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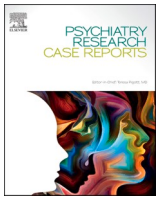

The use of external Trigeminal Nerve Stimulation as an initial treatment for ADHD symptoms in children: A qualitative study of case series reports

Christel-Mie Lykke Huus [a,*], Henriette Edemann-Callesen [a], Pernille Darling-Rasmussen [a,b], Ørjan G Martinsen [c,d], Aida Bikic [e,f], Ole Jakob Storebø [a,g,h]

[a] Center for Evidence-Based Psychiatry, Psychiatric Research Unit, Psychiatric Services, Psychiatry Region Zealand, Fælledvej 6, 4200, Slagelse, Denmark
[b] Private Hospital Hejmdal, Peter Bangs Vej 5D, 2000, Frederiksberg, Denmark
[c] Department of Physics, University of Oslo, Sem Sælands vei 24, 0371, Oslo, Norway
[d] Department of Clinical and Biomedical Engineering, Oslo University Hospital, 0372, Oslo, Norway
[e] Child and Adolescent Mental Health Services Southern Jutland, Kresten Phillipsens Vej 15, Aabenraa, Region of Southern Denmark, Denmark
[f] Department of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark, Winsløwparken 19, 3, Odense C, Denmark
[g] Department of Child and Adolescent Psychiatry, Psychiatric Services Region Zealand, 4000, Roskilde, Denmark
[h] Department of Psychology, University of Southern Denmark, 5000, Odense, Denmark

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ABSTRACT

The Monarch external Trigeminal Nerve Stimulation (eTNS) device has been approved by the U.S Food and Drug Administration (FDA) for non-pharmaceutical treatment of attention-deficit/hyperactivity disorder (ADHD) in children. Previous research into the use of eTNS to treat other psychiatric and neurological disorders has shown the device to be well-tolerated with few adverse events. Here, we report on the use of eTNS treatment in a case series of four children with ADHD in Denmark, using the NeuroSigma Monarch eTNS stimulator.

Four children aged 7–12 years, newly diagnosed with ADHD and treatment naïve, tested the device for four weeks. During the intervention the parents were interviewed three times, two and four weeks after the start of intervention and again two weeks after the end of intervention. In this qualitative study a semi-structured interview guide was used with topics including user friendliness, general experience with the intervention, potential adverse events and the parents' experience with changes in the children's ADHD symptoms, sleep and wellbeing.

Our results showed that the Monarch eTNS stimulator is user-friendly. It should be noted that one child, who is known to move excessively during sleep, got tangled in the cables. This required that the parents often checked him at night. Due to the novelty of this type of intervention, we observed that it was essential that the reason for using eTNS as a treatment is communicated appropriately at school and to the children's peers, for the child to feel understood and accepted. We found that the current intensity had to be increased for three out of the four children during the four-week experiment to enable the parents to report on potential changes in ADHD symptoms. The child who received the highest current intensity also displayed the most pronounced decrease in ADHD symptoms as indicated by the parents. The sleep patterns of three of the children potentially changed during the intervention. The parents of two children reported that they observed the children having a longer and deeper sleep. One child with bedtime avoidance improved, as he now went straight to bed and fell asleep much faster. Two children stopped waking up at night and going to their parents' beds. These observations indicate that they had a better sleep quality, and this is a topic for further investigation. Only few mild adverse events were reported.

* Corresponding author at: Center for Evidence-Based Psychiatry, Psychiatric Research Unit, Psychiatric Services, Region Zealand, Fælledvej 6, 4200, Slagelse, Denmark.
E-mail address: christelmie@gmail.com (C.-M.L. Huus).

