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ASSESSING THE EFFECTIVENESS AND SAFETY OF PHARMACOLOGICAL THERAPY IN CHILDREN DIAGNOSED WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDERS

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Abstract. Deficit Hyperactivity Disorder (ADHD) is considered to be a neurodevelopment condition with a worldwide prevalence between 3-10 % in children1 with symptoms that could continue into adolescence for 50-80% of cases and into adulthood for as many as 30 – 50 % of cases. The purpose of the research was to evaluate the efficacy and safety of pharmacological treatment in attention deficit hyperactivity children. A retrospective clinical research in 73 patients was designed and carried out at "Victor Gomoiu" Clinical Pediatric Hospital. The data was obtained from patients medical records. The study duration was 15 months from Jan 2013 to March 2014. The medical treatment was analysed: type of drugs given, dosage, pharmaceutical formulation, length of treatment. We also analysed the types of non-medical treatments associated: psychological therapy, logopedic therapy, occupational and cognitive stimulation therapy, other types of therapy. Monthly monitoring and identification of adverse events was done for each patient by analysing the type of medication given, adverse event onset, severity, dose optimization, withdrawal from treatment or change of medication. Data was stratified for three age groups: preschool children (< 7years old), 12 to 18 - year-olds and 7 to 11 - year- olds. Combined therapy (both medical and psychological) gave results but without being able to determine the measure in which either the psychological, pharmacological or combined treatment have influenced the end result. Early detection and management of side effects (dose optimization, change of medication, drug combinations that diminish or even eliminate the side effects, treatment interruption) improve compliance and adherence towards the given medical treatment but also improve the quality of life.
Key words: ADHD; efficacy; safety; pharmacological and non-pharmacologycal treatment

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is considered to be a neurodevelopment condition with a worldwide prevalence between 3 - 10% in children with symptoms that could continue into adolescence for 50 - 80% of cases and into adulthood for as many as 30 – 50 % of cases (Kristensen H.A., et al, 2014). The persistence of ADHD in these age groups was once debated between clinicians and researchers but it is a well-established fact now. Symptom severity decrease with time but patients continue to experience elevated levels of inattention, hyperactivity and impulsivity compared to typically developing peers. There seem to be three patterns of ADHD manifestations in patients: one consisting mostly of inattention, the second mostly of hyperactivity and/or impulsivity and the third type being a combination between these two. The findings are consistent with the current available guidelines: DSM V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) the 2013 update to the American Psychiatric Association's (APA) and the International Statistical Classification of Diseases and Related Health Problems (ICD 10) a medical classification list established by the World Health Organization (WHO).

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Etiology

ADHD is thought to be caused by abnormalities of neurotransmitter functions, which regulate the amount of dopamine and norepinephrine in the frontal lobe (Bron T.I., et al, 2014). Both are catecholamine-structured compounds that play an important role in the functionality of the sympathetic nervous system. Dopamine plays an important part in behaviours such

as learning, motivation, goals, drives and emotions while norepinephrine is involved in maintaining the organism in a state of alertness and awareness through detection of the correct stimuli that start the process. Other studies demonstrated increases in dopamine D2/D3 receptor activity in striatal regions in adolescence with ADHD (Ernst M., et al., 1999). The physiopathology of ADHD is complex and not fully understood but the genetic aspects account for around 75% of the disorder symptomatology. Other two important factors are the external ones and the social related ones. The genetic research for ADHD summarises a list of candidate genes that could be responsible for the disorder but most likely, there is a combination of genes linked to ADHD, which are involved in the function of several neurotransmitters (Voeller K.K.S., 2004). Other recent studies have shown a co-occurrence of ADHD and obesity in children due to common risk alleles. There is evidence that obesity genes such as FTO gene, which codes for the enzyme alpha-ketoglutarate - dependent dioxygenase, may affect ADHD risk. There is no clear picture concerning specific biomarkers, which could detect from early on a tendency towards developing ADHD in young patients but recent studies highlight that adiponectin and in particular, its high molecular weight form may be a possible marker for ADHD. The mechanisms underlying the association between adiponectin levels and psychiatric symptoms are largely unknown (Mavroconstanti T., et al, 2014). Early findings using magnetic resonance imaging (MRI) reported morphological differences in brain regions innervated by dopamine containing neurons in young patients with ADHD. Similar studies showed that children with ADHD have smaller volumes of total brain matter and subcortical regions but it is not clear yet whether these differences persist into adulthood or are simply a delayed maturation process. The most noticeable differences in ADHD compared to controls were found in the cerebellar regions, the splenium of the corpus callosum, total and right cerebral volumes and right caudate nucleus. The literature does not specify how abnormal childhood brain volumetric translates into adulthood. No difference between ADHD patients and healthy subjects were observed for total brain volume, grey matter or white matter volume (Marten A., et al, 2014).

