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ADHD and comorbidity: The role of pharmacotherapy

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Abstract. In recent years, there has been an increase in the incidence of ADHD in children and adolescents. Many learning and behavioral problems are associated with this disorder due to difficulties in cognitive and metacognitive functions. Only when individuals improve these functions will they be able to integrate in the social environment. Skills such as self-awareness, self-regulation, and self-control can help children with ADHD develop their emotional intelligence to control their cognitive deficits and adapt to diverse areas. With the rapid development of science, several medical and behavioral methods have been proposed to treat ADHD, which have contributed significantly to the control of symptoms. However, medication is considered as a first-choice treatment to reduce the symptoms. The present study investigates the comorbidity of ADHD with other mental and developmental disorders as also the role and effectiveness of drug intervention in order to improve the quality of life of these children.

Keywords. Attention Deficit Hyperactivity Disorder (ADHD), Social/Emotional Development, Pharmacotherapy, Methylphenidate, ADHD Comorbidity, Metacognition, Emotional Intelligence

1. Introduction

According to Drigas & Driga (2019), Attention Deficit Hyperactivity Disorder (ADHD) is a complex neurological disorder, which still lacks scientific data concerning its nature and treatment methods. Some factors, such as the family's socioeconomic status, the existence of a psychiatric disorder in the mother, or smoking and alcohol consumption during pregnancy, have been proved to play an important role. The main symptoms of ADHD are lack of attention and impulsivity, resulting from a malfunction in areas of the brain that control executive functions. These functions, such as memory and attention, lay the foundation for an individual's organizational skills, their ability to focus on tasks, control of emotions, and the ability to self-evaluate. Most difficulties in executive functions and subsequently in cognitive and metacognitive skills result from damage in the prefrontal cortex, an imbalance between the prefrontal cortex and the amygdala, or a malfunction of the dopamine system. In addition, the cerebellum plays a critical role, as, without its contribution, the prefrontal cortical networks malfunction, and, thus, individuals cannot develop hierarchically organized behaviors (Drigas & Mitsea 2020; Heatherton & Wagner, 2011).

In order to control the symptoms of ADHD, a therapy based on the development of cognitive and metacognitive skills is required. According to Drigas et al. (2021), cognitive and metacognitive skills evolve progressively via an individual's self-awareness of their strengths and weaknesses, their self-observation, self-regulation, adaptation and flexibility in diverse areas (cognitive, emotional, and behavioral), recognition, discernment and mindfulness. People with high social and emotional intelligence are capable of better self-monitoring, a skill that is necessary to control behavior in children with ADHD (Drigas & Papoutsi 2018). Emotional intelligence focuses also on the individual's character and aspects of self-control, such as regulating impulses, which is one of the predominant difficulties of these children (Matthews et al., 2004). According to the 9-level model (pyramid) of emotional intelligence of Drigas & Papoutsi (2018), a person must go through the following stages to reach the highest level of Emotional Intelligence, which is Emotional Unity:

1) Emotional Stimuli (coding of emotional senses, attention)
2) Emotions' Recognition, Perception/Expression of Emotions (memory, perception, recognition, emotions' identification)
3) Self-knowledge (self-perception, awareness, self-observation)
4) Self-management (self-regulation, flexibility, self-control)
5) Social Awareness, Empathy, Emotion Discernment (awareness, monitoring, social recognition & flexibility)
6) Social skills, Specialization in Emotions (reflection, management of social problems)
7) Universality of Emotions, Self-realization (self-perfection, self-completion)
8) Transcendence (self-reflection, transcendental knowledge)
9) Emotional Unity (pure consciousness & fullness)

Only when people with ADHD develop their emotional intelligence and improve their metacognitive skills with pharmacological, behavioral, or alternative interventions will they be able to incorporate the appropriate cognitive and socio-emotional skills that will enable them to integrate into the social environment. (Drigas & Mitsea 2020; Drigas & Mitsea 2021).