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with estimated prevalence around 5% (Polanczyk et al., 2007). ADHD can be present as Predominantly Inattentive, Predominantly Hyperactive-Impulsive or Combined (APA 2013). ADHD is linked to challenges with education, social relations and occupation according to ICD-11 (WHO, World Health Organization 2020). There is an increased risk of co-occurring conditions for people with ADHD, including depression, anxiety, sleep disturbance and personality disorders (Schmidt and Petermann, 2009). ADHD is often treated with medication, which is known to have adverse effects, uncertain long-term effect, and decreased efficacy over time (Pereira Ribeiro et al., 2021; Storebø et al., 2016; Rubia et al., 2021). A comprehensive Cochrane systematic review concluded that methylphenidate can have a small beneficial effect on ADHD symptoms, general behaviour and quality of life in short term trials. The review also concluded that methylphenidate does not seem to increase risk of serious adverse events in the short term, but found a relatively high risk of non-serious adverse events in general (Storebø et al., 2015). No evidence for benefits or adverse events was associated with methylphenidate over the longer term of more than 12 weeks. Furthermore a large network meta-analysis by Cortese and colleagues found no evidence from trials lasting longer than 12 weeks (Cortese et al., 2018). In a large review investigating nonpharmacological interventions for ADHD, Sonuga-Barke et al. found that there is a lack of evidence for behavioural interventions, neurofeedback, cognitive training, and restricted elimination diets and they can therefore not be supported as treatments for core ADHD symptoms. (Sonuga-Barke et al., 2013). The efficacy of fatty acid supplements on ADHD symptoms is questionable and thus needs further investigation (Händel et al., 2021). New treatment options appear warranted.

ADHD core symptoms have been linked to reduced activity in the prefrontal cortex (Cubillo et al., 2012). The current hypothesis is that external trigeminal nerve stimulation (eTNS) may reduce ADHD symptoms by activating the trigeminal nerve located in the forehead, and through this to indirectly modulate the activity in the prefrontal cortex (Cook et al., 2014).

Granted that this is the case, eTNS would offer a spatial treatment approach targeting pathology-relevant brain areas, which is an advantage compared to pharmaceutical interventions (Cook et al., 2014). More research is needed to investigate the mechanism of actions.

The Monarch eTNS stimulator from NeuroSigma is the first medical device to obtain FDA approval for treatment in children in the age range of 7–12 years. It is designed for nocturnal use at home, to be administered by parents or caregivers. The stimulator is placed close to the child's bed and attached with thin wires to a disposable patch electrode attached to the child's forehead. Electrical pulses are applied with a repetitive cycle of 30 s on/30 s off, and the device is powered by a rechargeable 9-volt lithium battery. The stimulus intensity is controlled by the parent. The current is increased until the child feels a small tickle, warmth or shiver below the electrode. The parents then lock the device and the child can fall asleep.

The blinded sham-controlled randomised controlled trial with 62 participants by McGough et al. (2019) (McGough et al., 2019) formed the basis for FDA approval of NeuroSigma's device. The study by McGough et al. 2019 found a general efficacy of eTNS treatment with the Monarch eTNS stimulator from NeuroSigma, where children showed a decrease in ADHD core symptoms and an increase in general functioning measured by ADHD-IV-RS, CGI-I and BRIEF while undergoing eTNS for four weeks. Furthermore, the results indicated only a minimal risk for mild adverse events, such as fatigue, headache and increased appetite for the active treatment and no participants reported serious adverse events (McGough et al., 2019) .

These promising findings call for more research to clarify whether eTNS treatment should be offered to children with ADHD in Denmark. This article describes four cases, where we tested the Monarch eTNS stimulator from NeuroSigma in preparation for a larger sham-controlled randomised trial. The aim of this project was to gather experience from families testing the device. The user-friendliness of the device, possible adverse events and the experiences of children and their families during and after the four-week intervention period were of special interest to the researchers. We primarily sought to learn about the children and their parents' reactions and attitudes towards this potential new eTNS treatment, as this would assist us in determining whether eTNS treatment is a realistic alternative for clinical use in the future. Four newly diagnosed and medicine naïve children were recruited through the Region Zealand mental health services for children and adolescents and the private hospital Hejmdal in Frederiksberg, Copenhagen. The study was approved by Regional Zealand committee on health research ethics (SJ-855).

