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Transcutaneous Auricular Vagus Nerve Stimulation in Pediatric Patients: A Systematic Review of Clinical Treatment Protocols and Stimulation Parameters

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ABSTRACT

Background: Noninvasive transcutaneous vagus nerve stimulation (tVNS) has promising therapeutic potential in a wide range of applications across somatic and psychiatric conditions. Compared with invasive vagus nerve stimulation, good safety and tolerability profiles also support the use of tVNS in pediatric patients. Potential neurodevelopment-specific needs, however, raise concerns regarding the age-appropriate adjustment of treatment protocols and applied stimulation parameters.

Objective: In this study, we aimed to review registered trials and published studies to synthesize existing tVNS treatment protocols and stimulation parameters applied in pediatric patients.

Materials and Methods: A systematic search of electronic data bases (PubMed, Scopus, MEDLINE, Cochrane Library, and PsycINFO) and ClinicalTrials was conducted. Information on patient and study-level characteristics (eg, clinical condition, sample size), the tVNS device (eg, brand name, manufacturer), stimulation settings (eg, pulse width, stimulation intensity), and stimulation protocol (eg, duration, dosage of stimulation) was extracted.

Results: We identified a total of 15 publications (four study protocols) and 15 registered trials applying tVNS in pediatric patients (<18 years of age). Most of these studies did not exclusively address pediatric patients. None of the studies elaborated on neurodevelopmental aspects or justified the applied protocol or stimulation parameters for use in pediatric patients.

Conclusions: No dedicated pediatric tVNS devices exist. Neither stimulation parameters nor stimulation protocols for tVNS are properly justified in pediatric patients. Evidence on age-dependent stimulation effects of tVNS under a neurodevelopment framework is warranted. We discuss the potential implications of these findings with clinical relevance, address some of the challenges of tVNS research in pediatric populations, and point out key aspects in future device development and research in addition to clinical studies on pediatric populations.

Keywords: Children and adolescents, neurodevelopment, pediatrics, transcutaneous vagus nerve stimulation

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INTRODUCTION

Noninvasive transcutaneous vagus nerve stimulation (tVNS) enables electrical stimulation of the vagus nerve while mitigating the risks associated with invasive vagus nerve stimulation (VNS).[1] tVNS is applied in a wide range of clinical fields with increasing evidence of its efficacy[2]; it also demonstrates good safety and tolerability.[3] Given its favorable risk-benefit profile, tVNS has potential for application in pediatric patients. However, for several reasons, it remains unclear whether treatment protocols and stimulation parameters require adjustment for use in this patient group. Concerning the underlying neurobiological mechanisms targeted by tVNS, children and adolescents are characterized by developmental specifics that need to be considered when contemplating tVNS as a treatment option in pediatric patients. Furthermore, pediatric populations pose considerable practical challenges to the application of stimulation, compliance monitoring, and the proper assessment of adverse events.

Early childhood is a critical time for brain development, marked by massive growth spurts (the human brain reaches approximately 90% of adult size by the age of six years), whereas a significant amount of remodeling in later childhood and throughout adolescence and young adulthood takes place before the brain can fully function as an adult brain.[4] Adolescence in particular is a period of dramatic neural reorganization owing to increased neural plasticity, whereas the maturation of various neural circuits also depends, to a large degree, on one's experiences on both physical and psychosocial levels.[5] In general, brain sites that involve primary functions, such as motor and sensory systems, are assumed to mature earlier than higher-order association areas that integrate these primary functions.[6,7] Pruning processes further allow for fine-tuning and strengthening of connections between prefrontal and subcortical regions.[4] Besides regional changes, pathways of connectivity continue to develop across childhood into adulthood in nonlinear fashion. Specifically, neural networks underlying social, emotional, and cognitive function exhibit heightened experience-dependent plasticity during sensitive periods that occur in different circuits and regions at specific periods of development.[5] Besides, adolescent sensitive periods are characterized by large interindividual differences.[8]

The afferent vagal system targeted by tVNS has widespread influence across major neural networks, and the mechanisms driving the beneficial effects of electrical stimulation of the vagus nerve as found across health conditions are assumed to overlap extensively[9]—yet, and critically, the specific mechanisms behind the therapeutic effects of tVNS are still not known.[10] Generally, and very briefly, the vagus nerve conveys information from diverse organ systems in the human body to the nucleus tractus solitarii (NTS) in the brainstem, where input is relayed directly and indirectly to diverse components of the brain. The synaptic projections from the NTS differentially modulate neuronal activity within key regions involved in affect/emotion regulation, pain modulation, or memory and attention processes[9]—as outlined earlier, most of these regions are subject to substantial neurodevelopmental growth and remodeling across childhood and adolescence into adulthood.