2. ADHD and comorbidity

According to Drigas & Mitsea (2020), the collapse of self-regulation, one of the essential metacognitive functions, is associated with most mental and developmental disorders, such as attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, anxiety disorders, and learning disabilities. Attention Deficit / Hyperactivity Disorder can coexist with various other diseases, some more common than others. According to Biederman, Newcorn, & Sprich (1991), ADHD is the disorder with the highest rates of comorbidity, ranging from 30% to 50%; most frequently co-exist behavioral disorders, learning disabilities, oppositional defiant disorder, anxiety disorders and mood disorders (Saul, 2015). These coexisting situations can complicate the social and school life of children with ADHD, resulting in low self-esteem, interpersonal relationship problems, and social withdrawal (Koumoula, 2012).

2.1. ADHD and Oppositional Defiant Disorder and Conduct Disorder

Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) coexist more often with ADHD. Up to the age of 7 years, 35-60% of children with ADHD may be diagnosed at the same time with ODD, and 30-50% may be diagnosed with CD (Biederman et al., 1991). Children with ADHD and ODD or CD belong to a reasonably vulnerable group. The symptoms are more severe because intense antisocial behavior occurs early on with tendencies to engage in conflict, theft, lying, or aggressive behavior (Hinshaw et al., 1993). According to Edelbrock (1989), there are four stages of aggressive behavior in children with ADHD. In the first stage, a child's impulsivity is the basis for their disobedience and their desire to be the center of attention.

In the second phase, they start lying, cheating and causing problems. Even more intense aggressive behavior emerges in the third phase, where conflicting relationships with others, destructive behavior, and a tendency to stealing occur. In the fourth and final phase, the symptoms worsen, as a strong antisocial behavior emerges, with more severe destructive activity and tendencies to run away from home and school.

Vitello & Stoff (1997) stress the importance of impulsivity as a symptom of ADHD, which is the one that determines the intensity of antisocial behaviors. Furthermore, according to Goldstein & Goldstein (1998), comorbidity of ADHD with ODD and CD seems absolutely expected, as children with ADHD often clash with their school or family environment. In addition, there is a negative correlation with their peers and adults. Finally, regarding Greece, according to research by Kakouros & Maniadakis (1998), adolescents who had been diagnosed with ADHD in their childhood and still having symptoms were also diagnosed with CD at a rate of 75%.

2.2. ADHD and Mood Disorders and Bipolar Disorder

Emotional disorders that coexist with ADHD occur at a rate of 30-50% (McClelland et al., 1989). Many argue that depression, as a type of mood disorder, results from the disappointment and frustration that children experience due to their poor school performance and their rejection by those around them (Ostrander et al., 2006). Also, their dysfunctional interpersonal relationships to others, their tendency to misinterpret the reactions of others as aggressive towards them, and the frequent criticism and punishments by others due to their behavior result in depression (Capaldi, 1992). Finally, the process of differential diagnosis is essential because ADHD and depression have many symptoms in common, such as disturbed sleep, difficulty in concentrating, reduced memory, restless mobility, and irritability (Mclntosh et al., 2009).

There is a significant difficulty in differential diagnosis regarding the comorbidity of ADHD with Bipolar Disorder. The symptoms of a chronic hypomanic phase, such as tachylalia, hyperactivity, and distraction are also present in ADHD (Lazaratou, 2012). Studies conducted in the United States report a 70% to 90% of comorbidity rates among child population and a 30% to 40% among adolescent population (Biederman et al., 1999). According to studies by Faraona et al. (1997, b), bipolar disorder is widely coexisting with ADHD, ergo it has been proposed to be characterized as an additional type of ADHD. Finally, according to Wozniak et al. (2010), children with ADHD and mania have an even more severe clinical picture with a high incidence of depression and psychosis that affects their emotional and social functioning.