2. Method

Participants were selected via staff referrals at the Region Zealand mental health services for children and adolescents and the private psychiatric hospital Hejmdal in Copenhagen after being diagnosed with ADHD. This case study was approved by the Regional Zealand Committee on Health Research Ethics (SJ-855).

The inclusion and exclusion criteria were the following:

Inclusion criteria

- Informed consent from parents/legal caretakers
- Age of children: 7 to 12 years
- Children with a confirmed ADHD diagnose based on the ICD10

Exclusion criteria

- Children receiving other treatment for ADHD.
  Children with epilepsy
- Children with other electronic or metallic implants.
  Children with other serious mental and/or somatic diseases.
- Children with an IQ below 70 measured by the Wechsler Intelligence Scale for Children (WISC) version III or IV.

All families interested in participating in the case trial were invited to a meeting where they were given information about the study, as well as an introduction to the Monarch eTNS stimulator from NeuroSigma. The families subsequently had the choice to participate or not. Before inclusion, parents or caregivers provided informed consent for participation. All families had a home visit from a member of the research group at the start of the four-week intervention where the families were taught proper electrode placement and device operation.

Two weeks after the start of the intervention, the parents participated in a semi-structured interview. This was repeated at the end of the four-week intervention and again two weeks after the intervention had ended to collect as many details as possible. The semi-structured interviews were conducted via Zoom or phone calls due to COVID-19 restrictions. The semi-structured interview guide was inspired by the findings reported in the McGough study. It included questions about impact on sleep quality, adverse events, experiences and changes at home and at school, changes in behaviour and well-being of the child, as well as the observed user-friendliness of the device, including administration of the device and adjustment of the current intensity.

Adverse events were both spontaneously reported by the parents as well as more directly inquired for in questions such as "How would you assess the severity of your child's ADHD symptoms? Have there been changes? Have you noticed any changes in the child's wellbeing?" Evaluation of user-friendliness relied on questions such as: "How was it to handle the device? Did the device provide the requested treatment every night as planned? Did you experience any surprises or issues with the device? Did you have any problems with administering the

treatment? How would you assess the user manual?" The questions provided a framework for the interview, however as this was a semi-structured interview, parents were able to talk freely about the trial and their reactions.

The same interview guide was used for every interview. All interviews were recorded and later transcribed (Brinkmann and Tanggaard, 2015). The transcripts were analysed once all participants had completed the intervention, by using colour codes to assign the parents' statements to different categories in order to provide an overview of the content. The major categories included potential impact on ADHD symptoms, impact on sleep, the user-friendliness of the device, the current intensity applied and reporting on adverse events. The findings were entered in a log document arranged by topic. The results were presented per participant, with the major categories presented for each participant in a consistent manner (Brinkmann, 2014).

3. Results

3.1. Case presentation: participant 1

Child 1 was an eight-year-old boy attending primary school, who lived with both parents and his younger brother. He had vocal and multiple motoric tics, but no other co-occurrent diagnoses. He was below average within the spectrum of normal scores on the WISC-IV. His-ADHD symptoms were severe and of both hyperactive and inattentive type. He was proud of participating in this research project and keen on integrating the device into his bedtime routine. His-mother reported that his long-term interest in a subject was not something that they normally experienced. He fully participated in the project and to a degree that surprised the parents. It meant a lot to him to be the first child who tried this treatment in Denmark. Before the intervention both parents and teachers described the situation as chaotic. Child 1 was involved in many conflicts, both at school and at home with his family, of both verbal and physical nature. This included constant nagging of his brother and frequent fights.

3.1.1. Results during the four weeks of intervention

After the first week of eTNS treatment Child 1 had calmed down and no conflicts or fights were experienced, neither at school nor at home, indicating an impact on ADHD symptoms. The family interpreted the change as a result of a new ability to keep focus and corresponding disappearance of his hyperactivity symptoms. This improved pattern continued throughout the 4-week intervention.