The development and application of specific medical devices are required to meet the development-specific needs of children and adolescents.[11] Yet development-specific needs, particularly those of adolescents, have long received very limited attention in the history of medical device development.[12–14] Considering children, in turn, medical device development has been described to simply "gravitate […] towards the repurposing of adult's applications, on the basis of the incorrect assumption that devices can simply be made smaller in line with a child's size, with little consideration for changes in anatomy and physiology through growth and development" (p. 17).[15] Critically, the development of tVNS devices, even though commercially available devices show no restrictions of application to exclusively adult populations, currently does not intend specific stimulation systems for children and young people.[16] This also might seem reminiscent of a past situation in which, alongside clinical practice experience in children and adolescents, the administration of psychotropic drugs in pediatric patients was usually guided by evidence extrapolated from adults, leading to substantial off-label use.[17] In part, this was due to a relative lack of high-quality pharmacokinetic, efficacy, and safety data, partly because drug regulatory authorities did not request evidence for this patient group until not much longer than a decade ago—which put pediatric patients at an increased risk of suboptimal treatment outcomes (eg, inefficacy of treatments, high rates of adverse effects). Respective studies now have demonstrated that, for example, children and adolescents experience higher rates of nausea and activation than adults when prescribed antidepressants,[18] antipsychotics are associated with higher rates of sedation, weight gain, prolactin elevation, and withdrawal dyskinesia in children than in adults, mood stabilizers have been associated with greater weight gain in children,[19] and children receiving lamotrigine experience serious dermatologic adverse effects at higher rates than adults.[20]

In sum, the consideration of development-specific needs seems equally critical when good adherence and clinical benefit are to be achieved through a treatment applying medical devices.[21–24] The development and application of medical devices should address changes in growth and psychosocial maturation, physiology, and pathophysiology and avoid inappropriate repurposing of adult technologies.[15] Regarding the development and application of treatment systems for auricular tVNS in pediatric patients, critical aspects include, among others, ear-anatomical changes in development (ie, electrode fit and engineering), increased needs for independence, especially during puberty (compliance and compliance monitoring), and the assessment of physical symptoms and mental distress, which might be hampered by an inability to communicate such symptoms in specific pediatric subpopulations (ie, affecting the assessment of adverse effects and adverse events). Addressing these aspects should not only be considered in the development of tVNS devices and systems but also should present a key priority in research studies producing relevant data on the clinical application of tVNS in pediatric populations—if really contributing to achieving good clinical benefit presents a primary aim in these studies.

Several comprehensive reviews of tVNS already exist, addressing, among others, current reporting standards and practice,[2] safety and tolerability,[3] the underlying anatomical rationale,[25] technical aspects and engineering,[16,26] physiological aspects,[27] neurophysiological underpinnings,[28] and clinical considerations[10,29,30] of tVNS. Yet none of these reviews specifically addresses aspects to be considered in the research and application of tVNS in pediatric patients. In this study, we aimed to systematically review existing tVNS treatment protocols and stimulation parameters used in pediatric patients, independent of the underlying condition. The primary aim of this review was to synthesize existing approaches concerning the dosage, frequency, and duration of stimulation and

to review standards in the use of selected stimulation parameters in children and young people. After the review of existing practice, we aim to provide recommendations to foster future ambitions in the field of pediatric tVNS.

Of note, current forms of tVNS can include both transcutaneous auricular VNS (applied to the external surface of the ear, in the areas innervated by the auricular branch of the vagus) and transcutaneous cervical VNS (applied to the surface of the neck over the cervical vagus nerve). In this study, we focus on auricular tVNS because it was shown that cervical tVNS can make selective transcutaneous stimulation of vagus nerve fibers difficult, with existing devices most likely indiscriminately stimulating afferent and efferent fibers alike[10,31]—impeding our objective to synthesize stimulation protocols of tVNS in children and youths that produce consistent and reproducible results. In principle, auricular tVNS is achieved by means of an ear electrode connected to the actual stimulation device.[2] The ear electrode, typically consisting of two surface electrodes, is placed at the target site, innervated by the auricular branch of the vagus.[32] In the clinical setting, patients are instructed to apply stimulation for a defined duration (minutes to hours) per day during a defined treatment period (weeks or months). Commercially available devices are handheld and allow stimulation during daily routine. Furthermore, these devices typically allow the adjustment of certain stimulation parameters (predominantly the stimulation intensity) according to individual needs by the user or as defined in treatment protocols based or not based on a clinical rationale. Custom-made devices (ie, modified devices for transcutaneous electrical nerve stimulation [TENS]) may come with restrictions concerning these degrees of freedom, explaining expected variance in stimulation parameters and treatment protocols.

