------------|-------------------|-------------------------------------------------|-------------------------------|-------------------|-----------------|
| I Microcephalia     | 6 (CS, CR)                  | very serious | very serious   | very serious | very serious | very serious       | –/–/–                                            | 14                            | No statistic outcome data available. Improvements in all items descriptively reported. | Very low           |
| II Down syndrome    | 2 (non-RCT, CBA)            | very serious | very serious   | very serious | very serious | very serious       | –/–/–                                            | 142                           | Measured outcomes documented only in one item. Improvements in all items descriptively reported. - decrease of DI90 (2.7 [SD 4.5] to 2.1 [SD 3.7], p < 0.05) [53] | Very low           |
| III Neurological disorders | 16 (non-RCT, retrospective self-controlled cohort study, CS, CR) | very serious | very serious | very serious | very serious | very serious       | –/–/–                                            | 28                            | Measured outcomes documented only in one item. Improvements in all items descriptively reported. - decrease of DI90 (2.7 [SD 4.5] to 2.1 [SD 3.7], p < 0.05) [53] | Very low           |

GRADE rate down for limitations, inconsistency, indirectness, imprecision, and publication bias (serious –1, very serious –2), and rates up in case of large magnitude, dose response, or if confounders likely to minimize the effect. The lowest assessment of each set of studies was used. a See results chapter and Tables 3 and 5 for details. b High heterogeneity in participants and inclusion criteria. c Differences in study population, intervention protocol, outcome measurements. d No precise outcome measurements available in the majority of each set of studies. e Reporting bias likely as documentation of outcomes and follow-up were poor in the majority of each set of studies. f IV is included in C (see Table 8).
| Quality assessment | Number of studies (design) | Limitationsa | Inconsistencyb | Indirectnessc | Imprecisiond | Publication biasp | Large magnitude effect/dose response/confounders likely to minimize the effect | Number of patients (after dropout) | Outcome measurement | Outcome quality |
|-------------------|---------------------------|--------------|---------------|--------------|--------------|----------------|-----------------------------------------------|---------------------------|------------------|-----------------|
| Domain            |                           |              |               |              |              |                |                                                              |                           |                  |                 |
| A.i               | Motoric dysfunction       | 11 (retrospective self-controlled cohort study, CS, CR) | very serious | very serious | very serious | very serious | very serious | –/–/– | 103 | Measured outcomes documented only in 1 item. Very low improvements in all items descriptively reported. – rise of AIMS [182] score [63] with serious imprecision |
|                   | Motoric development       |                           |              |              |              |                |                                                              |                           |                  |                 |
|                   | and coordination          |                           |              |              |              |                |                                                              |                           |                  |                 |
| A.ii              | Posture and axial         | 10 (non-RCT, CS, CR)     | very serious | very serious | very serious | very serious | very serious | –/–/– | 30 | Some statistical significance for single subitems. Very low improvements in all items descriptively reported. – no preferred side of chewing (p = 0.025), improved sitting posture (p = 0.046) [45] – reduced lateral posture (p = 0.029) [45] – improved axis symmetry of eyes (p = 0.038) [45] – zygomatic bone (p = 0.025) [45] and – shoulders (p = 0.026) [45] – rise of AIMS [182] score [63] |
|                   | symmetry impairment       |                           |              |              |              |                |                                                              |                           |                  |                 |
| B                 | Neuropsychomotoric        | 12 (retrospective self-controlled cohort study, CS, CR) | very serious | very serious | very serious | very serious | very serious | –/–/– | 113 | Some statistical significance for single subitems. Very low improvements in all items descriptively reported. – reduced habit of licking lips (p = 0.054) [45] – habit of biting objects reduced (p = 0.038) – Rise of AIMS [182] score [63] |
|                   | development disorder      |                           |              |              |              |                |                                                              |                           |                  |                 |
| C                 | Orofacial or myofunctional disorderf | 10 (pseudo-RCT, CBA, retrospective self-controlled cohort study, CS, CR) | very serious | very serious | very serious | very serious | very serious | –/–/– | 129 | Some statistical significance for single subitems. Very low improvements in all items descriptively reported. – changes of tongue and lip coordination exercises (tongue exercise 2 [195]), likelihood ratio test (LRT) $\chi^2(2, n = 12): p = 0.001$ [58] – swallowing examination (swallowing fluids [193]), t test for independent samples: t(10) = –5.331, p ≤ 0.000 [58] – position of tongue tip whilst swallowing [193], t test for independent samples: t(10) = –3.429, p = 0.006 [58] – position of tongue edge whilst swallowing [193], t test for independent samples: t(10) = –9.163, p < 0.001 [58] – Lip strength, T1 = initial examination: 500–1,017 g; T2 = examination after intervention: 850–1,367 g [58] – decrease of DI90 2.7 (SD 4.5) to 2.1 (SD 3.7), p < 0.05 [53] – Rise of AIMS [182] score [63] |
| D                 | Speech or articulation    | 6 (pseudo-RCT, CR)       | very serious | very serious | very serious | very serious | very serious | –/–/– | 16 | Some statistical significance for single subitems. Very low improvements in all items descriptively reported. – articulation s-sound formation [188], t test for independent samples: t(10) = –2.526, p = 0.010 [58] |