After the first night he had problems sleeping with the device and the wires attached to his forehead. He then got used to sleeping with the device and his sleep quality and length went back to his normal sleep pattern (20:00–6:30). He would however fall asleep much faster than before the start of the intervention, as he was calmer before bedtime.

The family found that the device was user-friendly and easy to handle after the child got used to the wires. The mother noticed the patch falling off once and attached it again, continuing the eTNS treatment the rest of the night.

The family started the treatment at a current intensity of 1.8 mA, which was increased during the intervention to 4.0 mA. Child 1 did not report any adverse events.

3.1.2. Results at two weeks follow-up after end of treatment

The positive change in behaviour decreased during the first week after the intervention ended. In the second week Child 1 reverted to the previous pattern of chaotic interactions with peers, teachers and family members that were exhibited before the start of the intervention. His-schoolteacher wrote a note to the parents recommending purchase of the device because no conflicts had been experienced at school during the 4 weeks of intervention.

3.2. Case presentation: participant 2

Child 2 was a ten-year-old boy attending primary school. He had no co-occurring conditions and was in the average spectrum on the WISC-IV scale indicating an IQ in the normal range. His-parents had 50/50 custody and he was staying with each parent and siblings for one week at a time. His-ADHD symptoms were severe, of both inattentive and hyperactive type. His-parents described him as having trouble sitting still, constantly fidgeting and having a low tolerance for frustration. He had previously changed to a school with better support. He was usually the one teasing other children in school and not used to being teased himself.

3.2.1. Results during the four weeks of intervention

Child 2 was very disappointed that he did not feel an effect of the eTNS treatment on his ADHD symptoms such as constant movements and irritability with others and it was hard for the parents to persuade him to continue the intervention. Before the intervention he slept very lightly and woke up very easily. Child 2 slept longer and deeper during the intervention and it was harder for the parents to get him up in the morning. During the intervention, he was fully rested when he woke up. Child 2 did not report any adverse events. The eTNS treatment was applied with a substantial variation in current intensity throughout the 4 weeks. The parents tested how much the child could tolerate each night, which led to an inconsistency in the stimulation applied. He started at 1.4 mA and at one point went up to 3.0 mA. The parents agreed that the Monarch eTNS stimulator was user-friendly and easy to use.

The parents informed the school that Child 2 was participating in the project. The treatment was subsequently explained to other children at the school as a form of electroshock therapy and the device was referred to as "the hat". Child 2 was teased very much about the treatment and he had a difficult time in school during the treatment period as a result.

3.2.2. Results at 2 weeks follow-up after end of intervention

Being teased with "the hat" caused aggravation to child 2, and it was a new experience for him to be teased instead of being the one teasing other children. The teachers and parents did not see any changes in his ADHD symptoms, and he himself did not feel any variation in the ADHD related symptoms after the end of intervention.

3.3. Case presentation: participant 3

Child 3 was a seven-year-old boy attending primary school. He joined a new school at the beginning of the school year, during the intervention. He had ADHD symptoms of moderate severity and both hyperactive and inattentive type, with no co-occurring conditions. He had difficulty sitting still, was easily distracted and would blame others for his behaviour. His-family consisted of an older brother and both parents. His-former school had been very dissatisfied with his behaviour due to his ADHD symptoms and had asked the parents to find him another school. The current teachers had not seen him prior to the eTNS intervention and they could therefore not assess the effectiveness of the treatment. Both the current and former schools are part of the normal school system and while his behaviour had been problematic, his academic performance was indicated to be normal for his age group.

3.3.1. Results during the four weeks of intervention

The father reported that the impact on ADHD symptoms was best in the morning, after which the positive impact on symptoms decreased during the day. In the evening he was more vulnerable and more liable to cry. According to Child 3 himself, he found it easier to remain calm during classes and that made school easier for him after beginning the eTNS treatment. This was confirmed by one of his teachers. His-former school had sent daily messages about his behaviour, but the new school did not send a single message to the parents during the four-week intervention period. The quality and length of the child's sleep were

not affected. He was able to get up, go to the toilet and proceed to his parent's bed with the device where he continued his sleep.