More and more evidence suggests a possible attentional phenotypic pattern for ADHD children. It seems that compared to typically developing peers, ADHD children are slower and less accurate in responding to invalidly cued left targets than compared to right ones.

Another difference was noted through positron emission tomography (PET) which showed that ADHD patients had an overall deficit in cerebral glucose metabolism compared to control subjects (Marten A., et al, 2014).

It is not surprising regarding the genetic nature of ADHD, that 25% of patients will have a parent who met the former diagnostic criteria for ADHD as well. Aside the genetic factors, social-environmental ones also play a very important part. Increased rates of attention deficit and hyperactivity have been observed in children who were raised in institutions. The educational background as well as the family upbringing influences the symptomatology but it also could affect the way a proper diagnosis will be given depending on the severity of the behaviour. There is growing concern that patients could be over-diagnosed due to a faulty therapeutic evaluation, which can lead also to inadequate therapy.

External factors have also been linked to ADHD or ADHD like behaviours. Some of these include multiple pre- and perinatal factors: foetal alcohol syndrome, maternal smoking, metabolic disorders of the mother (diabetes, phenylketonuria), injury to the medial temporal lobe during early development, hyperbilirubinemia (jaundice) in the newborn period, iron deficiency, hypoxia, particularly in the foetus or infant.

The risk of co morbidity is high in patients with ADHD. The most common condition in adult ADHD is Major Depressive Disorder (MDD), which was associated with smaller volumes of total and left hippocampus in subjects.

Developmental coordination disorder (DCD) is another neurodevelopmental disorder frequently associated with children with ADHD and it affects their ability to perform everyday tasks. There is a heightened risk of psychological distress for these patients, which can lead to more health problems than in children with ADHD only. Research indicates that the co morbidity between ADHD and DCD is very high, a "pure" ADHD being rather an exception than a rule (Missiuna C., et al, 2014).

ADHD has been also associated with autism spectrum disorders, epilepsy, anxiety, thus patients with such co morbidities experience a greater social, cognitive and psychological impairment.

Treatment

Controlled studies proved a lower efficacy only with behavioural therapy as compared to those where a medical treatment was associated. Combined therapy leads to variable results. The type of therapeutic approach depends on the patient's age, severity of symptoms and other known associated conditions.

Non-medical treatment

There are different types of approaches but the best thing for a young patient is to understand the condition, a step which can be done through counselling including through cognitive-behavioural therapy (ex: goal-setting, role-play, self-monitoring). The main aspect resides in organisation, routine and structure. The behaviour during school hours should be carefully monitored through noise and visual stimuli control, by establishing an adequate deadline for tasks, a diversity and innovation in them and also though the teacher's proximity and influence.

If difficulties persist in the home environment, parents are encouraged to seek additional professional help including through behavioural management techniques. Children with mostly hyperactive and impulsive type ADHD are often helped at home by having an organised schedule, established limits and through adequate parenting approaches.

It has been reported that patients with ADHD tend to be bored more easily and because of this fact, immediate rewards are preferred compared to delay ones, even if this choice would reduce overall size of the rewards.