GRADE rates down for limitations, inconsistency, indirectness, imprecision and publication bias (serious –1, very serious –2), and rates up, in case of large magnitude, dose response, or if confounders likely to minimize the effect. The lowest assessment of each set of studies was used. See results chapter and Tables 3 and 5 for details. High heterogeneity in participants and inclusion criteria. Differences in study population, intervention protocol, outcome measurements. No precise outcome measurements available in the majority of each set of studies. Reporting bias likely as documentation of outcomes and follow-up were poor in the majority of each set of studies. Contains also the studies of group IV of Table 7 but also further studies.
Table 9. Summary of findings – patients with microcephalia

Therapy according to Padovan-Method for patients with microcephalia

| Outcomes | Estimated comparative risks (95% CI) | Relative effect (95% CI) | No. of participants (studies) | Quality of evidence (GRADE) | Comment |
|----------|--------------------------------------|--------------------------|------------------------------|----------------------------|---------|
|          | control risk                          | intervention risk        |                               |                            |         |
| Response to treatment; condition improvement or alleviation of symptoms; follow-up: 2 months to 1 year | No study had a control group | Not estimable³ | Not estimable³ | 14 (6) | very low³ ●○○○ |
| Death due to intervention side effects | See comment | See comment | Not estimable¹ | – | See comment No study reported on this outcome |
| Quality of life | No study had a control group | improvements of quality of life described qualitatively in some studies | Not estimable¹ | – | low ●●○○ Improvements of quality of life described qualitatively in some studies |
| Acceptability of treatment; dropout for any reason; follow-up: 2 months to 1 year | NR 0 from 1,000 (0) | NR | 14 (6) | moderate³,⁴,⁵ ●●○○ |
| Overall tolerability; dropout due to adverse events; follow-up: 2 months to 1 year | NR 0 from 1,000 (0) | NR | 14 (6) | moderate³,⁴,⁵ ●●○○ |

GRADE Working Group grades of evidence. See Table B2 (online supplement B) for details. NR, not relevant. ¹ Outcomes were mainly qualitatively described or statistical outcomes had serious inconsistency, indirectness, and risk of publication bias. ² Methodological weakness of study design, unclear intervention protocol, poor outcome statistics. ³ Not a single study reported on this outcome. ⁴ Acceptability of treatment was measured indirectly by the number of participants leaving the studies prematurely. ⁵ Due to small sample size.