Child 3 started on current intensity 1.4 and went up to 1.8 mA during the 4 weeks.

Child 3 enjoyed switching on the Monarch eTNS stimulator device and falling asleep while listening to an audiobook on his tablet. His-parents found the device user-friendly and that it provided a reliable treatment, but they had problems understanding the "key invalid" message intermittently displayed on the screen. By consulting the manual, they found that this signified the periods between the active phases in the treatment, but they would have liked to have known this beforehand. The patches fell off twice during the four weeks, and each time the parents replaced them and continued the treatment without further incident.

3.3.2. Results at 2 weeks follow-up after end of intervention

The ADHD core symptoms worsened after the eTNS treatment stopped. The parents were uncertain whether this increase in ADHD symptoms after the intervention ended was related to the eTNS treatment or the change of school.

3.4. Case presentation: participant 4

Child 4 was a seven-year-old boy attending primary school, who was living at home with both parents and his older brother. He had severe ADHD symptoms of both hyperactive and inattentive types and no co-occurring conditions. His-symptoms included significant restlessness that made him appear hyperactive during personal interaction and he moved about excessively during sleep. The intervention took place during COVID-19 lock down and the child only went to school for part of the duration. He attended a normal school with his age group and received no special support.

3.4.1. Results during the four weeks of intervention

The family did not notice a change in the ADHD symptoms during the four weeks of treatment. The mother reported that the child got more irritable during the last four days of the intervention, wanting to argue with his mother, which has never occurred before. The school did not report any changes in the behaviour at school. Child 4 slept longer and deeper during the intervention. As the child's sleep is normally very restless, he could get tangled up in the cables, and on occasion inadvertently wrapped them around his neck. His-mother found a way to tape the cords to avoid that for the rest of the intervention and she frequently checked on him every night. During the four-week intervention, the child stopped going to his parent's bed, which he had normally done before.

The eTNS treatment was applied with a progressive current intensity over the four weeks from 1.2 to 2.6 mA. Parents reported that the Monarch eTNS stimulator was user-friendly.

3.4.2. Results at 2 weeks follow-up after end of intervention

The mother reported that after the 4-week treatment the parents noticed a strong increase in the child's ADHD symptoms. He was much more hyperactive, frequently speaking without considering the consequences and transcending other people's personal space. The mother was uncertain how the ADHD-symptoms related to the preintervention level.

3.5. Recruitment issues

It took a whole year to recruit four children for this study. Twenty requests were initially received from parents who were interested in the project but eleven families decided to opt for pharmacological treatment or for other reasons not to participate in the case study. The remaining nine requests led to separate information meetings with the parents. Five families decided not to participate because their children's ADHD symptoms were very stressful for both the children and their surroundings. This left the four children who took part in the case study. Their parents participated in the twelve semi-structured interviews we report on.

4. Discussion

In this qualitative case series we observed that progressive current intensity over four weeks may have positive impact on ADHD symptoms. The child who received the highest current intensity also displayed the most pronounced decrease in ADHD symptoms as indicated by his parents. Two of the children displayed a positive change in the observed ADHD symptoms during the trial, whereas no changes were seen in the remaining two children. Given that this is a non-controlled, unblinded case study, it may be speculated that the positive effects mentioned by the parents reflect a placebo effect. Indeed, a positive change in ADHD symptoms was described in Child 1 who also had a positive attitude towards the intervention from the beginning. A negative attitude was observed in Child 2 who likewise did not observe a positive treatment response.

