Vpliv kombiniranega nadaljevalnega zdravljenja na simptomatiko in kvaliteto življenja otrok s hiperkinetično motnjo: prospektivna opazovalna študija

Impact of Combined Continuous Treatment on the Symptoms and Quality of Life of Children with Attention Deficit Hyperactivity Disorder: A Prospective Observational Study

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Izvleček

Namen: *Čeprav je ADHD ena najpogostejših razvojnih motenj, so študije o dolgotrajnem učinku zdravljenja na simptomatiko in kvaliteto življenja (QOL) pičle in nasprotujoče. Namen te študije je bil raziskati učinek kombiniranega (farmakološkega in nefarmakološkega) nadaljevalnega zdravljenja na simptomatiko in QOL otrok z ADHD po začetni stabilizaciji simptomov.*

Metode: *Sedemnajst otrok z ADHD (M = 8,5 let; 15 dečkov in 2 deklici) je bilo vključenih v prospektivno opazovalno študijo, kjer smo jih ocenili v dveh časovnih razmakih z vprašalniki ADHD Rating Scale, Clinical Global Impression-Severity, Child Health and Illness Profile/Parent Report Form-76.*

Rezultati: *Po devetih mesecih zdravljenja je ADHD RS pokazal izboljšanje simptomatike v dveh postavkah, povezanih s pozornostjo ($p < 0,05$), pri*

Abstract

Purpose: *Although attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders, studies involving the long-term treatment effects on symptoms and quality of life (QOL) are few in number and the results are conflicting. The purpose of the current study was to determine the effect of combined (pharmacologic and non-pharmacologic) continuous treatment on the symptoms and QOL in children with ADHD after initial stabilization of symptoms.*

Methods: *Seventeen children with ADHD (mean age = 8.5 years; 15 boys and two girls) were included in this prospective observational study. The children were assesed at baseline and 9 months later based on the ADHD Rating Scale (RS), Clinical Global Impression-Severity (CGI-S), and Child Health and Illness Profile/Parent Re-*

tem je globalna vrednost ostala nespremenjena. Prav tako je CGI-S pokazal izboljšanje v izraženosti motnje ($p < 0,05$), CHIP-CE pa je pokazal stabilnost in tudi izboljšanje v QOL pri več kot 50 % udeležencev pri štirih od petih domen brez dokazane signifikantne razlike.

Zaključek: *Rezultati te raziskave kažejo, da je upravičeno nadaljevati z zdravljenjem ADHD tudi po začetni stabilizaciji simptomov ter da lahko pričakujemo nadaljnjo izboljšanje simptomatike in QOL, kadar je kombinacijsko zdravljenje nadaljevano.*

port Form-76 (CHIP-CE).

Results: *After 9 months of treatment, the ADHD RS showed improvement in symptoms in two items closely related to attention ($p < 0.05$); the global value remained unchanged. Furthermore, the CGI-S showed improvement in the severity of ADHD ($p < 0.05$). CHIP-CE showed stability and > 50% improvement in the QOL among participants in four of five domains with no statistically significant difference.*

Conclusion: *The results of this study suggested that continued treatment of ADHD was justified after initial stabilization of symptoms and further improvement in symptoms and QOL can be expected.*

INTRODUCTION

The recommended treatment of attention deficit hyperkinetic disorder (ADHD) is integrated and combined, thus covering every aspect of a child's psychosocial environment, including psychoeducation of the child and parents, parental training, behavioral interventions in the family, individualized adjustments, behavioral interventions in school, cognitive-behavioral therapy, and pharmacologic treatment (1,2). Psychoeducation is based on informing the children and parents about ADHD, in particular about the clinical presentation, treatment, and prognosis. The measures of behavioral interventions are individualized and aimed at rewarding appropriate behavior, and at the same time, reducing inappropriate behavior (2). Poor parenting can contribute to co-morbid psychopathology in children with ADHD, therefore parent training is considered reasonable (3). Adaptations in school, such as setting clear rules, a predictable workflow, and similar interventions are also necessary. Cognitive-behavioral therapy is individually tailored and concentrated on the areas where the most deficits are expressed (4). Given the effect of cognitive-behavioral therapy, Brown and colleagues reported that as an independent therapy, cognitive-behavioral therapy has little effect on symptoms and QOL; however, combination with pharmacologic treatment results in further improvement in functioning (5). Thus, lower doses of medication are needed for the treatment of ADHD (5). Salakari et al. confirmed that among 29 adults with ADHD, cognitive-behavioral group rehabilitation achieved improvement at the 6-month follow-up or at least retained the previously stabilized condition (6).