Medical treatment

A measure of ADHD and the responsiveness to

medication is through the electroencephalogram (EEG) which in ADHD has a consistent pattern of low frequency activity. In the diagnosis of ADHD, theta waves play an important role, being significantly increased in frontal regions in ADHD groups compared to the control group (Tye C., et al, 2014). The purpose of pharmacotherapy is to reduce symptoms and to bring the condition to a stable state, this being the case of long term ADHD with symptoms from moderate to severe. Studies have shown that ADHD is an independent risk factor for smoking with increased chances for an individual to start smoking earlier in life and with a higher risk of dependency. Although a precise mechanism has not been described, researchers consider that dopamine dysfunctions in the reinforcement processes might be a possible cause (Kollins S.H., et al, 2014). Besides smoking tendencies, individuals with ADHD are also at higher risk for substance abuse (Charach A., et al., 2011) and the use of psychostimulant drugs is controversial in patients that also have a substance-abusing problem.

The two main drugs prescribed in Romania are methylphenidate (MPH) and atomoxetine. MPH is a CNS stimulant, chemically related to amphetamine and by stimulating the central nervous system; it increases attention, alertness and lowers fatigue (Davițoiu A., ș.a., 2014). The long-term effects of MPH are unknown and treatment duration should not surpass 12 months, unless the physician considers there is an overall therapeutic benefit. Treatment for patients under 6 years old is not recommended. MPH is prescribed also off-label in MDD (major depressive disorder), in obesity, lethargy and bipolar disorders. Generally it is recommended for the last dose to be given at least 4 hours before going to bed, due to side effects (***., 2012). Sleep problems or difficulties with sleep onset and maintenance are reported within the use of psychostimulants. This problem can be also due to ADHD itself and it is often associated with anxiety or other behaviour disorders (parent reported prevalence ranging from 55% to 74%). Melatonin is prescribed in these cases, only for sleep onset while other drugs are prescribed also for a range of emotional and behavioural symptoms (clonidine/tricyclic antidepressants) (Efron D., et al., 2014). Atomoxetine is a selective norepinephrine reuptake inhibitor, used in the treatment of ADHD and has demonstrated efficacy, being preferred in individuals with co morbid anxiety, substance abuse, increased mood lability or tics. The mechanism of Atomoxetine is not completely understood but it acts as an indirect agonist of catecholamine signalling in the prefrontal cortex, modifying the signals to noise ratios, which are thought to influence the symptoms in the disorder. Benefits have been observed as early as one week after reaching therapeutic dose but evidence suggests that full effects may be observed after 6 weeks from the start of the treatment. Although ADHD was initially considered a developmental disorder, recent findings lean towards the idea of a disruptive disorder. Many researchers consider ADHD to be over diagnosed, especially due to inadequate diagnosis criteria (Leuchter A.F., et al., 2014).

Objective

This retrospective study of 73 paediatric patients was carried out in the Clinical Emergency Children's Hospital "Victor Gomoiu" in Bucharest and its main purpose was to evaluate the safety and effectiveness of treatment in children diagnosed with ADHD. The duration of the study was of 15 months, between January 2013 and March 2014. The study received approval from the Institutional Ethics Committee, and both parties (patients and their legal guardians) gave their consent to take part in the study by signing an Informed Consent Form.

Materials and methods

The study participants were ambulatory patients of the Emergency Children's Hospital "Victor Gomoiu". The study data was obtained from medical records pertaining to a variety of paediatric patients diagnosed with ADHD as well as other associated illnesses. Demographic features such as: age, sex, family background and social background were also recorded.

Subjects included in the study were paediatric patients diagnosed with ADHD according to DSM IV or DSM V or ICD-10 that tested positive for at least 3 out of 9 symptoms of inattention, at least 2 out of 5 symptoms of hyperactivity and at least one criteria out of 4 for impulsivity. The final diagnosis meant that symptoms should be present and identifiable for a minimum of 6 moths, and the condition should manifest in at least one of the following backgrounds: social, family or school. Autism, psychical illnesses and Down Syndrome were considered inclusion criteria.

There were no established exclusion criteria.