MATERIAL AND METHODS

Published studies on auricular tVNS in children and adolescents were searched in electronic data bases (PubMed, Scopus, MEDLINE, Cochrane Library, and PsycINFO). The following search strategy was applied: "transcutaneous vagus nerve stimulation" OR "taVNS" OR "tVNS" OR "t-VNS," AND "child*" OR "youth" OR "adolescen*." No additional search engine filters or restrictions were used. Empirical studies published in peer-reviewed journals in English, French, Spanish, or German language up to July 28, 2021 were considered for inclusion in the review. Duplicates were removed, followed by an initial screening of titles and abstracts to identify articles of relevance. All studies reporting on interventional studies using auricular tVNS in pediatric patients (<18 years of age) were included. Studies addressing a broader age range were considered if underage patients were part of the reported sample. Reference lists of all included articles were screened for additional papers published on the topic (snowballing). The following information was extracted from all eligible studies: clinical condition; sample size; sample composition in terms of sex; sample mean age and SD; tVNS device use (ie, brand name, manufacturer); electrode type for auricular stimulation; stimulation site; pulse width; stimulation intensity (in mA); stimulation frequency (in Hz); and dosage of stimulation. In cases where insufficient data were reported, authors were contacted, and data were requested. To complement the search in electronic data bases, ongoing clinical trials on tVNS in pediatric patients were searched on ClinicalTrials.gov.

RESULTS

Search Results

The systematic search and study selection procedure is depicted below (Fig. 1). The systematic search identified a total of 169 articles. After removal of duplicates, 79 articles (46.8%) remained for further screening. Finally, 13 published articles (7.7%) fulfilled the inclusion criteria. Two articles were further identified by snowballing of the reference lists of included studies (Table 1). A total of 15 registered trials were identified (Table 2). Data were requested and provided from one ongoing clinical trial (also included in Table 1).

Reported Study Protocols and Stimulation Parameters in Pediatric Patients

Stimulation Devices and Electrode Types

Of the 16 studies (including one ongoing trial) included, three failed to report any information on the tVNS device used.[33–35] In the remaining studies, most commonly, some devices for TENS were used: four studies[36–38] reported to have used a TENS-200 device (Suzhou Medical Appliance Co Ltd, Jinfeng Town, Zhangjiagang, China); two studies[39,40] used a TENS-sm device (Suzhou Medical Appliance Co Ltd, Jinfeng Town, Zhangjiagang, China); and three studies[41–43] reported to have used a TENS device, without providing further model specifications. One study[44] used a NEMOS Cerbomed device (tVNS Technologies GmbH, Erlangen, Germany) and one study[45] a VITOS Cerbotech device (tVNS Technologies GmbH, Erlangen, Germany). One study[46] reported to have used a Digitimer DS7AH device (Digitimer North America Ltd, Fort Lauderdale, Florida). Of note, some of the device types used have now been discontinued, and access to their technical specifications may be limited. Generally, the electrode type used varied widely between studies (Table 1). Although TENS and Digitimer devices often require custom-made electrodes, the manufacturers of NEMOS Cerbomed and VITOS Cerbotech devices provide an easy-to-use package including specific stimulation electrodes, targeting a prespecified stimulation location (ie, cymba conchae). Two studies[33,44] did not provide information on the electrodes used.

Reported Stimulation Locations

Generally, large discrepancies were seen between studies regarding reported stimulation locations and respective terminology. This was the case even when the same type of device was used and, presumably, the same location of the auricle was stimulated in some of these studies (Table 1). Two studies[33,44] failed to report the stimulation site.

Studies in Epilepsy

Rong et al[42] studied patients with drug-resistant epilepsy who received tVNS for 24 weeks in a nonrandomized, uncontrolled observational study. Initially, $N = 50$ patients were recruited, of whom $n = 3$ dropped out for adverse events ($n = 1$ severe dizziness, $n = 2$ red rashes and swelling). No specifics were reported concerning the adjustment of stimulation parameters in the included pediatric patients. In the same year, the authors published results from a randomized controlled trial (RCT) on tVNS[40] in patients aged between 12 and 65 years with refractory epilepsy. Initially, $N = 156$ patients were recruited, of whom $n = 12$ were excluded, for reasons that are not known. Auricular tVNS was compared with a sham non-VNS group receiving stimulation of the outer ear canal. The authors report on transient adverse events