According to ADHD guidelines, the duration of pharmacological treatment is not fixed in advance but should be individually tailored. After an adequate treatment response, drug treatment should be continued for as long as treatment remains clinically effective, but should be reviewed at least annually (1,2,7). Few studies have attempted to determine whether or not further improvement can be reasonably expected after an adequate treatment response is achieved. Young et al. reported continued improvement with atomoxetine from the 12-week evaluation point to the 24-week study end point; however, a multimodal treatment study involving children with ADHD (MTA) showed that the effect of the combined treatment at the 24-month assessment point is greater than after 36 months, which suggests that active treatment is effective but must be properly maintained. Van de Loo-Neus et al. selected relevant papers about the efficacy, safety, and tolerability with respect to the long-term advantage of treatment with medication and showed that intensive

management with medication results in a marked reduction in symptoms of ADHD for at least 2-5 years (8, 9, 10). There is limited and inconsistent evidence regarding the long-term advantage of treatment beyond symptom control, such as improved social functioning, academic achievement, and self-image.
Although the high burden of ADHD is associated with problems in the family and society as a whole, few studies have discussed the QOL in persons with ADHD. Escobar et al. compared the QOL of 120 children with newly-diagnosed ADHD with 2 control groups (93 children with asthma and 120 healthy children) (11). The results showed that children with ADHD function significantly worse in most areas (11). Coghill and Hodgkins compared the QOL of 213 children with ADHD to 58 children with type 1 diabetes and 117 healthy individuals (12). The responses of children and their parents correlated and showed a poorer QOL for children with ADHD compared to the group of children with diabetes type 1 and the healthy group (12). Klassen, Miller, and Fine compared 165 children with ADHD with two population samples of healthy children in the USA and Australia and found that children with ADHD have a poorer QOL in all psychosocial domains (13). Taken together, it has been determined that the QOL of individuals with ADHD is significantly worse than the QOL of healthy individuals (11–13).

Regarding the effect of treatment on the QOL in individuals with ADHD, a systematic review confirmed that QOL improves with effective treatment, but this evidence was almost entirely limited to pharmacologic treatment (14).
The primary aim of our study was to determine whether or not the symptoms and QOL of children with ADHD further improved when the initial treatment was continued. Our study was one of a few studies to determine the impact of continuous combined treatment on symptoms and QOL. We assumed that ADHD symptoms and QOL were connected so that changes in the severity of symptoms affected the change in QOL and vice versa. Therefore, we developed the following working hypotheses: 1) during 9 months of continuous combined treatment, further improvement in symptoms of ADHD will occur; and 2) during 9 months of continuous combined treatment, QOL will improve.

MATERIAL AND METHODS

We invited 19 children and adolescents who were diagnosed with ADHD according to DSM-5 and with hyperkinetic disorder (HK) according to ICD-10 to participate in the study. The children and adolescents were invited after initial stabilization of ADHD symptoms. A total of 17 (89.5%) children 15 (88.2%) boys and two (11.8%) girls, age range, 6–11 years; mean age, 8.5 years) responded to the oral invitation during a routine medical evaluation. All participants were stable on prior standard combined therapy before the first assessment (T1), which included pharmacotherapy, school adaptation, counseling and support for parents, teachers, and children, and other individualized behavioral measures. All of the participants were treated with pharmacotherapy (methylphenidate or atomoxetine) for at least 3–8 months prior to T1, thus ensuring that participants received therapeutic (rather than the initial) doses of medications. An initial improvement in symptoms was achieved, thus allowing us to fully assess the effect of standard combined therapy rather than the initial effect of pharmacotherapy. Accordingly, T1 does not represent the onset of treatment, but the start of the continuation of treatment. After 9 months of combined treatment (T2), participants were re-assessed with the same battery of tests as used at T1. Co-morbidity was not considered as exclusion criterion.