The children's symptoms were included in one of the following categories: attention deficit, hyperactivity or a combination of the two. The children selected in the study received medical treatment or other types of therapy, depending on the doctor's decision. The neuropsychiatric development was established by IQ measurement and by using the Portage Scale.

The Childhood Autism Rating Scale (CARS) was used to evaluate the symptoms of Autism. Other assessments were done to collect information regarding the quality of life as per the following procedures which will be discussed further on.

The medical treatment was analysed: type of drugs given, dosage, pharmaceutical formulation, length of treatment. We also analysed the types of non-medical treatments associated: psychological therapy, logopedic therapy, occupational and cognitive stimulation therapy, other types of therapy. Their inclusion in the overall treatment was the doctor's personal decision.

Monthly monitoring and identification of adverse events was done for each patient by analysing the type of medication given, adverse event onset, severity, dose optimization, withdrawal from treatment or change of medication.

Data was stratified for three age groups: preschool children (< 7years old), 12 to 18-year-olds and 7 to 11 - year-olds.

Results and discussions

Applying non-medical treatment or medical treatment in children diagnosed with ADHD, has the end purpose of reducing symptom severity and improving the

performance and task accomplishment at school, amongst family or any other social environment that the child is part of (Klassen AF et al, 2004). ADHD syndrome was diagnosed in 73 cases, out of which 63 patients (83.5%) had comorbidities. Only 10 patients appeared to be diagnosed with "pure" ADHD. The number of comorbidities was between 1 and 4 (Figure 1) out of which the most common were intellectual disability (ID), speech impediments and autism spectrum disorders (ASD).

Out of all study participants, 73.6% were males and 26.3% females (Figure 2). The average age for was 9.3 years (age range between 5 to 16 years) years for males and for females 8.7 years (age range between 3 to 13 years).

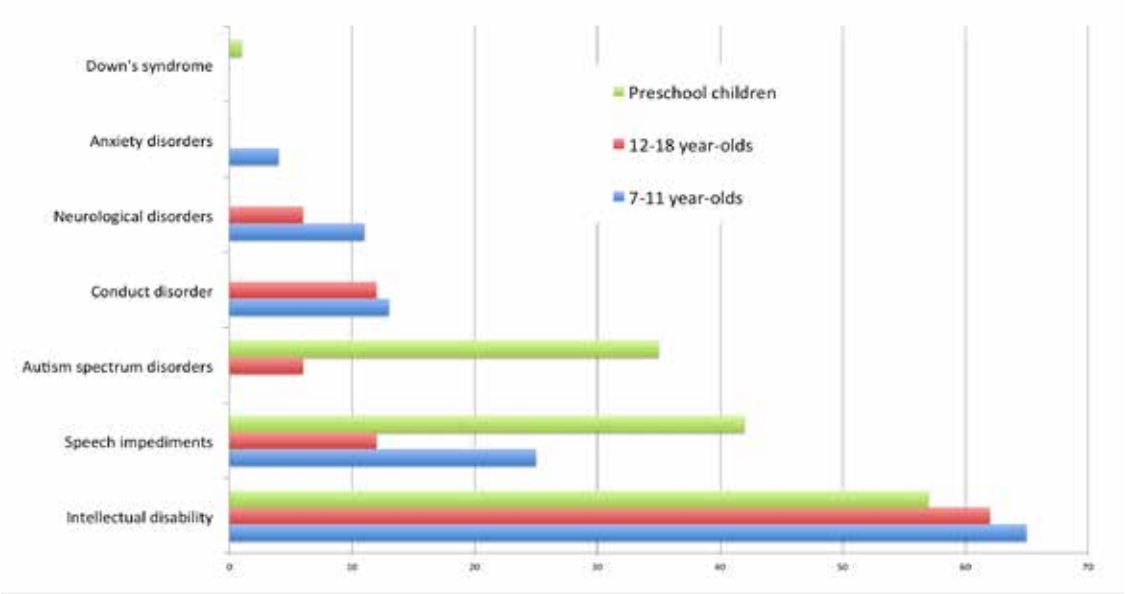

Figure 1. Comorbidities per age groups

Demographic, socio-economic and clinical characteristics of children with ADHD as well as their families are presented in Table I.