Table 10. Summary of findings – patients with Down syndrome

Therapy according to Padovan-Method for patients with Down syndrome

| Outcomes | Estimated comparative risks (95% CI) | Relative effect (95% CI) | No. of participants (studies) | Quality of evidence (GRADE) | Comment |
|----------|--------------------------------------|--------------------------|------------------------------|----------------------------|---------|
|          | control risk                          | intervention risk        |                               |                            |         |
| Response to treatment; condition improvement or alleviation of symptoms; follow-up: 1 week to 10 weeks | Not estimable³ | Not estimable³ | Not estimable³ | 52 (2 studies) | very low³ ●●○○ |
| Death due to intervention side effects | See comment | See comment | Not estimable¹ | – | See comment No study reported on this outcome |
| Quality of life | Not estimable¹ | See comment | Not estimable¹ | – | low ●●○○ Improvements of quality of life described qualitatively in some studies |
| Acceptability of treatment; dropout for any reason; follow-up: 1 week to 10 weeks | Not estimable³ | See comment | Not estimable¹ | 538 per 1,000 (24 to 52) | NR 52 (2 studies) moderate³,⁴,⁵ ●●○○ |
| Overall tolerability; dropout due to adverse events; follow-up: 1 week to 10 weeks | Not estimable³ | See comment | Not estimable¹ | 538 per 1,000 (24 to 52) | NR 52 (2 studies) moderate³,⁴,⁵ ●●○○ |

GRADE Working Group grades of evidence. See Table B2 (online supplement B) for details. NR, not relevant. ¹ A control group was not available to all included items. ² Outcomes were mainly qualitatively described or statistical outcomes had serious inconsistency, indirectness, and risk of publication bias. ³ Methodological weakness of study design, unclear intervention protocol, poor outcome statistics. ⁴ Not a single study reported on this outcome. ⁵ Acceptability of treatment was measured indirectly by the number of participants leaving the studies prematurely. ⁶ Due to small sample size.
The updated PICOT review question for further research is presented in Table D24 (online supplement D).

**Discussion**

**Summary of Main Results**

The Padovan-Method® is a rehabilitation approach used for neuro-rehabilitation in different countries. Its effects in general or compared to other therapies or placebo has to our knowledge not been assessed by a systematic review so far. Moreover the number of available studies about the method is very low. In this work a total of \( n = 18 \) reports and \( n = 196 \) participants indicate a possible contribution to a relief of symptoms or improvements of condition mainly in the context of mouth functions (swallowing, lip and tongue movement).

**Clinical Implications**

Although the available material provides now substance for strong recommendations, the absence of adverse effects, the resolution of symptoms, and the reported improvements of quality of life are desirable outcomes [207]. As shown in Table 16, in all listed symptom clusters (A–D) or diagnoses (I–III) application of therapy according to the Padovan-Method® by trained therapists might be considered by clinicians (weak recommendation) and a relief of some symptoms might be possible within a time span from a few days to 24 months.

For all recommendations further research is highly recommended and has a large potential in order to reduce the uncertainty.

**Evaluation of Side Effects and Contraindications**

Study quality and methodology implicate a reporting bias on potential side effects and contraindications of the therapy approach. The included studies provide poor information on the presence of side effects or contraindications (see Table D21 of online supplement D). A considerable amount of participants dropped out due to infectious reasons (\( n = 24 \) upper respiratory infections [53], \( n = 7 \) sepsis [57]). The data presented in the studies is too thin and does not provide any epidemiological context. Making a comparison to general numbers is therefore difficult. Relevant to look at are the cases of death. As the recruiting of patients was done within a neonatal intensive care unit [57], higher mortality rates compared to population in general is not out of the question. Reference
numbers are difficult to draw in, as many details of the setting of the study and the place of study are not clear or not given. In a study from 2018 carried out in Brazil, a neonatal mortality coefficient with sepsis involved of 2.3 deaths per one thousand live births was reported [208]. Given this context, the mortality in the cited study [57] appears high and further background and explanation would have been highly desired.

Even though no contraindications for the application of the Padovan-Method® were found in the included trials or reports, precaution is required in the case of broken bones. According to oral presentations during the annual conference of the German Padovan-Method® association (2019) instability and fracture of dens axis alike other spine instability are strict contraindications.