2.3. ADHD and Anxiety Disorders

According to Drigas & Mitsea (2021), uncontrollable stress is the "health epidemic" of our century. Mental disorders and mood disorders, premature aging, cognitive disorders, and learning disabilities are some of the implications associated with stress. The hormones of stress and happiness are a "hard" control system, as they play a crucial role in regulating emotions, mood, and behavior in various aspects. According to the research conducted to evaluate the coexistence of ADHD with anxiety disorders, the results are contradictory. According to Biederman (1991), anxiety disorders coexist with ADHD at a rate of 25% to 40%. Also, research by Russo & Biedel (1994) argues that the rates are higher in children belonging to the inattentive and distractible predominant type, with their anxiety symptoms significantly reducing in adolescence. Opposite studies observe that the coexistence rates of ADHD and anxiety disorders are higher in the combined type (Kakouros & Maniadaki, 1998).

2.4. ADHD and Learning Disabilities

Numerous studies support the correlation between ADHD and Learning Disabilities. Based on data from the National Institute of Mental Health (2012), 20% to 30% of children with ADHD also have Learning Disabilities. A survey conducted in Greece by Kakouros & Maniadakis (1998) observed 29 first and second grade school children diagnosed with ADHD. 50% of these children had a low performance in lessons and 75.9% had significant difficulty in meeting the school's learning requirements. The school performance of children with ADHD is disproportionate to their mental capacity. Also, they usually receive lower grades than their classmates, and it is very common that they are referred to special schools (Loe & Feldman 2007). According to Faraone et al. (1993), 56% of children with ADHD will require specialized support, 30% may have to attend the same class again, and 10% to 35% may drop out of school.

The most common particular learning difficulty that children with ADHD exhibit is dyslexia. More specifically, 8% to 39% of children have difficulty in writing and reading, 12% to 26% in spelling, and 12% to 33% in math (Willcutt & Pennington, 2000). Such highly frequent coexistence of ADHD with Special Learning Disabilities raises some concerns, as many argue that ADHD could be considered as a secondary condition of dyslexia (Pennington, 1991). In addition, many argue that school withdrawal that most children with learning disabilities experience due to their poor performance may lead to the difficulties in concentration and impulsivity. However, to date it remains unclear how these two disorders are related, while there's evidence that their etiology may be the same (Kakouros & Maniadaki 1998).

3. Pharmacotherapy

In their bibliographic research, Mohammadi and Akhondzadeh (2011) studied the forms of pharmacological interventions for ADHD and their effectiveness. Psychostimulants are the first choice of drugs for ADHD. About 70% of children treated showed an improvement in symptoms, and the benefits lasted up to two years. The most common side effects are reduced appetite, insomnia, increased anxiety and depression, tics, and irritability (Mohammadi & Akhondzadeh, 2007). Currently, methylphenidate (MPH) and amphetamine are the most widely used stimulants; they are relatively short-acting, lasting from 3 to 6 hours, and require two or three doses per day (May & Kratochvil, 2010). Dexmethylphenidate XR also seems to have similar efficacy to methylphenidate. However, its advantage is the longer-lasting effect at a lower dose (Greenhill et al., 2006). The symptoms usually subside within 30 minutes, and the effect lasts up to 10 hours.

Several non-stimulant drugs affecting noradrenergic and dopaminergic systems have proved to be effective too in treating ADHD. This group includes drugs with noradrenergic, dopaminergic, and serotonergic properties such as atomoxetine, venlafaxine, buspirone, cholinergic drugs, neuroleptics, and theophylline (Banaschewski et al., 2004). Atomoxetine is a selective norepinephrine reuptake inhibitor and it is the only non-stimulant drug approved by the FDA for treating ADHD (Wernicke & Kratochvil, 2002). Several studies have shown the efficacy of atomoxetine for ADHD, with daily doses ranging from 1 to 1.8 mg in total and with its beneficial effects lasting up to 24 months. In contrast to stimulants, which tend to treat the underlying symptoms of ADHD immediately after consumption, atomoxetine produce an improvement one to two months after reaching the recommended dosage (Wernicke &

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Kratochvil, 2002). However, common side effects include weight loss, poor appetite, nausea, insomnia, fatigue, dizziness, and irritability.