We couldn't establish a connection between socio economic influences, antecedents and ADHD subtype. XVIII The most frequent subtype of ADHD among subjects, in all three groups, was the Combined Type (Figure 3), followed by the Predominant Inattentive and the Hyperactive-Impulsive type.

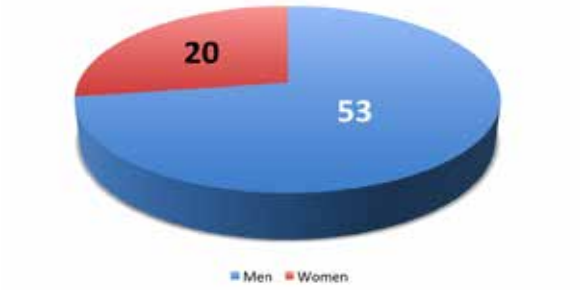

Figure 2. Gender of study participants diagnosed with ADHD

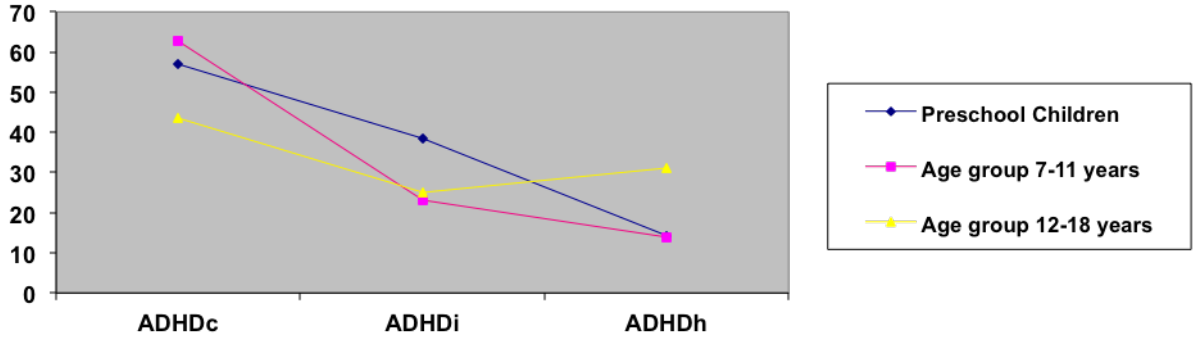

Figure 3. ADHD subtype amongst the three age groups

Feature	Number	%
Family status		
Nuclear family (two-parent family)	38	52.05
Single-parent family	22	30.13
Maternal assistant	5	6.84
Personal caregiver	8	10.95
Education		
Normal school/ kindergarten	68	93.15
Special school/ Special classes	5	6.8
Mistakes in educational assessment	20	27.39
Gender		
Male	53	73.6
Female	20	26.7
Age		
≤ 7 years	14	19,17
7 - 11 years	16	58.9
12 - 18 years	43	21.19
ADHD subtype		
ADHD, Combined Type	42	57.53%
ADHD, Predominantly Hyperactive-Impulsive Type	13	17.8%
ADHD, Predominantly Inattentive Type	18	24.65%
Types of associated illnesses		
Intellectual disability	46	63.01
Speech impediments	19	26.02
Autism spectrum disorders	10	13.69
Down's syndrome	1	1.36
Conduct disorder	10	13.69
Neurological disorders	7	9.58
Others	5	6.84
Antecedents		
Parent with ADHD	1	1.36
Prenatal seizures	3	4.1

Table I. Demographic, socio-economic and clinical status of children diagnosed with ADHD as well as their families

All age groups were confronted with socio economic issues: single-parent families (30.13%), personal caregivers (10.95%), maternal assistants (6.8%), all of these influencing the quality of life.