Permission to use the data acquired was obtained from a child and/or each participant's parent prior to inclusion in the study. All persons gave informed consent. The results of the questionnaires were combined as a group evaluation, which served to protect personal data. The observational study was approved by the Republic of Slovenia National Medical Ethics Committee (NMEC registration number, 0120-344/2017-5 on 13.06.2017). The NMEC reference number reads as follows: 0120-334/2017/5. The study was conducted in accordance with the ethical standards recommended in the 1995 Declaration of

Helsinki (revised in Edinburgh in 2005).The present study had a prospective, observational design. Three types of questionnaires were used to assess the symptoms and QOL of children with ADHD at the first assessment (T1) and after 9 months (T2). The severity of symptoms was assessed by the ADHD Rating Scale-IV: Home Version (ADHD-RS) and the Clinical Global Impression-Severity (CGI-S). At the same time, the Child Health and Illness Profile-Child Edition/Parent Report Form-76 (CHIP-CE) was used to assess the QOL.

ADHD-RS is a questionnaire designed to assess the severity of signs and symptoms of ADHD. The ADHD-RS consists of 18 items that described the most common signs and symptoms of ADHD (15). The questionnaire has demonstrated acceptable reliability, validity, internal consistency, and comparability in European and international populations (16,17).
The CGI-S is a questionnaire intended to allow rapid clinical assessment of disease severity. The CGI-S is intended for therapists who are well-acquainted with the patient and represents a summary of patient functioning (18).

The CHIP-CE questionnaire consisted of 76 items and covered five main domains that assessed the QOL (satisfaction, comfort, resilience, risk avoidance, and achievements). Riley et al. verified satisfactory reliability, validity, internal consistency, test-retest reliability, and comparability of the CHIP-CE questionnaire in multiple studies (19–21).

The ADHD-RS and CHIP-CE were completed by the child's parents, while the CGI-S was completed by the child's therapist. Hereafter, "parents" will also be used in reference to the child's caregivers. All questionnaires were completed as part of a routine follow-up visit in the Department of Child and Adolescent Psychiatry at the University Clinical Center (Maribor, Slovenia). The Wilcoxon test, which is known to be suitable for related and small samples, was used for analyses (22). All three questionnaires were analyzed separately. For the CHIP-CE questionnaire, we analyzed individual domains. The final score for each domain was obtained by averaging, with the sum of points of all items divided by the number of items. For the ADHD-RS questionnaire, individual items and a global score (i.e., the average of all items) were analyzed. For the CGI-S, individual items were analyzed. The requirement for the analysis of all questionnaires was at least 70% completion of the questionnaire or < 30% missing responses for each domain (the latter applied to the CHIP-CE questionnaire). A p-value <0.05 was defined as a statistically significant difference.

RESULTS

A total of 19 participants with ADHD were invited to participate in the survey, 17 of whom (89.5%) attended both follow-up visits. The age structure of the 17 participants included in the analysis was 8.5+/-1.5 years at T1. Fifteen (88.2%) participants were males and 2 (11.8%) were females. All participants were Caucasian. Fourteen (82.4%) participants received extended-release methylphenidate and three (17.6%) were treated with atomoxetine. ADHD-RS and CHIP-CE were completed by the participants' parents, 12 (70.6%) of whom were biological parents and 5 (29.4%) were caregivers. The CGI-S was always completed by the same therapist.

The ADHD-RS was used to assess the change in symptoms during continuous combined treatment. At T1 and T2, 18 individual items and the global value were compared. For items 1 (p=0.046) and 17 (p=0.029), statistically significant improvement was determined (p<0.05). The global value did not show statistically significant differences, and the average of all items for the majority of participants (70.6%) was unchanged (Table 1). Although no statistically significant differences existed, improved results in > 40% of participants were shown for six items (Nos. 1, 5, 6, 7, 15, and 17), and deterioration was shown in > 40% of participants for 4 items (Nos. 2, 3, 10, and 18). The remaining results of the individual items are listed in Table 1.