Several studies have shown the effectiveness of tricyclic antidepressants (TCAs) in treating ADHD, such as desipramine, imipramine, and nortriptyline. The advantages of TCAs include relatively long half-lives and positive effects on mood, stress, sleep, and tics (Mohammadi & Akhondzadeh, 2007). In addition, a few studies with monoamine oxidase inhibitors (MAOIs) have suggested that irreversible MAOIs and reversible MAOIs may improve the symptoms of ADHD. The mechanism of MAOIs in reducing the symptoms of ADHD is probably related to their ability to block the metabolism of noradrenaline and dopamine. However, the use of irreversible MAOIs (e.g., phenelzine, tranylcypromine) is severely limited, as they can cause hypertensive seizures. Therefore, reversible MAOIs (e.g., moclobemide, selegiline) need further evaluation.

While there is no doubt that medication is highly effective in treating ADHD, it is estimated however that 30% of children do not respond adequately to or cannot tolerate the medicine. On the other hand, herbal remedies have proved to improve ADHD-related behaviors (Brue & Oakland, 2002). For example, Ginkgo Biloba is somewhat effective in treating dementia and memory impairment. A review of 40 controlled trials with Ginkgo Biloba revealed a partial positive outcome in almost all individuals with cerebral palsy (e.g., concentration and memory difficulties). In addition, Ginkgo Biloba improves cerebrovascular blood flow and attention, and can help reducing hyperactivity. A study by Akhondzadeh et al. (2005) showed that Passiflora incarnata might be a new therapeutic agent for treating ADHD. In addition, Passiflora’s tolerable side effect profile is considered as an advantage in the treatment of ADHD.

Brown, Amler, Freeman, Perrin, Stein, Feldman, et al. (2005) researched therapeutic methods for children with ADHD. The purpose of their bibliographic research was to examine the short-term and long-term efficacy and safety of pharmacological and non-pharmacological interventions for ADHD, as well as the efficacy of a combined therapy. Three major data sources were reviewed for this purpose; the McMaster University Evidence-Based Practice Center, the British Columbia Institute for Child and Women's Health Research, and published reports of behavioral therapies in groups of school-age children with ADHD. A review by McMaster University Evidence-Based Practice Center on long-term studies of 12 weeks or more, examined 1) comparisons of drugs, such as stimulants versus antidepressants and 2) comparisons of different forms of the same drug. The tested stimulant drugs were methylphenidate (MPH), Dexedrine (DEX), and Pemoline (PEM). The review also compared tricyclic antidepressants versus placebo, and pharmacological versus non-pharmacological interventions (Brown et al., 2005).

The review concluded that the data supported consistently the efficacy of drug therapy in managing the underlying symptoms of ADHD, with no apparent differences between MPH, DEX, and PEM (Rapport et al., 1993). The most common side effects were loss of appetite, sleep difficulties, headaches, motor tics, abdominal pain, irritability, nausea, and fatigue (Brown et al., 2005). Methylphenidate has also proved to be more effective than desipramine (a tricyclic antidepressant) in improving children's alertness and their learning ability in couples (Quinn & Rapoport, 1975). The researchers did not reach further conclusions about the effectiveness of stimulants over tricyclic antidepressants in managing ADHD symptoms; however, they considered that antidepressants should be used in cases of severe side effects (Brown et al., 2005).

The researchers found that stimulant drugs are more effective than non-pharmacological interventions in controlling the underlying symptoms of ADHD. Numerous of research data confirm the effectiveness of methylphenidate in treating the symptoms of ADHD since it improves instantly the children's functionality in many areas. Even greater effects of the stimulant medication were observed with regard to attention, impulsivity, and social behavior in class. However, modest outcomes were reported on school performance (Brown et al., 2005). Also, they concluded that only drug treatment alleviated the underlying symptoms of ADHD in a consistent way. Behavioral interventions alone did not show any significant results as none were more effective in treating the symptoms than medication. Medication in combination with behavioral interventions has proved to be just as beneficial. In addition, some studies have found that combined therapies are better accepted by teachers and parents and can reduce the doses of medication required to achieve the same therapeutic goals. Based on long-term clinical experience, education and counseling of the patient, their family, and school staff are valuable and necessary complementary interventions in drug therapy, similar to most long-term treatments for chronic diseases (Brown et al., 2005).