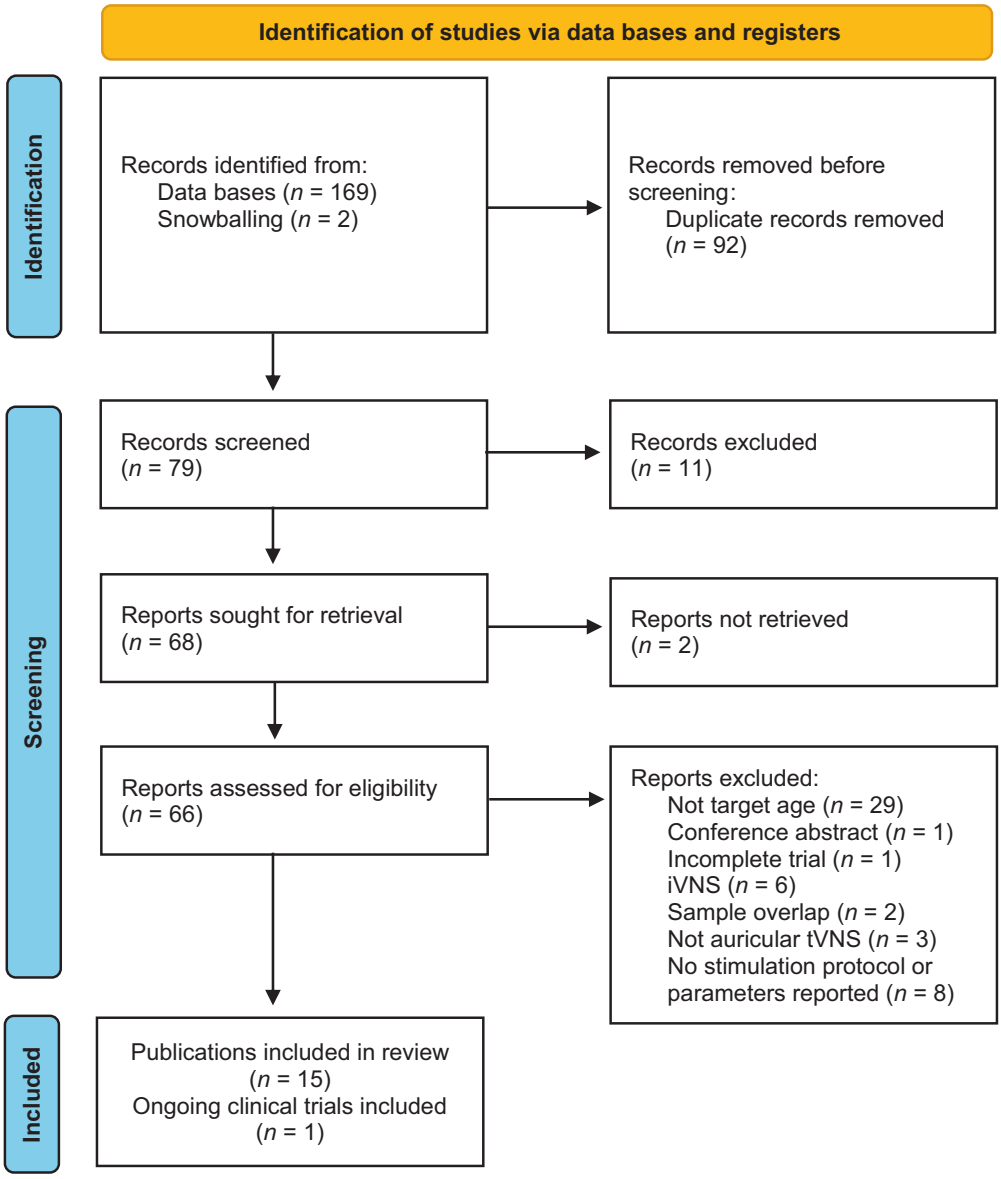

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram depicting the current systematic search and study selection procedure. iVNS, invasive vagus nerve stimulation. [Color figure can be viewed at www.neuromodulationjournal.org]

(skin itch, 6.2%; red rashes and swelling, 4.1%; dizziness, 1%). However, it is not specified whether these occurred in the tVNS or sham group. (Given the similarity in treatment protocol and stimulation parameters, an overlap in samples between Rong et al[40] and Rong et al[42] cannot be ruled out.) The same group[39] published another report on patients between 12 and 65 years of age with refractory epilepsy, receiving six months of tVNS. Initially, $N = 24$ patients were recruited, of whom $n = 3$ dropped out for poor compliance and $n = 1$ for inability to independently apply the stimulation. Two other patients dropped out for reasons unrelated to treatment. Adverse events of the stimulation were reported in one patient of unspecified age, who reported mild dizziness and dropped out of the study. No specifics concerning the adjustment of stimulation parameters in pediatric patients were reported. Another study on epilepsy was published earlier by the respective group of authors.[36] Here, $N = 60$ patients with pharmaco-resistant epilepsy, aged more than four years, were studied. In the RCT design, patients were allocated to the tVNS group, receiving bilateral tVNS over 12 months of treatment. $n = 1$ patient of the treatment arm dropped out owing to adverse events (dizziness). In $n = 3$ cases, reasons for loss to follow-up were not reported. Barbella et al[33] also applied tVNS in patients aged 16 years and older with refractory epilepsy in an open label pilot study. Six patients reported a reduction of seizure frequency >30% after six months of daily tVNS during the first trial epoch. Notably, none of the responders was a pediatric patient. Again, no adjustment of the stimulation protocol in pediatric subjects was reported. In a pilot study, He et al[37] specifically addressed pediatric epilepsy in patients aged two to 12 years. $n = 13$ patients completed the 24-week intervention period. Two patients reported adverse effects (ie,

Table 1. Summary of tVNS Treatment Protocols and Stimulation Parameters Reported in Registered Trials in Children and Adolescents.