Acceptability
The available data provides only little information about acceptability of the treatment, as comparison is difficult due to the fact of missing control groups in most of the included studies. \( n = 40 \) dropouts due to any reason in \( n = 187 \) treated patients (213 dropouts per 1,000) can be considered an indicator for acceptability and compliance although it presents a very indirect measurement.

Quality of Evidence
As it is difficult in rehabilitative medicine to set up trials especially with high level of evidence [108] it was not surprising not having RCTs amongst the included results. We emphasize that too little information on side effects and contraindications is available throughout the included material. It remains open if these outcomes were not measured or not reported as protocols are not available.

Overall Completeness and Applicability of Evidence
Although most of the included studies are published, only a small number of items underwent a peer review. Reliability and applicability of the results remain unsure underlined by the fact that the study with the lowest risk of bias [53] (see Table 3) presented only a marginal effect.

We emphasize that too little information on side effects and contraindications is available throughout the included material. It remains open if these outcomes were not measured or not reported as protocols are not available.

Table 12. Summary of findings – patients with motoric dysfunction

| Outcomes | Estimated comparative risks (95% CI) | Relative effect (95% CI) | No. of participants (studies) | Quality of evidence (GRADE) | Comment |
|----------|------------------------------------|--------------------------|-----------------------------|---------------------------|---------|
| Response to treatment; condition improvement or alleviation of symptoms; follow-up: 2 days to 2 years | Not estimable\(^a\) Not estimable\(^b\) | Not estimable\(^b\) 129 (13 studies) | very low\(^d\) ○○○ | One study (Pereira et al., 2015 [57]) reported death of patients due to sepsis in the setting of preterm newborn babies. A correlation to the treatment is not of clear evidence. |
| Death due to intervention side effects | See comment See comment | Not estimable\(^d\) – | See comment | |
| Quality of life | Not estimable\(^b\) See comment | Not estimable\(^d\) – | Low ○○○ | Improvements of quality of life described qualitatively in some studies |
| Acceptability of treatment; dropout for any reason; follow-up: 2 days to 2 years | Not estimable\(^a\) Not estimable\(^b\) | 884 per 1,000 (15 to 129) | NR 129 (13 studies) | moderate\(^a\)\(^e\)\(^f\) ○○○○ | |
| Overall tolerability; dropout due to adverse events; follow-up: 2 days to 2 years | Not estimable\(^a\) Not estimable\(^b\) | 884 per 1,000 (15 to 129) | NR 129 (13 studies) | moderate\(^f\) ○○○○ | 

GRADE Working Group grades of evidence. See Table B2 (online supplement B) for details. NR, not relevant. \(^a\) A control group was not available to all included items. \(^b\) Outcomes were mainly qualitatively described or statistical outcomes had serious inconsistency, indirectness, and risk of publication bias. \(^c\) Methodological weakness of study design, unclear intervention protocol, poor outcome statistics. \(^d\) Not a single study reported on this outcome. \(^e\) Acceptability of treatment was measured indirectly by the number of participants leaving the studies prematurely. \(^f\) Due to small sample size.
setup and reporting could be expected but revealed methodological flaws in most of the included items. Outcome measurement was difficult to compare due to different rating instruments used. The presentation of results was sometimes narrative. Concluding, according to our “summary of findings” tables (I–III) the evidence on “response to treatment” was very low and on “overall tolerability” and “acceptability of treatment” was only moderate, that on “quality of life” was low and no sufficient data on the other a priori defined outcome of the “summary of findings” tables, “death due to intervention side effects,” was provided.