In their research, Awami & Albanna (2020) studied the case of a 6-year-old boy who had ADHD with Autism Spectrum Disorder (ASD) and was treated with low-dose methylphenidate medication. ADHD treatment usually includes behavioral alteration methods and pharmacotherapy. Among the drug choices, stimulants are considered as first-line treatment for ADHD. However, while stimulant drugs are considered to be safe, they may have potential side effects (Plizska, 2007). Common side effects include anorexia, weight loss, poor growth, and emotional instability (Storeb et al., 2018).

The results of the research came after an interview with the parents. The boy was given a small dose of the drug, both in the long-acting form (controlled-release methylphenidate, 18 mg) and in short-acting forms (immediate-release methylphenidate, 2.5 mg). The child could not tolerate these drugs due to irritability, insomnia, and anorexia. Therefore, he received Adderall® XR at an initial dose of 5 mg. His parents reported that the child became lethargic about 1 hour after the first dose, showing reduced stimulation and excessive drowsiness. Therefore, after one day, the drug was re-administered in the form of Adderall® IR immediate release at 1.25 mg, and the child showed the same reaction. Due to parental concerns and possible side effects, the drug was then changed to atomoxetine 10 mg twice per day, to which the boy responded moderately in the following days, as his parents reported (Awami & Albanna 2020).

In their bibliographic research, Pitzianti, Spiridigliozzi, Bartolucci, Esposito & Pasini (2020) studied the effects of methylphenidate (MPH) on Attention-Deficit Hyperactivity Disorder (ADHD). Genetic research has revealed that dopaminergic and frontal system dysfunction is the neurobiological substrate of ADHD. In addition, the dopamine transporter (DAT) gene (SLC6A3) encodes the DAT protein, which controls the DAT concentration and determines ADHD-sensitivity, as well as response variability to methylphenidate (MPH) (Shang et al., 2010).

The researchers concluded that treatment with MPH in children with ADHD could improve attention and executive functions. Regarding the effectiveness of MPH, parents and teachers report that children improved their social interactions and their maladaptive and aggressive behavior in the classroom (Barkley, 1997). In addition, a previous study by Tucha et al. (2006) demonstrated that MPH reduces reaction time, improves alertness, attention, flexibility/shift of attention, and aspects of selective attention such as inhibition and focus in children with ADHD Although the improvement after using MPH is remarkable, children with

ADHD can improve further when cognitive and behavioral training programs are included in the therapy. Apart from the three major clinical symptoms (i.e., inattention, hyperactivity, and impulsivity), children with ADHD also have deficits in executive functions. A meta-analysis of the bibliography on ADHD showed that inhibition, working memory, and planning ability were the most substantial deficits found in all studies (Willcutt et al., 2005).

Also, scientific evidence has shown that dopamine transporter (DAT) genes could be considered as predictors of the MPH therapeutic response. Patients with ADHD who do not respond to MPH have a low DAT concentration, while patients who respond better to MPH therapy have a higher concentration. Finally, although further studies are needed on this matter, more advanced research has shown that Human Endogenous Retroviruses (HERVs) play a role in the etiology of ADHD, since their hyperactivity is typical in children with ADHD. MPH administration has been associated with decreased HERV-H activity, which coincides with the improvement of the underlying symptoms of the disorder (Pitzianti, Spiridigliozzi, Bartolucci, Esposito & Pasini, 2020).

Storebø, Krogh, Ramstad, Moreira-Maia, Holmskov, Skoog, et al. (2015) attempted to answer whether methylphenidate is beneficial or harmful in the treatment of ADHD in children and adolescents. For this purpose, a systematic review and meta-analysis of clinical trials was conducted, comparing all types of methylphenidate either with placebo or without drug intervention, in children and adolescents aged 3 to 18 years with ADHD or with tendencies for ADHD. The average age was 9.7 years.