Table 1: *ADHD Rating Scale-IV: Home Version (ADHD-RS)-Relative and p-values of individual items and global values*

ITEM	IMPROVEMENT (%)	DETERIORATION (%)	UNCHANGED (%)	P-VALUE
1	47.1	11.8	41.2	0.046
2	17.6	52.9	29.4	0.083
3	35.2	41.2	23.5	0.312
4	35.2	17.6	47.1	0.564
5	41.2	17.6	41.2	0.265
6	47.1	29.4	23.5	0.317
7	41.2	11.8	47.1	0.083
8	35.2	35.2	29.4	0.805
9	35.2	23.5	41.2	0.156
10	23.5	41.2	35.2	0.218
11	29.4	29.4	41.2	0.531
12	35.2	35.2	29.4	1.0
13	35.2	17.6	47.1	0.564
14	29.4	23.5	47.1	0.903
15	41.2	29.4	29.4	0.644
16	35.2	23.5	41.2	0.490
17	52.9	17.6	29.4	0.029
18	17.6	41.2	41.2	0.250
GLOBAL	11.8	17.6	70.6	0.655

Based on the CGI-S, the disease severity was clinically assessed by the therapist at T1 and T2. The overall results improved in 8 (47.1%) patients and was unchanged in 9 patients (52.9%). The calculated P-value was 0.005, which represents a statistically significant difference showing improvement in disease severity for the majority of symptoms (Table 2).

Table 2: *Clinical Global Impression: Severity ADHD (CGI-S)-Relative and p-values*

IMPROVEMENT (%)	DETERIORATION (%)	UNCHANGED (%)	P-VALUE
47.1	0	52.9	0.005

For the CHIP-CE, the QOL was assessed in five domains (Table 3). A statistically significant difference ($p < 0.05$) was not verified for any of these domains. In the first domain (satisfaction), the condition improved in 10 participants (58.8%), in remained unchanged in four participants (23.6%), and deteriorated in three participants (17.6%). The second domain (comfort) deteriorated in nine participants (52.9%), improved in seven participants (41.2%) and was unchanged in one participant (5.9%). In the third domain (resilience), the situation improved in nine participants (52.9%) and worsened in 8 participants (47.1%). The fourth domain (risk avoidance) yielded the best results. Specifically, the situation improved in 12 participants (70.6%) and deteriorated in five participants (29.4%). Due to > 30% missing answers, the questionnaires of two participants (11.8%) could not be analyzed for the 5th domain (achievements). Therefore, the analysis was completed for 15 participants (88.2%). Of the 15 participants, improvement occurred in 10 participants (66.7%) and deteriorated in five participants (33.3%).

Table 3: *Child Health and Illness Profile – Child Edition / Parent Report Form-76 (CHIP-CE)-Relative and p-values for individual domains*

DOMAIN	IMPROVEMENT (%)	DETERIORATION (%)	UNCHANGED (%)	P-VALUE
Satisfaction	58.8	17.6	23.5	0.206
Comfort	41.2	52.9	5.9	0.959
Resilience	52.9	47.1	0	1.000
Risk Avoidance	70.6	29.4	0	0.118
Achievement	66.7	33.3	0	0.138