Of the four children, three displayed an increase in ADHD symptoms after the intervention had ended. This increase in ADHD symptoms needs to be investigated further in a future randomised controlled trial. The worsening in symptoms after the trial had ended may indicate that eTNS only provides short-term effect, at least when applied as described here. For now, the Monarch eTNS stimulator from NeuroSigma is FDA approved for 4 weeks of treatment, however future research is needed to determine the optimal length and frequency of treatment as well as current intensity. Furthermore, there might be a difference in how well subgroups of patients responds to the eTNS treatment. Our intervention took place during COVID-19 lockdown, which entailed disruptions in the children's everyday life, making the effect of the treatment harder to discover. A school change or other personal life events during the intervention also made it more difficult to gauge the effect of the intervention.

Two out of four families reported that the children slept longer and more deeply. Furthermore, one child stopped his bedtime resistance during the intervention. Several parents reported that their child did not come to their parents' bed as frequently or not at all, as they no longer woke up at night. These findings are indications of better sleep. Sleep disturbances are known to be more frequent in children with ADHD (25–50%) than normal controls (7%) (Miano et al., 2012). Sleep disturbance decreases the wellbeing for both the children and their families and may worsen the ADHD symptoms.

Our observations contrast a case study about a boy with ADHD, a history of mild autism spectrum disorder and obsessive-compulsive behaviours (Shah et al., 2021). This study investigated eTNS impact on sleep architecture by means of EEG measurements while the child slept. The child served as his own control as he received active eTNS via the Monarch device during the first part of the night after which it was turned off during the last part of the night. Changes in sleep architecture were observed during active treatment, as EEG measurements showed that the participant did not reach REM sleep during the active eTNS treatment (Shah et al., 2021).

The families in our study did not report the children being less rested than before intervention. Instead the parents' reports were positive as the children experienced less sleep disturbance. Further investigation into impact on sleep is needed. As some of the families experienced problems with the device, including patches falling off as well as problems managing cables, we found it necessary that the parents would check up on the child after the child had fallen asleep. Such issues concerning the practical use of the device call for awareness, as this may constitute a burden for the families and thus impact the user-friendliness of the device.

We found that the degree and manner of communication with teachers matters, and it is important that the teachers understand the

treatment and provide support. Comparing the treatment to ECT or giving the device nicknames like "the hat" appears counterproductive. Potential for teasing by peers needs to be actively evaluated and managed to help the child feel comfortable and accepted while receiving this type of treatment.

Recruitment of participants was difficult and many of the prospective participants opted out. This happened despite a great interest for the project, with many interviews with families who subsequently decided not to participate as their situation was so challenging that they preferred to start medical treatment.

The findings will be used to improve a future feasibility trial protocol and to adjust information documents for parents participating in future research.

5. Conclusion

In this study we found that half of the children displayed a potential improvement in ADHD symptoms during the trial, whereas no improvements were found in the remaining two children. Given that this is a case series study, the positive effects mentioned by the parents may reflect a placebo effect. This needs to be investigated in a future randomised controlled trial.

The impact on sleep also needs to be further examined. We experienced that children who move excessively during sleep could get tangled up in the cables. We found that recruitment of drug naïve children via the child and adolescent's psychiatry health services is difficult. The children who reach these services tend to need immediate treatment due to their substantial burden of symptoms. We learned that the school can assist the treatment by supporting the participant through communication and understanding. These findings will need to be tested in a larger sample size with a control group. For this, we plan to do a feasibility trial, which will serve as the basis for a full size randomised controlled trial.

Ethical considerations

The data included in this article is published with the consent of the contributing individuals. The study was approved by Regional Zealand committee on health research ethics (SJ-855).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

APA, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychological Association, Arlington, VA, USA.

Brinkmann, S., 2014. The Qualitative Interview (DK: Det kvalitative Interview), 1. edition ed. CPH, Hans Reitzels Forlag.

Brinkmann, S., Tanggaard, L., 2015. Qualitative Methods (DK: Kvalitative metoder: En Grundbog), 2. edition ed. CPH.