**Agreements and Disagreements with Other Studies or Reviews**

To our knowledge, no systematic review investigated the effect of therapies according to the Padovan-Method®. da Silva Neto et al., 2016 [95] published an abstract stating a planned review, but it was not found published. Several articles or hints are found published promoting positive effects of the Padovan-Method® [10, 27, 29, 52, 65, 76, 78, 80, 82–85, 89, 93, 143–157] though not providing underlying studies. Ruben et al., 2014 [17] present results of an expert inquiry for treating myofunctional disorders where the Padovan-Method® was the second most used approach [17] and Klocke et al., 2000 [16] claim a multidisciplinary approach referring to the ideas of the Padovan-Method® in the context of treating myofunctional disorders [16]. Starrost and Schilling, 2013 [79] list and explain several methods for treating dysphagia including the Padovan-Method® [79] enumerated also by the AWMF Guideline for Down Syndrome in Childhood for treating orofacial dysfunctions regarding closure of mouth, tongue position, and speech development in early childhood [10].

Nevertheless critical voices are present, too. Candel and Bonilla, 2016 [91] provide an information brochure about the Padovan-Method® in the context of Down syndrome concluding with an advice against the method [91] because of lacking proof of evidence. Von Suchodoletz mentions the method in several of his works [92, 93, 156, 163, 164] and criticizes the theoretical fundament of the
method as outdated and refers to the Padovan-Method® with his critical opinion due to missing proof of evidence in the context of learning disabilities [92]. One of the included studies suggests nearly no effect by existing limitations due to too short intervention protocol [53]. This systematic review holds again the critical voices as it comes to the conclusion that the Padovan-Method® might be considered by clinicians if indicated and a relief of some symptoms might be possible, though further research and high-quality studies are necessary (see Table 16).

**Authors’ Conclusions**

This systematic review was set up to establish a preliminary evidence on the use of the Padovan-Method®. Considering the little available literature about the method, its potential outcomes, or suggested treatment protocol, the inclusion criteria of this review were wide-ranging. Thereby a broader range of facets of this particular approach could be explored.

Summarizing this review, the Padovan-Method® therapy approach is observed in several small-scale studies and case reports. Methodological weaknesses were existent in all items and accordingly rated or commented in the text. Whilst there were more studies not fulfilling the inclusion criteria, the included material allows at least a weak recommendation for the Padovan-Method® in patients with certain neuro-rehabilitative needs with a possible alleviation of symptoms.

However, no statement can be given regarding the theoretical framework and model of intervention as it remains a theoretical concept. Its proof was not the intent of this work and further investigation on this is incumbent to large-scale studies.

Thus a need for an intense research activity and setup of higher-graded methodological studies is indispensable to gain more certainty what kind of patients benefit most from the Padovan-Method®. By setting up new trials, special attention should be paid to the methodological challenges in the context of rehabilitative medicine [209]. The selection of outcomes and relevant measurements,
ies have to improve on reporting on ethical aspects. Using the work of Weingarten et al., 2004 [118] can help on this issue.

Regarding clear therapy description and how-to manuals further research is necessary and it is strongly recommended to present more details on duration, frequency, and intervention period of the therapy. The author group of this systematic review is currently working on a Delphi process to gain a treatment recommendation [220]. The knowledge of experienced trainers is needed. A subsequent set of studies will be required to proof the recommendations.

Regarding the training and certification process of the Padovan-Method® some clarifications are desirable [221]. There seems to be no admission restriction to take part and complete the certification courses. Hence a basic qualification in the therapeutic area should be the minimum to ensure quality and safety of the therapeutic process.

Patient and Public Involvement
There is no patient and public involvement in the conduction of this systematic review which aims to clarify the evidence of the Padovan-Method®. It is of use for academic and clinical audiences, patients’ associations, and

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**Table 15. Summary of findings – patients with speech or articulation difficulties**

| Outcomes | Estimated comparative risks (95% CI) | Relative effect (95% CI) | No. of participants (studies) | Quality of evidence (GRADE) | Comment |
|----------|-------------------------------------|--------------------------|--------------------------------|----------------------------|---------|
| Response to treatment; condition improvement or alleviation of symptoms; follow-up: 5 days to 2 years | Not estimable | Not estimable | 17 (6 studies) | very low | –
| Death due to intervention side effects | See comment | See comment | – | See comment | Improvements of quality of life described qualitatively in some studies |
| Quality of life | Not estimable | See comment | – | low | – |
| Acceptability of treatment; dropout for any reason; follow-up: 5 days to 2 years | Not estimable | 941 per 1,000 (1 to 17) | NR | moderate | – |
| Overall tolerability; dropout due to adverse events; follow-up: 5 days to 2 years | Not estimable | 941 per 1,000 (1 to 17) | NR | moderate | – |