Study	Clinical condition	Study design	Sample size (f)	Mean age (range)	tVNS device	Type of electrode	Stimulation site	Pulse width	Stimulation intensity (mA)	Stimulation frequency (Hz)	Stimulation duty cycle	Stimulation dose
Aihua et al[36]	Pharmaco-resistant epilepsy	RCT	26 (n.r.)	34.5 (16–60)	TENS-200, Hua Tuo brand	Bilateral (plug like)	Ramsay-Hunt zone	0.2 s	2 mA (increasing in steps of 2 mA until discomfort)	20 Hz	n.r. (likely constant stimulation)	20 min, 3 times per day, for 12 mo
Liu et al[39]	Refractory epilepsy	Observational study	17 (7)	27 (12–65)	TENS-sm, Suzhou Medical Audio Supplies Company Ltd, China	Clip electrode	Cavity of the auricular concha and the outside of the external ear canal	Biphasic waveform, 200 s*	4 mA (increasing in steps of 2 mA until individual tolerance level was reached)	10 Hz	n.r. (likely constant stimulation)	20 min, 3 times per day, for 6 mo
Badran et al[46]	Premature/HIE infants	Open label pilot study	14 (n.r.)	Preterm infants (<33 wk) and term i nfants suffering from HIE	Digitimer DS7AH	Custom ear electrode	Tragus	500 μs	0.1 mA	25 Hz	2 min on/15 s off	30 min per day
Barbella et al[33]	Refractory epilepsy	Prospective, open-label, single-center experimental trial	20 (10)	38.6 (16–57)	n.r.	n.r.	n.r. (placed according to the 10–20 System)	n.r.	0.6–0.8 mA		20 s on/5 min off	4 h in individual sessions (duration of 1 h minimum) per day, for 6 mo
Fang et al[34]	MDD	Single blind clinical trial	34 (24)	40.87 (16–70)	n.r.	Bilateral clip electrodes	Auricular concha	1 ms	4–6 mA	20 Hz	n.r.	30 min, 2 times per day, for 5 d a week, for 4 wk
Finetti[44]	Dravet syndrome	Case report	1 (1)	11 (n.r.)	NEMOS, Cerbomed	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	Daily stimulation time of 4 h
He et al[37]	Epilepsy	Pilot trial	14 (3)	7.8 (2–12)	TENS-200, Suzhou, China	Conductive rubber clips (5 mm diameter)	Concha cavity and cymba conchae	n.r.	0.4–1 mA (individual tolerance level)	20 Hz	n.r.	30 min, 3 times a day, for 24 wk
He et al[47]	Epilepsy	RCT (study protocol)	42 (n.r.)	n.r. (2–14)	TENS-200, Suzhou, Jiangsu, China	Conductive rubber clips (5 mm diameter)	Concha cavity and cymba conchae	n.r.	1 mA	20 Hz	n.r.	30 min, 3 times a day, for 6 mo
Koenig et al[45]	MDD	Preclinical experimental trial	63 (49)	n.r. (14–17)	VITOS, Cerbotech	Ear electrode "Legacy"	Cymba conchae	250 μs	0.5 mA	1 Hz	30 s on/30 s off	2 stimulation periods of 15 min duration

(Continued)

Table 1. *Continued*

Study	Clinical condition	Study design	Sample size (f)	Mean age (range)	tVNS device	Type of electrode	Stimulation site	Pulse width	Stimulation intensity (mA)	Stimulation frequency (Hz)	Stimulation duty cycle	Stimulation dose
Li et al[41]	Tinnitus	RCT (study protocol)	120 (n.r.)	n.r. (15–65)	TENS device; Suzhou Medical Appliance Co Ltd, China	Carbon-impregnated silicone connected by metal wire	Cymba conchae and the triangular fossa	<1 ms	1–5 mA	20 Hz	n.r.	30 min, every other day, for 8 wk
Mei et al[38]	Tinnitus	RCT	63 (34)	41.1 (17–63)	TENS-200, Suzhou, China	Electrode clip	Cavum conchae	1 ms	1 mA	20 Hz	n.r.	20 min, 2 times a day, for 8 wk
Rong et al[43]	Depression	Double-blinded RCT (study protocol)	60 (n.r.)	n.r. (16–70)	TENS device	2 carbon-impregnated silicone electrodes	Concha	<1 ms	1 mA (adjustable)	20 Hz	n.r.	30 min, 2 times a day, 5 days a week, for 12 wk
Rong et al[42]	Drug-resistant epilepsy	Observational study	50 (20)	25.2 (n.r.)	TENS device; Suzhou Medical Appliance Co Ltd, China	2 carbon-impregnated silicone electrodes	Triangular fossa of the auricle	≤1 ms pulse duration	1 mA	20–30 Hz	n.r. (likely constant stimulation)	30 min, 2 times a day, for 24 wk
Rong et al[40]	Refractory epilepsy	RCT	98 (34)	24.44 (n.r.)	TENS-sm; Suzhou Medical Appliance Co Ltd, China	3 carbon-impregnated silicone electrode tips	Triangular fossa off the auricle	≤1 ms pulse duration	1 mA	20–30 Hz	n.r. (likely constant stimulation)	30 min, 2 times a day, for 24 wk
Tauber[48,†]	Prader-Willi syndrome	Nonrandomized clinical trial	12 (n.r.)	n.r. (9–15)	Parasym™ tVNS Device	Ear clip electrode	Tragus of the left ear	200 μs	1–36 mA (until a tingling sensation was reported)	25 Hz	n.r.	60 min, 5 d a week, for 6 mo
Xiao et al[35]	Depression	RCT (study protocol)	120 (n.r.)	n.r. (12–16)	n.r.	Electrode clip	Cymba concha (auricular)	n.r.	Adjustable until discomfort	4 Hz for 5 s 20 Hz for 10 s	n.r.	30 min, 2 times a day (morning and evening), for 8 wk