The researchers found that methylphenidate reduced the symptoms of ADHD in children and adolescents and that it also had a small beneficial effect on their quality of life and general behavior. Methylphenidate use is also associated with a relatively high risk of non-severe side effects -such as decreased appetite and sleep problems- but not with severe ones. Just over 25% of the children and adolescents experienced non-serious side effects after treatment. Overall however, there is a lack of data on the long-term effects of methylphenidate in children and adolescents with ADHD (Storebø et al., 2015).

In their research, Knez, Stevanovic, Nasic, Doric, and Wentz (2021) studied the performance of children and adolescents with ADHD in the QbTest (Quantified Behavior Test) before and after a dose of methylphenidate (MPH). The QbTest consists of three primary parameters: 1) QbActivity, 2) QbImpulsivity, and 3) QbInattention, and is an approved tool by the US Food and Drug Administration (FDA) for the clinical evaluation of ADHD (Hollis et al., 2018). The most recent study by Ulberstad et al. (2020) showed that QbCheck, which is an online version of the QbTest, was able to distinguish between adolescents/adults with or without ADHD, with a diagnostic validity of 82.6%.

This study included data from 149 children and 215 adolescents who completed the QbTest. The main criteria for inclusion were children and adolescents aged between 6 and 18 years, with a confirmed ADHD diagnosis. The test was performed twice within the same day, before and up to three hours after MPH intake (Knez et al., 2021). QbTest provides data on the three main attributes of ADHD, namely attention, hyperactivity, and impulsivity (Hollis et al., 2018). During a test activity, a high-resolution infrared camera monitors the movements of the participant's head while stimuli appear on the computer screen. There are two versions of the test. One for children aged 6 to 12 years (QbTest) lasting 15 minutes and one for teens/adults aged 12 to 60 years (QbTest) lasting 20 minutes. The QbTest displays two different stimuli: a gray circle (target) and a gray circle with a cross (non-target). The QbTest plus consists of a rapid display of four different stimuli: a red and a blue circle, and a red and a blue square.

During the test, the participant is asked to press a button once every time a target signal appears that is of same color and shape as the preceding stimulus (Knez et al., 2021).

The results showed improved QbActivity scores in 71.7% of children and 76.2% of adolescents; improved QbImpulsivity scores in 50.4% of children and 44.7% of adolescents; and improved QbInattention scores in 85.1% of children and 91.1% of adolescents after drug administration. Improvements in one area were not necessarily producing an improvement in other areas, and no differences in response were observed in different ADHD subtypes. Also, the higher the QbTest score before the MPH uptake, the more notable the improvement in the respective area (Knez et al., 2021).

Grazioli et al. (2021) studied 24 children with ADHD compared to a control group of 25 peers with no diagnosis. The children with ADHD underwent a comprehensive clinical, cognitive and neurophysiological evaluation before MPH treatment and one month after treatment. For this purpose, a learning algorithm (ML) was used to categorize the responses to MPH. ML is a set of statistical procedures and algorithms that are increasingly used as a valuable tool for determining responses to medication (Wong et al., 2017). Symptoms were assessed by parents and clinicians before and after drug administration using questionnaires such as the Conners' Parent Rating Scale. Evaluations were performed during two time spots, one week before MPH and one month after continuous intake.

For all children, the diagnosis of ADHD was made according to the criteria DSM-5 (American Psychiatric Association, 2013). Specifically, 33% of children had ADHD with predominantly inattentive and distractible type, 11% with impulsive/hyperactive type, and 58% with combined type. Any diagnosis of other psychiatric disorders was not an exclusion criterion: 50% of participants were diagnosed with SLD, 17% of participants also had an Oppositional Defiant Disorder, 13% also suffered from an Anxiety Disorder, 8% of participants also had an Autism Spectrum Disorder, and 13% of participants also had a Mood Disorder. In total 21% of the children were diagnosed solely with ADHD.