DISCUSSION

Although ADHD affects 5% of children, studies involving the long-term effects of pharmacologic, non-pharmacologic, or combined treatment on symptoms and QOL are limited and conflicting. The purpose of this study was to determine whether or not continuation of combined treatment improves the symptoms and QOL of children with ADHD, even after the initial stabilization of symptoms. Based on the ADHD-RS, two inattentive symptoms showed a statistically significant improvement (attention to details/ a reduced number of unnecessary errors and less forgetfulness in daily activities; Table 1). Similar results, with a significant improvement in the attention domain, were described in a study by Weiss et al. (23). The Weiss et al. study involved 725 adults with ADHD and the ADHD-RS was used for assessment (23). Weiss et al. found that inattention is more closely related to QOL than hyperactivity and/or impulsivity, and inattention is the main cause of reduced QOL in individuals with ADHD (23). Our results are consistent with the finding of Weiss et al.; specifically, improving attention in individuals with ADHD also improves the QOL (23). Other items did not display statistically significant differences, but we assessed improvement in > 40% of participants in 4 items (Table 1). Of these, three items were within the domain of attention, which further supports our finding that attention symptoms continue to improve with continuation of treatment. Deterioration in four items in > 40% of participants was also demonstrated (Table 1). Among these items, three were within the domain of hyperactivity and impulsivity. According to the Weiss et al. study, hyperactivity and impulsivity have little effect on QOL compared to inattention symptoms, but are more often noticed by parents (23). We speculate that hyperactivity and impulsivity

were more disturbing to the parents who completed the questionnaire and scored the items as markedly deteriorated.

Moreover, unchanged results in other items indicated that continuous combined treatment may maintain the previously stabilized condition of the participants, which was also of great importance.

Global improvement in symptoms was also found in the majority of participants based on the CGI-S. As shown in Table 2, a statistically significant improvement in symptoms was achieved, with 47.1% of participants improved. Our findings are in agreement with the findings of Rostain and Ramsey, who demonstrated a significant global improvement in ADHD symptoms on combined therapy in adults with ADHD based on the CGI questionnaire (24).

The QOL improved in > 50% of participants in four of five domains in the CHIP-CE in our study (Table 3). In the satisfaction domain, parents assessed the child's happiness, well-being, general health, self-esteem, and self-satisfaction (19, 25, 26). During the 9-month period between T1 and T2, the above-listed subdomains improved in 58.8% of participants. The results are very encouraging, indicating that during continuous combined treatment, there is improvement in a child's self-esteem and self-satisfaction. This is crucial because better self-esteem and self-satisfaction lower the risk of co-morbidities, such as depression, anxiety, oppositional defiant disorder, and abuse of psychoactive substances. Considering the large study involving 1947 adolescents with ADHD, the concurrent internalizing symptoms (depression and anxiety) may underlie a negative relationship between ADHD symptoms and QOL in adolescents (27). The effect of combined treatment on improvement of the risk of co-morbidity is also stressed in a review of the evidence for treatment of ADHD (5).

In the resilience domain, parents assessed the child's participation in family and physical activity, the sense of family support, and the ability to actively solve interpersonal problems (19, 25, 26). The abovementioned domain improved in 52.9% of the participants. This result showed that during continuous combined therapy the children acquired communication skills and improved their participation in family activities, which improved the QOL not only of the child but also of the entire family. Furthermore, children with ADHD are often limited in their ability to participate in physical activities because they may be awkward and clumsy. With continued treatment, we established a greater participation in physical activity in our study, which also contributed to an improvement in family QOL. Improving the family life of children with ADHD is of great importance because parents of children with ADHD assess the impact of the interference of the disorder on the family as more severe compared to the parents of healthy and asthmatic children (11).

The risk avoidance domain evaluated the child's avoidance of situations that could induce injury or illness, or disrupt social development (19, 25, 26). Our results have shown the greatest improvement in this domain because the improvement occurred in 70.6% of the participants. The MTA study also noted a reduction in delinquent acts and abuse of psychoactive substances after the successful completion of a 14-month treatment (9). In their review article, Harstad and Levy concluded that treatment with stimulant medications and behavioral therapy significantly reduced the possibility of psychoactive substance abuse. Moreover, pharmacotherapy in combination with behavioral therapy has proven to have a greater impact on reducing risk-taking and abuse of psychoactive substances compared to autonomous pharmacologic treatment (9, 28). Our results are consistent with these studies and confirm that combined treatment reduces risk-taking behavior in children with ADHD.