HIE, Hypoxic-ischemic encephalopathy; MDD, major depressive disorder; n.r., not reported.
*Reported as seconds, likely a typographic error and actually reflecting 200 ms.
†Registered and ongoing trial.

mild ulceration of the skin). A subsequent protocol for an RCT was registered[47] but apparently not completed (Table 2). In 2015, Finetti[44] published an abstract reporting on a case study of an 11-year-old girl with Dravet syndrome who was treated with tVNS.

Studies in Depression

Four studies addressed patients with depression, one of which was an experimental trial in adolescents with depression, not applying long-term tVNS to therapeutically address depressive symptoms.[45] The protocol for one RCT including adolescents with depression was published.[43] However, although a later publication reported on the study registered under the same identifier (ChiCTR-TRC-11001201), the study was no longer an RCT and did not include pediatric patients as planned[49] because the inclusion criteria obviously changed (inclusion cirtiera: 18–70 years of age). To our surprise, another publication from the same group,[34] presumably reporting on that same sample, apparently included pediatric patients (inclusion criteria: 16–70 years of age). Neither of these studies mentioned the adjustment of stimulation parameters for pediatric patients. Another study protocol for a tVNS trial specifically in adolescent depression was published by Xiao et al.[35] The study has not been preregistered, and the status of recruitment is not known.

Tinnitus and Other Conditions

Two studies reported on tVNS in patients with tinnitus, also including adolescents. In a study by Mei et al,[38] again, no adjustments of stimulation parameters or protocol were reported in pediatric patients. Furthermore, no reporting of adverse effects was provided. In 2015, Li et al[41] published a study protocol for an RCT in patients with tinnitus, including pediatric patients. The study was registered in the Chinese Clinical Trials Register. Unfortunately, the registry was not accessible, and we were not able to confirm the status of the trial. Badran et al[46] addressed the effects of tVNS in $N = 14$ infants with feeding problems. The authors monitored safety aspects closely and report only one adverse event (bradycardia) during the intervention, likely not associated with tVNS. In some instances, excessive fussiness was linked to the intervention, which was transient once stimulation was stopped.

DISCUSSION

This systematic review aimed to provide a comprehensive overview of the current state of the art in pediatric tVNS research. We focused on existing treatment protocols and stimulation parameters used for auricular tVNS in the treatment of pediatric patients. tVNS has been applied in pediatric patients with various clinical conditions, mainly including epilepsy, depression, and tinnitus. Registered and ongoing studies investigate the use of tVNS in children and adolescents with other conditions, such as Prader-Willi syndrome, feeding problems, or opioid withdrawal syndrome. Most of the published studies including pediatric patients were not specifically designed for the age group of interest. The inclusion criteria of the respective studies considered a broad range of age groups, irrespective of potential age-related differences in tVNS effects. More recently, studies are specifically designed to address pediatric disorders, as illustrated by studies registered on ClinicalTrials.

Reviewing the stimulation protocols of published studies (that provided the respective information) illustrates that existing protocols in pediatric patients are characterized by great heterogeneity and are not readily distinguishable from those reported in adults.[2] Generally, existing studies are characterized by poor reporting standards. For several studies, not even central sample summary statistics, such as either sample mean age or the age range of participants, were provided. Generally, information provided for stimulation devices and electrodes is frequently insufficient, and several studies have failed to report which type of stimulation device and/or which ear electrode had been used. Furthermore, engineering aspects in adjusting adult products for the use in pediatric patients (eg, the size of electrodes) have not been disclosed. Crucially, none of the included studies addressed whether electrodes were adjusted specifically to the ears of pediatric patients (eg, in size, which should deviate from custom-made electrodes intended for use with adult patients). Such lack of reporting hampers scientific progress (eg, by limiting the interpretability, comparability, and reproducibility of study findings).