GRADE Working Group grades of evidence. See Table B2 (online supplement B) for details. NR, not relevant. A A control group was not available to all included items. Outcomes were mainly qualitatively described or statistical outcomes had serious inconsistency, indirectness, and risk of publication bias. Methodological weakness of study design, unclear intervention protocol, poor outcome statistics. Not a single study reported on this outcome. Acceptability of treatment was measured indirectly by the number of participants leaving the studies prematurely. Due to small sample size.

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For measuring the neurodevelopmental outcomes standardized and validated tests should be considered according to the age of the target group. Exemplarily named might be the Bayley Scales of Infant and Toddler Development, Third Edition [210], the McCarthy Scale of Children’s Abilities (MCMSA) [211], or Raven’s Coloured Progressive Matrices and Trail Making Tests [212] as exemplarily described and applied by Karakosta et al. [213], SETK 3-5 [192], PACST [199], amongst others.

An adherence to a methodological framework such as CONSORT [214] or CONSORT extensions for adaptive designs [215], adaptation for N-of-1 [216] or rehabilitation medicine [217] as well as CARE-Guidelines [117, 218] for case reports or the STROBE statement for observational studies (cohort, case-control studies, cross-sectional studies) [219] is highly recommended. This includes reporting on received funding and declaring competing interests, which was rare in the papers on hand.

According to the little reporting on ethical considerations or on adherence to the Declaration of Helsinki [129], it remains inevitable to point out that further studies have to improve on reporting on ethical aspects. Using the work of Weingarten et al., 2004 [118] can help on this issue.

Regarding clear therapy description and how-to manuals further research is necessary and it is strongly recommended to present more details on duration, frequency, and intervention period of the therapy. The author group of this systematic review is currently working on a Delphi process to gain a treatment recommendation [220]. The knowledge of experienced trainers is needed. A subsequent set of studies will be required to proof the recommendations.

Regarding the training and certification process of the Padovan-Method® some clarifications are desirable [221]. There seems to be no admission restriction to take part and complete the certification courses. Hence a basic qualification in the therapeutic area should be the minimum to ensure quality and safety of the therapeutic process.

**Patient and Public Involvement**
There is no patient and public involvement in the conduction of this systematic review which aims to clarify the evidence of the Padovan-Method®. It is of use for academic and clinical audiences, patients’ associations, and
policy makers. Guideline developers may be influenced in order to improve outcomes for patients according to re-
view results.

Limitations
Limitations are given due to the difficulties of evidence in rehabilitative medicine and missing concepts [101, 108]. The small available scientific background of the therapy approach made it difficult to set up a well defined PICOT question.

The language restrictions led to further reduction of included items.

The inclusion of studies despite the poor reporting on ethical standards has to be considered critically but may help to improve further investigation projects. Updates of this systematic review should handle this topic more stringently.

There was a small amount of available data and deficient reporting, as in many cases study results were not precisely documented. Results were partly incomplete and contained methodologic flaws. Classification of the items were often difficult due to unclear design, population, or outcomes. Inconsistency, indirectness, and publication bias made clear outcomes difficult. This aspects hindered drawing precise conclusions.

The described dropouts due to death caused by sepsis in preterm newborn intensive care babies [57] should be examined more closely and put in relation to general mortality numbers.

More research is highly recommended and might have an impact on the confidence of evidence of the therapy according to the Padovan-Method®.

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van-Method®. Many thanks to Prof. Dr. Thomas Ostermann and Dr. Dr. Katharina Fetz for their care and supervision and Hannah for a lot.