Initial treatment consisted in psychotherapy for preschool children. For the other age groups, the initial approach was a pharmacological one. The types of drugs administered were either Methylphenidate (71.4% -79.6%) or Atomoxetine (20.9% - 28.5%) – Figure 4.

The quality of life had suffered a severe impact for 50% of preschool children and for 60.4% of children between 7 and 11 years of age. For the other 50% of preschool children, 23.5% of the 7 to 11-year-olds and 100% of the 12 to 18-year-olds, the impact was of moderate proportions. 16.27% of the 7 to 11-year-olds, had the quality of life slightly affected by their condition.

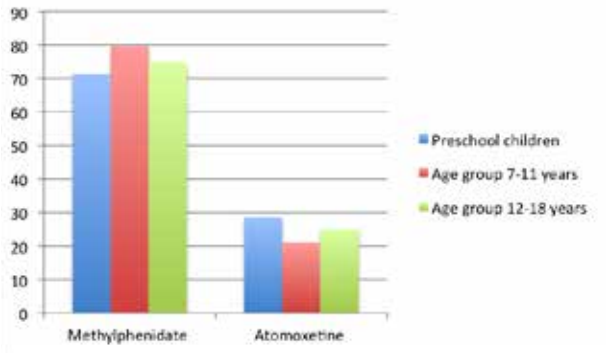

Figure 4. Pharmacological treatment for ADHD in the three age groups

The treatment improved the quality of life for 50% of preschool children and for 9.3% of children between 7-11 years old. For the rest of the children, there were no improvements concerning this issue.

Adverse events (AE) were reported in all three age groups: 25%, 23% and 30% - see Figure 5. The AE

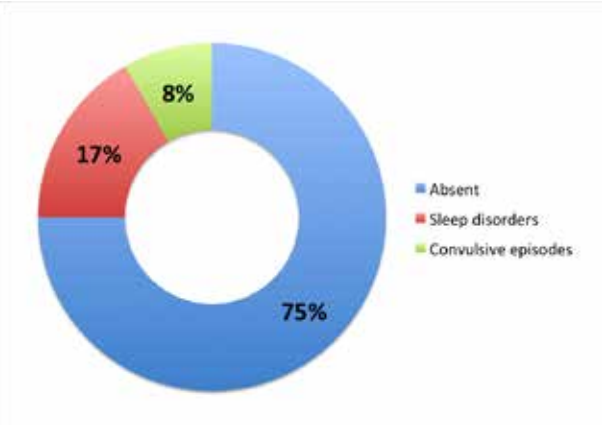

Figure 5. Adverse events reported in preschool children

reported amongst preschool children (a total of 14 children – 2 girls 14.28% and 12 boys – 85%) were sleep disorders (two cases – 14.28%) and convulsive episodes (one case – 7.1%). The two patients that were treated with methylphenidate, had sleep induction and sleep maintenance problems. The convulsive episode appeared after two months from the initial treatment with Atomoxetine and lead to the following therapeutic measures: discontinuity of Atomoxetine administration, the treatment of convulsions and continuity in cognitive behavioural therapies.

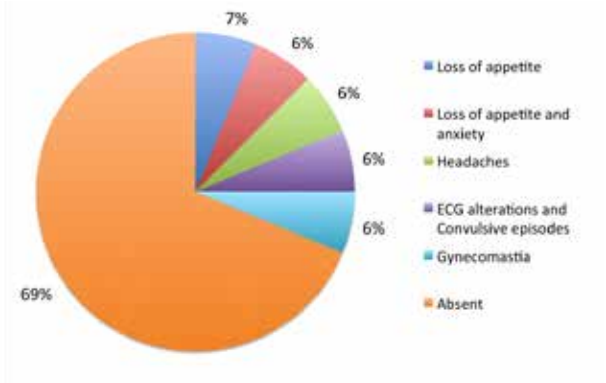

Figure 6. Adverse events reported in 12 to 18-year-olds

The total number of children with ages between 12 to 18 was 16: 4 girls, 12 boys with an average age of 13 years for girls and 14, 08 years for boys. The AE that were reported in this age group are presented in Figure 6. Five children that were receiving pharmacological treatment had an adverse event (31.25%). For these patients, symptoms appeared after treatment with Methylphenidate (2 patients - 12.5%) and after treatment with Atomoxetine (3 patients – 18.75%). Other adverse events reported were: headaches (1 subject) and ECG alterations associated with convulsive episode (1 subject) – for patients treated with Methylphenidate and loss of appetite (2 subjects), anxiety (1 subject) and gynecomastia (1 subject) for patients treated with Atomoxetine.