Applied daily doses of tVNS differ, ranging from as low as 30 minutes per day to four hours per day. Similarly, applied stimulation intensities vary from 0.1 mA to 6 mA, at varying stimulation frequencies. Of note, the task to define and justify stimulation parameters is not an issue specific to pediatric research but inherent to the tVNS field. In general, the selection of stimulation parameters for clinical application of VNS and tVNS currently relies on subjective sensations (eg, pain or sensory threshold) and benefits reported by patients. In part, this may ground on the fact that the effects of certain stimulation parameters such as frequency and duty cycle are observed postsynaptically in various brain structures and thus cannot be computationally modeled to determine optimal parameters.[50] Moreover, the various nerve fibers of the auricular branch of the vagus have not been investigated at a level detailed enough to consider computational modeling.[10] Recently suggested electrotechnical and software-based improvements to the state-of-the-art stimulators include the use of individualized tVNS therapy, using evolution algorithms that use device and subject data to optimize stimulation parameters.[16]

One approach to determine stimulation parameters and protocols is the use of biomarkers of tVNS.[51] Frequently discussed biomarkers of tVNS include heart rate variability (HRV),[52] event-related (P300) or somatosensory evoked potentials, pupil dilation, or salivary alpha-amylase. Importantly, these potential biomarkers show developmental specifics. HRV, for example, shows tremendous changes early in the course of life, characterized by an increase up to late adolescence and early adulthood, with a following decline during adulthood.[53] Similarly, the P300 cannot be considered a robust trait-like marker but differs as a function of age.[54] Diurnal profiles of alpha-amylase have been shown to differ across the adult lifespan,[55] and studies comparing alpha-amylase secretion in children and adults have shown mixed results—some illustrating differences, and others not.[56,57] These neurodevelopmental differences need to be considered in the search for a rationale to justify tVNS stimulation parameters in children and adolescents. Furthermore, differences in physiology and anatomy should inform the clinical application of tVNS. Likely, a one-size-fits-all approach is not in the best interest of pediatric patients.

Moreover, tVNS in pediatric patients bears some practical challenges that should be considered and addressed by empirical research. In the review of existing studies, it is evident that existing stimulators are not specifically built for pediatric patients. Alongside the practical issue mentioned earlier (ie, fitting the ear

Table 2. Summary of Pediatric tVNS Trials Currently Registered in ClinicalTrials.

Contact	Trial no.	Clinical condition	Study design	Enrollment (*N*)	Ages eligible for study	Status	Last update
Benner	NCT05129020	Neonatal opioid withdrawal syndrome	Randomized	80	33 wk–1 y	Not yet recruiting	February 25, 2022
Chelimsky	NCT04247100	Pediatric functional gastrointestinal disorders	Randomized	10	12–18 y	Terminated	December 21, 2021
Dijan	NCT04177511	Chronic pelvic pain caused by endometriosis	Randomized/open label	72	≥15 y	Recruiting	December 15, 2021
He	NCT02004340	Epilepsy	Randomized	120	2–18 y	Recruiting	February 13, 2015
Jenkins	NCT05101707	Unilateral upper extremity weakness	Nonrandomized/open label	5	6–18 mo	Not yet recruiting	February 25, 2022
Jenkins	NCT04643808	Poor oral feeding	Nonrandomized/crossover	40	Up to 5 mo	Recruiting	February 25, 2022
Jenkins*	NCT04632069	Poor oral feeding	Single group/open label	10	Up to 5 mo	Recruiting	January 24, 2022
Jenkins and Lubeskie	NCT04849507	Poor oral feeding	Randomized/crossover	20	Up to 5 mo	Not yet recruiting	March 11, 2022
Laurent	NCT04169776	Idiopathic nephrotic syndrome	Nonrandomized/open label	30	2–21 y	Recruiting	August 31, 2021
Ma	NCT05256173	Epilepsy	Randomized	100	7–65 y	Recruiting	February 25, 2022
Parker	NCT04396470	Prader-Willi syndrome	Randomized	30	8–14 y	Withdrawn	May 6, 2021
Sahn	NCT03863704	Pediatric inflammatory bowel disease	Randomized	30	10–21 y	Enrolling by invitation	February 2, 2022
Tauber and Valette	NCT04526379	Prader-Willi syndrome	Nonrandomized/open label	60 (30 with and 30 without Prader-Willi syndrome)	9–15 y	Recruiting	November 3, 2020
Van Diest	NCT02113306	Fear extinction (experimental study)	Randomized	50	16–50 y	Unknown	April 14, 2014
Yang	NCT03592446	Depression	Randomized crossover	60	15–70 y	Not yet recruiting	July 19, 2018

*One previous study protocol by the group (NCT0464380) no longer available at the time of submission.

electrode), future generations of medical devices for tVNS should have the interests of pediatric patients in mind concerning the handling of devices (beyond aesthetic aspects). Furthermore, compliance monitoring seems to be of particular interest in pediatric patients. We were not able to quantify compliance rates with certain protocols in this review. Alongside existing recommendations on minimum reporting standards,[2] we encourage transparent reporting of compliance rates in future clinical studies applying long-term tVNS in pediatric patients. These issues are of particular concern when applying tVNS in patients with limited capacity for self-application, when tVNS is applied through caregivers, and so on. Attention also should be paid to a detailed assessment and reporting of adverse events in pediatric patients, which in particular concerns those unable to articulate distress given their age or health condition. Potential adverse effects of tVNS in pediatric patients need to receive particular attention and careful monitoring in future studies.