Table 16. Clinical recommendations

| Condition/outcome                  | PICOT recommendation                                                                 |
|------------------------------------|---------------------------------------------------------------------------------------|
| I Microcephalia                    | In patients with microcephalia an application of therapy according to the Padovan-Method® by trained therapists might be considered by clinicians (weak recommendation) and a relief of some symptoms might be possible within a time span from 2 to 12 months. Further research and investigation are highly recommended to reduce the uncertainty of effect. |
| II Down syndrome                   | In patients with Down syndrome disorders an application of therapy according to the Padovan-Method® by trained therapists might be considered by clinicians (weak recommendation) and a relief of some symptoms might be possible within a time span from a few weeks to 6 months. Further research and investigation are highly recommended to reduce the uncertainty of effect. |
| III Neurological disorders         | In patients with neurological disorders an application of therapy according to the Padovan-Method® by trained therapists might be considered by clinicians (weak recommendation) and a relief of some symptoms might be possible within a time span from a few days to 24 months. Further research and investigation are highly recommended to reduce the uncertainty of effect. |
| IV Myofunctional disorders         | See section C in this table.                                                          |
| A Motoric dysfunction              | In patients with motoric dysfunction an application of therapy according to the Padovan-Method® by trained therapists might be considered by clinicians (weak recommendation) and a relief of some symptoms might be possible within a time span from a few days to 24 months. Further research and investigation are highly recommended to reduce the uncertainty of effect. |
| B Neuropsychomotoric development disorder | In patients with neuropsychomotoric development disorder an application of therapy according to the Padovan-Method® by trained therapists might be considered by clinicians (weak recommendation) and a relief of some symptoms might be possible within a time span from a few days to 24 months. Further research and investigation are highly recommended to reduce the uncertainty of effect. |
| C (IV) Orofacial or myofunctional disorder | In patients with orofacial or myofunctional disorders an application of therapy according to the Padovan-Method® by trained therapists might be considered by clinicians (weak recommendation) and a relief of some symptoms might be possible within a time span from a few days to 24 months. Further research and investigation are highly recommended to reduce the uncertainty of effect. |
| D Speech or articulation difficulties | In patients with speech or articulation difficulties an application of therapy according to the Padovan-Method® by trained therapists might be considered by clinicians (weak recommendation) and a relief of some symptoms might be possible within a time span from a few days to 24 months. Further research and investigation are highly recommended to reduce the uncertainty of effect. |

For all recommendations further research is highly recommended and has a large potential in order to reduce the uncertainty.
Statements of Ethics

Due to the scope of the project and its character, no human subject were involved. The paper is therefore exempt from ethical committee approval.

Conflict of Interest Statement

The authors declare that they have no conflict of interests.

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Author Contributions

D.V. and K.F. developed the search strategy. D.V. performed systematic searches, screened titles and abstracts for duplicates, and was the major contributor in writing the manuscript. Screening for eligibility was done by D.V. and H.V. K.L. was implicated as second independent reviewer of the literature. D.V. and K.L. extracted the data. H.V. and K.F. were consulted as third reviewer in case of disagreement. T.O. had an advisory function and mainly contributed to structure the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Preprint Statement

A preprint but not a published version of this article is available at Research Square [107].

Amendments

If amendments to the protocol [106] were necessary, we will note the date of each amendment as well as description of the change and the rationale in this section.

Date of Most Recent Amendment

September 1, 2020.

Date of Most Recent Substantive Amendment

September 1, 2020.

What’s New

Due to the SARS-CoV-2 pandemic there are delays in the process. The schedule therefore had to be changed. Further restrictions were also made regarding the included studies. Only studies in English, Portuguese, and German will now be included. Conference abstracts were not included because they could not provide sufficient information per se. The EPPI reviewer was not used due to difficulties in functionality and compatibility of operating platforms. As some of the included trials or reports extended over a long period, by derogation from the protocol [106] the section “follow-up response between 4 and 6 months” was extended to “long-term and follow-up response between 4 and 6 months and more.” The assessment of reporting on ethical standards was expanded according to [118] and [130] as the analysis of the included trials revealed relevant shortcomings on this topic.
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