Cook, I.A., Espinoza, R., Leuchter, A.F., 2014. Neuromodulation for depression: invasive and noninvasive (deep brain stimulation, transcranial magnetic stimulation, trigeminal nerve stimulation). Neurosurg. Clin. 25 (1), 103–116.

Cortese, S, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A.J., Carucci, S., Atkinson, L.Z., Tessari, L., Banaschewski, T., Coghill, D., Hollis, C., Simonoff, E., Zuddas, A., Barbui, C., Purgato, M., Steinhausen, H., Shokraneh, F., Xia, J., Cipriani, A., 2018. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 5 (9), 727–738.

Cubillo, A., Halari, R., Smith, A., Taylor, E., 2012. & Rubia, K, *A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention*. Cortex 48 (2), 194–215.

Händel, M.N., Rohde, J.F., Rimestad, M.L., Bandak, E., Birkefoss, K., Tendal, B., Lemcke, S., Callesen, H.E., 2021. Efficacy and safety of polyunsaturated fatty acids supplementation in the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents: a systematic review and meta-analysis of clinical trials. Nutrients 13 (4).

McGough, Sturm, A., Cowen, J., Tung, K., Salgari, G.C., Leuchter, A.F., Cook, I.A., Loo, S. K., 2019. Double-blind, sham-controlled, pilot study of trigeminal nerve stimulation for attention-deficit/hyperactivity disorder. J. Am. Acad. Child Adolesc. Psychiatry 58 (4), 403–411 e3.

Miano, S., Parisi, P., Villa, M.P., 2012. The sleep phenotypes of attention deficit hyperactivity disorder: the role of arousal during sleep and implications for treatment. Med. Hypothes. 79 (2), 147–153.

Pereira Ribeiro, J., Arthur, E.J., Gluud, C., Simonsen, E., Storebø, O.J., 2021. Does methylphenidate work in children and adolescents with attention deficit hyperactivity disorder? Pediatr. Rep. 13 (3), 434–443.

Polanczyk, G., de Lima, M.S., Horta, B.L., Biederman, J., Rohde, L.A., 2007. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am. J. Psychiatry 164 (6), 942–948.

Rubia, K., Westwood, S., Aggensteiner, P.-M., Brandeis, D., 2021. Neurotherapeutics for attention deficit/hyperactivity disorder (ADHD): a review. Cells (Basel, Switzerland) 10 (8), 2156.

Schmidt, S., Petermann, F., 2009. Developmental psychopathology: attention deficit hyperactivity disorder (ADHD). BMC Psychiatry 9 (1), 58.

Shah, Y.D., Kelly-Pieper, K., Kothare, S., 2021. eTNS used for ADHD can disrupt sleep architecture. Sleep Med. 83, 1–3.

Sonuga-Barke, E.J., Brandeis, D., Cortese, S., Daley, D., Ferrin, M., Holtmann, M., Stevenson, J., Danckaerts, M., van der Oord, S., Döpfner, M., Dittmann, R.W., Simonoff, E., Zuddas, A., Banaschewski, T., Buitelaar, J., Coghill, D., Hollis, C., Konofal, E., Lecendreux, M., Wong, I.C., Sergeant, J., 2013. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am. J. Psychiatry 170 (3), 275–289.

Storebø, O.J., Ramstad, E., Krogh, H.B., Nilausen, T.D., Skoog, M., Holmskov, M., Rosendal, S., Groth, C., Magnusson, F.L., Moreira-Maia, C.R., Gillies, D., Buch Rasmussen, K., Gauci, D., Zwi, M., Kirubakaran, R., Forsbøl, B., Simonsen, E., Gluud, C., 2015. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). Cochrane Database Syst. Rev. 2015 (11), Cd009885.

Storebø, O.J., Simonsen, E., Gluud, C., 2016. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents. JAMA 315 (18), 2009–2010.

WHO, World Health Organization, 2020. The ICD-11 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines, 1. World Health Organization, Geneva, Switzerland, p. 2020.