Another potentially relevant aspect that has not yet gained attention in tVNS research concerns engagement in specific physical, sensory, or mental processes concurrent with stimulation. The possibility of engaging in different kinds of activities (such as playing/listening to music, drawing, completing homework, going for a walk, etc) while applying tVNS provides a great advantage, especially in the treatment of children and adolescents. Evidence from other neuromodulatory techniques, such as repetitive transcranial magnetic stimulation (rTMS), indicates that differences in behavioral engagement/arousal cause a potential source of variability of treatment effects because factors such as attention, arousal, and mood state have been shown to affect modulation of excitability by rTMS.[58] It is currently not known whether and how such factors might affect tVNS treatment, and thus, this presents an important avenue for future tVNS research.

Importantly, the current practice of including patients across a broad age range (ie, pediatric and adult patients) in clinical trials and not reporting on age-related effects of the intervention limits the generalizability of findings and thereby progress in understanding which setting works for whom. Interestingly, one of the reviewed studies that included children, adolescents, and adults only reported adults to respond to the intervention.[33] However, the existing evidence is insufficient to 1) come to meaningful recommendations concerning a set of best practice parameters of tVNS in pediatric patients or 2) derive any meaningful insights on appropriate treatment protocols concerning the length and duration of treatment for specific indications in pediatric disorders. Thus, we echo the call for minimum reporting standards in the field.[2] Moreover, we encourage the adherence to principles in pediatric research considering specific needs of the target population. To iterate, "study protocols and study designs should be evaluated child-specifically and should not be simple modifications of study protocols for adults."[59]

CONCLUSIONS

This review illustrates an absence of justification of tVNS stimulation protocols and parameters in pediatric patients. Although the entire field of tVNS research has yet to agree on stimulation parameters and empirical ways to address respective differences to determine protocols of greater efficiency and clinical benefit, particular attention should be paid when targeting pediatric patients. tVNS protocol, stimulation site, applied electrode, frequency of stimulation, and dosage may all influence effect sizes in tVNS studies, and optimizing these factors in a neurodevelopmentally informed way could increase the observed treatment effects. Thus, instead of producing data that are neither reproducible nor consistent, the targeted development and clinical evaluation of tVNS for children and adolescents will require collaboration across multiple professional disciplines and must be informed by good scientific practice—because these ingredients are essential to facilitate and drive innovation. In the face of the window of opportunity that is inherently linked with the neurodevelopmental processes occurring across childhood into young adulthood, in combination with the remarkable excitatory, inhibitory, and reflexive properties of the vagus with the widely distributed anatomical and functional projections of its afferent system throughout the brain, tVNS should widely and actively be explored in the treatment of pediatric patients. Custom tVNS devices for use in pediatric patients are warranted, addressing specific needs of the target population by innovative engineering and patient involvement in their development.

Authorship Statements

Julian Koenig and Christine Sigrist conceptualized and designed the study, including literature search and study selection, data extraction, and presentation of results, with important intellectual input from Armin Bolz, Tobias Jeglorz, and Lars-Oliver Bolz. Bushra Torki conducted the literature search, identified relevant studies, performed the data extraction, and drafted the presentation of results. Julian Koenig and Christine Sigrist drafted the full manuscript. All authors critically revised the draft for important intellectual input and approved the final manuscript.

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COMMENTS

This is a comprehensive and astute review of transcutaneous auricular vagus nerve stimulation and its application in pediatric populations. The authors of this manuscript highlight the shortcomings of the current literature and evidence base, which is applicable to the broader field and not just pediatric populations. The authors also illustrate the growing need for developmentally aware treatments and devices to be used in this population. It was a pleasure to review this manuscript.

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In this review, the authors review registered trials and published studies to evaluate existing tVNS treatment protocols and stimulation parameters as used in children (subjects < 18 years). The authors provide a comprehensive overview of the noninvasive VNS literature with a particular emphasis on application to children. They point out the challenges that accompany certification and testing of medical devices for children and the fallacy of just scaling down adult devices for "smaller people." The authors specifically focus on tVNS in minors and point out that the published studies show very little consistency in reporting of important details regarding stimulus protocols, equipment, and statistical analyses. They provide the reader with a comprehensive overview of the gaps in current practice for using tVNS in minors and suggest future work to fill those gaps, improve transparency, and increase reproducibility across tVNS applications.

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