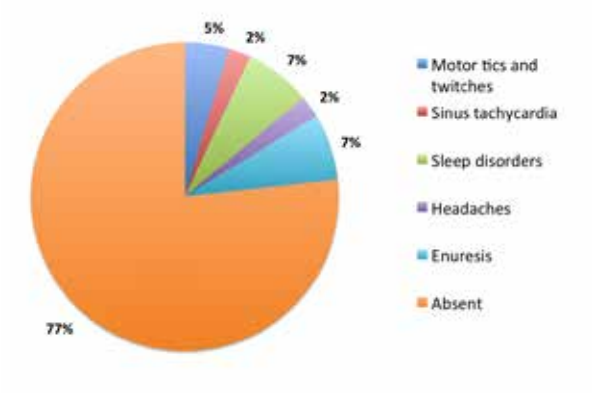

Figure 7. Adverse events reported in 7 to 11-year-olds

The AE reported in the 7 to 11 - year-olds group were the following: motor tics and twitches (1 subject), sinus tachycardia (1 subject), enuresis (2 subjects), diurnal enuresis (1 subject), headaches (1 subject), sleep disorders (2 subjects) and drowsiness (1 subject) – Figure 7.

In most cases (88.37% for 7 to 11 - year olds and 87.5% for 12 to 18 - year-olds) ADHD was diagnosed for the first time ("de novo") in children. Late diagnoses of this condition as well as a faulty education (20-27.39%) lead to increased rates of treatment abandonment and also difficulties in fitting in the family, school and other social environments.

Conclusions

Combined therapy (both medical and psychological) gave results but without being able to determine the measure in which either the psychological, pharmacological or combined treatment have influenced the end result.

Association between pharmacological and non-pharmacological treatment as well as family support contributed to the child's well-being and state of health.

A big contribution to a positive outcome in ADHD treatment belongs to a wide range of parties: medical specialists (the general practitioner, the pediatric doctor, the neuropsychiatrist), the psychologist, family members as well as the social environment surrounding the child.

We notice the absence of a National Therapeutic Guideline in our country as well as a common disinterest manifested by parents in following educational programmes and behavioural trainings for parents with children diagnosed with ADHD: manuals, videos on behavioral techniques and statements of other parents sharing positive experiences as an outcome, tips regarding practicing a balanced and a healthy diet with high quality nutrients, recommended regular exercises for children and teenagers diagnosed with ADHD as well as supervision of eating habits and the amount of fluids ingested and the relationship to ADHD. Fatty acid supplements are not recommended as a way of treatment.

Thus, the number of educational errors could be reduced or even be eliminated.

Training programs for schoolteachers would also improve the quality of life of children diagnosed with ADHD. The frequency of these trainings for both parents and teachers would delay the initiation of a pharmacological treatment, reducing thus the prevalence of adverse events and the costs of the treatment.

For a better assessment of safety and efficacy of pharmacological treatment in children diagnosed with ADHD, this study should be extended to other medical centres, interested in understanding better this condition. This would be a great contribution in solving the frequent impediments related to this disorder.

Early detection and management of side effects (dose optimization, change of medication, drug combinations that diminish or even eliminate the side effects, treatment interruption) improve compliance and adherence towards the given medical treatment but also improve the quality of life.

It is recommended, as a safety measure, to apply cognitive behavioural therapy as an elective treatment before any pharmacological approach - for preschool children and children younger than 12 years of age. In the case of teenagers, pharmacological treatment is recommended as a primary therapeutic measure.

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