In the achievement domain, school performance, engagement in school activities, and a sense of acceptance among peers was estimated (19, 25, 26). An improvement occurred in 66.7% of the participants, demonstrating that continuous combined treatment helped express the child's basic potentials, which could be reduced by ADHD. Similarly, the AUTOR study demonstrated that school performance was one of the main factors associated with stability of the disorder (29). We can assume that continued treatment helps to maintain the stability, and consequently the QOL. Furthermore, it has been shown that acceptance among peers is a very good predictor of later social functioning (30). The results

of our study are consistent with the findings of Hoza, indicating that better social functioning was achieved with continuous combined treatment (30).

The comfort domain evaluated the child's physical and mental state as well as the limitation of daily activities due to illness (19, 25, 26). The situation improved in 41.2% of participants, but deterioration occurred in 52.9%. Combined treatment requires order and routine in everyday life, which children often resist, resulting in family distress rather than increased comfort. There is evidence that parents often assess the QOL more negatively than do children with ADHD (14).

The risk avoidance and achievements domains showed the most improvement in the present study. The same domains were also estimated to be one of the most important prognostic factors related to QOL of ADHD by Montoya (26). Based on this finding, we speculate that continuous combined treatment also improved the prognosis of children with ADHD.

The strength of this study was that it was one of the few studies to explore the effect of continuous treatment of ADHD, not only on key symptoms, but beyond key symptoms (QOL, social functioning, school achievement, self-esteem, and family functioning). The focus was not on one specific treatment, but combined treatment was explored, which is the recommended treatment for ADHD. Because all participants also fulfilled the diagnostic criteria for hyperkinetic disorder, which constitutes the most severe presentation of symptoms of ADHD, pharmacotherapy was included in the combined treatment. Children included in this study all received the same package of therapies, which were individually tailored. We confirmed that it is justified to continue with the combined treatment of ADHD after initial stabilization of symptoms and that further improvement in symptoms (especially inattention) and QOL (child's happiness, well-being, general health, self-esteem, and self-satisfaction) can be expected when combined interventions are extended, leading to a better prognosis and lowering co-morbidities.

The limitation of the present study was the small sample size. This study involved 17 participants, which meant differences in the results of the questionnaires between T1 and T2 had to be much greater to achieve statistical significance than would be necessary for a study with a larger number of participants. Small samples can prevent the extrapolation of data (31, 32). Despite the small sample size, the proven calculated statistically significant values should be considered to be important. This study was started after the initial stabilization of symptoms. Therefore, even unchanged (i.e., stabile) results should be considered a good outcome; however, it would be wise to carry out a similar study with a larger number of participants. The study did not include a control group, mainly due to ethical reasons, because the control group should include children with ADHD, who did not receive continuous combined treatment, which is highly controversial.

The ADHD symptoms and QOL during therapy were estimated by the child's parents and therapist. As noted by Coghill and Hodgkins, the same was true for most of the comparative studies, although the child's view about his own symptoms and QOL was of vital importance (12). Therefore, it would be interesting to include the child's assessment in further studies.

In conclusion, our study demonstrated that after 9 months of combined treatment there was stability and further improvement in both symptoms of ADHD (overall and especially symptoms related to attention) and QOL. This was confirmed by a statistically significant reduction in the severity of the disorder on the CGI-S and a statistically significant improvement in two items from the field of attention on the ADHD-RS. The study also documented improvement in > 40% of participants in additional items on the ADHD-RS, three of which fall within the attention domain. Reducing the inattentive symptoms was found to be crucial for the QOL in both our study and other comparable studies (23, 27). The positive impact of continuous combined treatment on the child's overall functioning was also demonstrated by improvement in > 50% of participants in 4 of 5 domains on the CHIP-CE. The greatest improvement occurred in domains that are associated with inattention and impulsivity, which suggested that by reducing the symptoms of ADHD, improvement in QOL was achieved. We assumed that further improvement was the result of combined interventions, such as school adaptations, counseling and support for parents, teachers, and

children, other individualized behavioral measures, and pharmacotherapy, which all helped children and adolescents not only to lower the symptoms of ADHD, but to provide different, more encouraging experiences in the family, school, and peers.

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