All children completed four computer tasks using ANT (De Sonneville, 2000), which were administered in the following order: essential speed (BS), four letter focus (FA4L), shift focus (SSV), and prolonged focus (SAD). BS consisted of a simple reaction time (RT) task. During the FA4L, participants had to choose a target letter out of four when displayed in a relative diagonal position and ignore it when it appeared otherwise. SSV explored three different cognitive dimensions: vigilance, inhibition, and cognitive flexibility. Finally, SAD was used to assess attentiveness variability over time. NEPSY-II (Korkman, 2007) was also used, which is designed to evaluate neurocognitive abilities in children aged 3 to 16 years. In addition, a visual attention sub-test was included in this study, which assesses the speed and accuracy with which the child can focus selectively and maintain focus on visual targets. Finally, fNIRS (HbO) and deoxyhemoglobin oxyhemoglobin (HbR) data were processed using Homer2 v2.8 software (Huppert et al., 2009), measuring the average hemodynamic activation throughout the completion of tasks.

The results showed notable improvements in clinical and neuropsychological areas. Regarding the hemodynamic activation of the brain, no significant HbO changes were found after MPH administration. ANT scales also showed substantial improvements in children with ADHD. As expected, children with ADHD had also higher psychopathological characteristics and lower neuropsychological performance than the control group. Regarding their response to MPH, children with ADHD showed a significant improvement in clinical symptoms after one month of MPH administration.

Interestingly, the most severe symptoms were those that improved most after pharmacological treatment. As expected, a significant improvement in the neuropsychological profile of children with ADHD in all cognitive tasks was observed. In addition, according to CPRS (Conners' Parent Rating Scale) data, most children showed a remarkable improvement after MPH treatment, while a considerable improvement was also observed in the control group. Finally, the researchers concluded that MPH pharmacotherapy works in different areas of symptoms, while psychopathological comorbidity and neurophysiological characteristics may play a role in influencing the response (Grazioli et al., 2021).

4. Conclusions

The purpose of this study was the literature review of researches on pharmacological intervention methods for the socio-emotional development of children with ADHD, as well as the study of the comorbidity of ADHD with other mental and developmental disorders. Children with ADHD exhibit a set of symptoms. The main characteristics of the disease are inattention, hyperactivity, and impulsivity. To control these symptoms, it is necessary to develop emotional intelligence and to improve the cognitive and metacognitive skills, which are controlled and regulated by various parts of the brain.

Brown, Amler, Freeman, Perrin, Stein, Feldman, et al. (2005) concluded that stimulant drugs are more effective than non-pharmacological interventions in controlling the underlying symptoms of ADHD and that only drug therapy can produce a lasting improvement. Also, several studies (Knez, Stevanovic, Nasic, Doric and Wentz, 2021; Krogh, Ramstad, Moreira-Maia, Holmskov, Skoog, et al., 2015; Pitzianti, Spiridigliozzi, Bartolucci, Esposito & Pasini, 2020) argue that Methylphenidate (MPH) therapy in children with ADHD can improve attention and executive functions and has also a beneficial effect on the quality of life and behavior in general. The same view is shared by Knez, Stevanovic, Nasic, Doric, and Wentz (2021). They studied the performance of children and adolescents with ADHD in the QbTest (Quantified Behavior Test) before and after a dose of methylphenidate (MPH), observing an improvement in all symptoms. However, Awami & Albanna (2020), seem to have the opposite view concerning the administration of methylphenidate treatment, after studying the case of a 6-year-old boy with ADHD and Autism Spectrum Disorder (ASD), who was receiving the medication. The child became lethargic, exhibiting reduced stimulation, excessive drowsiness and anorexia, thus they are questioning the effectiveness of this drug. The discussion about the comorbidity of ADHD and the most appropriate rehabilitation methods has been of great concern to the scientific community. Further research is needed to clarify the mental and developmental disorders that coexist with ADHD and to develop more therapeutic approaches to improve cognitive and metacognitive skills in order to integrate these children into the social environment.

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